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LMC

LIPID MANAGEMENT-

FOR PREVENTION OF CARDIOVASCULAR EVENTS: RECENT TRIALS AND NEW APPROACHES

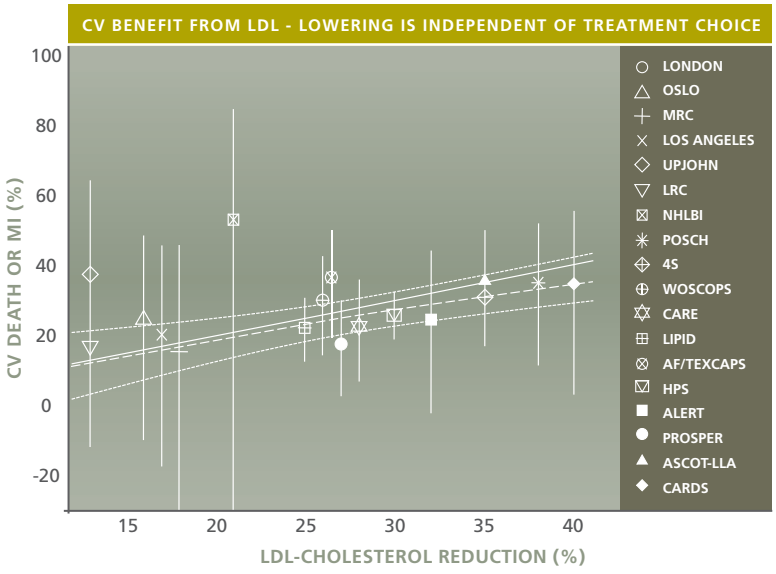
Robert Schlosser
MD, FRCPC

Cardiovascular (CV) disease is still the leading cause of death, particularly in patients with Diabetes and/or Metabolic Syndrome. Fortunately, both the incidence and mortality related to CV disease are declining due to factors such as lower smoking rates and CV prevention strategies, especially lipid-lowering therapies.

The 2008 CDA Guidelines reiterate that the primary target for diabetic patients at high risk (men > 45 years, women > 50 years, or younger patients with additional risk factors) is an LDL-cholesterol (LDL) < 2.0 mmol/L. For patients not at target on first-line statin therapy, combination therapy may play an important role in reaching target. Statins combined with each of Ezetimibe, fibrates or Niacin have been well-studied for safety and lipid outcomes with larger endpoint trials under way: IMPROVE-IT (Ezetimibe), ACCORD (fenofibrate), and AIM HIGH (extended-release Niacin).

To date, studies of a variety of LDL-lowering approaches have found a remarkably consistent and linear relationship between LDL reduction and CV risk reduction. A meta-regression analysis of 19 lipid lowering trials found that CV risk reduction is linearly related in an almost 1:1 ratio to the percent LDL reduction from baseline, irrespective of the method of cholesterol reduction (Figure 1). Therefore, it would seem prudent to achieve at least a 40 to 50% reduction from baseline LDL levels (in addition to an absolute goal LDL of < 2 mmol/L) in patients at high risk for CV events.

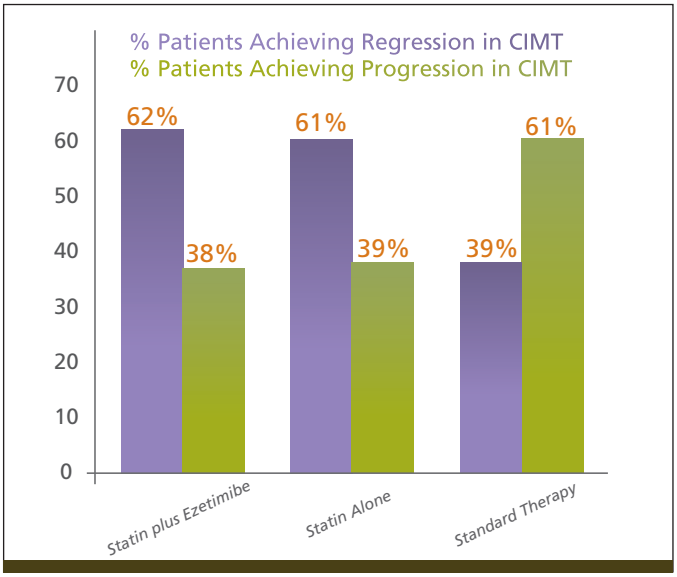
FIGURE 1



SANDS Trial

The Stop Atherosclerosis in Native Diabetic Study (SANDS trial) recently evaluated the effect of lower BP and LDL targets on carotid atherosclerosis in 499 diabetic American Indian patients. The aggressively-treated group targeted LDL < 1.8 mmol/L vs < 2.6 mmol/L in the standard group. Their BP goals were < 115/75 vs < 130/80 in the standard group. Baseline therapies were ACE-inhibitor/ARB and statins, with other therapies added by algorithm.

FIGURE 2 SANDS RESULTS:



At 3 years, the aggressively-treated group showed regression in carotid intima-media thickness (CIMT) (-0.012mm) vs progression (0.038mm) in the standard group. There were too few clinical CV events to assess differences between groups.

> "For a surrogate marker such as CIMT, there was identical clinical benefit, for similar absolute LDL reductions, in the combination Ezetimibe-plus-statin treated-patients as in the statin-alone patients."

A follow-up analysis compared "statins-plus-Ezetimibe" effect vs "statins-alone" in this population. In the aggressively-treated group, the Ezetimibe-treated patients had slightly higher baseline LDL (2.81 vs 2.63 mmol/l) and at 36 months (2.03 vs 1.77 mmol/l). Despite these higher starting and ending points, the CIMT regression in the aggressively-treated subjects were similar in both "statin-plus-Ezetimibe" patients vs "statin-alone".

For a surrogate marker such as CIMT, there was identical clinical benefit, for similar absolute LDL reductions, (0.8 mmol/L) in the combination Ezetimibe-plus-statin treated-patients as in the statin-alone patients.

JUPITER Study

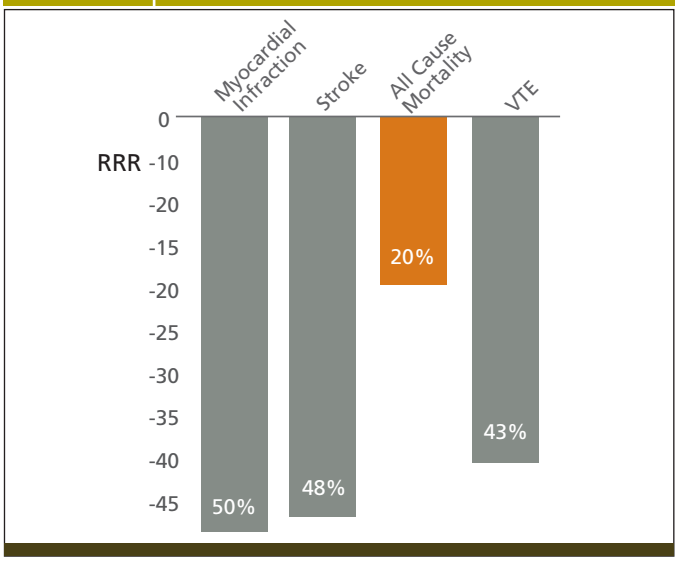
Nearly half of all CV events occur in patients with normal or low LDL. Inflammation is a known critical process in plaque formation and especially, in plaque rupture. Of the many markers of endovascular inflammation, high-sensitivity C-reactive protein (hs-CRP) has gained acceptance as a predictive biomarker of CV risk with clear evidence that lipid-lowering agents (both statins and Ezetimibe) lower CRP, in addition to lowering LDL.

> "designed to test the hypothesis of whether statin therapy decreases the rate of a first major CV event, in patients with low to normal LDL levels and elevated hs-CRP."

In re-examining the landmark 1° prevention study AFCAPS/TEXCAPS (Lovastatin vs placebo), patients with low LDL (<3.88 mmol/L) but high hs-CRP (greater than 1.6 mg/L) had the same CV benefit as patients with high LDL. Even in these healthy patients with low LDL, the "number needed to treat" (NNT) was only 33-58.

This post-hoc analysis led to a large prospective randomized trial, designed to test the hypothesis of whether statin therapy decreases the rate of a first major CV event, in patients with low to normal LDL levels and elevated hs-CRP. The JUPITER study (Justification for the Use of statins in Primary prevention: an InTERvention trial), evaluated Rosuvastatin in healthy

FIGURE 3 JUPITER: SUMMARY OF RESULTS TO DATE



men >50 and women >60 with hs-CRP > 2.0 mg/L but LDL <3.4 mmol/L. In these 17,802 patients, Rosuvastatin 20mg decreased LDL by 50% (to 1.4 mmol/l) and hs-CRP by 37% (to 2.2 mg/l) vs placebo. In 2008, the trial was stopped early (median follow-up 1.9 years) because of unequivocal benefit in the patients treated with Rosuvastatin.

> "In low- to moderate-risk patients, it may be reasonable to test hs-CRP and treat if this value is greater than 2.0 mg/l based on the JUPITER study."

The primary outcome was reduced by 44% (p<0.00001), producing a NNT of 95 over 2 years. Projected out to 5 years of therapy, the NNT is only 25. In addition, MI was reduced by 48%, stroke incidence by 50% and total mortality by 20%. Recently, DVT has even been reported to have been reduced by 43%.

All sub-groups benefited similarly, including men and women, as well as those with and without features of Metabolic Syndrome. Mild muscle complaints occurred in 16% of Rosuvastatin patients and in 15.4% of placebo-treated patients, with no serious MSK issues. One case of rhabdomyolysis occurred after the trial was stopped.

Nearly half of the patients in JUPITER who benefitted had a Framingham risk score < 10% (low risk). The Reynolds risk score (www.reynoldsriskscore.org) includes family history and CRP results and so may offer better 10-year risk prediction than Framingham. It remains to be seen how the Canadian guidelines will deal with the results of JUPITER. Clearly, the benefit of statin therapy extends to lower LDL levels than previously thought. A suggested approach would be to continue aggressive treatment of high-risk patients since these patients do not require hs-CRP testing to trigger the decision to treat with a statin. In low- to moderate-risk patients, it may be reasonable to test hs-CRP and treat if this value is greater than 2.0 mg/l based on the JUPITER study.

CRP: A Marker or a Target?

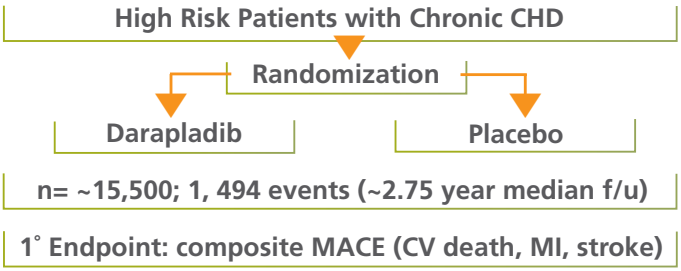
In JUPITER, CRP > 2 mg/L was a key entry criteria. Should CRP be used as a target as well? Unfortunately, no treat-to-target CRP trial exists to answer this question. Although high CRP is epidemiologically linked to high CVD prevalence, many similarly associated markers which have failed to show benefit of targeted lowering (eg homocysteine). In addition, other therapies (TZDs and COX-2 inhibitors) significantly lower CRP but have not been shown to provide CV benefit. A recent evaluation of CRP polymorphisms found that some very marked CRP elevations were unconnected to CVD risk. Clearly, the jury is still out as to whether CRP is a cause of CVD or simply an inflammatory marker.

> "Will chronic PLA2 inhibition with Darapladib stabilize high risk lesions and reduce CV events? The question is being addressed in the STABILITY trial. 15,500 patients with established CVD, plus at least one other risk factor…"

Lipoprotein-Associated Phospholipase A-2 (PLA2)

On entering a plaque, LDL becomes oxidized and the phospholipid portions are hydrolyzed by the enzyme PLA2 to oxidize free fatty acids. These are taken up by macrophages, yielding foam cells and ultimately, atherosclerotic plaques. Rupture-prone, and ruptured, plaques stain intensely for PLA2 leading to the hypothesis that this enzyme is related to plaque instability. PLA2 levels and activity have been associated with increased CV risk in various studies, including WOSCOPS. Although statins reduce PLA2 activity, specific inhibitors of this enzyme are being investigated to potentially decrease CV event rates.

FIGURE 4 STABILITY TRIAL: STUDY DESIGN



The selective PLA2 inhibitor Darapladib, at a daily dose of 160mg, added to Atorvastatin, inhibited PLA2 activity by 66% (and lowering CRP by 13%). The IBIS 2 study has already demonstrated that Darapladib was associated with a shift in plaque content over a 2 year exposure period – from fatty, vulnerable plaque to mature, fibrous plaque. Will chronic PLA2 inhibition with Darapladib stabilize high risk lesions and reduce CV events? The question is being addressed in the STABILITY trial. 15,500 patients with established CVD, plus at least one other risk factor will be treated with Darapladib vs placebo, and followed for ~ 3.5 years. Canadian cardiology sites and our LMC Endocrinology sites will be major contributors to this landmark trial, now underway for 4 months.

Getting Enough Omega 3

Choose High Omega-3, Low-Mercury Fish
(<0.2ppm)

- Salmon
- Mackerel
- Herring
- Sardines
- Oysters
- Shrimp
- Pollack
- Anchovy
- Rainbow Trout

Limit Higher-Mercury Fish
(>0.2ppm)

- Albacore Tuna
- Lake Trout
- Halibut
- Shark
- Escolar
- Orange Roughy
- Swordfish
- Marlin

Foods rich in omega-3, and omega-3 supplements, rank at the top of the "most healthy nutrient" list.

Omega-3 has beneficial effects in the prevention and treatment of heart disease, inflammation, and macular degeneration. There are three kinds: ALA, EPA and DHA.

ALA is an essential fat and is found in plant sources of omega-3. Through an inefficient process, the body can make its own EPA and DHA so these are not considered essential.

EPA and DHA are specifically linked to improvements in brain function, and to brain and eye development in children. Both fats are readily absorbed from the animal sources of these nutrients.

How much do we need?

Omega-3 is highest in fish, particularly mackerel and salmon, and to some degree, in omega-3 enriched eggs, enriched dairy, fortified grains, and vegetable sources. It is also best absorbed when eaten in the form of fish, rather than through a supplement or via the ALA in vegetable sources.

To meet the AHA heart-healthy recommended daily intake of 1.5g ALA and 4g DHA/EPA, we would need to eat 6 omega-3 enriched eggs (ALA) and 5 oz of salmon daily. Currently, Health Canada recommends at least 5oz of fish weekly. At higher levels, absorption of the neurotoxin methyl mercury from fish becomes a concern.

Victoria Tully
MSc, RD

Methyl Mercury and Fish Consumption

Advise patients to choose fish with the highest amounts of omega-3 and the lowest levels of mercury. The average Canadian should limit the consumption of higher-mercury fish to no more than 5oz/week. Pregnant women should limit higher-mercury fish to 5oz/month. Children and toddlers should limit higher-mercury fish to 2.5-4oz/month.

Bottom Line

Encourage your patients to eat more fish, achieving at least 2 servings a week through fish sandwiches, canned fish on salads, or fish entrees. Eating more than 2 servings a week is safe and encouraged, as long as the higher-mercury fish are avoided. Foods high in ALA-omega 3, such as walnuts, flax meal, canola oil and omega-3 enriched/fortified products contribute, but probably don't provide enough, omega-3 for conversion to EPA/DHA. If not enough fish is being consumed, then a 500mg/day supplement of omega-3 (not omega-6/9, not cod liver oil) is warranted. Vegetarians can use algal oil supplements, which is a plant-derived source of DHA.

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