Current perspective on the cardiovascular effects of coxibs

MARVIN A. KONSTAM, MD, AND MATTHEW R. WEIR, MD

ABSTRACT

Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory and analgesic effects. In addition, aspirin is documented to reduce cardiovascular events in selected populations, presumably because of inhibition of platelet aggregation. Yet these drugs are not without toxicity, particularly adverse effects on the gastric mucosa. The gastrointestinal toxicity of nonselective NSAIDs and aspirin derives from the inhibition of the cyclooxygenase (COX) enzyme, COX-1, which synthesizes gastroprotective prostaglandins, while the anti-inflammatory and pain-relieving effects are largely derived from inhibition of COX-2–derived prostaglandins. Available data indicate that the harmful gastric effects of nonselective NSAIDs are reduced by substitution of agents that only inhibit the COX-2 protein. The COX-2–selective inhibitors, however, have also been shown to inhibit the production of vascular prostacyclin, which has vasodilatory effects and inhibits platelet aggregation; unlike nonselective NSAIDs, they do not inhibit the production of thromboxane, an eicosanoid that promotes platelet aggregation. Whether these effects could potentially contribute to a prothrombotic environment is the subject of current, intensive debate. In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, there was a higher incidence of cardiovascular thrombotic events in the rofecoxib- vs the naproxen-treated group: 1.67 vs 0.70 per 100 patient years. However, in a pooled analysis of rofecoxib studies, the risk of sustaining a thrombotic cardiovascular event was similar when comparing patients receiving rofecoxib with those receiving placebo, or when comparing patients receiving rofecoxib with those receiving non-naproxen nonselective NSAIDs. These findings are likely to result, at least in part, from the antiplatelet action of naproxen, which has been shown to be potent and sustained during a typical dosing regimen (500 mg twice daily in VIGOR). In contrast, the other NSAID comparators effect weaker and/or nonsustained antiplatelet action. In the Celecoxib Long-term Arthritis Safety Study (CLASS) trial, there was no difference between celecoxib and the nonselective NSAIDs explored (which did not include naproxen) in cardiovascular event rates. Unlike those in VIGOR, patients in the CLASS trial were allowed to take low-dose aspirin. Thus, despite concerns raised by results of VIGOR, other existing data, including those pooled from existing placebo-controlled trials, do not support a clinically relevant prothrombotic effect of the COX-2 inhibitors. Additional placebo-controlled data, from patients at both high and low risk for cardiovascular events, are warranted to clarify the cardiovascular effects of this class of agents.

From the Tufts University School of Medicine and the New England Medical Center (M.A.K.) and the University of Maryland School of Medicine, Baltimore (M.R.W.).
Address correspondence to: M.A.K, New England Medical Center, 750 Washington Street, Box 108, Boston, MA 02111; e-mail: mkonstam@lifespan.org.

Disclosure. Dr. Konstam has indicated that he has been a consultant for Merck, Pfizer, and Pharmacia and is on the speakers' bureaus of Merck and Pfizer. Dr. Weir has indicated that he has received grant or research support from Pharmacia, has been a consultant for Merck and Pharmacia, and is on the speaker's bureau of Merck.

Aspirin and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory and analgesic effects. In addition, aspirin, an effective antiplatelet agent, is documented to reduce cardiovascular risk in select populations.[1,2] Yet these drugs are not without toxicity, particularly adverse effects on the gastric mucosa. The gastrointestinal side effects of aspirin and NSAIDs derive from the inhibition of cyclooxygenase (COX)-1–derived prostaglandin synthesis. COX-1 is an isoform constitutively expressed in many tissues.[3] It facilitates the production from arachidonic acid of homeostatic prostaglandins, which preserve gastrointestinal mucosal integrity and renal blood flow. This same isoform is also expressed in platelets, producing thromboxane A_2, which promotes platelet activation and aggregation. Nonselective NSAIDs also inhibit COX-2, an enzyme induced at sites of inflammation that facilitates the production of prostanoids, which mediate pain and inflammation.[3,4]

Identification of the COX-2 enzyme allowed the development of COX-2–selective inhibitors. It was believed that the harmful gastric effects of nonselective NSAIDs—those NSAIDs that inhibit both COX-1 and COX-2—would be alleviated by agents that selectively inhibited the COX-2 protein. The COX-2–selective inhibitors, however, have also been shown to inhibit the production of vascular prostacyclin, which has important vasodilatory properties and inhibits platelet aggregation. In the absence of significant inhibition of COX-1, these agents do not inhibit platelet thromboxane production.[5,6]

It has been theorized that by inhibiting production of prostacyclin but not thromboxane, COX-2 selective inhibitors could be prothrombotic. This article will summarize current findings regarding cardiovascular thrombotic events in patients taking nonselective NSAIDs and selective COX-2 inhibitors. We will review the data from major clinical trials and attempt to put the results of the VIGOR trial and other analyses into a useful perspective.

BACKGROUND

Cyclooxygenase is a family of enzymes that catalyze the metabolism of arachidonic acid to various eicosanoids or prostanoids including various prostaglandins, prostacyclins, and thromboxane.[4] To date, two distinct COX isoforms have been identified. COX-1 is expressed constitutively in many tissues, including platelets and the gastrointestinal mucosa. COX-2 is largely inducible and expressed at sites of inflammation, but is also a constitutive enzyme in some tissues[3,7] and is responsible for endothelial production of prostacyclin.

Aspirin serves as a useful model to illustrate the vascular protective effects of potent and sustained inhibition of platelet aggregation. As demonstrated convincingly in the Second International Study of Infarct Survival (ISIS 2), administration of aspirin, which irreversibly inhibits platelet aggregation, reduces the incidence of major cardiovascular thromboembolic events in patients with suspected myocardial infarctions (MIs).[1]

Although definitive studies are lacking, it is possible that some of the nonselective NSAIDs may also provide a variable degree of cardioprotection through their ability to inhibit platelet thromboxane. In contrast to aspirin, however, the antiplatelet action of these agents is reversible, with the duration of effect linked to the pharmacokinetics of each agent.[8] Naproxen is one agent that, when given in a typical dosage of 500 mg twice daily, produces greater than 90% inhibition of platelet thromboxane production throughout the dosing interval.[6] **Figure 1** shows the effects of typical doses of the nonselective NSAIDs—diclofenac, ibuprofen, and naproxen—and the COX-2–selective inhibitor rofecoxib on platelet aggregation. Using typical dosing, diclofenac produces minimal antiplatelet effect, and ibuprofen produces a significant effect but one which is not sustained. Only naproxen (dosed in a conventional, twice-daily manner) produces an antiplatelet effect comparable to that achieved with aspirin and sustained through its dosing interval. COX-2–selective inhibitors do not inhibit platelet function.[5,6]

Results of a recently published study investigating potential interactions between aspirin and commonly prescribed arthritis therapies found that, when administered with aspirin, ibuprofen (but not rofecoxib, acetaminophen, or diclofenac) antagonizes the irreversible platelet inhibition induced by aspirin.[9] This ex-vivo analysis tested platelet function in isolation. Further clinical evaluation is required to determine whether some NSAIDs limit the cardioprotective effects of aspirin.[10]

Figure 2 schematically illustrates the effects of aspirin, NSAIDs, and COX-2–selective inhibitors

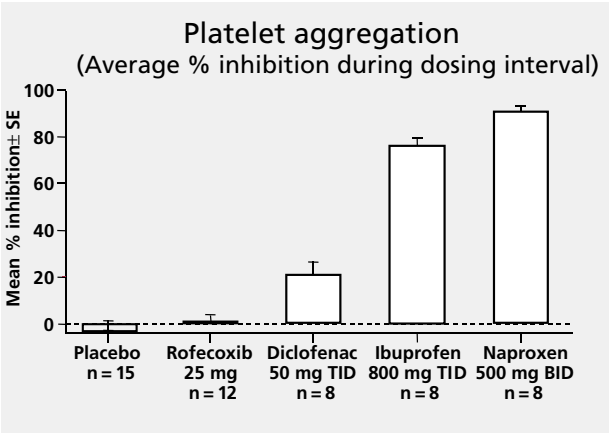

FIGURE 1. Platelet aggregation observed over 8 hours postdose on day 6 versus baseline.[6]

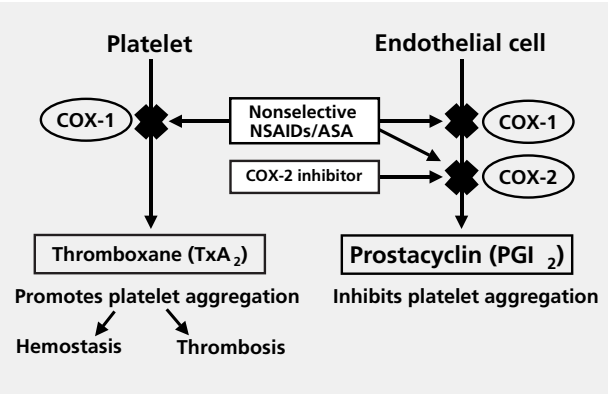

FIGURE 2. How aspirin, nonselective NSAIDs, and COX-2–selective inhibitors affect thromboxane and prostacyclin.

on thromboxane and prostacyclin. Like the nonselective NSAIDs, COX-2–selective inhibitors can inhibit production of systemic prostacyclin, a prostanoid that induces both vasodilation and inhibition of platelet aggregation. The ability of COX-2–selective inhibitors to inhibit endothelial cell prostacyclin without inhibiting platelet aggregation could theoretically create an imbalance resulting in a tendency toward increased thrombosis.[5] Because of this possibility, careful review of available data regarding the cardiovascular effects of COX-2–selective inhibitors is warranted.

EVIDENCE FROM MAJOR COX-2–SELECTIVE INHIBITOR CLINICAL TRIALS

The VIGOR trial. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study was carried out to test the hypothesis that administration of the COX-2–selective inhibitor, rofecoxib, is associated with a reduced incidence of major gastrointestinal adverse events relative to that seen with the nonselective NSAID, naproxen.[11]

Eight thousand seventy-six patients (mean age, 58 years) with rheumatoid arthritis were randomly assigned to receive either rofecoxib 50 mg once daily (a dosage which is 2 to 4 times higher than that indicated for chronic use) or naproxen 500 mg twice daily. Patients taking low-dose aspirin or other antiplatelet agents were excluded. Over a median follow-up of 9 months, compared with naproxen-treated patients, patients receiving rofecoxib had a statistically significantly lower rate of confirmed gastrointestinal events, defined as gastroduodenal perforation or obstruction, upper GI bleeding, and symptomatic gastroduodenal ulcers: 2.1 per 100 patient years with rofecoxib vs 4.5 per 100 patient years with naproxen ($P < .001$).[11]

Data on cardiovascular events were collected as adverse events during the VIGOR trial. Investigator-reported events were confirmed by an independent adjudication committee. The rate of confirmed cardiovascular thrombotic events was 0.70 and 1.67 per 100 patient years in the naproxen group and in the rofecoxib group, respectively.[12] In each group, 0.2% of patients experienced ischemic cerebrovascular events. The rate of death from cardiovascular causes was also 0.2% in each group. The incidence of MIs in the rofecoxib-treated group vs the naproxen group was 0.4% vs 0.1%, respectively.[11]

A post-hoc analysis found that 4% of the participants in the VIGOR trial met US Food and Drug Administration criteria for use of aspirin as a secondary cardiovascular prophylaxis. These aspirin-eligible patients accounted for 38% of the patients who had MIs. Although the event rate was lower in the remaining population, this population likewise displayed an imbalance, favoring naproxen, in the number of thrombotic events within the two groups. The rate of MIs in those patients who did not meet FDA criteria for low-dose aspirin was 0.2% and 0.1% in the rofecoxib and naproxen groups, respectively.[11]

Cardiovascular findings in VIGOR suggest three possible explanations: a prothrombotic effect of rofecoxib, an antithrombotic effect of naproxen, or the play of chance.[13] The potential for a cardiopro-

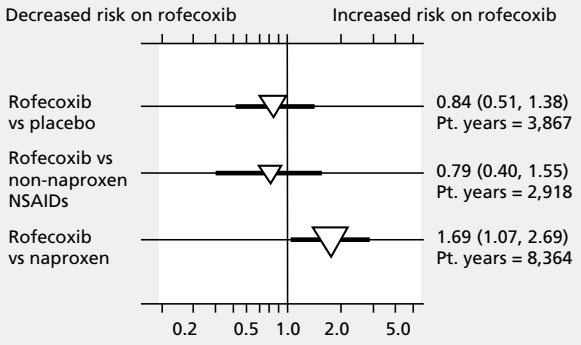

FIGURE 3. Relative risk of the APTC endpoint for rofecoxib relative to placebo, non-naproxen NSAIDs, and naproxen in the rofecoxib pooled analysis. Triangles represent relative risk, and triangle size represents patient-years of exposure. Bars indicate 95% CI. (Reprinted with permission from Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 2001; 104:2280–2288.)[12]

NSAIDs, coxibs, and cardiovascular risk

Aspirin reduces the incidence of major cardiovascular thromboembolic events in selected populations in the 81 to 162 mg/day dose range.

Possible explanations for the VIGOR trial results include the possibility that naproxen offered some cardioprotection; however, current data do not support naproxen for this use until properly evaluated in prospective trials.

Prophylactic use of aspirin against cardiovascular events was not permitted in the VIGOR trial, a possible confounding factor.

Clinicians should be aware that blood pressure may become elevated in some patients receiving an NSAID or COX-2–selective inhibitor. This BP-raising effect must be weighed against the therapeutic impact.

Clinicians should consider each individual patient's gastrointestinal and cardiovascular risk profile when selecting among nonselective NSAIDs and coxibs.

tective effect of naproxen is supported by the potent and sustained antiplatelet actions of this agent, cited above.[6] Alternatively, rofecoxib may have had a prothrombotic effect. To further explore the possibility of a prothrombotic effect of rofecoxib, we conducted a pooled analysis of cardiovascular events across the randomized controlled trials of rofecoxib.[12]

Rofecoxib pooled analysis. To further characterize the potential impact of rofecoxib on the incidence of thrombotic cardiovascular adverse events, we conducted a pooled analysis of data derived from the existing and ongoing randomized-controlled clinical trials involving rofecoxib.[12] We included the entire patient data set of randomized controlled trials of rofecoxib, except those of less than 4 weeks' duration and those in which the rofecoxib dosage was below 12.5 mg/day.[12] Patients were included in the analysis only if they received at least one dose of study drug.

Individual patient data were combined to explore the relative risk of cardiovascular thrombotic events among patients taking rofecoxib, placebo, naproxen, and other nonselective NSAIDs (diclofenac, ibuprofen, and nabumetone).[12] The endpoint investigated was that employed by the Antiplatelet Trialists Collaborative (APTC): cardiovascular, hemorrhagic, and unknown death, nonfatal MI, and nonfatal cerebrovascular accident. The pooled analysis included over 28,000 patients from 23 studies, representing more than 14,000 patient-years at risk (**Figure 3**). When comparing rofecoxib with placebo, there was no evidence of an increased incidence of APTC events (relative risk, rofecoxib vs placebo, 0.84). Similarly, there was no evidence of an increased incidence of APTC events for rofecoxib when compared with the non-naproxen NSAIDs (relative risk, 0.79) The analysis confirmed a significant disparity in events, favoring naproxen over rofecoxib (relative risk, 1.69), an effect which was primarily driven by the findings of VIGOR. These findings lend further credence to an antithrombotic effect of naproxen as the principal explanation for the cardiovascular findings seen in VIGOR.[12]

The CLASS study. The Celecoxib Long-term Arthritis Safety Study (CLASS) was a double-blind, randomized, controlled trial investigating the relative effects of celecoxib and nonselective NSAIDs on gastrointestinal events.[14] It enrolled 8,059 patients (mean age, 60.6 years) with osteoarthritis or rheumatoid arthritis who were randomized to receive celecoxib 400 mg twice daily or either ibuprofen 800 mg 3 times daily or diclofenac 75 mg twice daily. In contrast to VIGOR, use of aspirin as prophylaxis against cardiovascular events was permitted.

A total of 4,573 patients (57% of all patients randomized) received treatment for 6 months. The primary endpoint of the study was the number of com-

plicated ulcers. There was no statistically significant difference in treatment arms with regard to the primary endpoint. There was a lower incidence of symptomatic ulcers and ulcer complications with celecoxib, which was given at two to four times higher than clinically indicated dosages, compared with NSAIDs given at standard dosages.

No difference was observed between celecoxib and the nonselective NSAIDs with regard to incidence of cardiovascular events. MIs occurred in 0.3% of all patients taking either celecoxib or a nonselective NSAID. MIs occurred in less than 0.1% and 0.1% of patients not receiving aspirin within the celecoxib group and the nonselective NSAID group, respectively.[14]

There are several major differences between the VIGOR and CLASS trials, aside from the COX-2 inhibitor investigated. VIGOR exclusively enrolled patients with rheumatoid arthritis, whereas CLASS enlisted patients with either osteoarthritis or rheumatoid arthritis. This difference may be important, since rheumatoid arthritis is associated with an increased incidence of cardiovascular events, when correction is made for other population differences.[15-17] As noted, the two trials employed different comparator NSAIDs, a factor that is likely to be of critical importance given the difference in platelet inhibitory effects of these various agents. Finally, approximately 20% of patients in CLASS were taking aspirin for cardiovascular prophylaxis whereas VIGOR did not allow aspirin use. Nevertheless, analysis of cardiovascular endpoints from CLASS does not support the hypothesis of a prothrombotic action of selective COX-2 inhibitor agents.

Alternative analysis of rofecoxib/celecoxib cardiovascular data. Recently, Mukherjee and colleagues reviewed four published randomized controlled trials with COX-2–selective inhibitors, VIGOR, CLASS, and two smaller rofecoxib trials, each involving approximately 1,000 patients, to investigate a potential influence of COX-2–selective inhibitors on the rates of cardiovascular thrombotic events.[18] The authors observed that the annualized rates of MI for rofecoxib within VIGOR (0.74%) and for celecoxib within CLASS (0.80%) were higher than those observed within the pooled placebo group from a meta-analysis of four primary prevention trials (0.52%).[19] Conclusions must be drawn cautiously from these findings because of significant limitations to the analysis. These include 1) comparison of event rates across different trials is generally hazardous; 2) the populations within the primary prevention studies are likely to be substantially different from those within VIGOR and CLASS, which enrolled older patients with a variety of comorbidities (including rheumatoid arthritis, which is known to confer an increased risk of MI); and 3) in fact, the MI rates observed within VIGOR and CLASS fell within the range of those observed within the composite primary prevention trials utilized in this meta-analysis.

■ DISCUSSION AND CONCLUSIONS

The effect of COX-2–selective inhibitors on the incidence of cardiovascular events remains unresolved. Of the available clinical trial data, only those from the VIGOR trial provide reason for concern, based on an increased incidence of thrombotic events in patients randomized to rofecoxib compared with those randomized to naproxen. However, there is reason to anticipate a significant cardiovascular protective effect of naproxen, based on the potent and sustained antiplatelet effect achieved with this agent. Importantly, our pooled analysis of data from the randomized-controlled trials of rofecoxib provides no evidence for an increased incidence of cardiovascular events for rofecoxib relative to either placebo or non-naproxen NSAIDs. Likewise, data from CLASS provide no evidence for an excess of cardiovascular events for celecoxib relative to either diclofenac or ibuprofen, agents that do not produce sustained antiplatelet effect. This information, in aggregate, makes it likely that the results of VIGOR derive, at least in part, from a cardioprotective effect of naproxen. At present, low-dose aspirin should be prescribed in patients with an increased risk of cardiovascular events, since this agent has been shown to reduce the incidence of cardiovascular events in appropriate patient populations.

Additional prospective, placebo-controlled data are needed to fully clarify the cardiovascular effects of COX-2 inhibitors. Such data will be forthcoming from ongoing trials in disorders such as Alzheimer's disease and intestinal polyp disease. Randomized, controlled trials in patients with a high risk for cardiovascular events are also warranted.

REFERENCES

1. **ISIS-2 (Second International Study of Infarct Survival) Collaborative Group.** Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349–360.
2. **Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R, on behalf of the ISIS-2 (Second International Study of Infarct Survival) Collaborative Group.** ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. BMJ 1998; 316:1337–1343.
3. **Vane JR, Botting RM.** New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 1995; 44:1–10.
4. **Chan C-C, Boyce S, Brideau C, et al.** Rofecoxib [Voixx, MK-0966; 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5*H*)-furanone]: a potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and biochemical profiles. J Pharmacol Exp Ther 1999; 290:551–560.
5. **McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA.** Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci U S A 1999; 96:272–277.
6. **Van Hecken A, Schwartz JI, Depré M, et al.** Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol 2000; 40:1109–1120.
7. **Seibert K, Zhang Y, Leahy K, et al.** Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc Natl Acad Sci U S A 1994; 91:12013–12017.
8. **Patrono C, Coller B, Dalen JE, et al.** Platelet-active drugs: the relationships among dose, effectiveness, and side effects. Chest 1998; 114:470S–488S.
9. **Catella-Lawson F, Reilly MP, Kapoor SC, et al.** Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001; 345:1809–1817.
10. **Crofford LJ.** Rational use of analgesic and antiinflammatory drugs [editorial]. N Engl J Med 2001; 345:1844–1846.
11. **Bombardier C, Laine L, Reicin A, et al, for the VIGOR Study Group.** Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343:1520–1528.
12. **Konstam MA, Weir MR, Reicin A, et al.** Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 2001; 104:2280–2288.
13. **FitzGerald GA, Patrono C.** The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345:433–442.
14. **Silverstein FE, Faich G, Goldstein JL, et al.** Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. JAMA 2000; 284:1247–1255.
15. **Wolfe F, Straus WL.** Increased prevalence of cardiovascular and cerebrovascular disease in rheumatoid arthritis compared with osteoarthritis [abstract]. Arthritis Rheum 2000; 43:S133. Abstract 400.
16. **Myllykangas-Luosujärvi RA, Aho K, Isomäki HA.** Mortality in rheumatoid arthritis. Semin Arthritis Rheum 1995; 25:193–202.
17. **del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A.** High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001; 44:2737–2745.
18. **Mukherjee D, Nissen SE, Topol EJ.** Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954–959.
19. **Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE.** Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart 2001; 85:265–271.