



Opinion Paper

Post-the SAFARI STEMI study: Is there still a debate on radial vs. femoral access in STEMI?

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ABSTRACT

Despite the seminal trials on radial versus femoral access for percutaneous coronary intervention (PCI) in ST elevation myocardial infarction (STEMI) showing reduced bleeding, major adverse cardiovascular events and mortality; these outcomes were attributed by some to low usage of bivalirudin and an unnecessarily higher dose of Heparin, combined with high usage of GP IIb/IIIa inhibitors, as well as to the use of larger bore catheters in the femoral groups. To prove the point, a study comparing TF with TR access was mooted (Lee et al., 2013) 3; with bivalirudin instead of heparin, preferably with use of potent oral anti-platelets instead of GP IIb/IIIa inhibitors; and femoral vascular closure devices, ostensibly, to assess outcomes based on 'access-site alone'. With this intent, the SAFARI STEMI study was designed. In this article we discuss some of the major short-comings of this trial which raise significant questions on its results.

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1. Why SAFARI STEMI?

Following the publication of the seminal Radial Vs. Femoral STEMI studies in 2011 and thereafter,^{1,2} establishing the superiority of radial over femoral access for PCI in acute coronary syndromes (ACS); the conclusions of reduced bleeding, MACE and mortality were questioned³ by those who attributed them to low bivalirudin usage; an unnecessarily higher dose of Heparin, together with GPIIb/IIIa inhibitors, as well as to the use of larger bore catheters in the femoral groups; all of which were alleged to have been responsible for higher vascular complications, access-site bleeding and consequent mortality in the femoral groups of the trials. To prove the point, a study comparing transfemoral (TF) with transradial (TR) access was mooted,³ with bivalirudin instead of heparin, preferably with use of potent oral antiplatelets instead of GP IIb/IIIa inhibitors; and femoral vascular closure devices (VCDs), ostensibly,

to assess outcomes based on 'access-site alone' by containing bleeding risk which adversely affects TF access more.

With this intent, SAFARI STEMI⁴ was designed, and in order to minimize bleeding risk, the study also excluded higher bleeding risk (HBR) patients that could potentially have contributed to worse outcomes with femoral access, such as: (i) patients post-fibrinolytic therapy including those requiring rescue PCI; (ii) patients on oral anticoagulants, as in those with atrial fibrillation. It also excluded post-coronary artery bypass graft (CABG) patients. Since these patients form a significant part of the real-world scenario; their exclusion in the SAFARI STEMI study thus distracts from a real-world perspective. The HBR patients were however included in the seminal TR Vs. TF trials.^{1,2}

It is noteworthy that not only was the SAFARI STEMI study under-powered for bleeding; it wrongly included the bleeds from secondary femoral access for Intra-aortic balloon pumps (1.8%) and ECMO/Impella (0.26%) on to the TR group!

1.1. Limitations of the SAFARI STEMI study

In the SAFARI STEMI multicenter study,⁴ patient allocation was open-label, randomized, parallel. Patients were randomized to TR ($n = 1082$; 95.2%) or to TF access ($n = 1109$; 95.9%) for PCI with 30-

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day follow-up. Initially, the primary outcome was bleeding, but this outcome was later modified to 30-day all-cause mortality. Secondary outcomes included recurrent myocardial infarction, stroke, and Thrombolysis in Myocardial Infarction defined major or minor bleeding. 1001 patients (88.1%) in the TR group vs. 1068 patients (92.4%) in the TF group received bivalirudin; while glycoprotein IIb/IIIa inhibitors were administered in only 69 patients (6.1%) in the TR group and 68 patients (5.9%) in the TF group.

The MATRIX trial (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX),⁵ was multi-centre, prospective, randomized controlled trial (RCT), open-label, 2 by 2 factorial comparison of trans-radial vs. trans-femoral intervention and bivalirudin vs. unfractionated heparin and provisional use of glycoprotein IIb/IIIa inhibitor in patients presenting with ACS including patients with STEMI (47.7%/47.8% in TR/TF groups). The masking was single (Outcomes Assessor). The MATRIX trial showed that TR Vs. TF PCI reduced net adverse clinical events (NACE; 9.8% TR Vs. 11.7% TF (0.83, 95% CI 0.73–0.96; $p = 0.0092$)), via a reduction in non-coronary bypass surgery (non-CABG) Bleeding Academic Research Consortium (BARC) major bleeding (1.6% vs. 2.3%, RR 0.67, 95% CI 0.49–0.92; $p = 0.013$) and all-cause mortality (1.6% vs. 2.2%, RR 0.72, 95% CI 0.53–0.99; $p = 0.045$).

Interestingly, upto 8% of the study population of the seminal TR Vs TF trials^{1,2} comprised of patients with prior fibrinolytic therapy,⁶ which were excluded in SAFARI STEMI. This is particularly important because it is well-established that rescue PCI confers a higher risk of bleeding and mortality (20% with failed Vs. 4% with successful rescue PTCA, $p = 0.03$)⁷.

Another point of relevance is that in patients with uninterrupted warfarin therapy undergoing PCI, with mean international normalized ratio of ≥ 2.4 , TR access is associated with reduced bleeding and vascular complications compared to TF access⁸; but such patients were excluded from the SAFARI STEMI study, although they were included in the seminal TR Vs. TF trials (1.5%/1.6%, TR/TF in MATRIX study⁵).

Unlike the RIVAL⁹ (with 27.2% STEMI), MATRIX,⁵ RIFLE STEACS⁶ and STEMI-RADIAL¹⁰ trials which included 2.3%; 2.6%/3.5% (TR/TF); 1.4%/2.4% (TR/TF) and 0.8% patients with prior CABG; the SAFARISTEMI study excluded patients with prior CABG who are known to have a higher 90 day mortality, especially when the infarct-related artery (IRA) is a bypass graft (hazard ratio: 1.9, 95% confidence interval: 1.08–3.33, $p = 0.025$)¹¹.

Again, though patient demographics (age, body mass index (BMI) and sex distribution) in the SAFARI STEMI were comparable to the seminal TR Vs. TF studies; the SAFARI STEMI clearly had a lower proportion of patients with co-morbid risk factors compared to that in the seminal studies, including chronic obstructive pulmonary disease (None Vs. 8% in RIFLE STEACS,⁶ 6.7% in MATRIX⁵) chronic kidney disease (12.8% Vs. 25.3% in RIFLE STEACS⁶); peripheral vascular disease (PVD) (None Vs.; 14% in RIFLE-STEACS,⁶ 8.4% in MATRIX,⁵ 2.6% in RIVAL⁹), diabetes mellitus (18% Vs. 22.3% in RIVAL,⁹ 24.4% in RIFLE-STEACS,⁶ 22% in STEMI-RADIAL,¹⁰ 22.7% in MATRIX⁵). Also, compared to SAFARI STEMI,⁴ the prevalence of Killip class 2–4 heart failure was much higher in the seminal trials^{1,2} (7% Vs. 34.1% in RIFLE-STEACS,⁶ 15% in STEMI-RADIAL,¹⁰ 10% in MATRIX⁵). Further, in MATRIX,⁵ and RIFLE-STEACS⁶ 10% and 7% patients were in shock respectively, compared to 2% in SAFARI STEMI study.

Thus, because of the above exclusion criteria the SAFARI STEMI study population was low-risk, as reflected in the lower mortality in the study compared to that in the seminal studies (1.3% Vs. 1.5% compared to 2.7% Vs. 4.7% for radial Vs. femoral access respectively in the SAFARI STEMI Vs. seminal trials^{1,2}) and was like testing for crash safety of a car while driving it at low-speed! No surprise then, that, being a lower risk study population, the mortality in SAFARI

STEMI was lower; which led to the study being considered futile by the data surveillance monitoring board (DSMB) with respect to finding a difference in mortality between radial and femoral access. Only half the number of patients planned for the trial got enrolled. Hence, with a study power of 50%, it was like the toss of a coin. The SAFARI STEMI study was clearly underpowered for primary outcomes. For the sake of meaningful conclusions, the study should have been allowed to continue, to recruit the total number of patients (4884; 2242 in each group), as was planned, based on calculation of sample size, with 80% power and level of significance of 0.05; because there was no risk of harm to patients, even though the study was considered to be futile by DSMB, with regard to the end-point of mortality.

Another interesting point to note is that despite the lack of evidence for thrombo-aspiration,^{12,13} it was still used in a high proportion of patients in the SAFARI STEMI study (38.8 vs 42.9% patients in the TR vs. TF groups). With shorter median ischemia times of 166 vs. 161 min for radial Vs. femoral groups, which are not real-world for most centers; it is likely that thrombus build-up after plaque rupture was less, making the use of thrombo-aspiration ideal, thus reducing the need for bailout GP IIb/IIIa inhibitors and helping contain the risk of bleeding in the SAFARI STEMI study population, as intended, to the advantage of the TF group.

The intention of the study³ clearly was to reduce the need for bailout GP IIb/IIIa inhibitors (6.1% Vs. 5.9% TR Vs. TF) with bivalirudin, in an attempt to minimize the risk of bleed which would otherwise have adversely affected the primary outcome of bleeding for TF group. Though the use of thrombectomy and Gp2b3a inhibitor was high in earlier studies also (41% and 69% in RIFLE-STEACS; 28% and 45% in STEMI RADIAL; 28.6%/29.9% (TR/TF) and 13.7%/12.4% (TR/TF) in MATRIX trial respectively); these studies were completed before the data on the lack of survival advantage with thrombus-aspiration was published.^{12,13} The usage of Gp2b3a inhibitors was high in these trials, even with utilization of thrombo-aspiration.

Additionally, the estimated cost for containment of bleeding risk, by using bivalirudin (88.1%/92.4%, TR/TF), and VCD (in 68.3% in TF), combined with export thrombo-aspiration (38.8%/42.9%, TR/TF) as in the SAFARI STEMI study, would have been higher than that of TRPCI with heparin and supplemental GP IIb/IIIa inhibitors. Further, though a VCD was used in 38% patients in TF group in STEMI RADIAL study and was utilized only rarely in other seminal studies; in clinical practice, its use is less frequent because it is non-inferior to manual compression with regard to 30-day vascular complications.¹⁴ Further, in addition to cost, it has the risk of device-related complications.¹⁵

On the other hand, with TR access (TRA), hemostasis with gauze-ball and elastic bandage or compression band is inexpensive and effective. Major bleeding is significantly lower with TRA compared to TFA with VCD (odds ratio [OR] 0.22, 95% CI 0.11–0.44, $p < 0.00001$ with vessel plugs; OR 0.12, 95% CI 0.05–0.28, $p < 0.00001$ with suture devices). Vascular complications are also significantly lower with TRA compared to TFA and VCD (OR 0.25, 95% CI 0.13–0.49, $p < 0.0001$ with vessel plugs; OR 0.13, 95% CI 0.04–0.41, $p = 0.0005$ with suture devices).¹⁵

The seminal trials, without the above limitations; and their subsequent meta-analyses^{1,2} have already clearly established significant reduction in access-site bleeding, major bleeding and major adverse cardiac events (MACE) and mortality on conventional meta-analysis and trial sequential analysis (TSA).²

1.2. Differences in mortality between TR and TF access for STEMI

None of the TR Vs TF STEMI studies were powered for mortality, nor was SAFARI STEMI.

With a 50% power, no conclusion can be made from the SAFARI STEMI study regarding mortality.

A TSA² of the seminal trials showed that the z-curve crossed the conventional threshold ($p < 0.01$), and information size (IS) monitoring boundaries, conclusively indicating a clinically significant reduction in mortality with radial access for PCI in STEMI at 5% & 1% α errors.

The pooled effects of radial access on STEMI study outcomes and sensitivity analyses² showed significantly lower risk of death, MACE, major bleeding, access-site bleeding while lack of heterogeneity suggested that there was no variation in expertise in transradial vs. transfemoral access across trials. A 10% variation in access-site bleeding was because of variability in definition of access-site bleeding.² Further, mortality reduction with TR access was consistent across 7 trials, with low risk of bias.²

In summary, the evidence clearly supports radial access for STEMI with decreased risk of mortality [2.7% vs. 4.7%; odds ratio [OR]:0.55, 95% confidence interval [CI]: 0.40–0.76; $p < 0.001$], major bleeding [1.4% vs. 2.9%; OR: 0.51, 95%CI: 0.31–0.85; $p = 0.01$], access-site bleeding [2.1% vs. 5.6%; OR: 0.35, 95%CI: 0.25–0.50; and MACE [4.6% vs. 6.8%; OR: 0.64, 95%CI: 0.49–0.83; $p < 0.001$]².

2. Conclusion

There is neither a debate on TR vs. TF primary angioplasty in STEMI, radial access being clearly superior; nor is there any reason to advocate TF access with bivalirudin, vascular closure device, and thrombo-aspiration in STEMI patients, at a higher cost compared to TR PCI.

The SAFARI STEMI study has however brought into focus, the need for meticulous attention to access, use of vascular closure devices and restricted use of GP IIb/IIIa inhibitors, should TF access become necessary in the current era of wide-bore access for left ventricular mechanical support devices and structural interventions.

Declaration of competing interest

All authors have none to declare.

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