Mild renal disease increases major bleeding in patients with atrial fibrillation undergoing percutaneous coronary stenting

…or why clinical cardiologists and interventionists should be friends

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The Broadway musical OKLAHOMA depicted tensions which occurred during Western expansion in the United States in the early 1900’s. Two of the main protagonists were the farmers and the cowmen who had disagreements concerning fences. The farmers wanted fences to protect crops. The cowmen wanted cattle to roam the open range. In one scene after a boisterous confrontation at a country picnic, the two sides made temporary peace as they concluded in song that “the cowmen and farmer should be friends.”

Similar high drama is presented by Manzano-Fernández et al. (1) in the current issue of Thrombosis and Haemostasis, whereby the authors identified 285 patients with atrial fibrillation (AF) and a CHADS2 score which was high enough to warrant oral anticoagulation. These patients also had coronary artery disease severe enough to warrant percutaneous coronary intervention (PCI) and to be treated with a variety of antiplatelet and antithrombotic therapies. The authors then determined the rate of major bleeding after one year of follow-up and found that risk of major bleeding in patients with moderate to severe renal disease compared to those with normal renal function was high – a disturbing 17.6%. However, the interesting finding was that the rate of major bleeding in patients with mild renal impairment, defined as an estimated creatinine clearance of 60–89 ml/min/1.73 m², was 7.9% and significantly higher than the risk of bleeding in patients who had no renal dysfunction. Given the association of major bleeding with higher mortality in patients undergoing PCI (2) and in patients with AF (3), the findings are particularly relevant.

Patients with advanced renal disease are known to have a wide variety of endothelial, coagulant, and inflammatory markers which make them at higher risk for thromboembolic events. These patients are also at risk for increased bleeding due to a variety of abnormalities which continue to be defined and which include platelet abnormalities, defective coagulation parameters, altered blood rheology (related to anaemia), and concomitant drug therapy (4).

In the past, renal impairment had to be pretty severe to get the attention of the interventionalist. In addition, many pathology laboratories in the United States report a “normal” estimated creatinine clearance as >60 ml/min/1.73 m² without reporting a numerical value. Now it appears that even minor abnormalities in renal function might be important in this high-risk patient population. Their study is small, retrospective and from a single site. As such it is subject to all the biases inherent to this kind of analysis. Many of their patients received low-molecular-weight heparin and glycoprotein IIb/IIIa agents. It goes without saying that doses adjusted to renal function are important and often ignored, particularly in patients with acute coronary syndromes when the patient receives therapy before laboratory studies have been completed. In addition, their oral anticoagulant of choice was acenocoumarol and it is uncertain if these findings apply to other vitamin K antagonists. Because of these issues, the findings need to be confirmed with larger, preferably prospective studies.

Renal disease is associated with major bleeding in patient with AF. Based on randomised clinical trials, major bleeding rates for patients with AF treated with warfarin ranges form 1.5–3.5%/year (5). The bleeding rate is lower with the new novel anticoagulant agents but those with severe renal impairment were not studied in the recent trials. However, patients with end-stage renal disease requiring dialysis who receive warfarin have a yearly rate of major bleeding reported to be as high as 16.2% (6). Patients with less severe forms of renal disease also have substantial risks. Compared to patients with normal renal function, those with a serum creatinine >1.5 mg/dl have a three times higher risk of major bleeding; those with a serum creatinine >2.0 mg/dl have a 4.8 times higher risk of major bleeding (7).

Renal dysfunction is also associated with higher bleeding risks in patients undergoing PCI. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, patients with acute coronary syndromes, the majority of whom underwent PCI, the 30 day rate of major bleeding ranged from 3–5.7%, depending upon the type of antithrombotic therapy (2). However, the risk of major bleeding was nearly doubled in patients with moderate to severe renal dysfunction, defined as a creatinine clearance of <60 ml/min². As pointed out by the manuscript by Manzano-Fernández et al. (2), patients with the combination of unstable coronary artery disease with oral anticoagulation are at particularly high risk for major bleeding and even mild renal dysfunction intensifies the risk.
In addition to renal dysfunction, another factor emerged as a risk factor for major bleeding in the paper by Manzano-Fernández et al. (1), as triple antithrombotic therapy was associated with a 3.44 times greater risk of major bleeding. The interventionalist knows that dual antiplatelet therapy provides superior protection against stroke in patients with AF compared to antiplatelet therapy. The price paid by combining these therapies, so called “triple therapy,” is sobering and should open up a dialogue between the interventionalist and the clinical cardiologist in an effort to establish ways to minimise the risk. Indeed, such patients represent a complex management problem, leading to recent expert consensus recommendations from European (8) and North American (9) largely address some of these important issues with regard to vascular access and the regime of triple (and dual) antithrombotic therapy following coronary stenting.

Indeed, the European (8) and North American expert consensus documents (9, 10) largely address some of these important issues with regard to vascular access and the regime of triple (and dual) antithrombotic therapy following coronary stenting.

References


Conflict of interest

None declared.

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