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Radial Access Reduces Mortality in Patients With Acute Coronary Syndromes

Results From an Updated Trial Sequential Analysis of Randomized Trials

Giuseppe Andò, MD, PhD,[a] Davide Capodanno, MD, PhD[b]

ABSTRACT

OBJECTIVES The authors sought to investigate whether the cumulative evidence coming from randomized studies has reached the necessary power to consider radial access as a bleeding avoidance strategy that reduces mortality and ischemic endpoints in patients with acute coronary syndromes (ACS).

BACKGROUND Studies in ACS patients have reached conflicting conclusions about the impact of radial access in improving ischemic outcomes in addition to the established bleeding benefit.

METHODS English-language publications and abstracts of major cardiovascular meetings until October 2015 were scrutinized. Study quality, patient characteristics, procedural data, and outcomes were extracted. Data were pooled in random effects meta-analyses with classic and trial sequential techniques. Trial sequential analysis combines the a priori information size calculation needed to allow for clinically meaningful statistical inference with the adjustment of thresholds for which results are considered significant.

RESULTS Seventeen studies, encompassing data from 19,328 patients, were pooled. Radial access was found to reduce mortality (relative risk [RR]: 0.73; 95% confidence interval [CI]: 0.60 to 0.88; $p = 0.001$), major adverse cardiovascular events (RR: 0.86; 95% CI: 0.77 to 0.95; $p = 0.005$), and major bleeding (RR: 0.60; 95% CI: 0.48 to 0.76; $p < 0.001$). Multiple sensitivity analyses showed consistent results, and trial sequential analysis suggested firm evidence for a meaningful reduction in mortality with radial access.

CONCLUSIONS Radial access reduces mortality compared with femoral access in ACS patients undergoing invasive management. This benefit is paralleled by consistent reductions in major adverse cardiovascular events and major bleeding, supporting radial access as the default strategy for cardiac catheterization in patients with ACS.
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Combined use of potent antithrombotic drugs and early invasive management in patients with ACS have prompted a substantial reduction in adverse ischemic events, at the cost of increased bleeding (1). From being traditionally regarded as an inherent shortcoming of implementing life-saving procedures, bleeding is now appreciated as an important cause of negative outcomes (2).

The radial access site has been increasingly used as an alternative to the femoral access site both for diagnostic and interventional purposes. An earlier meta-analysis conducted across the broad spectrum of percutaneous coronary intervention (PCI) concluded that radial access reduces major bleeding (3). Yet, studies conducted in ACS have come to conflicting conclusions with respect to the efficacy of the radial approach in reducing ischemic events, or the

From the [a]Department of Clinical and Experimental Medicine, Section of Cardiology, University of Messina, Messina, Italy; and the [b]Department of General Surgery and Medical-Surgical Specialties, Ferrarotto Hospital, University of Catania, Catania, Italy.
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composite of ischemic or bleeding events, by parallel reductions in bleeding (4–10). A more recent meta-analysis (11) suggested a mortality benefit of radial access in patients with ST-segment elevation myocardial infarction (STEMI), although the significant heterogeneity of the studies included prevented a clear understanding of the mechanistic relation between bleeding and mortality (12). Notably, none of such meta-analyses has included data from the most recent trials in the field, and 1 recent article—including a concise meta-analysis of ACS trials—did not report pooled results of procedural outcomes nor explored potential sources of heterogeneity with sensitivity analyses (10).

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On this background, we conducted an updated, comprehensive meta-analysis of randomized studies comparing radial and femoral access in invasively managed patients with ACS. Given the small sample size of many of the earlier trials and to explore any chance of false-positive or false-negative findings in previous meta-analyses (13), we used a trial sequential methodology to critically evaluate whether the amount of the accumulated information has now reached the necessary power to support the systematic and routine use of radial access as a bleeding avoidance strategy to reduce mortality or other ischemic endpoints in patients with ACS undergoing invasive management.

METHODS

PROTOCOL AND REGISTRATION. The protocol of this study has been registered in the PROSPERO database (Time Sequential Meta-Analysis of Radial Versus Femoral Access in Invasively Managed Patients With Acute Coronary Syndromes; CRD42015022031) in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (14). Study selection, data sources and searches, data extraction and quality assessment, and data synthesis and analysis are reported in the Methods section of the Online Appendix.

TRIAL SEQUENTIAL ANALYSIS. The trial sequential analysis (TSA) combines the a priori information size (IS) calculation for a meta-analysis with the adjustment of the thresholds for which the results are considered statistically significant (15,16). The IS calculation is analogous to sample size calculation in a single trial aimed at estimating the number of events and patients needed to allow for reliable statistical inference. Similarly, in a meta-analysis, the IS calculation is on the basis of the expected incidence of events in the control group and the expected relative risk (RR) reduction of the experimental intervention. Estimating the IS for the purpose of a TSA is instrumental in quantifying the reliability of data pooled in the meta-analysis itself, as a function of the strength of the accumulating evidence over time, and the heterogeneity across included trial populations, interventions, and methods.

The TSA methodology is on the basis of the assumption that data will accumulate until the required IS has been exceeded and requires pre-specifying meaningful thresholds to control for the risk of false-positive (type I error) or false-negative (type II error) results. To that end, a monitoring boundaries methodology was used. Briefly, such approach has been originally developed for repeated significance testing in clinical trials in order to evaluate the accumulating data before the sample size has been reached and to avoid false-positive statistical test results, a phenomenon commonly known as "multiplicity due to repeated significance testing" (17). In other words, adjusted significance thresholds may eliminate early false-positive findings due to repeated significance testing when pooled estimates are on the basis of a still insufficient number of events and patients. Indeed, the possibility to calculate adjusted confidence intervals (CIs) serves to guard against spurious inferences at early stages of a meta-analysis: adjusted confidence intervals appropriately converge to resemble conventional CIs as the accrued number of patients approaches the required IS.

z-Curves were constructed for each explored outcome, and alpha conventional thresholds for significance testing at the 5% and 1% levels were displayed. Adjusted significance monitoring boundaries, as described above, were added by using the O'Brien-Fleming alpha-spending method under the assumption that significance testing may have been performed each time a new trial was sequentially added to the meta-analysis (16). Given the considerable amount of attention given to the access site debate over the last decade, this assumption appeared reasonable. The IS was calculated (Online Table 1) with 99% power for major adverse cardiovascular events (MACE) (defined as the composite of death, myocardial infarction, or stroke), access site bleeding and major bleeding, and 90% power for each of the MACE components. The control event rate was set to the proportion observed in the

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

IS = information size

MACE = major adverse cardiovascular event(s)

PCI = percutaneous coronary intervention

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RR = relative risk

STEMI = ST-segment elevation myocardial infarction

TSA = trial sequential analysis