American College of Cardiology 55th Annual Scientific Session

The ASTEROID trial, which showed regression of atherosclerosis by reducing low-density lipoprotein cholesterol to new lows and simultaneously improving high-density lipoprotein cholesterol, was one of the highlights of this year's American College of Cardiology meeting held in Atlanta, Georgia, US, on March 11–14th 2006. Other successes included two new antithrombotic regimens that improved outcomes compared with unfractionated heparin in ST-elevation myocardial infarction patients, while clopidogrel showed disappointing results in a large study of primary/secondary prevention.

CHARISMA: no benefit of clopidogrel in stable vascular disease

Adding clopidogrel to long-term aspirin therapy in patients with, or at high risk of, vascular disease is of no benefit, according to the results of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management, and Avoidance) trial. Clopidogrel also increased the risk of moderate to severe bleeding, and actually appeared harmful in the primary prevention patients.

Presenting the results, Dr Deepak L Bhatt (Cleveland Clinic, US) said: "Our findings do not support the use of dual antiplatelet therapy across the broad population tested".

The trial randomised 15,603 patients to clopidogrel 75 mg/day plus low-dose aspirin (75–162 mg/day) or to placebo plus low-dose aspirin. Around 12,000 patients already had evidence of vascular disease (secondary prevention) and 3,000 were primary prevention patients with multiple risk factors.

Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the primary end point – a composite of myocardial infarction, stroke or cardiovascular death (table 1).

Table 1. Composite and individual primary and secondary end points in CHARISMA

End point	Clopidogrel + aspirin (n=7,802)	Placebo + aspirin (n=7,801)	RR	P value
Primary end point	6.8%	7.3%	0.93	0.22
Severe bleeding	1.7%	1.3%	1.25	0.09
Moderate bleeding	2.1%	1.3%	1.62	<0.001

Different results for primary/secondary prevention

There was a suggestion of benefit in the secondary prevention group, in which the primary end point occurred in 6.9% of patients on clopidogrel and 7.9% on placebo (p=0.046). But primary prevention patients appeared to do worse on clopidogrel, with the primary end point occurring in 6.6% of patients versus 5.5% with placebo (p=0.20). But it was the rate of death from cardiovascular causes that caused the most concern in this group – 3.9% in the clopidogrel group versus 2.2% with placebo (p=0.01).

This suggestion of harm in asymptomatic patients means that "dual antiplatelet therapy should not be used in patients without a history of established vascular disease", Dr Bhatt said.

But he suggested that some secondary prevention patients may be candidates for the drug, and that further analyses of CHARISMA will attempt to establish which patients in particular benefited from taking clopidogrel. "We need to weigh the ischaemic risk against the risk of bleeding," he said. "If I had a patient who had had multiple myocardial infarctions in the past despite taking aspirin, I would consider adding clopidogrel. But if a patient was stable and had a bleeding ulcer, I would avoid clopidogrel."

Discussion

Dr Doug Weaver (Henry Ford Health System, Detroit, Michigan, US), one of the moderators of the session at which the CHARISMA results were presented, commented: "The primary end point was negative. I don't think it's even fair to look at secondary end points. Our indications for clopidogrel should not change after this study."

Full results of the CHARISMA trial were published online in the *New England Journal of Medicine* on March 12th 2006.

ASTEROID: high-dose rosuvastatin shows atheroma regression

Aggressive lipid lowering with rosuvastatin 40 mg showed a significant regression of coronary atherosclerosis as measured by intravascular ultrasound (IVUS) in the ASTEROID (A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) study.

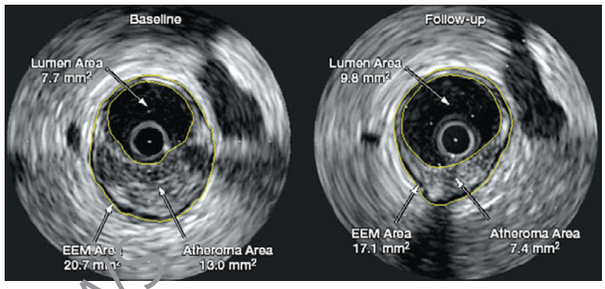
The high dose of rosuvastatin caused a large reduction in low-density lipoprotein cholesterol (LDL-C) and a significant 15% increase in high-density lipoprotein cholesterol (HDL-C), both of which are believed to be important in bringing about atheroma regression.

Presenting the results, Dr Steven Nissen (Cleveland Clinic, US) stated that this is the first time regression has been shown. "We concluded that if you lower LDL-C to these very low levels and keep it there for two years, particularly if accompanied by an increase in HDL-C, you could partially reverse coronary disease.

ASTEROID involved 349 patients who had more than a 20% luminal diameter narrowing in a coronary vessel, and who were not already taking statins. They were all treated with rosuvastatin 40 mg.

After two years of treatment with rosuvastatin, mean LDL-C was reduced from 130 mg/dL (3.36 mmol/L) to 60 mg/dL (1.55 mmol/L), the lowest level ever achieved in a statin trial. Mean HDL-C was increased from 42.1 mg/dL (1.09 mmol/L) to 49 mg/dL (1.27 mmol/L). IVUS results showed that there were significant decreases in the two primary end points: mean per cent atheroma volume and mean atheroma volume in the most diseased 10 mm vessel subsegment. In addition, there was a significant reduction in total atheroma volume. Figure 1 shows the effect statin therapy can have in reducing atheroma.

Figure 1. Examples of how statin therapy can reduce atheroma in a coronary vessel



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Regression of coronary atherosclerosis occurred in nearly all subgroups, including men and women, older and younger patients, and most subgroups defined by lipid levels. The drug was also said to be well tolerated, with rates of elevated hepatic enzymes comparable to other trials using maximum doses. There were no cases of rhabdomyolysis.

Dr Nissen said that the results of this one study would not be enough to alter guidelines but that individual doctors would have to decide 'how low to go' in terms of LDL-C.

"We did not show that these low levels reduce morbidity and mortality but we think that will follow," he commented.

Full results of ASTEROID were published online in *JAMA* on March 13 2006.

ASTEROID – a secondary care perspective

ASTEROID is the first intravascular ultrasound (IVUS) efficacy trial to show unequivocal evidence of significant coronary disease plaque regression of 7–9 % when patients with coronary heart disease (CHD) were treated with rosuvastatin 40 mg for two years.

IVUS is the first clinical technique to permit routine tomographic imaging of coronary arteries.[1] In a study recruiting patients with suspected coronary artery disease, 48 % of those with normal coronary arteries on angiography were shown to have atheroma using IVUS.[2] It is quite worrying to note that the majority of acute coronary events are caused by plaques producing only mild to moderate, often non-flow limiting, coronary lesions.[3]

So what are the clinical implications of ASTEROID for cardiologists? National and international guidelines for LDL-C and total cholesterol are taking targets lower and lower. Studies indicate that substantial LDL-C reductions, by 40% or to < 1.8 mmol/L, are needed to halt progression of atherosclerosis.[5] i.e. significantly lower than current guidance. The LDL-C levels achieved in the ASTEROID study were the lowest values ever observed in a statin atherosclerosis regression trial. The magnitude of the HDL-C increase was also unprecedented, exceeding, effects reported in previous statin trials.

This trial recruited patients with established CHD and therefore at significantly high risk of future cardiovascular events. These patients have the most to gain from intensive cholesterol lowering and the study indicates that clinicians should consider treating established CHD patients to as low an LDL-C level as can safely be achieved and should not adhere strictly to recommended targets. They should at least consider target acquisition as the bare minimum standard.

Another important message from the study is the importance of improving the whole lipid profile. Previous angiographic trials have focused on the importance of HDL-C in halting progression of atherosclerosis.[4,5] Trials of combination therapy designed to lower LDL-C and simultaneously raise HDL-C are underway and should report in the near future. In the meantime, it is imperative that clinicians prioritise LDL-C lowering, bearing in mind the importance of raising HDL-C to the best achievable level.

Despite the unique findings of ASTEROID, there are some study limitations that need to be taken into consideration when making clinical decisions. Ethical considerations meant the trial had no control group. The trialists compensated for bias by extensive blinding of information, and by resequencing IVUS examinations. Therefore ASTEROID did not test the probability of atheroma regression using a lower dose of study drug. The degree to which atheroma regression on IVUS will translate into reduction in morbidity and mortality also remains to be proven. Reduction in hard end points, however, is likely to follow significant atheroma regression.

Despite the favourable side-effect profile shown in this study, statins in general are known to exhibit a dose-related adverse effect profile.[6] At this stage, it seems reasonable to extrapolate from the study that patients achieving similar LDL-C reductions in addition to modest increases in HDL-C should realise similar benefits irrespective of the dose and statin used. Moreover, rosuvastatin at the usual starting dose of 10 mg has been shown to achieve LDL-C reductions in the order of 50%.[7,8]

'Clinicians must prioritise LDL-C lowering and bear in mind the importance of raising HDL-C to the best achievable level'
Lena Izzat

On a lighter note, patients constantly enquire whether there is anything we can do to help reduce the extent of the 'hardening of their arteries'. Until recently the answer has always been: "No, but we can try to halt it". We can now reply with considerably more optimism.

References
These are available from the editorial office on request.

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ASTEROID – a view from general practice

This study is breaking ground in medicine. It has entered the 'cyberspace' of vascular medicine and attempts to show us that perhaps we can go back to the low-density lipoprotein cholesterol (LDL-C) levels *Homo sapiens* had when attending the fields and living off the land. To slow down progression of atherosclerosis is an achievement but to actually reverse the process is extraordinary. It opens a new chapter in the management of atherosclerosis, which we hope will lead to a reduction in coronary events as the key outcome in future trials.

Multiple statin trials achieving very low LDL-C levels have shown reduction in cardiovascular events in the past. There is no reason why this should not apply to the ASTEROID patients. The question is whether the ASTEROID patients will do even better.

ASTEROID does not show so much a reversal of disease, rather a regression of atherosclerosis in the coronary artery wall. The previous study, REVERSAL, using atorvastatin 80 mg, showed a reduction of the atherosclerosis process down to zero. ASTEROID has gone further. It repeats the results obtained in the common carotid artery in ARBITER 3, where

'Could the 14.7% rise in HDL-C have helped to achieve the remarkable results in ASTEROID?'
George Kassianos

nicotinic acid was added to a statin. The result was regression in the common carotid intima-media thickness in the group taking nicotinic acid on top of their usual statin (~90% were on simvastatin).

In ARBITER 3 the driving force was the 24% further rise in high-density lipoprotein cholesterol (HDL-C). Could the 14.7% rise in HDL-C have helped to achieve the remarkable results in ASTEROID? Undoubtedly, it is the combined effect of rosuvastatin 40 mg on both LDL-C (down to 1.58 mmol/L) and HDL-C.

I was disappointed not to see the hs C-reactive protein (hsCRP) measured in ASTEROID. Cholesterol and inflammation play a very important role in the atheromatous plaque existence. Why measure one and not the other? Rosuvastatin is a potent inhibitor of hsCRP.

Although ASTEROID was a research and not an outcomes study, the results are good news for patients. It points a way to the future but it is not sufficient to alter guidelines. No doubt, individual physicians will make their own minds up about how compelling an argument can be made for reducing LDL-C lower, and raising HDL-C with potent statins, nicotinic acid or fibrates. The question is, should we have a target for LDL-C? Why not just take it to as low a level as we can, without creating safety problems?

It is my view that ASTEROID supports the idea that rather than the quality and outcomes framework (QOF) goal of total cholesterol $\leq$ 5 mmol/L being met in primary care, an LDL-C level of < 2 mmol/L should be our clinical target. We should be mindful, however, of the fact that the dose of 40 mg of rosuvastatin used in ASTEROID is, in the UK, reserved for patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who do not achieve their treatment goal on 20 mg.

George Kassianos
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OASIS 6: fondaparinux benefits in STEMI

The factor Xa inhibitor antithrombotic, fondaparinux reduced mortality and reinfarction without increasing bleeding compared with usual care in the OASIS 6 (Organisation to Assess Strategies for Ischaemic Syndrome) trial in a broad population of patients with ST-elevation myocardial infarction (STEMI). The drug was of benefit in all groups apart from those patients undergoing primary angioplasty (PCI), who had a higher risk of catheter thrombosis with fondaparinux, lead investigator, Dr Salim Yusuf (McMaster University, Hamilton, Canada) reported.

The OASIS-6 trial enrolled 12,092 STEMI patients who were randomised to fondaparinux (2.5 mg once daily given for up to eight days) or usual care – unfractionated heparin for up to 48 hours followed by placebo for up to eight days, or placebo for up to eight days for those in whom unfractionated heparin was not indicated.

The primary end point, a composite of death or reinfarction, was significantly reduced in the fondaparinux group at nine days, 30 days (table 1) and six months. Mortality was also significantly reduced throughout the study.

Fondaparinux showed benefits over usual care in patients receiving thrombolytic therapy and those not receiving any reperfusion therapy, but showed similar outcomes to unfractionated heparin in those patients who underwent primary PCI. In this group, there was a higher rate of guiding catheter thrombosis, and more coronary complications (abrupt coronary artery closure, new angiographic thrombus, catheter thrombus, no reflow, dissection, or perforation), with fondaparinux. But addition of UFH with fondaparinux during PCI largely avoided these complications.

Table 1. OASIS 6 primary end point: death/re-MI at 30 days

Time point	Fondaparinux (n=6,036)	Control (n=6,056)	HR	95% CI	P value
30 days	9.7%	11.2%	0.86	0.77–0.96	0.008

Key: MI = myocardial infarction; HR = hazard ratio; CI = confidence interval

The OASIS authors say: "Given the very limited time for antithrombotic therapy prior to the procedure and the need for UFH during the procedure, there is probably little advantage in using fondaparinux as the initial treatment in patients in whom primary PCI is intended". But they add that: "In all other patients (including those who may need a rescue PCI or other PCI after admission), initial management with fondaparinux followed by standard UFH during PCI is an attractive choice."

No bleeding problems

There was a tendency to fewer severe bleeds with fondaparinux. There were also significantly fewer cardiac tamponades with the factor Xa inhibitor, which the authors attribute to less intrapericardial bleeding or to smaller infarct size and therefore fewer cases of myocardial rupture.

Dr Yusuf said: "This pattern of reduction in mortality and reinfarction without an increase in bleeds is unique among antithrombotic agents".

Full results of OASIS-6 were published online in *JAMA* on March 14th 2006.

REACH: risk of events rises sharply if CAD patients also have cerebrovascular or peripheral arterial disease

The risk of cardiovascular events increases sharply with the number of vascular systems affected by atherothrombosis, one-year data from the REACH (REduction of Atherothrombosis for Continued Health) registry show.

While patients with coronary artery disease (CAD) alone had a 3% risk of having cardiovascular death, a myocardial infarction or a stroke at one year, this risk increased to 6.4% in those with coronary artery disease and cerebrovascular disease, and to more than 7% of those with CAD, cerebrovascular disease and peripheral arterial disease (PAD) (see table 1).

The registry, from 44 countries, enrolled patients with documented coronary artery disease, cerebrovascular disease or peripheral arterial disease, or at least three risk factors for atherothrombosis.

Lead investigator, Dr Gabriel Steg (Bichat-Claude Bernard Hospital, Paris, France) said: "We should stop looking at our patients as affected with one localised disease". He added that cardiologists should examine carotid arteries and peripheral vessels as well as coronary arteries, and that primary care physicians should look for signs of PAD in patients without chest pain. These patients should have their low-density lipoprotein cholesterol lowered as if they had coronary disease.

Table 1. Adjusted one-year rate of CV events by involved vascular-disease sites

Selected 1-year end points	Any 1 site	CAD alone	CVD alone	PAD alone	Any 2 or 3 sites	CAD+ CVD	CAD+ PAD	CAD+ PAD+ CVD
CV death	1.5%	1.5%	1.4%	1.2%	2.4%	2.0%	2.9%	3.6%
CV death/ MI/ stroke	3.4%	3.1%	4.5%	2.3%	6.0%	6.4%	4.8%	7.4%
CV death/ MI/ stroke/ CV hospitalisation	12.8%	13.3%	10.0%	18.2%	22.0%	20.0%	23.3%	26.9%

Key: CV = cardiovascular; CAD = coronary artery disease, PAD = peripheral arterial disease; MI = myocardial infarction; CVD = cardiovascular disease

REACH – a contemporary insight into the global management of atherothrombosis

Atherothrombosis, the unifying pathology underlying ischaemic cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral arterial disease (PAD), is the leading cause of death worldwide and accounts for 39% of all deaths and 31% of premature deaths in the UK.[1]

So much anticipation surrounded the presentation of the interim 12-month follow-up data of the REACH registry at the ACC. This international, prospective, observational registry has recruited more than 68,000 patients (aged 45 years or over) with either established atherothrombosis (CAD, CVD or PAD) or a high multi-factorial risk of atherothrombotic events (see table 1). Patients were recruited sequentially from 5,473 sites in 44 countries, with UK investigators contributing 620 patients from 51 centres.

It is an important and unique initiative that aims to identify the magnitude of the cardiovascular event risk in high-risk patients and, ultimately, the most effective ways of protecting them. Many studies and surveys have been undertaken in the past to investigate the incidence of vascular disease, but they have all had limitations:

'There is a need to address atherothrombosis as a 'global disease' rather than a disease of individual vascular beds'
Jonathan Morrell

- They have not specifically evaluated the broad population at risk of atherothrombotic events (e.g. the World Health Organization MONICA project[2])

Table 1. Definition of high multi-factorial risk in the REACH registry

Patients had to have at least three of the following risk factors:

- male aged ≥ 65 years or female aged ≥ 70 years
- current smoker
- diabetes mellitus (type 1 or 2)
- diabetic nephropathy
- hypertension
- hypercholesterolaemia
- ABPI (ankle brachial pressure index) < 0.9
- asymptomatic carotid stenosis or the presence of at least one carotid plaque

Key: CV = cardiovascular; CAD = coronary artery disease, PAD = peripheral arterial disease; MI = myocardial infarction

- They have focused on just one manifestation of the disease (e.g. acute coronary syndromes in ENACT[3])
- They have been geographically restricted to one country (e.g. Sweden[4])
- They have been restricted to secondary care settings (e.g. GRACE[5]).

In contrast, the REACH registry is not limited to a single subtype of patient, a single geographical area or to hospital in-patients.

The registry aims to study a contemporary, stable patient population from various regions of the world in order to describe the characteristics and management of these high-risk patients. This will include assessing the long-term risk of atherothrombotic events in both the global population and each subgroup, and assessing the amount of 'cross-risk' between subgroups. The study will compare outcomes within different subject profiles and will eventually define predictors of risk for subsequent atherothrombotic events. Follow-ups of these patients are planned at 12 and 21 months and have been extended to allow follow-ups at three and four years. Baseline data are summarised in table 2.

One-year data

The key data from the interim 12-month follow-up data of the REACH registry[7] indicate that the burden of atherothrombotic disease, both in the at-risk population and in the secondary prevention populations, is substantially larger than first recognised.

Despite contemporary interventions, both symptomatic and asymptomatic patients still encounter high annual cardiovascular event rates, with 3.9% and 1.7% respectively experiencing cardiovascular (CV) death, myocardial infarction (MI) or stroke. These hard event rates increase markedly with the number of symptomatic disease locations, ranging from 1.5% (risk factors only) to 7.1% (triple location). Overall, in patients with disease in one vascular bed, there was a 12.8% annual event rate of CV death/MI/stroke or hospitalisation (TIA, unstable angina, other ischaemic arterial event including worsening of PAD) compared to 22% in patients with polyvascular disease. Rather than the type of vascular bed initially affected, it is the overlap between symptomatic locations which affects and increases event rates.

Table 2. Baseline data in the REACH registry[6]

- 81.8% of patients had 'symptomatic' atherothrombosis. Of these 65.9% had established disease in one arterial bed and 15.9% had polyvascular disease with established disease in two or all three arterial beds
- 18.2% of patients had multiple risk factors ('asymptomatic')
- atherothrombotic patients throughout the world had similar risk profiles including a high proportion with:
  - hypertension (81.8%)
  - hypercholesterolaemia (72.4%)
  - diabetes (44.3%)
  - prevalence of overweight, obesity and morbid obesity was similar in most geographic locations but highest in North America
- patients were generally found to be undertreated with statins, antiplatelet agents and other evidence-based risk reduction therapies
- undertreated hypertension (50% with elevated blood pressure at baseline), undiagnosed hyperglycaemia (4.9%) and impaired fasting glucose (36.5% in those not known to be diabetic) were common

Rates of interventions are high, with 5% angioplasty/bypass surgery in CAD patients, 1.1% carotid stenting/surgery in CVD patients and > 10% peripheral interventions in PAD patients. A 1.3% yearly amputation rate among PAD patients was observed.

Not surprisingly, the annual CV death/MI/stroke event rate varied geographically, ranging from 2.2% in North America to 6.8% in Eastern Europe; Western Europe had a 3.7% event rate. Overall, the CV death/MI/stroke event rate in women was similar, but slightly lower than in men, at 3.6% *vs.* 3.9%.

Interestingly, patients with PAD showed the highest annual death rate (2.4%) and also a similar rate of chronic heart failure to patients with CAD of just over 4%. PAD is underdiagnosed in the UK, yet is a clear marker for serious underlying vascular disease. The exclusion of PAD from the Quality and Outcomes Framework of the new General Medical Services contract will only contribute to the continued under-recognition and poor prognosis of patients with the disease.

The preliminary results from the REACH registry demonstrate the high event rate in both symptomatic and high-risk asymptomatic patients despite current therapies. Importantly, they confirm the need to address atherothrombosis as a 'global disease' rather than a disease of individual vascular beds.

References

These are available from the editorial office on request.

Jonathan Morrell
General Practitioner and UK REACH Lead Investigator

ARMYDA-3: statins reduce AF post-CABG

Treatment with atorvastatin significantly reduced post-operative atrial fibrillation (AF) among patients undergoing elective coronary artery bypass grafting (CABG) or valve surgery in the ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery) trial.

Presenting the results, Dr Germano Di Sciascio (Bio-Medico University, Rome, Italy) noted that post-surgical AF occurs in about 40% of CABG patients (and even more valve surgery patients) and is associated with haemodynamic deterioration, stroke, other thromboembolic events, a prolongation of hospital stay, and increased costs. He said inflammation was suspected to be involved in the development of AF after cardiac surgery, and that statins are known to have anti-inflammatory effects.

In the study, 200 patients received either atorvastatin 40 mg or placebo for one week prior to surgery. Treatment with atorvastatin significantly reduced the incidence of post-operative atrial fibrillation and length of hospital stay (for results, see table 1).

Patients who developed atrial fibrillation had significantly higher levels of C-reactive protein than those who did not have the arrhythmia, adding weight to the belief that inflammatory mechanisms are involved. Dr Di Sciascio concluded that these results might prompt the use of statins before elective cardiac surgery procedures, but that larger trials were probably needed.

Table 1. ARMYDA-3 results

End point	Atorvastatin 40 mg	Placebo	P value
Incidence of post-operative in-hospital atrial fibrillation	35%	57%	0.003
Hospital stay	6.3 days	6.9 days	0.001

ExTRACT- TIMI 25: enoxaparin superior to heparin in thrombolysis patients

A new dosing regimen of enoxaparin was superior to unfractionated heparin in patients receiving thrombolysis for ST-elevation myocardial infarction in the ExTRACT-TIMI 25 (Enoxaparin and Thrombosis Reperfusion for Acute Myocardial Infarction Treatment: Thrombosis in Myocardial Infarction) study.

Presenting the study at the ACC meeting, Dr Elliott Antman (Brigham and Women's Hospital, Boston, US) explained that previous trials with enoxaparin in thrombolysis patients had shown bleeding concerns in certain patient groups, so in ExTRACT TIMI-25, the dose of enoxaparin was reduced in elderly patients and those with renal dysfunction. This did translate into a reduction in bleeding compared with previous trials but enoxaparin was still associated with an increase in major bleeding compared with unfractionated heparin (UFH) in this study. Nonetheless, the low molecular weight heparin did reduce the primary end point of death or non-fatal recurrent myocardial infarction (MI), and was associated with a net clinical benefit when the efficacy and bleeding results were combined.

The trial involved 20,506 patients with ST-elevation MI (STEMI) who were scheduled to undergo thrombolysis. They were randomised to receive enoxaparin (until hospital discharge or for a maximum of eight days, whichever came first) or UFH for at least 48 hours. The primary end point – death or non-fatal recurrent MI at 30 days – was significantly reduced in the enoxaparin group (table 1).

"Our results suggest that a strategy of administering enoxaparin throughout the index hospitalisation is superior to the current strategy of administering UFH for 48 hours as adjunctive therapy for patients with STEMI who undergo pharmacologic reperfusion with a thrombolytic," Dr Antman said.

"For every 1,000 patients treated with the enoxaparin strategy, there would be 15 fewer non-fatal reinfarctions, seven fewer episodes of urgent revascularisation and six fewer deaths, at the cost of four additional episodes of non-fatal major bleeding (with no increase in the number of non-fatal intracranial haemorrhages)," he added.

Full results of the ExTRACT TIMI-25 trial were published online in the *New England Journal of Medicine* on March 14th 2006.

Table 1. ExTRACT TIMI-25 results at 30 days

Outcome at 30 days	Enoxaparin (n=10,256)	UFH (n=10,223)	Relative risk	P value
Primary end point (death or MI)	9.9%	12.0%	0.83	<0.001
Major bleeding	2.1%	1.4%	1.53	<0.001
Net clinical benefit – death, non-fatal MI or non-fatal major bleeding	11.0%	12.8%	0.86	<0.001

Key: UFH = unfractionated heparin; MI = myocardial infarction

MIST: Mixed results for PFO closure in migraine prevention

Closing a patent foramen ovale (PFO) reduced the occurrence of migraine but did not completely cure the headaches in the MIST (Migraine Intervention with Starflex®Technology) trial.

The trial was conducted after observations that people found to have PFOs also often suffer from migraine with aura, and patients who undergo PFO closure often report a reduction in migraine following the procedure.

The MIST trial involved 147 patients with large PFOs, who suffered from migraine with aura that was refractory to at least two classes of migraine medication.

They were randomised to either PFO closure with the Starflex® septal-repair implant or to a sham procedure, consisting of general anaesthesia and groin incision. All patients were prescribed aspirin and clopidogrel for three months, and were followed for an additional three months.

Reporting the results at the ACC meeting, Dr Andrew Dowson (King's College Hospital, London) noted that three patients in each arm of the trial achieved the primary end point of complete cessation of headache. But more patients who had their PFOs closed had a 50% or greater reduction in headache days (42% *vs.* 23%), and more PFO closure patients had a reduction in headache burden (headache frequency multiplied by duration) – (37% *vs.* 17%).

The cardiologist involved in the study, Dr Peter Wilmshurst (Royal Shrewsbury Hospital, Shropshire), pointed out that some patients may have residual shunts and the data on this have not yet been analysed. "If bloodborne substances are responsible for migraine, significant residual shunting would influence the results", he said. A larger trial – MIST II – is now planned with a longer follow-up period.

TROPHY: treating 'prehypertension' may be beneficial

People with blood pressures that are in the range of 'prehypertension' (high normal) could benefit from treatment with antihypertensive medication, according to the results of the TROPHY (TRial Of Preventing HYpertension) trial.

The trial randomised prehypertensive patients to two years' treatment with candesartan followed by placebo for two years, or to placebo for the whole four-year study period.

"Two years of treatment with candesartan in patients with prehypertension delayed onset of stage 1 hypertension beyond two years after discontinuation of treatment, substantially suppressed onset of stage 1 hypertension during the two years of treatment, substantially prolonged the hypertension-free period, and the treatment was well-tolerated," reported lead investigator, Dr Stevo Julius (University of Michigan, Ann Arbor, US).

But he added that they are not recommending intermittent drug treatment for all prehypertensive patients on the basis of this one trial. They are, however, recommending more frequent follow up (three-monthly intervals) of patients whose pressures are in the range they studied.

The threshold for prehypertension may be defined as 120/80 mmHg and this trial involved individuals in the higher half of the prehypertension range. To enter the trial, they had to have repeated blood pressure measurements of 130 to 139 mmHg for systolic and 89 mmHg or lower for diastolic, or a systolic pressure of 139 mmHg or lower and a diastolic pressure of 85 to 89 mmHg.

The study randomised 809 such individuals to receive 16 mg/day of candesartan or placebo for two years, then all patients were switched to placebo for an additional two years. The primary end point of the trial was the development of stage 1 hypertension, which occurred significantly more frequently in the placebo group than in the candesartan group (table 1).

Table 1. TROPHY: risk for hypertension after two years with candesartan versus placebo, followed by two years of placebo versus placebo

Time point	Candesartan	Placebo	Relative risk (95% CI)	P value
At two years	53	154	66.3	<0.001
At four years	208	240	15.6	<0.007

Serious adverse events were similar in the two groups – occurring in 3.5% of candesartan patients and 5.6% of those on placebo, not a significant difference.

Dr Julius concluded that these findings generate a variety of other questions, such as whether results would be better in younger subjects with prehypertension, whether a longer period of treatment or a large degree of blood pressure lowering would give better results, whether the results would be the same with other antihypertensive agents, and whether early treatment of prehypertension will ultimately decrease target organ damage and improve cardiovascular outcomes.

Full results were published online in the *New England Journal of Medicine* on March 14th 2006.

ACC in briefs

● **UNLOAD: ultrafiltration looks good in acute heart failure**

Ultrafiltration of peripheral venous blood removed more fluid and led to significantly fewer rehospitalisations compared to standard diuresis in the UNLOAD study in patients with acute decompensated heart failure.

Chief investigator, Dr Maria Rosa Costanzo (Edward Hospital Center, Naperville, US) said: "Ultrafiltration is more effective than diuretics for removal of excess salt and water, and this strategy is associated with sustained clinical benefits. We believe that the results are immediately applicable to a large proportion of patients that are admitted with decompensated heart failure."

The trial randomised 200 patients to ultrafiltration or standard diuretic therapy. They were evaluated at 48 hours and at 90 days. Fewer patients in the ultrafiltration group required rescue therapy with vasoactive drugs, and the procedure was not associated with hypokalaemia or adverse changes in serum creatinine. In addition, ultrafiltration allowed patients to take lower dosages of oral diuretics after discharge.

● **Ablation better than drugs in paroxysmal AF**

Catheter ablation appears to be superior to drug therapy for the treatment of paroxysmal atrial fibrillation (AF), according to the first head-to-head randomised trial of the two approaches.

In the APAF study, almost 90% of catheter ablation patients were in normal sinus rhythm at nine months. "This suggests it is possible to cure atrial fibrillation," said lead investigator, Dr Carlo Pappone (San Raffaele University Hospital, Milan, Italy).

Dr Pappone noted that until recently, the only option for paroxysmal AF was drug treatment. But he added that antiarrhythmic drugs have an intrinsic limitation due to side effects and the increase in mortality associated with their use.

The APAF trial enrolled 199 patients with paroxysmal AF who were experiencing, on average, three episodes of AF per month and were previously shown to be unable to control their AF with medication. They were randomised to one of three drugs – amiodarone, flecainide or sotalol – or to circumferential pulmonary vein ablation.

Patients underwent daily ECG monitoring by telephone for one year. At the time of the presentation, complete data on 150 patients were available. This showed that 87% of patients were free of AF at nine months compared with 29% of patients treated with antiarrhythmic drug therapy. No serious adverse events were reported, including no reported cases of pulmonary vein stenosis.

● **Waist circumference is better CVD predictor than BMI**

Waist size is an independent risk factor, and a better predictor than body mass index (BMI) for cardiovascular disease (CVD), according to results of the IDEA (International Day for the Evaluation of Abdominal Obesity) study presented at the meeting. "Both were strong predictors," reported lead investigator Professor Steve Haffner, University of Texas, US). "However, the association between waist circumference and CVD was stronger than for BMI."

IDEA included 177,340 patients recruited from 6,000 primary care physicians all over the world but excluding the US. Every adult patient visiting their general practitioner (GP) on selected days had waist circumference, weight and height measured. GPs also recorded the presence of established CVD or risk factors such as smoking status, dyslipidaemia, hypertension and diabetes for each patient.

UK IDEA study leader Jonathan Morrell, a Hastings GP and hospital practitioner in cardiology, said: "Waist circumference measures abdominal obesity, reflecting presence of visceral fat, a major underlying driver of cardiovascular risk. BMI is not a good marker for CVD risk or diabetes in short, squat muscular people."

Results of the UK IDEA study, involving 70 GPs and 1,800 patients, will be presented separately later this year.

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● **Rimonabant improves metabolic profile**

Rimonabant, a weight-loss drug that targets the endocannabinoid system, achieves a 50% greater improvement in metabolic profile than weight loss alone. Pooled one-year data from four phase III clinical trials, which were presented at the meeting, compared the effects of placebo and rimonabant on high-density lipoprotein (HDL) cholesterol, triglycerides, fasting insulin, HbA_{1C} and adiponectin, where patients achieved exactly the same percentage weight loss.

Dr Xavier Pi-Sunyer (Columbia University, New York, US) said: "For any level of weight loss, rimonabant achieved additional improvement in lipid profile over placebo and consistently and significantly reduced HbA_{1C} to a greater extent."

The percentage overall increase in HDL attributable to rimonabant over weight loss alone was 45%, while for adiponectin it was 57%. Rimonabant also caused reductions in triglycerides, fasting insulin and HbA_{1C} of 46%, 49% and 55%, respectively.

An article on rimonabant and the endocannabinoid system appears on pages 113–20 of this issue.

● The first chair in Cardiometabolic Risk has been established at Laval University, Quebec, Canada. Announcing the development at the ACC, Dr Jean-Pierre Despres, the first incumbent, said his faculty would study prevention, assessment and clinical management of cardiometabolic risk factors.

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