Targeting Better Lipid Control —Combination Therapy

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The importance of statin therapy in reducing cardiovascular (CV) risk in post myocardial infarction patients is well established. Now, both secondary prevention and primary prevention studies—randomized clinical trials (RCT)—have shown that aggressive lipid-lowering with statins decreases CV morbidity and mortality. Results of more recent RCTs suggest even greater benefits (30% CV risk reduction) for patients with LDL-C levels well below 100mg/dL. NCEP and the American Diabetic Association (ADA) continue to focus on LDL-C control as the primary target of therapy and are moving toward endorsement of an LDL-C goal of ≤ 70mg/dL.

"The lower the LDL-C the lower the CAD risk", is the accepted mantra. Statins lower LDL-C and CAD risk (30%) better than any other drug. But the story isn't really over. *What about the other 70%?* This *Heartbeat* will explain why we should be looking at global vascular risk and other lipid parameters to better determine when a patient should be on a statin and when they may need other drugs. A case will be made for the importance and safety of combination therapy to treat the multiple components of dyslipidemia just as we use combination therapy for diabetes and hypertension.

Treat Vascular Disease Risk, Not Cholesterol

Professor Rory Collins, the lead investigator of the Heart Protection Study, says that we should treat vascular risk regardless of cholesterol. In Collin's view, cholesterol lowering should be prescribed based on the patient's estimated risk for heart attack, stroke and revascularization—not just heart attack risk. Patients who are at higher CV risk for any reason—whether they have CV disease, diabetes, metabolic syndrome (MetS), tobacco dependence, or hypertension—putting them at risk for vascular disease—should be considered for lipid-lowering therapy. Clinical data have proven that using an effective and safe regimen to lower LDL-C is one way to lower risk substantially, irrespective of starting LDL-C levels, age, sex or other treatments. This philosophy fits with NCEP ATP III Guidelines for risk identification. Treatment is beneficial regardless of baseline lipid levels. But treatment goals are needed to maximize this benefit. How much treatment is enough? The NCEP ATP III Guidelines, using LDL-C and non-HDL-C as goals, provides a plan. This is also why the guidelines want you to treat higher risk patients (like diabetics) who already have an LDL-C at goal. These patients, despite a *normal* LDL-C, have increased atherogenic lipoproteins.

Parameters

Statin monotherapy may not be sufficient to reach serum LDL-C targets in many patients, especially those with combined lipid abnormalities. LDL-C goal, NCEP's primary surrogate for the atherogenic beta-lipoproteins (ApoB)—because of cost and reliability of measurement considerations—continues to become lower and lower (< 70mg/dL) in very high-risk situations. This necessitates higher statin doses, usage of more potent statins, and/or a combination of medical treatments (statin plus ezetimibe or colesevelam) to achieve these goals.

Elevated non-high-density lipoprotein cholesterol (non-HDL-C)–NCEP's secondary surrogate goal—has frequently been shown to have a greater predictive value for CV risk (ApoB levels) than LDL-C, especially in those with abnormalities of the triglyceride (TG)/ high density lipoprotein (HDL) axis. Many patients fall into this category and the count is rising, including diabetics and those with MetS or insulin resistance, who are at very high CV risk but have LDL-C levels that aren't usually very high. Most experts feel that adding other medications (fenofibrates or niacin) to low dose statins might be more beneficial in these situations because they are more effective in decreasing TG or elevating HDL-C, even though we don't have specific treatment goals for these lipids. (NCEP states that risk begins with TG > 150mg/dL and high-risk > 200mg/dL. NCEP states an HDL-C < 40mg/dL is associated with high-

risk. The NCEP goal of therapy for a TG between 200 to 500mg/dL is to normalize LDL-C and non-HDL-C. There is no TG goal of therapy if baseline is 200 to 500mg/dL. There is no specific NCEP HDL-C goal of therapy. Suggested targets are LDL-C and non-HDL-C.)

Non-HDL-C (Total cholesterol [TC] minus the HDL-C) should be calculated anytime TG is > 200mg/dL. The non-HDL-C goal, which is 30mg/dL higher than the LDL-C goal, obviously continues to be lowered as the LDL-C is lowered. High non-HDL-C can alert the physician that a person is high-risk despite a "normal" LDL-C level. The underlying concept here is that LDL-C is an inaccurate index of LDL particle number when small, dense LDL-C and other atherogenic particles containing ApoB are present—when non-HDL-C is high. When TG is elevated, non-HDL-C is a much better surrogate of the all important apoB level, than is LDL-C. Dr Thomas Dayspring believes that non-HDL-C is a better surrogate of apoB than is LDL-C at any TG > 70mg/dL (for sure when TG is > 100 to 130mg/dL). By the time TG is > 200mg/dL, most people are drowning in apoB particles. Unfortunately, this surrogate, too, is frequently insufficient, as many on the fringes will be missed. Dr Dayspring comments, "You would be amazed at how many small LDL particles can exist in patients with very nice LDL-C and non-HDL-C."

This is where advanced lipoprotein analysis can be helpful. Nuclear magnetic resonance spectroscopy (NMR Lipoprofile) from LipoScience (www.lipoprofile.com) directly measures the lipoprotein particles responsible for CAD. Both LDL particle concentration (LDL-P) and size are listed by NCEP as emerging risk factors. We need to know them to truly estimate risk. This data enhances the clinical management of CAD risk by identifying patients whose risk is higher or lower than that assessed by routine LDL-C and non-HDL-C testing. Treatment of at risk patients can be improved by directing therapy to reduce overall numbers of LDL particles and small LDL particles, the primary agents of atherosclerosis–the lipoproteins that enter the vascular wall (refer back to Heartbeat 99).

Combination Therapy

Combination therapy offers a means to get more people to goal. Like with diabetes and hypertension, combination therapy offers us the chance to use lower doses of medications with less downside risk and to take advantage of the synergistic and complementary effects of different medications to get to goal. Unlike diabetes and hypertension, dyslipidemia has multiple components. Combination therapy is implemented for two main reasons:

(1) to achieve a lower LDL-C goal (mostly with statin alone or with statin plus ezetimibe).
(2) to control LDL-C, non-HDL-C, TG and HDL-C in combined dyslipidemia (mostly with statin plus fenofibrates or niacin).

Sometimes a combination of three agents is necessary to reach recommended treatment goals with improved safety and better tolerance.

NIACIN: The particular goal should determine the choice of combination therapy, i.e. match the lipid or metabolic abnormality with the therapeutic agent most likely to correct it. Niacin is currently the most potent agent for elevating HDL-C in addition to having a significant lowering effect on TG. Meta-analysis data via an epidemiologic presumption indicate that every 1mg/dL incremental increase in HDL-C is associated with a 3% incremental decrease in the incidence of CAD events. There are no clinical trials to document this.

Unfortunately there is no true goal of therapy for HDL-C. In addition, niacin is not well tolerated. Several studies using extended release (ER) niacin (best tolerated) have examined the potential lipid-modifying effects of combination therapy with niacin ER and statin treatment. In terms of lipid-modifying effect, the combination appears to have significant TG-lowering and HDL-raising effects, superior to statin monotherapy. The LDL-C effects were comparable. Long-term CV outcome data are not available. Niacin ER is preferred when the HDL-C is low but TG and LDL-C are near normal (abnormal TC/HDL-C ratio > 4 or elevated non-HDL-C, 30mg/dL higher than the LDL-C goal). Most of these patients aren't diabetic so we don't have to worry about elevation of sugars—a common side effect of niacin. If they have known CV disease, niacin could be added in combination with a statin if you think HDL-C is important.

FIBRATES

Concern about developing myopathy with the statin-fibrate combination has lessened somewhat by the recent finding that one fibrate (fenofibrate) does not interfere with catabolism of statins and is therefore

less likely to increase the risk of myopathy in patients treated with moderate doses of statins. Fibrates are the most potent TG-lowering drugs available, with effects ranging from 50% to 80%, depending on patient compliance with medication, diet and exercise. Fibrates also raise HDL-C levels. The effects on LDL-C vary, depending largely on the baseline hypertriglyceridemia, the degree of reduction, and the type of fibrate. Fenofibrate can reduce total and LDL cholesterol, whereas gemfibrozil has a neutral effect. However, with either medication, if the reduction of TG is large and sudden, the accelerated lipolysis will produce a transient elevation of LDL-C (beta-shift phenomenon).

Fibrates are clearly the drug of choice for treatment of severe hypertriglyceridemia (TG > 500mg/dL). They should be used with extreme care in patients with renal failure as they are excreted through the urine. An important aspect of LDL metabolism in patients with abnormalities of the TG/HDL axis is the accumulation of small, dense LDL particles. Fenofibrate decreases small dense LDL in favor of larger, more buoyant LDL particles, which are less susceptible to oxidation and less atherogenic.

In a secondary prevention trial, the Veterans Administration HDL Intervention Trial (VA-HIT) evaluated the effect of gemfibrozil in CAD patients with type 2 Diabetes or MetS and low HDL-C. There was a significant reduction of coronary and cerebrovascular events (22% and 31% respectively). Sanders Robbins (lead author of VA-HIT) thinks that much of the CV protection a fibrate brings to the table cannot be ascertained just by looking at the lipid profile. Fibrates improve outcomes in these patients through their pleiotropic (non lipid-lowering effects) on the vascular wall and by decreasing cardio C-reactive protein (CRP), in addition to improving the lipid abnormality most likely to respond to it. At a time when new trials and guidelines are moving toward endorsement of lower LDL-C goals, the danger is under-treatment of the atherogenic dyslipidemia of diabetes—including MetS and insulin resistance. Fenofibrates are preferred when TG is high (non-HDL-C is your best lipid surrogate in these patients) to get non-HDL-C to goal in conjunction with statins.

Summary/Plan

- Obtain a baseline lipid profile, access global CV risk and treat per NCEP ATP III Guidelines (Attachment 1). LDL-C (primary goal) and non-HDL-C (secondary goal) are NCEP surrogates for apoB—the atherogenic transport vehicle carrying cholesterol into the vessel wall. LDL-C is a decent surrogate of apoB if TG or TG/HDL-C axis is normal. In this situation treat LDL-C aggressively to goal according to risk. Lower is definitely better the higher the risk, and this is supported by the RCTs. Combination therapy is preferred with a statin and ezetimibe both for their synergistic effects and low downside risk when large reductions are necessary. The side effects of statins are dose related. NCEP provides goals of therapy but do not specify how you achieve those goals as long as FDA approved therapies are utilized.

- In TG/HDL-C axis disorders, which are becoming more prevalent, LDL-C is simply not as good a surrogate for apoB. Non-HDL-C is better. Calculate the TC/HDL-C ratio (abnormal > 4) and the non-HDL-C (TC-HDL-C) if TG > 200mg/dL (abnormal is > 30mg/dL higher than the LDL-C goal).

- Clues in the routine lipid analysis that should make you realize that you're dealing with elevated apoB or small LDL-P elevations when LDL-C is near *normal* are:
  (1) Abnormal TC/HDL-C ratio (> 4) in the face of an LDL-C < 100-130mg/dL.
  (2) Abnormal TG/HDL-C ratio >3.8 women, >4 men.
  (3) Increased non-HDL-C in the presence of a normal LDL-C (<100-130mg/dL).

  If you don't want to risk patients' lives on NCEP III lipid surrogates, order an NMR Lipoprofile by LipoScience (and now LabCorp). On the LabCorp form, request "884247" NMR LipoProfile. This will assist to accurately determine and treat risk, especially in high-risk patients (as identified above).

- In TG/HDL-C axis disorders, it seems logical that a combination of a statin and a fenofibrate would provide additional risk reduction compared with a statin. Fibrates and statins regulate serum lipids by different mechanisms, have pleiotropic effects and significantly

decrease cardio CRP. This combination will offer more benefits in patients with combined dyslipidemia—specifically those with normal or only mildly elevated LDL-C, high TG and low HDL-C—a pattern particularly common to the high-risk diabetic/Met S subset of patients. Our recommendation is to use a combination of rosuvastatin (Crestor) and ezetimibe (Zetia) or simvastatin/ezetimibe (Vytorin) because of the synergistic effects—decreasing LDL-C, increasing HDL-C and decreasing cardio-CRP. Atorvastatin (Lipitor) is not associated with increased HDL-C at high doses. If non-HDL-C or LDL-P is still high, add a fenofibrate (Antara 130mg, Tricor 145mg, or Triglide 160mg). Because statins, absorption inhibitors or bile-acid sequestrants, and fenofibrates each regulate serum lipids by different mechanisms, combination therapy may offer particularly desirable benefits in patients with combined dyslipidemia.

- Dyslipidemia is an important modifiable risk factor. Key elements of lipid control remain diet and exercise (to avoid high-risk status or lower risk). Unfortunately we don't have a pill for diet and exercise and "Willpower only lasts for three weeks and in addition, it's alcohol soluble".

- Global risk assessment determines the intensity of intervention. If patients fall into high-risk categories that require reaching the lowest mandated LDL-C and non-HDL-C targets, combination therapy can assist reaching these targets. Continuous monitoring of patients is necessary in maintaining these goals to ensure that we are tailoring therapeutic care to the metabolic abnormality and the absolute risk for developing CAD. A frequently unmentioned risk CV risk factor is non-compliance. Conscientious implementation of current evidence-based guidelines can markedly decrease the CV risk of tens of thousands of individuals.

Cost Saver Message:
Splitting statin tablets can save millions for our patients!!
Benefits are the same.

We again would like to express our thanks to Dr Thomas Dayspring for his expertise and his Lipidaholics Weekly newsletter from which a lot of this information comes. His cases of the week discussions can be found at http://www.nypcvs.org/pages/1/index.htm .

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ATTACHMENT 1 How to determine the goal LDL-C level and whether to start drug therapy: Assess Risk

(Everything NCEP III advises is based on the risk of the individual patient. The higher the risk the earlier we start interventions and the more strict are the goals of therapy.)

If any…

- Coronary artery disease
- Peripheral vascular disease
- Abdominal aortic aneurysm
- Symptomatic carotid disease
- Diabetes mellitus

→ LDL-C goal < 100mg/dl—(**HIGH-RISK**)
(< 70mg/dL optional if ACS or CVD with other risk factors like DM, Met S, tobacco dependence)–(**VERY HIGH-RISK)**
All should be on a statin regardless of LDL level.

If none of the above, count risk factors below

- Hypertension (blood pressure ≥140/90 mm Hg or taking meds)
- Cigarette smoking
- HDL-C < 40 mg/dL (subtract 1 risk factor if HDL-C is ≥60)
- Age ≥40 years (men) or ≥55 years (women)
- Family history of coronary artery disease (before age 55 in a male first-degree relative or before age 65 in a female first-degree relative)

0-1 risk factor → **LDL-C goal < 160mg/dL**
Meds if > 190mg/dL
Optional if 160-189
(LOW- RISK)

≥ 2 risk factors → **Calculate 10 yr CHD risk (ATTACHMENT 2)**

< 10% → **LDL-C goal < 130mg/dL**
Meds if > 160mg/dL
(MODERATE-RISK)*

10-20 % → **LDL-C goal < 130mg/dL**
Optional < 100mg/dL
Meds if ≥ 130mg/dL
Optional @ 100-129mg/dL
(MODERATELY HIGH-RISK)

> 20 % → **LDL-C goal < 100mg/dL**
Meds if ≥ 100mg/dL
(HIGH-RISK [CAD risk equivalent])

*The following *practical* **EMERGING RISK FACTORS** should be checked in patients in the **MODERATE-RISK** subset—especially those with strong family history—to more accurately determine risk—bumping them to **MODERATELY HIGH-RISK** subset and the optional < 100mg/dL LDL-C goal.

- TG > 150mg/dL; Cholesterol/HDL ratio < 4 (just a marker of risk – not a treatment goal); FBS > 100mg
- High *hs*-CRP (cardio)—3 to 10 (the most proven and easily attainable marker (not a treatment goal) of vascular inflammation). This particular marker can be used as a clinical decision tool to bump any subset to higher risk.
- Coronary Calcium scoring or carotid ultrasonography is recommended to further ascertain risk especially in patients in the moderate risk or moderately high risk category If the test is significantly positive, they would become in effect coronary heart disease equivalents.

If LDL-C goal is reached, treat secondary targets. NCEP target if HDL-C is low is normalize LDL-C then check
Triglycerides: If triglyceride level is ≥200 mg/dL, calculate non-HDL-C level (total cholesterol minus HDL-C);
Non-HDL-C goal is 30 mg/dL higher than the LDL-C goal. (ApoB surrogate in abnormalities of TG/HDL-C axis).

Metabolic syndrome (Insulin resistance)---usually abnormalities in the triglyceride/HDL axis: If three or more of the following are present, treat with Therapeutic Lifestyle Changes (TLC)—weight reduction, increased physical activity, antihypertensive treatment (if blood pressure is elevated—some form of A II blockade), aspirin—low dose (if coronary disease is present), and therapy to reduce LDL-C and non-HDL-C—statin in combination with a fenofibrate and/or ezetimibe.

- Waist > 40 inches (men) or > 35 inches (women)
- Triglyceride level ≥ 150 mg/dL
- HDL-C level < 40 mg/dL (men) or < 50 mg/dL (women)
- Blood pressure ≥130/85 mm Hg
- Glucose level >100 mg/dL

TLC should be part of every risk reduction program. For patients at high and moderate risk requiring drug therapy, clinicians should seek to lower LDL-C levels 30% to 40%.

NCEP ATP III Guidelines: *JAMA* May 2001; 285: 2486-97. NCEP ATP III Updated Guidelines Report: *Circulation* July 2004; 110: 227-39.

ATTACHMENT 2 SJHG

Coronary Heart Disease Calculator

Men ☐
Women ☐

1. Age		
Age	Points	
20-34	-9	-7
35-39	-4	-3
40-44	0	0
45-49	3	3
50-54	6	6
55-59	8	8
60-64	10	10
65-69	11	12
70-74	12	14
75-79	13	16

2. Systolic Blood Pressure				
Systolic BP	Treated		Untreated	
Under 120	0	0	0	0
120-129	1	3	0	1
130-139	2	4	1	2
140-159	2	5	1	3
>160	3	6	2	4

3. HDL-C Level		
HDL	Points	
60 or more	-1	-1
50-59	0	0
40-49	1	1
Less than 40	2	2

4. Tobacco Use				
Age	Smoker		Non-smoker	
20-39	8	9	0	0
40-49	5	7	0	0
50-59	3	4	0	0
60-69	1	2	0	0
70-79	1	1	0	0

5. Total Cholesterol Level										
AGE	Under 160		160-199		200-239		240-279		280 or more	
20-39	0	0	4	4	7	8	9	11	11	13
40-49	0	0	3	3	5	6	6	8	8	10
50-59	0	0	2	2	3	4	4	5	5	7
60-69	0	0	1	1	1	2	2	3	3	4
70-79	0	0	0	1	0	1	1	2	1	2

1. Age points ___
2. Systolic BP points ___
3. HDL-C points ___
4. Tobacco points ___
5. Total Cholesterol points ___

(Adding 1 thru 5) **Total Points** = ____*

Chances of developing CHD in the next 10 years:

*(Using the point total (1-5) from above**)**

Men		Women		Treatment
Total pts	Risk	Total pts	Risk	
< 0	< 1%	< 9	< 1%	No treatment necessary
0-4	1%	9-12	1%	
5-6	2%	13-14	2%	
7	3%	15	3%	
8	4%	16	4%	
9	5%	17	5%	
10	6%	18	6%	
11	8%	19	8%	
12	**10%**	**20**	**11%**	**Diet and/or Drug treatment**
13	**12%**	**21**	**14%**	
14	**16%**	**22**	**17%**	
15	**20%**	**23**	**22%**	**Start Drug Treatment**
16	**25%**	**24**	**27%**	
≥17	**≥30%**	**≥25**	**≥30%**	

Success of treatment is measured in part by the level of LDL-C achieved. Patients with >20% 10 year risk and diabetics are CHD risk equivalents and these patients along with those with known CVD (coronary, carotid, cerebral or peripheral) and AAA are <u>all</u> high-risk—Goal LDL-C<100mg/dL…the **new** guidelines give an additional *option to lower LDL-C to <70mg/dL in the very high-risk (those with known dx. plus diabetes, persistent tobacco dependence, uncontrolled BP, MetS or recent MI or ACS.*

For risk of 10-20%, the goal LDL-C is <130mg/dL. *For those with LDL-C levels between 100-129mg/dL and multiple risk factors or modifiers (FH, ↑ Lp(a), ↑ hs-CRP, inactivity, overweight or MetS*), a new option is *to lower LDL-C to < 100mg/dL*. For risk <10% and 2 risk factors, goal LDL-C is <130mg/dL.

Modified for easier use from NCEP ATP III Updated Guidelines Report. Circulation July 13 2004; 110: 227-239.