



# Therapeutics Today

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**Anyone for Aspirin?** The use of aspirin to prevent future cardiovascular (CV) events in patients with a prior history of CV disease is recommended by all relevant guidelines and is supported by a strong evidence base. However, recent publications have given conflicting results on the benefit/risk of aspirin (taking into account the potential risk of GI bleeding) when used in patients with no prior risk of CVD, and particularly in patients with diabetes mellitus. The British Hypertension Society (BHS) recently updated its statement on the use of aspirin (*BMJ* 2010; 340: c1183; [www.bhsoc.org](http://www.bhsoc.org)). It refers to a recently published meta-analysis using individual participant data from trials of primary prevention with aspirin (*Lancet* 2009; 373: 1849-60). Results showed an overall risk reduction of serious vascular events of 12% (due mainly to a reduction in non-fatal myocardial infarction), however this use was associated with a significant increase in major GI and extracranial bleeds. Therefore the absolute reduction in the risk of CV events was only about twice as large as the absolute increase in bleeding. Another recent meta-analysis of aspirin in primary prevention in diabetic patients showed a non-significant trend for benefit on CV events (with significant reduction in MI in men but not women) and inconsistent safety results from the different studies (*BMJ* 2009; 339: b4531). The most recent study (*JAMA* 2010; 303: 841-8) has shown no benefit of aspirin 100mg/day vs. placebo in 28,980 patients with asymptomatic atherosclerosis during a mean follow-up of 8.2 years, in terms of fatal and non-fatal CV events. There was a non-significant increase in major haemorrhage cases (34 vs. 20) requiring hospital admission with aspirin. Following this review the BHS reaffirms the following recommendations:

- Low dose aspirin use is recommended in patients with known CV disease (secondary prevention)
- Aspirin for primary prevention (including those with diabetes) should be restricted to those > 50 years, with a 10-year CV risk of at least 20%.
- Physicians should weigh up the benefits and risks of low dose aspirin in each individual



**Never too old for a statin!** With increased life expectancy, the population of older patients is growing and cardiovascular disease (CVD) remains the major cause of mortality in this age group. Although it is known that use of lipid-lowering statins significantly reduces CVD mortality in post-myocardial infarction (MI) patients, observational studies suggest that <40% of post MI patients >75 years are prescribed statins at discharge. Reasons for this under-prescribing include a fear of increased toxicity in the elderly patient and a potential increased risk of cancer suggested by a previous study. A recent large observational study included all eligible patients >80 years who presented with an MI between 1999 and 2003 in Sweden (*J Am Coll Cardiol* 2010; 55: 1362-9). The study group (n=14,907) were followed up until time of first event (CVD or other chronic disease or cancer) for a maximum of 5 years (median 294 days); statin usage was recorded during the study. Results showed that 59% of patients (n=8,817) died during follow-up. Of these, 79% were due to CVD (of which n=4,423 had an MI) and 5.4% (n=477) due to cancer. **Statin treatment at discharge was associated with a reduction of fatal CVD by 41% in the overall group and by 37% in the cohort of patients surviving at least one year.** These figures are similar to the benefits noted for middle-aged patients on statins. In terms of cancer risk, **the study showed no difference in the relative risk of cancer mortality between statin-treated and non statin-treated patients.** Although this was an observational study, it included a large number of patients, followed up for periods of up to 5 years. The authors contend that these results strongly support the concept that statin treatment provides cardiovascular protection, even in very elderly post-MI patients, without increasing the risk of cancer. Therefore the results should be supportive of the overall benefits of statin treatment in this age group.



**Safety Update for Clopidogrel and PPIs.** The European Medicines Agency has recently issued a public statement ([www.ema.europa.eu](http://www.ema.europa.eu); [www.imb.ie](http://www.imb.ie)) to update its safety warning regarding the concomitant use of clopidogrel and proton pump inhibitors (PPIs) as a result of the emergence of new data on this topic. **Clopidogrel is a pro-drug which requires activation in the body (via CYP2C19).** Several observational studies, published in early 2009 had suggested that PPIs might reduce the effectiveness of clopidogrel by reducing conversion into its active form. As a result, in May 2009, the Agency recommended that PPIs and clopidogrel should not be used concomitantly unless absolutely necessary. The Agency has kept this issue under review (See *Therapeutics Today* Newsletters 2009: 5,6,12) and has recently become aware of **a number of new studies, which called into question the clinical relevance of this potential interaction for PPIs as a class.** Moreover, two new studies confirmed that omeprazole could reduce blood levels of the active form of clopidogrel and reduce its antiplatelet effects. After taking all available data into account, the Agency and its scientific committees have concluded that the relevant prescribing information should be amended to remove the "class" warning advising against use of clopidogrel with any PPI. **The updated recommendation is to avoid concomitant use of clopidogrel with either omeprazole or esomeprazole only.** [Editor's note: This clarification should be helpful for prescribers whose patients need GI cover when taking clopidogrel. The Agency has recommended that full details of the two studies that showed the interaction between clopidogrel and omeprazole / esomeprazole should be added to the prescribing information in the near future.]



**Pharmacoeconomic Evaluation in Ireland.** Expenditure on medicines in Ireland continues to rise year on year. In 2008, expenditure under the various community drug schemes was €1.9 billion, a >6 fold increase over the decade 1998-2008. The National Centre for Pharmacoeconomics (NCPE) in Ireland evaluates cost-effectiveness of new medicines prior to reimbursement and conducts pharmacoeconomic (P/E) evaluations to inform public policy (e.g. infant pneumococcal vaccination) and prescribing in primary care (e.g. statins for primary and secondary prevention of coronary heart disease). A recent paper reviewed the P/E evaluations (n=12) undertaken by NCPE, at the request of the HSE, from 2006-9 and subsequent reimbursement decisions by the HSE (*Pharmacoeconomics 2010; 28: 307-22*). The products included anti-cancer agents (n=3), anti-thrombotic agents (n=2), treatments for multiple sclerosis, opiate addiction, primary insomnia, pulmonary arterial hypertension, a grass pollen allergy vaccine, rimonabant (now withdrawn from the market) and chondroitin sulfate. The companies were asked to provide evidence of cost-effectiveness and an estimate of the potential budget impact of the product in the Irish setting. The NCPE undertook a critical appraisal of these data, using a multidisciplinary team (clinician, pharmacists, research scientist, health economist and statistician). Results showed that 8 of the medicines were either recommended as a cost-effective use of resources or recommended with certain restrictions; all were subsequently funded by the HSE. Of the 4 medicines that were not considered cost-effective, 2 were subsequently reimbursed after further negotiations: a price reduction was agreed for the grass pollen allergy vaccine and the opiate addiction treatment was restricted to those for whom methadone treatment is not suitable. The other 2 medicines (chondroitin sulphate, melatonin) were not reimbursed. The average time from the issue of the product licence to reimbursement was 7 months (average duration of the P/E process was 2.7 months). Of interest, the review noted that the NCPE recommendations concurred with those of the UK evaluation agencies (the National Institute for Health & Clinical Excellence, the Scottish Medicines Consortium and the All Wales Medicines Strategy Group), with the exception of two anti-cancer agents sunitinib and lapatinib, which were reimbursed in Ireland.

[Editor's note: The NCPE publishes all of its pharmacoeconomic evaluations on its website: check out [www.ncpe.ie](http://www.ncpe.ie)]