GRIGORE T. POPA UNIVERSITY OF MEDICINE AND PHARMACY IASI

Cardio-nephrology

– a complex interplay between cardiovascular diseases management and chronic kidney disease distinctive milieu

HABILITATION THESIS

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Contents

ABBREVIATION LIST

2D-STE	Two-Dimensional Speckle Tracking Echocardiography
ACC	American College of Cardiology
ACEi	Angiotensin Converting Enzyme inhibitors
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
AI	Artificial Intelligence
AKI	Acute Kidney Injury
AKI-D	AKI requiring Dialysis
AMI	Acute Myocardial Infarction
ANP	Atrial Natriuretic Peptide
ARB	Angiotensin Receptor Blockers
ARVD	Atherosclerotic Renovascular Disease
AUC	Area Under the Curve
BAT	Baroreflex Activation Therapy
BMS	Bare-Metal Stent
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CA	Carotid Atherosclerosis
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CAr	Cardiac Arrest
CAS	Carotid Artery Stenting
CCB	Calcium Channel Blocker
CCS	Chronic Coronary Syndromes
CEA	Carotid Endarterectomy
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKRT	Continuous Kidney Replacement Therapy
COPD	Chronic Obstructive Pulmonary Disease
CPM	Calcium-Phosphorus Metabolism
CS	Cardiovascular Surgery
CS-AKI	Acute kidney Injury following Cardiac Surgery
CTO	Chronic Total Occlusions

CVD	Cardiovascular Disease
DAPT	Dual Antiplatelet Therapy
DES	Drug-Eluting Stent
DGF	Delayed Graft Function
DM	Diabetes Mellitus
DOACs	Direct Oral Anticoagulants
E/e’	Early Mitral Inflow Velocity and Mitral Annular Early Diastolic Velocity
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ESC	European Society of Cardiology
ESKD	End-Stage Kidney Disease
FAC	Fractional Area Change
FDA	U.S. Food and Drug Administration
FFR	Fractional Flow Reserve
GI	Gastrointestinal
Hb	Hemoglobin
HD	Hemodialysis
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HGM	Heparin-Grafted Membrane
HOCM	Hypertrophic Obstructive Cardiomyopathy
Hs-CRP	High-sensitivity C-Reactive Protein
Hs-tnT	High-sensitivity-troponin T
HR	Hazard Ratio
HRV	Heart Rate Variability
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IQR	Inter Quartile Range
IL-18	Interleukin-18
ILR	Implantable Loop Recorder
INR	International Normalized Ratio
IVUS	Intravascular Ultrasound
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1
KRT	Kidney Replacement Therapy

KT	Kidney Transplantation
LA	Left Atrium
LAA	Left Atrial Appendage
LAAO	Left Atrial Appendage Occlusion
LAGS	LA Global Strain
LASr	LA Strain
LAS-a	LA late diastolic strain
LAS-e	LA early diastolic strain
LAS-s	LA Systolic Strain
LAVI	LA Volume Index
LF/HF	Low Frequency to High Frequency
LIDI	Longer Interdialytic Interval
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
LVGLS	LV Global Longitudinal Strain
LVMI	LV Mass Index
LVSRA	LV late diastolic Strain Rate
MACE	Major Adverse Cardiovascular Events
MD	Mean Difference
MDT	MultiDisciplinary cardio-nephrology Team
METs	Metabolic Equivalents
MI	Myocardial Infarction
ML	Machine Learning
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NHHD	No-Heparin Hemodialysis
NIH	National Institutes of Health
NKF-KDOQI	National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
NOAF	New-Onset AF
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OAT	Oral Anticoagulation Therapy
OSA	Obstructive Sleep Apnoea
PALS	Peak LA Longitudinal Strain
PCI	Percutaneous Coronary Intervention
PCWP	Pulmonary Capillary Wedge Pressure
PD	Peritoneal Dialysis
PH	Pulmonary Hypertension
PINNR	Percentage of INR readings in the therapeutic Range

PPI	Proton Pump Inhibitors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTRA	Percutaneous Transluminal Renal Angioplasty
PVD	Peripheral Vascular Disease
RAASi	Renin-Angiotensin-Aldosterone System inhibitors
RCT	Randomized Controlled Trial
RD	Renal Denervation
RH	Resistant Hypertension
ROI	Region Of Interest
ROS	Reactive Oxygen Species
RR	Risk Ratio
RV	Right Ventricular
RVFWLS	Right Ventricular Free Wall Longitudinal Strain
RVSP	Right Ventricular Systolic Pressure
SAVR	Surgical Aortic Valve Replacement
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SD	Standard Deviation
SDANN	Standard Deviation of the Averages of NN (Normal Sinus to Normal Sinus)
STEMI	ST-Elevation Myocardial Infarction
TAPSE	Tricuspid Annular Plane Systolic Excursion
TAT	Triple Antithrombotic Therapy
TRJV	Tricuspid Regurgitation Jet Velocity
TTE	TransThoracic Echocardiography
TTR	Target Therapeutic Range
Tx	Transplant recipients
UACR	Urine Albumin-Creatinine Ratio
UFH	Unfractionated Heparin
VF	Ventricular Fibrillation
VKAs	Vitamin K Antagonists
VT	Ventricular Tachycardia

REZUMATUL TEZEI

Această teză de abilitare, cu titlul „*Cardio-nefrologia – o interacțiune complexă între managementul bolilor cardiovasculare și mediul distinctiv al bolii cronice de rinichi*” oferă o prezentare generală și sintetică a principalelor mele preocupări dintr-un domeniu extrem de nou, cardio-nefrologia, o (potențială) supra-specializare care se ocupă cu managementul (epidemiologia, particularitățile de diagnostic, terapiile medicamentoase și intervenționale / chirurgicale) pacienților cu boală renală cronică (incluzând aici pe pacienții dializați și cei cu transplant renal) care prezintă patologie cardiovasculară.

Au fost abordate mai multe aspecte din perspectiva recomandărilor de diagnostic și tratament din cele mai noi ghiduri Europene de Cardiologie, cu sublinierea mai ales a lipsurilor de evidențe în ceea ce privește pacienții renali avansați (care adeseori au fost excluși din studiile clinice care fundamentează indicațiile) și a imposibilității de administrare a unora din terapii (limitări date de funcția deficitară a rinichilor). Această perspectivă a tezei este a unui medic cardiolog bun cunoscător și al ghidurilor nefrologice, dar și cu experiență în colaborarea cu centre nefrologice și de transplant renal de elită (atât din țară, cât și din Europa – EuDial).

Această teză de abilitare este structurată în conformitate cu recomandările Consiliului Național pentru Atestarea Titlurilor, Diplomelor și Certificatelor (CNATDCU). Prin urmare, ea trece în revistă activitatea mea profesională, academică și științifică din perioada post-doctorală (2018-2022), din cadrul Universității de Medicină și Farmacie „Grigore T. Popa” din Iași și a Institutului de Boli Cardiovasculare „Prof. Dr. George IM Georgescu”, Iași.

După actualul Rezumat, teza este alcătuită din patru secțiuni, după cum urmează:

Secțiunea I oferă un sumar al realizărilor mele profesionale, academice și științifice din ultimii 5 ani, după obținerea titlului de doctor în medicină din 2018.

Secțiunea II prezintă, pe scurt, una dintre cele mai importante direcții ale activității mele de cercetare postdoctorală, centrată pe diverse aspecte (de diagnostic și tratament) ale cardio-nefrologiei. Cercetările și investițiile din acest domeniu cardio-nefrologic (care nu are doar un singur sens – din perspectiva pacientului renal care dezvoltă patologie cardiacă, ci și perspectiva inversă – pacienți cardiovasculari care suferă o afectare reversibilă sau nu a funcției rinichilor) sunt extinse și incumbă multe resurse din mai multe motive: pacienți numeroși, patologie cardiacă variată, intervenții cardiovasculare complexe, medicație modernă și insuficient studiată.

Această secțiune are **8 capitole**:

- **Capitolul 1.** *Introducere în cardio-nefrologie* (în care descriu ce reprezintă această potențială supra-specialitate, de ce este nevoie de ea și cum se privesc diferite aspecte de epidemiologie, de diagnostic și de tratament medicamentos, intervențional percutan sau chirurgical – atât din perspectiva cardiologului, cât și a nefrologului). Cardio-nefrologia ar trebui nu doar să pună întrebări cu privire la pacienții cu patologie complexă, ci și să ofere soluții și să propună studii care să crească nivelul de evidență al terapiilor actuale.
- **Capitolele 2-4** pot fi privite ca un tot unitar pentru că prezintă din mai multe perspective o problemă foarte des întâlnită la pacienții cu boală renală avansată, și anume *indicația de tratament complex antitrombotic* (fie antiplachetar, fie anticoagulant, fie ambele), după cum urmează: capitolul 2: întregul spectru al bolii coronariene la pacienții renali – sinteza

evidențelor și propuneri de rezolvare a controverselor terapeutice existente; capitolul 3: modalități de reducere a riscului trombotic la acești pacienți cu indicație de anticoagulare; capitolul 4: problema (delicată) a *sângerării* la pacienții dializați, în condițiile unei indicații ferme de tratament antitrombotic (particularități de încadrare în grupe de risc, modalități de definire a sângerărilor, precum și modalitățile alternative de prevenție a trombilor. Ideea centrală este că pacienții renali avansați manifestă o coagulopatie divergentă (fie predispuși la sângerare, fie la tromboză), și atunci medicația antitrombotică (care adeseori nu este studiată la dializați) trebuie ajustată sau chiar exclusă.

- **Capitolul 5** tratează problema prevenției (primare și secundare) a *diferitelor forme de stroke* la pacienții renali (atât accidentul vascular ischemic, cât și cel hemoragic), iar în ultimul subcapitol atinge problema indicației de implantare percutană de ocluder de urechiușă atrială în cazul imposibilității anticoagulării orale cronice.
- **Capitolul 6** detaliază problema *morții subite cardiace* la pacienții cu boală renală în stadiul G5D (mecanisme fiziopatologice, practicile din timpul dializei, medicația antiaritmică, indicația de defibrilator implantabil).
- **Capitolul 7** este axat pe folosirea *tehnicilor moderne de ultrasonografie* (cardiacă și coronariană) ca predictori în boala renală avansată sau post-transplant renal (evaluarea funcționalității ventriculului drept și a atriului stâng după inițierea dializei, măsurarea non-invazivă a presiunii din artera pulmonară ca predictor al evenimentelor adverse post-transplant renal; și folosirea tehnicii de IVUS intracoronarian pentru a implanta un stent fără uzitarea substanței de contrast care ar putea agrava disfuncția renală preexistentă).
- **Capitolul 8** tratează două aspecte legate de *chirurgia cardiacă la pacienții renali*: (a) predictorii preoperatori de dezvoltare a injuriei acute renale; (b) o meta-analiză a principalelor complicații postoperatorii cardiovasculare la pacienții care deja au un transplant de organ (rinichi sau ficat).

Secțiunea III cuprinde obiectivele și direcțiile viitoare de perfecționare profesională, academică și științifică.

În ceea ce privește activitatea didactică, intenționez să includ studenții, medicii rezidenți și doctoranzii în cursuri dedicate pe teme de cardio-nefrologie (medicație și intervenții coronariene), mai ales că activitatea mea medicală este în continuare în cadrul laboratorului de Cardiologie Intervențională al IBCV Iași.

În ceea ce privește activitatea științifică, îmi propun să continui direcțiile lansate și prezentate până la momentul actual și să dezvolt altele noi:

- studierea tehnicilor de denervare renală la pacienții cu hipertensiune arterială rezistentă la tratament;
- utilizarea tehnicilor de inteligență artificială pentru generarea unor profile de risc hemoragic/trombotic la pacienții dializați cu indicație de tratament antitrombotic complex;
- întocmirea și analiza unui registru cardio-renal cu pacienții renali sau cu disfuncție renală care sunt revascularizați cu stent în centrul IBCV Iași;
- efectuarea de măsurători coronariene de înaltă performanță (rezerva fracțională de flux și ecografia intracoronariană) la pacienții dializați cu angina stabilă și leziuni coronariene intermediare.

Secțiunea IV include o listă de referințe bibliografice citate în prezenta teză de abilitare.

SUMMARY OF THE THESIS

This habilitation thesis, entitled "*Cardio-nephrology – a complex interplay between cardiovascular diseases management and chronic kidney disease distinctive milieu*" provides an overview and a summary of my main concerns in an extremely new field, cardio-nephrology, a (potential) sub-specialization that tackle the management (epidemiology, diagnostic features, drugs and interventional/surgical therapies) of patients with chronic kidney disease (including dialysis or kidney transplantation patients) who have cardiovascular disease.

Several aspects of the diagnosis and treatment recommendations in the latest European Guidelines for Cardiology were addressed, with particular emphasis on the lack of evidence for advanced renal patients (who have often been excluded from clinical trials underpinning the indications) and the inability to administer some of the therapies (limitations due to impaired kidney function). This perspective of the thesis is of a cardiologist well versed in nephrological guidelines and, but also with experience in collaboration with elite nephrological and kidney transplant centers (both in the country and in Europe - EuDial).

This habilitation thesis is structured in accordance with the recommendations of the National Council for the Attestation of Titles, Diplomas and Certificates (CNATDCU). Therefore, it reviews my professional, academic and scientific activity during the post-doctoral period (2018-2022), from the University of Medicine and Pharmacy "Grigore T. Popa" in Iasi and the Institute of Cardiovascular Diseases "Prof. Dr. George IM Georgescu" Iasi (IBCV).

Following this Abstract, the Thesis consists of four sections, as follows:

Section I provides a summary of my professional, academic, and scientific accomplishments over the past 5 years, following my 2018 doctorate in medicine.

Section II briefly presents one of the most important directions of my postdoctoral research activity, focusing on various aspects (diagnosis and treatment) of cardio-nephrology. Research and investment in this cardio-nephrological field (which has not only one meaning - from the perspective of the renal patient who develops cardiac pathology, but also the reverse perspective - cardiovascular patients with reversible/or not kidney dysfunction) is extensive and involves many resources for several reasons: numerous patients, various cardiac pathology, complex cardiovascular interventions, modern and insufficiently studied medication.

This section has 8 chapters:

- **Chapter 1.** *Introduction to cardio-nephrology* (describing what this potential sub-specialty is, why it is needed and how it looks at different aspects of epidemiology, diagnosis and drug treatment, percutaneous or surgical intervention – both from the perspective of a cardiologist as well as nephrologist). Cardio-nephrology should not only ask questions about patients with such complex pathology, but also provide solutions and propose studies that increase the level of evidence of current therapies.
- **Chapters 2-4** should be considered as a whole because they present from several perspectives a very common problem in patients with advanced kidney disease, namely the indication for complex antithrombotic treatment (either antiplatelet, anticoagulant, or both), as follows: chapter 2: the whole spectrum of coronary heart disease in renal patients – synthesis of evidence and proposals for resolving existing therapeutic controversies; chapter 3: modalities to reduce thrombotic risk in these patients receiving anticoagulation; chapter 4: The

(sensitive) problem of bleeding in dialysis patients (with a solid indication for antithrombotic treatment): features of risk groups, defining bleeding, and alternative ways to prevent thrombus formation). The central idea is that patients with advanced kidney disease manifests a divergent coagulopathy (either prone to bleeding or thrombosis), hence antithrombotic medication (which is often not studied in dialysis patients) should be adjusted or even ruled out.

- **Chapter 5** deals with the (primary and secondary) prevention of various forms of stroke in renal patients (both ischemic and hemorrhagic stroke; in the last subchapter deals with the issue of the indication of percutaneous implantation of left atrial appendage occluder in case of contraindication of oral anticoagulation.
- **Chapter 6** details the problem of sudden cardiac death in patients with G5D kidney disease (pathophysiological mechanisms, dialysis practices, antiarrhythmic medication, and indications for implantable defibrillator).
- **Chapter 7** focuses on the use of modern (cardiac and coronary) ultrasonography techniques as predictors in advanced kidney disease or post-renal transplantation (e.g., assessment of right ventricular and left atrium function after initiation of dialysis, non-invasive measurement of pulmonary artery pressure as predictor of post-renal transplant adverse events, and the use of the intracoronary IVUS technique to implant a stent without the use of a contrast agent that could aggravate pre-existing renal dysfunction).
- **Chapter 8** deals with two aspects of cardiac surgery in renal patients: (a) preoperative predictors of the development of acute renal injury; (b) a meta-analysis of major postoperative cardiovascular complications in patients who already have an organ transplant (kidney or liver).

Section III sets out the objectives and future directions for professional, academic and scientific development.

Regarding the didactic activity, I intend to include students, resident doctors and doctoral students in dedicated courses on cardio-nephrology (medication and coronary interventions), especially since my medical activity is within the Interventional Cardiology laboratory of IBCV Iasi.

Regarding the scientific activity, I propose to continue the directions launched and presented until the present moment and to develop new ones:

- study of renal denervation techniques in patients with treatment-resistant hypertension;
- the use of artificial intelligence techniques (machine learning) to generate hemorrhagic / thrombotic risk profiles in dialysis patients with indication for complex antithrombotic treatment;
- design and analysis of a cardio-renal registry with kidney dysfunction patients who received a percutaneous coronary intervention with a stent in the IBCV Iasi center;
- performing high-performance coronary measurements (fractional flow reserve and intracoronary ultrasound) in dialysis patients with stable angina and intermediate coronary lesions.

Section IV includes a list of bibliographic references cited in this habilitation thesis.

SECTION I. Overview of personal professional, academic, and scientific accomplishments

I am an Associate Professor at the Department of Internal Medicine, Nephrology and Geriatry at "Grigore T. Popa" University of Medicine and Pharmacy from Iasi, and a senior interventional cardiologist at the Institute of Cardiovascular Diseases "Prof. Dr. George IM Georgescu", Iasi, Romania.

My career path started with one desire (to learn to be a better human being) and two main strengths (enthusiasm and discipline). During my professional journey, esteemed mentors, colleagues, dear patients, and students shaped my scientific, medical, and academic skills and helped me reinforce the value of authenticity and honesty in science, medicine, and academia. These values are central to the structure of my habilitation thesis and constitute the framework I wish to inspire and pass on to my students, colleagues, and future doctoral students.

1. Professional road map: from residency to senior FESC interventional cardiologist and public health management specialist

My option for Cardiology was outlined during my university years (I graduated from the Faculty of Medicine of the "Gr. T. Popa" University of Medicine and Pharmacy in Iasi, in 2004, as Head of Promotion). After a cardiology scholarship in 2003 at the "Alberts-Ludwigs Universitat" and University Hospital of Freiburg, Germany, inspired by prof. George IM Georgescu's rigor and passion for medicine at the patient's bedside, working with students, and his scientific research, I decided to pursue Cardiology as a specialty in 2005.

My residency in cardiology started at the University Emergency Hospital - Bucharest, at the Internal Medicine III and Cardiology II Clinics. The meeting with the academician professor Dr. Leonida Gherasim (a man who, through his high academic and human stature, inspired me and helped me in the different stages of my career) has contributed fundamentally to my training as a doctor and university professor.

I gained clinical experience in USTACC after my activity at SUUB (at least five-night shifts per month in the period 2005-2010) and, especially since 2008, in the Cardiac Catheterization Laboratory, where I entered daily all the procedures of coronary angiography and various arterial percutaneous angioplasties.

The next stage in my professional development was my return in 2011 to Iasi, to the Institute of Cardiovascular Diseases, as a cardiologist in the department of Interventional Cardiology, to substantiate an essential event for the region of Moldova, at the initiative of Professor Dr. Grigore Tinică: implementation of the national program/priority action for percutaneous dilation of patients with STEMI, funded by the Ministry of Health. Thus, being one of the four interventional cardiologists on the team, we ensured the non-stop on-call program and 24/7 availability and contributed to increasing the number of patients who benefited from interventions (from 400 STEMI interventions-year in 2011 to up to 1,050 interventions in 2018).

An important element leading me to follow a specialization in acute myocardial infarction was the completion of the postgraduate intervention course *"CardioSkills"* –

"Frankfurt 2010: European specialization course in interventions for acute myocardial infarction (emergency PCI for STEMI)". Subsequently, I performed as an independent operator approx. 200 STEMI interventions per year and 250-300 elective percutaneous coronary dilations per year in the last 10 years.

At the same time, in 2013, I was appointed by competition as the medical director of the "Providența" Polyclinic. In addition to the medical activity as a primary care cardiologist (consultations, echocardiography, and ECG effort tests daily, over 2500 / year), I provided the medical coordination activity in over 26 specialties and 44 medical staff in 20 medical offices. This activity lasted for four years, helping me extend my vision regarding health policies and shaping my ability to coordinate a large medical team. I mention that I currently hold a Health Services Management Certificate issued by the Ministry of Health.

The most important event of my career was the meeting with Professor Dr. Adrian Covic that led to the start of my academic career (assistant professor 2016 – present), the intensification of my medical career, and the reinforcement of my scientific activities.

My appointment as Head of the Department of Interventional Cardiology at the Institute of Cardiovascular Diseases between 2018 and 2021 opened up numerous medical and scientific opportunities to implement several projects. In addition, for three years, I became the regional head of the action program – priority AP-IMA, being responsible for virtually all cases of acute myocardial infarction in the Moldova region.

Between 2019 and 2021, I was appointed National Coordinator of the Cardiology Program – percutaneous interventional treatment of cardiovascular diseases at the National Health Insurance House level. We started updating the protocols for including patients in programs and resizing funding by regional centers from this position.

Also, I am a Fellow of the European Society Cardiology (FESC) professional member and also a member in the Workgroup of Thrombosis from the ESC.

2. Academic activity: from teaching assistant to associate professor

Few interventional cardiologists across the country also make teaching and communicating with students an active concern. My teaching activity started in 2005 to 2010 when I was a resident at SUUB when together with Prof. Dr. Vinereanu participated in the composition of courses, internships, case presentations, and workshops for cardiology and internal medicine students. For the past five years, along with Prof. Dr. A. Covic, I have been involved in all three levels of medical education at the University of Iasi: students, residents, and doctors in post-university education. I participated in the elaboration of teaching materials and knowledge verification tests. I guided undergraduate papers (10 students) and involved the residents in documentaries and syntheses on various topics.

One of the recent development directions (both scientific research and academic practice) is to explore the significant achievements of artificial intelligence in the medical field. In 2020, with Prof. Dr. Adrian Covic, I managed to propose for approval at UMF Iasi an optional course in *Artificial Intelligence in Medicine* for 5th-year medical students, where I was appointed course holder.

I am the sole organizer of interventional cardiology workshops for students in Iasi. Also, I am currently the only mentor to guide residents in interventional cardiology.

3. Scientific accomplishments: publications and research (team and projects)

My research activity was greatly influenced by the collaboration with Prof. Dr. Adrian Covic and his coordinated research team. Under his leadership, I completed my doctoral thesis in 2018, with a topic on the interface between emergency cardiology - interventional cardiology, and nephrology: "*Renal and metabolic morpho-functional profile of patients with AMI revascularized by primary coronary angioplasty*". I started with three studies that targeted acute myocardial infarction patients, focusing on different metabolic and vascular parameters (with renal function and renal artery stenosis in the foreground).

Thus, in 2015, we were the first from the international academic community to publish data on the incidence of renal artery stenosis in patients who have suffered from acute infarction and primary angioplasty in the Journal of American Heart Association (ClinicalTrials.gov identifier: NCT02388139). We also developed a project to assess hydration status (ClinicalTrials.gov Identifier: NCT02655341) by which we proposed to measure the hydration of patients with STEMI both before and after the acute percutaneous dilation procedure, a factor incriminated in STEMI cause. Another important project carried out under my coordination (and published in a journal with a high impact factor) was aimed to optimize the prediction power of the complexity scores of coronary lesions (SYNTAX and clinical SYNTAX) that predict the presence of renal artery stenosis.

The collaboration with the *Cardiovascular Surgery Clinic* in Iasi resulted in another important project, its topic being the only one of its kind in the country: the structure and functioning of the Heart Team at the institutional level. The need for a multidisciplinary approach is also highlighted by numerous reviews, which show that: A) for 20-40% of coronary patients, revascularization procedures are under-used; b) medical discussions in complex situations are absent, and revascularization techniques are inadequately used. Team discussions can prevent *"specialty bias",* with many patients being advised and treated according to what the specialist knows better. We have obtained the approval of the Ethics Committee of UMF and IBCV Iasi for this project, and we have implemented procedures for operating and optimizing decisions at the institutional level.

At the beginning of 2017, I was part of an internal grant team at UMF Iasi for the project: "*Morphoatomical and Pathophysiological aspects of coronary Artery Bypass Graphing in terms of long-term outer (CABOT) 29031/12.2016*", as an interventional cardiologist alongside cardiovascular surgeons and radiologists. We monitored the patency of arterial grafts on coronary arteries in the long term by combining images acquired at the cardiac catheterism with those obtained at the coronary CT of IBCV Iasi.

At IBCV Iasi, one of the most significant projects with European funding was implemented under the Romanian Academy of Medical Sciences (ASM) coordination. This project is the second-largest in Romania, after the one with the Măgurele laser. It has more than 12 million EUR in funding. In this project, I am employed as a specialist doctor and researcher, managing the external relationship with the coordinating staff in Bucharest. It is to be noted that the center in Iasi benefits from a new Siemens angiography, modern angiography materials, and a high-performance IT system. The Funding Contract is 2/Axa 1/31.07.2017/107124 SMIS, Signed with the Ministry of Regional Development, Public Administration and European Funds (MDRAPFE) as Managing Authority for the

Competitiveness Operational Program 2014-2020 and with the Ministry of Research and Innovation as Intermediate Body for Competitiveness Operational Program 2014-2020.

The project title is: *"Development of public infrastructure for research, development, and creation of a new infrastructure" – project co-financed by the European Regional Development Fund (ERDF) through the Competitiveness Operational Program 2014-2020*. The project's general objective is to increase the research capacity of 17 Romanian medical centers (research centers) in the field of angiography using the angiography systems purchased in Phase 1 of the project. With the involvement of 100 patients on average in each research center, the clinical research is part of the *emerging cluster AngioNET. The role of the cluster is to stimulate the medical research activity in Romania, with direct effects on improving the quality of life*. (see https://angionet.ro)

The current European project where I am involved is CARDIO SCARS IN CKD (PN-III-P4-ID-PCE-2020-2393). The main aim of the study is to holistically assess the CV risk in a CKD population, following COVID-19 SARS-CoV-2 infection, with a focus on the endothelial dysfunction as compared to a control group of matched CKD patients by using clinical evaluation, flow-mediated dilatation, carotid-femoral pulse wave velocity, intima-media thickness, echocardiographic parameters, lung ultrasound, bioimpedance spectroscopy and a series of novel biomarkers, to determine the long-term impact of this disease on CV and renal outcomes (see https://cardioscarsinckd.grant.umfiasi.ro).

I am employed as a researcher at ASM, and I am a founder and delegate member of UMF Iasi in this newly established ANGIONET CLUSTER. The ANGIONET cluster aims to access European funding for multiple national centers and underpin competitive European scientific research projects in the health sector. My presence at UMF Iasi as a member of the founding committee of the cluster will ensure our presence and visibility in future research directions funded by the Romanian Academy of Medical Sciences.

In the following lines, I present my scientific research projects based on Artificial Intelligence that I completed after fruitful cooperation with Prof. Dr. Adrian Covic and a team of collaborators, leading to the publication of several scientific articles:

1. Using Artificial Intelligence Resources in Dialysis and Kidney Transplant Patients: A Literature Review. Burlacu A., Covic A. https://doi.org/10.1155/2020/9867872
   [Impact Factor: 3.411]
2. Challenging the supremacy of evidence-based medicine through artificial intelligence: the time has come for a change of paradigms. https://doi.org/10.1093/ndt/gfz203
   [Impact Factor: 5.992]
3. Curbing the AI-induced enthusiasm in diagnosing COVID-19 on chest X-Rays: the present and the near-future. https://doi.org/10.1101/2020.04.28.20082776
4. The collaboration with the Clinic of Gastroenterology at St Spiridon Hospital in Iasi led to the implementation of several AI algorithms (artificial neural networks) aimed to be used in the non-invasive diagnosis of endoscopic and histologic activity in inflammatory bowel diseases: A machine Learning model Accuracy Predicts Ultrasound Colitis activity at one year in patients treated with anti-tumor necrosis factor α agents. https://doi.org/10.3390/medicina56110628
   [Impact Factor: 2.430]

The collaboration with the Dialysis Center within C.I. Parhon Hospital in Iasi resulted in elaborating at least three directions.

Firstly, we have compiled a *register of dialyzed patients* who have received a coronarography indication, and we have separated these patients into different batches: dialysis with normal coronary heart, dialysis with tricoronary lesions, or stenting lesions. Beyond the follow-up they receive at the dialysis center, coronary dispensation provides additional information on patients who have often been excluded from clinical trials and do not have clear treatment indications.

The *FIDEL project* (Ffr&IVUS in Dialysed patients with ELective indication of coronary angiography) is the first to combine high-performance coronary measurements (fractional flow reserve and intra-coronary ultrasound at dialytic patients with stable angina and intermediate coronary lesions). Patients to be stented or those with normal angiographic epicardial coronary arteries are excluded. This is a pilot project which will include 15 patients and for which I intend to obtain funding through a national grant.

In collaboration with Prof. Dr. Adrian Covic, we also started a project for dialysis patients to catheterize pulmonary artery with the aim to obtain measurements of pulmonary pressures and resistances. This patient category seems to have a multi-factorial aggravating pulmonary arterial hypertension, which we intend to explore. Arterial-venous fistula, variations in hydration status, or the dialysis regime may be incriminated in the etiology of pulmonary hypertension.

We have recently initiated another research project on dialyzed patients requiring chronic oral anticoagulation for atrial fibrillation. Considering the context of hematological complications (excess thrombosis but also higher hemorrhagic risk) in advanced renal disease and the unpredictable response to anticoagulant treatment, it has been observed that the permeability of thrombus can have predictable power for ischemic or hemorrhage events. In collaboration with the Hematology Clinic at the Regional Oncology Institute, we intend to measure this permeability coefficient in dialysis patients. We initiate treatment with antivitamin K or apixaban and follow the correlation between this parameter thrombotic or hemorrhage events. For this project, we will apply for an internal UMF grant.

In collaboration with the San Gerardo di Monza University Center and Hospital, Ospedale, Italy, and the Nephrology and Internal Medicine Clinic - Geriatrics at the C.I. Parhon Hospital, I was included as the principal investigator in the AGE-AF-OAT Multi-ventricular observational study. This study aims to identify clinical, cognitive, and socio-demographic factors associated with chronic oral anticoagulation strategies in elderly patients with AF and moderate-severe chronic kidney disease (CKD) (glomerular filtration rate of 15-50 $ml/min/m^2$). Our objective is to assess the safety and effectiveness of these patients' different thrombosis prevention strategies.

My most important concern, which has resulted in 10 articles with IFs over 5, is the research of the European Cardiology Society and KDIGO (Kidney Disease Improving Global effects) guidelines and the important nephrology studies on the protocols of antithrombotic treatment (classical anticoagulants, oral or subcutaneous, antiplatelets and combinations, and triple therapy) in patients with chronic renal disease. We have explored antiplatelet therapy (according to the DAPT guidelines over the last three years) for dialysis patients requiring stents, translating the protocols and algorithms recommended by the ESC for the general

population to the population of patients with advanced renal disease. The latest Article (as the leading author) is currently being published in the Nephrology Dialysis and Transplantation journal and is endorsed and supported by EuDial (European Dialysis working Group) in a team of highly competent authors.

My current position places the Department of Cardiac Catheterization and Angiography on a spinning plate between the Clinics of Cardiovascular Surgery, Cardiology, Nephrology, Dialysis, Geriatrics, and Hematology, each completed and future projects.

Another project initiated recently is based on a collaboration between the Institute of Macromolecular Chemistry "Petru Poni" from Iasi (an Institute of the Romanian Academy, represented by the Researcher Mariana Pinteala), CEMEX (Advanced Research and Development Center in Experimental Medicine) and the Department of Interventional Cardiology. The researchers at Petru Poni have the capacity to generate nanoparticles to magnetize and "cover" with drugs (modern anticoagulants, antiplatelets). The goal is to cover the architecture of metal stents with these nanoparticles and evaluate their relationship with the endothelium in laboratory animals within CEMEX. To date, there is exceptionally recent research with preliminary studies that somehow places us among the first teams to study this. I also intend to attract funding from a national grant for this project.

In line with my latest published articles, together with Prof. Dr. A. Covic and the Cardiology Centers in Iasi, Timisoara, and Bucharest, we intend to start a collaboration between the Romanian Cardiology Society and the Romanian Nephrology Society for the development of antithrombotic treatment protocols (antiplatelets and anticoagulants) for patients with chronic renal disease and acute coronary syndrome or atrial fibrillation. These protocols are of extreme use in clinical practice.

Moreover, I have been in contact with the private IT industry and the Computer Science Faculty within "A. I. Cuza" University in Iasi to develop dedicated software (via OWL programming) to be available to the medical practice and on-call rooms. The software is integrated with the medical algorithms from the guidelines, and by straightforward questions facilitated by the software, doctors can decide which anticoagulant/antiplatelet treatment to administer and for what duration in patients with varying degrees of renal dysfunction.

At this point, the articles I published as the leading author in collaboration with the teams mentioned above have a cumulative impact factor (FCIAP) of 300, as follows:

Hirsch index (Clarivate Analytics)	11
Number of publications in Clarivate Analytics	70
FCIAP	220
Total number of citations (Clarivate Analytics)	320
Hirsch index (Google Scholar)	14
Hirsch index (Scopus)	11
ORCID	https://orcid.org/0000-0002-3424-1588

In conclusion, considering all the projects I have been involved in and the projects I plan to initiate, I can provide the premises for personal development in all three directions of my career: clinical medicine, academia, and science.

SECTION II. Scientific achievements

Chapter 1. Introduction. What is cardio-nephrology and what should it be?

Interactions between the heart and the kidneys will exist and manifest whether one wants them to or not; physiological as well as pathological. Similarly, the (hopefully good) crossroads of cardiologist and nephrologist. From both a theoretical (pathophysiological) and clinical (pathological) standpoint, the requirement for a cardio-nephrology specialization (or "supra-specialty") appears to be well warranted.

A recent paper raised the issue regarding the "*need for a cardio-nephrology subspecialty*" [1]. Another first-class editorial published in 2017, raised "*a call to action to stimulate universities, medical schools, and teaching hospitals to create a core curriculum for cardiorenal medicine, as has been done for critical care nephrology, cardiac critical care, and other disciplines that bridge the knowledge and skills between fields of cardiology and nephrology"* [2].

Examining the historical background of specialty areas such as cardiology (17th century) [3], nephrology (1960) [4], gastroenterology (1980) [5], there are parallels between the current situation and specialties that were originally introduced in internal medicine training. Internal medicine branched off into cardiology, nephrology, and gastroenterology at the right time, when specific guidelines and technology advancements in certain diagnostic and therapeutic techniques permitted them to self-delimit as different medical fields (e.g., assessment of blood circulation and cardiac anatomy and pathology, auscultation, cardiac catheterization [3], biopsy needle, hemodialysis, microscopy, organ transplantation [4], or the pioneering of endoscopy [5]).

Furthermore, scientific research revealed that hospital admissions to standard clinical specialties were inappropriate and overwhelming, that total assessment was required for optimum patient management, and that there was a level of lack of education and ignorance among medical staff on the principles of care of a particular missing medical field [6].

Modern diagnostic and therapeutic methods have been developed that are friendly and safe for cardio-renal patients, such as the low-contrast percutaneous coronary interventions (PCI) using intravascular ultrasound (IVUS) [7], drug-eluting stents (DES) requiring a short course of dual antiplatelet therapy (DAPT), which may be ideal for patients with end-stage kidney disease (ESKD) [8], or advanced heart failure therapies such as the left ventricular assist device implantation [9]. These contemporary technologies may form an arsenal for a responsible and safe fight against cardio-renal conditions, laying the groundwork for an unique and sustainable medical field.

Taking into account the current state of the junction of cardiology and nephrology, it is clear that all of the patterns listed above are also being recognized in the cardio-renal sphere. To begin, I coined the nomenclature and developed this central theme in the following papers.

1. **Burlacu A.**, McCullough PA, Covic A. *Cardionephrology from the point of view of the cardiologist: no more agree to disagree-getting to "yes" for every patient*. Clinical Kidney Journal, Volume 14, Issue 9, September 2021, Pages 1995–1999. https://doi.org/10.1093/ckj/sfab092
   [Impact Factor: 4.452]
2. **Burlacu A.**, Covic A. *The Devil Is in the Details When Considering the OAC Efficacy-Safety Equation in Dialysis Patients*. Journal of the American College of Cardiology, Volume 76, Issue 3, 21 July 2020, Pages 349-350, https://doi.org/10.1016/j.jacc.2020.03.085
   [Impact Factor: 24.093]

From a nephrologist's perspective, *"cardiovascular aspects do not receive the attention that corresponds to their burden of disease*". Additionally, many less studies address the inverted context of CKD risk in predominantly cardiovascular patients. Specifically, the majority of acute heart failure (HF) research focused on short-term consequences such as acute kidney injury (AKI) [10, 11]. Three out of four studies examining the likelihood of developing ESKD in cardiovascular patients investigated just a subset of individuals (those with comorbidities such as diabetes mellitus (DM) or CKD), leaving the broader population untouched [12-14].

At the very least, the cardiologist's perspective is worth examining, as cardiovascular disorders appear to be associated with an increased risk of kidney failure as well [15, 16]. HF, atrial fibrillation (AF), coronary heart disease, or stroke were all related with the progression of CKD and development of ESKD, with heart failure being the most robust predictor [15]. It is critical to emphasize that evidence of the effect of cardiovascular illness on the long-term risk of CKD development is being ignored at the moment, both in the scholarly literature and in clinical practice.

All of these factors contribute to suboptimal, unsafe, and ignorant patient management in nephrology and cardiology departments, where inter-specialty disagreements are the norm rather than the exception; one can easily see this omission in the unexpectedly and unjustifiably high rates of mortality and cardiovascular events in advanced kidney patients in the twenty-first century [17].

Inter-specialist conflicts often arise as a result of divergent perspectives on pathophysiology, risk factors, diagnostic procedures, and specific treatment responses in overlapping cardiovascular and renal illnesses. On the one hand, Diez and Ortiz concisely and precisely describe the major pathophysiological pathways underlying systemic macro and microvascular damage in patients with CKD and other uremic variables, which may eventually result in cardiac dysfunction.

On the other hand, the cardiologist's perspective emphasizes how increased renin-angiotensin-aldosterone system activity may result in inflammation, oxidative stress, and endothelial dysfunction, all of which have a detrimental effect on the kidney [18]. Additionally, numerous commonly used cardiovascular drugs, such as loop diuretics and contrast agents, are nephrotoxic [19]. Due to concerns about treatment dangers and technical challenges, some cardiologists may treat renal patients with less zeal than non-renal patients. (e.g., "*therapeutic nihilism*") [20].

To manage a cardio-renal patient successfully from a comprehensive, unified perspective, a cardio-renal specialist must grasp both disease perspectives, such as: "*diastolic malfunction contributes to the risk of pulmonary edema, on the one hand, and to the risk of hypotension during volume subtraction by ultrafiltration, on the other hand.*"[20] The accumulating evidence in the contemporary setting, combined with the existing knowledge gaps, all point in the same direction. As expected, a cardio-nephrology specialization evolves naturally. Beyond the veracity of this remark, a body of evidence in the form of clinical protocols [21], growing evidence-based literature [22], and medical books [23] exist exclusively addressing this specialty niche. However, because the evidence to date is unsystematized and disorganized, considerable knowledge gaps, a dearth of studies, and suggestions for the management of such a small patient population emerge.

Perhaps only through the eyes of a committed physician can sufficient clinical experience in this niche specialty be gained in order to systematize and organize knowledge and develop the most authentic and reliable management guidelines. The rationale for this entire approach is to minimize mortality and complications (in cardiac patients with renal dysfunction or in renal patients with cardiac problems – which frequently appear to be synonymous).

A cardio-nephrology specialty will largely allow for the resolution of inter-disciplinary controversies by moving beyond the "agree to disagree" notion to a consistent, unique, and accurate perspective of illness management. Cardio-nephrologists will also benefit from a more full understanding of the patient's history and thorough surveillance of the illness course, whereas nephrology experts will lack access to the complete patient picture.

Not the scientific foundations of this new discipline are one of the critical concerns we wish to discuss ("*initially sustained by passionate specialists interested in the cross-fertilization between the two fields, cardiorenal medicine is now a discipline whose time has come*" [2]), but the operationality and applicability of the aforementioned principles. That instance, if asked who should manage cardio-renal pathology, I would argue that a cardiologist with nephrology expertise should.

Where cardiology Guidelines recommend against referring renal patients for PCIs or maximization of cardiological medication in acute coronary syndromes (ACS) (so-called "*therapeutic nihilism*"), clear evidence-based indications must support the necessity of a written cardio-nephrologist's opinion. This would be a positive step toward increasing adherence to guidelines in the management of complicated patients and (presumably) lowering key clinical endpoints.

Another thought-provoking question is: *do one really need a subspecialty in cardio-nephrology, or is it enough to operationalize a nephro-heart team on the Heart Team model?* [24] The solution is not easy, as both instances have their advantages and disadvantages. There is some evidence of the usefulness of a multidisciplinary cardio-nephrology team (MDT). MDT meetings were reported to be critical in addressing cardio-renal syndrome, resulting in improved care outcomes and more efficient use of healthcare resources through evidence-based management [25-27].

While good consensus decisions by the MDT are probably the best-case scenario (at the moment), real-world clinical settings may face a variety of difficulties due to the role that divergent interpretations of scientific data or clinical guidelines, professional conflicts, toxic

interpersonal relationships, or personal motivations play [28]. These distinctions may result in conflict among a team, which may have a detrimental effect on patient management.

A multi-perspective, team-based interview study explored how cardiology and nephrology teams collaborate to manage patients with severe heart failure. Despite a shared narrative of common purpose, this study observed that care activities were fraught with communal tension as a result of "*asynchronous clinical interpretations, geographically distributed specialist care, fragmented forms of communication, and uncertainty due to clinical complexity*" [29]. When comparing therapies indicated by a Heart Team to those recommended by the original treating interventional cardiologist, all 30% of cases of divergent viewpoints (Heart Team vs. interventional cardiologist) entailed a significant degree of disagreement within the Heart Team [30].

Additionally, MDT's general opinion is not yet clearly defined in terms of applicability, reproducibility, decision-making processes, shared metrics, internal- and external validity [28, 31]. Substantial disagreement was reported between cardiologists within various hospitals when asked whether a Heart Team existed in their hospital [32]. The survey's findings emphasize the importance of further refining the definition of a Heart Team and the metrics for effective implementation.

These findings lead me to believe that a cardio-nephrology expertise could assist in overcoming the challenges to MDT implementation. However, because the unifying goal is beneficial outcomes for patients, additional prospective and randomized trials are necessary to make clear findings. Additionally, given the history of incorporating the Heart Team into the Guidelines, and with a specific focus on this issue, one might easily incorporate a suggestion to seek the opinion of a cardio-nephrologist into the next cardiovascular Guidelines.

To the subject of where a cardio-nephrologist should work or be integrated, I would provide several examples from seemingly disparate contexts that share a high volume of difficult patients.

The first scenario concerns the therapy of ACS. There are two types of patients who account for a sizable proportion of individuals diagnosed with ACS. One is represented by patients with ACS who develop renal impairment as a result of regular testing, whereas the other is represented by patients with known CKD who display an acute coronary event.

These numerous patients can only be treated in the same circuits: interventional cardiology, coronary care units, cardiology ward, and potentially cardiovascular rehabilitation. All of these institutions are not simply replaceable, and integrating a cardio-renal unit into their operative flow is somewhat complex. Rather than that, a cardio-renal expert affiliated to the entire department would be ideal here to focus exclusively on the management and supervision of renal failure, including medication adjustment, treatment protocols, dialysis decisions, and specific prevention of AKI. We believe that by doing so, positive changes in cardiovascular outcomes can be seen immediately.

A second component is primary prevention of cardiovascular events in two (big) subgroups of patients: those with advanced renal disease who have not experienced (yet) cardiovascular events; and those with multiple cardiovascular risk factors and mild renal insufficiency who are asymptomatic. Thus far, the overwhelming data indicates that the presence of (even modest) renal impairment greatly raises the risk of serious cardiovascular events in both categories. Again, I believe that a specialist cardio-nephrologist could

dramatically improve mortality and major adverse cardiovascular events in these two groups of patients.

Two settings are proposed as reasons for the lack of agreement between cardiologists and nephrologists. The clinical issue that is causing inter-specialty tension is discontinuing renin-angiotensin-aldosterone system inhibitors (RAASi) in heart failure patients with CKD; these drugs are frequently withdrawn anticipatorily out of concern for hyperkalemia, azotemia, or hypotension. As shown by several studies [33-35] this management strategy is frequently associated with poor results, as quitting RAASi in heart failure may result in rapid hemodynamic worsening and increased mortality [36, 37]. Several solutions have been proposed to solve the clinical dilemma of stopping RAASi. Strong evidence suggested that the use of potassium binders enables the safe continuation of RAASi therapy [38]. Moreover, evidence underlines that RAASi "*have come to be widely but wrongly seen as 'nephrotoxic'"* despite the absence of evidence of RAASi discontinuation benefits in preventing AKI [39].

The communication gaps between the two specialties and their disparate attitudes toward a single illness (e.g., acute renal damage, acute tubular injury) result in unjustifiably high death rates. While the cardiologist is limited to repeated measurements of serum creatinine (an insensitive and unreliable biomarker, as its concentration does not significantly increase until approximately half of the kidney function is lost) [40], the nephrologist employs a "*double-edged sword"* (e.g., fluid overload), which results in additional cardiovascular complications [41].

While monitoring hemodynamic parameters, updating echocardiography parameters, and adjusting cardiovascular medication, a dedicated cardio-nephrologist could easily investigate the utility of novel biomarkers (e.g., kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), or interleukin-18 (IL-18),) which may be critical for early diagnosis and clinical course [40, 42].

To summarize, the issue/necessity of a cardio-nephrologist must be approached from two angles:

1. From an operational standpoint, a practitioner's perspective, or an organizational standpoint:
    - Where does a cardio-nephrologist work?
    - Should patients be admitted to a separate Cardio-renal Sector or should a dedicated cardio-nephrologist be available in present care settings?
    - Whose interests should a cardio-nephrologist pursue: acute patients or chronic conditions?
    - How will the final curricula look: enlarged cardiology or a nephrologist with additional cardiac competencies?
    - The consequence of this specialization is a physician who is also a nephrologist, or should we state clearly from the start that a cardio-nephrologist will treat specific disorders, not "pure" cardiac or "pure" kidney pathology?
2. From a scientific standpoint:
    - What aspects remain unresolved with regard to highlight-based management of these patients?
    - Which studies have not yet been initiated?
    - Who will make the ultimate recommendation: a multidisciplinary team of cardiologists and nephrologists or a single cardio-nephrologist?

Chapter 2. Evidence synthesis and controversies regarding coronary artery disease management in advanced chronic kidney disease patients

2.1. Introduction

In individuals with ESKD, cardiovascular disease (CVD) is the leading cause of morbidity and mortality. Dialysis patients over the age of 65 have a 50% chance of developing coronary artery disease (CAD). Additional non-traditional risk factors for CVD in patients with CKD include increased inflammation, elevated levels of reactive oxygen species (ROS), aberrant calcium-phosphorus metabolism (CPM) (besides diabetes and arterial hypertension) [43].

The likelihood of getting CAD increases linearly as glomerular filtration rate decreases [44]. Dialysis patients (CKD stage G5D) with CAD have a greater mortality rate, with cardiac death being the primary cause of death in these patients [45]. Patients with CKD typically have coronary calcification in many coronary arteries [46]. Acute myocardial infarction (AMI) has a worse short- and long-term prognosis if the patient has a high uric acid level [47]. Clinical trials that would have provided evidence for G5D-CKD patients were not conducted (studies that have addressed the problem of anticoagulation have excluded these patients) [48]. As a result, proven therapies (especially antiplatelet and anticoagulant treatment, but also invasive revascularization therapies) tested in non-CKD populations cannot be extrapolated to CKD patients, which could lead to disappointing or inconclusive results in terms of survival and other outcomes like quality of life.

There is a lack of information about dialysis patients with CAD in general (see Table I). There are also significantly more complications in this group than in non-CKD patients (due to medical or invasive treatments) [49]. The "*therapeutic nihilism*" of dialysis patients is typically accepted by clinicians, as they do not recommend or implement most of the general population standards of care (e.g., management of either chronic or acute CAD) [50]. In G5D-CKD patients, therapeutic nihilism has been frequently linked to worse outcomes [51]. This is not just because of a lack of information; it seems to be also because of the uncertainty created by not including dialysis patients in clinical trials (e.g., "*no evidence, hence, no prescribing*").

Table I. Uncertainties regarding dialysis patients with high probability of CAD.

?	What is the best way to establish a correct diagnosis?
	In the case of a confirmed CAD, should an angiographic investigation be performed or not?
	If Yes, then When it should be done?
	Which treatment option is preferable in the context of significant coronary artery stenosis: coronary artery bypass grafting (CABG) or coronary stenting?
	What is the most effective medical treatment for these patients?
	For how long DAPT after DES implantation in advanced CKD?

Abbreviations: DAPT- Dual Antiplatelet Therapy, DES – Drug-Eluting Stent.

Given my concerns in the field of antithrombotic and interventional percutaneous coronary treatment in dialysis patients, as well as the unclear issues addressed above, I have summarized the main observations and comments on better advanced CKD patient with CAD management in the following articles.

1. **Burlacu A.**, Genovesi S., Basile C., Ortiz A, Mitra S, Covic A. *Coronary artery disease in dialysis patients: evidence synthesis, controversies and proposed management strategies*. Journal of Nephrology 34, 39–51 (2021). https://doi.org/10.1007/s40620-020-00758-5
   [Impact Factor: 3.902]
2. **Burlacu A**., Covic A. *Longer or shorter dual antiplatelet therapy in dialysis patients receiving a coronary drug-eluting stent? A rope game still ongoing*. Clinical Kidney Journal, Volume 13, Issue 5, October 2020, Pages 749–752, https://doi.org/10.1093/ckj/sfaa040
   [Impact Factor: 4.452]
3. Covic A., Genovesi S., Rossignol P., Kalra PA, Ortiz A, Banach M, **Burlacu A**. Practical issues in clinical scenarios involving CKD patients requiring antithrombotic therapy in light of the 2017 ESC guideline recommendations. BMC Medicine 16, 158 (Indexed 2018-12). https://doi.org/10.1186/s12916-018-1145-0
   [Impact Factor: 8.285]
4. **Burlacu A.**, Artene B., Covic C. *A Narrative Review on Thrombolytics in Advanced CKD: Is it an Evidence-Based Therapy?* Cardiovasc Drugs Therapy 32, 463–475 (2018-12-28). https://doi.org/10.1007/s10557-018-6824-8
   [Impact Factor: 4.181]

2.2. Search strategy and selection criteria

My primary research goal was in evaluating the validity of all new recommendations from the ESC Guidelines involving CAD (CCS and ACS) with a focus on the specific subgroup of CKD patients, which was my primary research emphasis. We assessed all of the provided references from the standpoint of kidney function for each recommendation by extracting baseline estimated glomerular filtration rate (eGFR) data and the presence or absence of albuminuria in all included patients, as well as by reviewing exclusion criteria. The same examination as described in the “web addenda” of the Guidelines (particularly the studies listed in the Tables) was also carried out, with the goal of determining the existence and size of any CKD / ESKD subgroup.

2.3. Features of Chronic coronary syndromes in advanced kidney disease setting

Since 2019, Cardiology Guidelines have focused on the new term chronic coronary syndromes (CCS) instead of stable CAD [52]. Previously, the guidelines were referred to as the 2013 European Society of Cardiology Guidelines on the Management of Stable Coronary Artery Disease [53]. The term "*stable coronary artery disease*" has been replaced by the term "*chronic coronary syndrome*," signifying the beginning of a new era in the care of CAD.

The emphasis is now on CAD as one of several diseases on a continuum (see Table II). It is possible for patients with CAD to develop acute coronary syndromes at any stage during the evolution of their disease. As a result, the term "*chronic stable angina*" is currently out of favor because of the implications it has for the therapy of persistent ischemic symptoms. CAD is a dynamic process that is the result of a variety of interactions, some of which are environmental and genetic in nature. As a result, the illness process can be stable for long periods of time, but it can also become unstable at any point during that time. Acute atherothrombotic events, such as plaque rupture or erosion, are the most common cause of this condition. The phrase "*stable*" is sometimes used to imply that the complex pathological process that underpins angina is inactive, which is far from the case in the majority of cases, especially in the early stages.

The clinical picture of CAD in patients with CKD and kidney failure (G5D) is frequently misconstrued because it mirrors symptoms of fluid overload or intradialytic hypotension. Particular emphasis should be made to the relatively high incidence of silent myocardial ischemia in the general population, despite the fact that the exact frequency of this condition is currently unclear.

Table II. Chronic coronary syndrome categories according to the last ESC guidelines [52].
*including dyspnea as angina equivalent.

Category	Description
1	Patients with suspected CAD and "stable" angina symptoms*
2	Patients with new onset of heart failure or left ventricular dysfunction and suspected CAD
3	Asymptomatic and symptomatic patients <1 year after an ACS or recent revascularization
4	Patients >1 year after initial angina diagnosis or revascularization
5	Patients with angina and suspected vasospastic or microvascular disease
6	Asymptomatic patients in whom CAD is detected at screening

Abbreviations: ACS - acute coronary syndrome, CAD - coronary artery disease.

In part because of the atypical presentation of stable angina in patients with CKD and G5D, the true prevalence of CCS in this population is likely to be underestimated. Periodic electrocardiogram (ECG) monitoring for conduction abnormalities, AF, and silent myocardial infarction (MI) in asymptomatic non-CKD patients with diabetes is recommended by the recently published ESC Guidelines [54]. It seems fair to extend this policy to diabetic patients with silent CKD-G5D.

The evidence for screening CAD in asymptomatic hemodialysis (HD) patients is limited. A report from the 2011 KDIGO Conference on Cardiovascular Disease in Chronic Kidney Disease [55] said that the data available on this topic was insufficient to recommend screening in asymptomatic CKD patients. When a patient has three cardiovascular risk factors,

such as DM, prior CVD, >1 year on dialysis, left ventricle (LV) hypertrophy, LV ejection fraction (LVEF) 40%, age > 60 years, smoking, hypertension, or dyslipidemia, they should be considered at very high cardiovascular risk [56]. If this criterion were adopted, at least 70% of dialysis patients should be thoroughly checked for the presence of CAD, even if they have no symptoms. As a conclusion, a lack of data (e.g., no randomized controlled trial (RCT) on the topic) on HD patients makes it difficult to make "*generalizable therapy recommendations*" according to current guidelines.

Dialysis patients who underwent invasive operations performed no better than patients who received merely drugs and lifestyle recommendations. There was no reduction in the occurrence of cardiovascular death, heart attack, hospitalization for unstable angina, hospitalization for HF, or resuscitation after cardiac arrest in the study participants [57].

In conclusion, a high index of clinical suspicion is required for the timely diagnosis of CCS in G5D-CKD patients, as clinical signs and symptoms can range from symptoms of fluid overload or intradialytic hypotension to silent myocardial ischemia, which occurs more frequently in diabetics than in the general population. Patients exhibiting symptoms and/or indicators of CCS, as well as those who have previously been diagnosed with CCS but have had a change in symptoms, should be assessed using non-invasive diagnostics. A more aggressive strategy, which may involve the use of cardiac angiography techniques, does not appear to be justified because it does not appear to provide any advantages over effective medical management in this situation. In addition, it is unclear if periodic monitoring for myocardial ischemia in asymptomatic G5D-CKD patients is beneficial. Research should be aimed toward determining the most effective medical treatment for CCS in people with G5D-CKD.

2.4. Acute coronary syndromes management in G5D-CKD: evidence and gaps

Because so few dialysis patients have the traditional history of central chest pain spreading into the arm (41.4 percent vs to 61.6 percent in non-dialysis/non-CKD patients), diagnosing non-ST-elevation myocardial infarction (STEMI) in these patients might be problematic. When compared to the general population, more dialysis patients present with clinical signs of congestive HF (42.2 percent vs. 27.2 percent), pulmonary edema (15.4 percent vs 8.1 percent), pulmonary rales, and jugular vein distension (25.5 percent vs. 17.6 percent) at the time of their appointment.

Furthermore, when compared to non-dialysis/non-CKD patients, they are accurately diagnosed as having AMI less frequently on admission to the hospital (19.8 percent versus 36.8 percent) [58]. As a result, the cutoff for high-sensitivity-troponin T (hs-tnT) increases with the progression of the CKD stages; a higher hs-tnT cut-off (149.4 ng/L) has been proposed for the identification of AMI in dialysis patients [59].

Plethora of challenges impair the management of non-STEMI in patients with CKD-G5D, including lack of evidence to support an interventional approach, timing of PCI and subsequent risk stratification), and a lack of evidence-based antithrombotic regimens.

The results of a large propensity score–matched comparison between invasively and conservatively managed CKD patients in 2018 revealed two major conclusions: a) in-hospital mortality is higher in non-STEMI patients with greater severity of CKD, regardless of treatment strategy; and b) PCI appears to be more beneficial than medical therapy alone in

CKD patients presenting with non-STEMI (even in the CKD-G5D population) [60, 61]. The same journal and authors also presented the most comprehensive guidance to date, namely: "*prospective studies and RCTs are warranted to substantiate these findings and to assess the best revascularization strategies for this highly vulnerable population*."

Regarding the timing of intervention in dialysis patients who manifest non-STEMI, there are no clear guidelines available at this time. According to the 2015 ESC guidelines, dialysis patients are deemed to be at high- to extremely high cardiovascular risk, necessitating an early invasive approach (24 to 72 h). The two meta-analyses favouring these indications, however, did not include individuals with G5D-CKD [62, 63]. According to another recent systematic review, early invasive treatment for severe CKD patients, particularly those who are managed with dialysis or kidney transplantation (KT), is not recommended [64]. In conclusion, to date, no clear recommendations can be made regarding the timing of interventional therapy and the best revascularization strategies in non-STEMI dialysis patients.

G5D-CKD patients are under-represented and excluded in evidence-based trials of STEMI treatment as they are considered a complex patient group with a poor health status. Any CKD stage in patients with STEMI is associated to higher mortality and morbidity [65]. Because of the delay in diagnosis, the atypical presentation symptoms, and the presence of many concomitant diseases, this may be the case. Although patients with ESKD who suffer from STEMI have a significant death rate, there is no consensus on the best treatment and care options for them.

As a result of poor outcomes and high risks associated with invasive coronary revascularization and evidence-based pharmacotherapy, there is no consensus among cardiologists regarding the management of dialysis patients with STEMI. Correct patient selection, precise healthcare, and a decision about when to intervene are all required. Patients with ESKD, who received PCI sooner after STEMI had a greater cumulative survival [65].

No specific indication about reperfusion therapy in G5D-CKD patients is proposed. The guidelines indicate reperfusion therapy in all patients with symptoms of ischemia of <12 h duration and persistent ST-segment elevation [66]. If timely primary PCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications [67]. There seems to be no reason to consider ESKD a contraindication to thrombolysis, as major bleeding occurrence is not increased in this population [68].

Guidance in drug therapy for STEMI in G5D-CKD patients is limited. Only aspirin and unfractionated heparin (UFH) (no dose adjustment for both) are accepted. Ticagrelor, prasugrel, enoxaparin, or fondaparinux are not recommended, while the reference to clopidogrel is less clear (no information). However, clopidogrel appears to be less effective in CKD-G5D patients than in patients with preserved renal function and a small RCT performed in dialysis subjects without AMI demonstrated a superiority of ticagrelor in inhibiting platelet function with respect to clopidogrel [69, 70].

The PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) is a five-item score (age, estimated creatinine clearance, hemoglobin, white blood cell count, and previous bleeding) predicting bleeding events in patients treated with DAPT. For patients with a score ≥ 25, the suggested decision-making cut-off is short DAPT (i.e., 3 - 6 months), while for those with score

< 25 a standard/long DAPT (12 - 24 months) is proposed [71]. The optimal duration of DAPT following PCI in dialysis patients is debatable and lack supportive trials. Based on the PRECISE-DAPT score, most dialysis patients should be considered at high risk of bleeding and prescribed 3-6 months of DAPT.

2.5. Controversies: longer or shorter dual antiplatelet therapy?

Even while ESKD is still in the center of a rope game, it is being dragged to one side or the other-by-other characteristics that are predisposing to higher bleeding risk or to higher ischemia risk.

The difference between an acute and an elective presentation (see above) appears to have an impact on the choice of an antiplatelet regimen. The "*one-size-fits-all technique*" is not appropriate for this particular set of individuals. Practitioners will most likely be presented with decision paths developed by artificial intelligence (AI) algorithms, which will result in *"fully customized"* DAPT treatments for each and every patient in the future, according to predictions.

At present, fewer revascularization interventions are performed in stage G5D CKD patients than in non-CKD patients [72] because multivessel atherosclerosis, small diffuse obstructive disease, and severe calcifications are common in ESKD, often resulting in poor PCI outcomes [73]. However, a recent study from the United States, which included nearly 900,000 patients admitted for ACS has revealed a significant upward trend in the use of PCI in dialysis patients [74], with a marked reduction in mortality risk.

Due to the fact that nearly half of dialysis patients have asymptomatic coronary artery stenosis [75] and that stage G5D CKD is associated with accelerated atherosclerosis and coronary calcifications, there has been a significant mobilization of resources aimed at improving quality of life and extending survival, particularly in patients with ACS.

The controversy and uncertainty around the duration of antiplatelet medication after PCI in dialysis patients, which I compared to a rope game, was the inspiration for one of the publications mentioned above. On the one hand, this equation is hampered by the higher thrombotic risk associated with this group of patients, and on the other hand, their high bleeding risk necessitates the reduction in the duration of the DAPT regimen.

Since the era of the „*12 months after DES*" dogma has passed, two divergent tendencies emerged. In an excellent review study, Becker et al considered the question: „*Are at least 12 months of Dual Antiplatelet Therapy needed for all patients with Drug-Eluting Stents?* And offered the conclusion in the title: "*Not all patients with DES need at least 12 months of DAPT*" [76]. This statement can be supplemented by two (equally accurate, but diametrically opposed) responses: there are groups of patients who require only a few months of DAPT, and other groups who require more than 12 months.

Further evidence supports this conclusion, as demonstrated by a recent robust meta-analysis [77] and a nationwide cohort study [78], which found that the use of DES was associated with a significant reduction in all-cause and cardiovascular mortality in dialysis patients compared to the use of metal-only stenting (BMS). Looking into the studies further, it becomes clear that neither was randomized. The first research included 60 percent of ESKD patients who had ACS, whereas the second included only one-third of patients who had ACS.

Despite this, the well-documented benefits of DES treatment in dialysis have been extended to non-acute patients in recent years.

However, according to the results of the only randomized trial (ISCHEMIA-CKD) involving stable angina patients with advanced CKD (and not just ESKD) that was presented at the 2019 American Heart Association Scientific Sessions in Philadelphia in November 2019, the results of the trial failed to demonstrate that stenting was superior to optimal medical therapy in terms of mortality and angina symptoms [79]. This was the first time that this had been demonstrated. It is evident that not all DES procedures are linked with the same long-term thrombosis risk; nevertheless, it should be noted that the interventional arm of the ISCHEMIA-CKD study got only short-term DAPT, whereas the control arm had no DAPT.

The ISCHEMIA trial was designed to address problems left unanswered by the 2007 COURAGE trial, which demonstrated no benefit from PCI over medical therapy in patients with stable coronary artery disease. Nevertheless, the COURAGE trial was limited to only 16 patients with advanced CKD [80], and there is no evidence-based information to guide medical therapy for dialysis patients with CAD (as blood pressure and cholesterol targets, the benefits of the new antiplatelet agents, angiotensin converting enzyme inhibitors (ACEi) / receptor blockers (ARBs), and the newer neutral endopeptidase inhibitors are still debated and unstudied in randomized trials).

Howard et al. identified a number of clinical characteristics that benefit from extended DAPT based on the findings of several subgroup analyses from the PEGASUS-TIMI 54 trial. The authors listed ACS presentation as the first clinical characteristic to benefit from extended DAPT [81], followed by peripheral arterial disease, diabetes, renal dysfunction, current cigarette use, LVEF less than 30%, increased procedure complexity, high CAD burden, and stent diameter less than 3mm.

And so, it seems to us that ESKD is still caught in the center of this rope game, being tugged to one side or the other by other significant traits that point toward increased bleeding risk or greater risk of heart attack and stroke.

In particular, the study by Park et al [82] is significant because it provided the first convincing evidence of a significant advantage of prolonged DAPT in dialysis patients who are receiving a DES, the majority of whom are suffering from an ACS. As the Authors argue (and as a result, pull the rope in the game), "*risk scores [should] weight dialysis as an increased risk for ischemia rather than bleeding.*" It appears to be a bold statement, one that will almost certainly elicit criticism and a second trial to demonstrate the contrary.

At the other end of the rope game, one may discover Table 5 from the ESC focused update on DAPT in CAD, which lists high-risk characteristics of stent-driven recurrent ischemic episodes (which necessitate a longer DAPT strategy) such as longer stents, diffuse multivessel disease, and advanced CKD [83] (see Table III).

Considering that more than half of the ESKD patients included in the study of Park et al had diabetes, 85 percent had hypertension, and 60 percent had dyslipidemia [82], it is likely that the majority of the ESKD patients included in the study had high-risk coronary thrombosis characteristics. Furthermore, extended DAPT was found to reduce events more gradually in patients with greater procedural complexity (complex PCI was defined elsewhere as having at least 1 of the following features: 3 vessels treated, 3 stents implanted, 3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, or chronic total occlusion) [84].

According to Mavrakanas, the "*one size fits all technique*" is not appropriate for this particular set of people [85]. Practitioners will most likely be provided with decision pathways generated by AI algorithms (rather than by clinical trials) in the future, which will result in "*truly individualized"* DAPT protocols for each and every patient, in a way that is not possible using the current Guidelines' recommendations.

2.6. Conclusions

CKD is connected with a very high risk of CAD. Dialysis patients pose a greater incidence, severity, and death from CAD than non-CKD patients. CKD patients are exposed to nontraditional, uremia-related CVD risk factors such as inflammation, oxidative stress, and aberrant calcium-phosphorus metabolism, in addition to the high incidence of classic CAD risk factors such as DM and hypertension. Because of concomitant diseases, the unpredictable response to medication, and probable adverse effects during therapies, CAD therapy in CKD patients is complex.

Patients with G5D-CKD are more likely to be asymptomatic, complicating the accurate detection of CAD, which is required for proper risk stratification and therapy. This may result in "*therapeutic nihilism*" which has been linked to worse results. Guidelines typically fail to address G5D-CKD patients or extrapolate recommendations from non-dialysis research. Furthermore, there are relatively few RCTs concentrating on CAD in ESKD. Additional prospective studies focused on the diagnosis, prevention, and therapy of CAD in G5D-CKD patients are required.

Chapter 3. How to reduce thrombotic risk in advanced CKD patients with oral anticoagulant therapy

3.1. Introduction

The main idea behind the thrombotic risk problem (especially in the indication of chronic oral anticoagulation therapy (OAT), but also the combinations with antiplatelets) is that the renal population is a special one (which behaves differently to anticoagulants and has no solid evidence behind it to support protocols for clear treatment schemes).

Table III. High-risk features of stent-driven recurrent ischemic events (according to the ESC focused update on DAPT in CAD [86]).

• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• **Chronic kidney disease** (i.e., creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stent length >60 mm
• Treatment of a chronic total occlusion

Firstly, there are no RCT investigating the efficacy and safety of antiplatelet and antithrombotic medications in G5D-CKD patients, including both traditional (aspirin and warfarin) and new (P2Y12 inhibitors and direct oral anticoagulants, DOACs) antiplatelet and antithrombotic drugs. The guidelines are therefore of limited use in the management of ESKD patients who present with CVD and require antithrombotics [87].

Heart disease is particularly common among people with CKD who require kidney replacement therapy (KRT), with the frequency and incidence of heart disease indicating the need for antiplatelet and/or anticoagulant medications being extremely high among these patients. Atherosclerotic heart disease is prevalent in approximately 40% of HD patients and 30% of those on peritoneal dialysis (PD) patients, according to statistics [88]. An AF diagnosis is made in one out of every five HD patients, and the frequency of arrhythmias is 15 percent in the PD population.

Aspirin is the only antiplatelet medicine approved by cardiology guidelines for G5D-CKD patients with ACS, and UFH is the sole anticoagulant, despite the fact that there are no RCTs demonstrating its efficacy in this population [89]. Dialysis patients are also overlooked when it comes to therapeutic recommendations for DAPT, such as following a PCI.

Regarding G5D-CKD patients with AF, in their 2014 guidelines, the Canadian Cardiovascular Society states that, due to a lack of RCTs data, routine anticoagulation cannot be recommended for AF patients on dialysis [90]. The 2018 ESC guidelines advocate against the use of DOACs and recommend that vitamin K antagonists be used with considerable caution (VKAs) [91].

The position taken by the Kidney Disease Improving Global Outcomes (KDIGO) consensus in 2018, specifically stated that there is insufficient high-quality data to recommend warfarin or other VKAs for the prevention of stroke in patients with G5D-CKD [92]. It is even more difficult to make a therapeutic decision in clinical settings when there is an indication for the combined use of antiplatelet and anticoagulant medications (the so-called "*triple therapy*").

The recommended thrombotic risk scores by the ESC provide minimal support for nephrologists. Patients with any degree of CKD perform poorly on current commonly used prediction scores for thromboembolic and bleeding events [93]. The performance of classical thromboembolic scores, on the other hand, is not significantly improved by the addition of one or two points to account for renal failure [94].

3.2. Material and methods

We searched the literature (MEDLINE, Cochrane, Embase, Scopus databases) to find clinical studies investigating safety and efficacy of different antithrombotic agents and regimens in patients with advanced CKD, including patients undergoing dialysis. We also searched the references from ESC and American College of Cardiology (ACC) guidelines on atrial fibrillation and antithrombotic therapy in ESKD patients. In addition, a search was performed in an international database of clinical trials (ClinicalTrials.gov) to retrieve ongoing studies on antithrombotic therapy in CKD patients.

We revised currently available data regarding not only VKAs, but also DOACs in this particular subset of patients. We also focused on antiplatelet drugs benefits and risks, including more potent P2Y12 inhibitors, as a single or dual antiplatelet regimen. Finally, we provided

recommendations concerning triple antithrombotic therapy in advanced CKD patients, based on investigated clinical studies.

This is why both cardiologists and nephrologists frequently face tough clinical and therapeutic decisions in G5D-CKD patients, and they often find themselves on their own in their everyday clinical practice decisions because there are no guidelines to follow. The interest for this topic of research was materialized in the following high-IF ISI papers:

1. **Burlacu A.**, Genovesi S., Ortiz A., Combe C, Basile C, Schneditz D, Morosanu C, Covic A. *Pro and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update*. Nephrology Dialysis Transplantation, Volume 34, Issue 6, June 2019, Pages 923–933, https://doi.org/10.1093/ndt/gfz040
   [Impact Factor: 4.531]
2. Covic A., Genovesi S., Rossignol P., Kalra PA, Ortiz A, Banach M, **Burlacu A**. *Practical issues in clinical scenarios involving CKD patients requiring antithrombotic therapy in light of the 2017 ESC guideline recommendations*. BMC Medicine 16, 158 (2018.12). https://doi.org/10.1186/s12916-018-1145-0
   [Impact Factor: 8.285]
3. **Burlacu A.**, Covic A. *The Devil Is in the Details When Considering the OAC Efficacy-Safety Equation in Dialysis Patients*. J Am Coll Cardiology 2020 Jul 21;76(3):349-350. https://doi.org/10.1016/j.jacc.2020.03.085
   [Impact Factor: 24.093]

3.3. Pro and cons using Vitamin K Antagonists for OAT in dialysis

A. In patients AF who did not have CKD, oral anticoagulation reduced the risk of stroke and systemic thromboembolism by two-thirds, whereas antiplatelet medications were much less effective [95]. When OAT should be used, it is determined by the individual's embolism risk. In all stroke risk strata, CKD is related with a greater risk of stroke / thromboembolism [96]. Patients with G5D-CKD who have high CHADS2 or CHA2DS2-VASc values are at higher risk of stroke, despite the fact that the thromboembolic cardiological scores have not been validated in this group of patients as in the general population [97-99].

A large number of RCTs and observational studies have demonstrated that VKAs reduce thromboembolic events in patients with G3/4-CKD [96, 100, 101]. Several studies have also demonstrated a reduction in the incidence of stroke related with VKAs medication, even in patients undergoing dialysis [102-104]. Other research, on the other hand, pointed in the opposite direction [97, 98]. As a result of this heterogeneity, meta-analyses have revealed that individuals with G5D-CKD who use warfarin do not benefit from the medication in terms of thromboembolic risk reduction [105]. This inefficiency in dialysis patients is still under investigation, and the exact cause is unknown.

The difficulty is that the majority of the studies that have been published in the literature have significant biases. In fact, less than one in every four dialysis patients with AF is prescribed warfarin [104, 106] and 70 percent of those who do are forced to stop taking the medication within the first year [107], generally due to bleeding episodes. Despite the fact that patients whose International Normalized Ratio (INR) is maintained between 2-3 and whose

Target Therapeutic Range time (TTR) is high [108] have a much lower risk of bleeding, data on INR and TTR are rarely reported in the research literature.

The INR was only reported for some of the individuals in the Chan's historical study; which found an elevated rate of stroke in patients using warfarin and no INR values. Patients who did not have this information had the greatest rate of stroke [97]. Because of these factors, it is extremely difficult to accurately assess the effectiveness of VKAs in reducing thromboembolic events in CKD patients undergoing dialysis. Good anticoagulation control, on the other hand, may minimize the risk of ischemic stroke without raising the risk of bleeding [109].

Even in individuals with G5D-CKD, the prevalence of AF was associated with an increased all-cause and cardiovascular mortality [110, 111]. In recent studies, researchers used a statistical approach to mitigate selection bias associated with the prescription or non-prescription of VKAs ("*propensity score"* and "*marginal structural models"*) to conclude that patients with ESKD who take VKAs have a lower mortality risk than those who do not take oral anticoagulants, particularly in the presence of a high TTR [99, 104, 107, 112-114] (see also Table IV).

Table IV. Selected recent guidelines on anticoagulant therapy.

Guideline/ Year	Disease condition	Recommendation/Suggestion	Comment	Ref
Canadian Cardiovascular Society Guidelines 2014	Nonvalvular AF	Most patients with nonvalvular AF and CKD who are not dialysis-dependent have sufficient risk for stroke to consider OAT. However, there are no RCT data for nonvalvular AF patients who are dialysis-dependent, and therefore cannot be recommend their routine anticoagulation	G5D-CKD patients excluded from trials.	[90]
European Society of Cardiology (ESC) 2018	Nonvalvular AF	Given the lack of strong evidence for VKAs in HD patients, the decision to anticoagulate remains a very individualized one requiring a multidisciplinary approach considering and respecting patients' preferences. In the absence of hard endpoint studies, the routine use of DOACs in patients on dialysis is best avoided.	Lack of evidence for VKAs and G5D-CKD. Patients exclusion from trials for DOACs.	[91]
Kidney Disease: Improving Global Outcomes (KDIGO) 2018	Nonvalvular AF	There is insufficient high-quality evidence to recommend warfarin or other VKAs for prevention of stroke in G5D-CKD patients. Consideration of the lower dose of apixaban 2.5 mg orally twice daily in G5D-CKD until clinical safety data are available is suggested.	Lack of evidence for VKAs and G5D-CKD. Pharmacokinetic study for apixaban.	[92]
European Society of Cardiology (ESC) 2018	ACS	In G5D-CKD only UFH, without dose adjustment, is recommended in the treatment of ACS.	The type and dose of antithrombotic agent should be considered based on renal function.	[66, 87, 115]

Abbreviations: VKA – Vitamin K antagonist; DOAC – Direct Oral Anticoagulant; ACS – acute coronary syndrome; AF – atrial fibrillation; UFH – unfractionated heparin

It should be noted that there is no conclusive evidence that VKAs enhance the risk of vascular calcifications in patients with ESKD and AF, as this risk is already extremely high in this particular population [116]. Furthermore, fast deterioration of renal function is a rare occurrence that should be taken seriously.

B. Warfarin has a limited therapeutic window and must be monitored on a regular basis to ensure proper treatment. Improvements in the quality of anticoagulation control, as defined by TTR or the percentage of INR readings in the therapeutic range (PINNR), are highly associated with increased stroke prevention in the general population. Unfortunately, maintaining an acceptable INR range in individuals with advanced CKD is more challenging, and the poorer the renal function, the lower the TTR [117, 118].

Patients with G5D-CKD who have malnutrition, unique dietary requirements, dysbiosis of the intestinal microbiome, or who have been exposed to antibiotics on a regular basis find it particularly challenging to maintain a narrow INR range [119, 120].

Another factor that prevents nephrologists from prescribing VKAs to patients with ESKD is the concern that they will favor the development of vascular calcifications. It has been demonstrated that VKAs are related with an increase in coronary calcium score in individuals with maintained renal function, regardless of their age [121].

Patients with ESKD develop extra-skeletal calcifications, which increase arterial stiffness, raise the risk of CVD, and ultimately increase mortality [122]. Dialysate magnesium supplementation, which looks to have the potential to displace calcium, appears to be an appealing alternative for patients with ESKD who are at risk of calcification [123]. In any event, according to the 2018 KDIGO CKD-MBD guidelines suggest restricting calcium-based phosphate binder to all CKD patients [92].

Notably, a novel study mentioned that eGFR loss was faster in patients on VKAs than in those on DOACs [124]. So, if DOACs look better, what do we recommend? VKA or DOAC? Subjects that do not have a prohibitive hemorrhagic risk and ensure a good compliance by INR monitoring of warfarin therapy, also considering the proven benefits in terms of survival [125], warfarin prescription should be considered. In order to be accurate, statements such as "*there is no link between OAT use and a reduced risk of stroke or death*" should be qualified by the type and efficacy of the medications taken [126].

A 2017 meta-analysis which included 17,380 patients from more current dialysis cohorts, found that VKAs were used in suboptimal fashion, suggesting that the genuine protective impact of VKAs was underestimated [127]. The opposite end of the efficacy-safety spectrum, a recent large Medicare cohort of dialysis patients using OAT discovered that apixaban use (in 2,351 patients) was linked with a decreased risk of bleeding when compared to warfarin use (with similar reductions in thromboembolic and mortality risk) [128].

3.4. Should one recommend DOACs instead of VKAs?

There is currently no EMA (European Medicine Agency) approval for the use of any of the four DOACs (dabigatran, edoxaban, apixaban, rivaroxaban) in G5D-CKD patients, but the U.S. Food and Drug Administration (FDA) stated that apixaban (5 mg twice daily, or 2.5 mg twice daily for patients older than 80 years or with a body weight less than 60 kg) and

rivaroxaban (15 mg once daily) can be used in such patients. Considering that G5D-CKD patients were not included in the clinical efficacy and safety studies conducted with apixaban and rivaroxaban, the FDA's indication is based on data from pharmacokinetic studies demonstrating that these doses result in plasma concentrations and pharmacodynamic activity that are comparable to those observed in the RCTs [129, 130].

The 2018 KDIGO guidelines [131] suggest a reduced dose of apixaban (2.5 mg twice daily) in this population. This dose reduction is based on a recent study showing that in HD patients apixaban 5 mg twice daily led to supra-therapeutic anticoagulation levels [132].

Small trials conducted in G5D-CKD patients with AF in recent years have compared the outcomes of warfarin and apixaban, with apixaban demonstrating similar or superior safety and no difference in effectiveness [133, 134]. The first real-world study on apixaban in a large cohort of G5D-CKD patients with AF provided more convincing data [135]. The risk of bleeding was decreased in people using apixaban compared to those taking warfarin (hazard ratio - HR - 0.72, p 0.001), while the risk of thromboembolic events was equivalent in both groups. Moreover, patients receiving 5 mg twice daily of the anticoagulant showed lower thromboembolic risk and mortality than those receiving warfarin (HR 0.64, p = 0.04, and HR 0.63, p = 0.003, respectively) or 2.5 mg twice daily of the anticoagulant (HR 0.61, p = 0.04, and HR 0.64, p = 0.01, respectively).

A recent study in patients with CKD stage G3b-4 tested the hypothesis that using rivaroxaban was linked with a reduction in heart valve calcification deposition and progression when compared to warfarin in a cohort of patients with CKD stage G3b-4 [136].

The recent ESC guidelines emphasized that, in the absence of rigorous endpoint studies, the routine use of DOACs in dialysis patients should be avoided [91]. In individuals with G5D-CKD, dabigatran and rivaroxaban were found to be associated with a greater risk of hospitalization or mortality from bleeding compared to warfarin (rate ratio, 1.48 and 1.38, respectively). It was found that dabigatran and rivaroxaban increased the risk of hemorrhagic mortality even more so when compared to warfarin (rate ratios of 1.78 and 1.71, respectively) [137].

To illustrate this point, the open label, parallel-group, single-dose pharmacokinetic research that provided evidence to justify the FDA's approval of apixaban comprised only 8 patients undergoing HD [129]. Each patient was given two doses of apixaban 5 mg, separated by a seven-day washout interval between each dosage (in period 1, the dose was given 2 hours prior to HD; in period 2, the dose was given immediately after HD).

It was found that the area under the curve (AUC) of apixaban concentration was 36 percent larger in G5-CKD patients compared to those with normal renal function. Also, it was discovered that when apixaban was provided before to HD, the AUC was reduced by 14 percent. A labeling update for apixaban 5 mg twice daily in G5D-CKD patients without dose changes for renal impairment was authorized by the FDA early in 2014 based on the findings of this small trial [93]. That this is the case is surprising given that the use of DOACs in patients with G5D-CKD is not suggested by the drug's manufacturer.

Real life studies might be of great interest to nephrologists because they suggest that the position of KDIGO regarding apixaban may be too conservative [135]. In fact, in patients who could take the full dose of the drug, there would be benefits in terms of thromboembolic events and mortality, in the absence of an increased risk of bleeding.

3.5. "Triple" antithrombotic therapy (DAPT plus an oral anticoagulant)

There are no evidence-based recommendations regarding antithrombotic therapies in dialysis patients with AF and PCI, rather "*only extrapolation from the overall data can be made in context of stable CAD*" and "*in anticoagulated patients developing ACS, suggestions are based on observational studies and expert opinion*" [138].

Nephrologists caring for a G5D-CKD patient with AF, ACS, and/or PCI should understand that the first step is to determine whether risk factor is more prevalent: thrombotic risk or high bleeding risk. Almost often, the HAS-BLED risk calculator indicates a high risk of bleeding in G5D-CKD patients. This elevated risk must be weighed against the complexity of the PCI procedure (number and location of stents: left main stenting, proximal left anterior descendent artery stenting, proximal bifurcation stenting, and recurrent myocardial infarction/stent thrombosis) or the magnitude of ischemic risk (GRACE or SYNTAX score) [139]. This choice should be made either by a multidisciplinary team for each individual patient (nephrologist, cardiologist, interventional cardiologist), or by a cardio-nephrologist (see Chapter II, 1).

The practitioner can choose among three scenarios (Figure 1):

a) **an overt very high bleeding risk**: Triple Antithrombotic Therapy (TAT) should be avoided (recommending only dual therapy with an oral anticoagulant and P2Y12 inhibitor for 12 months);

b) **a high bleeding risk** (prevailing over thrombotic risk): TAT for one month, then dual therapy as above, up to one year;

c) **prevailing high thrombotic risk**: TAT up to 6 months, then dual therapy as above, up to one year.

It should be underlined the fact that clinicians have been given the opportunity to choose among different scenarios, each of them having limitations and not being free of harm. This could mean: "*whatever one chooses (covered by an agreed algorithm) is good and beneficial for the patient, even though it is not free of harm*".

Every clinician should accept that at present there is no clear limit between extrapolating indications from general population to G5D-CKD and considering that HD group should benefit from specific and different recommendations. This seems a dead-end road in an "*evidence-based*" maze, which could be solved for good only by solid RCTs.

One should note that he stratification of bleeding risk in "*very high*" and "*high*" cannot be made by any available risk score. It is more a matter of subjective perception of the clinician/team. Moreover, it is not supported by HAS-BLED score, which only provides risk percentages for a given risk factor, and does not categorize scores into low/medium/high. A valuable remark from the score creator himself is that "*the most important pitfall is using HAS-BLED as an absolute cut-off to withhold or withdraw anticoagulation. Instead, HAS-BLED should be used as an alarm bell which assists in minimizing the potential risk of bleeding by signaling risk factors that can be avoided or reversed*." Unfortunately, age, G5D-CKD, indication for antiplatelet agent indication, bleeding predisposition and labile INR are unmodifiable elements in dialysis patients.

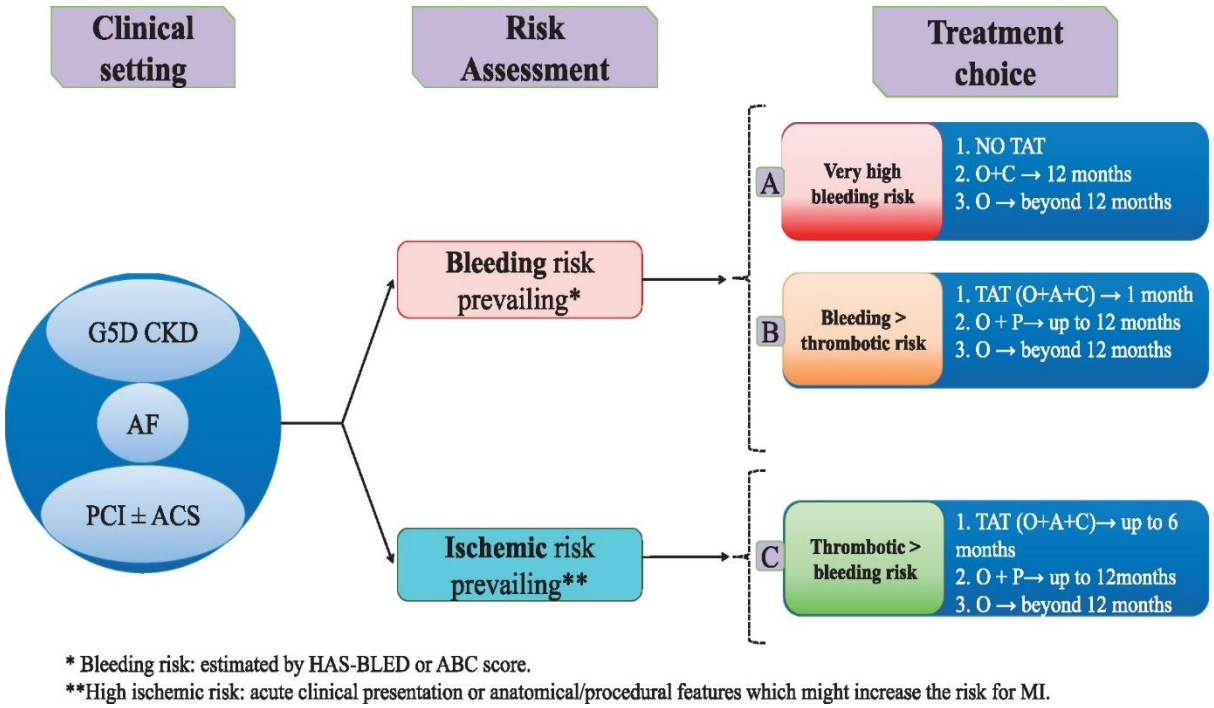


Figure 1. Treatment choices in different bleeding risk scenarios (according to [140]).

Importantly, the association between OAT and antiplatelet medication increases the absolute risk of major bleeding in all patients [141, 142]. Unfortunately, there is no dedicated score for this therapy. The only existing functional assessment tool is the HAS-BLED score, while CRUSADE and ACUITY do not have predictive value on patients with OAT [143]. For the advanced CKD patient on OAT requiring DAPT, the HAS-BLED score starts already from a value of 4 points (Table V), and if we add one single variable, such as age over 65, the (already) high risk for major bleeding increases significantly (4 points - 8.7 bleeds per 100 patient-years vs. 5 points - 12.5 bleeds per 100 patient-years) [144].

Moreover, I believe that HAS-BLED score is not refined enough and the binary stratification, in low or high levels should be further enhanced, in order to reflect various contexts and situations.

Table V. HAS-BLED score calculation in advanced CKD patients with chronic AF and recent PCI.

HAS-BLED [144, 145]	Low – intermediate risk: 1 – 2 points **High risk ≥ 3 points**	
Hypertension (uncontrolled)	No 0	Yes +1
Renal disease	No 0	Yes +1
Liver disease	No 0	Yes +1
Stroke history	No 0	Yes +1
Prior major bleeding or **predisposition to bleeding[146]**	No 0	Yes +1
Labile INR (TTR<60%)[147]	No 0	Yes +1
Age > 65	No 0	Yes +1
Medication prone to bleeding	No 0	Yes +1
Alcohol / drug use	No 0	Yes +1
	TOTAL: 4 points	

3.6. Conclusions

Prescription of an evidence-based antithrombotic medication to a G5D-CKD patient is a difficult challenge. This task is made extremely difficult by contradictory and insufficient facts. Various clinical scenarios frequently test the practitioner's ability to employ the "Procrustes bed" recommended by the last Guidelines. Even worse, there are clinical circumstances in which there are no clear guidelines at all. Furthermore, the cardiological and nephrological criteria are extensive and complicated. Given this backdrop, our research presented both nephrologists and cardiologists with pro and con reasons, as well as expert-provided algorithms based on numerous studies regarding antiplatelet and anticoagulant medication in dialysis patients. One should keep in mind that the goal of antithrombotic therapy should be to reduce thrombotic risk while minimizing bleeding occurrences.

Chapter 4. Bleeding issues in advanced CKD patients receiving antithrombotic treatment

4.1. Introduction and Methodology

Bleeding is a critical concern in daily medical practice and management of advanced CKD patients since it increases morbidity and death. As a result of the absence of medical evidence-based foundation for particular recommendations about antithrombotic medication in this particular high bleeding risk context, these patients are mostly omitted from major randomized clinical trials.

There is no defined set of algorithms and measurements for the experts to use in this framework to explore and balance the risks of bleeding and thrombosis. I covered a wide range of clinical and practical circumstances, from patients with CAD or/and atrial fibrillation to those taking antiplatelet treatment or/and OAT, all of whom having advanced CKD. Recent research and therapy gaps in the ESC Guidelines are both highlighted in our study.

A bleeding risk assessment tool's strength, reliability, and usefulness are all factors I took into account. After doing a risk assessment, I outlined all of the actions that need to be taken, including specific plans, dosage changes, and specific therapeutic techniques. Finally, I offered advice on how to better care for this particular group of patients.

This issue of exploring the risk of bleeding in the context of complex cardiovascular medication in dialysis patients, I have explored in several articles in journals with high ISI impact factor, as follows:

1. **Burlacu A.**, Genovesi S., Goldsmith D., Rossignol P., Ortiz A., Kalra PA., Małyszko J., Banach M., Kanbay M., Covic A. *Bleeding in advanced CKD patients on antithrombotic medication – A critical appraisal*. Pharmacological Research Vol. 129 (Indexed 2018-12-28), Pages 535-543, https://doi.org/10.1016/j.phrs.2017.12.004
   [Impact Factor: 5.574]
2. **Burlacu A.**, Covic A. *The Devil Is in the Details When Considering the OAC Efficacy-Safety Equation in Dialysis Patients*. Journal of the American College of Cardiology, Volume 76, Issue 3, 21 July 2020, Pages 349-350, https://doi.org/10.1016/j.jacc.2020.03.085

[Impact Factor: 24.093]

3. Covic A., Genovesi S., Rossignol P., Kalra PA, Ortiz A, Banach M, **Burlacu A**. *Practical issues in clinical scenarios involving CKD patients requiring antithrombotic therapy in light of the 2017 ESC guideline recommendations*. BMC Medicine 16, 158 (Sept 2018). https://doi.org/10.1186/s12916-018-1145-0

[Impact Factor: 8.285]

CKD patients with advanced stages (stages G4, 5 and 5D) are more likely to have CVD that necessitates antiplatelet and/or anticoagulant medication, which increases their risk of bleeding. Added to that, this considerable risk typically happens in a vulnerable population that already carries a heavy load of illness.

Antithrombotic drugs guidelines from the ESC contain notable gaps when it comes to treating patients with advanced CKD, due to a lack of solid data about the risks and benefits. The lack of solid evidence from RCTs (as these patients have been excluded from protocols), along with appropriate bleeding risk scores and clear management algorithms, creates a void that hinders an effective and safe approach in medical care, when using antithrombotic medication [148].

As CKD progresses, the problem of bleeding risk assessment must be addressed in light of the state of the art, or lack thereof. Proton-pump inhibitors (PPIs) have been shown in multiple studies [149] to reduce bleeding risk in individuals on antiplatelet medication, but their use may have unexpected adverse effects, especially in those with kidney disease. Hemorrhage is the great unknown in this framework, and it is often overlooked in favor of thrombosis, simply because we know and can do more about it. However, bleeding is an important factor that can significantly alter the delicate balance in the health of advanced CKD patients, and it is important to recognize this.

My focus was to:

a) describe the hemorrhagic risk in advanced CKD patients on antiplatelet (mono/dual) and/or anticoagulant medication (VKAs/DOACs);

b) examine all of the primary bleeding scores and list their advantages and disadvantages;

c) recognize and address all gaps in the evidence and management techniques / Guidelines suggestions;

d) suggest new directions in order to improve quality of care.

4.2. Hemorrhagic risk in advanced CKD with antithrombotic therapy

Several standardized bleeding definitions from clinical trials rank the severity of bleeding in three categories (TIMI, GUSTO) or five types (BARC), one of the five being lethal bleeding (Table VI) [150-152].

The ESC Guidelines proposed five categories, encompassing trivial, mild, moderate, severe and life-threatening (Table VII) [115]. Mild bleeding requires medical attention, while in moderate and severe bleeding the patient is hemodynamically stable and not rapidly evolving but hemoglobin levels have fallen >3 or >5 g/dL, respectively. Life-threatening bleeding is severe, active and puts the patient life immediately at risk. Each category is associated to recommendations regarding DAPT, OAT and general measures.

The key decision to be taken is whether to withhold or continue DAPT. Additionally, the type, dose, and duration of DAPT should be reassessed. These decisions should be individualized based on the relative risks of thrombosis and continuous or recurrent bleeding. A flow chart is provided, according to the severity of bleeding. Regarding DAPT prescription upon a bleeding episode, potential actions include shortening DAPT duration, stopping DAPT and continuing with a single antiplatelet agent, preferably with the $P2Y_{12}$ inhibitor, switching to a less potent $P2Y_{12}$ inhibitor (e.g., from ticagrelor or prasugrel to clopidogrel) or stopping all anti-thrombotic medication, at least transitorily. Since patients in CKD categories G5 and G5D are not expected to be on ticagrelor or prasugrel, the range of options for these patients is reduced.

Guidance for the management of bleeding are especially relevant for CKD patients, mainly for those with more severe CKD. As an example, the incidence of upper gastrointestinal bleeding in HD patients was estimated at 6 to 33 episodes per 100 person-years, with an overall 30-day mortality of 12% [153]. CKD patients, especially those on HD, may have lower baseline hemoglobin values, since they frequently need therapy with erythropoiesis stimulating agents and guidelines suggest target hemoglobin levels of 9.0 or 10.0 to 11.5 or 12.0 g/dL[154]. Recent reports indicate that since the publication of KDIGO guidelines mean hemoglobin levels have dropped and HD patients with Hb <10 g/dL increased from 9% in 2009 to 20% by 2012 (http://www.dopps.org/annual report/).

Thus, the potential impact of a >3 g/dL drop in hemoglobin levels (e.g., from 10 g/dl to 6 g/dl) may be higher than for individuals without baseline anemia (e.g., from 14 to 10 g/dL). Furthermore, a low hematocrit (below 30%, roughly equivalent to a hemoglobin level below 10 g/dL) favours bleeding in uremia [146]. The severity thresholds based on the fall in hemoglobin levels proposed by the ESC to categorize the severity of bleeding may not be appropriate in CKD patients, especially in those with most advanced CKD, and decisions for action should be individualized, but may consider milder decreases in hemoglobin levels as thresholds to take action.

Table VI. Standardized bleeding definitions (according to BARC, TIMI, GUSTO).

BARC	TIMI	GUSTO
Type 1 Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by healthcare professional	**Minimal:** Any overt bleeding event that does not meet the criteria below	**Mild:** Bleeding that does not meet below criteria
Type 2 Any overt, actionable sign of hemorrhage that does not fit the criteria for type 3, 4 or 5 but does meet at least one of the following criteria: (1) requiring non-surgical medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation	**Minor:** Clinically overt bleeding resulting in Hb drop of 3 to <5 g/dL	**Moderate:** Bleeding requiring blood transfusion but not resulting in hemodynamic instability

BARC	TIMI	GUSTO
Type 3 **3a:** Overt bleeding plus Hb drop of 3 to <5g/dL or any transfusion with overt bleeding **3b:** Overt bleeding plus Hb drop ≥5 g/dL, cardiac tamponade, bleeding requiring survival intervention for control or bleeding requiring intravenous vasoactive agents **3c:** Intracranial hemorrhage or intraocular bleed compromising vision	**Major:** Fatal bleeding, intracranial bleeding or clinically overt signs of bleeding associated with a drop in Hb of ≥5 g/dL	**Severe or life-threatening:** Intracranial hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment
Type 4 CABG-related bleeding including perioperative intracranial bleeding with 48 hours, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period, chest tube output ≥2 L within a 24-hour period		
Type 5: Fatal bleeding **5a:** Probable fatal bleeding, no autopsy or imaging confirmation but clinically suspicious **5b:** Define fatal bleeding, overt bleeding or autopsy or imaging confirmation		

Abbreviations: BARC = Bleeding Academic Research Consortium; CABG = Coronary Artery Bypass Graft surgery; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; TIMI = Thrombosis In Myocardial Infarction; GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; Hb = hemoglobin.

For OAT, the range of actions includes downgrading from triple to dual therapy, preferably with clopidogrel and OAT, considering OAT discontinuation or even reversal until bleeding has stopped unless very high thrombotic risk, with re-initiation when bleeding has stopped and if the patient is in dual therapy, consider stopping antiplatelet agent.

The only absolute indication to stop and reverse OAT is life-threatening bleeding, while for moderate and sere bleeding, stopping OAT may be considered until bleeding is controlled unless the thrombotic risk is prohibitive (mechanical mitral valve, cardiac assist device) for severe bleeding or very high (mechanical heart valve, cardiac assist device, CHA2DS2-VASC≥4) for moderate bleeding. CKD patients are expected to be overrepresented among those with CHA2DS2-VASC≥4, given the association of CKD with age, cardiac failure, hypertension, diabetes, stroke and vascular disease.

Additional actions may be considered, depending on the severity and persistency of bleeding, that include intravenous PPIs, specific hemostatic interventions depending on the site of bleeding, transfusion of platelets or red blood cells and fluid replacement if hypotension.

In G5D-CKD patients, additional options can be found in the literature, upon a severe, life-threatening bleeding episode, including the administration of desmopressin, which are not mentioned by the ESC Guidelines [155]. As a potential complication of desmopressin administration is thrombosis, this should be considered a high-risk intervention.

For reinitiating anticoagulation following moderate, severe and life-threatening bleeding, guidance includes both considering an INR target of 2.0-2.5 unless there are overriding indications, such as mechanical heart valves and cardiac assist device, as well as switching from triple to double therapy.

Table VII. Standardized bleeding definitions (according to the ESC [156]).

ESC/EACTS 2017	
Trivial bleeding Any bleeding not requiring medical intervention or further evaluation	e.g., skin bruising or ecchymosis, self-resolving epistaxis, minimal conjunctival bleeding
Mild bleeding Any bleeding that requires medical attention without requiring hospitalization	e.g., not self-resolving epistaxis, moderate conjunctival bleeding, genitourinary or upper/lower GI bleeding without significant blood loss, mild haemoptysis
Moderate bleeding Any bleeding associated with a significant blood loss (>3 g/dL Hb) and/or requiring hospitalization, which is hemodynamically stable and not rapidly evolving	e.g., genitourinary, respiratory or upper/lower GI bleeding with significant blood loss or requiring transfusion
Severe bleeding Any bleeding requiring hospitalization, associated with a severe blood loss (>3 g/dL Hb) which is hemodynamically stable and not rapidly evolving	e.g., severe genitourinary, respiratory or upper/lower GI bleeding
Life-threatening bleeding Any severe active bleeding putting patient's life immediately at risk	e.g., massive overt genitourinary, respiratory or upper/lower GI bleeding, active intracranial, spinal or intraocular hemorrhage, or any bleeding causing hemodynamic instability
Abbreviations: GI = gastrointestinal; Hb = hemoglobin.	

4.3. Bleeding events in CAD strata of ESKD patients

In the Table VIII below, I have summarized the recommendations from the ESC Guidelines for adjusting antithrombotic medication in order to reduce the risk of bleeding for various categories of CVD that require medication in patients with ESKD.

Table VIII. Guidelines recommendations for different categories of CKD patients.

1. Antithrombotic therapy for chronic stable angina in advanced CKD patients
The prescription of low-dose aspirin is probably safe in most patients with CKD. Based on these considerations it is reasonable to recommend that decisions about antiplatelet therapy for preventing CVD in patients with CKD should be individualized depending upon each patient's overall risk for CVD and for bleeding. Of note, the 2016 European Guidelines on CVD prevention [157] consider that patients with advanced CKD should be classified in the "*very high risk*" category of CVD-related mortality, which could make prescription of low-dose aspirin mandatory in this population. In addition to CVD, aspirin therapy may reduce the risk of cancer incidence. This should also be considered in the decision about whether or not to use aspirin in patients with CKD. This suggestion is broadly consistent with guidelines made by the KDIGO report on the management of CKD [158].
2. Antithrombotic therapy for advanced CKD patients with ACS / non-STEMI
For the effective management of this population, it is essential to design and implement new risk scores, starting from RCTs based on patient-related parameters, coronary and renal pathology, and medication. Moreover, a solid assessment test for the bleeding risk of this population should also allow for the accurate quantification of the impact of specific measures, such as dose adjustment or removing certain medication. It is imperative to establish a relevant set of guidelines, with concrete measures and clear algorithms, effective and easy to use in current practice.
3. Antithrombotic therapy in advanced CKD patients with STEMI
Due to the current lack of information, adequate scoring system and effective Guidelines, the experts should decide on a routine algorithm applicable for clinicians confronted with a patient with advanced CKD and STEMI. Moreover, in the absence of an adequate assessment tool, and on the basis of very recent research, we recommend the routine usage of CRUSADE or ACTION score for stratification of hemorrhagic risk [159], and STEMI Guidelines should include at least one discussion on the issue of bleeding in the context of advanced CKD.
4. Advanced CKD patients requiring chronic oral anticoagulation
Currently, evidence is against of the use of DOACs in patients with advanced CKD or ESKD. For this population vitamin K inhibitors remain the only pharmacological choice. However, the ongoing trials can provide additional elements for the therapeutic approach in these patients.
5. Association of double antiplatelet and anticoagulant medication („triple therapy")
Based on a class IIb observation from AF Guidelines ("*dual therapy with any OAC plus clopidogrel may be considered as an alternative to initial triple therapy in selected patients*") and the lack of evidence for advanced CKD patients, in this group double therapy (OAT + C) [160] should be considered from the very beginning as an alternative to triple therapy.

4.4. Managing anticoagulants for reducing major bleeding in G5D-CKD patients

Patients with ESKD are more likely than the general population to experience excessive bleeding when using anticoagulant medications. Data from several studies, including those involving patients who were taking OAT for the prevention of HD access thrombosis, revealed that warfarin use, both full and low-intensity, was associated with a two-fold increase in bleeding risk when compared with no warfarin or subcutaneous heparin use, respectively [105, 161].

The use of chronic oral anticoagulants in patients with AF with a thromboembolic score (CHA2DS2-VASc – see Table IX) more than 2, mechanical prosthetic valves, or recurrent deep vein thrombosis is strongly recommended. The majority of this population consists of patients with AF and for whom the ESC Guidelines recommend anticoagulant therapy based on thromboembolic risk [162].

Table IX. CHA2DS2-VASc score.

Condition	$CHADS_2$ score	Points	CHA_2DS_2-VASc score	Points
Congestive heart failure (or Left ventricular systolic dysfunction)	C	1	C	1
Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	H	1	H	1
Age ≥75 years	A	1	A_2	2
Diabetes Mellitus	D	1	D	1
Stroke or TIA or thromboembolism in history	S_2	2	S_2	2
Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)			V	1
Age 65–74 years			A	1
Sex category (i.e. female gender)			Sc	1

This table shows the components of the $CHADS_2$ (Gage et al., JAMA 2001 [36]) and CHA_2DS_2-VASc scores (Lip et al., Chest 2010 [41]) tools to assess stroke risk in patients with AF. These risk assessment tools help to determine who should and who should not receive anticoagulation. CHA_2DS_2-VASc improves risk stratification in patients with $CHADS_2$=0 or 1, and allows for identification of patients at truly low risk.

Reduced kidney function is associated with an increased risk of major bleeding among older adults with AF starting warfarin, most pronounced during the first 30 days of treatment [163]. DOACs are associated with a reduced risk of major bleeding and hemorrhagic stroke compared to warfarin in subjects with mild or moderate renal impairment [164]. However, the use of DOACs in ESKD patients is associated with a higher risk of hospitalization or death from bleeding when compared with warfarin [137].

Table X. HAS-BLED score.

Clinical characteristic			Points
Hypertension	Uncontrolled, >160 mmHg systolic)	H	1
Abnormal renal and liver function (1 point each)	Dialysis, transplant, Cr >200 µmol/L, Cirrhosis, bilirubin >2x normal, AST/ALT/AP >3x normal)	A	1 or 2
Stroke history		S	1
Bleeding or predisposition to bleeding		B	1
Labile INR	Unstable/high INRs, time in therapeutic range < 60%)	L	1
Elderly	Age > 65	E	1
Drugs or alcohol (1 point each)	Antiplatelet agents, NSAIDs, ≥ 8 alcohol drinks/week	D	1 or 2

This table shows the components of the HAS-BLED score (Pisters et al, Chest 2010 [45], Camm et al., Eur H J 2010 [2]), used to assess bleeding risk.

Although there are several scores [144, 165, 166] for the assessment of the bleeding risk in patients on OAC, the only one that seems to have an adequate predictive power in patients with advanced CKD [108] is the HAS-BLED score, currently recommended by ESC Guidelines for hemorrhagic risk stratification as well (see Table X).

In patients taking warfarin, ESC Guidelines advise to keep the INR between 2 and 3 to ensure anticoagulant efficacy with reduced risk of hemorrhagic episodes. They also indicate that presence of high hemorrhagic risk is not considered a reason to deny the OAC to a patient if there is an indication, and the recommendation is to identify hemorrhagic risk factors and, whenever possible, to modify them [167]. Although CKD is associated with low TTR despite comparable INR monitoring intensity [117], bleeding episodes are inversely correlated to TTR [108], even in advanced stages of CKD.

The ESC AF guidelines discourage the use of DOACs in the setting of severe CKD, since there are no published RCTs addressing this subject. However, there is an ongoing observational prospective study aimed at assessing the efficacy and safety of rivaroxaban 15 mg once daily in patients with eGFR between 15 and 49 mL/min/1.73m^2 (XARENO, NCT02663076). Moreover, there are two ongoing prospective, randomized trials assessing the safety of apixaban versus warfarin in patients with AF and ESRD on hemodialysis (AXADIA NCT02933697 and RENAL-AF NCT02942407), which will provide us with important information on the use of DOACs in patients with advanced CKD and on RRT.

4.5. Novel methods to reduce hemorrhagic risk

A. *Radial versus femoral percutaneous approach*

Both the ESC STEMI and Non-STEMI Guidelines recommend the use of a radial approach in order to reduce the risk of bleeding [168, 169]. This is a technique that, when performed in the frail and unstable setting of advanced kidney disease, which is further complicated by a variety of cardiovascular issues, has been shown to significantly reduce the rate of adverse events and mortality by lowering the incidence of vascular bleeding complications. However, because the radial artery is involved in arterial-venous bypass and HD, it is generally avoided; nonetheless, because of the influence on the potentially fatal risk of vascular complications, it is not considered a strict contraindication [170].

B. *No-heparin hemodialysis (NH-HD)*

No-heparin hemodialysis (NH-HD) treatment with predilution is a procedure used in some dialysis facilities for prevention of clotting in the extracorporeal circuit. However, fluid infusion is far from optimal because of the increased volume load that has to be removed during dialysis session, and implies an additional logistic burden for healthcare staff [171]. Another alternative for NH-HD is to bind heparin on the blood side of the dialyzer membrane (i.e., a heparin-grafted membrane (HGM)).

Regional anticoagulation or tight heparinization are not confidently safe for patients with active bleeding or those at risk of bleeding. Various solutions have been attempted to prevent clotting of the extracorporeal circuit. No-heparin infusion using regular saline flushes

is one of the methods of choice. Alternatively, regional citrate anticoagulation can be used. Both methods are currently recommended by the 2002 European Best Practice Guidelines for hemodialysis) [172] although the level of evidence is weak [173].

An international RCT [171] evaluated the NH-HD treatment options of an HGM and standard of care (defined by the usual procedure in place at each study site (i.e., saline flushes or predilution) for 251 patients with end-stage renal disease requiring a NH-HD (being at high (68.1%) or very high (11.6%) bleeding risk, none being critically ill). The trial showed a statistically significant non-inferiority of HGM over the controls (primary outcome). Moreover, the success rate in the HGM group was 20% higher, with a very small number (n=5) of patients needed to treat to avoid one failure.

C. *Left atrial appendage occlusion and exclusion in ESKD patients with AF*

An experimental procedure consisting in the anatomical exclusion of the site of thrombus formation with percutaneous left atrial appendage occlusion (LAAO) [174, 175] could have similar efficacy and safety profile in patients with or without advanced CKD [176] and represents a future alternative to OAT for stroke prevention in patients with advanced CKD and AF. The most common justification for LAA occlusion/exclusion in clinical practice is a perceived high bleeding risk or, less often, contraindications for OAT.

The ESC indication for percutaneous LAAO (Class IIbB recommendation [177]) is not (yet) so strong ("*in patients with a high stroke risk and contraindications for long-term oral anticoagulation"*) because RCTs comparing LAAO vs warfarin have been performed on populations that did not have a contraindication to OAC, while the populations most likely to benefit from LAAO, i.e. patients with high hemorrhagic risk like those with severe CKD, were excluded from the trials.

4.6. Conclusions

Advanced CKD patients have a significant risk of bleeding, which necessitates a precise diagnostic and individualized treatment plans, none of which are currently accessible. We believe that carefully designed RCTs are achievable and should be initiated as soon as possible, in order to provide the clinician with a clear set of measures and a distinct trajectory in the exploration and balancing of bleeding and thrombosis risks. Clinical circumstances addressed in our research provided light on the complication and lack of solid scientific evidence.

Chapter 5. Stroke prevention in CKD setting: a sensitive concern with major implications

5.1. Introduction

CKD has been identified as an independent risk factor for stroke by the American Heart Association (AHA) [178]. In fact, the incidence of stroke is disproportionately higher in CKD patients and especially in ESKD patients: 14.9 to 49 per 1000 person-years in ESKD [179, 180], compared to 0.41 to 2.38 per 1000 person-years in the general population worldwide

[181]; concurrently, stroke may cause renal impairment [182], and figures describing the two-way "*cerebro-renal*" relationship are similar: CKD stage 3 or higher increases the the risk for stroke by 43% [183], while post- (ischaemic) stroke kidney dysfunction occurs in up to 40% stroke survivors in the general population [182].

In spite of this, it is frequently difficult to incorporate measures for preventing a first stroke in patients with CKD due to a lack of sufficient data: guidelines are inadequate in providing recommendations in this population, and as a result, clinicians frequently face significant dilemmas such as the decision to use OAT or antiplatelet agents, the decision between medical and interventional management, the decision between two different types of interventional procedures that carry significant risks, and so on (Figure 2).

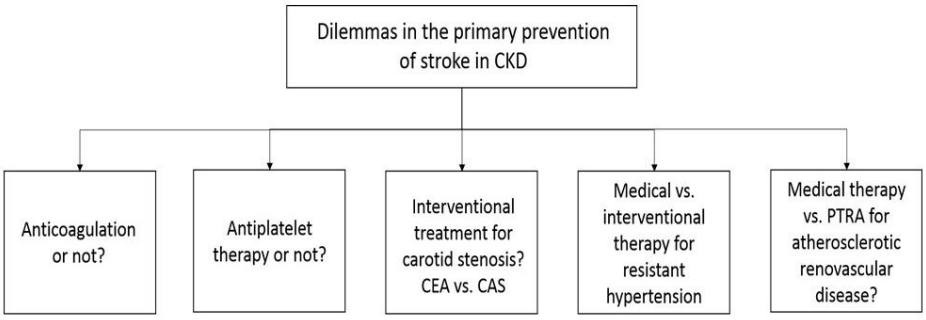


Figure 2. Main issues regarding primary prevention of stroke in CKD.

In this chapter I intended to discuss the most recent evidence-based approaches for preventing a first stroke in people with CKD. Particular emphasis will be placed on specific conditions that are highly prevalent in people with CKD and have a significant impact on the risk for stroke (e.g., AF, carotid atherosclerosis – CA, and resistant hypertension – RH), but which also raise significant concerns about their management. The research was organized according to the kind of stroke in general (ischaemic and hemorrhagic), in the CKD setting. Treatment-resistant hypertension and bleeding while on antithrombotic therapy are addressed in the ischemic stroke part, whereas the hemorrhagic stroke section addresses treatment-resistant hypertension and bleeding while on antithrombotic therapy.

My interest for this theme of research was materialized in the following articles, published in high IF journals.

1. Bilha S.C., **Burlacu A.**, Siriopol D., Voroneanu L., Covic A. *Primary prevention of Stroke in chronic kidney disease patients: a scientific update.* Cerebrovasc Diseases 2018; 45:33–41. Indexed 2018-12-28. https://doi.org/10.1159/000486016
   [Impact Factor: 2.681]
2. **Burlacu A.**, Covic A. "*Some doors are better left closed": Using LAA occluders as an alternative to warfarin in very high-risk dialysed patients with atrial fibrillation*. Int J of Cardiology volume 262, p 43-44, July 01, 2018. https://doi.org/10.1016/j.ijcard.2018.03.123

[Impact Factor: 3.471]

3. **Burlacu A.**, Genovesi S., Artene B., Covic A. "*Will the king ever be dethroned?" The relationship and the future of oral anticoagulation therapy versus LAA closure devices.* Expert Review of Cardiovascular Therapy volume 19, 2021 - Issue 1
https://doi.org/10.1080/14779072.2021.1850267
4. Kalra PA., **Burlacu A**., Ferro CJ., Covic A. *Which anticoagulants should be used for stroke prevention in non-valvular atrial fibrillation and severe chronic kidney disease*? Current Opin Nephrol Hypertens 2018 Nov;27(6):420-425.
https://doi.org/10.1097/mnh.0000000000000443

[Impact Factor: 3.013]

5.2. Search strategies

Two search strategies were used in two of my most important papers on this topic.

Firstly, the electronic databases of PubMed and ISI Web of Science were searched using the search terms "*primary prevention and stroke*"/ "*atrial fibrillation*"/ "*resistant hypertension*"/ "*cardiovascular disease*"/ "*carotid*"/ "*peripheral artery disease*" and "*chronic kidney disease*"/ "*dialysis*", with and without "*guidelines*". RCTs, observational studies, reviews, meta-analyses and guidelines were included if referring to measures of stroke prevention or to the treatment of stroke-associated risk factors (CVD in general and AF, arterial hypertension or carotid/peripheral artery disease in particular) in the CKD population; if highly relevant or if CKD data were very scarce or lacking, data regarding the general population was also referred to. Relevant references from the selected articles and guidelines were also searched manually afterwards.

In the second approach, a literature search was done that included all new oral anticoagulant publications since January 2016. The title/abstract of the articles were retrieved from PubMed using the keywords "*oral anticoagulation*", "*novel or direct oral anticoagulants*", or "*non-vitamin K antagonists"*, or "*vitamin K antagonists"*, or "*warfarin"*, and "*atrial fibrillation"*, and "*severe CKD*", "*dialysis"*, and "*left atrial apendage occluder"*. There were 395 articles discovered, 51 of which were deemed relevant to the topic. These publications were analyzed, and only the most noteworthy or innovative ones are discussed in the review.

5.3. Cardioembolic and atherothrombotic stroke in CKD: dilemmas in primary prevention

Cardioembolic stroke: AF

CKD patients with AF (approximately a quarter of all renal patients) [88] are more prone to experiencing both stroke and bleeding, which makes the use of oral anticoagulants a subtle art in managing stroke risk in this population (Figure 3) [89, 184].

Non-ESKD patients

Anticoagulation is safe for an eGFR ≥15ml/min/1.73m^2, according to the 2016 ESC Guidelines for the management of AF [185].

There is currently no restriction to using VKAs in non-ESKD CKD [186]. The classic treatment of AF with VKAs (namely warfarin) significantly reduces the risk of stroke in non-end stage CKD, without significantly impacting the risk for major bleeding [105]. VKA have a renal elimination of only 10-15% [187]; however, a creatinine clearance under 30 ml/min was shown to be an independent predictor of warfarin-associated hemorrhagic risk [165] and therefore, careful dose titration is needed in patients with advanced kidney impairment [187]. This observation is also supported by a 2017 research which demonstrated that severe non-ESKD CKD patients treated with warfarin have a labile INR with a significantly lower time-in-therapeutic range and a higher adverse events risk [188].

Atrial fibrillation	– Both high thromboembolic and bleeding risks; – Anticoagulation is generally safe for an eGFR ≥15 mL/min (ESC guidelines) [10]; – Decision to use anticoagulants should be individualized and based, preferably, on stratification algorithms (Fig. 2) [20]; – Careful monitoring of bleeding risk is mandatory [18]; NOACs: – Are generally preferred over VKAs in mild and moderate CKD [10]; – Need dose adjustment (Table 1); – Generally not suitable for CKD stage 5 [10] (apixaban and/or rivaroxaban might be considered); VKAs: – Need careful titration in advanced CKD (delayed achievement of therapeutic INR) [13];
CS	– No official firm recommendations for CKD; Aspirin: – AHA/ASA guidelines [22]: eGFR <45 mL/min, but not for CKD stages 4 and 5; – KDIGO guidelines [23]: for secondary prevention only; – Clopidogrel is not an alternative [23]; Revascularization techniques (CEA or CAS): – Higher risk for adverse events with worsening renal function [28], but reported overall stroke and death rate within the safety limits of under 3% [29]; – "May be considered in symptomatic patients with moderate to severe carotid stenosis" [25]; – CEA is generally preferred over CAS [25]; – CAS is an option in selected symptomatic high-risk patients if CEA is not suitable [25, 29, 32];
Resistant hypertension	Medical therapy: – 4th line therapy (aldosterone antagonists, centrally acting alpha-adrenergic agonists, alpha-blockers): limited use [38, 39]; Interventional approaches: – If truly resistant hypertension with systolic BP ≥160 mm Hg and failure of medical treatment [36]; Renal Denervation: – For truly resistant hypertension if eGFR ≥45 mL/min/1.73 m^2 (expert consensus of the ESC) [44]; – Consistent data in the more advanced stages of CKD are lacking [44]; – Also has renoprotective effects [41]; – BAT is becoming a promising option (also has renoprotective effects) [47, 49]; PTRA: – RCTs did not include high-risk patients with refractory hypertension and rapidly declining kidney function; – Observational studies: improves BP control and kidney function in CKD stages 4–5 [56]; – High chances of response if recent high BP (particularly over 180 mm Hg systolic) reluctant to medical therapy and prior progressive CKD [58, 59]; – Need for benefit stratification [30].

AHA/ASA, American Heart Association/American Stroke Association; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BAT, baroreflex activation therapy; BP, blood pressure; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; CKD, chronic kidney disease; CS, carotid stenosis; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; KDIGO, Kidney Disease Improving Global Outcomes; NOAC, non-vitamin K antagonist oral anticoagulants; PTRA, percutaneous transluminal renal angioplasty; RAS, renal artery stenosis; RCTs, randomized controlled trials; VKA, vitamin K antagonist.

Figure 3. Primary prevention of stroke in CKD: dilemmas (according to [189]).

The novel DOACs are associated with lower risks for stroke and major bleeding compared to warfarin in patients with mild and moderate renal impairment [164]. Nonetheless, definite dose adjustment is needed as they have variable renal elimination [185]. The 2016 ESC Guidelines do not support the use of NOACs in CKD stages 4 and 5 due to little evidence [185],

but the EMA and the FDA also spread the indications to CKD stage G4 based on pharmacokinetic studies [89].

There is currently insufficient evidence to recommend single or dual anti-platelet therapy for stroke prevention in patients with AF and stages G4/5 or G5D CKD even when OAT is undesirable. Bleeding risk appears to be increased and there is no evidence for efficacy. It is recommended that their combined use with OAT should be avoided in severe CKD unless in specific situations (e.g., recent coronary stent) [190].

ESKD patients

In the absence of RCTs regarding stroke prevention in dialysis patients with AF, the decision to use oral anticoagulants should be made on an individualized basis [186]. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) controversies report published in September 2017, is the first official taskforce that discusses the existing observational studies that examine warfarin use and associated stroke and bleeding risks in adults with G5D-CKD and AF [191]. Strict monitoring due to the increased bleeding risk is mandatory (the KDOQI clinical practice guidelines for CVD in dialysis patients) [192].

Warfarin was reported to increase the risk of major bleeding by 30% in ESKD without having any effect on the risk of stroke [105]. Since the ESC and the EMA do not support the use of DOACs in ESKD due to lack of sufficient data [89, 185] and there are no RCTs of DOACs in patients with severe CKD, warfarin still remains the only choice for OAT [185]. Nonetheless, the FDA supplemented the indications for apixaban and low dose of rivaroxaban usage in dialysis patients based on pharmacokinetic and pharmacodynamic studies [89, 193].

Ischemic and bleeding risk stratification

The use of individualized stratification models should be encouraged as refraining CKD patients from standard therapies ("*therapeutic nihilism*") worsens their prognosis [89, 194].

Reinecke et al. [194] have proposed a stratification algorithm for CKD patients (Figure 4) to better identify those that would mostly benefit from anticoagulation: if [1] CHADS2 score (Congestive heart failure, Hypertension, Age ≥75 years, DM, Stroke [double weight]) ≥2 or [2] under 2 but age≥75 or [3] ≥1 and age between 65-74 years/female sex/vascular heart disease, bleeding risk should be calculated (HAS-BLED score -Hypertension, Abnormal renal and liver function, Stroke, Bleeding Labile INR, Elderly, Drugs or alcohol - with recurrent falls, dementia and cancer as additional factors) for the opportunity of oral anticoagulation; if the bleeding risk is low-to-intermediate (HAS-BLED = 0-2), than anticoagulation with DOAC or VKA is proposed [194].

Atherothrombotic stroke: Carotid stenosis (CS)

CKD patients display advanced carotid atherosclerosis with more frequently unstable or ruptured plaques due to composition changes (less collagen, more calcified) and this explains the 3-fold higher prevalence of remote cerebrovascular events in these patients compared to non-CKD [195].

Specific guidelines for the medical treatment of CS in CKD do not exist. The AHA/ASA Guidelines allow the use of aspirin for preventing a first stroke when eGFR is under

45 ml/min/1.73 m^2, but not for CKD stages 4 and 5 [196]; at the same time, KDIGO 2012 Guidelines suggest prescribing aspirin to CKD patients "*at risk for atherosclerotic events*" only for secondary prevention and if there is no increased bleeding risk [197]. Antiplatelet drugs increase the risk for major and minor bleeding (by 33% and 49%, respectively) but do not significantly reduce the risk for stroke, all-cause and cardiovascular mortality [198]. Clopidogrel is generally not a practicable alternative to aspirin: it brings no benefits over placebo for reducing stroke risk in CKD, possibly due to an occurring clopidogrel resistance [197].

The ESC do not address the puzzle of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) in CKD patients; the North American Society for Vascular Surgery Guidelines state that „*among asymptomatic patients with cardiac or renal insufficiency, best medical therapy may be preferable to CAS or CEA*", while „*CEA or CAS may be considered among symptomatic high-risk patients with moderate to severe carotid stenosis*" [199].

Clinical trials investigating CEA or CAS in CKD are missing but retrospective studies have shown that worsening renal function is generally associated with an increased risk of myocardial infarction, stroke and death after both CEA (9% for CKD versus 2.6% for controls 30 days after CEA) [200] and CAS (HR 2.97 for CKD versus no CKD 6 months after CAS) [201], with dialysis patients being at the highest risk [202].

Despite this, Klarin et al. [203] recently reported an overall 30-day stroke and death rate of less than 3% for CEA and CAS combined across all CKD stages which meets the criteria endorsed by the guidelines [196, 204]. Moreover, CKD stage 3 patients with symptomatic high-grade (70-99%) CS were shown to greatly benefit from CEA, with a relative stroke risk reduction of 82% compared to medical therapy [205]. CAS requires iodinated contrast and is associated with higher rates of major adverse cardiovascular and cerebrovascular events and 2-fold higher 30-day mortality compared to CEA in both moderate and severe CKD [203, 206]. Therefore, CAS becomes a viable option only in symptomatic patients at high-risk for CEA, especially if there is severe cardiac impairment [199].

5.4. Hemorrhagic stroke in renal patients

Resistant Hypertension

Hypertension is both responsible for ischemic [207] and hemorrhagic stroke [208]. As a well-known CVD risk factor, high blood pressure (BP) is strongly corelated with the development of atherosclerosis and ischemic stroke. However, since uncontrolled hypertension is the most common cause of spontaneous intracerebral hemorrhage [209], for scientific clarity we decided to discuss here the hemorrhagic stroke causality. In fact, the main interest in the "*equation of RH*" is to lower the BP values by all means.

As defined in the 2013 ESH/ESC Guidelines, RH is contemplated when a therapy with 3 drugs (diuretic and two other antihypertensive drugs belonging to different classes at adequate doses) fails to lower BP to 140 and 90 mmHg, respectively [210].

One third of the patients with an eGFR under 45 ml/min and almost half of patients with an urinary albumin-to-creatinine ratio >300 mg/g have RH, a major cause of hemorrhagic stroke in the CKD population [211].

When the addition of the "fourth line" medical therapies (e.g. aldosterone antagonists, centrally acting alpha-adrenergic agonists, alpha blockers) recommended by the CKD dedicated guidelines (KDIGO, KDOQI) [212, 213] fails to efficiently lower BP, invasive procedures such as renal denervation (RD) or baroreceptor stimulation represent an alternative [210]. Revascularization of the renal artery in patients with RH secondary to atherosclerotic renovascular disease (ARVD) is also an option.

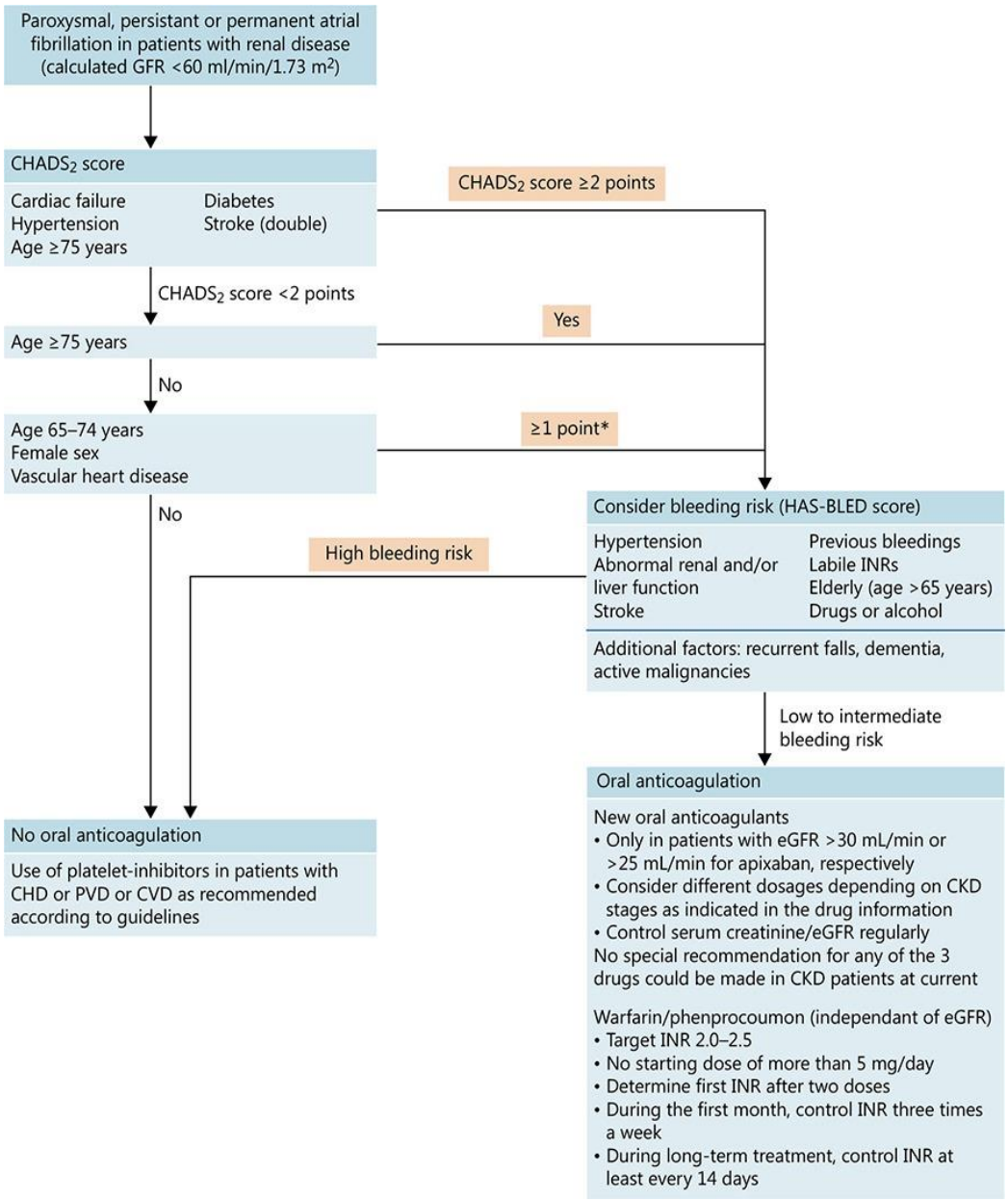


Figure 4. Risk stratification algorithm for anticoagulation in CKD according to Reinecke et al. [194] (reproduced with permission of the publisher. ©Stroke, Lippincott Williams and Wilkins 2013). CKD, chronic kidney disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PVD, peripheral vascular disease.

Renal denervation

Even though there is limited evidence that RD controls the BP (and could have renoprotective effects: eGFR stabilization/increase and/or lower albuminuria) [214, 215], two major 2017 reviews [216, 217] questioned the benefits of RD on renal function and major cardiovascular events. According to the expert consensus of the ESC, RD may be performed for truly RH if eGFR≥45 ml/min/1.73m^2 (consistent data in the more advanced stages of CKD are lacking) [218, 219]. However, renal arteries with stenosis are not eligible for RD [218] and prophylaxis of contrast-induced nephropathy is necessary [218].

Baroreflex activation therapy (BAT)

Even if there are not yet important studies and clear protocols, BAT could become a promising option [220] in the treatment of RH. Particularly interesting for CKD patients is that BAT was not only shown to decrease office BP values in small prospective trials on CKD non-dialysis and dialysis patients [221, 222], but also to have renoprotective effects by significantly reducing proteinuria and improving eGFR [221]. BAT would be an option when RD is not possible or inefficient [223].

Renal artery stenting

When declining kidney function impairs the efficacy of medical treatment in controlling BP or limits the use of ACEi or ARBs in ARVD, percutaneous transluminal renal angioplasty (PTRA) with stenting is usually proposed as the alternative method of choice [224].

Data from RCTs failed to demonstrate a clear benefit of stenting regarding BP, renal function and cardiovascular morbidity and mortality outcomes [225-228] and therefore renal revascularisation is not endorsed by the 2017 ESC Guidelines for the management of renovascular hypertension (with few specific exceptions) [204].

However, relevant gaps in evidence are represented by RCTs not addressing high-risk patients with refractory hypertension and rapidly declining kidney function. Revascularisation was shown in observational studies to improve BP control and kidney function in CKD stages 4-5 and to have a major impact upon survival [229, 230]. The 2017 ESC Guidelines draw the attention towards the need for stratification of patients based on the estimated benefits of renal revascularisation [204]. As such, PTRA with stenting seems to be most beneficial in those patients with recent high BP (particularly over 180 mm Hg systolic) that is reluctant to medical therapy and prior progressive kidney function impairment [204, 231, 232].

Cerebral bleeding in antithrombotics overdosing

The risk of major bleeding in advanced CKD patients without anticoagulant treatment is twice as high as in the general population [233]. Even when thrombotic and haemorrhagic risks are estimated according to the Guidelines, the indication of antithrombotic treatment is solid, and the drugs are chosen and dosed accordingly, anticoagulation therapy in CKD patients can promote bleeding episodes, as these substances can accumulate or directly interfere with an already changed hemostatic system [234, 235]. For primary prevention of cerebral haemorrhage in DOACs overdosing, there are new recommendations in the ESC Guidelines

for antithrombotic therapy and very good local anticoagulant reversal protocols (e.g., idarucizumab administration in dabigatran reversal).

5.5. Left atrial appendage closure devices: alternatives to anticoagulation for stroke prevention

Since 2011, when the EMA endorsed the treatment with DOACs for essential anticipation of cardio-embolic stroke in patients with AF, a sensible address more than once emerged: "*will NOACs become the new standard of care in anticoagulation therapy*?" [236]. However, dialysis patients still rely on VKAs as the only oral anticoagulant therapy available, especially in Europe. In the 2020 guidelines, AHA advocated for adjusted Apixaban dose in patients with ESKD requiring OAT, as an alternative to VKAs [237].

One of the few alternatives to oral anticoagulation is percutaneous LAAO with various devices, an idea taken from the LAA surgical exclusion from the '50s. It seems that surgical exclusion of LAA led to a decrease in the rate of stroke or systemic embolism, including mortality from all causes, even though it was not documented in RCTs [238].

Planned and utilized within the final decade as a surrogate for oral anticoagulation in high-risk patients, transcatheter LAA occluders appeared to be a compromise between bleeding and thrombo-embolic events. LAA percutaneous exclusion is designed not only to reduce the stroke risk, but also to improve hemorrhagic profile induced by OAT. According to the 2020 European guidelines, LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (IIb class recommendation, level of evidence B) [239]. Though anticoagulation therapy could be discontinued after percutaneous LAA occlusion, antiplatelet therapy should be continued indefinitely (Aspirin 75-325 mg/day) [239].

However, ESKD and dialysis patients are not the single high-risk population to benefit from percutaneous LAA occlusion. Other categories of patients in which LAAO could be very helpful are patients with previous intracranial hemorrhage(s), patients with major gastrointestinal bleeding due to non-removable causes (esophageal varices, colon angiodysplasia, hereditary hemorrhagic telangiectasia), patients with cerebral amyloid angiopathy, patients with recurrences of ischemic stroke despite taking oral anticoagulants and frail elderly patients with high risk of bleeding and falling. Nevertheless, factual data on the efficacy and safety of LAAO in these populations are currently lacking.

Two major studies (PREVAIL and PROTECT AF) [240, 241] which included 2400 patients, and a meta-analysis [242] compared implantation of LAA occluder with conventional pharmacological anticoagulation therapy, and reported an implantation success rate of 95%. Most of the complications (between 2.2 and 5%) occurred in the periprocedural period. In addition, the optimistic perspective of a "*few-complications*" percutaneous occlusion should be interpreted in the context of cautious attitude of the European guidelines.

The operators' experience is another key element in a multidisciplinary team, guiding the selection of patients, as well as influencing the success of the procedure and post-procedural management. Therefore, an extended MDT (nephrologist, interventional cardiologist, clinical cardiologist, the echocardiographer, the anaesthetist, cardiac surgeon) might be required to ensure good procedural outcomes. Careful selection of very high-risk patients who would

benefit most from LAA occlusion seems more reasonable than to relax the criteria and to extend the indications of the procedure.

Careful selection of dialysis patient combined with experience of the operator team should provide beneficial long-term outcomes, allowing for a better level of indication in the guidelines and a more refined post-procedural antithrombotic protocol.

Some limitations of LAA occlusion should be addressed. One limitation attributed to percutaneous closure is represented by the fact that not all thrombi form in the left atrial appendage [243, 244]. Thus, LAAO may not protect against thromboembolic stroke's overall risk related to atrial cardiomyopathy. Moreover, following the procedure, optimal therapy consists of one or two antiplatelet agents [245, 246]. This therapeutic approach could prove inefficient in atrial cavity thrombosis and could carry an additional hemorrhagic risk in the case of dual antiplatelet therapy (Figure 5).

Regimen
Warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely
Warfarin for 45 d followed by aspirin and clopidogrel for 6 mo, then aspirin indefinitely
warfarin in 16%, NOAC in 11%, DAPT in 60%, SAPT in 7%, and no therapy in 6%
OACs in 28.8%, SAPT in 36.2%, DAPT in 23.2%, OACs plus DAPT in 4.3%, and no therapy in 7.5%.
DAPT for 6 mo followed by aspirin indefinitely
DAPT for 1 to 6 mo followed by aspirin indefinitely

Figure 5. Different antithrombotic regimens following LAA occlusion used in clinical trials (modified from Pacha et al., 2019 [246]).

Another problem resides in the functional and endocrine properties of the LAA. Since it is 2.6 times as compliant as the left atrial body, LAA contributes significantly to left atrial reservoir function. Therefore, LAA is important for the adaption to pressure and volume overload [247]. In addition, LAA contributes to the release of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Following LAA exclusion, a significant decrease of ANP- and BNP-serum levels has been described [248]. Notably, the question of whether or not LAAO favors the onset of HF remains a matter of debate [249]. Unfortunately, the development and aggravation of HF was not consistently assessed in any trial on LAA occlusion and is not planned to be registered as an endpoint or adverse event in ongoing studies.

Considering all potential benefits and risks, in our opinion only patients who truly cannot take OAT should undergo LAA occlusion. Thus, if they do not undergo the procedure they would be doomed to have no protection against thromboembolic risk. Consequently, this technique has a more significant potential than guidelines claim nowadays. Ongoing studies could help to introduce a stronger indication in future guidelines and select the patients who would have clear benefits from LAA occlusion.

Chapter 6. Sudden cardiac death and end-stage kidney disease: answering to contemporary practical questions

6.1. Background and epidemiology

Sudden cardiac death (SCD) is defined as an unexpected death from cardiac causes in a person with known or undiagnosed cardiac illness, occurring within 1 hour of symptom start (witnessed SCD), or within 24 hours of the last proof of life (unwitnessed SCD). Because cause of death is sensitive to interobserver heterogeneity, SCD can be misclassified [250]. SCD is the most common cause of mortality in the general population, accounting for up to 15% of all fatalities [251]. SCD is a leading cause of mortality in patients with ESKD [252], but determining its exact frequency is challenging since research on the incidence of SCD in ESKD are frequently mixed with those on sudden cardiac arrest (SCA) during a HD session. However, extradialysis SCD and intradialysis SCA are separate clinical conditions that should be distinguished.

In reality, aside from the patient's clinical circumstances, the dialysis session may promote the start of life-threatening arrhythmias. Furthermore, hypotension and syncope are widespread during HD sessions, highlighting a number of risk factors [253]. Their emergence necessitates quick action by healthcare specialists in order to make an accurate diagnosis and distinguish these occurrences from SCA.

My research, as a fellow of the prestigious European Dialysis (EuDial) Working Group, was to conduct a critical review of the recent scientific literature on the causes of extradialysis SCD and intradialysis SCA in ESKD patients, as well as potential management strategies to reduce the occurrence of such events. This work was recently published in a high IF journal [254].

Genovesi S., Boriani G., Covic A., Vernooij RW, Combe C., **Burlacu A.**, Davenport A., Kanbay M., Kirmizis D., Schneditz D., van der Sande F., Basile C., the EuDial Working Group of ERA-EDTA, *Sudden cardiac death in dialysis patients: different causes and management strategies*. Nephrology Dialysis Transplantation, Volume 36, Issue 3, March 2021, Pages 396–405, https://doi.org/10.1093/ndt/gfz182

[Impact Factor: 5.992]

Arrhythmia and cardiac arrest were the leading causes of mortality in the US Renal Data System database, accounting for 40% of all known causes of death among dialysis patients and over 78 percent of all cardiovascular causes of death [252]. When compared to PD, the risk of SCD in HD patients is 50% greater three months after dialysis begins, albeit these rates equalize after two years. Although SCD is responsible for a significant number of deaths in ESKD patients, it is somewhat surprising that the number of such deaths during dialysis sessions is not higher, given the increased prevalence of left ventricular hypertrophy, and CAD in HD patients, as well as changes in cardiac perfusion and electrolyte fluxes.

Karnik et al. [255] reported an intradialysis SCA rate of 7.0/100 000 HD sessions, whereas Pun et al. [256] reported a rate of 4.5 per 100 000 dialysis treatments. As a result, the occurrence of such occurrences is rather uncommon, but the prognosis following an

intradialysis SCA is exceedingly bad. According to Karnik et al. [255] just 40% of patients were successfully resuscitated and were still alive after two days. Of the 60% who died within 48 h of the arrest, 13% died in the dialysis unit.

6.2. Sudden cardiac arrest in G5D-CKD: pathophysiological mechanisms

When confronted with sudden cardiac death, determining which arrhythmia caused death is difficult. It is conceivable that when the initial ECG is done, it is hard to determine whether any documented asystolic bradyarrhythmia is the source of the event or a result of a ventricular fibrillation episode (VF). This uncertainty may be addressed only if a device was already recording the fatal event [e.g., an ECG Holter, an intracardiac device, or an implanted loop recorder (ILR)] [257].

VF appears to be the most readily documented rhythm in cardiopathic individuals during SCD [258, 259]. Cobb et al. [260] showed, however, that VF events may account for a lesser proportion of SCD than previously believed. It is unknown what type of lethal arrhythmia occurs in dialysis patients undergoing SCD. According to Wan et al. [261], 78.6 percent of SCAs in 75 HD patients using a wearable cardioverter defibrillator were caused by ventricular tachycardia (VT) or VF, whereas only 21.4 percent were caused by asystole. The research population's average LVEF was 27.4 percent, with 19 percent of patients having an LVEF more than 35 percent. Eight unexpected SCDs were documented in later research in HD patients with an implanted cardiac monitor as a result of severe bradycardia with asystole. One of the exclusion criteria in this cohort was the existence of an LVEF of less than 35% [262].

Two recent investigations in HD patients with ILRs have bolstered the notion that SCDs are mostly caused by bradyarrhythmias. Sacher et al. [263] investigated 71 HD patients over a 21-month period and discovered four SCDs in diabetic individuals as a result of increasing bradycardia followed by asystole. Three of the four individuals had an LVEF of greater than 50% (for one of them, LVEF was not known).

Additionally, Roy-Chaudhury et al. [264] reported 14 instances of asystole and just one of prolonged VT in a group of 66 younger HD patients implanted with an implantable loop recorder (ILR) and observed for six months. None of these arrhythmias was life-threatening. Eighty-six percent of patients with clinically significant arrhythmia were diabetic, and their mean LVEF was 55%.

Numerous publications have proposed a correlation between SCDs and dialysis sessions in HD patients, demonstrating two frequency peaks at the end of the longer interdialytic interval (LIDI) and immediately following the first dialysis session of the week [265, 266]. Wong et al [267] .'s investigation revealed that the risk of SCD increased during the LIDI.

Furthermore, Sacher et al. [263] observed that all episodes occurred during the LIDI, and Roy-Chaudhury et al. observed that clinically significant arrhythmias occurred most frequently during the final 12 hours of the LIDI. None of the research mentioned could establish a link between plasma electrolyte levels and catastrophic occurrences.

However, the study by Sacher et al. demonstrated that a plasma potassium concentration greater than 5.0 mmol/L was associated with an increased risk of cardiac conduction disorders and a plasma K+ concentration less than 4.0 mmol/L was associated with

an increased risk of ventricular arrhythmia. Epidemiological studies indicated a statistically significant connection between pre-dialysis hyperkalemia levels and SCD [266].

By combining all of this information, we anticipate that during the first brief interdialysis interval of the week, HD patients have a significant reduction in plasma K+ concentration, but by the conclusion of the LIDI, they may present with substantial hyperkalemia and acidosis. Both of these diseases can result in cardiac electrical instability, which can result in potentially fatal arrhythmias (i.e., VF or bradyarrhythmia with asystole).

However, additional risk factors associated with cardiac comorbidities and uraemia may lead to sudden death in ESKD patients. Indeed, PD patients who do not have fast electrolyte concentration changes also have a high prevalence of SCD [268]. PD is less intense than HD: therapy is more or less constant with minor modifications due to the various types of PD. As a result, establishing a causal link between the actual therapy and treatment-induced SCD is even more challenging. Nonetheless, the fatality risk associated with aberrant plasma K+ concentrations may be even greater in PD patients than in HD patients, since PD patients are predisposed to hypokalaemia, a clinical condition that can result in deadly tachyarrhythmias [269].

There has been a link established between SCD and reduced LVEF in PD patients with elevated plasma levels of pro-BNP and tn-T, implying a significant role for HF and ischemic heart disease as risk factors for increased sudden mortality in this population [270]. SCD has also been connected with some CVD in individuals receiving HD. After controlling for potential confounding variables, a greater incidence of SCD was seen in incident HD patients with obstructive sleep apnea (OSA) compared to participants without OSA [271]. Furthermore, the incidence of SCD was notably significant among HD patients with severe aortic stenosis who did not have an aortic valve replacement [272].

In conclusion, SCD in ESKD patients may be caused by both brady - and tachyarrhythmias. Recent findings indicate that the former may be the most often occurring cause of death in HD patients, and a correlation between SCD and dialysis time has been established. Diabetic individuals appear to be more vulnerable to this sort of mortality, even with a normal LVEF, and should thus be closely watched.

6.3. Safe practices during dialysis

In Table XI, I tried to summarize the main recommendations of the EuDial group (of which I was also part of the elaboration of this Guideline) regarding the management of the dialysis procedure in order to reduce the risk of SCD.

6.4. Drugs and devices for SCD prevention

There is conflicting and insufficient data about the efficacy and safety of anti-arrhythmic medicines in HD patients in terms of SCD or fatal cardiovascular events. Additionally, dialysis patients have a low rate of long-term adherence to medication therapy [273, 274], which may restrict the findings' applicability to everyday clinical practice. As a result, no firm recommendations can be made in favor of any particular treatment or kind of therapy, and large, high-quality RCTs in HD patients are required.

Drugs

HD patients may benefit from cardiovascular medicines, however there is little evidence to support this claim. This is largely because RCTs seldom include people with HD. For HD patients, below is a brief review of the effectiveness, safety, and efficacy of medicines that affect electrophysiology and/or the sympathetic-vagal control of the heart and arteries in terms of specific HD patient populations.

Table XI. Dialysis treatment practices (according to [254]).

Dialysate potassium	- One of the main goals of HD is the removal of K+ that has accumulated in the body in the interval between two dialysis sessions; - The frequency of arrhythmias is greater during the last 2 h of dialysis and immediately post-dialysis; [275] - There is no good evidence that intradialysis ventricular arrhythmias are associated with an increased risk of overall mortality or sudden mortality;[276] - In conclusion, the true challenge in HD patients is to avoid both life-threatening pre-dialysis hyperkalaemia (plasma K+ level >6 mmol/L) and post-dialysis relative hypokalaemia (or at least a very rapid decrease of plasma K+ concentration and the related risk of lethal arrhythmias).
Dialysate calcium	- A lower Ca2+D concentration may induce an increase in myocardial repolarization time and QT-interval; [275, 277] - Ca2+D deficiency should be avoided in individuals with a prolonged baseline QT interval and should not be utilized in conjunction with a deficiency of K+D. Ca2+D concentrations should be chosen in such a way that they do not deplete serum Ca2+, particularly in individuals at risk of hypokalaemia following dialysis.
Dialysate bicarbonates	- The main potential adverse effects associated with a high dialysate bicarbonate (D_{BIC}) concentration are increased carbon dioxide formation, electrolyte imbalances and QT prolongation; [278] - During HD, an increase in serum bicarbonate levels leads to a decrease in serum Ca2+ concentration. This phenomenon is primarily caused by an alkalosis-induced change in the electrical charge of proteins, which increases the amount of complexed calcium. - This phenomenon causes an increase in ventricular repolarization time and prolongation of the QT interval, potentially increasing the risk for life-threatening arrhythmias. It is therefore advisable not to combine lower $Ca^{2+}D$ and $K^{+}D$ concentrations with high D_{BIC}concentrations, particularly in patients with a prolonged basal QT interval.
Dialysate magnesium	- A large observational study from Japan using data from 142 555 HD patients reported a J-shaped curve between magnesium concentrations and all-cause mortality (both cardiovascular and non-cardiovascular); [279] - It has been shown that serum magnesium concentrations are independently and inversely associated with all-cause mortality, cardiovascular mortality and sudden death in European HD patients. [280]
Ultrafiltration	- An ultrafiltration volume >5.7% of body weight has been related to a higher risk for SCD [HR 1.13 95% CI 1.00–1.27]; P = 0.04 [281]. - Pun *et al*. [256] found an association between intradialysis SCA and percent volume removed during the dialysis session [OR 1.11 95% CI 1.02–1.20).

β-blockers

There have been conflicting findings on the effectiveness and safety of β-blockers in people with HD. For example, a systematic review containing three RCTs that demonstrated a substantial risk reduction for cardiovascular mortality and cardiovascular events with β-blockers, but also nine observational studies that revealed no effect on these outcomes [282].

In comparison, three further observational studies found that β-blockers were related with a decreased incidence of SCD in individuals with HD [281] or a reduction in all-cause mortality [283, 284]. In another RCT with 114 HD patients, it was discovered that carvedilol treatment resulted in a substantial reduction in all-cause and cardiovascular mortality, but not a statistically significant reduction in SCD [285]. There was no correlation between β-blocker intake and SCD in a post-hoc study of the Hemodialysis Study, which included 1747 patients [286].

Inhibitors of the angiotensin-converting enzyme / blockers of the angiotensin receptor

There is currently no clear evidence that ACEis or ARBs are beneficial in avoiding SCD in HD patients. A comprehensive study showed no evidence of a substantial decrease in the risk of cardiovascular events in the ACEi or ARB therapy group [287]. For example, RCTs with fosinopril and olmesartan failed to demonstrate a decrease in the incidence of cardiovascular events or all-cause mortality in HD patients [288, 289]. Similarly, another trial found no statistically significant reduction in the probability of SCD in HD patients treated with spironolactone [290]. However, two observational studies revealed that HD patients treated with an ACEi experienced a decrease in cardiovascular or total mortality [291, 292].

Potassium binding agents

Although sodium polystyrene sulphonate and calcium polystyrene sulphonate are frequently used in the general population to treat chronic hyperkalemia [293, 294], contradictory effects of fludrocortisone or sodium zirconium cyclosilicate (ZS-9) on plasma K+ levels have been observed in HD patients [295, 296]. SCD and cardiovascular mortality outcomes were not reported in these two RCTs [293, 294].

Calcium channel blockers (CCBs)

An observational research discovered a favorable, albeit not statistically significant, impact of CCBs on mortality 24 hours after SCA in HD patients [297]. Similarly, another observational trial with 4065 HD patients found that the use of CCBs was related with a 23% reduction in the risk of cardiovascular death [298].

Calcimimetics

Ballinger et al. [299] showed no effect on all-cause or cardiovascular mortality in individuals treated with cinacalcet. SCD was not included as an outcome measure in this review and was examined in only one trial, which reported no difference in SCD between cinacalcet and usual care [300]. In two RCTs, etelcalcetide considerably lowered parathyroid hormone levels; nevertheless, hypocalcaemia was more prevalent in the etelcalcetide group, resulting in QT-interval lengthening in many patients. There were no reports of death or adverse cardiovascular events [301].

Amiodarone

Despite the possibility of side effects (on the thyroid gland, lungs and liver), amiodarone is commonly used to treat both atrial and ventricular tachyarrhythmias. However, there has been no consistent evidence of its efficacy in avoiding SCD in people with HD. Amiodarone was related with an increased risk of SCD in HD patients in a DOPPS study [HR 1.44 (95 percent CI 1.16–1.81)] [281]. However, as is the case with any observational study, no causal inferences can be formed. A Cochrane systematic review [302] of 24 studies found that amiodarone was associated with a significant reduction in the risk of SCD, cardiac, and all-cause mortality in individuals at high risk (primary prevention) or who had recovered from a SCA (secondary prevention). However, these studies did not include specific subgroups of ESKD or HD patients.

Digoxin

Digoxin usage was related with a 28% higher risk of death in a retrospective observational cohort analysis of 120 864 incident HD patients, with the risk of death being greatest in patients with lower pre-dialysis blood K+ levels [303].

In conclusion, contradictory and limited data has been discovered regarding the effectiveness and safety of antiarrhythmic medications in individuals with HD in terms of SCD or fatal cardiovascular events. Additionally, dialysis patients have a low rate of long-term adherence to medication therapy, which may restrict the findings' applicability to everyday clinical practice. As a result, no firm recommendations can be made in favor of any particular treatment or kind of therapy, and large, high-quality RCTs in HD patients are required.

Implantable cardioverter defibrilators (ICDs).

In general, the decision to implant an ICD in the setting of ESKD and dialysis is clinically challenging and should be made through an interdisciplinary approach involving close collaboration between nephrologists and cardiologists, with the goal of weighing the risk–benefit of each specific treatment option on an individual basis [304] Clinical decision-making may become even more challenging in the event of life-threatening VT that appear to be assisted by temporary but not completely correctable causes [305].

Clinically, the difficulty in deciding whether to implant an ICD is that, given the significant comorbidities that typically occur in ESKD patients, the benefit of ICD therapy may be diminished by competing causes of mortality. This critical issue may also be related to a number of other issues, including electrolyte imbalances, which raise the likelihood of ineffective shock treatment or the formation of non-shockable rhythms (asystole/pulseless electrical activity) as a pathophysiological cause of arrhythmic SCD (Figure 6).

A significant issue is the high occurrence of ICD-related problems in dialysis patients. A meta-analysis revealed a substantial increase in infectious complications in patients with ESKD [HR 8.73 (95 % CI 3.42–22.31)] [306]. Infections of the ICD system need the device's total removal, an operation fraught with inherent danger and consequences [304]. Additional common problems include lead dislodgment necessitating revision, lead malfunction necessitating extraction, hemorrhage, and venous thrombosis [307, 308]. Although it has been hypothesized that subcutaneous ICDs may have a benefit over endocardial ICDs with

transvenous leads in terms of minimizing the risk of central venous stenosis and infection, this kind of device may be ineffective in cases of severe bradyarrhythmias [309].

The major cardiology societies' Guidelines for sudden death prevention recommend implanting an ICD for primary prevention in patients with an LVEF of less than 35% and a life expectancy of at least one year, and in secondary prevention in patients with documented VF or haemodynamically intolerable VT in the absence of reversible causes [310]. However, the presence of ESKD was an exclusion criterion in the RCTs that demonstrated that the ICD confers a survival benefit in populations with a high risk of SCD [311-313].

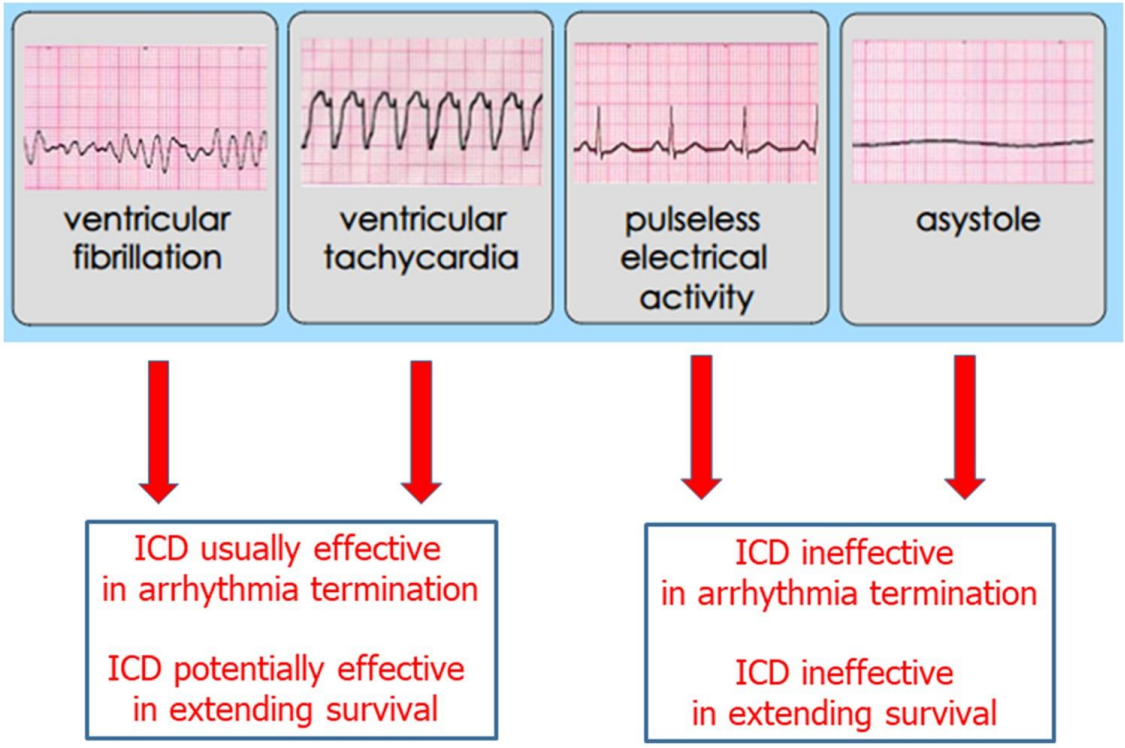


Figure 6. Arrhythmias potentially leading to SCD and the role of ICD therapy.

Numerous observational studies have demonstrated that the presence of ESKD is a poor predictive factor for death in patients implanted with an ICD for primary prevention [314, 315]. When populations of dialysis patients with ICD indications are compared, however, statistics are inconsistent. Hiremath et al. [316] demonstrated that an ICD implant is related with improved survival in ESKD patients with left ventricular dysfunction (LVEF < 35%) when compared to those without the device [HR 0.40 (95 % CI 0.19–0.82)] [316].

Clearly, the danger of bias and unmeasured confounding is a significant constraint, and propensity score matching may be used to mitigate this risk. Indeed, Pun et al. [317] found no difference in mortality between two propensity-matched cohorts of ESKD patients, one of whom got an ICD for primary prevention and the other who did not (43.4 percent in the ICD cohort versus 39.7 percent in the control group). Due to the lack of proof, only a fraction of ESKD patients with an indication for ICD placement receive the device.

There might be various explanations for the ICD strategy's inability to reduce overall and SCD mortality: To begin, we must consider the possibility of device failure due to the presence of non-shockable rhythms (asystole/pulseless electrical activity) or an arrhythmia

occurring in the presence of hyperkalemia and/or severe acid–base balance disturbances [267, 318] resulting in ineffective ICD shock termination or immediate reinitiation following shock delivery. Only post-mortem examination of intracardiac ECGs (which was actually anticipated as part of the ICD2 trial design) revealed which arrhythmia was related with SCD.

6.5. Conclusions

In spite of current attempts to prevent and identify people at increased risk of SCD in the ESKD community, SCD remains a major cause of mortality. Certain modifiable risk factors have been discovered, such as low K+D and Ca2+D concentrations, and some benefits connected to the availability of AEDs in dialysis units have been recorded with regard to patients with intradialysis SCA. However, it is important to remember that the arrhythmia that leads to the fatal event is not always shockable.

Extradialysis SCD is a more complicated issue, and its underlying causes are still a mystery. There are just a small number of HD patients with SCD that have a lower LVEF than normal. Patients with ischemic heart disease and/or heart failure who were not influenced by ESKD had distinct features of SCD than ESKD patients. Recent research reveals that bradyarrhythmias may be more common in this population than tachyarrhythmias as the fatal arrhythmia.

As a result, it's possible that ICDs aren't better at avoiding SCD in people with ESKD because of this. The link between SCD and HD session timing suggests that electrolyte abnormalities, which are common in HD patients, might explain some of the arrhythmic occurrences. Uraemic individuals have a high rate of sudden death, but this does not always mean that other causes are not at play.

Chapter 7. Perspectives opened by novel cardiovascular ultrasound techniques used in CKD patients

7.1. Introduction

Echocardiographic evaluation plays a pivotal role in establishing the diagnosis of myocardiopathy of ESKD patients as well as in stratifying risk and defining the impact of various interventions. Much less work has been devoted to uncovering and evaluating the processes of myocardial dysfunction in advanced CKD, as well as the impact of therapies for this condition. Modern echocardiographic techniques for assessing the strain and strain-rate have allowed the exploration of the so-called neglected cardiac cavities, and I am referring here to the left atrium (LA) and right ventricle (RV). Both the left atrium [319] and the right ventricle [320] appear to be cardiac structures that are particularly affected by advanced CKD. Their study may facilitate a deeper understanding of how renal-heart disease sets in and the (possibly) degree of reversibility in the context of initiating dialysis or KRT.

Moreover, we identified an association between pre-existing pulmonary hypertension (PH) documented by transthoracic echocardiography (TTE) or invasively and adverse

outcomes following KT. It seems that routine assessment of PH in patients on the KT waitlist might be an extensively available and valuable tool for risk stratification in KT patients.

In addition, I presented a recent study coordinated by me, in which the usefulness of IVUS extends to performing percutaneous coronary angioplasties without contrast, in patients with advanced CKD, which could massively impair residual kidney function.

All these concerns have materialized in the publication of recent articles in journals with IF ISI.

1. Tanasa A., **Burlacu A.**, Popa IV, Covic A. *Right Ventricular Functionality Following Hemodialysis Initiation in End-Stage Kidney Disease-A Single-Center, Prospective, Cohort Study*. Medicina (Kaunas) 2021 Jul 10;57(7):704. https://doi.org/10.3390/medicina57070704
   [Impact Factor: 2.430]
2. Tanasa A., **Burlacu A.**, Popa C., Kanbay M., Brinza C., Macovei L., Covic A. *A Systematic Review on the Correlations between Left Atrial Strain and Cardiovascular Outcomes in Chronic Kidney Disease Patients*. Diagnostics (Basel) 2021 Apr 8;11(4):671. https://doi.org/10.3390/diagnostics11040671
   [Impact Factor: 3.706]
3. Brinza C., Covic A., Stefan AE., Floria M., Popa IV., Scripcariu DV., **Burlacu A.** *Pulmonary Arterial Hypertension and Adverse Outcomes after Kidney Transplantation: A Systematic Review and Meta-Analysis*. J. Clin. Med. **2022**, *11*(7), 1944; https://doi.org/10.3390/jcm11071944
   [Impact Factor: 4.242]
4. **Burlacu A**., Tinica G., Brinza C., Crisan-Dabija R., Popa IV., Covic A. *Safety and Efficacy of Minimum- or Zero-Contrast IVUS-Guided Percutaneous Coronary Interventions in Chronic Kidney Disease Patients: A Systematic Review*. Journal of Clinical Medicine 2021 May 6;10(9):1996. https://doi.org/10.3390/jcm10091996
   [Impact Factor: 4.242]

7.2. Right ventricular functionality following hemodialysis initiation - a single-center, prospective, cohort study

7.2.1. Background

The beginning of HD treatments is a particularly traumatic and difficult time in the life of an ESKD patient [321]. In this situation, the patient gets reliant on medical technology, which results in negative psychological and even pathophysiological reactions in the patient. Only a few studies have looked at the precise changes in cardiovascular function that occur following the commencement of dialysis.

Conventional echocardiography may not be capable enough to expose precocious cardiac abnormalities in CKD patients [322], but two-dimensional speckle tracking echocardiography (2D-STE) is viewed as an outstanding technique in the recent past competent of uncovering subclinical myocardial anomalies in LV even when the LVEF is average [323, 324].

A small number of studies have also used 2D-STE to assess the RV function in people with ESKD [325]. No published prospective investigation on an adult ESKD cohort has examined the effects of elective HD on RV, and we are not aware of any such study now underway.

The purpose of this study was to investigate the changes in RV function and mechanics in a prospective manner, utilizing both standard and 2D-STE parameters, after the onset of HD in ESKD stable patients.

7.2.2. Study design

We enrolled 79 consecutive patients with ESKD starting HD and assessed in 4 steps – at baseline, before HD, and at 3, 6, and 12 months. The current investigation was conducted between December 2019 to December 2020 at the "Dr. C.I. Parhon" Hospital, Department of Nephrology, Iasi, Romania. Of 79 patients, only 62 of them finished the study at 12 months, with 17 deaths recorded from CV causes.

In this study, the participants were included in a prospective cohort. The local Ethical Commission has approved the design of the research. Patients who met the eligibility criteria were recorded after studying principles and signing the informed consent. There was no interference to correct the subjects' routines regarding their medication or water drinking constraints for the duration of the study.

Patients started HD with central venous catheters and transitioned to arteriovenous fistula access within 90 days. HD sessions were programmed as three hours and a half. All the recruited subjects received periodical clinical and echocardiography evaluation at three, six, and twelve months.

Our primary objective was to discover if HD can have a beneficial effect on the RV's function and mechanics, including subclinical impairment as measured by 2D-STE. Additionally, each parameter evaluated was analyzed for a possible predictive function.

7.2.3. Methodology

The strain appraisal was made on an offline groundwork. We manually traced the RV endocardium at the end of the ventricular diastole by selecting 3 or 6 points of interest (usually basal, medial, and apex); the software automatically draws the desired contour on adjacent images. Region of interest (ROI) is estimated, manually tailored to fit the thickness of the RV free wall as well as of the interventricular septum.

Subsequently, the specific deformation curves are displayed, with automatic calculation of the global RV strain and the free wall (RVFWLS). Fractional Area Change (FAC) is defined as (end-diastolic area − end-systolic area)/end-diastolic area × 100. RVFWLS is defined as the mean longitudinal peak systolic strain of three segments of the RV free wall, according to the established guidelines [326].

Our study used the prospective analysis of only the free RV wall strain, according to international recommendations, to avoid interfering with LV systole. Although an international agreement for normal values is currently deficient, we considered a value of RV free wall strain below 19% to be pathological, as suggested by larger, recent published multicenter studies [327].

7.2.4. Results

Tricuspid annular plane systolic excursion (TAPSE), FAC, and strain values evaluated with 2D-STE at baseline (before the initiation of the first session of HD) and 3, 6, and 12 months are depicted in Table XII.

Table XII. Dynamic evolution of RVFWLS, FAC, TAPSE values from baseline to 3/6/12 months.

Parameter/Value (N=62)		**Baseline**	**3 months**	**6 months**	**12 months**	**p***
RVFWLS	Average ± SD	31.06 ± 3.5	35.17 ± 4.03	39.72 ± 4.53	39.72 ± 4.58	<0.001
	Median (IQR)	30.7 (27.9-34)	35.1 (31.6-38.4) †	39.8 (35.8-43.4) †,**	39.6 (36-43.6) †, ‡	
FAC	Average ± SD	30.7 ± 3.8	34.7 ± 4.38	39.2 ± 4.96	39.13 ± 4.96	<0.001
	Median (IQR)	30.5 (27.1-33.7)	34.3 (30.1-38.4) †	39 (34-43.4) †,**	38.9 (34.1-43.1) †, ‡	
TAPSE	Average ± SD	20.8 ± 2.34	23.57 ± 2.71	26.63 ± 3	26.62 ± 3	<0.001
	Median (IQR)	20.5 (18.7-22.9)	23.3 (21.1-26) †	26.3 (23.9-29.5) †,**	26.3 (23.9-29.3) †, ‡	

*Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, † ($p<0.001$ – In comparison to baseline values), ‡ ($p>0.05$ – 12 months values vs. 6 months values), ** ($p<0.001$ – 3 months values vs. 6 months values)

Data from Figures 7-9 show the dynamic evolution of RVFWLS, FAC, TAPSE values from baseline to 3/6/12 months. The distribution of parameters was assessed as non-parametric according to the Shapiro-Wilk test ($p<0.05$).

The differences between the parameters measured at different times were significant according to Friedman's tests ($p<0.001$), RVFWLS, FAC, and TAPSE values having a significant increase at 3/6/12 months from baseline ($p<0.001$) and a significant increase at 6 months from 3 months ($p<0.001$), the differences between 12 months and 6 months, however, were not significant ($p>0.05$), according to the Dunn-Bonferroni posthoc tests.

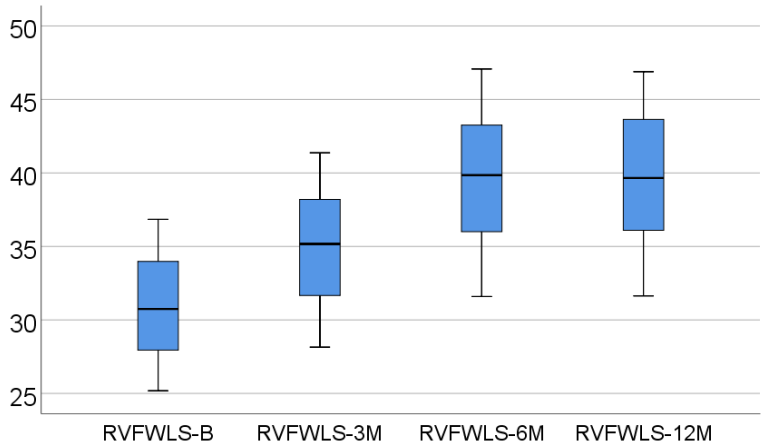


Figure 7. Box-plot representation of RVFWLS evolution.

Data from Table XIII and Figures 10-11 show RVFWLS, FAC, TAPSE evolution values compared to mortality. The distribution of parameters was assessed as non-parametric according to the Shapiro-Wilk test ($p<0.05$).

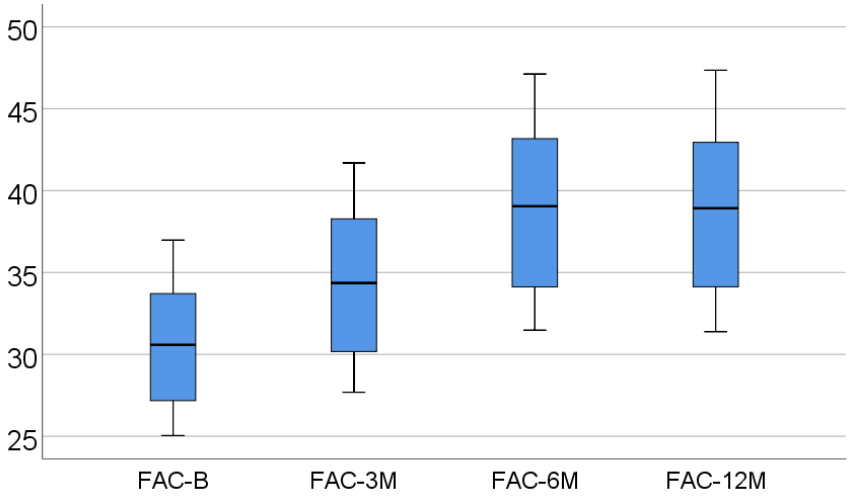


Figure 8. Box-plot representation of FAC evolution.

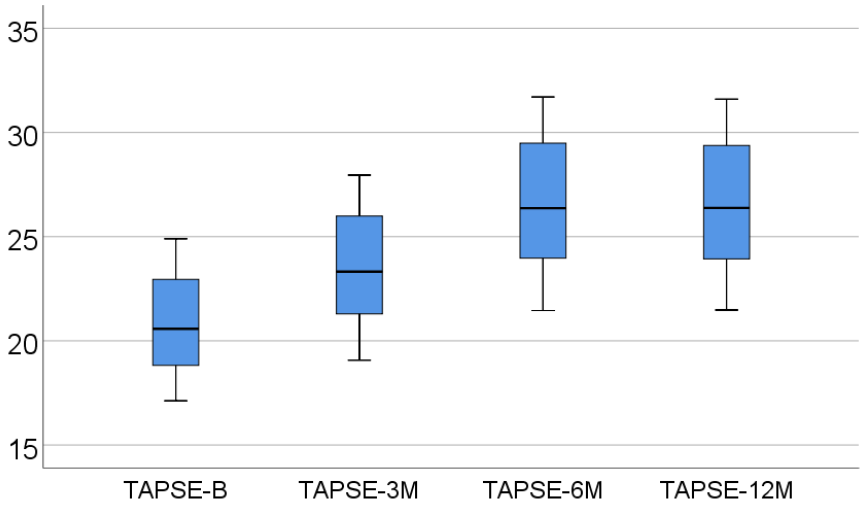


Figure 9. Box-plot representation of TAPSE evolution.

Table XIII. Comparison of RVFWLS, FAC, TAPSE evolution values in comparison to mortality

Parameter/Value/Mortality (N=71)			**3 Months - Baseline**	**6 Months – 3 Months**	**6 Months - Baseline**
RVFWLS (%)	Average ± SD	-	13.21 ± 1.8	12.96 ± 0.61	27.89 ± 2.11
	Median (IQR)	-	13.2 (11.6-15.01)	13 (12.34-13.58)	27.8 (26.08-29.84)
	Average ± SD	+	-1.53 ± 1.56	-0.93 ± 1.24	-2.45 ± 2.1
	Median (IQR)	+	-1.84 (-2.82 - -0.11)	-1.36 (-1.92 – 0.5)	-2.5 (-4.45 - -0.65)
	p*		<0.001	<0.001	<0.001

Parameter/Value/Mortality (N=71)			**3 Months - Baseline**	**6 Months – 3 Months**	**6 Months - Baseline**
FAC (%)	Average ± SD	-	12.93 ± 1.62	12.98 ± 0.5	27.6 ± 1.93
	Median (IQR)	-	12.65 (11.72-14.41)	12.94 (12.61-13.38)	27.45 (25.88-29.52)
	Average ± SD	+	-1.44 ± 1.26	-1.66 ± 1.24	-3.08 ± 2
	Median (IQR)	+	-1.87 (-2.6 - -0.02)	-1.93 (-2.42 - -0.5)	-3.29 (-4.48 - -1.35)
	p*		<0.001	<0.001	<0.001
TAPSE (%)	Average ± SD	-	13.33 ± 1.52	13 ± 0.52	28.05 ± 1.82
	Median (IQR)	-	13.45 (12.02-14.66)	12.91 (12.7-13.42)	28.02 (26.75-29.5)
	Average ± SD	+	-1.22 ± 1.61	-1.4 ± 1.1	-2.6 ± 2.11
	Median (IQR)	+	-1.25 (-2.74 – 0.28)	-1.3 (-2.16 - -0.7)	-2.91 (-4.37 - -0.28)
	p*		<0.001	<0.001	<0.001

*Mann-Whitney U Test

The differences observed of the evolution values in comparison to mortality were statistically significant according to the Mann-Whitney U tests ($p<0.001$), showing that the RVFWLS, FAC, TAPSE values had a higher increase at 3 months from baseline, 6 months from 3 months and 6 months from baseline in survivor patients than in deceased patients (where these parameters had a decrease over time).

7.2.5. Discussions

The purpose of this study was to determine if initiating HD improves RV function as measured by conventional techniques (TAPSE or FAC) as well as by current RV strain measurement utilizing 2D-STE. Additionally, we concentrated on determining which RV systolic function metrics had predictive significance for one-year mortality.

Our research adds to the body of knowledge in an area where worldwide recommendations describe significant uncertainty regarding the cardiovascular risks and benefits of dialysis beginning. There is a widespread belief that the first few months on dialysis are associated with an increased risk of cardiovascular events, while it is unknown whether these adverse events are caused by dialysis beginning. [328, 329]. HF during dialysis treatment is associated with high mortality [330].

High uncertainties derive from a few studies with extremely heterogeneous results that evaluated longitudinal changes in subclinical HF after initiation of dialysis: the CRIC study reports a decline in LVEF [331], the CASCADE [332] and IDEAL [333] trials showed no change in LVEF, while a study [334] reported improvement in LV parameters after HD initiation.

These contradictions may support the notion of reverse causality, as patients with higher eGFR levels who begin dialysis may face greater health risks as a result of frailty and cumulative comorbidities, rather than as a result of HD beginning. [335].

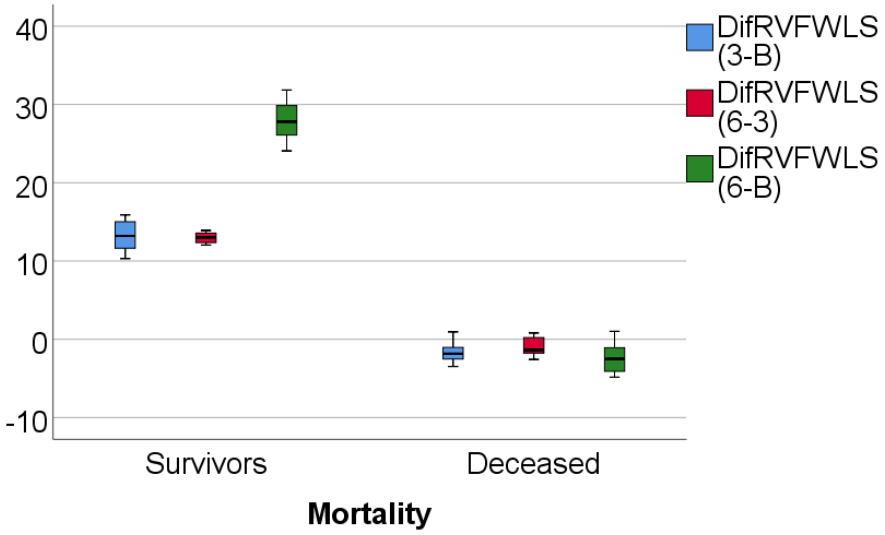


Figure 10. Box-plot representation of RVFWLS evolution in comparison with mortality.

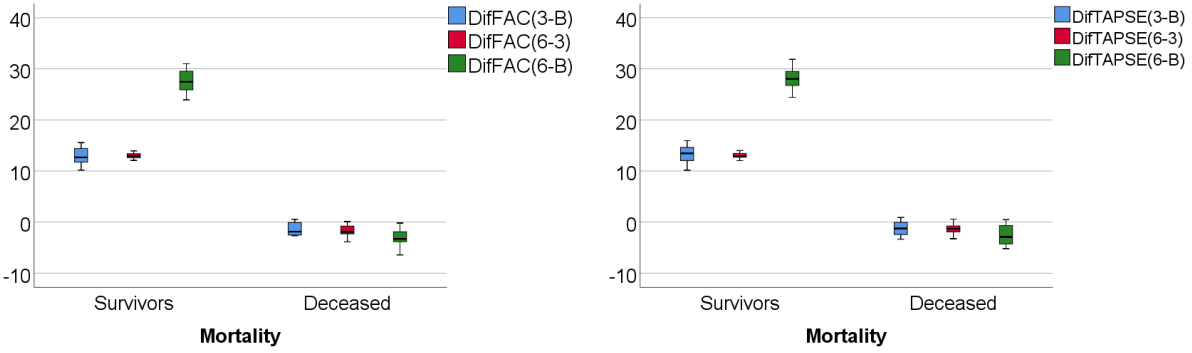


Figure 11. Box-plot representation of FAC and TAPSE evolution in comparison with mortality.

As a consequence of these important inconsistencies, KDIGO guidelines encourage further clinical trials in which patients are followed beyond dialysis initiation [335]. As a result, our article adds significant new evidence to the scholarly literature on post-HD cardiovascular surveillance. RV function appears to be a critical factor in the decline of post-HD cardiovascular function. A regression analyses [330] showed that arteriovenous fistula-induced RV dysfunction may contribute to LV dysfunction in dialysis patients, playing an essential role in triggering LV dysfunction through right-to-left ventricular interdependence.

Conversely, LV dysfunction did not significantly influence RV parameters [330]. As a result, our primary focus has been on assessing post-HD RV systolic function and mechanics. Our research offers three significant advantages. It is the first clinical trial to evaluate long-term RV function following the commencement of HD. Second, it presents a fresh, modern method for evaluating RV function using 2D-STE. Thirdly, our findings demonstrate that a low RV strain has significant predictive value for death regardless of the presence of HD, indicating that the elevated health risks associated with HD onset may not be causally related.

In our prospective study, we observed a statistically significant rise in RVFWLS, FAC, and TAPSE values at 3/6/12 months from baseline ($p<0.001$), and, most intriguingly, a

statistically significant increase in all parameters at 6 months (when compared to the 3 months analysis, $p<0.001$). RVFWLS, FAC, and TAPSE did not show any further variance at the conclusion of the trial compared to the 6-month evaluation ($p>0.05$). There are conflicting findings in the current literature about the sensitivity of TAPSE and FAC assessment to preload reduction by commencing HD. All of them, however, are short-term trials examining TAPSE or FAC within hours or days of HD onset, not months later. [336-339].

Although strain is considered independent of loading conditions, some studies reported a bettering in strain values ensuing elective HD within minutes or days [340]. We believe that the amelioration seen in all studied parameters at 6 months after HD initiation is a milestone in the life of an ESKD patient.

Hemodialysis can improve myocardial perfusion with a steady reduction amid the interdialytic hiatus [341, 342]. In time this reduction could lower the cardiac chamber size or the pulmonary circulation loading [343], ultimately improving all the RV systolic indices, as confirmed by our outcomes. Furthermore, concerning mortality, RVFWLS, FAC, and TAPSE values significantly decreased at 3 and 6 months in all 17 deceased patients.

We determined that a baseline FAC of less than 25.62 percent has a sensitivity of 88.2 percent and a specificity of 90.1 percent for the prediction of mortality, and that a baseline TAPSE of less than 18mm has a sensitivity of 88.2 percent and a specificity of 85.5 percent for the prediction of mortality, our findings correlating with those previously validated in larger studies and across different population groups [326]. Nevertheless, these indicators may bear limitations for different reasons, such as – patients with worse image quality, ventricular loading conditions, or even overall heart motion [344].

In opposition, speckle-tracking echocardiography grants appraisal of the myocardial mechanics in an angle-independent fashion. Our study depicts the fact that if a baseline RVFWLS value is less than 18.5%, this carries a sensitivity of 94.1% and specificity of 100% for the prediction of mortality at 6 or 12 months, an outcome which is similar with other different studies, although different populations or results whatsoever [345, 346]. As stated above, this issue may suggest that a low value of an RV strain carries the burden of mortality, irrespective of HD or any other aggravating or ameliorating factor.

7.2.6. Conclusions

Our work is the first to characterize and examine RV function in patients with ESKD using 2D-STE and to connect it with traditional echocardiography techniques both before and after the commencement of HD. RV function improved considerably at 3/6 and 12 months as compared to baseline levels (pre-HD). We discovered that TAPSE, FAC, and RVFWLS all have a significant role in predicting one-year death in this fragile group.

7.3. Left atrial strain and cardiovascular outcomes in advanced CKD patients

7.3.1. Introduction

Because CKD has a detrimental effect on cardiovascular risk and mortality, the underlying structural and functional abnormalities of cardiac remodeling have been extensively

studied in the literature. Numerous physiopathological mechanisms have been implicated in the development of cardiovascular disease, including uremic toxins, left ventricular hypertrophy, myocardial fibrosis, inflammation, oxidative stress, growth factors, Klotho proteins, fibroblast growth factor 23, and the soluble receptor for advanced glycation end products [347].

The volume and dimensions of the LA as determined by two-dimensional transthoracic echocardiography are recognized imaging indicators linked with an elevated risk of CVD, mortality, and AF in patients with CKD, including ESKD [348-350]. Once speckle tracking echocardiography became accessible, clinical trials shown that it outperformed standard echocardiogram in detecting heart dysfunction by evaluating ventricular and atrial myocardial deformation [351-353].

As new evidence supporting deformation imaging emerged, the European Association of Cardiovascular Imaging/American Society of Echocardiography/Industry Task Force published a consensus statement on the standardization of left atrial, right ventricle, and right atrial deformation imaging in order to improve the quality and reproducibility of future research [354]. To summarize, the Task Force advises that LA strain (LASr) be determined using an apical four-chamber view, while a biplane technique incorporating a two-chamber view may also be adequate. Endocardial and epicardial boundaries are defined manually or mechanically, such that the analysis includes just the LA wall and excludes the pericardium. The Task Force advises that, given the available characteristics, LA global strain (LAGS) be used instead of radial or transverse strain assessment.

LASr is a relatively new yet promising approach for assessing LA and LV function [355]. A recent research found a greater correlation between LASr and mean pulmonary arterial wedge pressure assessed invasively (AUC 0.80, $p<0.001$) than with conventional echocardiographic measurements [356]. Additionally, LASr was substantially associated with myocardial fibrosis (p 0.0001) and endocardial thickness ($p = 0.0001$), indicating that LASr may be useful in detecting subclinical cardiac dysfunction [357]. LASr has a good discriminating power (AUC 0.86–0.91) for evaluating LV diastolic dysfunction [358].

Our aims were to determine the effect of LASr on cardiovascular outcomes as reported in clinical studies, including individuals with CKD.

7.3.2. Materials and Methods

We searched in PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials. The time of publication was restricted to the interval between January 2000 and January 2021. The following terms were used in searching process: "*left atrium*", "*strain*", "*deformation imaging*", "*chronic kidney disease*", "*cardiovascular*", "*outcomes*", "*risk*" and "*mortality*".

We assessed the quality of non-randomized studies in the systematic review using the Newcastle-Ottawa scale, a star-based tool that evaluates studies at three different levels: selecting groups, comparability of groups, and outcome of interest. It comprises eight essential items, for which stars are assigned, and the quality is judged according to the total number of stars. In studies without a control group, quality was assessed using a tool designed by the National Institutes of Health (NIH), encompassing 14 key questions.

The following data were extracted from included studies: year of publication, study design, number of patients, patients' age, clinical setting, CKD definition, outcomes investigated, duration of follow-up, odds ratio (OR), risk ratio (RR), hazard ratio (HR), confidence intervals (CIs), p-value, predictive power, and AUC – when available. Whenever possible, data are presented as percentages, mean or median values, ranges of variation.

7.3.3. Results

We searched the prespecified databases and identified 893 references. After screening for duplicates, 118 citations were excluded. Additional 743 citations were excluded based on title and abstract, leaving 32 articles for eligibility assessment. Six studies were included in our systematic review after excluding 26 references because the inclusion criteria were not met (Figure 12).

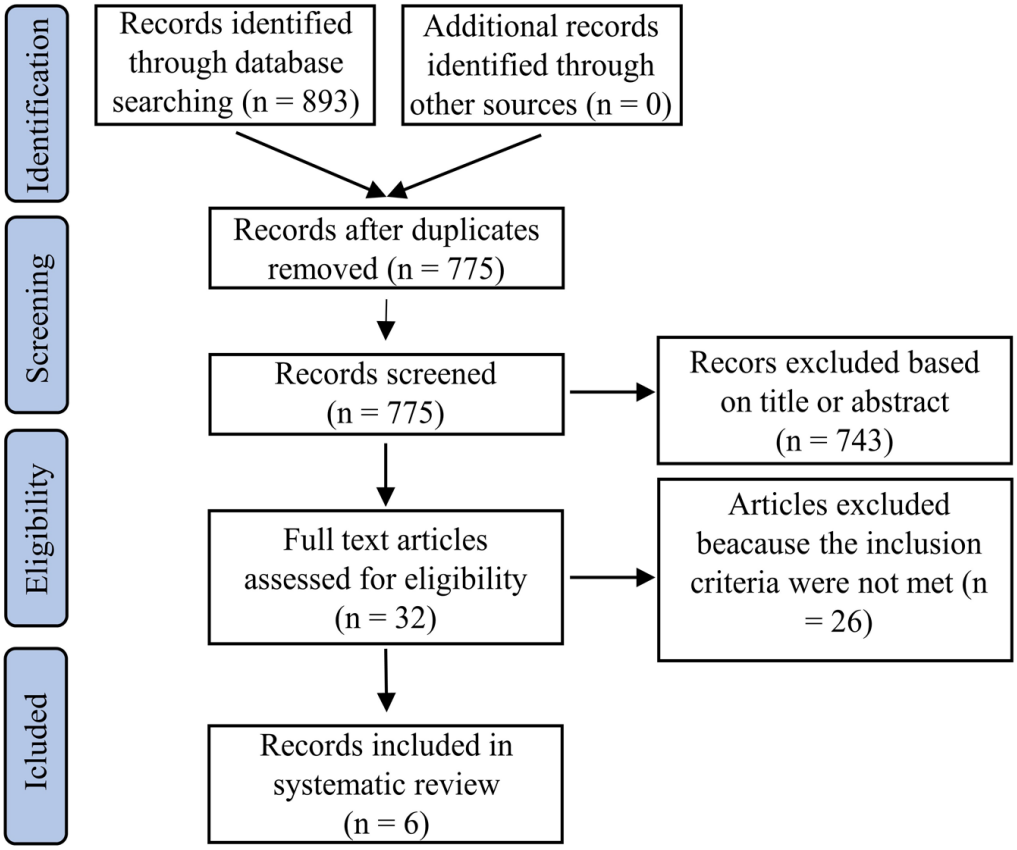


Figure 12. Flow diagram of selected studies for inclusion in the systematic review.

The characteristics of studies and population included and the outcomes measured were summarized in Table XIV.

Table XIV. General characteristics of studies included in present systematic review.

Author, Year	Design	Patients, no	Age (Years), Median/ Mean	Parameters	Software	Setting	Outcomes	Follow-up
Gan et al., 2020	Observational, prospective	243	59.2 ± 14.4	LASr E/e' LV mass LAV LVGLS	EchoPAC Version BT13, GE	CKD stage 3–4, without previous cardiac disease	Primary end point: CV death and MACE Secondary end point: composite of all-cause death and MACE	3.9 ± 2.7 years
Gan et al., 2021	Observational, prospective	218	63.9 ± 11.7	LASr LVGLS LV mass LAVI E/A E/e'	EchoPAC Version BT13, GE Healthcare	CKD stage 3–4, without prior cardiac history	Exercise capacity	NA
Papadopoulos et al., 2018	Observational, prospective	79	57 ± 17	LASr LASr rate LAVI LVMI E/e'	EchoPAC Version 113, GE Healthcare	ESRD + HD, preserved LV systolic function	Paroxysmal AF	16 ± 5 months
Kadappu et al., 2016	Observational, prospective	86	–	LAGS LVSRa LAVI	NA	CKD stage 3	Composite of MACE (death, CV events or ESKD)	60 months
Li et al., 2019	Observational	59 ESRD	44.41 ± 16.28 ESRD – group C	PALS LA stiffness LAVI LVMI	Philip Qlab 10.0, Andover	ESKD, LVEF > 50%, without symptoms of CV disease	Diastolic dysfunction	NA
		30 healthy controls	40.55 ± 11.4 controls					
Altekin et al., 2013	Observational	85 ESRD	33.79 ± 9.08 ESRD	LASr LA stiffness LAVI LVMI E/A E/e' E-DecT IVRT	EchoPAC Version 8, GE Healthcare	ESKD + HD, preserved LVEF	Estimated pulmonary capillary wedge pressure	NA
		60 healthy controls	39.17 ± 10.08 healthy controls					

Abbreviations: CKD—chronic kidney disease; CV—cardiovascular; E-DecT—E wave deceleration time; ESKD—end-stage kidney disease; HD—hemodialysis; IVRT—isovolumetric relaxation time; MACE—major adverse cardiovascular events; LA—left atrium; LAGS—left atrial global strain; LASr—left atrial strain; LAV—left atrial volume; LAVI—left atrial volume index; LV—left ventricle; LVEF—left ventricular ejection fraction; LVGLS—left ventricular global longitudinal strain; LVMI—left ventricular mass index; LVSRa—left ventricular late diastolic strain rate; PALS—peak left atrial longitudinal strain.

Results reported in studies included in the systematic review were summarized in Table XV.

Table XV. Results reported in studies included in present systematic review.

Study, Year	Outcomes	Parameter	Results	
Gan et al., 2021	Cardiovascular death and MACE	LASr	HR 0.89 (95% CI, 0.840.93)	$p < 0.01$
		LAVI	HR 1.02 (95% CI, 0.99–1.05)	$p = 0.31$
		E/e'	HR 1.03 (95% CI, 0.98–1.09)	$p = 0.25$
	Composite of all-cause death and MACE	LASr	HR 0.87 (95% CI, 0.82–0.92)	$p < 0.01$
		LAVI	HR 1.01 (95% CI, 0.98–1.04)	$p = 0.44$
		E/e'	HR 1.04 (95% CI, 0.98–1.11)	$p = 0.22$
Gan et al., 2021	Reduced exercise capacity	LASr	$r = 0.70$	$p < 0.01$
			AUC, 0.83 (95% CI, 0.78–0.88)	$p < 0.01$
		E/e' (exercise)	$r = -0.65$	$p < 0.01$
			AUC, 0.79 (95% CI, 0.73–0.85)	$p < 0.01$
		E/e' (resting)	AUC, 0.67 (95% CI, 0.60–0.73)	$p < 0.01$
		LAVI	$r = -0.18$	$p < 0.01$
Papadopoulos et al., 2018	Paroxysmal atrial fibrillation	Mean LASr	OR 0.847 (95% CI, 0.760–0.944)—univariate analysis	$p = 0.003$
		Mean LASr rate	OR 0.03 (95% CI, 0.002–0.416)—multivariate analysis	$p = 0.010$
		LAVI	OR 1.049 (95% CI, 1.000–1.101)	$p = 0.05$
Kadappu et al., 2016	MACE (death, cardiovascular events, ESRD)	LAGS	HR 3.8 (95% CI, 1.5–9.9)	$p = 0.006$
		LVSRa	HR 2.9 (95% CI, 1.1–7.5)	$p = 0.03$
		LAVI	HR 0.38 (95% CI, 0.16–0.94)	$p = 0.04$
Li et al., 2019	Diastolic dysfunction	PALS	33.33 ± 9.30 (grade II diastolic disfunction) vs. 51.75 ± 5.82 (control group)	$p < 0.05$
			36.37 ± 8.59 (grade I diastolic dysfunction) vs. 51.75 ± 5.82 (control group)	$p < 0.05$
Altekin et al., 2013	Estimated pulmonary capillary wedge pressure	LA_{S-S}	β 0.409 (95% CI, 0.140–0.246)	$p < 0.001$
		LA_{S-E}	β –0.125 (95% CI, –0.139–−0.019)	$p = 0.01$
		LA_{S-A}	β 0.461 (95% CI, 0.3–0.498)	$p < 0.001$

Abbreviations: AUC—area under the curve; ESRD—end-stage renal disease; LA_{S-A}—left atrial late diastolic strain; LA_{S-E}—left atrial early diastolic strain; LA_{S-S}—left atrial systolic strain; LAGS—left atrial global strain; LAVI—left atrial volume index; LASr—left atrial strain; LVSRa—left ventricular late diastolic strain rate; MACE—major adverse cardiovascular events; PALS—peak left atrial longitudinal strain.

Gan et al. [359] evaluated LASr as a predictor for major adverse cardiovascular event (MACE: AF, HF, MI, coronary revascularization and non-fatal stroke), CV mortality and all-cause mortality in patients with CKD stage 3-4, without pre-existing cardiac disease. During the follow-up interval, 54 adverse events were documented (deaths, n = 8; MACE, n = 46). Of all echocardiographic parameters investigated, only LASr was associated with the primary outcome (after adjustment for other variables, HR 0.89, 95% CI, 0.84 – 0.93, $p < 0.01$). As regarding prediction of the primary outcome, LASr had a better discriminatory power, with AUC 0.84 (95% CI, 0.761 – 0.900, $p < 0.001$), in comparison with LV global longitudinal strain (LVGLS) – AUC 0.696 (95% CI, 0.605 – 0.776, $p = 0.016$), LA volume index (LAVI) – AUC 0.671 (95% CI, 0.580 – 0.754, $p < 0.001$) and LV mass index (LVMI) – AUC 0.658 (95% CI, 0.566 – 0.741, $p = 0.006$). Moreover, patients with LASr ≤ 20.46 were at particular high risk, as 42% of them had an adverse event during 3 years (MACE or CV death).

Gan et al. [359] explored the utility of echocardiographic parameters (including LASr) in evaluating CKD patients' exercise capacity without pre-existing cardiac disease. Although three parameters (LASr, E/e' and LAVI) were initially associated with metabolic equivalents (METs) achieved, after integrating them in the final clinical model, only LASr remained an independent predictor of METs achieved ($p < 0.01$). The predictive performance of LASr was better (AUC 0.83, 95% CI, 0.78 – 0.88) than in case of E/e' ratio during exercise (AUC 0.79, 95% CI, 0.73 – 0.85) or rest (AUC 0.67, 95% CI, 0.60–0.73), suggesting a clear advantage of LASr.

Kadappu et al. [360] evaluated the correlation between LASr and MACE, reporting similar results: LA global strain being associated with an increased risk of MACE ($p = 0.006$). Notably, this study included stage 3 CKD patients, highlighting the usefulness of LASr even in the early stages of renal disease. Other parameters associated with MACE during follow-up were LAVI ($p = 0.04$) and LV late diastolic strain rate (LVSRA) ($p = 0.03$).

The relationship between LASr and the risk of paroxysmal AF in patients with ESKD and hemodialysis was explored by Papadopoulos et al. [361]. The authors included patients with preserved LV systolic function and excluded those with cardiac structural abnormalities (altering LA anatomy). After univariate analysis, several echocardiographic measures were found to increase the risk of AF: LASr ($p = 0.003$), LASr rate ($p = 0.001$), E/e' (0.005), LAVI ($p = 0.05$) and LVMI ($p = 0.005$). In the multivariate analysis, the LASr rate remained strongly associated with an increased AF risk ($p = 0.010$). Nevertheless, limited by a small number of patients (n = 79), LASr proves to be a better marker than traditional echocardiographic measures in the CV risk stratification of ESKD patients.

A case-control study dealing with ESKD patients and preserved ejection fraction without CV disease symptoms investigated the relationship between peak LA longitudinal strain (PALS) and diastolic dysfunction [362]. Interestingly, PALS was reduced in ESKD compared to controls, even when LA pressure was normal (40.23 ± 12.72, $p < 0.05$). Also, PALS was significantly reduced in patients with diastolic dysfunction grade I (36.37 ± 8.59, $p < 0.05$) and grade II (33.33 ± 9.30, $p < 0.05$). Moreover, eGFR was independently correlated with PALS ($B = 0.084$, $p = 0.046$).

Altekin et al. [363] evaluated the association between LASr and pulmonary capillary wedge pressure (PCWP) based on echocardiographic measures. Notably, the authors investigated LASr parameters according to the cardiac cycle timing (LA_{S-S}, left atrial systolic

strain; LA_{S-A}, left atrial late diastolic strain; LA_{S-E}, left atrial early diastolic strain). All three components of LASr were strongly associated with PCWP, suggesting that LASr could be used as a marker to predict LV dysfunction in ESKD patients. However, this study limitation is represented by estimating PCWP using a formula, which could differ from the values measured invasively. The quality assessment used the Newcastle-Ottawa scale and NIH tool for observational studies. Overall, as none of the studies was radomized, the quality was judged as fair to low.

7.3.4. Discussions

LASr and CV outcomes in patients with CKD have not previously been studied in a systematic review, to our knowledge. Recent years have seen an increase in interest in LA structure and function evaluation as a possible early indication of a complicated underlying cardiac illness with prognostic implications. The LA acts as a reservoir, conduit, and booster pump in direct relation to the LV's compliance and function, hence modulating the preload. In the last several years, the role of the LA in risk classification of individuals with and without CVD has been intensively explored [364].

The Dallas Heart Study [365] found that over the course of an eight-year follow-up, both the maximal LA volume and the LA emptying fraction were linked with all-cause death in a variety of general population clinical models. In contrast to echocardiography, which is less costly and more widely available, cardiac magnetic resonance was used to assess LA parameters. In another study involving the general population [366], LASr was associated with a composite cardiovascular outcome (ischemic heart disease, heart failure, or CV death) but only in women (HR 1.46, 95% CI, 1.05 – 2.02, p = 0.025).

AF prediction is another important clinical use of LASr in the general population [367]. Univariable analysis found an increased incidence of AF in those with lower PALS scores, however this impact persisted only in those under 65 years old (HR 1.46, 95 percent CI 1.06–2.02, p = 0.021 for every 5% drop in PALS). Moreover, LASr was linked to an increase in thrombotic events and unsuccessful electrical cardioversion in patients with AF or atrial flutter, suggesting the utility of LASr in therapeutic decision-making regarding rhythm control [368]. LA deformation parameters could guide anticoagulant therapy initiation, as LASr measures were associated with increased stroke risk [369].

LASr involvement in CKD has only been partially verified despite all the promising therapeutic uses of LA parameters discussed above. LASr and MACE or (all-cause) mortality were shown to be associated in two of the studies included in our systematic review. LASr has been linked to long-term cardiovascular outcomes in individuals with CKD stage 3–4 in one study [359]. When all the echocardiographic data was taken into account, only LASr remained a significant predictor of the primary result (CV mortality and MACE). LVMI, LAVI, and even LVGLS did not reach statistical significance. Another research that looked at the relationship between LASr and MACE came to the same conclusion: LAGS was linked to an increased risk of MACE [360].

These data support the utility and feasibility of LASr parameters in clinical practice for an accurate CVD risk stratification of CKD patients (even in the early stages). Furthermore, LASr could be integrated into future prediction models and other clinical and imagistic

variables, as it could detect CKD patients at high risk even better than LVGLS. In addition, even in individuals with ESKD and normal LV ejection fraction, LA deformation imaging was linked to LV diastolic dysfunction [362]. A gradual reduction of PALS was noticed along with diastolic dysfunction progression ($p < 0.001$). Conversely, LAVI and LVMI were higher in the presence of diastolic dysfunction ($p < 0.05$).

Finally, the calculation of LV filling pressures is an appealing application of LA deformation imaging. There was a substantial association between LASr and estimated PCWP in patients who had ESKD, dialysis, and a preserved LV ejection fraction [363].

7.3.5. Conclusions

To better predict and assess the risk of cardiovascular events in patients with CKD, LASr has emerged as a potential marker in the age of personalized treatment and new imagistic approaches. The detection of individuals with a high risk of MACE, CV mortality, and all-cause mortality through the use of LASr in CKD is an important clinical application. Anticoagulant treatment can be started more quickly if AF can be predicted with LASr, which has important practical consequences. More prospective trials are needed to see if include LASr in future clinical models improves prediction accuracy.

7.4. Pre-existing pulmonary hypertension – a robust predictor for adverse events after kidney transplantation

7.4.1. Introduction

Clinical investigations revealed a very high frequency of PH in patients with CKD, particularly those receiving RRT. A meta-analysis found a 30% prevalence of PH in individuals with CKD, which was considerably higher in the ESKD subgroup (35 percent) [370]. Another research found a 34.6% prevalence of PH among dialysis patients, which was consistent with the results of the meta-analysis reported previously [371]. According to these findings, PH affects more than one-third of individuals with ESKD, indicating that it is not an uncommon illness.

Furthermore, individuals with ESKD who have PH are more likely to suffer from a range of negative effects. A higher death rate from any cause and cardiovascular disease was seen in individuals with CKD and PH, as previously reported (respectively, Risk Ration (RR) 2.08, 95% CI, 1.06-4.08 and RR 3.77, 95% CI, 2.46-5.78) [370]. A recent study with a larger sample size (30,052 CKD patients with PH) confirmed that PH was linked to greater mortality risk during five years of follow-up (HR 1.47, 95% CI, 1.40-1.53). Apart from death, PH patients had a higher chance of hospitalization, mostly for cardiovascular reasons (rate ratio 4.61) [372].

Pre-existing PH and its possible influence on short- and long-term KT outcomes are of special attention. Apart than invasive procedures, PH may be readily evaluated non-invasively in a pre-KT environment using TTE [373]. Thus, PH may be a widely available and helpful tool for risk classification in patients with KT.

Regretably, the majority of research examining pre-existing PH as a predictor of adverse outcomes following KT use observational data. Concerning the prognostic usefulness of PH in KT candidates, a 2017 meta-analysis concluded that patients with PH had a greater mortality risk than those without PH (OR 3.15, 95% CI, 1.42-6.97, p = 0.005). However, this paper included only three studies with a small sample analyzed (n = 502) [374]. Moreover, one of the included study did not specify if all KT candidates underwent KT during follow-up [375]. As a result, the efficacy of pre-existing PH in identifying high-risk KT users has to be clarified.

We conducted a systematic review of the literature to determine the relationship between pre-existing PH (as determined by TTE or invasive methods) and unfavorable outcomes following KT.

7.4.2. Materials and Methods

The protocol was registered in PROSPERO database (CRD42022306978).

We searched in MEDLINE (PubMed), Embase, Cochrane, and Scopus. Language filters were not applied in the search process. In addition to the sources mentioned above, Google Scholar and ClinicalTrials.gov databases were screened for additional citations. References from representative studies were also searched to retrieve further studies for eligibility assessment. We used different combinations of keywords and controlled vocabulary to create a comprehensive search strategy: *"pulmonary hypertension", "pulmonary pressure", "echocardiography", "kidney transplant", "renal transplant", "kidney graft", "renal graft", "outcomes", "mortality", "survival", "kidney graft dysfunction", "renal graft dysfunction", "kidney graft survival" and "renal graft survival."*

The primary composite outcome included mortality from any cause following KT and delayed graft function (DGF), graft dysfunction, or graft failure. The secondary outcomes were represented by individual components of the primary composite outcome, respectively, any-cause mortality and delayed graft function, graft dysfunction, or graft failure.

7.4.3. Results

General data (PH definition used, investigated outcomes) and results reported in analyzed studies were presented in Table XVI.

Table XVI. Results reported in studies included in present systematic review and meta-analysis

Author, year	Parameters	Outcomes	Results	
Issa et al, 2008	RVSP > 50 mmHg	Reduced recipient survival	HR 3.75 (95% CI, 1.17-11.97)	P = 0.016
Nguyen et al, 2021	PH	Delayed graft function	OR 1.23 (95% CI, 1.10-1.36)	P < 0.001
		Mortality	HR 1.56 (95% CI, 1.44-1.69)	P < 0.001
		Death-censored graft failure	HR 1.23 (95% CI, 1.11-1.38)	P < 0.001

Author, year	Parameters	Outcomes	Results	
Obi et al, 2020	PASP ≥ 35mmHg		*Univariate analysis:*	
		Mortality (1 year)	HR 1.16 (95% CI, 0.33-4.04) –	P = 0.82
		Mortality (3 years)	HR 1.71 (95% CI, 0.84-3.47) –	P = 0.14
		Mortality (5 years)	HR 1.98 (95% CI, 1.11-3.56) –	P = 0.02
		Composite of death or graft loss (5 years)	HR 1.69 (95% CI, 1.03-2.78) –	P = 0.04
			Multivariate analysis:	
		Mortality (5 years)	HR 1.26 (95% CI, 0.66-2.41)	P = 0.49
		Graft failure (5 years)	HR 0.77 (95% CI, 0.31-1.91)	P = 0.57
Rabih et al, 2022	RVSP ≥ 35 mmHg and/or TRJV ≥ 2,9m/s	Death, graft dysfunction, or failure	RR 1.432 (95% CI, 1.189-1.724)	P < 0.001
	LV systolic dysfunction	Death, graft dysfunction, or failure	RR 0.672 (95% CI, 0.347-1.302)	P = 0.239
	LV diastolic dysfunction	Death, graft dysfunction, or failure	RR 1.073 (95% CI, 0.824-1.399)	P = 0.600
Sadat et al, 2021	PASP ≥ 40 mmHg	Mortality	30.7% in patients without PH vs 37.7% in patients with PH	P = 0.334
Goyal et al, 2018	PASP ≥ 35 mmHg	Delayed graft function	OR 8.75 (95% CI, 1.05-72.75) – univariate analysis	P = 0.017
			On multivariate analysis PH was not associated with delayed graft function	
Wang et al, 2018	PASP ≥ 37 mmHg	Death or graft loss (> 2 years)	7.090% in patients without PH vs 9.800% in patients with PH	P = 0.536
		Mean eGFR (2 years)	60.28 mL/min ± 20.94 in patients without PH vs 51.04 ± 15.07 in patients with PH	P = 0.006
Zlotnick et al, 2010	PASP ≥ 35 mmHg	Early graft dysfunction	OR 15.0 (95% CI, 1.2-188.9) – adjusted for multiple variables	P = 0.03
			AUROC 0.74 (95% CI, 0.58-0.91)	
Caughey et al, 2020	TRJV: ≥ 2.9 m/s ± other signs	Mortality	8% in patients without PH and normal left atrial pressure vs 17% in patients with PH with normal left atrial pressure	
Abasi et al, 2020	PASP ≥ 35 mmHg	Delayed graft function	39.5% in patients with PH vs 24% in patients without PH	P < 0.05
Foderaro et al, 2017	RVSP ≥ 40 mmHg	Death-censored allograft failure	Three-fold higher risk in PH group (95% CI, 1.20-7.32)	P = 0.02
		Mortality	5% in patients with PH vs 3% in patients without PH	P = 0.80
Joseph et al, 2021	RV dilation and dysfunction	Composite of delayed graft function, graft failure and all-cause mortality	100% in patients with RV dysfunction vs 60% in patients without RV dysfunction	

Abbreviations: AUROC = the area under the receiver operating characteristic; eGFR = estimated glomerular filtration rate; LV = left ventricle; PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; RV = right ventricle; RVSP = right ventricular systolic pressure; TRJV = tricuspid regurgitation jet velocity.

In the pooled analysis, the primary composite outcome was observed in 2064 patients with KT and PH, compared to 54942 patients with KT, but no documented signs of PH. Patients with PH exhibited a two-fold higher risk of primary composite outcome occurrence (OR 2.01, 95% CI, 1.53-2.64), P < 0.00001 (Figure 13), with moderate heterogeneity (I^2 = 42%).

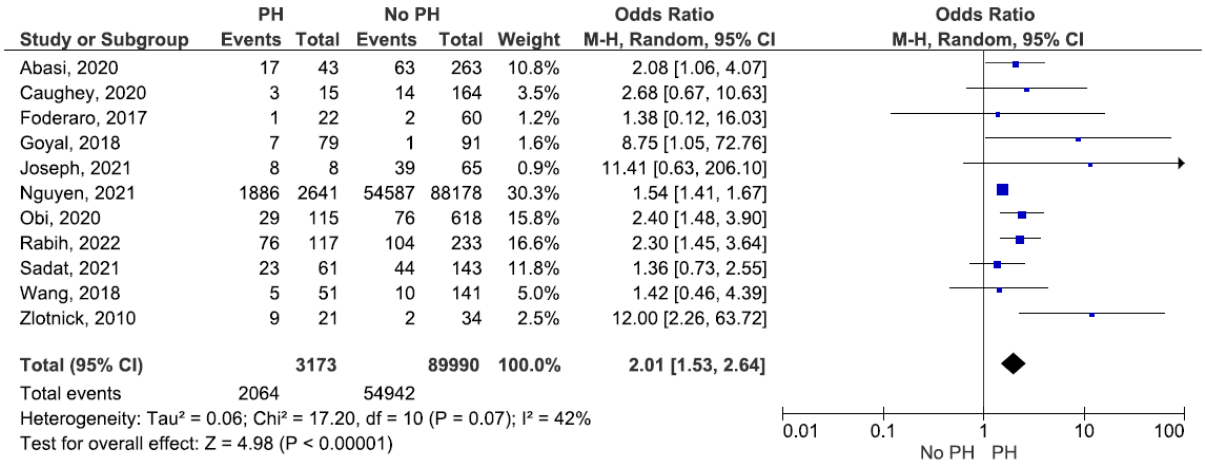


Figure 13. Primary composite outcome (mortality from any cause following KT and delayed graft function (DGF), graft dysfunction, or graft failure).

Patients with KT and documented PH prior to surgery were at increased risk of DGF, graft dysfunction, or failure (OR 2.26, 95% CI, 1.49-3.42), P = 0.0001 (Figure 14).

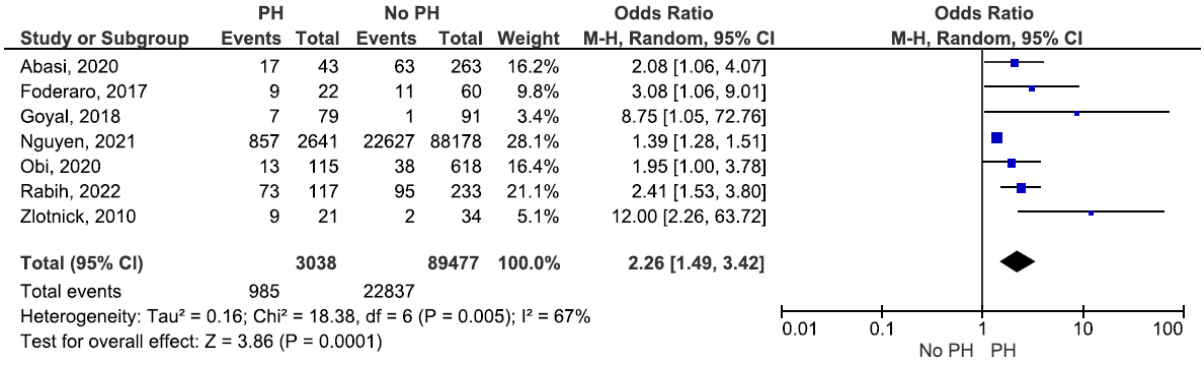


Figure 14. Graft dysfunction or failure.

Patients with PH documented by TTE or invasively were associated with an increase in mortality risk after surgery (OR 1.46, 95% CI, 1.05-2.03), P = 0.02 (Figure 15), with moderate heterogeneity across studies (I^2 = 42%).

7.4.4. Discussions

Our meta-analysis included the most recent clinical research addressing the efficacy of PH evaluation in predicting negative outcomes following KT.

The primary conclusion of this systematic review and meta-analysis is that pre-existing PH is related with a greater risk of death and a higher likelihood of delayed graft function,

kidney graft malfunction, and failure in KT recipients. The impact was significant for all outcomes regardless of whether PH was evaluated invasively or by TTE. As a result, individuals with PH characterized only by TTE had a significantly increased risk of mortality, DGF, or graft failure. Although right heart catheterization is the gold standard for diagnosing PH, TTE indicators including as PASP, RVSP, and TRJV may be useful in predicting adverse events in KT patients.

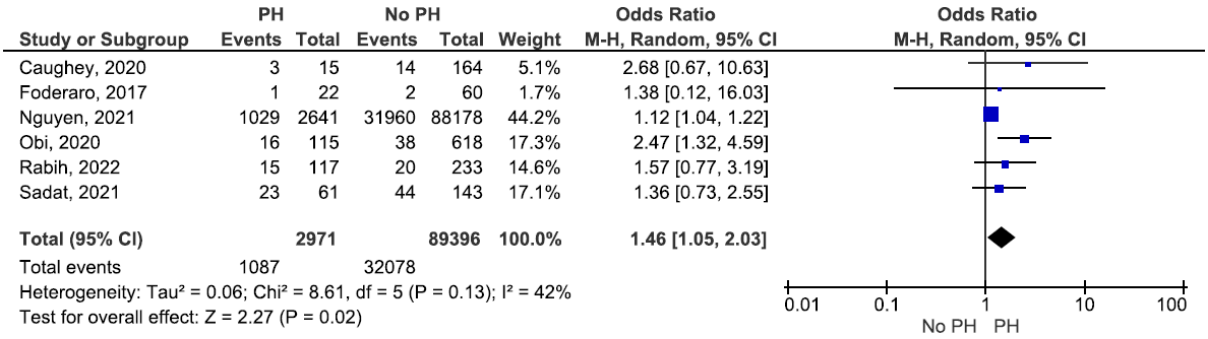


Figure 15. Mortality.

Early results from 2008 [376] and 2010 [377] shown an elevated risk of death and DGF in individuals with pre-existing PH. The effect on mortality was unrelated to other risk variables (age, left ventricular ejection fraction, and serum albumin), providing a baseline and impetus for further research [376]. Since then, further evidence has become available, however data has occasionally been inconsistent. As a result, a quantitative investigation is necessary to determine the predictive value of PH for bad outcomes following KT.

The most often utilized parameter for defining PH in the studied research was PASP as determined by TTE. However, the PASP cut-off values used in the included research differed. The majority of publications utilized the 35 mmHg PASP cut-off to classify patients as having or not having PH [377-380], while the others adopted different values, respectively 40 mmHg [381] or 37 mmHg [382]. As a result, consistent cut-off values for TTE parameters and measurement methodologies are essential for future clinical investigations to produce generalizable and repeatable results.

Along with PASP, RVSP and TRJV were useful indicators of PH, but their cut-off values were similarly subject to variation. RVSP cut-off values of > 50 mmHg, > 40 mmHg, or greater than 35 mmHg were used to diagnose PH patients [376, 383, 384]. Thus, we also analyzed clinical trials that focused exclusively on PASP in order to diminish the variety of PH evaluation approaches. Nonetheless, the presence of PH (as defined by the PASP) was related with an elevated risk of both primary composite and individual secondary outcomes (mortality, DGF, or kidney graft failure). Notably, pre-existing PH, but not left ventricular systolic or diastolic dysfunction was associated with worse outcomes in KT patients in multivariable analysis (respectively, RR 1.432, 95% CI, 1.189-1.724, $P < 0.001$ and RR 1.031, 95% CI, 0.844-1.258, $P = 0.767$) [383]. These data highlight the importance of PH evaluation in patients waiting for KT, more than other echocardiographic parameters.

Along with specific main and secondary outcomes, one research examined the connection between PH and perioperative complications in patients undergoing KT [379].

Patients with PH experienced perioperative hypotension at a higher rate than those without PH (26.6 % vs. 9.9%, P = 0.004), which imposed hemodynamic support.

While pre-existing PH was related with inferior short- and long-term results, it should not be viewed as a contraindication to KT policies. According to one study, KT enhanced survival rates in patients with PH when compared to those on the waitlist who did not get KT (respectively, 70.9 percent and 53 percent at five years). Additionally, mortality was 46 percent lower following KT than in patients awaiting KT with pre-operatively confirmed PH [385]. As a result, PH evaluation before to KT should not preclude surgical intervention. Nonetheless, PH might be used clinically in this cohort as a risk factor for future adverse outcomes.

7.4.5. Conclusions

We found that pre-existing PH (as determined by TTE or invasive methods) was linked with an increased risk of all-cause mortality, DGF, kidney transplant malfunction, or failure following KT. Notably, individuals with PH characterized solely by TTE or PASP had a greater risk of poor follow-up outcomes. PASP, RVSP, and TRJV, which are now utilized as TTE indicators of PH, might be used to predict adverse outcomes in KT patients in the pre-surgical environment. While the presence of PH should not exclude KT indication, patients with pre-existing PH may benefit from more intensive postoperative and long-term follow-up surveillance to detect possible problems early. Our findings suggest regular PH testing in patients on the KT waitlist, but these findings should be validated in large prospective clinical studies.

7.5. Zero-contrast intravascular ultrasound–guided percutaneous coronary interventions in CKD setting

7.5.1. Introduction

Two of the most recent ESC clinical practice guidelines on coronary syndromes (acute from 2020 [386] and chronic from 2019 [52]) made prominent and reliable recommendations (class I, level of evidence A) on minimizing the use of iodinated contrast agents during PCIs in patients with advanced CKD to avoid further deterioration and a subsequent increase in deaths. Furthermore, in this context, the same texts strongly advocated for the use of low- or iso-osmolar contrast media in the smallest feasible volume (class I indication, level of evidence A).

With a large number of patients receiving PCI worldwide and a sizable proportion of patients with CKD, the issue of contrast volume becomes problematic, even more so when the incidence of AKI increases from 5% to 15% in the general population (elective versus acute settings) [387]. Additionally, recent studies have shown that about one-third of patients with severe CKD develop AKI following PCI [388], resulting in a considerable increase in both short- and long-term mortality [5, 7]. Even a pre-procedural serum creatinine level more than 2.0 mg/dL was shown to be a marker of AKI, as it was found to be significantly associated with increased intra- and post-hospitalization mortality [387].

In summary, the options include conducting PCI utilizing digitally rebuilt roadmaps, IVUS, and real-time fractional flow reserve (FFR) measurements, after a prior angiography with low contrast (ultra-low contrast with 10 mL contrast) in another session [389].

With the goal of preventing further renal deterioration and the necessity for renal replacement treatment in patients with severe CKD, this relatively new technique appears exceedingly appealing and has been studied in several trials.

Our systematic review of articles addressing low-contrast IVUS PCIs in the setting of CKD is a world first. Conducting this research is critical to determining the current level of evidence and publication quality, as well as to highlighting any gaps in knowledge prior to more extensive use in clinical practice. This is a significant step toward safer interventional cardiovascular procedures in patients with CKD and greater usage of PCIs in patients with CKD who have coronary syndromes (as PCIs tend to be under-utilized in this high risk setting [390]).

Our approach was to conduct a systematic review of the most recent literature, focusing on trials (randomized or observational) that reported data and outcomes (e.g., safety and efficacy) for minimal- to no-contrast PCIs explicitly performed in patients with CKD who have acute or CCS.

7.5.2. Data sources, extraction and outcomes

The following search statement was used for the Embase, PubMed, and Cochrane library databases: "('percutaneous coronary intervention'/exp OR 'percutaneous coronary intervention') AND ('chronic kidney disease'/exp OR 'chronic kidney disease' OR 'CKD' OR 'nephropathy' OR 'kidney injury' OR 'kidney disease') AND ('low contrast' OR 'zero contrast' OR 'low-contrast' OR 'zero-contrast')".

For Pubmed, the search was conducted using the following filters: "('percutaneous coronary intervention'[MeSH Terms] OR 'percutaneous coronary intervention') AND ('chronic kidney disease'[MeSH Terms] OR 'chronic kidney disease' OR 'CKD' OR 'nephropathy' OR 'kidney injury' OR 'kidney disease') AND ('low contrast' OR 'zero contrast' OR 'low-contrast' OR 'zero-contrast')". The Cochrane database was searched using the following statement: "'percutaneous coronary intervention' AND ('chronic kidney disease' OR 'CKD' OR 'nephropathy' OR 'kidney injury' OR 'kidney disease') AND ('low contrast OR 'zero contrast' OR 'low-contrast' OR 'zero-contrast')". Both MeSH and Emtree terms were used in the systematic search.

The inclusion criteria are summarized in Table XVII according to the PICOS statement.

We evaluated the cardiovascular effectiveness outcomes of IVUS-guided PCI in patients with CKD and ACS or CCS as reported in clinical studies, which included at least one of the following: cardiac mortality, all-cause death, stent thrombosis, revascularization, and myocardial infarction. Additionally, we evaluated safety outcomes reported in clinical studies, including AKI following the surgery, the need for RRT, and deterioration of renal function.

Table XVII. Inclusion criteria for selected studies according to the PICOS statement**.**

Criteria	
Population	Patients (aged > 18 years) with chronic kidney disease and acute or chronic coronary syndromes
Intervention	Minimum-contrast or zero-contrast intravascular ultrasound guided percutaneous coronary interventions
Comparators	Angiography guided percutaneous coronary interventions
	None
Outcomes	Efficacy and/or safety
Type of **S**tudy	Randomized or non-randomized studies, observational studies, case series, and case reports
Language	English

7.5.3. Results

Our search in prespecified databases retrieved 970 citations. After excluding 181 duplicates, 789 publications left for screening. Other 749 citations were excluded after title or abstract screening leaving 40 articles for full-text assessment. Additional 36 references were excluded after full-text reading, with reasons: meta-analysis (2), abstract only (2), and inclusion criteria were not met (32), leaving six studies included in the systematic review

General characteristics of the studies and the population included were summarized in Table XVIII. Outcomes of interest, as well as results reported in each study, were summarized in Table XIX.

Sakai et al. [390] excluded individuals on HD from their analysis since they had advanced CKD (eGFR < 30 mL/min/1.73 m^2). In both groups, IVUS-guided PCI and angiography-guided PCI, the authors included patients with three-vessel coronary disease and unprotected left main trunk disease. Patients had conventional angiography first, followed by IVUS-guided PCI with minimal contrast injection at end of the intervention to rule out distal coronary issues. Patients treated with IVUS-guided PCI required less contrast volume than those treated with angiography led PCI (22 ± 20 mL compared 130 ± 105 mL, $p < 0.001$), with identical PCI success rates (99 percent vs. 100 percent, $p = 0.35$).

Table XVIII. General characteristics of studies included in systematic review.

Study, year	**Design**	**Patients, no**	**Age (years), median/ mean**	**Setting**	**Intervention**	**Comparator**	**Outcomes**	**Follow-up**
Ali et al, 2016 [391]	Retrospective analysis (case series), single center	31	66 ± 11	Patients with advanced CKD (stages 4-5) and stable CAD	Zero-contrast IVUS guided PCI	N/A	- Requirement of KRT - Stent thrombosis - Revascularization - Myocardial infarction - Death	79 days (median)

Study, year	Design	Patients, no	Age (years), median/ mean	Setting	Intervention	Comparator	Outcomes	Follow-up
Sakai et al, 2018 [390]	Non-randomized, multicenter	184	74 ± 7 (angiography guided PCI) 76 ± 9 (IVUS guided PCI)	Patients with CAD, elective PCI and CKD stages 4-5 (excluding HD)	IVUS guided minimum-contrast PCI (98 patients)	Angiography guided PCI (86 patients)	- All-cause mortality - Cardiac death - Non-cardiac death - Requirement of KRT	12 months
Sacha et al, 2019 [392]	Retrospective analysis, single center	20	73.7 ± 12.8	Patients with CKD (eGFR < 45 mL/min/1.73 m^2) including HD (preserved urine output) admitted due to ACS or in elective setting	Zero-contrast IVUS guided PCI	N/A	During hospitalization: -Change in creatinine/ eGFR - AKI - Requirement of KRT (in patients without dialysis) - Periprocedural myocardial infarction - Distal embolization During follow-up: Acute coronary syndrome Stent thrombosis Repeat revascularization Stroke Requirement of KRT (in patients without dialysis) Death	3.2 months (median)
Kumar et al, 2020 [393]	Case report	1	54	CKD patient with recent history of few cycles of hemodialysis for acute on CKD	IVUS guided rota assisted left main zero-contrast PCI	N/A	During hospitalization: - Post stenting pericardial effusion - Post intervention symptoms - Hemodynamic instability - Change in creatinine	-

Study, year	Design	Patients, no	Age (years), median/ mean	Setting	Intervention	Comparator	Outcomes	Follow-up
Patel et al, 2020 [394]	Case report	1	70	CKD stage 4 and history of hypertension type 2 DM	IVUS guided PCI of RCA with zero-contrast, and PCI of distal LM to LAD using minimum contrast	N/A	During hospitalization: - Changes in renal function - Post intervention symptoms During follow-up: - Changes in renal function - Post intervention symptoms	1 week
Rahim et al, 2019 [389]	Case report	1	57	CKD stage 4 and a history of HIV, DM	Zero-contrast PCI of LM (bifurcation), LAD with LV support	N/A	During hospitalization: - Procedural harm - Procedural success	6 months

CAD – coronary artery disease; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; IVUS – intravascular ultrasound; LAD – left anterior descending artery; LM – left main trunk; LV – left ventricle; PCI – percutaneous coronary intervention; RCA – right coronary artery; KRT – kidney replacement therapy.

Additionally, the IVUS group had a considerably lower risk of contrast-induced AKI than the angiography group (2% versus 15%, p = 0.001). At one year, the minimum-contrast group had a lower rate of KRT (2.7 percent versus 13.6 percent, p = 0.01), though the composite endpoint of all-cause mortality, myocardial infarction, and KRT was similar in both groups (10.7 percent for IVUS-guided PCI versus 19.9 percent for angiography-guided PCI, p = 0.09). In terms of stent placement precision, five side-branch occlusions were found in patients treated with standard angiography-guided PCI, compared to just one in patients treated with IVUS-guided PCI. However, the study's limitations include a small number of adverse events and a non-randomized methodology.

Table XIX. Results reported in studies included in systematic review.

Author, year	Outcomes	Results	
Sakai et al, 2018 [390]	*IVUS guided PCI versus Angiography guided PCI*		
	All-cause death	6 (6.4%) vs 6 (7.8%) patients	p = 0.85
	Cardiac death	2 (2.2%) vs 2 (2.6%) patients	p = 0.98
	Non-cardiac death	4 (4.4%) vs 4 (5.3%) patients	p = 0.79
	Requirement of KRT	3 (3.2%) vs 11 (13.6%) patients	p = 0.01
Ali et al, 2016 [391]	Stent thrombosis	0 (0%) patients	
	Revascularization	0 (0%) patients	
	Myocardial infarction	0 (0%) patients	
	Death	0 (0%) patients	
	Requirement of KRT	0 (0%) patients	

Author, year	Outcomes	Results	
Sacha et al, 2019 [392]	*During hospitalization*		
	Change in creatinine (mg/dL)	0.1 ± 0.31	p = 0.2
	Change in eGFR (mL/min/1.73m^2)	–0.7 ± 10.9	p = 0.8
	AKI after zero-contrast PCI	2 (10%) patients	
	Requirement of KRT	0 (0%) patients	
	Periprocedural myocardial infarction	1 (5%) patient	
	Distal embolization	1 (5%) patient	
	During follow-up		
	Acute coronary syndrome	0 (0%) patients	
	Stent thrombosis	0 (0%) patients	
	Repeat revascularization	0 (0%) patients	
	Stroke	0 (0%) patients	
	Requirement of KRT	0 (0%) patients	
	Death	1 (5%) patient	
Kumar et al, 2020 [393]	*During hospitalization*		
	Post stenting pericardial effusion	0	
	Post intervention symptoms	0	
	Hemodynamic instability	0	
	Change in creatinine	0.2 mg/dL	
Patel et al, 2020 [394]	*During hospitalization*		
	Changes in renal function	0	
	Post intervention symptoms	0	
	During follow-up		
	Changes in renal function	0	
	Post intervention symptoms	0	
Rahim et al, 2019 [389]	*During hospitalization*		
	Procedural harm	0	
	Procedural success	0	

AKI – acute kidney injury; eGFR – estimated glomerular filtration rate; IVUS – intravascular ultrasound; PCI – percutaneous coronary intervention; KRT – kidney replacement therapy.

Ali et al. also included patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2) and CCS [391], but in contrast to the previous study, the authors used a zero-contrast IVUS-guided PCI technique. Patients had low-contrast coronary angiography prior to the index PCI (at least 1 weak time gap between interventions), with no deterioration of kidney function 21 hours after angiography (creatinine = 3.9 mg/dL, IQR 2.9-4.9 and eGFR = 18 8 mL/min/1.73 m^2, p > 0.05). During the 79-day median follow-up period, kidney function remained steady, with no statistically significant changes (creatinine = 3.7 mg/dL, IQR 3.0-4.5, p = 0.69; eGFR = 18 mL/min/1.73 m^2, IQR 14-22 mL/min/1.73 m^2, p = 0.70).

Furthermore, no patient experienced major cardiovascular or renal events during the follow-up period, including KRT, stent thrombosis, revascularization, myocardial infarction, or death, indicating that a zero-contrast IVUS-guided PCI technique with a favorable safety profile could be used in patients with advanced CKD. The study, however, was limited by its

non-randomized design, small patient population, and absence of a comparator, which is represented by conventional coronary angiography-guided PCI.

Sacha et al. also evaluated patients with chronic renal disease, but they used a slightly different cut-off (eGFR < 45 mL/min/1.73 m^2) [392]. A critical point to note is that people undergoing hemodialysis (with preserved diuresis, 500 mL/day) were also included in accordance with the procedure. Patients with CCS were included in the trial, however patients with myocardial infarction were also included in situations when PCI was performed in stages. While the authors investigated the effectiveness and safety of no-contrast PCI, a modest volume of contrast media (3.5–9 mL) was administered at the end of the coronary intervention to rule out distal problems.

Another two case reports (Patel et al. and Rahim et al.) [389, 394] included patients with stage 4 CKD, diabetes mellitus, and complex coronary lesions: severe lesions of distal left main trunk, proximal LAD and mid- RCA in one case, and lesions of left main trunk (bifurcation), proximal and mid LAD in the other one. In both situations, the IVUS-guided PCI procedure was safely performed, and kidney function was stable during follow-up, denoting this approach's safety even in complex coronary lesions.

7.5.4. Discussions

This is the first systematic review to include studies evaluating the effectiveness and safety of percutaneous coronary procedures in patients with CKD utilizing IVUS with minimal- or zero-contrast.

The overarching conclusion of our systematic review is that, based on the available evidence, contrast-free and IVUS-guided PCI procedures in patients with CKD appear to be safe (both in terms of cardiac and renal outcomes, without renal adverse events and greater kidney preservation) and effective, even in complex atherosclerotic lesions. This strategy appears to be promising in renal patients who develop coronary syndromes, since an invasive operation without the hazards associated with media contrast results in a decreased risk of future worsening of renal function, as well as likely cardiovascular benefits (due to the use of IVUS).

The concept of IVUS-guided low-contrast coronary procedures is applicable not just to individuals with chronic kidney disease, but also to other patients who have risk factors for developing AKI following PCI. Thus, patients with advanced age, diabetes, intra-aortic balloon pump usage, cardiogenic shock, or a high number of revascularized arteries may benefit from IVUS-guided PCI with minimal or no contrast [395].

Notably, we discovered that none of the patients involved in the aforementioned trials experienced a decline in renal function and did not require renal replacement treatment following the zero-contrast IVUS-guided percutaneous operations. Additionally, this approach has been shown to be safe in terms of cardiovascular results.

At the moment, it appears that at least one randomized controlled study with a large number of patients with advanced CKD is needed to compare zero-contrast IVUS-guided PCIs to traditional angiography and to extend the follow-up time. The (positive) outcomes of this study would serve as the foundation for an indication in the European Guidelines (given that the “zero-contrast” method is not currently used to manage renal patients requiring PCI).

Additionally, given physicians' well-documented reluctance to refer renal patients with CAD for angiography ("therapeutic nihilism"), a paradigm shift away from contrast might very well alter physicians' perspectives and prognoses of these patients.

While Sakai et al. reported excellent results a year after the zero-contrast treatment in advanced CKD patients, they remain skeptical about the ease with which the stent may be positioned without contrast [390], a problem handled by other operators using "*dynamic roadmap*" technology [389]. Even if they did not have complications, the same authors would discuss the IVUS method's limitations in rapidly detecting acute complications such as coronary perforation, extensive coronary dissection, or slow-flow or no-flow phenomena, technical issues that appear to be "*critical drawbacks*" for widespread implementation of the technique. Additionally, Sacha et al. were more hopeful about the "*steep curve*" of the interventional cardiologists learning program, noting that the research group did not convert to routine PCI. This excitement is reinforced by the positive outcomes observed in difficult left main and saphenous vein graft lesions [392].

With this evidence, we believe that using functional assessments such as FFR/iFR and intravascular imaging such as IVUS would play a critical role in developing a more accurate PCI optimization tool and could also be applicable to patients with CKD. Thus, we emphasize the need of combining functional ischemia and imaging modality assessment in order to ensure the success of low contrast treatments.

7.5.5. Conclusions

Apart from its burden and setbacks, CKD imposes a hefty weight of an increased risk of cardiovascular consequences, the most common of which are coronary syndromes. While conventional percutaneous angiographic interventions are intended to save lives, they may paradoxically have a detrimental effect on the mortality of CKD patients due to recurrent contrast-induced acute renal injury. Following a mandatory and rigorous evidence-based validation, these complex and bidirectional consequences may soon be effectively mitigated by safer low-to-zero contrast IVUS-guided PCI procedures.

Chapter 8. Open heart surgery and kidney disease

8.1. Introduction

Acute kidney injury following cardiac surgery (CS-AKI) represents a severe postoperative complication, negatively impacting short-term and long-term mortality. Due to the lack of a specific treatment, effective prevention remains the most powerful tool to overcome the CS-AKI burden. Improving the preventive strategies is possible by establishing appropriate preoperative risk profiles. No externally validated and universally accepted risk models currently exist.

Firstly, we attempted a systematic approach to review all proposed preoperative risk factors and their predictive power. Our strategy was the starting point for selecting and comparing the predictive elements to be integrated into future risk models. The clinical

judgment and a good knowledge of the preoperative risk factors in the light of new evidence may help personalize preoperative risk profiles as the cornerstone of prevention measures.

The second study is a meta-analysis which evaluated the short- and long-term consequences of open cardiac surgery in solid abdominal organ transplant patients versus non-transplant patients. This meta-analysis reveals that prior solid abdominal organ transplantation is associated with higher long-term mortality after major cardiac surgery. However, in the short term, not mortality but infectious complications are significantly higher in the group of transplanted individuals. Our meta-analysis sheds light on the short-term significant infectious risks and increased long-term mortality induced by open heart surgery in kidney and liver transplant patients.

We believe that alternatives to classical surgery (such as minimally invasive surgery or transcutaneous interventions) must be found, especially where solid evidence predicts major and unjustified complications.

Both researches stated above were published in good impact factor journals, as follows.

1. Tinica G., Brinza C., Covic A., Popa IV., Tarus A., Bacusca AE., **Burlacu A**. *Determinants of acute kidney injury after cardiac surgery: a systematic review*. Rev Cardiovasc Med 2020 Dec 30;21(4):601-610. https://doi.org/10.31083/j.rcm.2020.04.206
   [Impact Factor: 2.930]
2. Bacusca AE., Enache M., Tarus A., Litcanu CI, **Burlacu A.**, Tinica G. *Cardiac surgery outcomes in patients with antecedent kidney, liver, and pancreas transplantation: a meta-analysis.* Rev Cardiovasc Med 2020 Dec 30;21(4):589-599.
https://doi.org/10.31083/j.rcm.2020.04.192
   [Impact Factor: 2.930]

8.2. Acute kidney injury following cardiac surgery: personalizing preoperative risk profiles

8.2.1. Background

AKI is a serious postoperative complication that has a detrimental effect on both short- and long-term mortality following open-heart surgery. Given the huge volume of patients having cardiovascular surgery (CS), the incidence of postoperative AKI is considerable, ranging from 20% to 70% of cases [396]. Severe forms of CS-AKI necessitating KRT have a lower prevalence (≤ 4%) but are subject to high mortality rates ranging from 40% to 70% [396, 397].

However, increased mortality has been recorded in less severe CS-AKI forms, with a 0.5 mg/dL rise in serum creatinine associated with a nearly threefold increase in thirty-day death [398, 399]. Additionally, a minor rise in blood creatinine (0.3 mg/dl) postoperatively is related with a considerably increased risk of long-term mortality and a threefold increased chance of developing ESKD [400].

Numerous critical processes are involved in the development of CS-AKI: renal hypoperfusion (HF, cardiopulmonary bypass, hemorrhage events during surgery), inflammation and oxidative stress (tissue damage, blood passage through cardiopulmonary bypass circuit), use of nephrotoxic drugs and agents (ACEIs, ARBs, nonsteroidal anti-

inflammatory drugs (NSAIDs), exposure to contrast agents), embolic factors and genetic predisposition [401-403].

Numerous clinical models have been developed to aid clinicians in risk stratification for CS-AKI: the Cleveland and modified Cleveland scores, the Mehta score, and the Simplified Renal Index (SRI) score [396, 404, 405]. These scores, however, are utilized to predict severe forms of CS-AKI, although their prognostic ability for moderate forms is limited. There is an urgent need for more effective ways for preventing, diagnosing, and treating AKI associated with open-heart surgery. Early detection of AKI is critical, as the cornerstone of CS-AKI care is prevention, as there is no particular therapy.

In this revised systematic review, the goal was to assess the significance of all previously identified risk variables in the development of CS-AKI and to pave the path for the creation of more effective preventative interventions.

8.2.2. Materials and Methods

Data Sources

We performed a systematic search in PubMed, ScienceDirect and Cochrane databases for articles published from January 2005 until October 2020 using the following query terms: *"Preoperative risk factors", "Cardiac surgery related acute kidney injury", "Heart failure", "BNP", "NT-proBNP"," hs-cTnT", "cTnI", "CK-MB", "Type 1 diabetes mellitus", "Type 2 diabetes mellitus", "Hemoglobin A_{1c}", "Chronic hyperglycemia", "Anemia", "Obesity", "ACEi", "ARB", "Cardiac catheterization", "Coronary angiography", "High-sensitivity C-reactive protein", "C-reactive protein", "Red blood cell distribution width", "Cystatin C", "Creatinine", "eGFR", "Galectin-3", "Urine albumin to creatinine ratio", "Mild proteinuria", "Heavy proteinuria", "Coronary artery bypass graft surgery"*. The search was restricted to trials published in English. Disagreements were resolved by consensus.

Study selection

Studies involving ≥ ten patients over 18 years of age that reported original data regarding the preoperative risk factors for the development of AKI related to specific cardiac surgery types were eligible. Trials were included if adverse renal outcome was defined according to KDIGO, AKIN, or RIFLE criteria [406, 407]. Non-human studies, papers available only in abstract, letters, case reports, and meta-analysis were excluded.

Data extraction

Data extracted from each included study were: authors' last name, year of publication, type of study, the preoperative risk factors being evaluated, number of patients, age median/mean, the proportion of patients exposed to a particular risk factor (when available), type of surgical intervention, criteria used to define CS-AKI, number of CS-AKI events. When available, data are presented as percentages, mean/median values, risk ratio, odds ratio, and range of variation. Also, when reported, the ability of a particular preoperative risk factor to improve the prediction power of a clinical model was documented.

Outcomes

We assessed the risk of developing CS-AKI in relation to the various preoperative risk factors reported in the included trials.

Quality assessment

The quality of the non-randomized included trials was assessed using the Newcastle-Ottawa scale for cohort studies concerning three criteria (study group selection, the comparability of the study groups, and the evaluation of the outcome of interest).

8.2.3. Results

Our database search retrieved 841 results. The study selection process is illustrated in Figure 16. After removing titles and abstracts irrelevant to the topic (n=756), duplicates (n = 5), meta-analysis (n = 4), and studies that did not meet the inclusion criteria (n = 53), 23 papers were included for the systematic review. Study design, patients' characteristics, the number of CS-AKI events and the AKI definition for each included study are summarized in Table XX.

The evaluated preoperative risk factors (Figure 17) and their relation with CS-AKI varied across studies: three studies assessed hemodynamic risk factors [408-410], six papers evaluated metabolic risk factors [411-416], seven studies analyzed nephrotoxic drugs and agents [417-423], one paper studied inflammatory risk factors [424], and four papers examined other comorbidities [425-428].

The AKI definitions differed between studies, KDIGO and AKIN being the most used ones.

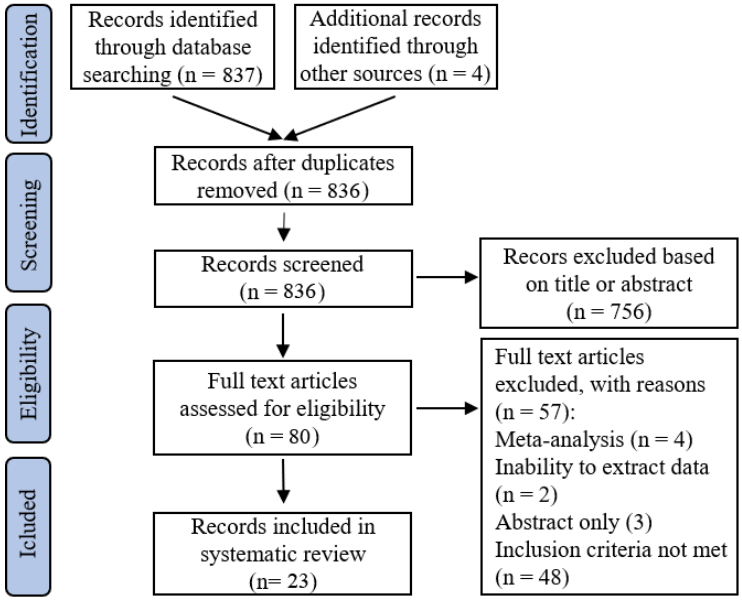


Figure 16. Flow diagram of the selection process.

8.2.4. Discussions

Our research is the first to take a thorough look at all proposed preoperative risk variables and their predictive value. Our technique serves as a foundation for identifying and comparing the predictive factors that will be included in future risk models. Without a

particular therapy, CS-AKI is a common consequence. Thus, effective prevention remains the most effective approach for resolving this issue. By developing suitable preoperative risk profiles, it is feasible to improve preventative efforts.

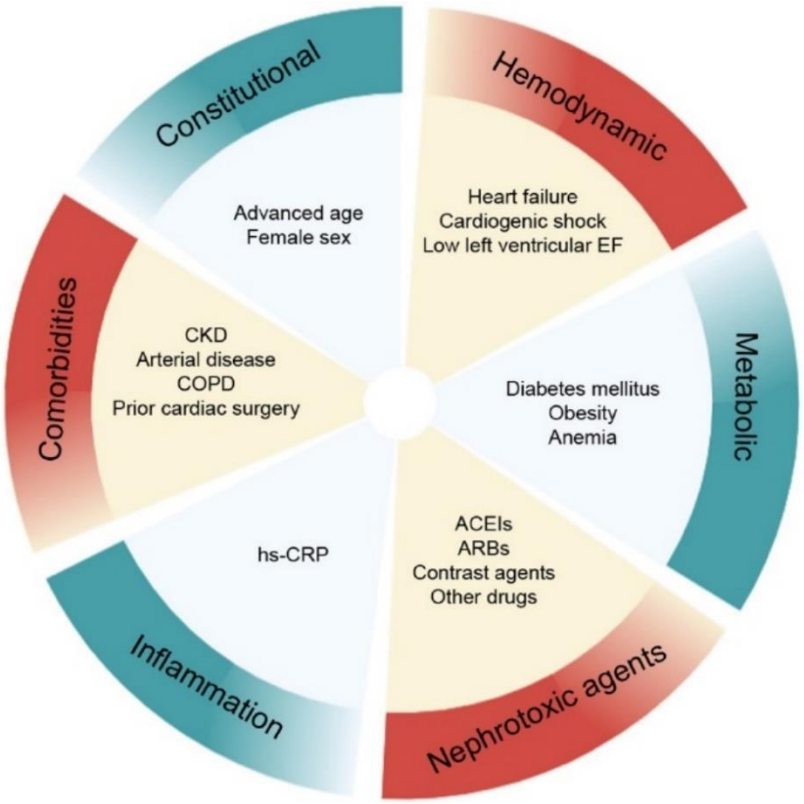


Figure 17. Known preoperative risk factors for CS-AKI grouped into six categories (EF – ejection fraction; ACEIs - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; hs-CRP - High-sensitivity C-reactive protein; CKD - chronic kidney disease; COPD - chronic obstructive pulmonary disease.

Current clinical models have a limited predictive value for milder forms of CS-AKI, despite the fact that milder forms are more prevalent and have a detrimental effect on short- and long-term mortality. As a result, new and integrative models are required to effectively estimate risk across all severity categories. Prior to developing new models, it is critical to do a thorough evaluation of all published original research on preoperative risk factors for CS-AKI. Pre-existing heart failure must be managed carefully since it is related with a greater incidence of postoperative CS-AKI.

Hertzberg et al. [408] stratified the CS-AKI risk according to the LVEF. Patients with a LVEF lower than 30% had a greater risk of CS-AKI than those with a higher LVEF (OR 1.32, 95% CI 1.06-1.65). Additionally, heart failure was linked to an increased risk of 30-day death. However, a significant weakness of this study is that it did not address left ventricular filling pressures and relaxation. Also, patients with elevated BNP and NT-proBNP levels had a higher rate of postoperative CS-AKI, as reported by Patel et al. [409], and Belley-Cote et al. [410]. BNP levels improved the prediction performance of the clinical model given by Patel et al. [409].

In addition, Belley-Cote et al [410] reported a higher 1-year mortality in patients with elevated NT-proBNP (OR 1.70, 95% CI 1.35-2.14, P < 0.0001), especially for the NT-proBNP highest tertile (OR 27.2, 95% CI 3.46-213.5, P = 0.002). Both trials, however, involved patients at high risk of CS-AKI, limiting its applicability to individuals with a modest preoperative risk profile.

Table XX. Characteristics of included studies in present systematic review.

Author, year	Type of study	RF evaluated	Patients, no	Patients with RF, no (%)	Type of surgical intervention	Age median/ mean	Acute kidney injury	
							Definition used	Events, no (%)
Hemodynamic risk factors								
(1) Hertzberg et al, 2018	Cohort study	Heart failure	36403	3914 (11)	First isolated CABG	67.0	KDIGO	4432 (14) no RF 1000 (26) with RF
(2) Patel et al, 2012	Cohort study	BNP levels	1139	Stratified in quintiles	CABG only, valve only, or both	72.0	AKIN	465 (41)
(3) Belley-Cote et al, 2016	Cohort study	NT-proBNP hs-cTnT cTnI CK-MB	960	Stratified in tertiles	CABG only, valve only, or both	71.53 (no AKI) 70.7 (severe AKI)	Severe AKI – doubling in SCr from baseline, or RRT	37 (3.9) – severe AKI
Metabolic risk factors								
(4) Hertzberg et al, 2015	Cohort study	Diabetes mellitus	36106	5581 (15.3)	Primary nonemergent isolated CABG	67.4	AKIN	5199 (14)
(5) Kocogullari et al, 2017	Cohort study	Hemoglobin A_{1c}	202	90 (44.5) – with $HbA_{1c} \geq 5.6$ %	Isolated CABG	63.0 ($HbA_{1c} < 5.6$ %) 60.0 ($HbA_{1c} \geq 5.6$ %)	KDIGO	19 (9.4)
(6) Oezkur et al, 2015	Cohort study	Chronic hyperglycemia	307	165 (53.7)	Isolated CABG or combination procedures	69	KDIGO	148 (48.2)
(7) De Santo et al, 2009	Cohort study	Anemia	1047	320 (28)	Isolated CABG	63.2	RIFLE	42 (4)
(8) Karkouti et al, 2011	Cohort study	Anemia	12388	2287 (18.4)	Isolated CABG, valve surgery or other procedures	66 (anemia) 62 (no anemia)	RIFLE	256 (2)

Author, year	Type of study	RF evaluated	Patients, no	Patients with RF, no (%)	Type of surgical intervention	Age median/ mean	Acute kidney injury	
							Definition used	Events, no (%)
(9) O'Sullivan et al, 2015	Cohort study	Obesity	432	128 (29.6)	Isolated CABG, CABG and concomitant procedure, valve surgery, pericardiectomy, Redo procedure, subaortic membrane resection	65.29 (obesity) 66.37 (no obesity)	AKIN and KDIGO	57 (13.2)
Use of nephrotoxic drugs and agents								
(10) Coca et al, 2013	Cohort study	ACEi/ARB	1594	231 (14.5) with continued ACEi/ARB	CABG and/or valve surgery	73 (no ACEi/ ARB) 70 (with ACEi/ ARB)	↑SCr ≥ 50% or ≥ 0.3 mg/dL from baseline	543 (34.7)
(11) Barodka et al, 2011	Cohort study	ACEi/ARB	346	122 (35.26)	CABG or valve surgery	74	↑SCr > 2.0 mg/dL or 2x times from baseline, RRT	19 (5.5)
(21) Diepen et al, 2018	Randomized study	ACEi/ARB	126	60 (47.6) with continued ACEi/ARB	CABG and/or valve surgery	67 (with ACEi/ ARB) 64 (no ACEi/ ARB)	↑SCr 2x times baseline or ↓GFR > 50%	2 (1.6)
(12) Jiang et al, 2018	Cohort study	Cardiac catheterization	1069	888 (83.1) surgery ≤ 7 days 181 (16.9) surgery > 7 days	Isolated CABG, valve surgery or both	61.3 surgery ≤ 7 days 63.9 surgery > 7 days	KDIGO	412 (38.5)
(13) Ranucci et al, 2013	Cohort study	Coronary angiography	4440	552 (12.4)	Isolated CABG, valve surgery, CABG and other procedures	65.8 (no AKI) 69.8 (with AKI)	AKIN	961 (21.7)
(14) Borde et al, 2019	Cohort study	Coronary angiography	900	210 (23.3) surgery ≤ 7 days 690 (76,7) surgery > 7 days	Isolated CABG	60	KDIGO	214 (24)
(15) Ozkaynak et al, 2014	Cohort study	Cardiac catheterization	573	Stratified in groups	CABG and/or valve surgery or other procedures	59.3	AKIN	233 (41)

Author, year	Type of study	RF evaluated	Patients, no	Patients with RF, no (%)	Type of surgical intervention	Age median/ mean	Acute kidney injury	
							Definition used	Events, No (%)
Inflammatory risk factors								
(16) Han et al, 2017	Cohort study	High-sensitivity C-reactive protein	1656	Stratified in tertiles	Isolated CABG	64.7	KDIGO	549 (33.2)
Other comorbidities								
(17) Shlipak et al, 2011	Cohort study	Pre-existing kidney disease (creatinine, eGFR, cystatin C)	1147	Stratified in quintiles	Isolated CABG, valve surgery or both	71	AKIN	407 (36)
(18) Ballmoos et al, 2018	Cohort study	Galectin-3	1498	Stratified in tertiles	Isolated CABG	64.02 (no AKI) 68.08 (with AKI)	KDIGO	568 (37.9)
(19) Coca et al, 2012	Cohort study	Urine albumin to creatinine ratio	1159	Stratified in groups	Isolated CABG, valve surgery or both	Stratified in groups	AKIN	409 (35.2)
(20) Huang et al, 2011	Cohort study	Proteinuria (dipstick)	1052	315 (29.9) with mild proteinuria 138 (13.1) with heavy proteinuria	Isolated CABG	65.7	AKIN	183 (17.4)
(21) Zou et al, 2018	Cohort study	RDW	13420	10274 (76) unmatched cohort 3146 (24) matched cohort	Isolated CABG	53.3	KDIGO	32.8%
(22) Duchnowski et al, 2020	Cohort study	RDW	751	Stratified in groups	Valve surgery	63.5	↑SCr > 0.3 mg/dL or urine volume <0.5	46 (6%)

Diabetes mellitus is another key risk factor for CS-AKI in a considerable proportion of patients following cardiac surgery. Hertzberg et al. [411] demonstrated that the therapy regimen had an effect on the risk of developing CS-AKI in diabetic individuals. A higher risk was identified in individuals treated with insulin, whether or not they were also using oral antidiabetic medications (OR 1.82, 95% CI 1.61-2.06) compared to those treated with oral antidiabetic medication only (OR 1.23, 95% CI 1.08-1.41) or diet only (OR 1.13, 95% CI 0.93-1.38). Moreover, Kocogullari et al. [412] and Oezkur et al. [413] observed that persistent hyperglycemia (defined as a high preoperative hemoglobin A1c level) was related with postoperative CS-AKI, regardless of whether diabetes mellitus was verified. This indicates that hemoglobin A1c values may be relevant for risk classification prior to surgery, even in non-diabetic individuals. Nonetheless, increasing hemoglobin A1c levels were not associated with

an increased risk of postoperative death or the need for KRT. Additionally, obesity is a potentially modifiable risk factor for postoperative CS-AKI emphasizing the critical nature of body weight management [416].

De Santo et al. [414] and Karkouti et al. [415] identified an increased incidence of postoperative CS-AKI in patients with anemia or who had erythrocyte transfusions. These findings suggest that early treatment of anemia may be critical for minimizing postoperative risk. International consensus guidelines advocate for preoperative discontinuation of ACEIs and ARBs [397], although data regarding their CS-AKI development risk is discordant.

Coca et al. [417] reported an increased risk of CS-AKI for patients treated with ACEIs or ARBs. Conversely, a randomized trial [423] revealed similar risks after medication discontinuation. Surprisingly, Barodka et al. [418] revealed a protective effect of the preoperative treatment with ACEIs or ARBs against CS-AKI development. However, the latter study only included patients over 65 years, limiting the results' interpretation for the younger population.

Although studies are contradictory, the worldwide consensus recommends against contrast agent exposure 24 to 72 hours before to heart surgery (2C level of evidence) [397]. According to a single-center research from China [419], the amount of the contrast agent is also critical, with patients receiving doses greater than 240 mg/kg being advised to postpone surgery (> 7 days). Ranucci et al. [420] reported an elevated incidence of postoperative CS-AKI in individuals who had contrast agents administered on the day of surgery.

In contrast, two investigations [421, 422] found that contrast exposure had no effect on the incidence of CS-AKI. However, when surgery was performed within seven days of coronary angiography, patients with pre-existing renal illness (eGFR < 50 mL/min) had a significantly increased risk of postoperative CS-AKI (OR 2.70, 95 percent CI 1.4-5.4, P = 0.005). Thus, a tailored approach that considers the time interval between the two procedures, the kind and amount of contrast agent, and preoperative kidney function may show to be more beneficial than a time interval strategy alone.

After eliminating septic patients, a South Korean observational study [424] discovered that patients with elevated hs-CRP levels had a higher risk of postoperative CS-AKI (OR 1.88, 95 percent CI 1.392-2.525, P < 0.001). Additionally, a preoperative hs-CRP level greater than 1 mg/dL was associated with an increased risk of long-term death (HR 1.55, 95% CI 1.261-1.914, P < 0.001). High sensitivity CRP is a cost-effective, commonly accessible biomarker for risk stratification of CS-AKI in preoperative situations.

Preoperative kidney function is critical because it reflects the patient's baseline functional reserve and may identify individuals at increased risk of CS-AKI. Serum creatinine, cystatin C, and eGFR are used to assess kidney function preoperatively. Cystatin C, in particular, has a greater connection with postoperative CS-AKI than the others [425]. However, only serum creatinine and eGFR are routinely used due to lower costs.

Galectin-3 is a novel biomarker linked to chronic kidney disease, heart failure, and inflammation. Ballmoos et al. [426] reported that patients with a high concentration of Galectin-3 had a greater incidence of CS-AKI, and the addition of Galectin-3 improved the predictive power of the existing clinical models.

Coca et al. [427] and Huang et al. [428] reported that urine albumin-creatinine ratio (UACR) and dipstick proteinuria was associated with a higher risk of CS-AKI. However, there

was no association between proteinuria and CS-AKI in patients with eGFR < 45 ml/min/1,73m^2 [427]. These findings show that proteinuria should be included in clinical models for CS-AKI prediction. Dipstick proteinuria is a less costly method of determining proteinuria than UACR. Its economic viability may ease its incorporation into clinical risk models.

Regarding preoperative intra-aortic balloon pump (IABP) placement, the international consensus position [397] is that IABP could have a beneficial effect on postoperative CS-AKI incidence. This is based on the results of a meta-analysis of 17 studies [429] reporting that the preoperative placement of IABP in patients at high risk was associated with a lower incidence of AKI after CABG (OR 0.54, 95% CI 0.36-0.79, P = 0.002).

8.2.5. Conclusions

Our findings may be used to analyze previous studies on the risk variables for AKI following heart surgery. AKI is a common and serious complication of heart surgery. Given the lack of a particular therapy, preventative strategies aimed at identifying and mitigating preoperative risk factors are critical.

A higher incidence of postoperative CS-AKI is related with heart failure, chronic hyperglycemia, anemia, obesity, preoperative exposure to nephrotoxic medications or contrast media, inflammation, proteinuria, and preexisting kidney disease.

There are currently no externally verified or widely recognized clinical models that accurately predict the incidence of postoperative CS-AKI, particularly in non-severe clinical manifestations. As a result, clinical judgment and an up-to-date understanding of preoperative risk variables may aid in personalizing preoperative risk profiles as the cornerstone of preventative strategies.

8.3. Major cardiac surgical procedures in kidney transplant recipients: a meta-analysis on long- / short-term postoperative outcomes

8.3.1. Background and Aims

According to the Global Observatory on Donation and Transplantation's most recent global report, 139,024 transplantation operations were done globally in 2017, with 90,306 kidney transplants, 32,348 liver transplants, and 2243 pancreas transplants [430]. End-stage organ failure is responsible for an increased mortality rate in the general population. The replacement of dysfunctional organs with healthy equivalents through transplantation represents the gold standard treatment. Each year, the number of patients on the waiting list continues to be much larger than both the number of donors and transplants [431].

Cardiovascular risk factors are more prevalent in the majority of individuals having abdominal organ transplantation. Coronary artery disease, stroke, hypertension, dyslipidemia, and diabetes mellitus are the leading causes of late mortality among transplant recipients [432-434]. The incidence of cardiovascular events appears to be underestimated, indicating that other transplant-specific variables may contribute to cardiovascular risk either alone or in combination with "conventional" risk factors such as immunosuppressive medications [435, 436].

Cardiac surgery following organ donation is not rare, although it proved to be more difficult and risky than in the general population [437, 438]. Improved surgical methods, immunosuppressive regimes, and perioperative care have led in improved early and late outcomes for transplant recipients undergoing nontransplant-related surgical operations.

However, a few studies have revealed that the incidence of postoperative complications and death is much greater in kidney and liver transplant patients undergoing major cardiac surgery than in individuals with normal organ function [437-440]. There are presently no clear recommendations or methods for determining the risk-benefit ratio of cardiac surgery in patients undergoing abdominal transplantation.

The purpose of our meta-analysis is to determine the safety of cardiac surgery in abdominal solid organ transplant recipients by comparing postoperative outcomes (in terms of major adverse cardiovascular and cerebrovascular events, short- and long-term mortality) in adult patients who had previously undergone kidney, liver, pancreas, or pancreas-kidney transplant surgery to those who had not previously undergone transplant surgery.

8.3.2. Methods

Three electronic databases were searched: PubMed, EMBASE, and SCOPUS from beginnings from the inception of these databases to September 1st, 2020. We used the following query terms: "cardiac surgery", "heart surgery", "solid organ transplantation", "liver transplantation"," kidney transplantation", "pancreas transplantation". Two researchers independently scanned titles and abstracts and performed an additional check of references in relevant articles. When there was a lack of consensus, we asked the opinion of the third senior reviewer. The literature's systematic search was performed following PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

The endpoints were as follows: the overall rate of postprocedural infection, pneumonia, stroke, cardiac tamponade, acute kidney failure, 30-days, 5-years, and 10-years mortality between patients with previous solid abdominal organ transplantation and patients without a history of transplantation, undergoing heart surgery.

Review Manager (RevMan) Version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen, Denmark) software was used to generate the pooled effect size with OR and 95% CI by Mantel-Haenszel method and random effect model for dichotomous data. For continuous data, we used mean difference (MD) and 95% confidence intervals by the Inverse Variance method and random effect model. I^2 statistics were used to evaluate the heterogeneity of studies. We considered 0% to 25% as low, 26% to 50% as moderate, 51% to 75% as high, and >75% as very high heterogeneity.

The risk of publication bias was assessed Newcastle-Ottawa Quality Assessment Scale for cohort studies.

8.3.3. Results

Five full-text articles that compared clinical outcomes, early and late mortality after cardiac surgical procedures in solid abdominal organ transplant recipients with patients without transplantation history were retrieved [441-445].

The final analysis included 1,711,189 patients with 3826 transplant recipients (Tx) and 1.707.363 patients without transplantation history (N-Tx). Only patients with solid abdominal organ transplants (kidney, liver, pancreas, kidney-pancreas) were included in the Tx group. All types of cardiac surgery were taken into account. Baseline characteristics and periprocedural data distinguishing each group are summarized in Table XXI.

Table XXI. Summary of individual pooled data and comparison between groups.

Parameters	No. of studies	No. of Tx patients	No. of N-Tx patients	Tx Mean±SD or (%)	N-Tx Mean±SD or (%)	p-value
Demographics						
Age	5	3826	1.707.363	58.06 ± 10.55	65.50±11.80	<0.0001
Male	5	3826	1.707.363	66.28%	68.36%	0.006
Congestive Heart Failure	3	3675	1.706.914	28.97%	23.4%	<0.0001
NYHA – class IV	2	185	2135	16.75%	11.89%	NS
Previous myocardial infarction	4	291	1414	31.27%	38.33%	0.03
Peripheral vascular disease	5	3826	1.707.363	10.29%	9.98%	NS
Prior Stroke	5	3826	1.707.363	6.61%	7.56%	0.03
Diabetes mellitus	5	3825	1.707.363	27.42%	26.53%	NS
Hypertension	4	291	1414	88.31%	74.82%	<0.0001
Obesity	2	185	415	28.64%	27.95%	NS
BMI	2	185	1240	26.42±5.76	28.51 ±5.67	
COPD	3	3641	1.706.123	10.73%	21.22%	<0.0001
Smoking history	3	176	1069	37.5%	51.07%	0.001
Dyslipidaemia	3	176	1069	59.09%	68.38%	0.002
Type of surgery						
CABG only	5	3826	1.707.363	59%	70%	<0.0001
Valve surgery only	5	3826	1.707.363	25.37%	16%	<0.0001
CABG and Valve surgery	4	3756	1.707.293	14.8%	13%	0.002
Intraoperative data						
CPB time-minutes	4	291	1414	132.375 ± 65.9417	147.1262± 65.3887	0.0005
Aortic cross-clamp time-minutes	4	291	1414	86.1653±45.527	102.9047±49.266	<0.0001

We aimed to compare the difference in periprocedural data between the liver and a kidney transplant cohort. Except that renal transplant recipients were younger (62.42±7.15 vs. 57.38 ± 11.12, p=0.04), no significant differences were reported (Table XXII).

Table XXII. Comparison between liver transplant and kidney transplant recipients.

Risk Factor	TOTAL LIVER Tx Kohmoto-Vargo-Sharma	TOTAL KIDNEY Tx Kohmoto-Vargo-Sharma	P-value
Demographics			
Number of patients	762	2824	
Age at heart surgery (years)	62.42±7.15	57.3839±11.130	0.0357
Gender (males)	19/24 (79.16%)	84/112 (75%)	0.8657
Cardiac procedure			
CABG	471/762 (61.81%)	1635/2824 (57.89%)	0.0563
CABG and Valve	4/24 (16.66%)	15/112 (13.39%)	0.9244
Valve	183/762 (24.01%)	710/2824 (25.14%)	0.5532
Other	1/24 (4.16%)	11/112 (9.82%)	0.6236
Comorbidities			
Previous MI (%)	8/24 (33.33%)	31/112 (27.67%)	0.7683
PVD (%)	6/24 (25%)	26/112 (23.21%)	0.9382
Stroke (%)	1/24 (4.16%)	17/112 (15.17%)	0.2658
Diabetes mellitus (%)	13/24 (54.16%)	51/112 (45.53%)	0.5869
Hypertension (%)	20/24 (83.33%)	101/112 (90.17%)	0.5409

The meta-analysis revealed that the infectious postoperative complications such as wound infection (Tx vs. N-Tx: OR: 2.03, 95%CI: 1.54 to 2.67, I2 = 0%) and septicemia (Tx vs N-Tx: OR: 3.91, 95% CI: 1.40 to 10.92, I2 = 0%) had significant lower rates in patients without transplantation history. Despite that, there was no difference pneumonia occurrence (OR: 0.95, 95%CI: 0.71 to 1.27, I2 = 0%).

Cardiac tamponade (Tx vs. N-Tx: OR: 1.83, 95%CI: 1.28 to 2.62, I2 = 0%) and kidney failure (Tx vs. N-Tx: OR: 1.70, 95%CI: 1.44 to 2.02, I2 = 89%) had also a higher incidence in transplant recipients, but no significant difference in post-procedural stroke rate (OR: 0.89, 95% CI: 0.54 to 1.48, I2 = 78 %) was noticed (Figure 18).

No significant difference in 30-day mortality was observed (OR: 1.92, 95% CI, 0.97 to 3.80, I2 = 0%). Meanwhile, 5-years (OR: 3.74, 95%CI, 2.54 to 5.49, I2 = 0%) and 10-years mortality rates were significantly lower in the N-Tx group (OR: 3.32, 95%CI, 2.35 to 4.69, I2 = 0%).

8.3.4. Discussions

Our meta-analysis demonstrates an association between past solid abdominal organ transplantation and an increased risk of long-term mortality following major heart surgery. However, not death, but infectious problems, are much greater in the transplanted group in the short term. This is the first meta-analysis to compare the short- and long-term outcomes of open cardiac surgery in patients with solid abdominal organ transplantation against non-transplant patients.

The (abdominal) transplanted population is more prone to cardiovascular events than the general population, with an estimated risk of 19% [432]. Additionally, the yearly cardiovascular death rate of renal recipients is increased from 0.28 percent (in the general population) to 0.54 percent, accounting for 55% of total mortality. By comparison, cardiovascular disorders have been attributed to up to 10% of late mortality in the same patient group [446, 447].

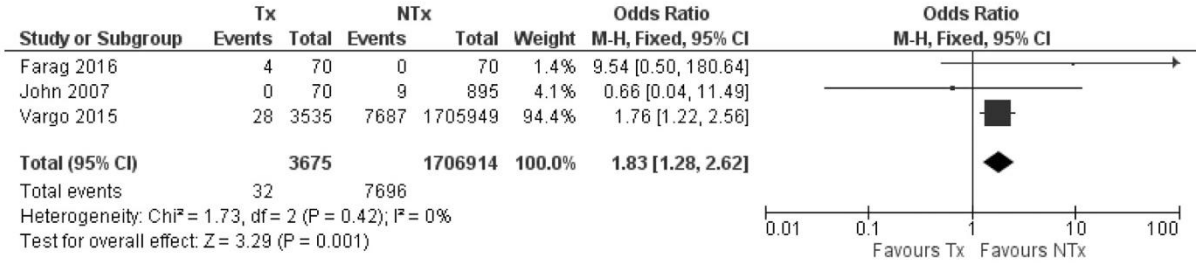
A particularly distinct risk factor that appears to multiply the prevalence of cardiovascular risk factors and thus the development of cardiovascular disease is pharmacological immunosuppression in transplanted individuals, with the use of calcineurin inhibitors being directly associated with severe hypertension and dyslipidemia [446].

Hypertension is prevalent in >70% of transplant recipients and is associated with allograft failure, death with a functioning allograft, atherosclerotic cardiovascular diseases, and disorders of cardiac function [448]. Meanwhile, between 50% and 60% of kidney transplant recipients had dyslipidemia, which is highly related with atherosclerotic cardiovascular disease in both CKD and non-CKD patients [449]. Obesity is another common posttransplantation consequence, with a cumulative incidence of 5.9 percent at six months and 29.8 percent at 15 years [450].

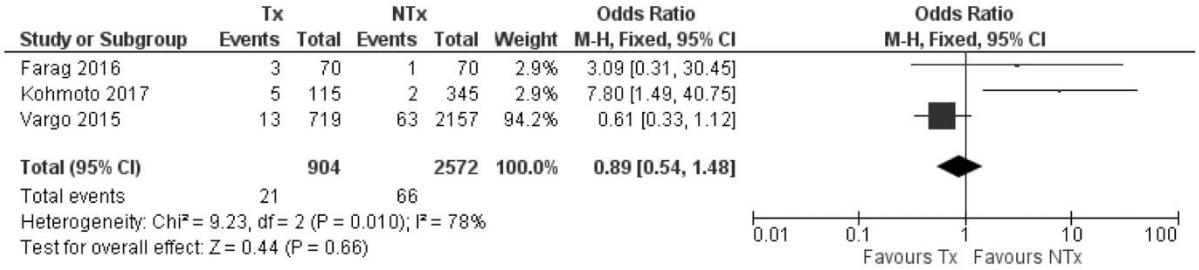
As with dyslipidemia, new-onset diabetes has been linked to allograft loss and mortality while an allograft is functioning [451-453]. There was a substantial difference in the prevalence of hypertension and congestive heart failure between the two groups in our research, although, contrary to earlier reports, obesity and dyslipidemia were less prevalent in the transplanted population. Three of the five trials included data on the average time period between heart surgery and transplantation. The mean and standard deviation together amounted to nearly eight years.

Musci et al. similarly found comparable findings in a renal transplant sample with a 7.26-year delay [454]. The effect of this variable on short- and long-term outcomes cannot be adequately evaluated since no comparable data exist for the control group. Additionally, no comparisons were made among the transplanted population using the average delay between transplantation and heart surgery. Additional research comparing the effect of transplanted graft age on postoperative outcomes is warranted, since this might be a source of lead-time bias.

A



B



C

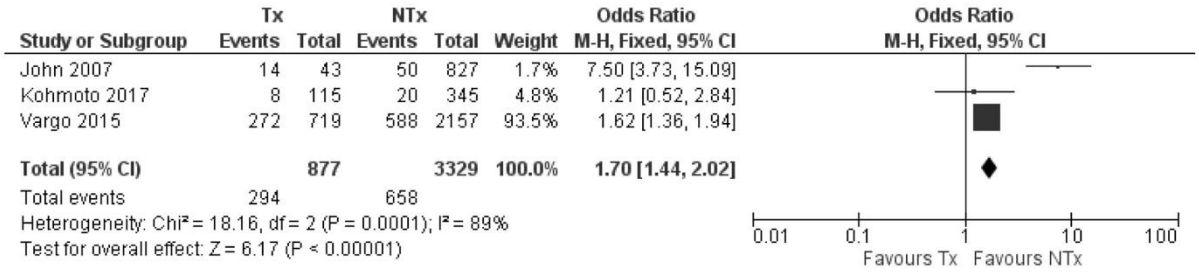


Figure 18. Postprocedural cardiovascular and renal complications. (A) Tamponade. (B) Stroke. (C) Kidney failure.

Forest plot of the meta-analysis depicting the comparison of postoperative kidney failure after cardiac surgery in solid abdominal organ transplant recipients with patients without abdominal transplantation history.

Our meta-analysis demonstrated that open heart surgery in abdominal transplant patients may be difficult and dangerous due to an increased risk of infection, as seen by increased rates of septicemia and wound infections. Opportunistic infections, in particular, are one of the most feared complications in transplant patients due to immunosuppressive medication [455]. Although the authors of the included studies mentioned lower respiratory tract infections, we observed no difference in pneumonia across groups [456] [457]. Cardiovascular tamponade and kidney failure were also more prevalent in transplant patients, albeit this might be explained by the increased frequency of long-term chronic kidney dysfunction in renal transplant recipients.

We discovered no statistically significant difference in 30-day mortality. According to some researchers, individuals with past transplants who undergo valve replacement surgery had a 100 percent survival rate after 30 days [458]. This finding led to the conclusion that there

would be no justification for the delays that frequently accompany the application of appropriate therapy in patients who have previously undergone transplantation, given the relative impunity with which cardiac therapeutic interventions could be performed [457].

When it comes to long-term mortality, a considerable difference is evident, with considerably higher rates after 5- and 10-year follow-up. This might be a compelling justification for reconsidering the appropriate surgical strategy to treating cardiac diseases in this population in favor of less invasive transcatheter options. A propensity-matched control research based on six years of registry data demonstrated the importance of accounting for kidney transplantation status when deciding between open heart surgery and transcatheter coronary revascularization.

The purpose of this study was to determine the incidence of postoperative renal dysfunction in patients with a history of kidney transplantation who underwent coronary revascularization therapy via PCI or CABG between 2008 and 2014. There was a substantially increased incidence of acute renal damage (OR 2.20, 95% CI 1.91 to 2.54, p=0.0001) and AKI requiring dialysis (OR 2.50, 95% CI 1.49 to 4.19, p = 0.001) in patients who received CABG compared to those who underwent PCI. Despite this, no statistically significant difference in in-hospital mortality was seen between the PCI and CABG populations (OR 1.33, 95% CI 0.94–1.87, p = 0.104) [459].

Transcatheter valve implantation operations have been shown to be a safe and successful means of treating kidney transplant patients with severe aortic stenosis, with a lower rate of morbidity and mortality than conventional open-heart surgery. There were no serious problems such as acute renal failure (post-intervention creatinine [mg/dl] at 24 h 1.88±0.77; 48 h 1.93±0.84; 72 h 1.81±0.78; discharge 1.87±0.76), nosocomial infection, or in-hospital mortality, and a one-year follow-up revealed a 100 percent survival rate. Meanwhile, the same authors observed an 11.1 percent 30-day death rate and a 16.7 percent 1-year mortality rate in a group of patients who underwent surgical aortic valve replacement (SAVR). Acute renal failure, sepsis, cerebral hemorrhage, re-thoracotomy, and extended hospitalization were additional postoperative problems in the SAVR group [460].

8.3.5. Conclusions

Given the increasing incidence of abdominal organ transplant operations and difficult cardiovascular illnesses requiring open-heart surgery in this subgroup of patients, a strong evidence base and indications/contraindications are required for appropriate care of these challenging cases. Our meta-analysis elucidates the considerable short-term infection hazards and higher long-term mortality associated with open heart surgery in transplant recipients. We think that alternatives to conventional surgery (such as minimally invasive surgery or transcutaneous procedures) must be developed, particularly in cases where sufficient evidence indicates considerable and unjustifiable consequences.

SECTION III. Future directions in the academic, professional and research domains

Chapter 1. Future projects in the academic field

My main goal in terms of teaching is to train students, resident physicians and future researchers and Ph.D students in the field of scientific research methodology, to be a facilitator for each of our future doctors and researchers to have their own research projects and to publish their findings in high IF journals.

I will invest a significant part of my time and energy resources in this educational vocation. As Prof. Daniel David wrote about the research methodology, it "*addresses intelligent consumers of science who like to think and like science*", especially in the contemporary context where "*one is witnessing an offensive of non-science and pseudo - science.*"

Since two years ago, a number of over 50 students from the medical faculty of UMF Iasi take part in the Artificial Intelligence course every week, where I invited expert lecturers in the field of AI both from the connected university field of Iasi (Prof. Dr. Marin Fotache from FEAA - UAIC, as well as Prof. Dr. Adrian Iftene from the Faculty of Informatics - UAIC), as well as from the private and entrepreneurial environment.

The objectives of this first AI course in medicine in Romania within the medical university are to integrate the main concepts of AI used in modern medicine; presentation of various medical pathologies where AI solutions have been implemented; facilitating the use of AI concepts in medicine for future research projects of students / future physicians. Thus, in an original way the student will acquire the necessary knowledge to conduct a scientific research in the field of AI / ML by writing articles and will have knowledge about the limits of the use of AI in medicine and possible ethical slippage.

The future plan is to explain to students / PhD fellows the use of NLP (Natural language processing), the notions of Data Science in medicine; the use of AI in cardiology, pulmonology and nephrology, in medical imaging as well as the impact of AI in the diagnosis, treatment and prevention of cancer. I also aim to invite readers to explain how the artificial pancreas works through AI, medical robotics and virtual healthcare - Siri, Alexa and the Google Health project. I will also explore the issue of data, confidentiality and GDPR in the field of AI.

Another didactic development project (but aimed at training young doctors and students passionate about scientific research through Artificial Intelligence), is the inauguration of the recent "*Center for Innovation and Technology Transfer MAVIS*" from UMF Iasi, an *Artificial Intelligence club in Medicine*, where young students and residents can work informally in the sense of exchanging ideas and applying them in a benchmark that allows them to progress from idea to solution, from model to final result. I believe that this approach is a medium and long-term investment both locally and nationally, allowing both the education of young students and the emergence of new methods of diagnosis and therapies through AI.

Considering that there is currently no training center for residents in the field of interventional cardiology in the area of Moldova, I propose that together with Mr. Dr. Igor Nedelciuc to substantiate this *Residency Training Center* for training in Interventional

Cardiology and training specialists for this sub-specialization; I have already conducted several workshops for English language medical students under my leadership under the auspices of UMF Iasi and EMSA.

By attracting European funding and supporting the private sector, I intend to develop a *Simulation Hub in Interventional Cardiology*, following an American model that entered the curriculum of cardiology training in the USA (Center of Advanced Clinical Skills, Cedars-Sinai); I myself studied in Frankfurt on simulators of preparation for rapid reaction in STEMI, simulation of placement of temporary stimulation probe, simulation of radial and femoral vascular access. This hub will be able to educate both students interested in modern techniques of the future and residents and specialists in the module of interventional cardiology training.

Students and residents are in constant need of teaching materials. I will get involved in capitalizing on the experience of my predecessors and, possibly, creating new, updated editions of the courses / treaties already developed. Given my current experience (I wrote a Chapter on the European Treatment of Resistant Hypertension at Springer Publishing House and attended a Renal Denervation Course in Berlin) I intend to write with Prof. Adrian Covic a *Manual on Renal Arteries Pathology*, being in the project at the Springer publishing house.

In terms of cardio-nephrology, I also propose the elaboration, together with colleagues from the Cardiology and Nephrology Clinics, of *specific materials for common cardiovascular and renal pathology*. In the future, I also consider making a "*Compendium of Clinical Cases*" relevant to cardiac and nephrological pathology that have benefited from arterial / coronary / percutaneous valvular interventions.

The current experience together with the team from the Nephrology clinic in teaching the internships and courses of Research Methodology (under the coordination of Prof. A. Covic), raised my idea to draw up a Collective Manual of Research Methodology. I believe that the large number of team publications, as well as the high impact factor of articles published by me as the lead author, reflect my ability to manage information and structure it in a modern format appropriate for students. This direction is one of my top priorities for the future, because educating future physicians to critically interpret medical information and studies will really improve the level of science and the quality of medical decisions, as well as rising the international ranking of our own University (UMF Iasi).

I believe that together with the other profile clinics in the country we will have to develop *a common material with the course subjects in Interventional Cardiology*, as well as with the techniques (including catheterization, stenting, post-dilation), maneuvers and practical activities (especially in emergency) provided for in the module of the Specific Training Curriculum.

I will be involved – along with my colleagues – in all teaching activities with students (courses, internships, bachelor's theses, scientific circles) and residents (presentations, papers) including verification actions (discussions, grid tests) and "*feedback*" consultations, for the continuous improvement and adaptation of the content and methods of teaching activities to the requirements of students and young doctors.

Chapter 2. Future plans in the clinical field

One of the main concerns for medical development is the elaboration of the *Nephro-Heart Team project*, a project initiated by me in the Institute of Cardiovascular Diseases in collaboration with the Nephrology and Transplant Clinic at Parhon Iasi Hospital (Prof. A. Covic) and the Cardiac Surgery Clinic from IBCV Iasi; this project is based on the latest recommendations of complex medical practice in the European Guidelines, facilitating the meeting of a team of cardiologists, emergency physicians, ultrasonographers, nephrologists, interventional cardiologists and surgeons, to make complex decisions on the treatment of the latest generation of patients with complex cardiovascular and renal pathology. All patients who have kidney dysfunction and receive a percutaneous coronary intervention in IBCV Iasi are included in our databases and analyzed later.

Within this Nephro-Heart Team (see above, MDT) , those sensitive situations that are located in the "*gray area*" of the Guidelines are most competently discussed. The existence of the Heart Team confirms that there are no diseases, but patients, and that the multitude of situations encountered in current clinical practice cannot be covered by the Clinical Practice Guidelines, no matter how elaborate they may be. I will continue to work with the team coordinated by me to publish high IF scientific articles exploring the usefulness of antithrombotic medication in advanced and kidney transplant patients. I mention that currently our team has over 20 articles with IF published only on the topic of antithrombotic drugs in (advanced) CKD patients.

Given that I personally established connections with the Center for Chronic Occlusion from Szeged, Hungary (Dr. Imre Ungi and Dr. Andrasy Katona) in December 2018, and that I proposed the arrival of several specialists trained in Japan to instruct fellow interventionists in special techniques for CTOs, this project will certainly be a priority for the team coordinated by me at this time. It should be mentioned that there is currently no center in Romania specialized in this type of coronary interventions and that the respective patients must be referred to centers outside the country, or private practice centers.

Another sensitive aspect is the treatment of patients with essential arterial hypertension resistant to conventional medical treatment, for which there is currently no state center in Romania to practice an interventional technique of renal denervation. Through the project I am considering with the head of the Nephrology Clinic, I believe that we will be the first center in the country to practice renal denervation as a solution to intractable cases. There is currently no registry of secondary RD. In our collaborative practice, the nephro-cardiology team started under my coordination the steps for the preparation of this follow-up register of patients with secondary hypertension due to reno-vascular diseases as well as the stents used for their treatment. We will therefore be a first Romanian reply to STAR, ASTRAL and CORAL initiatives.

Since I have started the protocols for the Coronary FFR and IVUS assessment procedures, I will follow up on a project to perform FFR and IVUS in dialysis patients with stable angina who have intermediate coronary lesions (so they do not require stenting) to see if these lesions deserve to be stented or have active criterion (e.g., treated with medication or the intensification of the dialysis regimen).

Chapter 3. Future projects in the research field

3.1. Ongoing projects in cardio-nephrology

Since, my most important concern (i.e., sensitive issues in **cardio-nephrology**, which has resulted in 10 articles with ISI IF more than 5), is the research of the ESC and KDIGO guidelines and the most important nephrological studies on protocols or lack of evidence in the treatment and antithrombotic medication (either anticoagulants, or antiplatelet agents and/or combinations, as well as TAT) in patients with CKD.

We explored various aspects of antiplatelet therapy (according to the last Guidelines) in dialysis patients requiring stenting, translating or adapting the protocols and algorithms recommended by the ESC for the general population to the population of patients with advanced CKD.

My next project (in collaboration with the EuDial Working Group of the European Renal Association) is aiming to disentangle the complex epidemiological, pathophysiological, and prognostic relations between acute kidney injury and cardiac arrhythmias.

AKI is generally characterized by an abrupt rise in the serum creatinine level, decreased urinary output, or both. Advances in critical care and KRT have provided tools that can support patients through most of the immediate complications of AKI, such as uremia or hyperkalemia, which could be rapidly fatal. Nevertheless, mortality from AKI remains high. AKI has an overall 21% prevalence among hospitalized patients, with 2% to 5% requiring KRT, and bears a significant adverse prognostic impact [461]. Depending on specific clinical settings (e.g., general medical wards or intensive care units – ICUs -), in-hospital death may occur in 16% to 49% of these patients [462].

Acute kidney injury has been shown to promote cardiac injury and dysfunction (myocardial ischemia and heart failure). In patients with AKI, the pathophysiological sequence connecting the initial event causing the abrupt decrease in kidney function with death may include the onset of cardiac arrhythmias [463]. Multiple comorbidities (e.g., underlying cardiovascular diseases, post-surgical conditions, sepsis, and drug- or toxic-related effects) are potential causes of both the development of AKI during the hospital stay and the triggering of supraventricular arrhythmias (e.g., AF), life-threatening ventricular arrhythmias and severe bradyarrhythmias. Reciprocally, cardiac arrhythmias increase the risk of adverse kidney outcomes, including AKI. This specific population has not investigated the incidence and prognostic impact of arrhythmia events.

Therefore, there is an urgent need to closely inspect the available evidence concerning the association between AKI and cardiac arrhythmias.

a) AKI and arrhythmogenesis: pathophysiological mechanisms of electrolyte and acid-base disorders.

Complex arrhythmias may arise due to electrolyte and acid-base derangements in patients with AKI and represent a potentially lethal complication. Potassium and calcium are

directly involved in the genesis of myocardial action potential, and hyperkalemia and hypocalcemia are important risk factors for the onset of arrhythmic events. In addition, hyper- or hypophosphatemia, hypomagnesemia, and metabolic acidosis may complicate the clinical course of AKI and trigger or favor arrhythmogenic mechanisms [464]. It is essential to note that ECG changes induced by metabolic acidosis can be modified by acidosis-induced modifications in serum concentrations of potassium and ionized calcium [465].

b) AKI and Atrial Fibrillation.

The relationship between AKI and AF is complex and bidirectional, especially in the ICU setting: on the one hand, AKI can promote AF development; on the other hand, AF may be regarded as a risk factor for AKI occurrence. Notably, treatment with β-blockers and non-VKAs were protective factors for AKI development [466]. AKI requiring dialysis (AKI-D) can be a serious complication in critically ill patients with AF. Moreover, in patients with AKI, new onset AF (NOAF) is associated with a high incidence of KRT. Chan et al. described an increase from 0.3/1000 in 2003 to 1.5/1000 in 2012 of AKI-D among patients hospitalized because of AF [467]. underscore that the association between NOAF and AKI is dynamic, as AKI patients had a higher risk of NOAF, while NOAF was linked to a greater incidence of AKI, including AKI requiring KRT. Also, AF occurrence could be regarded as a promoter of adverse events, mortality, and poor prognosis during follow-up in patients with AKI. Therefore, early AF detection and timely therapeutic intervention could significantly impact patients' outcomes. However, more studies are required to confirm these observations.

c) AKI and bradyarrhythmias (cardiac conduction disorders and cardiac arrest).

In patients who survive a cardiac arrest (CAr), the incidence of AKI is high and varies depending on the criteria for defining AKI. After a CAr, the onset of AKI is an early event that occurs within 24-48 hours [468-470]. A number of risk factors predictive of the onset of post-arrest AKI have been described. Older age is associated with an increased risk of developing AKI, ranging from 2 to 3% per year [470, 471]. Other predictors of AKI risk include worse kidney function at hospital admission [468, 470-474], longer duration of CAr [471, 474], and higher blood lactate levels measured within 12 hours of recovery of spontaneous circulation [470-472].

d) AKI and ventricular arrhythmias.

Life-threatening ventricular arrhythmias leading to CAr represent a significant cause of death in patients with severe CKD and those with AKI due to impaired fluid, electrolyte, and acid-base homeostasis [475]. The risk of occurrence of ventricular arrhythmias increases along with worsening kidney function [475, 476]. Also, the prognosis of patients with ventricular arrhythmias and impaired kidney function is poorer compared with patients with preserved kidney function, especially in those who survived a CAr event [476].

e) Pharmacological therapy for the prevention and treatment of arrhythmias in AKI patients.

The presence of AKI represents a challenge in cardiac arrhythmias management due to accumulating uremic toxins, acidosis, electrolyte disorders, and fluid overload. The coexistence of AKI with structural heart disease, such as ACS or CCS, may further contribute to treatment complexity. Pharmacological treatment of arrhythmias in the AKI setting could have several purposes: 1) ensuring adequate tissue perfusion by maintaining an optimal heart rate; 2) bridge (life-saving) therapy before etiologic and pathophysiologic interventions; 3) preventing thromboembolic events; 4) prophylaxis of arrhythmic recurrences.

A summary of the main recommendations, advantages, and disadvantages of antiarrhythmic drugs in the AKI context are presented in Table XXIII.

Table XXIII. Recommendations for antiarrhythmic drug use in AKI).

Drug	Advantages	Disadvantages
Amiodarone	Metabolized by the liver [477] Can be administered in AKI	Can cause hypotension and severe bradycardia [477] Can prolong QT interval (increased risk of torsade des points) [477] Not significantly removed by hemodialysis [478]
Sotalol	Removed by dialysis [479]	Excreted by the kidneys [239] Not recommended in AKI Contraindicated in left ventricular hypertrophy, HFrEF, eGFR < 30/mL/min/1.73m^2 [477]
Vernakalant	Eliminated by the liver [477] Can be administered in AKI	Contraindicated in severe hypotension, ACS, severe aortic stenosis, NYHA class III and IV heart failure [480] Not recommended in LVEF < 35%, HOCM, advanced hepatic impairment, restrictive cardiomyopathy, constrictive pericarditis, significant valvular stenosis [480]
Propafenone	Metabolized by the liver [477] Can be administered in AKI (with caution)	Contraindicated in ischemic heart disease, HFrEF, severe left ventricular hypertrophy Not removed by dialysis [481]
Flecainide	Metabolized by the liver + excreted unchanged by the kidneys [477]	Not recommended in AKI (higher risk of ventricular arrhythmias) Contraindicated in ischemic heart disease, HFrEF, severe left ventricular hypertrophy, eGFR < 50 mL/min/1.73m^2 [477] Not significantly removed by dialysis [481]
Metoprolol	Eliminated by the kidney to a lower extent (< 5%) [482] Can be administered in AKI	Not significantly removed by dialysis [481]
Bisoprolol	Can be administered in AKI (reduced dose, with caution)	Almost 50% eliminated unchanged by the kidneys [482] Not significantly removed by dialysis [481]
Carvedilol	16% eliminated by the kidneys [482] Can be administered in AKI	Not significantly removed by dialysis [481]
Labetalol	< 5% eliminated unchanged by the kidneys Can be administered in AKI	Not significantly removed by dialysis [481]
Diltiazem	2-4% eliminated unchanged by the kidneys Can be administered in AKI (with caution)	Not significantly removed by dialysis [481]
Verapamil	Can be administered in AKI (reduced dose, with caution)	Eliminated by the kidneys in a greater proportion (70%) [482] Reduced dose if eGFR < 10 mL/min/1.73m^2 [482] Not significantly removed by dialysis [239]
Digoxin	Mainly eliminated by the kidneys [482]	Contraindicated in acute myocardial infarction, myocarditis, and ventricular fibrillation Electrolyte disorders could increase toxicity

	Might be used in AKI (reduced dose, with caution)	Not significantly removed by dialysis [481]
Mexiletine	10-15% eliminated unchanged by the kidneys [483] Might be used in AKI (reduced dose, with caution)	Contraindicated in HFrEF, sinus node dysfunction, severe atrioventricular conduction abnormalities, long QT syndrome [484] Not significantly removed by dialysis [481]
ACS = acute coronary syndrome; AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HOCM = hypertrophic obstructive cardiomyopathy; LVEF = left ventricular ejection fraction.		

f) KRT in the prevention of life-threatening arrhythmias in AKI patients.

KRT can promote or rectify electrolyte and acid-base problems in AKI dependent on unique operational parameters and patient comorbidities, hence possibly raising or decreasing the incidence of arrhythmias. Indeed, depending on the severity of the patient's condition and the clinical setting (i.e., nephrology wards vs. intensive care units), KRT can be administered via intermittent HD or hemodiafiltration (IHDF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) or hemodiafiltration (CVVHDF), or "hybrid" techniques such as sustained low-efficiency dialysis (SLED).

In **Conclusion,** arrhythmias are a serious complication that can occur in hospitalized AKI patients. Diverse and varied situations related with the development of AKI or pathogenetically connected with it may encourage arrhythmogenesis. These problems include pre-existing or AKI-induced heart damage and myocardial dysfunction, fluid overload, and electrolyte and acid-base disturbances, all of which complicate the clinical course of individuals with AKI.

Cardiovascular arrhythmias, on the other hand, increase the risk of severe renal outcomes, including AKI. Additionally, depending on the kind of KRT employed in later AKI stages, a fast fall in blood potassium during IHD with a large dialysate-to-serum potassium gradient or the development of hypophosphatemia, hypocalcemia, and hypomagnesemia during cKRT or SLED may promote arrhythmias.

Minimizing these electrolyte imbalances by careful selection of dialysis/replacement fluid composition may help lower the risk of arrhythmia in AKI patients receiving KRT. AF is by far the most often reported rhythm abnormality in individuals with AKI. In these individuals, severe hyperkalemia, possibly in combination with hypocalcemia, induces severe bradyarrhythmias. Although the risk of life-threatening ventricular arrhythmias is reported to be low, the combination of myocardial ischemia and a specific electrolyte (e.g., hypocalcemia and/or hypomagnesemia) or acid-base (e.g., metabolic acidosis) disorder may increase the risk, particularly in patients with AKI requiring KRT. Amiodarone and β-blockers had the greatest safety/effectiveness profile for avoiding VT or VF recurrence in AKI patients. It should be emphasized that the majority of existing epidemiological data on arrhythmias in AKI patients and speculations about the pathogenetic processes behind arrhythmogenesis in this scenario come from retrospective investigations.

Thus, caution is required when interpreting these findings due to the heterogeneity of patient features, several possible biases, and confounding by latent variables not included in

multivariable analysis. There are still clinically significant information gaps, most notably regarding the antiarrhythmic effectiveness of a personalized KRT strategy in critically sick patients with severe AKI stages. To this end, future well-designed and suitably powered controlled trials evaluating the incidence of arrhythmias in critically ill patients with AKI receiving continuous kidney replacement therapy (CKRT) or "hybrid" treatments using a variable mix of dialysis/replacement fluids are eagerly expected.

3.2. Heart rate variability: new implications in STEMI

One of my major concerns in an innovative field of cardiology represents the HRV (heart rate variability).

HRV defines the changes in the time interval of cardiac sinus node depolarization, thus reflecting a balance between sympathetic and parasympathetic nervous systems activity [485]. It seems that HRV is impacted by stress, current neurobiological evidence supporting its use for the objective assessment of psychological health, stress, and fatigue [486].

Neglected since the last guidelines published in 1996 by The Task Force of the ESC and The North American Society of Pacing and Electrophysiology, HRV represents a reliable marker of cardiac function [487]. In the last decade, researchers revisited the idea of HRV measurement, as it could help to monitor vital signs, stress levels, and fatigue using adapted sensors, which are supported by technological progress.

Moreover, it seems that HRV could have important clinical implications in various pathological conditions involving the heart, the brain, or the kidney [488, 489].

During 2021, me and our team already published three papers, as follows:

1. **Burlacu A.**, Brinza C., Popa IV., Covic A., Floria M. *Influencing Cardiovascular Outcomes through Heart Rate Variability Modulation: A Systematic Review*. Diagnostics 2021, *11*(12), 2198; https://doi.org/10.3390/diagnostics11122198
   [Impact Factor: 3.706]
2. Brinza C., Floria M., Covic A., **Burlacu A.** *Measuring Heart Rate Variability in Patients Admitted with ST-Elevation Myocardial Infarction for the Prediction of Subsequent Cardiovascular Events: A Systematic Review***.** Medicina 2021, 57(10), 1021; https://doi.org/10.3390/medicina57101021
   [Impact Factor: 2.430]
3. **Burlacu A**., Brinza C., Brezulianu A., Covic A. Accurate and early detection of sleepiness, fatigue and stress levels in drivers through Heart Rate Variability parameters: a systematic review. Rev. Cardiovasc. Med. 2021, 22(3), 845–852; https://doi.org/10.31083/j.rcm2203090
   [Impact Factor: 2.930]

My next project is "*The Usefulness of Assessing Heart Rate Variability in Patients With Acute Myocardial Infarction (HeaRt-V-AMI)*." This study protocol was registered in the ClinicalTrials.gov registry (NCT05098977). https://clinicaltrials.gov/ct2/show/NCT05098977

and published in the *Sensors* 2022, 22(9), 3571 https://doi.org/10.3390/s22093571 [Impact Factor: 3.576].

To date, HRV proves to be an excellent prognostic element for mortality in patients with acute myocardial infarction or end-stage kidney disease. Previous research showed it could have independent and critical prognostic values in patients admitted for STEMI. There are limited data in the literature regarding HRV assessment and utility in STEMI setting. Thus, we aim to investigate the potential correlations between HRV and adverse outcomes in a contemporary cohort of patients presenting with STEMI undergoing primary percutaneous coronary intervention.

We will perform a **prospective, observational cohort study** in a single healthcare center. Adult patients aged ≥ 18 years presenting with STEMI in sinus rhythm will be enrolled for primary PCI within 12 hours from symptoms onset. HRV will be assessed in addition to the medical and interventional therapy for myocardial infarction according to the latest ESC guidelines.

The objectives of our study are:

1) **HRV measurement in patients presenting with STEMI revascularized by primary PCI using a wearable medical device**;

2) Correlation assessment between HRV and short- and long-term adverse clinical events, including different subgroups of patients (chronic kidney disease, diabetes mellitus, elderly);

3) Development of a registry which will include HRV parameters measured in a contemporary cohort of patients with STEMI.

Time-domain, frequency-domain, and non-linear HRV parameters will be measured using a medically approved wrist-wearable device on 5-minute segments during myocardial revascularization by primary PCI.

Additional HRV measurements will be performed at one- and six months from the index event. We will evaluate the envisioned correlations between HRV parameters and pre-specified primary and secondary outcomes. The primary composite outcome will include all-cause mortality and MACE (during the hospital stay, at one month, and one year following the admission). Several secondary outcomes will be analyzed: individual components of the primary composite outcome, target lesion revascularization, hospitalizations for HF, ventricular arrhythmias, LVEF, and LV diastolic function.

We aim to disseminate the results in the scientific medical community through publishing articles in journals with appropriate objectives and scope. Also, the results will be presented at national or international medical conferences.

HRV was established as a prognostic marker in the case of patients with end-stage kidney disease undergoing hemodialysis. In this regard, a recent meta-analysis showed increased all-cause mortality (HR 1.63, 95% CI, 1.11 – 2.39) linked, mainly, to lower Standard Deviation of the Averages of NN (Normal Sinus to Normal Sinus) (SDANN) and Low Frequency to High Frequency (LF/HF) ratio values [490]. Similar results are expected to be documented in the case of patients presenting with STEMI.

3.3. Challenging the supremacy of evidence-based medicine through Artificial Intelligence: changing paradigms

The third direction of research (besides the concerns of the EuDial, and HRV) is the use of Artificial Intelligence in medicine.

There are already several publications from our group in this field and my desire is to develop in this direction as well.

1. **Burlacu A**., Iftene A., Busoiu E., Cogean D., Covic A. *Challenging the supremacy of evidence-based medicine through artificial intelligence: the time has come for a change of paradigms.* Nephrology Dialysis Transplantation, Volume 35, Issue 2, February 2020, Pages 191–194, https://doi.org/10.1093/ndt/gfz203
   [Impact Factor: 5.992]
2. **Burlacu A.**, Iftene A., Popa IV., Crisan-Dabija R., Brinza C., Covic A. *Computational Models Used to Predict Cardiovascular Complications in Chronic Kidney Disease Patients: A Systematic Review.* Medicina 2021, 57(6), 538; https://doi.org/10.3390/medicina57060538
   [Impact Factor: 2.430]
3. **Burlacu A.**, Iftene A., Jugrin D., Popa IV., Lupu PM., Vlad C., Covic A., *Using Artificial Intelligence Resources in Dialysis and Kidney Transplant Patients: A Literature Review*. Biomed Res Int 2020 Jun 10;2020:9867872 https://doi.org/10.1155/2020/9867872
   [Impact Factor: 3.411]
4. Popa IV., **Burlacu A.**, Gavrilescu O., Dranga M., Cijevschi C., Mihai C. *A new approach to predict ulcerative colitis activity through standard clinical-biological parameters using a robust neural network model*. Neural Computing and Applications (2021) 33:14133–14146 https://doi.org/10.1007/s00521-021-06055-x
   [Impact Factor: 5.606]
5. Popa IV., Diculescu M., Mihai C., Prelipcean C., **Burlacu A**. *Developing a Neural Network Model for a Non-invasive Prediction of Histologic Activity in Inflammatory Bowel Disease.* Turk J Gastroenterol 2021 Mar;32(3):276-286. https://doi.org/10.5152/tjg.2021.20420
   [Impact Factor: 1.852]
6. Popa IV., **Burlacu A**., Mihai C., Cijevschi-Prelipcean C. *A Machine Learning Model Accurately Predicts Ulcerative Colitis Activity at One Year in Patients Treated with Anti-Tumour Necrosis Factor α Agents*. Medicina (Kaunas) 2020 Nov 20;56(11):628. https://doi.org/10.3390/medicina56110628
   [Impact Factor: 2.430]

Nowadays, each European Medical Society (e.g., nephrology or cardiology) adopts additional Clinical Guidelines that are produced by subject-matter specialists and regularly updated with fresh data from medical databases and published literature [491]. All of these Guidelines commence their texts with two Tables: the classes of recommendations and the levels of evidence [492]. According to the definition, Evidence-Based Medicine is the practice of integrating clinical expertise, patient values, and the best available evidence into health care decision-making. The greatest scientific evidence is defined as data generated from many RCTs

or meta-analyses done on populations and demonstrating the efficacy of a specific (new) treatment / intervention, as well as the harm and inefficacy of others in compared to the best available therapy [493].

A relevant example is that the majority of RCTs on antithrombotic medicine (anticoagulant and antiplatelet treatment) in patients with ACS, post-PCI, AF, or both, excluded patients with severe CKD [494]. Additionally, none of the risk ratings (for bleeding or ischemic events) has been verified in the G5D-CKD group, resulting in a dearth of medical data to support particular recommendations [87, 495]. In other words, in the twenty-first century, the majority of advanced CKD patients are treated with antithrombotics (antiplatelets or anticoagulant combos) on the basis of observational studies or expert position statements [495]. Many of the most anticipated RCTs will undoubtedly be postponed for many years due to ethical or practical concerns.

On the other hand, employing a variety of data sources (experimental, environmental, clinical, biological, or wearable devices), particular "*machine learning algorithms*" might and would be used to make medical diagnostic or therapeutic decisions (ensemble decision trees, support vector machines, neural networks, deep learning and topological data analysis) [496].

In this way, in our specific case, physicians will be provided with new bleeding risk algorithms based on a) "*Big Data*" [497] a phrase describing a massive volume of both structured and unstructured data, an assemblage of vast information that it is difficult to process using traditional database and software techniques [498]; Big Data main characteristics are: volume, velocity, variety, variability and complexity [499]), and b) Decision Pathways generated by AI algorithms (not by RCTs-derived evidence).

Indeed, the responses provided by such algorithms will be really personalized for each patient in a manner that a Guideline cannot. For example, the current Cardiology and Nephrology Guidelines lack the authority to provide evidence (or even advice) on how to treat an 80-year-old woman with G5D-CKD, chronic AF, and a recent primary PCI (because bleeding / thrombotic risk scores do not apply in this context, and the existing antithrombotics lack study-based evidence in a "*triple association*" at this age and advanced kidney disease on dialysis) [494].

In this very specialized context, a sophisticated AI system will identify bleeding patterns and forecast (in a novel and "deep" manner) whether or not this woman would experience serious side effects when given certain medicine combinations. In other words, the medical community will be supplied not only (limited) "RCT data," but also enhanced (and self-improving) AI tools with increased accuracy and predictive capacity. The scientific community's attention will shift away from evidence generation and toward building self-learning and pattern-detection AI solutions.

SECTION IV. References

1. Díez, J. and A. Ortiz, *The Need For A Cardio-Nephrology Subspecialty.* Clinical Kidney Journal, 2021.
2. Ronco, C., F. Ronco, and P.A. McCullough, *A Call to Action to Develop Integrated Curricula in Cardiorenal Medicine.* Blood Purification, 2017. **44**(4): p. 251-259.
3. Kittleson, M., J. Patel, J. Kobashigawa, V. Fuster, R. Harrington, J. Narula, and Z. Eapen, *Hurst's the Heart.* 2017.
4. Hardy, A., *A New Chapter in Medical History.* The Journal of Interdisciplinary History, 2009. **39**(3): p. 349-359.
5. Telleman, H., T.F. Burger, and C.J.J. Mulder, *Evolution of gastroenterology training.* World journal of gastroenterology, 2009. **15**(15): p. 1793-1798.
6. Williamson, J., *Three views on geriatric medicine: 3: Notes on the historical development of geriatric medicine as a medical speciality.* Age and Ageing, 1979. **8**(3): p. 144-148.
7. Sacha, J., M. Gierlotka, P. Lipski, P. Feusette, and D. Dudek, *Zero-contrast percutaneous coronary interventions to preserve kidney function in patients with severe renal impairment and hemodialysis subjects.* Postepy w kardiologii interwencyjnej = Advances in interventional cardiology, 2019. **15**(2): p. 137-142.
8. Bhatti, N.K., K.K. Galougahi, Y. Paz, T. Nazif, J.W. Moses, M.B. Leon, G.W. Stone, A.J. Kirtane, D. Karmpaliotis, S. Bokhari, et al., *Diagnosis and Management of Cardiovascular Disease in Advanced and End-Stage Renal Disease.* Journal of the American Heart Association, 2016. **5**(8): p. e003648.
9. Rangaswami, J., S. Soman, and P.A. McCullough, *Key Updates in Cardio-Nephrology from 2018: Springboard to a Bright Future.* Cardiorenal Medicine, 2019. **9**(4): p. 222-228.
10. Damman, K., G. Navis, A.A. Voors, F.W. Asselbergs, T.D. Smilde, J.G. Cleland, D.J. van Veldhuisen, and H.L. Hillege, *Worsening renal function and prognosis in heart failure: systematic review and meta-analysis.* J Card Fail, 2007. **13**(8): p. 599-608.
11. Damman, K., M.A. Valente, A.A. Voors, C.M. O'Connor, D.J. van Veldhuisen, and H.L. Hillege, *Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis.* Eur Heart J, 2014. **35**(7): p. 455-69.
12. Charytan, D.M., S.D. Solomon, P. Ivanovich, G. Remuzzi, M.E. Cooper, J.B. McGill, H.H. Parving, P. Parfrey, A.K. Singh, E.A. Burdmann, et al., *ESRD After Heart Failure, Myocardial Infarction, or Stroke in Type 2 Diabetic Patients With CKD.* Am J Kidney Dis, 2017. **70**(4): p. 522-531.
13. Sud, M., N. Tangri, M. Pintilie, A.S. Levey, and D.M. Naimark, *ESRD and death after heart failure in CKD.* J Am Soc Nephrol, 2015. **26**(3): p. 715-22.
14. Sud, M., N. Tangri, M. Pintilie, A.S. Levey, and D. Naimark, *Risk of end-stage renal disease and death after cardiovascular events in chronic kidney disease.* Circulation, 2014. **130**(6): p. 458-65.
15. Ishigami, J., L.T. Cowan, R.T. Demmer, M.E. Grams, P.L. Lutsey, J.J. Carrero, J. Coresh, and K. Matsushita, *Incident Hospitalization with Major Cardiovascular Diseases and*

Subsequent Risk of ESKD: Implications for Cardiorenal Syndrome. J Am Soc Nephrol, 2020. **31**(2): p. 405-414.

16. Kajimoto, K., N. Sato, T. Keida, Y. Sakata, and T. Takano, *Associations of anemia and renal dysfunction with outcomes among patients hospitalized for acute decompensated heart failure with preserved or reduced ejection fraction.* Clin J Am Soc Nephrol, 2014. **9**(11): p. 1912-21.
17. Tong, J., M. Liu, H. Li, Z. Luo, X. Zhong, J. Huang, R. Liu, F. He, and J. Fu, *Mortality and Associated Risk Factors in Dialysis Patients with Cardiovascular Disease.* Kidney and Blood Pressure Research, 2016. **41**(4): p. 479-487.
18. Szymanski, M.K., R.A. de Boer, G.J. Navis, W.H. van Gilst, and H.L. Hillege, *Animal models of cardiorenal syndrome: a review.* Heart Fail Rev, 2012. **17**(3): p. 411-20.
19. Testani, J.M., J. Chen, B.D. McCauley, S.E. Kimmel, and R.P. Shannon, *Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival.* Circulation, 2010. **122**(3): p. 265-72.
20. Ritz, E. and A. Remppis, *What have nephrologists and cardiologists learnt from each other?* Nature Clinical Practice Nephrology, 2009. **5**(1): p. 1-1.
21. Ponikowski, P., C. Ronco, and S.D. Anker, *Cardiorenal syndromes–recommendations from clinical practice guidelines: the cardiologist's view*, in *Cardiorenal Syndromes in Critical Care*. 2010, Karger Publishers. p. 145-152.
22. Rangaswami, J., S. Soman, and P.A. McCullough, *Key updates in Cardio-Nephrology from 2018: springboard to a bright Future.* Rev Cardiovasc Med, 2018. **19**(4): p. 113-116.
23. Rangaswami, J., E.V. Lerma, and C. Ronco, *Cardio-nephrology: confluence of the heart and kidney in clinical practice*. 2017: Springer.
24. Burlacu, A., S. Genovesi, A. Ortiz, C. Combe, C. Basile, D. Schneditz, F. van der Sande, G.T. Popa, C. Morosanu, A. Covic, et al., *Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update.* Nephrology Dialysis Transplantation, 2019. **34**(6): p. 923-933.
25. Sankaranarayanan, R., H. Douglas, and C. Wong, *Cardio-nephrology MDT meetings play an important role in the management of cardiorenal syndrome.* Br J Cardiol, 2020. **27**: p. 80-82.
26. Bayliss, E.A., B. Bhardwaja, C. Ross, A. Beck, and D.M. Lanese, *Multidisciplinary team care may slow the rate of decline in renal function.* Clin J Am Soc Nephrol, 2011. **6**(4): p. 704-10.
27. Burlacu, A., A. Covic, M. Cinteza, P.M. Lupu, R. Deac, and G. Tinica, *Exploring Current Evidence on the Past, the Present, and the Future of the Heart Team: A Narrative Review.* Cardiovascular therapeutics, 2020. **2020**: p. 9241081-9241081.
28. Kornowski, R. and G. Witberg, *The pros and cons of the Heart Team.* Future Cardiology, 2019. **15**(4): p. 255-258.
29. McDougall, A., M. Goldszmidt, E.A. Kinsella, S. Smith, and L. Lingard, *Collaboration and entanglement: An actor-network theory analysis of team-based intraprofessional care for patients with advanced heart failure.* Social science & medicine (1982), 2016. **164**: p. 108-117.

30. Tsang, M.B., J.D. Schwalm, S. Gandhi, M.G. Sibbald, A. Gafni, M. Mercuri, O. Salehian, A. Lamy, D. Pericak, S. Jolly, et al., *Comparison of Heart Team vs Interventional Cardiologist Recommendations for the Treatment of Patients With Multivessel Coronary Artery Disease.* JAMA Network Open, 2020. **3**(8): p. e2012749-e2012749.
31. Coylewright, M., M.J. Mack, D.R. Holmes, and P.T. O'Gara, *A Call for an Evidence-Based Approach to the Heart Team for Patients With Severe Aortic Stenosis.* Journal of the American College of Cardiology, 2015. **65**(14): p. 1472-1480.
32. Bruckel, J.T., H.S. Gurm, M. Seth, R.L. Prager, A. Jensen, and B.K. Nallamothu, *Use of a Heart Team in Decision-Making for Patients with Complex Coronary Disease at Hospitals in Michigan Prior to Guideline Endorsement.* PLOS ONE, 2014. **9**(11): p. e113241.
33. McCullough, P.A. and J. Rangaswami, *Real or Perceived: Hyperkalemia Is a Major Deterrent for Renin-Angiotensin Aldosterone System Inhibition in Heart Failure.* Nephron, 2018. **138**(3): p. 173-175.
34. Oliveros, E., E.T. Oni, A. Shahzad, A.Y. Kluger, K.B. Lo, J. Rangaswami, and P.A. McCullough, *Benefits and Risks of Continuing Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Antagonists, and Mineralocorticoid Receptor Antagonists during Hospitalizations for Acute Heart Failure.* Cardiorenal Med, 2020. **10**(2): p. 69-84.
35. Singhania, G., A.A. Ejaz, P.A. McCullough, A.Y. Kluger, S. Balamuthusamy, B. Dass, N. Singhania, and A. Agarwal, *Continuation of Chronic Heart Failure Therapies During Heart Failure Hospitalization - a Review.* Rev Cardiovasc Med, 2019. **20**(3): p. 111-120.
36. Epstein, M., N.L. Reaven, S.E. Funk, K.J. McGaughey, N. Oestreicher, and J. Knispel, *Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors.* Am J Manag Care, 2015. **21**(11 Suppl): p. S212-20.
37. Edner, M., L. Benson, U. Dahlström, and L.H. Lund, *Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study.* Eur Heart J, 2015. **36**(34): p. 2318-26.
38. Pitt, B., S.D. Anker, D.A. Bushinsky, D.W. Kitzman, F. Zannad, and I.Z. Huang, *Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial.* Eur Heart J, 2011. **32**(7): p. 820-8.
39. Tomson, C. and L.A. Tomlinson, *Stopping RAS Inhibitors to Minimize AKI.* Clinical Journal of the American Society of Nephrology, 2019. **14**(4): p. 617.
40. Medić, B., B. Rovcanin, K.S. Vujovic, D. Obradovic, D. Duric, and M. Prostran, *Evaluation of Novel Biomarkers of Acute Kidney Injury: The Possibilities and Limitations.* Curr Med Chem, 2016. **23**(19): p. 1981-97.
41. Patil, V.P. and B.G. Salunke, *Fluid Overload and Acute Kidney Injury.* Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine, 2020. **24**(Suppl 3): p. S94-S97.

42. Beker, B.M., M.G. Corleto, C. Fieiras, and C.G. Musso, *Novel acute kidney injury biomarkers: their characteristics, utility and concerns.* Int Urol Nephrol, 2018. **50**(4): p. 705-713.
43. Sarnak, M.J., K. Amann, S. Bangalore, J.L. Cavalcante, D.M. Charytan, J.C. Craig, J.S. Gill, M.A. Hlatky, A.G. Jardine, U. Landmesser, et al., *Chronic Kidney Disease and Coronary Artery Disease.* Journal of the American College of Cardiology, 2019. **74**(14): p. 1823.
44. Manjunath, G., H. Tighiouart, H. Ibrahim, B. MacLeod, D.N. Salem, J.L. Griffith, J. Coresh, A.S. Levey, and M.J. Sarnak, *Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community.* J Am Coll Cardiol, 2003. **41**(1): p. 47-55.
45. Saran, R., B. Robinson, K.C. Abbott, L.Y.C. Agodoa, J. Bragg-Gresham, R. Balkrishnan, N. Bhave, X. Dietrich, Z. Ding, P.W. Eggers, et al., *US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States.* Am J Kidney Dis, 2019. **73**(3s1): p. A7-a8.
46. Nakano, T., T. Ninomiya, S. Sumiyoshi, H. Fujii, Y. Doi, H. Hirakata, K. Tsuruya, M. Iida, Y. Kiyohara, and K. Sueishi, *Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study.* Am J Kidney Dis, 2010. **55**(1): p. 21-30.
47. Herzog, C.A., K. Littrell, C. Arko, P.D. Frederick, and M. Blaney, *Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction.* Circulation, 2007. **116**(13): p. 1465-72.
48. Charytan, D. and R.E. Kuntz, *The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease.* Kidney Int, 2006. **70**(11): p. 2021-30.
49. Hammes, M.S., *Medical complications in hemodialysis patients requiring vascular access radiology procedures.* Semin Intervent Radiol, 2004. **21**(2): p. 105-10.
50. Shroff, G.R. and C.A. Herzog, *Acute myocardial infarction in patients with chronic kidney disease: how are the most vulnerable patients doing?* Kidney International, 2013. **84**(2): p. 230-233.
51. Ortiz, A., A. Covic, D. Fliser, D. Fouque, D. Goldsmith, M. Kanbay, F. Mallamaci, Z.A. Massy, P. Rossignol, R. Vanholder, et al., *Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure.* Lancet, 2014. **383**(9931): p. 1831-43.
52. Knuuti, J., W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, E. Prescott, R.F. Storey, C. Deaton, T. Cuisset, et al., *2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC).* European Heart Journal, 2019. **41**(3): p. 407-477.
53. Members, T.F., G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, A. Budaj, R. Bugiardini, F. Crea, T. Cuisset, et al., *2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology.* European Heart Journal, 2013. **34**(38): p. 2949-3003.

54. Knuuti, J., W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, E. Prescott, R.F. Storey, C. Deaton, T. Cuisset, et al., *2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.* Eur Heart J, 2019.
55. Herzog, C.A., R.W. Asinger, A.K. Berger, D.M. Charytan, J. Diez, R.G. Hart, K.U. Eckardt, B.L. Kasiske, P.A. McCullough, R.S. Passman, et al., *Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO).* Kidney Int, 2011. **80**(6): p. 572-86.
56. Bhatti, N.K., K. Karimi Galougahi, Y. Paz, T. Nazif, J.W. Moses, M.B. Leon, G.W. Stone, A.J. Kirtane, D. Karmpaliotis, S. Bokhari, et al., *Diagnosis and Management of Cardiovascular Disease in Advanced and End-Stage Renal Disease.* J Am Heart Assoc, 2016. **5**(8).
57. Maron, D.J., J.S. Hochman, H.R. Reynolds, S. Bangalore, S.M. O'Brien, W.E. Boden, B.R. Chaitman, R. Senior, J. López-Sendón, K.P. Alexander, et al., *Initial Invasive or Conservative Strategy for Stable Coronary Disease.* N Engl J Med, 2020. **382**(15): p. 1395-1407.
58. Shroff, G.R., P.D. Frederick, and C.A. Herzog, *Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction.* Am Heart J, 2012. **163**(3): p. 399-406.
59. Yang, H., J. Liu, H. Luo, X. Zeng, X. Tang, L. Ma, H. Mai, S. Gou, F. Liu, and P. Fu, *Improving the diagnostic accuracy of acute myocardial infarction with the use of high-sensitive cardiac troponin T in different chronic kidney disease stages.* Sci Rep, 2017. **7**: p. 41350.
60. Shroff, G.R., S. Li, and C.A. Herzog, *Trends in Mortality Following Acute Myocardial Infarction Among Dialysis Patients in the United States Over 15 Years.* J Am Heart Assoc, 2015. **4**(10): p. e002460.
61. Bhatia, S., S. Arora, S.M. Bhatia, M. Al-Hijji, Y.N.V. Reddy, P. Patel, C.S. Rihal, B.J. Gersh, and A. Deshmukh, *Non-ST-Segment-Elevation Myocardial Infarction Among Patients With Chronic Kidney Disease: A Propensity Score-Matched Comparison of Percutaneous Coronary Intervention Versus Conservative Management.* J Am Heart Assoc, 2018. **7**(6).
62. Bavry, A.A., D.J. Kumbhani, A.N. Rassi, D.L. Bhatt, and A.T. Askari, *Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials.* J Am Coll Cardiol, 2006. **48**(7): p. 1319-25.
63. Fox, K.A., T.C. Clayton, P. Damman, S.J. Pocock, R.J. de Winter, J.G. Tijssen, B. Lagerqvist, and L. Wallentin, *Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data.* J Am Coll Cardiol, 2010. **55**(22): p. 2435-45.
64. Shaw, C., D. Nitsch, J. Lee, D. Fogarty, and C.C. Sharpe, *Impact of an Early Invasive Strategy versus Conservative Strategy for Unstable Angina and Non-ST Elevation Acute Coronary Syndrome in Patients with Chronic Kidney Disease: A Systematic Review.* PLoS One, 2016. **11**(5): p. e0153478.

65. Ismail, M.D., M. Jalalonmuhali, Z. Azhari, J. Mariapun, Z.V. Lee, I. Zainal Abidin, W.A. Wan Ahmad, and A.S.M. Zuhdi, *Outcomes of STEMI patients with chronic kidney disease treated with percutaneous coronary intervention: the Malaysian National Cardiovascular Disease Database - Percutaneous Coronary Intervention (NCVD-PCI) registry data from 2007 to 2014.* BMC Cardiovasc Disord, 2018. **18**(1): p. 184.
66. Ibanez, B., S. James, S. Agewall, M.J. Antunes, C. Bucciarelli-Ducci, H. Bueno, A.L.P. Caforio, F. Crea, J.A. Goudevenos, S. Halvorsen, et al., *2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC).* Eur Heart J, 2018. **39**(2): p. 119-177.
67. Burlacu, A., B. Artene, and A. Covic, *A Narrative Review on Thrombolytics in Advanced CKD: Is it an Evidence-Based Therapy?* Cardiovasc Drugs Ther, 2018. **32**(5): p. 463-475.
68. Newsome, B.B., D.G. Warnock, C.I. Kiefe, N.W. Weissman, T.K. Houston, R.M. Centor, S.D. Person, W.M. McClellan, and J.J. Allison, *Delay in time to receipt of thrombolytic medication among Medicare patients with kidney disease.* Am J Kidney Dis, 2005. **46**(4): p. 595-602.
69. Park, S.H., W. Kim, C.S. Park, W.Y. Kang, S.H. Hwang, and W. Kim, *A comparison of clopidogrel responsiveness in patients with versus without chronic renal failure.* Am J Cardiol, 2009. **104**(9): p. 1292-5.
70. Jeong, K.H., J.H. Cho, J.S. Woo, J.B. Kim, W.S. Kim, T.W. Lee, K.S. Kim, C.G. Ihm, and W. Kim, *Platelet reactivity after receiving clopidogrel compared with ticagrelor in patients with kidney failure treated with hemodialysis: a randomized crossover study.* Am J Kidney Dis, 2015. **65**(6): p. 916-24.
71. Costa, F., D. van Klaveren, S. James, D. Heg, L. Raber, F. Feres, T. Pilgrim, M.K. Hong, H.S. Kim, A. Colombo, et al., *Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials.* Lancet, 2017. **389**(10073): p. 1025-1034.
72. McCullough, P.A. and R.C. Maynard, *Treatment disparities in acute coronary syndromes, heart failure, and kidney disease.* Contrib Nephrol, 2011. **171**: p. 68-73.
73. Schiffrin, E.L., M.L. Lipman, and J.F. Mann, *Chronic kidney disease: effects on the cardiovascular system.* Circulation, 2007. **116**(1): p. 85-97.
74. Patel, B., M. Shah, R. Dusaj, S. Maynard, and N. Patel, *Percutaneous coronary intervention and inpatient mortality in patients with advanced chronic kidney disease presenting with acute coronary syndrome.* Proc (Bayl Univ Med Cent), 2017. **30**(4): p. 400-403.
75. Ohtake, T., S. Kobayashi, H. Moriya, K. Negishi, K. Okamoto, K. Maesato, and S. Saito, *High Prevalence of Occult Coronary Artery Stenosis in Patients with Chronic Kidney Disease at the Initiation of Renal Replacement Therapy: An Angiographic Examination.* Journal of the American Society of Nephrology, 2005. **16**(4): p. 1141-1148.
76. Becker, R.C. and T. Helmy, *Are at Least 12 Months of Dual Antiplatelet Therapy Needed for All Patients With Drug-Eluting Stents?* Circulation, 2015. **131**(22): p. 2010-2019.

77. Galiffa, V.A., G. Crimi, V. Gritti, V. Scotti, M. Ferrario, A. Repetto, M. Ferlini, B. Marinoni, G.M. De Ferrari, S. De Servi, et al., *Drug-eluting compared to bare metal stents in patients with end-stage renal disease on dialysis: a meta-analysis.* Journal of cardiovascular medicine (Hagerstown, Md.), 2019. **20**(5): p. 313-320.
78. Lee, H.-F., L.-S. Wu, Y.-H. Chan, C.-H. Lee, J.-R. Liu, H.-T. Tu, M.-S. Wen, C.-T. Kuo, W.-J. Chen, Y.-H. Yeh, et al., *Dialysis Patients with Implanted Drug-Eluting Stents Have Lower Major Cardiac Events and Mortality than Those with Implanted Bare-Metal Stents: A Taiwanese Nationwide Cohort Study.* PloS one, 2016. **11**(1): p. e0146343-e0146343.
79. Bangalore, S., D.J. Maron, S.M. O'Brien, J.L. Fleg, E.I. Kretov, C. Briguori, U. Kaul, H.R. Reynolds, T. Mazurek, M.S. Sidhu, et al., *Management of Coronary Disease in Patients with Advanced Kidney Disease.* New England Journal of Medicine, 2020. **382**(17): p. 1608-1618.
80. Boden, W.E., R.A. O'Rourke, K.K. Teo, P.M. Hartigan, D.J. Maron, W.J. Kostuk, M. Knudtson, M. Dada, P. Casperson, C.L. Harris, et al., *Optimal medical therapy with or without PCI for stable coronary disease.* N Engl J Med, 2007. **356**(15): p. 1503-16.
81. Howard, C.E., V. Nambi, H. Jneid, and U. Khalid, *Extended Duration of Dual‐Antiplatelet Therapy After Percutaneous Coronary Intervention: How Long Is Too Long?* Journal of the American Heart Association, 2019. **8**(20): p. e012639.
82. Park, S., Y. Kim, H.A. Jo, S. Lee, M.-S. Kim, B.R. Yang, J. Lee, S.S. Han, H. Lee, J.P. Lee, et al., *Clinical outcomes of prolonged dual antiplatelet therapy after coronary drug-eluting stent implantation in dialysis patients.* Clinical kidney journal, 2020. **13**(5): p. 803-812.
83. Valgimigli, M., H. Bueno, R.A. Byrne, J.-P. Collet, F. Costa, A. Jeppsson, P. Jüni, A. Kastrati, P. Kolh, L. Mauri, et al., *2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS).* European heart journal, 2018. **39**(3): p. 213-260.
84. Giustino, G., A. Chieffo, T. Palmerini, M. Valgimigli, F. Feres, A. Abizaid, R.A. Costa, M.-K. Hong, B.-K. Kim, Y. Jang, et al., *Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI.* Journal of the American College of Cardiology, 2016. **68**(17): p. 1851-1864.
85. Mavrakanas, T.A., Y.S. Chatzizisis, K. Gariani, D.J. Kereiakes, G. Gargiulo, G. Helft, M. Gilard, F. Feres, R.A. Costa, M.-C. Morice, et al., *Duration of Dual Antiplatelet Therapy in Patients with CKD and Drug-Eluting Stents: A Meta-Analysis.* Clinical journal of the American Society of Nephrology : CJASN, 2019. **14**(6): p. 810-822.
86. Regitz-Zagrosek, V., J.W. Roos-Hesselink, J. Bauersachs, C. Blomström-Lundqvist, R. Cífková, M. De Bonis, B. Iung, M.R. Johnson, U. Kintscher, P. Kranke, et al., *2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC).* European Heart Journal, 2018. **39**(34): p. 3165-3241.

87. Covic, A., S. Genovesi, P. Rossignol, P.A. Kalra, A. Ortiz, M. Banach, and A. Burlacu, *Practical issues in clinical scenarios involving CKD patients requiring antithrombotic therapy in light of the 2017 ESC guideline recommendations.* BMC Med, 2018. **16**(1): p. 158.
88. Saran, R., B. Robinson, K.C. Abbott, L.Y. Agodoa, P. Albertus, J. Ayanian, R. Balkrishnan, J. Bragg-Gresham, J. Cao, J.L. Chen, et al., *US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States.* Am J Kidney Dis, 2017. **69**(3 Suppl 1): p. A7-a8.
89. Burlacu, A., S. Genovesi, A. Ortiz, M. Kanbay, P. Rossignol, M. Banach, J. Malyszko, D. Goldsmith, and A. Covic, *The quest for equilibrium: exploring the thin red line between bleeding and ischaemic risks in the management of acute coronary syndromes in chronic kidney disease patients.* Nephrol Dial Transplant, 2017. **32**(12): p. 1967-1976.
90. Verma, A., J.A. Cairns, L.B. Mitchell, L. Macle, I.G. Stiell, D. Gladstone, M.S. McMurtry, S. Connolly, J.L. Cox, P. Dorian, et al., *2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation.* Can J Cardiol, 2014. **30**(10): p. 1114-30.
91. Steffel, J., P. Verhamme, T.S. Potpara, P. Albaladejo, M. Antz, L. Desteghe, K.G. Haeusler, J. Oldgren, H. Reinecke, V. Roldan-Schilling, et al., *The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation.* Eur Heart J, 2018. **39**(16): p. 1330-1393.
92. Turakhia, M.P., P.J. Blankestijn, J.J. Carrero, C.M. Clase, R. Deo, C.A. Herzog, S.E. Kasner, R.S. Passman, R. Pecoits-Filho, H. Reinecke, et al., *Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.* Eur Heart J, 2018. **39**(24): p. 2314-2325.
93. McAlister, F.A., N. Wiebe, M. Jun, R. Sandhu, M.T. James, M.S. McMurtry, B.R. Hemmelgarn, and M. Tonelli, *Are Existing Risk Scores for Nonvalvular Atrial Fibrillation Useful for Prediction or Risk Adjustment in Patients With Chronic Kidney Disease?* Can J Cardiol, 2017. **33**(2): p. 243-252.
94. Friberg, L., L. Benson, and G.Y. Lip, *Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study.* Eur Heart J, 2015. **36**(5): p. 297-306.
95. Hart, R.G., O. Benavente, R. McBride, and L.A. Pearce, *Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis.* Ann Intern Med, 1999. **131**(7): p. 492-501.
96. Bonde, A.N., G.Y. Lip, A.L. Kamper, P.R. Hansen, M. Lamberts, K. Hommel, M.L. Hansen, G.H. Gislason, C. Torp-Pedersen, and J.B. Olesen, *Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study.* J Am Coll Cardiol, 2014. **64**(23): p. 2471-82.
97. Chan, K.E., J.M. Lazarus, R. Thadhani, and R.M. Hakim, *Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation.* J Am Soc Nephrol, 2009. **20**(10): p. 2223-33.
98. Wizemann, V., L. Tong, S. Satayathum, A. Disney, T. Akiba, R.B. Fissell, P.G. Kerr, E.W. Young, and B.M. Robinson, *Atrial fibrillation in hemodialysis patients: clinical*

features and associations with anticoagulant therapy. Kidney Int, 2010. **77**(12): p. 1098-106.

99. Genovesi, S., P. Rebora, M. Gallieni, A. Stella, F. Badiali, F. Conte, S. Pasquali, S. Bertoli, P. Ondei, G. Bonforte, et al., *Effect of oral anticoagulant therapy on mortality in end-stage renal disease patients with atrial fibrillation: a prospective study.* J Nephrol, 2017. **30**(4): p. 573-581.
100. Hart, R.G., L.A. Pearce, R.W. Asinger, and C.A. Herzog, *Warfarin in atrial fibrillation patients with moderate chronic kidney disease.* Clin J Am Soc Nephrol, 2011. **6**(11): p. 2599-604.
101. Carrero, J.J., M. Evans, K. Szummer, J. Spaak, L. Lindhagen, R. Edfors, P. Stenvinkel, S.H. Jacobson, and T. Jernberg, *Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation.* Jama, 2014. **311**(9): p. 919-28.
102. Olesen, J.B., G.Y. Lip, A.L. Kamper, K. Hommel, L. Kober, D.A. Lane, J. Lindhardsen, G.H. Gislason, and C. Torp-Pedersen, *Stroke and bleeding in atrial fibrillation with chronic kidney disease.* N Engl J Med, 2012. **367**(7): p. 625-35.
103. Chan, P.H., D. Huang, P.S. Yip, J. Hai, H.F. Tse, T.M. Chan, G.Y. Lip, W.K. Lo, and C.W. Siu, *Ischaemic stroke in patients with atrial fibrillation with chronic kidney disease undergoing peritoneal dialysis.* Europace, 2016. **18**(5): p. 665-71.
104. Kai, B., Y. Bogorad, L.N. Nguyen, S.J. Yang, W. Chen, H.T. Spencer, A.Y. Shen, and M.S. Lee, *Warfarin use and the risk of mortality, stroke, and bleeding in hemodialysis patients with atrial fibrillation.* Heart Rhythm, 2017. **14**(5): p. 645-651.
105. Dahal, K., S. Kunwar, J. Rijal, P. Schulman, and J. Lee, *Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease: A Meta-Analysis of Observational Studies.* Chest, 2016. **149**(4): p. 951-9.
106. Winkelmayer, W.C., J. Liu, A.R. Patrick, S. Setoguchi, and N.K. Choudhry, *Prevalence of atrial fibrillation and warfarin use in older patients receiving hemodialysis.* J Nephrol, 2012. **25**(3): p. 341-53.
107. Shen, J.I., M.E. Montez-Rath, C.R. Lenihan, M.P. Turakhia, T.I. Chang, and W.C. Winkelmayer, *Outcomes After Warfarin Initiation in a Cohort of Hemodialysis Patients With Newly Diagnosed Atrial Fibrillation.* Am J Kidney Dis, 2015. **66**(4): p. 677-88.
108. Genovesi, S., E. Rossi, M. Gallieni, A. Stella, F. Badiali, F. Conte, S. Pasquali, S. Bertoli, P. Ondei, G. Bonforte, et al., *Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation.* Nephrol Dial Transplant, 2015. **30**(3): p. 491-8.
109. Potpara, T.S., C.J. Ferro, and G.Y.H. Lip, *Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction.* Nat Rev Nephrol, 2018. **14**(5): p. 337-351.
110. Genovesi, S., A. Vincenti, E. Rossi, D. Pogliani, I. Acquistapace, A. Stella, and M.G. Valsecchi, *Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients.* Am J Kidney Dis, 2008. **51**(2): p. 255-62.
111. Tanios, B.Y., H.S. Itani, and D.L. Zimmerman, *Clopidogrel use in end-stage kidney disease.* Semin Dial, 2015. **28**(3): p. 276-81.
112. Brancaccio, D., L. Neri, F. Bellocchio, C. Barbieri, C. Amato, F. Mari, B. Canaud, and S. Stuard, *Patients' Characteristics Affect the Survival Benefit of Warfarin Treatment for*

Hemodialysis Patients with Atrial Fibrillation. A Historical Cohort Study. Am J Nephrol, 2016. **44**(4): p. 258-267.

113. Tan, J., S. Bae, J.B. Segal, J. Zhu, G.C. Alexander, D.L. Segev, and M. McAdams-DeMarco, *Warfarin Use And the Risk Of Stroke, Bleeding, And Mortality In Older Adults On Dialysis With Incident Atrial Fibrillation.* Nephrology (Carlton), 2017.
114. Jun, M., M.T. James, Z. Ma, J. Zhang, M. Tonelli, F.A. McAlister, B.J. Manns, P. Ravani, R.R. Quinn, N. Wiebe, et al., *Warfarin Initiation, Atrial Fibrillation, and Kidney Function: Comparative Effectiveness and Safety of Warfarin in Older Adults With Newly Diagnosed Atrial Fibrillation.* Am J Kidney Dis, 2017. **69**(6): p. 734-743.
115. Valgimigli, M., H. Bueno, R.A. Byrne, J.P. Collet, F. Costa, A. Jeppsson, P. Juni, A. Kastrati, P. Kolh, L. Mauri, et al., *2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS).* Eur Heart J, 2018. **39**(3): p. 213-260.
116. Fusaro, M., M. Gallieni, P. Rebora, M.A. Rizzo, M.C. Luise, H. Riva, S. Bertoli, F. Conte, A. Stella, P. Ondei, et al., *Atrial fibrillation and low vitamin D levels are associated with severe vascular calcifications in hemodialysis patients.* J Nephrol, 2016. **29**(3): p. 419-426.
117. Limdi, N.A., T.D. Nolin, S.L. Booth, A. Centi, M.B. Marques, M.R. Crowley, M. Allon, and T.M. Beasley, *Influence of kidney function on risk of supratherapeutic international normalized ratio-related hemorrhage in warfarin users: a prospective cohort study.* Am J Kidney Dis, 2015. **65**(5): p. 701-9.
118. Szummer, K., A. Gasparini, S. Eliasson, J. Arnlov, A.R. Qureshi, P. Barany, M. Evans, L. Friberg, and J.J. Carrero, *Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction.* J Am Heart Assoc, 2017. **6**(3).
119. Vaziri, N.D., J. Wong, M. Pahl, Y.M. Piceno, J. Yuan, T.Z. DeSantis, Z. Ni, T.H. Nguyen, and G.L. Andersen, *Chronic kidney disease alters intestinal microbial flora.* Kidney Int, 2013. **83**(2): p. 308-15.
120. Khoury, T., K. Tzukert, R. Abel, A. Abu Rmeileh, R. Levi, and Y. Ilan, *The gut-kidney axis in chronic renal failure: A new potential target for therapy.* Hemodial Int, 2017. **21**(3): p. 323-334.
121. Weijs, B., Y. Blaauw, R.J. Rennenberg, L.J. Schurgers, C.C. Timmermans, L. Pison, R. Nieuwlaat, L. Hofstra, A.A. Kroon, J. Wildberger, et al., *Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients.* Eur Heart J, 2011. **32**(20): p. 2555-62.
122. Cozzolino, M., D. Brancaccio, M. Gallieni, and E. Slatopolsky, *Pathogenesis of vascular calcification in chronic kidney disease.* Kidney Int, 2005. **68**(2): p. 429-36.
123. Bressendorff, I., D. Hansen, M. Schou, A. Pasch, and L. Brandi, *The Effect of Increasing Dialysate Magnesium on Serum Calcification Propensity in Subjects with End Stage Kidney Disease: A Randomized, Controlled Clinical Trial.* Clin J Am Soc Nephrol, 2018. **13**(9): p. 1373-1380.

124. Yao, X., N. Tangri, B.J. Gersh, L.R. Sangaralingham, N.D. Shah, K.A. Nath, and P.A. Noseworthy, *Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation.* J Am Coll Cardiol, 2017. **70**(21): p. 2621-2632.
125. Brancaccio, D., L. Neri, F. Bellocchio, C. Barbieri, C. Amato, F. Mari, B. Canaud, and S. Stuard, *Warfarin in CKD patients with atrial fibrillation.* Kidney Int, 2017. **92**(3): p. 766-767.
126. Burlacu, A. and A. Covic, *The Devil Is in the Details When Considering the OAC Efficacy-Safety Equation in Dialysis Patients.* Journal of the American College of Cardiology, 2020. **76**(3): p. 349-350.
127. Van Der Meersch, H., D. De Bacquer, and A.S. De Vriese, *Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: A systematic review and meta-analysis.* American heart journal, 2017. **184**: p. 37-46.
128. Siontis, K.C., X. Zhang, A. Eckard, N. Bhave, D.E. Schaubel, K. He, A. Tilea, A.G. Stack, R. Balkrishnan, and X. Yao, *Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States.* Circulation, 2018. **138**(15): p. 1519-1529.
129. Wang, X., G. Tirucherai, T.C. Marbury, J. Wang, M. Chang, D. Zhang, Y. Song, J. Pursley, R.A. Boyd, and C. Frost, *Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis.* J Clin Pharmacol, 2016. **56**(5): p. 628-36.
130. De Vriese, A.S., R. Caluwe, E. Bailleul, D. De Bacquer, D. Borrey, B. Van Vlem, S.J. Vandecasteele, and J. Emmerechts, *Dose-finding study of rivaroxaban in hemodialysis patients.* Am J Kidney Dis, 2015. **66**(1): p. 91-8.
131. Heine, G.H., V. Brandenburg, and S.H. Schirmer, *Oral Anticoagulation in Chronic Kidney Disease and Atrial Fibrillation.* Dtsch Arztebl Int, 2018. **115**(17): p. 287-294.
132. Mavrakanas, T.A., C.F. Samer, S.J. Nessim, G. Frisch, and M.L. Lipman, *Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients.* J Am Soc Nephrol, 2017. **28**(7): p. 2241-2248.
133. Stanton, B.E., N.S. Barasch, and K.B. Tellor, *Comparison of the Safety and Effectiveness of Apixaban versus Warfarin in Patients with Severe Renal Impairment.* Pharmacotherapy, 2017. **37**(4): p. 412-419.
134. Sarratt, S.C., R. Nesbit, and R. Moye, *Safety Outcomes of Apixaban Compared With Warfarin in Patients With End-Stage Renal Disease.* Ann Pharmacother, 2017. **51**(6): p. 445-450.
135. Siontis, K.C., X. Zhang, A. Eckard, N. Bhave, D.E. Schaubel, K. He, A. Tilea, A.G. Stack, R. Balkrishnan, X. Yao, et al., *Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States.* Circulation, 2018. **138**(15): p. 1519-1529.
136. Di Lullo, L., G. Tripepi, C. Ronco, G. D'Arrigo, V. Barbera, D. Russo, B.R. Di Iorio, M. Uguccioni, E. Paoletti, M. Ravera, et al., *Cardiac valve calcification and use of anticoagulants: Preliminary observation of a potentially modifiable risk factor*. Int J Cardiol, 2018.

137. Chan, K.E., E.R. Edelman, J.B. Wenger, R.I. Thadhani, and F.W. Maddux, *Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis.* Circulation, 2015. **131**(11): p. 972-9.
138. Lip, G.Y.H., J.P. Collet, M. Haude, R. Byrne, E.H. Chung, L. Fauchier, S. Halvorsen, D. Lau, N. Lopez-Cabanillas, M. Lettino, et al., *2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA).* Europace, 2018.
139. Fauchier, L., C. Lecoq, Y. Ancedy, K. Stamboul, C. Saint Etienne, F. Ivanes, D. Angoulvant, D. Babuty, Y. Cottin, and G.Y. Lip, *Evaluation of 5 Prognostic Scores for Prediction of Stroke, Thromboembolic and Coronary Events, All-Cause Mortality, and Major Adverse Cardiac Events in Patients With Atrial Fibrillation and Coronary Stenting.* Am J Cardiol, 2016. **118**(5): p. 700-7.
140. Burlacu, A., S. Genovesi, D. Goldsmith, P. Rossignol, A. Ortiz, P.A. Kalra, J. Małyszko, M. Banach, M. Kanbay, and A. Covic, *Bleeding in advanced CKD patients on antithrombotic medication–a critical appraisal.* Pharmacological Research, 2018. **129**: p. 535-543.
141. Dewilde, W.J., T. Oirbans, F.W. Verheugt, J.C. Kelder, B.J. De Smet, J.P. Herrman, T. Adriaenssens, M. Vrolix, A.A. Heestermans, M.M. Vis, et al., *Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial.* Lancet, 2013. **381**(9872): p. 1107-15.
142. Lamberts, M., G.H. Gislason, J.B. Olesen, S.L. Kristensen, A.M. Schjerning Olsen, A. Mikkelsen, C.B. Christensen, G.Y. Lip, L. Kober, C. Torp-Pedersen, et al., *Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention.* J Am Coll Cardiol, 2013. **62**(11): p. 981-9.
143. Roffi, M., C. Patrono, J.P. Collet, C. Mueller, M. Valgimigli, F. Andreotti, J.J. Bax, M.A. Borger, C. Brotons, D.P. Chew, et al., *2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC).* Eur Heart J, 2016. **37**(3): p. 267-315.
144. Lip, G.Y., L. Frison, J.L. Halperin, and D.A. Lane, *Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score.* J Am Coll Cardiol, 2011. **57**(2): p. 173-80.

145. Pisters, R., D.A. Lane, R. Nieuwlaat, C.B. de Vos, H.J. Crijns, and G.Y. Lip, *A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey.* Chest, 2010. **138**(5): p. 1093-100.
146. Kaw, D. and D. Malhotra, *Platelet dysfunction and end-stage renal disease.* Semin Dial, 2006. **19**(4): p. 317-22.
147. Yang, F., J.A. Hellyer, C. Than, A.J. Ullal, D.W. Kaiser, P.A. Heidenreich, D.D. Hoang, W.C. Winkelmayer, S. Schmitt, S.M. Frayne, et al., *Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease.* Heart, 2017. **103**(11): p. 818-826.
148. Rossignol, P., R. Agarwal, B. Canaud, A. Charney, G. Chatellier, J.C. Craig, W.C. Cushman, R.T. Gansevoort, B. Fellstrom, D. Garza, et al., *Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints.* Eur Heart J, 2017.
149. Li, L., O.C. Geraghty, Z. Mehta, and P.M. Rothwell, *Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study.* Lancet, 2017.
150. Chesebro, J.H., G. Knatterud, R. Roberts, J. Borer, L.S. Cohen, J. Dalen, H.T. Dodge, C.K. Francis, D. Hillis, P. Ludbrook, et al., *Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge.* Circulation, 1987. **76**(1): p. 142-54.
151. *An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction.* N Engl J Med, 1993. **329**(10): p. 673-82.
152. Hansson, E.C., L. Jideus, B. Aberg, H. Bjursten, M. Dreifaldt, A. Holmgren, T. Ivert, S. Nozohoor, M. Barbu, R. Svedjeholm, et al., *Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study.* Eur Heart J, 2016. **37**(2): p. 189-97.
153. Yang, J.Y., T.C. Lee, M.E. Montez-Rath, J. Paik, G.M. Chertow, M. Desai, and W.C. Winkelmayer, *Trends in acute nonvariceal upper gastrointestinal bleeding in dialysis patients.* J Am Soc Nephrol, 2012. **23**(3): p. 495-506.
154. Locatelli, F., P. Barany, A. Covic, A. De Francisco, L. Del Vecchio, D. Goldsmith, W. Horl, G. London, R. Vanholder, and W. Van Biesen, *Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement.* Nephrol Dial Transplant, 2013. **28**(6): p. 1346-59.
155. Svensson, P.J., P.B. Bergqvist, K.V. Juul, and E. Berntorp, *Desmopressin in treatment of haematological disorders and in prevention of surgical bleeding.* Blood Rev, 2014. **28**(3): p. 95-102.
156. Baumgartner, H., V. Falk, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, B. Iung, P. Lancellotti, E. Lansac, D. Rodriguez Muñoz, et al., *2017 ESC/EACTS Guidelines for the management of valvular heart disease.* European Heart Journal, 2017. **38**(36): p. 2739-2791.
157. Piepoli, M.F., A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, M.T. Cooney, U. Corra, B. Cosyns, C. Deaton, et al., *2016 European Guidelines on*

cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J, 2016. **37**(29): p. 2315-81.

158. Kidney International Supplements. *Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. 2012 [cited 2017 28 June]; Available from: http://kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.
159. Flores-Rios, X., D. Couto-Mallon, J. Rodriguez-Garrido, M. Garcia-Guimaraes, P. Gargallo-Fernandez, P. Pinon-Esteban, G. Aldama-Lopez, J. Salgado-Fernandez, R. Calvino-Santos, N. Vazquez-Gonzalez, et al., *Comparison of the performance of the CRUSADE, ACUITY-HORIZONS, and ACTION bleeding risk scores in STEMI undergoing primary PCI: insights from a cohort of 1391 patients.* Eur Heart J Acute Cardiovasc Care, 2013. **2**(1): p. 19-26.
160. Liu, J., M. Fan, J. Zhao, B. Zhao, C. Zhang, C. Liu, and Y. Dong, *Efficacy and safety of antithrombotic regimens after coronary intervention in patients on oral anticoagulation: Traditional and Bayesian meta-analysis of clinical trials.* Int J Cardiol, 2016. **205**: p. 89-96.
161. Elliott, M.J., D. Zimmerman, and R.M. Holden, *Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates.* Am J Kidney Dis, 2007. **50**(3): p. 433-40.
162. Kirchhof, P., S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, M. Castella, H.C. Diener, H. Heidbuchel, J. Hendriks, et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* Eur Heart J, 2016. **37**(38): p. 2893-2962.
163. Jun, M., M.T. James, B.J. Manns, R.R. Quinn, P. Ravani, M. Tonelli, V. Perkovic, W.C. Winkelmayer, Z. Ma, and B.R. Hemmelgarn, *The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study*. Bmj, 2015. **350**: p. h246.
164. Del-Carpio Munoz, F., S.M. Gharacholou, T.M. Munger, P.A. Friedman, S.J. Asirvatham, D.L. Packer, and P.A. Noseworthy, *Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for Atrial Fibrillation.* Am J Cardiol, 2016. **117**(1): p. 69-75.
165. Fang, M.C., A.S. Go, Y. Chang, L.H. Borowsky, N.K. Pomernacki, N. Udaltsova, and D.E. Singer, *A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study*. J Am Coll Cardiol, 2011. **58**(4): p. 395-401.
166. Hijazi, Z., J. Oldgren, J. Lindback, J.H. Alexander, S.J. Connolly, J.W. Eikelboom, M.D. Ezekowitz, C. Held, E.M. Hylek, R.D. Lopes, et al., *The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study*. Lancet, 2016. **387**(10035): p. 2302-11.
167. Kirchhof, P., S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, M. Castella, H.C. Diener, H. Heidbuchel, J. Hendriks, et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the*

management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). Europace, 2016.

168. Piccolo, R., G. Galasso, E. Capuano, S. De Luca, G. Esposito, B. Trimarco, and F. Piscione, *Transradial versus transfemoral approach in patients undergoing percutaneous coronary intervention for acute coronary syndrome. A meta-analysis and trial sequential analysis of randomized controlled trials.* PLoS One, 2014. **9**(5): p. e96127.
169. Lee, M.S., M. Wolfe, and G.W. Stone, *Transradial versus transfemoral percutaneous coronary intervention in acute coronary syndromes: re-evaluation of the current body of evidence.* JACC Cardiovasc Interv, 2013. **6**(11): p. 1149-52.
170. Faurie, B., *[Transradial approach and kidney disease].* Ann Cardiol Angeiol (Paris), 2009. **58**(6): p. 348-54.
171. Laville, M., M. Dorval, J. Fort Ros, R. Fay, J. Cridlig, J.L. Nortier, L. Juillard, A. Debska-Slizien, L. Fernandez Lorente, D. Thibaudin, et al., *Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis.* Kidney Int, 2014. **86**(6): p. 1260-7.
172. *Section V. Chronic intermittent haemodialysis and prevention of clotting in the extracorporal system.* Nephrol Dial Transplant, 2002. **17 Suppl 7**: p. 63-71.
173. Rossignol, P., M. Dorval, R. Fay, J.F. Ros, N. Loughraieb, F. Moureau, and M. Laville, *Rationale and design of the HepZero study: a prospective, multicenter, international, open, randomized, controlled clinical study with parallel groups comparing heparin-free dialysis with heparin-coated dialysis membrane (Evodial) versus standard care: study protocol for a randomized controlled trial.* Trials, 2013. **14**: p. 163.
174. Reddy, V.Y., S.K. Doshi, H. Sievert, M. Buchbinder, P. Neuzil, K. Huber, J.L. Halperin, and D. Holmes, *Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial.* Circulation, 2013. **127**(6): p. 720-9.
175. Reddy, V.Y., H. Sievert, J. Halperin, S.K. Doshi, M. Buchbinder, P. Neuzil, K. Huber, B. Whisenant, S. Kar, V. Swarup, et al., *Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial.* Jama, 2014. **312**(19): p. 1988-98.
176. Kefer, J., A. Tzikas, X. Freixa, S. Shakir, S. Gafoor, J.E. Nielsen-Kudsk, S. Berti, G. Santoro, A. Aminian, U. Landmesser, et al., *Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation.* Int J Cardiol, 2016. **207**: p. 335-40.
177. Hindricks, G., T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, G. Boriani, M. Castella, G.-A. Dan, P.E. Dilaveris, et al., *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC.* European Heart Journal, 2020. **42**(5): p. 373-498.

178. Benjamin, E.J., M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, S.D.d. Ferranti, J. Floyd, M. Fornage, C. Gillespie, et al., *Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association.* 2017. **135**(10): p. e146-e603.
179. Nayak-Rao, S. and M.P. Shenoy, *Stroke in Patients with Chronic Kidney Disease…: How do we Approach and Manage it?* Indian J Nephrol, 2017. **27**(3): p. 167-171.
180. Fu, J., J. Huang, M. Lei, Z. Luo, X. Zhong, Y. Huang, H. Zhang, R. Liu, J. Tong, and F. He, *Prevalence and Impact on Stroke in Patients Receiving Maintenance Hemodialysis versus Peritoneal Dialysis: A Prospective Observational Study.* PLoS One, 2015. **10**(10): p. e0140887.
181. Thrift, A.G., T. Thayabaranathan, G. Howard, V.J. Howard, P.M. Rothwell, V.L. Feigin, B. Norrving, G.A. Donnan, and D.A. Cadilhac, *Global stroke statistics.* Int J Stroke, 2017. **12**(1): p. 13-32.
182. Chwojnicki, K., E. Król, Ł. Wierucki, G. Kozera, P. Sobolewski, W.M. Nyka, and T. Zdrojewski, *Renal Dysfunction in Post-Stroke Patients.* PLoS One, 2016. **11**(8): p. e0159775.
183. Lee, M., J.L. Saver, K.H. Chang, H.W. Liao, S.C. Chang, and B. Ovbiagele, *Low glomerular filtration rate and risk of stroke: meta-analysis.* Bmj, 2010. **341**: p. c4249.
184. Reinecke, H., E. Brand, R. Mesters, W.R. Schäbitz, M. Fisher, H. Pavenstädt, and G. Breithardt, *Dilemmas in the management of atrial fibrillation in chronic kidney disease.* J Am Soc Nephrol, 2009. **20**(4): p. 705-11.
185. Kirchhof, P., S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, M. Castella, H.-C. Diener, H. Heidbuchel, J. Hendriks, et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* European Heart Journal, 2016. **37**(38): p. 2893-2962.
186. Dad, T. and D.E. Weiner, *Stroke and Chronic Kidney Disease: Epidemiology, Pathogenesis, and Management Across Kidney Disease Stages.* Semin Nephrol, 2015. **35**(4): p. 311-22.
187. Harenberg, J., V.A. Hentschel, S. Du, S. Zolfaghari, R. Krämer, C. Weiss, B.K. Krämer, and M. Wehling, *Anticoagulation in patients with impaired renal function and with haemodialysis. Anticoagulant effects, efficacy, safety, therapeutic options.* Hamostaseologie, 2015. **35**(1): p. 77-83.
188. Szummer, K., A. Gasparini, S. Eliasson, J. Ärnlöv, A.R. Qureshi, P. Bárány, M. Evans, L. Friberg, and J.J. Carrero, *Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction.* J Am Heart Assoc, 2017. **6**(3).
189. Bilha, S.C., A. Burlacu, D. Siriopol, L. Voroneanu, and A. Covic, *Primary Prevention of Stroke in Chronic Kidney Disease Patients: A Scientific Update.* Cerebrovascular Diseases, 2018. **45**(1-2): p. 33-41.
190. Burlacu, A., S. Genovesi, D. Goldsmith, P. Rossignol, A. Ortiz, P.A. Kalra, J. Małyszko, M. Banach, M. Kanbay, and A. Covic, *Bleeding in advanced CKD patients on antithrombotic medication - A critical appraisal.* Pharmacol Res, 2018. **129**: p. 535-543.
191. Bansal, V.K., C.A. Herzog, M.J. Sarnak, M.J. Choi, R. Mehta, B.G. Jaar, M.V. Rocco, and H. Kramer, *Oral Anticoagulants to Prevent Stroke in Nonvalvular Atrial Fibrillation*

in Patients With CKD Stage 5D: An NKF-KDOQI Controversies Report. Am J Kidney Dis, 2017. **70**(6): p. 859-868.

192. *K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients.* Am J Kidney Dis, 2005. **45**(4 Suppl 3): p. S1-153.
193. Dias, C., K.T. Moore, J. Murphy, J. Ariyawansa, W. Smith, R.M. Mills, and M.R. Weir, *Pharmacokinetics, Pharmacodynamics, and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis.* Am J Nephrol, 2016. **43**(4): p. 229-36.
194. Reinecke, H., C. Engelbertz, and W.R. Schäbitz, *Preventing stroke in patients with chronic kidney disease and atrial fibrillation: benefit and risks of old and new oral anticoagulants.* Stroke, 2013. **44**(10): p. 2935-41.
195. Pelisek, J., I.N. Hahntow, H.H. Eckstein, S. Ockert, C. Reeps, P. Heider, P.B. Luppa, and H. Frank, *Impact of chronic kidney disease on carotid plaque vulnerability.* J Vasc Surg, 2011. **54**(6): p. 1643-9.
196. Meschia, J.F., C. Bushnell, B. Boden-Albala, L.T. Braun, D.M. Bravata, S. Chaturvedi, M.A. Creager, R.H. Eckel, M.S. Elkind, M. Fornage, et al., *Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2014. **45**(12): p. 3754-832.
197. *Notice.* Kidney International Supplements, 2013. **3**(1): p. 1.
198. Palmer, S.C., L. Di Micco, M. Razavian, J.C. Craig, V. Perkovic, F. Pellegrini, M.J. Jardine, A.C. Webster, S. Zoungas, and G.F. Strippoli, *Antiplatelet agents for chronic kidney disease.* Cochrane Database Syst Rev, 2013(2): p. Cd008834.
199. Ricotta, J.J., A. Aburahma, E. Ascher, M. Eskandari, P. Faries, and B.K. Lal, *Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease.* J Vasc Surg, 2011. **54**(3): p. e1-31.
200. Tarakji, A., A. McConaughy, and G.G. Nicholas, *The risk of carotid endarterectomy in patients with chronic renal insufficiency.* Curr Surg, 2006. **63**(5): p. 326-9.
201. Saw, J., H.S. Gurm, R.B. Fathi, D.L. Bhatt, A. Abou-Chebl, C. Bajzer, and J.S. Yadav, *Effect of chronic kidney disease on outcomes after carotid artery stenting.* American Journal of Cardiology, 2004. **94**(8): p. 1093-1096.
202. Adil, M.M., F. Saeed, S.A. Chaudhary, A. Malik, and A.I. Qureshi, *Comparative Outcomes of Carotid Artery Stent Placement and Carotid Endarterectomy in Patients with Chronic Kidney Disease and End-Stage Renal Disease.* J Stroke Cerebrovasc Dis, 2016. **25**(7): p. 1721-1727.
203. Klarin, D., R.T. Lancaster, E. Ergul, D. Bertges, P. Goodney, M.L. Schermerhorn, R.P. Cambria, and V.I. Patel, *Perioperative and long-term impact of chronic kidney disease on carotid artery interventions.* J Vasc Surg, 2016. **64**(5): p. 1295-1302.
204. Aboyans, V., J.B. Ricco, M.E.L. Bartelink, M. Björck, M. Brodmann, T. Cohnert, J.P. Collet, M. Czerny, M. De Carlo, S. Debus, et al., *2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of*

Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J, 2018. **39**(9): p. 763-816.

205. Mathew, A., M. Eliasziw, P.J. Devereaux, J.G. Merino, H.J. Barnett, and A.X. Garg, *Carotid endarterectomy benefits patients with CKD and symptomatic high-grade stenosis.* J Am Soc Nephrol, 2010. **21**(1): p. 145-52.
206. Lima, F.V., T.Y. Yen, J. Butler, J. Yang, J. Xu, and L. Gruberg, *Impact of chronic kidney disease in patients undergoing percutaneous or surgical carotid artery revascularization: Insights of the healthcare cost and utilization Project's National Inpatient Sample.* Cardiovasc Revasc Med, 2016. **17**(8): p. 560-565.
207. Hung, C.Y., K.Y. Wang, T.J. Wu, Y.C. Hsieh, J.L. Huang, W. Loh el, and C.H. Lin, *Resistant hypertension, patient characteristics, and risk of stroke.* PLoS One, 2014. **9**(8): p. e104362.
208. Dandapani, B.K., S. Suzuki, R.E. Kelley, Y. Reyes-Iglesias, and R.C. Duncan, *Relation between blood pressure and outcome in intracerebral hemorrhage.* Stroke, 1995. **26**(1): p. 21-4.
209. Brott, T., K. Thalinger, and V. Hertzberg, *Hypertension as a risk factor for spontaneous intracerebral hemorrhage.* Stroke, 1986. **17**(6): p. 1078-83.
210. Mancia, G., R. Fagard, K. Narkiewicz, J. Redón, A. Zanchetti, M. Böhm, T. Christiaens, R. Cifkova, G. De Backer, A. Dominiczak, et al., *2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).* J Hypertens, 2013. **31**(7): p. 1281-357.
211. Tanner, R.M., D.A. Calhoun, E.K. Bell, C.B. Bowling, O.M. Gutiérrez, M.R. Irvin, D.T. Lackland, S. Oparil, D. Warnock, and P. Muntner, *Prevalence of apparent treatment-resistant hypertension among individuals with CKD.* Clin J Am Soc Nephrol, 2013. **8**(9): p. 1583-90.
212. Wheeler, D.C. and G.J. Becker, *Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease?* Kidney Int, 2013. **83**(3): p. 377-83.
213. *K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease.* Am J Kidney Dis, 2004. **43**(5 Suppl 1): p. S1-290.
214. Persu, A., Y. Jin, M. Azizi, M. Baelen, S. Völz, A. Elvan, F. Severino, J. Rosa, A. Adiyaman, F.E. Fadl Elmula, et al., *Blood pressure changes after renal denervation at 10 European expert centers.* J Hum Hypertens, 2014. **28**(3): p. 150-6.
215. Hering, D., P. Marusic, J. Duval, Y. Sata, G.A. Head, K.M. Denton, S. Burrows, A.S. Walton, M.D. Esler, and M.P. Schlaich, *Effect of renal denervation on kidney function in patients with chronic kidney disease.* Int J Cardiol, 2017. **232**: p. 93-97.
216. Sanders, M.F., J.B. Reitsma, M. Morpey, H. Gremmels, M.L. Bots, A. Pisano, D. Bolignano, C. Zoccali, and P.J. Blankestijn, *Renal safety of catheter-based renal denervation: systematic review and meta-analysis.* Nephrol Dial Transplant, 2017. **32**(9): p. 1440-1447.
217. Coppolino, G., A. Pisano, L. Rivoli, and D. Bolignano, *Renal denervation for resistant hypertension.* Cochrane Database Syst Rev, 2017. **2**(2): p. Cd011499.

218. Mahfoud, F., T.F. Lüscher, B. Andersson, I. Baumgartner, R. Cifkova, C. Dimario, P. Doevendans, R. Fagard, J. Fajadet, M. Komajda, et al., *Expert consensus document from the European Society of Cardiology on catheter-based renal denervation.* Eur Heart J, 2013. **34**(28): p. 2149-57.
219. Veelken, R. and R.E. Schmieder, *Renal denervation--implications for chronic kidney disease.* Nat Rev Nephrol, 2014. **10**(6): p. 305-13.
220. Yoruk, A., J.D. Bisognano, and J.P. Gassler, *Baroreceptor Stimulation for Resistant Hypertension.* Am J Hypertens, 2016. **29**(12): p. 1319-1324.
221. Wallbach, M., L.Y. Lehnig, C. Schroer, G. Hasenfuss, G.A. Müller, R. Wachter, and M.J. Koziolek, *Impact of baroreflex activation therapy on renal function--a pilot study.* Am J Nephrol, 2014. **40**(4): p. 371-80.
222. Beige, J., M.J. Koziolek, G. Hennig, A. Hamza, R. Wendt, G.A. Müller, and M. Wallbach, *Baroreflex activation therapy in patients with end-stage renal failure: proof of concept.* J Hypertens, 2015. **33**(11): p. 2344-9.
223. Hoppe, U.C., M.C. Brandt, R. Wachter, J. Beige, L.C. Rump, A.A. Kroon, A.W. Cates, E.G. Lovett, and H. Haller, *Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial.* J Am Soc Hypertens, 2012. **6**(4): p. 270-6.
224. Herrmann, S.M., A. Saad, and S.C. Textor, *Management of atherosclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL).* Nephrol Dial Transplant, 2015. **30**(3): p. 366-75.
225. Bax, L., A.J. Woittiez, H.J. Kouwenberg, W.P. Mali, E. Buskens, F.J. Beek, B. Braam, F.T. Huysmans, L.J. Schultze Kool, M.J. Rutten, et al., *Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial.* Ann Intern Med, 2009. **150**(12): p. 840-8, w150-1.
226. Wheatley, K., N. Ives, R. Gray, P.A. Kalra, J.G. Moss, C. Baigent, S. Carr, N. Chalmers, D. Eadington, G. Hamilton, et al., *Revascularization versus medical therapy for renal-artery stenosis.* N Engl J Med, 2009. **361**(20): p. 1953-62.
227. Cooper, C.J., T.P. Murphy, D.E. Cutlip, K. Jamerson, W. Henrich, D.M. Reid, D.J. Cohen, A.H. Matsumoto, M. Steffes, M.R. Jaff, et al., *Stenting and medical therapy for atherosclerotic renal-artery stenosis.* N Engl J Med, 2014. **370**(1): p. 13-22.
228. Misra, S., A. Khosla, J. Allred, W.S. Harmsen, S.C. Textor, and M.A. McKusick, *Mortality and Renal Replacement Therapy after Renal Artery Stent Placement for Atherosclerotic Renovascular Disease.* J Vasc Interv Radiol, 2016. **27**(8): p. 1215-24.
229. Kalra, P.A., C. Chrysochou, D. Green, C.M. Cheung, K. Khavandi, S. Sixt, A. Rastan, and T. Zeller, *The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease.* Catheter Cardiovasc Interv, 2010. **75**(1): p. 1-10.
230. Herrmann, S.M. and S.C. Textor, *Current Concepts in the Treatment of Renovascular Hypertension.* Am J Hypertens, 2018. **31**(2): p. 139-149.
231. Jaff, M.R., M. Bates, T. Sullivan, J. Popma, X. Gao, M. Zaugg, and P. Verta, *Significant reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: results from the HERCULES trial.* Catheter Cardiovasc Interv, 2012. **80**(3): p. 343-50.

232. Anderson, J.L., J.L. Halperin, N.M. Albert, B. Bozkurt, R.G. Brindis, L.H. Curtis, D. DeMets, R.A. Guyton, J.S. Hochman, R.J. Kovacs, et al., *Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.* Circulation, 2013. **127**(13): p. 1425-43.
233. Parikh, A.M., F.A. Spencer, D. Lessard, C. Emery, A. Baylin, C. Linkletter, and R.J. Goldberg, *Venous thromboembolism in patients with reduced estimated GFR: a population-based perspective.* Am J Kidney Dis, 2011. **58**(5): p. 746-55.
234. Lutz, J., K. Jurk, and H. Schinzel, *Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations.* Int J Nephrol Renovasc Dis, 2017. **10**: p. 135-143.
235. Dager, W.E. and T.H. Kiser, *Systemic anticoagulation considerations in chronic kidney disease.* Adv Chronic Kidney Dis, 2010. **17**(5): p. 420-7.
236. Oktay, E., *Will NOACs become the new standard of care in anticoagulation therapy?* International Journal of the Cardiovascular Academy, 2015. **1**(1): p. 1-4.
237. Chen, A., E. Stecker, and A.W. B, *Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges.* J Am Heart Assoc, 2020. **9**(13): p. e017559.
238. Johnson, W.D., A.K. Ganjoo, C.D. Stone, R.C. Srivyas, and M. Howard, *The left atrial appendage: our most lethal human attachment! Surgical implications.* Eur J Cardiothorac Surg, 2000. **17**(6): p. 718-22.
239. Hindricks, G., T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, G. Boriani, M. Castella, G.A. Dan, P.E. Dilaveris, et al., *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC.* Eur Heart J, 2021. **42**(5): p. 373-498.
240. Holmes, D.R., S. Kar, M.J. Price, B. Whisenant, H. Sievert, S.K. Doshi, K. Huber, and V.Y. Reddy, *Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy: The PREVAIL Trial.* Journal of the American College of Cardiology, 2014. **64**(1): p. 1-12.
241. Holmes, D.R., V.Y. Reddy, Z.G. Turi, S.K. Doshi, H. Sievert, M. Buchbinder, C.M. Mullin, and P. Sick, *Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial.* The Lancet, 2009. **374**(9689): p. 534-542.
242. Holmes, D.R., S.K. Doshi, S. Kar, M.J. Price, J.M. Sanchez, H. Sievert, M. Valderrabano, and V.Y. Reddy, *Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis.* Journal of the American College of Cardiology, 2015. **65**(24): p. 2614-2623.
243. Mahajan, R., A.G. Brooks, T. Sullivan, H.S. Lim, M. Alasady, H.S. Abed, A.N. Ganesan, S. Nayyar, D.H. Lau, K.C. Roberts-Thomson, et al., *Importance of the underlying*

substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure. Heart, 2012. **98**(15): p. 1120-6.

244. Cresti, A., M.A. García-Fernández, H. Sievert, P. Mazzone, P. Baratta, M. Solari, A. Geyer, F. De Sensi, and U. Limbruno, *Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study.* EuroIntervention, 2019. **15**(3): p. e225-e230.
245. Meier, B., Y. Blaauw, A.A. Khattab, T. Lewalter, H. Sievert, C. Tondo, and M. Glikson, *EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion.* EuroIntervention, 2015. **10**(9): p. 1109-25.
246. Moussa Pacha, H., Y. Al-Khadra, M. Soud, F. Darmoch, A. Moussa Pacha, and M.C. Alraies, *Percutaneous devices for left atrial appendage occlusion: A contemporary review.* World J Cardiol, 2019. **11**(2): p. 57-70.
247. Davis, C.A., 3rd, J.C. Rembert, and J.C. Greenfield, Jr., *Compliance of left atrium with and without left atrium appendage.* Am J Physiol, 1990. **259**(4 Pt 2): p. H1006-8.
248. Behnes, M., B. Sartorius, A. Wenke, S. Lang, U. Hoffmann, C. Fastner, M. Borggrefe, T. Roth, J. Triebel, T. Bertsch, et al., *Percutaneous Closure of Left Atrial Appendage affects Mid-Term Release of MR-proANP.* Scientific Reports, 2017. **7**.
249. Granier, M., G. Laugaudin, F. Massin, S. Cade, P.F. Winum, C. Freitag, and J.L. Pasquie, *Occurrence of Incomplete Endothelialization Causing Residual Permeability After Left Atrial Appendage Closure.* J Invasive Cardiol, 2018. **30**(7): p. 245-250.
250. Takeda, K., A. Harada, S. Okuda, S. Fujimi, Y. Oh, F. Hattori, K. Motomura, H. Hirakata, and M. Fujishima, *Sudden death in chronic dialysis patients.* Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association-European Renal Association, 1997. **12**(5): p. 952-955.
251. Stecker, E.C., K. Reinier, E. Marijon, K. Narayanan, C. Teodorescu, A. Uy-Evanado, K. Gunson, J. Jui, and S.S. Chugh, *Public health burden of sudden cardiac death in the United States.* Circulation: Arrhythmia and Electrophysiology, 2014. **7**(2): p. 212-217.
252. Saran, R., B. Robinson, K.C. Abbott, L.Y. Agodoa, P. Albertus, J. Ayanian, R. Balkrishnan, J. Bragg-Gresham, J. Cao, and J.L. Chen, *US renal data system 2016 annual data report: epidemiology of kidney disease in the United States.* American journal of kidney diseases, 2017. **69**(3): p. A7-A8.
253. Ligtenberg, G., M. Barnas, and H. Koomans, *Intradialytic hypotension: new insights into the mechanism of vasovagal syncope.* Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association-European Renal Association, 1998. **13**(11): p. 2745-2747.
254. Genovesi, S., G. Boriani, A. Covic, R.W.M. Vernooij, C. Combe, A. Burlacu, A. Davenport, M. Kanbay, D. Kirmizis, D. Schneditz, et al., *Sudden cardiac death in dialysis patients: different causes and management strategies.* Nephrology Dialysis Transplantation, 2019. **36**(3): p. 396-405.
255. Karnik, J.A., B.S. Young, N.L. Lew, M. Herget, C. Dubinsky, J.M. Lazarus, and G.M. Chertow, *Cardiac arrest and sudden death in dialysis units.* Kidney international, 2001. **60**(1): p. 350-357.

256. Pun, P.H., R.W. Lehrich, E.F. Honeycutt, C.A. Herzog, and J.P. Middleton, *Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics.* Kidney international, 2011. **79**(2): p. 218-227.
257. Poulikakos, D., K. Hnatkova, S. Skampardoni, D. Green, P. Kalra, and M. Malik, *Sudden Cardiac Death in Dialysis: Arrhythmic Mechanisms and the Value of Non-invasive Electrophysiology.* Front Physiol, 2019. **10**: p. 144.
258. Luu, M., W.G. Stevenson, L.W. Stevenson, K. Baron, and J. Walden, *Diverse mechanisms of unexpected cardiac arrest in advanced heart failure.* Circulation, 1989. **80**(6): p. 1675-80.
259. Bayés de Luna, A., P. Coumel, and J.F. Leclercq, *Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases.* Am Heart J, 1989. **117**(1): p. 151-9.
260. Cobb, L.A., C.E. Fahrenbruch, M. Olsufka, and M.K. Copass, *Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000.* Jama, 2002. **288**(23): p. 3008-13.
261. Wan, C., C.A. Herzog, W. Zareba, and S.J. Szymkiewicz, *Sudden cardiac arrest in hemodialysis patients with wearable cardioverter defibrillator.* Ann Noninvasive Electrocardiol, 2014. **19**(3): p. 247-57.
262. Wong, M.C., J.M. Kalman, E. Pedagogos, N. Toussaint, J.K. Vohra, P.B. Sparks, P. Sanders, P.M. Kistler, K. Halloran, G. Lee, et al., *Temporal distribution of arrhythmic events in chronic kidney disease: Highest incidence in the long interdialytic period.* Heart Rhythm, 2015. **12**(10): p. 2047-55.
263. Sacher, F., L. Jesel, C. Borni-Duval, V. De Precigout, F. Lavainne, J.P. Bourdenx, A. Haddj-Elmrabet, B. Seigneuric, A. Keller, J. Ott, et al., *Cardiac Rhythm Disturbances in Hemodialysis Patients: Early Detection Using an Implantable Loop Recorder and Correlation With Biological and Dialysis Parameters.* JACC Clin Electrophysiol, 2018. **4**(3): p. 397-408.
264. Roy-Chaudhury, P., J.A. Tumlin, B.A. Koplan, A.I. Costea, V. Kher, D. Williamson, S. Pokhariyal, and D.M. Charytan, *Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle.* Kidney Int, 2018. **93**(4): p. 941-951.
265. Bleyer, A.J., J. Hartman, P.C. Brannon, A. Reeves-Daniel, S.G. Satko, and G. Russell, *Characteristics of sudden death in hemodialysis patients.* Kidney Int, 2006. **69**(12): p. 2268-73.
266. Genovesi, S., M.G. Valsecchi, E. Rossi, D. Pogliani, I. Acquistapace, V. De Cristofaro, A. Stella, and A. Vincenti, *Sudden death and associated factors in a historical cohort of chronic haemodialysis patients.* Nephrol Dial Transplant, 2009. **24**(8): p. 2529-36.
267. Wong, M.C., J.M. Kalman, E. Pedagogos, N. Toussaint, J.K. Vohra, P.B. Sparks, P. Sanders, P.M. Kistler, K. Halloran, and G. Lee, *Temporal distribution of arrhythmic events in chronic kidney disease: highest incidence in the long interdialytic period.* Heart Rhythm, 2015. **12**(10): p. 2047-2055.
268. Genovesi, S., L. Porcu, M.C. Luise, H. Riva, E. Nava, G. Contaldo, A. Stella, C. Pozzi, P. Ondei, C. Minoretti, et al., *Sudden Death in End Stage Renal Disease: Comparing Hemodialysis versus Peritoneal Dialysis.* Blood Purif, 2017. **44**(1): p. 77-88.

269. Torlén, K., K. Kalantar-Zadeh, M.Z. Molnar, T. Vashistha, and R. Mehrotra, *Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort.* Clin J Am Soc Nephrol, 2012. **7**(8): p. 1272-84.
270. Wang, A.Y., C.W. Lam, I.H. Chan, M. Wang, S.F. Lui, and J.E. Sanderson, *Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis.* Hypertension, 2010. **56**(2): p. 210-6.
271. Kerns, E.S., E.D. Kim, L.A. Meoni, S.M. Sozio, B.G. Jaar, M.M. Estrella, R.S. Parekh, and G. Bourjeily, *Obstructive Sleep Apnea Increases Sudden Cardiac Death in Incident Hemodialysis Patients.* Am J Nephrol, 2018. **48**(2): p. 147-156.
272. Kawase, Y., T. Taniguchi, T. Morimoto, K. Kadota, K. Iwasaki, A. Kuwayama, M. Ohya, T. Shimada, H. Amano, T. Maruo, et al., *Severe Aortic Stenosis in Dialysis Patients.* J Am Heart Assoc, 2017. **6**(7).
273. Chiu, Y.-W., I. Teitelbaum, M. Misra, E.M. De Leon, T. Adzize, and R. Mehrotra, *Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients.* Clinical Journal of the American Society of Nephrology, 2009. **4**(6): p. 1089-1096.
274. Burnier, M., M. Pruijm, G. Wuerzner, and V. Santschi, *Drug adherence in chronic kidney diseases and dialysis.* Nephrology Dialysis Transplantation, 2015. **30**(1): p. 39-44.
275. Genovesi, S., C. Dossi, M.R. Vigano, E. Galbiati, F. Prolo, A. Stella, and M. Stramba-Badiale, *Electrolyte concentration during haemodialysis and QT interval prolongation in uraemic patients.* Europace, 2008. **10**(6): p. 771-777.
276. Sforzini, S., B. Redaelli, R. Latini, A. Vincenti, G. Mingardi, and F.G.E.P. Cardiovascolari, *Ventricular arrhythmias and four-year mortality in haemodialysis patients.* The Lancet, 1992. **339**(8787): p. 212-213.
277. Näppi, S.E., V.K. Virtanen, H.H. Saha, J.T. Mustonen, and A.I. Pasternack, *QTc dispersion increases during hemodialysis with low-calcium dialysate.* Kidney international, 2000. **57**(5): p. 2117-2122.
278. Basile, C., L. Rossi, and C. Lomonte. *Dialysate bicarbonate concentration: too much of a good thing?* in *Seminars in dialysis*. 2018. Wiley Online Library.
279. Sakaguchi, Y., N. Fujii, T. Shoji, T. Hayashi, H. Rakugi, and Y. Isaka, *Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis.* Kidney international, 2014. **85**(1): p. 174-181.
280. de Roij van Zuijdewijn, C.L., M.P. Grooteman, M.L. Bots, P.J. Blankestijn, S. Steppan, J. Büchel, R.H. Groenwold, V. Brandenburg, M.A. van den Dorpel, and P.M. Ter Wee, *Serum magnesium and sudden death in European hemodialysis patients.* PLoS One, 2015. **10**(11): p. e0143104.
281. Jadoul, M., J. Thumma, D.S. Fuller, F. Tentori, Y. Li, H. Morgenstern, D. Mendelssohn, T. Tomo, J. Ethier, and F. Port, *Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study.* Clinical Journal of the American Society of Nephrology, 2012. **7**(5): p. 765-774.
282. Jin, J., X. Guo, and Q. Yu, *Effects of beta-blockers on cardiovascular events and mortality in dialysis patients: a systematic review and meta-analysis.* Blood Purification, 2019. **48**(1): p. 51-59.

283. Nakao, K., H. Makino, S. Morita, Y. Takahashi, T. Akizawa, A. Saito, Y. Asano, K. Kurokawa, S. Fukuhara, and T. Akiba, *Beta-blocker prescription and outcomes in hemodialysis patients from the Japan Dialysis Outcomes and Practice Patterns Study.* Nephron Clin Pract, 2009. **113**(3): p. c132-9.
284. Foley, R.N., C.A. Herzog, and A.J. Collins, *Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study.* Kidney Int, 2002. **62**(5): p. 1784-90.
285. Cice, G., L. Ferrara, A. D'Andrea, S. D'Isa, A. Di Benedetto, A. Cittadini, P.E. Russo, P. Golino, and R. Calabrò, *Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial.* J Am Coll Cardiol, 2003. **41**(9): p. 1438-44.
286. Tangri, N., S. Shastri, H. Tighiouart, G.J. Beck, A.K. Cheung, G. Eknoyan, and M.J. Sarnak, *β-Blockers for prevention of sudden cardiac death in patients on hemodialysis: a propensity score analysis of the HEMO Study.* Am J Kidney Dis, 2011. **58**(6): p. 939-45.
287. Tai, D.J., T.W. Lim, M.T. James, B.J. Manns, M. Tonelli, and B.R. Hemmelgarn, *Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis.* Clin J Am Soc Nephrol, 2010. **5**(4): p. 623-30.
288. Iseki, K., H. Arima, K. Kohagura, I. Komiya, S. Ueda, K. Tokuyama, Y. Shiohira, H. Uehara, and S. Toma, *Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial.* Nephrol Dial Transplant, 2013. **28**(6): p. 1579-89.
289. Zannad, F., M. Kessler, P. Lehert, J.P. Grünfeld, C. Thuilliez, A. Leizorovicz, and P. Lechat, *Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies.* Kidney Int, 2006. **70**(7): p. 1318-24.
290. Matsumoto, Y., Y. Mori, S. Kageyama, K. Arihara, T. Sugiyama, H. Ohmura, T. Yakushigawa, H. Sugiyama, Y. Shimada, Y. Nojima, et al., *Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients.* J Am Coll Cardiol, 2014. **63**(6): p. 528-36.
291. Efrati, S., R. Zaidenstein, V. Dishy, I. Beberashvili, M. Sharist, Z. Averbukh, A. Golik, and J. Weissgarten, *ACE inhibitors and survival of hemodialysis patients.* Am J Kidney Dis, 2002. **40**(5): p. 1023-9.
292. Berger, A.K., S. Duval, and H.M. Krumholz, *Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction.* J Am Coll Cardiol, 2003. **42**(2): p. 201-8.
293. Packham, D.K., H.S. Rasmussen, P.T. Lavin, M.A. El-Shahawy, S.D. Roger, G. Block, W. Qunibi, P. Pergola, and B. Singh, *Sodium zirconium cyclosilicate in hyperkalemia.* N Engl J Med, 2015. **372**(3): p. 222-31.
294. Kosiborod, M., H.S. Rasmussen, P. Lavin, W.Y. Qunibi, B. Spinowitz, D. Packham, S.D. Roger, A. Yang, E. Lerma, and B. Singh, *Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial.* Jama, 2014. **312**(21): p. 2223-33.

295. Singhal, P.C., L. Desroches, J. Mattana, M. Abramovici, J.D. Wagner, and J.K. Maesaka, *Mineralocorticoid therapy lowers serum potassium in patients with end-stage renal disease.* Am J Nephrol, 1993. **13**(2): p. 138-41.
296. Ash, S.R., B. Singh, P.T. Lavin, F. Stavros, and H.S. Rasmussen, *A phase 2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient.* Kidney Int, 2015. **88**(2): p. 404-11.
297. Pun, P.H., R.W. Lehrich, S.R. Smith, and J.P. Middleton, *Predictors of survival after cardiac arrest in outpatient hemodialysis clinics.* Clin J Am Soc Nephrol, 2007. **2**(3): p. 491-500.
298. Kestenbaum, B., D.L. Gillen, D.J. Sherrard, S. Seliger, A. Ball, and C. Stehman-Breen, *Calcium channel blocker use and mortality among patients with end-stage renal disease.* Kidney Int, 2002. **61**(6): p. 2157-64.
299. Ballinger, A.E., S.C. Palmer, I. Nistor, J.C. Craig, and G.F.M. Strippoli, *Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients.* Cochrane Database of Systematic Reviews, 2014(12).
300. Messa, P., F. Macário, M. Yaqoob, K. Bouman, J. Braun, B. von Albertini, H. Brink, F. Maduell, H. Graf, J.M. Frazão, et al., *The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism.* Clin J Am Soc Nephrol, 2008. **3**(1): p. 36-45.
301. Block, G.A., D.A. Bushinsky, J. Cunningham, T.B. Drueke, M. Ketteler, R. Kewalramani, K.J. Martin, T.C. Mix, S.M. Moe, U.D. Patel, et al., *Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: Two Randomized Clinical Trials.* Jama, 2017. **317**(2): p. 146-155.
302. Claro, J.C., R. Candia, G. Rada, F. Baraona, F. Larrondo, and L.M. Letelier, *Amiodarone versus other pharmacological interventions for prevention of sudden cardiac death.* Cochrane Database of Systematic Reviews, 2015(12).
303. Chan, K.E., J.M. Lazarus, and R.M. Hakim, *Digoxin associates with mortality in ESRD.* J Am Soc Nephrol, 2010. **21**(9): p. 1550-9.
304. Boriani, G., I. Savelieva, G.-A. Dan, J.C. Deharo, C. Ferro, C.W. Israel, D.A. Lane, G. La Manna, J. Morton, and A.M. Mitjans, *Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society.* Ep Europace, 2015. **17**(8): p. 1169-1196.
305. Boriani, G., L. Fauchier, L. Aguinaga, J.M. Beattie, C. Blomstrom Lundqvist, A. Cohen, G.-A. Dan, S. Genovesi, C. Israel, and B. Joung, *European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS).* Ep Europace, 2019. **21**(1): p. 7-8.
306. Polyzos, K.A., A.A. Konstantelias, and M.E. Falagas, *Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis.* Ep Europace, 2015. **17**(5): p. 767-777.

307. Jukema, J.W., R.J. Timal, J.I. Rotmans, L.C. Hensen, M.S. Buiten, M.K. de Bie, H. Putter, A.H. Zwinderman, L. van Erven, and M.J. Krol-van Straaten, *Prophylactic use of implantable cardioverter-defibrillators in the prevention of sudden cardiac death in dialysis patients: the prospective, randomized, controlled ICD2 Trial.* Circulation, 2019. **139**(23): p. 2628-2638.
308. Dasgupta, A., J. Montalvo, S. Medendorp, D.M. Lloyd-Jones, C. Ghossein, J. Goldberger, and R. Passman, *Increased complication rates of cardiac rhythm management devices in ESRD patients.* American Journal of Kidney Diseases, 2007. **49**(5): p. 656-663.
309. Dhamija, R.K., H. Tan, E. Philbin, R.O. Mathew, M.S. Sidhu, J. Wang, B. Saour, S.S. Haqqie, G. Beathard, and A.S. Yevzlin, *Subcutaneous implantable cardioverter defibrillator for dialysis patients: a strategy to reduce central vein stenoses and infections.* American Journal of Kidney Diseases, 2015. **66**(1): p. 154-158.
310. Priori, S., C. Blomström-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, P. Elliott, D. Fitzsimons, R. Hatala, and G. Hindricks, *Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC).* Europace, 2015. **17**(11): p. 1601-87.
311. Moss, A.J., W.J. Hall, D.S. Cannom, J.P. Daubert, S.L. Higgins, H. Klein, J.H. Levine, S. Saksena, A.L. Waldo, and D. Wilber, *Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia.* New England Journal of Medicine, 1996. **335**(26): p. 1933-1940.
312. Moss, A.J., W. Zareba, W.J. Hall, H. Klein, D.J. Wilber, D.S. Cannom, J.P. Daubert, S.L. Higgins, M.W. Brown, and M.L. Andrews, *Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction.* New England Journal of Medicine, 2002. **346**(12): p. 877-883.
313. Bardy, G.H., K.L. Lee, D.B. Mark, J.E. Poole, D.L. Packer, R. Boineau, M. Domanski, C. Troutman, J. Anderson, and G. Johnson, *Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure.* New England Journal of Medicine, 2005. **352**(3): p. 225-237.
314. Khan, F., E. Adelstein, and S. Saba, *Implantable cardioverter defibrillators confer survival benefit in patients with renal insufficiency but not in dialysis-dependent patients.* Journal of interventional cardiac electrophysiology, 2010. **28**(2): p. 117-123.
315. Hess, P.L., A.S. Hellkamp, E.D. Peterson, G.D. Sanders, H.R. Al-Khalidi, L.H. Curtis, B.G. Hammill, P.H. Pun, J.P. Curtis, and K.J. Anstrom, *Survival after primary prevention implantable cardioverter-defibrillator placement among patients with chronic kidney disease.* Circulation: Arrhythmia and Electrophysiology, 2014. **7**(5): p. 793-799.
316. Hiremath, S., S.R. Punnam, S.S. Brar, S.K. Goyal, J.C. Gardiner, A.J. Shah, and R.K. Thakur, *Implantable defibrillators improve survival in end-stage renal disease: results from a multi-center registry.* American journal of nephrology, 2010. **32**(4): p. 305-310.

317. Pun, P.H., A.S. Hellkamp, G.D. Sanders, J.P. Middleton, S.C. Hammill, H.R. Al-Khalidi, L.H. Curtis, G.C. Fonarow, and S.M. Al-Khatib, *Primary prevention implantable cardioverter defibrillators in end-stage kidney disease patients on dialysis: a matched cohort study.* Nephrology Dialysis Transplantation, 2015. **30**(5): p. 829-835.
318. Hsu, J.C., G.M. Marcus, S.M. Al-Khatib, Y. Wang, J.P. Curtis, N. Sood, M.W. Parker, J. Kluger, R. Lampert, and A.M. Russo, *Predictors of an inadequate defibrillation safety margin at ICD implantation: insights from the National Cardiovascular Data Registry*. Journal of the American College of Cardiology, 2014. **64**(3): p. 256-264.
319. Paoletti, E. and C. Zoccali, *A look at the upper heart chamber: the left atrium in chronic kidney disease.* Nephrology Dialysis Transplantation, 2013. **29**(10): p. 1847-1853.
320. Dini, F.L., R.T. Demmer, A. Simioniuc, D. Morrone, F. Donati, G. Guarini, E. Orsini, P. Caravelli, M. Marzilli, and P.C. Colombo, *Right ventricular dysfunction is associated with chronic kidney disease and predicts survival in patients with chronic systolic heart failure.* Eur J Heart Fail, 2012. **14**(3): p. 287-94.
321. McIntyre, C.W. and S.J. Rosansky, *Starting dialysis is dangerous: how do we balance the risk?* Kidney Int, 2012. **82**(4): p. 382-7.
322. Edwards, N.C., A. Hirth, C.J. Ferro, J.N. Townend, and R.P. Steeds, *Subclinical abnormalities of left ventricular myocardial deformation in early-stage chronic kidney disease: the precursor of uremic cardiomyopathy?* J Am Soc Echocardiogr, 2008. **21**(12): p. 1293-8.
323. Chiu, D.Y., D. Green, N. Abidin, S. Sinha, and P.A. Kalra, *Cardiac imaging in patients with chronic kidney disease.* Nat Rev Nephrol, 2015. **11**(4): p. 207-20.
324. Liu, Y.W., C.T. Su, E.J. Song, W.C. Tsai, Y.H. Li, L.M. Tsai, J.H. Chen, and J.M. Sung, *The role of echocardiographic study in patients with chronic kidney disease.* J Formos Med Assoc, 2015. **114**(9): p. 797-805.
325. Unger, E.D., R.F. Dubin, R. Deo, V. Daruwalla, J.L. Friedman, C. Medina, L. Beussink, B.H. Freed, and S.J. Shah, *Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction.* Eur J Heart Fail, 2016. **18**(1): p. 103-12.
326. Rudski, L.G., W.W. Lai, J. Afilalo, L. Hua, M.D. Handschumacher, K. Chandrasekaran, S.D. Solomon, E.K. Louie, and N.B. Schiller, *Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography.* J Am Soc Echocardiogr, 2010. **23**(7): p. 685-713; quiz 786-8.
327. Morris, D.A., M. Krisper, S. Nakatani, C. Köhncke, Y. Otsuji, E. Belyavskiy, A.K. Radha Krishnan, M. Kropf, E. Osmanoglou, L.H. Boldt, et al., *Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study.* Eur Heart J Cardiovasc Imaging, 2017. **18**(2): p. 212-223.
328. Eckardt, K.-U., I.A. Gillespie, F. Kronenberg, S. Richards, P. Stenvinkel, S.D. Anker, D.C. Wheeler, A.L. de Francisco, D. Marcelli, M. Froissart, et al., *High cardiovascular event rates occur within the first weeks of starting hemodialysis.* Kidney International, 2015. **88**(5): p. 1117-1125.

329. Robinson, B.M., J. Zhang, H. Morgenstern, B.D. Bradbury, L.J. Ng, K.P. McCullough, B.W. Gillespie, R. Hakim, H. Rayner, J. Fort, et al., *Worldwide, mortality risk is high soon after initiation of hemodialysis.* Kidney International, 2014. **85**(1): p. 158-165.
330. Paneni, F., M. Gregori, G.M. Ciavarella, S. Sciarretta, F. Palano, G. Pignatelli, L. Castello, A. Domenici, G. Punzo, G. Tocci, et al., *Relation between right and left ventricular function in patients undergoing chronic dialysis.* J Cardiovasc Med (Hagerstown), 2013. **14**(4): p. 289-95.
331. Bansal, N., M. Keane, P. Delafontaine, D. Dries, E. Foster, C.A. Gadegbeku, A.S. Go, L.L. Hamm, J.W. Kusek, A.O. Ojo, et al., *A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study.* Clin J Am Soc Nephrol, 2013. **8**(3): p. 355-62.
332. Cai, Q.-Z., X.-Z. Lu, Y. Lu, and A.Y.-M. Wang, *Longitudinal changes of cardiac structure and function in CKD (CASCADE study).* Journal of the American Society of Nephrology : JASN, 2014. **25**(7): p. 1599-1608.
333. Whalley, G.A., T.H. Marwick, R.N. Doughty, B.A. Cooper, D.W. Johnson, A. Pilmore, D.C. Harris, C.A. Pollock, and J.F. Collins, *Effect of early initiation of dialysis on cardiac structure and function: results from the echo substudy of the IDEAL trial.* Am J Kidney Dis, 2013. **61**(2): p. 262-70.
334. Ganda, A., S.D. Weiner, N.L. Chudasama, A.M. Valeri, A. Jadoon, D. Shimbo, and J. Radhakrishnan, *Echocardiographic changes following hemodialysis initiation in patients with advanced chronic kidney disease and symptomatic heart failure with reduced ejection fraction.* Clin Nephrol, 2012. **77**(5): p. 366-75.
335. Eckardt, K.U., N. Bansal, J. Coresh, M. Evans, M.E. Grams, C.A. Herzog, M.T. James, H.J.L. Heerspink, C.A. Pollock, P.E. Stevens, et al., *Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.* Kidney Int, 2018. **93**(6): p. 1281-1292.
336. Pelà, G., G. Regolisti, P. Coghi, A. Cabassi, A. Basile, A. Cavatorta, C. Manca, and A. Borghetti, *Effects of the reduction of preload on left and right ventricular myocardial velocities analyzed by Doppler tissue echocardiography in healthy subjects.* Eur J Echocardiogr, 2004. **5**(4): p. 262-71.
337. Kjaergaard, J., E.M. Snyder, C. Hassager, J.K. Oh, and B.D. Johnson, *Impact of preload and afterload on global and regional right ventricular function and pressure: a quantitative echocardiography study.* J Am Soc Echocardiogr, 2006. **19**(5): p. 515-21.
338. Akyüz, A., A. Yıldız, M.A. Akıl, M.Z. Bilik, Ü. İnci, F. Kayan, İ. Yıldız, Z. Yılmaz, Y. Yıldırım, and M.S. Ülgen, *[Assessment of right ventricular systolic function in patients with chronic renal failure before and after hemodialysis by means of various echocardiographic modalities].* Turk Kardiyol Dern Ars, 2014. **42**(8): p. 717-25.
339. Akkaya, M., E. Erdoğan, S. Sağ, H. Arı, Y. Türker, and M. Yılmaz, *[The effect of hemodialysis on right ventricular functions in patients with end-stage renal failure].* Anadolu Kardiyol Derg, 2012. **12**(1): p. 5-10.
340. Ünlü, S., A. Şahinarslan, G. Gökalp, Ö. Seçkin, S.T. Arınsoy, N.B. Boyacı, and A. Çengel, *The impact of volume overload on right heart function in end-stage renal disease patients on hemodialysis.* Echocardiography, 2018. **35**(3): p. 314-321.

341. Georgianos, P.I., P.A. Sarafidis, A.B. Haidich, A. Karpetas, D. Stamatiadis, P. Nikolaidis, and A.N. Lasaridis, *Diverse effects of interdialytic intervals on central wave augmentation in haemodialysis patients.* Nephrol Dial Transplant, 2013. **28**(8): p. 2160-9.
342. De Blasio, A., M. Sirico, L. Di Micco, and B. Di Iorio, *[Hemodialysis improves the subendocardial viability ratio].* G Ital Nefrol, 2013. **30**(6).
343. Loutradis, C., P.A. Sarafidis, C.E. Papadopoulos, A. Papagianni, and C. Zoccali, *The Ebb and Flow of Echocardiographic Cardiac Function Parameters in Relationship to Hemodialysis Treatment in Patients with ESRD.* J Am Soc Nephrol, 2018. **29**(5): p. 1372-1381.
344. Giusca, S., V. Dambrauskaite, C. Scheurwegs, J. D'Hooge, P. Claus, L. Herbots, M. Magro, F. Rademakers, B. Meyns, M. Delcroix, et al., *Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring.* Heart, 2010. **96**(4): p. 281-8.
345. Haeck, M.L., R.W. Scherptong, N.A. Marsan, E.R. Holman, M.J. Schalij, J.J. Bax, H.W. Vliegen, and V. Delgado, *Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension.* Circ Cardiovasc Imaging, 2012. **5**(5): p. 628-36.
346. Fine, N.M., L. Chen, P.M. Bastiansen, R.P. Frantz, P.A. Pellikka, J.K. Oh, and G.C. Kane, *Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension.* Circ Cardiovasc Imaging, 2013. **6**(5): p. 711-21.
347. Kaesler, N., A. Babler, J. Floege, and R. Kramann, *Cardiac Remodeling in Chronic Kidney Disease.* Toxins (Basel), 2020. **12**(3).
348. Tripepi, G., F.A. Benedetto, F. Mallamaci, R. Tripepi, L. Malatino, and C. Zoccali, *Left atrial volume monitoring and cardiovascular risk in patients with end-stage renal disease: a prospective cohort study.* J Am Soc Nephrol, 2007. **18**(4): p. 1316-22.
349. Sciacqua, A., M. Perticone, G. Tripepi, S. Miceli, E.J. Tassone, N. Grillo, G. Carullo, G. Sesti, and F. Perticone, *Renal disease and left atrial remodeling predict atrial fibrillation in patients with cardiovascular risk factors.* Int J Cardiol, 2014. **175**(1): p. 90-5.
350. Chan, M.Y., H.B. Wong, H.Y. Ong, and T.C. Yeo, *Prognostic value of left atrial size in chronic kidney disease.* Eur J Echocardiogr, 2008. **9**(6): p. 736-40.
351. Kimura, K., K. Takenaka, A. Ebihara, T. Okano, K. Uno, N. Fukuda, J. Ando, H. Fujita, H. Morita, Y. Yatomi, et al., *Speckle tracking global strain rate E/E' predicts LV filling pressure more accurately than traditional tissue Doppler E/E'.* Echocardiography, 2012. **29**(4): p. 404-10.
352. Amundsen, B.H., T. Helle-Valle, T. Edvardsen, H. Torp, J. Crosby, E. Lyseggen, A. Støylen, H. Ihlen, J.A. Lima, O.A. Smiseth, et al., *Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging.* J Am Coll Cardiol, 2006. **47**(4): p. 789-93.
353. Pastore, M.C., G. De Carli, G.E. Mandoli, F. D'Ascenzi, M. Focardi, F. Contorni, S. Mondillo, and M. Cameli, *The prognostic role of speckle tracking echocardiography in clinical practice: evidence and reference values from the literature.* Heart Fail Rev, 2020.
354. Badano, L.P., T.J. Kolias, D. Muraru, T.P. Abraham, G. Aurigemma, T. Edvardsen, J. D'Hooge, E. Donal, A.G. Fraser, T. Marwick, et al., *Standardization of left atrial, right*

ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging, 2018. **19**(6): p. 591-600.

355. Donal, E., A. Behagel, and D. Feneon, *Value of left atrial strain: a highly promising field of investigation.* Eur Heart J Cardiovasc Imaging, 2015. **16**(4): p. 356-7.
356. Lundberg, A., J. Johnson, C. Hage, M. Bäck, B. Merkely, A. Venkateshvaran, L.H. Lund, A.I. Nagy, and A. Manouras, *Left atrial strain improves estimation of filling pressures in heart failure: a simultaneous echocardiographic and invasive haemodynamic study.* Clin Res Cardiol, 2019. **108**(6): p. 703-715.
357. Cameli, M., M. Lisi, F.M. Righini, A. Massoni, B.M. Natali, M. Focardi, D. Tacchini, A. Geyer, V. Curci, C. Di Tommaso, et al., *Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse.* Am J Cardiol, 2013. **111**(4): p. 595-601.
358. Singh, A., K. Addetia, F. Maffessanti, V. Mor-Avi, and R.M. Lang, *LA Strain for Categorization of LV Diastolic Dysfunction.* JACC Cardiovasc Imaging, 2017. **10**(7): p. 735-743.
359. Gan, G.C.H., K.K. Kadappu, A. Bhat, F. Fernandez, K.H. Gu, L. Cai, K. Byth, S. Eshoo, and L. Thomas, *Left Atrial Strain Is the Best Predictor of Adverse Cardiovascular Outcomes in Patients with Chronic Kidney Disease.* J Am Soc Echocardiogr, 2021. **34**(2): p. 166-175.
360. Kadappu, K., L. Cai, W. Xuan, J. French, and L. Thomas, *LEFT ATRIAL STRAIN AN EARLY MARKER OF FUTURE ADVERSE CARDIOVASCULAR EVENTS IN CHRONIC KIDNEY DISEASE.* Journal of the American College of Cardiology, 2016. **67**(13_Supplement): p. 1704-1704.
361. Papadopoulos, C.E., E. Pagourelias, C. Bakogiannis, K. Triantafyllou, K. Baltoumas, E. Kassimatis, D. Zioutas, D. Siskos, S. Tzikas, N. Fragakis, et al., *Left atrial deformation as a potent predictor for paroxysmal atrial fibrillation in patients with end-stage renal disease.* Int J Cardiovasc Imaging, 2018. **34**(9): p. 1393-1401.
362. Li, C., J. Zhang, R. Fan, W. Li, Y. Liu, D. Liu, H. Lin, F. Yao, M. Ye, and W. He, *Left atrial strain associated with alterations in cardiac diastolic function in patients with end-stage renal disease.* The International Journal of Cardiovascular Imaging, 2019. **35**(10): p. 1803-1810.
363. Altekin, R.E., A. Yanikoglu, M.S. Karakas, D. Ozel, H. Yilmaz, and I. Demir, *Evaluation of left atrial function using two-dimensional speckle tracking echocardiography in end-stage renal disease patients with preserved left ventricular ejection fraction.* Kardiol Pol, 2013. **71**(4): p. 341-51.
364. Hoit, B.D., *Assessment of Left Atrial Function by Echocardiography: Novel Insights.* Curr Cardiol Rep, 2018. **20**(10): p. 96.
365. Gupta, S., S.A. Matulevicius, C.R. Ayers, J.D. Berry, P.C. Patel, D.W. Markham, B.D. Levine, K.M. Chin, J.A. de Lemos, R.M. Peshock, et al., *Left atrial structure and function and clinical outcomes in the general population.* Eur Heart J, 2013. **34**(4): p. 278-85.

366. Modin, D., S.R. Biering-Sørensen, R. Møgelvang, A.S. Alhakak, J.S. Jensen, and T. Biering-Sørensen, *Prognostic value of left atrial strain in predicting cardiovascular morbidity and mortality in the general population.* Eur Heart J Cardiovasc Imaging, 2019. **20**(7): p. 804-815.
367. Alhakak, A.S., S.R. Biering-Sørensen, R. Møgelvang, D. Modin, G.B. Jensen, P. Schnohr, A.Z. Iversen, J.H. Svendsen, T. Jespersen, G. Gislason, et al., *Usefulness of left atrial strain for predicting incident atrial fibrillation and ischaemic stroke in the general population.* Eur Heart J Cardiovasc Imaging, 2020.
368. Costa, C., T. González-Alujas, F. Valente, C. Aranda, J. Rodríguez-Palomares, L. Gutierrez, G. Maldonado, L. Galian, G. Teixidó, and A. Evangelista, *Left atrial strain: a new predictor of thrombotic risk and successful electrical cardioversion.* Echo Res Pract, 2016. **3**(2): p. 45-52.
369. Shih, J.Y., W.C. Tsai, Y.Y. Huang, Y.W. Liu, C.C. Lin, Y.S. Huang, L.M. Tsai, and L.J. Lin, *Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation.* J Am Soc Echocardiogr, 2011. **24**(5): p. 513-9.
370. Bolignano, D., A. Pisano, G. Coppolino, G.L. Tripepi, and G. D'Arrigo, *Pulmonary Hypertension Predicts Adverse Outcomes in Renal Patients: A Systematic Review and Meta-Analysis.* Ther Apher Dial, 2019. **23**(4): p. 369-384.
371. Zhang, Y., X.-H. Ding, R. Rao, Y. Wang, F. Pang, S. Tang, L. Nie, and S.-Z. Bian, *The Prevalence of Pulmonary Hypertension Among Maintenance Dialysis Patients With ESRD and Its Associated Factors: A Retrospective Study.* Frontiers in Medicine, 2020. **7**.
372. Navaneethan, S.D., C.P. Walther, L.P. Gregg, S. Bansal, W.C. Winkelmayer, V. Nambi, and J. Niu, *Mortality, Kidney Failure, and Hospitalization Among Medicare Beneficiaries With CKD and Pulmonary Hypertension.* Am J Kidney Dis, 2021. **78**(5): p. 700-708.e1.
373. Augustine, D.X., L.D. Coates-Bradshaw, J. Willis, A. Harkness, L. Ring, J. Grapsa, G. Coghlan, N. Kaye, D. Oxborough, S. Robinson, et al., *Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British Society of Echocardiography.* Echo research and practice, 2018. **5**(3): p. G11-G24.
374. Moza, A., A. Khan, R. Parashar, S. Khan, S. Khouri, J. Ortiz, D. Malhotra, M. Rees, and G. Moukarbel, *Pulmonary hypertension in renal transplant candidates: A systematic review and meta-analysis of the available evidence and a proposed algorithm for pre-transplant management.* Trends in Transplantation, 2017. **10**.
375. Ribeiro, A.R. and M.M. Knorst, *Pulmonary Hypertension Identified By Echocardiography With Color Doppler In Renal Transplant Candidates: Prevalence And Outcome,* in *C65. ASSESSMENT OF PULMONARY HYPERTENSION*. p. A4690-A4690.
376. Issa, N., M.J. Krowka, M.D. Griffin, L.J. Hickson, M.D. Stegall, and F.G. Cosio, *Pulmonary hypertension is associated with reduced patient survival after kidney transplantation.* Transplantation, 2008. **86**(10): p. 1384-8.
377. Zlotnick, D.M., D.A. Axelrod, M.C. Chobanian, S. Friedman, J. Brown, E. Catherwood, and S.P. Costa, *Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction.* Nephrol Dial Transplant, 2010. **25**(9): p. 3090-6.
378. Obi, C., A.E. Frost, E.A. Graviss, D.T. Nguyen, A.O. Gaber, and W.N. Suki, *The Association of Pretransplant Pulmonary Hypertension With Patient and Graft Survival*

After Kidney Transplantation: A Retrospective Cohort Study. Transplant Proc, 2020. **52**(10): p. 3023-3032.
379. Goyal, V.K., S.L. Solanki, and B. Baj, *Pulmonary hypertension and post-operative outcome in renal transplant: A retrospective analysis of 170 patients.* Indian J Anaesth, 2018. **62**(2): p. 131-135.
380. Abasi, K., Z. Lotfi, M. Ahmadi, H.M. Majd, and B. Hasanzamani, *Relationship Between Pulmonary Hypertension Before Kidney Transplantation and Early Graft Dysfunction.* Iran J Kidney Dis, 2020. **14**(5): p. 399-404.
381. Sadat, B., D. Tirunagari, V. Karthikeyan, A. Patel, M. Van Harn, M.M. Saleem, and K. Ananthasubramaniam, *Clinical impact of pre-kidney transplant pulmonary hypertension on post-transplant outcomes.* Int J Cardiovasc Imaging, 2021. **37**(6): p. 1979-1986.
382. Wang, S.C., R. Garcia, M. Torosoff, S.A. Fein, A. Ashar, N. Chandolias, D. Conti, and R. Lyubarova, *Influence of mildly and moderately elevated pulmonary artery systolic pressure on post-renal transplantation survival and graft function.* Echocardiography, 2019. **36**(1): p. 22-27.
383. Rabih, F., R.L. Holden, P. Vasanth, S.O. Pastan, M.R. Fisher, and A.W. Trammell, *Effect of pulmonary hypertension on 5-year outcome of kidney transplantation.* Pulmonary Circulation, 2022. **12**(1): p. e12010.
384. Foderaro, A.E., G.L. Baird, A. Bazargan-Lari, P.E. Morrissey, R.Y. Gohh, A. Poppas, J.R. Klinger, and C.E. Ventetuolo, *Echocardiographic Pulmonary Hypertension Predicts Post-transplantation Renal Allograft Failure.* Transplant Proc, 2017. **49**(6): p. 1256-1261.
385. Nguyen, M., T. Chiang, A. Massie, S. Bae, J. Motter, D. Brennan, N. Desai, D. Segev, and J. Garonzik Wang, *Kidney Transplantation Confers Survival Benefit for Candidates With Pulmonary Hypertension.* Transplantation Direct, 2021. **7**: p. e738.
386. Collet, J.P., H. Thiele, E. Barbato, O. Barthélémy, J. Bauersachs, D.L. Bhatt, P. Dendale, M. Dorobantu, T. Edvardsen, T. Folliguet, et al., *2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.* Eur Heart J, 2020.
387. Rihal, C.S., S.C. Textor, D.E. Grill, P.B. Berger, H.H. Ting, P.J. Best, M. Singh, M.R. Bell, G.W. Barsness, V. Mathew, et al., *Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention.* Circulation, 2002. **105**(19): p. 2259-64.
388. Gaipov, A., M.Z. Molnar, P.K. Potukuchi, K. Sumida, Z. Szabo, O. Akbilgic, E. Streja, C.M. Rhee, S.K.G. Koshy, R.B. Canada, et al., *Acute kidney injury following coronary revascularization procedures in patients with advanced CKD.* Nephrol Dial Transplant, 2019. **34**(11): p. 1894-1901.
389. Rahim, H., S. Sethi, D. Karampaliotis, and Z. Ali. *Imaging and physiology-guided PCI without contrast administration in advanced renal failure*. 2019 [cited 2021 11th of February]; Available from: https://www.pcronline.com/Cases-resources-images/Cases/Read-share-cases/2019/Imaging-and-physiology-guided-PCI-without-contrast-administration-in-advanced-renal-failure?auth=true.
390. Sakai, K., Y. Ikari, M. Nanasato, H. Umetsu, M. Okutsu, T. Takikawa, S. Sumitsuji, K. Sadamatsu, M. Takada, Y. Kato, et al., *Impact of intravascular ultrasound-guided minimum-contrast coronary intervention on 1-year clinical outcomes in patients with*

stage 4 or 5 advanced chronic kidney disease. Cardiovasc Interv Ther, 2019. **34**(3): p. 234-241.
391. Ali, Z.A., K. Karimi Galougahi, T. Nazif, A. Maehara, M.A. Hardy, D.J. Cohen, L.E. Ratner, M.B. Collins, J.W. Moses, A.J. Kirtane, et al., *Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study.* Eur Heart J, 2016. **37**(40): p. 3090-3095.
392. Sacha, J., M. Gierlotka, P. Lipski, P. Feusette, and D. Dudek, *Zero-contrast percutaneous coronary interventions to preserve kidney function in patients with severe renal impairment and hemodialysis subjects.* Postepy Kardiol Interwencyjnej, 2019. **15**(2): p. 137-142.
393. Kumar, P., B. Jino, M. R, S. Roy, and S.G. Villoth, *IVUS guided rota assisted left main zero-contrast PCI in a patient with CKD.* IHJ Cardiovascular Case Reports (CVCR), 2020. **4**(2): p. 49-52.
394. Patel, N.J., C. Jost, M.D. Barry, S. Lipskind, and R.R. Heuser. *Zero Contrast PCI Using SyncVision Precision Guidance*. 2020 [cited 2021 15th of February]; Available from: https://www.cathlabdigest.com/content/zero-contrast-pci-using-syncvision-precision-guidance.
395. Fan, P.C., T.H. Chen, C.C. Lee, T.Y. Tsai, Y.C. Chen, and C.H. Chang, *ADVANCIS Score Predicts Acute Kidney Injury After Percutaneous Coronary Intervention for Acute Coronary Syndrome.* Int J Med Sci, 2018. **15**(5): p. 528-535.
396. Vives, M., A. Hernandez, F. Parramon, N. Estanyol, B. Pardina, A. Muñoz, P. Alvarez, and C. Hernandez, *Acute kidney injury after cardiac surgery: prevalence, impact and management challenges.* Int J Nephrol Renovasc Dis, 2019. **12**: p. 153-166.
397. Nadim, M.K., L.G. Forni, A. Bihorac, C. Hobson, J.L. Koyner, A. Shaw, G.J. Arnaoutakis, X. Ding, D.T. Engelman, H. Gasparovic, et al., *Cardiac and Vascular Surgery-Associated Acute Kidney Injury: The 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group.* J Am Heart Assoc, 2018. **7**(11).
398. Lassnigg, A., D. Schmidlin, M. Mouhieddine, L.M. Bachmann, W. Druml, P. Bauer, and M. Hiesmayr, *Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study.* J Am Soc Nephrol, 2004. **15**(6): p. 1597-605.
399. Duchnowski, P., T. Hryniewiecki, M. Kuśmierczyk, and P. Szymański, *The usefulness of selected biomarkers in patients with valve disease.* Biomark Med, 2018. **12**(12): p. 1341-1346.
400. Rydén, L., U. Sartipy, M. Evans, and M.J. Holzmann, *Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease.* Circulation, 2014. **130**(23): p. 2005-11.
401. Mariscalco, G., R. Lorusso, C. Dominici, A. Renzulli, and A. Sala, *Acute kidney injury: a relevant complication after cardiac surgery.* Ann Thorac Surg, 2011. **92**(4): p. 1539-47.
402. Wang, Y. and R. Bellomo, *Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment.* Nat Rev Nephrol, 2017. **13**(11): p. 697-711.
403. Tecson, K.M., D. Brown, J.W. Choi, G. Feghali, G.V. Gonzalez-Stawinski, B.L. Hamman, R. Hebeler, S.R. Lander, B. Lima, S. Potluri, et al., *Major Adverse Renal and*

Cardiac Events After Coronary Angiography and Cardiac Surgery. Ann Thorac Surg, 2018. **105**(6): p. 1724-1730.
404. O'Neal, J.B., A.D. Shaw, and F.T.t. Billings, *Acute kidney injury following cardiac surgery: current understanding and future directions.* Crit Care, 2016. **20**(1): p. 187.
405. Huen, S.C. and C.R. Parikh, *Predicting acute kidney injury after cardiac surgery: a systematic review.* Ann Thorac Surg, 2012. **93**(1): p. 337-47.
406. Khwaja, A., *KDIGO clinical practice guidelines for acute kidney injury.* Nephron Clin Pract, 2012. **120**(4): p. c179-84.
407. Lopes, J.A. and S. Jorge, *The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review.* Clin Kidney J, 2013. **6**(1): p. 8-14.
408. Hertzberg, D., U. Sartipy, L.H. Lund, L. Rydén, J.W. Pickering, and M.J. Holzmann, *Heart failure and the risk of acute kidney injury in relation to ejection fraction in patients undergoing coronary artery bypass grafting.* Int J Cardiol, 2019. **274**: p. 66-70.
409. Patel, U.D., A.X. Garg, H.M. Krumholz, M.G. Shlipak, S.G. Coca, K. Sint, H. Thiessen-Philbrook, J.L. Koyner, M. Swaminathan, C.S. Passik, et al., *Preoperative serum brain natriuretic peptide and risk of acute kidney injury after cardiac surgery.* Circulation, 2012. **125**(11): p. 1347-55.
410. Belley-Côté, E.P., C.R. Parikh, C.R. Shortt, S.G. Coca, A.X. Garg, J.W. Eikelboom, P. Kavsak, E. McArthur, H. Thiessen-Philbrook, and R.P. Whitlock, *Association of cardiac biomarkers with acute kidney injury after cardiac surgery: A multicenter cohort study.* J Thorac Cardiovasc Surg, 2016. **152**(1): p. 245-251.e4.
411. Hertzberg, D., U. Sartipy, and M.J. Holzmann, *Type 1 and type 2 diabetes mellitus and risk of acute kidney injury after coronary artery bypass grafting.* Am Heart J, 2015. **170**(5): p. 895-902.
412. Kocogulları, C.U., A.T. Kunt, R. Aksoy, C. Duzyol, H. Parlar, H. Saskın, and O. Fındık, *Hemoglobin A1c Levels Predicts Acute Kidney Injury after Coronary Artery Bypass Surgery in Non-Diabetic Patients.* Braz J Cardiovasc Surg, 2017. **32**(2): p. 83-89.
413. Oezkur, M., M. Wagner, D. Weismann, J.H. Krannich, C. Schimmer, C. Riegler, V. Rücker, R. Leyh, and P.U. Heuschmann, *Chronic hyperglycemia is associated with acute kidney injury in patients undergoing CABG surgery--a cohort study.* BMC Cardiovasc Disord, 2015. **15**: p. 41.
414. De Santo, L., G. Romano, A. Della Corte, V. de Simone, F. Grimaldi, M. Cotrufo, and M. de Feo, *Preoperative anemia in patients undergoing coronary artery bypass grafting predicts acute kidney injury.* J Thorac Cardiovasc Surg, 2009. **138**(4): p. 965-70.
415. Karkouti, K., D.N. Wijeysundera, T.M. Yau, S.A. McCluskey, C.T. Chan, P.Y. Wong, and W.S. Beattie, *Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients.* Anesthesiology, 2011. **115**(3): p. 523-30.
416. O'Sullivan, K.E., J.S. Byrne, A. Hudson, A.M. Murphy, D.M. Sadlier, and J.P. Hurley, *The effect of obesity on acute kidney injury after cardiac surgery.* J Thorac Cardiovasc Surg, 2015. **150**(6): p. 1622-8.
417. Coca, S.G., A.X. Garg, M. Swaminathan, S. Garwood, K. Hong, H. Thiessen-Philbrook, C. Passik, J.L. Koyner, and C.R. Parikh, *Preoperative angiotensin-converting enzyme*

inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant, 2013. **28**(11): p. 2787-99.

418. Barodka, V., S. Silvestry, N. Zhao, X. Jiao, D.J. Whellan, J. Diehl, and J.Z. Sun, *Preoperative renin-angiotensin system inhibitors protect renal function in aging patients undergoing cardiac surgery.* J Surg Res, 2011. **167**(2): p. e63-9.
419. Jiang, W., J. Yu, J. Xu, B. Shen, Y. Wang, Z. Luo, C. Wang, X. Ding, and J. Teng, *Impact of cardiac catheterization timing and contrast media dose on acute kidney injury after cardiac surgery.* BMC Cardiovasc Disord, 2018. **18**(1): p. 191.
420. Ranucci, M., A. Ballotta, B. Agnelli, A. Frigiola, L. Menicanti, and S. Castelvecchio, *Acute kidney injury in patients undergoing cardiac surgery and coronary angiography on the same day.* Ann Thorac Surg, 2013. **95**(2): p. 513-9.
421. Borde, D.P., B. Asegaonkar, P. Apsingekar, S. Khade, B. Khodve, S. Joshi, A. George, A. Pujari, and A. Deodhar, *Influence of time interval between coronary angiography to off-pump coronary artery bypass surgery on incidence of cardiac surgery associated acute kidney injury.* Indian J Anaesth, 2019. **63**(6): p. 475-484.
422. Ozkaynak, B., N. Kayalar, F. Gümüş, C. Yücel, B. Mert, K. Boyacıoğlu, and V. Erentuğ, *Time from cardiac catheterization to cardiac surgery: a risk factor for acute kidney injury?* Interact Cardiovasc Thorac Surg, 2014. **18**(6): p. 706-11.
423. van Diepen, S., C.M. Norris, Y. Zheng, J. Nagendran, M.M. Graham, D. Gaete Ortega, D.R. Townsend, J.A. Ezekowitz, and S.M. Bagshaw, *Comparison of Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Management Strategies Before Cardiac Surgery: A Pilot Randomized Controlled Registry Trial.* J Am Heart Assoc, 2018. **7**(20): p. e009917.
424. Han, S.S., D.K. Kim, S. Kim, H.J. Chin, D.W. Chae, and K.Y. Na, *C-Reactive Protein Predicts Acute Kidney Injury and Death After Coronary Artery Bypass Grafting.* Ann Thorac Surg, 2017. **104**(3): p. 804-810.
425. Shlipak, M.G., S.G. Coca, Z. Wang, P. Devarajan, J.L. Koyner, U.D. Patel, H. Thiessen-Philbrook, A.X. Garg, and C.R. Parikh, *Presurgical serum cystatin C and risk of acute kidney injury after cardiac surgery.* Am J Kidney Dis, 2011. **58**(3): p. 366-73.
426. Wyler von Ballmoos, M., D.S. Likosky, M. Rezaee, K. Lobdell, S. Alam, D. Parker, S. Owens, H. Thiessen-Philbrook, T. MacKenzie, and J.R. Brown, *Elevated preoperative Galectin-3 is associated with acute kidney injury after cardiac surgery.* BMC Nephrol, 2018. **19**(1): p. 280.
427. Coca, S.G., D. Jammalamadaka, K. Sint, H. Thiessen Philbrook, M.G. Shlipak, M. Zappitelli, P. Devarajan, S. Hashim, A.X. Garg, and C.R. Parikh, *Preoperative proteinuria predicts acute kidney injury in patients undergoing cardiac surgery.* J Thorac Cardiovasc Surg, 2012. **143**(2): p. 495-502.
428. Huang, T.M., V.C. Wu, G.H. Young, Y.F. Lin, C.C. Shiao, P.C. Wu, W.Y. Li, H.Y. Yu, F.C. Hu, J.W. Lin, et al., *Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting.* J Am Soc Nephrol, 2011. **22**(1): p. 156-63.
429. Wang, J., W. Yu, M. Gao, C. Gu, and Y. Yu, *Preoperative Prophylactic Intraaortic Balloon Pump Reduces the Incidence of Postoperative Acute Kidney Injury and Short-Term Death of High-Risk Patients Undergoing Coronary Artery Bypass Grafting: A Meta-Analysis of 17 Studies.* Ann Thorac Surg, 2016. **101**(5): p. 2007-19.

430. 1. Carmona, M., November 05). 2017 Global Report. Retrieved September 16, 2020, from http://www.transplant-observatory.org/download/2017-activity-data-report/.
431. Transplantation, U.S.G.I.o.O.D.a. *Organ Donation Statistics*. Organ Donation Statistics 2020 [cited 2020 September 1st]; Available from: https://www.organdonor.gov/statistics-stories/statistics.html.
432. de Mattos, A.M., J. Prather, A.J. Olyaei, Y. Shibagaki, D.S. Keith, M. Mori, D.J. Norman, and T. Becker, *Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors.* Kidney Int, 2006. **70**(4): p. 757-64.
433. Watt, K.D., R.A. Pedersen, W.K. Kremers, J.K. Heimbach, and M.R. Charlton, *Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study.* Am J Transplant, 2010. **10**(6): p. 1420-7.
434. Johnston, S.D., J.K. Morris, R. Cramb, B.K. Gunson, and J. Neuberger, *Cardiovascular morbidity and mortality after orthotopic liver transplantation.* Transplantation, 2002. **73**(6): p. 901-6.
435. Miller, L.W., *Cardiovascular toxicities of immunosuppressive agents.* Am J Transplant, 2002. **2**(9): p. 807-18.
436. Kasiske, B.L., H.A. Chakkera, and J. Roel, *Explained and unexplained ischemic heart disease risk after renal transplantation.* J Am Soc Nephrol, 2000. **11**(9): p. 1735-43.
437. Yamamura, M., Y. Miyamoto, M. Mitsuno, H. Tanaka, M. Ryomoto, S. Fukui, N. Tsujiya, T. Kajiyama, and M. Nojima, *Open heart surgery after renal transplantation.* Asian Cardiovascular and Thoracic Annals, 2014. **22**(7): p. 775-780.
438. Mitruka, S.N., B.P. Griffith, R.L. Kormos, B.G. Hattler, F.A. Pigula, R. Shapiro, J.J. Fung, and S.M. Pham, *Cardiac operations in solid-organ transplant recipients.* Annals of Thoracic Surgery, 1997. **64**(5): p. 1270-1278.
439. Giakoustidis, A., T.P. Cherian, N. Antoniadis, and D. Giakoustidis, *Combined cardiac surgery and liver transplantation: Three decades of worldwide results.* Journal of Gastrointestinal and Liver Diseases, 2011. **20**(4): p. 415-421.
440. Alfaro Sanchez, C.I., M.J. Molina Higueras, J.P. Moiron Fernandez-Felechosa, J.M. Mora Gutierrez, P.L. Martin Moreno, N. Garcia Fernandez, F.J. Lavilla Royo, and P. Errasti Goenaga, *Short-Term Outcomes of 100 Consecutive Kidney Transplantations in a 3-Year Period: A Single-Center Experience.* Transplant Proc, 2016. **48**(9): p. 2906-2909.
441. Kohmoto, T., S. Osaki, D.B. Kaufman, G. Leverson, N. DeOliveira, S.A. Akhter, S. Ulschmid, L. Lozonschi, and E.B. Lushaj, *Cardiac Surgery Outcomes in Abdominal Solid Organ Transplant Recipients.* Annals of Thoracic Surgery, 2018. **105**(3): p. 757-762.
442. Farag, M., M. Nikolic, R. Arif, B. Schmack, A. Sabashnikov, M. Zeriouh, A.F. Popov, A. Ruhparwar, M. Karck, and A. Weymann, *Cardiac Surgery in Patients With Previous Hepatic or Renal Transplantation: A Pair-Matched Study.* Annals of Thoracic Surgery, 2017. **103**(5): p. 1467-1474.
443. Vargo, P.R., N.K. Schiltz, D.R. Johnston, N.G. Smedira, N. Moazami, E.H. Blackstone, and E.G. Soltesz, *Outcomes of Cardiac Surgery in Patients With Previous Solid Organ Transplantation (Kidney, Liver, and Pancreas).* Am J Cardiol, 2015. **116**(12): p. 1932-8.
444. Sharma, R., C. Hawley, R. Griffin, J. Mundy, P. Peters, and P. Shah, *Cardiac surgical outcomes in abdominal solid organ (renal and hepatic) transplant recipients: A case-matched study.* Interactive Cardiovascular and Thoracic Surgery, 2013. **16**(2): p. 103-111.

445. John, R., K. Lietz, S. Huddleston, A. Matas, K. Liao, S. Shumway, L. Joyce, and R.M. Bolman, *Perioperative outcomes of cardiac surgery in kidney and kidney-pancreas transplant recipients.* Journal of Thoracic and Cardiovascular Surgery, 2007. **133**(5): p. 1212-1219.
446. Rabkin, J.M., C.L. Corless, H.R. Rosen, and A.J. Olyaei, *Immunosuppression impact on long-term cardiovascular complications after liver transplantation.* Am J Surg, 2002. **183**(5): p. 595-9.
447. Rabkin, J.M., V. de La Melena, S.L. Orloff, C.L. Corless, H.R. Rosen, and A.J. Olyaei, *Late mortality after orthotopic liver transplantation.* Am J Surg, 2001. **181**(5): p. 475-9.
448. Kasiske, B.L., S. Anjum, R. Shah, J. Skogen, C. Kandaswamy, B. Danielson, E.A. O'Shaughnessy, D.C. Dahl, J.R. Silkensen, M. Sahadevan, et al., *Hypertension after kidney transplantation.* Am J Kidney Dis, 2004. **43**(6): p. 1071-81.
449. Kasiske, B.L., *Clinical practice guidelines for managing dyslipidemias in kidney transplant patients.* Am J Transplant, 2005. **5**(6): p. 1576.
450. Friedman, A.N., D.C. Miskulin, I.H. Rosenberg, and A.S. Levey, *Demographics and trends in overweight and obesity in patients at time of kidney transplantation.* Am J Kidney Dis, 2003. **41**(2): p. 480-7.
451. Kasiske, B.L., J.J. Snyder, D. Gilbertson, and A.J. Matas, *Diabetes mellitus after kidney transplantation in the United States.* Am J Transplant, 2003. **3**(2): p. 178-85.
452. Cosio, F.G., T.E. Pesavento, S. Kim, K. Osei, M. Henry, and R.M. Ferguson, *Patient survival after renal transplantation: IV. Impact of post-transplant diabetes.* Kidney Int, 2002. **62**(4): p. 1440-6.
453. Gill, J.S., *Cardiovascular disease in transplant recipients: current and future treatment strategies.* Clin J Am Soc Nephrol, 2008. **3 Suppl 2**(Suppl 2): p. S29-37.
454. Musci, M., C.A. Yankah, H. Klose, R. Baretti, Y. Weng, R. Meyer, and R. Hetzer, *Heart valve operations in solid organ recipients: an 18-year single-center experience.* Transplantation, 2007. **84**(5): p. 592-597.
455. Christiansen, S., F.H. Splittgerber, G. Marggraf, M. Claus, T. Philipp, H.R. Zerkowski, and J.C. Reidemeister, *Results of cardiac operations in five kidney transplant patients.* Thorac Cardiovasc Surg, 1997. **45**(2): p. 75-7.
456. Basic-Jukic, N., R. Ivanac-Jankovic, B. Biocina, and P. Kes, *Cardiovascular surgery after renal transplantation--indications, complications and outcome.* Ren Fail, 2015. **37**(6): p. 1020-1.
457. Bolman, R.M., 3rd, R.W. Anderson, J.E. Molina, J.S. Schwartz, B. Levine, R.L. Simmons, and J.S. Najarian, *Cardiac operations in patients with functioning renal allografts.* J Thorac Cardiovasc Surg, 1984. **88**(4): p. 537-43.
458. Bozso, S.J., J.J.H. Kang, D. Al-Adra, Y. Hong, M.C. Moon, D.H. Freed, J. Nagendran, and J. Nagendran, *Outcomes following bioprosthetic valve replacement in prior non-cardiac transplant recipients.* Clin Transplant, 2019. **33**(11): p. e13720.
459. Taduru, S.S., M. Ramakrishnan, R.A. Mustafa, and P.S. Baweja, *Comparison of the Frequency of Acute Kidney Injury in Patients With Renal Transplant Who Underwent Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graft Surgery.* Am J Cardiol, 2017. **120**(7): p. 1104-1109.

460. Fox, H., S. Büttner, K. Hemmann, A. Asbe-Vollkopf, M. Doss, A. Beiras-Fernandez, A. Moritz, A.M. Zeiher, E. Scheuermann, H. Geiger, et al., *Transcatheter aortic valve implantation improves outcome compared to open-heart surgery in kidney transplant recipients requiring aortic valve replacement.* J Cardiol, 2013. **61**(6): p. 423-7.
461. Susantitaphong, P., D.N. Cruz, J. Cerda, M. Abulfaraj, F. Alqahtani, I. Koulouridis, and B.L. Jaber, *World incidence of AKI: a meta-analysis.* Clin J Am Soc Nephrol, 2013. **8**(9): p. 1482-93.
462. Mehta, R.L., J. Cerdá, E.A. Burdmann, M. Tonelli, G. García-García, V. Jha, P. Susantitaphong, M. Rocco, R. Vanholder, M.S. Sever, et al., *International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology.* Lancet, 2015. **385**(9987): p. 2616-43.
463. Patschan, D., B. Marahrens, M. Jansch, S. Patschan, and O. Ritter, *Experimental Cardiorenal Syndrome Type 3: What Is Known so Far?* J Clin Med Res, 2022. **14**(1): p. 22-27.
464. Faubel, S. and P.B. Shah, *Immediate Consequences of Acute Kidney Injury: The Impact of Traditional and Nontraditional Complications on Mortality in Acute Kidney Injury.* Adv Chronic Kidney Dis, 2016. **23**(3): p. 179-85.
465. Surawicz, B., *Electrolytes and the Electrocardiogram.* Postgraduate Medicine, 1974. **55**(6): p. 123-129.
466. Wang, G., L. Yang, N. Ye, W. Bian, C. Ma, D. Zhao, J. Liu, Y. Hao, N. Yang, and H. Cheng, *In-hospital acute kidney injury and atrial fibrillation: incidence, risk factors, and outcome.* Ren Fail, 2021. **43**(1): p. 949-957.
467. Chan, L., S. Mehta, K. Chauhan, P. Poojary, S. Patel, S. Pawar, A. Patel, A. Correa, S. Patel, P.S. Garimella, et al., *National Trends and Impact of Acute Kidney Injury Requiring Hemodialysis in Hospitalizations With Atrial Fibrillation.* J Am Heart Assoc, 2016. **5**(12).
468. Kim, Y.W., K.C. Cha, Y.S. Cha, O.H. Kim, W.J. Jung, T.H. Kim, B.K. Han, H. Kim, K.H. Lee, E. Choi, et al., *Shock duration after resuscitation is associated with occurrence of post-cardiac arrest acute kidney injury.* Journal of Korean medical science, 2015. **30**(6): p. 802-807.
469. Domanovits, H., M. Schillinger, M. Müllner, J. Thoennissen, F. Sterz, A. Zeiner, and W. Druml, *Acute renal failure after successful cardiopulmonary resuscitation.* Intensive Care Med, 2001. **27**(7): p. 1194-9.
470. Tujjar, O., G. Mineo, A. Dell'Anna, B. Poyatos-Robles, K. Donadello, S. Scolletta, J.-L. Vincent, and F.S. Taccone, *Acute kidney injury after cardiac arrest.* Critical care (London, England), 2015. **19**(1): p. 169-169.
471. Geri, G., L. Guillemet, F. Dumas, J. Charpentier, M. Antona, V. Lemiale, W. Bougouin, L. Lamhaut, J.P. Mira, C. Vinsonneau, et al., *Acute kidney injury after out-of-hospital cardiac arrest: risk factors and prognosis in a large cohort.* Intensive Care Med, 2015. **41**(7): p. 1273-80.
472. Chua, H.R., N. Glassford, and R. Bellomo, *Acute kidney injury after cardiac arrest.* Resuscitation, 2012. **83**(6): p. 721-7.
473. Patyna, S., K. Riekert, S. Buettner, A. Wagner, J. Volk, H. Weiler, J.W. Erath-Honold, H. Geiger, S. Fichtlscherer, and J. Honold, *Acute kidney injury after in-hospital cardiac*

arrest in a predominant internal medicine and cardiology patient population: incidence, risk factors, and impact on survival. Ren Fail, 2021. **43**(1): p. 1163-1169.

474. Strand, K., E. Søreide, H. Kirkegaard, F.S. Taccone, A.M. Grejs, C.H.V. Duez, A.N. Jeppesen, C. Storm, B.S. Rasmussen, T. Laitio, et al., *The influence of prolonged temperature management on acute kidney injury after out-of-hospital cardiac arrest: A post hoc analysis of the TTH48 trial.* Resuscitation, 2020. **151**: p. 10-17.
475. Bonato, F.O.B. and M.E.F. Canziani, *Ventricular arrhythmia in chronic kidney disease patients.* J Bras Nefrol, 2017. **39**(2): p. 186-195.
476. Whitman, I.R., H.I. Feldman, and R. Deo, *CKD and sudden cardiac death: epidemiology, mechanisms, and therapeutic approaches.* J Am Soc Nephrol, 2012. **23**(12): p. 1929-39.
477. Dan, G.A., A. Martinez-Rubio, S. Agewall, G. Boriani, M. Borggrefe, F. Gaita, I. van Gelder, B. Gorenek, J.C. Kaski, K. Kjeldsen, et al., *Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP).* Europace, 2018. **20**(5): p. 731-732an.
478. Matzke, G.R., *Status of Hemodialysis of Drugs in 2002.* Journal of Pharmacy Practice, 2002. **15**(5): p. 405-418.
479. Roberts, H. and N. Stallard, *Clearance of Sotalol on continuous venovenous haemofiltration.* Critical Care, 2005. **9**(1): p. P355.
480. Hall, A.J. and A.R. Mitchell, *Introducing Vernakalant into Clinical Practice.* Arrhythm Electrophysiol Rev, 2019. **8**(1): p. 70-74.
481. Ashley, C. and A. Dunleavy, *The Renal Drug Handbook.* 2017.
482. Boriani, G., I. Savelieva, G.A. Dan, J.C. Deharo, C. Ferro, C.W. Israel, D.A. Lane, G. La Manna, J. Morton, A.M. Mitjans, et al., *Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society.* Europace, 2015. **17**(8): p. 1169-96.
483. Woosley, R.L., T. Wang, W. Stone, L. Siddoway, K. Thompson, H.J. Duff, I. Cerskus, and D. Roden, *Pharmacology, electrophysiology, and pharmacokinetics of mexiletine.* Am Heart J, 1984. **107**(5 Pt 2): p. 1058-65.
484. Priori, S.G., C. Blomström-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, P.M. Elliott, D. Fitzsimons, R. Hatala, G. Hindricks, et al., *2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC).* Eur Heart J, 2015. **36**(41): p. 2793-2867.
485. Natarajan, A., A. Pantelopoulos, H. Emir-Farinas, and P. Natarajan, *Heart rate variability with photoplethysmography in 8 million individuals: a cross-sectional study.* Lancet Digit Health, 2020. **2**(12): p. e650-e657.

486. Kim, H.-G., E.-J. Cheon, D.-S. Bai, Y.H. Lee, and B.-H. Koo, *Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature.* Psychiatry investigation, 2018. **15**(3): p. 235-245.
487. *Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.* Circulation, 1996. **93**(5): p. 1043-65.
488. Thio, C.H.L., A.M. van Roon, J.D. Lefrandt, R.T. Gansevoort, and H. Snieder, *Heart Rate Variability and Its Relation to Chronic Kidney Disease: Results From the PREVEND Study.* Psychosomatic medicine, 2018. **80**(3): p. 307-316.
489. Ernst, G., *Heart-Rate Variability-More than Heart Beats?* Front Public Health, 2017. **5**: p. 240.
490. Yang, L., Y. Zhao, B. Qiao, Y. Wang, L. Zhang, T. Cui, and P. Fu, *Heart Rate Variability and Prognosis in Hemodialysis Patients: A Meta-Analysis.* Blood Purification, 2021. **50**(3): p. 298-308.
491. *Evidence-based medicine, in its place.* Lancet, 1995. **346**(8978): p. 785.
492. Neumann, F.J., M. Sousa-Uva, A. Ahlsson, F. Alfonso, A.P. Banning, U. Benedetto, R.A. Byrne, J.P. Collet, V. Falk, S.J. Head, et al., *2018 ESC/EACTS Guidelines on myocardial revascularization.* Eur Heart J, 2019. **40**(2): p. 87-165.
493. Sackett, D.L., W.M. Rosenberg, J.A. Gray, R.B. Haynes, and W.S. Richardson, *Evidence based medicine: what it is and what it isn't.* Bmj, 1996. **312**(7023): p. 71-2.
494. Burlacu, A., S. Genovesi, D. Goldsmith, P. Rossignol, A. Ortiz, P.A. Kalra, J. Malyszko, M. Banach, M. Kanbay, and A. Covic, *Bleeding in advanced CKD patients on antithrombotic medication - A critical appraisal.* Pharmacol Res, 2018. **129**: p. 535-543.
495. Burlacu, A., S. Genovesi, A. Ortiz, C. Combe, C. Basile, D. Schneditz, F. van der Sande, G.T. Popa, C. Morosanu, and A. Covic, *Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update.* Nephrol Dial Transplant, 2019. **34**(6): p. 923-933.
496. Johnson, K.W., J. Torres Soto, B.S. Glicksberg, K. Shameer, R. Miotto, M. Ali, E. Ashley, and J.T. Dudley, *Artificial Intelligence in Cardiology.* J Am Coll Cardiol, 2018. **71**(23): p. 2668-2679.
497. Yang, C., G. Kong, L. Wang, L. Zhang, and M.H. Zhao, *Big data in nephrology: are we ready for the change?* Nephrology (Carlton), 2019.
498. Krumholz, H.M., *Big data and new knowledge in medicine: the thinking, training, and tools needed for a learning health system.* Health Aff (Millwood), 2014. **33**(7): p. 1163-70.
499. SAS-Institute. *What is Big Data?* 2019 [cited 2019 August 15th]; Available from: https://www.sas.com/en_us/insights/big-data/what-is-big-data.html.