Treatment of non-ST-elevation myocardial infarction and ST-elevation myocardial infarction in patients with chronic kidney disease

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Abstract

Renal dysfunction is frequent in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Chronic kidney disease (CKD) is associated with very poor prognosis and is an independent predictor of early and late mortality and major bleeding in patients with NSTE-ACS. Patients with NSTE-ACS and CKD are still rarely treated according to guidelines. Medical registers reveal that patients with CKD are usually treated with too high doses of antithrombotics, especially anticoagulants and inhibitors of platelet glycoprotein (GP) IIb/IIIa receptors, and therefore they are more prone to bleeding. Drugs which are excreted mainly or exclusively by the kidney should be administered in a reduced dose or discontinued in patients with CKD. These drugs include enoxaparin, fondaparinux, bivalirudin, and small molecule inhibitors of GP IIb/IIIa inhibitors. In long-term treatment of patients after myocardial infarction, anti-platelet therapy, lipid-lowering therapy and β-blockers are used. Chronic kidney disease patients before qualification for coronary interventions should be carefully selected in order to avoid their use in the group of patients who could not benefit from such procedures. This paper presents schemes of non-ST and ST-segment elevation myocardial infarction treatment in CKD patients in accordance with the current recommendations of the European Society of Cardiology (ESC).

Keywords: bleeding, chronic kidney disease, management, myocardial infarction, treatment.

Introduction

Renal dysfunction is present in 30–40% of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) [1, 2]. In patients with chronic kidney disease (CKD), heart failure (HF) with lack of typical chest pain is frequent [3]. Chronic kidney disease is usually associated with very poor prognosis [1, 2, 4] and is an independent predictor of early and late mortality and major bleeding in patients with NSTE-ACS [2]. According to studies the risk of cardiac death is increased 46% in those with a glomerular filtration rate (GFR) between 60 ml/min and 90 ml/min and 131% in those with GFR between 30 ml/min and 60 ml/min, independent of traditional cardiovascular (CV) risk factors including diabetes and hypertension [5, 6]. Biomarkers of CKD (such as proteinuria, estimated GFR (eGFR) [7, 8]) are easy and relatively inexpensive to detect, and...
there is evidence that screening for CKD in global health programs will significantly improve the outcomes of not only renal disease, but also diabetes and CVD [5]. Moreover, more attention should be put on the treatment of CKD patients with NSTE-ACS since they are rarely treated according to guidelines.

Non-ST-elevation myocardial infarction in chronic kidney disease patients

Although patients with NSTE-ACS and CKD are often underestimated in clinical trials, there is no particular rationale to treat them in a different way than patients without renal dysfunction. However, due to the risk of bleeding complications, anticoagulation therapy should be used with caution.

According to data from medical registers, patients with CKD are frequently treated with too high doses of antithrombotics, especially anticoagulants and inhibitors of platelet glycoprotein (GP) IIb/IIIa receptors, and therefore they are more prone to bleeding. According to studies, aspirin can be safely and effectively used in patients with CKD in the management of acute coronary syndromes without the need for dose modification [9].

Many drugs which are excreted mainly or exclusively by the kidney should be administered in a reduced dose or discontinued in patients with CKD. These drugs include enoxaparin, fondaparinux, bivalirudin, and small molecule inhibitors of GP IIb/IIIa inhibitors (Table I).

In severe renal failure, when fondaparinux or enoxaparin is contraindicated, unfractionated heparin (UFH) use is recommended. According to the GRACE (Global Registry of Acute Coronary Events) registry UFH does not protect against bleeding complications. In patients receiving UFH, a gradual increase in the bleeding risk along with the progression of renal dysfunction is observed. The same tendency was seen in the case of low-molecular-weight heparin (LMWH) use [10]. The EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment)–TIMI 25 sub-study demonstrated that every 30 ml/min decrease in creatinine clearance (CrCl) increased the risk of major and minor bleeding by 50% [11]. The benefits of UFH therapy in CKD patients in comparison to other antithrombotics are associated with the fact that while using UFH anticoagulant activity can be easily monitored on the basis of activated partial thrombin.

Table I. Recommendations concerning the use of antithrombotic drugs in patients with chronic kidney disease according to ESC guidelines

| **Antiplatelet therapy** |  |
|-------------------------|--|
| **ASA** | Lack of specific recommendations |
| **Clopidogrel** | Lack of recommendations for CKD patients |
| **Prasugrel** | Lack of information concerning the reduction of dose in patients with GFR 30–60 ml/min/1.73 m² |
| **Ticagrelor** | There is no need to adjust the dose in CKD patients |

| **GP IIb/IIIa antagonists** |  |
|---------------------------|--|
| **Abciximab** | Lack of recommendations concerning the use or dose reduction in CKD patients |
| **Tirofiban** | In CKD patients the dose should be reduced; 50% of the standard dose should be used in patients with GFR < 30 ml/min/1.73 m² |
| **Eptifibatide** | It should be used with caution in CKD patients. Dose reduction in patients with GFR < 50 ml/min/1.73 m² by 25% is required |
| **Contraindicated in patients with GFR < 30 ml/min/1.73 m²** |  |

| **Antithrombotic therapy** |  |
|---------------------------|--|
| **Unfractionated heparin** | The dose should be adjusted (reduced) on the basis of frequently measured aPTT in order to maintain drug efficiency |
| **Enoxaparin and other low molecular weight heparins** | In CKD patients with GFR 30–60 ml/min/1.73 m² the dose should be reduced by 25% |
| **Contraindicated in patients with GFR < 30 ml/min/1.73 m² or 50% dose reduction is required depending on drug registration in the given country** |  |
| **Therapeutic concentration can be controlled on the basis of anti-Xa activity** |  |
| **Fondaparinux** | Drug of choice in patients with GFR 30–60 ml/min/1.73 m² due to lower risk of bleeding complications in comparison to enoxaparin |
| **Contraindicated in patients with GFR < 30 ml/min/1.73 m²** |  |
| **Bivalirudin** | In CKD patients with GFR 30 ml/min/1.73 m² the infusion rate should be reduced to 1.0 mg/kg/h |
| **The use of this drug in patients with NSTEMI and CKD should be carefully considered** |  |
boplatin time (aPTT) level and that it can be quickly neutralized in the case of bleeding. Fondaparinux has a much safer profile than enoxaparin in patients with CKD, as evidenced by significantly lower risk of bleeding complications seen in the OASIS-5 trial. In the PLATO (Study of Platelet Inhibition and Patient Outcomes) study, ticagrelor significantly reduced the incidence of ischemic end points and mortality in comparison to clopidogrel, without increasing the risk of major bleeding [12, 13]. It was thought that clopidogrel, which is metabolized in the liver, requires no dose adjustment in patients with renal failure. However, a sub-study of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial demonstrated that clopidogrel may have decreased effectiveness in patients with mild-to-moderate CKD and that this effect was not related to increased bleeding in that group [14]. Also Park et al. [15], who compared the responsiveness of clopidogrel in CKD patients and healthy persons, observed that platelet inhibition was decreased in patients with renal insufficiency, even when doubling the dose of clopidogrel. The scheme of ACS treatment in CKD patients with the division into high and low risk patients (according to European Society of Cardiology (ESC) recommendations) is presented in Figure 1 [16, 17].

The analyses of data from large registry and clinical trials concerning NSTE-ACS revealed that improved prognosis of patients with CKD following invasive treatment was observed not only in end-stage renal disease, but also in patients with moderate CKD [16, 17]. Observational studies demonstrated that the implementation of invasive treatment is associated with better 1-year survival in patients with mild to moderate kidney disease. However, these benefits became less pronounced as renal function decreased and were doubtful in patients with renal failure or on dialysis. It should also be kept in mind that CKD patients are at risk of contrast-induced nephropathy. This risk is much higher in the elderly and in patients with diabetes. In the case of emergency angiography the ratio between the risk of contrast-induced nephropathy and risk of ischemia should be assessed. It was shown that proper irrigation of the patient 12 h before and 24 h after angiography or angioplasty has the greatest impact on reduction of the risk of contrast-induced nephropathy. The amount of contrast medium should be maintained at < 4 ml/kg [18, 19].

**ST-elevation myocardial infarction in chronic kidney disease patients**

The reduction in GFR increases the risk of serious cardiovascular complications by about 20% (compared to subjects with normal renal function). A reduction in GFR < 70 ml/min/1.73 m² is found in approximately 40% of patients with ST-segment elevation myocardial infarction (STEMI). Along with the progression of kidney damage the risk of serious complications such as heart failure, cardiac shock, cardiac arrhythmias and atrioventricular block increases. Worse prognosis is also associated with the fact that patients with chronic kidney disease are usually more advanced in age and often suffer from diabetes, coronary artery disease and heart failure [16]. The clinical picture of myocardial infarction (MI) may be similarly atypical in renal failure as in diabetes. Lower predictive value of commonly used diagnostic markers of myocardial necrosis in patients with chronic kidney disease pose an additional problem [20, 21]. The treatment of myocardial infarction in patients with chronic kidney disease does not differ significantly from the procedure used in patients with normal renal function. However, many authors recommend more aggressive treatment, particularly angioplasty, as a method of restoration of infarct-related artery patency in CKD patients. The risk of surgery is greater than in the population with normal renal function, but the benefits are much better than in the case of conservative treatment.

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**Figure 1.** ACS treatment in CKD patients with the division into high and low risk patients according to European Society of Cardiology (ESC) 2011 recommendations

*Indicated for people in high risk group*
The treatment with intravenous antagonists of GP IIb/IIIa in patients with CKD is associated with a higher risk of bleeding complications, but it also significantly reduces the risk of in-hospital deaths. Treatment with unfractionated heparin with the monitoring of aPTT is recommended in this group of patients. It should be kept in mind that ACE inhibitors and sartans may aggravate renal impairment [16, 17, 20]. According to Swanepoel [20] the use of β-blockers following ST segment elevation MI in hemodialysis patients is beneficial and recommended partly due to great sympathetic overactivity of catecholamine release in this group of patients. The scheme of the ESC recommendations concerning ACS treatment in CKD patients is presented in Figure 2.

**General long-term treatment (secondary prevention)**

In long-term treatment of patients after MI, antiplatelet therapy, lipid-lowering therapy and β-blockers are used [21, 22]. According to studies, the rates of aspirin use are low in patients with CKD mainly due to increased risk of bleeding. In the Wright et al. [23] study, the rate of aspirin use was only 61% in dialysis patients and 74% in patients with a GFR of < 35 ml/min, compared to 89% in patients with a normal GFR. The UK-HARP study (Study of Heart and Renal Protection) revealed that the use of low-dose aspirin (100 mg) in severe CKD (pre-dialysis, dialysis or functioning transplant) increased the risk of minor bleeding three-fold (15% vs. 5%), but did not influence the rate of major bleeding [24]. The Antithrombotic Trialists’ Collaboration (ATT) meta-analysis showed that low-dose aspirin (75 mg to 160 mg) is as efficacious as high-dose aspirin (325 mg) beyond the acute phase for secondary prevention of coronary artery disease in patients with CKD and end-stage renal disease [25]. Moreover, another study conducted on 1,000 end-stage renal disease (ESRD) patients and 145,000 controls who underwent MI revealed that the efficacy and benefit of aspirin treatment for 30-day mortality were similar to those in patients with normal renal func-

![Image of the diagram](image_url)
enzyme inhibitors (ACEI) should be used to avoid recurrent ischemic events and their efficient types and doses should be applied [36]. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril found that in patients with coronary artery disease 95% CI 0.2-1.0; \( p = 0.05 \) [27]. However, one study found that in patients with coronary artery disease platelet responsiveness to acetylsalicylic acid was reduced compared to controls without coronary artery disease (CAD) [28].

The efficacy of anti-platelet therapy with parenteral GP IIb/IIIa inhibitors in patients with CKD is not established. The ESPRIT study (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrin Therapy) [29] demonstrated that eptifibatide therapy during percutaneous coronary intervention (PCI) in CKD patients reduced the number of CAD events and the need of further revascularization procedures over the next 12 months to the same degree as in the non-CKD population. Moreover, no increase in the risk of bleeding was observed in this study [29]. However, Freeman et al. [30] demonstrated doubled risk of major bleeding following the use of GP IIb/IIIa. Despite this adverse event, they still observed reduced in-hospital mortality following ACS in CKD patients (eGFR < 60 ml/min) [30]. Also, the subanalysis of TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcome) study [31] showed that patients with lower CrCl had more ischemic and bleeding events. Moreover, the PROTECT trial (Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy) [31] and the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Registry demonstrated that bleeding risk was higher in patients receiving excess doses of GP IIb/IIIa inhibitors (OR: 1.36; 95% CI: 1.10-1.68), and it is further increased in patients with renal insufficiency (OR 4.12; 95% CI: 2.65-5.75) [32, 33].

The use of ACE inhibitors is according to guidelines recommended within 24 h in all patients with left ventricular ejection fraction (LVEF) \( \leq 40\% \) and in patients with HF, hypertension or CKD unless contraindicated [34, 35]. Angiotensin-converting-enzyme inhibitors (ACEI) should be used to avoid recurrent ischemic events and their efficient types and doses should be applied [36]. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril treatment of CKD patients resulted in similar reduction in the frequency of cardiovascular events to that seen in people with normal renal function [37]. Moreover, the CKD group benefited more from ACEI therapy when the influence of ramipril on total mortality, heart failure related hospitalization and cardiovascular mortality was considered. This therapy was not associated with increased risk of acute renal failure [37]. The use of ACEI in dialysis patients should be carefully weighed since experimental data concerning such therapy are conflicting. A small, retrospective study revealed that dialysis patients treated with an ACE inhibitor had a 52% relative risk reduction for mortality over 5 years (\( p < 0.0019 \)) [38]. However, the prospective Fosinopril in Dialysis (FOSIDIAL) study demonstrated no differences in cardiovascular deaths or morbidity rates (heart failure hospitalization/non-fatal cardiovascular events) over the 2-year follow-up [39, 40].

In patients who do not tolerate ACEI, \( \beta \)-blockers should be used [40]. \( \beta \)-Blockers are also recommended in all patients with dysfunction of LV systolic function (LVEF \( \leq 40\% \)) [41, 42]. The study of McCullough et al. [43] demonstrated that across the range of GFR values, combined effects of \( \beta \)-blockers and aspirin were associated with reduced in-hospital mortality after NSTEMI by 78% in patients on dialysis, 64.3% in those with GFR < 46 ml/min, 69% in those with GFR 46–63 ml/min, and 75% in those with GFR 63–81.5 ml/min. Better survival (a 22% reduction in mortality) of dialysis patients treated with \( \beta \)-blockers after STEMI was observed by Berger et al. [26]. Moreover, retrospective analysis revealed a lower risk of new heart failure and cardiac death (adjusted hazard ratio (aHR) 0.77, \( p = 0.02 \)) as a result of \( \beta \)-blocker treatment [44].

Statin therapy should be used soon after admission to hospital [45]. The target concentration of low-density lipoprotein cholesterol (LDL-C) was established at < 1.8 mmol/l [46]. Post hoc analysis of lipid-lowering trials, enrolling patients with mild CKD, revealed that the effects of statins may be comparable with those observed in patients with normal renal function [47, 48]. According to a retrospective sub-group analysis from the Cholesterol And Recurrent Events (CARE) trial [49], pravastatin reduced cardiovascular death and non-fatal MI. Another retrospective analysis of pravastatin intervention trials demonstrated that it reduced relative risk in patients with CKD (eGFR 30–59 ml/min) with a similar manner to that observed in the overall trial cohorts, including a reduction in total mortality [50]. Analysis of data concerning the use of statins in hemodialysis patients revealed that they were safe for dialysis patients and that they might reduce the incidence of CV deaths by 36% [51, 52]. However, Deutsche Diabetes Dialyse Studie (4D), in which hemodialysis patients with diabetes obtained either atorvastatin or placebo, failed to show any significant difference in the CV event rate or total mortality in the treatment group over a follow-up period of 5 years [53]. On the other hand, the Lescol Intervention Prevention Study (LIPS) demonstrated that CKD patients (eGFR < 55.9 ml/min) undergoing percutaneous coronary intervention (PCI) gained near equal benefit from statin therapy to that seen.
in patients with normal renal function [54]. The most recent meta-analyses from the Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group suggest univocally that statins are very effective, in terms of lipid parameters, renal outcomes, as well as cardiovascular endpoints and all-cause mortality, only in patients without renal replacement therapy. What is more, it seems that long-term therapy with statins in dialysis patients might even worsen the lipid parameters. Therefore the authors do not recommend initiating statin treatment in ESRD patients requiring dialysis. On the other hand, they suggest that there are not enough data to stop treatment in patients who are already on statins. They also emphasize that large, well-designed, randomized trials in well-selected CKD patients on dialysis are necessary, in order to finally confirm or refute the limited benefits of statin therapy [55–58]. These data are strictly in line with the most recent KDIGO recommendation [59].

Myocardial revascularization in patients with chronic kidney disease

Patients with chronic kidney disease with glomerular filtration rate 30–90 ml/min/1.73 m²

According to recommendations, coronary artery bypass grafting (CABG) is a better way of treatment than PCI, especially when CKD is a result of diabetes. When surgical revascularization is required, surgery without cardiopulmonary bypass can be considered [60]. If there are indications for PCI, there is weak evidence that drug-eluting stents (DES) are more beneficial than bare-metal stents (BMS) since their implantation is associated with lower frequency of recurrent ischemic events. However, it should be kept in mind that DES implantation is associated not only with benefits but also with some adverse effects due to the need for long-term use of dual antiplatelet therapy as well as increased risk of late thrombosis and higher susceptibility to restenosis in complex calcified changes. Percutaneous coronary intervention in CKD patients is associated with increased risk of death and major adverse cardiac events during and after the procedure and this risk rises gradually with the degree of renal impairment [61]. Patients with CKD often experience peri-procedural MI, ischemia and target vessel revascularization [62].

Patients with severe chronic kidney disease (GFR < 30 ml/min/1.73 m²), end-stage renal disease or on hemodialysis

The benefits of CABG treatment in comparison to PCI are less unequivocal. Surgical treatment is associated with better survival in long-term observation, but in-hospital mortality and the incidence of complications are greater. When choosing the most appropriate revascularization strategy, the patient’s general condition and his life expectancy must be considered. In patients in a very serious general condition and in those most susceptible to complications, the least invasive treatment should be carried out. In these patients, no advantages of DES over BMS were found and they all should not be used without limitations [60]. Patients eligible for kidney transplantation should be screened to assess the incidence of myocardial ischemia. Patients with significant CAD should not be deprived of the potential benefits of myocardial revascularization. If kidney transplantation is possible during a year, PCI with BMS implantation should be considered [63, 64].

The Global Registry of Acute Coronary Events (GRACE) study confirmed higher mortality and lower reperfusion rates in patients with CKD undergoing primary PCI for STEMI. It demonstrated that adverse outcomes became more frequent along with renal function deterioration [65]. Dewey et al. [66] in their study demonstrated that off-pump revascularization in patients with ESRD on hemodialysis is associated with better perioperative morbidity and mortality compared with conventional surgery with cardiopulmonary bypass (CPB). However, their results clearly indicated that long-term survival was significantly better in the on-pump patients, probably due to incomplete revascularization in the off-pump cohort. Moreover, revascularization with the use of CPB was shown to increase the life expectancy of patients with ESRD and coronary artery disease in comparison to patients with no interventions [66].

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**Figure 3.** Schemes of invasive treatment in accordance with recommendations of European Society of Cardiology
Chronic kidney disease patients before qualification for CABG should be carefully selected in order to avoid its use in the group of patients who could not benefit from such a procedure. Moreover, patients who underwent off-pump bypass grafting should be followed up to ensure that the benefits seen in the perioperative period translate into long-term results equivalent to conventional revascularization [66]. Schemes of invasive treatment in accordance with recommendations of the ESC are presented in Figure 3.

Conclusions

Non-ST elevation myocardial infarction and STEMI occur frequently in CKD patients. Although the results of numerous studies and meta-analyses are conflicting, it seems that CKD patients should not be deprived of standard cardiovascular treatment but the doses ought to be titrated to avoid adverse effects. Also the standard procedures should be implemented in CKD patients but only in those in whom the benefits outweigh the risks [67–74].

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