News

Prasugrel approved in Europe

The new antiplatelet agent, prasugrel (Lilly/Daiichi Sankyo), has been approved in the European Union for the prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI).

This follows a positive recommendation from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency at the end of last year.

Prasugrel, which will be marketed in Europe as Efient®, will be the first major competitor to clopidogrel, which has a much broader range of indications and is one of the world's best selling pharmaceuticals. Prasugrel is a more potent antiplatelet agent than clopidogrel and is not thought to be associated with so much variability as clopidogrel.

The increased antiplatelet potency of prasugrel would be expected to translate into a higher efficacy in preventing ischaemic events, but also a higher risk of bleeding.

This is exactly what was seen in the large-scale TRITON-TIMI 38 trial, on which the approval of prasugrel is based.

In the trial, which was conducted in 13,608 moderate-to-high-risk ACS patients scheduled for PCI, prasugrel given at a 60 mg loading dose followed by a 10 mg daily maintenance dose) was compared to clopidogrel (300 mg loading dose /75 mg maintenance dose). Results showed a significant reduction in the primary end point (cardiovascular death/non-fatal myocardial infarction/non-fatal stroke), but at the expense of a significant increase in major bleeding, life-threatening bleeding, and fatal bleeding.

In the paper, published in 2007 (*N Engl J Med* 2007;**357:**2001-15), the TRITON-TIMI 38 authors report that for every 1,000 patients treated with prasugrel as compared with clopidogrel, 23 myocardial infarctions were prevented, with an excess of six non-CABG-related TIMI major bleeds. They concluded that: "When considering the choice of antiplatelet regimens for the treatment of patients with ACS who are undergoing PCI, clinicians need to weigh the benefits and risks of intensive inhibition of platelet aggregation".

Writing in an accompanying editorial, Dr Deepak Bhatt (Cleveland Clinic, US) suggested that: "Prasugrel would probably benefit patients with ACS who are undergoing PCI and who are at high risk of ischaemic events and low risk for bleeding, although those with a lower risk for ischaemic events and a high risk of bleeding may be better served with clopidogrel".

In the TRITON-TIMI 38 trial, an increased risk of serious bleeding with prasugrel was seen in certain patient groups; patients who weighed less than 60 kg, patients who were 75 years of age or older and those who had had a prior transient ischaemic attack (TIA) or stroke. Consequently, it is recommended that patients with prior TIA or stroke should not be treated with prasugrel, and the drug is also generally not recommended for use in patients aged 75 years or older; but if it is used in this elderly group, a lower maintenance dose (5 mg) should be used. This lower maintenance dose is also recommended if prasugrel is given to patients who weigh less than 60 kg.

Approval also likely in the US

Prasugrel also received a positive recommendation from the US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee in early February for a similar indication, suggesting that US approval will follow shortly. But the FDA advisory committee meeting attracted some controversy when it was revealed that one expert, Dr Sanjay Kaul, an outspoken critic of prasugrel, was dropped from the committee after a phone call to the FDA from Lilly, questioning his inclusion.

Tricyclic antidepressants increase blood pressure

It has long been thought that depression is associated with increased blood pressure, but a new study suggests that it is not the condition itself, but the drugs used to treat it, that can lead to hypertension.

The study, published online in the journal, *Hypertension,* found that depression itself was actually associated with low blood pressure, but that taking tricyclic antidepressants tends to raise blood pressure and increase the risk of hypertension.

The study included 2,618 subjects who were divided into three groups: those with no history of anxiety or depressive disorder (controls); patients with a depressive or anxiety disorder who did not take antidepressants; and patients with a depressive or anxiety disorder who were taking antidepressants. Blood pressure was measured in all patients and was adjusted for use of antihypertensive drugs.

Results showed that compared with healthy controls, patients with depression had a significantly lower mean systolic blood pressure. In contrast, patients taking a tricyclic antidepressant had up to a 9% higher mean systolic blood pressure and an 11% higher mean diastolic blood pressure compared with healthy controls and patients with depression who were not taking any medication. However, the use of selective serotonin re-uptake inhibitor (SSRI) antidepressants was not significantly associated with increased blood pressure.

The study authors, led by Dr Carmilla Licht (VU University Medical Center, Amsterdam, The Netherlands) conclude that doctors should be aware of a potential blood pressure rise with tricyclic antidepressants, especially for patients with cardiovascular disease or hypertension. Doctors need to carefully monitor blood pressure in patients prescribed these drugs, or they could consider prescribing another antidepressant medication, they add.

Calorie reduction key to weight loss with heart healthy diets

Four different heart-healthy diets showed similar degrees of weight loss in a new study, leading to the conclusion that the type of foods eaten is not as important as generally just reducing calorie intake.

The study, published in the February 26 issue of the *New England Journal of Medicine*, included 811 overweight adults who were randomised to one of four different diets each emphasising different levels of fat, protein, and carbohydrates.

On average, patients lost 6 kg in the first six months, but gradually began to regain weight after 12 months, regardless of which type of diet they were following.

The diets tested in the study included the same types of foods, but in different proportions, and were aimed to reduce overall calorie consumption by approximately 750 calories per day. Participants were advised to take moderate exercise for at least 90 minutes per week, and were offered counselling sessions to help aid compliance to the diets.

Results showed that 80% of subjects completed the trial, and 15% managed to lose at least 10% of their initial body weight. Similar levels of satisfaction and hunger were reported in all four groups. All four diets reduced risk factors for diabetes and cardiovascular disease at six months and two-year follow-up. The low-fat diets produced the best reductions in low-density lipoprotein cholesterol, but the lowest carbohydrate diet improved high-density lipoprotein cholesterol the most.

Don't take proton pump inhibitors with clopidogrel

New evidence has been reported suggesting that use of proton pump inhibitors (PPIs) such as omeprazole can reduce the effectiveness of clopidogrel.

In a recent study (*JAMA* 2009; **301**:937–44), there was an increased risk of future cardiovascular events in acute coronary syndrome (ACS) patients taking both clopidogrel and a PPI compared with those taking clopidogrel alone.

PPIs are often prescribed for patients treated with clopidogrel and aspirin following ACS to reduce the risk of gastrointestinal bleeding. But it is thought that they can inhibit the cytochrome P450 isoenzymes that convert clopidogrel to its active metabolite, and these latest results suggest that such prophylactic prescribing of PPIs in this group of patients is not recommended, and that other gastro-protective agents may be preferable, the study authors comment.

For their study, they identified 8,205 patients with ACS taking clopidogrel after hospital discharge, of whom 64% were prescribed a PPI. The primary end point, the risk of death or re-hospitalisation for ACS, was increased by 25% in patients taking a PPI. This was driven by re-hospitalisation for ACS, which was increased by 86%, while mortality was not significantly different between the two groups.

Professor Peter Weissberg, Medical Director at the British Heart Foundation, pointed out that the reduction in effectiveness was modest, adding: "Many patients may need the PPI to protect their stomachs and a prospective trial is necessary to quantify the risks and benefits before there is any change in prescribing practice".

Diabetes rising dramatically in UK

There was a 63% increase in the incidence of diabetes in the UK in the ten years between 1996 and 2005, a new study shows.

The study, published online in the *Journal of Epidemiology and Community Health*, used data on 49,999 prevalent cases and 42,642 incident cases (1,256 type I diabetes and 41,386 type 2 diabetes) in UK patients aged 10 to 79 contained in The Health Improvement Network (THIN) database.

During the 10-years examined, the prevalence increased from 2.8% to 4.3% while the incidence rose from 2.71 per 1,000 person-years to 4.42 per 1,000 person-years.

Type 2 diabetes accounted for most of the increase, and the proportion of patients newly diagnosed with type 2 diabetes who were obese increased from 46% to 56% during the decade.

"Our results suggest that, although the incidence of diabetes remains lower in the UK than in the US or Canada, it appears to be increasing at a faster pace," the authors state.