Risk Reduction Beyond the Boundaries of Current Practice

Satellite Symposium
of the
Canadian Cardiovascular Congress 2003

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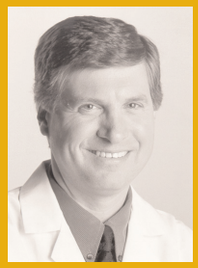

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At this Satellite Symposium, leading experts discussed the most recent prevention and treatment advances, as well as patient care alternatives, for dyslipidemia and cardiovascular disease. Current trial data and new disease management guidelines were explored.

Victor Huckell, MD, Clinical Professor of Medicine, University of British Columbia, Vancouver, chaired the session. He verified that the goal was accomplished of addressing the continuum of cardiovascular disease, beginning with identification of risk factors and progressing to:

- **atherosclerosis**
- **left ventricular hypertrophy**
- **coronary artery disease**
- **heart failure**
- **end-stage microvascular heart disease**
- **and finally, death.**

Overview of New Canadian Dyslipidemia Guidelines

Jacques Genest, MD, Professor of Medicine McGill University, and Director, Division of Cardiology, Royal Victoria Hospital, Montreal, is a co-author of the *Recommendations for the Management of Dyslipidemia and the Prevention of Cardiovascular Disease: 2003 update* (1).

The guidelines are simplified and include three levels of risk of coronary artery disease (CAD) and two treatment targets (Table 1).

Dr Genest noted, topics addressed in the revised guidelines include the management of patients at high risk of CAD who have a low-density lipoprotein cholesterol (LDL-C) level at target (2.5 mmol/L) and the management of patients who have combined dyslipidemia and low high-density lipoprotein cholesterol (HDL-C) levels. The guidelines also describe the optimal noninvasive assessment of cardiovascular disease and other risk factors, including the metabolic syndrome and levels of apoliprotein B, lipoprotein(a), homocysteine and C-reactive protein.

Diet and exercise are still considered to be of prime importance in both primary and secondary prevention of heart disease. The new recommendations call for increasing fruit and vegetable intake, as well as the proportion of mono- and

Table 1

Risk Categories and Target Lipid Levels

Risk Category	LDL-C Level, mmol/L	Total Cholesterol:HDL-C Ratio
High* (10-year risk of coronary artery disease ≥ 20%, or history of diabetes mellitus† or any atherosclerotic disease)	<2.5 *and*	< 4
Moderate (10-year risk 11%-19%)	< 3.5 *and*	< 5
Low‡ (10-year risk ≤ 10%)	< 4.5 *and*	< 6

*Note: LDL-C = low-density lipoprotein cholesterol.*Apolipoprotein B can be used as an alternative measurement, particularly for follow-up of patients treated with statins. An optimal level of apoliprotein B in a patient at high risk is < 0.9 g/L, in a patient at moderate risk < 1.05 g/L and in a patient at low risk < 1.2 g/L. †Includes patients with chronic kidney disease and those undergoing long-term dialysis. ‡In the "very low" risk stratum, treatment may be deferred if the 10-year estimate of cardiovascular disease is < 5% and the LDL-C level is < 5.0 mmol/L.*

polyunsaturated fats in the diet. Concurrently, saturated fats and trans-fatty acids should be decreased to < 7% of total calories. The guidelines also suggest body mass index should be < 25 kg/m^2.

If a patient crosses a threshold of a 20% 10-year CAD risk, medical therapies should be instituted concurrently with lifestyle modification, said Dr Genest. The new guidelines list six statins, two bile-acid-binding resins, one cholesterol absorption inhibitor, three fibrates and niacin as the currently used lipid-lowering medications. The priority for treatment is reduction of the LDL-C level to < 2.5 mmol/L and the total cholesterol (TC):HDL-C ratio to < 4.0.

"My preference is robust monotherapy with a statin, not because it can raise HDL but because it can truly lower LDL very satisfactorily, and I can reduce the cholesterol-to-HDL ratio." concluded Dr Genest. "We have taken the TG out of the guidelines because the data suggest that once you've removed the small LDL particles, the remaining V[very]LDL particles are not that atherogenic," he added.

The guidelines also stipulate men 40 years of age or older should be screened, as should women who are postmenopausal or over 50 years of age. Indicators for screening are diabetes mellitus; presence of risk factors such as hypertension, smoking or abdominal obesity; a strong family history of premature cardiovascular disease; manifestations of hyperlipidemia; or evidence of symptomatic or asymptomatic atherosclerosis. The guidelines also recommend the calculation of 10-year risk of CAD in patients without diabetes or clinically evident cardiovascular disease – using data from the Framingham Heart Study – should be based on age, TC level, whether the person smokes tobacco, HDL-C level and degree of treatment of hypertension.

STELLAR – Head-to-Head Comparison of Effects of Statins on Lipids

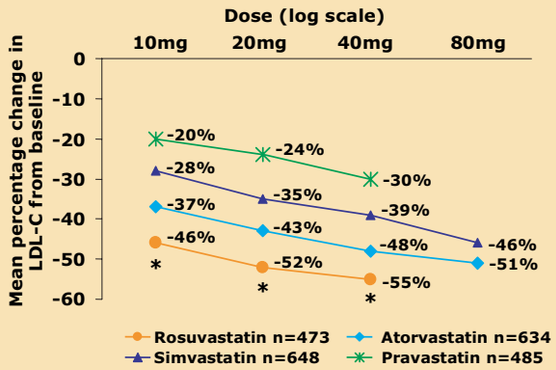
The results of this landmark trial were summarized by Michael Davidson, MD, Director, Preventive Cardiology Center, and Associate Professor of Medicine, Rush University Medical Center, Chicago, Illinois.

"I am very pleased to present the STELLAR trial on behalf of my fellow investigators in the United States," said Dr Davidson in prefacing his remarks. "It was the largest comparative trial of statins across the dose range."

STELLAR (Statin Therapies for Elevated Lipid Levels compared Across Doses to Rosuvastatin) was a six-week, open-label study comparing 10 mg, 20 mg and 40 mg rosuvastatin to 10 mg, 20 mg , 40 mg and 80 mg atorvastatin, 10 mg, 20 mg and 40 mg pravastatin and 10 mg, 20 mg, 40 mg and 80 mg simvastatin (2). The 2431 subjects were adults with hypercholesterolemia (LDL cholesterol ≥ 160 and < 250 mg/dL) and triglyceride (TG) levels of < 400 mg/dL. They discontinued all of their cholesterol-lowering medications and dietary supplements at study entry and participated in a dietary lead in period of six weeks.

Figure 1

LDL-C: Percentage Change from Baseline at Week 6



*p<0.002 RSV 10mg vs ATV 10mg, SIM 10, 20 & 40mg, PRA 10, 20 & 40mg; RSV 20mg vs ATV 20 & 40mg, SIM 20, 40 & 80mg, PRA 20 & 40mg; RSV 40mg vs ATV 40mg, SIM 40 & 80mg, PRA 40mg

Over the entire dose range, rosuvastatin provided an additional 8.2% reduction in LDL-C compared with atorvastatin (P<0.001) at Week 6, an additional 12-18% reduction compared with simvastatin and an extra 26% reduction over pravastatin. Figure 1 demonstrates the LDL-C reductions with rosuvastatin compared with those of the other medications.

"Ten milligrams of Crestor (rosuvastatin) is significantly better than 10 mg of atorvastatin, all the doses of simvastatin up to 40 mg and all the doses of pravastatin," commented Dr Davidson. "And looking at the 20 and 40 mg doses of Crestor, they are significantly better than 20 or 40 mg of atorvastatin, better than all the doses of simvastatin up to 80 mg, and also better than the 20 and 40 mg doses of pravastatin."

Dr Davidson also noted rosuvastatin produced significantly greater elevations of HDL-C than its comparators in the STELLAR trial. For example, increasing doses of atorvastatin were associated with a decline in increase of HDL levels, while the elevation of HDL with rosuvastatin continued at the highest doses. Moreover, the reductions in TG levels associated with rosuvastatin also were greater than with simvastatin or pravastatin, and comparable to those with atorvastatin. Dr Davidson added that rosuvastatin reduced both non-HDL-C levels and the ratio of apolipoprotein B to apolipoprotein A-1 more than did any of its comparators.

Eight of 10 patients taking 10 mg rosuvastatin also reached the 2000 Canadian and NCEP (National Cholesterol Education Program) Adult Treatment Panel (ATP) III goals for LDL-C reduction.

The trial treatments were well tolerated. The percentages of patients who reported adverse events were similar among groups. The percentages of patients who withdrew from treatment because of adverse events were also similar among the groups.

"So the results indicate Crestor achieves impressive LDL reductions, of about 50% at the 10 mg dose, approximately 55% at the 20 mg dose and of approximately 60% at the 40 mg dose," concluded Dr Davidson. "I think the medication

provides us with another efficacious statin to help achieve our very ambitious new goals for reduction of both LDL and the TC-to-HDL-C ratio."

CHARM – Multi-pronged Examination of Candesartan in Heart Failure

Salim Yusuf, DPhil, Director of McMaster University's Division of Cardiology, Hamilton, Ontario, was one of the lead investigators in the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) trials. He provided attendees with highlights and updates from this recently published series of studies.

The CHARM program (3-5) was a set of three independent but coordinated double-blind, placebo-controlled clinical trials including more that 7600 patients with New York Heart Association Class II to IV heart failure (HF). Each study examined a distinct patient group. The primary objective was to assess the effect of candesartan ≤ 32 mg once/day on the risk of cardiovascular (CV) death or hospitalization for management of HF. The primary outcome of the overall program was all-cause mortality.

The CHARM program incorporated three trials comparing candesartan with placebo in patients with symptomatic heart failure. CHARM-Alternative involved 2028 patients with a left ventricular ejection fraction (LVEF) of ≤ 40 who were intolerant to angiotensin converting enzyme (ACE) inhibitors (3). In CHARM-Added, 2548 patients were enrolled who had an LVEF of ≤ 40 and were being actively treated with an ACE inhibitor (4). CHARM-Preserved involved 3023 patients with an LVEF of > 40% who were either being treated or not treated with an ACE inhibitor (5).

CHARM-Alternative

Figure 2 shows the results of the CHARM-Alternative study (3). After 34 months of follow-up, candesartan use resulted in a highly statistically significant 23% relative risk reduction (RRR; P=0.004) in the composite primary endpoint of CV death or hospitalization.

"The risk reductions of CV death or hospitalization for chronic heart failure were highly, highly significant. So there's no doubt that if you can't use an ACE inhibitor, certainly do use an angiotensin receptor blocker (ARB)," commented Dr Yusuf.

CHARM - Added

The significant advantage conferred by candesartan was corroborated by the results of CHARM-Added, which had a median follow-up of 41 months (Figure 3). Candesartan administration resulted in a 15% reduction in the relative risk reduction (RRR) of CV death/HF hospitalization (P=0.011) (4).

Furthermore, the proportion patients hospitalized was 30% in placebo patients and 25% in those taking candesartan, while more than 800 placebo subjects were hospitalized compared with 600 among those taking candesartan (both P<0.001). Dr Yusuf noted the results were similar among both patients who were or were not taking an optimal dose of an ACE inhibitor.

He concluded by noting that, just as in cancer therapy, a number of medications in several courses appear to be necessary in heart failure risk reduction.

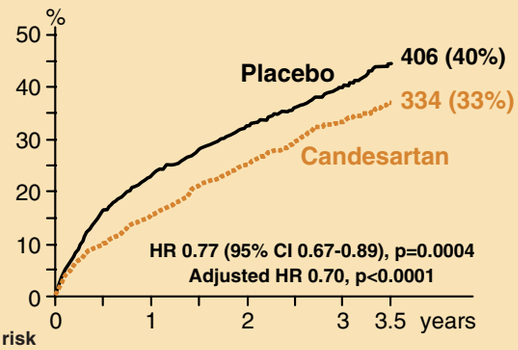
The latest information from CHARM-Added also indicates that clinicians can consider double or even triple therapy - with a beta-blocker, ACE inhibitor and an ARB – in patients who have NYHA Class III or IV heart failure. With careful monitoring, physicians can thus help their patients preserve heart function and quality of life.

CHARM-Preserved

The results of the CHARM-Preserved study also demonstrated a lower rate of CV death or chronic heart failure (CHF) hospitalization among candesartan subjects, although the difference was not statistically significant (P=0.051). Furthermore, 40% fewer patients taking candesartan were diagnosed as having new onset diabetes than in the placebo patients (P=0.005).

Figure 2

CHARM-Alternative: CV Death or CHF Hospitalization

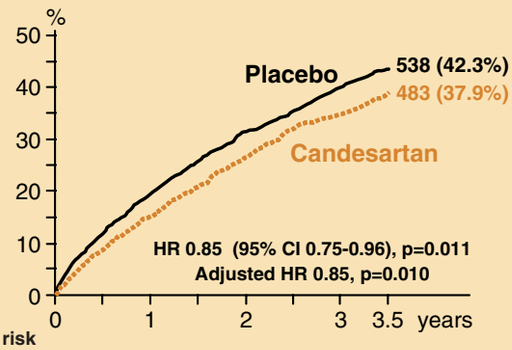


Number at risk					
Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

CHARM ESC Hotline 030824-3

Figure 3

CHARM-Added: CV Death or CHF Hospitalization



Number at risk					
Candesartan	1276	1176	1063	948	457
Placebo	1272	1136	1013	906	422

CHARM ESC Hotline 030824-3

At the end of 37 months, 366 individuals in the placebo group (24.3%) and 333 (22%) of the candesartan-treated patients experienced the primary endpoint of CV death or hospitalization for HF (5). Although the two groups did not differ in terms of mortality, candesartan treatment resulted in a statistically significant decrease in the number of hospitalizations for HF management (402 vs 566, P=0.014).

"But we recently discovered that the method of randomization led to a large imbalance in the trial with respect to level of morbidity of patients in each arm," said Dr Yusuf. "So we performed a retrospectively stratified analysis and found a 14% risk reduction with candesartan, which is very close to the CHARM-Added result of 15%."

Summary and Conclusions

Attendees of the Satellite Symposium received a comprehensive view from leading experts on the latest trials and clinical guidelines for patients with dyslipidemia and cardiovascular disease. Furthermore, the experts outlined the key objectives in stratifying patients based on their risk factors and treating them accordingly. For example, in the new Canadian guidelines, placement of patients in one of three levels of risk of coronary artery disease guides their management towards lipid-level targets.

Results from the latest CV clinical trials offer physicians and patients valuable options in treatment of this condition and point to optimal approaches for reducing CV mortality and morbidity.

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