5 Monitoring the Progression and Regression of Coronary Atherosclerosis with Intravascular Ultrasound

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Introduction

Atherosclerosis and its thrombotic complications remains the commonest cause of death in western societies [1]. This pattern of disease is soon to be replicated worldwide [2], due in part to the obesity epidemic and its related metabolic disorders [3]. HMG-CoA reductase inhibitors, or statins, remain the backbone of our treatment for atherosclerosis, with major benefits observed across many clinical trials powered for hard clinical endpoints and burden of disease [4, 5]. Statins were introduced into clinical practice in the 1980s, and since then, a number of experimental anti-atherosclerotic compounds have reached phase 1–4 clinical trial evaluation in humans. Most, if not all of these compounds have either failed due to futility or toxicity. Hence, there remains a large unmet clinical need for the development of novel anti-atherosclerotic compounds to combat the residual risk of cardiovascular events observed despite statin therapy. In addition, current risk prediction algorithms are somewhat limited in their ability to deal with fluctuating, or modifiable risk factors, as well as novel and emerging biomarkers of risk. As such, considerable attention has focused on direct atherosclerosis imaging, as a complementary means of evaluating cardiovascular risk. This rationale stems from necropsy studies and a variety of vascular imaging modalities that show a strong, consistent association between a greater burden of atherosclerosis in those individuals succumbing to a cardiovascular event [6–11].

The last decade has been witness to the pertinent role of atherosclerosis imaging for providing mechanistic insights into the natural history of the disease process, as well as the utility of serial plaque quantification for measuring the efficacy of novel anti-atherosclerotic compounds. Intravascular ultrasound (IVUS), in particular, has evolved as an imaging modality that generates high-resolution, precise volumetric quantification of epicardial coronary atherosclerosis, the vascular bed responsible for a majority of the morbidity and mortality arising from atherosclerosis. By measuring the change in coronary atheroma volume over time, IVUS can evaluate the potential anti-atherosclerotic efficacy of interventions on plaque development. Clinical trials of this nature have served as gatekeepers, with the findings of plaque progression (or lack of regression) providing important information

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regarding mechanistic efficacy of the studied compound. Lack of efficacy observed in such imaging trials, allows the drug-developer to halt the development program of the studied compound, not only saving millions of dollars, but most importantly, preventing the public from being exposed to a futile or unsafe compound. On the other hand, proof of a compounds mechanistic efficacy and safety provides a supportive signal to further invest in a large-scale clinical trial to test the clinical efficacy of a compound. With ongoing technological advancements in plaque imaging, there remains significant interest in the role that IVUS and affiliated intravascular imaging technologies will play in drug development programs, as well as improving our understanding of the serial behavior of potential high-risk, unstable plaques in at-risk patients.

Angiographic Plaque Imaging

For over 50 years, angiography has been the preferred imaging modality for the detection of atherosclerosis within the coronary vasculature. It remains fundamental for clinical decision making and guiding PCI within patients with symptomatic coronary artery disease. Coronary angiography has provided us with important insights into the temporal behavior of complex coronary lesions identified during acute infarct angioplasty [12]. Earlier studies also showed that the number of diseased vessels on angiography predicted clinical outcome [13]. However, the angiographic severity of lesions detected via coronary angiography has not been shown to be an accurate predictor of future ischemic coronary events [14, 15]. Angiography is simply a 2-dimensional (2D) lumen-based imaging modality that fails to directly image plaque. Given that angiography detects luminal encroachment of plaque (percent stenosis) expressed in proportion to the lumen diameter of an apparently normal reference segment (which itself may contain a substantial amount of plaque), angiography typically underestimates the true amount of plaque present [16]. Although angiography has been utilized in clinical trials to evaluate the effects of medical therapies, its indirect approach to atherosclerosis imaging has limited the justification to use this modality for quantifying changes in disease burden [17].

Intravascular Ultrasound

IVUS is a high-frequency imaging modality that provides high-resolution, cross-sectional, topographic images of the vascular lumen and each component of the vessel wall. IVUS has provided a unique insight into the burden and distribution of atherosclerotic plaque, allowing for a comprehensive characterization of the vessel wall, demonstrating the ubiquitous presence of plaque in regions that appear normal on angiography [18] (Fig. 5.1). This phenomenon has been explained by the ability of the artery (as determined by IVUS) to adapt to plaque accumulation within the vessel wall in order to preserve lumen encroachment—which is termed "adaptive" or "positive" remodeling [19]. Originally described by Glagov and colleagues following analysis of arterial necropsy specimens [20], IVUS has accurately characterized patterns of coronary arterial remodeling in vivo. Luminal dimensions are typically preserved via the expansion of the external elastic membrane (EEM) in response to atheroma formation within the arterial wall. As a result, a significant amount of atheroma can accumulate within the arterial wall without angiographic evidence of a significant stenosis. Angiographic-detected stenoses (lumen constriction) typically appear once a substantial amount of atheroma has accumulated within the arterial wall. In addition, the EEM can constrict in response to atheroma accumulation, further compromising luminal dimensions. This response has been termed negative (or "constrictive") remodeling. Indeed, the dynamic nature of the arterial wall in response to atheroma burden may play an important role in the propensity of particular plaque segments to undergo biological transformations that result in a corresponding clinical syndrome [21].

The high-resolution images attained from IVUS allow for the accurate identification of the lumen–plaque (or lumen–intima) interface, as

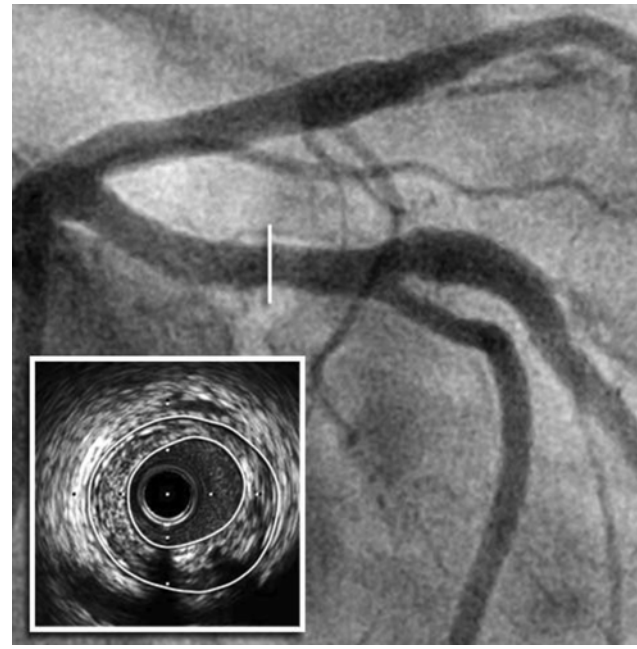

Fig. 5.1 IVUS-derived plaque evident in angiographically normal segments. A coronary angiogram showing minimal atherosclerotic disease within the mid portion of the left circumflex artery. *Inset* shows the corresponding IVUS cross-sectional view highlighting significant plaque burden (Adapted from Puri R, Tuzcua EM, Nissen SE, et al. Exploring coronary atherosclerosis with intravascular imaging. Int J Cardiol. 2013. doi.org/10.1016/j.ijcard.2013.03.024. With permission from Elsevier)

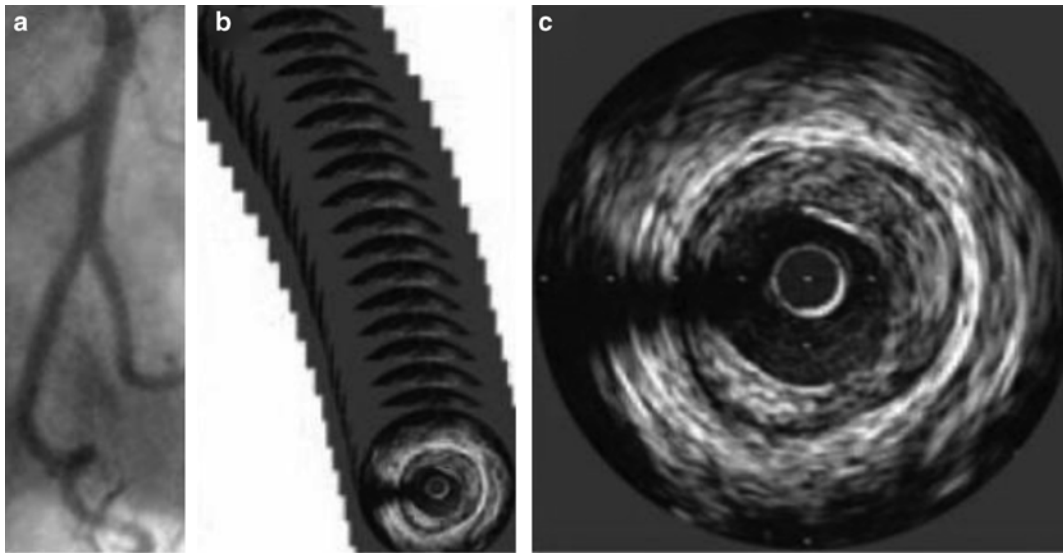

Fig. 5.2 Generation of images by intravascular ultrasound. Pullback of the ultrasound transducer through the artery (**a**) generates a series of tomographic images (**b**). Images separated by 1-mm intervals are then used for measurements (**c**) (Adapted from Nicholls SJ, Sipahi I, Schoenhagen P, et al. Application of intravascular ultrasound in anti-atherosclerotic drug development. Nat Rev Drug Discov. 2006;5(6):485–92. With permission from Nature Publishing Group)

well as the EEM. Allowing for the negligible thickness of the media, guidelines issued by the American College of Cardiology and European Society of Cardiology have endorsed the calculation of the area between the EEM and lumen edges as being the area occupied by plaque [22]. A constant automated transducer pull-back speed permits the volumetric quantification of atheroma burden with IVUS (Figs. 5.2 and 5.3). The ability to image anatomically matched arterial

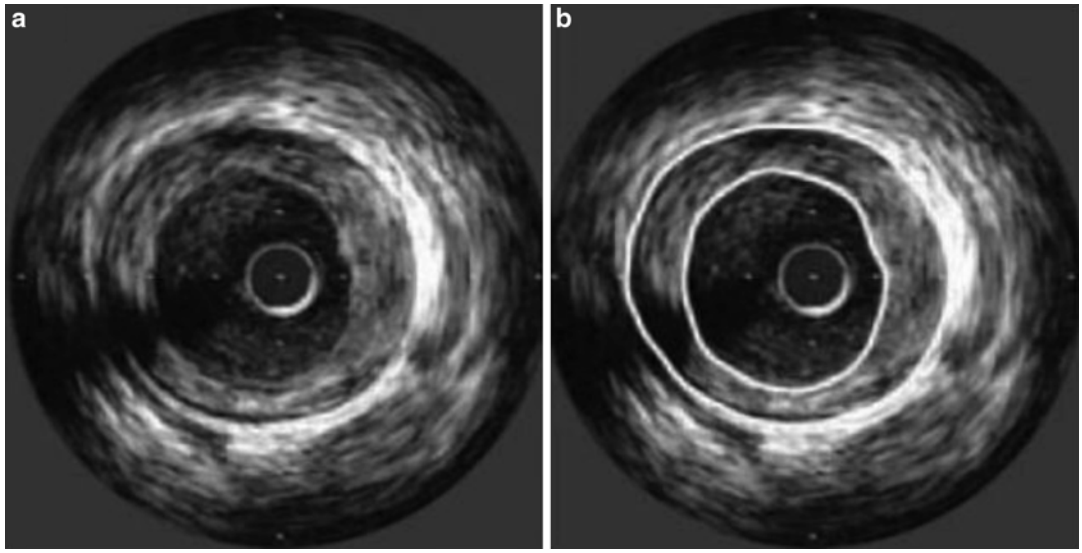

Fig. 5.3 Images from intravascular ultrasound. (**a**) Representative example of a cross-sectional tomographic image of a coronary artery acquired by intravascular ultrasound. (**b**) The panel illustrates the standard measurements that are made by manual planimetry of the leading edges of the external elastic membrane (*outer circle*) and lumen (*inner circle*). The area between these leading edges represents the plaque area (Adapted from Nicholls SJ, Sipahi I, Schoenhagen P, et al. Application of intravascular ultrasound in anti-atherosclerotic drug development. Nat Rev Drug Discov. 2006;5(6):485–92. With permission from Nature Publishing Group)

segments at different time points also provided the opportunity to accurately measure the effect of various therapeutic strategies on disease progression (Fig. 5.4).

A number of experimental models and serial imaging studies in humans had previously suggested that atherosclerosis is a potentially reversible disease. In turn, numerous studies have been designed to assess the impact of favorably modifying one or more of the known traditional cardiovascular risk factors and the resulting influence upon the natural history of coronary atherosclerotic plaque. As a result, several drug classes have been tested in large-scale trials to determine whether they can halt the progression of atherosclerosis. A number of these trials have employed IVUS to detect changes in atheroma burden.

Low-Density Lipoprotein Cholesterol and Atherosclerosis Progression

Lowering serum low-density lipoprotein cholesterol (LDL-C) levels with statins has known anti-atherosclerotic effects, demonstrated in large-scale atherosclerosis imaging trials [5, 23–25], which support the consistent findings of reductions in hard clinical endpoints in both primary [26–28] and secondary disease prevention [29–33]. Most notably, these clinical benefits appear most pronounced in the setting of intensive LDL-C lowering [4]. However the precise mechanism(s) as to how statin therapy contributes to these benefits remains unclear. The degree of atheroma regression appears more modest than the magnitude of clinical benefit accrued from statins, as well as the residual burden of disease that persists during therapy. Prior angiographic studies had not shown consistent atherosclerosis regression with statin monotherapy to corroborate the profound impact that statin therapy had shown upon clinical event rates. With the known limitations of angiography in mind, trials were designed to test the hypothesis that intensive LDL-C lowering with statins would significantly alter the rate of coronary atheroma progression evaluated with serial IVUS.

A consistent observation in IVUS trials is the linear relationship between mean LDL-C levels achieved on statin therapy and the median

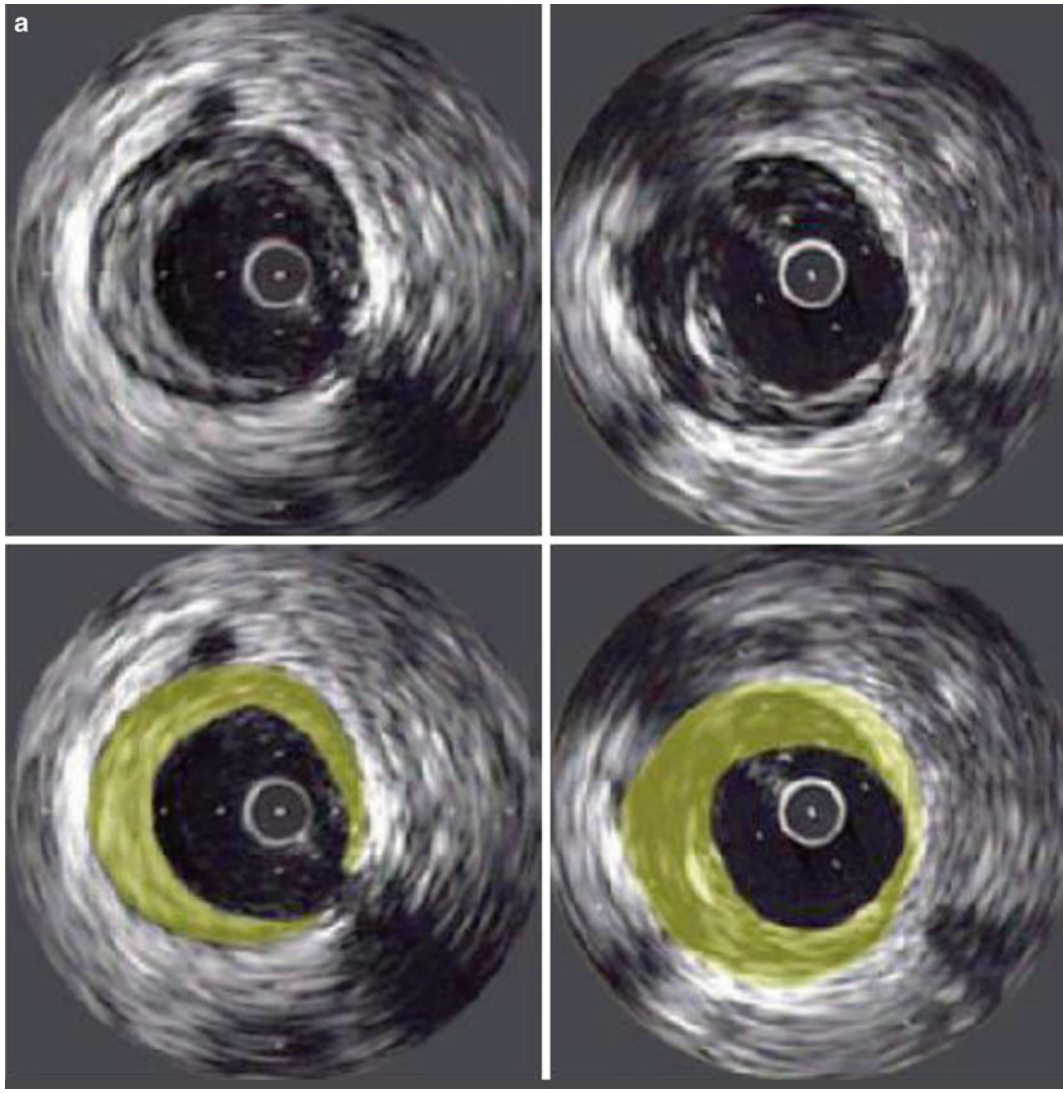

Fig. 5.4 Plaque progression and regression assessed by intravascular ultrasound. (**a**) Illustrative example of plaque progression at a matched site from IVUS studies performed in the same arterial segment a baseline (*left panels*) and follow-up (*right panels*).(**b**) Illustrative example of plaque regression at a matched site from IVUS studies performed in the same arterial segment at baseline (*left panels*) and follow-up (*right panels*). The shading in the *lower panels* highlights the plaque area at each time point (Adapted from Nicholls SJ, Sipahi I, Schoenhagen P, et al. Application of intravascular ultrasound in anti-atherosclerotic drug development. Nat Rev Drug Discov. 2006;5(6):485–92. With permission from Nature Publishing Group)

progression–regression rate of atherosclerosis (Fig. 5.5). In the Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, 18 months of moderate LDL-C reduction (pravastatin 40 mg) resulting in a mean on-treatment LDL-C level of 110 mg/dL associated with significant disease progression [23]. Intensive LDL-C lowering (atorvastatin 80 mg) on the other hand, resulted in a mean on-treatment LDL-C level of 79 mg/dL, halting the natural progression of disease. Interestingly, despite there being a direct relationship between LDL-C lowering and slowing of disease progression, C-reactive protein lowering, a marker of systemic

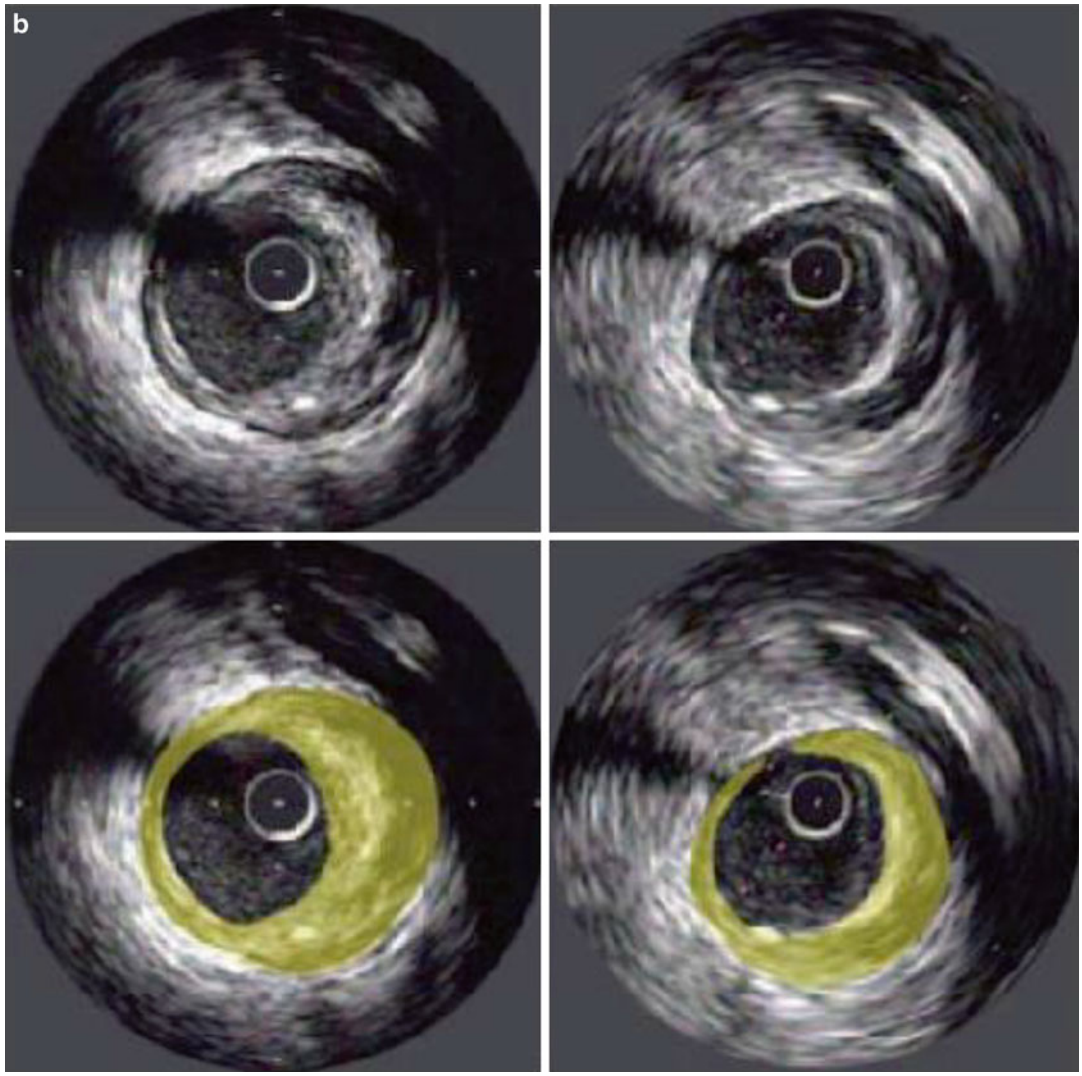

Fig.5.4 (continued)

inflammation, also independently associated with less disease progression [34]. This suggests that non-cholesterol mediated, or pleiotropic effects of statins, are likely to be important in mediating the progression of disease.

The ASTEROID (A study to evaluate the effect of rosuvastatin on IVUS-derived coronary atheroma burden) trial was designed to test the hypothesis that lowering LDL-C levels to below those achieved in REVERSAL might regress plaque. Unequivocal LDL-C reductions to a mean on-treatment level of 61 mg/dL were achieved with rosuvastatin 40 mg daily for 24 months. As predicted by the regression line, this degree of LDL-C lowering associated with significant plaque regression [24]. On the basis of these findings, SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) was performed to directly compare the anti-atherosclerotic efficacy of rosuvastatin 40 mg daily and atorvastatin 80 mg daily for 24 months [5]. Marked regression of coronary atherosclerosis was evident in each treatment group, following the

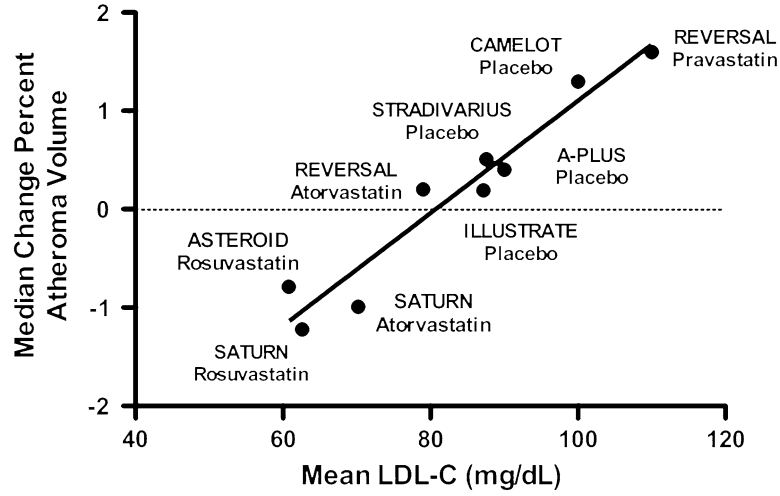

Fig. 5.5 The relationship between plaque regression and achieved LDL-C levels in clinical trials. Line of regression highlighting the relationship between on-treatment mean LDL-C vs. median change in atheroma volume (Adapted from Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease. N Eng J Med 2011;365:2078–87. With permission from Massachusetts Medical Society)

achievement of very low on-treatment LDL-C levels (62 mg/dL vs. 70 mg/dL) in the rosuvastatin and atorvastatin arms, respectively, with two-thirds of the SATURN population demonstrating disease regression. These findings highlight the benefit of high-intensity statin therapy in patients with coronary artery disease, particularly when achieved LDL-C levels are consistent with or lower than those recommended by current treatment guidelines [35, 36]. It remains to be seen however, whether a ceiling effect of the magnitude of plaque regression exists, or whether further degrees of regression are achievable when on-treatment LDL-C levels are driven below those achieved in SATURN. Clinical trials are currently underway to test this hypothesis. The finding that a proportion of individuals continue to demonstrate disease progression despite significant LDL-C lowering with high-intensity statin therapy also highlights the multifactorial nature of the disease process [37], the need to globally intensify risk-factor control in these patients, as well as the importance of identifying novel anti-atherosclerotic strategies to tackle the residual risk and disease burden following statin therapy.

High-Density Lipoprotein Cholesterol and Atherosclerosis Progression

A number of animal and population-based studies have demonstrated the protective effects of high-density lipoprotein cholesterol (HDL-C) [38, 39]. The inverse relationship between HDL-C levels and cardiovascular risk holds true even in the setting of very low LDL-C [40]. A meta-analysis of several trials that employed serial IVUS measures of coronary atheroma volume identified that plaque regression was most likely to occur in patients who, despite achieve LDL-C levels below 87.5 mg/dL, also experienced an increase in HDL-C from baseline of at least 7.5 % [41]. As a result, considerable attention has focused upon developing biological strategies of elevating HDL-C levels and/or promoting HDL particle functionality.

IVUS-based trials, that have tested the anti-atherosclerotic efficacy of direct HDL infusions in humans, have collectively demonstrated safety and potential benefit. Rapid and large amounts of coronary atheroma regression was demonstrated

in relatively few patients afflicted with acute coronary syndrome who underwent weekly intravenous infusions of reconstituted HDL, vs. placebo infusion, over a 5-week period [42]. Further analysis revealed that this degree of plaque regression occurred in concert with preservation of lumen size [43], indicative of reverse remodeling of the coronary arterial wall, most likely a result of rapid plaque delipidation. Similar, beneficial effects have been observed following infusion of apoA-1 particles or autologous, delipidated HDL particles [44, 45]. Whether these favorable effects upon the arterial wall will translate into clinical benefit, remains to be investigated.

The ability to substantially raise HDL-C levels stimulated enthusiasm for the development of cholesteryl ester transfer protein (CETP) inhibitors. This enzyme is responsible for the transfer of esterified cholesterol from HDL-C to atherogenic LDL-C particles in exchange for triglyceride [46]. This pathway seemed an attractive target, as inhibition of CETP would not only result in preventing the cholesterol enrichment of atherogenic lipoproteins, but also substantially raise HDL-C levels, with concomitant modest LDL-C lowering. To add support to this hypothesis, lower cardiovascular event rates have been observed in populations with a genetic predisposition for CETP inhibition, and elevated CETP levels associated with increasing risk of cardiovascular events [47, 48]. However, the first tested CETP inhibitor, torcetrapib, failed to alter the natural progression of coronary atherosclerosis [49], and a parallel run large-scale phase 4 clinical trial was prematurely terminated due to molecule-specific toxicity related to torcetrapib's activation of the renin–angiotensin–aldosterone system [50]. A post hoc analysis however, revealed that those with the highest achieved HDL-C levels demonstrated atheroma regression, indicative of intact HDL functionality in mobilizing lipid from the coronary arterial wall in such patients [51]. Next-generation CETP inhibitors are subsequently under clinical investigation.

Another therapeutic approach involving HDL is to promote the generation of functional HDL particles in vivo, via the up-regulation of endogenous hepatic ApoA-1 synthesis. The theory being that this would result in the generation of nascent HDL particles that would have the ability to undertake the variety of known anti-atherosclerotic functions of HDL, such as reverse cholesterol transport and anti-inflammatory effects. The implications of an oral ApoA-1 inducer (RVX-208) upon the progression of coronary plaque is currently being tested in a serial IVUS study called ASSURE (ApoA-1 Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation) [52].

Blood Pressure

Little is known about the direct anti-atherosclerotic effects of systemic blood pressure lowering, with a study employing serial carotid intima-medial thickening measurements demonstrating attenuation of disease progression following commencement of antihypertensive therapy [53]. Contrary to current national blood pressure lowering guidelines, it remains unclear as to what the optimal or target blood pressure should be in patients afflicted with coronary artery disease. The Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial was designed to assess the effect of blood pressure reduction with amlodipine or enalapril (compared to placebo) in patients with coronary artery disease [54]. An embedded IVUS substudy within CAMELOT demonstrated that blood pressure lowering with amlodipine of the magnitude of 5/3 mmHg corroborated a halting of atheroma progression, compared with the placebo group whose atheroma burden progressed significantly. A further analyses revealed a direct relationship between the degree of systolic blood pressure lowering and plaque volume, with a trend towards plaque regression in patients with a systolic BP < 120 mmHg [55]. A post hoc analysis examined the effect of intensive control of both LDL and blood pressure upon atheroma progression in coronary artery disease patients. Patients with on-treatment serum LDL levels $\leq$70 mg/dL and systolic blood pressure $\leq$120 mmHg experienced less disease progression and more frequent atheroma regression [56]. These findings suggest

the need for such patients to have their blood pressure lowered to levels below those endorsed by current national blood pressure guidelines. As such, there is currently no consensus of the optimal blood pressure target in patients with demonstrable coronary disease, particularly when guidelines currently recommend a treatment goal of systolic blood pressure of <140 mmHg.

Diabetes and Obesity

As the incidence of diabetes mellitus continues to rise, parallel increases in the rates of diabetic atherosclerotic vascular disease are projected to impart major health and socioeconomic challenges for authorities worldwide. Atherosclerosis is the predominant disease phenotype in diabetic individuals, particularly within the coronary, cerebrovascular, and peripheral arterial territories. Diabetic individuals display progressive coronary atherosclerosis, despite LDL-C lowering [57], emphasizing the importance of evaluating novel therapies that reduce the burden and progression of diabetic atherosclerosis. Whilst controversy exists regarding the safety of rosiglitazone [58], IVUS has yielded important mechanistic insights into the anti-atherogenic effects of the PPAR-γ agonist pioglitazone in diabetic patients with coronary artery disease. PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) was a trial that compared the effects of pioglitazone to the insulin secretagogue, glimepiride, upon atherosclerosis progression. The pioglitazone group demonstrated a significantly lower rate of plaque progression when compared to the glimepiride group, who demonstrated plaque progression. These results were supported by the clinical results from the PROACTIVE (Prospective Pioglitazone Clinical Trial In Macrovascular Events), a trial that demonstrated a reduction in hard clinical endpoints with pioglitazone [59].

The increasing prevalence of abdominal obesity is a major factor for the worldwide increase in metabolic syndrome, insulin resistance, and atherosclerotic cardiovascular disease. The Strategy To Reduce Atherosclerosis Development Involving Administration of Rimonabont—the Intravascular Ultrasound Study (STRADIVARIUS) tested the hypothesis that a medication that selectively antagonized the cannabinoid type 1 receptor over an 18-month period might reduce the progression of coronary artery disease in abdominally obese individuals with metabolic syndrome [60]. Rimonabant, however, had no significant effect upon the primary endpoint of change in percent atheroma volume (PAV) from baseline, but had a significant effect on the secondary endpoint, reduction of total atheroma volume (TAV). More frequent psychiatric adverse effects were also reported in the rimonabont group, despite more favorable changes in HDL-C and triglyceride levels, weight loss, and waist circumference reduction compared to the placebo group. Nevertheless, the lack of an overt anti-atherosclerotic effect from rimonabont led to cessation of development of this compound.

Non-Lipid Plaque-Modifying Therapies

IVUS has also been instrumental in outlining the effects of non-lipid modifying compounds on plaque. Inhibition of acyl-coenzyme A:cholesterol acyltransferase (ACAT) promised to be an exciting therapeutic target. The lack of a direct effect on serum LDL-C or HDL-C concentrations made the dose-finding exercise of the potential anti-atherosclerotic effects of this class of compound difficult. Imaging endpoints were thus considered the most appropriate technique for demonstration of mechanistic efficacy. Despite demonstrative anti-atherosclerotic properties of ACAT inhibitors in animal models of disease, the failure to observe disease regression on serial IVUS with ACAT inhibition in two separate clinical trials resulted in halting the development programs of ACAT inhibitors [61, 62].

The mechanical strain of the arterial wall, coupled with local tissue deformation can be determined by the cross-correlation analysis of the radiofrequency IVUS signal, to derive localized strain maps of the arterial wall. The imputed

degree of radial strain can be incorporated within the plaque area to determine the local elastography of the segment, or upon the luminal boundary (to a depth of 450 μm) to determine the local palpography of the respective plaque segment. As such, these elastic properties of the coronary arterial wall have been proposed to predict plaque vulnerability [63]. Subsequently, the Integrated Biomarker and Imaging (IBIS-2) trial was designed to assess for changes in plaque deformability (utilizing IVUS-palpography) in response to the lipoprotein-associated phospholipase A2 inhibitor, darapladib [64]. This was the first drug-intervention trial designed to explore if a therapeutic intervention could modulate plaque composition, and subsequent plaque phenotype. Although it was postulated that darapladib would lower the deformability/strain of coronary atherosclerotic plaques, the results of this trial failed to show any overall significant effect of darapladib upon plaque mechanical strain, despite changes in atheroma composition, which was an exploratory endpoint. The total atheroma burden in the treatment group also remained unchanged, questioning the anti-atherosclerotic potential of this compound, although further clinical trials are currently underway to assess the anti-atherosclerotic and clinical efficacy of this compound.

Cardiac Allograft Vasculopathy

IVUS has also yielded significant insights into the pathogenesis and modulation of cardiac allograft vasculopathy, the single greatest determinant of allograft failure and overall mortality within this patient group. Moreover, serial IVUS imaging has been employed to assess the progression of cardiac allograft vasculopathy [65]. Everolimus-based immunosuppressive therapy following cardiac transplantation was demonstrated to show a beneficial impact upon the rate of progression of intimal thickening within cardiac allograft recipients [66]. Moreover, this was associated with fewer episodes of rejection and the need for repeat transplantation when compared to a standard azathioprine-based immunosuppressive regimen. A separate study identified the rate of intimal thickening seen on IVUS at the 1-year mark following cardiac transplantation to predict 5-year mortality [67].

Clinical Implications of the Burden and Plaque Progression–Regression on IVUS

Although IVUS has been instrumental in enabling us to determine the efficacy of anti-atherosclerotic strategies, the clinical relevance of such an approach lies in the ability to demonstrate an association between the burden of atherosclerotic disease, its rate of progression and subsequent clinical outcomes. A number of studies employing IVUS, that have either measured plaque burden of defined lesions in a non-volumetric fashion [68, 69], or via a volumetric analysis of whole vessel segments [10, 70], have described an association between IVUS-derived plaque burden and incident clinical events, driven largely by an increased risk of coronary revascularization. In addition, a pooled analysis revealed that the rate of progression of IVUS-derived plaque volume independently associated with the composite risk of death, myocardial infarction, and coronary revascularization [10]. Further studies, with larger numbers of enrolled patients, with longer duration of clinical follow-up, will be required to confirm these associations in a single trial.

Conclusions

IVUS-derived plaque burden and its rate of change are well-established imaging biomarkers used in clinical trials to test the efficacy of currently utilized and experimental anti-atherosclerotic therapies. Indeed, changes in plaque volume have been largely congruent to the clinical findings of experimental agents, such that IVUS-based trial results have been fundamental in determining the fate of these compounds. Serial coronary imaging with IVUS however, has affirmed the importance of stringent and global atherosclerosis risk-factor modification in order

to attenuate, and even regress the disease process. Further refinements in ultrasound technologies will enable enhanced plaque characterization, which will continue to promote the role of direct coronary imaging for not only future drug development programs, but also to better risk-stratify individuals. Whether this information will be strong enough to alter clinical practice remains to be seen.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125:e2–220.
2. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation. 2001;104:2855–64.
3. Bandyopadhyay P. Cardiovascular diseases and diabetes mellitus. Drug News Perspect. 2006;19:369–75.
4. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376: 1670–81.
5. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011;365:2078–87.
6. Cliff WJ, Heathcote CR, Moss NS, Reichenbach DD. The coronary arteries in cases of cardiac and noncardiac sudden death. Am J Pathol. 1988;132:319–29.
7. Dalager S, Falk E, Kristensen IB, Paaske WP. Plaque in superficial femoral arteries indicates generalized atherosclerosis and vulnerability to coronary death: an autopsy study. J Vasc Surg. 2008;47:296–302.
8. Ringqvist I, Fisher LD, Mock M, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). J Clin Invest. 1983;71:1854–66.
9. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115:459–67.
10. Nicholls SJ, Hsu A, Wolski K, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. J Am Coll Cardiol. 2010;55:2399–407.
11. Lin FY, Shaw LJ, Dunning AM, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. J Am Coll Cardiol. 2011;58:510–9.
12. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med. 2000;343:915–22.
13. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data. Circulation 1983;68:939–50.
14. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation. 1995;92:657–71.
15. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003;108:1664–72.
16. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995;92:2333–42.
17. Ballantyne CM. Clinical trial endpoints: angiograms, events, and plaque instability. Am J Cardiol. 1998;82: 5M–11.
18. Mintz GS, Painter JA, Pichard AD, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: an intravascular ultrasound study with clinical correlations. J Am Coll Cardiol. 1995;25:1479–85.
19. Schoenhagen P, Ziada KM, Vince DG, Nissen SE, Tuzcu EM. Arterial remodeling and coronary artery disease: the concept of "dilated" versus "obstructive" coronary atherosclerosis. J Am Coll Cardiol. 2001;38: 297–306.
20. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316:1371–5.
21. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes : an intravascular ultrasound study. Circulation. 2000;101:598–603.
22. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2001;37:1478–92.
23. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291: 1071–80.
24. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295:1556–65.
25. Crouse 3rd JR, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007; 297:1344–53.

26. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333:1301–7.
27. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007;357:1477–86.
28. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
29. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344: 1383–9.
30. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998; 339:1349–57.
31. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
32. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001–9.
33. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35.
34. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352: 29–38.
35. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227–39.
36. Smith Jr SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011;58:2432–46.
37. Bayturan O, Kapadia S, Nicholls SJ, et al. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. J Am Coll Cardiol. 2010;55:2736–42.
38. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989;79:8–15.
39. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circ Res. 2004;95:764–72.
40. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357:1301–10.
41. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007;297:499–508.
42. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA. 2003;290:2292–300.
43. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Relationship between atheroma regression and change in lumen size after infusion of apolipoprotein A-I Milano. J Am Coll Cardiol. 2006;47:992–7.
44. Tardif JC, Gregoire J, L'Allier PL, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA. 2007;297:1675–82.
45. Waksman R, Torguson R, Kent KM, et al. A first-in-man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. J Am Coll Cardiol. 2010;55:2727–35.
46. Barter PJ, Brewer Jr HB, Chapman MJ, Hennekens CH, Rader DJ, Tall AR. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. Arterioscler Thromb Vasc Biol. 2003;23:160–7.
47. Boekholdt SM, Kuivenhoven JA, Wareham NJ, et al. Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: the prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study. Circulation. 2004;110:1418–23.
48. Johannsen TH, Frikke-Schmidt R, Schou J, Nordestgaard BG, Tybjaerg-Hansen A. Genetic inhibition of CETP, ischemic vascular disease and mortality, and possible adverse effects. J Am Coll Cardiol. 2012;60:2041–8.
49. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med. 2007;356:1304–16.
50. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357:2109–22.
51. Nicholls SJ, Tuzcu EM, Brennan DM, Tardif JC, Nissen SE. Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis: insights from ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation). Circulation. 2008;118:2506–14.
52. ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression

Evaluation (ASSURE I). http://clinicaltrials.gov/ct2/show/NCT01067820?term=ASSURE&rank=4 2011. Last accessed on July 5th, 2013.
53. Zanchetti A. Antiatherosclerotic effects of antihypertensive drugs: recent evidence and ongoing trials. Clin Exp Hypertens. 1996;18:489–99.
54. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292:2217–25.
55. Sipahi I, Tuzcu EM, Schoenhagen P, et al. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. J Am Coll Cardiol. 2006;48:833–8.
56. Chhatriwalla AK, Nicholls SJ, Wang TH, et al. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. J Am Coll Cardiol. 2009;53:1110–5.
57. Nicholls SJ, Tuzcu EM, Kalidindi S, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. J Am Coll Cardiol. 2008; 52:255–62.
58. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457–71.
59. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366:1279–89.
60. Nissen SE, Nicholls SJ, Wolski K, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA. 2008;299:1547–60.
61. Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. N Engl J Med. 2006;354:1253–63.
62. Tardif JC, Gregoire J, L'Allier PL, et al. Effects of the acyl coenzyme A: cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. Circulation. 2004;110:3372–7.
63. de Korte CL, van der Steen AF, Cespedes EI, Pasterkamp G. Intravascular ultrasound elastography in human arteries: initial experience in vitro. Ultrasound Med Biol. 1998;24:401–8.
64. Serruys PW, Garcia-Garcia HM, Buszman P, et al. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. Circulation. 2008;118:1172–82.
65. Kapadia SR, Nissen SE, Tuzcu EM. Impact of intravascular ultrasound in understanding transplant coronary artery disease. Curr Opin Cardiol. 1999;14:140–50.
66. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med. 2003; 349:847–58.
67. Kobashigawa JA, Tobis JM, Starling RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. J Am Coll Cardiol. 2005;45:1532–7.
68. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364:226–35.
69. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. Circulation. 2012;126:172–81.
70. Puri R, Wolski K, Uno K, et al. Left main coronary atherosclerosis progression, constrictive remodeling, and clinical events. JACC Cardiovasc Interv. 2013;6: 29–35.