

BRIEF COMMUNICATION

# Factor V Leiden Does Not Modify the Phenotype of Acute Coronary Syndrome or the Extent of Myocardial Necrosis

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**BACKGROUND:** The prothrombotic defect factor V Leiden (FVL) may confer higher risk of ST-segment–elevation myocardial infarction (STEMI), compared with non–ST-segment–elevation acute coronary syndrome, and may be associated with more myocardial necrosis caused by higher thrombotic burden.

**METHODS AND RESULTS:** Patients without history of cardiovascular disease were selected from 2 clinical trials conducted in patients with acute coronary syndrome. FVL was defined as G-to-A substitution at nucleotide 1691 in the factor V (factor V R506Q) gene. Odds ratios were calculated for the association of FVL with STEMI adjusted for age and sex in the overall population and in the subgroups including sex, age ( $\geq 70$  versus  $< 70$  years), and traditional cardiovascular risk factors. The peak biomarker levels (ie, creatine kinase-myocardial band and high-sensitivity troponin I or T) after STEMI were contrasted between FVL carriers and noncarriers. Because of differences in troponin assays, peak high-sensitivity troponin levels were converted to a ratio scale. The prevalence of FVL mutation was comparable in patients with STEMI (6.0%) and non–ST-segment–elevation acute coronary syndrome (5.8%). The corresponding sex- and age-adjusted odds ratio was 1.06 (95% CI, 0.86–1.30;  $P=0.59$ ) for the association of FVL with STEMI. Subgroup analysis did not show any differences. In patients with STEMI, neither the median peak creatine kinase-myocardial band nor the peak high-sensitivity troponin ratio showed any differences between wild-type and FVL carriers ( $P$  for difference: creatine kinase-myocardial band=0.33; high sensitivity troponin ratio=0.54).

**CONCLUSIONS:** In a general population with acute coronary syndrome, FVL did not discriminate between a STEMI or non–ST-segment–elevation acute coronary syndrome presentation and was unrelated to peak cardiac necrosis markers in patients with STEMI.

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**Key Words:** cardiovascular disease ■ cardiovascular disease risk factors ■ coagulation/thrombosis ■ factor V Leiden ■ genetic polymorphism

Acute coronary syndrome (ACS) is one of the leading causes of death in developed countries. ACS is generally subdivided in non–ST-segment–elevation acute coronary syndrome (NSTEMI) and ST-segment–elevation myocardial infarction (STEMI).<sup>1,2</sup> Nearly all cases of ACS are

caused by the slowly progressive process of atherosclerosis, followed by an acute rupture or erosion of an atherosclerotic plaque with subsequent thrombus formation.<sup>1,2</sup> It is, however, unknown why in some cases plaque rupture leads to high thrombotic burden with total artery occlusion leading to STEMI,

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whereas in the setting of NSTEMI-ACS, plaque rupture is usually associated with limited and nonobstructive thrombus.

Whereas hereditary thrombophilic defects such as factor V Leiden predisposes to  $\approx$ 4-fold higher risk of venous thrombosis,<sup>3</sup> arterial thrombosis is considered less likely to be influenced by hereditary thrombophilic defects. Platelet aggregation seems to be more important in the pathogenesis of arterial thrombosis.<sup>4</sup> In several meta-analyses, factor V Leiden showed only weak, if any, association with the occurrence of myocardial infarction.<sup>5–7</sup> This may be because the plaque rupture itself is generally caused by atherosclerosis, which is mainly driven by traditional cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking.<sup>1,2</sup> Moreover, these and other acquired risk factors for arterial thrombosis may overrule the impact of hereditary thrombophilic defects.<sup>4</sup> Nevertheless, coagulation activation is a pivotal component of thrombus formation and stabilization at the site of vascular injury following platelet aggregation.<sup>1,2</sup> Hence, thrombophilic conditions such as factor V Leiden may play a more important role in determining the phenotype rather than the incidence of ACS, that is, STEMI versus NSTEMI-ACS, because patients with a factor V Leiden may have higher thrombus formation at the site of plaque rupture and therefore more often STEMI. Moreover, patients with STEMI with factor V Leiden may have higher levels of myocardial necrosis biomarkers attributable to higher thrombus burden. On the other hand, a few studies reported the opposite, that is, higher prevalence of factor V Leiden in patients with myocardial infarction with nonobstructive (<50% stenosis) epicardial coronary arteries (MINOCA) compared with patients with one or more flow-limiting epicardial coronary stenosis.<sup>4,8,9</sup>

In the current study we assess whether factor V Leiden mutation modifies the risk of STEMI compared with NSTEMI-ACS, and whether patients with STEMI carrying this thrombophilic defect have more myocardial necrosis based on the levels of peak creatine kinase-myocardial band (CK-MB) and high-sensitivity troponin (hs-troponin).

## METHODS

In accordance with Transparency and Openness Promotion guidelines, summary-level data supporting the findings of this study could be made available upon reasonable request to the corresponding author. Requests for individual participant data require formal assessment by the steering committee of each study that could be submitted to the principal investigators (L.W. for the PLATO [Study

of Platelet Inhibition and Patient Outcomes] trial, Lars.Wallentin@ucr.uu.se; J.M.t.B for the POPular Genetics trial, jurtenberg@gmail.com).

## Participants

The first question on whether factor V Leiden mutation modifies the type of ACS was addressed in the PLATO trial,<sup>10</sup> and the second question on biomarker levels in patients with STEMI was assessed in the POPular Genetics trial.<sup>11</sup> Detailed study protocols of these clinical trials have been published previously.<sup>10,11</sup> The PLATO trial was an international randomized, double-blind, double-dummy phase III study comparing ticagrelor plus aspirin with clopidogrel plus aspirin in patients with either STEMI intended for primary percutaneous intervention or with NSTEMI-ACS.<sup>10</sup> A total of 18 624 patients from 862 centers in 43 countries were enrolled between 2006 and 2008. DNA samples for genetic analyses were available from centers and patients consenting to participation in the genetics sub-study. The POPular Genetics trial was a multicenter, open-label, assessor-blinded trial comparing ticagrelor or prasugrel plus aspirin with clopidogrel plus aspirin based on rapid genetic testing for clopidogrel resistance in patients with STEMI undergoing primary percutaneous intervention.<sup>11</sup>

Patients requiring oral anticoagulants and patients with high bleeding risk, such as those with recent (<24 hours) fibrinolytic therapy, were excluded from these trials. Patients with prior cardiovascular event (ie, stroke, myocardial infarction, or coronary revascularization) at baseline were excluded from the current analysis to avoid overlap such that a STEMI patient could have had a prior NSTEMI-ACS and vice versa, and to limit a possible selection bias caused by prior stroke. The study protocols of each study were approved by ethical review boards, and only patients who had provided informed consent for genetic studies at the time of enrollment were eligible for inclusion. Both studies were conducted in agreement with the Declaration of Helsinki.

## Measurements

Factor V Leiden was defined as the presence of a single nucleotide mutation, that is, G-to-A substitution at nucleotide 1691 in the factor V (factor V R506Q) gene (SNP rs6025). This was documented by direct DNA sequencing using commercially available targeted sequencing kits. In the POPular Genetics trial, peak (highest value) CK-MB or peak hs-troponin, or both, were measured every 6 hours after the primary percutaneous coronary intervention until these markers reached decreasing values. Because of differences in troponin assays among the hospitals participating in the POPular Genetics trial, such as difference in

the normal ranges or troponin T versus troponin I assays, we used the ratio of peak hs-troponin by dividing the peak hs-troponin value obtained during the index hospitalization for STEMI by the upper limit of the normal range for that specific hospital, as previously reported.<sup>12</sup>

## Statistical Analysis

Prevalence of factor V Leiden was contrasted between patients with STEMI and NSTEMI-ACS and tested using a  $\chi^2$  test. Age- and sex-adjusted odds ratios accompanied by 95% CIs and *P* values for STEMI compared with NSTEMI-ACS were calculated using logistic regression models for the overall population and for several subgroups. Subgroups consisted of patient-level characteristics measured at baseline, including sex, age ( $\geq 70$  years versus  $< 70$  years), hypertension (physician diagnosed or treated), type 2 diabetes mellitus (physician diagnosed or treated), hyperlipidemia (physician diagnosed or treated), and current smoking.

To assess whether factor V Leiden is associated with more myocardial necrosis in patients with STEMI, median and interquartile ranges of peak CK-MB and hs-troponin levels were calculated for wild-type and factor V Leiden carriers. Differences in levels of these cardiac markers between patients with versus without factor V Leiden were tested by Wilcoxon rank sum test. In all analyses, a *P* value of  $< 0.05$  was considered statistically significant. All analyses were conducted using the R software package (R Foundation for Statistical Computing, Vienna, Austria).<sup>13</sup>

## RESULTS

A total of 9980 patients in the PLATO trial and 2304 patients in the POPular Genetics trials had data on factor V Leiden status (ie, PLATO trial: 563 heterozygous and 17 homozygous; POPular Genetics trial: 128 heterozygous and 1 homozygous). After exclusion of patients with prior cardiovascular disease and unknown ACS type, a total of 3792 patients with NSTEMI-ACS and 3273 patients with STEMI contributed to the analysis of whether factor V Leiden modifies ACS type, assessed in the PLATO trial population. A total of 1825 patients from the POPular Genetics trial had data on biomarkers and had no history of prior cardiovascular disease. Clinical characteristics of the study participants for NSTEMI-ACS versus STEMI in the PLATO and POPular Genetics trials are summarized in Table. Compared with patients with NSTEMI-ACS, patients with STEMI in the PLATO trial were on average younger and had a higher prevalence of male sex and current smoking ( $P < 0.001$ ). Hypertension,

**Table. Baseline Characteristics of the Study Population**

|                                  | PLATO Trial |            | POPular Genetics Trial |
|----------------------------------|-------------|------------|------------------------|
|                                  | NSTEMI-ACS  | STEMI      | STEMI                  |
| Patients, n                      | 3792        | 3273       | 1825                   |
| Factor V Leiden, n (%)           | 220 (5.8)   | 198 (6.0)  | 107 (5.9)              |
| Mean age, y (SD)                 | 64 (10.6)   | 59 (10.8)  | 62 (11.3)              |
| Male sex, n (%)                  | 2389 (63)   | 2462 (75)  | 1379 (76)              |
| Hypertension, n (%)              | 2514 (66)   | 1799 (55)  | 642 (36)               |
| Diabetes mellitus, n (%)         | 853 (22)    | 520 (16)   | 187 (10)               |
| Hyperlipidemia, n (%)            | 1576 (42)   | 1062 (32)  | 1181 (66)              |
| Current smoking, n (%)           | 1176 (31)   | 1607 (49)  | 824 (46)               |
| Mean BMI, kg/m <sup>2</sup> (SD) | 28.1 (4.6)  | 28.0 (4.3) | 27.1 (4.0)             |

BMI indicates body mass index; NSTEMI-ACS, non-ST-segment-elevation acute coronary syndrome; PLATO, Study of Platelet Inhibition and Patient Outcomes; and STEMI, ST-segment-elevation myocardial infarction.

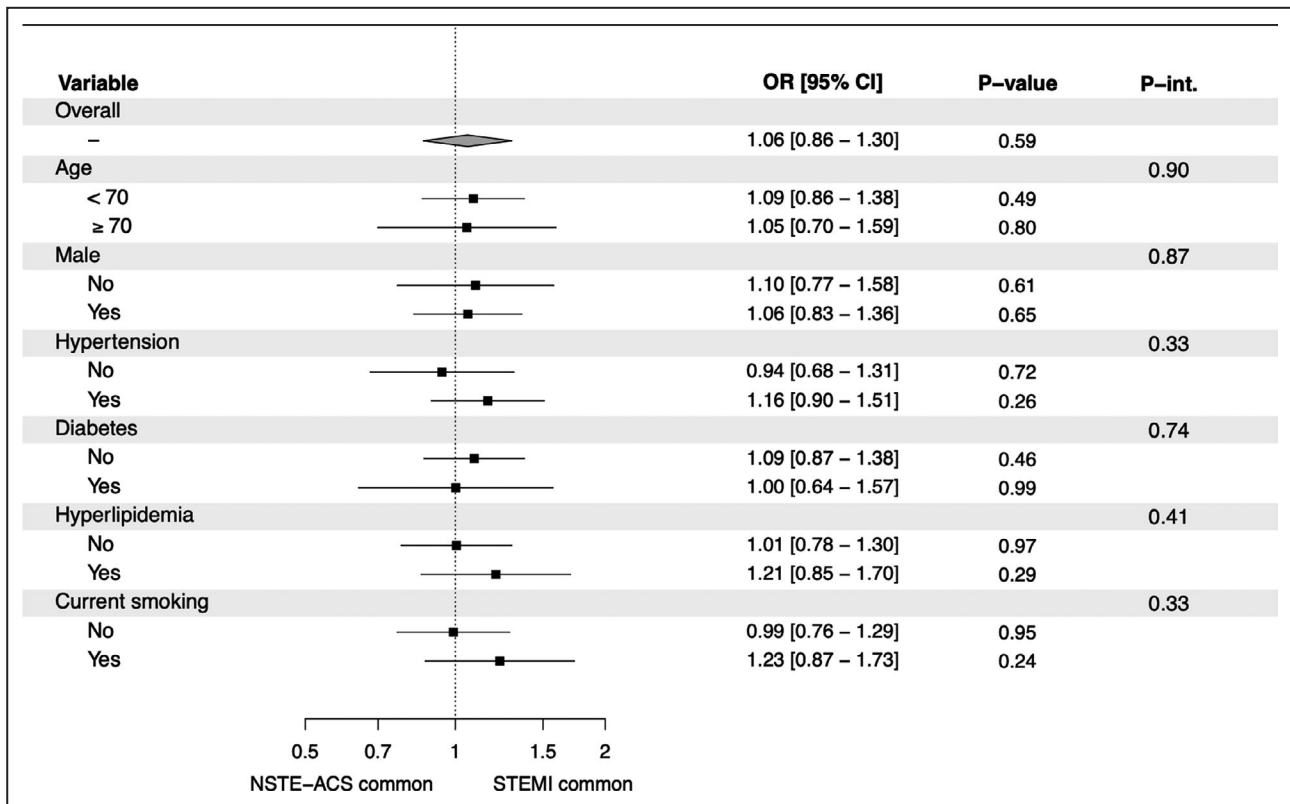
hyperlipidemia, and diabetes mellitus were more prevalent in the NSTEMI-ACS group ( $P < 0.001$ ), and body mass index was similar between patients with STEMI and NSTEMI-ACS ( $P = 0.21$ ).

## Prevalence of Factor V Leiden in STEMI Versus NSTEMI-ACS (PLATO Trial)

The prevalence of factor V Leiden mutation was comparable in patients with STEMI (6.0%) compared with NSTEMI-ACS (5.8%; Table). Moreover, a similar prevalence of factor V Leiden (5.9%) was observed in the POPular Genetics trial (Table). The corresponding age- and sex-adjusted odds ratio for the association of factor V Leiden with STEMI was 1.06 (95% CI, 0.86–1.30;  $P = 0.59$ ; Figure 1). Further adjustment for hypertension, diabetes mellitus, hyperlipidemia, current smoking, and body mass index did not change this risk estimate (adjusted odds ratio, 1.07; 95% CI, 0.87–1.32;  $P = 0.51$ ). Subgroup analysis according to sex, age categories, hypertension, diabetes mellitus, hyperlipidemia, and smoking status did not show any differences (Figure 1).

## Factor V Leiden Mutation Association With Myocardial Necrosis (POPular Genetics Trial)

In the POPular Genetics trial, for a total of 1670 patients with STEMI, peak CK-MB values were available, and for 957 patients with STEMI, peak hs-troponin values were available. Figure 2 shows the peak CK-MB and hs-troponin ratio values in patients with wild-type (CK-MB, median 138 U/L; interquartile



**Figure 1.** Association of factor V Leiden mutation with ST-segment-elevation myocardial infarction (STEMI) compared with non-ST-segment-elevation acute coronary syndrome (NSTEMI-ACS) in the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial.

P-int denotes P value for interaction, that is, the difference between the strata. Estimates are adjusted for sex and age, when appropriate. OR indicates odds ratio.

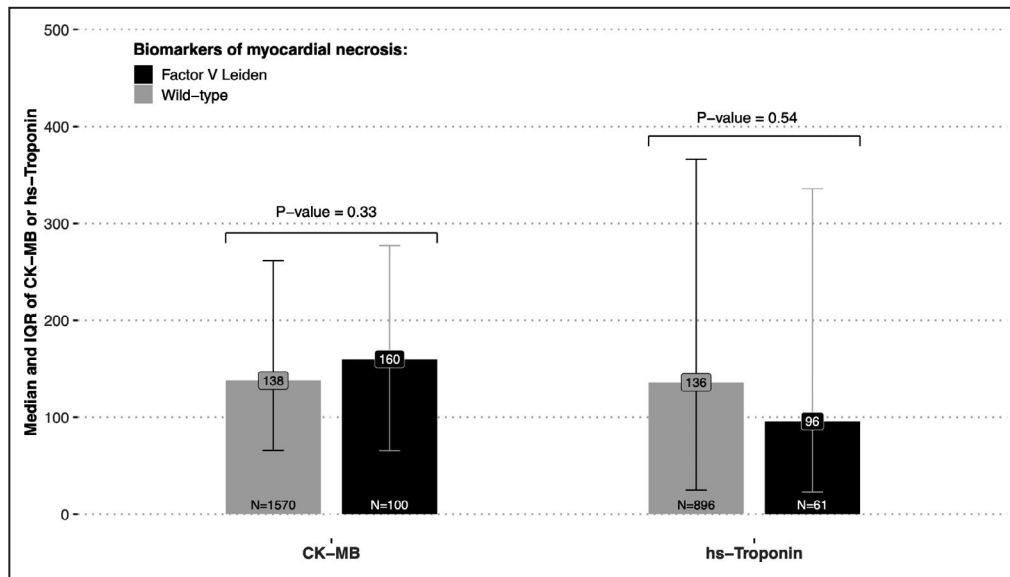
range, 66–263 U/L; hs-troponin ratio, median 141; interquartile range, 24–370) versus factor V Leiden carriers (CK-MB, median 160 U/L; interquartile range, 67–277 U/L; hs-troponin ratio, median 96; interquartile range, 23–329). Both CK-MB ( $P=0.33$ ) and hs-troponin ratio ( $P=0.54$ ) levels did not vary according to factor V Leiden status. Similarly, the peak levels of CK-MB and hs-troponin did not differ ( $P\geq 0.40$ ) in subgroups consisting of women, young age (ie, <55 years), individuals with positive family history for premature atherothrombotic events, and individuals without traditional cardiovascular risk factors (ie, hypertension, hyperlipidemia, diabetes mellitus, and smoking; data not shown).

## DISCUSSION

Factor V Leiden mutation was not associated with higher risk of STEMI compared with NSTEMI-ACS in a total of 3273 patients with STEMI and 3792 patients with NSTEMI-ACS, respectively. Neither was the extent of myocardial necrosis higher in patients with STEMI with versus without factor V Leiden, as quantified by peak CK-MB and hs-troponin. There was no evidence

for significant effect modification according to sex, age categories ( $\geq 70$  versus <70 years), hypertension, diabetes mellitus, hyperlipidemia, and current smoking status.

Prior studies on the association of the factor V Leiden mutation with atherothrombotic outcomes, including myocardial infarction and stroke, showed contradictory results ranging from no evidence for increased risk in cohort studies to a pooled odds ratio of  $\approx 1.20$  for factor V Leiden.<sup>5–7</sup> Recently, we performed a large individual patient-level meta-analysis of prospective studies including clinical trials in patients with established coronary heart disease, which also showed no evidence of increased risk of atherothrombotic events in these patients.<sup>7</sup> Studies investigating factor V Leiden mutation contrasting overall STEMI versus NSTEMI-ACS or assessing myocardial necrosis burden during STEMI in patients with versus without factor V Leiden are lacking. However, several studies reported the prevalence of thrombophilic defects in patients with MINOCA.<sup>4,8,9</sup> Factor V Leiden was more prevalent in patients with MINOCA compared with patients with one or more flow-limiting epicardial coronary stenosis.<sup>4,8,9</sup> In a systematic review and meta-analysis,<sup>9</sup>



**Figure 2. Median and interquartile range (IQR) of the peak creatine kinase-myocardial band (CK-MB) and high-sensitivity (hs)-troponin ratio in the POPular Genetics trial.**

CK-MB values are measured in units per liter, and the hs-troponin values are ratio of the peak hs-troponin divided by the upper limit of the normal range of the same hs-troponin assay. Whiskers represent IQR. N indicates the number of patients contributing data in each group.

patients with MINOCA were younger, often women, and had a lower prevalence of hyperlipidemia compared with patients with one or more flow-limiting epicardial coronary stenosis. Possibly, the prothrombotic state associated with hereditary thrombophilic defects is overruled by other potentially stronger risk factors in the setting of atherothrombotic events.<sup>4</sup> The average prevalence of MINOCA is about 6%, with two thirds of these patients being presented as NSTEMI-ACS and one third as STEMI.<sup>9</sup> Our current study failed to demonstrate any role of factor V Leiden in determining the ACS phenotype by comparing the overall STEMI to the overall NSTEMI-ACS population without subdividing by angiographic characteristics such as stratifying by MINOCA. Similarly, the extent of myocardial necrosis, as measured by peak CK-MB or hs-troponin, did not differ in patients with STEMI, with versus without factor V Leiden. The later analysis was performed in the POPular Genetics trial,<sup>11</sup> which only included patients with flow-limiting epicardial coronary stenosis who underwent primary percutaneous intervention with stent implantation. Of note, the overall prevalence of factor V Leiden in the POPular Genetics trial was the same compared with the PLATO trial, which did not exclude patients with MINOCA.

This study has several limitations. First, our study is underpowered for detecting small differences, because this study had only 76% power to detect an odds ratio of 1.30. Though we aimed to contrast clinical phenotypes of ACS, instead of looking at the true burden of thrombus as documented by angiography,

or more sensitive methods such as optical coherence tomography and intravascular ultrasound, exclusion of patients without significant epicardial coronary stenosis may have led to a more uniform comparison. In the PLATO trial, information on the angiographic characteristics was not available to perform subgroup analysis, for instance, for MINOCA versus obstructive epicardial coronary disease. Nevertheless, given the prevalence of MINOCA (~6%) and factor V Leiden (~6%), our study was likely underpowered for such a comparison. Based on prior literature, factor V Leiden is more prevalent in patients with MINOCA.<sup>4,8,9</sup> The lack of difference in the levels of myocardial necrosis markers in patients with STEMI with factor V Leiden, compared with wild-type, may have been blunted by the primary percutaneous intervention. However, this would have occurred nondifferentially, because factor V Leiden status was unknown at presentation, and the time to reperfusion was similar between factor V Leiden carriers versus noncarriers. There are multiple other factors that could have also influenced the peak cardiac necrosis markers levels such as blood flow before/after coronary intervention, size/location of the thrombus in the target coronary artery, and peripheral embolization after percutaneous coronary intervention. However, our aim was to assess whether myocardial necrosis is influenced by the presence of factor V Leiden in the overall STEMI population undergoing primary percutaneous intervention without searching for subgroups, for which our sample size was underpowered. Finally, our results are not applicable

to non-White populations, because our study participants were almost exclusively (>98%) White.

In conclusion, in a general ACS population, factor V Leiden did not discriminate between a STEMI or NSTEMI presentation and was unrelated to peak cardiac necrosis markers in patients with STEMI.

## ARTICLE INFORMATION

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Author contributions: Dr Mahmoodi developed the analysis script and performed the analysis in the POPular Genetics trial. Dr Eriksson prepared the data sets and applied the analysis script to the PLATO trial. Dr Mahmoodi drafted the manuscript. Drs Wallentin and ten Berg supervised the preparation of the manuscript. All authors took part in the interpretation of the data, and all authors provided critical revisions of the manuscript for important intellectual content.

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