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PRESIDENT'S PAGE

Acute Coronary Syndromes and Renal Disease

Patients with chronic renal disease have an increased risk of cardiovascular disease compared to the general population.[1] Ischemic heart disease is the most common cause of death in patients with chronic renal disease, and patients with acute coronary syndromes (ACS) usually suffer from chronic renal disease.[2,3] Furthermore chronic renal disease is associated with poor survival in patients with acute coronary syndrome with greater mortality and reinfarction rates.[4,5]

The presence of chronic renal disease in patients with ACS is common and is an independent unfavorable prognostic factor. The National Cardiovascular Data Registry-Acute Coronary Treatment and Intervention Outcomes Network (NCDR-ACTION) registries indicated that 42.9% of patients with NSTEMI and 30.5% of patients with STEMI have chronic renal disease, defined as a GFR $<$ 60 ml/min/1.73 m^2.[6] Alternatively, acute renal failure in patients with acute coronary syndromes has been studied less systematically. Most data come from retrospective studies, as the presence of renal dysfunction is often a criterion for exclusion from large prospective clinical trials.

Chronic kidney disease (CKD), defined as renal damage of $\geq$ 3 months duration, characterized by structural or functional abnormalities of the kidney with or without a reduction in glomerular filtration rate (GFR). For the evaluation of renal function, several indicators are used as the estimated glomerular filtration rate (GFR), based on equations such as the MDRD equation or the Cockroft-Gault equation, and the CKD-EPI.

Several mechanisms have been proposed regarding the interaction between the heart and kidneys, where both organs are affected when one of them suffers. This phenomenon has been described as cardiorenal syndrome.[7] Characteristics of this phenomenon are the residual confounding cardiovascular risk factors in patients with chronic kidney disease, such as older age, diabetes, hypertension, dyslipidemia, LV hypertrophy, hyperhomocysteinemia, oxidative stress and high levels of inflammatory markers. Additionally, complex interactions observed between anemia and resistance to erythropoietin, malnutrition, calcium and phosphorus disorders, sodium and volume overload, endothelial dysfunction due to uremia, oxidation of LDL and oxidative stress by stimulating monocytes leads to the proliferation of smooth muscle cells, accelerated atherosclerosis, calcification of the coronary vessels, remodeling of the left ventricle, reduced blood supply to the coronary and systolic and diastolic dysfunction. On the other hand, suboptimal therapy in patients with chronic renal disease and acute coronary syndromes affect the unfavorable prognosis. However, it is important to note that patients with chronic kidney disease have a poor prognosis, even when they receive the best treatment.

1. CKD and STEMI

Myocardial reperfusion seems to be used often in patients with chronic kidney disease.[8,9] Most studies are retrospective or registries. While there are a few prospective reperfusion studies, chronic kidney disease is an exclusion criterion. In patients with acute coronary syndromes, registries of large populations illustrate that short- and long-term survival with early reperfusion is better compared to drug therapy at all stages of renal disease.[10] The indication for angioplasty is preferable, with coated intracoronary prosthesis (drug-eluting stent, DES) preferred over uncoated (bare metal stent, BMS) because of a lower risk of restenosis.[11]

Several studies have highlighted that STEMI patients with chronic renal disease less frequently receive evidence-based therapy compared to patients with normal renal function, despite the evidence of superiority.[12] In a study in which the US Renal Data System database was matched with the National Registry of Myocardial Infarction (NRMI), patients on hemodialysis had more pre-hospital delays, fewer recognized as suffering from AMI and less frequently had ST-segment elevation or LBBB at baseline compared with patients without dialysis. They also had higher mortality. At discharge, CKD patients were less likely to receive aspirin or beta-bockers.[13] In the Global Registry of Acute Coronary Events (GRACE) registry, the hospital mortality

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was 30% in patients with STEMI or AMI with a LBBB and stage 4 or 5 chronic kidney disease. Both thrombolysis and primary angioplasty were associated with increased incidence of bleeding complications in patients with severely impaired renal function.[4] Moreover, the progressive renal dysfunction is a predictor of bleeding in patients receiving anticoagulant therapy, which may be linked to both the intrinsic renal impairment and antithrombotic failure or avoidance of antithrombotics that are dependent on excretion through renal dialysis.[14]

Additionally, acute renal failure in STEMI patients is related to such factors as patient age, pre-hospital renal function, medication, contrast volume and hemodynamic state. Contrast nephropathy after coronary angiography and intervention for STEMI is always a risk and requires attention to both the volume of contrast and appropriate hydration.[15] In addition, patients may have other comorbidities resulting in increased risk of periprocedural bleeding or ischemic events.

2. Chronic Kidney Disease and NSTEMI

Based on the evaluation of renal function guidelines of 2015,[16] it is necessary in all patients with NSTEMI to perform an eGFR evaluation, especially in elderly women with low weight. Patients with CKD are less likely to receive the proper anticoagulant therapy and less likely reperfusion therapy also.[17]

The diagnosis of NSTE-ACS in these patients presents challenges because small variations of cardiac enzymes and ECG changes are common. In most cases, increasing myocardiac enzymes should not be attributed only to the reduced creatinine clearance and considered "innocent", but instead a workup should be performed for cardiac conditions such as chronic coronary artery disease or cardiomyopathy of hypertension.[18] Mainly in patients with severe renal impairment (eGFR $<$30 mL/min/1.73 m^2), it is possible that an increased troponin can be due to renal disease. The high-sensitivity troponin maintains a high diagnostic value and clinical utility in patients with renal dysfunction. Thus, the most likely diagnosis for a patient with renal dysfunction and increased troponin is acute myocardial infarction (45–80%).[19]

Prospectively, the effect of interventional therapy or anticoagulant therapy has not been studied in patients with renal impairment and NSTE-ACS. The SWEDEHAERT study examined patients with kidney disease and NSTE-ACS and showed that the more impaired the renal function of the patient, the less likely the patient would undergo invasive treatment and revascularization. Only 14% of patients with an eGFR between 15–29 mL/min/1.73 m^2 submitted for interventional therapy.[9] In a recent meta-analysis of observational studies,[20] it was recorded that early revascularization therapy in patients with NSTE-ACS or unstable angina leads to better survival in patients with mild or moderate renal dysfunction. In patients with severe kidney disease or dialysis or after renal transplantation, data were missing, resulting in unclear data on whether early reperfusion therapy is the proper therapy.

In patients with chronic kidney disease, selection and dosage of antithrombotic drugs must be carefully selected. While most anticoagulants need dosage adjustment, this is not correct for the new oral antiplatelets.[21] In patients with end-stage renal disease (eGFR $<$15 mL/min/1.73 m^2) the data are incomplete. Therefore, the antiplatelet P2Y12 inhibitors used in high-risk patients for the prevention of thrombosis should be used with caution in patients with a bleeding risk. Clopidogrel exhibits a better safety profile compared with ticagrelor or prasugrel. Several anticoagulants are available for parenteral use, such as eptifibatide, tirofiban, bivalirudin, enoxaparin and fondaparinux. Most of them require adjustment for renal function. Regarding abciximab, no adjustment is required, but in stage 4 kidney disease the risks and benefits should be taken into account. Corresponding adjustments for renal function are required in newer anticoagulants.

3. Acute Renal Failure and ACS

In contrast to CKD, the available data on the effect of acute renal failure (absolute increase $\geq$0.3 mg/dL, $\geq$50% increase in baseline serum creatinine (1.5 times) in a 48 hour period or reduction in urine output with documented oliguria ($<$0.5 ml/kg per hour for $>$ 6 hours)) in the clinical setting of acute coronary syndromes are limited.

The incidence of acute renal failure is increasing in patients with acute coronary syndromes.[22] This situation presents a complex pathogenesis, has an incidence of over 30% and is associated with higher short- and long-term morbidity and mortality. Acute renal failure precedes renal failure as an index for disease severity, and it also constitutes a causative factor for acceleration of cardiovascular damage by neurohormonal activation, immune and inflammatory pathways. Recent data suggest that patients with acute renal failure after acute coronary syndrome, even those with fully recovered renal function, are at increased risk of future acute injury and the development of chronic kidney disease. Therefore, these patients require both regular renal monitoring after hospital discharge and secondary prevention measures.

4. Contrast Agent Nephropathy

Contrast agent nephropathy is defined as an increase in serum creatinine of $\geq$0.5 mg/dL or $\geq$25% within 48–72 hours after exposure to the contrast agent. It is the main cause of acute renal failure after catheterization in patients with acute coronary syndromes. Risk factors are age, pre-existing renal disease, diabetes mellitus, cardiogenic shock/cardiac insufficiency, anemia and the volume and type of contrast. Prevention, especially in patients with a GFR $<$40 mL/min/1.73 m^2, requires the administration of isotonic saline 12 hours before and 24 hours after angiography in order to reduce the risk of kidney disease. However, caution must be exercised in fluid administration to patients with heart failure. In addition, administration of high dosages of statins before diagnostic catheterization is a preventive measure in patients without contraindications. Finally, the use of other agents, such as ascorbic acid, have shown inconsistent results, while the effect of N-acetylcysteine is undisputed. Particularly important is the role of minimization of the volume of contrast to $<$4 ml/kg.

Additionally, it seems that isosmotic agents are preferred over low-osmolality contrast agents. Furthermore, the risk for kidney disease greatly increases when the ratio of the contrast volume to GFR is $> 3.7:1$.[23,24]

5. Conclusions

- Chronic kidney disease is a powerful risk factor for death in acute coronary syndromes and affects clinical decisions.
- It is important to identify the baseline serum creatinine with ACS patients and monitor the course of renal function during hospitalization.
- Beware of contrast nephropathy and use preventive measures.
- Encourage the use of more aggressive therapies when they can be implemented at an acceptable level of safety.
- There is a need for randomized prospective clinical studies evaluating the therapeutic strategies in these patients.

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