Diabetics with acute coronary syndrome: advances, challenges, and uncertainties

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This editorial refers to ‘Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATElet inhibition and patient Outcomes (PLATO) trial’, by S. James et al., on page 3006.

Outcomes of patients with acute coronary syndrome (ACS) and myocardial infarction have dramatically improved over recent decades as a result of implementing novel infrastructures (i.e. coronary care units with continuous ECG monitoring), devices (i.e. external defibrillator), drugs (i.e. thrombolytic agents), and treatment strategies (i.e. invasive treatment) (Figure 1). During the long course of this unquestionable success story, diabetic patients always demonstrated a worse outcome compared with their non-diabetic counterparts. The reasons for the increased risk are plentiful (i.e. co-morbidities like renal impairment or heart failure). Of particular interest in this setting are the pro-inflammatory and pro-thrombotic states as well as the increased platelet reactivity in diabetics potentially necessitating a more aggressive anti-platelet regimen in such high-risk patients. Indeed, a recent subanalysis of the landmark Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) has shown a greater reduction in the primary endpoint (cardiovascular death, myocardial infarction, stroke) with prasugrel as compared with clopidogrel in diabetic patients with ACS.3

In this issue, James and co-workers present a substudy of the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial using ticagrelor, a novel reversible inhibitor of the adenosine diphosphate (ADP) receptor P2Y12 on platelets.4 As compared with clopidogrel, ticagrelor reduced ischaemic events in both diabetic and non-diabetic patients with ACS irrespective of the diabetes status and glycaemic control, without an increase in major bleeding.

These results, clearly, are of clinical relevance and may lead to a shift from clopidogrel to third-generation anti-platelet agents as the new standard of therapy in a large number of diabetic patients with ACS. Probably even more important, careful dissection of the data guides us to better appreciate advances, challenges, and remaining uncertainties associated with the treatment of diabetics presenting with ACS.

Advances: ‘the enemy of good is better’5

Clopidogrel together with aspirin has been the backbone of anti-platelet therapy in ACS patients over the past decade.6 Unfortunately, clopidogrel has a number of drawbacks including delayed onset of action and irreversibility of its inhibitory effects. Furthermore, the large interindividual variability in platelet response to clopidogrel as a result of a two-step activation process involving a series of cytochrome P-450 (CYP) isoenzymes poses a major concern.7 As a result, prasugrel and ticagrelor accomplished a reduction in ischaemic events as compared with clopidogrel in TRITON-TIMI 38 and PLATO.9 In diabetic patients, prasugrel use led to an even greater reduction in ischaemic endpoints than clopidogrel with a comparable bleeding risk whereas ticagrelor led to a comparable reduction in ischaemic events and a reduction in coronary artery bypass surgery-related bleeding.7 The latter effect is likely the result of reversible drug-binding to the P2Y12 receptor.

How should we translate the given evidence into our clinical pathways? Is there still a place for clopidogrel? Should ticagrelor or prasugrel be used preferentially? First, limitations of the TRITON-TIMI 38 and the PLATO diabetes substudies should not be forgotten. Even though pre-specified groups were analysed, randomization was not performed. Importantly, most outcome differences in relation to the randomized treatment did not reach statistical significance.

Therefore, trials exclusively addressing diabetic patients are necessary, specifically in the light of the dramatically increasing prevalence of diabetes in ACS patients (Figure 1).

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Second, data from the recent OASIS-7 (CURRENT) trial indicate that a high-dose clopidogrel regimen (600 mg loading, 150 mg/day for the first 7 days after intervention) in patients with ACS undergoing invasive treatment reduces ischaemic endpoints as compared with ‘standard’ dosing (300 mg loading, 75 mg/day maintenance dose). Therefore, the relative benefit of prasugrel and ticagrelor as compared with high-dose clopidogrel treatment at least during the first 30 days after intervention remains unclear.

Final answers to the above questions, therefore, cannot be provided yet. Clearly, contraindications limit the use of prasugrel (i.e. status after stroke or transient ischaemic attack). Ticagrelor treatment, in contrast, is associated with certain side effects and should be discouraged in patients with severe chronic pulmonary disease, or bradyarrhythmias. Therefore, individualization of treatment seems appropriate but necessitates a deep understanding of the evidence from studies and individual patient characteristics.

Challenges: it’s all about implementation

Adherence to guidelines improves the prognosis of patients with ACS. In the case of diabetic patients, an early invasive treatment strategy as well as the use of glycoprotein (GP) IIb/IIIa inhibitors (GPIs) are associated with an improved outcome; however, these treatments are underutilized in the real world. The article by James and co-workers, however, does provide data clearly indicating that these evidence-based therapies are also underutilized in randomised clinical trials. Therefore, implementation of evidence into clinical routine seems to be challenging, even in controlled trials performed in selected centres.

Unfortunately, no study has specifically addressed the value of an early invasive strategy in diabetic patients with ACS. Subgroup analyses of large-scale randomized trials like the Fragmin and Fast Revascularization Drug Instability in Coronary Artery Disease (FRISC II) and the Treat Angina with Aggrastat to Determine Cost of Therapy with Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) trial, however, indicate that the relative benefit of an early invasive strategy is greater in diabetic as compared with non-diabetic patients with ACS.

Likewise, GP IIb/IIIa receptor antagonists also provide greater benefit in diabetics as compared with non-diabetics with ACS when undergoing early invasive treatment. However, as seen with early invasive treatment, patients with diabetes receive GPIs less frequently than their non-diabetic counterparts in clinical routine. It has to be appreciated, however, that the effect of GPIs might be far less pronounced in patients receiving a fast-acting and potent oral anti-platelet drug like ticagrelor.

As a matter of fact, however, in the PLATO study planned invasive treatment (67% vs. 74%, \( P < 0.0001 \)), coronary angiography before discharge (77% vs. 83%, \( P < 0.0001 \)) and percutaneous coronary intervention (PCI) before discharge (54% vs. 63%, \( P < 0.0001 \)) were all performed significantly less often in diabetic patients as compared with non-diabetic subjects. Common reasons for not offering early invasive treatment in diabetics are related to moderate to severe renal impairment; however, the mean creatinine clearance in diabetics was \( \approx 76 \) mL/min in PLATO. Furthermore, GPIs were also underutilized in diabetic patients (24% vs. 28%, \( P < 0.0001 \)).

The clinical relevance of evidence based medicine is obvious: however, the patient can only benefit when it is offered to him: it is all about implementation.
Uncertainties: what we still don’t know yet

Despite clear messages from randomized trials in the context of diabetes and ACS, a number of clinically relevant uncertainties remain.

First, management of patients presenting with an ACS and an indication for oral anticoagulation (OAC) therapy (i.e. atrial fibrillation, mechanical valves) poses management complexities, especially when patients are treated with PCI (indication for dual anti-platelet therapy). It is unclear at present, however, how more potent anti-platelet agents like prasugrel and ticagrelor will affect bleeding when administered as triple therapy together with OAC and aspirin.16

Second, it remains to be proven how the risk–benefit ratio will be affected in this relevant patient population when new oral anticoagulants (i.e. dabigatran) will be available. Clearly, there is a definite need for large scale registries and prospective clinical studies to determine the optimal antithrombotic management of patients with indication for OAC presenting with ACS undergoing coronary interventions.

Thirdly, data on long-term treatment using ticagrelor are missing. This may be of particular interest in patients with ACS undergoing implantation of drug-eluting stents with an indication of prolonged dual anti-platelet therapy.

Finally, as ticagrelor binds reversibly to the platelet P2Y12 receptor, careful surveillance of patient compliance with the drug is absolutely mandatory.

Conclusions

Novel anti-platelet drugs like ticagrelor are able to further improve the care of patients with ACS and diabetes. As the increase in antithrombotic efficacy compared with clopidogrel is not associated with an overall higher bleeding risk, ticagrelor—comparable to prasugrel—has set new standards in the treatment of this high-risk patient population. At present, individualization of treatment seems appropriate, but necessitates a deep understanding of clinical evidence and individual patient characteristics. Furthermore, we need to try hard to improve guideline adherence in diabetic patients. They need our special attention.

References