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EDITORIAL COMMENT

# Is Patient Frailty the Unmeasured Confounder That Connects Subacute Stent Thrombosis With Increased Periprocedural Bleeding and Increased Mortality?*

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Stent thrombosis is an uncommon but serious complication of coronary artery stenting that frequently presents as death or nonfatal myocardial infarction (MI), often with ST-segment elevation. Apprehension regarding stent thrombosis influences which patients are candidates for coronary interventions and alters the strategy by which stents are deployed (1). Adjunctive pharmacology is profoundly altered due to these potential consequences: both the routine administration and duration of dual antiplatelet therapy (DAT) and other anticoagulants center on the prevention of stent thrombosis (2).

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The generally held conception of the equilibrium between hemostasis and intravascular thrombosis is that the patients who bleed are the same patients who develop stent thrombosis and, hence, have a higher rate of mortality, particularly in the setting of an acute ST-segment elevation myocardial infarction (STEMI). However, recent findings of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, published in this issue of the *Journal* (3), raise serious doubts regarding the completeness of this explanation to characterize the relation among mortality, stent thrombosis, and bleeding. The scenario of DAT cessation is actually rarely encountered in acute stent thrombosis, but is common in late stent thrombosis. The inability to elucidate the operational sequence of events or clarify the association of bleeding, stent thrombosis distant from the periprocedural bleeding, and mortality suggests that the data collected in clinical trials and registries cannot fully account for these relationships. Therefore, an unmeasured confounder must be involved, which either completely, or in combination with other factors, accounts for these connections. The possibility that patient frailty is the missing variable should be tested prospectively in future studies.

**Early versus late stent thrombosis: pathogenesis.** The causes of early and late stent thrombosis are disparate. When large retrospective analyses and randomized clinical trials are analyzed for risk factors that predispose to stent thrombosis, there are recurring patient-specific and procedure-related factors that seem to convey greater risk (4–7) (Table 1). Early and late stent thrombosis shares a common final pathway: poor neointimal coverage leading to a thromboembolic milieu, which in turn leads to activation of platelets and thrombus formation.

**Relative mortality of stent thrombosis presentations.** Stent thrombosis is associated with increased mortality, whether early or late (7). It might be expected that late stent thrombosis would be associated with higher mortality, as it occurs out of hospital and unrelated to an index STEMI. However, acute stent thrombosis carries a higher risk (5). Another study showed no difference in death at 1 year between early versus late stent thrombosis, but the composite endpoint of death, MI, and recurrent stent thrombosis was higher in early stent thrombosis (8). Moreover, patients with early stent thrombosis had higher rates of cardiogenic shock (39.2% vs. 20%, $p = 0.042$), suggesting a more dire presentation.

**Major bleeding increases mortality.** Excess bleeding in acute coronary syndromes is associated with higher mortality. In a study of 30,000 patients at 350 hospitals (9), patients with higher rates of major bleeding had higher mortality. Eikelboom et al. (8) found that patients with major bleeding experienced a 5-fold higher incidence of death during the first 30 days and 50% higher risk between 30 days and 6 months.

The controversial question is whether relatively minor episodes of bleeding are actually responsible for later mortality. The most obvious potential relationship is if bleeding leads to early cessation of DAT. However, there are other potential mechanisms that have been considered. Experimental data suggest that increased synthesis of erythropoetin in response to anemia caused by bleeding might sustain a systemic prothrombotic state beyond the acute phase by causing platelet activation and inducing plasminogen activator 1 (11).

Finally, several investigators have noted a relationship with blood transfusions. In a retrospective analysis of non-STEMI patients, Rao et al. (10) showed that transfusion was associated with increased adverse events and 30-day mortality.

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**Table 1 Mechanisms of Early and Late Stent Thrombosis**

| | Early Stent Thrombosis | Late Stent Thrombosis |
|---|---|---|
| Stent factors | Incomplete stent apposition<br>Stent undersizing or underexpansion<br>Post-PCI minimal lumen CSA $<5\ mm^2$ | Hypersensitivity to drug coating<br>Incomplete endothelialization<br>Stent design<br>Covered stents |
| Patient factors | Bleeding<br>Age<br>Frailty | PCI for ACS/STEMI<br>DM<br>Renal failure<br>Impaired LV function<br>Premature cessation of antiplatelet therapy<br>Aspirin nonresponsiveness<br>Clopidogrel nonresponsiveness<br>GP IIb/IIIa inhibitors<br>Malignancy<br>Saphenous vein grafts |
| Lesion characteristics | Local thrombus<br>Impaired distal flow due to distal embolization<br>Presence of vulnerable plaque at the site of stent placement | Lesion/stent length<br>Vessel/stent diameter<br>Complex lesions (bifurcation lesion, chronic total lesions)<br>Stasis<br>Stenting over a side branch |

ACS = acute coronary syndrome(s); CSA = cross-sectional area; DM = diabetes mellitus; GP = glycoprotein; LV = left ventricular; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

**The HORIZONS-AMI trial.** The HORIZONS-AMI trial previously reported that patients with major bleeding after primary percutaneous coronary intervention (PCI) have significantly increased 3-year rates of morbidity and mortality (13). The survival curves show a rapid early separation in curves, which continues to diverge throughout the 36-month period. Landmark analysis shows 3 separate statistically significant breakpoints: at 30 days, 12 months, and 3 years. When the hazard ratios for 3-year mortality are compared, major bleeding, stent thrombosis, and age are the 3 most powerful independent predictors. Whether bleeding is the primary event that drives mortality or just a surrogate marker that denotes a sicker population is a crucial point of contention (14), especially because it is difficult to explain how bleeding, considered to be an acute, short-lived, "reversible" event, can lead to increased mortality years after hospital discharge.

Dangas et al. (3) further explore this surprising observation. Mortality at 1 year in patients with in-hospital stent thrombosis was 27.8% compared with 10.8% in patients with late stent thrombosis ($p = 0.007$). Despite the observation that the rate of major bleeding was higher in patients who experienced in-hospital stent thrombosis (21.2% vs. 6% $p = 0.006$), major bleeding was not an independent predictor of mortality at 1 year (see Table 5 in Dangas et al. [3]). By multivariable analysis, 1-year mortality was significantly increased in patients with in-hospital compared with out-of-hospital stent thrombosis (adjusted hazard ratio: 4.69, 95% confidence interval: 2.00 to 11.01, $p < 0.01$). The acute stent thrombosis group had a mortality of 7.1%, the subacute thrombosis group had a mortality of 50% in-hospital and 27.6% out-of-hospital, mortality was 3.3% in the late stent thrombosis group, and mortality was 8.0% the very late stent thrombosis group; hence, it was the subacute thrombosis cohorts, in- and out-of-hospital, with the worst outcomes. Two-thirds of the stent thromboses occurred after hospital discharge. The breakdown of stent thrombosis timing as in- versus out-of-hospital, when combined with the Academic Research Consortium definitions (see Fig. 3 in Dangas et al. [3]), shows that even in the subacute stent thrombosis group, mortality was highest in patients still hospitalized. Figure 3 (3) further illustrates that with out-of-hospital stent thrombosis, mortality was highest if the event occurred within 30 days after the index procedure. The HORIZONS-AMI trial was unique in that rates of DAT remained high throughout the follow-up period, and thus any analysis in respect to bleeding/stent thrombosis are independent of this factor. Age was not a predictive factor.

There does seem to be a confusing difference between the 2 publications, in that a univariate, unadjusted association between bleeding in-hospital and subsequent stent thrombosis within the 3-year follow-up period of the HORIZONS-AMI trial was originally reported (13). However, in the current paper (3), after multivariate adjustment, bleeding was not associated with in-hospital or out-of-hospital stent thrombosis. The authors clarify this problem in the discussion; the key point is that the relationship between bleeding and subsequent stent thrombosis is not necessarily causal.

**Implications.** These new observations are inconsistent with current characterizations of the relation between mortality, stent thrombosis, and bleeding. Specifically, there is no known pathophysiologic mechanism that explains how periprocedural bleeding and 1- and 3-year mortality can be related, or that explains exceptionally high mortality in subacute stent thrombosis. Although bleeding risk in acute coronary syndromes can be predicted (14,15), there is no known connection with risk for stent thrombosis. Either this relationship is based on a complex, previously unde-

scribed mechanism, or there is some missing piece of information that ties together the clues already identified.

We believe it is likely that the usual variables collected in clinical trials and interventional registries are not sufficiently powerful to explain these associations, and suggest that an unmeasured confounder must be involved. Although cessation of DAT and transfusions may be contributory, they cannot explain the observations made in the HORIZONS-AMI trial. Age and factors related to risk and extent of disease may also be related, but are inadequate to explain the findings in isolation. There is some common systemic factor at play that is upsetting the fragile balance between clotting and bleeding, as that is the most apparent pathophysiologic connection among these conditions.

Patient frailty is the variable most likely to be the missing confounder. It is intuitive that the fragile balance sought between thrombosis and bleeding is most apt to be easily disrupted by acute illness in a delicate, less active, less vigorous person. This makes sense both from a technical/procedural viewpoint as well as from the pharmacology aspect. Even among older patients (>65 years of age) there are subgroups with different cardiovascular outcomes after percutaneous revascularization. Using a frailty index, Singh et al. (14) were able to identify a subgroup at higher risk: at 35-month follow-up, 28% of patients identified as frail had died compared with 6% of nonfrail patients. Adding frailty, quality of life, and comorbidity to the Mayo Clinic PCI Risk Score conferred a discernible improvement to predict death and death/MI.

Obviously, a fundamental problem lies in how to objectively evaluate frailty. Gharacholoulou et al. (16) combined the Fried criteria to assess frailty, which includes assessment of 5 items: unintended weight loss (>10 lb in the preceding year), exhaustion (by 2 questions), physical activity, time required to walk 15 feet, and hand grip strength combined with the Charlson index for comorbidity and the SF-36 questionnaire for quality of life. This approach was strongly supported for elderly patients (17) but probably should be included in a general assessment of all patients undergoing any form of revascularization. A telephone interview was used to assess cognition in STEMI patients (18). Cognitive impairment was associated with less invasive care, lower rates of referral and participation in cardiac rehabilitation, and worse risk-adjusted 1-year survival. Frailty has also been identified as a substantial issue in selection of patients for bypass surgery.

**Conclusions.** In the new analyses from the HORIZONS-AMI trial, major in-hospital bleeding was associated with increased mortality at times distant from the acute event. This observation is incomprehensible without implicating a previously unmeasured patient related factor that links with the fragile balance of bleeding and thrombosis inherent in interventional coronary procedures.

Future pharmacologic studies, PCI clinical trials, and registries such as the National Cardiovascular Data Registry should be amended to include simple subjective clinical variables such as frailty that have not been collected traditionally due to the difficulty in their objective definition. It may be that the explanation for an otherwise perplexing clinical observation is discernible only at the most primitive level.

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**Key Words:** PCI ■ STEMI ■ stent thrombosis.