Fibrin clot strength measured by thromb-elastography and outcomes after percutaneous coronary intervention

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Dear Sirs,

High thrombin induced clot strength in whole blood measured by thrombelas tography (TEG) has been associated with increased risk for recurrent thrombotic events after percutaneous coronary intervention (PCI) (1, 2). Whole blood TEG incorporates both the component of platelet aggregation by thrombin, as well as contribution of fibrin to tensile force of whole blood thrombus. We have recently explored the use of plasma fibrin TEG measured in platelet-poor plasma to examine the component of clot strength attributable to fibrin alone in absence of platelets (3–5). We hypothesized that high mechanical strength of cross linked fibrin clot is associated with increased risk of recurrent myocardial infarction (MI) and cardiovascular death (CVD).

We enrolled subjects before or in follow up to a cardiac catheterisation. All subjects had angiographically established coronary artery disease and had undergone percutaneous coronary intervention. Mean time of follow-up was 2.9 years. Kaolin-activated TEG was performed according to the manufacturer's instructions using platelet-poor citrate plasma (Haemonetics, Brain-tree, MA, USA) as previously described (3, 5, 6). The primary combined clinical endpoint was defined as first occurrence CVD or MI (7). Secondary endpoints included CVD, MI, stent thrombosis, and severe or life-threatening bleeding according to GUSTO criteria (8, 9). Clinical endpoints were evaluated by review of electronic medical records, with last known clinical follow-up as last censored time event. Coronary angiograms were reviewed to ascertain stent thrombosis events, available. The study protocol was approved by the Indiana University institutional review board and written informed consent was obtained from all subjects.

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A total of 270 subjects were included the analysis. The mean age of patients was 57.1 ± 9.8 years. Details of clinical variables are available in the Suppl. Material (available online at www.thrombosis-online.com).

The primary endpoint of CVD and MI occurred in 14.4 % of subjects. Definite stent thrombosis occurred in 3 % and possible, probable, or definite stent thrombosis in 3.7 % of subjects. Subjects with occurrence of the primary endpoint during follow up (CVD or MI) had significantly higher maximal fibrin clot strength (TEGMA: 39.6 ± 7.4 vs 35.4 ± 7.4 mm; p=0.001) and shorter clot formation time (TEG-K: 1.14 ± 0.5 vs 1.49 ± 1.3 min; p=0.002) than patients without events during follow up, while time to fibrin formation was similar (TEG-R: 6.7 ± 2.9 vs 7.0 ± 2.9 min; p=0.55) (▶Figure 1). Patients with possible, probable, or definite stent thrombosis during follow up demonstrated significantly higher fibrin MA than subjects without stent thrombosis (TEG-MA: 43.8 ± 9.1 vs 35.7 ± 7.3 mm; p=0.001), but no significant difference in TEG-K (1.1 ± 0.6 vs 1.45 ± 1.2 min; p=0.1) or TEG-R (6.6 ± 3 vs 7 ± 3 min; p=0.67) (▶Figure 1). Patients with definite stent thrombosis during follow up also demonstrated significantly higher fibrin MA than subjects without stent thrombosis (TEG-MA: 41.5 ± 8.6 vs 35.8 ± 7.6 mm; p=0.037). Fibrinogen levels were not significantly different between subjects with CVD or MI versus those without events (Median [interquartile range]: 3.6 [2.1–5.1] vs 3.6 [2–5.2] mg/ml; p=0.95). Fibrinogen was modestly correlated with plasma fibrin TEG-MA (r=0.2; p=0.028).

Optimal cut-off for high fibrin clot strength (MA 35.35 mm) was determined by receiver-operating curve (ROC) analysis for the primary endpoint (area under curve (AUC)=0.652, p=0.002). The sensitivity for high MA (35.35 mm) was 80 % (CVD and MI) and 90 % (definite, probable, possible stent thrombosis), and the specificity was 52 % (CVD and MI) and 46 % (stent thrombosis). Subjects with high MA (35.35 mm) exhibited higher body mass index, and higher prevalence of diabetes mellitus, while there was no significant difference in other baseline variables (see Suppl. Material, available online at www.thrombosis-online.com).

Kaplan-Meier survival analysis and Cox regression analysis was performed with forward conditional adjustment for baseline clinical variables. Subjects with high MA demonstrated significantly increased risk for the primary combined endpoint of CVD and MI (adjusted hazard ratio [HR] (95 % confidence interval [CI]): 3.8 (1.7–8.3);p=0.001), as well as MI (adjusted HR (95 % CI): 3.0 (1.3–6.9); p=0.008) (▶Figure 1). In contrast, bleeding was not significantly different between subjects with high or low MA (adjusted HR (95 % CI): 0.21 (0.04–1.2); p=0.082); however, bleeding events tended to occur more often in subjects with low MA. Four patients with low MA had intracranial bleeding events versus one patient with high MA who was being treated with warfarin at the time. Definite stent thrombosis (adjusted HR (95 % CI): 5.1 (0.7–47); p=0.145; log-rank p=0.041), as well as definite, probable, or possible stent thrombosis (adjusted HR (95 % CI): 6.3 (0.8–51); p=0.08; log-rank p=0.014) occurred more often in subjects with high MA (▶Figure 1).

The results of our study indicate that subjects who experience recurrent ischemic cardiovascular events after PCI show increased maximal fibrin clot strength at baseline as compared to subjects without adverse ischaemic events. The importance of the fibrin

component in the prothrombotic environment of atherosclerotic cardiovascular disease is illustrated by the findings of Ang et al., who demonstrated an increased risk of MI after PCI in a cohort of subjects with increased fibrinogen, but not increased platelet reactivity during treatment with clopidogrel (10). Fibrinogen concentration was not significantly different between subjects with and without recurrent ischaemic events in our study; however, fibrinogen was correlated with TEG-MA. Differences in fibrin stabilisation and cross-linking could potentially account for higher event rates in individuals with high plasma clot strength in our study.

The risk of stent thrombosis is significantly reduced with use of more potent $P2Y_{12}$ platelet inhibitors, such as prasugrel and ticagrelor; however, stent thrombosis continues to occur in a significant number of subjects (11, 12). In addition, increased bleeding risk can be observed in a minority of patients, thus substantiating the need for better characterisation of subjects at risk with current standard medical therapy used in secondary prevention after PCI (11, 13). A validated *ex vivo* measure of intrinsic coagulation that is strongly associated with clinical risk of thrombosis and/or bleeding may be critical in further developing personalised antithrombotic treatment after PCI. TEG may be able provide such an integrated assessment of thrombotic risk. The functional fibrinogen assay in whole-blood TEG is similar to the measurement of TEG in platelet-poor plasma; however, there are some differences. In particular, in the functional fibrinogen assay, red blood cells are still present, but platelets are inhibited by addition of glycoprotein (GP)IIb/IIIa inhibitor. The functional fibrinogen assay thus measures the strength of clot that includes incorporated red cells, which has been shown to be dependent of factor XIIIa activity and fibrin α-chain crosslinking (14). In contrast, plasma TEG measures cross-linked fibrin strength in absence of red cells and without GPIIb/IIIa antagonist, which could influence the final MA measurement. Functional fibrinogen TEG assays based on GPIIb/IIIa inhibition have also been shown to overestimate fibrin strength in patients with high platelet counts, possibly due to incomplete platelet inhibition (15).Limitations of our study that diminish the strength of our conclusions include the study size, the imbalance of diabetics between subjects with and without high clot strength, and relatively low predictive value of the cut-off for MA.

In conclusion, the results of our analysis suggest that measurement of high plasma fibrin clot strength by TEG may identify subjects at increased risk of recurrent CVD, MI, and stent thrombosis treated with standard dual antiplatelet therapy after PCI. Further studies are needed to examine the utility of plasma TEG in tailored antithrombotic treatment strategies after PCI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support:

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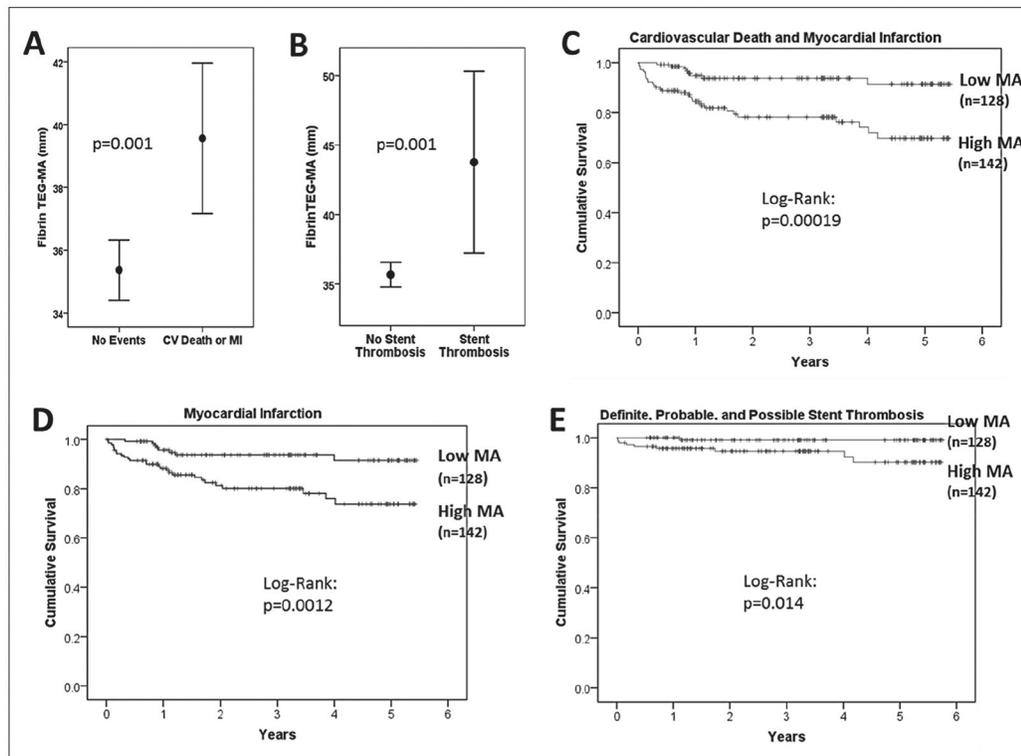
Figure 1:

Thrombelastography (TEG) maximal fibrin clot strength (MA) in A) subjects without events vs subjects with cardiovascular death or MI and B) subjects without stent thrombosis vs subjects with possible, probable, or definite stent thrombosis during follow-up. C-E) Kaplan-Meier survival analysis according to high MA (35.35 mm) vs low MA (<35.35 mm) for primary endpoint of CVD and MI (C), MI (D), and definite, probable, or possible stent thrombosis (E). Values are mean ± 95 % confidence interval.