

Does TORCH shed light on COPD management?

The TORCH study (TOWards a Revolution in Chronic obstructive pulmonary disease [COPD] Health)¹ was a randomised double-blind study in 6,112 patients with COPD. It compared the effects of inhaled salmeterol plus fluticasone (50/500mcg) with placebo, salmeterol (50mcg) alone or fluticasone (500mcg) alone. The primary outcome was death from any cause for the comparison between the combination regimen and placebo. After three years, the proportion of deaths in the combination treatment group was not statistically significantly lower than in the placebo group (12.6% vs. 15.2%, respectively; hazard ratio 0.83, 95%CI 0.68 to 1.00, P=0.052).¹

Other findings were statistically significant improvements in some secondary outcomes among patients treated with the salmeterol-fluticasone inhaler when compared with placebo, balanced by some adverse events.¹ Compared with placebo, the annual rate of moderate or severe exacerbations was reduced with the combination regimen (1.13 vs. 0.85; rate ratio 0.75, 95%CI 0.69 to 0.81, P<0.001); lung function was improved (adjusted mean change in post bronchodilator forced expiratory volume in one second [FEV₁] over three years -0.062L vs. +0.029L; rate ratio 0.092, 95%CI 0.075 to 0.108, P<0.001); and health status was improved by an average of 3 units on the St. George's Respiratory Questionnaire over three years (+0.2 vs. -3.0; difference -3.1, 95%CI -4.1 to -2.1, P<0.001). However, the latter result did not reach the threshold of 4 units that is generally considered to be clinically relevant on this 100-unit scale, and which was specified in the trial protocol. Also, it is worth noting that, in the year before the study, more than half of the participants had used inhaled corticosteroids (ICSs), long-acting beta agonists (LABAs), or both.¹ As these were stopped, patients receiving placebo may have been more likely to experience worse outcomes, such as exacerbations.

Given the severity of COPD in the patients recruited to TORCH, and the current NICE guidance² on the stages of drug therapy for COPD, a more helpful comparison is between the combination of salmeterol-fluticasone and

single therapy, particularly with a long-acting bronchodilator. In the TORCH study, combination therapy was not significantly better than salmeterol on the risk of death from any cause (P=0.48).¹ Combination therapy did significantly reduce the annual rate of exacerbations but, importantly, not the rate of severe exacerbations requiring hospitalisation, compared with salmeterol. In addition, although it did not seem to cause an increase in the number of deaths, pneumonia occurred more frequently in the combination and fluticasone groups, than in the salmeterol and placebo groups (19% vs. 13%).¹ This means that, for every 17 people treated for three years with an inhaler containing fluticasone, instead of salmeterol alone or placebo, one suffered pneumonia.

When should combinations be used?

NICE recommends that an ICS should be prescribed in addition to a long-acting bronchodilator (i.e. a LABA or tiotropium) for patients with moderate or severe COPD (FEV₁ ≤ 50% predicted) who have had two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period.² They also suggest that there may be benefits in adding an ICS to a long-acting bronchodilator where patients with moderate or severe COPD are still breathless despite monotherapy with a LABA or tiotropium. However, combination treatment should be discontinued if there is no benefit after four weeks.²

In summary, compared with placebo or salmeterol alone, combination therapy did not significantly reduce mortality. Salmeterol-fluticasone reduced moderate to severe exacerbations, but not exacerbations requiring hospitalisation, compared with salmeterol alone. Also, the combination significantly increased the risk of pneumonia. TORCH supports NICE guidance² and the cautious approach previously outlined by the NPC concerning the place in therapy of ICSs in COPD (see MeReC Briefing No. 33).³ The editorial, which accompanied the publication of the TORCH study, suggests that combination therapy should be used cautiously and recommends that the risk of pneumonia with ICSs should be investigated further.⁴



Combination therapy did not significantly reduce mortality

The risk of pneumonia with inhaled corticosteroids should be investigated further

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References

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When using aspirin with warfarin, any benefit in reducing the risk of thromboembolism must be put in the context of an increased risk of bleeding

When should aspirin be added to warfarin?

Combined oral anticoagulant and antiplatelet therapy may be considered for patients who are at high risk of having a thromboembolism. However, any benefit in reducing the risk of these events has to be put in the context of an increased risk of bleeding. A recent systematic review and meta-analysis¹ quantified the relative risks and harms of aspirin plus warfarin (see footnote*) compared with warfarin alone. Bearing in mind the increased risk of bleeding, the review questioned the practice of adding aspirin to warfarin except for patients with mechanical heart valves.

The review included ten randomised controlled trials (n=4,180) with at least three months of follow up that compared aspirin plus warfarin with warfarin alone, with the same intensity of anticoagulation in each of the treatment arms (i.e. warfarin was administered to achieve the same target international normalised ratio or was given at the same fixed dose in each group).¹ Five of the studies (n=990) were of patients with mechanical heart valves, two were of patients with atrial fibrillation (n=495), two were of patients with coronary artery disease (n=150), and one was a primary prevention study of patients at high risk of cardiovascular

(CV) disease (n=2,545). Aspirin was used at a dose of 75 to 300mg daily in eight of the studies, with the other studies (both in patients with mechanical heart valves) using 500mg and 1000mg daily.¹

Overall, the study identified a significant reduction in the risk of arterial thromboembolism (defined as myocardial infarction, unstable angina requiring hospitalisation, stroke, transient ischaemic attack, or systemic embolism) for the combined therapy compared with warfarin alone (6.3% vs. 8.8%; OR 0.66, 95%CI 0.52 to 0.84; NNT=40), but not for all-cause mortality (both 6.7%; OR 0.98, 95%CI 0.77 to 1.25).¹ There was a greater incidence of major bleeding with warfarin plus aspirin compared with warfarin alone (3.8% vs. 2.8%; OR 1.43, 95%CI 1.00 to 2.02, P=0.05).^{1,2}

Secondary analysis only identified a significant advantage for combination therapy in reducing arterial thromboembolism in the subgroup of patients with mechanical heart valves. (OR 0.27, 95%CI 0.15 to 0.49).¹ The risk of major bleeding in these patients was similar to that seen in the overall analysis (OR 1.49, 95%CI 1.00 to 2.23, P=0.05).^{1,2}

American College of Cardiology/American Heart Association 2006 guidelines recommend the addition of aspirin (75 to 100mg daily) to warfarin for all patients with mechanical heart valves and those patients with biological valves who have additional CV risk factors (including atrial fibrillation, previous thromboembolism, left-ventricular dysfunction, and hypercoagulable condition).³

References

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* Although the term 'warfarin' is used throughout this article, the meta-analysis reports the results for oral anticoagulants without specifying the type. The exact proportion of patients included in the meta-analysis who used warfarin is not known.²

New from the National Prescribing Centre

Two new MeReC *Bulletins* will shortly be available on the NPC website at www.npc.co.uk/merec.htm. The first *Bulletin* covers the **role of newer insulins in diabetes** and the second discusses some of the current issues in the management of **rheumatoid arthritis**. A CD-ROM containing the entire MeReC portfolio produced during 2006/7 will be distributed over the summer.

To provide support for continuing professional development and local implementation of the evidence base, a range of complementary education and implementation resources, such as slide sets, case studies and learning quizzes, now accompanies each MeReC *Bulletin*. Resources to support the three most recent *Bulletins* covering **hypertension, contraception and common infections**, are available at www.npc.co.uk/merec.htm.

A unique e-Learning environment, *NPCi*, is coming soon from the NPC. This will provide summarised evidence and information in 'bite-sized' chunks in a variety of learning formats. Once testing is complete, details of how to access *NPCi* will be posted on our website (www.npc.co.uk).

From autumn, the NPC therapeutic workshop programme is evolving. Over the summer, all PCTs will have the chance to nominate an *NPC Associate*. *Associates* will participate in a regular programme of e-Learning and local workshops and, with support, take their learning back to their own organisations. *NPCi* will provide *Associates* with tools to promote clinically and cost effective therapeutics and medicines management. Further details will be available on our website soon, and will be mailed directly to the organisations from whom we hope to recruit *Associates*.

The National Institute for Health and Clinical Excellence (NICE) is associated with MeReC Publications published by the NPC through a funding contract. This arrangement provides NICE with the ability to secure value for money in the use of NHS funds invested in its work and enables it to influence topic selection, methodology and dissemination practice. NICE considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery. This publication represents the views of the authors and not necessarily those of the Institute.