

Implications of the obesity epidemic for lipid-lowering therapy: Non-HDL cholesterol should replace LDL cholesterol as the primary therapeutic target

Michel R Hoenig

Royal Brisbane and Women's Hospital,
Herston, Queensland, Australia

Abstract: Obesity, metabolic syndrome and diabetes are conditions with increasing prevalence around the world. Cardiovascular risk in diabetics is often so high as to overlap with event rates observed in those with established coronary disease and this has led to diabetes being classified as a coronary risk equivalent. However, despite the elevated risk of cardiovascular events associated with diabetes and the metabolic syndrome, these patients often have normal low density lipoprotein (LDL) cholesterol despite frequent increases in apolipoprotein B, triglycerides and nonhigh density lipoprotein (HDL) cholesterol. In contrast to LDL cholesterol, non-HDL cholesterol represents cardiovascular risk across all patient populations but is currently only recommended as a secondary target of therapy by the ATP III report for patients with hypertriglyceridemia. This article provides an overview of the studies that shown non-HDL cholesterol to be superior to LDL cholesterol in predicting cardiovascular events and presents the case for non-HDL cholesterol being the more appropriate primary target of therapy in the context of the obesity pandemic. Adopting non-HDL cholesterol as the primary therapeutic target for all patients will conceivably lead to an appropriate intensification of therapy for high risk patients with low LDL cholesterol.

Keywords: obesity, coronary artery disease, non-HDL cholesterol, LDL cholesterol, metabolic syndrome, diabetes

LDL cholesterol: The current target of therapy

Epidemiologic data from populations with and without coronary artery disease (CAD) have highlighted the importance of reducing low density lipoprotein cholesterol (LDL-C) in preventing both new-onset CAD and recurrent ischemic events (Stamler et al 1986, 1984b, 1984a; Rossouw et al 1990; Wong et al 1991; Wilson et al 1998). Indeed, there is a log-linear relationship between LDL-C and CAD risk, and this relationship holds true at low LDL-C levels (Grundy et al 2004). Not surprisingly, LDL-C was identified by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) reports as being the primary focus of cholesterol-reducing therapy and successive NCEP ATP reports have recommended successively lower LDL-C goals for high risk patients (ATP III 2002). However, the ATP-III report acknowledges that when serum triglycerides (TG) are >200 mg/dl, increased remnant atherogenic lipoproteins greatly heighten risk predicted by LDL-C and this is associated with a substantially elevated very low density lipoprotein cholesterol (VLDL-C) (ATP III 2002). VLDL-C is not accounted for by the calculation of LDL-C in standard lipid panels. When serum TG is <150 mg/dl, VLDL-C is usually <30 mg/dl and hence VLDL-C arguably makes a small contribution to the atherogenic cholesterol pool

Correspondence: Michel R Hoenig
Clinical Sciences Building, D Floor, D7
Office, Royal Brisbane and Women's
Hospital, Herston Qld 4029, Australia
Tel +61 411 024 177
Fax +61 7 3636 3251
Email drmhoenig@yahoo.com.au

(1979). However, for patients with TG > 200 mg/dl, non high density lipoprotein cholesterol (non-HDL-C) is identified as a secondary target of therapy with the target being < 30 mg/dl greater than the LDL-C target (ATP III 2002). Non-HDL-C is simply calculated from a standard lipid panel as total cholesterol (TC) minus HDL-C and accounts for LDL-C, VLDL-C, IDL-C, chylomicron remnants, and lipoprotein a. Non-HDL-C is highly correlated with apolipoprotein B (apoB) and therefore provides a more accurate measure of the cholesterol in atherogenic particles (ATP III 2002). While non-HDL-C is highly correlated with LDL-C ($r = 0.94$), at TG > 150 mg/dl, non-HDL-C becomes displaced upwards and the correlation weakens (Abate et al 1993). Since hypertriglyceridemia affects 16% of the American population and 37% of diabetics (Shepherd 2005), non-HDL-C may be a more appropriate primary target of therapy since LDL-C may be less reliable for risk prediction in a sizeable proportion of the population (Pischon et al 2005). Moreover, non-HDL-C may be a superior predictor of CAD events regardless of TG; a 5794 person cohort from the Framingham study showed non-HDL-C to be a superior predictor of CAD events compared with LDL-C and also showed VLDL-C to predict CAD events after adjusting for LDL-C in patients with TG > 200 mg/dl and in patients with TG < 200 mg/dl (Liu et al 2006). Further, VLDL-C correlated poorly ($r = 0.08$) with LDL-C and an advantage of a non-HDL-C target is that it incorporates both LDL-C and VLDL-C. The triglyceride-rich lipoproteins which are not accounted for by LDL-C measurement have been associated with both increased angiographic progression of CAD and hard clinical end points (Phillips et al 1993; Mack et al 1996; Sacks et al 2000). Further, non-HDL-C is inversely correlated to HDL-C in adults and children (Gordon et al 1989, Srinivasan et al 2002). The need to change the primary target of therapy is arguably more pressing given the increasing prevalence of obesity, diabetes, the metabolic syndrome and hypertriglyceridemia;

this paper proposes that non-HDL-C should be the primary target of therapy for all patients.

Diabetes, obesity, metabolic syndrome, atherogenic dyslipidemia and cardiovascular events

Recent data from the Framingham Offspring study have shown that the incidence of type 2 diabetes in the 1990s has doubled when compared to the 1970s, with most of the absolute increase in diabetes incidence occurring in the obese as determined by body mass index (BMI) of greater than 30 (Fox et al 2006). This finding is concordant with secular trends found in the San Antonio Heart Study from 1987–1996 (Burke et al 1999). Data collected from the Framingham cohort over 5 decades has shown that the burden of cardiovascular disease is increasingly attributable to diabetes mellitus (Fox et al 2007a). Some studies have shown diabetics without previous myocardial infarction to harbor the same risk of cardiovascular death and myocardial infarction as non-diabetic patients with previous myocardial infarction (Haffner et al 1998). However, this high risk of cardiovascular events in diabetics depends on co-existing cardiovascular risk factors as shown in the Strong Heart Study and the Multiple Risk Factor Intervention Trial (MRFIT) (Vaccaro et al 1998; Howard et al 2006). Similarly, in an National Health and Nutrition Examination Survey (NHANES III) analysis, patients with diabetes but without the metabolic syndrome (only 14% of diabetics) did not have an increased risk of CAD (Alexander et al 2003). The diagnosis of the metabolic syndrome (criteria in Table 1) describes the clustering of central adiposity with impaired fasting glucose, elevated blood pressure, high TG, and low HDL-C (Grundy 2005; Zimmet et al 2005; Pladevall et al 2006) and, like diabetes, is associated with an increased risk of cardiovascular events (Bonora et al 2000; Lakka et al 2002; Malik et al 2004; Butler et al 2006; Nigam et al 2006). Individual components of the

Table 1 ATP III and IDF Definitions of the metabolic syndrome (ATPIII 2002; Liberopoulos et al 2005).

IDF Criteria (first criterion compulsory plus any additional 2)	ATP III Criteria (3/5 required for diagnosis)
Waist circumference >94 cm in Europid males or > 80 cm in Europid females (with ethnic-specific values for other groups)	Waist circumference >102 cm in males or > 88 cm in females
Triglycerides >150 mg/dl or specific treatment for lipid abnormality	Triglycerides >150 mg/dl
HDL cholesterol <40 mg/dl in a male or <50 mg/dl in a female or specific treatment for lipid abnormality	HDL cholesterol <40 mg/dl in a male or <50 mg/dl in a female
Blood pressure >130/85 or antihypertensive medications	Blood pressure >130/85 or anti-hypertensive medications
Fasting glucose >100 mg/dl or previously diagnosed type 2 diabetes	Fasting glucose >110 mg/dl

metabolic syndrome, like impaired fasting glucose have been shown to be independently associated with an increased risk of cardiovascular death (Barr et al 2007). This clustering of risk factors is ultimately driven by visceral adiposity which can be quantified by waist circumference measurements or imaging studies which, with insulin resistance, drives the increased risk of cardiovascular events (Carr et al 2004; Grundy et al 2005; Zimmet et al 2005; Bonora 2006; Grundy 2006). Since obesity, metabolic syndrome, and diabetes are common conditions, treating the ensuing increased risk of cardiovascular events is of great public health significance.

NHANES data has shown roughly one third of American adults over the age of 20 to be obese, 9.3% of Americans to be diabetic with another 26% having impaired fasting glucose, and a nearly double prevalence of diabetes in minorities (Cowie et al 2006; Ogden et al 2006). The metabolic syndrome is similarly prevalent and affects roughly a quarter of Americans above the age of 20 (Ford et al 2004) and 44% of Americans over the age of 50 (Alexander et al 2003). The purpose of this paper is to discuss the alterations in lipid parameters that occur with obesity and to argue that non-HDL-C is a more appropriate target for lipid-lowering therapy than LDL-C given that, as societies, we are becoming fatter and more diabetes-prone (Flegal et al 2002; Ford et al 2003). This is especially topical as absolute risk for cardiovascular events in primary prevention and secondary prevention increasingly overlap, largely driven by the increase in obesity, metabolic syndrome and diabetes in the primary prevention setting (Vaccaro et al 1998; Howard et al 2000, 2006; ATP III 2002).

The lipid profile of obesity

In an analysis of men enrolled in the NHANES II database, increasing BMI was associated with higher TC, TG, and non-HDL-C, but with lower HDL-C. In middle-aged and older men, LDL-C did not vary with BMI (Denke et al 1993). Indeed, while excess body weight has been consistently associated with increases in TG, VLDL-C, TC, and decreased HDL-C, the effects of body weight on LDL-C have been variable (Foster et al 1987; Jacobs et al 1988; Meilahn et al 1988; Denke et al 1994). Further, while TC and LDL-C generally correlate on a population level, this correlation weakens at higher body weights where VLDL-C makes a larger contribution to TC (Wolf and Grundy 1983a). Similarly, obese children have higher TC and TG than non-obese children with no significant difference in LDL-C (Friedland et al 2002). In a pediatric population, non-HDL-C correlated with BMI and with waist circumference while LDL-C did

not (Srinivasan et al 2002). Such observations in children are highly relevant to preventative cardiologists since children with higher non-HDL-C are more likely as adults to have high non-HDL-C, to be obese adults, to have hypertriglyceridemia, impaired fasting glucose, hyperinsulinemia, and low HDL-C while LDL-C levels in children are not similarly predictive (Srinivasan et al 2006). An analysis of adults in the NHANES III dataset corroborated these findings in children and showed non-HDL-C to be a significantly stronger correlate with BMI than LDL-C (Gardner et al 2000). Similarly, the accumulation of visceral adipose tissue which drives the metabolic syndrome and diabetes is associated with the lipoprotein profile of obesity which includes a normal LDL-C despite elevated cardiovascular risk (Yusuf et al 2005). Intra-abdominal fat, quantified with computed tomography scanning, correlates with insulin resistance and patients with high amounts of intra-abdominal fat and greater degrees of insulin resistance have elevated TC, TG, ApoB, VLDL-C, and less HDL-C (Nieves et al 2003). Similarly, in the Framingham cohort, TC and TG were shown to correlate positively with visceral adipose tissue while HDL-C correlated negatively (Fox et al 2007b). Determination of LDL-C is not informative of these changes in lipid parameters that are concomitants of the accumulation of visceral fat.

The NHANES III data set suggests that at least 13 million US adults with CAD or CAD risk equivalents have an LDL-C of <130 mg/dl while 5 million US adults have an LDL-C <100 mg/dl (Case et al 2003) and hence may not qualify for drug therapy based on current ATP III guidelines. Further, most patients who develop ischemic heart disease have LDL-C levels in the 'normal' range (Stamler et al 1993) and a cross-sectional analysis from the Framingham cohort showed that men with CAD have LDL-C that is no different from those without CAD (Schaefer et al 1994). Importantly, non-HDL-C was significantly higher in CAD than in control subjects (Schaefer et al 1994) and hence the adoption of non-HDL-C as a primary target of therapy may lead to appropriate intensification of therapy. From a pathophysiologic perspective, non-HDL-C better reflects the increased cardiovascular risk associated with high apoB levels and small LDL particle size which are hallmarks of obesity.

Cholesterol metabolism in obesity and insulin resistance

Lipoprotein kinetic studies show that the liver overproduces apoB and triglycerides in the VLDL fraction in obesity and the two drivers of this process are hypertriglyceridemia and insulin resistance (McNamara et al 1987; Barrett and Watts

2003; Chan et al 2003). Further, obesity is associated with an increase in cholesterol synthesis and a decrease in intestinal absorption (Nestel et al 1969; Miettinen 1971; Kempen et al 1988; Hoening et al 2007) and these variables are responsive to weight loss (Miettinen 1971). In 2000, Miettinen suggested that low cholesterol absorption is a component of the metabolic syndrome (Simonen et al 2000). Not surprisingly, the changes in cholesterol metabolism in type 2 diabetics are similar to those seen in obese individuals; namely a lowered cholesterol absorption efficiency, decreased absorption marker ratios (Briones et al 1986; Gylling and Miettinen 1997; Simonen et al 2000, 2002) and increased levels of synthesis markers and cholesterol synthesis determined with sterol balance (Bennion and Grundy 1977; Gylling and Miettinen 1997; Simonen et al 2002; Nathan et al 2005; Hoening et al 2007). The significance of these observations is that VLDL-C is an independent predictor of CAD events, after adjustment for LDL-C (Liu et al 2006). Conversely, weight loss has been shown to produce consistent reductions in VLDL-C, TG levels and increases in HDL-C with variable effects on LDL-C (Brownell and Stunkard 1981; Wolf and Grundy 1983b; Follick et al 1984; Wood et al 1988). Measuring non-HDL-C includes the cholesterol in the VLDL fraction and therefore better capitulates this shift in phenotype to increased cholesterol synthesis with obesity whereas considering LDL-C alone is uninformative. Higher BMI is associated with increases in non-HDL-C, TC, VLDL-C, and apoB, reflecting higher hepatic synthesis of VLDL and an increased number of atherogenic particles (Lamon-Fava et al 1996). In contrast to non-HDL-C, LDL-C often remains unchanged in obesity and insulin resistance.

Non-HDL-C correlates better than LDL-C with apoB

Patients with the metabolic syndrome have an increased concentration of apoB and TC despite no difference in LDL-C compared with individuals without the metabolic syndrome (Hulthe et al 2000). In this context, it is hardly surprising that apoB concentrations added to the predictive value of LDL-C in the Quebec Heart Study which was a prospective cohort followed for 13 years (St-Pierre et al 2006). Further, there was poor concordance between LDL-C and apoB values in this population, especially amongst the majority of the population in the middle quintiles of LDL-C. Non-HDL-C was a superior correlate to ApoB than LDL-C and those with disproportionately elevated apoB were those with higher BMI, higher TG, lower HDL-C, and smaller LDL particles, ie, features of the metabolic syndrome (Sniderman

et al 2003b). The superior correlation of non-HDL-C with apoB compared to LDL-C is also illustrated by data from the Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS) investigators. Non-HDL-C correlated better with apoB than LDL-C, especially in patients with CAD and non-HDL-C correlated with ApoB ($r > 0.90$) across all TG strata while the correlation between LDL-C and apoB deteriorated as TG increased ($r = 0.81$ if $TG > 250$ mg/dl) and was poorer in those with CAD ($r = 0.81$) than in lower risk patients without CAD ($r = 0.86$) (Ballantyne et al 2001). The measurement of apoB levels for cardiovascular risk prognostication has its supporters, especially in Canada (Genest et al 2003) and is the 'gold standard' for cardiovascular risk management according to its proponents (Walldius et al 2001; Sniderman et al 2003a). ApoB assays have been standardized and several experts have championed the inclusion of apoB measurement in treatment guidelines (Barter et al 2006). While non-HDL-C correlates well with apoB, its concordance has been relatively poorer (Barter et al 2006). However, the prognostic utility of non-HDL-C in predicting the hard clinical endpoint (discussed below) is perhaps the primary consideration for the clinician. Moreover, on a worldwide basis, the standard lipid panel remains the mainstay of lipid assessment and the adoption of non-HDL-C as the primary therapeutic target would not require clinician re-education to the same extent that adoption of apoB as a therapeutic target would. As such, to replace LDL-C as the primary therapeutic target with non-HDL-C instead of apoB may be based more on pragmatism than evidence per se.

Non-HDL-C correlates better than LDL-C with small dense LDL particles

As well as being associated with increased apoB, obesity and diabetes have been associated with a preponderance for small, dense LDL particles. Just as non-HDL-C is a better correlate of apoB than LDL-C, elevated non-HDL-C is associated with smaller LDL particle size while elevated LDL-C is not. Prospective cohort data from the Quebec Cardiovascular Study show that an increased risk of cardiovascular events is associated with a preferential accumulation of small dense LDL particles $<255\text{\AA}$ (St-Pierre et al 2001, 2005). While LDL-C in patients who developed CAD was a mere 8% higher than those without disease, the increase in cholesterol carried in small LDL particles ($<255\text{\AA}$) was 40% (St-Pierre et al 2001). As expected, individuals with a preferential accumulation of cholesterol in small dense LDL particles had higher BMI, elevated TG, lower HDL-C and higher insulin levels, which

are all features of the metabolic syndrome (St-Pierre et al 2005). Conversely, the preferential accumulation of cholesterol in larger LDL particles (>260Å) was associated with a relatively reduced incidence of ischemic heart disease and fewer features of the metabolic syndrome (St-Pierre et al 2005). Similarly, in the Framingham cohort, LDL-C was not significantly different in men with and without the metabolic syndrome although those with the metabolic syndrome had a greater number of small LDL particles, a smaller average LDL size and greater apoB (Kathiresan et al 2006). While LDL particle size bears no correlation to LDL-C, patients with smaller LDL particles had higher TC, non-HDL-C and TG with lower HDL-C than those with larger LDL particle size (Hulthe et al 2000). Similarly, data from the EPIC-Norfolk Prospective Population Study has shown non-HDL-C to correlate inversely with LDL particle size ($p < 0.01$) while there was no correlation between LDL-C and LDL particle size ($p = 0.6$) (El Harchaoui et al 2007). Given that determination of LDL size is not part of routine patient care and LDL-C levels are usually normal or mildly elevated in those with diabetes, an alternative to LDL-C to quantify risk appears to be warranted.

Non-HDL-C is superior to LDL-C in cardiovascular risk prediction

While non-HDL-C has been correlated to cardiovascular events in epidemiologic studies (Keys et al 1984; Pocock et al 1986; Menotti et al 1992; Bos et al 2003), the purpose of this section is to describe studies that have compared the predictive value of non-HDL-C with LDL-C. Where data is available, the predictive value of non-HDL-C is also compared with apoB. While non-HDL-C levels have been associated with fatty streaks, vascular stenoses, angiographic progression of CAD, and carotid IMT (Bittner 2004), the linking of non-HDL-C to the hard clinical endpoint is of greater prognostic and therapeutic value and is crucial to effecting guideline change. Hence, this section only deals with studies that have reported hard clinical end points. These are summarized in Table 2 and selected studies are discussed herein. To the author's knowledge, this is the most comprehensive assimilation of such studies.

In a 5794 patient cohort from Framingham who were initially free from CAD, VLDL-C predicted CAD events after adjustment for LDL-C (Liu et al 2006). Further, within each LDL-C category (<130 mg/dl, 130–159 mg/dl, >160 mg/dl), non-HDL-C (<160 mg/dl, 160–189 mg/dl, >190 mg/dl) was additionally predictive of CAD event rates but within each non-HDL-C category, LDL-C was not predictive

of event rates (Liu et al 2006). As expected, LDL-C predicted CAD events in patients with TG <200 mg/dl (RR 1.009 per mg/dl increase, $p < 0.01$) as did non-HDL-C (RR 1.008 per mg/dl increase, $p < 0.01$). However, LDL-C lost predictive value in patients with TG > 200 mg/dl while non-HDL-C remained predictive (RR 1.006 per mg/dl increase, $p < 0.01$) (Liu et al 2006). Hence, non-HDL-C is a better predictor of CAD events and can be utilized 'across the board' regardless of TG. Interestingly, a study of diabetic women enrolled in the Nurses' Health study showed the predictive value of non-HDL-C to interact with TG. For the population as a whole ($n = 921$), the multivariate hazard ratio for a fourth: first quartile non-HDL-C value was 1.97 ($p = 0.016$) but in those with a TG > 200 mg/dl, the hazard ratio for a fourth: first quartile non-HDL-C was 3.80 ($p = 0.046$) with a p for interaction of 0.045 (Schulze et al 2004). The confidence intervals for the hazard ratios were however wide and overlapping. Hence while available studies have suggested that non-HDL-C is predictive regardless of TG, of some concern are studies that have suggested that LDL-C loses predictive value in people with hypertriglyceridemia and this has been found in multiple studies. For instance, in a cohort from the Lipid Research Clinics prevalence study, increasing increments of non-HDL-C by 30 mg/dl were associated with an increasing risk of cardiovascular death (Cui et al 2001) as outlined in Table 2. However, men with LDL-C < 100 mg/dl, had an increased cardiovascular mortality when compared with men with LDL-C in the 100–130 mg/dl range. Careful analysis of the group of men with LDL-C < 100 mg/dl showed the increased mortality to be confined to the group who also had TG > 200 mg/dl. Similarly, an analysis of diabetics (average TG 254 mg/dl) also suggests a dissociation between CAD death and LDL-C. Diabetics with LDL-C 100–129 mg/dl had a lower 13-year CAD mortality than diabetics with LDL-C < 100 mg/dl; however, the confidence intervals were wide (Liu et al 2005). Given that hypertriglyceridemia affects 16% of the American population and 37% of diabetics (Shepherd 2005), there is a potentially large population in which LDL-C does not reflect the risk of CAD events. Indeed, some analyses have suggested that TG can add prognostic information to LDL-C but not to non-HDL-C (Pischon et al 2005). Other studies have also compared the predictive value of non-HDL-C to apoB.

In 15,632 females followed in the Women's Health study, non-HDL-C and apoB were the strongest lipid measures associated with cardiovascular end points and these two measures were highly correlated ($r = 0.87$) (see Table 2) (Ridker et al 2005). ApoB was not superior to non-HDL-C in

Table 2 A summary of studies that have compared non-HDL-C to either LDL-C or ApoB for prediction of cardiovascular events

Population	N	End point	Average follow up (years)	Type of analysis and reference (comparator) group for the cohort	HR (95% CI or p value)			Reference
					Non-HDL-C	LDL-C	ApoB	
Men and women in the Framingham cohort, Framingham Offspring cohort, Lipid Research Clinics Prevalence Study and the Multiple Risk Factor Intervention Trials; 5% diabetics; average BMI 26.0; average TG 157 mg/dl; average VLDL-C 29 mg/dl	19381; 18363	CAD death	13	Multivariate; Comparator for analyses is non-diabetics with LDL-C <100 mg/dl or non-diabetics with non-HDL-C <130 mg/dl	DIABETICS Non-HDL-C <130 mg/dl; 2.73 (1.27–5.87) Non-HDL-C 130–159 mg/dl; 2.73(1.60–4.66) Non-HDL-C >160 mg/dl; 3.68 (2.51–5.39) NON-DIABETICS Non-HDL-C 130–159 mg/dl; 0.95(0.65–1.39) Non-HDL-C >160 mg/dl; 2.11 (1.52–2.91)	DIABETICS LDL-C <100 mg/dl; 4.63 (2.21–9.70) LDL-C 100–129 mg/dl; 2.93 (1.53–5.61) LDL-C >130 mg/dl; 5.94 (3.64–9.69) NON-DIABETICS LDL-C 100–129 mg/dl; 1.73 (1.07–2.81) LDL-C >130 mg/dl; 3.02(1.94–4.72)	NA	Liu et al 2005
Women free of cardiovascular disease at baseline enrolled in the Women's Health Study; 3% diabetics; average BMI 26.3	15632	Cardiovascular death or non-fatal myocardial infarction, stroke or coronary revascularization.	10	Multivariate; in each analysis, the fifth quintile (Q5) is compared to the reference first quintile (Q1)	Q5:Q1 (>191 mg/dl versus <123 mg/dl); 2.51 (1.69–3.72)	Q5:Q1 (>154 mg/dl versus <98 mg/dl); 1.62 (1.17–2.25)	Q5:Q1 (>126 mg/dl versus <79 mg/dl); 2.50 (1.68–3.72)	Ridker et al 2005
Men and women free of CAD at baseline; Framingham cohort; 6.8% diabetics; average BMI 24; average TG 111 mg/dl; average VLDL-C 25 mg/dl	5794	Fatal and non-fatal myocardial infarction, acute coronary insufficiency or sudden cardiovascular death	22	Multivariate; Comparator for LDL-C analysis is LDL-C <130 mg/dl and for non-HDL-C <160 mg/dl	Non-HDL-C 160–189 mg/dl; 1.64 (1.13–2.40) Non-HDL-C >190 mg/dl; 2.21 (1.57–3.11) 1.008 per mg/dl TG < 200 mg/dl (p < 0.01) 1.006 per mg/dl TG > 200 mg/dl (p < 0.01)	LDL-C 130–159 mg/dl; 1.50 (1.05–2.15) LDL-C >160 mg/dl; 2.04 (1.44–2.90) 1.009 per mg/dl TG < 200 mg/dl 1.004 per mg/dl TG > 200 mg/dl (p = NS)	NA	Liu et al 2006
Patients enrolled in the SHEP trial; age > 60 with mean blood pressure 170/77 mmHg; 10% diabetics; average BMI 27.5; average TG 144 mg/dl; 13% on lipid-lowering therapy	4736	Non-fatal myocardial infarction, CAD death	4.5	Multivariate; risk is expressed per 40 mg/dl increase in lipid parameters	1.32 (1.13–1.54)	1.30 (1.09–1.54)	NA	Frost et al 1996

(Continued)

Table 2 (Continued)

Population	N	End point	Average follow up (years)	Type of analysis and reference (comparator) group for the cohort	HR (95% CI or p value)			Reference
					Non-HDL-C	LDL-C	ApoB	
Men and women free of cardiovascular disease at baseline; individuals enrolled in the Lipid research clinics prevalence program; 4% diabetics; average BMI 26.2; average TG 136 mg/dl; average VLDL-C 27 mg/dl; 2% on lipid-lowering therapy	4462	Cardiovascular death	19	Corrected for age; comparator for LDL-C analysis is LDL-C <130 mg/dl and for non-HDL-C <160 mg/dl	30 mg/dl increments correspond to a 19% increase in cardiovascular death in men and 11% in women	30 mg/dl increments correspond to a 15% increase in cardiovascular death in men and 8% in women	NA	Cui et al 2001
Chinese men and women free of cardiovascular disease at baseline; 13% diabetics; average BMI 23.5; average TG 127 mg/dl.	3568	non-fatal myocardial infarction, fatal CAD or coronary revascularization	13.6	Multivariate; in each analysis, the fifth quintile (Q5) is compared to the reference first quintile (Q1)	Q5:Q1; 1.98 (1.00–3.92)	Q5:Q1; 1.86 (1.00–3.46)	Q5:Q1; 2.74 (1.45–5.19)	Chien et al 2007
Men and women free of CAD at baseline; Framingham cohort; 4% diabetics. This Framingham cohort is different to that studied by Liu et al (13).	3322	myocardial infarction, angina pectoris, coronary insufficiency or cardiovascular death	15	Multivariate; Hazard ratios expressed per increase in one standard deviation of the population. Analyses were stratified based on sex.	MALE 1.22 (1.06–1.40) per one standard deviation increase FEMALE 1.28 (1.06–1.56) per one standard deviation increase	MALE 1.11 (0.97–1.27) per one standard deviation increase FEMALE 1.20 (0.99–1.46) per one standard deviation increase	MALE 1.37 (1.20–1.57) per one standard deviation increase FEMALE 1.38 (1.15–1.67) per one standard deviation increase	Ingelsson et al 2007
1003 men and women with a CAD event and 1885 matched controls enrolled in the EPIC-Norfolk study designed to study determinants of cancer. Participants were apparently healthy and free of cardiovascular disease at baseline. 3% diabetics; average BMI 27;	2888	Hospital admission for CAD or death secondary to CAD.	6 years follow up; case control design	Multivariate; in each analysis, the fourth quartile (Q4) is compared to the reference first quartile (Q1). This study reported odds ratio and not hazard ratios (HR)	Q4:Q1; 1.63(1.26–2.11)	Q4:Q1; 1.55 (1.22–1.96)	NA	El Harchaoui et al 2007

(Continued)

Table 2 (Continued)

Population	N	End point	Average follow up (years)	Type of Analysis and reference (comparator) group for the cohort	HR (95% CI or p value)			Reference
					Non-HDL-C	LDL-C	ApoB	
average TG 148 mg/dl; 0% using lipid-lowering therapy								
Men and women with myocardial infarction or angina pectoris enrolled in the placebo arm of the 4S study; TG <220 mg/dl for enrolment;	2223	CAD death or non-fatal myocardial infarction	5.4	Multivariate; data reported as relative risk reductions	16.4% risk reduction (p = 0.002) per 39 mg/dl decrease in non-HDL-C	12.8% risk reduction (p = 0.024) per 39 mg/dl decrease in LDL-C	5.3% risk reduction (p = 0.0025) per 10 mg/dl decrease in ApoB	Pedersen et al 1998
Men and women with myocardial infarction or angina pectoris enrolled in the treatment arm (Simvastatin 20 or 40 mg; average 27 mg) of the 4S study; TG <220 mg/dl for enrolment;	2221	CAD death or non-fatal myocardial infarction	5.4	Multivariate; data reported as relative risk reductions. The absolute reductions in lipid parameters at one year post-randomization were assessed for prognostic significance over the study period	24.9% risk reduction (p = 0.002) per 39 mg/dl decrease in non-HDL-C 1.7% reduction in events (0.9–2.4) per 1% reduction in non-HDL-C	27.8% risk reduction (p = 0.024) per 39 mg/dl decrease in LDL-C 1.7% reduction in events (1.0–2.4) per 1% reduction in LDL-C	8.8% risk reduction (p = 0.0025) per 10 mg/dl decrease in ApoB 1.1% reduction in events (0.3–1.8) per 1% reduction in ApoB	Pedersen et al 1998
Diabetics free of cardiovascular disease at baseline from American Indian Communities (Strong Heart Study); 100% diabetics; average BMI 32; average TG 144 mg/dl;	2108	Cardiovascular death or non-fatal CAD, myocardial infarction or stroke.	9	Multivariate; values of LDL-C or non-HDL-C were divided into tertiles and in each analysis, the third tertile (T3) is compared to the reference first tertile (T1)	T3:T1 (>161 mg/dl versus <127 mg/dl); 2.23 (1.41–3.43) in men; 1.80 (1.32–2.46) in women T3:T1; 1.80 (1.27–2.54) TG<150 mg/dl; 1.52 (1.12–2.07) TG>150 mg/dl	T3:T1 (>115 mg/dl versus <91 mg/dl); 1.71 (1.17–2.48) in men; 1.61 (1.19–2.17) in women T3:T1; 1.66 (1.17–2.34) TG<150 mg/dl; 1.58 (1.16–2.16) TG>150 mg/dl	NA	Lu et al 2003
Men of Japanese ancestry living in Oahu (The Honolulu Heart Study) free of CAD at baseline	1751	Fatal CAD event or non-fatal myocardial infarction	16	Multivariate; risk is expressed per 20 mg/dl increase in lipid parameters; stratified as middle aged (50–64 years old) or elderly (65–74 years old)	MIDDLE AGE 1.18 (1.09–1.29) ELDERLY 1.30 (1.11–1.53)	MIDDLE AGE 1.12 (1.02–1.23) ELDERLY 1.24 (1.05–1.48)	NA	Reed and Benfante 1992

(Continued)

Table 2 (Continued)

Population	N	End point	Average follow up (years)	Type of analysis and reference (comparator) group for the cohort	HR (95% CI or p value)			Reference
					Non-HDL-C	LDL-C	ApoB	
Mediterranean men and women followed prospectively; 100% diabetics; average BMI 27; average TG 138 mg/dl	1565	Cardiovascular mortality	11	Multivariate; analyses stratified based on age <70 and >70 years old comparator for LDL-C analysis is <111 mg/dl and for non-HDL-C <137 mg/dl and for ApoB <77 mg/dl	AGE <70 Non-HDL-C 137–163 mg/dl; 1.25 (0.54–2.87) Non-HDL-C 164–197 mg/dl; 1.47(0.69–3.12) Non-HDL-C >198 mg/dl; 1.52 (0.72–3.23) AGE >70 Non-HDL-C 137–163 mg/dl; 0.80 (0.53–1.19) Non-HDL-C 164–197 mg/dl; 0.80(0.54–1.19) Non-HDL-C >198 mg/dl; 0.58 (0.36–0.93)	AGE <70 LDL-C 111–136 mg/dl; 0.71 (0.31–1.63) LDL-C 137–165 mg/dl; 1.00(0.49–2.06) LDL-C >166 mg/dl; 1.03 (0.52–2.08) AGE >70 LDL-C 111–136 mg/dl; 0.96 (0.64–1.42) LDL-C 137–165 mg/dl; 0.84 (0.56–1.28) LDL-C >166 mg/dl; 0.59 (0.38–0.95)	AGE <70 ApoB 78–101 mg/dl; 1.33 (0.56–3.15) ApoB 101–126 mg/dl; 1.94(0.84–4.49) ApoB >127 mg/dl; 2.86 (1.22–6.67) AGE >70 ApoB 78–101 mg/dl; 1.18 (0.73–1.91) ApoB 101–126 mg/dl; 1.69(1.08–2.63) ApoB >127 mg/dl; 1.50 (0.93–2.41)	Bruno et al 2006
Patients enrolled in the BARI trial; all had multi-vessel CAD; 18% diabetics; average TG 184 mg/dl; 13% on lipid-lowering therapy	1514	non-fatal myocardial infarction	5	Multivariate; risk is expressed per 10 mg/dl increase in lipid parameters	1.049 (1.006–1.093)	NS 1.033 (0.981–1.088)	NA	Bittner et al 2002
Diabetic cohort 16% with previous myocardial infarction; 100% diabetics; average BMI 29; average TG 230 mg/dl	1059	CAD death	7	Multivariate;	1.6 (1.2–2.3); for non-HDL-C >200 mg/dl versus <200 mg/dl;	NS 1.3 (0.9–1.8); for LDL-C >160 mg/dl versus <160 mg/dl	NA	Lehto et al 1997
Diabetic women free of cardiovascular disease at baseline enrolled in the Nurses' Health study; 100% diabetics; average BMI 30; average TG 200 mg/dl; 4% using lipid-lowering therapy	921	Fatal CAD event, non-fatal myocardial infarction or coronary revascularization	10	Multivariate; in each analysis, the fourth quartile (Q4) is compared to the reference first quartile (Q1). Non-HDL-C is even more predictive in those with TG>200 mg/dl; discussed in text.	Q4:Q1 (quartile median 224 mg/dl versus 126 mg/dl); 1.97 (1.14–3.43)	Q4:Q1 (quartile median 179 mg/dl versus 98 mg/dl); 1.93 (1.15–3.22)	Q4:Q1 (quartile median 131 mg/dl versus 74 mg/dl); 1.78 (1.02–3.11)	Schulze et al 2004

(Continued)

Table 2 (Continued)

Population	N	End point	Average Follow up (years)	Type of analysis and reference (comparator) group for the cohort	HR (95% CI or p value)			Reference
					Non-HDL-C	LDL-C	ApoB	
Diabetic men free of cardiovascular disease at baseline enrolled in the Health Professionals' follow up study; 100% diabetics; average BMI 27.1; average TG 182 mg/dl; 9% on lipid-lowering therapy	746	Fatal CAD, non-fatal myocardial infarction, fatal stroke, non-fatal stroke, coronary revascularization	6	Multivariate; in each analysis, the fourth quartile (Q4) is compared to the reference first quartile (Q1)	Q4:Q1 (>195 mg/dl versus <143 mg/dl); 2.25 (1.24–4.08)	Q4:Q1 (>149 mg/dl versus <102 mg/dl); NS 1.63 (0.94–2.81)	Q4:Q1 (>119 mg/dl versus <89 mg/dl); 2.31 (1.25–4.27)	Jiang et al 2004
243 men with a CAD event enrolled in the Health Professionals' follow up study and 496 matched controls; 6% diabetics; average BMI 25.8; average TG 130mg/dl; 0% on lipid-lowering therapy	739	Fatal CAD or non-fatal myocardial infarction	6 years follow up; case control design	Multivariate; in each analysis, the fifth quintile (Q5) is compared to the reference first quintile (Q1)	Q5:Q1; 2.75 (1.62–4.67)	Q5:Q1; 2.07 (1.24–3.45)	Q5:Q1; 2.98 (1.76–5.06)	Pischon et al 2005
100 patients with non-fatal myocardial infarction before the age of 36 and 100 matched controls (n = 100); 2% diabetics; average BMI 29; average TG 143 mg/dl	200	Non-fatal myocardial infarction	Case control	Multivariate; risk is expressed per 1 mg/dl increase in lipid parameters	1.03 (1.01–1.05) per 1mg/dl increase	1.02 (1.01–1.03) per 1mg/dl increase	1.02 (1.01–1.04) per 1 mg/dl increase	Rallidis et al 2005

Abbreviations: BMI, body mass index; CAD, coronary artery disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NS, not significant; NA, not available; HR, hazard ratio; TG, triglycerides.

predicting cardiovascular events in this primary prevention, female cohort. Likewise, in a diabetic male cohort (n = 746) with high TG (average 182 mg/dl), apoB was not superior to non-HDL-C in predicting cardiovascular events (Jiang et al 2004). In contrast, other studies have suggested that apoB is a superior predictor of cardiovascular events than non-HDL-C (Pischon et al 2005, Bruno et al 2006, Chien et al 2007) and a stronger correlate with markers of obesity (Sattar et al 2004). Further, apoB may be the superior risk marker in those aged >70 years since there is a well described 'reverse epidemiology' that occurs in elderly populations whereby high lipids may be protective and hypocholesterolemia may represent a measure of frailty or selection bias (Bruno et al 2006).

Perspective

While multiple prospective cohort studies show that non-HDL-C is superior to LDL-C in cardiovascular risk prognostication, to become the primary target of therapy non-HDL-C would also have to predict cardiovascular events in patients on statins. As shown in Table 2, the 4S investigators have shown non-HDL-C to predict cardiovascular events in patients using Simvastatin (Pedersen et al 1998). Also, an analysis from the Greek Atorvastatin and Coronary Heart Disease evaluation (GREACE) study showed that the relative risk reduction of cardiovascular events in patients prescribed Atorvastatin was highly correlated with percentage reductions in non-HDL-C (Athysos et al 2003). Further, in this study, the percentage reduction in hard clinical endpoints correlated more strongly with reductions in non-HDL-C than LDL-C (Athysos et al 2003). Hence, the familiar linear relationship between relative risk reduction in CAD death or non-fatal myocardial infarction and LDL-C reduction with statins (Robinson et al 2005), if repeated with non-HDL-C may show stronger correlation and higher concordance. In this context, retrospective analyses of existing data and future inclusion of non-HDL-C as a primary outcome of lipid-lowering trials is strongly encouraged. The implications of such a shift in the primary target of therapy would probably mean intensification of lipid lowering therapy for patients with CAD or those who are at high risk for CAD. For instance, in the ACCESS program, patients with CAD had higher non-HDL-C (and ApoB) relative to LDL-C and since fewer patients reached non-HDL-C targets than LDL-C, the use of a non-HDL-C could conceivably lead to the appropriate intensification of therapy for a large number of patients (Ballantyne et al 2001). Data from the NCEP Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II Survey also

support the notion that the adoption of non-HDL-C would lead to the appropriate intensification of therapy in patients with CAD or its risk equivalents. For instance, the NEPTUNE II survey reported that in the cohort of CAD patients with TG >200 mg/dl, 57% were at the LDL-C goal of <100 mg/dl while a mere 33% of patients achieved both LDL-C <100 mg/dl and non-HDL-C <130 mg/dl (Davidson et al 2005). Hence, the adoption of non-HDL-C as the primary target of therapy could have multiple advantages. Firstly, it is easier to calculate and its routine measurement is not limited to patients with TG <400 mg/dl or fasting specimens (Hsia 2003). Secondly, it is superior to LDL-C in determining cardiovascular risk 'across the board'. Thirdly, its superiority over LDL-C seems to be especially pertinent to the obese, which is a considerable proportion of the world. Fourthly, it appears that non-HDL-C predicts events in patients on statin therapy although this point in particular requires further clarification. Without doubt, non-HDL-C will be the lipid target of the future. With time, the definition of obesity has evolved from an assessment of body mass to BMI to the current assessment with waist circumference. Similarly, the primary target of lipid lowering therapy will have to evolve in a society that is increasingly obese.

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