Combined Type 2 Diabetes and Ischemic Heart Disease: Double Jeopardy

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Type 2 diabetes increases the risk of coronary heart disease by a factor of 2–4. Haffner et al. [1] demonstrated that the 7-year mortality among type 2 diabetics without established ischemic heart disease (IHD) was similar to that of nondiabetics who had experienced a prior myocardial infarction (MI). The combination of type 2 diabetes and IHD further increased mortality by a factor of 2 [1]. Other long-term post-MI studies have demonstrated an approximately double mortality rate in diabetics versus nondiabetics [2].

The poor prognosis in diabetes is probably mainly due to both the high frequency of risk factors for IHD as well as more widespread coronary artery disease in diabetics, as also demonstrated in two articles in this issue of *Heart Drug* [3, 4].

Conventional pharmacological treatment modalities, such as fibrinolysis, ASA, statins, beta-blockers and ACE inhibitors, have proven their efficacy in high-risk patients with diabetes, IHD, or both, and a general pattern is that for any given treatment the effect is greater in diabetics than in nondiabetics, i.e. numbers needed to treat are smaller among diabetics. Despite this fact, diabetics are in general treated to a lesser extent than nondiabetics [2, 5]. This might simply be because physicians do not realize the severity of the diabetic disease, and because of prob-

lems with compliance in these patients due to the many drugs prescribed.

In case of an acute MI, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction I (DIGAMI I) study [6] suggested a beneficial effect on survival of acute glucose-insulin infusion in diabetics. This hypothesis is now being tested prospectively in the larger, ongoing DIGAMI II study, which also focuses on long-term glycemic control.

The beneficial effect of prolonged good glycemic control on the development of IHD in diabetics has been a matter of controversy. In large prospective trials, both in type 1 diabetics – Diabetes Control and Complications Trial (DCCT) [7] – and type 2 diabetics – United Kingdom Prospective Diabetes Study (UKPDS) [8] – good glycemic control tended to, but did not conclusively demonstrate a beneficial effect on the development of cardiovascular disease (CVD). However, in the UKPDS trial in type 2 diabetics, the patients were at low risk of CVD, and established CVD at entry was an exclusion criterion. In contrast, in the follow-up of the Kumamoto trial [9] good glycemic control in type 2 diabetics conclusively demonstrated reduced events of CVD, and in the UKPDS a subgroup of overweight patients demonstrated a quite substantial benefit from metformin treatment on the devel-

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opment of CVD [10]. Of particular interest, the UKPDS trial demonstrated no adverse effects of insulin or sulfonylureas (SU) on the development of CVD [8]. It has otherwise been argued that glucose-lowering treatment increases the risk of mortality from CVD, insulin being atherogenic by itself [11], and SU reducing preconditioning in the ischemic heart [12].

In the present issue of *Heart Drug*, Hasdai et al. [3, 4] extract data on the outcome of percutaneous transluminal coronary angioplasty (PTCA) from an impressively large register from the Mayo Clinic. They find that diabetics treated with insulin have an approximately 60% higher risk of death or MI than those treated with oral agents or just diet. However, this is probably not due to insulin per se, but to the fact that these patients have more advanced diabetic disease, with more complications, especially of macrovascular type, which was indeed the case. The type of diabetes was not given, nor was the duration of disease or the degree of metabolic control (HbA1c). However, the majority of these patients most likely were type 2 diabetics on insulin. Five to ten percent of type 2 diabetics develop secondary therapeutic failure per year, and many of these end up on insulin, i.e., the fact that these patients were on insulin indicated longer duration of the disease, and thus probably more advanced disease. Nevertheless, the data are important from a clinical point of view, since they identify a group of diabetics with a particularly high risk of complications/death due to invasive therapy for IHD.

The type of invasive therapy – coronary artery bypass graft (CABG) or PTCA with or without stent – selected for the diabetic patients with IHD has been a matter of debate. In general diabetics should be offered the same treatment modality as nondiabetics, but on the basis of several recent studies and most impressively by the BARI I trial (although a posthoc analysis) [13], it emerges that diabetics offered PTCA have a much higher mortality than those offered CABG, particularly if the patients had a Q wave infarction [14]. This difference seems more moderate if the patients suffered a non-Q wave infarction. The reason for the poor prognosis using PTCA is complex, but it might be due to an inappropriate intimal hyperplasia after PTCA induced by the diabetic state [15]. Whether stenting is better than conventional balloon angioplasty is not clear. However, stenting does not obviate accelerated restenosis in diabetes [6]. In the article by Hasdai et al. [3] reported in this issue, the diabetic patients submitted for PTCA had an almost two-fold in-hospital mortality, and an almost double mortality rate during long-term follow-up. As proposed by the authors,

the adverse prognosis is probably not directly related to the procedure itself, but more likely owing to the more extensive coronary artery disease as well as to the less complete revascularization achieved during intervention. These findings could explain the results of a better outcome after CABG than PTCA in the Bypass Angioplasty Revascularization Investigation I (BARI I) trial.

Of interest is a new class of drugs, the glitazones, which are insulin sensitizers acting by reducing insulin resistance through a reduction of free fatty acids in plasma. These drugs reduce rather than stimulate insulin secretion, as other drugs do (equivalent to exogenous insulin), and have been shown to reduce carotid artery intimal thickness [15, 16]. The BARI II trial will test whether the effect of these drugs on coronary heart disease differs from that of SU or exogenous insulin.

In conclusion, the combination of diabetes and IHD is double jeopardy, and aggressive management of all risk factors for CVD as well as hyperglycemia should be undertaken in order to reduce the risk of new events of CVD. The choice of glucose-lowering drugs is at present less essential, although overweight patients should be urged to take metformin, and older SU should be avoided due to the risk of inhibiting preconditioning in the ischemic heart. Decisions to perform invasive therapy for IHD should rest on the same principles as for nondiabetics, but at present CABG should be considered preferable to angioplasty for the management of IHD.

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