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REVIEW

Coronary artery disease in dialysis patients: evidence synthesis, controversies and proposed management strategies

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Abstract

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with end-stage renal disease (ESRD). Clustering of traditional atherosclerotic and non-traditional risk factors drive the excess rates of coronary and non-coronary CVD in this population. The incidence, severity and mortality of coronary artery disease (CAD) as well as the number of complications of its therapy is higher in dialysis patients than in non-chronic kidney disease patients. Given the lack of randomized clinical trial evidence in this population, current practice is informed by observational data with a significant potential for bias. Furthermore, guidelines lack any recommendation for these patients or extrapolate them from trials performed in non-dialysis patients. Patients with ESRD are more likely to be asymptomatic, posing a challenge to the correct identification of CAD, which is essential for appropriate risk stratification and management. This may lead to "*therapeutic nihilism*", which has been associated with worse outcomes. Here, the ERA-EDTA EUDIAL Working Group reviews the diagnostic work-up and therapy of chronic coronary syndromes, unstable angina/non-ST elevation and ST-elevation myocardial infarction in dialysis patients, outlining unclear issues and controversies, discussing recent evidence, and proposing management strategies. Indications of antiplatelet and anticoagulant therapies, percutaneous coronary intervention and coronary artery bypass grafting are discussed. The issue of the interaction between dialysis session and myocardial damage is also addressed.

Keywords Chronic kidney disease · Chronic coronary syndrome · Coronary artery disease · Dialysis · End-stage renal disease · Myocardial infarction

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with end-stage renal disease (ESRD). Coronary artery disease (CAD) is a key disease process, present in 50% of the dialysis population ≥ 65 years of age. Besides the high prevalence of traditional CAD risk factors, such as diabetes and hypertension, patients affected by chronic kidney disease (CKD) are also exposed to other non-traditional uremia-related CVD risk factors, including inflammation, increased oxidative stress, and abnormal calcium-phosphorus metabolism [1].

As glomerular filtration rate (GFR) declines, the probability of developing CAD increases linearly [2]. Furthermore, mortality is higher in dialysis patients (CKD stage G5D) with CAD, cardiac death representing the first cause of mortality in these patients [3]. CAD in CKD patients usually has a pattern of multi-vessel involvement with coronary calcification [4]. Uremia status per se leads to a more severe manifestation of acute myocardial infarction (AMI) including a worse short- and long-term prognosis [5].

CKD-G5D patients were excluded from evidence-generating clinical trials [6], hence, proven therapies tested in non-CKD population can at most be extrapolated, which could potentially yield unsatisfactory or inconclusive results in terms of survival and other outcome benefits such as quality of life. There is general paucity of data in

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dialysis patients. Moreover, the complication rate (either due to drugs or invasive interventions) is significantly higher in this group compared with non-CKD patients [7]. Clinicians caring for dialysis patients often accept the so-called "*therapeutic nihilism*" [8] and refrain from recommending or implementing most of the therapies advised by the general population guidelines. *Therapeutic nihilism* has been repeatedly associated with worse outcomes in CKD-G5D patients [9]. In fact, this approach is not merely due to a lack of knowledge, but to the ambiguity generated by the exclusion of dialysis patients from the clinical trials.

Several questions could be raised when a dialysis patient shows a clinical picture which may suggest CAD occurrence. How to establish a correct diagnosis? In case of ascertained CAD, to prescribe or not an angiographic investigation? In presence of significant coronary artery stenosis is a coronary stent or coronary artery bypass grafting (CABG) most appropriate? What is the optimal medical therapy in these patients?

Here, the ERA-EDTA EUDIAL Working Group reviews the diagnostic work-up and therapy of chronic coronary syndromes (CCSs) (clinical pictures of CAD, excluding the situations of acute coronary event), unstable angina/non-ST elevation myocardial infarction (non-STEMI) and ST-elevation myocardial infarction (STEMI) in dialysis patients, outlining unclear issues and controversies, discussing recent evidence, and proposing management strategies. Specifically, indications of antiplatelet and anticoagulant therapies, percutaneous coronary intervention (PCI) and CABG are discussed. Our review gives due consideration to new and updated cardiology guidelines [10, 11] against a backdrop of paucity of evidence from randomized clinical trials (RCTs) in prescribing drugs or interventions for the very niche category of CKD-G5D patients with CAD. Issues such as epidemiology, risk prediction, pathophysiology and the relationships between CKD and atherosclerosis are considered outside the scope of this review and can be referred to in other recent publications [1].

CCSs in CKD-G5D patients

The European Society of Cardiology (ESC) recently released the 2019 Guidelines on the diagnosis and management of CCS and on the use of cardiac imaging in patients with suspected or known CCS [10, 11].

Chronic coronary syndrome (CCS) in hemodialysis (HD) patients can manifest with a typical exercise-induced chest discomfort or dyspnea, but also with intradialytic or interdialytic symptoms of arterial hypotension or cardiac arrhythmias [12]. HD patients presenting with this symptomatology should be evaluated for CAD, as it is done for patients with known stable CAD, if any symptoms change. In CKD-G5D patients, the clinical picture of CAD may be quite often misinterpreted as it mimics symptoms of fluid overload or intradialytic hypotension (IDH). Furthermore, special attention should be paid to the quite high occurrence of silent myocardial ischemia compared to the general population, although the exact prevalence is yet unknown [13]. In these cases, there may be objective evidence of myocardial ischemia in the absence of any symptoms at all. This can occasionally occur in the context of significantly poor tolerance to exercise due to comorbidities such as anemia, peripheral arterial disease, malnutrition and poor conditioning. Because of the quite atypical presentation of stable angina in CKD-G5D patients, the actual prevalence of CCS in this population is probably underestimated.

The recently published ESC Guidelines recommend periodical screening with ECG for assessment of conduction abnormalities, atrial fibrillation, and silent myocardial infarction (MI) for asymptomatic non-CKD patients with diabetes [10]. We find it reasonable to extend this policy to asymptomatic CKD-G5D diabetic patients. A more advanced assessment with functional non-invasive tests (stress cardiac magnetic resonance imaging scan or stress echocardiography, or perfusion changes by single-photon emission computed tomography, or coronary computed tomography angiography) is recommended for patients at very high cardiovascular risk by ESC Guidelines [10]. The cardiovascular risk in the ESC Guidelines is defined according to the ESC SCORE-European Risk Chart, which is based on gender, age, systolic blood pressure, serum total cholesterol and smoking status (https://www.heartscore.org). In all HD patients, particularly if male and elderly, a careful assessment of cardiovascular risk factors is needed: their removal, if possible (e.g., smoking) or the achievement of their target (e.g., blood pressure and serum cholesterol levels) are mandatory, since ESRD itself is a cardiovascular risk factor.

Limited is the evidence with regards to screening for CAD in asymptomatic HD patients. The 2011 KDIGO Conference on CVD in CKD stated that the data available on this topic were insufficient to advocate screening in asymptomatic CKD patients [14]. Currently, such a screening is not routine in clinical practice except for patients being evaluated for kidney transplantation [13, 15, 16], mainly due to the lack of any compelling evidence that early detection and intervention improve outcomes in this population [19], but also to the lack of reliable risk estimate tools for this population [20], as the majority of patients may be classified as high risk by the ESC SCORE-European Risk Chart. Moreover, non-invasive stress testing has shown reduced accuracy in CKD patients [21]. Dialysis patients are often unable to perform an exercise ECG and sensitivity and specificity for pharmacological stress echocardiography are reduced [22]. In elderly patients, ESC Guidelines suggest to base

"diagnostic and revascularization decisions on symptoms, the extent of ischemia, frailty, life expectancy, and comorbidities" [10]. We could suggest to adopt a similar approach for HD patients.

It has been proposed that CKD-G5D patients should be considered at very high cardiovascular risk when they have ≥ 3 cardiovascular risk factors, including diabetes mellitus, prior cardiovascular disease, > 1 year on dialysis, left ventricle (LV) hypertrophy, LV ejection fraction ≤ 40%, age > 60 years, smoking, hypertension, or dyslipidemia [13]. If this criterion were used, at least 70% of dialysis patients should be fully investigated, even in the absence of symptoms, for the presence of CAD [23, 24]. In the absence of a demonstration that such an aggressive attitude translates into a positive cost/benefit ratio for our patients, we refrain to adopt such an invasive approach. Even though cardiac troponin (cTnT) levels are commonly elevated in asymptomatic ESRD patients, cTnT has evolved from a marker of "no significance", into a "diagnostic and prognostic marker" even without acute coronary syndrome (ACS) [27]. Moreover, it seems that the magnitude of high-sensitivity (hs)-cTnT variations both during and between HD sessions may predict clinically important events [28]. Two solid meta-analyses demonstrated that elevated cTnT levels identified a subgroup of CKD-G5D patients who had poor survival and a high risk of cardiac death despite being asymptomatic [29, 30]. However, it is not clear whether such stratification can help identify CAD and guide treatment in those at highest risk for death [29].

Two important RCTs showed that outcomes on optimal medical therapy are not different from outcomes on optimal medical therapy plus revascularization in patients with stable CCS [31, 32]. Namely, they are the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial which included revascularization plus intensive medical therapy versus intensive medical therapy alone in Class I to III angina [31] and the BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) Trial, which included revascularization versus medical therapy in asymptomatic or mildly symptomatic angina in diabetic patients with objective evidence of ischemia [32]. CKD-G5D patients were notably under-represented in both RCTs, making any assessment of the conclusions of both studies to CKD-G5D patients somehow problematic [31, 32]. Current guidelines openly admit that "data on patients on HD are very limited, making generalizable treatment recommendations difficult" [10].

Since the COURAGE Trial reported no difference in mortality or AMI when performing PCI in addition to medical therapy compared with optimised medical therapy alone for CCS in the general population [33], there is a justified questioning of the benefits of PCI in CKD-G5D patients with CCS. The number of PCIs in patients with CCS declined after the publication of the COURAGE Trial [34]. In addition, in patients with diabetes in the BARI-2D Trial, a strategy of revascularization with CABG or PCI resulted in no difference in mortality compared with optimal medical therapy [32].

The 2018 ESC/EACTS Myocardial Revascularization Guidelines dedicated a specific section to CAD management in CKD patients [35]. However, too few practical aspects were covered in that chapter, since the 2018 Task Force relied only on "on retrospective analyses of RCTs and data from large registries", quoting the previous version published in 2014 [36], and waiting for a first RCT dealing with revascularization strategies in advanced CKD [35].

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) Trial was designed to determine the best management strategy for higher-risk patients with stable CCS. Eligible participants were randomly assigned to an invasive strategy with cardiac catheterization followed by revascularization, if feasible, plus optimal medical therapy or to a conservative strategy of optimal medical therapy [37]. The results showed that patients undergoing invasive procedures fared no better than patients receiving only medications and lifestyle advices. No reduction in the rate of occurrence of cardiovascular death, heart attack, hospitalization for unstable angina, hospitalization for heart failure, or resuscitation after cardiac arrest was observed [38].

The ISCHEMIA Trial included also a sub-study to evaluate the two treatment strategies in patients with advanced CKD who also had significant but stable CCS, the ISCHEMIA-CKD Trial [39]. The recently published results showed that the primary outcome, death or MI at 2.3 years, occurred in 36.4% of the routine invasive group compared with 36.7% of the medical therapy group (p = 0.95). The invasive/medical hazard ratio (HR) was 0.70 with 95% confidence interval (CI) 0.46–1.05 in patients with severe ischemia and 1.30 (95% CI 0.94–1.79) in those with moderate ischemia [40].

There is currently not enough RCT-derived information to determine what the optimal medical therapy for CKD-G5D patients should be. The 2019 ESC Guidelines suggested that "drug therapies must be adapted to each patient's characteristics and preferences" [10]. The lack of specific RCTs on this issue in CKD-G5D patients and the encouraging results obtained by the ISCHEMIA-CKD Trial [40] induce us to accept the algorithm proposed by the ISCHEMIA-CKD Trial researchers (Table 1). Debate remains as far as blood pressure and lipid profile targets, the benefits of antiplatelet agents, relative importance of β-blockers compared to calcium channel antagonists and angiotensin converting enzyme inhibitors (ACE-Is)/receptor blockers (ARBs) and the newer neutral endopeptidase inhibitors are concerned. β-blockers are recommended as

Table 1 Optimal medical management for dialysis patients with chronic coronary syndromes

Lifestyle counselling focused on smoking cessation, nutrition, physical activity, and medication adherence with weight loss targets
Pharmacologic interventions:
Serum LDL cholesterol control: statin with or without ezetimibe
Blood pressure control: angiotensin converting enzyme inhibitors/receptor blockers
β-blockers if history of myocardial infarction or left ventricular ejection fraction < 40%
Antiplatelet agents: aspirin, P2Y12 receptor antagonist if contraindication to aspirin
Treatment of CKD-related conditions, including anemia and bone and mineral disorders
Glycemia control in diabetic patients

the first choice in anti-ischemic therapy [10]. It has been shown that in HD patients β-blocker use was associated with lower risks of sudden cardiac death (irrespective of CAD presence) and death from all causes. β-blockers may substantially improve outcomes in this high-risk population [41, 42]. One study reported that the use of carvedilol represented 85% of all β-blockers [41]. Carvedilol and metoprolol are the most commonly lipophilic β-blockers prescribed to US HD patients; there is evidence that metoprolol is even better than carvedilol [43]. Potential explanations for these findings could be the increased occurrence of IDH after carvedilol [43] and the low dialysis clearance of carvedilol compared with the high dialysis clearance of metoprolol [44].

Although ACE-Is are good first-line antihypertensive agents, most of them are actually removed by the dialyzer. This could help to prevent IDH. However, patients experiencing intradialytic hypertension should be switched to either an ARB or a non-dialyzable ACE-I (i.e., fosinopril) [45]. Most of the ACE-Is should be administered daily, preferably at night in order to minimize the occurrence of both nocturnal arterial hypertension observed in many dialysis patients and IDH [46].

Conclusions

- A high index of clinical suspicion is necessary for a timely diagnosis of CCS in CKD-G5D patients, as clinical pictures can range from symptoms of fluid overload or IDH to silent myocardial ischemia, which occurs especially in diabetics. Patients with symptoms and/or signs of CCS or with already known CCS that show a change in symptoms should be evaluated with non-invasive tests. A more aggressive approach, which includes the use of cardiac angiography techniques, does not seem justified as it does not offer advantages over optimal medical therapy.
- The usefulness of a periodical screening in asymptomatic CKD-G5D subjects for myocardial ischemia is uncertain.
- Research should be directed to define the optimal medical treatment of CCS in CKD-G5D patients.

Unstable angina/non-STEMI in CKD-G5D patients

The in-hospital mortality of dialysis patients admitted with unstable angina/non-STEMI remains greater than that of non-CKD patients, but less than that of patients with STEMI. Dialysis patients with non-STEMI are more likely to be managed conservatively than the non-dialysis patients [47]. The number of CKD-G5D patients with non-STEMI is increasing in the US [48].

The diagnosis of non-STEMI in dialysis patients is difficult, as few of them show the classic history of central chest pain radiating into the arm (41.4% vs. 61.6% in non-dialysis/non-CKD patients). Compared to the general population, more dialysis patients have clinical signs of congestive heart failure (42.2% vs. 27.2%), pulmonary edema (15.4% vs. 8.1%), pulmonary rales and jugular vein distension (25.5% vs. 17.6%) at presentation. Furthermore, they are correctly diagnosed less frequently as affected by AMI on admission to the hospital (19.8% vs. 36.8%) compared to non-dialysis/non-CKD patients [49]. In addition, the cut-off for hs-cTnT increases with the progression of the CKD stages; a higher hs-cTnT cut-off (149.4 ng/L) was suggested in order to make a diagnosis of AMI in dialysis patients [50]. Several issues limit the management of non-STEMI in CKD-G5D patients: lack of evidence to support an interventional approach, timing of PCI and subsequent risk stratification, lack of evidence-based antithrombotic regimens.

In the absence of RCTs prospectively evaluating the impact of invasive strategies, the 2015 ESC Guidelines supported the conclusions of SWEDEHEART registry [51] on dialysis patients: there is no survival benefit of invasive strategies in CKD-G5D patients with non-STEMI [52]. However, a 2018 large propensity score–matched comparison between invasively- and conservatively-managed CKD patients yielded two major conclusions: (a) in-hospital mortality is greater in non-STEMI patients with more severe CKD regardless of treatment strategy; (b) CKD patients presenting with non-STEMI appear to benefit from PCI compared with medical therapy only (even in CKD-G5D population) [53, 54]. Moreover, the same publication and authors provided the most summative advice to date, i.e.: "prospective studies

and RCTs are warranted to substantiate these findings and to assess the best revascularization strategies for this highly vulnerable population" [54].

There are no clear recommendations regarding the timing of intervention in dialysis patients with non-STEMI. In the 2015 ESC Guidelines, dialysis patients are considered at high- to very high cardiovascular risk, therefore requiring an early invasive approach (24–72 h) [52]. However, two meta-analyses supporting these indications did not include CKD-G5D patients [55, 56]. A further recent systematic review did not support an early invasive treatment for severe CKD patients and in particular for those managed with dialysis or renal transplantation [57]. Thus, the impact of early invasive approach remains less clear, requiring future trials and a collaboration between "renal and cardiology specialities" [57].

Conclusions

- Non-STEMI often occurs with atypical symptoms and non-specific ECG changes in CKD-G5D patients.
- No clear recommendations can be made regarding the timing of interventional therapy and the best revascularization strategies in non-STEMI dialysis patients. However, the Eudial Working Group considers reasonable performing angiography in the first 24 h as in high risk, non-CKD-G5D, patients affected by a heart disease.
- Drug treatment of non-STEMI does not differ from that of STEMI in CKD-5GD patients (see next section).

STEMI in CKD-G5D patients

Acute myocardial infarction (AMI) is frequent in ESRD patients, although STEMI is not a frequent presentation of AMI. Data of AMI hospitalizations collected from the US Renal Data System (USRDS) database hospitalizations from April through June 2000 showed that 19.1% of dialysis patients had ST elevation *vs.* 35.9% of non-dialysis patients [5]. Moreover in the US, among 86,305,292 discharge records of 11 years (2003–2013) from National Inpatient Sample, 30,072 were represented by CKD-G5D patients hospitalized with STEMI [58]. In a large Swedish population (n = 57,477) hospitalized for ACS only 22% of patients with estimated GFR (eGFR) < 15 mL/min (n = 806) had a STEMI) [59]. In a more recent update of the Swedish register, out of 289,699 patients with AMI, 1,398 were on dialysis and 21.0% of them had STEMI [60]. Similar data are those of a US cohort (n = 274,777 patients with AMI, of which 2390 were CKD-G5D patients). Few dialysis patients had STEMI: 17.6% were ESRD patients, whereas 32.5% were non-CKD patients [49].

Interestingly, CKD-G5D 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 [61]. This is possibly due to delay in the diagnosis, atypical presentation symptoms and higher comorbid conditions. Despite the high mortality rate of ESRD patients with STEMI, there are no clear treatment and management recommendations for them.

In-hospital mortality rate of CKD-G5D patients with STEMI was 23.7%, which was higher than that of non-CKD and renal transplant patients (8.4% and 8.5%, respectively; renal transplant *vs.* CKD-G5D adjusted odds ratio (OR): 0.37, 95% CI 0.33–0.43; P < 0.001) [58]. There is no consensus among cardiologists about the management of dialysis patients with STEMI due to poor outcomes and the high risks of invasive coronary revascularization and evidence-based pharmacotherapy, that necessitate correct patient selection, precise healthcare and decision about timing of intervention. However, earlier post-STEMI PCI was associated with better cumulative survival of CKD patients including ESRD patients [61].

Currently, statin, aspirin, thrombolytic therapies and other evidence-based treatments are less frequently administered to dialysis patients than to the general population. Of 30,072 ESRD patients with STEMI, 65.2% received reperfusion therapy whilst only 2.1% received thrombolysis; 50.5%, 32.2% and 6.3% of the ESRD cohort underwent coronary angiography, PCI and CABG, respectively [58].

Two sequential scenarios should be considered with regards to treatment in CKD-G5D patients with STEMI: a) treatment in the coronary care unit; b) treatment after discharge from the coronary care unit.

a) Treatment in the coronary care unit

Both the European [59] and the American study [49] reported a lower percentage of reperfusion therapy in ESRD patients hospitalized for an ACS compared to non-CKD patients (both studies did not analyse the STEMI and non-STEMI populations separately). The Swedish study reported reperfusion therapy in 49.4% of CKD-G5D patients vs. 77.3% of patients with a eGFR > 90 mL/min [OR 0.49 (95% CI 0.31–0.79)] [59]. In addition, the percentage of ESRD patients undergoing primary PCI versus thrombolysis was also lower (42.5% in ESRD patients vs. 70.3% in patients with eGFR > 90 mL/min [OR 0.41 (95% CI 0.21–0.79)] [59]. Similarly, Shroff et al. reported an immediate reperfusion strategy in 42.9% of ESRD patients *vs.* 70.8% in non-CKD patients (P < 0.001) [8]. Thrombolysis and primary PCI were performed in 26.4% and 15.6%, respectively, of CKD-G5D patients *vs.* 41.9% and 27.9% respectively, of non-CKD patients (P < 0.001) [37]. An update of the Swedish register was recently published [60]: CKD-G5D patients were treated more

invasively in 2012–2013 than in 1995–1996. In-hospital PCI increased from 1.1% (1996–1997) to 40.0% (2012–2013), in-hospital CABG from 0.0% (1996–1997) to 4.0% (2012–2013) and reperfusion therapy in STEMI patients from 27.8% (1996–1997) to 56.0% (2012–2013) ($P < 0.01$ for all). However, dialysis patients continued to receive fewer invasive therapies than non-dialysis patients: 40.0% vs. 60.0% in-hospital PCI and 56.0% vs. 81.3% reperfusion for STEMI (2012–2013) [60].

The recent 2017 ESC Guidelines on STEMI stated that decisions on reperfusion in patients with STEMI have to be made independently from any assessment of renal function [62]. However, it is important to estimate the eGFR as soon as possible. No specific indication about reperfusion therapy in CKD-G5D patients was proposed. The guidelines indicate reperfusion therapy in all patients with symptoms of ischemia of < 12 h duration and persistent ST-segment elevation [62]. If timely primary PCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications [63]. There seems to be no reason to consider ESRD a contraindication to thrombolysis, as major bleeding occurrence is not increased in this population [64]. Many studies performed in populations with heart disease demonstrated that PCI is more effective than thrombolytic therapy for the treatment of STEMI [65]. In the US, between 2003 and 2011, the use of in-hospital PCI in ESRD patients with STEMI increased from 18.6 to 37.8% ($P < 0.001$) [66]. A reduction of major bleeding episodes has been described in AMI patients in recent years, likely due to the shift in reperfusion method from thrombolysis to PCI with a resulting reduction in thrombolysis interventions [67].

Guidance in drug therapy for STEMI in CKD-G5D patients is limited. Only aspirin and unfractionated heparin (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 [68, 69].

Conclusions

- STEMI is not a frequent clinical presentation of AMI in CKD-G5D patients.
- Immediate reperfusion for STEMI has lower uptake in dialysis than in non-CKD patients, although there is a recent trend towards increased use of immediate invasive procedures also in dialysis patients.
- The EUDIAL Working Group supports the suggestion/recommendation of the ESC Guidelines [62], that the decision on immediate reperfusion with PCI should be independent of the severity of renal impairment.
- If immediate (< 2 h) PCI cannot be performed, CKD-G5D should not be considered a contraindication to thrombolysis [63].
- Aspirin and unfractionated heparin are the preferred agents for STEMI in ESRD patients.

b) Treatment after the discharge from the coronary care unit

Dual antiplatelet therapy (DAPT) reduces the risk of stent thrombosis and the rate of spontaneous AMI in patients undergoing PCI and coronary stenting [70]. However, it is necessary to weigh the hemorrhagic risk against the potential benefit, because DAPT is associated with an increase in bleeding events, particularly in high-risk population like CKD-G5D patients. The ESC Guidelines validated a hemorrhagic risk score for DAPT duration decision-making at the time of coronary stenting [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 suggested [71].

As CKD-G5D patients have virtually no renal function, they start with a PRECISE-DAPT score of 25. Since dialysis patients are often elderly, anemic and with previous bleeding episodes, the score is not usable in this population. A Swedish prospective cohort study of 36,001 patients compared DAPT prolonged after 3 months with DAPT stopped at 3 months in patients with ACS and known serum creatinine [72]. Primary study outcome was the composite of death, AMI, or ischemic stroke within day 111 and 365 from discharge. A longer DAPT duration, as compared with the 3-month DAPT, was associated with lower HR for study outcomes in each CKD stratum. However, statistical significance was lost in patients with eGFR < 30 mL/min [HR 0.93 (95% confidence interval 0.70–1.24)] [72].

Testing even shorter periods of DAPT in patients at high bleeding risk (including also patients with advanced CKD), two RCTs showed that one-month DAPT is as safe as longer therapy if dedicated stents are used (a polimer-free biolimus-drug coated stent in LEADERS FREE trial [73], and

a polymer-based zotarolimus-eluting stent in ONYX ONE trial [74]). However, it must be underlined that both trials included patients with creatinine clearance < 40 mL/min, not specifying how many were CKD-G5D patients and, in this case, if the results were comparable to those of non-dialysis patients.

Even if, from a theoretical point of view, all ESRD patients should have a short DAPT, some authors investigated the benefits and risks of long DAPT compared to short DAPT after coronary drug-eluting stent implantation in patients undergoing HD. A nested case–control Taiwan study compared the long-term benefits and risks of prolonged (> 6 months) and ≤ 6 months DAPT use, the primary outcomes being death and AMI [75]. The study conclusion was that > 6 months of DAPT use was not associated with primary or secondary outcomes different from shorter-term use. However, an increase in bleeding events was not observed in patients treated with long DAPT [75]. In conclusion, scarce and conflicting evidence exists about safety and optimal duration of DAPT in CKD-G5D patients with ACS.

End-stage renal disease (ESRD) patients with ACS are often under-treated as far as other cardioprotective drugs are concerned. Shroff et al. showed that, after AMI, dialysis patients were discharged from the hospital with a significantly lower prescription of aspirin (66.1% vs. 78.3%, P < 0.001), β-blockers (56.2% vs. 62.7%, P < 0.001) and ACE-Is (40.1% vs. 62.4%, P < 0.001) compared to patients with preserved renal function [49]. Similar data were reported by the Swedish register [crude OR 0.60 (95% CI 0.51–0.68)] [59].

The update of the Swedish register showed that dialysis patients received more medication at hospital discharge in the most recent years: prescription of aspirin increased from 67.3 to 90.9%, of β-blockers from 59.3 to 86.4%, of ACE-I from 21.4 to 54.5%, from 1996 to 2013 [60]. Furthermore, DAPT prescription increased from 0.0 to 61.7% (P < 0.001 for all prescriptions). While the use of secondary preventive drugs at the end of the study period (2012/2013) was comparable among dialysis and non-dialysis patients for aspirin (90.9% vs. 92.6%) and β-blockers (86.7% vs. 88.3%), the use of DAPT (61.7% vs. 78.0%) and ACE-Is (54.5% vs. 77.9%) was still lower in dialysis patients [60].

As expected, the long-term outcomes of revascularization in dialysis patients with ACS are worse than in patients with preserved or less compromised renal function. This applies to both CABG and PCI [76, 77].

Less clear is whether it is better to perform PCI or CABG within the CKD-G5D population. Some studies suggest that short-term mortality is greater in patients undergoing CABG, but that CABG provides an advantage in terms of long-term survival. Chang, based on recommendations made by the 2014 ESC Myocardial Revascularization Guidelines [36], described a higher mortality rate at 6 months in dialysis patients with previous ACS and undergoing CABG compared to those who had PCI (HR 1.08, 95% CI 1.01–1.16), but a lower mortality rate at 5 years (HR 0.86, 95% CI 0.82–0.90) [78]. A meta-analysis comparing the benefits of PCI with drug-eluting stents (DES) versus CABG in CKD patients with multi-vessel disease showed that HD patients with DES had higher long-term all-cause mortality (OR 1.26, 95% confidence interval 1.19–1.34) and repeat revascularization (OR 2.83, 95% CI 2.61–3.07), but lower short-term mortality (OR 0.31, 95% CI 0.27–0.36) compared to HD patients who underwent CABG [79]. A more recent meta-analysis confirmed a better survival in CKD-G5D patients undergoing CABG compared to those who had PCI, also considering the increase of the number of PCIs over time (HR 0.92, 95% CI 0.89–0.96) [80]. The lack of RCTs and the fact that patients who underwent CABG were probably those with lesser comorbidity suggests caution in interpreting these data. Moreover, it appears that within the dialysis population undergoing PCI, the benefit from DES is higher compared to bare metal stents [81].

Few data are available regarding revascularization procedures in the kidney transplant population. One study showed that renal transplant recipients in the US have comparable long-term survival after both PCI and CABG; however, the relative risk of cardiac death or AMI was lower after CABG with internal mammary grafting than after PCI [82].

Conclusions

- The optimal duration of DAPT following PCI in dialysis patients is debated because of the lack of supportive trials.
- Based on the PRECISE-DAPT score, most of dialysis patients should be considered at high risk of bleeding. Scarce and conflicting evidence exists about safety and optimal duration of DAPT in CKD-G5D patients with ACS. Some observational data suggest that short-term DAPT is effective in this population.
- Other therapeutic measures such as ACE-Is or β-blockers were traditionally under-used in dialysis patients. The recent trend towards a larger use is supported by the EUDIAL Working Group.
- Observational studies suggest that PCI is associated with better short-term survival, but with greater long-term mortality compared to CABG in CKD-G5D patients. When evaluating a revascularization strategy, the least invasive approach should be advised in the most fragile patients, taking into account their clinical conditions and life expectancy.
- DES are associated with better outcomes than metal stents in CKD-G5D patients.

Interaction between myocardial damage and the HD session

The HD treatment per se may induce myocardial ischemia [83]. From a hemodynamic point of view, the increased preload, due to hypervolemia and to the high blood flow rates of arterio-venous fistulas, is a major risk factor [84]. McIntyre et al. showed that global myocardial blood flow is acutely reduced during the HD treatment [85]. A decrease of LV systolic function during the dialysis session is associated with an increase in serum levels of myocardial injury enzymes, suggesting a HD-related acute myocardial stress [86]. Several studies demonstrated a deterioration of ventricular diastolic function during the dialysis session [87, 88]. Furthermore, ventricular diastolic dysfunction could be a complication of transient myocardial ischemia [89]. Owing to the fact that coronary perfusion occurs mainly during the diastolic phase of the cardiac cycle, the ventricular diastolic dysfunction related to the HD session may favour cardiac ischemia and myocardial stunning [90].

Fluid overload is associated with alteration of both systolic and diastolic cardiac function in HD patients [91] and the correction of fluid overload with careful attention to the assessment of the dry weight results in an improvement of these parameters [92]. An excessive interdialytic weight gain requires a high ultrafiltration rate during the HD session. This is the main cause of too a rapid intravascular volume depletion leading to hemodynamic alterations, such as IDH and marked heart rate increase. Both may be stressful for the myocardial perfusion, particularly in the presence of pre-existing CAD.

The occurrence of episodes of IDH can be a serious clinical problem in CAD patients. CVD, including systolic and diastolic dysfunction and ischemic heart disease, are important risk factors for the development of IDH, which is associated with poor cardiovascular outcomes [93]. Moreover, IDH is independently associated with myocardial stunning [94, 95]. Repetitive intradialytic reversible ischemic episodes due to IDH could lead to myocardial fibrosis and systolic dysfunction [96]. All interventions aimed to prevent the onset of IDH such as optimization of the dialysis prescription and interventions to achieve a lower weight gain during the interdialytic interval, may be helpful in CAD patients undergoing HD. Finally, the potential interactions between the HD session and the antihypertensive drugs have been previously described.

Conclusions

- The HD session may induce myocardial ischemia leading to ventricular systolic and diastolic dysfunction.
- Recurrent IDH episodes may lead to irreversible myocardial damage. Particular attention must be paid to optimize the dialysis prescription and the assessment of the dry weight in HD patients with CAD.

Conclusions

Chronic kidney disease (CKD) is associated with a very high risk for CAD. The incidence, severity and mortality of CAD is higher in dialysis patients than in non-CKD patients. Besides the high prevalence of traditional CAD risk factors, such as diabetes and hypertension, CKD patients are also exposed to other non-traditional, uremia-related CVD risk factors, including inflammation, oxidative stress, and abnormal calcium-phosphorus metabolism [1].

Coronary artery disease (CAD) management is complicated in CKD patients, due to comorbid conditions and potential side effects during interventions. Patients with CKD-G5D are more likely to be asymptomatic, posing a challenge to the correct identification of CAD, which is essential for appropriate risk stratification and management. This may lead to "*therapeutic nihilism*", which has been associated with worse outcomes.

Guidelines frequently do not mention CKD-G5D patients or extrapolate recommendations from trials performed in non-dialysis patients. Furthermore, there are very few RCTs focusing on CAD in CKD-G5D patients. Additional prospective studies focusing on diagnosis, prevention, and treatment of CAD are needed in CKD-G5D patients.

Given the lack of evidence in this population, current practice is informed by observational data with a significant potential for bias; then, unanswered key questions in CKD-G5D patients with CAD remain (Table 2).

Table 2 Unanswered key questions in CKD-G5D patients with CAD

CCS
Optimize definition of the very high-risk population that may benefit from extensive testing for CAD while still asymptomatic
Define optimal management strategy for patients with CCS: optimal medical therapy alone or in combination with early intervention?
Are there specific optimal medical therapy strategies in CKD-G5D patients?
Non-STEMI
Define optimal timing of intervention
Define the optimal intervention
Define the optimal antithrombotic regimen
Are there specific optimal medical therapy strategies in CKD-G5D patients?
STEMI
Acute setting
Identify and correct the factors that underlie the lower rates of primary reperfusion in CKD-G5D patients
Define the optimal antithrombotic regimen
Outpatient follow-up
Optimal duration of DAPT following PCI
Identify and correct the factors that underlie the frequent under-treatment of CKD-G5D patients
Are there specific optimal medical therapy strategies in CKD-G5D patients?

CKD chronic kidney disease, *G5D category* GFR < 15 mL/min/1.73 m^2 and on dialysis, *CAD* coronary artery disease, *CCS* chronic coronary syndrome, *non-STEMI* non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, *DAPT* dual antiplatelet therapy, *PCI* percutaneous coronary intervention

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals (1) Statement of human rights. (2) Statement on the welfare of animals. This article does not contain any studies with human participants or animals performed by any of the authors.

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