Not Too Fast: The Case Against Immediate Cardiac Angiography After Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation

August 2019 Annals of Emergency Medicine Journal Club

Guest Contributors
Christopher S. Evans, MD, MPH; Ryan P. Radecki, MD, MS; Rory J. Spiegel, MD

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2019.06.001

Editor's Note: *You are reading the 73rd installment of* Annals of Emergency Medicine *Journal Club. As the Journal Club enters its second decade of publication, we are making a number of changes to the format. The Journal Club format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. *N Engl J Med.* 2019;380:1397-1407.

What Question Did This Investigation Aim to Answer?

In adult patients with out-of-hospital cardiac arrest, an initial shockable rhythm, and no ST-segment elevation on postreturn of spontaneous circulation ECG, does immediate coronary angiography improve mortality compared with delayed coronary angiography?

What Study Design Did the Authors Choose?

Design: Prospective, multicenter, open-label, investigator-initiated, randomized clinical trial. Netherlands Trial Register Number: NTR4973.

Setting: Nineteen hospitals in the Netherlands.

Population: Five hundred thirty-eight adult patients with out-of-hospital cardiac arrest with an initial shockable rhythm, Glasgow Coma Scale score less than 8 after return of spontaneous circulation, and no signs of ST-segment elevation on ECG.

Intervention: Immediate coronary angiography (within 2 hours) versus delayed coronary angiography after neurologic recovery.

Primary and Secondary Outcomes: Primary outcome was overall survival at 90 days. Secondary outcomes included 90-day survival with good cerebral performance (using Cerebral Performance Category, myocardial injury [as measured by troponin level, creatine kinase, and creatine kinase-MB], acute kidney injury, need for dialysis, time to target temperature, time spent on catecholamine infusions or inotropes, neurologic status at discharge from the ICU, markers of shock as measured by mean arterial pressures and lactate level, recurrence of ventricular tachycardia, duration of mechanical ventilation, and major bleeding).

Sponsors: Netherlands Heart Institute, Biotronik, and AstraZeneca.

How Did the Authors Interpret the Results?

Among 538 adults with out-of-hospital cardiac arrest and no signs of ST-segment elevation on postreturn of spontaneous circulation ECG, the authors found no statistically significant difference in survival at 90 days between immediate angiography versus delayed angiography (90-day survival 64.5% in immediate angiography versus 67.2% in delayed angiography; odds ratio 0.89; 95% confidence interval 0.62 to 1.27). Time to targeted temperature management was 0.7 hours shorter in the delayed angiography group (ratio of geometric means 1.19 (95% confidence interval 1.04 to 1.36) and was the only secondary outcome found to be statistically significant between treatment strategies.

Immediate angiography showed no survival benefit at 90 days compared with delayed angiography in adults with out-of-hospital cardiac arrest and no signs on ECG of ST-segment elevation.

How Might This Study Affect Your Clinical Practice in the Emergency Department?

In this prospective randomized clinical trial, there was no survival benefit to immediate angiography in out-of-hospital cardiac arrest patients without signs of ST-segment elevation. These data are contrary to those of observational studies suggesting more liberal early cardiac catheterization of such patients. This study supports continued efforts to identify which patients are most likely to benefit from emergency cardiac catherization, a resource-intensive intervention for emergency departments and hospitals.

DISCUSSION POINTS

1. *This is the earliest randomized trial evidence addressing this specific research question; how should we interpret these data in the context of the previous evidence informing practice?*

Previous studies suggesting benefit for early angiography after out-of-hospital cardiac arrest and ECGs without ST-segment elevation have been observational.[1,2] Inherent in any observational study are many limitations, including the potential for selection bias. Lack of randomization can lead to a study population or study arm with baseline imbalances favoring the primary outcome, different than if investigators had enrolled the entire population the study question is trying to target. A potential explanation for the differences in this study's findings compared with previous observational data is simply that there were favorable characteristics based on unmeasured clinical features, which led to important contrasts between patients selected for early or delayed coronary angiography.

This study, in contrast with previous work, was a prospective randomized clinical trial using a 1:1 randomization algorithm to allocate patients evenly between treatment arms. By using randomization, the investigators limited the aforementioned potential confounding between treatment arms. Although statistical adjustments are becoming more sophisticated in observational study designs, the process of randomization continues to be the best way to account for nonrandom error or bias.[3] In a systematic review on this topic before this study, Khan et al[2] appropriately pointed out that the favorable outcomes in previous studies attributed to early angiography may have been misattributed if early angiography was more likely to be performed in younger patients, those with witnessed arrest or bystander cardiopulmonary resuscitation, those with shorter time to return of spontaneous circulation, and other important clinical characteristics.

Additionally, although these data are in contrast to the observational data in out-of-hospital cardiac arrest as outlined above, these findings are consistent with those of multiple randomized controlled trials of immediate versus late coronary angiography in non–ST-segment elevation myocardial infarction among patients who did not present after a cardiac arrest.[4,5]

In summary, considering the inherent strengths of a well-designed randomized clinical trial limiting confounding and selection bias, the findings from this study represent a higher level of evidence than those reflected in previous observational data.

2. *The trial was powered to detect a 40% relative difference in mortality at 90 days, but also incorporated an "adaptive design" to allow for increasing the sample size. How do adaptive designs work, and what was this type of design's effect on this trial?*

The power calculation of this study used a 40% relative difference in mortality at 90 days, based on a meta-analysis of 10 nonrandomized studies that suggested survival benefit of immediate angiography,[6] but also incorporated an option for increasing the sample size with an adaptive design. Adaptive study designs are an increasingly used method that allows modification of key study components according to a predefined analysis of interim data. Ideally, such designs are intended to increase the efficiency of a study in terms of time and resources required. In cases of clear benefit of treatment strategy, adaptive designs mitigate the ethical dilemmas of continuing long-term conventional controlled trials when clear benefit is shown before completion of the study.[7] Conversely, interim analyses may also protect study participants from undue burdens related to study procedures when the ultimate analysis is known to be statistically futile. Adaptive trial designs can be used in both exploratory trials including dose-response modeling and in confirmatory clinical trials using one or more of the following components: seamless phase 2 to 3 designs, sample size reestimation, group-sequential designs, and population-enrichment designs.[8] To limit the potential for biased results after an interim adaption, a key component to adaptive trial planning is using simulations to better understand how potential adaptions may alter the study findings. Predetermined decision rules of how and when a study will be adapted also play a key role in reducing bias.

This trial used an adaptive design allowing the option of increasing the sample size if "the survival benefit was substantial but smaller than the 40% difference," after an interim analysis of the outcome in the first 400 patients. The authors do not explicitly define "substantial," or a protocol for adaptation, in this study or the accompanying methods article.[9] Ultimately, after review of the data at the interim analysis, no change in the sample size was recommended.

It is unclear what effect an adaptive design with sample size reestimation had on the results of this study. One could argue that the validity of the findings is strengthened because the study had an option to increase the sample size, but did not, and found no mortality benefit of immediate angiography with the original methods. Although the exact methods of this component of the study are vague, the study used the original sample size calculation until completion of the study.

Section editors: Tyler W. Barrett, MD, MSCI; Ryan P. Radecki, MD, MS; Rory J. Spiegel, MD

Author affiliations: From the Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN (Evans); Department of Emergency Medicine, Northwest Permanente, Portland, OR, and The University of Texas Health Science Center at Houston, Houston, TX (Radecki); and the Department of Emergency Medicine, University of Maryland, Baltimore, MD (Spiegel).

Authorship: All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Hollenbeck RD, McPherson JA, Mooney MR, et al. Early cardiac catheterization is associated with improved survival in comatose survivors of cardiac arrest without STEMI. *Resuscitation*. 2014;85:88-95.
2. Khan MS, Shah SMM, Mubashir A, et al. Early coronary angiography in patients resuscitated from out of hospital cardiac arrest without ST-segment elevation: a systematic review and meta-analysis. *Resuscitation*. 2017;121:127-134.
3. Altman DG, Bland JM. Uncertainty beyond sampling error. *BMJ*. 2014;349:g7065.
4. Riezebos RK, Ronner E, Ter Bals E, et al. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart*. 2009;95:807-812.
5. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for non-STEMI patients: the RIDDLE-NSTEMI study. *JACC Cardiovasc Interv*. 2016;9:541-549.
6. Larsen JM, Ravkilde J. Acute coronary angiography in patients resuscitated from out-of-hospital cardiac arrest—a systematic review and meta-analysis. *Resuscitation*. 2012;83:1427-1433.
7. Thorlund K, Haggstrom J, Park JJ, et al. Key design considerations for adaptive clinical trials: a primer for clinicians. *BMJ*. 2018:360:k698.
8. Bhatt DL, Mehta C. Adaptive designs for clinical trials. *N Engl J Med*. 2016;375:65-74.
9. Lemkes JS, Janssens GN, Straaten HMO van, et al. Coronary angiography after cardiac arrest: rationale and design of the COACT trial. *Am Heart J*. 2016;180:39-45.

IMAGES IN EMERGENCY MEDICINE

(continued from p. 306)

DIAGNOSIS:

Ovarian mucinous cystadenoma. CT of the abdomen and pelvis revealed a 35×20×17-cm cystic mass with multiple thin enhancing septations in its top left portion (Figures 1 and 2). The mass appeared to arise from the pelvis and extend into the upper abdomen. The patient underwent surgical drainage of the mass, in which 6 L of serous fluid was drained and the tumor was dissected from the surrounding structures (Figure 3). Final pathology was consistent with ovarian mucinous cystadenoma, which appeared to be intestinal, with no areas of invasion.

Ovarian mucinous tumors represent a spectrum of neoplastic disorders, including benign mucinous cystadenoma, pseudomyxoma peritonei, mucinous tumors of low malignant potential (borderline), and invasive mucinous ovarian carcinoma.[1] Mucinous cystadenomas usually occur as a large, multiloculated, cystic mass with mucus-containing fluid. The mean size at presentation is 18 cm, and mucinous tumors can become extremely large and fill the entire abdominopelvic cavity. The large size can itself sometimes suggest a mucinous histology. Most mucinous tumors are unilateral, especially when primarily ovarian in origin.[2]

Author affiliations: From the Department of Emergency Medicine (Zhang) and Department of Surgery (Liu, Wang), First Hospital of Jilin University–Eastern Division, Changchun City, Jinlin Province, People's Republic of China.

REFERENCES

1. Dougherty D, Onyemkpa C, Engel M, et al. A case report of an incidental Brenner tumor found after resection of a large ovarian mucinous neoplasm. *Int J Surg Case Rep*. 2018;49:40-43.
2. Brown J, Frumovitz M. Mucinous tumors of the ovary: current thoughts on diagnosis and management. *Curr Oncol Rep*. 2014;16:389-397.