

Prostate cancer screening: no compelling evidence that benefits outweigh harms

The value of prostate cancer screening is still unclear. Interim results from a large European randomised controlled trial¹ and a large US study² show that screening with prostate-specific antigen (PSA) testing (combined with digital rectal examination [DRE] in the US study) detects many more cancers than usual care. However, whether or not this translates into a survival benefit from prostate cancer remains uncertain.

Action

NHS policy is that only men who have made an informed choice based on the Prostate Cancer Risk Management Programme³ materials should receive a PSA screening test - this was recently confirmed in a letter from the Chief Medical Officer (CMO).⁴ NICE advises that men with symptoms suggesting prostate cancer should have DRE and a PSA test after counselling.⁵ The results of these investigations will guide referral and further action.

What is the background to this?

At present there is no national screening programme for prostate cancer in the UK, as there is no clear evidence of benefit. Interim results from the European study¹ (n=162,243) suggest that, over nine years, 1,410 men would need to be screened with PSA testing to

prevent one death from prostate cancer. Interim data from a US study² (n=76,693) identified no reduction in deaths from prostate cancer from a formal screening programme compared with usual care, which did not exclude ad hoc screening, over a ten-year period. More information can be found in *MeReC Rapid Review Blog No. 322*.

The CMO has stated that the Department of Health will ask the UK National Screening Committee to review this new evidence and make recommendations. There is an excellent review of the dilemmas in prostate cancer in the CMO's Annual Report entitled "What to do with the pussycats?".⁶

Further information on the background, diagnosis and treatment of prostate cancer can be found in the NICE clinical guideline on prostate cancer⁷ and on the prostate cancer floor of NPCi.

References

1. Schröder FH, Hugosson J, Roobol MJ, et al, for the ERSPC investigators. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320–8
2. Andriole GL, Crawford ED, Grubb RL, et al, for the PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310–9
3. NHS Cancer Screening Programmes. Prostate cancer risk management programme
4. CMO. Prostate cancer screening. CEM/CMO/2009/04. 18th March 2009
5. NICE. Referral guidelines for suspected cancer. Clinical Guideline 27. June 2005
6. CMO. Annual Report. 16th March 2009
7. NICE. Prostate cancer: diagnosis and treatment. Clinical Guideline 58. February 2008



Rosuvastatin gives a small reduction in VTE in people at low risk of CV disease

In this analysis¹ of the JUPITER study,² compared with placebo, rosuvastatin 20mg daily produced a small absolute reduction in the risk of symptomatic venous thromboembolism (VTE) in people with few cardiovascular (CV) risk factors.¹ This is in addition to the previously reported small absolute reduction in CV events. There was an increase in reports of diabetes in people taking rosuvastatin.²

Action

The results of this study do not justify the use of statins for prevention of VTE in the general population. Participants in the JUPITER study were apparently healthy men and women but with increased levels of high sensitivity C-reactive protein (hs-CRP). It is argued that this is a marker for having an increased risk of CV events, although this is not widely accepted in the UK. Common risk assessment tools,

e.g. Framingham, which is recommended by NICE, would predict the study population in Jupiter to be at low risk of CV disease. Most of these people would be below the threshold recommended in the NICE guidance on lipid modification³ for consideration of primary prevention with statins, although some may have particular risk factors that put them above this threshold. Individualised risk assessment, using a recommended Framingham-based tool, should be used to inform treatment decisions.

What does this study claim?

The JUPITER randomised controlled trial (RCT) (n=17,802) investigated the effect of rosuvastatin 20mg daily on the risk of major CV events in apparently healthy individuals with no previous history of CV disease who had elevated hs-CRP levels.²

This publication was correct at the time of preparation: July 2009

Over a median follow-up period of 1.9 years, the incidence of symptomatic VTE was reduced by 43% (relative risk reduction [RRR]) with rosuvastatin compared to placebo (0.38% vs 0.67%, hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.37 to 0.86; P=0.007).¹ However, because the baseline risk of VTE was low, the number needed to treat (NNT) was high: 342 people would need to take rosuvastatin 20mg daily for 1.9 years for one to benefit. The main JUPITER study showed that rosuvastatin treatment reduced the risk of major CV events compared with placebo (NNT=82), so the NNT overall to obtain a clinically relevant benefit will be lower if VTE is also taken into consideration.²

Harms other than bleeding rates, which were not significantly different between groups, were not reported in this paper, but the main JUPITER study reported there was a 25% relative increase in the risk of physician-diagnosed diabetes in the rosuvastatin group: 3.0% vs 2.4% in the control group (relative risk (RR) 1.25, P=0.01; number needed to harm [NNH] =165).²

The MHRA has advised caution in initiating the dose of rosuvastatin used in this trial: patients should start on 5mg or 10mg daily (5mg for Asian patients and those with pre-disposing factors for myopathy), including patients switched from other statins, and the dose should be titrated up only if necessary and after a four week trial.⁴

Further details of the JUPITER study are available in *MeReC Rapid Review Blog No. 236*. Further details of this analysis are discussed in *MeReC Rapid Review Blog No. 324* and a recent NPCi podcast.

References

1. Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *New Engl J Med* 2009;360:1851–61
2. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med* 2008;359:2195–207
3. NICE. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. *Clinical Guideline* 67. May 2008
4. MHRA. *Current Problems in Pharmacovigilance* 2006;31:4

Is clopidogrel ACTIVE for atrial fibrillation?

The ACTIVE A study found that clopidogrel plus aspirin reduced the risk of a composite vascular endpoint compared with aspirin alone, in AF patients at increased risk of stroke and for whom warfarin-like drugs were unsuitable. However, this benefit should be balanced against a similar increased magnitude of risk of major bleeding with the combination.

Action

Currently clopidogrel is not licensed in atrial fibrillation (AF). Should it receive such a licence, then any potential benefit would need to be weighed against the risk of major bleeding, taking into account the patient’s baseline risk of a vascular event as well as their risk of bleeding.

What does this study claim?

The ACTIVE A study included patients with AF, at least one risk factor for stroke (n=7,554), and who were unsuitable for warfarin. The primary outcome of any major vascular event (stroke, non-central nervous system embolism, myocardial infarction, or death from vascular causes) was reduced in patients taking clopidogrel plus aspirin. There were 832 events in the combined group (n=3,772) compared to 924 in the aspirin-only group (n=3,782) (RR 0.89, 95% CI 0.81 to 0.98; P=0.01). The absolute risk reduction is 2.4%

giving an NNT of 42 over 3.6 years. The difference in the primary outcome was mainly due to a reduction in the risk of stroke.¹

There were 251 major bleeding events in the clopidogrel plus aspirin group and 162 in the aspirin only group. The increased risk of 2.4% in the clopidogrel plus aspirin group compared to the aspirin-only group gives an NNH of 42 over 3.6 years for those taking clopidogrel in addition to aspirin.¹

Although warfarin therapy is not ideal, its potential benefits and risks in AF are well known. The ACTIVE A study has shown that if 100 people who are unsuitable for warfarin are treated with clopidogrel plus aspirin, rather than aspirin alone, two will be prevented from having a major vascular event but two will have a major bleed.

Details about the study can be found in *On the Horizon Rapid Review No. 331*. Information about AF and the use of anticoagulation is available on NPCi and in the NICE clinical guideline on the management of AF.²

References

1. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066–78
2. NICE. The management of atrial fibrillation. *Clinical Guideline* 36. June 2006

What’s new from the National Prescribing Centre?

This is a selection of some recent items that can be found on the NPC (www.npc.co.uk) and NPCi (www.npci.org.uk) websites.

MeReC Blogs www.npci.org.uk/blog/

- Improving communication skills and measuring CRP may facilitate appropriate antibiotic prescribing
- Cholinesterase inhibitors associated with syncope in patients with dementia
- New Drug Safety Update from MHRA/CHM (May 2009)
- What’s new on NPCi this month? - April 2009

New Medicines Blogs www.npci.org.uk/blog/

- Scottish Medicines Consortium reviews fluticasone furoate ▼ nasal spray for allergic rhinitis

Podcasts www.npci.org.uk/podcast/

The NPCi’s Evidence-Based Therapeutics team discuss the latest bumper edition of the Drug Safety Update Bulletin from the MHRA

MeReC Monthly www.npc.co.uk/ebt/merec.htm

No. 14. May 2009; No. 15. June 2009

MeReC Bulletin www.npc.co.uk/ebt/merec.htm

Vol 19. No.4. April 2009. Recent safety issues with inhaled treatments for COPD

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