Pursuit of the Optimal Antithrombotic Regimen for Patients With Non−ST-Segment Elevation Acute Coronary Syndrome Who Undergo Subsequent Percutaneous Coronary Intervention

We are intrigued by the recent Chen, et al., research publication, "Association of Parenteral Anticoagulation Therapy with Outcomes in Chinese Patients Who Underwent Percutaneous Coronary Intervention (PCI) for Non−ST-Segment Elevation Acute Coronary Syndrome (NSTE-ACS).[1]" That research challenges current guidelines[2] for the management of patients presenting with NSTE-ACS (in particular, anticoagulation therapy in the setting of concurrent dual oral antiplatelet therapy). We have complementary information published in this journal some time ago[3,4] that may prove useful for the design of further investigations into optimization of antithrombotic regimens in the medical management of patients with NSTE-ACS who undergo subsequent PCI.

Thrombosis occurs through 2 interrelated mechanisms[5]: first, the adhesion, activation, secretion, and aggregation of platelets; and second, amplification of the coagulation cascade - which requires an activated platelet surface for the development of thrombin. If adequate antiplatelet therapy is provided, then thrombosis does not occur, even in the absence of specific antithrombin therapy directed toward the coagulation cascade. This has been observed both in vitro[6] and in vivo.[7]

However, the presence of thrombus before initiation of antiplatelet therapy, for example at the site of plaque rupture in patients admitted with biomarker-positive NSTE-ACS, appears to require the addition of antithrombin therapy for successful clinical stabilization.[8] Antithrombin therapy is, to date, a Guideline Class I recommended treatment for patients admitted with NSTE-ACS (as well as for subsequent PCI).[2] An effective drug in this context is enoxaparin (Level of Evidence, A), which a majority of the anticoagulated Chen, et al., patients received.[1]

When confronted with the challenge of minimizing further ischemia against bleeding risk in this same patient population some 20 years ago, we noted that the then contemporary Dose-Ranging Trial of Enoxaparin for Unstable Angina (TIMI 11A)[9] showed 1.0 mg/kg subcutaneously every 12 hours to be similarly efficacious but with less major hemorrhage compared with 1.25 mg/kg subcutaneously every 12 hours. However, no other dose-ranging studies were available. Our approach, as published in this journal,[3] therefore involved using a reduced dose of enoxaparin (0.5 mg/kg) with dual oral antiplatelet therapy (aspirin + clopidogrel) for medical stabilization followed by triple antiplatelet therapy alone (adding intravenous eptifibatide) without anticoagulation for PCI. Our observational results were salutary, including a major bleeding complication rate of 0.1%, at a trade-off of 0.6% "failed" medical management mandating emergency PCI, and 0.1% peri-PCI major ischemic complication. This remains the default approach for one author (SJD), without a detectable change in outcomes.

Because the optimal antithrombotic regimen for the medical management of patients with NSTE-ACS who undergo subsequent PCI has not been determined, we would suggest further incremental investigations, starting with a randomized trial comparing our approach − without additional enoxaparin or unfractionated heparin at the time of PCI[3,4] − with more conventional dosing of enoxaparin pre- and peri-PCI. If positive, then further work would follow to address the foundational question of Chen, et al., "Is parenteral anticoagulation therapy actually beneficial for patients with NSTE-ACS who undergo subsequent PCI?"

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Prolonged Benefit of Radial Access Beyond 30 Days: Fact or Fiction?

We read with great interest the study by Kim et al[1] recently published in the Journal. The authors have compared the outcomes of patients with acute myocardial infarction receiving transradial intervention (TRI) or transfemoral intervention (TFI) with or without the use of vascular closure device (VCD)

in a retrospective observational nationwide registry in Korea. After propensity matching, they have found that TFI with VCD is associated with a comparable incidence of MACCE (including mortality and major bleeding) than TRI, thus offering an alternative bleeding avoidance strategy to patients deemed not suitable for TRI.[1] This study is largely consistent with the recently published final 1 year analysis of the MATRIX program, that demonstrated that TRI provides a sustained benefit at 1 year compared with TFI,[2] a finding that is evident in the study by Kim et al[1] as well. Unfortunately, to assess the impact of the VCD was not a prespecified outcome in the MATRIX-access study, as all procedural choices beyond vascular access and anticoagulation were left to the discretion of the attending interventional cardiologist.[3]

The landmark analysis after 30 days in the study by Kim et al[1] is an intriguing result deserving attention. Indeed, the authors observed a reduced incidence of repeated revascularization after 30 days in patients having received TRI as compared with TFI (1.4% vs 2.3%, $p < 0.001$) in the index procedure. This implies a sort of additional benefit of TRI beyond that offered in the peri-intervention period by the reduction in major bleeding, which is known to explain the large short-term mortality benefit of TRI in patients with acute myocardial infarction.[4] This observed reduction of revascularization beyond 30 days should be considered hypothesis generating. Indeed, it remains unclear whether the increased number of procedures is related to urgent revascularizations, thus suggesting that the TFI procedure has somehow resulted less effective, or to elective staged procedures, and whether the same vascular access has been used in the repeated intervention. It cannot be ruled out that residual unmeasured confounders, not totally accounted by propensity matching, have determined this result. Importantly, MATRIX investigators did not observe an increase of stent thrombosis or urgent revascularization or any MACE after 30 days in patients having received TFI.[2] In other words, although the possibility of further benefits of TRI beyond 30 days remains a speculation, a loss of the treatment effect observed soon after the intervention is unlikely to exist.

In conclusion, Kim et al should be congratulated for their comprehensive study that contributes to fill a major knowledge gap. Their study definitely underscores that radial access not only provides sustained benefits at 1 year compared with femoral access but also does not expose patients to a rebound of ischemic or bleeding events after the peri-intervention period.

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