Effective Lipid-lowering Therapy in High-risk Patients

Benoit J Arsenault, PhD1,2, John J.P. Kastelein, MD, PhD1 and Jean-Claude Tardif, MD2

ABSTRACT

Cardiovascular disease (CVD) is the primary cause of mortality in developed and developing societies. Identifying patients at high CVD risk is important but challenging. Measurement of classical risk factors is crucial for this assessment. Also, next to traditional factors such as lipids or lipoprotein levels, apolipoproteins or Lp(a) plasma levels may be important for such purposes. Moreover, the use of emerging biomarkers such as C-reactive protein is likely to gain importance in upcoming years in an attempt to better identify subgroups of patients that may be at increased cardiovascular risk. Our review will focus on novel tools that are, or will become available to identify patients at high CVD risk; and to discuss the potential usefulness of statins in these patients, with a particular focus on potent statin therapy.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the world according to the World Health Organization (1). Each year, more deaths occur from CVD than from any other disease. Although low- and middle-income countries are proportionally more affected by CVD as a result of access to treatment, the risk factors for CVD are similar across gender, ethnicity and region of the world.

Most of these risk factors have been identified in the 1950s by the investigators of the Framingham Heart Study and include age, male gender, elevated blood pressure, smoking, blood lipid levels, poor diet and physical inactivity; the last two being the root causes of chronic conditions such as metabolic syndrome, systemic inflammation, insulin resistance and diabetes, which are also important risk factors for CVD (2). Over the past decade, numerous genetic variants have also been linked to the development of CVD and the role of genetics in CVD risk prevention and treatment is expected to receive more consideration in the future (3).

Nevertheless, in a study cohort representative of the worldwide population, the INTERHEART study, it has been suggested that more than 90% of heart attacks are attributable to modifiable risk factors (4). Although the most important risk factors for CVD are well known, it is important to highlight the fact that several individuals carrying a number of CVD risk factors, the so-called “high-risk” individuals will not undergo a cardiovascular event while an important proportion of “low-risk” individuals will suffer cardiovascular complications.

This puzzling situation has led the medical and scientific communities to seek for additional CVD risk factors. Keeping this notion in mind and witnessing the increasing body of literature associating systemic inflammation with the development of atherosclerosis and CVD risk, investigators have suggested that biological markers, or biomarkers, reflecting this inflammatory state may be useful in terms of CVD risk prediction and treatment (5).

Given the substantial number of studies that have described the predictive value of high-sensitivity C-reactive protein (CRP), as summarised in a recent meta-analysis (6), this biomarker has been considered the most appropriate marker of systemic inflammation influencing CVD risk prediction. Recently, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial has shown that asymptomatic individuals with high CRP levels experienced significant cardiovascular risk reduction when treated with rosuvastatin (44% compared to placebo), suggesting a role for CRP in identifying individuals or patients who are likely to benefit from statin therapy (7).

The debate surrounding the JUPITER study has drawn attention to the challenge of evaluating and managing patients at high risk of having their first cardiovascular event, and the importance of considering the overall risk to the individual patient rather than isolated risk factors. Based on the findings of the JUPITER study, rosuvastatin has recently been approved in the US and the EU for primary prevention of cardiovascular events as an adjunct to other risk-modifying measures.

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Our objective is to summarise the evidence supporting a holistic approach to evaluating cardiovascular risk, including the Framingham Risk and SCORE methods as well as discussing the appropriate use of potent statin therapy in reducing CVD risk burden in “forgotten” at-risk patients such elderly patients, women and those with other chronic illnesses.

**Improving the definition of cardiovascular risk with emerging biomarkers**

Plasma cholesterol is one of the major risk factors for CVD identified by the investigators of the Framingham Heart Study in 1964 (8). All around the world, beyond age, blood pressure and smoking status, CVD risk prevention national guideline rate lipid levels (mainly low-density lipoprotein [LDL] cholesterol) as highly important for assessing cardiovascular risk and making clinical decisions in both primary and secondary prevention (9-12). The Framingham Heart Study investigators have also pioneered the notion that independently of plasma LDL cholesterol levels, high-density lipoprotein (HDL) cholesterol levels were inversely related to CVD risk (13). Overall, it is well accepted that cardiovascular risk is more appropriately evaluated when a combination of risk factors is taken into account; as CVD risk is rarely attributed to isolated variables (the exception being patients with genetic disorders such as familial hypercholesterolemia).

In 1998, Wilson and other investigators of the Framingham Heart Study created an algorithm based on the most important CVD risk factors, known today as the Framingham risk score (2). In Western medicine, this algorithm is used by most clinicians to estimate a patient's 10-year CVD risk. The Framingham risk score is also justifiably used to identify patients who are likely to obtain the most significant benefits from lipid-lowering therapy. In Europe, the SCORE project (14) was initiated to develop a similar risk scoring system derived from a pool of datasets originating from 12 large-scale European cohort studies for use in the clinical management of cardiovascular risk. Additionally, the Prospective Cardiovascular Münster (PROCAM) study as shown that on top of the above-mentioned CVD risk factors, plasma triglycerides and family history of premature myocardial infarction were important risk factors to be incorporated in such risk scoring systems (15).

Among the key findings of PROCAM, the identification of the total cholesterol/HDL cholesterol ratio as one of the best predictors of CHD risk certainly represented an important step in the field of CVD risk prediction (16). Over time the prevalence of lifestyle-associated risk factors for CVD such as abdominal obesity, metabolic syndrome and type 2 diabetes has entered unprecedented epidemic proportions (17). These clinical phenotypes are all associated with an increased CVD risk (18-20). Interestingly, an increasing body of literature suggest that such associations may be explained to a great extent by biological pathways linking CRP to atherosclerotic plaque development (21). The concentration of apoB is highly correlated with non-HDL cholesterol levels, and it has been suggested that these two parameters are interchangeable although this proposition is not unanimously accepted (24).

Similarly, individuals with either low levels of either HDL cholesterol or apolipoprotein A-I are also more likely to suffer cardiovascular events, despite having optimal LDL cholesterol levels (25). It is generally accepted that lipids and lipoproteins show stronger association with CVD risk when they are used as ratio. Although most studies have shown that apoB/apoA-I ratio better discriminates CVD risk compared to cholesterol-based lipid ratio (26), it is unknown if adding the apoB/apoA-I ratio to either traditional lipids or currently used CVD risk prediction algorithms will result into a more accurate prediction of CVD risk (27,28).

**Lipoprotein(a)**

Lipoprotein(a) (Lp[a]) represents an LDL-like particle with the apolipoprotein(a) (apo(a)) covalently bound to the apoB molecule. Two recent meta-analyses have provided evidence that both the Lp(a) concentration as well as the different apo(a) isoforms are associated with CVD risk, and that these associations are consistent, yet modest. Since levels of Lp(a) range over 1000 fold between individuals and that such levels are stable over the lifespan of each individual, it has been suggested that genetics may have an important role to play in determining Lp(a) levels (29). Recently the Preoccussion Coronary Artery Disease (PROCARDIS) study has shown that the LPA locus on 6q26–27 which encodes apo(a) has a strong association with both Lp(a) levels and CVD risk, a relationship that appears to be mediated by Lp(a) levels (30). This confirms the results of a Danish group published a few months earlier last year (31). The European Atherosclerosis Society was the first organisation to recommend screening for elevated concentrations of Lp(a) during their 2010 meeting.

**C-reactive protein**

The body of literature linking plasma levels of high-sensitivity CRP with CVD risk is impressively coherent. Recently, the Emerging Risk Factor Collaboration has provided convincing evidence that the relationship between CRP and CVD risk is consistent and that the extent of this relationship is as strong as that of major lipids and blood pressure with CVD risk (6). Specialists expressing certain concerns about the clinical use of hsCRP and its role in cardiovascular disease management often discuss the uncertainties about the causality of CRP. Since the CRP gene contains a few single nucleotide polymorphisms that are associated with CRP levels, a number of Mendelian randomisation studies have sought to establish the consistency of associations among genetic variants, CRP plasma levels and CVD risk. Unlike Lp(a), most of them have shown that these associations were not entirely consistent, a finding that has brought additional arguments against causality of CRP (32-34).

Nonetheless, irrespective of causality, CRP is a strong and consistent risk marker for CVD risk and the Framingham Heart Study as well as the Women's Health Study have shown that including CRP levels in CVD risk prediction algorithms (namely the Framingham risk score) may improve CVD risk prediction in men and women, respectively (35,36). Investigators that have taken side against the use of CRP in CVD risk assessment often refer to the fact that the biological pathways linking CRP to atherosclerotic plaque development is somewhat obscure and that the usefulness of CRP may reside in the fact that it may be a good marker of abdominal obesity and/or insulin resistance, two emerging risk factors for CVD (37,38).
In that context, it has been shown that interleukin-6 (IL-6), a visceral adipose tissue-derived hormone, reaches the portal vein at high concentration to upregulate the hepatic production of CRP. Interestingly, investigators of the Québec Cardiovascular Study have provided evidence that the relationship between CRP and CVD risk is abolished after statistical adjustment for plasma IL-6 concentrations whereas the strong relationship between IL-6 and CVD risk was merely affected upon adjustment for CRP levels (39).

**Fibrinogen**

Fibrinogen, a liver-derived plasma glycoprotein that is converted by thrombin into fibrin, is at the frontline of biomarkers of the prothrombotic state that may be useful for cardiovascular risk prediction (40). Fibrinogen has been shown to be an independent predictor of CVD more than 20 years ago by the investigators of the Framingham Heart Study (41). Even then, these investigators have suggested that fibrinogen should be routinely measured to identify individuals at increased CVD risk. Genetic variations in the beta-fibrinogen gene have been shown to be associated with the risk of coronary atherosclerosis (42).

**Homocysteine**

Homocysteine is a circulating amino acid with apparently no known biologic function. Moderately elevated homocysteine levels have been shown to be an independent predictor for atherosclerosis, CVD and thromboembolism. In a study by de Ruijter et al. (43), concentrations of this hotly debated marker were able to accurately identify those at a high risk of cardiovascular mortality in elderly patients with no history of cardiovascular disease. However, a randomised clinical trial performed in more than 12,000 patients with coronary disease has shown that long-term reductions in homocysteine levels with folic acid and vitamin B-12 supplementation did not have beneficial effects on vascular outcomes, thereby questioning the relevance of homocysteine in CVD risk management (44).

**Cystatin C**

Cystatin C, a protease inhibitor synthesised in all nucleated cells, is a novel marker of renal function that has shown to improve the identification of individuals at a higher risk for cardiovascular events (45). Shilpak et al. (46) found cystatin C to be a strong and independent predictor of overall mortality and cardiovascular mortality in ambulatory elderly individuals. Cystatin C levels appear to provide a stronger estimate of the risk of cardiovascular events and death among elderly persons than either the creatinine level or the estimated glomerular filtration (GFR) (46). Among patients belonging to a relatively low-risk category as assessed by both creatinine and estimated GFR values, cystatin C could identify individuals at a higher CV risk (45).

**Troponin I**

Cardiac troponins are regulatory proteins that control the calcium-mediated interaction between actin and myosin. Predominantly used in clinical settings to diagnose myocardial infarction and to risk-stratify patients with suspected acute coronary syndrome (47), recent data suggest the possibility that troponin testing may be of value for population screening (48).

Zethelius et al. (49) reported that elevated cardiac troponin I was found to be an independent predictor of CHD events and mortality in a community-based cohort. In another population-based cohort, Daniels and colleagues (50) reported that those with elevated troponin T levels had an increased risk of cardiovascular death.

More sensitive assays for cardiac troponins are currently in development, the application of which has been shown to strongly predict risk in patients with chronic heart failure (51) and CHD (52). These diagnostically tools are currently expected to provide a more robust performance for population screening than currently available assays.

**Natriuretic peptides**

Brain-type natriuretic peptide (BNP), a neurohormone mainly synthesised by the myocardium, is an effective predictor of cardiovascular events. Investigators of the Framingham Heart Study found BNP to be the best of an expanded panel of circulating biomarkers examined (53). However, this association was apparently not strong enough to support routine measurement of this biomarker in healthy people for future cardiovascular risk assessment. The amino-terminal fragment of the BNP molecule, N-terminal prohormone BNP (NT-proBNP), has also been identified as a predictor of CV risks in a large sample of a general population (54). Furthermore, NT-proBNP was able to improve risk stratification beyond that of traditional risk factors in the multimarker study performed by Blakenberg et al. (55).

This mechanism helps to open the L type Ca channels, due to local increase of the calcium ions; followed by the active transport of the ion back into the lumen of the sarcoplasmatic reticulum, initiating the myocyte relaxation.

**MANAGING HIGHER-RISK PATIENTS**

Several pharmacological strategies are currently available to reduce CVD event rates in patients classified at higher risk of CVD. Although it is beyond the scope of this review to discuss these strategies, one should acknowledge that statin therapy is an essential part of preventing cardiovascular disease in patients with known risk factors, as recommended by most if not all health organisations, including NCEP-ATP III (9). Statins are supported by a wealth of clinical evidence confirming their role in reducing cardiovascular mortality and morbidity (56).

In 2005, the Cholesterol Treatment Trialists (CTT) have published a large-scale meta-analysis of 14 prospective clinical trials evaluating the efficiency of statin therapy on cardiovascular outcomes (57). In this study, which included more than 90,000 participants, they have shown that irrespective of baseline patients characteristics (including lipid profile), each 1 mmol/L reduction in LDL cholesterol levels provided a 12% reduction in all-cause mortality, a 19% reduction in cardiovascular mortality and a 23% reduction in incident CVD. The currently marketed statins are also licensed for primary prevention, based on the CTT findings.

In the same timeframe, a few additional prospective randomised clinical trials have shown that uptitrating statin dosage may provide additional benefit. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial, patients with a recent myocardial infarction were randomised to receive moderately (pravastatin 40 mg) or highly (atorvastatin 80 mg) intense statin therapy.
With a significant 16% risk reduction in the primary composite endpoint observed in the high-dose arm, this study was amongst the first to document the benefits of intensive statin therapy. Subsequently, two trials performed in stable coronary patients have confirmed these findings. The Treating to New Targets (TNT) trial has shown that high-dose atorvastatin (80 mg) therapy provided a 22% risk reduction of major cardiovascular events compared to low-dose atorvastatin (10 mg) statin therapy (58). Later on in 2005 the results of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial were published, which compared the efficacy of more intense (atorvastatin 80 mg) versus less intense (simvastatin 20-40 mg) therapy in patients who had had a myocardial infarction (59).

Although this trial did not show that high-dose statin reduced significantly the risk of major coronary events (hazard ratio = 0.89 [95%CI, 0.78-1.01], p=0.07), the study did show that atorvastatin 80 mg significantly reduced the risk of major coronary events (hazard ratio = 0.89 (95% CI, 0.88-1.01) (60).

The publication of these trials has provided strong clinical evidence that intensive lipid-lowering therapy with statins, to achieve lower plasma lipid levels, reduced the risk of clinical events. In other words, these studies have provided the scientific basis of the “lower is better” concept, which is now well-accepted in contemporary preventive medicine (61). An updated meta-analysis of the CTT has also been published in late 2010 (62). On top of re-emphasising that statin therapy provides a significant risk reduction, they have shown that compared to less intensive statin regimens, more intensive statin regimens provided a 15% additional risk reductions in major vascular events.

**FOCUS ON ROSUVASTATIN**

The clinical use of rosuvastatin is supported by a comprehensive clinical development programme (GALAXY), which aims at investigating its efficacy on lipid levels and cardiovascular outcomes in various clinical settings. However, these differences were not observed at three months. In the “Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy” (MERCURY) I trial, the effect of switching from commonly used doses of atorvastatin, simvastatin, and pravastatin to low doses of rosuvastatin on LDL cholesterol goals achieved was investigated in more than 3,000 high-risk patients around the world (63).

That study did meet its primary endpoint by showing that LDL-C goal achievement was more frequent for patients who switched to rosuvastatin 10 mg, compared with patients who remained on atorvastatin 10 mg (86% vs. 80%, P <0.05), simvastatin 20 mg (86% vs. 72%, P <0.0001), and pravastatin 40 mg (88% vs. 66%, P <0.0001). Additionally, patients who switched to rosuvastatin 20 mg and those who remained on atorvastatin 20 mg also had increased likelihood of meeting their LDL cholesterol goal (90% vs. 84%, P <0.01).

The benefits of rosuvastatin on atherosclerosis in the coronary and carotid arteries have been confirmed in two key clinical trials. The “Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin” (METEOR) study showed (using B-mode ultrasound) that rosuvastatin slowed progression of atherosclerosis in the carotid arteries in individuals at low CVD risk (64).

In METEOR, 984 individuals without any CVD risk factors (except age) or with a Framingham risk score <10% and high LDL cholesterol levels were randomised to rosuvastatin 40 mg or placebo. The benefits of rosuvastatin were extended to patients at higher CVD risk who participated in “A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden” (ASTEROID) trial, in which significant regression of coronary atherosclerosis (estimated by the change in percent atheroma volume) was observed with intravascular ultrasonography (65). In ASTEROID, 507 patients with coronary artery disease received rosuvastatin 40 mg for two years in this single-arm study and 349 patients were analysed.

Despite the absence of evidence showing that high-dose rosuvastatin may be better than other statins in improving mortality, morbidity or cardiovascular outcomes, a few outcomes studies have been conducted using rosuvastatin. In the “Controlled Rosuvastatin in Multinational Trial in Heart Failure” (CORONA) study, rosuvastatin 10 mg did not improve cardiovascular outcomes in patients with heart failure and left ventricular systolic dysfunction compared to placebo (66). The results of “A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events” (AURORA) trial, which assessed the same drug regimen in patients undergoing haemodialysis, were also neutral (67).

In 2008 the results of JUPITER were published, which provided documented pos- of rosuvastatin’s effects in primary cardiovascular prevention for patients with normal serum LDL cholesterol levels, deemed at high cardiovascular risk based on CRP levels (7). JUPITER was a large, multinational, long-term, double-blind, placebo-controlled, randomised clinical trial that included 17,802 healthy men and women assigned to rosuvastatin 20 mg or placebo. Among patients treated with rosuvastatin, LDL cholesterol concentrations were reduced by almost half, decreasing from 108 mg/dL at baseline to 55 mg/dL at one-year. High-sensitivity CRP levels were also reduced from 4.2 mg/L at baseline to 2.2 mg/L at one-year.

After just under two years of follow-up, treatment with rosuvastatin provided a significant reduction of 44% compared with placebo in the incidence of the primary composite endpoint of nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, revascularisation, and confirmed death from cardiovascular causes. This reduction was observed among nearly all of the individual endpoints, including a 55% reduction in nonfatal myocardial infarction and a 48% reduction in the risk of nonfatal stroke. The results of a pre-specified analysis of JUPITER have also provided convincing evidence that individuals who have had substantial reductions in both LDL cholesterol and CRP levels had the lowest odds of developing CVD (68). One of the key drawbacks of the CTT meta-analysis was the lack of primary prevention efficacy in women and the elderly (57).

Interestingly, JUPITER demonstrated sustained efficacy of rosuvastatin in these groups of patients (69,70). The publication of the JUPITER results has brought significant change for clinicians. For instance, in early 2010 the use of rosuvastatin was approved for patients who are at increased risk of heart disease such as men 50 years of age and older and women 60 years of age and older who have CRP levels >2.0 mg/L and at least one additional traditional cardiovascular risk factor such as smoking, high blood pressure, a family history of premature heart disease or low amounts of HDL cholesterol. Additionally, following the publication of JUPITER, the Canadian guidelines were the first to suggest considering the measurement of high-sensitivity CRP levels in specific subgroups such as individuals at moderate CVD risk to determine whether lipid-lowering therapy is warranted.
Those guidelines recommend considering statin therapy in individuals at moderate risk if their CRP levels exceed 2 mg/L. Additional organisations are likely to adapt their guidelines and add recommendations on the use of high-sensitivity CRP in clinical practice. Based on the findings of JUPITER, European Health Authorities have approved the use of rosuvastatin to reduce the risk of CVD in primary prevention in individuals at high risk based on Framingham or SCORE. In fact, it has recently been shown that individuals with a SCORE risk ≥5%, the risk reduction association with the use of rosuvastatin 20 mg was 43% and 50%, respectively for the extrapolated and capped models.

CONCLUSIONS

In summary, the Framingham risk score or any other cardiovascular risk algorithm such as SCORE should be used to identify individuals at higher cardiovascular risk and patients in whom lipid-lowering therapy should be initiated or intensified. However, on top of traditional risk factors, circulating biomarkers such as CRP and others discussed above are already available for potential use in primary and secondary care settings for these purposes. In both cases, robust LDL cholesterol lowering such as with potent statins is useful and secondary care settings for these purposes. In both cases, robust LDL cholesterol lowering such as with potent statins is useful and secondary care settings for these purposes.

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