A new look at benefits of drug therapy in silent myocardial ischaemia

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This editorial refers to ‘Effects of anti-ischaemic drug therapy in silent myocardial ischaemia type I: the Swiss Interventional Study on Silent Ischaemia type I (SWISS I): a randomized, controlled pilot study’ by P. Erne et al., on page 2110.

Over 25 years ago we prepared a classification system for silent myocardial ischaemia that we hoped would make it easier for future researchers to study the pathophysiological basis for the syndrome, establish prognosis, and determine appropriate management protocols. In our categorization, Cohn Type I refers to asymptomatic individuals without known coronary artery disease (CAD) and Cohn Types II and III to patients with known CAD. Those with prior myocardial infarctions (MIs) who are asymptomatic are Type II, and those with CAD and both silent and symptomatic ischaemic episodes are Type III. In the last decade a dedicated group of Swiss cardiologists led by Dr Mathias Pfister of the Basel University Hospital have conducted a long-term series of clinical studies involving patients with Types I and II silent ischaemia. By providing a ‘new look’ at the syndrome of silent ischaemia they have contributed important clinical data to aid in its management. They have now described the results of anti-ischaemia drug therapy in Type I patients (studied in their SWISS I trial); their SWISS II data dealing with Type 2 patients and also recently published will be commented on later in this editorial.

Investigations into silent ischaemia have been centred on either its pathophysiology, prevalence, prognosis, or treatment, or the effect of treatment on prognosis. Although recent pain studies have not yet been able to pinpoint the exact nature of the cardiac pain mechanism, there is increasing evidence linking adenosine to the process as a chemical mediator. Fortunately, much more is known about the cardiac haemodynamic abnormalities associated with silent ischaemic episodes than its causation. The prevalence of the three types has been estimated with a variety of techniques, and prognostic data are also abundant, but controversies arise when the therapeutic aspects are considered, especially as they apply to the totally asymptomatic Type I patients. Whereas Type 2 and 3 patients have known CAD, and treatment guidelines for silent ischaemia conform to those accepted for symptomatic patients, this is not true for Type I patients. This is why the studies of the Swiss investigators are so important. There is a distinct paucity of data in Type I patients even when CAD is diagnosed by multiple non-invasive tests and/or coronary angiography. In one of the most significant previous series of Type I patients, Erikson and Thaulow followed a group of 50 patients with angiographically proven CAD for 15 years and found that 14 out of 50 had died (including eight with three-vessel disease). No attempt was made to randomize medical or surgical therapy in this group once the diagnosis was made, but yearly mortality in the three- vessel group was computed to be 3% compared with 1% in the combined one- and two-vessel disease subgroups. These figures provide a yardstick to measure the effect of subsequent natural history and/or treatment/interventional studies.

In their current report, the study population of Erne et al. consisted of 263 asymptomatic persons with at least one risk factor for CAD (plus a stress test with abnormal ECG and imaging results). Unfortunately, only 54 (21%) consented to randomization and the authors acknowledge this limitation. This was also a very well motivated subgroup, and for purposes of a pilot study this ‘bias’ is probably a plus rather than a minus. Clearly the 26 patients in the antianginal drug therapy group did better during the 11.2 year mean follow-up period in terms of mortality, morbidity, and the results of repeated non-invasive procedures than did the control group. There was no mortality in this group compared with 1.1% yearly for the control group. If anything, the full effects of medical therapy may have been underestimated over time, since patients in the control group often had anti-anginal drugs added as the years went by (see Fig. 2 in Erne et al.).

What are the clinical implications of this study? Do the results mean that asymptomatic individuals with similar risk factor profiles to those in this report should be screened for silent ischaemia? Does the drug therapy used in this study employ the ‘correct’ anti-ischaemic agents? The prognostic significance of silent ischaemia in middle-aged and elderly persons with no apparent heart disease has most recently been evaluated in the Danish study of Sajadieh et al.
Sajadieh et al. used ambulatory monitoring to document silent ischaemia—a useful technique but not as accepted as the exercise test protocol used in the Swiss study—and found a >3-fold increase in the cardiac event rate in the positive responders. This latest Holter study confirms earlier prognostic data in other patient populations using a variety of Holter and stress tests.

As far as ‘routine’ screening is concerned, however, even in the most aggressive quarters the emphasis is only on testing healthy patients at the highest risk for CAD, based on risk factor profiles. Certainly diabetes fits this description of high risk, yet even here the pros and cons of appropriate screening procedures are still debated.6–8 The argument against screening relies on aggressive treatment (with statins) for all diabetics, not just those with silent ischaemia.8 As far as the ‘correct’ drug treatment is concerned, few would argue that the combination of a b-blocker and aspirin is a good start. This was the basis for management in the ASIST10 trial where—like SWISS I—significant improvement was achieved in combined ‘hard’ cardiac end-points (death, non-fatal MIs, and unstable angina) although the patient population was slightly different.

What is the role of percutaneous coronary intervention (PCI)? This was not specifically evaluated in the SWISS I or ASIST trials, but it has been addressed in asymptomatic patients with silent ischaemia and prior MIs in the SWISS II trial. Erne et al.3 randomized 201 patients to a PCI subgroup (96 patients) and an anti-ischaemic drug therapy subgroup (105 patients). The latter group did not do as well as the former in terms of cardiac death, non-fatal recurrent MIs, or need for revascularization. This is similar to what was found in the ACIP study,11 though the patient populations also differed somewhat (the latter had a mixture of silent and symptomatic ischaemia). The SWISS II result argues that in addition to drug therapy there is a role for an ischaemia-targeted approach to PCI in asymptomatic survivors of MI.3 Just as the SWISS I pilot study results suggest that an ischaemia-targeted approach (i.e. more than just risk factor modification) can be helpful in totally asymptomatic persons with evidence of silent ischaemia. The Swiss investigators are to be congratulated for their perseverance in these studies, but their ‘new look’ should not end there since all clinicians interested in this syndrome look forward to continued productivity from their Swiss colleagues!

Conflict of interest: none declared.

References