European Heart Journal (1996) **17**, 1463–1465

Clinical Perspectives

Interpretation of trials with drugs and devices; a double standard?

Recently, results have been presented of two major trials which, appropriately, received considerable attention in both the professional and lay press. The West of Scotland Coronary Prevention study (WOSCOP) demonstrated a reduction of coronary events at 5-year follow-up through treatment with a cholesterol lowering drug (pravastatin), and the Bypass surgery Angioplasty Revascularisation Investigation (BARI) reported a similar outcome with coronary angioplasty and bypass surgery after 5 years[1,2]. The interpretation of the results, as presented by the investigators at the 1995 sessions of the American Heart Association, suggests that different standards are applied to studies with drugs and devices.

Lipid lowering therapy

The West of Scotland study randomized 6595 male subjects without previous myocardial infarction and with serum LDL levels between 4·5 and 6·0 mmol . l^{-1} to treatment with pravastatin (40 mg) or placebo[1]. After average follow up of 4·9 years, approximately 70% of the participants were using study medication. The primary endpoint of definite non-fatal myocardial infarction or death from coronary heart disease was reduced by pravastatin from 7·9% to 5·5% at 5 years. This 31% relative reduction was statistically significant; 95% confidence interval 17–43%, $P<0·001$. Furthermore, reductions were observed in coronary revascularization procedures (2·5% vs 1·7%, $P=0·009$) and in total mortality at 5 years (4·1% vs 3·2%, $P=0·051$, see Table 1). The findings were consistent among many subgroups.

The results of the West of Scotland study are consistent with those of the recently published Scandinavian Simvastatin Survival Study (4S) in 4444 patients with documented coronary artery disease[3]. In 4S, total mortality was reduced after 6 years' treatment with simvastatin from 12·4% to 8·7%. This corresponds to a relative mortality reduction of 30%, a 95% confidence interval of 15–42%, and $P=0·0003$. Furthermore, a combined analysis of 14 angiographic studies revealed retardation of progression and in some of the patients regression of coronary lesions, associated with a 22% relative reduction of mortality and reinfarction after 2 to 5 years[4]. A pooled analysis of other smaller studies with pravastatin yielded similar reduction of cardiovascular events[5].

Coronary revascularization

The Bypass surgery Angioplasty Revascularisation Investigation (BARI) enrolled 1829 patients with angina pectoris or documented myocardial ischaemia during exercise and multivessel coronary artery disease. These patients were selected from approximately 12 530 candidates for bypass surgery (CABG) of whom 4530 were eligible for angioplasty (PTCA). Their mean age was 61 years, 27% were female and 55% had had a previous myocardial infarction. Survival at 5 years was reported as 89·3% after CABG and 86·3% after PTCA[5]. This was statistically not significant, although the relative reduction in mortality by CABG was 22%.

Non-significant trends to lower survival rates after PTCA were also observed in the Emory Angioplasty versus Surgery Trial (EAST)[6]) at 3 years and in the European Coronary Angioplasty vs Bypass Revascularisation Investigation (CABRI[7]) at 5 years (preliminary data presented by M. Bertrand at AHA, 1995), while survival after 2·5 years was slightly better after PTCA in the Randomized Intervention Treatment of Angina (RITA[8]) trial. Two meta-analyses of comparative studies of PTCA and CABG concluded similar survival and reinfarction rates at 1 to 3 years, although the risks after the initial procedure tended to be lower after CABG, which may explain the trends favouring CABG at longer follow-up[9,10,11].

Double standards?

In Table 1 the main results of WOSCOP and BARI are presented. In both studies the first treatment

Correspondence: Prof. M. L. Simoons, Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Postbus 1738, 3000 DR Rotterdam, The Netherlands.

0195-668/96/101463+07 $18.00/0

Table 1 Main results of the West of Scotland Coronary Prevention Study comparing placebo or pravastatin therapy in men with moderately elevated cholesterol levels and of the BARI study comparing coronary angioplasty (PTCA) and coronary bypass surgery (CABG) in patients with multivessel coronary artery disease. Preliminary BARI data were presented at the 1995 Scientific Sessions of the American Heart Association, and may appear in an altered form in subsequent publications

	WOSCOP		BARI	
	Placebo	Pravastatin	PTCA	CABG
Patients	3293	3302	915	914
5 year				
death (%)	4·1	3·2	13·7	10·7
death or MI (%)	10·9	9·2	21·3	19·6
revascularization (%)	2·5	1·7	52	7

(placebo, PTCA) resulted in higher rates of mortality, infarction and revascularization than with pravastatin and CABG. The relative reductions of mortality by pravastatin and CABG were similar: 22% in both studies. However, different conclusions were drawn: a beneficial effect of pravastatin therapy and no differences between the two intervention methods.

The WOSCOP as well as the 4S studies were designed with adequate power to detect a small difference in at 4–5 years follow-up in subjects without or in patients with coronary artery disease (primary and secondary prevention)[1,3]. In contrast, the trials comparing CABG and PTCA were underpowered to document small differences in survival. Accordingly, the conclusion of equivalence seems premature. Furthermore, the reported follow-up is too short in view of the higher procedure-related death and infarction rates with CABG with possible lower event rates during follow-up[8]. The total number of patients enrolled in randomized comparisons of the two revascularization procedures is approximately 4800. A pooled analysis of the individual data (clinical data and angiography) at 5 year follow-up might allow an adequately powered comparison of both approaches.

The initial presentations of the coronary intervention trials included cost-comparisons. As expected, the initial costs of CABG exceeded those for PTCA, although part of this advantage for the percutaneous approach was lost because of higher rates of subsequent hospital admissions and repeat procedures. In contrast, no costs were mentioned in the initial presentations and publications of the trials on lipid lowering therapy[1,3]. However, it should be appreciated that the reported 20 fewer myocardial infarctions, 14 fewer revascularization procedures and nine fewer deaths per 1000 patients treated[1] were achieved when the patients were treated for an average of 4 years, which corresponds to 4000 treatment years, taking into account the observed drop-outs. Accordingly, the costs per life year gained for primary prevention by therapy with HMG-CoA reductase inhibitors will be high! In The Netherlands it was estimated that the cost of preventing one death or one infarct would amount to approximately Dfl250 000!![12]. However, these costs would be lower in subgroups of patients with a higher risk for coronary events, including secondary prevention such as those in 4S[14]. Indeed, individual risk estimates may help to select patients in whom prevention with HMG-CoA inhibitors would be cost effective[12].

Conclusions

As discussed above, the trials were presented differently and had different viewpoints. The drug study (WOSCOP) was adequately powered, but did not present the financial implications of the statistically significant but small differences in survival and cardiovascular complications. On the other hand, the revascularization intervention studies appeared underpowered to detect similarly small relative differences in survival rates, but did present cost-effectiveness analyses. It seems that the high costs of drug therapy were neglected in the initial presentation of WOSCOP, in view of the perceived clinical benefit, while the possible differences in outcome in the BARI presentation were not highlighted in view of the lower costs and less invasive nature of PTCA. A 'double standard' indeed!

It should be appreciated that the comparison made in this commentary is based on a simplified view of the various treatments. First, it is understood that the techniques for both percutaneous intervention and surgery are changing rapidly. In particular the widespread use of stents and the use of arterial grafts may improve the results of PTCA and CABG in comparison with the presented trials[6–10]. Further trials to compare these procedures in patients with multivessel coronary disease are certainly warranted!

Furthermore, many patients could be treated before extensive stenoses develop in different branches of the coronary arteries. In the near future, non-invasive imaging of the coronary arteries through magnetic resonance imaging or electronic beam tomography may offer early (timely) detection of significant coronary lesions in high risk patients.

Repetitive intervention of single coronary lesions, once detected, may avoid the dilemma of

whether to choose PTCA or CABG for multivessel disease as studied in BARI. Finally, the focus on survival in this comparison does not account for other aspects of coronary intervention, such as 'quality of life'. Patients might prefer a slightly higher risk of PTCA at follow-up, with the risk of restenosis necessitating repeat intervention, to avoid a full surgical procedure.

In view of rapid developments, it is recommended that additional trials be performed to compare percutaneous/endovascular intervention and coronary surgery, and that such trials should be adequately powered to demonstrate equivalence or superiority in comparison with the reference method. Devices should be tested using standards similar to those used for drugs. Equivalence studies for different interventions require the inclusion of several thousands of patients[13]. Drug trials should report the costs of therapy, particularly if large patient groups are included to achieve a relatively small absolute event reduction in primary and secondary prevention.

The author is grateful for the constructive remarks by his colleagues J. R. T. C. Roelandt, P. W. Serruys and J. W. Deckers, although they did not share all views expressed in this commentary.

M. L. SIMOONS

Thoraxcenter,
Erasmus University and
University Hospital Dijkzigt,
Rotterdam, The Netherlands

References

[1] Shepherd J, Cobbe SM, Ford I *et al.* for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with Pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301–7.

[2] The Bypass Angioplasty Revascularisation (BARI) Investigators. A clinical trial comparing bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996; 335: 217–25.

[3] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.

[4] Simoons ML, Vos J, Deckers JW, De Feyter PJ. Clinical perspective. Coronary artery disease: prevention of progression and prevention of events. Eur Heart J 1995; 16: 729–33.

[5] Byington RTP, Jukema JW, Salonen JT *et al.* Reduction in cardiovascular events during Pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation 1995; 92: 2419–25.

[6] Weintraub WS, Mauldin PD, Becker E, Kosinski AS, King III SB. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). Circulation 1995; 92: 2831–40.

[7] CABRI Trial Participants. First year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). Lancet, 1995; 346: 1179–84.

[8] RITA Trial Participants. Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial. Lancet 1993; 341: 573–80.

[9] Sim I, Gupta M, McDonald K, Bourassa MG, Hlatky MA. A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. Am J Cardiol 1995; 76: 1025–9.

[10] Pocock SJ, Henderson RA, Rickards AF *et al.* Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. Lancet 1995; 346: 1184–9.

[11] Simoons ML. Myocardial revascularisation in bypass surgery or angioplasty. N Engl J Med 1996; 335: 275–7.

[12] Pravastatine en voedingsmiddelen bij afwezigheid van coronaire aandoeningen. GEBU Prikbord 1996; 30: 9–10.

[13] INJECT investigators. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. International Joint Efficacy Comparison of Thrombolytics. Lancet 1995; 346: 329–36.

[14] Jönsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H, for the Scandinavian Simvastatin Survival Study Group. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). Eur Heart J 1996; 17: 1001–7.

European Heart Journal (1996) **17,** 1465–1469

Percutaneous mitral commissurotomy

Percutaneous mitral commmissurotomy has been used in a considerable number of patients in the 10 years since the first publication on its implementation by Inoue[1]. Numerous reports are now available, enabling us to evaluate its immediate and mid-term results. Predictors have also been identified and thus we are much better placed today to select appropriate candidates for this procedure.

Correspondence: Dr A. Vahanian, Cardiology Department, Hôpital Tenon, 4 rue de la Chine, 75970 Paris Cedex 20, France.

Immediate and mid-term results

The failure rates range from 1 to 17% and they mostly occur in the early stage of the practitioner's experience.