Second, we previously demonstrated that intravascular ultrasound is able to depict significant underlying mechanical problems in most patients with ST (stent underexpansion, malapposition, dissections, inflow/outflow stenoses) (2). Because these findings, which require specific therapy, are frequently undetected by angiography, a description of the ultrasonic data of these patients (if available) would be helpful. Third, information on the reason for initial stent implantation would be appreciated because it has been suggested that acute coronary syndromes (with the associated platelet hyperactivity) may be a predisposing factor for ST (2).

Moreover, detailing whether some episodes of ST were secondary to antiplatelet therapy withdrawal would also be of great interest.

Finally, considering the potentially catastrophic consequences of recurrent ST, it would be important to define precisely when clopidogrel therapy was discontinued in the study in order to evaluate platelet aggregation with aspirin alone. The potential benefit of a higher dose of clopidogrel has been suggested (3,4), and this strategy appears especially attractive for high-risk patients. Therefore, from a pragmatic standpoint, it will be critical to determine whether the relative inefficacy of a conventional clopidogrel regimen (1) can be overcome with higher doses (3,4). Eventually, unraveling the multifaceted etiology of ST is urgently required to prevent and successfully treat this challenging problem.

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REPLY

We thank Dr. Alfonso for his interest in our work (1). We agree with him that the phenomenon of "stent thrombosis" is a multifactoral process and that mechanical factors play an important role, especially in the setting of an acute stent thrombosis (within 24 h), whereas for subacute (1 to 30 days) or late stent thrombosis (>30 days) a more complex etiology has been postulated. In our case-control study no patient with an acute stent thrombosis was included (1). Platelet aggregation was assessed several months after stent thrombosis to avoid confounding factors such as platelet activation induced by thrombotic stent occlusion. Dr. Alfonso cites four issues in his letter. We address each one here.

First, we fully agree that an optimal angiographic result is a key factor in the prevention of stent thrombosis (2). In our study population two patients showed a suboptimal angiographic result (one had a distal residual dissection with Thrombolysis In Myocardial Infarction [TIMI] flow grade 2; another showed a no-reflow phenomenon).

Second, intravascular ultrasound was not routinely performed after stent implantation in our institution. Therefore, we cannot exclude stent underexpansion or stent malapposition.

Third, acute coronary syndromes have been previously identified as potential risk factors for stent thrombosis (2,3). In our study population, 83% of the patients in the stent thrombosis group suffered from an acute coronary syndrome at time of stent implantation, whereas only 43% of patients in the control group were affected ($p < 0.001$). This highlights the importance of activated platelets in the setting of an acute coronary syndrome and the role of an effective antithrombotic regimen in the prevention of stent thrombosis. Therefore, a resistance to antiplatelet therapy may represent an additional risk factor for stent thrombosis.

Fourth, all patients in our study population were on lifelong aspirin therapy; however, at the time of stent thrombosis 26% were off thienopyridine treatment. We agree that this may be another risk factor, although the rate of clopidogrel resistance was lowest in stent thrombosis patients. According to our protocol all patients were first examined under aspirin therapy alone, followed by a second measurement under aspirin and clopidogrel.

Finally, the etiology of stent thrombosis is multifaceted, and we agree that mechanical risk factors should be avoided. Nevertheless, the efficacy of our standard (dual) antiplatelet treatment might not be as good as wished for. A higher dose of clopidogrel or new antithrombotic drugs as alternative treatment in patients with resistance to antiplatelet therapy warrant further evaluation to prevent stent thrombosis and its high morbidity and mortality.

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