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# Cardiovascular Disease: A Comprehensive Primer for Clinicians

by Thomas D. Dayspring, MD

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*For decades there have been few data on gender differences with respect to cardiovascular disease. In recent years, randomized clinical trial evidence has emerged that shows clear distinctions between women and men. These data have the potential to impact both risk assessment and treatment. It is important for clinicians to be aware of these gender differences and apply the evidence from the emerging trials when assessing and treating their female patients.*

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**W**ith 5,000 women entering the menopause every day, and with coronary heart disease (CHD) and cerebrovascular disease incidence, when combined, representing the number-one cause of morbidity and mortality among women in the United States, it is incumbent upon practicing clinicians to understand the paradigm shifts that have occurred and are occurring in both risk assessment and treatment options. After decades without gender-specific evidence on CHD in women, data are finally emerging from randomized clinical trials. Gender-specific advice has finally been provided by the American Heart Association (AHA)<sup>1,2</sup> and in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).<sup>3</sup> This article will review outcome evidence from the randomized, controlled clinical trials and will review current data regarding lipoprotein and vascular biologic forces, with the aim of enhancing understanding of disease etiology, risk assessment and effective therapies.

## Etiology Overview

For decades it has been assumed that gender difference, with respect to the age at

which CHD develops, is hormonal. Estrogen has beneficial effects on many cardiovascular (CV) risk surrogates, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), nitric oxide (NO)-dependent vasodilation, selectins and many inflammatory cytokines. However, findings from autopsy studies of children and young adults now reveal that many females have significant plaque in major vessels by the second and third decades of life, when reproductive steroids are at normal physiologic levels.<sup>4</sup> How is this possible if endogenous estrogen is truly cardioprotective?

Paradoxically, the current prevailing opinion is that androgens adversely affect lipids in men. Gender-related lipid differences are not seen until puberty, when the appearance of testosterone in males causes a 20% drop in cardioprotective HDL-C. With less effective reverse cholesterol transport, plaque becomes more severe and unstable earlier in life in men than in women. This hormone-related reduction in HDL-C may explain the different age-of-onset gender differences in CV events.<sup>5</sup>

When the endothelial lining of arteries is subjected to irritants, such as inhalants, abnormal lipoproteins, oxidative and

thrombotic forces, various cytokines, homocysteine and other risk factors, the development of plaque is initiated. The earliest abnormalities are the upregulation of surface selectins, intercellular adhesion molecules (ICAMs), which trap lipoproteins where they attach to intimal proteoglycans. Monocyte chemotactic proteins are released, and arriving monocytes transform into macrophages and engulf the lipoproteins with their lipid load, generating foam cells. Such plaque consists of a central core of cholesterol ester (CE) covered by a connective-tissue cap. Under inflammatory conditions, this cap begins to fissure (upon the action of metalloproteinase), and at the cap's shoulder regions, which are most subject to rheologic forces, a rupture occurs. Thrombotic lipids and tissue factors pour out into the arterial lumen and initiate the coagulation cascade. Platelets, and then fibrinogen, clump at the site, and a thrombosis develops. A minor thrombosis adds to the size of the original plaque; a thrombosis of significant size partially or completely occludes the arterial lumen, leading to acute coronary syndromes or infarction.<sup>6</sup>

The injured or inflamed endothelium

*Continued.*

also releases several proinflammatory cytokines, the most prominent of which are interleukins 1 and 6 (IL-1, IL-6). These cytokines cause increased hepatic production of both amyloid and C-reactive protein (CRP), which can be easily measured in the serum, leading to their use in risk assessment. In the Women's Health Study of 28,000 women followed prospectively, high-sensitivity C-reactive protein (hs-CRP) was twice as proficient in identifying patients with CV events as low-density lipoprotein cholesterol (LDL-C). CRP also was predictive of CHD events, even in the absence of severe lipid abnormalities.<sup>7</sup> Hs-CRP is a new assay capable of measuring previously undetectable levels of CRP (<4.0 mg/dl).

This story has become much more fascinating in the wake of accumulating evidence that CRP is also involved in the atherothrombotic process. CRP has thrombotic properties, enhancing blood coagulation; it attaches to degraded LDL particles in vessel walls, where it upregulates complement and is chemotactic to monocytes. Persons with chronic inflammatory conditions (e.g., rheumatoid arthritis, lupus or gingivitis) have perpetual increases in CRP and have very high incidences of premature CHD.<sup>8</sup> Almost all of the FDA-approved cardioprotective therapies (statins, niacin, fibrates, beta blockers, aspirin, omega-3 fatty acids) reduce CRP levels.

### Lipids and Risk Assessment

Traditionally, CV risk assessment has depended heavily upon analysis of lipids: TC, HDL-C, LDL-C and triglycerides (TGs). Unfortunately for women, the standard guidelines are based on studies of men with elevated LDL-C. Recent data from the Framingham Heart Study, however, have shown that 80% of the women in that cohort would never have qualified for a primary-prevention lipid intervention trial; of the women who went on to develop CHD, two thirds would not have qualified for such trials. The new data revealed the most common lipid abnormality in women with CHD is

isolated hypertriglyceridemia at levels >200 mg/dl; the second most common lipid abnormality was elevated TG with reduced HDL-C.<sup>9</sup> Hokanson and Austin's meta-analysis of multiple studies demonstrated that, in women, an 80 mg/dl increase in TG elevates CV risk by 75%.<sup>10</sup>

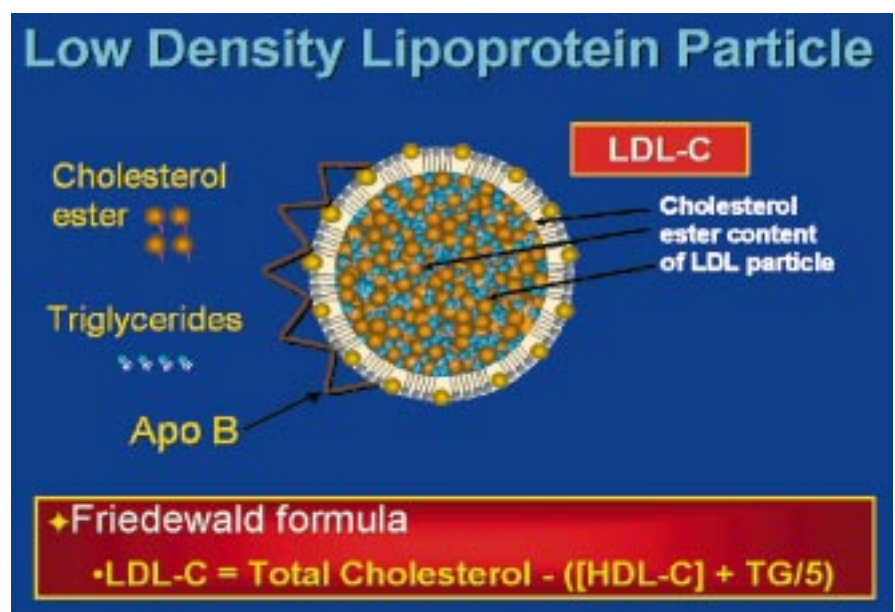
Unfortunately, most of the existing guidelines on risk assessment are heavily based on LDL-C. The NCEP ATP III has lowered desirable TG levels to 150 mg/dl. When TGs are elevated to >200 mg/dl, the NCEP recommends calculation of non-HDL cholesterol (TC minus HDL-C). This value represents the cholesterol present in the more likely atherogenic LDL and very low-density lipoprotein (VLDL) particles. When non-HDL cholesterol is more than 30 mg/dl above the desired level, more aggressive therapy is indicated.<sup>3</sup>

Low levels of HDL-C have long been recognized as being predictive of CHD risk; there are, however, gender differences. High risk is currently listed as <40 mg/dl for both sexes, with the stipulation that women with the metabolic syndrome are at risk with levels <50 mg/dl.<sup>3</sup> Data from the Heart and Estrogen/progestin Replacement Study (HERS) revealed that the most common HDL-C level in women with CHD is 40 to 50 mg/dl (followed by 50 to 60 mg/dl), and that 20% of the

cohort had levels between 60 and 80 mg/dl.<sup>11</sup> Unfortunately, many practicing physicians believe levels >60 mg/dl are always protective.

Guidelines for risk assessment have traditionally been based on LDL-C; this is, in part, because LDL-C is an easily obtained number, calculated via the Friedewald formula using TC, HDL-C and TG levels (Figure 1). In reality, LDL-C leaves much to be desired as a risk factor for predicting CHD in individual patients. Distinguished lipidologist Gerd Assman recently stated that "there is no doubt that LDL-C is causal for myocardial infarction but it is also not debatable that measurement of LDL-C is insufficient for risk analysis."<sup>12</sup> Kannel published fascinating data showing an 80% overlap between the total and LDL-C levels in Framingham Heart Study participants with no CHD versus patients at Tufts University with CHD. This overlap ranged from LDL-C levels of 80 to 280 mg/dl.<sup>13</sup> Current guidelines call for an LDL-C "goal" of <100 mg/dl in high-risk patients (those with a 20% chance of a CV event over a decade) and <130 mg/dl in those at lesser risk (a 10 to 20% chance).<sup>3</sup>

For more than 40 years it has been known that it is the lipoproteins transporting the lipids that determine CHD

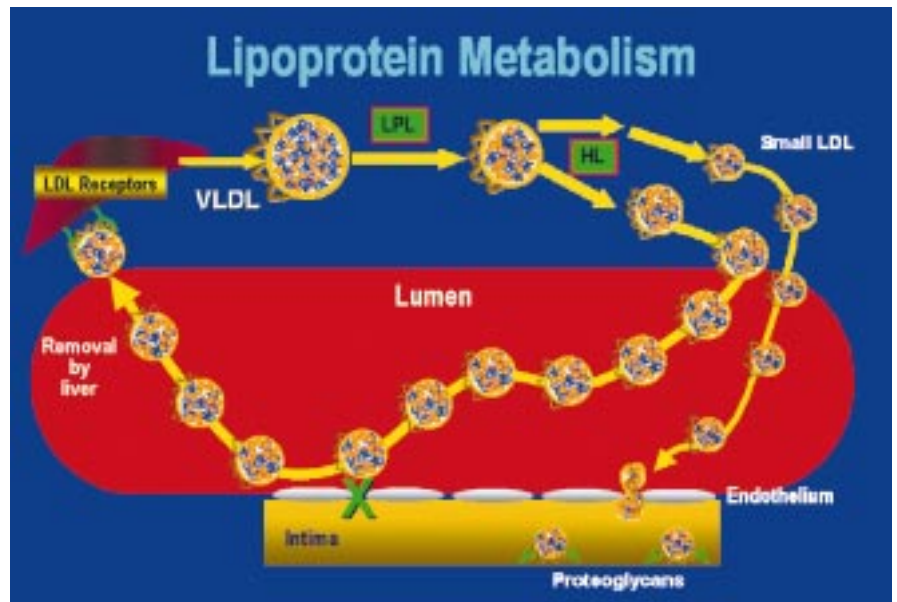


**Figure 1.** Low-density lipoprotein cholesterol levels are obtained using the Friedewald formula.

risk; the amount of lipid transported is of lesser importance.<sup>14</sup> CE and TG are lipids (oils) and are thus insoluble in aqueous solutions such as plasma; they are rendered soluble by their encasement in lipoproteins (HDL, LDL and VLDL). The laboratory reports HDL-C, LDL-C or VLDL-C, which is the amount of CE inside the various lipoprotein particles (Figure 1). CV risk actually depends on whether the lipoprotein is removed by the liver or steroid-producing tissue (where the cholesterol becomes a bile salt or steroid), or invades the arterial endothelium, where the cholesterol initiates plaque development.

The major determinants of lipoprotein particle atherogenicity are its plasma concentration, its size and its possible attachments. In most studies of lipoprotein atherogenicity, LDL particle concentration (as measured by apolipoprotein B [Apo B], one molecule of which exists on the surface of each LDL particle), outperforms other lipid measurements.<sup>15-17</sup> A level >120 mg/dl is associated with risk. Drugs that upregulate LDL receptors (e.g., statins) facilitate removal of LDL particles and, thus, reduce Apo B concentrations. Lipoproteins are heterogeneous in size and density; there are mixtures of large buoyant (pattern or phenotype A) and small dense (pattern or phenotype B) particles, and each individual particle has a predominant size. Pattern A LDLs are less atherogenic and create risk only if their levels are too high. Pattern B particles are at least six times more atherogenic when present in increased quantities.<sup>18</sup>

Larger LDL particles are much less atherogenic than smaller ones. The large size contorts the surface Apo B into a shape easily recognized by hepatic LDL receptors; this facilitates removal of particles, and their larger size makes it more difficult for the LDL particles to penetrate the endothelium.<sup>19</sup> Conversely, the smaller LDL particles are prone to oxidative forces and easily invade the endothelium. Because the smaller particles are not readily recognized by hepatic LDL receptors, their removal from the circula-



**Figure 2.** Invasion of the endothelium by LDL particles: The large LDL particles encounter resistance at the endothelium, while the smaller particles are prone to oxidative forces and easily penetrate.

tion is impaired<sup>19</sup> (Figure 2). Since large LDL particles carry more cholesterol, patients with these particles can have elevated LDL-C while not being at very high risk. In patients with too many large LDL particles, the CHD risk is double compared to those with normal concentrations. In contrast, small LDL particles do not transport large amounts of CE, and although LDL-C may be normal or only slightly high, the patient has a six-fold risk of CHD compared to those with normal concentrations. This partly explains the paradox of women with borderline or normal LDL-C levels having CHD and why not all persons with elevated LDL-C are subject to CHD.

TGs are the main determinant of lipoprotein particle sizes. Parent VLDL particles that are TG rich are quite large and have lower levels of CE (to make room for the TGs). VLDLs undergo lipolysis or hydrolysis of TGs to free up fatty acids for energy or storage in adipocytes. When TG-rich, CE-poor VLDL particles are "delipidated" of TG, the resultant lipoprotein (LDL) is small and dense (pattern B). If the parent VLDL is small (TG poor and CE rich) lipolysis results in a large, CE-laden, more buoyant (pattern A) LDL particle. It is for this reason that the factors that elevate TGs

(e.g., diet, insulin resistance, oral estrogen use and heredity) ultimately lead to the development of LDL particles that are smaller, denser and more atherogenic.<sup>20</sup> Interestingly, however, the creation of small LDL particles may actually result in a paradoxical decrease in LDL-C that would actually not be cardioprotective. One must view with caution an ERT or HRT reduction in LDL-C, as the cholesterol might then reside in atherogenic LDL particles.<sup>21</sup>

A recent trial demonstrated that a conjugated equine estrogen (CEE)- or CEE/medroxyprogesterone acetate (MPA)-induced TG rise of only 15 mg/dl can reduce LDL size.<sup>21</sup> In addition, it is because of LDL particle size that diabetics typically have normal or only slightly elevated LDL-C levels but have excessive CV risk. The hypertriglyceridemia so common in diabetics is associated with small, dense LDL particles.<sup>22</sup>

HDL-C tends to inversely parallel TG concentrations. When TG levels are high and intermediate density lipoproteins (IDL), VLDL and LDL particles have to make room for the TG, CE via cholesterol ester transfer protein (CETP) is shifted to HDL particles. Small HDL particles (HDL<sub>2</sub>) become larger (HDL<sub>3</sub>), facilitating removal by hepatic scavenger

B1 (HDL) receptors. When the HDL particles are "delipidated," the resultant smaller particle, apolipoprotein A (Apo A), is easily excreted by the kidney. This explains the reduced HDL-C levels seen in hypertriglyceridemic patients, such as those with diabetes and metabolic syndromes.<sup>23</sup>

Many women lack the genes that transcribe enzymes necessary to convert small HDL particles to large HDL particles. Such women can have high levels of total HDL-C (the sum of the cholesterol in both large and small HDL particles), yet they lack large particles, thus impairing reverse cholesterol transport. This helps to explain the occasional paradox of women with normal or elevated HDL-C who experience CV events.<sup>24</sup>

Lipoprotein(a) [Lp(a)] (referred to as "little a") is an abnormal, inherited LDL particle that has an abnormal surface protein, termed apoprotein A. Apo A interferes with fibrinolysis and, thus, adds to blood coagulability. In Caucasians and Asians, there has been demonstrated to be at least a tripling of CV risk associated with concentrations of Lp(a) >25 mg/dl.<sup>25</sup> The presence of different isoforms (large) of Apo A may not convey such risks in African-Americans. Interestingly, in the HERS trial most of the women with elevated Lp(a) had "late benefit" of HRT and were not subject to the increased adverse relative risk seen in the participants during year 1 of the trial.<sup>26</sup> CEE/MPA lowered Lp(a) by 25%.<sup>26</sup> One study showed the Lp(a)-lowering effect, and the mechanism of action is thought to be through reduced flow of Lp(a) from the liver into the plasma.<sup>27</sup>

### Preventive and Therapeutic Interventions

**Lipid-modifying drugs.** Among the lipid interventions currently available are several lipid-modifying drugs, the most commonly used of these being *statins* or HMG-CoA reductase inhibitors. Statins inhibit hepatic cholesterol synthesis, thereby depleting hepatic levels of free cholesterol; hepatic LDL receptors are upregulated, enhancing removal of CE-laden LDL

particles and, thus, significantly decreasing Apo B levels. Nicotinic acid (vitamin B<sub>3</sub>), especially the extended-release formulation, lowers LDL-C and TG and, most significantly, elevates HDL-C.

**Fibrates or fibric acids** (gemfibrozil and fenofibrate) are very effective at lowering TG and raising HDL-C; fenofibrate also quite effectively lowers Apo B and LDL-C. All of these drugs have pleiotropic effects (e.g., coagulation benefits and C-reactive protein reduction). Fenofibrate is effective for diabetics or those with the metabolic syndrome who do not have significantly elevated Apo B or LDL-C (>130 mg/dl). In view of emerging data showing that the most common CV risk in postmenopausal women is elevated TGs, with or without reductions in HDL-C, fenofibrate may be an ideal medication for those whose risk assessment mandates pharmacologic therapy.

**Resins**, the best tolerated of which is colestevam, interfere with the enterohepatic circulation of bile salts necessary for hepatic cholesterol synthesis and, thus, cause hepatic LDL receptor upregulation. This facilitates LDL particle removal. It should be noted that resins can aggravate TGs and are relatively contraindicated with TG >200 mg/dl.<sup>28</sup>

The NCEP ATP III guidelines suggest that pharmacotherapy be used when existing CHD or CHD equivalents (20% decade risk of CV event) are present as well as abnormalities of LDL-C (>100 mg/dl), HDL-C (<40 mg/dl) or non-HDL-C (>30 mg/dl above LDL-C goal). Pharmacotherapy is also indicated in those with less than a 20% 10-year risk, where 6 months of therapeutic lifestyle changes (TLC) is ineffective in normalizing LDL-C, HDL-C or non-HDL-C. The first goal of therapeutic intervention is to lower LDL-C or LDL particle concentration to normal. Once this has been achieved, the goal shifts to correcting HDL-C and TG abnormalities. If TG is >200 mg/dl, the non-HDL-C value should be evaluated and treated so that it never exceeds 30 mg/dl above the desired LDL-C. The NCEP advises that an elevated non-HDL-C level is an indication for aggres-

sive statin dosing or for combination lipid therapy with statins/niacin or statins/fibrates.<sup>3</sup>

Pending outcome studies, pravastatin/fenofibrate may be the most likely safe statin/fibrate combination; neither drug has significant hepatic metabolism using the cytochrome P450 3A (CYP4503A) enzymes and, thus, may be less likely to be associated with drug-drug interactions of the type associated with myositis.

Before prescribing any lipid-modifying drug other than a resin, liver-function testing must be done. No subsequent testing is required if pravastatin is used, unless the dose is changed. With all lipid-modifying drugs, a three-fold elevation in aminases requires halting the drug. Hepatic steatosis is not a contraindication to lipid-lowering medication, but liver function must be monitored. It should be noted that, to date, there has not been a published clinical-outcome trial looking at any lipid medication in substantial numbers of postmenopausal women.

In addition to the above-mentioned interventions, another approach that has been shown effective in reducing CV events in individuals with risk factors and in those with established CHD involves therapeutic lifestyle changes.

### HRT for Cardioprotection?

The most challenging aspect of dealing with the postmenopausal woman with CV risk is the decision related to estrogen-receptor modulation. Whereas once estrogen was considered standard of care, its use solely as a cardioprotective agent is no longer advised by the AHA, American College of Cardiology (ACC) or the NCEP. Indeed, the most dramatic change in the 2001 NCEP ATP III guidelines is the statement that "despite the previous belief that the gender difference reflects the protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt about the use of HRT to reduce CHD in women."<sup>3</sup> The 2001 AHA Statement to Healthcare Professionals on HRT concludes that estrogen should not be initiated in women with CHD who

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have never used HRT, and that it should be stopped in those who develop an acute coronary or cerebrovascular event. The statement also concludes that there is no evidence from randomized controlled trials to suggest estrogen's cardioprotection in the primary prevention of CHD.<sup>2</sup> Of note, however, there also are no studies suggesting a worse outcome in women who reinstate ERT after the coronary disease is stabilized with lipid-lowering therapy. Both AHA and NCEP guidelines recommend proven interventions, such as TLC and the medications described above.

The AHA statement concludes by noting that "the majority of the data available to make clinical recommendations are based on standard doses of CEE/MPA. Evidence is insufficient to determine whether different preparations, routes of delivery, doses or different progestins have a more favorable or more adverse effect on clinical CVD endpoints." In a recent editorial, Mendelsohn and Karas note that HRT in the United States

has become synonymous with CEE/MPA although this is not the only HRT regimen available.<sup>29</sup> They conclude that the hope remains "that HRT or SERMs will prove beneficial in the primary prevention of CHD once further studies are done."<sup>29</sup> Indeed, various HRTs and SERMs are quite distinct and different with respect to their modification of lipids, lipoproteins and other risk factors.

In a recently published analysis of CHD events at 4 years in the large Multiple Outcomes of Raloxifene Effects (MORE) trial, raloxifene had a null effect on CV outcomes (a secondary endpoint of the trial) in the overall cohort. In the 1,000 women with CV risk, raloxifene was associated with a 40% relative risk reduction in CV events compared to placebo. In the women without CV risk, there was no evidence of early or late CV harm or benefit. Even though these data are a secondary endpoint, the findings offer optimism that the Raloxifene Use in the Heart Trial (RUTH), a large interna-

tional trial designed to determine the CV effects of raloxifene, also may be successful. The current data support the contention that raloxifene can be used with a high degree of CV safety in postmenopausal women regardless of their CV risk.<sup>30</sup>

Four randomized, controlled, prospective trials and three subtrials looking at HRT and clinical outcomes in women with CHD have now been completed.<sup>31-37</sup> Not one, including a trial of transdermal ERT and HRT, has been successful. The HRT arm of the Women's Health Initiative (WHI), a large primary-prevention trial involving 16,608 women, demonstrated significant coronary (RR 29%) and cerebrovascular (RR 41%) adversity. After 5.2 years of study, the National Institutes of Health announced in July 2002 that it had terminated the study.<sup>36,37</sup> The ERT (CEE alone) arm of the study remains ongoing. The authors conclude that CEE/MPA should not be used for cardioprotection in healthy women. The

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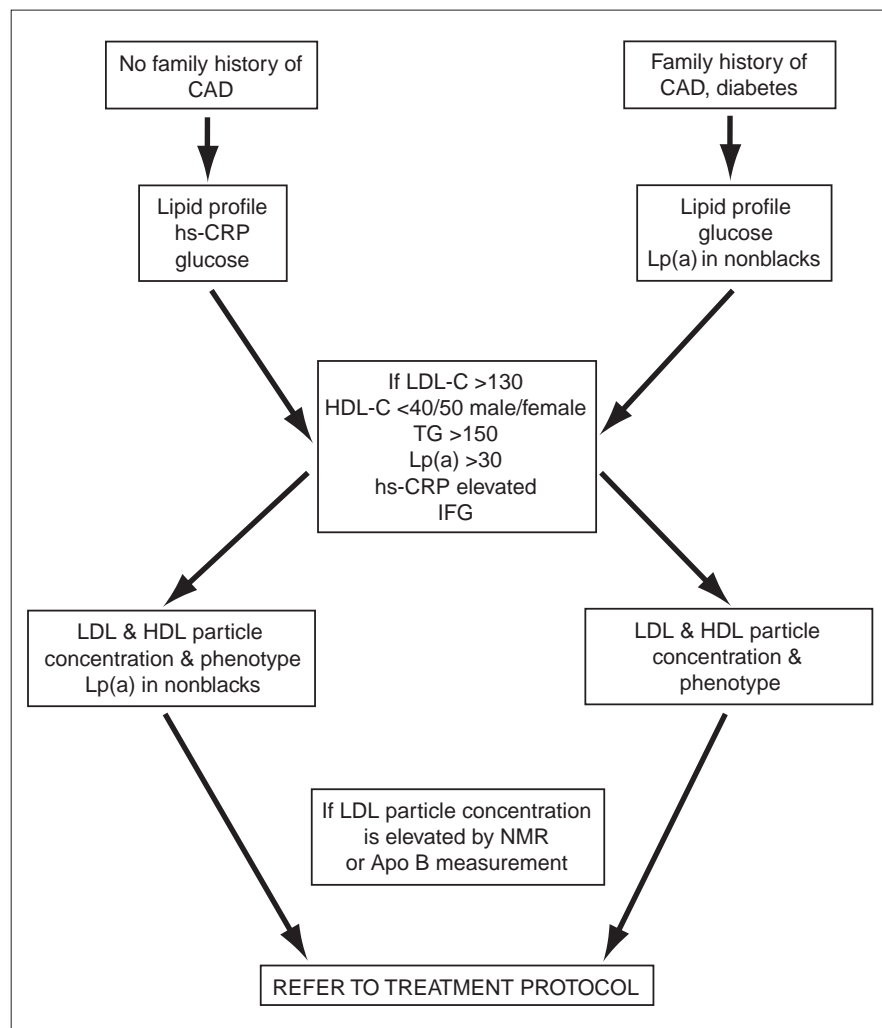
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diol has been shown to be beneficial to TG.<sup>56</sup> The most interesting progestin is norethindrone acetate (NETA). In the Continuous Hormones as Replacement Therapy (CHART) study, using varying doses of ethinyl estradiol and NETA, Speroff et al demonstrated that 1 mg of NETA reduced the ethinyl-estradiol-induced TG elevation (except for the 10µg EE dose).<sup>57</sup> In the Davidson study of estradiol with NETA, the 0.5 mg dose of NETA significantly reduced TG. The authors conclude that the 0.5 mg dose of NETA is, thus, the only commercially available oral HRT with a beneficial effect on TG.<sup>58</sup> Raloxifene does not cause hepatic synthesis of TG and has been shown in studies to be TG-neutral or to result in small reductions in TG.<sup>59</sup>

Estrogen causes elevations of HDL particles (large and small) and HDL-C. This has been accepted almost universally as a benefit. Rodent data, however, show that the HDL elevation is caused by hepatic downregulation of hepatic HDL receptors (scavenger receptors B1); thus, HDL particle concentration and HDL-C are elevated, but reverse cholesterol transport may be hindered in the process.<sup>60</sup> In the recent EURALOX 1 study, raloxifene elevated HDL-C.<sup>61</sup> Prior to this study, Walsh and colleagues demonstrated that the SERM shifts HDL size from smaller HDL<sub>3</sub> particles, which are less capable of reverse cholesterol transport, to the larger HDL<sub>2</sub> particles, which are more beneficial.<sup>59</sup> Paradoxically, this intervention may enhance reverse cholesterol transport, yet have no effect on HDL-C values.

The estrogen-induced HDL changes appear to be profoundly affected by progestogen use. Adding transdermal norethindrone to transdermal estradiol lowers HDL-C.<sup>62</sup> In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, MPA reduced CEE-induced HDL-C elevation, whereas micronized progesterone did so to a lesser degree.<sup>55</sup> Norgestimate, a nonandrogenic progestin, does not negate the estradiol-induced rise in HDL-C. NETA's effects are quite interesting. In the CHART trial, for example,



**Figure 3.** Lipid Work-up Flowsheet. hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a); IFG = impaired fasting glucose; NMR = nuclear magnetic resonance spectroscopy (available at LipoScience, Raleigh, N.C.); Apo B = apolipoprotein B

the 1-mg dose of NETA, but not the 0.5-mg dose, more significantly lowered the ethinyl-induced rise of HDL-C by 6.7%.<sup>57</sup> Likewise, in the Davidson study, the 0.5-mg dose did not abnormally lower HDL-C below baseline.<sup>58</sup> Use of testosterone preparations, alone or in combination with HRT, has been shown to lower HDL-C; lipids should be monitored carefully in such women.<sup>63</sup>

All ERTs, and most HRTs, lower TC and LDL-C. As with the rise in HDL-C, this has been presumed to be a universal benefit. We now know there are “good and bad” ways of modifying LDL-C. Removing LDL particles and their CE content reduces CV events. Lowering LDL-C by reducing the size of LDL particles, rendering them more arthro-

genic, is unlikely to be of benefit and may be harmful. Lowering LDL-C by removing circulating LDL particles (upregulation of LDL receptors) or inhibiting synthesis of VLDL or LDL particles is beneficial and is the mechanism of action of statins, niacin fibrates and resins. Significant data have been accumulating on the effect of estrogen-receptor modulation on lipoprotein particle concentrations and size.

Like statins, estrogen and raloxifene upregulate hepatic LDL receptors and cause removal of Apo B-containing LDL particles and their load of CE and TG. However, Davidson notes that most HRT studies of Apo B demonstrate no or little reduction of LDL particle concentration, and he recently concluded that the

**Table 1.**  
**Helpful Hints for CV Risk Assessment.**

- Do not be fooled by an innocuous or normal LDL-C level in women.

- The most and next most frequent lipid abnormalities in women with CHD are:

isolated hypertriglyceridemia (>200 mg/dl)  
hypertriglyceridemia with low HDL-C (<45 mg/dl)

- Non-HDL-C = Total Cholesterol (TC) – HDL-C

This represents the cholesterol in LDL and VLDL particles. It should never be more than 30 mg/dl higher than the desirable LDL-C.

High risk (20% 10-year risk)	LDL-C <100	Non-HDL-C <130
Moderate risk (10%)	LDL-C <130	Non-HDL-C <160
Low risk (<10%)	LDL-C <160	Non-HDL-C <190

- TC/HDL-C ratio, <4.0 desirable

- LDL-C/HDL-C ratio, <5.0 desirable

- Apo B/Apo A ratio, <0.90 desirable

- LDL-C/Apo B ratio >1.0 suggests large LDL particles.

- LDL-C/Apo B ratio <1.0 suggests small LDL particles.

- Apo B is a measure of total LDL and VLDL particles (the most likely atherogenic particles); <100 to 120 mg/dl is desirable.

- Apo A is a measure of HDL particles (the most likely protective particles).

- The presence of small LDL particles and absence of large HDL particles is a strong clue that the metabolic syndrome or insulin resistance is present.

- An abnormal level of high-sensitivity C-reactive protein (hs-CRP) in women is a strong indicator that significant CV risk is present.

Oral HRT and oral contraceptives can cause elevated hs-CRP; SERMs cannot.

Perform a thorough lipid and/or lipoprotein assessment in women with abnormal hs-CRP.

- Lipoprotein(a) is an LDL particle with an abnormal surface attachment (Apo A). This particle is associated with arterial thrombosis in Caucasians and Asians, but not in African-Americans (because of isoform sizes).

failure of HRT to lower Apo B may help explain its failure to reduce clinical events in randomized, controlled trials of CV outcomes in women with CHD.<sup>64</sup> One reason for the lack of reduction in Apo B is that ERT or HRT that induces hepatic synthesis of TG also causes hepatic synthesis of Apo-B-containing VLDL particles. In effect, these drugs remove

LDL particles through estrogen-induced upregulation of hepatic LDL receptors but add VLDL particles to the circulation. The result is an overall null effect on Apo B. Neither 1 mg estradiol/0.5 mg NETA nor raloxifene causes TG or VLDL particle production, but both therapies lower Apo B (9% and 12%, respectively).<sup>58,59</sup> This is a potentially

distinct advantage for a very important CV risk surrogate. Since transdermal estrogen does not have a first-pass effect on the liver, there is less upregulation of LDL receptors and lowering of Apo B, a distinct disadvantage for this mode of administration.

Oral estrogen induces hepatic synthesis of TG and, subsequently, TG-rich,

**Table 2.**  
**Lipid-Modifying Drug Selection by Particle Size (Pattern A).**

Large (pattern A) LDL particle excess:

Elevated LDL-C  
Elevated LDL particle concentration (Apo B)  
Normal TG and HDL-C

Statin monotherapy  
Fenofibrate  
Niacin (extended-release)  
Resins, plant stanols  
Combination therapy (severe cholesterol elevations: familial hyperlipidemia)

**Table 3.**  
**Lipid-Modifying Drug Selection by Particle Size (Pattern B).**

Large (Pattern B) LDL particle excess:

Elevated LDL-C may or may not be present  
Elevated LDL particle concentration (Apo B)  
TG usually >150 mg/dl  
HDL-C usually <45 mg/dl  
Non-HDL-C often 30 mg/dl above desired LDL-C

Fenofibrate  
Gemfibrozil (does not lower LDL-C)  
Niacin (extended-release)  
Statins  
Combination therapy  
Statin plus fenofibrate or extended-release niacin

cholesterol-poor large VLDL particles. After being released into the circulation, these particles undergo immediate lipolysis, with hydrolysis of the TG by lipoprotein lipase. The resultant fatty acids are used by muscles for energy or are reconverted into TGs by adipocytes for storage. Once the TGs are gone, the VLDLs reduce in size; the more TGs originally present, the smaller the resultant particle (LDL) will become. A TG rise of only 15 mg/dl (via CEE) converts large, non-atherogenic LDL particles to smaller, denser atherogenic particles.<sup>21</sup> When LDL size is reduced, the LDL-C value is decreased, as well. This is another paradox; even though the LDL-C has lessened, the CE now resides in a more atherogenic particle. New data show that, unlike other oral HRT products, the 1-mg estradiol/0.5 mg NETA formulation re-

duces TGs and does not reduce LDL particle size.<sup>65</sup> This HRT formulation lowers LDL-C via its estradiol-induced hepatic LDL-receptor removal of LDL particles, not by reducing the size of the LDL particles, as is the case with other HRTs. Raloxifene has a mechanism of action similar to estradiol/NETA with regard to lowering of LDL-C.

### Conclusions

A practical approach to CV risk assessment is presented in Figure 3 and Table 1, and a treatment regimen is outlined in Tables 2 and 3. Both the risk assessment and treatment regimen are based on the most cutting-edge evidence available at this time; recommendations will likely change as newer and more thorough clinical-outcome trials on women emerge. Future trials will continue to answer many

existing questions. In the meantime, clinicians have at their disposal CV risk-assessment tools and therapies for women that are more effective than ever before.

A statement attributed to Confucius says: "He who learns, but does not think, is lost. He who thinks, but does not learn, is dangerous." In her restatement of these words, Nanette Wenger, MD, of Emory University eloquently depicts the optimal approach that we, as clinicians, should adapt in the care of all of our patients, including midlife women with, or at risk for, heart disease. "I therefore hope," says Dr. Wenger, "that if we both learn and think we will neither be lost nor dangerous to our postmenopausal women patients."<sup>66</sup> ■

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