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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

therapeutics letter
July - August 2007

Clinical implications of recent key therapeutic trials

Randomised controlled clinical trials (RCTs) are critical in determining the net health effect of a therapy (benefit minus harm). When the primary outcome of the trial is the reduction in one or more serious adverse events, the best measure of the net health effect of the drug is the total number of people with at least one serious adverse event (see Therapeutics Letter 42). When the total number of people with at least one serious adverse event is not reported, total mortality is the next best measure of net health effect. In this Letter we use this analytic perspective to interpret the results and clinical implications of four recent RCTs.

Torcetrapib for prevention of cardiovascular events

The Investigation of Lipid Level management to Understand its iMpact IN ATherosclerotic Events (ILLUMINATE) study has not yet been published. This RCT was designed to test whether the new drug torcetrapib, a cholesteryl ester transfer protein inhibitor, reduced mortality and morbidity as compared to placebo. In prior studies torcetrapib, 30 to 90 mg/day, caused a dose-related increase in HDL of up to 55% and a dose-related reduction in LDL of up to 19%.[1,2] ILLUMINATE investigators randomized about 15,000 patients at high risk of coronary artery disease to atorvastatin or combination atorvastatin and torcetrapib, 60 mg, with plans to follow subjects for 4 to 5 years. On December 2, 2006, a little over a year into the trial, Pfizer terminated the study and all further development of torcetrapib.[3] This decision was made at the request of the trial Data Safety and Monitoring Board (DSMB) who discovered a statistically significant increase in mortality in the patients randomised to torcetrapib (82 deaths) as compared to placebo (51 deaths). This outcome occurred despite the fact that torcetrapib raised HDL and reduced LDL.

Clinical implications

Torcetrapib increases mortality as compared to placebo in patients at high risk of coronary artery disease. Drug induced changes in surrogate outcomes, such as raising HDL and lowering LDL, are insufficient to know whether a drug is beneficial or harmful.

Comment

This trial "illuminates" how the system should work. The trial was initiated relatively early in the development of the drug, as the FDA had indicated that it would probably require proof of a reduction in mortality and morbidity before approval of torcetrapib. The DSMB did their job in identifying and reporting the problem and the company responded appropriately. **Thus a harmful drug was identified relatively early in development and the number of patients exposed to and harmed by the drug was minimized.** It remains critical that this trial is published and that the report includes all serious adverse events, to allow assessment of possible mechanisms for the harm caused by torcetrapib.

Percutaneous coronary intervention (PCI) for stable angina [4]

In this RCT, 2,287 patients with myocardial ischemia and significant coronary artery disease were randomized to PCI (1,145) or no intervention (1,138). Both groups received evidence-based drug therapy (acetylsalicylic acid, statin, beta blocker and angiotensin converting enzyme inhibitor) and lifestyle interventions. During a median of 4.6 years of follow-up, PCI had no effect on the primary outcome, death from any cause or non-fatal myocardial infarction: 19.0% in the PCI group and 18.5% in the control group, Hazard Ratio (HR) 1.05 [0.87 - 1.27]. No secondary outcomes were statistically different between the two groups. The control group experienced more angina and received more nitrates (ARI 14%) and calcium channel blockers (ARI 8%) than the PCI group. However, the percentage free from angina at 5 years was not different in the two groups, 74% PCI and 72% control. Total mortality, the only net health effect outcome reported, was 7.4% in the PCI and 8.3% in the control group, HR 0.87 [0.65 - 1.16].

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Clinical implications

PCI does not reduce mortality or cardiovascular serious adverse events as compared to no intervention as an initial management strategy in patients with stable angina due to coronary artery disease.

Comment

The wide confidence intervals particularly for total mortality in this trial leave some uncertainty as to the net health effect. The report published in the New England Journal of Medicine would have been more informative if it had included the total number of people with at least one serious adverse event in each group.

Eicosapentaenoic acid (EPA) for hypercholesterolemia [5]

EPA is a long chain omega-3 fatty acid commonly found in fish oils. This open label RCT randomized 18,645 people in Japan with total cholesterol ≥ 6.5 mmol/L to EPA, 600 mg TID, or nothing, and followed them for an average of 4.6 years. Both groups were treated with a low dose statin, either pravastatin 10 mg daily or simvastatin 5 mg daily. The trial used blinded clinical endpoint assessment to reduce bias. Of the people randomized 20% were secondary prevention and 80% were primary prevention. The composite primary endpoint: sudden cardiac death, fatal or non-fatal myocardial infarction, unstable angina pectoris, angioplasty and stenting, or coronary artery bypass grafting, occurred in 2.8% of the EPA group and 3.5% of the control group, HR 0.81 [0.69-0.95] ARR 0.7% NNT 143. The ARR for the primary outcome was 2% and statistically significant in the secondary prevention subgroup (p=0.048) and 0.3% and not statistically significant in the primary prevention subgroup (p=0.132). Withdrawals due to adverse events were 11.7% in the EPA group and 7.2% in the control group, RR 1.6 [1.5 - 1.8], ARI 4.5%, NNH = 22 for 5 years. Total mortality, the only net health effect outcome reported, was 3.1% for EPA and 2.8% for control, HR 1.09 [0.92 - 1.27].

Clinical implications

EPA does not affect mortality as compared to placebo in a Japanese primary and secondary prevention population. EPA reduces cardiac SAEs as compared to placebo in a secondary prevention population, ARR 2%, NNT 50 for 5 years.

Comment

This large trial has the potential of providing a precise estimate of the net health effect of EPA in a primary and secondary prevention population. It is unfortunate that the report published in the Lancet did not include the total number of people with at least one serious adverse event for each group and subgroup.

Oral anticoagulant plus antiplatelet for peripheral vascular disease [6]

This open label RCT randomized 2,161 patients with peripheral arterial disease of the lower extremities, carotid or subclavian vessels to antiplatelet alone or a combination of oral anticoagulant plus antiplatelet, and followed them for 2.9 years. The antiplatelet drugs used were acetylsalicylic acid, 81-325 mg/day or clopidogrel or ticlopidine, and the oral anticoagulant drugs used were warfarin or acenocoumarol. Myocardial infarction, stroke, severe ischemia or death from cardiovascular cause occurred in 15.9% of the combination group and 17.4% of the antiplatelet group, RR 0.91 [0.74 - 1.12]. Life threatening bleeding occurred in 4% of the combination group and 1.2% of the antiplatelet group, RR 3.4 [1.8 - 6.4], ARI 2.8%, NNH 36 for 3 years. Total mortality, the only net health effect outcome reported, was 9.2% for combination and 8.9% for antiplatelet, RR 1.04 [0.79 - 1.38].

Clinical implications

Adding an oral anticoagulant to an antiplatelet increases life threatening bleeds and does not affect mortality or cardiovascular serious adverse events as compared to an antiplatelet alone in patients with peripheral vascular disease.

Comment

Once again, reporting the total number of people with at least one serious adverse event in each group would have provided a more precise measure of the net health effect in this trial.

HR = Hazard ratio
RR = Relative risk
ARI = Absolute risk increase
ARR = Absolute risk reduction
NNH = Number needed to harm
NNT = Number needed to treat

The draft of this Therapeutics Letter was submitted for review to 40 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

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