Clopidogrel in unstable angina: ‘Clear benefit with an acceptable safety risk’

Clopidogrel, in addition to standard medications, confers significant benefits to patients with acute coronary syndromes. Salim Yusuf (McMaster University, Hamilton, Canada) presented results from CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) study for the first time. Compared with placebo, clopidogrel was shown to reduce, by 20%, the risk of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS).

Clopidogrel is an advanced antiplatelet agent that works by direct blockade of adenosine diphosphate receptors. It is currently indicated for the prevention of atherosclerotic events in patients with atherosclerotic disease, documented by recent myocardial infarction (MI) or ischemic stroke, or peripheral arterial disease. The CURE study involved 12,562 patients in 28 countries and ran from December 1998 to December 2000. “It provides important new findings that constitute a major step forward and could lead to a very significant improvement in the treatment of patients at risk of heart attack, stroke, and cardiovascular death” said Yusuf.

In the study, subjects who were admitted to hospital with suspected ACS were given aspirin (75–325 mg/day) then randomised to receive either clopidogrel (75 mg/day) or placebo. Subjects also received an initial loading dose of clopidogrel 300 mg orally (or matching placebo) within 24 hours of symptom onset. Treatment was continued for three months to one year, and the primary endpoint was a...
composite of MI, stroke (any type), cardiovascular death (CVD), and refractory ischemia.

Treatment with clopidogrel was found to confer a risk reduction of 20% on the composite endpoint, at a highly significant \( P = 0.00005 \). This benefit was incremental and independent of concomitant drug treatment and revascularization. Importantly, high and low risk patients showed a similar reduction in events. Also, the effects on the endpoints became apparent within two hours and continued to 30 days and beyond. The major side effect was bleeding, which was independent of dose. The incidence of major bleeding increased by 30% in the treatment group (similar to aspirin), while the incidence of life-threatening bleeding increased by 15% (non-significant). Yusuf felt the risk-benefit ratio, both early and late, was ‘favourable’ and the side-effect profile was ‘acceptable’ and far outweighed by the savings in lives and cardiac events.

The widespread use of clopidogrel in addition to aspirin in ACS could prevent about 50,000–100,000 heart attacks or deaths every year in North America. Over the study duration, the investigators found the drug was ‘cost-neutral’ and, compared with percutaneous transluminal coronary angioplasty (PTCA) and glycoprotein IIb/IIIa blockers, was cost-saving.

**Cardiac resynchronisation in HF confers ‘clinically and statistically meaningful’ benefit**

A new type of pacemaker has shown ‘markedly positive’ results in patients with heart failure. Results from MIRACLE (Multicenter InSync Randomized Clinical Evaluation), a large, randomized, double-blind study, were reported by William Abraham (University of Kentucky College of Medicine, Lexington, USA). He presented six-month clinical, functional, and quality of life data.

Cardiac resynchronisation therapy (CRT) is an innovative methodology to resynchronise the heart, in which a left ventricular (LV) lead is placed into a cardiac vein via the coronary sinus. After promising pilot studies, MIRACLE was designed to evaluate CRT in patients with heart failure (HF), complicated with intraventricular conduction delays or ventricular dysynchrony. In all, 266 patients were enrolled at 44 centres in the USA and Canada. To ensure blinding, the device was implanted in all patients, but only half were switched on.

Overall, the implant success rate was 93%, “far exceeding expectations,” Abraham said. There were statistically significant improvements in all primary and secondary endpoints compared with the control group. In particular, more patients had an improvement of at least 1 New York Heart Association (NYHA) class (69% vs 44%). Active treatment also improved a combined endpoint, improvement in NYHA \( \geq 1 \) class and six minute walk \( \geq 50 \) meters, which was achieved by 41% of the CRT group versus 15% in the controls \( P<0.001 \). Patients who received the active device were also more likely to show improved quality of life (47% vs 22%, \( P<0.001 \) and reduced QRS duration \( P<0.001 \).

Other clinical measures – LV dimensions and function, peak VO\(_2\) and plasma norepinephrine – showed significant benefits with active treatment versus control. Cost-effectiveness analyses showed that CRT is associated with significant reductions in healthcare utilisation, while the application of a composite outcome measure also favoured the device over placebo. No long-term deleterious effects of CRT have been seen so far and it was stressed that the results were clinically and statistically meaningful. Abraham predicted that CRT could potentially benefit 0.75 to 1.5 million patients in the United States.

**CAPRICORN: Carvedilol saves lives and reduces risk of second MI**

Carvedilol offers ‘dramatic’ protection against death and second MI in patients with postinfarction left ventricular dysfunction. Results presented from the CAPRICORN (Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction) trial show that treating post-MI patients with the beta-blocker carvedilol reduces the risk of another MI by 41% and the risk of dying by 23%. Data firmly support the addition of carvedilol to standard therapy in MI patients. Lead author Henry Dargie (University of Glasgow, UK) commented: “Until now, we have had little evidence to determine the additional benefits of beta blockers used in combination with modern standard therapy in patients with acute MI and confirmed LV systolic dysfunction and/or clinical evidence of heart failure.”

CAPRICORN is the first large multicentre placebo-controlled study to examine beta blockade post-MI, since the widespread introduction of thrombolytics and angiotensin converting enzyme (ACE) inhibitors. It is also the first trial to focus on a population with postinfarction LV dysfunction, regardless of clinical evidence of heart failure. A total of 1,959 patients in over 160 sites in 17 countries, were prospectively enrolled within 21 days of suffering an MI and randomly assigned to either carvedilol or placebo. Since CAPRICORN was an event-driven study, follow-up stopped in March 2000 when the predefined number of endpoints (633) had occurred. The co-primary endpoints were all-cause mortality/ cardiovascular hospitalisation and all-cause mortality; secondary endpoints were sudden death and hospitalisation for HF.

Treatment with carvedilol reduced the risk of all-cause death from 15 to 12% \( (P = 0.031) \). This represents a 23% relative risk reduction in mortality and was associated with a 41% \( (P = 0.014) \) reduction in risk of recurrent non-fatal MI and a 29% \( (P = 0.002) \) reduction in the risk of all-cause
mortality or non-fatal MI. As in previous trials, carvedilol was well-tolerated, with 75% of patients being uptitrated to the maximum dose (25 mg twice daily) by four weeks.

Dargie described the implications of the CAPRICORN results for clinical practice as ‘clear and far reaching’. Based on this data he said: “Carvedilol should be considered in all patients following MI with significant LV dysfunction. The results are extremely good news for patients in terms of markedly reduced chance of additional heart attacks and greater likelihood of survival.”

**Intracoronary gamma radiation ‘safe and effective’ for in-stent restenosis**

Ron Waksman (Washington Hospital Center, Washington DC, USA) presented results from SVG WRIST (Washington Radiation for In-Stent Restenosis Trial). This is the first multicentre double-blind randomised trial to examine the usefulness of gamma radiation in patients who have developed diffuse in-stent restenosis following coronary artery bypass surgery. Gamma radiation is already approved for the treatment of in-stent restenosis (ISR) in native coronaries, but these results support the extension of this therapy to patients with in-stent restenosis in saphenous vein bypass grafts (SVG).

SVG WRIST involved 120 patients with angina and diffuse ISR in SVGs. Subjects were aged 65–67 and almost all had hyperlipidemia and hypertension. All patients initially underwent PTCA with laser ablation, atherectomy, or stenting, before randomisation to receiving either 192Ir-labelled seeds or placebo. Radiation (14 or 15 Gy) was delivered for a mean dwell time of 22 ± 0.7 minutes, and was well tolerated.

At 30 days, no adverse events related to radiation therapy had occurred. At six months, the restenosis rate was significantly lower in the radiation group compared with the placebo group (16% vs 43%, \( P = 0.004 \)). Radiation therapy reduced by 78% the need for repeat revascularization; only 10% of the irradiated patients required further intervention, versus 48% in the placebo group (\( P = 0.001 \)). The rate of major cardiac events (death, MI) was lower in the gamma radiation group (20%) than in the placebo group (55%); \( P = 0.001 \). Finally, radiation therapy was associated with a reduction in late thrombosis (1.7% vs 6.7%) with no excess of edge effect compared with control.

Conventional treatment of ISR in bypass grafts is associated with a high recurrence rate however, Waksman concluded that the SVG WRIST study demonstrated that catheter-based radiation therapy was safe and effective for the reduction of the overall restenosis rate, and the need for repeat revascularization. These results support expanding the indications for gamma radiation therapy to patients with ISR following bypass grafting.

**Endothelin receptor antagonist stabilises acute HF without inducing arrhythmias**

Patients with acute decompensated heart failure (ADHF) gain substantial benefits from rapid administration of tezosentan, a potent intravenous dual endothelin receptor antagonist.

Guillermo Torre-Amione (Baylor College of Medicine, Houston, USA) presented results from the Randomised Intravenous Tezosentan (RITZ) 2 study. It suggests that tezosentan not only improves hemodynamic variables but also confers benefit on clinical parameters such as dyspnea and death. There have been few, if any, major advancements in the treatment of acute HF during the last decade but it was felt that tezosentan may offer a new approach to treating this disease. Torre-Amione described the data as ‘compelling’ but cautioned that the study was not designed to assess clinical endpoints. These will be provided by RITZ 1, a 650-patient study evaluating the drug’s ability to relieve the symptoms of congestive heart failure. RITZ 4 and 5 will complete the program as supporting studies.

In RITZ 2, 292 patients at 32 centres in the USA, Europe, and Israel were randomised to receive either tezosentan 50 mg/h or 100 mg/h or placebo for 24 hours after admission for ADHF. The study’s primary endpoint was the change in cardiac index (CI) six hours after the start of treatment, while secondary endpoints included other hemodynamic variables, dyspnea, time to death, and worsening of HF at 24 hours.

Both doses of tezosentan improved CI and pulmonary capillary wedge pressure significantly more than placebo (\( P < 0.0001 \)). The effect was maintained for the duration of treatment and for at least six hours thereafter. Tezosentan was also associated with a dose-related decrease in arterial pressure, and, importantly, no changes in heart rate. In terms of clinical benefit, patients who received active treatment were less likely to experience a worsening in dyspnea, and more likely to have an improvement (\( P = 0.048 \) and nonsignificant, respectively). In addition, a clear tendency for improvement in time to worsening of HF or death was observed over the 24 hours of treatment with tezosentan (\( P = 0.06 \)) compared with placebo.

The safety profile was generally favourable, with no difference in the incidence of serious adverse events up to 28 days after treatment. Patients in the treatment group were more likely to experience headaches and symptomatic hypotension, although this was experienced only at the higher dose. Torre-Amione stated that the R&D efforts would now concentrate on the 50 mg/hr dose, which had a safety profile similar to placebo. “When treating patients with acute HF, every second counts,” he added. “Quickly improving the heart’s pumping ability can prevent the
Inclusion of troponin status improves accuracy of TIMI Risk Score

Troponin testing only identifies around half of patients presenting with acute coronary syndromes who are at high risk of mortality. Data presented suggest that, while troponin testing is not a definitive tool for risk stratification in patients with ACS, it provides useful additional information about patients who warrant aggressive therapy.

Lead investigator Christopher Cannon (Brigham and Women’s Hospital, Boston, USA) presented the new data, which comes from Orbofiban in Patients with Unstable Coronary Syndromes-TIMI (OPUS-TIMI) 16 trial. He explained that, while patients who are troponin-positive are known to be at high risk of mortality and recurrent cardiac events, there is debate about patients who are troponin-negative. OPUS-TIMI 16 used a case-control design and a composite endpoint (death, MI, urgent revascularization, recurrent ischemia, stroke) to test whether all patients who are troponin-negative are at low risk. Levels of troponin I were measured in 2,241 patients on hospital admission and converted into a Thrombolysis in Myocardial Infarction (TIMI) Risk Score.

As expected, a positive troponin test was associated with a significantly increased relative risk (RR) of all endpoints at 10 months (RR 1.6-1.82), but only weakly for the composite endpoint including angina requiring hospitalisation. Among patients who were troponin-negative (≤0.1 ng/ml), the TIMI Risk Score identified a graded increase in the relative risk of the composite endpoint to 10 months. Patients who scored 0 had a RR of 1, while a score of 6 had a RR of 2.6 (P for trend = 0.002).

Cannon said that the incorporation of troponin tests into routine risk-stratification of patients with suspected MI would both improve diagnosis and facilitate early, aggressive medical therapy. He also noted that the number of lives saved offsets the cost of testing.

PRINCE: Inflammation in atherosclerosis a ‘very real phenomenon’

Paul Ridker (Brigham and Women’s Hospital, Harvard Medical School, Boston, USA) announced results from PRINCE (Pravastatin Inflammation CRP Evaluation). Pravastatin was associated with a highly significant reduction in C-reactive protein (CRP) levels becoming apparent at four weeks and present for the duration of the study.

PRINCE had two tiers: an open-label evaluation of pravastatin 40 mg/day in 898 patients with known CVD (secondary prevention cohort) and a double-blind trial of pravastatin 40 mg versus placebo in 1,339 apparently healthy men and women (primary prevention cohort). In both groups, pravastatin reduced median CRP levels by 13.2% (P< 0.001), while no change was observed with placebo. The effect was independent of gender, age, smoking status, body mass index, baseline lipid levels, and the presence of diabetes. Stratification of CRP response according to lipid levels revealed no association with either baseline or final LDL cholesterol (LDL-C).

In addition to the primary findings, the PRINCE study results also provides physicians with additional information that can be useful in evaluating patients in everyday practice. The study demonstrated that the reduction in CRP levels was similar in magnitude among patients with and without a history of heart disease. The investigators found it intriguing that the reductions in CRP levels were minimally related to changes in LDL cholesterol levels. Inflammatory processes are thought to be critical in driving the progression of atherosclerosis, as well as predisposing plaques to rupture. However, it is not known yet if reducing CRP itself reduces heart risk. This is a key question for the future. Ridker emphasised that lipid-lowering strategies are underused in both the USA and Europe, and hoped that these results would encourage more widespread, and more aggressive, use of statins.

In response to a question regarding the biological basis of these results, Ridker admitted that there are no clear-cut answers at present. He speculated that, while changes in CRP are not directly linked to changes in LDL-C, this could be a surrogate for changes in oxidised LDL-C – which cannot be measured. The data suggest that several pathways are involved, one or more of which may be a direct anti-inflammatory route. He admitted that although statins are known to decrease cholesterol levels and cholesterol drives the response to vascular injury, separating the two processes is difficult. Finally, Ridker highlighted another paradox: statins are known to reduce the risk of stroke, but LDL-C is not a risk factor for this condition. Results from other trials are needed to confirm or refute the hypothesis that lowering CRP levels reduces the risk of thrombotic events.

Experimental drug lowers BP, improves vascular compliance

David Kass (Johns Hopkins University, Baltimore, USA) presented data on an experimental drug ALT-711, which has shown promising results in a small trial of patients with age-related vascular stiffening.

Vascular stiffening and the associated increase in pulse pressure and systolic blood pressure is a huge epidemiological problem, affecting about half of all individuals aged over 60 years. ALT-711 may represent a novel therapeutic approach for patients with arterial stiffness associated with ageing, diabetes, and systolic hypertension.
In the study, the oral compound, ALT-711, or matching placebo were given to 93 patients with systolic blood pressure ≥140 mmHg and evidence of vascular stiffening. After eight weeks, patients who received the active compound had a significant reduction in arterial pulse pressure. These patients also showed an improvement in vascular compliance of up to 18%.

Previous drugs to treat this common blood pressure abnormality have mostly focused on lowering the mean or average pressure by relaxing the peripheral resistance arteries, but Kass’s results showed that ALT-711 appears to be different. It appeared to act on the larger vessels that regulate stiffness.

ALT-711 works by breaking advanced glycosylated crosslink endproducts (AGE) that form between proteins. The crosslinks particularly target proteins that are long-lived, such as structural proteins in the artery wall that confer the ability to stretch. In the cardiovascular system, AGE results in a loss of elasticity, which in turn causes raised pulse pressure (a major risk factor for atherosclerosis and vascular disease) and increases the heart’s workload (a risk factor for MI, heart failure, and coronary artery disease).

The results of this study has paved the way for a major multicentre clinical trial involving hundreds of patients with age-related vascular stiffening.

**Surgery has slight advantage over stenting – but data are inconclusive**

One-year results from the Stent or Surgery (SoS) trial, presented by Rodney Stables (Royal Liverpool University Hospital, UK), show a slight advantage for bypass surgery over stenting. Surprisingly, there appears to be a mortality advantage in patients managed with bypass. The mortality rate was 1.2% with CABG versus 4.1% with angioplasty.

In the SoS trial, 988 patients with multivessel coronary disease were recruited at 53 centres in Europe and Canada. They were randomised in equal proportion to initial therapy with CABG or percutaneous coronary intervention (PCI) and stent implantation. All patients were followed for at least one year, with an average follow-up of two years. Dr Stables reported that both procedures were associated with low rates of major adverse cardiac events (death, MI, and repeat revascularization). The rate of the combined endpoint, death and nonfatal MI, was similar in the two groups, at 9.5%.

Dr Stables said the mortality advantage seen with CABG was ‘surprising’ and cautioned that since the overall death rate in this group was extremely low at 0.8%, the results are prone to skew. He labelled this figure ‘extremely unusual’ and ‘out of step with other clinical trials in the area’, and stressed that SoS was not designed to assess mortality as a primary endpoint. In addition, there was an unusually high number of carcinoma-related deaths in the angioplasty group compared with the surgery group, which could have further distorted the data.

Continuing analysis of the SoS data will provide information about healthcare costs and cost-benefit, patient-reported symptoms, and quality of life. In particular, Dr Stables said that neuropsychological outcomes are due to be assessed in a sub-study (n=172) where cerebral function will be tested at baseline, 6, and 12 months. “Only then will we know the true role of PCI in revascularization in the multivessel arena,” Stables stressed. These results are due to be presented at the European Society for Cardiology’s meeting later this year.