Outcome of coronary revascularisation in diabetes

P. Smits

Departments of Pharmacology and Toxicology, and General Internal Medicine, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands

In this issue, Timmer et al. present interesting data on the outcome of coronary revascularisation in diabetic patients in the Netherlands. Based on the recommendation of an expert panel, they assigned all enrolled patients to one of three treatment options: coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or pharmacotherapy without revascularisation. In total 872 patients were analysed, 107 of whom had diabetes. The investigators concluded that patients with diabetes experience worse outcomes compared with nondiabetic subjects. Interestingly, the increased long-term mortality in diabetes held true for the PCI subgroup (41% vs 24%) as well as for the pharmacotherapy subgroup (65% vs 31%), but not for the CABG-treated patients. Long-term mortality after CABG appeared to be exactly the same in diabetic vs nondiabetic subjects (24% vs 24%). So, the overall conclusions of the authors were 1) long-term mortality of revascularisation procedures is relatively high in diabetes, and 2) total revascularisation by CABG may be superior to PCI or to a conservative pharmacological approach in diabetes.

The first conclusion of Timmer et al., a higher long-term mortality after coronary revascularisation in patients with diabetes vs nondiabetics, is a well-known phenomenon. Further analysis of this increased cardiovascular mortality shows that this is at least based on three independent mechanisms.

- Type 2 diabetes accounts for up to 95% of all cases with diabetes. Type 2 diabetes often involves the combination of classical risk factors such as hypertension and dyslipidaemia resulting in a relatively advanced state of atherosclerosis in this particular group of patients. Timmer et al. did not discriminate between type 1 and type 2 diabetes, but their data clearly show a higher incidence of risk factors in the diabetic patients, suggesting a predominance of type 2 diabetes in their group. Accordingly, the signs of macrovascular disease were much more frequent in the diabetes group as compared with the nondiabetic patients.
- Apart from the concurrence of risk factors in type 2 diabetes, the disease itself appears to be an important independent risk factor for cardiovascular events. Apparently, the atherosclerotic process in diabetic patients has particular features that contribute to a worse prognosis and a worse response to revascularisation. The majority of mechanistic studies point towards a toxic role for high glucose in the vascular complications. Pathophysiological mechanisms such as endothelial dysfunction, increased platelet aggregation, inflammation and advanced glycosylation end products seem to be crucial in glucose-accelerated atherogenesis. These mechanisms are also relevant for type 1 diabetes. In the DCCT trial, intensive glucose lowering was associated with a significant decrease in carotid artery intima-media thickness, and reduced cardiovascular disease by 42%. Although the progression of atherosclerosis in diabetes is often impressive, there does not seem to be a specific feature that enables us to distinguish the diabetic atherosclerotic plaque from a nondiabetic lesion.
- Vascular disease ultimately results in cardiovascular events. The outcome of such an event is not only dependent on the severity of the atherothrombotic process, but is also determined by mechanisms that modulate ischaemia-reperfusion injury. Animal experiments have convincingly shown that a certain vascular obstruction of a coronary artery results in a larger myocardial infarction under hyperglycaemic conditions than under normoglycaemic conditions. Apparently, the diabetic or hyperglycaemic state inhibits endogenous cardioprotective mechanisms. One of the most important protective mechanisms against ischaemia is the well-described phenomenon of ‘ischaemic preconditioning’. Ischaemic preconditioning is defined as an increased tolerance to ischaemia and reperfusion induced by a previous sublethal period of ischaemia. Other than timely reperfusion, ischaemic preconditioning is the most powerful mechanism for...
limiting infarct size. The myocardial ATP-dependent potassium channel (K<sub>ATP</sub> channel) plays a crucial role in the cellular signalling of ischaemic preconditioning. Recent research has shown that diabetes attenuates K<sub>ATP</sub> channel function, thereby explaining reduced ischaemic preconditioning in these patients. It is interesting to realise that all three aforementioned mechanisms may have been modulated by the use of prescribed drugs in the study of Timmer et al. For example, blood pressure and cholesterol-lowering drugs would certainly reduce the impact of the concurring risk factors in type 2 diabetes. From a theoretical point of view, blood glucose lowering drugs are expected to reduce glucose-accelerated atherogenesis, and the positive clinical data of the biguanide derivative metformin on cardiovascular complications may be compatible with this view. Interestingly, blood glucose lowering drugs may also affect ischaemic preconditioning. Sulphonylurea derivatives, and in particular glibenclamide, have been shown to block the myocardial K<sub>ATP</sub> channel, thereby resulting in a negative effect on ischaemia-reperfusion injury in the human in vitro setting. Indeed, the use of sulphonylurea drugs is associated with an increased mortality in patients with diabetes mellitus after direct angioplasty following acute myocardial infarction. In contrast, insulin, metformin and thiazolidinedione derivatives appear to limit ischaemia-reperfusion injury in experimental conditions. Unfortunately, the study by Timmer et al. did not analyse the different pharmacotherapeutic regimens of the included patients. As such, the impact of the aforementioned drug-induced mechanisms cannot be evaluated in their set of data.

The second conclusion of Timmer et al. refers to the superiority of CABG vs PCI. In a recent article, Flaherty and Davidson reviewed the outcome of subgroups of diabetic patients in six randomised clinical trials comparing CABG with PCI in a total of 950 patients. This overview confirms the superiority of CABG vs PCI as far as balloon-only PCI is concerned. However, the data do not support a superiority of CABG vs stent-assisted PCI. It seems important to realise that the use of drug-eluting stents has led to dramatic reductions in restenosis in diabetes. Finally, the use of glycoprotein IIb/IIIa antagonists has improved the outcome of PCI in diabetes. As such, the conclusion on the superiority of CABG vs PCI may not hold for current strategies with drug-eluting stents and with new pharmacological agents to inhibit coagulation.

In conclusion, studies have shown that the outcome of coronary revascularisation, in particular of balloon-only PCI, is relatively poor in patients with diabetes. However, a thorough analysis of the respective factors that are considered to contribute to this poor outcome can help to optimise the chance of long-term survival after coronary revascularisation.

REFERENCES

5. Hearse DJ, Stewart DA, Chain EB. Diabetes and the survival and recovery of the anoxic myocardium. J Mol Cell Cardiol 1975;7:397-419.