Imaging Progression of Coronary Atherosclerosis – Lessons Learned and Ongoing Challenges –

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Advances in arterial wall imaging permit direct visualization of the full burden of atherosclerosis within the coronary arteries. When performed serially, these studies have demonstrated the importance of targeting major cardiovascular risk factors and provide an important opportunity for evaluation of novel therapies. The findings of these studies, the clinical implications and ongoing advances will be reviewed. (*Circ J* 2013; **77**: 3–10)

Key Words: Atherosclerosis; Intravascular ultrasound; Risk factors

Large, randomized controlled trials have demonstrated the benefits of medical therapies that target blood pressure¹ and dyslipidemia.² Despite the widespread use of these agents, atherosclerotic cardiovascular disease remains a major public health challenge worldwide. The overall prevalence of disease continues to rise in parallel with the global spread of abdominal obesity. Furthermore, many patients continue to experience clinical events despite the use of established therapies.³ This ongoing disease risk presents a considerable challenge in terms of the need to develop more effective forms of risk prediction and preventive therapies. With technological advances in atherosclerotic plaque imaging, there is increasing interest in the role it might play in achieving more effective reductions in cardiovascular risk.

Traditional Approach to Plaque Imaging

Since its inception in 1958, coronary angiography (CAG) has been widely used to diagnose and quantify the extent of obstructive disease within the coronary arteries. This has guided a range of medical and revascularization strategies, largely on the basis of observations of a relationship between the extent of angiographic disease and the incidence of adverse cardiovascular events.⁴ Serial CAG has also been used in clinical trials to evaluate the effect of medical therapies on the progression of obstructive disease.⁵ However, there are several limitations to the relationship between angiographic findings and atherosclerotic disease. A number of groups have reported that the ability of CAG to predict outcomes at a focal level is limited, with many patients found to have mildly stenotic culprit lesions at the time of an episode of acute coronary syndrome (ACS).⁶ Furthermore, it has become increasingly apparent that CAG generates a 2-D silhouette of the arterial lumen and does not image the vessel wall, the site at which plaque accumulates. In other words, CAG does not directly image

plaque; rather, it visualizes the obstructive complications of the disease. Such observations have stimulated the need to develop imaging modalities that directly visualize plaque in the vessel wall.

Intravascular Ultrasound (IVUS)

Initially conceptualized in the 1970s, IVUS enables catheter placement of high-frequency ultrasound transducers within the coronary artery lumen. Being able to perform high-frequency ultrasonography in close proximity to the artery wall generates high-resolution cross-sectional images of the full thickness of the vessel. Enthusiasm for this approach was stimulated by interest in its ability to guide more optimal percutaneous coronary interventions. In parallel, it was appreciated that the ability to image the entire artery wall permitted quantitation of the burden of atherosclerotic plaque contained within. Investigations revealed the presence of far more extensive atheroma than suggested by CAG,⁷ and the early prevalence of coronary atherosclerosis in adolescence,⁸ and confirmed observations from pathology studies of compensatory remodeling of the artery wall in response to plaque accumulation⁹ (Figure 1). The ability to image anatomically matched arterial segments at different time points also provided the opportunity to more precisely evaluate the effect of medical therapies on disease progression. This led to a large number of clinical trials that have primarily investigated the effect of targeting major cardiovascular risk factors on atherosclerotic disease burden.

Lowering Low-Density Lipoprotein (LDL)

Clinical trials have consistently demonstrated that lowering the level of LDL cholesterol (LDL-C) reduces cardiovascular event rates.² Early studies with quantitative CAG demonstrated

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Figure 1. Examples of intravascular ultrasound imaging of atherosclerotic plaque in a region that appears to be free of obstructive disease on coronary angiography (**Left**). Plaque (yellow), lumen (red) and catheter (black) imaging within each ultrasound image (**Right**) are delineated.

that LDL-C lowering is associated with less progression of obstructive disease.⁵ Coronary IVUS imaging has been used to extend these observations further, particularly in the setting of use of high-intensity statin therapy. The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study¹⁰ directly compared the effects of moderate lipid-lowering with pravastatin 40mg and intensive lipid-lowering with atorvastatin 80mg for 18 months. Achieving a lower LDL-C level with atorvastatin (79 vs. 110mg/dl) was associated with halting the progression of coronary atherosclerosis. Although a direct relationship was demonstrated between the degree of LDL-C lowering and slowing of disease progression, it was also reported that lowering the inflammatory biomarker, C-reactive protein (CRP), was independently associated with slower disease progression.¹¹ These findings affirmed the benefits of aggressive lipid-lowering, but also the potential pleiotropic effects, with high-intensity statin therapy.

Supporting data for the benefits of statin therapy on coronary plaque progression have been provided by a demonstration of the benefits of simvastatin in a Danish cohort¹² and in a number of important studies from Japan.^{13,14} In fact, the studies in Japan typically reveal disease regression in a much shorter time frame, when focusing primarily on the shorter, higher disease burden, culprit lesions of patients with ACS. Although these findings suggest that the potential benefits of statin therapy in patients with ACS may occur relatively quickly, the relative linearity of these benefits has not been demonstrated because of the inability to conduct invasive imaging of patients on more than 2 occasions.

This relationship was further explored in the ASTEROID (A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden) study,¹⁵

in which patients were treated with rosuvastatin 40mg for 24 months. Lowering LDL-C to 61mg/dl and raising high-density lipoprotein cholesterol (HDL-C) to 49mg/dl was associated with regression of coronary atherosclerosis. A subsequent pooled analysis of 1,455 statin-treated patients demonstrated that both LDL-C lowering and modest HDL-C raising were independent predictors of the ability of statins to slow disease progression.¹⁶ In fact, the finding that lowering the ratio of apolipoprotein B/A-I was the strongest predictor of benefit in these studies¹⁶ affirms the pivotal role played by lipoprotein particles in atherogenesis and supports the need to therapeutically target both atherogenic and protective lipid particles.

On the basis of these findings, SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin)¹⁷ was performed to directly compare the effects of atorvastatin 80mg and rosuvastatin 40mg for 24 months, in order to determine whether different lipid profiles with high-intensity statin regimens influenced the progression of coronary atherosclerosis. Achieving low levels of LDL-C (62 vs. 70mg/dl) and more optimal levels of HDL-C (48 vs. 50mg/dl) with rosuvastatin and atorvastatin, respectively, was associated with marked regression of coronary atherosclerosis. In addition to the observation of a greater magnitude of regression than in previous studies, it was also reported that two-thirds of individual patients demonstrated regression with these therapies. These studies provide further evidence for the benefits of high-intensity statin therapy in patients with established coronary artery disease. The finding that in many individuals the disease continue to progress, despite achieving low levels of LDL-C, highlights the multifactorial nature of atherosclerosis and the need to target patients' global risk.¹⁸

Targeting HDL

A large body of evidence suggests that HDL may play a protective role in atherosclerosis. Population studies consistently demonstrate an inverse relationship between HDL-C levels and prospective cardiovascular risk.¹⁹ This association continues to be demonstrated in patients with very low LDL-C levels.²⁰ Promoting HDL via direct infusion or transgenic expression of its major proteins has a favorable effect on the size and composition of atherosclerotic lesions in animal models.^{21–27} The finding that modest increases in HDL-C independently predict the ability of statins to slow plaque progression¹⁶ complements similar findings from clinical event studies.^{28,29} These observations provide the rationale for the development of HDL targeted therapies as a potential new strategy for patients with coronary disease.

Three clinical studies have demonstrated the potential benefits of infusing HDL in humans. In the first of these studies, patients with ACS underwent IVUS imaging at baseline and following 5 weeks of treatment with intravenous infusions of reconstituted HDL containing apoA-IMilano (AIM) or saline.³⁰ Patients receiving the AIM infusions demonstrated rapid regression of coronary atherosclerosis. These benefits were observed, without any change in lumen size, suggesting that they would not have been detected by angiographic evaluation and supporting the concept that regression is accompanied by reverse remodeling of the artery wall.³¹ Similar findings have been reported from studies that evaluated the effect of infusing HDL particles containing wild-type apoA-I³² or autologous preparations of delipidated HDL.³³ In total, these findings support the concept that delipidated HDL promotes rapid cholesterol efflux³⁴ and improved endothelial function.^{35,36} The therapeutic potential of any of these strategies awaits further evaluation in phase 3 clinical trials.

Increasing interest in the ability to substantially raise HDL-C levels has focused primarily on the development of cholesteryl ester transfer protein (CETP) inhibitors. CETP facilitates the transfer of esterified cholesterol from HDL to both very-LDL and LDL particles in exchange for triglyceride.³⁷ Although the physiological role of CETP remains uncertain, interest in its inhibition has developed because that would substantially raise HDL-C levels and prevent cholesterol enrichment of atherogenic lipoproteins. Supporting evidence for this approach was provided by observations that populations with a high prevalence of low CETP activity appear to be associated with less cardiovascular events, when accompanied by high HDL-C levels³⁸ and that inhibiting CETP in animal species that endogenously express CETP is atheroprotective.^{39–41}

Although early clinical development of CETP inhibitors resulted in favorable effects on both HDL-C and LDL-C levels, the first large-scale clinical trial with torcetrapib was prematurely terminated because of high rates of mortality and cardiovascular events.⁴² In parallel, imaging studies had been conducted to evaluate the effects of torcetrapib on disease progression; the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) study⁴³ with used IVUS to compare the effects of torcetrapib 60 mg and placebo on progression of coronary atherosclerosis in patients treated with atorvastatin for a LDL-C goal of 100 mg/dl. Although the torcetrapib group demonstrated a 61% increase in HDL-C and incremental lowering of LDL-C to 70 mg/dl in combination with atorvastatin, no effect was seen in terms of either slowing disease progression or promoting

regression. Similar findings were observed in 2 studies that measured carotid intima-medial thickness.^{44,45} Subsequent analyses from the IVUS study revealed that as HDL-C levels increased with torcetrapib treatment, disease progression rates declined, with evidence of regression in the patients who achieved very high levels of HDL-C.⁴⁶ This finding is important because it suggests an intact capacity of HDL to promote lipid transport and shrink plaque size with torcetrapib treatment and suggests that the adverse effects may reflect a molecule-specific problem. This is further supported by observations that HDL efflux capacity is intact in CETP-deficient and torcetrapib-treated individuals⁴⁷ and that torcetrapib has a number of off-target toxicities at the level of both the adrenal gland and artery wall.⁴⁸ These observations have permitted the opportunity for ongoing clinical development of other CETP inhibitors that lack such toxicity.

An alternative approach to targeting HDL is to focus primarily on the generation of nascent functional HDL particles. The benefits of HDL infusions have been demonstrated, with no steady state increase in HDL-C levels, suggesting that provision of functional HDL may enhance cholesterol transport. Strategies such as CETP inhibition impair physiologic remodeling pathways, artificially raising HDL-C levels, the implications of which remain uncertain. The ability to upregulate endogenous hepatic synthesis of apoA-I should, theoretically, create nascent HDL particles that would carry out physiological activities, including cholesterol efflux and antiinflammatory functions, once they enter the systemic circulation. Preclinical studies of an apoA-I inducer (RVX-208) reveal increased cholesterol efflux capacity of serum of treated non-human primates.⁴⁹ Early studies of statin-treated patients with coronary artery disease demonstrated that administration of RVX-208 resulted in modest increases in HDL-C, predominantly because of increases in the number of larger HDL particles.⁵⁰ These observations are consistent with facilitation of cholesterol efflux, the implications of which are being further evaluated in the ASSURE (ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation) study, in which the ability of RVX-208 to promote atheroma regression in patients with coronary disease is being evaluated with serial IVUS imaging.⁵¹

Blood Pressure (BP)

BP is the major contributing risk factor to the proliferation of cardiovascular disease worldwide, with evidence of marked clinical benefit with use of BP-lowering therapies in hypertensive patients.⁵² However, the effect of BP and its modification on disease progression has been relatively poorly studied. Limited studies have revealed that progression of carotid intima-medial thickening is highly sensitive to BP, with studies that imaged the artery wall suggesting that lowering BP is beneficial.⁵³

The CAMELOT (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis) study⁵⁴ evaluated the effect of amlodipine, enalapril and placebo in patients with established coronary artery disease and BP that was considered to be optimally controlled, defined as a diastolic BP <100 mmHg, on clinical event rates. An IVUS imaging sub-study⁵⁴ demonstrated that treatment with amlodipine slowed disease progression, in parallel with lower cardiovascular event rates. A direct relationship was observed between achieved levels of systolic BP and disease progression, with a trend towards regression observed in patients with a BP <120 mmHg.⁵⁵ The finding of a greater benefit at BPs lower than the current

Figure 2. Examples of atherosclerotic plaque imaging with near-infrared spectroscopy demonstrating lipid content (**Upper**) and ultrasonic radiofrequency analysis represented as a spectral tissue map demonstrating fibrotic, fibrocalcific, pathological intimal thickening, thick-cap fibroatheroma and thin-cap fibroatheroma phenotypes (**Lower**, L to R).

treatment goal of 140 mmHg adds to the controversy of how aggressively to manage BP in patients with established coronary disease. This is being further evaluated in AQUARIUS (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study),⁵⁶ in which the effects of the renin inhibitor, aliskerin, on plaque progression is being assessed in patients with BPs in the prehypertensive range. The observation of a greater benefit in patients who achieve aggressive control of both LDL-C and BP supports the need for modification of global risk, rather than focusing on a specific risk factor.⁵⁷

Diabetes

An increasing prevalence of type 2 diabetes, in association with abdominal obesity, is a major factor underlying the global spread of atherosclerotic disease. The adverse prognosis in patients with diabetes is accompanied by greater plaque burden and disease progression, in association with impaired compensatory remodeling of the artery wall.⁵⁸ Although aggressive lowering LDL-C is associated with slowing of disease progression, the finding that plaque continues to accumulate emphasizes the need to develop additional therapeutic strategies to reduce cardiovascular risk in diabetic patients.⁵⁸

The PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study⁵⁹ directly compared the effects of glimepiride and pioglitazone in patients with type 2 diabetes. Favorable effects on HDL-C, triglycerides and CRP were associated with halting of disease progression in the pioglitazone group. The observation that lowering the triglyceride/HDL-C ratio was

the strongest predictor of slowing progression underscores the importance of atherogenic dyslipidemia in the propagation of coronary disease in diabetes.⁶⁰ The incremental benefit of targeting multiple metabolic risk factors further supports the need for aggressive management of cardiovascular risk in patients with diabetes.⁶¹

Experimental Therapies

Serial plaque imaging provides an additional opportunity to evaluate the effects of novel antiatherosclerotic agents. The ability to determine whether such an agent has a favorable effect on plaque progression can provide important support to either advance or halt clinical development of new therapies. This is particularly important, given the large expense and time required to assess new therapies in large, phase 3 clinical trials. This approach has been used in several programs, where the lack of benefit of acyl:cholesterol acyltransferase inhibitors^{62,63} and endocannabinoid receptor antagonists³⁰ led to cessation of development of these compounds.

Clinical Implications of Plaque Progression Studies

The ultimate relevance of the findings of such studies is determined by the ability to demonstrate an association between measures of plaque burden and clinical outcome. Early studies of cross-sectional images within the left main coronary artery demonstrated that disease progression was associated with the incidence of cardiovascular events during the next 12 months.⁶⁴ These findings were extended to volumetric analyses, in which

Figure 3. Examples of coronary artery imaging with optical coherence tomography demonstrating atherosclerotic plaque with a large lipid pool and thin fibrous cap (**Left**), and stent struts with neointimal hyperplasia (**Right**).

both baseline plaque burden and the rate of progression in serial observations were associated with a greater likelihood of death, myocardial infarction and coronary revascularization.⁶⁵

Novel Measures of Plaque Composition

Increasing interest has focused on the potential role of plaque composition in determining the propensity of plaque to rupture and promote acute ischemic events. Pathologic studies have consistently demonstrated that lesions containing more lipid, inflammation and necrotic material are more vulnerable.⁶ Although conventional ultrasonography can characterize both the degree of echogenicity and calcification of plaque, these techniques lack the resolution to monitor therapeutic-induced changes in plaque composition. Recent studies have demonstrated that lesions containing spotty calcification, which has been reported as associated with vulnerability, identify patients that are more likely to undergo disease progression on serial observation.⁶⁶

Additional intravascular measures have been developed with the aim of more accurate characterization of plaque composition. Advances in analysis of both radiofrequency signals⁶⁷ or integrated backscatter⁶⁸ of ultrasound have been reported to distinguish fibrotic, fibrofatty, calcific and necrotic components. Further analysis enables phenotypic categorization of individual lesions, including identification of thin-cap fibroatheromas (**Figure 2**). Early studies have demonstrated potential benefits of statin therapy⁶⁹ and the lipoprotein-associated phospholipase A2 inhibitor, darapladib,⁷⁰ on plaque composition. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) registry⁷¹ demonstrated that the presence of a thin-cap fibroatheroma identified by radiofrequency analysis was associated with a greater rate of cardiovascular events, when observed in patients with a greater plaque burden. However, a greater need for histologic validation is required, with inconsistent reports in the literature⁷² confounding interpretation of these findings. The potential relevance and utility of evaluation of novel therapies remain to be determined.

Near-infrared spectroscopy (NIRS) permits characterization of the chemical components of tissue samples. Advances in catheter techniques enable performance of NIRS imaging within the coronary arteries.⁷³ Early development of this ap-

proach permits quantitation of the lipid content within atherosclerotic plaque. Although early reports that open-label statin therapy reduces the lipid content of plaque,⁷⁴ the potential utility of this approach in the evaluation of antiatherosclerotic agents remains uncertain.

Optical coherence tomography (OCT) permits intravascular imaging with light rather than ultrasound, generating greater imaging resolution, but at the expense of reduced tissue penetration. Although the full vessel wall is suboptimally imaged, OCT does enable high-resolution imaging of the lumen surface, with superior characterization of intravascular stents and fibrous cap thickness.⁷⁵ Early reports suggested potential evaluation of lipid pools and macrophage deposits beneath the fibrous cap, but this remains to be validated.⁷⁵ Accordingly, serial OCT imaging is likely to play an important role in the evaluation of novel stents. The potential utility of OCT in the early evaluation of novel antiatherosclerotic agents is unknown (**Figure 3**).

Non-Invasive Imaging

Although intravascular techniques provides the greatest imaging resolution of the artery wall, each technique requires an invasive catheterization procedure, which limits the potential pool of patients for study and the number of time points for evaluation. There is increasing interest in the potential of emerging non-invasive modalities of imaging atherosclerotic plaque. Computed tomography provides a number of options for evaluation of atherosclerotic plaque. Quantitation of plaque calcification has been consistently reported as associated with cardiovascular risk.^{76,77} However, the utility of these measurements in clinical trials is limited by reports that statins have no effect on progression of the calcification of coronary plaque.^{78,79} Computed tomography illustrates obstructive lesions within the coronary vasculature, with a high negative predictive value in intermediate-risk patients.⁸⁰ However, the limited ability to image the full burden of plaque in the vessel wall raises further uncertainty over its potential utility for evaluating new therapies. Fusion imaging with positron emission tomography (PET) enables anatomical location of the plaque with CT and then evaluation of macrophage glucose uptake with PET.⁸¹ The potential to evaluate changes in plaque inflammation with this approach has generated considerable interest.

Magnetic resonance imaging enables characterization of plaque burden and composition, with early studies reporting the favorable effects of statins⁸² and niacin.⁸³ However, this technique is limited to imaging larger arteries and at this point in time evaluation of the effect of novel therapies on coronary atherosclerosis is not possible. The ability to combine these non-invasive techniques with molecular targeted agents will enable study of the effects of therapies on specific factors in atherosclerotic plaque that is involved in rupture.⁸⁴ This potentially provides incremental information regarding the effect of new therapies.

Summary

Significant advances in arterial wall imaging have expanded our ability to visualize the full extent of atherosclerotic plaque. These studies have affirmed the importance of aggressive targeting of major risk factors in order to slow disease progression and, in some cases, effect regression of atherosclerotic plaque. Ongoing technical advances will provide a greater role for imaging of various aspects of the disease in a range of vascular beds and improve the ability to evaluate novel anti-atherosclerotic therapies.

Disclosures

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References

- Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362**: 1527–1535.
- Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, 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**: 1670–1681.
- Libby P. The forgotten majority: Unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol* 2005; **46**: 1225–1228.
- Ringqvist I, Fisher LD, Mock M, Davis KB, Wedel H, Chaitman BR, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest* 1983; **71**: 1854–1866.
- Ballantyne CM. Clinical trial endpoints: Angiograms, events, and plaque instability. *Am J Cardiol* 24 1998; **82**: 5M–11M.
- Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; **92**: 657–671.
- Lavoie AJ, Bayturan O, Uno K, Hsu A, Wolski K, Schoenhagen P, et al. Plaque progression in coronary arteries with minimal luminal obstruction in intravascular ultrasound atherosclerosis trials. *Am J Cardiol* 2010; **105**: 1679–1683.
- Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: Evidence from intravascular ultrasound. *Circulation* 2001; **103**: 2705–2710.
- 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.
- Nissen SE, Tuzcu EM, Schoenhagen P, Brown G, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial. *JAMA* 2004; **291**: 1071–1080.
- Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005; **352**: 29–38.
- Jensen LO, Thayssen P, Pedersen KE, Stender S, Haghfelt T. Regression of coronary atherosclerosis by simvastatin: A serial intravascular ultrasound study. *Circulation* 2004; **110**: 265–270.
- Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: The ESTABLISH Study. *Circulation* 2004; **110**: 1061–1068.
- Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: Multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Circ J* 2009; **73**: 2110–2117.
- Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA* 2006; **295**: 1556–1565.
- Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007; **297**: 499–508.
- Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011; **365**: 2078–2087.
- Bayturan O, Kapadia S, Nicholls SJ, Tuzcu EM, Shao M, Uno K, et al. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. *J Am Coll Cardiol* 2010; **55**: 2736–2742.
- Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease: The Framingham Study. *Am J Med* 1977; **62**: 707–714.
- Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007; **357**: 1301–1310.
- Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit. *J Clin Invest* 1990; **85**: 1234–1241.
- Badimon JJ, Badimon L, Galvez A, Dische R, Fuster V. High density lipoprotein plasma fractions inhibit aortic fatty streaks in cholesterol-fed rabbits. *Lab Invest* 1989; **60**: 455–461.
- Nicholls SJ, Cutri B, Worthley SG, Kee P, Rye KA, Bao S, et al. Impact of short-term administration of high-density lipoproteins and atorvastatin on atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol* 2005; **25**: 2416–2421.
- Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. *Proc Natl Acad Sci USA* 1994; **91**: 9607–9611.
- Rubin EM, Krauss RM, Spangler EA, Verstuyft JG, Clift SM. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. *Nature* 1991; **353**: 265–267.
- Rong JX, Li J, Reis ED, Choudhury RP, Dansky HM, Elmaleh VI, et al. Elevating high-density lipoprotein cholesterol in apolipoprotein E-deficient mice remodels advanced atherosclerotic lesions by decreasing macrophage and increasing smooth muscle cell content. *Circulation* 2001; **104**: 2447–2452.
- Shah PK, Yano J, Reyes O, Chyu KY, Kaul S, Bisgaier CL, et al. High-dose recombinant apolipoprotein A-I Milano mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein E-deficient mice. *Circulation* 2001; **103**: 3047–3050.
- Cui Y, Watson DJ, Girman CJ, Shapiro DR, Gotto AM, Hiserote P, et al. Effects of increasing high-density lipoprotein cholesterol and decreasing low-density lipoprotein cholesterol on the incidence of first acute coronary events (from the Air Force/Texas Coronary Atherosclerosis Prevention Study). *Am J Cardiol* 2009; **104**: 829–834.
- Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Mercouris BR, Pehlivaniadis A, et al. Effect of atorvastatin on high density lipoprotein cholesterol and its relationship with coronary events: A subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study. *Curr Med Res Opin* 2004; **20**: 627–637.
- Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: A randomized controlled trial. *JAMA* 2003; **290**: 2292–2300.
- Nicholls SJ, Tuzcu EM, Sipahi I, Schoenhagen P, Crowe T, Kapadia S, et al. Relationship between atheroma regression and change in lumen size after infusion of apolipoprotein A-I Milano. *J Am Coll Cardiol* 2006; **47**: 992–997.
- Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Lesperance J, Heinson TM, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: A randomized controlled trial. *JAMA* 2007; **297**: 1675–1682.

33. Waksman R, Torguson R, Kent KM, Pichard AD, Suddath WO, Satler LF, 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**: 2727–2735.
34. Rye KA, Barter PJ. Formation and metabolism of pre-beta-migrating, lipid-poor apolipoprotein A-I. *Arterioscler Thromb Vasc Biol* 2004; **24**: 421–428.
35. Bisoendial RJ, Hovingh GK, Levels JHM, Lerch PG, Andresen I, Hayden MR, et al. Restoration of endothelial function by increasing high-density lipoprotein in subjects with isolated low high-density lipoprotein. *Circulation* 2003; **107**: 2944–2948.
36. Spieker LE, Sudano I, Hurlimann D, Lerch PD, Lang MG, Binggeli C, et al. High-density lipoprotein restores endothelial function in hypercholesterolemic men. *Circulation* 2002; **105**: 1399–1402.
37. Barter PJ, 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**: 160–167.
38. Boekholdt SM, Kuivenhoven JA, Wareham NJ, Peters RJ, Jukema JW, Luben R, 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**: 1418–1423.
39. Sugano M, Makino N, Sawada S, Tsuchida K, Makino N, Kamada M, et al. Effect of antisense oligonucleotides against cholesteryl ester transfer protein on the development of atherosclerosis in cholesterol-fed rabbits. *J Biol Chem* 1998; **273**: 5033–5036.
40. Rittershaus CW, Miller DP, Thomas LJ, Picard MD, Honan CM, Emmett CD, et al. Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2000; **20**: 2106–2112.
41. Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. *Nature* 2000; **406**: 203–207.
42. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; **357**: 2109–2122.
43. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007; **356**: 1304–1316.
44. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): A randomised, double-blind trial. *Lancet* 2007; **370**: 153–160.
45. Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med* 2007; **356**: 1620–1630.
46. 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**: 2506–2514.
47. Tall AR, Yvan-Charvet L, Wang N. The failure of torcetrapib: Was it the molecule or the mechanism? *Arterioscler Thromb Vasc Biol* 2007; **27**: 257–260.
48. Vergeer M, Stroes ES. The pharmacology and off-target effects of some cholesterol ester transfer protein inhibitors. *Am J Cardiol* 2009; **104**(Suppl): 32E–38E.
49. Bailey D, Jahagirdar R, Gordon A, Hafiane A, Campbell S, Chatur S, et al. RVX-208: A small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo. *J Am Coll Cardiol* 2010; **55**: 2580–2589.
50. Nicholls SJ, Gordon A, Johannsson J, Wolsky K, Ballantyne CM, Kastelein JJ, et al. Efficacy and safety of a novel oral inducer of apolipoprotein A-I synthesis in statin-treated patients with stable coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 2011; **57**: 1111–1119.
51. Nicholls SJ, Gordon A, Johannsson J, Ballantyne CM, Barter PJ, Brewer HB, et al. ApoA-I induction as a potential cardioprotective strategy: Rationale for the SUSTAIN and ASSURE studies. *Cardiovasc Drugs Ther* 2012; **26**: 181–187.
52. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: Results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; **165**: 1410–1419.
53. Zanchetti A. Antiatherosclerotic effects of antihypertensive drugs: Recent evidence and ongoing trials. *Clin Exp Hypertens* 1996; **18**: 489–499.
54. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, 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**: 2217–2225.
55. Sipahi I, Tuzcu EM, Schoenhagen P, Wolski K, Nicholls SJ, Balog C, et al. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. *J Am Coll Cardiol* 2006; **48**: 833–838.
56. Safety and Efficacy of Aliskiren on the Progression of Atherosclerosis in Coronary Artery Disease Patients (AQUARIUS). <http://clinicaltrials.gov/ct2/show/NCT00853827> (accessed October 23, 2012).
57. Chhatrwalla AK, Nicholls SJ, Wang TH, Wolski K, Sipahi I, Crowe T, et al. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. *J Am Coll Cardiol* 2009; **53**: 1110–1115.
58. Nicholls SJ, Tuzcu EM, Kalidindi S, Wolski K, Moon KW, Sipahi I, 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**: 255–262.
59. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: The PERISCOPE randomized controlled trial. *JAMA* 2008; **299**: 1561–1573.
60. Nicholls SJ, Tuzcu EM, Wolski K, Bayturan O, Lavoie A, Uno K, et al. Lowering the triglyceride/high-density lipoprotein cholesterol ratio is associated with the beneficial impact of pioglitazone on progression of coronary atherosclerosis in diabetic patients: Insights from the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study. *J Am Coll Cardiol* 2010; **57**: 153–159.
61. Kataoka Y, Shao M, Wolski K, Uno K, Puri R, Tuzcu EM, et al. Multiple risk factor intervention and progression of coronary atherosclerosis in patients with type 2 diabetes mellitus. *Eur J Prev Cardiol* 2012 January 31 [Epub ahead of print].
62. Nissen SE, Tuzcu EM, Brewer HB, Sipahi I, Nicholls SJ, Ganz P, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. *N Engl J Med* 2006; **354**: 1253–1263.
63. Tardif JC, Gregoire J, L'Allier PL, Anderson TJ, Bertrand F, Reeves F, et al. Effects of the acyl coenzyme A: Cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. *Circulation* 2004; **110**: 3372–3377.
64. von Birgelen C, Hartmann M, Mintz GS, Baumgart D, Schmermund A, Erbel R. Relation between progression and regression of atherosclerotic left main coronary artery disease and serum cholesterol levels as assessed with serial long-term (> or =12 months) follow-up intravascular ultrasound. *Circulation* 2003; **108**: 2757–2762.
65. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, et al. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010; **55**: 2399–2407.
66. Kataoka Y, Wolski K, Uno K, Puri R, Tuzcu M, Nissen SE, et al. Spotty calcification as a marker of accelerated progression of coronary atherosclerosis: Insights from serial intravascular ultrasound. *J Am Coll Cardiol* 2012; **59**: 1592–1597.
67. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radio-frequency data analysis. *Circulation* 2002; **106**: 2200–2206.
68. Kawasaki M, Takatsu H, Noda T, Sano K, Ito Y, Hayakawa K, et al. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angiographic findings. *Circulation* 2002; **105**: 2487–2492.
69. Kawasaki M, Sano K, Okubo M, Yokoyama H, Ito Y, Murata A, et al. Volumetric quantitative analysis of tissue characteristics of coronary plaques after statin therapy using three-dimensional integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2005; **45**: 1946–1953.
70. Serruys PW, Garcia-Garcia HM, Buszman P, Erne P, Verheye S, Aschermann M, et al. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008; **118**: 1172–1182.
71. Stone GW, Maehara A, Lansky AJ, Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364**: 226–235.
72. Thim T, Hagensen MK, Wallace-Bradley D, Granada JF, Kaluza GL, Drouet L, et al. Unreliable assessment of necrotic core by virtual

- histology intravascular ultrasound in porcine coronary artery disease. *Circ Cardiovasc Imaging* 2010; **3**: 384–391.
73. Waxman S, Dixon SR, L'Allier P, Moses JW, Petersen JL, Cutlip D, et al. In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: Initial results of the SPECTACL study. *JACC Cardiovasc Imaging* 2009; **2**: 858–868.
 74. <http://www.theheart.org/article/1381907> (accessed October 24, 2012).
 75. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012; **59**: 1058–1072.
 76. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004; **291**: 210–215.
 77. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: A systematic review and meta-analysis. *Arch Intern Med* 2004; **164**: 1285–1292.
 78. Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). *Circulation* 2005; **112**: 563–571.
 79. Schmermund A, Achenbach S, Budde T, Buziashvili Y, Forster A, Friedrich G, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: A multicenter, randomized, double-blind trial. *Circulation* 2006; **113**: 427–437.
 80. Hoffmann U, Moselewski F, Cury RC, Ferencik M, Jang IK, Diaz LJ, et al. Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: Patient-versus segment-based analysis. *Circulation* 2004; **110**: 2638–2643.
 81. Hacker M. Monitoring anti-inflammatory therapies in patients with atherosclerosis: FDG PET emerges as the method of choice. *Eur J Nucl Med Mol Imag* 2012; **39**: 396–398.
 82. Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Smith D, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: Two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation* 2002; **106**: 2884–2887.
 83. Lee JM, Robson MD, Yu LM, Shirodaria CC, Cunningham C, Kyllintreas I, et al. Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: A randomized, placebo-controlled, magnetic resonance imaging study. *J Am Coll Cardiol* 2009; **54**: 1787–1794.
 84. Hyafil F, Cornily JC, Feig JE, Gordon R, Vucic E, Amirbekian V, et al. Noninvasive detection of macrophages using a nanoparticulate contrast agent for computed tomography. *Nat Med* 2007; **13**: 636–641.