

Early diagnosis of silent coronary artery disease in diabetic subjects – are intense efforts worth while?

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The prevalence of diabetes is increasing at present, affecting 3–5% of Western populations. Most of the increase is due to type 2 diabetes which seems to be a predominantly vascular disease, since the incidence of all manifestations of macrovascular disease is at least two-fold higher in patients with type 2 diabetes than in corresponding non-diabetic subjects. When it comes to coronary artery disease, it is noteworthy that not only the occurrence of the disease is increased, but also the prognosis seems to be worse than in non-diabetic subjects with atherosclerosis accounting for up to 60% of all diabetes-related deaths. It is also a widely accepted dogma that the coronary artery disease of diabetic patients often presents with atypical symptoms, and even advanced disease may be completely asymptomatic making the disease more frightening and mysterious for the patient and the doctor.

In view of the above mentioned high prevalence and poor prognosis of coronary artery disease in diabetes it makes good sense to develop strategies for early diagnosis of the disease to prevent later fatal and irreversible complications. In this issue, Zellweger and Pfisterer have put together current knowledge on silent coronary artery disease in diabetic subjects. Their review shows that in spite of good intentions many open questions remain and need to be answered before solid, evidence-based recommendations can be given on many aspects of the topic.

The prevalence of silent myocardial ischaemia and infarction is increased in diabetic subjects and autonomic neuropathy has been suggested as causing the lack of symptoms. This relationship is, however, controversial, although it is tempting to speculate that the neuropathic process leads to abnormalities in sympathetic afferent nerves, which are the main pathways for the transmission of cardiac pain [1]. This controversy is not surprising, since the mechanisms of silent myocardial ischaemia are complex and controversial even in non-diabetic patients [1–3]. The available epidemiological and clinical data suggest that increased incidence of asymptomatic myocardial

infarctions, coronary artery disease and myocardial ischaemia in diabetic patients *mainly* reflects accelerated coronary atherosclerosis and is not due to autonomic neuropathy, ie, since the symptomatic forms of the disease are common in diabetes, earlier asymptomatic forms should be as well [1]. Even if diabetic subjects do often have asymptomatic coronary artery disease, myocardial infarctions and episodes of myocardial ischaemia, there is no evidence to prove that the *proportion* of silent disease relative to symptomatic disease or episodes is significantly increased in diabetic patients.

Strategies aimed at large-scale early diagnosis of silent coronary artery disease may give rise to multiple problems both in diabetic and non-diabetic populations. First, non-invasive diagnosis of asymptomatic coronary artery disease is uncertain using current methods. This inaccuracy leads to numerous false diagnoses and unnecessary pain in populations with low likelihood of occlusive coronary artery disease unless invasive methods are used for the confirmation of the findings [4]. On the other hand, even coronary angiography has serious drawbacks in this context. The silhouette of contrast medium in the coronary tree cannot exclude atherosclerosis or even identify vulnerable plaques at risk of imminent rupture. This is clinically important if the aim is to prevent sudden death or acute myocardial infarction. It is well-known that vulnerable plaques at risk to cause future vessel occlusion are common also in angiographically normal coronary segments [5] and abrupt coronary occlusion caused by rupture in non-obstructive plaques is a common cause of sudden cardiac death and the first (and only) clinical manifestation of coronary artery disease in as many as 20–25% of patients [6]. In this respect it is noteworthy that the risk of early sudden death before hospital admission may be even higher in diabetic than non-diabetic men with acute myocardial infarction [7].

Another problem arises when we find a traditional, *haemodynamically* significant coronary artery disease in an asymptomatic diabetic subject. What should we do in such case? Of course, we can

change our aggressive primary prevention for aggressive secondary prevention of the disease, but what about invasive treatment of such lesions? The early CASS study showed that coronary artery bypass surgery gives no prognostic benefit, unless left ventricular function is depressed in addition to 3-vessel or left main coronary artery disease. Similarly, in the recent AVERT study “cosmetic” treatment of coronary stenosis by modern angioplasty offered no prognostic advantage in patients with mild or no symptoms, but may expose the patient to procedure-related complications [8].

In my view, large-scale hunting for silent coronary artery disease in diabetic or non-diabetic populations with normal exercise tolerance, a sign of good prognosis, is not justified [9]. At present we do not know if we do more harm than good with the goal of making asymptomatic people (= “healthy” in their own perception) feel they are sick and start to treat them with methods not proven to be useful. On the other hand, even with uncertainty on specific coronary anatomy we know that the prognosis of asymptomatic diabetic subjects used to be comparable to non-diabetic patients with a history of myocardial infarction [10]. How-

ever, a lot of work has been published since the publication of Haffner et al. and prognosis can be improved by starting aggressive primary prevention of established risk factors including, for example, statin therapy. Furthermore, the recent MICRO-HOPE study showed that ACE-inhibition is useful in diabetic patients with coronary risk factors [11]. Secondly, when symptoms develop we should not delay diagnosis and treatment, since recent studies have shown that many evidence-based treatments of acute or chronic symptomatic coronary artery disease are currently under-used in diabetic patients, despite the absolute (and often relative) benefits of the treatments being even larger than in non-diabetic patients [12–14].

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References

- 1 Airaksinen KEJ. Silent coronary artery disease in diabetes – a feature of autonomic neuropathy or accelerated atherosclerosis? *Diabetologia* 2001;44:259–66.
- 2 Malliani A, Lombardi F. Consideration of the fundamental mechanisms eliciting cardiac pain. *Am Heart J* 1982;103:575–8.
- 3 Rosen SD, Paulesu E, Frith CD et al. Central nervous pathways mediating angina pectoris. *Lancet* 1994;44:147–50.
- 4 Koistinen MJ. Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. *Br Med J* 1990;301:92–5.
- 5 Lichtlen PR, Nikutta P, Jost S, Deckers J, Wiese B, Rafflenbeul W. Anatomical progression of coronary artery disease in humans as seen by prospective, repeated, quantitated coronary angiography. Relation to clinical events and risk factors. The INTACT Study Group. *Circulation* 1992;86:828–38.
- 6 Kannel WB, Doyle JT, McNamara PM, Quickenton P, Gordon T. Precursors of sudden coronary death. Factors related to the incidence of sudden death. *Circulation* 1975;51:606–13.
- 7 Miettinen H, Lehto S, Salomaa V, et al for the FINMONICA myocardial infarction register study group. Impact of diabetes on mortality after the first myocardial infarction. *Diabetes Care* 1998;21:69–75.
- 8 Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med* 1999;341:70–6.
- 9 Thompson GA, Jabbour S, Goldberg RJ et al. Exercise performance-based outcomes of medically treated patients with coronary artery disease and profound ST segment depression. *J Am Coll Cardiol* 2000;36:2140–5.
- 10 Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–34.
- 11 Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–9.
- 12 Kendall MJ, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. *Ann Intern Med* 1995;123:358–67.
- 13 Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study [4S]. *Diabetes Care* 1997;20:614–20.
- 14 Hildebrandt P. Diabetic patients and acute coronary syndromes. *Eur Heart J* 2001;22:887–8.

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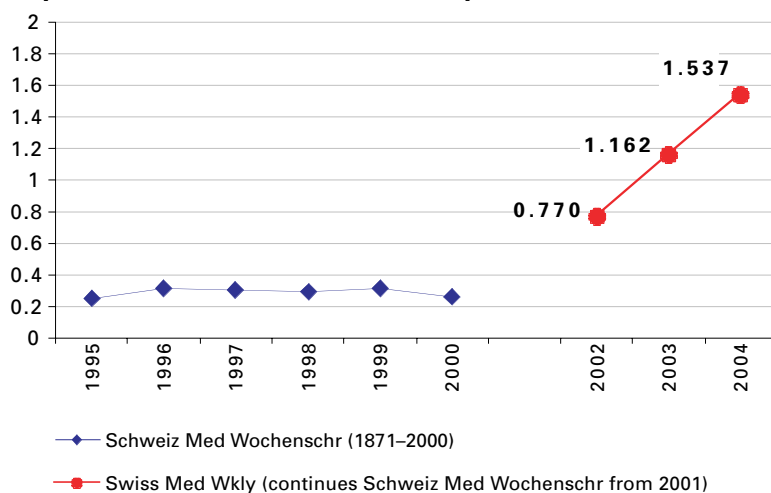
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