Ultrasound imaging techniques for the evaluation of cardiovascular therapies

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Cardiovascular disease remains a substantial cause of morbidity and mortality in the developed world, and is becoming an increasingly important cause of death in developing countries too. While current cardiovascular treatments can help to reduce this disease burden, a substantial number of patients still retain a high risk of experiencing a life-threatening cardiovascular event. Thus, the development of new therapies capable of reducing this residual risk remains an important healthcare objective. The time taken to bring new therapies to the patient in need is lengthened by the unavoidable requirement to demonstrate a statistically significant benefit in terms of clinical events beyond that achievable with current treatments. However, clinical trials utilizing surrogate endpoints—biomarkers of disease progression that manifest before potentially fatal cardiovascular events occur—have the potential to enhance the process of drug development by enabling a statistically sound assessment of the efficacy of new therapies several years in advance of the availability of data from clinical endpoint trials. Two vascular ultrasound imaging techniques, measurement of carotid intima-media thickness (CIMT) and intravascular ultrasound (IVUS) of the coronary arteries, are increasingly being used to assess novel cardiovascular therapies in surrogate endpoint trials forming integral components of larger trial programmes utilizing both surrogate and clinical endpoints. The rationale for the use of CIMT- and IVUS-based surrogates, with supporting evidence from historical and recent trials, is presented in this review article.

Keywords

Cardiovascular disease • Coronary heart disease • Atherosclerosis • Intravascular ultrasound • B-mode ultrasound • Carotid intima-media thickness

Introduction

Mortality levels because of cardiovascular disease (CVD) remain high, with CVD accounting for the deaths of 16.7 million people worldwide in 2003; it remains the single biggest cause of global mortality.1 Despite the progress that has been made in developing treatments for CVD, prevailing social, demographic, and lifestyle factors in the developed world, along with changing habits and economic improvement, will almost certainly mean that the prevalence of CVD risk factors will increase, thereby ensuring the position of CVD as the biggest global cause of death for the foreseeable future. Indeed, projections by the World Health Organization suggest that CVD deaths will reach a total of 25 million per year by 2020.2 Clearly, therefore, in order to combat this problem, there is an urgent need for newer, more effective CVD treatments.

Historically, the efficacy of new drug therapies for CVD has been evaluated in trials employing clinical endpoints such as cardiovascular mortality and events. Such trials currently require tens of thousands of patients to be followed over many years to provide the statistical power necessary to detect differences in outcomes between treatment arms. The use of surrogate endpoints—measurable biomarkers predictive of future cardiovascular events—can facilitate shorter, smaller, and less resource-intensive clinical trials,3 and may help to provide an early test of potential efficacy before clinical outcomes data are available.

Atherosclerosis is well recognized as the pathological cause of the majority of cardiovascular events and progression of atherosclerosis has been shown to increase the risk of experiencing future cardiovascular events.4,5 Consequently, there is a growing trend towards employing change in atherosclerotic disease status as a surrogate endpoint in clinical trials of novel CVD therapies alongside ongoing clinical endpoint trials as part of a comprehensive trial programme. As this review will discuss, vascular ultrasound techniques are now commonly used as surrogate markers for this purpose.

Cited references were identified for inclusion by a search of the PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez/) using the following keywords: intravascular ultrasound, carotid ultrasound, intima-media thickness, IVUS, and CIMT. The results are...
Atherosclerotic disease progression as a surrogate marker for CVD

Several intervention studies in individuals at risk of CVD have demonstrated that progression of atherosclerosis, as measured by coronary angiography, increases the risk of future cardiovascular events. A similar finding was shown in the Cholesterol Lowering Atherosclerosis Study (CLAS) of colestepl/niacin therapy of 162 patients who had previously undergone coronary artery bypass graft (CABG) surgery. In this instance, progression of coronary atherosclerosis during 2 years of therapy significantly predicted clinical coronary events over 7 years of subsequent follow-up. Angiographically determined progression of atherosclerosis was also used as a surrogate marker in the HDL-Atherosclerosis Treatment Study (HATS) to assess simvastatin–niacin combination therapy for the secondary prevention of CVD in 160 patients with coronary artery disease (CHD). The active treatment group exhibited a 3.9% increase in average stenosis and 24% experienced a clinical cardiovascular event, whereas those in the placebo arm had a 0.4% decrease in average stenosis over 3 years and only 3% experienced a clinical cardiovascular event.

Atherosclerotic disease progression in asymptomatic patients whose atherosclerotic disease burden did not increase.

Limitations of angiography

While coronary angiography has been important in revealing the association between atherosclerotic progression and risk of CVD, current understanding of atherogenesis has revealed fundamental limitations of the technique. It is now understood that atherosclerotic plaques develop within the arterial wall, which initially expands outwards (positive remodelling) to accommodate the growing plaque, causing stenosis only during advanced stages of disease. Positively remodelled lesions may have minimal stenotic effect, these plaques have been shown to be significantly associated with acute coronary syndromes. As angiography provides a two-dimensional view (silhouette) of the arterial lumen, but no quantitative or qualitative information on the vessel wall itself, it is an inherently limited technique for accurately assessing atherosclerotic disease burden. Angiography often fails to detect new, non-stenotic plaques, or advanced atherosclerosis that impacts upon the entire length of an artery. Generally, reliance on angiography alone to assess atherosclerosis results in underestimation of disease burden, as studies comparing post-mortem histology with angiographic measurements have demonstrated. Angiography also suffers from technical limitations, including a low resolution that precludes the detection of clinically important structural features such as intracoronary thrombi or small focal calcifications. Importantly, the risks associated with both the invasiveness of the procedure and exposure to X-ray radiation generally restrict its application for studying atherosclerotic disease progression in asymptomatic patients. Further discussion of these issues can be found in the comprehensive review by Topol and Nissen.

Although angiography is still considered by many to be the gold standard for diagnosis of CHD, its limitations have generated interest in other cardiovascular imaging techniques for measurement of prognostic changes in atherosclerosis. These include magnetic resonance imaging, cardiac computed tomography, and techniques based on ultrasonography.

Ultrasonography for assessment of atherosclerosis

Currently, the two leading ultrasound-based techniques for clinical assessment of atherosclerosis are B-mode ultrasound measurement of carotid artery intima-media thickness (CIMT) and intravascular ultrasound (IVUS). Ultrasonod determination of CIMT is a non-invasive procedure in which an ultrasound transducer is placed sequentially over the skin above extracranial segments of each of the carotid arteries, with images recorded from multiple segments. CIMT may be determined by a single measurement from a pre-defined site, or a mean of multiple values from the same artery or different branches (Figure 1). Both far wall and near wall measurements may be taken.

In IVUS imaging, a coronary artery is selectively cannulated and a catheter containing a miniature transducer emitting high-frequency ultrasound is advanced over the wire and then slowly pulled back. An external computer converts ultrasonic reflections into a series of images; each of which comprises a 360° cross-sectional view of the three layers of the arterial wall (intima, media, and adventitia) as well as the lumen. Planimetry of the leading edge of the blood-intima acoustic border is used to calculate lumen cross-sectional area (LCSA); similarly, the media-adventitia cross-sectional area (MCSA) is calculated by planimetry of the intimal leading edge and the adventitia. Atheroma volume is calculated as the sum of the differences in cross-sectional area between MCSA and LCSA for all evaluable cross-sectional images (Figure 2).

Advantages of ultrasound imaging

The fundamental advantage of ultrasonography over angiography for measuring atherosclerosis is that the penetrating nature of ultrasound enables direct visualization of the arterial wall itself (i.e. the site of disease). This is true for both IVUS and measurement of CIMT. Each technique, however, has several additional advantages over angiography. For example, CIMT measurement is a more sensitive measure of early atherosclerosis than angiography; it is non-invasive, does not expose patients to X-ray radiation, and is associated with high inter- and intra-observer reproducibility in well-controlled research settings. This permits multiple serial measurements to accurately monitor changes in atherosclerosis. Furthermore, the procedure is relatively simple and inexpensive. Unfortunately, however, the routine monitoring of...
CIMT in clinical practice is currently limited by a lack of consensus on standardized protocols. When standardized protocols are followed, however, the reproducibility is greatly enhanced. Unlike measurement of CIMT, IVUS provides a direct assessment of atherosclerosis in the coronary vasculature and, unlike angiography, IVUS can reliably enable the detection of the remodelling of the arterial wall that occurs during early atherosclerosis, as well as diffuse advanced disease. The advantages of IVUS over angiography are not limited to its ability to visualize atherosclerotic progression in the arterial wall, as it is also a more sensitive method for detecting stenosis. Thus, IVUS tends to present a more clinically relevant assessment of atherosclerotic disease burden than angiography (Figure 3).

Although the invasive nature of IVUS poses some risks, its safety is well established, with major complications of vessel dissection or closure occurring in <0.5% of procedures (and usually during surgical intervention rather than diagnostic imaging). As well as a limited number of qualified imaging sites, a lack of standardization for acquisition of images and reporting of results has hindered the clinical application of IVUS. In response to this, the American College of Cardiology has issued consensus guidelines on the use of IVUS.

Change in carotid intima-media thickness as a surrogate marker for cardiovascular disease

There is a wealth of evidence from both observational and intervention studies validating change in CIMT measured by ultrasound as a surrogate marker for CVD, and though CIMT measurement does not directly visualize coronary arteries, its application in studies of coronary atherosclerosis is based on the dual premise that (a) carotid plaques indicate the presence of coronary

Figure 1 B-mode ultrasound measurement of the distance between the line indicated by Arrow 1 (lumen-intima interface) and the line marked by Arrow 2 (media-adventitia interface) provides a value for the carotid intima-media thickness (CIMT), a well-validated measure of the progression of atherosclerosis. Increasing CIMT over time correlates with increasing atherosclerosis, whereas a decrease in CIMT is indicative of atherosclerotic regression.

Figure 2 Intravascular ultrasound image showing determination of atheroma cross-sectional area by subtracting the lumen cross-sectional area from the media-adventitia cross-sectional area.
atherosclerosis and (b) changes in CIMT predict clinical coronary events.

**Evidence from observational studies**

Over the past 10–15 years, several large observational studies have demonstrated that baseline CIMT significantly predicts future clinical cardiovascular events. In the prospective Kupio Ischemic Heart Disease Risk Factor Study (KIHD) of 1288 Finnish men followed for up to 2.5 years, a CIMT of greater than 1 mm at baseline was associated with a 2.2-fold [95% confidence interval (CI) 0.7–6.74] increased risk of myocardial infarction (MI). Furthermore, the Rotterdam study of 8000 individuals at least 55 years of age found that baseline CIMT in those who had experienced cardiovascular events at an average follow-up of 2.7 years was significantly greater than in asymptomatic individuals. A difference in CIMT of 0.163 mm was associated with an odds ratio of 1.41 (95% CI, 1.30–2.51) for stroke and 1.43 (95% CI, 1.16–1.78) for MI. The predictive association between CIMT progression and coronary events was also demonstrated in the Atherosclerosis Risk in Communities (ARIC) study. In this study of 12 800 individuals aged 45–64 years without CVD at baseline, a mean CIMT of >1 mm at baseline was associated with a significantly increased risk for clinical coronary events >4–7 years of follow-up compared with a mean CIMT of ≤1 mm. The Cardiovascular Health Study of 5858 individuals aged at least 65 years with no history of CVD found that those with the greatest CIMT at baseline experienced a significantly higher incidence of cardiovascular events over 6 years of follow-up. An association between baseline CIMT and increased CVD risk has also been observed in healthy young adults.

**Evidence from intervention studies**

Evidence from intervention studies reinforces the observational data linking CIMT with cardiovascular events. Long-term follow-up of patients in the CLAS trial who received colesteipol–niacin or placebo following CABG surgery indicated a significant positive association between progression of CIMT over the 2–4 years of therapy and combined incidence of non-fatal MI or coronary
death over a subsequent mean follow-up of 8.8 years.\textsuperscript{31,32} The combined relative risk was 2.2 (95% CI, 1.4–3.6) for each annual increase of 0.03 mm.

More recently, in several placebo-controlled clinical trials, statin therapy was found to slow or reverse progression of CIMT and reduce the incidence of cardiovascular events (reviewed by Grobbee and Bots).\textsuperscript{12} Nevertheless, these studies did not specifically relate changes in CIMT with cardiovascular event rates. However, a recent meta-analysis of seven of these statin trials has revealed a statistical link between progression of CIMT and incidence of cardiovascular events.\textsuperscript{33} A mean annual decrease in CIMT thickness of 0.012 mm (95% CI, –0.016 to –0.007) was associated with an odds ratio of 0.48 (95% CI, 0.30–0.78) for cardiovascular events. The authors of this meta-analysis concluded that ultrasound-measured CIMT met all the clinical criteria, and most or all of the statistical criteria, for use as a surrogate endpoint for cardiovascular events in clinical trials of statins.

Use of carotid intima-media thickness as a surrogate endpoint for cardiovascular disease

The aforementioned body of evidence validating B-mode ultrasound-measured CIMT as a predictive marker for CVD has led to its application as a surrogate endpoint in several recently completed and ongoing clinical intervention studies. Both The Atorvastatin vs. Simvastatin on Atherosclerosis Progression (ASAP) study\textsuperscript{34} and Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial\textsuperscript{35} compared the effects of aggressive lipid-lowering vs. moderate lipid-lowering on CIMT. In the 2-year ASAP study of 325 patients with familial hypercholesterolemia, the mean change in CIMT from baseline was significantly different between treatment groups ($P = 0.0001$). Patients treated with atorvastatin 80 mg daily exhibited a significant mean reduction in CIMT from baseline of 0.031 mm (95% CI, 0.007–0.055; $P = 0.0017$). In comparison, patients treated with simvastatin 40 mg daily had a significant mean increase from baseline of 0.036 mm (95% CI, 0.014–0.058; $P = 0.0005$).\textsuperscript{34} Interestingly, in a 2-year extension study in which all patients received atorvastatin 80 mg/day, CIMT did not change further in patients previously receiving atorvastatin, but significantly decreased in those previously receiving simvastatin.\textsuperscript{36}

A similar pattern emerged from the ARBITER study in which 161 patients with hypercholesterolemia were treated with atorvastatin 80 mg or pravastatin 40 mg daily. After 1 year, CIMT had decreased by a mean of 0.034 mm in atorvastatin patients but had not significantly changed in pravastatin recipients ($P = 0.03$ for between-group comparison).\textsuperscript{35} The ARBITER 2 study investigated the effect of adding niacin 1000 mg daily to statin therapy in 167 patients with CHD and dyslipidaemia. After 1 year, CIMT had not changed in patients receiving statin/niacin combinations, but had increased by a mean of 0.044 mm in those receiving statin plus placebo, although the between-group difference showed only a trend towards statistical significance ($P = 0.08$). Three patients (3.8%) on combination therapy experienced clinical cardiovascular events compared with seven (9.6%) patients on statin monotherapy ($P = 0.20$).\textsuperscript{37}

The Measuring Effects on intima-media Thickness: an Evaluation Of Rosuvastatin (METEOR) study employed B-mode ultrasound measurement of CIMT to assess the impact of rosuvastatin on progression of subclinical atherosclerosis in 984 asymptomatic subjects at low risk of CVD.\textsuperscript{38} The results showed that treatment with rosuvastatin 40 mg/day halted progression of atherosclerosis. The primary outcome measure of annualized change in CIMT for the rosuvastatin treatment group was –0.0014 (95% CI, –0.0041 to 0.0014) vs. 0.0131 (95% CI, 0.0087–0.0174) for placebo-treated subjects ($P < 0.001$).

Torcetrapib/atorvastatin was, until December 2006, a new therapy in development that combined the proven ability of atorvastatin to prevent CVD\textsuperscript{39,40} with the potential cardiovascular benefits of torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP) that elevates HDL-C levels.\textsuperscript{51,42} Clinical development of torcetrapib was halted, however, when the independent Data and Safety Monitoring Board of the ongoing clinical outcomes trial, ILLUMINATE (the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events), recommended terminating the study because of a statistically significant imbalance in all-cause mortality between patients receiving torcetrapib/atorvastatin and those receiving atorvastatin alone.\textsuperscript{43} The full cause of this imbalance has yet to be determined, however, two randomized, double-blind trials—the Rating Atherosclerotic Disease change by Imaging with A New CETP inhibitor (RADIANCE 1 and 2) studies—which employed change in CIMT to compare the effects of torcetrapib/atorvastatin vs. atorvastatin monotherapy had completed before clinical development of torcetrapib ceased (Figure 4).\textsuperscript{44} The results from RADIANCE 1, in which 850 patients with heterozygous familial hypercholesterolaemia were treated with either torcetrapib/atorvastatin or atorvastatin alone, indicated that treatment with torcetrapib/atorvastatin did not result in a reduction of progression of atherosclerosis as determined by CIMT measurement. The increase in the primary outcome of maximum CIMT was 0.0053 \pm 0.0028 mm/year in the atorvastatin treatment group and 0.0047 \pm 0.0028 mm/year in the torcetrapib/atorvastatin group. Similarly, the results from RADIANCE 2, in which 752 patients with mixed dyslipidaemia were randomized to treatment with torcetrapib/atorvastatin or atorvastatin alone, failed to demonstrate a beneficial effect of torcetrapib treatment on atherosclerosis assessed by CIMT despite an increase in HDL-C of 63.4%, and a decrease in LDL-C of 17.7%, relative to atorvastatin treatment alone. The primary endpoint of change in maximum CIMT was 0.025 (SD 0.005) mm/year in the torcetrapib/atorvastatin group vs. 0.030 (SD 0.005) mm/year in the atorvastatin alone group, a difference of –0.005 mm/year (95% CI, –0.018 to 0.008).\textsuperscript{45}

Other studies employing CIMT endpoints include the AUDITOR study, which is examining the effects of rimonabant—the first-in-class cannabinoid-1 receptor antagonist—on atherosclerotic progression in obese patients with metabolic syndrome (ClinicalTrials.gov Identifier: NCT00228176), and the ENHANCE trial, assessing the effect of treatment with simvastatin plus ezetimibe vs. simvastatin alone on progression of atherosclerosis in familial hypercholesterolaemia patients.\textsuperscript{46}
Intravascular ultrasound-based surrogate markers of cardiovascular disease

As progression of coronary atherosclerosis measured by angiography is associated with an increased risk of cardiovascular events, a similar, or stronger, predictive relationship might be expected for the more sensitive technique of IVUS. Several studies support this hypothesis. In a study of 107 patients with angiographically insignificant coronary atherosclerosis who underwent percutaneous coronary intervention (PCI), left main coronary artery disease detected by IVUS during PCI was significantly associated with future coronary events. Mean area stenosis determined by IVUS and quantitative coronary angiography (QCA) was 30.2 and 18.2%, respectively. Follow-up of 102 patients was conducted for a median of 29 months, during which time the major clinical coronary events recorded were death (n = 6), MI (n = 4), repeat PCI (n = 13), and CABG (n = 16). By univariate analysis, these events were associated with IVUS minimum (P = 0.01) and mean (P = 0.01) lumen area, as well as angiographic minimum lumen diameter (P = 0.04), female sex (P = 0.04), and diabetes (P = 0.02). For every 5 mm² increase in IVUS minimum and mean lumen area, the hazard ratio (HR) was 0.59 (P = 0.01) and 0.62 (P = 0.01), respectively. However, multivariate analysis revealed that only minimum lumen area by IVUS (HR = 0.59 for every 5 mm² increase; P = 0.015) and diabetes (HR = 2.69; P = 0.014) independently predicted coronary events.

A link between increased atherosclerotic burden, as assessed by serial IVUS, and risk of cardiovascular events was found in a small study involving 56 patients with angiographic evidence of CHD. Patients at greatest risk of cardiovascular events, as determined by the PROCAM, SCORE, and Framingham CVD algorithms, exhibited significantly greater plaque progression by IVUS from the initial to the repeat intervention (at median 14 months) than patients at lowest risk (P < 0.01 and <0.05 for absolute and percent increases in atheroma cross-sectional area, respectively). The 18 patients who experienced cardiovascular events during follow-up had a significantly greater annual plaque progression by IVUS than asymptomatic patients (P < 0.001), despite there being no significant difference in length of follow-up between the groups.

Further evidence to support IVUS-determined coronary atherosclerosis as a predictive marker for CVD comes from recent intervention studies. In the Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study in 1991 normotensive patients with QCA-documented coronary atherosclerosis, therapy with amlodipine reduced both cardiovascular events and IVUS-detected atherosclerotic progression. Patients were randomized to 24 months of therapy with amlodipine, enalapril or placebo, and IVUS was conducted at baseline and at study completion in a subgroup of 274 patients (the NORMALIZE study). At study end, the cumulative incidences of cardiovascular events in the amlodipine, enalapril, and placebo groups, respectively, were 16.6% (HR = 0.69 vs. placebo; 95% CI, 0.54–0.88; P = 0.003), 20.2% (HR = 0.85 vs. placebo; 95% CI, 0.67–1.07; P = 0.16), and 23.1%. There was no progression of IVUS-assessed atherosclerotic burden in the amlodipine group (P = 0.31), a trend towards progression in the enalapril group (P = 0.08), and progression in the placebo group (P < 0.001).

Taken together, the findings from the Reversal of Atherosclerosis with Aggressive Lipid Lowering trial (REVERSAL) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in MI 22 (PROVE IT-TIMI 22) trial strongly suggest that IVUS-measured stabilization of atherosclerosis with high-dose statin therapy is associated with a reduced incidence...
of cardiovascular events. After 18 months of therapy in 654 patients with CHD in the REVERSAL study, atheroma volume decreased by 0.4% (95% CI, −2.4 to 1.5%; \( P = 0.98 \)) in those receiving atorvastatin 80 mg but increased by 2.7% (95% CI, 0.2–4.7%; \( P = 0.001 \)) in those receiving pravastatin 40 mg. In the PROVE IT-TIMI 22 study, which evaluated the same treatment regimens, there was a significantly reduced incidence of cardiovascular events in patients with acute coronary syndromes who were treated with atorvastatin 80 mg compared with those treated with pravastatin 40 mg.

IVUS-based surrogate endpoints have also been employed in several other completed trials of statin-based treatment regimens in patients with acute or stable CHD. Since the results of REVERSAL were published, two further studies employing IVUS have reported their effects on atherosclerotic plaque volume. In a study conducted by Nissen et al., a total of 57 patients with acute coronary syndromes were randomized to double-blind treatment with weekly infusions of recombinant Apo A-I Milano (a genetically engineered version of a naturally occurring mutant form of apo A-I) or placebo. After 6 weeks, atheroma volume measured by IVUS had decreased by a mean of 4.2% (\( P < 0.001 \)) in patients receiving Apo A-I Milano, but had not changed significantly in those receiving placebo. ASTEROID (A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden) was a 24-month single-arm study examining the effects of therapy with rosuvastatin 40 mg on IVUS-derived measures of coronary disease progression in 346 patients requiring coronary angiography for a clinical indication. Results showed that rosuvastatin produced a significant reduction from baseline in LDL-C (−53%) and also a significant increase from baseline in HDL-C (15%). In terms of the two IVUS-derived primary endpoints—change in per cent atheroma volume and change in atheroma volume in the 10 mm subsegment with the greatest disease—there was a significant reduction in both endpoints compared with baseline.

As with the RADIANCE studies described previously, the ILLUSTRATE trial (Investigation of Lipid Level management using coronary UltraSound To assess Reduction of Atherosclerosis by cETp inhibition and HDL Elevation), which used IVUS endpoints to compare the effects of torcetrapib/atorvastatin vs. atorvastatin alone, found no strong beneficial effect of torcetrapib treatment on progression of atherosclerosis despite an \( \sim 61\% \) increase in HDL levels in the torcetrapib/atorvastatin treatment group relative to the atorvastatin alone group. The primary outcome of per cent atheroma volume increased by 0.19% in the atorvastatin alone treatment group and by 0.12% in the torcetrapib/atorvastatin group (\( P = 0.72 \)).

The ERASE study employed IVUS assessed atherosclerotic plaque volume as a means of assessing the efficacy of infusion of reconstituted HDL in patients with acute coronary syndromes. The results showed that short-term infusions of reconstituted HDL did not result in a significantly greater per cent change in atheroma volume than did infusions of saline placebo. The per cent change in atheroma volume was \( 3.4\% \) for treatment with reconstituted HDL vs. \( −1.6\% \) for placebo infusion (\( P = 0.48 \)).

Other ongoing trials employing IVUS-measured progression of atherosclerosis to evaluate novel CVD therapies include the APPROACH study of rosiglitazone vs. glipizide in patients with type 2 diabetes and CHD (ClinicalTrials.gov identifier: NCT00116831), and the STRADIVARIUS study of rimonabant in patients with CHD and abdominal obesity (ClinicalTrials.gov identifier: NCT00124332).

Conclusions

The increasing global burden of CVD necessitates the need for more effective CV risk-reducing therapies. Many new therapies are likely to be administered in addition to the most effective cardiovascular risk-reducing therapies currently available (e.g. statins), in order to produce maximal reductions in CV risk. A comprehensive assessment of the efficacy and safety of new CVD therapies will necessitate the use of lengthy clinical endpoint trials involving follow-up study of tens of thousands of patients over many years, in order to provide enough statistical power to determine incremental benefits over the best current therapies. This inevitably lengthens the time taken to bring effective new remedies to patients in dire need of further CV risk-reducing treatments. Therefore, to test potential drug efficacy more quickly, new therapies are increasingly being assessed by surrogate endpoint trials, conducted while clinical endpoint trials are ongoing. Such surrogate endpoint trials allow assessment of progression of pathology at stages of disease prior to those that precipitate some of the CV events typically employed as clinical endpoints, thereby enabling a robust test of potential efficacy ahead of the availability of clinical endpoint data.

Ultrasound imaging techniques can be used to determine the presence or extent of atherosclerosis, or to assess disease progression over time, and represent an effective means of determining surrogate endpoints. There is a growing body of evidence validating CIMT measured by B-mode ultrasound and coronary atheroma burden measured by IVUS as predictive markers for future cardiovascular events. These ultrasound techniques offer substantial advantages over the traditional method of coronary angiography for imaging atherosclerosis: they allow direct visualization of atherosclerotic plaques in situ, and they can detect early stages of atherosclerosis that cannot be detected by angiography.

Despite the usefulness of CIMT- and IVUS-based surrogate endpoint trials, however, they are unlikely to completely replace traditional clinical endpoint trials, as the need for a comprehensive assessment of the safety of a novel therapy will still require the long-term monitoring of clinical endpoints. CIMT- and IVUS-based endpoints provide a valuable insight into one aspect of disease progression, but by no means do they reveal the whole story. Only a large, well-designed clinical endpoint study can provide a body of data sufficient for a proper safety assessment. Furthermore, the relative lack of standardized protocols and assessment criteria remain important limitations that must be addressed. Nevertheless, progress is being made in this regard and consensus statements on standards for acquisition, measurement, and reporting of both IVUS and CIMT data have been published.

The use of CIMT- and IVUS-based surrogate endpoint trials can augment clinical endpoint trials as part of a broader trial programme to hasten the evaluation of the potential efficacy of novel therapies. The advantage of this approach is evident in the
increasing use of B-mode ultrasound measurement of CIMT or IVUS to clinically evaluate novel CVD therapies in surrogate endpoint trials forming integral parts of wider trial programmes. Indeed, the advantages conferred by such an approach are so great that, in the near future, it may be largely inconceivable that any novel CVD therapy would be assessed by clinical endpoint trials alone.

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Conflict of interest

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