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Delay in reperfusion with transradial percutaneous coronary intervention for ST-elevation myocardial infarction: Might some delays be acceptable?

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Abstract

Background—Randomized clinical trials (RCTs) suggest benefits for the transradial approach to percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI). However, transradial PCI may delay reperfusion, leading to its avoidance. We sought to quantify the delay in reperfusion from transradial PCI (“transradial delay”) that would need to be introduced to offset the potential mortality benefit of transradial PCI, compared with transfemoral, observed in RCTs.

Methods—We developed a decision-analytic model to compare transfemoral and transradial PCI in STEMI. 30-day mortality rates were estimated by pooling STEMI patients from two RCTs comparing transfemoral and transradial PCI. We projected the impact of transradial delay using estimates of the increase in mortality associated with door-to-balloon time delays. Sensitivity analyses were performed to understand the impact of uncertainty in assumptions.

Results—In the base case, a transradial delay of 83.0 minutes was needed to offset the mortality benefit of transradial PCI. When the mortality benefit of transradial PCI was one-quarter that observed in RCTs, the delay associated with equivalent mortality was 20.9 minutes. In probabilistic sensitivity analyses, transradial PCI was preferred over transfemoral PCI in 97.5% of

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simulations when transradial delay was 30 minutes and 79.0% of simulations when delay was 60 minutes.

Conclusions—A substantial transradial delay is required to eliminate even a fraction of the mortality benefit observed with transradial PCI in RCTs. Results were robust to changing multiple assumptions and have implications for operators reluctant to transition to transradial PCI in STEMI due to concern for delaying reperfusion.

Keywords

transradial; percutaneous coronary intervention; ST-segment elevation myocardial infarction; door-to-balloon time; decision analysis

Introduction

The use of transradial arterial access during percutaneous coronary intervention (PCI) has been growing steadily but varies greatly among operators, hospitals, and geographic location.(1-4) Compared with transfemoral PCI, transradial access causes fewer vascular access site complications, allows more rapid ambulation post-procedure, and offers greater post-procedural comfort.(5,6) In several randomized clinical trials (RCTs), it has been suggested that transradial PCI may confer a mortality benefit compared with transfemoral PCI for patients with ST-segment myocardial infarction (STEMI), although these data are controversial.(6-8) Despite the limitations of these, and other, data a recently published consensus statement from several European professional societies advocates a “default radial approach” in the performance of PCI.(1)

Across countries, the rate of transradial PCI varies.(4) In 2011, transradial access was used for primary PCI in only 6.4% of STEMI cases in the United States,(2) whereas in the United Kingdom, transradial PCI was used in 39.1% of STEMI from 2006 to 2010.(9) Of note, when performed by experienced operators in clinical trials, there are few delays associated with transradial PCI.(7,8) In “real world” practice, however, there may be increases in reperfusion time with transradial PCI as less experienced operators attempt the technique. Among proceduralists accustomed to transfemoral PCI, reluctance to adopt a radial-first approach in STEMI may result from concerns that transradial PCI will delay reperfusion in instances where even short time delays will negatively impact patient outcomes. Reporting of door-to-balloon time as a quality metric or performance measure may further reduce operator interest.

In this study, we sought to quantify the potential delay in reperfusion associated with transradial PCI (“transradial delay”) that would offset the mortality benefit associated with transradial PCI for STEMI that was observed in RCTs. In addition, we sought to examine the sensitivity of our findings to a range of assumptions, including substantially more conservative estimates of the mortality benefit of transradial PCI.

Methods

We developed a decision analytic model comparing two strategies of primary PCI in patients with STEMI: transradial PCI and transfemoral PCI. The model's primary outcome was 30-day mortality. Model probabilities were derived from published reports. Based on the model, we sought to quantify the delay in reperfusion associated with transradial PCI (compared with transfemoral PCI) required to offset the mortality benefit observed with transradial PCI when reperfusion times were equivalent. The model describes a typical patient presenting with STEMI to a PCI-capable facility who was eligible for PCI via either a transradial or transfemoral approach.

Decision Model

We created a decision tree to estimate 30-day mortality with primary PCI in STEMI. Figure 1 depicts the therapeutic decision to use either transradial or transfemoral arterial access. Patients could be either alive or dead 30 days after presentation.

Within the model, we created a variable representing the additional time to reperfusion in the transradial arm compared to the transfemoral arm – the transradial delay. An increase in the transradial delay would amplify the probability of 30-day mortality within the transradial arm based on the associated per-minute increase in mortality that occurs with delays in door-to-balloon time. The model also allowed for crossover from the transradial approach to the transfemoral approach, but not vice versa. This node allows for increases in mortality based on the additional delay in reperfusion associated with cases that require transradial to transfemoral crossover.

Although transradial PCI reduces vascular access complications compared with transfemoral PCI,(5,6) we elected not to model differences in vascular access complications explicitly for several reasons. First, in our model, access complications influencing mortality were already reflected in 30-day mortality estimates. Second, when described on the same scale (e.g. quality-adjusted life-years), the transient impact of non-fatal vascular access complications on quality of life is dwarfed by the mortality differences associated with the selection of vascular access or increasing door-to-balloon time.(10)

Data Sources

Estimates for model inputs were taken from the literature and are in Table 1. Rates of death at 30-days were calculated by combining primary data from the two largest, published, multicenter RCTs that compared transradial versus transfemoral PCI in patients with STEMI: the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE STEACS) and the STEMI patient subset from the Trial of Trans-radial Versus Trans-femoral Percutaneous Coronary Intervention Access Site Approach in Patients with Unstable Angina or Myocardial Infarction Managed with an Invasive Strategy (RIVAL).(7,8,11) We pooled 30-day mortality rates in the RIVAL STEMI sub-study (transradial, 1.3%; transfemoral, 3.2%) with cardiac mortality rates at 30-days in RIFLE STEACS (transradial, 5.2%; transfemoral, 9.2%) and generated a relative risk (RR) for mortality with transradial PCI. Because these studies were analyzed with the intention-

to-treat principle, mortality estimates reflect the constitutive rate of access site crossover observed in the trials (9.4% in RIFLE STEACS and 7.0% in RIVAL). The pooled rate crossover rate was 7.8%. Any transradial delay observed in these trials would also be reflected in the mortality estimates. However, because door-to-balloon time and door-to-PCI times did not differ between the transradial and transfemoral arms of RIFLE STEACS (transradial door-to-balloon time, 60 minutes; transfemoral door-to-balloon time, 53 minutes) and RIVAL (transradial door-to-PCI, 85 min; transfemoral door-to-PCI, 85 min), our base case assumed no transradial delay (0 minutes).

Multiple studies have attempted to quantify the relationship between reperfusion delays and mortality in STEMI.(12) However, only two studies examined the relationship in a manner allowing estimation of the per-minute increase in mortality associated with delays in reperfusion within 30-days from the index event. One study was derived from National Cardiovascular Data Registry (NCDR) and one was from patients 65 years of age or older from the US Medicare program.(13,14) We used the per-minute increase in in-hospital mortality associated with reperfusion delays from the NCDR study population as our base case estimate as it was observed in a broadly representative STEMI population. (13) Linear regression was performed on the published data relating door-to-balloon time with mortality from presentation through 150 minutes to generate estimates of the per-minute relationship between delays in reperfusion and mortality. Because the vast majority of 30-day mortality after STEMI occurs during the index hospitalization, we assumed that the incremental effect of reperfusion delay on in-hospital mortality would lead to proportional increases in 30-day mortality. We made this assumption because the analysis in the NCDR population reported in-hospital mortality and the RCTs reported 30-day outcomes.

Primary analysis and base case

The base case used pooled mortality data from RIFLE STEACS and the RIVAL STEMI sub-study, assumed no additional transradial to transfemoral crossover apart from that observed in these trials, and used a per-minute incremental mortality estimate based on the aforementioned study by Rathore et al.(13) Because our interest was quantifying the threshold where transradial delay would offset the mortality benefit of transradial access, the primary analysis was a one-way sensitivity analysis where the transradial delay was increased over a broad range.

Elderly population

Because the impact of reperfusion delays may be different across populations, we also modeled transradial delay in a Medicare-like population. For this analysis, we estimated the incremental increase in 30-day mortality associated with reperfusion delay observed in the Medicare population, which was more than 3 times that observed in the NCDR population (1.7% increase in mortality per 15 minute delay compared with 0.5% per 15 minutes within the NCDR).(13,14) In addition, we assumed higher rates of 30-day mortality in the elderly independent of arterial access site based on the estimated 30-day mortality (and 95% confidence interval) of those with door to balloon times of 30 minutes in the Medicare analysis. (14)

Sensitivity Analyses

For the base case and Medicare case, we conducted analyses to examine the sensitivity of our findings to other assumptions. First, because the magnitude of the mortality difference between transradial and transfemoral PCI observed in trials has been questioned,^(15,16) we conducted a deterministic sensitivity analysis by decreasing the mortality benefit of transradial versus transfemoral PCI. We also conducted analyses where the transradial to transfemoral crossover rate was increased to reflect rates observed in routine practice.

Finally, probabilistic sensitivity analyses were performed using Monte Carlo simulation. For each analysis, 1000 Monte Carlo simulations were performed across a range of transradial delays to estimate the proportion of simulations that favored transradial compared with transfemoral access. The distributions used for the Monte Carlo simulations are described in Table 1 and incorporate the uncertainty observed in the RCT estimates of the mortality benefit of transradial PCI and in the per-minute mortality impact in delays in reperfusion. Parameters for the continuous distributions were generated based on reports of means and 95% confidence intervals of the estimated parameters in the literature. Analyses were performed using TreeAge Pro 2012 (Williamstown, MA).

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Results

Under base case assumptions, a transradial delay of 83.0 minutes was needed to fully offset the mortality benefit of transradial PCI observed in randomized trials. Thus, for a typical patient presenting with STEMI eligible for transradial or transfemoral PCI, the transradial approach would be preferred even if this added up to 83 additional minutes to the door-to-balloon time.

Because doubt has been cast on the magnitude of the mortality benefit of transradial PCI [44% reduction in the RIVAL STEMI sub-study, 60% reduction in RIFLE STEACS, pooled RR for 30-day mortality 0.50 (95% confidence interval; 0.33 to 0.76)], we examined the impact of reducing the mortality benefit on the transradial delay threshold. (Figure 2) When the benefit associated with transradial PCI was reduced to half of that observed in RCTs (RR for 30-day mortality = 0.75), the transradial delay associated with equivalent mortality outcomes between transradial and transfemoral PCI decreased to 41.8 minutes. The threshold value for transradial delay was 20.9 minutes when the RR of 30-day mortality was reduced by 75% to 0.88.

Finally, because access site crossover rates are likely to be higher in routine practice than those observed in RCTs, we examined the impact of increasing crossover (Figure 3). The transradial delays associated with equivalent mortality outcomes between transradial and transfemoral PCI were 81.5 minutes when the rate of crossover from transradial to transfemoral access was increased by 5% (to 12.8%) and 79.7 minutes when crossover was increased by 10% (to 17.8%).

Elderly population

When the analysis was based on a population of patients all ≥ 65 years of age, a transradial delay of 61.5 minutes with transradial PCI was needed to fully offset the projected mortality benefit of transradial PCI compared with transfemoral PCI. When the benefit associated with transradial PCI was reduced to half of that observed in RCTs (RR of 30-day mortality = 0.75), the transradial delay associated with equivalent mortality outcomes between transradial and transfemoral PCI decreased to 30.8 minutes (Figure 4). The threshold value for transradial delay was 14.8 minutes when the RR of 30-day mortality was reduced by 75% to 0.88. The transradial delays associated with equivalent mortality outcomes between transradial and transfemoral PCI were 60.0 minutes when the rate of crossover was increased by 5% and 58.2 minutes when crossover was increased by 10% (Figure 5).

Probabilistic sensitivity analyses

Figure 6 shows the results of probabilistic sensitivity analyses which account for uncertainty in the assumptions used in the model. Among 1,000 simulations at each transradial delay value, the proportion of simulations favoring transradial PCI declined as transradial delay increased. Under base case assumptions, transradial PCI was preferred over transfemoral PCI in 97.5% of simulations when the transradial delay was 30 minutes and 79.0% of simulations when the delay was 60 minutes. Under the assumptions for the elderly population, transradial PCI was preferred over transfemoral PCI in 98.5% of simulations when the transradial delay was 30 minutes and 52.0% of simulations when the delay was 60 minutes.

Discussion

Use of transradial access for PCI has grown significantly over the prior 5 years.^(2,9) However, despite the growing recognition of the feasibility and benefits of this approach, ^(17,18) substantial variation in its use exists between operators, hospitals, and countries, particularly in STEMI.^(2-4,9,19) Low rates of transradial PCI may reflect operator discomfort with this approach when the stakes of prolonging door-to-balloon time are high. The major finding of our study is that operators would need to introduce a substantial delay in door-to-balloon time through the performance of transradial PCI, compared with transfemoral PCI, to neutralize the mortality benefit of transradial arterial access in STEMI seen in published RCTs. These results were robust to changes in several important assumptions, including the mortality benefit of transradial compared with transfemoral PCI in STEMI, the estimated mortality increase associated with delayed reperfusion, and the transradial to transfemoral crossover rate.

These results may be surprising to many practitioners and reflect the large relative risk reduction seen with transradial PCI in the RIVAL STEMI substudy and RIFLE-STEACS trials. Although these studies represent the best sources of data from which to estimate the treatment effect, it is important to note that these observed benefits were larger than anticipated, and in the case of one study, the one positive subgroup analysis of several performed.⁽¹⁵⁾ Multiple hypotheses have been generated to account for the observed mortality benefit of transradial access. The simplest is that access site bleeding differs

between transradial and transfemoral PCI and is causally linked to excess short-term mortality.(20) The observed mortality benefit for transradial PCI, however, seems out of proportion to differences in bleeding observed between the two approaches.(15) Differences in early ambulation, more rapid hospital discharge, or possible reductions in renal failure(21) are also possible underlying mechanisms. Given the uncertainty surrounding the trial data, it is reassuring that our results were robust to analyses in which the mortality benefit with transradial PCI was as little as one-quarter of that seen in the RCTs. It is also reassuring that the threshold transradial delay of ~21 minutes under this alternative scenario is far greater than the 4 minute difference in door-to-balloon time that was recently reported from contemporary practice in the United States, where rates of transradial PCI have lagged. (2) These results were also robust in the elderly population where mortality is higher than that observed in RCTs and the impact of reperfusion delay is greater. Nevertheless, it is important to recognize that these results are meant to be hypothesis-generating, and should be interpreted cautiously in the context of the limitations of the current data.

The recent European consensus statement that advocates a default-radial approach for PCI recommends a stepwise framework for developing competency in new transradial programs. (1) STEMI patients are the last step in that framework due to complexity, acuity, and the need for rapid procedural completion. The data we have developed can reassure operators that a meaningful mortality benefit with transradial PCI in STEMI is likely to persist even if there are delays in reperfusion associated with transradial PCI. Recent data questioning the clinical impact of further reductions in reperfusion times in primary PCI in STEMI(22) would also support the use of transradial PCI if operators are hesitant to transition to a transradial approach due to concerns about short delays in reperfusion. Because studies assessing the relationship between door-to-balloon time and mortality largely been observational in nature, they may overestimate the true impact of small delays in reperfusion on survival. A flatter relationship between reperfusion time and outcomes would further support the conclusions of this analysis.

One additional implication of our findings is that the focus on reducing door-to-balloon time may lead to perverse incentives for operators caring for STEMI patients. Both European and US guidelines on the management of STEMI include goals for reducing door-to-balloon time, to less than 60 minutes in Europe and to less than 90 minutes in the US.(23,24) Operator attempts to gain small improvements in reperfusion times may be at the expense of greater benefits with a transradial approach. To provide a more balanced assessment, we propose that door-to-balloon time metrics be integrated with other quality measures in patients with STEMI. In light of our results, it may even be worth considering an alternative door-to-balloon time metric for patients treated with transradial PCI should the mortality benefit of transradial PCI in STEMI be confirmed.

Operators performing PCI for STEMI are under pressure to perform life-saving interventions under the duress of time. Notwithstanding this study, we do not recommend that inexperienced operators uncomfortable with transradial PCI in general transition to a “radial-first” approach in the STEMI patient subset. However, our results should be reassuring to less experienced radial operators and may lower the perceived barrier to integrating transradial primary PCI into interventional practice.

Finally, we observed that less delay was tolerated in the elderly cohort compared to the overall study population, due principally to the steeper relationship between door-to-balloon time and mortality observed in this population. This finding supports the notion that there may be different thresholds for the use of transradial PCI among different patient populations, based on the anticipated transradial delay as well as the expected impact of delay on mortality.

As with all modeling studies, there are important assumptions inherent to our approach that may impact the interpretation of our results. First, our model assumes that there is truly a mortality benefit with a transradial approach over a transfemoral approach in primary PCI. These data reflect the best estimates from current data, both randomized and observational. Should additional RCTs show a smaller reduction in mortality for transradial primary PCI than has been observed in studies thus far, our model results can be adjusted to estimate the transradial delay threshold based on these new data. Second, our analysis hinges on there being a true per-minute mortality impact of reperfusion delays in patients with STEMI. Both of the studies that we have highlighted and used in our analyses to define the relationship between door-to-balloon time and mortality have allowed for complex relationships between these variables, and both have found that any delay in primary PCI in STEMI is associated with higher mortality. Additionally, we have assumed a linear relationship between mortality outcomes and delays in the door-to-balloon time relationship. While several studies suggest that the exact relationship is not linear across the entire range of door-to-balloon time, (13,14,25) most have shown a near linear relationship across the range of times used in this analysis. Finally, we intentionally did not account for the non-mortality benefits of transradial access for PCI, thus biasing our analysis slightly in favor of transfemoral PCI.

Conclusions

Based on the best data currently available from RCTs and population-level observational studies, our model suggests that a substantial delay in door-to-balloon time would need to be introduced during transradial PCI to eliminate the observed mortality benefits of a transradial approach compared with a transfemoral approach for primary PCI. These results were robust to changes in multiple assumptions, and have implications for operators reluctant to transition to a “radial-first” approach in STEMI due to concern for potentially prolonging time to reperfusion.

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Figure 1. Decision tree

Decision-analytic model representing the choice of transradial or transfemoral PCI for STEMI. In the model, a box represents a decision node, a circle represents a chance node, and a triangle represents a terminal node. The probabilities of each event are under each limb. # represents the term “1- the probability of the opposite limb.” DBT-death relationship represents the per-minute mortality associated with delays in door-to-balloon time.

Figure 2. Two-way sensitivity analysis varying the transradial delay and the mortality benefit of transradial vs. transfemoral PCI in the base case

As the mortality benefit of transradial PCI is reduced, the transradial delay that would offset this mortality differences declines. The dashed lines represent the base case. RR = relative risk.

Figure 3. Two-way sensitivity analysis varying the transradial delay and varying transradial to transfemoral crossover in the base case

The base case has 7.8% crossover inherent from the analysis of the RIFLE STEACS and RIVAL studies.

Figure 4. Two-way sensitivity analysis varying the transradial delay and the mortality benefit of transradial access vs. transfemoral PCI in the elderly population
The dashed lines represent the elderly case. RR = relative risk.

Figure 5. Two-way sensitivity analysis varying the transradial delay and varying additional transradial to transfemoral crossover in the elderly population
 The base case has 7.8% crossover inherent from the analysis of the RIFLE STEACS and RIVAL studies.

Figure 6. Probabilistic sensitivity analysis

Each point along the curves represents 1,000 Monte Carlo simulations of the base case or the elderly case at a given transradial delay.

Table 1

Inputs from the literature for base case and sensitivity analyses.

Input	Case	Distribution Type	Details	Reference(s)
Mortality at 30-days for base case				
Radial PCI	Base case	Beta	38 deaths, 1455 patients	RIFLE STEACS,(8) RIVAL(7)
Femoral PCI	Base case	Beta	78 deaths, 1504 patients	RIFLE STEACS,(8) RIVAL(7)
Mortality at 30-days for elderly case	Medicare	Continuous	7.3% 95% CI: 6.1-8.6%)	Medicare analysis(14)
		Continuous		
Per-minute door-to-balloon mortality-relationship	Base case	Continuous	0.00031 (95% CI: 0.00021-0.00041) 0.00041	NCDR analysis(13)
	Medicare sensitivity analysis	Continuous	0.00117 (95% CI: 0.00017-0.00217)	Medicare analysis(14)
Crossover rate beyond RIFLE STEACS/RIVAL	Base case	-	7.8% implicit in model	
	12.8% Crossover	Continuous	0.128 (95% CI: 0.078-0.178)	Multiple cohorts(18,26,27)
	17.8% crossover	Continuous	0.178 (95% CI: 0.128-0.228)	Multiple cohorts(18,26,27)
Crossover time delay (minutes)	Additional crossover analyses	Continuous	30 minutes (95% CI: 10-50 minutes)	Expert opinion of authors

95% CI represents 95% confidence interval