www.medscape.com

Darapladib: An Emerging Therapy for Atherosclerosis

Marshall A. Corson, MD

Posted: 11/24/2010; Ther Adv Cardiovasc Dis. 2010;4(4):241-248.

Abstract and Introduction

Abstract

Despite a reduction in cardiovascular risk conferred by therapies that modify circulating lipids, a need remains for novel treatments to further decrease the occurrence of complications of atherosclerotic cardiovascular diseases. Lipoprotein-associated phospholipase-A_2 is an important regulator of lipid metabolism and inflammation that circulates with lipoprotein particles and is carried into the arterial wall with low-density lipoprotein particles during the progression of atherosclerosis. Within the vessel wall, lipoprotein-associated phospholipase-A_2 releases small molecules that stimulate macrophage recruitment and evolution to foam cells, leading to plaque vulnerability. Epidemiologic studies demonstrate that elevated circulating levels of lipoprotein-associated phospholipase-A_2 predict an increased risk of myocardial infarction and stroke, whereas histologic examination of diseased human coronary arteries reveals intense presence of the enzyme in atherosclerotic plaques that are prone to rupture. These considerations suggest lipoprotein-associated phospholipase-A_2 as a promising therapeutic target, and a specific inhibitor, darapladib, has been under development for this application. This review summarizes the completed preclinical and early phase clinical studies that underlie two recently commenced phase III clinical trials that will investigate the efficacy and safety of darapladib in nearly 13,000 individuals with coronary heart disease. When completed, these trials should provide important insights into the utility of darapladib to reduce myocardial infarction, stroke and cardiovascular death.

Introduction: Defining the Unmet Clinical Need in Atherosclerosis

The 1994 publication of the Scandinavian Simvastatin Survival Study (4S) heralded a new era in the treatment of atherosclerosis. In a population of individuals with stable coronary heart disease (CHD), elevated circulating cholesterol levels and other cardiovascular disease (CVD) risk factors, treatment with simvastatin resulted in a highly significant reduction of myocardial infarction, revascularization and mortality (both total and due to CVD) [4S Study Group, 1994]. Subsequent trials with this and other statins (e.g. CARE [Sacks *et al.* 1996], LIPID [LIPID Study Group, 1998], HPS [HPS Collaborative Group, 2002], TNT [Larosa *et al.* 2005]) for secondary prevention demonstrated a log-linear relationship between treatment-dependent reductions in lowdensity lipoprotein (LDL) cholesterol (LDLc) and achieved reductions in recurrent CHD events [Hayward *et al.* 2006]. Along with aspirin and beta-blockers, statins became cornerstone agents in the therapeutic regimen for individuals with CHD, with the added benefit of reducing incident stroke.

However, certain limitations of statin therapy bear further consideration. First, with regard to efficacy, individuals with starting LDLc levels in the 150–200 mg/dl range, who experience a 35–50% LDLc reduction, attain a quantitatively similar reduction in subsequent CVD event risk, with an absolute reduction of around five CVD events per 100 individuals treated for 5 years. While the relative risk reduction would be similar for individuals with starting LDLc levels of ~100 mg/dl, the absolute risk reduction would be in the range of only ~1.5 events prevented per 100 people treated for 5 years [Hayward *et al.* 2006]. Furthermore, in spite of large mean LDLc reductions in the aforementioned secondary prevention trials, 60–75% of aggressively treated participants still experienced recurrent CHD events, suggesting that other treatment modalities should be sought to improve prognosis. Other lipid-targeted therapies, such as fibrates, have shown utility in some studies (e.g. FIELD [Keech *et al.* 2005], ACCORD [ACCORD Study Group, 2010]) particularly in higher-risk subgroups (e.g. those with highest triglyceride/HDLc ratios), but these agents have not demonstrated a universal benefit for all dyslipidemic individuals. Likewise, several diverse studies have shown event reduction with niacin preparations, without or with statins (e.g. CDP [CDP Research Group, 1975], HATS [Brown *et al.* 2001]), but in order to demonstrate convincing CVD event reduction that could move niacin-based therapy into the mainstream the ongoing AIM-HIGH trial has been undertaken, powered to provide sufficient endpoints to examine major outcome benefit of such therapy (ClinicalTrials.gov: NCT00120289). Taken together these observations/considerations indicate that therapies targeting other mechanisms in atherosclerosis are needed to yield further improvements in outcomes.

Lipoprotein-associated Phospholipase-A_2 in Atherosclerosis

An ideal target for inhibitory therapy would be a molecule or pathway shown to mediate events necessary for the

progression of atherosclerotic plaque and its subsequent evolution to a vulnerable state with increased risk of rupture, the proximate cause of myocardial infarction (MI) and many ischemic strokes. One such candidate is lipoprotein-associated phospholipase-A_2 (Lp-PLA_2), a specific member of a large family of enzymes that share the ability to hydrolyze glycerophospholipids at the *sn*-2 position to liberate lysophospholipids and free fatty acids [Schaloske and Dennis 2006]. Originally described as platelet-activating factor acetylhydrolase (PAF-AH) based on its ability to metabolize and inactivate the inflammatory autocoid PAF, Lp-PLA_2 is distinctive from other A2-phospholipases in several aspects, notably its molecular size (~45 kD), constitutively active state with regulation by localization and substrate availability, and its strict preference for substrates with short-chain, oxidized moieties in the *sn*-2 position [Zalewski and Macphee 2005]. Lp-PLA_2 is synthesized by leukocytes and through incompletely understood mechanisms becomes associated with lipoproteins; in humans approximately 70–80% is associated with LDL and the remainder with high-density lipoprotein (HDL). In circulating LDL, Lp-PLA_2 is localized to a microdomain that is rich in lipoprotein(a), where it appears to function in an atheroprotective manner, possibly by serving as a scavenger for oxidized/damaged phospholipids [Tsimikas *et al.* 2007]. Consistent with a dual functional role for Lp-PLA_2 is the finding that a significant proportion of Asian individuals possess a mutation rendering it catalytically inactive, and this group has an increased risk of experiencing CHD events [Karasawa *et al.* 2003].

As LDL becomes smaller and denser through remodeling processes that are likely proportional to an individual's overall inflammatory state, its content of Lp-PLA_2 increases, simultaneous with its increasing propensity for entry into the vascular wall. The evolution of human atherosclerosis starts with the influx of LDL particles from the circulation into the subintimal space, where particles are susceptible to oxidation of surface phospholipids by tissue oxidases. The resultant oxidized phospholipids are favored substrates for Lp-PLA_2, whose actions generate lysophosphatidylcholine (lyso-PC) and oxidized fatty acids. Lyso-PC stimulates multiple signal events in vascular cells that are pro-inflammatory, such as increasing expression of endothelial adhesion molecules (e.g. vascular cell adhesion molecule-1) and chemoattractants for inflammatory leukocytes (e.g. monocyte chemoattractant protein-1), stimulation of vascular smooth muscle cell (VSMC) migration and proliferation of tissue macrophages (reviewed by Zalewski and Macphee [2005]). Oxidized fatty acids stimulate VSMC proliferation and upregulate local inflammatory cytokine production.

A specific role for vessel wall Lp-PLA_2 in the progression of atherosclerotic lesions was suggested by human studies performed at the Mayo Clinic by Lerman and colleagues, reviewed in this section. Using the combination of quantitative coronary angiography, intravascular ultrasound (IVUS) and measurement of acetylcholine-dependent change in coronary flow to characterize endothelial function, these investigators demonstrated that elevated circulating levels of Lp-PLA_2 predict the likelihood of endothelial dysfunction, manifested by vasoconstriction in response to acetylcholine infusion [Yang *et al.* 2006]. Furthermore, in subsequent studies in which Lp-PLA_2 levels in coronary arterial and venous blood were measured, this group demonstrated that individuals with evidence of nonobstructive atherosclerosis by IVUS become net producers of Lp-PLA_2 and its byproduct lyso-PCwithin the coronary circulation, but no evidence of coronary production of C-reactive protein (CRP) could be obtained [Lavi *et al.* 2007].

A body of research studies using techniques such as optical coherence tomography, in which the reflectance of light off the vessel endothelial surface is used to interrogate the composition of mural atherosclerosis, has shown a high correlation of the advanced atherosclerotic lesion known as thin-cap fibroatheroma with a highly attenuated (<65 mm) fibrous cap thickness and susceptibility to plaque rupture, leading to acute MI [Jang *et al.* 2005]. In a clinical–pathologic correlative study, Vermani's group performed immunostaining with a highly specific monoclonal antibody to assess the localization of Lp-PLA_2 in lesions of early, intermediate and advanced stages of atherosclerosis. In early (intimal thickening) and intermediate (fibroatheroma with thick fibrous cap) stage lesions, immunostaining showed only minimal Lp-PLA_2 presence. In contrast, advanced stage thin-cap fibroatheroma lesions demonstrated massive staining for Lp-PLA_2 [Kolodgie *et al.* 2006]. Thus, atherosclerotic plaques with a high content of Lp-PLA_2 correlate with the high-risk vulnerable phenotype.

Numerous observational and epidemiologic studies in diverse populations have shown that elevated circulating Lp-PLA_2 mass or activity (or both) predicts an increased risk for incident MI or stroke (reviewed by Corson *et al.* [2008]), typically remaining significant even after multivariable adjustment for other CVD risk factors. In general populations without known CVD at baseline, Lp-PLA_2 in the upper tertile or quartile versus the lowest quantile predicts a hazard ratio for subsequent events ranging from ~1.2 to 2, whereas in populations with established CVD the hazard ratio is even greater, ranging from ~1.4 to 4 [Corson *et al.* 2008]. Several studies have demonstrated that individuals with both upper quantile Lp-PLA_2 and highsensitivity CRP (hsCRP) have a risk of subsequent CVD events ranging from 3- to 10-fold increased over those with low quantile values for both markers [Crandall and Corson 2008]. Taken together, these epidemiologic studies, the functional studies by Lerman and colleagues and clinical–pathological correlative studies by Vermani's group support an active role for Lp-PLA_2 in furthering the vulnerability of atherosclerotic plaque and suggest that this enzyme is an

appropriate target for inhibitory therapy to reduce the risk of plaque rupture and clinical events.

Development of Darapladib

Preclinical

Darapladib became the lead compound amongst a series of substituted pyrimidones observed to have inhibitory activity towards Lp-PLA_2 *in vitro* [Blackie *et al.* 2003]. Favorable characteristics of darapladib amongst the original family of candidate compounds included its relatively straightforward chemical synthesis and minimal interactions with cytochrome P450 isozymes. Darapladib inhibits the phospholipase activity of recombinant Lp-PLA_2 with an IC50 value of 0.25 nM and was demonstrated to be lipophilic with good cell membrane permeability. When assessed for its activity towards another class of circulating A_2-phospholipases implicated in atherogenesis (soluble PLA_2, $sPLA_2$), darapladib (1 mM) demonstrated minimal inhibition of recombinant human isotypes $sPLA_2$-IIa (0%), $sPLA_2$-V (0%) and $sPLA_2$-X (8.7%) (reviewed by Riley and Corson [2009]).

Treatment of hyperlipidemic rabbits with oral darapladib (10 mg/kg) reduced plasma Lp-PLA_2 activity, which was maintained at >60% inhibition for 24 h and within atherosclerotic plaques a 95% reduction in Lp-PLA_2 activity was seen 2 h after oral administration (30 mg/kg) [Blackie *et al.* 2003]. Wilensky and colleagues utilized a porcine model of accelerated atherosclerosis in which animals become diabetic following streptozotocin treatment, and hypercholesterolemic on a high-fat diet. Such diabetic hypercholesterolemic (DM-HC) animals showed average increases in glucose (~550%), cholesterol (~875%) and plasma Lp-PLA_2 activity (~230%) relative to control non-DM-HC animals [Wilensky *et al.* 2008]. The model is relevant for study of mechanisms of human atherosclerosis in that the primary lipid alteration is an increase in apo-B-containing lipoproteins that carry the bulk of Lp-PLA_2. DM-HC animals may also develop advanced stage partially occlusive atherosclerotic plaques of the coronary arteries with necrotic core resembling advanced human lesions. Treatment with daily oral darapladib (10 mg/kg) starting 4 weeks after DM-HC induction markedly reduced Lp-PLA_2 activity in both plasma and artery wall (by 89%, $p<0.00001$ and 84%, $p<0.001$, respectively) after 24 weeks of therapy compared with placebo treatment of DM-HC animals. Plasma and tissue Lp-PLA_2 activity levels were reduced to those observed in control non-DM-HC animals. As a further measure of the specific targeting of Lp-PLA_2 by darapladib, reduction in the major Lp-PLA_2 product lyso-PC was observed in the plasma and arteries of actively treated animals.

When the coronary arteries of experimental animals were examined histologically it was found that median plaque area was smaller in darapladib-treated DM-HC animals compared with the untreated DM-HC animals (0.086 versus 0.222mm^2, $p<0.05$). Atherosclerotic coronary lesions similar to advanced human fibrous or thin fibrous cap atheroma were detected in 7 of 17 DM-HC animals but in only 2 of 20 darapladib-treated DM-HC animals ($p=0.05$), and immunohistochemical staining showed macrophage predominance in the plaques of untreated DM-HC pigs with predominance of VSMC in lesions from darapladib-treated DM-HC pigs. Using quantitative polymerase chain reaction (PCR) analysis it was found that coronary artery expression of 87 genes implicated in inflammation, leukocyte function and atherogenesis was increased in DM-HC animals. Darapladib treatment was associated with significant reduction in expression of 24 of these genes, including 8 of 14 that were most increased by DM-HC induction. In particular, there was a substantial reduction in expression of several markers associated with monocyte and T-helper type-1 lymphocyte recruitment and activation, including Lp-PLA_2, CD68 and cathepsin S. The macrophage content present in combined intimal and medial areas of coronary lesions was also reduced by 59% in darapladib-treated DM-HC animals compared with untreated animals (0.71 versus 1.78%, $p=0.036$) mirroring the observed effect on macrophage gene expression. This landmark study demonstrated that oral administration of darapladib to DM-HC animals reduces circulating and tissue Lp-PLA_2 activity and attenuates the development of coronary lesions resembling human atherosclerosis, in conjunction with restoring multiple measures of plaque progression to levels seen in control non-DM-HC animals, setting the stage for investigation of the efficacy of darapladib in humans with atherosclerosis.

Completed Clinical Studies

Following several phase I trials in normal volunteers showing that daily administration of oral darapladib was acceptably tolerated, without effects on platelet function or lipid values, an important proof of concept trial was performed in subjects who were scheduled to undergo carotid endarterectomy [Johnson *et al.* 2004]. Daily administration of either low-dose (40mg daily, $n=29$) or high-dose (80mg, $n=29$) darapladib for 2 weeks resulted in reduction of plasma Lp-PLA_2 activity (57%, 82% respectively, p for trend <0.001 by analysis of variance [ANOVA]) and, importantly, reduction in plaque Lp-PLA_2 activity (55%, 81% respectively, p for trend <0.001 by ANOVA).

A phase II trial [Mohler *et al.* 2008] in subjects ($n=959$) with coronary heart disease or a CHD risk equivalent compared

several darapladib doses with placebo for reduction of Lp-PLA_2 activity, in the presence of aggressive LDLc lowering with atorvastatin. The latter was administered daily for 4 weeks at either low-dose (20 mg) or high-dose (80 mg) and subjects then received 0, 40, 80 or 160 mg darapladib daily. Plasma Lp-PLA_2 activity was unchanged in the placebo group, but was decreased in a dose-dependent manner following 4 and 12 weeks of darapladib treatment, by 43%, 55% and 66% at 12 weeks (p<0.001 for all darapladib doses at both timepoints versus placebo). Plasma Lp-PLA_2 mass was also reduced after 12 weeks of darapladib treatment (10%, 13% and 9% reductions observed with the 40, 80 and 160 mg doses, respectively; p<0.001 for all doses versus placebo). While both total cholesterol and triglyceride levels continued to decline during placebo or darapladib treatment, there were no differences between placebo- and darapladib-treated groups, suggesting that changes were due to the continued treatment with atorvastatin.

Given that a secondary objective for this study was to determine the effects of darapladib treatment on other inflammatory biomarkers, the investigators observed a reduction in hsCRP in the group that received 160 mg of darapladib (20% decrease, p=0.003 versus baseline, a 13% nonsignificant decrease compared with placebo). Interleukin-6 was reduced in the group receiving 160 mg darapladib (22% compared with baseline, p<0.001, 12% compared with placebo, p=0.028). No significant changes were observed in other inflammatory (myeloperoxidase, matrix metalloproteinase-9) or platelet-related (P-selectin, CD40-L and 11-dehydrothromboxane B_2) plasma biomarker levels. Tolerability of darapladib in this trial was good, with angina being the most common serious adverse event reported in two placebo-treated subjects (n=177), one receiving 40mg darapladib (n=162), none receiving 80mg darapladib and three subjects receiving 160mg darapladib daily (n=151). Elevations in alanine transaminase (ALT) levels to more than threefold the upper limit of normal were observed in <1% of subjects receiving 0, 40 or 80mg darapladib and in 1% receiving 160mg darapladib daily. A higher occurrence of urinary or fecal malodor or altered taste events was reported by all darapladib groups (33–36%) compared with placebo treatment (21% incidence). The incidence of adverse events leading to discontinuation of study drug was ≤1% across all treatment groups, with the exception of a 3% incidence (n=6) of withdrawal due to gastrointestinal symptoms in the darapladib 160 mg group.

A second phase II trial, the Integrated Biomarker and Imaging Study-2 (IBIS-2), utilized surrogate endpoints for outcome benefit in a group of individuals with angiographically documented CHD who were receiving other contemporary standard-of-care treatments [Serruys *et al*. 2008]. After baseline angiography, assessment of plaque composition using a special modification of IVUS (IVUS-palpography) to assess atheroma deformability, and assay of Lp-PLA_2 and other inflammatory biomarkers, subjects (n=330) were randomized to daily oral darapladib (160 mg) or placebo for 1 year. As in previous trials darapladib treatment was associated with sustained reduction in plasma Lp-PLA_2 activity (59% reduction at 1 year compared with placebo, p<0.001) and the effects on Lp-PLA_2 mass were not reported. Neither of the coprimary endpoints for the trial, a reduction in plaque deformability by IVUS-palpography nor reduction in hsCRP, was achieved, however analysis of vessel wall changes in both groups indicated that the necrotic core volume in the placebo group had increased significantly (+4.5mm^3 from baseline, p=0.009) but was not significantly changed in the darapladib-treated subjects (−0.5mm^3 from baseline, p=0.71). No change in total atheroma volume was observed between the treatment groups (p=0.95), thus a qualitative change in plaque composition with worsening of necrotic core content in placebo-treated subjects was attenuated by the darapladib treatment. When other plaque characteristics were compared it was seen that the increase in necrotic core volume observed in the placebo group was accompanied by a similar decrease in atheroma fibrous content (decreased from 41% at baseline to 32%) indicating that a larger amount of fibrous tissue was converted into necrotic core with placebo compared with darapladib treatment.

In the IBIS-2 trial the incidence of adverse events in the placebo and darapladib groups (72% and 70%, respectively) and serious adverse events (30% and 28%, respectively) were similar. However, the incidence of any adverse event leading to discontinuation was low, 7% in the placebo group and 4% in the darapladib group. There was an increase in the incidence of urine or fecal malodor in the darapladib versus placebo group (16% and 3%, respectively), although this lead to discontinuation of therapy in only 2% of the darapladib group. Changes in mean systolic blood pressure (BP) included an increase in the placebo group from 125.7±16.9 to 129.6±17.2mmHg and an increase from 128.0±16.1 to 133.3±18.5mmHg in the darapladib group. Increases in transaminases or bilirubin were rare and not different between the groups and the incidence of major adverse CVD events (the composite of CVD death, MI, stroke and coronary revascularization) was 19% and 17% in the placebo and darapladib groups, respectively.

Ongoing Phase III Trials: STABILITY and SOLID-TIMI 52

Encouraged by the results of the developmental studies described above, the manufacturer of darapladib, GlaxoSmithKline, is moving ahead with two phase III clinical trials designed to be adequately powered to compare the efficacy and safety of darapladib versus placebo to reduce CVD events in individuals with chronic phase CHD, and in

those with recent acute coronary syndromes (ACSs).

The STabilization of Atherosclerotic Plaque By Initiation of DarapLadIb TherapY (STABILITY) Trial will evaluate whether daily administration of darapladib (160mg po) versus placebo to subjects with chronic stable CHD will reduce the risk of CHD death, MI, hospitalization for ACS or coronary revascularization in 15,500 subjects treated for ~3 years (ClinicalTrials.gov: NCT00799903). Candidates for inclusion are adults with chronic CHD, on statin therapy unless deemed not appropriate, with at least one of the following risk-enhancing characteristics: age ≥60, diabetes requiring pharmacotherapy, HDLc <40 mg/dl, smoker of five or more cigarettes daily (currently or within 3 months), stage III chronic kidney disease (CKD) or microalbuminuria, or cerebrovascular or peripheral arterial disease. Investigators are encouraged to utilize other proven risk-reducing therapies and enrollment for this trial has been completed.

The Stabilization Of PLaques usIng Darapladib – Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) Trial will test whether daily administration of darapladib (160mg po) versus placebo when treatment is initiated within 30 days after an ACS will reduce the risk of CVD death, nonfatal MI or nonfatal stroke in 11,500 participants treated for ~3 years (ClinicalTrials.gov: NCT01000727). Candidates for this study are adults with hospitalization for ACS within 30 days prior to study entry, deemed clinically stable for 24 h, with at least one of the following risk-enhancing characteristics: age≥60, diabetes requiring pharmacotherapy, MI prior to the qualifying ACS event, stage III CKD or microalbuminuria, or cerebrovascular or peripheral arterial disease. Individuals for whom percutaneous coronary intervention has been planned must undergo this procedure prior to study entry, whereas the need for coronary bypass graft surgery between the qualifying event and enrollment would exclude an individual's participation. Recruitment for this study is currently underway.

Future Prospects for Darapladib

The stage is now set to determine, in two well-powered placebo-controlled phase III clinical trials, whether darapladib, a selective inhibitor of the inflammatory enzyme Lp-PLA_2, will reduce the complications of atherosclerosis, such as MI, stroke and cardiovascular death. As described above, following the demonstration of Lp-PLA_2's role as a marker of CVD risk, a series of mechanistic animal and human studies have implicated Lp-PLA_2 in the vessel wall as an appropriate target for inhibitory therapy. However, several questions arise in this context. For example, if circulating Lp-PLA_2 confers protection from atherosclerosis, will the benefits of inhibiting Lp-PLA_2 within atherosclerotic lesions be outweighed by attenuating the function of the circulating Lp-PLA_2 component? Will the agent prove to be safe and acceptably tolerated by the –13,000 subjects to be enrolled and actively treated in the phase III STABILITY and SOLID Trials? Concerns about gastrointestinal toleration and BP-modifying effects will need to be mitigated by the data obtained in this markedly expanded group of human subjects.

Finally, the enrollment strategy for these two ongoing trials bears consideration. In contrast to the 4S and other statin trials discussed above, in which an elevated level of the target of therapy, i.e. cholesterol (or, in some trials, LDLc), was a key requirement for inclusion, the two phase III darapladib trials do not specify a requirement for elevated Lp-PLA_2 level as an enrollment criteria in all subjects. Rather, the approach has been to select individuals with high clinically defined risk, for whom the need for efficacious novel therapeutics may be greatest. However, it is possible that the role of Lp-PLA_2 in disease progression may be relatively less important in some of these participants, who may have intermediate or low circulating Lp-PLA_2 activity levels, potentially leading to a dilution of the treatment effect. If darapladib is shown to be efficacious and safe within the context of both trials then it might be expected to move ahead rapidly into the clinical arena. If, however, the primary endpoint for one or both trials is not met and post-hoc analysis of subgroups according to baseline Lp-PLA_2 activity levels demonstrates benefit only in the high or high and intermediate subgroups, then additional prospective studies may be required.

References

- 4S Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4s). *Lancet* 344: 1383–1389.
- ACCORD Study Group, Ginsberg, H.N., Elam, M.B., Lovato, L.C., Crouse 3rd, J.R., Leiter, L.A., Linz, P. *et al*. (2010) Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 362(17): 1563–1574 [Epub 2010 March 14]. Erratum in: N Engl J Med. 2010 May 6; 362(18): 1748.
- Blackie, J.A., Bloomer, J.C., Brown, M.J., Cheng, H.Y., Hammond, B., Hickey, D.M. *et al.* (2003) The identification of clinical candidate Sb-480848: a potent inhibitor of lipoprotein-associated phospholipase A2. *Bioorg Med Chem Lett* 13: 1067–1070.
- Brown, B.G., Zhao, X.Q., Chait, A., Fisher, L.D., Cheung, M.C., Morse, J.S. *et al.* (2001) Simvastatin and niacin,

antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 345: 1583–1592.
- CDP Research Group (1975) Clofibrate and niacin in coronary heart disease. *JAMA* 231: 360–381.
- Corson, M.A., Jones, P.H. and Davidson, M.H. (2008) Review of the evidence for the clinical utility of lipoprotein-associated phospholipase A2 as a cardiovascular risk marker. *Am J Cardiol* 101: 41F–50F.
- Crandall, M.A. and Corson, M.A. (2008) Use of biomarkers to develop treatment strategies for atherosclerosis. *Curr Treat Options Cardiovasc Med* 10: 304–315.
- Hayward, R.A., Hofer, T.P. and Vijan, S. (2006) Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med* 145: 520–530.
- HPS Collaborative Group (2002) MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 360: 7–22.
- Jang, I.K., Tearney, G.J., Macneill, B., Takano, M., Moselewski, F., Iftima, N. *et al.* (2005) In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* 111: 1551–1555.
- Johnson, A., Zalewski, A., Janmohamed, S., Sawyer, J., Rolfe, T., Staszkiewicz, W. *et al.* (2004) Lipoprotein-associated phospholipase A2 activity, an emerging CV risk marker, can be inhibited in atherosclerotic lesions and plasma by a novel pharmacologic intervention: the results of a multicenter clinical study. *Circulation* 110: 17–22.
- Karasawa, K., Harada, A., Satoh, N., Inoue, K. and Setaka, M. (2003) Plasma platelet activating factoracetylhydrolase (PAF-AH). *Prog Lipid Res* 42: 93–114.
- Keech, A., Simes, R.J., Barter, P., Best, J., Scott, R., Taskinen, M.R. *et al.* (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomised controlled trial. *Lancet* 366: 1849–1861.
- Kolodgie, F.D., Burke, A.P., Skorija, K.S., Ladich, E., Kutys, R., Makuria, A.T. *et al.* (2006) Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 26: 2523–2529.
- Larosa, J.C., Grundy, S.M., Waters, D.D., Shear, C., Barter, P., Fruchart, J.C. *et al.* (2005) Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 352: 1425–1435.
- Lavi, S., Mcconnell, J.P., Rihal, C.S., Prasad, A., Mathew, V., Lerman, L.O. *et al.* (2007) Local production of lipoprotein-associated phospholipase A2 and lysophosphatidylcholine in the coronary circulation: association with early coronary atherosclerosis and endothelial dysfunction in humans. *Circulation* 115: 2715–2721.
- LIPID Study Group (1998) 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* 339: 1349–1357.
- Mohler III, E.R., Ballantyne, C.M., Davidson, M.H., Hanefeld, M., Ruilope, L.M., Johnson, J.L. *et al.* (2008) The effect of darapladib on plasma lipoproteinassociated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: the results of a multicenter, randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 51: 1632–1641.
- Riley, R.F. and Corson, M.A. (2009) Darapladib, a reversible lipoprotein-associated phospholipase A2 Inhibitor, for the oral treatment of atherosclerosis and coronary artery disease. *IDrugs* 12: 648–655.
- Sacks, F.M., Pfeffer, M.A., Moye, L.A., Rouleau, J.L., Rutherford, J.D., Cole, T.G. *et al.* (1996) 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* 335: 1001–1009.
- Schaloske, R.H. and Dennis, E.A. (2006) The phospholipase A2 superfamily and its group numbering system. *Biochim Biophys Acta* 1761: 1246–1259.
- Serruys, P.W., Garcia-Garcia, H.M., Buszman, P., Erne, P., Verheye, S., Aschermann, M. *et al.* (2008) Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 118: 1172–1182.
- Tsimikas, S., Tsironis, L.D. and Tselepis, A.D. (2007) New insights into the role of lipoprotein(a)-associated lipoprotein-associated phospholipase A2 in atherosclerosis and cardiovascular disease. *Arterioscler Thromb Vasc Biol* 27: 2094–2099.
- Wilensky, R.L., Shi, Y., Mohler III, E.R., Hamamdzic, D., Burgert, M.E., Li, J. *et al.* (2008) Inhibition of lipoprotein-associated phospholipase A2 reduces complex coronary atherosclerotic plaque development. *Nat Med* 14: 1059–1066.
- Yang, E.H., Mcconnell, J.P., Lennon, R.J., Barsness, G.W., Pumper, G., Hartman, S.J. *et al.* (2006) Lipoprotein-associated phospholipase A2 is an independent marker for coronary endothelial dysfunction in humans. *Arterioscler Thromb Vasc Biol* 26: 106–111.
- Zalewski, A. and Macphee, C. (2005) Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol* 25: 923–931.

Conflict of interest statement
The author has no conflicts of interest related to this publication.

Funding
This research received no specific grant support from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments
The administrative assistance of Carla Griswold as gratefully acknowledged.

Ther Adv Cardiovasc Dis. 2010;4(4):241-248.