Calcium channel blockers or beta receptor antagonists for patients with ischaemic heart disease. What is the best choice?

See pages 76, 96, 104 for the articles to which this Editorial refers

The safety of calcium channel blockers has recently been challenged. A case-control study by Psaty et al.\(^{[1]}\) and a new meta-analysis by Furberg et al.\(^{[2]}\) of 16 randomized secondary-prevention trials with nifedipine initiated this debate. In the case-control study, antihypertensive therapy based on calcium channel blockers increased the risk for a subsequent myocardial infarction compared with the outcome for therapy based on diuretics or beta-blockers. In the meta-analysis, nifedipine used for secondary prevention in patients with ischaemic heart disease was associated with an increase in total mortality. Both studies claimed that an unfavourable outcome was more prevalent with increasing dosages. Furberg and co-workers\(^{[2]}\) are of the opinion that 'mortality data from randomized clinical trials of short acting nifedipine are alarming' and their review 'suggests that the problem may go beyond short-acting nifedipine' while 'extrapolation to slow release dihydropyridines and non-dihydropyridines represents a greater leap'. The authors also discuss mechanisms which may contribute to the increased risk such as pro-ischaemia, negative inotropism, neuroendocrine activation, nocturnal hypotension and increased risk for bleedings.

Not surprisingly, these two reports initiated a vigorous debate, followed by several editorials in leading medical journals. Yusuf\(^{[3]}\) correctly emphasizes that no study of calcium antagonists in patients with coronary artery disease has yet demonstrated a convincing reduction of morbidity or mortality. His opinion, obviously influenced by the case-control study and the meta-analysis, is therefore that it 'at present is prudent to use drugs from alternative classes of agent as initial treatment for angina pectoris and hypertension'. He also claims that widespread use of calcium antagonists should await results of ongoing trials. Horton\(^{[4]}\) shares the opinion that concerns raised by the new data are serious. Opie and Messeri\(^{[5]}\), Buring et al.\(^{[6]}\) and Klener\(^{[7]}\) would also like to see prospective mortality studies on the subject. These authors are hesitant, however, about some of the conclusions made by Psaty et al.\(^{[1]}\) and Furberg et al.\(^{[2]}\), who they consider overemphasize and generalize the risks. It is, nevertheless, admitted that there may be risks associated with the use of nifedipine, in particular with high dosages of short acting formulations.

Case-control studies have their well known limits. One of the most apparent is the problem of adjusting for confounding factors. In contrast to Psaty et al.\(^{[1]}\), Aurnes et al.\(^{[8]}\) in another recent case-control study, could not verify that calcium antagonists increased the risk for myocardial infarction. One reason for these conflicting results may be the inherent problems with this type of analysis. Even meta-analyses have their flaws. In particular, Opie and Messeri\(^{[5]}\) are critical of the way Furberg et al.\(^{[2]}\) handled the data upon which their conclusions were based. The choice of studies that were cited, the interpretation of end-points and the time when end-points were calculated are some aspects on which they expressed a difference in opinion. Diverging opinions regarding details always exist. The point is, however, that neither case-control studies nor meta-analyses are capable of giving us a final solution to a problem. Their strength is to create hypotheses to be tested in subsequent prospective, clinical trials. Accordingly, the debate regarding benefits and drawbacks with calcium antagonists will continue until the release of data from such investigations.

In this issue there are two well conducted trials of considerable importance in this context. Fox et al.\(^{[9]}\) and Dargie et al.\(^{[10]}\) present the results of the Total Ischaemic Burden European Trial (TIBET). Atenolol, nifedipine SR and their combination were given to patients with chronic, stable angina pectoris. In all, 682 patients with an established diagnosis of mild to moderate angina pectoris were recruited to a randomized, double-blind, parallel group study. The beta-blocker atenolol was given in a dosage of 100 mg daily and nifedipine SR in a dose of 40 mg daily. The same dosages were used in the combined atenolol+nifedipine group. The two drugs and their
combination were equally effective in significantly reducing all markers of reversible myocardial ischaemia during exercise testing and ambulatory electrocardiographic monitoring. During an average follow-up period of 2 years (range 1–3 years) there was no statistically significant difference in ‘hard’ end-points defined as cardiac death, non-fatal myocardial infarction and unstable angina pectoris. Furthermore there was no evidence of an association between the presence, frequency or total duration of ischaemic events and these outcomes.

The APSIS study presented by Rehnqvist et al.\textsuperscript{[11]} is a mono-centre randomized double-blind study recruiting 809 patients with stable angina pectoris. They were treated with either metoprolol (Seloken ZOC) 200 mg daily or verapamil (Isoptin Retard) 240 mg daily. During a median follow-up period of 3-4 years (range 6-75 months) there were no differences in fatal or non-fatal cardiovascular events. Among the latter were non-fatal myocardial infarctions, incapacitating or unstable angina pectoris and cerebrovascular or peripheral vascular events.

It should be emphasized that serious events were fairly infrequent in both studies, mortality approaching 1-2\% per year. In this respect, verapamil did not differ from metoprolol and nifedipine was equal to atenolol. It is interesting to notice that both studies, although using different drugs, basically arrived at the same conclusion, namely that treatments with a beta-blocker or a calcium channel blocker were equally effective as regards symptomatic relief.

One of the assumptions upon which these studies were based were that beta-blockers are cardio-protective as learnt from studies in post-myocardial infarction patients. Following the recent case-control study and meta-analysis, it may have been argued that calcium channel blockers would be harmful, in particular in patients with established ischaemic heart disease. There is, however, no evidence that this was the case. Both types of drugs, actually two different beta-blockers and two different calcium antagonists, gave the same outcome as regards mortality and serious cardiovascular morbidity. The dosages of the calcium antagonists were rather high, but administered as slow release formulations, which may have been of considerable importance.

Following TIBET and APSIS it therefore seems quite safe to use certain formulations and types of calcium channel blockers in patients with moderately severe angina pectoris. Many of the patients in these two studies were also hypertensives and some had a previous myocardial infarction. It should be emphasized, considering the size of the patient populations, that the power in APSIS is higher than that in TIBET. The safety issue regarding treatment with calcium antagonists in patients with stable angina pectoris is therefore possibly better documented for verapamil than nifedipine. If anything, these studies support the conclusion that generalization of risks from one type and amount of a compound to a class of pharmacological agents should not be done. It should not be forgotten that TIBET and APSIS do not address the issue of safety during unstable coronary syndromes, for instance acute myocardial infarction.

Another message is that protection from signs of silent ischaemia, as demonstrated in Holter-monitored ECG, appeared to be of limited value from a prognostic point of view in patients with stable ischaemic heart disease. If so, this will simplify the handling of these patients and limit the demand for such investigations.

In the light of TIBET and APSIS it may be asked whether drugs improve prognosis in patients with moderately severe angina pectoris. A study comparing the outcome of revascularization with bypass surgery or angioplasty and drugs could be of considerable interest. Mortality is low and it seems unreasonable that invasive or surgical procedures would be superior to drugs in this respect. It also seems that although drugs of various types do not differ in efficacy, they may differ as regards tolerability, as demonstrated in TIBET. Therefore, measures other than efficacy must be carefully evaluated in future trials of pharmacological treatment of angina pectoris.

In conclusion, the therapeutic goal in angina pectoris is to relieve symptoms and improve quality of life and longevity. It is difficult to further decrease the already low mortality among pharmacologically treated patients with mild to moderate angina. It is, however, mandatory that alternative therapy, besides relieving symptoms and improving quality of life, does not increase morbidity and mortality. TIBET and APSIS strongly support the view that the calcium antagonists tested did not differ as regards the outcome of therapy based on beta-blockade. The authors of the two reports are to be congratulated for timely and carefully conducted studies of major clinical relevance. Many patients with angina pectoris are treated with drugs. So far, few studies have addressed mortality and morbidity issues as raised in these studies.

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References


Selecting the most appropriate reperfusion therapy for acute myocardial infarction. How useful are guidelines?

See page 64 for the article to which this Editorial refers

Widely different therapies are currently being given to patients with an acute myocardial infarction. For those presenting with ST segment elevations or new bundle branch block within 6 to 12 h from the onset of symptoms, pharmacological and mechanical reperfusion strategies can be considered. For both strategies, impressive survival advantages have been demonstrated in clinical trials. Based on the clinical condition of the patient and, perhaps even more, on non-medical considerations, simple treatment with aspirin and streptokinase, or very aggressive and complicated treatment consisting of direct angioplasty followed by stent deployment associated with aPTT-adjusted heparin, aspirin and ticlopidin, may be chosen. Obviously, the efficacy of early reperfusion, the clinical benefit/risk ratio and the cost-effectiveness of these treatments differ enormously.

The increasing availability of catheterization laboratories providing 24 h service for emergency coronary artery interventions and the growing number of thrombolytic regimens with which reperfusion can be obtained pharmacologically, on the one hand, and the increasing constraints on health care expenses on the other, make it very difficult for the practising physician to choose. Boersma et al., in this issue offer a number of guidelines to select the most appropriate reperfusion strategy for an individual patient. They developed a model to calculate the expected gain in life expectancy by reperfusion therapy based on patients’ characteristics (of which age is by far the most important factor), predicted infarct size (using the amount of ST-segment elevations) and time to treatment. The expected benefits range from less than one month to more than 3 years. These data (which can be printed on a card) are very helpful for the physician who is often confronted with budgetary and organizational constraints and who has to select, on the spot, the best available treatment. Perhaps these guidelines are even more valuable for health authorities who have to take decisions on reimbursement policies for new reperfusion techniques. Indeed, the times are over when the medical community takes only a limited interest in the costs of a new therapy leading to a survival advantage.

Using these tables for their own patients, the authors recommend not giving any reperfusion therapy to 5 or 10% of patients in whom the estimated gain is negligible, and to perform direct angioplasty in the 5 or 10% with the highest expected gain in life expectancy or with a markedly increased risk for cerebral bleeding. For half of the remaining 80 or 90% of patients with the highest expected clinical benefit, front-loaded rt-PA is recommended and for the other half, streptokinase.

Obviously these practical recommendations are very arbitrary and are not useful in every hospital: a 24 h service for direct angioplasty is available in only a limited number of hospitals throughout the world and in countries with very limited resources for health care even rt-PA is out of the question. Furthermore, the decision