CHALLENGES OF ACUTE CORONARY SYNDROME IN DIABETIC PATIENTS: HOW TO IMPROVE CARDIOVASCULAR OUTCOME

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INTRODUCTION
Outcomes of patients with acute coronary syndrome (ACS) and myocardial infarction have dramatically improved over recent decades as a result of implementing novel infrastructures (coronary care units with continuous ECG monitoring), devices (external defibrillator), drugs (thrombolytic agents), and treatment strategies (invasive treatment). 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 include 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. 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) is associated with an improved outcome; but, these treatments are underutilized in the real world. However, that the effect of GPIs might be far less pronounced in patients receiving a fast-acting and potent oral anti-platelet drug.

BURDEN OF DIABETES
Atherosclerosis is responsible for 80% of all deaths in diabetic patients. As the prevalence of diabetes is estimated to double by the year 2025, the burden of cardiovascular disease with this condition will dramatically increase. Compared with non-diabetic individuals, diabetic patients have a two- to four-fold increased risk of coronary heart disease, two fold-higher risk of short-term mortality after acute myocardial infarction, and poorer results when submitted to angioplasty with increased risk of restenosis. Inflammatory activity is increased in individuals with type 1 and type 2 diabetes and strongly associated with risk of atherothrombosis.

Increased levels of C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with higher incidence of adverse cardiac events in patients with acute coronary syndromes, as well as in patients undergoing coronary stenting. Aggarwal et al found increased CRP levels (two fold) in diabetic than in non-diabetic subjects with acute coronary syndrome before and after coronary stenting. The negative impact of DM on outcomes is maintained across the ACS spectrum, including unstable angina and non-ST-elevation MI (NSTEMI), ST elevation MI (STEMI) treated medically, and ACS undergoing percutaneous coronary intervention (PCI).

Platelets of DM patients are characterized by dysregulation of several signaling pathways, both receptor (e.g., increased expression) and intracellular downstream signaling abnormalities, which leads to increased platelet reactivity. This may play a role not only in the higher risk of developing ACS and the worse outcomes observed in DM, but also in the larger proportion of DM patients with inadequate response to antiplatelet agents compared with non-DM subjects, which may also contribute to the impaired outcomes observed in DM patients despite compliance with recommended antiplatelet treatment regimens.

Characteristics of coronary arteries in diabetics include
• Diffuse coronary artery disease
• More small vessels and microvascular involvement
• High thrombogenesity
• High rate of restenosis after PCI
• High rate of occlusive restenosis resulting in poor prognosis
• More total and distal plaque burden with necrotic core and multiple vulnerable plaques

EARLY INVASIVE STRATEGY
Diabetes mellitus has been identified as an independent predictor of long-term mortality in the setting of non-ST-segment elevation acute coronary syndromes (NSTEMI). Several biological and metabolic abnormalities may enhance the vulnerability of individuals with diabetes for cardiovascular events in the presence of ACS and potentially influence outcomes following revascularization. Of particular interest in this setting are the pro-inflammatory and pro-thrombotic states described in diabetes.

FRISC II randomized 2457 patients to either an invasive or conservative strategy and demonstrated a benefit, and even a reduction in mortality, associated with an early invasive management. The benefit in terms of 1-year death or myocardial infarction (MI) was dramatic among patients with diabetes (n=299), both in terms of relative risk reduction (RRR, 39%) and absolute risk reduction (ARR, 9.3%); among individuals without diabetes, the efficacy was less pronounced (RRR, 28%; ARR, 3.1%). Owing to differences in sample size, the benefit observed did not reach statistical significance in patients with diabetes (P=0.07), while it was significant among individuals without diabetes (P=0.02).

In the TACTICS TIMI 18 trial (n=2220), an early invasive strategy was associated with a significant reduction in death, MI, or rehospitalization for ACS at 6 months, compared with an early conservative strategy. In contrast to FRISC II, in TACTICS TIMI 18, all patients received platelet glycoprotein (GP) IIb/IIIa receptor inhibitors. Again, patients with diabetes derived a greater benefit than those without diabetes from the early invasive strategy, in terms of both RRR (27 and 13%, respectively) and ARR (7.6 and 1.8%, respectively). The benefit reached statistical significance in diabetes (n=613), but not in non-diabetics (n=1607).

Revascularization in diabetic patients causes specific problems. CAD is typically diffuse and extensive, and restenosis as well as occlusion rates after PCI and CABG are higher. Repeat revascularization procedures are more frequent after PCI, compared with CABG. An early invasive approach has been shown to be beneficial in this high risk subgroup, with greater benefit in diabetic than in non-diabetic patients.

European Society of Cardiology Guidelines for NSTEMI (2011) have recommended an early invasive therapy as IA for diabetics.

PCI VERSUS CABG
In a meta-analysis of individual data from 7812 patients in 10 randomized trials, CABG was associated with significantly lower mortality at 5.9-year follow-up than with PCI in diabetic patients. Overall there was no difference in mortality with CABG vs. PCI (15% vs. 16%; HR 0.91; 95% CI 0.82–1.02; P=0.12), but mortality was significantly lower for CABG among 1233 patients with diabetes [23% vs. 29%; HR 0.70; 95% 0.56–0.87; P = 0.05; numbers needed to treat (NNT) = 17].

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, diabetic patients with stable angina were randomized to either intensive medical therapy or intensive medical therapy plus revascularization with either CABG or PCI (physician’s choice). At 5-year follow-up, in 763 patients in the CABG group, the rates of all cause mortality or MI were significantly lower in the CABG group vs. intensive medical therapy alone (21.1% vs. 29.2%; P<0.010), as well as the rate of cardiac death or MI (15.8% vs.21.9%; P<0.03) and MI (10% vs. 17.6%; P<0.003). There was no significant difference in outcome between intensive medical therapy alone and intensive medical therapy plus PCI. In SYNTAX—a trial comparing CABG with PCI with DESs in main stem and multivessel disease—the difference in major adverse cardiac and cerebrovascular events at 1-year follow-up between CABG and PCI groups was doubled in the pre-defined diabetes cohort, mostly driven by repeat revascularization. However, there was no significant difference in rates of death or MI. In SYNTAX trial 3-year follow-up, there were no significant interactions observed for the diabetic status and treatment group for 3-year MACCE or any of the components; the treatment effect of PCI compared with CABG was not different based on the diabetic status. The presence of diabetes was associated with increased rates of repeat revascularization and, consequently, MACCE in the PCI arm without increasing the rates of death/stroke/MI over 3 years of follow-up. Cardiac death was not significantly different between treatment groups in the subset of diabetic patients (4.8 vs. 8.8%, P=0.10). Finally, in the New York Registry, a trend to improved outcomes in diabetic patients treated with CABG compared with DESs (OR for death or MI at 18 months 0.84; 95% CI 0.69–1.01) was reported.

All of these studies suggest that CABG offers a better outcome compared with PCI in diabetic patients. However, it has to be pointed out that these trials incorporated mostly—if not only—chronic stable patients, and it is unclear whether these data can be extrapolated to patients with ACS.

CHOICE OF STENTS AND CONDUITS
In a meta-analysis a DES proved to be at least as safe as a BMS provided that DAPT is continued for >6 months,
which is indicated in ACS anyway.\textsuperscript{16} Repeat target vessel revascularization was considerably less frequent with a DES than a BMS (OR 0.29 for sirolimus eluting; 0.38 for paclitaxel eluting). It may be assumed that this is similar in diabetic patients with ACS. In the HORIZONS-AMI trial, implantation of PES compared to BMS in diabetic pts resulted in a 70% reduction in TLR, 61% reduction in TVR and a 46% reduction in MACE at 3 years, with comparable rates of safety outcomes including ST. The absolute benefits of PES were greater in DM than non-DM patients.\textsuperscript{17} European Society of Cardiology Guidelines for NSTEMI (2011) have recommended DES, to reduce rates of repeat revascularization, as I-A for diabetics.

Regarding the choice of conduits, observational studies suggest that arterial grafts offer better outcome compared with saphenous vein grafts. The impact of revascularization with bilateral arterial grafting on long-term outcome and risk of mediastinal infections is still debated. Again, no data confined to ACS patients alone are available.

**ANTITHROMBOTICS**

There is no indication that the antithrombotic regimen should differ between diabetic and non-diabetic patients. However, in the TRITON-TIMI 38 trial, prasugrel was shown to be superior to clopidogrel in reducing the composite endpoint of cardiovascular death or MI or stroke without excess major bleeding.\textsuperscript{18} The primary end point was reduced significantly with prasugrel in subjects with DM (12.2% versus 17.0%; HR=0.70; \textit{P}<0.001). This benefit was consistent in patients with (14.3% versus 22.2%; HR=0.63; \textit{P}=0.009) and without (11.5% versus 15.3%; HR=0.74; \textit{P}=0.009) insulin treatment. Prasugrel also improved the risk of stent thrombosis in the DM subgroup (overall DM cohort: 2.0% versus 3.6%; HR=0.52; \textit{P}=0.007; insulin-dependent patients: 1.8% versus 5.7%; HR=0.31; \textit{P}=0.008).

Similarly, ticagrelor, when compared with clopidogrel in the PLATO trial, reduced the rate of ischaemic events in ACS patients irrespective of diabetic status and glycaemic control, without an increase in major bleeding events.\textsuperscript{19} Ticagrelor reduced all-cause mortality in patients with haemoglobin A1c above the median (>6%).

Although GPIIb/IIIa receptor inhibitors were shown in an earlier meta-analysis (without concomitant use of thienopyridines) to have a favourable impact on outcome in diabetic patients,\textsuperscript{20} routine upstream treatment was not confirmed to be beneficial in the more recent EARLY-ACS trial.\textsuperscript{21} Therefore, with the current use of high dose oral antiplatelet agents, diabetic patients do not seem to benefit from the routine addition of GP IIb/IIIa receptor inhibitors.

Prevention of contrast-induced nephropathy is particularly important in diabetic patients undergoing angiography and/or PCI. There are no data to support delay of angiography in patients treated with metformin as the risk of lactate acidosis is negligible.\textsuperscript{22} Renal function should be monitored closely following contrast exposure.

**GLYCAEMIC CONTROL**

Recent studies have not shown improved outcomes with tight glycaemic control, but rather an excess of events related to more frequent hypoglycaemic episodes in patients allocated to tight blood glucose control.\textsuperscript{23} Until more data become available the treatment target should be to avoid severe hyperglycaemia [glucose concentration >10–11 mmol/L (>180–200 mg/dL)] as well as hypoglycaemia [<5 mmol/L (<90 mg/dL)]. There is no evidence that glucose–insulin–potassium improves outcome, but may be even deleterious.\textsuperscript{24}

**UNCERTAINTIES**

a. 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 effect bleeding when administered as triple therapy together with OAC and aspirin.

b. 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.

c. 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.

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

**CONCLUSION**

Diabetic patients with ACS are at high risk for subsequent cardiovascular events. They derive greater benefit than non-diabetic counterparts from aggressive therapy with an early invasive strategy and broad use of drug-eluting stents. Sirolimus-eluting stent appears to be of similar efficacy to the paclitaxel-coated one. In diabetic patients, prasugrel use leads to an even greater reduction in ischaemic endpoints than clopidogrel with a comparable bleeding risk. Ticagrelor leads to a comparable reduction in ischaemic events and a reduction
in coronary artery bypass surgery-related bleeding. Studies suggest that CABG offers a better outcome compared with PCI in diabetic patients. However, it has to be pointed out that these trials incorporated mostly—if not only—chronic stable patients, and it is unclear whether these data can be extrapolated to patients with ACS.

REFERENCES


