

# The British Journal of Diabetes & Vascular Disease

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*British Journal of Diabetes & Vascular Disease* 2007; 7; 142

DOI: 10.1177/14746514070070030801

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# Voodoo medicine – cardiovascular trials jinxed in New Orleans

## Dr Anthony Wierzbicki discusses highlights of the 56th Annual Scientific Session of American College of Cardiology held at Morial Conventions Centre in New Orleans March 24th–27th, 2007

### The heart of New Orleans

New Orleans is famous for its music and its ambience. In popular culture it is also famous for its graveyards, voodoo and recently for its devastation induced by hurricane Katrina. The American College of Cardiology meeting in 2007 was notable for the waves of disappointment that broke over a variety of novel therapies. Trials were presented of antidiuretic hormone therapy in cardiac failure, novel lipid lowering and atherosclerosis-modifying methods and coronary intervention.

### Cardiac failure

The treatment of heart failure is one where new treatments are required as the benefits of increasing inhibition of the renin-angiotensin system have been exhausted in combination therapy trials. Yet other potential avenues for neurohormonal intervention exist. Hyponatraemia is a feature of cardiac failure and recently specific vasopressin antagonists have become available. EVEREST which recruited 4,133 patients was analysed for both short-term and long-term outcomes. The two short-term studies showed improvements in the

primary end point composite end point of global clinical status and in symptoms including dyspnoea and oedema at 24 hours as well as raising sodium levels by 2.87 mmol/L but at the cost of causing dry mouth, thirst and polyuria. However, after 9.9 months average follow-up there was no benefit on all-cause mortality (25.9 vs. 26.3%; RR=0.98 [0.87–1.11];  $p=0.68$ ), cardiovascular death or hospitalisation (42.0 vs. 40.2%; RR=1.04 [0.95–1.14],  $p=0.55$ ).

Trial data were also presented on chronic nesiritide (synthetic recombinant brain natriuretic peptide) therapy in the FUSION-2 trial in 605 patients. There was no difference in mortality, cardiovascular events or cardiorenal events (36.7 vs. 36.8%;  $p=0.79$ ) or days in hospital (72.5 vs. 74.9;  $p=0.09$ ). In another small scale trial nesiritide was shown not to worsen renal function in patients with renal impairment.

### Lowering LDL-C

In the field of lipid-lowering the LDL-C lowering trials were predictable. In the ARMYDA trial pre-treatment with atorvastatin 80 mg 12 hours, then 40 mg immediately prior to intervention

reduced the incidence of peri-procedural events (5% vs. 15%;  $p=0.01$ ) especially myocardial infarction (5% vs. 15%) including post-procedural myocardial enzymes.<sup>1</sup> Further data substantiated the benefits of statin therapy on atherosclerosis even in low risk patients. In a population of 984 patients randomised 2.5:1 to active drug therapy, with initial Framingham algorithm calculated risk < 10%, 40 mg rosuvastatin therapy lowered LDL-C by 2 mmol/L from an initial level of 4.01 mmol/L. This intervention reduced progression of atherosclerosis as measured by maximum CIMT by 0.0014 mm/year compared to a 0.0131 mm/year increase in the placebo group ( $p<0.001$ ).<sup>2</sup>

### Raising HDL-C

There is extensive epidemiological and animal evidence for raising HDL-C.<sup>3,4</sup> Numerous drugs have been developed to raise HDL-C<sup>5</sup> and many agents raise HDL-C as part of their action.<sup>6</sup> Proof for the concept that raising HDL-C would affect rates of atherosclerosis was provided by IVUS of the effects of weekly infusions of a hyper-functional apoA-1<sub>Milano</sub>.<sup>7</sup> However, recombinant HDL

(rHDL) in 183 patients with established coronary heart disease with a LDL-C of 2.11 mmol/L using a similar infusion protocol in the ERASE trial showed borderline benefit (3.41 vs. 1.62%;  $p=0.07$ ) on inter-group IVUS analysis indicating either a different protocol or different doses were required. It was interesting that in contrast to the ETC-216 study, high dose rHDL induced transaminitis in 50% of patients when added to underlying statin therapy and had to be discontinued.

Fibrates showed benefits with the gemfibrozil trials in a general population and in secondary prevention with low HDL-C.<sup>8</sup> However, in the FIELD study fenofibrate reduced cardiovascular events in some unexpected groups in a very confusing study showing little benefit on HDL-C.<sup>8,9</sup> Yet there is still interest in more selective peroxisomal proliferators activating receptor alpha (PPAR- $\alpha$ ) agonists and results of phase 2 trial with LY518674 have been announced. It was approximately equivalent to fenofibrate in raising HDL-C (15.8–2.1% vs. 14.4%) but with a decline at higher doses (100  $\mu$ g) and was superior in reducing LDL-C (19.5% vs. 2.3%). It had a

**Abbreviations**

AGI	Agilent Technologies
ApoA-1	Apolipoprotein A-1
CETP	cholesteryl ester transfer protein
CIMT	carotid intima media thickening
ETC	Esperion Therapeutics Compound
HDL-C	high density lipoprotein-cholesterol
LDL-C	low density lipoprotein-cholesterol
PCI	percutaneous intervention
rHDL	recombinant HDL

**Acronyms**

ARISE	Aggressive Reduction of Inflammation Stops Events trial
ARMYDA	Atorvastatin for Reduction of MYocardial Damage during Angioplasty trial
COURAGE	Clinical Outcomes Utilizing Revascularisation and Aggressive Drug Evaluation trial
ERASE	Effect of Reconstituted high-density lipoprotein on Atherosclerosis-Safety and Efficacy trial
EVEREST	The Efficacy of Vasopressin antagonism in heart failure outcome Study with Tolvaptan Heart Attack Trial
FIELD	Fenofibrate Intervention in End point Lowering in Diabetes study
FUSION-2	Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure trial
ILLUMINATE	Investigation of Lipid Level management to Understand its IMpact IN Atherosclerotic Events study
ILLUSTRATE	Investigation of Lipid Level management Using coronary ultrasound. To assess Reduction of Atherosclerosis by CETP inhibition and HDL Elevation trial
IVUS	Intravascular ultrasound study
RADIANCE 1	Rating Atherosclerotic Disease by Imaging with A New CETP Inhibitor study
RITA-2	The Second Randomised Intervention Treatment of Angina study

similar effect in raising creatinine but differed in not raising creatine kinase, which has been an issue with highly specific PPAR- $\alpha$  agonists.<sup>5</sup>

However, none of the current HDL-C raising agents increase levels by more than 25%.<sup>10</sup> Animal experiments suggested that inhibition of CETP would reduce progression of atherosclerosis. Data on the relationship between CETP deficiency and coronary events in man were more controversial.<sup>11</sup> Torcetrapib raised HDL-C levels by 70%, though early studies did not show the characteristic rise

in faecal sterol excretion seen with other lipid-lowering therapies. The results were sufficiently encouraging for both surrogate marker and endpoint studies to be commenced. Unfortunately the ILLUMINATE study of 15,000 secondary prevention patients was discontinued after one year due to a 30% excess of cardiovascular deaths (82 vs. 51) in the torcetrapib arm. The surrogate marker studies were also disappointing. In the ILLUSTRATE trial with intravascular ultrasound torcetrapib raised HDL-C by 61% and reduced LDL-C by

20% but had no significant effect on atheroma volume. It was notable in this 2-year study of 1,188 patients that torcetrapib therapy was associated, as usual with hypertensive changes (4.6/2.0 mmHg). A blood pressure rise of > 15 mmHg was recorded in 6% of patients. An increase was seen in rates of acute coronary syndromes (8.0% vs. 5.7%) and revascularisation (19.3% vs. 15.9%) suggesting that torcetrapib may be having adverse effects on plaque stability. Similarly in the RADIANCE 1 study of torcetrapib on CIMT in 850 patients with familial hypercholesterolaemia on top of 56.5 mg atorvastatin raised HDL-C by 51.9% and reduced LDL-C by 20.6% yet CIMT increased by a non-significant 0.0047 mm/year. Results of the RADIANCE 2 study in 2,918 patients with mixed hyperlipidaemia (triglycerides 1.75–5.65 mmol/L) on a baseline of 13.5 mg atorvastatin were similar as torcetrapib therapy raised HDL-C by 63.4% and reduced LDL-C by 17.7% but CIMT increased by 0.0049 mm/year.

**Vascular protectants**

Another area of interest has been the concept of vascular protectants. These are drugs that uncouple the inflammation pathway and thus reduce atherosclerosis. The first of these to reach large scale trials is AGI-1067, which turns out to be related to the old lipid drug probucol. Probuco showed some success in preventing atherosclerosis in arteries subject to intervention as does AGI-

1067.<sup>12,13</sup> The ARISE trial recruited 6,144 patients with prior acute coronary syndromes on optimal background therapies including a HDL-C of 1.2 mmol/L and LDL-C of 2.2 mmol/L. The primary end point of the study was combined cardiovascular events and repeat intervention. AGI-1067 had little effect on the primary end point (17.3% vs. 17.2%;  $p=0.99$ ). However, in the secondary end points of the primary end point, excluding PCI, were reduced non-significantly (293 vs. 334;  $p=0.09$ ) and further excluding unstable angina i.e. hard cardiovascular events were significantly reduced (207 vs. 232;  $p=0.03$ ). The lipid effects of AGI-1067 were a 0.25 mmol/L increase in LDL-C and a 0.13 mmol/L decrease in HDL-C. Unexpectedly, AGI-1067 therapy was associated with a decrease in the incidence of diabetes (34 (1.6%) vs. 82 (4.2%);  $p<0.001$ ) and HbA<sub>1c</sub> was decreased by 0.4%.

RITA-2 study suggested that though PCI would not improve hard cardiovascular events it would result in symptomatic benefit in patients with stable angina.<sup>14,15</sup> The COURAGE trial randomised 2,287 patients with angina either to PCI plus optimal medical therapy or to optimal medical therapy alone.<sup>16</sup> Over a follow-up period of a median 4.6 years, rates of all-cause death or non-fatal myocardial infarction were similar in both groups (19% vs. 18.7%;  $p=0.62$ ). The only significant difference between the 2 treatment strategies was a reduced prevalence of angina in the PCI group at one and



### Key messages

- Intervention with vasopressin analogues not beneficial in heart failure
- Raising HDL-C by inhibiting CETP does not prevent progression of atherosclerosis
- Vascular protectants have little effect on cardiovascular outcomes
- Medical therapy is as good as angioplasty in preventing symptomatic angina

three years, again as reported in the 7-year data from RITA-2.<sup>14,17</sup> However, by five years in COURAGE there was no significant difference in freedom from angina, with 73% of both groups reporting no angina at five years. It is estimated that 30–40% of stable CHD patients are treated with PCI, so if the COURAGE – results are implemented in clinical practice most of these patients could now only be treated with drugs with expected substantial health care savings.

### In conclusion

Just as the oldest sections of New Orleans (French Quarter and the Garden District) survived the hurricane test, the lessons of the American College of Cardiology were

that old ideas were best and that novelty had little to offer.

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*Br J Diabetes Vasc Dis*

2007; **7**:142–4