Prognostic Utility of Secretory Phospholipase A₂ in Patients with Stable Coronary Artery Disease

Michelle O'Donoghue, Ziad Mallat, David A. Morrow, Joelle Benessiano, Sarah Sloan, Torbjørn Omland, Scott D. Solomon, Eugene Braunwald, Alain Tedgui, and Marc S. Sabatine

BACKGROUND: Secretory phospholipase A₂ (sPLA₂) may contribute to atherogenesis. To date, few prospective studies have examined the utility of sPLA₂ for risk stratification in coronary artery disease (CAD).

METHODS: We measured plasma sPLA₂ activity at baseline in 3708 subjects in the PEACE randomized trial of trandolapril vs placebo in stable CAD. Median follow-up was 4.8 years. We used Cox regression to adjust for demographics, clinical risk factors, apolipoprotein B, apolipoprotein A1, and medications.

RESULTS: After multivariable adjustment, sPLA₂ was associated with an increased risk of cardiovascular death, myocardial infarction, or stroke (adjusted hazard ratio Q4:Q1 1.55, 95% CI 1.13–2.14) and cardiovascular death or heart failure (1.91, 1.20–3.03). In further multivariable assessment, increased activities of sPLA₂ were associated with the risk of cardiovascular death, myocardial infarction, or stroke (adjusted hazard ratio 1.47, 95% CI 1.06–2.04), independent of lipoprotein-associated phospholipase A₂ mass and C-reactive protein, and modestly improved the area under the curve (AUC) beyond established clinical risk factors (AUC 0.668–0.675, P = 0.01). sPLA₂, N-terminal pro–B-type natriuretic peptide, and high-sensitivity cardiac troponin T all were independently associated with cardiovascular death or heart failure, and each improved risk discrimination (P = 0.02, P < 0.001, P < 0.001, respectively).

CONCLUSIONS: sPLA₂ activity provides independent prognostic information beyond established risk markers in patients with stable CAD. These data are encouraging for studies designed to evaluate the role of sPLA₂ as a therapeutic target.

The phospholipase A₂ enzymes are members of a large family that hydrolyze the sn-2 ester of glycerophospholipids to release free fatty acids and lysophospholipids. The secretory phospholipase A₂ (sPLA₂) family consists of 10 isoenzymes that are involved in a variety of biological processes that include hydrolysis of phospholipids, release of arachidonic acid, and eicosanoid generation (1). sPLA₂ enzymes are distinct from lipoprotein-associated phospholipase A₂ (Lp-PLA₂), another biomarker that has been extensively studied for risk stratification and is now being evaluated as a potential therapeutic target (2).

Growing evidence suggests that sPLA₂ may play a causal role in the development of atherosclerosis. sPLA₂-X has been shown to promote macrophage foam cell formation in murine models (3), and up-regulated sPLA₂-IIA or sPLA₂-V expression has been shown to increase atherosclerotic lesion size in transgenic mice (4, 5). Additionally, genetic deletion of sPLA₂-V or direct inhibition of sPLA₂ activity has been shown to reduce atherosclerotic lesion progression in animals (5–7).

To date, a small number of studies have evaluated the utility of sPLA₂ for risk stratification in primary prevention populations and in patients with acute coronary syndrome (ACS) (1). However, the prognostic utility of sPLA₂ activity has not been well established in a large population of patients with stable coronary artery disease (CAD). Determination of this association.

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is particularly relevant given the interest in sPLA₂ as a possible therapeutic target for helping to delay the progression of atherosclerosis (8). Furthermore, the relative prognostic utility of sPLA₂ compared with other well-established markers of risk, including those measured using new high-sensitivity assays, remains unknown. We hypothesized that sPLA₂ activity would provide incremental information for risk stratification beyond established clinical risk factors and biomarkers in a large cohort of subjects with stable CAD.

Methods

PATIENT POPULATION
The design and results of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial have been reported (9). In brief, the PEACE trial was a double-blind, phase III trial that randomized patients with stable CAD and preserved left ventricular function to trandolapril vs placebo. The median duration of follow-up was 4.8 years.

ENDPOINTS
Clinical endpoints for this analysis included cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, and heart failure (HF). Cardiovascular death, MI, and stroke were adjudicated by an independent clinical events committee who were blinded to assigned treatment arm. HF was classified by centrally trained local investigators and confirmed by outcomes staff through a review of hospital records at the coordinating center.

BIOMARKER ANALYSES
As per study protocol, a sample of venous blood was obtained in EDTA-treated tubes from subjects at the time of enrollment. The plasma component was frozen and shipped to a central laboratory where samples were stored at −70 °C or colder. Plasma sPLA₂ activity was measured using a selective fluorescent substrate (Aterovax). Results are expressed in U/mL of sample, with 1 unit defined as the amount of sPLA₂ enzyme that catalyzes the release of 1 nmol product in 1 min. The mean intraassay CV for individual human plasma samples was 8.46%. We evaluated the interassay variability by determining the average CV calculated from CV of 8 plasma samples from human subjects run by 2 operators, on 3 different days, on 2 different fluorometers, using 2 different batches of assay substrate and reagents. Total interassay CV for individual human plasma samples ranged from 1.05% to 13.08%, with a mean interassay CV of 5.24%. The mean sPLA₂ activity of the 8 plasma samples was 71.2, 73.9, 87.3, 113.6, 148.0, 184.2, 208.7, and 235.9 U/mL. The minimal detectable activity was 10 U/mL. The standard sPLA₂ used in the assay was stabilized and presented on liposomes supported by latex beads to optimize activity measurement.

We assessed high-sensitivity cardiac troponin T by use of an autoanalyzer (Cobas e 411, Roche Diagnostics). The lower limit of detection for this high-sensitivity precommercial assay was 0.001 μg/L (10). We performed Lp-PLA₂ mass measurements using the PLAC™ test at diaDexus (11) and measured N-terminal pro–brain natriuretic peptide (NT-proBNP) concentrations in plasma with an electrochemiluminescence immunoassay on a modular platform (Roche Diagnostics). High-sensitivity C-reactive protein (hsCRP) measurements were performed with the CRP-Latex (II) immunoturbidimetric assay (Denka Seiken) on a Hitachi 911 immunoanalyzer (Roche Diagnostics) at the Thrombolysis in Myocardial Infarction (TIMI) Clinical Trials laboratory (Boston, MA). This assay has a minimal detectable concentration of 0.03 mg/L. All biomarker testing was performed by personnel who were blinded to treatment arms, outcomes, and results of other biomarker testing.

STATISTICAL ANALYSIS
We compared baseline characteristics using the Wilcoxon rank sum test for continuous measures and the χ² test for trend for categorical variables. We assessed correlations between sPLA₂ activity and other biomarker concentrations using Spearman’s correlation coefficient.

Event rates at 5 years were estimated using the Kaplan–Meier method. sPLA₂ was modeled by categorization into quartiles of activity. We constructed Cox proportional hazard models to estimate the hazard ratios (HRs) and 95% CIs for clinical events associated with increasing activity levels of sPLA₂. The following covariates were included in all multivariable models: age, sex, hypertension, diabetes mellitus, tobacco use (current, prior, never), history of coronary revascularization, use of lipid-lowering therapy, body mass index, systolic blood pressure, estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease equation, apolipoprotein B (apoB), apoA1, and randomized treatment arm (note: there was no evidence of effect modification between sPLA₂ activity and randomized treatment arm when an interaction term was included in the model). Additional model permutations included the addition of established biomarkers, such as hsCRP, Lp-PLA₂ mass, NT-proBNP, and high-sensitivity cardiac troponin T (by quartiles of biomarker concentration). We also generated covariate-adjusted ROC curves for models with known risk factors with or without the inclusion of sPLA₂ and...
other established biomarkers. Comparisons between ROC curves were determined using the method described by DeLong et al. (12).

Because all analyses were considered to be exploratory, a $P$ value $<$ 0.05 was considered to be statistically significant. Analyses were performed using Stata/SE 9.2 (Stata Corp.).

Results

Baseline Demographics and Clinical Presentation

sPLA$_2$ activity was available in 3708 subjects who provided a blood sample at randomization. There were no clinically relevant differences in the baseline characteristics of patients who did and did not participate in the biomarker study (10). The baseline characteristics of the study population by quartile of sPLA$_2$ activity are displayed in Table 1. Patients with increasing plasma sPLA$_2$ activity levels were more likely to be female and have a history of hypertension, diabetes mellitus, current tobacco use, and a lower eGFR. Subjects with higher sPLA$_2$ activity were more likely to have higher concentrations of apoB, apoA1, cardiac troponin T, hsCRP, Lp-PLA$_2$ mass, and NT-proBNP.

Association of sPLA$_2$ Activity with Clinical Outcomes

There was a stepwise increase in the risk of cardiovascular death, MI, or stroke by quartile of sPLA$_2$ activity ($P$ for trend $<$ 0.001) (Table 2). The cumulative incidence of cardiovascular events by quartile of sPLA$_2$ activity is displayed in Fig. 1. Directional consistency was observed across all elements of the composite endpoint (Table 2). In particular, subjects with sPLA$_2$ activity levels in the highest quartile had a 2-fold higher risk of cardiovascular death (HR 2.00, 95% CI 1.18–3.37, $P = 0.01$) compared with patients with sPLA$_2$ in the lowest quartile. A strong association was also observed between increasing sPLA$_2$ and the risk of heart failure, such that subjects with sPLA$_2$ activity levels in the highest quartile had nearly a 3-fold higher incidence of heart failure during follow-up (HR Q4:Q1 2.73, 95% CI 1.38–5.38, $P = 0.004$).

Table 1. Baseline characteristics by quartile of sPLA$_2$ activity (U/mL).a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1, $&lt;$18.4 U/mL</th>
<th>Quartile 2, 18.5–30.9 U/mL</th>
<th>Quartile 3, 31.0–45.7 U/mL</th>
<th>Quartile 4, $\geq$45.7 U/mL</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>928</td>
<td>926</td>
<td>927</td>
<td>927</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>64 (8.3)</td>
<td>64 (8.4)</td>
<td>64 (8.2)</td>
<td>64 (7.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Female sex</td>
<td>13.3</td>
<td>13.5</td>
<td>19.7</td>
<td>29.3</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40.2</td>
<td>44.8</td>
<td>44.9</td>
<td>48.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current tobacco use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>53.3</td>
<td>56.5</td>
<td>57.7</td>
<td>57.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Prior PCI or coronary artery bypass graft surgery</td>
<td>80.0</td>
<td>75.5</td>
<td>70.3</td>
<td>64.36</td>
<td>$&lt;0.001$</td>
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<tr>
<td>Medications before randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin or antiplatelet drug</td>
<td>91.0</td>
<td>92.0</td>
<td>90.5</td>
<td>91.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>61.2</td>
<td>60.0</td>
<td>61.7</td>
<td>65.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>75.3</td>
<td>72.0</td>
<td>71.6</td>
<td>67.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Data at randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>132 (16)</td>
<td>133 (16)</td>
<td>134 (17)</td>
<td>135 (18)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>eGFR</td>
<td>80 (20)</td>
<td>77 (18)</td>
<td>79 (20)</td>
<td>76 (20)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>28 (4.3)</td>
<td>28 (4.5)</td>
<td>29 (4.8)</td>
<td>29 (5.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>102 (22)</td>
<td>105 (22)</td>
<td>110 (23)</td>
<td>112 (23)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>ApoA1, mg/dL</td>
<td>136 (22)</td>
<td>137 (23)</td>
<td>140 (25)</td>
<td>140 (27)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac troponin T, $\mu$g/L</td>
<td>7.1 (5.7)</td>
<td>7.8 (7.2)</td>
<td>7.4 (5.9)</td>
<td>8.0 (6.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>2.2 (3.3)</td>
<td>2.4 (3.6)</td>
<td>3.3 (5.6)</td>
<td>5.5 (8.8)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Lp-PLA$_2$ mass, ng/mL</td>
<td>226 (68)</td>
<td>230 (74)</td>
<td>228 (73)</td>
<td>237 (74)</td>
<td>0.002</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>225 (294)</td>
<td>221 (274)</td>
<td>255 (373)</td>
<td>278 (384)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a Data are mean (SD) or %.
**MULTIVARIABLE ANALYSES**

After adjusting for known clinical risk factors and potential confounders, sPLA$_2$ activity remained independently associated with an increased risk of cardiovascular death, MI, or stroke during long-term follow-up (adjusted HR 1.55, 95% CI 1.13–2.14, $P = 0.007$) (Table 2) compared with patients with the lowest activity levels of sPLA$_2$. Directional consistency was also seen for sPLA$_2$ and the risk of individual endpoints, including cardiovascular death (adjusted HR Q4:Q1, 1.66, 95% CI 0.95–2.88), MI (1.49, 0.96–2.32), and stroke (1.59, 0.74–3.41). Likewise, increased activity levels of sPLA$_2$ were independently associated with an increased risk of CVD or HF (adjusted HR 1.91, 95% CI 1.20–3.03) and HF alone (2.63, 1.19–5.80).

**MULTIMARKER ASSESSMENTS**

We subsequently evaluated the independent prognostic utility of sPLA$_2$ activity compared with other established biomarkers of cardiovascular risk and clinical risk factors. These included biomarkers of inflammation (hsCRP and Lp-PLA$_2$ mass), and biomarkers of hemodynamic stress (NT-proBNP) and myonecrosis (high-sensitivity cardiac troponin T).

**Biomarkers of Inflammation.** There was a modest correlation between sPLA$_2$ activity and concentrations of hsCRP ($r = 0.26$, $P < 0.001$). Although statistically significant, only a weak correlation was found between sPLA$_2$ activity and Lp-PLA$_2$ mass ($r = 0.05$, $P < 0.001$). After inclusion of hsCRP and Lp-PLA$_2$ in a multivariable model that included established clinical risk factors, sPLA$_2$ activities in the highest quartile remained significantly associated with an increased risk of cardiovascular death, MI, or stroke (adjusted HR Q4:Q1 1.47, 1.06–2.04, $P = 0.019$) (Fig. 2). In contrast, the association with hsCRP, Lp-PLA$_2$ mass, and the risk of cardiovascular death, MI, or stroke was attenuated (Fig. 2).

In ROC analyses, sPLA$_2$ activity was the only marker of inflammation to significantly improve the area under the curve (AUC) for identifying patients at increased risk of cardiovascular death, MI, or stroke (0.668–0.675, $P = 0.01$) compared with clinical risk factors alone.

**Biomarkers of Hemodynamic Stress and Myonecrosis.** We observed a weak but statistically significant correlation between sPLA$_2$ activity and concentrations of NT-proBNP ($r = 0.06$, $P < 0.001$) and high-sensitivity cardiac troponin T ($r = 0.05$, $P = 0.002$).

Because NT-proBNP and high-sensitivity cardiac troponin T have been shown to be associated with the risk of cardiovascular death or heart failure (rather than MI or stroke), we evaluated NT-proBNP, high-sensitivity cardiac troponin T, and sPLA$_2$ in the context of this endpoint. In a model that included both NT-proBNP and cardiac troponin T, sPLA$_2$ activities in the highest quartile remained significantly associated with an increased risk of cardiovascular death or HF (adjusted HR 1.79, 95% CI 1.12–2.86, $P = 0.015$) compared with patients with the lowest activities of sPLA$_2$. There also existed a strong and independent association between NT-proBNP and cardiac troponin T concentrations in the highest quartile and the risk of cardiovascular death or HF (Fig. 2), thereby suggesting that all 3 markers provided complementary information for risk stratification.

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**Table 2. Kaplan–Meier event rates and hazard ratios (95% Is) by quartile of sPLA$_2$ activity.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Kaplan-Meier event rate by quartiles of sPLA$_2$ activity at 5 years</th>
<th>Unadjusted HR (95% CI), Q4:Q1</th>
<th>Adjusted HR (95% CI), Q4:Q1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>928</td>
<td>926</td>
<td>927</td>
</tr>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>7.84</td>
<td>9.20</td>
<td>10.2</td>
</tr>
<tr>
<td>Cardiovascular death or HF</td>
<td>3.26</td>
<td>5.05</td>
<td>5.52</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.51</td>
<td>2.71</td>
<td>3.19</td>
</tr>
<tr>
<td>MI</td>
<td>4.54</td>
<td>4.70</td>
<td>6.59</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.26</td>
<td>1.92</td>
<td>1.20</td>
</tr>
<tr>
<td>HF</td>
<td>1.22</td>
<td>2.43</td>
<td>2.84</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>20.7</td>
<td>16.7</td>
<td>20.3</td>
</tr>
</tbody>
</table>

* MV model: age, sex, tobacco use (current, former, never), eGFR, body mass index, systolic blood pressure, apoB, apoA1, history of hypertension, diabetes mellitus, lipid-lowering therapy, history of coronary revascularization, randomized treatment arm.
Compared with clinical risk factors alone, the addition of sPLA₂ significantly improved model discrimination (AUC 0.734 – 0.742, P < 0.02). When considered individually, both NT-proBNP (AUC 0.734 – 0.765, P < 0.001) and high-sensitivity cardiac troponin (AUC 0.734 – 0.757, P < 0.001) also increased the AUC compared with clinical risk factors alone. Moreover, the inclusion of sPLA₂ activity into a model that already included both NT-proBNP and cardiac troponin T further improved model discrimination (AUC 0.778 – 0.782, P < 0.03).

Discussion

The current findings demonstrate that higher levels of plasma sPLA₂ activity are associated with an increased risk of cardiovascular events in a large population of patients with stable CAD. In particular, higher levels of sPLA₂ activities were associated with an increased risk of cardiovascular death, MI, or stroke and cardiovascular death or heart failure, independent of traditional risk factors. Moreover, sPLA₂ provided modest additive information for risk stratification beyond several established markers of risk, including hsCRP, Lp-PLA₂ mass, NT-proBNP, and high-sensitivity cardiac troponin T.

Prior studies have evaluated the prognostic utility of sPLA₂ in primary and secondary prevention populations. In 2 nested case-control studies in the European Prospective Investigation of Cancer (EPIC)-Norfolk, increasing sPLA₂ mass and activity were associated with the first occurrence of a coronary event during 6 years of follow-up in otherwise healthy individuals (13, 14). As well, higher sPLA₂ concentrations, but not mass, were shown to be associated with a higher risk of recurrent cardiovascular events in patients hospitalized with ACS (15).

Three prior studies have examined the prognostic role of sPLA₂ in patients with stable CAD. In a retrospective case-control study of 142 patients with angiographically proven CAD, sPLA₂ mass was significantly higher in cases than controls and independently asso-
CAD, sPLA2 was measured in a cohort of 1024 subjects, the largest prior study to date of patients with stable CAD. We found that inpatient coronary revascularization after ACS. Higher sPLA2 activities or mass were associated with an increased risk of cardiovascular events after adjustment for traditional risk factors and markers including hsCRP, cystatin C, Lp-PLA2 mass, and NT-proBNP (18). The study population proved to be at relatively low risk, however, and few fatal events occurred during study follow-up (2.8% incidence of cardiovascular death after median follow-up of 4.6 years). Additionally, the study design did not allow for adjudication of nonfatal events, and the incidence of HF was not reported.

The current analysis is, to our knowledge, the largest study to date to evaluate the prognostic utility of sPLA2 activity vs mass for risk assessment. In the current study population, the current analysis is exploratory, and future studies will be required to validate our findings or to consider potential cut points for clinical use.

There exist limitations to the current analysis that warrant consideration. Because we did not quantify sPLA2 mass, we are unable to evaluate the relative prognostic utility of sPLA2 activity vs mass for risk assessment in this study population. Furthermore, the current analysis is exploratory, and future studies will be required to validate our findings or to consider potential cut points for clinical use.

In summary, we have demonstrated that sPLA2 activity is associated with an increased risk of cardiovascular events in patients with stable CAD and provides incremental and complementary information for risk stratification beyond several established risk markers, including hsCRP, Lp-PLA2 mass, NT-proBNP, and high-sensitivity cardiac troponin T. These data not only strengthen the association between sPLA2 activity and the risk of CV outcomes, but also are encouraging for clinical trials of an sPLA2 inhibitor (8). If such trials show a clinical benefit, then measuring sPLA2 might be useful for targeting therapy.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References