News from the 2007 Congress of the European Society of Cardiology

Highlights of the European Society of Cardiology meeting held in Vienna, Austria, in September included a new study showing the benefits of reducing blood pressure in patients with diabetes, and of screening for peripheral arterial disease. But there was more controversy over drug-eluting stents and more disappointment over the idea of facilitated angioplasty.

ADVANCE – lowering blood pressure reduces events in diabetes

Routine administration of a fixed combination of perindopril and indapamide to a broad range of patients with type 2 diabetes, whatever their blood pressure at baseline, was associated with reduced risks of major vascular events, including death, in the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN MR Controlled Evaluation) study.

Presenting the results, Dr Steve MacMahon (University of Sydney, Australia) explained that using a fixed-dose combination of blood pressure-lowering drugs, irrespective of initial blood pressure level or the use of other antihypertensive drugs, would shift the entire distribution of blood pressure values down in patients with diabetes, with minimum requirements for titration. He added that if just half the population with diabetes worldwide took this drug combination, more than a million deaths would be avoided over five years. But other experts at the meeting and an editorial accompanying the *Lancet* publication of the ADVANCE study suggested that other drugs that lower blood pressure would probably be just as effective.

The ADVANCE trial included 11,140 type 2 diabetes patients who underwent a six-week active run-in period, and were then randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. The combination therapy was given at a dose of perindopril (2 mg) and indapamide (0·625 mg) for the first three months and then the dose of both agents was doubled. The use of concomitant treatments during follow-up, including blood pressure-lowering therapy, remained at the discretion of the responsible physician but use of thiazide diuretics was not allowed, and perindopril was the only angiotensin-converting enzyme (ACE) inhibitor allowed.

Results showed that after a mean of 4.3 years of follow-up, compared with patients assigned placebo, those assigned active therapy had a mean reduction in systolic blood pressure of 5.6 mmHg and diastolic blood pressure of 2.2 mmHg. The relative risk of a major macrovascular or microvascular event was significantly reduced by 9%; death from cardiovascular and from any cause was also reduced in the active treatment group (see **table 1**).

Dr MacMahon said the results built on those from UKPDS (the United Kingdom Prospective Diabetes Study), which had established that reducing systolic blood pressure from 155 mmHg to 145 mmHg produced benefits in patients with diabetes. He noted that ADVANCE extended these findings to lower pressures, as in this study average blood pressure was lowered from 145/81 mmHg to 135/75 mmHg in the active treatment group and to 140/77 mmHg in the placebo group.

The fixed combination regimen was well tolerated, he said, with only 3·6% of patients withdrawn because of suspected side effects during the pre-randomisation run-in period, and at the end of the study, adherence to active treatment was 73%, only 1% less than adherence to placebo. He concluded that: "These results support the provision of treatment, not on the basis of arbitrary cutoffs for blood pressure, but rather on assessment of vascular risk, which is raised in patients with type 2 diabetes, even in the absence of hypertension".

Discussant of the study, Dr Sydney Smith (University of North Carolina, Chapel Hill, US) said the trial "filled the evidence gap" for recommending a target blood pressure of 130/80 mmHg in the population with diabetes but he did not believe it supported treating absolutely all patients with diabetes, and that it was still not known whether ACE inhibitors have benefits over antihypertensives in this population.

Table 1. ADVANCE study results

End point	Perindopril/ indapamide	Control	HR	95% CI	P value
Major macrovascular or microvascular event (%)	15.5	16.8	0.91	0.83–1.00	0.04
Macrovascular event (%)	8.6	9.3	0.92	0.81–1.04	0.16
Microvascular event (%)	7.9	8.6	0.91	0.80–1.04	0.16
CV death (%)	3.8	4.6	0.82	0.68–0.98	0.03
Death from any cause (%)	7.3	8.5	0.86	0.75–0.98	0.03

Key: HR = hazard ratio; CI = confidence interval; CV = cardiovascular

Death rates with drug-eluting stents worse in STEMI patients

A new analysis of GRACE (the Global Registry for Acute Coronary Events) has shown that mortality risk with drug-eluting stents is four to six times higher than with bare-metal stents in patients with ST-elevation myocardial infarction (STEMI).

Presenting the results, Professor Gabriel Steg (University of Paris, France) said: "With all the caveats of observational datasets, this suggests that drug-eluting stents should be used with caution in patients with STEMI, at least until evidence of long-term safety is actually seen in large cohorts or large trials".

Table 1. Hazard ratio for death with drug-eluting compared to bare-metal stents in STEMI patients

End point	Hazard ratio	P
Death, 180–730 days	4.67	0.0170
Death, 180–730 days adjusted for GRACE risk score	6.022	0.002

Professor Steg explained that as there are few randomised controlled trials of drug-eluting stents in patients with acute coronary syndrome (ACS), information regarding their use in this population was gleaned from GRACE, which included 569 STEMI patients given a drug-eluting stent and 1,729 STEMI patients given a bare-metal stent between 2004 and 2006. The investigators found that there were no significant differences in deaths in STEMI patients given drug-eluting and bare-metal stents at 180 days follow-up, but the death rate between 180 days and 730 days was significantly higher in drug-eluting stent patients (8.6% *vs.* 1.6% for bare-metal stent patients).

Professor Steg suggested that these results may be explained by the large thrombus burden in STEMI patients, which is an independent predictor of complications and increased mortality, and to the fact that drug-eluting stents are known to delay re-endothelialisation in the stented segment.

There was no difference in mortality rates between drug-eluting stents and bare-metal stents in non-STEMI ACS patients.

SCAAR – more reassuring

More reassuring data came from four-year results from SCAAR (Swedish Coronary Angiography and Angioplasty Registry) of all drug-eluting stent use suggesting that that overall mortality is not higher in patients receiving drug-eluting stents than those receiving bare-metal stents.

Presenting the latest data from this registry, Dr Stefan James (Academic Hospital, Uppsala, Sweden), said he believed drug-eluting stents still had a role, but that patients must be selected carefully. He added that non-STEMI patients with longer lesions, smaller vessels, and complex lesions were more likely to be good candidates for drug-eluting stents but they must be judged able to take long-term clopidogrel.

Women with ACS do worse with PCI

Contrary to men, women having an acute coronary syndrome (ACS) do not seem to benefit from an early invasive strategy, new data from the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial show.

Dr Eva Swahn (University Hospital, Linkoping, Sweden) reported data from 184 women in the trial, half of whom received a routine early invasive strategy (routine angiography) and half a selective invasive strategy (angiography only with symptoms). In the early invasive group, 58% underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) compared with 31% in the selective invasive group. The early invasive group showed a higher mortality rate (8 deaths *vs.* 1; HR 4.65), and a higher bleeding rate (HR 6.90). "With these alarming results in this very small trial, we need to conduct a large randomised trial to determine the safety and efficacy of an early invasive approach in women," Dr Swahn said.

She also presented a meta-analysis of women in the major trials of testing routine versus selective invasive strategies – FRISC II, RITA-3, TACTICS-TIMI-18 and OASIS-5 –which showed a hazard ratio for death of 1.5 for the routine invasive strategy (p=0.07). "This suggests that the results from men do not necessarily apply to women and that large scale randomised trials in women are needed to determine the optimal strategy in non-ST-elevation ACS," Dr Swahn said.

EUROASPIRE: lifestyle issues cancel out treatment benefits

Although use of cardiovascular drugs has increased markedly over the past 12 years, any benefits seem to have been balanced by the failure to address lifestyle issues, new results from the EUROASPIRE survey suggest.

The current analysis examined trends among 8,547 coronary heart disease patients from eight European countries. Presenting the results, Professor David Wood (Imperial College, London) reported that smoking rates have remained unchanged (at around 20%) over the 12-year time period studied, and that body weight has increased dramatically (by an average of 4.9 kg), with 80% of patients now overweight and more than a third clinically obese. Diagnosed diabetes has also increased from 17% to 28% and when undetected diabetes is included, the figure reaches 43%.

In contrast, lipid levels have improved, with 72% of patients now achieving targets versus 13% at the start of the study. This has been driven by statin use which has increased from 18% to 87%. Reaching blood pressure targets have not followed the same trend, with no change seen over the study period and half of all patients still above the recommended target of 140/90 mmHg.

Professor Wood concluded that prevention was still being neglected. "Doctors must take some of the blame. Writing a prescription is absolutely not sufficient. We need multi-disciplinary rehabilitation programmes with regular monitoring."

FINESSE: another trial fails to show benefit of facilitated PCI

There was no benefit of facilitated percutaneous coronary intervention (PCI) with half-dose reteplase plus abciximab or abciximab alone in the FINESSE (The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial.

Presenting the results, Dr Stephen Ellis (Cleveland Clinic, US) noted that FINESSE joined several other trials, which have not managed to show any role for facilitated PCI in ST-elevation myocardial infarction (STEMI) patients.

FINESSE enrolled 2,452 STEMI patients who were estimated to have between one to four hours to get to a cath lab. They were randomised to primary PCI with abciximab in the cath lab, or to one of two facilitated regimens – half-dose reteplase/abciximab or abciximab alone before travelling to the cath lab for PCI.

At 90 days, there were no differences between the three treatment arms for the primary composite end point of the trial: all-cause mortality, readmission for heart failure, ventricular fibrillation, or cardiogenic shock. There were also no differences in all-cause mortality, complications of myocardial infarction (MI), or any of the independent components of the primary composite end point. But both major bleeding and minor bleeding were increased in the reteplase/abciximab arm compared with primary PCI alone, and there was also a strong trend towards increased intracranial haemorrhage in this combination group.

Dr Ellis said the trial results confirm that primary angioplasty alone should remain the default strategy for all, with two possible exceptions – those patients who present within one hour of symptom onset in whom lytics may be just as good, and those with very long transfer times for PCI (more than four hours) in whom lysis or a facilitated strategy may be preferable.

Discussant of the study, Dr Frans Van de Werf (University of Leuven, Belgium), agreed that all the results to date from facilitated PCI trials do not recommend such a strategy. But he suggested that there was still a chance that an early lytic-based treatment preceding PCI may be beneficial in certain patients – those presenting early (within two to three hours), with a large amount of viable myocardium, an anticipated long delay to PCI, who also receive adequate antithrombotic co-therapy, and in whom PCI is postponed if there is evidence of successful TIMI 3 reperfusion after lysis. He is conducting a new trial – STREAM – to look at this question.

CARESS

Another trial – CARESS (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis) – suggested that in patients undergoing thrombolysis in local community hospitals, immediate transfer for PCI is beneficial. The trial included 600 STEMI patients under 75 years old within 12 hours of symptom onset who had been admitted to hospitals without PCI facilities. They all received half-dose lytic therapy (reteplase), aspirin, heparin and abciximab bolus plus infusion, and were then randomised to immediate transfer for PCI or transfer for PCI only if they had persistent ST-elevation at 90 minutes (rescue PCI).

Results showed a significantly better outcome in the immediate transfer group, with a large reduction in the primary outcome of death/MI/refractory ischaemia at 30 days (4.1% *vs.* 11.1%), although this group also showed an increase in bleeding rate (any bleed 12.2% *vs.* 7.4%; p = 0.032). Stroke and transfusions were non-significantly increased.

No need for clopidogrel pre-treatment in stable patients

Routinely pre-treating stable coronary artery disease patients prior to angiography with clopidogrel did not reduce the risk of ischaemic complications, and increased the risk of bleeding in the PRAGUE-8 study.

Presenting the results, Dr Peter Widimsky (Charles University, Prague, Czech Republic) said that pretreatment with clopidogrel prior to coronary angiography is not justified in stable patients and that clopidogrel can safely be given to these patients after angiography and prior to the percutaneous coronary intervention (PCI). But he warned that these results do not apply to unstable patients, who stand to benefit much more from PCI, as well as from clopidogrel.

The trial involved 1,000 stable coronary artery disease patients who were either treated with clopidogrel more than six hours before the elective coronary angiography or just given clopidogrel in the lab after angiography if PCI was to be performed. There was no difference between the two groups in the primary end point of death, periprocedural myocardial infarction, stroke or transient ischaemic attack, or re-intervention within seven days but there was significantly more bleeding in the clopidogrel pretreatment group.

Atheroma regression with angiotensin receptor blockade

Two years of treatment with the angiotensin receptor blocker (ARB), olmesartan, appears to significantly reduce atherosclerotic plaque volume, according to a study presented by Professor Enrico Agabiti-Rosei (University of Brescia, Italy).

The MORE (Multicentre Olmesartan Atherosclerosis Evaluation) study compared the effects of olmesartan and atenolol in 165 middle-aged to older hypertensive patients, with increased cardiovascular risk, using a non-invasive three-dimensional ultrasound imaging system. Intima-media thickness (IMT) of the common carotid artery was measured at baseline, and at 28, 52 and 104 weeks. While blood pressure reduction was similar in both groups, preliminary findings showed that, in patients with larger plaque volumes, olmesartan significantly reduced the plaque volume compared to atenolol, an effect which was evident from 28 weeks onwards.

Professor Agabiti-Rosei told the *BJC* that, while ARBs have been shown to effectively reduce blood pressure and markers of inflammation, this is the first study showing reduction in plaque size using this imaging modality in a "respectable number " of patients.

Smoking ban reduces ACS

There was a significant reduction in hospital admission for acute coronary syndromes in Ireland in the year following the smoking ban in public places, a new study showed.

Dr Edward Cronin (Cork University Hospital, Ireland) reported that Ireland was the first country in Europe to impose an outright ban on smoking in public places, which came into effect in March 2004. He noted that Ireland has the second highest rate of cardiovascular deaths in Western Europe, after Finland, but that the rate of hospitalisations for acute coronary syndromes (ACS) declined by 11% the year following the smoking ban. "While we can't prove that the smoking ban decreased the admissions, this study should encourage other countries to consider implementing smoking bans," he said.

GetABI – screening for peripheral arterial disease would save lives

Patients with peripheral arterial disease (PAD) often have no symptoms, but are at a substantially increased risk of death, according to the results of GetABI (the German epidemiological trial on Ankle Brachial Index). The study found that simple screening of the ankle brachial index (ABI) by general practitioners can help identify patients with the condition. An ABI of less than 0.9 indicates PAD.

Lead investigator, Dr Curt Diehm (Affiliated Teaching Hospital, Karlsbad-Langensteinbach, Germany) called for screening of all elderly patients and for younger patients with cardiovascular risk factors, with those found to have PAD treated in the same way as patients with coronary artery disease. The study also found that while PAD is traditionally viewed as a smoker's disease, actually half the patients with the condition had never smoked.

GetABI included a total of 6,880 unselected patients (mean age 72 years) who underwent ABI testing by their primary care physician. At the five-year follow-up, all-cause mortality was substantially increased in patients with symptomatic and asymptomatic PAD (**table 1**).

Noting that ABI screening was simple and cheap, DrDiehm said: "We need to implement ABI as a screening tool in GPs offices to identify high-risk patients, and we have to make this happen now". He added that patients found to have PAD should be treated with aspirin or clopidogrel, plus a statin, beta blocker and ACE inhibitor. "A huge number of lives could be saved if patients with atherosclerosis would be identified with ABI and treated timely," he concluded.

Table 1. All-cause mortality in patients in the GetABI study

	Patients with symptomatic PAD	Pateints with asymptomatic PAD	Patients without PAD
All-cause mortality	23.9	19.1	9.4
Hazard ratio	1.8	1.6	1

Key: PAD = peripheral arterial disease

Bosentan beneficial in inoperable pulmonary arterial hypertension?

The endothelin antagonist, bosentan, improved haemodynamic outcomes in patients with inoperable pulmonary arterial hypertension in the BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension) trial. But there was no improvement in exercise duration after short-term follow-up.

In the study, 157 patients with inoperable chronic thromboembolic pulmonary hypertension or with post-pulmonary endarterectomy pulmonary hypertension were randomised to either 62.5 mg of oral bosentan per day or placebo. Dr Irene Lang (University of Vienna, Austria) reported that at 16 weeks, there were improvements in pulmonary vascular resistance, cardiac index, mean pulmonary arterial pressure and NT-Pro BNP in the bosentan group. There was no significant difference in six-minute walk time between the two arms. Dr Lang said that improvements in exercise capacity may not show up until much longer follow-up.

Discussant, Dr Nazzareno Galie (University of Bologna, Italy), noted that there have been multiple attempts to transfer the effects of targeted treatment for pulmonary arterial hypertension to inoperable patients, but that this is the first time a randomised study has shown any favourable effects in this group.

ARRIVE and REPLACE are announced

Details of the ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) study were announced at the meeting. This study will assess low-dose aspirin use to reduce the risk of a first cardiovascular or cerebrovascular event in some 12,000 men and women, at moderate risk (i.e. 20–30% 10-year cerebrovascular disease risk; 10–20% 10-year coronary heart disease risk) in 400 centres throughout Germany, Italy, Spain, UK and the US over a five-year period. ARRIVE, sponsored by Bayer HealthCare, will expand the already existing body of evidence supporting aspirin use in primary prevention. To date, meta-analysis of primary prevention trials show a 23% risk reduction of a first myocardial infarction in patients without known cardiovascular disease. The first patient was enrolled in July 2007.

The first patient has also been enrolled in to the REPLACE Registry, the first and largest prospective clinical trial, focusing on the complications associated with replacements and system upgrades of implantable pacemakers and defibrillators, independent of the manufacturers. Sponsored by BIOTRONIK, the trial principle investigator, Dr Charles Haffajee (Caritas St. Elizabeth Medical Centre, Boston, US) indicated that the study was "long overdue" and said that the actual complication rates, some of which are life-threatening, are often unreported and have never been collected prospectively in an unbiased registry. The REPLACE Registry will comprise 1,750 patients who will be monitored in up to 100 centres across the US.

MERLIN suggests ranolazine may have anti-arrhythmic properties in acute coronary syndrome

Further data on the possible anti-arrhythmic effects of the angina drug, ranolazine, were presented at the meeting. The main results of the MERLIN TIMI-36 trial, previously reported, showed no difference in event rates in acute coronary syndrome (ACS) patients between ranolazine and placebo, putting paid to a possible ACS indication for the drug. But there was a reduction in recurrent ischaemia, confirming its anti-anginal role.

As ranolazine prolongs the QT interval, there had been concerns that it may cause arrhythmias and it has been restricted to second-line use in angina patients, but new data from the MERLIN (Metabolic Efficiency with Ranolazine for Less Ischaemia in NSTE-ACS) trial suggest that ranolazine may actually have anti-arrhythmic properties.

Dr Ben Scirica (Brigham and Women's Hospital, Boston, US) reported that patients treated with ranolazine in the MERLIN study had fewer episodes of ventricular tachycardia, supraventricular tachycardia, and ventricular pauses (**table 1**). "These results suggest that further studies designed to evaluate the potential role of ranolazine as an antiarrhythmic agent are warranted," he said. Designated discussant, Dr John Camm (St George's Hospital Medical School, London), said the reduction in arrhythmia was an important secondary end point, and that this new data should move ranolazine up as a first-line anti-anginal agent since the drug cannot seriously be considered proarrhythmic.

Table 1. MERLIN: arrhythmic end points

Arrhythmic end point	Ranolazine	Placebo	P value
Ventricular tachycardia ≥ 3 beats (%)	52.0	60.6	<0.001
Ventricular tachycardia ≥ 8 beats (%)	5.3	8.3	<0.001
Supraventricular tachycardia ≥ 4 beats (%)	44.7	55.0	<0.001
New-onset atrial fibrillation (%)	1.7	2.4	0.08
Bradycardia < 45 beats per minute, complete heart block, or pause ≥ 2.5 sec (%)	39.8	46.6	<0.001
Pause ≥ 3 sec (%)	3.1	4.3	0.01