Hotline Editorials

Optimizing cholesterol lowering therapy: contribution of the Post Coronary Artery Bypass Graft Trial

Accelerated atherosclerosis and thrombosis occur in saphenous vein coronary artery bypass grafts in over 60% of patients by 10–12 years after grafting, and lead frequently to deterioration of the excellent early clinical results[1]. This complication is frequently associated with coronary heart disease risk factors, especially hyperlipidaemia. The Post Coronary Artery Bypass Graft trial (Post CABG) studied whether or not intensive low density lipoprotein cholesterol lowering and low-dose oral anticoagulation could delay this late saphenous vein graft disease[2].

Numerous trials based on angiographic findings have clearly shown that progression of atherosclerosis in the native coronary arteries can be delayed by lipid lowering[3]. Similarly, several trials with clinical endpoints have reported significant decrease of total mortality and major coronary events associated with cholesterol lowering therapy[4–6]. In contrast with these trials, two lowering goals of low density lipoprotein cholesterol were compared in Post CABG to determine instead the most beneficial or optimal lowering strategy. A moderate lowering goal of 3–4 to 3–6 mmol.l⁻¹ was consistent with the recommendations of the National Cholesterol Education Program (NCEP) Adult PANEL I in the U.S.A.[7] and the Therapeutic Guidelines of the European Society of Atherosclerosis[8]. A much lower low density lipoprotein cholesterol goal of 1–6 to 2–2 mmol.l⁻¹ was selected to minimize the coronary heart disease risk associated with an elevated low density lipoprotein cholesterol blood concentration which starts from a level as low as 1–6 mmol.l⁻¹ and increases in a near-linear fashion without a clear threshold, according to most epidemiological surveys[2].

Post CABG is a multicentre, randomized and double blind trial that included 1351 men and women aged 21–74 years who had at least two patent (one in women) saphenous vein grafts placed 1–11 years previously. The low density lipoprotein cholesterol at the first qualifying visit had to be between 3–4 and 5–2 mmol.l⁻¹ and between 3–4 and 4–6 mmol.l⁻¹ in at least one of the blood determinations before enrolment. The aggressive-treatment group was prescribed 40–80 mg of lovastatin daily (mean, 76 mg) whereas the moderate-treatment group was given 2.5–5 mg (mean, 4 mg). Cholestyramine was also prescribed to 30% of patients in the aggressive group and to 5% of the patients in the moderate group, although 35% discontinued in both groups because of drug intolerance. During this 4–5-year trial (mean, 4.3 years), the low density lipoprotein cholesterol in the aggressive group decreased by 37–40% from a mean of 4 mmol.l⁻¹ to 2.4–2.5 mmol.l⁻¹, while it fell by 13–15% to 3.4–3.5 mmol.l⁻¹ in the moderate-treatment group. Of the 1351 participants, 1192 (88%) had a final angiogram. Quantitative (computer-assisted) interpretation of baseline and follow-up angiograms revealed that 27% of grafts per patient in the aggressive group showed substantial progression compared to 39% in the moderate group (P<0.001), a relative difference of 31%. Substantial progression was defined as a decrease in the graft lumen diameter ≥0.6 mm, including new lesions, worsening lesions and occlusions. Risk reductions of 52% and 37.5% were noted, respectively, for new lesions and occlusions. Although this angiographic study was not powered to evaluate clinical events, it showed a lesser incidence of re-operation or angioplasty in the aggressive group: 6.5% vs 9.2% (P=0.03), a relative difference of 29%. This trial clearly showed that aggressive low density lipoprotein cholesterol lowering to 2.4–2.5 mmol.l⁻¹ was more beneficial in Post CABG patients than a moderate reduction to 3.4–3.5 mmol.l⁻¹. This lower low density lipoprotein cholesterol target is consistent with the most recent NCEP Adult PANEL II guidelines for secondary prevention[9].

The Cholesterol and Recurrent Events Trial (CARE)[9] randomly assigned post-myocardial infarction patients with low density lipoprotein cholesterol baseline levels between 3 and 4.5 mmol.l⁻¹ (mean, 3.6) to either 40 mg of pravastatin per day or to placebo for 5 years. The trial showed a significant decrease in major coronary events by reducing the low density lipoprotein cholesterol by 32% to a mean level below 2.6 mmol.l⁻¹, as in Post CABG.

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Although it would appear that 'lower is better' according to epidemiological studies\(^2\), the magnitude of low density lipoprotein cholesterol reduction has been thus far emphasized as the treatment goal, instead of the in-trial blood level.

A meta-analysis of angiographic changes in trials concerning the effect of lipid lowering on the progression of atherosclerosis in native coronary arteries suggested that a low density lipoprotein cholesterol reduction of 20\% was beneficial and that a further reduction added only a modest gain\(^3\). Two large trials with clinical endpoints have also shown great benefit associated with in-trial low density lipoprotein cholesterol levels of only 3.2 and 3.6 mmol. \(1^{-1}\) following a low density lipoprotein cholesterol reduction of 35\% and 24\%, respectively. These trials have shown for the first time that total mortality and incidence of non-fatal myocardial infarction could be decreased\(^4\). In both of these trials, the Scandinavian Simvastatin Survival Study (4S)\(^4\) and The West of Scotland Coronary Prevention Study (WOSCOPS)\(^5\), the mean low density lipoprotein cholesterol at baseline was 4.9 ± 0.9 and 5 ± 0.4 mmol. \(1^{-1}\), much higher than that of Post CABG and CARE. In the 4S trial, significant and similar reductions of major coronary events were observed following a low density lipoprotein cholesterol decrease of 32–37\%, irrespective of the pre-treatment low density lipoprotein cholesterol levels from <4.4 to >5.4 mmol. \(1^{-1}\)\(^6\). This observation implies that the in-trial low density lipoprotein cholesterol level in patients whose baseline level was <4.4 mmol. \(1^{-1}\) would have been less than 2.9 mmol. \(1^{-1}\) with a 35\% low density lipoprotein cholesterol reduction; it would have been more than 3.5 mmol. \(1^{-1}\) in patients with low density lipoprotein cholesterol levels >5.4 mmol. \(1^{-1}\), suggesting that similar percent reductions in risk are obtained by equal low density lipoprotein cholesterol reductions irrespective of the lowering target. However, the beneficial effect obtained in these two trials by reducing the low density lipoprotein cholesterol levels by 25–35\% without reaching a during-trial low density lipoprotein cholesterol level <2.6 mmol. \(1^{-1}\) may not have been optimal with regard to the small absolute difference observed for the primary endpoint between treatment and placebo groups, 2.4% in WOSCOPS and 4% in 4-S.

Aggressive lowering below 2.6 mmol. \(1^{-1}\) appears indicated for optimal results in patients with a pre-treatment level between 3 and 5 mmol. \(1^{-1}\), as in the selected study populations of Post CABG and CARE. Further studies, however, are required to ascertain the desirability of such a low target beyond a 30–40\% low density lipoprotein cholesterol reduction in patients with a pre-treatment low density lipoprotein cholesterol above 5 mmol. \(1^{-1}\). Such a goal may require low density lipoprotein cholesterol reductions up to 60–70\%; a decrease of 60\% in a pre-treatment level of 6 mmol. \(1^{-1}\), for example, would lower low density lipoprotein cholesterol to 2.4 mmol. \(1^{-1}\). These large reductions may eventually be safely achieved with a single drug, as suggested by the limited experience with 160 mg of simvastatin per day (four times the currently recommended dose) and the new HMG-CoA reductase inhibitor, atorvastatin\(^1\).\(^2\).

Post CABG evaluated two interventions in a 2 × 2 factorial design: aggressive low density lipoprotein cholesterol lowering, as described, and low-dose anticoagulation (warfarin vs placebo). No beneficial effect was associated with a mean trial international normalized ratio of only 1.4 (35\% of patients had an international normalized ratio ≥1.5). The effect on late saphenous vein graft disease of oral anticoagulation with a higher international normalized ratio remains unknown.

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**References**


Digoxin in heart failure: results of the recent digoxin investigation group trial in the context of other treatments for heart failure

Although digoxin has been widely used to treat patients with heart failure, its use has been surrounded by considerable controversy. The first controversy was whether its symptomatic benefits were only observable in patients with concomitant atrial fibrillation or whether patients in sinus rhythm and heart failure would also benefit. This issue was addressed in two well designed randomized trials, the RADIANCE study\(^1\) in patients on an angiotensin converting enzyme (ACE) inhibitor; and the PROVED study\(^2\) in those not receiving an ACE inhibitor. (See Appendix A on page 1688 for the full trial names) In both studies, patients with a low ejection fraction who were on digoxin were withdrawn and received a placebo or continued digoxin for 12 weeks. Patients who were randomized to continue digoxin demonstrated better exercise tolerance and less symptomatic deterioration in heart failure. However, these studies were too short and too small to assess the impact of digoxin on mortality or hospitalizations for heart failure. Furthermore, the withdrawal design and the inclusion of patients with low ejection fraction limited the generalizability of the results to a broader population.

A second controversy that has surrounded the use of digoxin was its impact on mortality.\(^3\) Several analyses of databases of patients with coronary artery disease suggested that patients using digoxin had a higher mortality compared to those not taking digoxin. Such studies cannot reliably distinguish whether the higher mortality was due to the drug or because sicker patients were prescribed the agent. In order to resolve this, the U.S. National Heart Lung and Blood Institute, the U.S. Veterans Affairs Department and investigators from over 300 hospitals in the U.S.A. and Canada collaborated in the Digitalis Investigation Group (DIG) trial, the largest clinical trial of heart failure, with 7788 patients.\(^4\) This study has several unusual features. First, it included patients irrespective of ejection fraction (2035 had ejection fraction over 0.35 and 988 over 0.45). Patients were recruited mainly from community hospitals so that the results have considerable generalizability. Treatment was prolonged with a mean duration of 37 months (range of 24 to 60 months), so that the true long-term effects of treatment could be assessed.

Over the entire course of the study there was a neutral impact on mortality with a 33.3% death rate in those allocated digoxin compared to 33.6% in the control group; (but an apparent beneficial effect over the first 12 months; death rates of 10.1% vs 11.5%, respectively; risk ratio of 0.87; P<0.032), which contrasts with the concerns that led to the establishment of the trial. This overall neutral effect also contrasts with the consistent adverse effect on mortality seen with a number of other inotropic agents such as the phosphodiesterase inhibitors or \(\beta\)-receptor antagonists.\(^5\)\(^6\) There was a significant and substantial

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