Can Lipoprotein-associated Phospholipase A2 be Used as a Predictor of Long-term Outcome in Patients with Acute Coronary Syndrome?

Sine Holst-Albrechtsen¹, Maria Kjaergaard¹, Anh-Nhi Thi Huynh¹, Johanne Kragh Sorensen¹, Susanne Hosbond² and Mads Nybo*¹

¹Dept. of Clinical Biochemistry and Pharmacology, ²Dept. of Cardiology, Odense University Hospital, Denmark

Abstract: Studies indicate that elevated plasma concentrations of lipoprotein-associated phospholipase A2 (Lp-PLA₂) is associated with increased risk of cardiovascular disease. Lp-PLA₂ seems to play a crucial role in the formation of plaques and acute inflammation, and plasma Lp-PLA₂ could therefore potentially be used as a predictor of long-term outcome in ACS patients. To evaluate this, data concerning Lp-PLA₂ as a predictor in ACS patients was gathered through a systematic literature review, and studies on this issue were extracted from relevant databases, incl. PubMed and Cochrane. A total of 14 articles were retrieved, but after thorough evaluation and elimination of irrelevant articles only seven studies were eligible for the literature review. All studies except two showed significant correlation between Lp-PLA₂ and CV events in ACS patients. Only one study found an independent value to predict CV events 30 days after ACS. Altogether, there was inconsistency in the findings regarding the potential use of Lp-PLA₂ and a lack of knowledge on several issues. Lp-PLA₂ seems to give valuable information on which ACS patients are prone to new events and also provides important information on plaque size. However, more focused studies concerning genetic variations, time-window impact, patients with and without CV risk factors (e.g. diabetes), and treatment effects are needed. In conclusion, Lp-PLA₂ offers new insight in the pathophysiological development of ACS, but until the aforementioned issues are addressed the biomarker will mainly be of interest in a research setting, not as a predictive parameter in a clinical setting.

Keywords: Acute coronary syndrome, biomarker, Lp-PLA₂, mortality, plaque rupture, prospective studies, statins.

INTRODUCTION

Today, the diagnostic criteria for myocardial infarction (MI) is detection of a rise or fall of cardiac biomarkers (especially troponins) and one of the following: symptoms of ischemia, electrocardiography (ECG) changes, development of pathological Q-waves in the ECG, and imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Further individual diagnostic criteria for MI are sudden unexpected cardiac death, percutaneous coronary intervention (PCI) patients, coronary artery bypass graft (CABG) patients and pathological findings of MI [1].

Cardiac troponins as an early diagnostic biomarker has major relevance in the diagnosis of MI, but is only available in a limited time window and does only provide limited information for some patient categories [2]. Several other biomarkers, e.g. C-reactive protein (CRP) and interleukin 6 (IL-6), have been identified also to indicate acute coronary syndrome (ACS) [3]. However, in order to identify the patients at risk and prevent development of ACS, it is important to have a biomarker that indicates the presence of a thin fibrous cap and rupture-prone plaques [3]. A good candidate for this is lipoprotein-associated phospholipase A2 (Lp-PLA₂), also known as platelet activating factor-acetylhydrolase (PAF-AH). It is a member of the phospholipase A₂ superfamily and is secreted by macrophages and foam cells in atherosclerotic plaques [4, 5]. In humans, approximately 80% of Lp-PLA₂ is bound to apolipoprotein B in circulating low density lipoprotein (LDL) cholesterol particles [6]. The oxidation of LDL to oxLDL provides oxidized phospholipids, which is hydrolyzed by Lp-PLA₂. This produces lysophosphatidylcholine and non-esterified fatty acids, important mediators of inflammation that up-regulates the expression of adhesion molecules activating leukocytes and recruiting macrophages and monocytes to atherosclerotic plaques [4]. Importantly, Lp-PLA₂ has been found strongly expressed in the vicinity of macrophages of vulnerable and ruptured plaques [3]. Lp-PLA₂ therefore seems to play a crucial role in the formation of plaques and acute inflammation.

Studies have shown that elevated plasma Lp-PLA₂ levels are associated with increased risk of cardiovascular disease (CVD) in a healthy population as well as in patients with vascular disease [4]. The West of Scotland Coronary Prevention Study (WOSCOPS) was the first study that showed an association between Lp-PLA₂ and CVD risk. Hereafter, several other epidemiological studies have found the same association between elevated plasma Lp-PLA₂ and the development of coronary heart disease (CHD) or CVD [5, 7]. Recently, studies on plasma Lp-PLA₂ as a possible predictor of long-term outcome in ACS patients have emerged, but the evidence has not yet been evaluated in a structured fashion [3]. The aim of this systematic literature review was to assess, whether plasma Lp-PLA₂ can be used as a biomarker to...
Lp-PLA₂ and Acute Coronary Syndrome

predict outcome in ACS patients in order to optimize medical care in this vulnerable patient category.

MATERIALS AND METHODS

A systematic search was conducted on PubMed and The Cochrane Library with no date restriction to retrieve all articles that had investigated the use of Lp-PLA₂ in patients with ACS. Studies investigating Lp-PLA₂ and ACS were extracted. The search strategy was: “Lipoprotein associated phospholipase A2” AND “acute coronary syndrome” [Limits: none]. Both searches were also conducted using the MeSH database. The search was conducted October 2012 and resulted in 14 publications including nine clinical studies, four reviews and one clinical trial commentary. All reviews and clinical trial commentaries were excluded and used as secondary literature. All the articles identified according to these search criteria were systematically assessed for quality by all according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist criteria. Studies not focusing on Lp-PLA₂ were excluded [8, 9] (Fig. 1). In order to evaluate significance of the biomarker and analytical issues concerning e.g. predictive values, the following aspects were thoroughly described: Study population, ACS diagnosis, time window for the analysis, the biomarker assay, and the statistical methods used.

RESULTS

The seven articles fulfilling the criteria for a prospectively designed study are summarised in Table 1. We here give a short description of the main findings:

Blankenberg et al., 2003 [10]: In a cross-sectional descriptive study the association between platelet activating factor-acetylhydrolase (PAF-AH) activity, inflammatory markers (CRP and IL-6) and coronary artery disease (CAD) were investigated. Additionally, PAF-AH activity was investigated in ACS patients compared with stable angina pectoris (SAP) and healthy objects. Patients with PAF-AH activity in the highest quartile had an almost twofold increased risk of CAD (p = 0.048). The authors concluded that PAF-AH activity increases gradually in patients with CAD compared with healthy controls. Furthermore, there was no correlation between PAF-AH activity and the inflammatory markers.

O’Donoghue et al., 2006 [11]: In this longitudinal study with 24 months follow-up focus was on the association between plasma Lp-PLA₂ and subsequent outcome in ACS patients. The study showed a significantly increased risk of CV events for patients in the highest quintile of Lp-PLA₂ after 30 days compared to the lowest quintile after adjustment for numerous risk factors (HR = 1.33, p = 0.002). Of note, there was no significant increase in risk of CV events with increased Lp-PLA₂ values at baseline. The authors concluded that an early measurement of Lp-PLA₂ did not add to the risk stratification, while Lp-PLA₂ activity measured after 30 days associated independently with an increased risk of CV events.

Möckel et al., 2007 [12]: The efficiency of Lp-PLA₂ as part of a multi-marker approach for risk stratification of ACS patients was the key issue in this paper. Patients with elevated Lp-PLA₂ levels had a significantly higher prevalence of elevated Troponin I (TnI) (p = 0.021) and ST-segment depression (NSTEMI) (p = 0.034). A significant improvement in diagnostic classification was achieved using Lp-PLA₂ in addition with NT-proBNP (RR = 2.6), but when investigated with logistic regression Lp-PLA₂ did not add significantly to the risk assessment. Despite this, the authors concluded that Lp-PLA₂ was a possible biomarker in a multi-marker approach for risk stratification of ACS patients.

Fig. (1). Flow chart of the search strategy as described in Materials and Methods.
| Study             | Type                | Year | Place     | Study population | Follow-up | Marker     | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Adjustments                                                                 | Primary endpoint                                                                 |
|-------------------|---------------------|------|-----------|------------------|-----------|------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Ryu et al.        | RCT                 | 2012 | International | MIRACL L trial: 2587 | 16 weeks | Lp-PLA<sub>2</sub> mass and activity | UAP or non-Q-wave acute MI                                                         | Elevated serum cholesterol, previous MI, PCI, treatment with lipid-lowering drugs | Age, sex, entry event, treatment group, baseline TnT, smoking, systolic blood pressure, hypertension, DM, previous MI, BMI, LDL-cholesterol, and CRP | CV events: death, non-fatal acute MI, and cardiac arrest with resuscitation or re-hospitalization for UAP |
| Dohi et al.       | RCT                 | 2011 | Japan     | 40 patients       | 6 months | Lp-PLA<sub>2</sub> activity and PV | ACS, coronary plaque of a non-PCI site in a culprit vessel                        | -                                                                               | -                                                                               | -                                                                               |
| Li et al.         | Case-control study  | 2011 | China     | 152 patients and 142 controls | 6 months | Lp-PLA<sub>2</sub> activity | ACS diagnosed by ECG and troponins                                                | Infection, systemic immune disease, liver cirrhosis, renal dysfunction, DM, malicious tumor, and cerebrovascular disease | Age and sex                                                                    | MACE: CV death, non-fatal MI, and target vessel re-vascularization |
| Oldgren et al.    | Case-control study  | 2007 | International | FRISC-II: 1362 patients GUSTO IV: 904 patients SWISH study: 435 controls | FRISC-II: 6 months and 2 years GUSTO IV: 30 days | Lp-PLA<sub>2</sub> mass | FRISC II: Symptoms of ischemia within 48 h before the start of dalteparin or unfractionated heparin treatment GUSTO IV: Over 21 years with chest pain lasting > 5 min and either positive troponins or NSTEMI | FRISC-II: raised risk of bleeding episodes, server cardiac disease, renal or hepatic insufficiency, patients with previous open-heart surgery etc. GUSTO-IV: MI precipitated by other disorders than atherosclerotic CAD, persistent STEMI, newly or planned PCI or CABG, history of stroke etc. | -                                                                               | CV events: death, MI and mortality |
| Möckel et al.     | Prospective study   | 2007 | Germany   | 429 patients      | 42 days | Lp-PLA<sub>2</sub> mass | Suspicion of ACS diagnosed by the attending physician                           | Severe anaemia, age of less than 18 years etc.                                   | -                                                                               | MACE: Death, non-fatal MI, UAP requiring admission, PCI, CABG, etc. |

Table 1. Articles retrieved in the systematic literature search.
**Oldgren et al., 2007 [13]:** This study investigated Lp-PLA₂ as an independent biomarker of CV events in ACS patients. Furthermore, they evaluated the relationship between Lp-PLA₂ mass and other known risk markers (e.g. CRP, Troponin T (TnT), and IL-6) in ACS patients compared to healthy subjects. The study showed no significant correlation between Lp-PLA₂ and CV events after 30 days (p = 0.5) or six months (p = 0.8), and furthermore, they could not show any associations between Lp-PLA₂ and risk of mortality or future CV events (p = 0.5). The authors concluded that Lp-PLA₂ correlated with and depended on several other inflammatory risk markers, but were not related to CV events or mortality.

**Li et al., 2010 [14]:** Here, the prognostic significance of plasma Lp-PLA₂ as a risk factor for ACS was investigated. Additionally, the study also evaluated Lp-PLA₂ as a risk factor for major adverse cardiac events (MACE) in patients with ACS. The study found elevated Lp-PLA₂ activity in patients with ACS at baseline (p = 0.027). Elevated Lp-PLA₂ was associated with higher risk of MACE at follow up (p = 0.033). Patients with a new event had higher Lp-PLA₂ activity compared to those without (p = 0.04). The authors concluded that Lp-PLA₂ concentrations contributed to risk discrimination by the strong and independent association with MACE.

**Dohi et al., 2011 [15]:** The relationship between circulating Lp-PLA₂ and plaque volume (PV) was investigated in ACS patients following PCI. Circulating Lp-PLA₂ levels and PV decreased significantly during six months (p < 0.001). The change in PV significantly correlated with the change in Lp-PLA₂ (r = 0.496, p < 0.001). The authors concluded that circulating Lp-PLA₂ levels were associated with changes in the coronary plaque volume in ACS patients.

**Ryu et al., 2012 [16]:** This study investigated the use of soluble PLA₂ and Lp-PLA₂ levels as biomarkers in risk prediction and association to CV events in patients with ACS. There was no association between the baseline levels of Lp-PLA₂ and the primary end points death and ACS after 16 weeks, neither for Lp-PLA₂ mass nor for Lp-PLA₂ activity. However, baseline sPLA₂ mass did predict risk of death after multivariable adjustment (p = 0.004). The authors did not conclude whether levels of Lp-PLA₂ could predict CV events, but the results of the study showed no association.

**DISCUSSION**

This is the first systematic review of the use of the new biomarker Lp-PLA₂ as a predictor of long-term outcome in ACS patients. The main message is that plasma Lp-PLA₂ concentrations indeed seems to reflect changes in the coronary plaque, but due to the contradictory results in the studies it is far to early to think of using Lp-PLA₂ as a predictor in this patient category. For example, some studies found that Lp-PLA₂ concentrations correlated with and depended upon several other inflammatory risk markers [12, 13], while other studies found no correlation between the Lp-PLA₂ levels and risk of MACE [13, 16]. Interestingly, a majority of the studies found that plasma Lp-PLA₂ did provide valuable information on, which ACS patients were prone to new events and also could provide valuable information on plaque volume; the latter could be highly interesting in order to monitor treatment efficiency of ACS patients. But despite these promising features, there is no evidence for the use of Lp-PLA₂ as a predictor in this setting.

In our systematic literature review we find several issues in the retrieved studies that must be addressed – issues that...
all ought to be considered before the use of Lp-PLA₂ as a predictive biomarker can be recommended.

**STUDY POPULATION**

The inclusion criteria of the studies were ACS verified by symptoms, ECG or biomarkers. However, different exclusion criteria were used. For example, Li et al. excluded patients with diabetes mellitus [14], while other studies excluded patients at young age [11-13]. Importantly, Dohi et al. did not describe any exclusion criteria at all [15]. Therefore, it is relevant to consider whether Lp-PLA₂ is usable for risk stratification in all ACS patients or only in a selected population of ACS patients without certain CV risk factors.

Only three studies included a multinational study population [11, 13, 16]. On the contrary, Dohi et al. only included a Japanese population [15], which could be problematic as previous studies have indicated that a genetic mutation (V279F) present in 30% of the Japanese population leads to a reduced risk of CVD/CHD [18]. Furthermore, Li et al. included a Chinese population [14], but the prevalence of the mentioned mutation is unknown in this population. It is therefore mandatory to examine differences between nationalities to clarify this issue.

**ACS DEFINITION IN THE STUDY POPULATIONS**

When comparing these studies it is relevant to evaluate the definition of ACS and the similarity in the study populations. According to the European Society of Cardiology ACS are defined as a syndrome consisting of acute myocardial infarction with ST-segment elevation (STEMI), acute myocardial infarction without ST-segment elevation (NSTEMI) and unstable angina (UAP) [17]. Several of the studies define ACS according to this [11, 13-16], but Möckel et al. included patients with suspected ACS only defined as STEMI and NSTEMI [12], while the ACS definition was not described at all in the study by Blankenberg et al. [10]. Except for the latter, the clinical trials thus seem comparable despite the small differences between the studies regarding the European guidelines. Therefore, uniformity in the classification used is mandatory if results from a future multicentre study are to be interpreted.

**TIME WINDOW**

Unfortunately, there is very little information regarding the definition of “baseline” in the studies: Is baseline at symptom debut, at the admission time at the hospital, at the blood sampling time, or at the time of diagnosis? Oldgren et al. investigated the time delay from symptom debut to blood sampling [13], but did not find any alterations in Lp-PLA₂ levels. Another time aspect to consider is the length of the follow-up period. Also, when is the best time to measure Lp-PLA₂ levels? O’Donoghue et al. found a difference between Lp-PLA₂ levels after 7 and 30 days [11]. As the time window is only investigated in two studies, it seems relevant to examine how Lp-PLA₂ changes over time by conducting a series of more frequent measurements in the follow-up period. A recent study by Ostadal et al. [19] demonstrated dynamic alterations in Lp-PLA₂ levels during the early stages of ACS, which indirectly support the hypothesis of an active role for Lp-PLA₂ in the pathogenesis of ACS. But without a secure knowledge on alterations over time it will be difficult to interpret findings as earlier described for e.g. cardiac troponins.

**ASSAY PERFORMANCE**

A high degree of assay reproducibility is needed in order to provide secure clinical information. Many studies have however found this problematic as mean levels vary considerably from study to study dependent on the assay used. Of note, a recent meta-analysis revealed a significant variation in both mass and activity between assays and studies [20] and in another study the preanalytical stability has been questioned [21]. Altogether, the lack of standardization of assay calibration clearly limits the clinical utility of this biomarker, and effort must be put into constructing a more solid assay with a standardized setup.

**THE CLINICAL USE OF Lp-PLA₂**

To evaluate the clinical use of Lp-PLA₂ it is important to consider the usability of Lp-PLA₂ as a risk marker of new CV events in ACS patients, the optimal time window and whether it is independent or should be part of a multi-marker approach. Most studies used a direct approach to show a positive correlation between elevated Lp-PLA₂ plasma concentrations and CV events [10, 12-14, 16], and Dohi et al. also evaluated plaque volume, an indirect risk factor of developing ACS [15]. O’Donoghue et al. showed that Lp-PLA₂ was not an effective marker for risk stratification of ACS patients in the acute phase [11]. However, after 30 days Lp-PLA₂ seemed to be a potential independent marker for CV events. Three of the studies described that independent biomarkers such as TnI, CRP, IL-6 and Lp-PLA₂ reflected different pathways in the pathophysiology of ACS [10, 12, 13]. It therefore seems relevant to investigate whether Lp-PLA₂ is usable as an independent biomarker or if a multi-marker approach will give the most applicable results. But before this is possible, the aforementioned issues need to be dealt with.

**STATINS**

It is known that Lp-PLA₂ activity and mass both are strongly associated with various lipid markers due to a physical binding to LDL cholesterol. Studies have evaluated whether statins or direct Lp-PLA₂ inhibitors lowering the level of serum Lp-PLA₂ could be used to minimize plaque volume and thereby the risk of a CV event. At present the direct Lp-PLA₂ inhibitor Darapladib (a selective blocker of the active serine residue in Lp-PLA₂ which decreases the activity) is investigated in a phase III study that examines the effect of Darapladib on different cardiovascular outcomes [4, 22-24]. This type of study will be able to tell us whether Lp-PLA₂ also can be used for monitoring the treatment efficiency.

**CONCLUSIONS**

Despite promising results in some of the retrieved studies and a feeling of excitement over this “new-kid-on-the-block” biomarker, there are inconsistencies in the findings regarding a potential use of Lp-PLA₂ in this setting. Also, there is a
huge need for focused studies on the issues lined out above, primarily genetic variations, time-window impact, patients with and without CV risk factors (diabetic patients?), and the assay performance. Nevertheless, if Lp-PLA₂ really does reflect threatening plaque rupture it still offers new insight in the pathophysiological development of ACS. This will however mainly be of interest in a research setting and not in a clinical setting. For the time being this marker must therefore remain an interesting candidate in this relation.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Thygesen K, Alpert J, Harvey D. Universal definition of myocardial infarction. Eur Heart J 2007; 28: 2525-38.
[2] Collinson P. Sensitive troponin assays. J Clin Pathol 2011; 64: 845-9.
[3] Searle J, Danne O, Müller C, Möckel M. Biomarkers in acute coronary syndrome and percutaneous coronary intervention. Minerva Cardioangiol 2011; 59: 203-23.
[4] Epps KC, Wilensky RL. Lp-PLA₂ – a novel risk factor for high-risk coronary and carotid artery disease. J Intern Med 2011; 269: 94-106.
[5] Lee JH, Engler MM. Lipoprotein-Associated Phospholipase A₂: A promising vascular-specific marker for screening cardiovascular risk. Progr Cardiovasc Nurs 2009; 24: 181-9.
[6] Khakpour H, Frishman WH. Lipoprotein-Associated Phospholipase A₂: An independent predictor of cardiovascular risk and a novel target for immunomodulation therapy. Cardiol Rev 2009; 17: 222-9.
[7] Cook NR, Paynter NP, Manson JE, et al. Clinical utility of lipoprotein-associated phospholipase A₂ for cardiovascular disease prediction in a multiethnic cohort of women. Clin Chem 2012; 58: 1352-63.
[8] Rosenson RS, Hislop C, Elliott M, Statis Y, Goulder M, Waters D. Effects of varespladib methyl on biomarkers and major cardiovascular events in acute coronary syndrome patients. J Am Coll Cardiol 2010; 56: 1079-89.
[9] Papathanasiou AI, Lourida ES, Tsiroonis LD, Goudevenos JA, Tselipis AD. Short- and long-term elevation of autoantibody titers against oxidized LDL in patients with acute coronary syndromes. Role of the lipoprotein-associated phospholipase A₂ and the effect of atorvastatin treatment. Atherosclerosis 2008; 196: 289-97.
[10] Blankenberg S, Stengel D, Rupprecht JJ, et al. Plasma PAF-acetylhydrolase in patients with coronary artery disease: results of a cross-sectional analysis. J Lipid Res 2004; 44: 1381-6.
[11] O’Donoghue M, Morrow DA, Sabatine MS, et al. Lipoprotein-Associated Phospholipase A₂ and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy - Thrombolysis In Myocardial Infarction) Trial. Circulation 2006; 113: 1745-52.
[12] Möckel M, Muller R, Vollert JO, et al. Lipoprotein-associated phospholipase A₂ for early risk stratification in patients with suspected acute coronary syndrome: a multimarker approach. Clin Res Cardiol 2007; 96: 604-12.
[13] Oldgren J, James SK, Siegbahn A, Wallentin L. Lipoprotein-associated phospholipase A₂ does not predict mortality or new ischaemic events in acute coronary syndrome patients. Eur Heart J 2007; 28: 699-704.
[14] Li N, Li S, Yu C, Gu S. Plasma Lp-PLA₂ in acute coronary syndrome: Association with major adverse cardiac events in a community-based cohort. Postgr Med 2010; 122: 200-5.
[15] Dohi T, Miyazaki K, Okazaki S, et al. Decreased circulation lipoprotein-associated phospholipase A₂ levels are associated with coronary plaque regression in patients with acute coronary syndrome. Atherosclerosis 2011; 219: 907-12.
[16] Ryu SK, Mallat Z, Benessiano J, et al. Phospholipase A₂ enzymes, high-dose atorvastatin, and prediction of ischemic events after acute coronary syndromes. Circulation 2012; 125: 757-66.
[17] Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 32: 2999-3054.
[18] Jang Y, Kim OY, Koh SJ, et al. The Val279Phe Variant of the Lipoprotein-Associated Phospholipase A₂ gene is associated with catalytic activities and cardiovascular disease in Korean men. J Clin Endocrinol Metab 2006; 91: 3521-7.
[19] Ostadal P, Vondraková D, Kruger A, Janotka M, Psothova H, Prucha M. Alteration in lipoprotein-associated phospholipase A₂ levels during acute coronary syndrome and its relationship to standard biomarkers. Lipids Health Dis 2012; 11: 153.
[20] Lip-PLA₂ Studies Collaboration, Thompson A, Gao P, et al. Lipoprotein-associated phospholipase A₂ and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010; 375: 1536-44.
[21] Oliver LK, Vokoboev N, Heser D, et al. Assessment of clinical performance without adequate analytical validation: A prescription for confusion. Clin Biochem 2011; 44: 1247-52.
[22] Rosenson RS. Future role for selective phospholipase A₂ inhibitors in the prevention of atherosclerotic cardiovascular disease. Cardiovasc Drugs Ther 2009; 23: 93-101.
[23] Bui QT, Wilensky RL. Darapladib. Expert Opin Invest Drugs 2010; 19: 161-8.
[24] White H, Held C, Stewart R, et al. Study design and rationale for the clinical outcomes of the STABILITY Trial (Stabilization of the Atherosclerotic Plaque By initiation of darapLadib TherapY) comparing darapladib versus placebo in patients with coronary heart disease. Am Heart J 2010; 160: 655-61.