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The treatment of coronary artery disease in patients with chronic kidney disease: gaps, challenges and solutions.

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Running title: treatment of coronary artery disease in patients with kidney disease
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Abstract:
Background: Chronic kidney disease (CKD) is associated with a high burden of coronary artery disease (CAD), which remains the leading cause of death in CKD patients. Despite the high cardiovascular risk, ACS patients with renal dysfunction are less commonly treated with guideline-based medical therapy and are less frequently referred for coronary revascularization.
Summary: The management of CAD is more challenging in patients with CKD than in the general population due to concerns regarding side effects and renal toxicity as well as uncertainty regarding clinical benefit of guideline-based medical therapy and interventions. Patients with advanced CKD and especially those receiving dialysis have not traditionally been represented in randomized trials evaluating either medical or revascularization therapies. Thus, only scant data from small prospective studies or retrospective analyses are available. Recently published studies suggest that there are significant opportunities to substantially improve both cardiovascular and renal outcomes of patients with CAD and CKD including new medications and interventions. Thus, the objective of this review is to summarize the current evidence regarding the management of CAD in CKD patients, in particular with respect to improvement of both cardiovascular and renal outcomes.
Key massages: Adequate medical therapy and coronary interventions using evidence based strategies can improve both cardiac and renal outcomes in patients with CAD and CKD.

Introduction:

Cardiovascular disease is the leading cause of morbidity and mortality among patients with chronic kidney disease (CKD). Even after adjustment for known cardiovascular risk factors, including diabetes and hypertension, mortality risk progressively increases with worsening CKD . As glomerular filtration rate (GFR) declines the probability of developing coronary artery disease increases linearly, and patients with GFR<60ml/min/1.73 m^2 have 2 to 3 fold increased CV mortality risk, relative to patients without CKD [1]. Management of CAD is complicated in CKD patients due to the likelihood of comorbid conditions and potential for side effects. Despite their high cardiovascular risk, ACS patients with renal dysfunction are less commonly treated with guideline-based medical therapy and are less frequently referred for coronary revascularization. This observation, referred to as the "treatment risk paradox," has been well described and may be explained by physicians' concerns regarding possible non-renal side effects as well as renal toxicities. Furthermore, patients with severe CKD have traditionally been underrepresented in most large cardiovascular clinical trials [2]. Therefore, recommendations for both medical and revascularization of CAD have relied heavily on extrapolation of results from the non-CKD population. This review summarizes the available updated data regarding the treatment of coronary artery in patients with CKD and also identifies knowledge gaps and areas of controversy.

Medical treatment of cardiovascular disorders in patients with CKD

Medical treatment remains the cornerstone of treatment for patients with coronary artery disease and has been associated with improved survival and quality of life. Adequate control of traditional risk factors including hypertension, dyslipidemia and diabetes in patients with coronary artery disease and CKD is of particular importance since it not only protects from adverse cardiovascular outcomes, but may also delay CKD progression. In this section we present clinical data and recommendations regarding medical therapy of patients with CAD and CKD, while focusing on new medications. An algorithm for medical therapy of CKD patients with CAD is presented in figure-1.

Treatment of cardiovascular risk factors

Anti-hypertensive medications: Recommended blood pressure targets for patients with CKD vary in the different international clinical guidelines. While the 2018 ESC/ESH guidelines recommended a systolic blood pressure target of 130-139 mmHg (with a lower target of <130mmHg in diabetics) the 2017 ACC/AHA offered a target of <130/80mmHg and the more recent 2021 KDIGO guidelines recommended a systolic blood pressure target of <120mgHg [3,4]. For patients with hypertension and CKD there are randomized controlled trials testing outcomes for renin-angiotensin system inhibitors, calcium channel and beta blockers [4]. In a large meta-analysis including approximately 65,000 patients with or without diabetes and with or without albuminuria, the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in people with CKD reduced the risk for kidney failure and cardiovascular events as compared to placebo or other anti-hypertensive drugs [5]. Among patients with CAD, treatment with ACE-Inhibitors or ARBs has been associated with improved cardiovascular outcomes, mainly in patients with reduced left ventricular function. Accordingly, ACE-inhibitors or ARBs should be considered as first line drugs for blood pressure control in patients with concomitant CAD and CKD. While advanced renal failure is not a contraindication for ACE inhibitors or ARBs, special attention to prevent hyperkalemia is warranted. Patiromer, a sodium free potassium binding polymer has been demonstrated to be effective in maintaining lower serum potassium levels and allowing optimization of renin-angiotensin system inhibitors dose in patients with heart failure [6]. Recent data support similar effects of patiromer in CKD patients treated with renin-angiotensin system inhibitors for other types of cardiovascular diseases [6].

Lipid lowering therapy: Statin therapy has been associated with improved cardiovascular outcomes in patients with coronary artery disease and is therefore recommended to all patients including those with concomitant CKD. Nevertheless, the cardiovascular benefit with statins decreases with decline of GFR, especially among patients on hemodyalysis. The AURORA study was a randomized, double-blind, prospective trial involving 2776 patients who were undergoing maintenance hemodialysis. Of them, 40% had a history of cardiovascular disease. Patients were randomly assigned to receive rosuvastatin, 10 mg daily, or placebo. Treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke [7]. The SHARP study investigated the cardiovascular effect of ezetimibe therapy in addition to a statin in patients with advanced CKD, including those on dialysis. The addition of ezetimibe to simvastatin reduced the rate of major atherosclerotic events compared with placebo among a wide range of patients with CKD including those on dialysis [8]. In recent years there has been a growing interest in the treatment with PCSK9 inhibitors in addition to statin therapy for further reduction of cardiovascular risk in patients with coronary artery disease. A subanalysis of the FOURIER study showed that LDL lowering therapy with evolocumab was effective and safe across all CKD groups. Interestingly, absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was greater in patients with more advanced CKD [9].

SGLT2 inhibitors: This new class of drugs was initially developed for glucose lowering in patients with type 2 diabetes. However, results from randomized controlled trials have demonstrated a significant reduction of different cardiovascular outcomes including cardiovascular mortality, heart failure hospitalizations and myocardial infarction in different populations of high risk patients regardless of the presence of diabetes [10-19]. Furthermore, the SGLT-2 inhibitor studies have demonstrated a consistent renoprotective effect regardless of the presence of diabetes, cardiovascular disease or renal dysfunction at baseline. Among patients with CKD, both empagliflozin and dapagliflozin reduced the risk of the composite outcome of kidney disease progression or cardiovascular death**.** Accordingly, The 2021 ESC guidelines recommended that an SGLT2 inhibitor with proven outcome benefits should be considered for the prevention of renal deterioration and mortality in patients with CKD regardless of the presence of diabetes [20]. A summary of renal and cardiovascular outcomes of the different SGLT-2 inhibitors randomized control trails is presented in table-1.

Anti-platelet therapy: In patients with established cardiovascular disease antiplatelet therapy significantly reduced the yearly risk of major cardiovascular events. The different pathophysiology of cardiovascular disease and abnormal platelet function has resulted in substantial uncertainty concerning the risks and benefits of antiplatelet therapy in patients with CKD. Some randomized control trials involving CKD population showed that more intensive anti-platelet therapy could be of reduced benefit in preventing major cardiovascular events [21] whereas others suggested benefits of similar or even greater magnitude [22,23]. A large meta-analysis including 27,773 patients with CKD with and without co-existing coronary artery disease who were treated with different anti-platelet drugs including aspirin and P2Y12 receptor inhibitors demonstrated the association of antiplatelet therapy with a 15% reduction in the risk of major cardiovascular events and a 48% reduction of dialysis access failure [24]. Antiplatelet therapy had no significant effect on all-cause death or kidney failure events. Not surprisingly, both major and minor bleeding events were significantly more common with antiplatelet therapy. For every 1000 persons with CKD treated with antiplatelet therapy for 12 months, 23 major cardiovascular events will be prevented while nine major bleeding events will occur. These data suggest that patients with coronary artery disease and concomitant CKD should receive anti-platelet therapy. However, special attentions should be given to bleeding risk assessment and strategies to prevent bleeding events. Among CKD patients with ACS or those following coronary revascularization, the decision regarding the type of P2Y12 receptor inhibitor (prasugrel, ticagrelor or clopidogrel) in addition to aspirin should be made following a careful assessment of bleeding and thrombotic risks. Among patients on hemodialysis, clopidogrel should be preferred over prasugrel and ticagrelor.

Treatment for patients with diabetes mellitus

Glucagon like protein -1 (GLP-1) receptor agonists: Liraglutide, semaglutide and dulaglutide have been associated with a reduction in the risk of major adverse cardiovascular events among diabetic patients at high cardiovascular risk including those with concomitant coronary artery disease. The cardiovascular benefit with GLP-1 receptor agonists treatment remained constant in patients with CKD. Moreover, treatment with GLP-1 receptor agonists has been associated with a significant reno-protective effect including a lower rate of new onset or worsening proteinuria. Accordingly, GLP-1 receptor agonists have been approved for high risk diabetic patients with an eGFR>15ml/min/1.73m² [25].

Fineranone, a new non-steroidal mineralocorticoid receptor antagonist has recently demonstrated a significant improvement in renal and cardiovascular outcomes in diabetes patients with CKD [26,27]. The FIDELIO-DKD study included 5,734 diabetic patients with CKD (a UACR of 30- 300 with eGFR of 25-59 ml/min/1.73 m^2, or UACR of >300 with an eGFR of 25-75 ml/min/1.73 m^2) who were randomly assigned to receive finerenone or placebo. Of them 2605 (45.9%) had a history of cardiovascular disease. The study demonstrated that in diabetic patients with predominantly stage 3-4 CKD , treatment with finerenone resulted in a lower risk of CKD progression (end stage renal failure, a sustained decrease of at least 40% in the eGFR from baseline or death from renal causes) and cardiovascular events (the composite of CV death, nonfatal myocardial infarction, stroke or hospitalization for heart failure) than placebo [26]. The FIGARO-DKD study randomly assigned 7,437 diabetic patients with a wide range of CKD to receive finerenone or placebo. Eligible patients had stage 2-4 CKD with moderate albuminuria or stage 1- 2 CKD with severe albuminuria. Of them, 3,330 (45.3%) had a history of cardiovascular disease. The study demonstrated that among diabetic patients with a wide range of CKD, treatment with finerenone significantly reduced the primary cardiovascular composite outcome as well as the secondary composite renal outcome [27]. These consistent results strongly support finerenone treatment in diabetic patients with CKD, including those with previous coronary artery disease, for the reduction of both cardiovascular and renal adverse outcomes.

Coronary revascularization:

The choice of medical therapy alone or revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in symptomatic patients with CKD is controversial. Despite the lack of dedicated data , CKD patients presenting with a STEMI undergo primary PCI similar to those with normal kidney function. Among patients with non–ST-segment elevation–ACS, observational studies support an early invasive strategy with coronary angiography and subsequent coronary revascularization over a conservative approach [28]. However, the early invasive approach was not associated with survival benefit among patients with eGFR<60 ml/min/1.73 m^2.

Short and long term procedural risks of both PCI and CABG are greater among patients with CKD compared to those with normal renal function. The data to support PCI or CABG in patients with CKD are limited and are taken mainly from observational studies. A meta-analysis including 3993 patients encompassing 526 patients with stage 3 to 5 CKD

suggested some benefits to CABG over PCI in moderate CKD [29]. Among dialysis patients, observational studies suggest a short-term higher risk of mortality and stroke with CABG versus PCI, but a long-term higher risk of adverse outcomes with PCI versus CABG. Decisions regarding the type of revascularization (surgical versus percutaneous) should be made individually for each patient following consideration of short- and long-term risks and benefits of each intervention. Special attention should be given to comorbidity burden, CKD and overall related-prognosis, frailty and patient preference.

Percutaneous Coronary interventions:

Patients with CKD who are planned for coronary angiography and subsequent PCI represent an important high risk group for both cardiovascular and renal adverse outcomes. Main causes of acute kidney injury (AKI) in patients undergoing PCI include the exposure to contrast media, hemodynamic instability and athero-embolization. Contrast-induced nephropathy (CIN) is defined as the development of AKI following contrast media administration in the absence of an alternative etiology [30]. The most widely adopted definition of CIN is the Kidney Disease Improving Global Outcomes (KDIGO) definition: an increase in serum creatinine by ≥0.3 mg/dl within 48 h after contrast media exposure, or an increase to ≥50% within 7 days [31]. The incidence of CIN in patients undergoing percutaneous coronary intervention (PCI) varies in different populations and may be as high as 15% in high risk groups. In the majority of patients with CIN, renal function returns to baseline values. However, the development of CIN has been associated with worse outcomes, including prolonged hospital stay, irreversible kidney injury including the need for dialysis, and death [30,31].

Several risk factors for the development of CIN have been identified. Of them, baseline renal function appears to be the strongest predictor. Patients with estimated glomerular filtration rates (eGFRs) ≥ 45mL/min/1.73m^2 are at negligible risk for CIN, while in patients with eGFRs<30mL/min/1.73m^2 the risk for CIN may be as high as 27% [32]. The presence of diabetes mellitus may further increase this risk. Other risk factors include renal hypoperfusion (due to volume depletion, cardiogenic shock, acute heart failure etc), advanced age, diabetes mellitus, anemia and low left ventricular ejection fraction [33]. CIN risk assessment can be done using validated scores which incorporate the aforementioned predictors [34,35].

Once the diagnosis of CIN is established there is no specific treatment; hence the main goal is prevention. Prevention of CIN is based on pre-procedural, procedural and post procedural strategies.

Prevention of PCI related AKI

Pre-procedural strategies

Discontinuation of nephrotoxic medications: Ideally, in non-urgent cases, potentially nephrotoxic medications (metformin, non-steroidal anti-inflammatory drugs, diuretics etc) should be discontinued at least 48 h before exposure to contrast media [36].

Intravenous fluids: Adequate hydration with intravenous infusion of normal saline remains a key instrument for CIN prevention. While the dosing, duration, or injection rate for pre and post procedural fluid administration have not been well established, the European Society of Cardiology guidelines recommend the routine administration of intravenous isotonic saline at a rate of 1 to 1ml/Kg/hour for 12 hours before and up to 24 hours after the procedure [37]. Several studies have demonstrated that tailoring hydration rate and total volume according to invasive left ventricular end-diastolic or central venous pressure monitoring [38,39] or bioimpedance vector analysis [40] can reduce the risk of CIN compared with a standard hydration protocol. Moreover, the RenalGuard system (RenalGuard Solutions, Milford, Massachusetts) is a novel device that allows the maximization of intravenous hydration by matching the infused volume to the patient's urine output that allow the dilution of contrast media without volume overexpansion according to urine output. Randomized trials showed benefit in CI AKI prevention using RenalGuard vs standard hydration protocols [41].

High dose statins are the only pharmacological agents that have been shown to decrease the risk of CIN in different randomized controlled trials on patients with CKD undergoing coronary interventions [42]. Possible mechanisms for this reno-protective effect may include improved endothelial function, antioxidant, anti-inflammatory, and antithrombotic effects. Therefore, in statin-naïve patients pre- treatment with high dose statins (rosuvastatin 20/40mg or atorvastatin 80mg) should be strongly considered. Other pharmacological agents including N-acetylcysteine, bicarbonate, trimetazidine and fenoldopam, have failed to show consistent reno-protective effect and are therefore not recommended.

Procedural strategies

Vascular access: Several large trials have showed that radial access is associated with lower incidence of PCI related AKI as compared with femoral access [43]. The mechanism behind this benefit appears to be multifactorial and includes lower rates of major bleeding and hemodynamic instability and reduction of atheroma embolization to the renal arteries by avoiding manipulating the abdominal aorta [42] Therefore, radial access should be preferred over femoral access, when feasible, to decrease the risk of AKI.

Contrast media volume reduction: There is a direct association between contrast media volume and the risk of CIN [44]. A contrast-volume-to-creatinine-clearance (CV/CrCl) ratio >2 has been identified as an independent predictor of CI-AKI in patients with an eGFR <30 ml/min/1.73m² [45]. Coronary procedures using ultra-low contrast volume techniques with CV/CrCl ratio <1 are ideal to minimize the risk for CI-AKI. Several studies have demonstrated that these techniques may be successfully utilized in most patients with CKD undergoing PCI with excellent renal outcomes and without jeopardizing coronary outcomes. The reduction of contrast media administration can be achieved by using diluted contrast, 5-French catheters with no side holes, avoidance of test injections, use of biplane angiography and stent enhancement techniques, increased acquisition rates (15 or 25 frames/s) to improve image quality during diagnostic angiogram and extensive use of intra-coronary imaging with intravascular ultrasound (IVUS) and dextran-based optical coherence tomography (OCT). The latter may allow zero contrast PCI procedures that can be performed if coronary anatomy is known. In the MOZART trial, zero contrast PCI was safely performed through IVUS imaging and significantly reduced the dose of iodine contrast in comparison to an angiography-only approach. However, no clinical benefit (including reduction of CIN) was observed [46].

Several other technologies for the reduction of contrast media exposure have been introduced. Among them are the DyeVert PLUS system that collects contrast media from the aortic root into a reservoir chamber which leads to 15%-40% reduction of contrast media exposure and contrast media aspiration from the coronary sinus immediately following contrast injection. However, both technologies have not shown any clinical benefit yet [47].

Type of contrast media: Recent data on patients with CKD undergoing PCI have showed no significant benefit of the iso-osmolar iodixanol over low osmolar contrast media in preventing CI-AKI [48]. Accordingly, there is no evidence to recommend iodixanol over low-osmolar CM for CI-AKI prevention.

Hemodynamic support: Hypotension during coronary procedures is an important cause of AKI. Hemodynamic support with a percutaneous left ventricular assist device such as Impella (Abiomed, Danvers, Massachusetts), is a feasible strategy for maintaining hemodynamic stability during high-risk PCI. In a single-center retrospective study on 230 patients with left ventricular ejection fraction <35% including 115 subjects supported with Impella and 115 unsupported matched controls undergoing high-risk PCI, CI-AKI was observed in 5.2% of Impella-supported subjects vs. 27.8% in the unsupported group (adjusted OR: 0.13; 95% confidence interval: 0.09 to 0.31; $p < 0.001$) [49]. Impella use was associated with lower incidence of all stages of AKI, including AKI requiring dialysis and there was no association between CKD severity and CI-AKI in the Impella-supported group. The promising result of this study warrants confirmation in large prospective registries. Currently there are no studies showing any effect of hemodynamic support during high risk PCI using intra aortic balloon pump on the risk of AKI .

Remote ischemic conditioning: The mechanism of the reno-protective effect of remote ischemic conditioning remains largely unknown but may include reduced renal ischemia/reperfusion injury [50]. Pre-conditioning with alternating 5-min inflation and 5-min deflation of an upper-arm blood pressure cuff or by inflating/deflating the stent balloon for 30 s after stenting the culprit lesion were associated with a significant reduction of AKI. Nevertheless, given the relatively small studies on remote ischemic conditioning, the feasibility and efficacy of this technique in routine clinical practice remains to be proven.

Cardiac surgery and renal failure

Acute kidney injury (AKI) complicates recovery from cardiac surgery in up to 30 % of patients [51]. Renal ischemia, reperfusion, inflammation, hemolysis, oxidative stress, cholesterol emboli, and toxins contribute to the development and progression of AKI. As many as 2-5% of patients with cardiac surgery-related AKI require renal replacement therapy and this serious complication is associated with a 10-fold increased mortality [52]. In a propensity-matched cohort based on a nationally representative database in the US, CABG for multi-vessel disease was associated with twice more likelihood of developing post-procedural AKI including the need for renal replacement therapy as compared with PCI [53]. Therefore, in patients with CKD and multi-vascular coronary artery disease who may be

treated with either surgical or percutaneous revascularization, the presence of high risk for procedure-related AKI is a strong argument supporting PCI.

Risk factors for cardiac surgery-related AKI may be divided into preoperative (urgent surgery, advanced age, female gender, pre-existing CKD, diabetes mellitus and anemia) intraoperative (Cardiopulmonary bypass (CPB) duration and a need to return to CPB, hypovolemia and hypoperfusion) and postoperative factors (shock, use of inotropes ,vasopressors or diuretics). Several risk stratification systems exist for prediction of cardiac surgery related AKI [54-56]. Of them, the Cleveland Clinic score offers the best prediction [56].

Prevention of cardiac surgery related AKI:

Timing of surgery: The association between the time from coronary angiography to cardiac surgery and the risk for cardiac surgery related AKI is controversial. While some studies have demonstrated that a short period (<3 days) was associated with increased risk of AKI, other studies have failed to show such an association [57,58]. Accordingly, surgical intervention should not be delayed in emergency or urgent cases. The optimization of renal function and correction of other predisposing factors seem to be the correct strategy in clinically stable patients with risk factors for AKI.

Pre-procedural prevention of cardiac surgery related AKI:

Discontinuation of potentially nephro-toxic drugs including NSAIDS, metformin, and diuretics prior to surgery is strongly recommended [59]. Recommendations regarding discontinuation of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are less clear end evidence exists suggesting that these drugs may be safely continued until the day of surgery [60]. Some evidence exists regarding renal protective effect of preoperative statin therapy [61].

Anemia and Transfusion: Studies have demonstrated that preoperative anemia is significantly associated with AKI during cardiac surgery [62]. Decreased hemoglobin concentration with an effect cut-off value of < 9 g/dl and volume of transfused RBC, especially on the day of surgery were independent risk factors for cardiac surgery related AKI [63] . Accordingly, severe hemodilution and blood transfusion in patients with hemoglobin levels > 8 g/dl should be avoided. When RBC transfusion cannot be avoided, it should be minimized and administered at least 1–2 days before surgery [64]. Among elective patients, the preoperative optimization of anemia using the infusion of erythropoietin (300 IU/kg) reduced the risk of AKI and improved postoperative renal function [65].

Hydration: Maintenance of volume status is extremely important in the prevention of AKI in cardiac surgery. Appropriate fluid management after cardiac surgery is complex, especially in patients in whom the cardiopulmonary bypass machine is used since fluid can be sequestered in the extracellular space while intravascular space remains volume depleted. Using diuretics in these patients leads to further intravascular dehydration. A low urine flow rate after furosemide administration was independently associated with AKI in post cardiac surgery patients [66]. The RenalGuard is a novel device that allows the maximization of intravenous hydration by matching the infused volume to the patient's urine output. It has been shown to reduce the rate of AKI and is safe to use in patients undergoing cardiac surgery [67].

Cardiopulmonary bypass: May contribute to the pathogenesis of AKI by activating a systemic inflammatory response, altering regional blood flow and vasomotor tone in kidneys and generating microemboli [67]. The duration of cardiopulmonary bypass is an important independent risk factor for AKI in the postoperative setting [68]. On the other hand, the routine use of pulsatile perfusion during cardiopulmonary bypass and a target MAP>60mmHg might be beneficial in renal preservation [69]. Off-pump cardiac surgery appears to be a logical step toward minimizing the risk of postoperative AKI. However, studies have provided conflicting results. The CORONARY trial found that off-pump compared with on-pump CABG surgery reduced the risk of postoperative AKI, but did not alter one year kidney function [70]. These findings were further supported by other studies [71, 72]. Evidence from small studies have suggested that minimally invasive surgery might also be renoprotective [73].

Conclusions:

The combination of CKD with CAD is associated with poor outcomes and poses a great challenge to the treating physician. Treatment decisions should be tailored individually to each patient following a multi-disciplinary discussion and consideration of relevant risks and benefits, as well as patient preference. While the clinical benefit from several guideline-based therapies may be unclear, several studies suggest that there are significant opportunities to substantially improve both cardiovascular and renal outcomes of these patients, including treatment with new lipid-lowering medications, SGLT-2 inhibitors GLP-1 receptor agonists and fineranone. Furthermore, several strategies

have resulted in lower rates of both CABG and PCI related AKI. Ongoing work is needed for further understanding of the efficacy and safety of different interventions and drugs that may further improve the outcome of patients with CAD and CKD.

Conflict of Interest

The authors have no conflicts of interest to declare

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Author contribution

Ilya Losin - Data collection, manuscript design, manuscript writing, critical revision of the manuscript approval of final version

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David Pereg - Data collection, manuscript design and conception, manuscript writing, approval of final version

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Figure legend:
Figure-1: An algorithm for medical therapy of CKD patients with coronary artery disease.
CKD – chronic kidney disease
DAPT – dual antiplatelet therapy
eGFR - estimated glomerular filtration rate
LDL-C – low-density lipoprotein cholesterol
PCSK9 - Proprotein convertase subtilisin/kexin type 9
SGLT2 - Sodium Glucose co-Transporter 2
CV – Cardiovascular
ACE-I - Angiotensin-converting-enzyme inhibitor
ARB - Angiotensin II receptor blockers
GLP-1 RA - Glucagon-like Peptide-1 receptor agonist

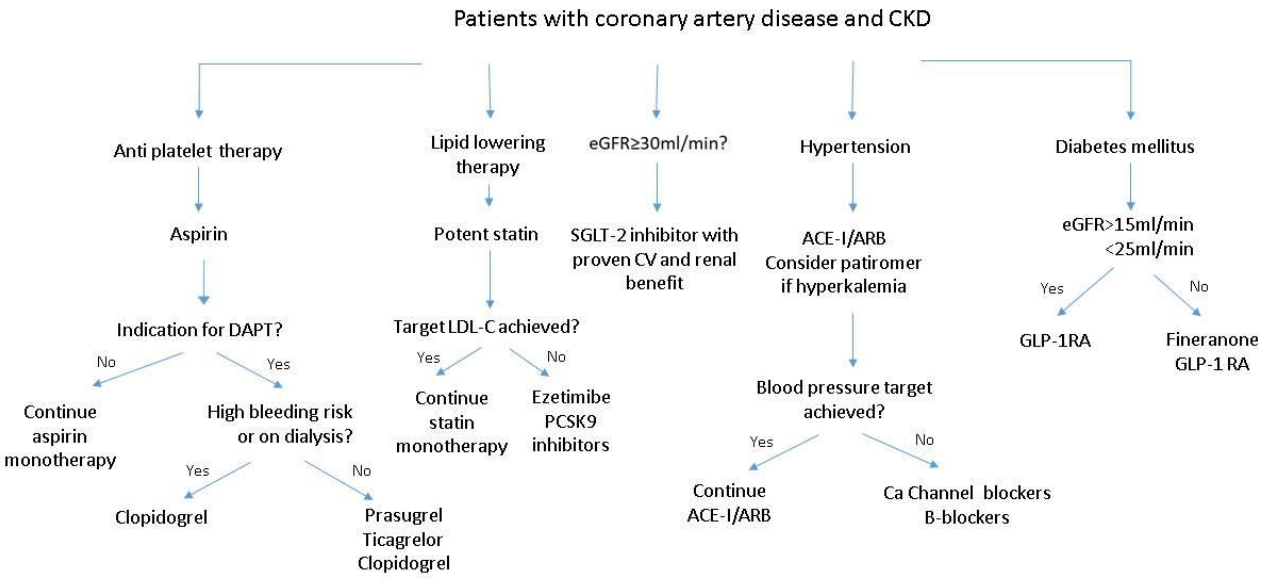

Table-1: Summary of cardiovascular and renal outcomes of the different SGLT-2 inhibitors RCTs

Study	Drug	Patient characteristics	N	Cardiovascular outcomes	Renal outcomes
EMPA-REG OUTCOMES [10]	Empagliflozin	Diabetic patients with CV disease eGFR>30 ml/min/1.73m^2 History of CAD:77%	7,020	14 % reduction of MACE (0.74-0.99) 34% reduction of heart failure hospitalizations (0.5-0.85)	39% reduction of Incident or worsening nephropathy
DECLARE [11]	Dapagliflozin	Diabetic patients who had or were at risk of CV disease eGFR>60 ml/min/1.73m^2 History of CV disease:40% History of CAD: 33%	17,160	17% reduction in the composite of CV death or hospitalization for heart failure	26% reduction in the composite renal outcome (≥40% decrease in eGFR to <60 ml/min/1.73m^2 , new ESRD, or death from renal or CV causes
DAPA-CKD [12]	Dapagliflozin	Diacetics and non-diabetics. eGFR=25-75 l/min/1.73m^2 and a UACR= 200-5000 History of CV disease: 37%	4,304	29% reduction of CV death +hospitalization for HF .	46% reduction in progression of CKD (composite of eGFR decline≥50%, ESRD, or death from renal causes)
DAPA-HF [13]	Dapagliflozin	Symptomatic HF patients with an EF ≤40% eGFR>30 ml/min/1.73m^2 (eGFR<60 in 41%) History of CAD:56%	4,744	26% reduction of CV death +hospitalization for HF.	
EMPEROR REDUCED [14]	Empagliflozin	Symptomatic HF patients with an EF ≤40% eGFR>20 ml/min/1.73m^2 (GFR <60 in 48%) History of CAD:52%	3,730	25% reduction for CV death +hospitalization for HF	50% reduction of composite renal outcome (chronic dialysis or renal transplantation or a sustained profound reduction in the eGFR).
EMPEROR PRESERVED [15]	Empagliflozin	Symptomatic HF patients with an EF >40%. eGFR>20 ml/min/1.73m^2 (GFR <60 in 50%) History of CAD:35%	5,988	21% reduction of CV death+hospitalizations for HF	Annual rate of decline in eGFR was slower in the empagliflozin group than in the placebo group (–1.25 vs. –2.62 ml/min/1.73m^2 /year; P<0.001)
EMPULSE [16]	Empagliflozin	Acute heart failure regardless of EF	530	36% increase in clinical benefit - composite of death, hospitalizations for HF and improved symptoms	
CANVAS [17]	Canagliflozin	Diabetic patients who had or were at risk of CV disease eGFR>30 ml/min/1.73m^2 History of CAD:56%	10,142	14 % reduction of MACE. 33% reduction of heart failure hospitalizations.	40% reduction of composite renal outcome (sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes
CREDENCE [18]	Canagliflozin	Diabetic patients with albuminuria eGFR>30 ml/min/1.73m^2 History of CV disease: 37%	4,401	20 % reduction of MACE. 39% reduction of heart failure hospitalizations.	34% reduction of composite renal outcome (ESRD, a doubling of the creatinine level, or death from renal causes)

EMPA-KIDNEY [19]	Empagliflozin	Patients with CKD: eGFR 20-45 ml/min/1.73 m^2, or eGFR 45-90 ml/min/1.73 m^2 with a urinary albumin-to-creatinine ratio >200.	6,609	28% reduction of kidney disease progression or death from cardiovascular causes	29% reduction of kidney disease progression

ASCVD – atherosclerotic cardiovascular disease

CHF – chronic heart failure

CKD – chronic kidney disease

CV- cardiovascular

DM – diabetes mellitus

eGFR – estimated glomerular filtration rate

EF – ejection fraction

ESRD – end stage renal disease

HF – heart failure

MACE – major adverse cardiovascular events

CAD: Coronary artery disease

UACR: urinary albumin-to-creatinine ratio