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Time for a Reappraisal: How much has the Last 10 Years of "Mainstream" STEMI Research Impacted on STEMI Outcome?

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Editorial

Evidenced based management of STEMI reperfusion is built on large-scale randomized trials with solid clinical endpoints. Promptly performed primary PCI, as measured by the door-to-balloon time within 90 minutes, is the current treatment standard. This key quality metric is tracked by many hospital databases, clinical registries etc., and is even made publicly available in some places.

Funded by the National Cardiovascular Data Registry of the American College of Cardiology Foundation, an analysis of the Cath-PCI registry reported unchanged in-hospital mortality (both observed and risk-adjusted mortality) from July 2005 through June 2009 for STEMI despite significant shortened door-to-balloon time from 83 minutes to 67 minutes in America [1]. The authors suggested that additional strategies were needed to reduce mortality.

A re-analysis of the same data by another group of investigators (adding at both ends of an extended period to include all complete years 2005 - 2011) [2] "vindicated" the importance of door-to-balloon time showing the positive and almost linear relationship between door-to-balloon time and observed in-hospital mortality within every calendar year. However, for the same door-to-balloon time when it was over ~70 minutes, mortality was consistently higher in later years than in earlier years. The net effect combining all patients was that over the 7 years door-to-balloon time had shortened from ~90 to ~65 minutes but mortality had not declined. Risk-adjusted in-hospital mortality showed a trend of an increase (from 4·7% to 5·3%) and risk-adjusted 6-month mortality showed an increase from 12·9% to 14·4% (p=0·001) [2].

Although more patients underwent PCI in later than in earlier years, there were only small variations in patient demographics. Their mean age was 61 years. To explain the paradoxical higher mortality over the more recent years among those patients with door-to balloon time over ~70 minutes, the investigators suggested a "survivor-cohort effect" that some of these patients might not have PCI performed in earlier years when primary PCI therapy was less prevalent. They further suggested that the expected increased mortality from this high-risk subset had offset the "gains" from shorter door-to-balloon times explaining why overall mortality had not fallen in later years [2].

This explanation however did not ensure that primary PCI performed in more recent years was better than PCI in earlier years. There is another more pertinent interpretation for the "worsening" mortality - recent mainstream research has not targeted the critical "link" between STEMI management and STEMI outcome – i.e., reducing the total time duration between STEMI onset and successful myocardial reperfusion of which door-to-balloon time only constitutes a (small) portion.

As shown in both studies [1,2] on the Cath-PCI registry over 2005 to 2011 there was an increasing use of thrombectomy (from ~10% to ~40%) and direct thrombin inhibitor bivalirudin (from ~10% to ~40%) and a decreasing use of glycoprotein 2B3A inhibitors (from ~70% to ~40%). However, these are areas where despite intensive research the "state-of-the-art" treatment still touches the realm of uncertainties.

In 2014, a meta-analysis was performed involving 33958 patients undergoing PCI [3]. A bivalirudin-based regimen, as compared to a heparin-based regimen, was found to increase the risk of (recurrent) myocardial infarction and stent thrombosis but decrease the risk of bleeding, with the magnitude of the reduction depending on the use of concomitant glycoprotein 2B3A inhibitor. The choice of an optimal anticoagulant in STEMI remains hotly debated today, and will certainly be altered in the future with more widespread use of newer antiplatelet drugs such as cangrelor and vorapaxar.

In 2015, the 10732 patient TOTAL trial was reported [4] showing that routine manual thrombectomy during primary PCI did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days.

Because STEMI is an ongoing process (hence the vogue for shortening door-to-balloon time) the inevitable delay with primary PCI as compared to immediately administered fibrinolysis can be the Achiles' heel of the primary PCI reperfusion approach. During the "PCI-related delay" (i.e., door-to-balloon time for patients undergoing PCI minus door-to-needle time for patients undergoing fibrinolysis) ongoing myocardial necrosis could have pushed the STEMI (and the patient) into an irrecoverable stage. This is particularly so with younger patients especially when having anterior STEMI. In the earlier NRMI-2,3,4 registries involving 192,509 STEMI patients, the "PCI-related delay" that gave the equipoise in mortality between primary PCI and fibrinolysis was found to be as short as 41 minutes for anterior STEMI and 71 minutes for non-anterior STEMI in patients aged <65 [5,6] (i.e., the age for most STEMI patients in the Cath-PCI registry analyses [1,2]).

The intense research effort in primary PCI in recent 10 years [1-4] stands in stark contrast to the paucity in fibrinolysis where questions remain even on the optimal dose. In the most recent 1892 patient STREAM trial comparing early fibrinolysis approach (mostly administered pre-hospitalisation) versus primary PCI, the Data Safety Monitoring Board advised the executive committee to amend the protocol (after ~1/5 of patient enrolment) in halving the dose of tenecteplase in patients aged 75 or above because of excess intracranial haemorrhage [7]. In this trial, outcome appeared best for patients with fibrinolysis and subsequent (>6 hours after fibrinolysis) PCI and worse for patients with rescue PCI. The outcome of those with primary PCI

was in between [8]. A pre-specified analysis showed that identical 30-day primary composite outcome was observed between patients randomized to primary PCI and patients randomized to initial fibrinolysis when the PCI-related delay was 55 minutes [9], a comparable number to findings from the earlier NRMI-2,3,4 registries [5,6].

In contrast to primary PCI, there is more limited research done for rescue PCI where full-strength fibrinolytics are still on-board during the procedure. Fibrinolysis facilitated PCI (full dose or half dose fibrinolytic plus abximicab) have generally failed and post-PCI myocardial haemorrhage might be one important component of the "reperfusion injury" [10,11].

Failure to have an early 12-lead ECG is clearly an important missing "link" in expediting STEMI diagnosis, but with minimal training this can be easily acquired even by many non-medical persons [12]. With a prompt diagnosis made the reperfusion strategy should be immediately planned. In situations where timely primary PCI cannot be arranged, (pre-hospital) fibrinolysis in suitable patients is a good alternative.

In the field of cardiovascular pharmacology, dedicated research may not end up with substantial clinical impact, as discussed earlier in the article. An editorial in this journal 3 years ago questioned whether measuring platelet reactivity after clopidogrel (a common research topic in those times) could be reaching the end of the road [13], giving way to newer and more efficacious antiplatelet medications.

Despite our reluctance to accept - the strategy of "primary PCI" has not completely won the battle against the life-threatening condition of STEMI. Perhaps STEMI patients need to be classified not only according to patient age and STEMI location (which dictate the equipoise point of PCI-related delay when PCI and fibrinolysis give equivalent outcome [5,6]), but also by widely available electrocardiographic characteristics of STEMI.

From prior experience in a large fibrinolytic cohort, sometimes determining ST level (elevation) can be tricky [14] and certainly other parameters including pathologic Q waves [15] and bundle branch blocks strongly influence prognosis [16]. As discussed previously from the STREAM trial [7] the dosage of fibrinolytic drug should be adjusted according to age and bleeding risks. Newer fibrinolytic regimes (including modified dosage of the traditional regimes to be used together with the newer more efficacious antiplatelet drug ticagrelor) and newer procedural method and pharmacology of rescue PCI deserve focussed research. This may make significant impact on outcomes, at least in some selected patient subgroups according to age and electrocardiographic characteristics.

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