Featured research

Abstracts and commentaries

Comparison of coronary flow reserve and fractional flow reserve in patients with versus without diabetes mellitus and having elective percutaneous coronary intervention and abciximab therapy (from the PREDICT Trial)

Kini AS, Kim MC, Moreno PR, Krishnan P, Ivan OC, Sharma SK. *Am J Cardiol*. 2008;101:796–800.

Patients with diabetes mellitus have poor long-term outcome after percutaneous coronary intervention (PCI), partly because of microvascular disease and distal embolization. Microvascular obstruction can be assessed by measuring coronary flow reserve (CFR). The Prediction of CK-MB Release During Successful Stenting Correlating with Indicators of Microvascular Obstruction (PREDICT) trial compared the CFR in patients with and without diabetes mellitus during PCI. Patients undergoing elective PCI were prospectively enrolled according to diabetic ($n = 36$) and non diabetic ($n = 36$) status. All patients received a drug-eluting stent with abciximab and were followed for 30 days for major adverse cardiac events. CFR and fractional flow reserve (FFR) before and after stenting were measured before and after administration of an intracoronary bolus of adenosine. Procedural success, concentrations of the MB enzyme of creatine kinase (CK-MB) and troponin I, increases in high-sensitive C-reactive protein, vascular complications, and major adverse cardiac events were not different between the groups. Before stenting, FFR was 0.77 ± 0.03 in patients with diabetes mellitus and 0.76 ± 0.02 in those without it ($P = 0.69$); after stenting it was 0.97 ± 0.03 and 0.99 ± 0.01 ($P = 0.26$), respectively. CFR before stenting was 1.36 ± 0.31 in patients with diabetes mellitus and 1.49 ± 0.25 in patients without it ($P = 0.064$); however, after stenting CFR was significantly lower in patients with diabetes mellitus than in those who were not diabetic (1.89 ± 0.30 compared with 2.44 ± 0.67; $P < 0.001$, respectively). CFR after stenting only moderately correlated with CK-MB and high-sensitive C-reactive protein after PCI, but did not correlate with 30-day major adverse cardiac events. It was concluded that patients with diabetes mellitus have significantly lower CFR after stenting, despite equivalent FFR and myonecrosis, compared with patients without diabetes mellitus, indicating greater microvascular obstruction after PCI despite treatment with abciximab.

Commentary

Diabetic patients with ischemic heart disease have a worse prognosis than those who are not diabetic, regardless of the type of treatment (medical, PCI, or bypass surgery). Several factors have been proposed to explain this poor outcome, including microvascular dysfunction. In this study by Kini et al, FFR and CFR were measured in diabetic and non diabetic patients undergoing PCI. FFR expresses the resistance to flow across the epicardial stenosis, and CFR expresses the vasodilating capability of the coronary microcirculation. Coronary stenting abolished the epicardial obstruction and normalized FFR in both groups. Conversely, CFR remained significantly lower in individuals with diabetes than in those who were not diabetic, suggesting a persistent microvascular dysfunction, despite equivalent FFR, similar amount of myocardial damage, and abciximab administration. The authors attribute the lower CFR after stenting that was observed in diabetic patients to greater microvascular obstruction secondary to distal embolization of atherosclerotic or thrombotic material, or to exaggeration of the microvascular disease itself, or a combination of both.

The observation that CFR tended to be lower in individuals with diabetes, even before stenting, is consistent with the hypothesis that a diffuse microvascular dysfunction pre-exists in these patients, but does not exclude the possibility of a worsening associated with the PCI procedure. This point could be clarified by the measurement of CFR in the non target

reference vessel. Unfortunately, this measurement was performed only at the end of the study, and the data are not reported in detail.

In conclusion, the findings of this study support the concept that the worse prognosis of ischemic heart disease in patients with diabetes relates to the presence of a severe microvascular dysfunction, which precedes the revascularization procedure, prevents recovery of CFR after stenting, and is diffuse to non target vessels.

Mario Marzilli

Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study

Mentzer RM Jr, Bartels C, Bolli R, et al, for the EXPEDITION Study Investigators. *Ann Thorac Surg*. 2008;85:1261–1270.

The EXPEDITION study addressed the efficacy and safety of inhibiting the sodium-hydrogen exchanger isoform-1 (NHE-1) by cariporide in the prevention of death or myocardial infarction in patients undergoing coronary artery bypass graft surgery. The premise was that inhibition of NHE-1 limits the intracellular accumulation of sodium and thereby limits Na^+–Ca^+-exchanger-mediated calcium overload to reduce infarct size. High-risk coronary artery bypass graft (CABG) surgery patients ($n = 5761$) were randomly allocated to receive either intravenous cariporide (180 mg in a 1 h preoperative loading dose, then 40 mg/h over 24 h and 20 mg/h over the subsequent 24 h) or placebo. The primary composite endpoint of death or myocardial infarction was assessed at 5 days, and patients were followed for as long as 6 months. At 5 days, the incidence of death or myocardial infarction was reduced from 20.3% in the placebo group to 16.6% in the treatment group ($P = 0.0002$). Paradoxically, myocardial infarction alone declined from 18.9% in the placebo group to 14.4% in the treatment group ($P = 0.000005$), whereas mortality alone increased from 1.5% in the placebo group to 2.2% with cariporide ($P = 0.02$). The increase in mortality was associated with an increase in cerebrovascular events. Unlike the salutary effects that were maintained at 6 months, the difference in mortality at 6 months was not significant. The EXPEDITION study is the first phase-3 myocardial protection trial in which the primary endpoint was achieved and proof of concept demonstrated. As a result of the increased mortality associated with an increase in cerebrovascular events, it is unlikely that cariporide will be used clinically. The findings suggest that NHE-1 inhibition holds promise for a new class of drugs that could significantly reduce myocardial injury associated with ischemia-reperfusion injury.

Commentary

The NHE-1 isoform is a cell membrane protein expressed in various organs and cells, including the heart and cardiac myocytes. As its name suggests, it exchanges hydrogen ions for sodium ions. During ischemia, the protons accumulating within cardiac myocytes are exchanged for external sodium. The intracellular sodium ions then accumulate as a result of the coincident decrease in high-energy phosphate charge, preventing active extrusion through the sodium pump (Na^+–K^+-ATPase). The accumulation of intracellular sodium, in turn, causes the accumulation of intracellular calcium, through reduced calcium efflux and increased influx through the Na^+–Ca^+ exchanger. The accumulation of intracellular calcium is very damaging, contributing to hypercontracture, mitochondrial calcium overload, and myocyte death. A wealth of preclinical studies have investigated these events during ischaemia and demonstrated without doubt that NHE-1 inhibition reduces infarction. The maximum cardioprotective effect is seen in animal studies when the NHE-1 inhibitor is present throughout ischemia and when definite reperfusion occurs. These two key criteria were absent in some of the groups of patients investigated in previous large-scale clinical studies of NHE-1 inhibition – a deficiency that probably contributed to their negative findings (reviewed in [1]).

Cariporide is a selective and potent inhibitor of NHE-1, previously investigated in a dose-ranging phase 2/3 study, GUARDIAN, that recruited patients who had evolving myocardial infarction, or were undergoing high-risk percutaneous coronary intervention or CABG surgery [2]. It was only in this last group, fulfilling the key criteria of cariporide being present throughout ischemia and definite reperfusion, that possible protection was seen. This ''signal'' provided the basis for the EXPEDITION study [3].

As can be seen, EXPEDITION was a positive study in that the incidence of the primary composite endpoint was significantly lower in the cariporide group than in the placebo group. Although all components of a primary endpoint contribute equally to the accrual of events, they obviously are not biologically equivalent. This was the problem in EXPEDITION.

The rationale behind EXPEDITION was that cariporide, given 2 h before CABG surgery and continued for 2 days, would reduce perioperative myocardial infarction to such an extent that this would be

reflected in all-cause mortality. Although cariporide was associated with a marked and highly significant reduction in the incidence – and the severity – of myocardial infarction, it increased mortality! The incidence of myocardial infarction, assessed 5 days after surgery, was reduced from 18.9% to 14.4%, a relative risk reduction of 24% that was statistically highly significant ($P = 0.000005$). At the same time point, mortality increased from 1.5% to 2.2% – an escalation in relative risk of 53.5% that was statistically significant ($P = 0.028$). The determination of cause-specific mortality was not mandated in the trial protocol. However, it seems likely that the excess deaths in the cariporide group were related to cerebrovascular events. Focal persistent neurological deficits occurred in 4.5% of the cariporide group, compared with 2.5% of the placebo group, an approximate 80% increase in relative risk that was statistically highly significant ($P = 0.0001$). There were similarly statistically significant increases in postoperative confusional states without focal neurological deficits. The increase in mortality together with these non fatal, but serious, adverse events more than offset the benefit of cariporide on non fatal myocardial infarction and, even though the investigational agent met its primary efficacy endpoint, it is not being developed further by its manufacturer, Sanofi-Aventis. I consider this to be a reasonable decision, given the clinical importance of death and disabling cerebrovascular accident over non fatal myocardial infarction.

Despite the unpredicted effects of cariporide in increasing mortality, confusional states, and cerebrovascular events, there are aspects of the trial that offer encouragement. First, to my knowledge, this is the first large phase-3 trial that demonstrates unequivocally that it is possible to increase myocardial resistance to ischemia and thereby reduce infarction. Moreover, this increased resistance is manifest with a definition of myocardial infarction that did not involve minor increases in troponin, but a 10-fold increase in CK-MB above the upper limit of normal or the postoperative appearance of new Q-waves using a conservative objective ECG scoring system. Secondly, it leaves the door open for further studies. At present it is not known whether the excess mortality and adverse cerebrovascular effects are the result of NHE-1 inhibition or an off-target action specific to the cariporide molecule. Although there is no doubt that the cloud of the EXPEDITION study will cast a shadow over the concept of cardioprotection, it is important not to ignore its very silver lining.

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