Contribution of novel biomarkers to incident stable angina and acute coronary syndrome: the PRIME Study

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Aims

To compare whether novel inflammatory and haemostatic biomarkers are more predictive of well-characterized incident acute coronary syndrome (ACS) than stable angina (SA).

Methods and results

We used data from the PRIME Study, a prospective cohort of 9758 asymptomatic middle-aged men recruited in Northern Ireland and France between 1991 and 1993. A nested case–control study was established with the baseline plasma sample of 269 incident cases and 538 matched controls. Odds ratios (ORs) for SA and ACS were estimated by conditional logistic regression analysis. After 5 years of follow-up, 107 incident SA and 162 ACS cases were validated. After adjustment for traditional risk factors, higher circulating levels of hs-CRP, ICAM1, interleukin 6 and interleukin 18 were equally predictive of SA and ACS (all P-values of OR comparison >0.05). In contrast, elevated levels of fibrinogen, von Willebrand factor, and possibly higher level of D-dimers and lower level of tissue factor pathway inhibitor were associated with ACS only. The comparison of the ORs showed a statistically significant difference for von Willebrand factor only [OR4th vs. 1st quartile = 2.99 (1.49–6.02) for ACS vs. 0.80 (0.33–1.94) for SA; Pz-test = 0.02].

Conclusion

This is the first population-based study suggesting that higher levels of circulating haemostatic markers and of von Willebrand factor, in particular, are significantly more predictive of incident ACS than SA.

Keywords

Epidemiology • Biomarkers • Angina pectoris • Acute coronary syndrome • Atherothrombosis

Introduction

Although stable angina (SA) on exertion is one of the most frequent initial clinical presentations of coronary heart disease (CHD), the search for specific risk factors has so far received little attention.¹ In most earlier population studies investigating risk factors for CHD, coronary events were grouped together on the assumption that they all had shared the same risk factors.²–⁴ However, the pathogenesis of the various phenotypes of CHD may differ. In particular, plaque rupture and subsequent thrombosis formation are thought to trigger the occurrence of the acute coronary syndrome (ACS) including unstable angina...
(UA) and myocardial infarction (MI), but not SA.5–7 This suggests that ACS and SA may not share all the same risk factors. A few cohort studies have shown that some conventional risk factors, including cigarette smoking consumption and blood pressure, are more predictive of incident ACS than SA.8–10 Systemic inflammatory and haemostatic markers may represent additional candidates to be assessed. In addition to potentially contributing to atherosclerosis, they are also involved in acute processes, i.e. plaque rupture (inflammatory markers) and thrombosis (haemostatic markers).11 Several large prospective studies, including the PRIME Study (Etude Prospective de l’Infarctus du Myocarde), have shown that those markers are independent predictors of CHD in healthy populations.12–14 However, to the best of our knowledge, whether those biomarkers are more likely to predict incident ACS rather than incident SA has not yet been established in population studies.

Therefore, we have used the multicentre PRIME prospective cohort of initially asymptomatic men,15 to assess whether systemic inflammatory and haemostatic markers measured at baseline examination were differentially predictive of well-characterized SA on exertion and ACS as a first manifestation of CHD over 5 years of follow-up.

Methods

Study population

The PRIME Study is a prospective cohort designed to identify the risk factors for CHD and to explain the gradient in CHD incidence between Belfast (Northern Ireland) and France. Details on recruitment, baseline examination, and follow-up of the PRIME Study have been previously described.15 Overall, 10 600 men aged 50–59 years were recruited between 1991 and 1993 in Lille, Strasbourg, and Toulouse in France, and Belfast in Northern Ireland. Among them, 842 had coronary disease as self-reported at baseline examination and were excluded since the coronary event leading to death was not documented, leaving 7588 men (7399 in France and 2359 in Northern Ireland) without coronary disease at baseline. These men were followed up for 5 years of occurrence of CHD events, including SA and UA, non-fatal MI, and coronary death.

Baseline examination in the entire cohort

General characteristics

Subjects who agreed to take part in the study were given a morning appointment and asked to fast for at least 12 h. A full description of clinical and laboratory measurements has been published elsewhere.16 Briefly, a self-administered health questionnaire was completed at home by the participants and was subsequently checked by trained interviewers at the clinic. It covered a broad range of clinical information including family and personal clinical history completed by interviewers at the clinic. It covered a broad range of clinical information including family and personal clinical history completed by the Rose Questionnaire, tobacco consumption, and drug intake. Diabetes mellitus was defined by the current intake of oral hypoglycaemic drugs or insulin. Blood pressure was measured twice in the sitting position with the same automatic device (Spengler SP9). A 12-lead ECG was also recorded. Plasma lipid analyses were centralized (SERLIA INSERM U545, Institut Pasteur de Lille, France).

Biological measurements

A subset of biological measurements was performed in the entire cohort at baseline. Total cholesterol and triglycerides were measured by enzymatic methods using commercial kits in an automatic analyser (Boehringer, Mannheim, Germany). High-density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein B by enzymatic methods (Boehringer). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Fibrinogen was measured according to the method of Clauss.

Follow-up and ascertainment of cases

During the 5-years of follow-up, subjects were contacted annually by letter and asked to complete a clinical event questionnaire. For all subjects reporting a possible event, clinical information was sought directly from the hospital or general practitioner records. All details of ECGs, hospital admissions, enzymes, surgical intervention, angioplasty, treatments, etc., were collected. Whenever possible, circumstances of death were obtained from the practitioner or the family. In the few cases where the circumstances surrounding the death were not available from the practitioner or the family, death certificates were checked for supporting clinical and post-mortem information on cause of death. A medical committee comprising one member from each PRIME centre and the coordinating centre and three cardiologists (two from France and one from the UK) was established, in order to provide an independent validation of coronary events. A description of the coronary end-point definitions has been published elsewhere.15

Angina pectoris was defined not only by the presence of chest pain at rest and/or on exertion, but also by one of the following criteria: (1) angiographic stenosis over 50%; (2) a positive scintigraphy (if no angiographic data); (3) a positive exercise stress (if no angiographic or scintigraphy data); (4) electrocardiogram changes at rest (if no angiographic, scintigraphy, or exercise stress test data) but without MI and no evidence of a non-coronary cause in the clinical history. UA was defined as a crescendo pain or chest pain at rest, with either enzyme changes or electrical changes. In the absence of enzyme or electrical data, the diagnosis was not upheld.

MI was defined by one of the following conditions: (1) new diagnostic Q-wave or other fresh typical electrocardiographic signs of necrosis; (2) typical or atypical pain symptoms and new (or increased) ischaemia and myocardial enzyme levels higher than twice the upper limit; (3) post-mortem evidence of fresh MI or thrombosis.

Coronary death was defined as death with a documented coronary event.

After 5 years of follow-up, the CHD event status was available for more than 98% of the cohort and 317 incident CHD events had been validated. However, 25 suspected coronary deaths were excluded since the coronary event leading to death was not documented, leaving 292 well-characterized incident events for analysis. There were 13 subjects who developed different types of CHD event during follow-up, but only the first one was considered for analysis including first SA (n = 7) and first MI (n = 6).

Taken together, two diagnosis categories were constructed: SA on exertion and ACS including UA and MI (fatal and non-fatal).

The case–control study

A nested case–control study within the PRIME prospective cohort study was conducted using the baseline plasma samples from the 292 study participants who subsequently developed an incident coronary event during follow-up and from 584 matched controls (two controls per case). Matched controls were study participants recruited in the same centre on the same day (±3 days) and of the same age (±3 years) as the corresponding case, and were free of the CHD phenotype under consideration (SA, UA, or MI) at the date of the ischaemic event of the case. The inflammatory assays and internal validation of
the measures in each laboratory have been previously described. High-sensitivity CRP (hs-CRP) was measured by immuno-nephelometry (Dade Behring, Reuil-Malmaison, France), IL-6 and IL-18 by ELISA (R&D Systems), and ICAM-1 using a commercially available ELISA (Innogenetics, Brugelette, Belgium). Haemostatic factors including D-dimers, vWF, free tissue factor pathway inhibitor (TFPI) were mainly assessed at the Laboratory of Hemostasis of La Timone Hospital in Marseille, France, using commercially available ELISAs from Diagnostica Stago. Internal validation of the measures has been previously published.

Statistical analysis
To limit the possibility that we included men with an underlying infectious disease or an inflammatory condition, we excluded 23 cases and 46 matched controls who had a baseline hs-CRP value above 10 mg/L, leaving 269 first coronary events and 538 matched controls for analysis. In descriptive analysis, the baseline characteristics of men who developed incident SA and ACS were compared with those of their respective matched controls using univariate conditional logistic regression that accounted for the matching variables. The odds ratios (ORs) and their 95% confidence interval (CI) of each biomarker for SA, on the one hand, and for ACS, on the other hand, were estimated on separate conditional logistic regression analyses. The quartiles of each biomarker were determined in the overall group of controls, and ORs of the second, third, and fourth over the first quartiles were estimated by including three indicator (dummy) variables of the biomarker in the conditional logistic regression model. For ease of the presentation, only the OR of the fourth over the first quartile was reported. For TFPI, however, the 10th percentile was used as the cut-off based on earlier results from the PRIME Study. In addition, the ORs were given for 1 standard deviation (SD) increase in the logarithm of each biomarker (except for TFPI), which was calculated in the overall group of controls. Multivariable adjustment was made for conventional risk factors measured at baseline examination and included smoking status, family history of early MI, systolic blood pressure, diabetes, body mass index (BMI), HDL and LDL cholesterol, triglycerides (which was log-transformed). The multivariable-adjusted ORs for SA and ACS associated with a given biomarker were compared using the standardized difference between the regression coefficients (z test). To obtain a clinical view of the incremental value of a biomarker, we also evaluated whether its addition in a risk model with established risk factors improved the ability of that model to discriminate between those men who will develop an ACS from those who will not. To this end, we calculated a net reclassification improvement (NRI) using the methods recently described by Pencina et al. This method evaluates whether the model containing the biomarker reclassified ACS cases and their matched controls into higher and lower predicted risk categories, respectively, compared with the model with established risk factors but without the biomarker. We also estimated the change in the C-statistic index associated with the addition of the biomarker in a multivariable model with established risk factors.

All comparisons were two-sided and a P-value <0.05 indicated a statistically significant difference. Analyses were performed using STATA software version 9.0.

Results
Baseline clinical characteristics of the cohort
The present study population consists of 269 first coronary events, 107 SA on exertion and 162 ACS events (34 UA, 128 MI), respectively, and a total of 538 matched controls. The mean age (SD) of the cohort was 55.0 years (2.9). The baseline clinical characteristics of those who developed SA or ACS and of their respective matched controls are described in Table 1. As expected, men who developed SA or ACS had a worse cardiovascular risk profile than their respective controls. The data also suggested that antihypertensive treatment including β-blockers and calcium-channel inhibitors were more often used in men who developed SA than in those who developed ACS. The same trend was found for lipid-lowering treatment but such an analysis was based on a much lower number of subjects. In addition, the mean levels of the risk factors were comparable in the two groups of controls.

Distribution of circulating inflammatory and haemostatic markers
Table 2 compares the distribution of the biomarkers among men with incident SA or ACS and that of respective matched controls. Except for CRP and IL-6 (borderline significance), the distribution of the biomarkers was not clearly different between those with SA and their matched controls. In contrast, the biomarkers were all significantly higher (lower for TFPI; borderline significance) in men with ACS compared with that of matched controls.

Associations of circulating inflammatory and haemostatic markers with SA and ACS
Table 3 reports and compares the univariate ORs of each systemic biomarker for SA and ACS. For the inflammatory markers, higher levels of CRP, ICAM-1, IL-6, and IL-18 were associated with ACS, whereas significant and near-significant association with SA was found for higher CRP and higher IL-6, respectively. Nevertheless, the comparison of the ORs for SA or ACS did not indicate any statistically significant difference (all P-values >0.05). For the haemostatic markers, higher levels of fibrinogen, D-dimers, vWF, and lower level of TFPI were associated significantly with ACS (near significance for TFPI), but not with SA. The comparison of the ORs for SA and ACS showed a statistically significant difference for vWF only (P = 0.03 and 0.048 for vWF considered in quartiles and as a continuous variable, respectively).

Figures 1 and 2 depict the multivariable associations of the above inflammatory and haemostatic markers with SA and ACS after adjustment for smoking, family history of early MI, BMI, systolic blood pressure, diabetes, LDL and HDL cholesterol, and triglycerides (log-transformed). The same trends as in the above analyses were observed. In particular, the significant stronger association of vWF with SCA (compared with SA) persisted: men with baseline vWF in the fourth quartile of the distribution had a three-fold increased risk of SCA compared with men with baseline vWF in the first quartile (OR = 2.99; 95% CI: 1.49–6.02), whereas no increased risk was found for SA (OR = 0.80; 95% CI: 0.33–1.94; P for the comparison between ORs = 0.02). Corresponding ORs for a TSD increase in the logarithm of vWF were 1.31 (1.02–1.69) and 0.82 (0.59–1.14), respectively (P for the comparison between ORs = 0.021). Similar findings were observed after subsequent adjustment for statins (not shown).
Moreover, the association of vWF with ACS persisted after additional adjustment for hs-CRP (OR 4th vs. 1st quartile $= 2.83; 95\% \text{ CI: } 1.39–5.73$), hs-CRP and IL-6 (OR 4th vs. 1st quartile $= 2.59; 95\% \text{ CI: } 1.23–5.45$), and hs-CRP, IL-6, and IL-18 (OR 4th vs. 1st quartile $= 2.34; 95\% \text{ CI: } 1.08–5.07$). Consistent results were observed when vWF was considered as continuous (not shown).

Adding vWF in a multivariable model with established risk factors yielded an overall NRI of 11.6% ($P = 0.02$), meaning that 11.6% of men were reclassified into adequate risk categories (higher and lower risk categories for cases and controls, respectively). In contrast, the c-statistic was virtually unchanged (from 0.69 to 0.70) after the inclusion of vWF in the aforementioned multivariable model with established risk factors (not shown).

Among the 128 men who developed an incident MI, 58 were non-Q-wave MIs and 70 Q-wave MIs. Associations between the haemostatic and inflammatory biomarkers with each ACS phenotype including UA, non-Q-wave and Q-wave MIs were of the same order of magnitude (not shown).

In sensitivity analysis where ACS cases were directly compared with SA cases, we found consistent results. There still was a trend toward a stronger association of haemostatic markers with ACS. In particular, the OR for ACS of the fourth over the first quartile of vWF was 2.14 (0.97–4.74, $P = 0.06$, after multivariable adjustment. The corresponding OR for 1SD increase in the logarithm of vWF was 1.28 (0.95–1.73, $P = 0.08$).

**Discussion**

The present population-based observational study conducted in initially asymptomatic middle-aged men indicates that systemic levels of CRP, ICAM-1, IL-6, and IL-18 are equally predictive of incident SA or ACS over 5 years. In contrast, it suggests that higher level of vWF is significantly more predictive of ACS than SA.
Table 2 Baseline distribution of inflammatory and haemostatic markers in men who developed incident stable angina or acute coronary syndrome over 5 years of follow-up and in their respective matched controls (the PRIME Study)

<table>
<thead>
<tr>
<th></th>
<th>Stable angina</th>
<th>Acute coronary syndrome</th>
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<tbody>
<tr>
<td></td>
<td>Cases (N = 107)</td>
<td>Controls (N = 214)</td>
</tr>
<tr>
<td>hs-CRP (mg/L), med (IQ range)</td>
<td>1.86 (0.72–3.26)</td>
<td>1.33 (0.62–2.61)</td>
</tr>
<tr>
<td>ICAM-1 (ng/L), med (IQ range)</td>
<td>589 (521–681)</td>
<td>548 (478–667)</td>
</tr>
<tr>
<td>IL-6 (pg/L), med (IQ range)</td>
<td>1.26 (0.94–1.96)</td>
<td>1.18 (0.82–1.81)</td>
</tr>
<tr>
<td>IL-18 (pg/ml), med (IQ range)</td>
<td>233 (163–292)</td>
<td>193 (150–280)</td>
</tr>
<tr>
<td>Fibrinogen (g/L), med (IQ range)</td>
<td>3.28 (2.79–3.78)</td>
<td>3.11 (2.72–3.65)</td>
</tr>
<tr>
<td>D-dimers (ng/L), med (IQ range)</td>
<td>256 (199–375)</td>
<td>259 (204–340)</td>
</tr>
<tr>
<td>von Willebrand factor (UI/mL), med (IQ range)</td>
<td>1.11 (0.85–1.47)</td>
<td>1.16 (0.88–1.41)</td>
</tr>
<tr>
<td>Tissue factor pathway inhibitor (ng/dL), 10th percentile (min–max)</td>
<td>12.0 (7.4–100)</td>
<td>11.8 (7.1–100)</td>
</tr>
</tbody>
</table>

*P-value from univariate conditional logistic regression.

Inflammatory and haemostatic factors were not differentially associated with patients with chronic SA.

Conversely, vWF was associated with ACS but not SA, and the comparison of the ORs showed a statistically significant difference that was independent of conventional risk factors and novel inflammatory biomarkers.

The PRIME Study is one of the few prospective, population-based studies in which the various phenotypes of ischaemic heart disease including SA on exertion, UA, and MI have been disaggregated. In previous studies, SA on exertion has been mostly defined on the basis of self-reported pain symptom only, whereas in the PRIME Study, more stringent criteria including enzymatic, invasive (angiography), and, if not available, non-invasive tests (stress test) have been applied limiting the false-positive rate for SA. Usually, clinical studies separate ACS with or without ST elevation based on ACS presentation at hospital admission. In the PRIME Study all available documented hospitalization were used and final classification of events was mostly based on hospital discharge data rather than admission data. Some differences might be expected between the two classifications. For instance, a recent analysis of the Euro Heart Survey indicates that among subjects presenting with ST elevation ACS at hospital admission, 22 and 13% were discharged with a non-Q-wave acute MI and UA diagnosis, respectively. For those presenting with ST depression ACS, 27% were discharged with a final diagnosis of non-Q-wave acute MI and 9% with a diagnosis of Q-wave acute MI.

In the present study, higher systemic levels of hs-CRP, IL-6, IL-18, and ICAM-1 were equally predictive of SA and ACS. Inflammatory cells have been observed in eroded or ruptured atherosclerotic plaques not only in patients with ACS, but also in those with chronic SA, although less frequently, suggesting that the supposed triggering effect of inflammation on the erosion or the rupture of an atherosclerotic plaque is not so specific to unstable coronary artery disease (CAD). Moreover, in addition to its acute effects, inflammation has been involved in the development of atherosclerosis, a process that is common to stable and unstable CAD.

Conversely, vWF was associated with ACS but not SA, and the comparison of the ORs showed a statistically significant difference that was independent of conventional risk factors, vWF is an endothelial cell marker involved in acute thrombosis formation, a process that is thought to be characteristic of ACS, and less so to SA. We also found that association of vWF with ACS remained significant after additional adjustment for several inflammatory markers, suggesting that vWF acts through pathways that are
different from inflammation. For instance, vWF has three major activities: (1) mediating platelet adhesion to damaged arterial walls, (2) mediating platelet aggregation at high shear stress, and (3) binding and stabilizing factor VIIIc.\textsuperscript{23} From a clinical point of view, the present study suggests that vWF may help in better discriminating men who will develop ACS from those who will not, as the addition of vWF in a risk prediction model containing established risk factors improved the classification of cases and controls into higher and lower predicted risk categories, respectively. As already mentioned, NRI is a more sensitive index of discrimination than the c-statistic, which was virtually unchanged in the present study when vWF was added in the model.\textsuperscript{17,24}

Also, higher fibrinogen level and lower TFPI level tended to be more predictive of ACS than SA, but the difference in the ORs did

<table>
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<tr>
<th>Table 3</th>
<th>Unadjusted odds ratios and 95% confidence interval of inflammatory and haemostatic biomarkers for incident stable angina and acute coronary syndrome (the PRIME Study)</th>
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<tbody>
<tr>
<td></td>
<td>Stable angina (N = 107)</td>
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<tr>
<td><strong>Inflammatory markers</strong></td>
<td></td>
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<tr>
<td>hs-CRP (mg/L)</td>
<td></td>
</tr>
<tr>
<td>1st quartile (&lt;0.60)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;2.49)</td>
<td>2.15 (1.07–4.30)</td>
</tr>
<tr>
<td>For 1SD increase of log CRP (1.02)</td>
<td>1.32 (0.94–1.82)</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td></td>
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<tr>
<td>1st quartile (&lt;477)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;665)</td>
<td>1.91 (0.84–4.33)</td>
</tr>
<tr>
<td>For 1SD increase of log ICAM-1 (0.29)</td>
<td>1.28 (0.91–1.81)</td>
</tr>
<tr>
<td><strong>IL-6 (pg/mL)</strong></td>
<td></td>
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<tr>
<td>1st quartile (&lt;0.83)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;1.95)</td>
<td>2.14 (0.97–4.72)</td>
</tr>
<tr>
<td>For 1SD increase of log IL-6 (0.70)</td>
<td>1.35 (0.91–1.97)</td>
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<tr>
<td><strong>IL-18 (pg/mL)</strong></td>
<td></td>
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<tr>
<td>1st quartile (&lt;145)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;269)</td>
<td>1.67 (0.74–3.79)</td>
</tr>
<tr>
<td>For 1SD increase of log IL-18 (0.53)</td>
<td>1.29 (0.96–1.73)</td>
</tr>
<tr>
<td><strong>Haemostatic markers</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td></td>
</tr>
<tr>
<td>1st quartile (&lt;2.73)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;3.68)</td>
<td>1.63 (0.87–3.48)</td>
</tr>
<tr>
<td>For 1SD increase of log fibrinogen (0.26)</td>
<td>1.10 (0.80–1.51)</td>
</tr>
<tr>
<td>D-dimers (ng/L)</td>
<td></td>
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<tr>
<td>1st quartile (&lt;197)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;344)</td>
<td>1.43 (0.65–3.11)</td>
</tr>
<tr>
<td>For 1SD increase of log D-dimers (0.48)</td>
<td>1.09 (0.78–1.52)</td>
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<tr>
<td>von Willebrand factor (U/L)</td>
<td></td>
</tr>
<tr>
<td>1st quartile (&lt;0.85)</td>
<td>1.0</td>
</tr>
<tr>
<td>4th quartile (&gt;1.41)</td>
<td>0.87 (0.43–1.79)</td>
</tr>
<tr>
<td>For 1SD increase of log von Willebrand factor (0.39)</td>
<td>0.90 (0.68–1.19)</td>
</tr>
<tr>
<td>Tissue factor pathway inhibitor (ng/dL)</td>
<td></td>
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<tr>
<td>≥10th percentile (≥12)</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;10th percentile (&lt;12)</td>
<td>0.88 (0.37–2.10)</td>
</tr>
</tbody>
</table>

SD: standard deviation. SD of the logarithm of each biomarker was taken in the overall group of controls. ORs and their 95% confidence intervals were estimated by univariate conditional logistic regression.

*Standardized difference between the regression coefficients for SA and ACS (z test).
not reach statistical significance. The apparent absence of statistical difference may be due to a lack of statistical power to detect smaller differences. Results for fibrinogen may also be due to the fact that this biomarker is relevant to atherosclerosis development, a process that is common to ACS and SA.

The present study has several strengths. It is a large, prospective, population-based study in which CHD end-points were validated using standardized and stringent criteria. In addition to the measurement of conventional risk factors, a large set of systemic biomarkers were measured at baseline examination.

The present study has also some limitations. Serial examination was not performed in the PRIME Study so that changes in risk factor levels and therapy during follow-up were not controlled for. Some true but potentially smaller differential association of some biomarkers with SA and ACS may have been masked by a lack of statistical power. A new definition of MI was recently proposed in 2007. It should be kept in mind, however, that in the current study, we used diagnosis criteria available when the 5 years of follow-up of the PRIME Study was completed in 1998. Finally, our sample only included middle-aged men and therefore further studies should also include older men and women.
Novel biomarkers and first coronary event

1973

Conclusion
In conclusion, this is the first population-based study assessing the contribution of novel biomarkers to first SA and ACS. The results suggest that haemostatic markers and VWF, in particular, are more predictive of ACS than SA.

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Conflict of interest: none declared.

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Appendix
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The Lille MONICA Project, INSERM, U744, Lille, France; Institut Pasteur de Lille, Lille, France; Université de Lille 2, Lille, France (F. Amouyel, M. Montaye).

The Department of Epidemiology and Public Health, Queen’s University, Belfast, Northern Ireland (A. Evans, J. Yarnell, F. Kee).

The Department of Atherosclerosis, INSERM, U545; Lille; Institut Pasteur de Lille, Lille; Université de Lille 2, Lille, France (F. Amouyel, M. Montaye).

The Department of Haematology, INSERM, U626, Marseille, Hôpital La Timone, Marseille, France (J. Juhan-Vague, Pierre Morange).

The Laboratory of Endocrinology, INSERM U563, Toulouse, France (B. Perret).

The Vitamin Research Unit, The University of Bern, Bern, Switzerland (F. Gey).

The Nutrition and Metabolism Group, Centre for Clinical and Population Sciences, Queen’s University, Belfast, Northern Ireland (Jayne Woodside, Ian Young).

The DNA Bank, INSERM U525, Paris, France (F. Cambien).

The Coordinating Center, INSERM, Unit 909, Villejuif, F-94807, France; Univ Paris-V, Faculty of Medicine, Villejuif, F-94807, France (P. Ducimetiere, A. Bingham).

The Strasbourg MONICA Project, Laboratoire d’Épidémiologie et de Sante Publique, EA1801, Strasbourg, F-67085, France (J. Ferrieres, JB. Ruidavets).

The Lille MONICA Project, INSERM, U744, Lille, France; Institut Pasteur de Lille, Lille; Université de Lille 2, Lille, France (F. Amouyel, M. Montaye).

The Department of Atherosclerosis, INSERM, U545; Lille; Institut Pasteur de Lille, Lille; Université de Lille 2, Lille, France (F. Amouyel, M. Montaye).

The Department of Epidemiology and Public Health, Queen’s University, Belfast, Northern Ireland (A. Evans, J. Yarnell, F. Kee).

The Department of Atherosclerosis, INSERM, U545; Lille; Institut Pasteur de Lille, Lille; Université de Lille 2, Lille, France (D. Arveiler, B. Haas).

The Toulouse MONICA Project, INSERM U558; Departement d’Épidémiologie, Universite Paul Sabatier - Toulouse Purpan, Toulouse, France (J. Ferrières, JB. Ruidavets).

The Lille MONICA Project, INSERM, U744, Lille, France; Institut Pasteur de Lille, Lille, France; Université de Lille 2, Lille, France (D. Arveiler, B. Haas).

Appendix
The PRIME Study is organized under an agreement between INSERM and the Merck, Sharpe, and Dohme-Chibret Laboratory, with the following participating laboratories.

The Strasbourg MONICA Project, Laboratoire d’Épidémiologie et de Sante Publique, EA1801, Strasbourg, F-67085, France; Universite Louis Pasteur, Faculte de Medecine, Strasbourg, F-67085, France (D. Arveiler, B. Haas).

The Toulouse MONICA Project, INSERM U558; Departement d’Épidémiologie, Universite Paul Sabatier - Toulouse Purpan, Toulouse, France (J. Ferrières, JB. Ruidavets).

The Lille MONICA Project, INSERM, U744, Lille, France; Institut Pasteur de Lille, Lille, France; Université de Lille 2, Lille, France (D. Arveiler, B. Haas).

The Department of Epidemiology and Public Health, Queen’s University, Belfast, Northern Ireland (A. Evans, J. Yarnell, F. Kee).

The Department of Atherosclerosis, INSERM, U545; Lille; Institut Pasteur de Lille, Lille; Université de Lille 2, Lille, France (G. Luc, JM. Bard).

The Laboratory of Haematology, INSERM, U626, Marseille, Hôpital La Timone, Marseille, France (J. Juhan-Vague, Pierre Morange).

The Laboratory of Endocrinology, INSERM U563, Toulouse, France (B. Perret).

The Vitamin Research Unit, The University of Bern, Bern, Switzerland (F. Gey).

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The DNA Bank, INSERM U525, Paris, France (F. Cambien).
Primary chylopericardium due to lymphangiectasias: the crucial role of lymphangiography

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A 24-year-old woman was referred to our Cardiology Department because of cardiomegaly at a routine chest X-ray. She was asymptomatic except for some fatigability. Physical examination was unremarkable. Electrocardiogram showed only low QRS voltages. Echocardiography revealed large pericardial effusion with right atrial and ventricular collapse. Pericardiocentesis was performed and 1100 mL of milky fluid were removed, suggesting chylopericardium. The chylous nature of the fluid was confirmed by high content of triglycerides (1200 mg/dL) and by cholesterol/triglyceride ratio <1. Sudan III stain of the fluid revealed fat globules. Bacterial and tuberculous cultures were negative. Cytology demonstrated abundance of lymphocytes, with no tumour cells. A subxiphoid exterior tube drainage was maintained and alipidic diet was started. After an initial success of this treatment, significant chylopericardium recurred. Thoracic computed tomography was negative. Thus, lymphangiogram was performed by slow injection of ethiodized oil into a cannulated lymphatic vessel of the right foot showing an open thoracic duct with lymphangiectasias at pericardial level (Figure). Left thoracotomy was indicated. The pleural cavity appeared normal; the pericardium appeared thickened with numerous lymphangiectasias. Ligation of the thoracic duct, closure between metallic clips of lymphangiectasias, and pericardial fenestration were performed. Pericardial biopsies showed a chronic inflammatory process with haemorrhagic infiltrate and a large number of lymphangiectasias. After 15 days, the patient was discharged and in 4 weeks she returned to normal diet, full-time work, and full activities. Echocardiography showed no recurrence of chylopericardium at late follow-up.

Panel A. Ascending phase at abdominal level of the lymphangiographic agent after cannulation of a right foot lymphatic vessel.

Panels B and C (detail). Diagnostic lymphangiogram in antero-posterior view showing the presence of lymphangiectasias at pericardial level (arrows).

Panel D. Diagnostic lymphangiogram in lateral view showing the thoracic duct (arrow heads) and the presence of lymphangiectasias at pericardial level (arrows).