

TABLE 1 Risk of Acute Kidney Injury Among Patients Receiving DOACs Versus Warfarin Overall and Stratified According to eGFR

	N	DOAC* (n = 3,206) Versus Warfarin (n = 3,206)		Dabigatran (n = 852)† Versus Warfarin (n = 852)		Rivaroxaban (n = 1,325)† Versus Warfarin (n = 1,325)		Apixaban (n = 1,029)† Versus Warfarin (n = 1,029)	
		HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Overall	6,412	0.79 (0.68-0.92)	0.003	0.70 (0.52-0.96)	0.025	0.83 (0.66-1.05)	0.114	0.86 (0.68-1.10)	0.233
eGFR ≥60 ml/min/1.73 m ²	4,169	0.72 (0.57-0.91)	0.007	0.66 (0.43-1.02)	0.063	0.79 (0.50-0.98)	0.037	0.67 (0.45-1.00)	0.052
eGFR 30-59 ml/min/1.73 m ²	1,990	0.80 (0.64-1.01)	0.067	0.60 (0.37-0.98)	0.040	0.95 (0.68-1.33)	0.764	1.01 (0.72-1.41)	0.956
eGFR <30 ml/min/1.73 m ²	253	1.31 (0.81-2.13)	0.271	1.52 (0.53-4.38)	0.440	1.48 (0.63-3.49)	0.368	1.23 (0.58-2.61)	0.593

*DOACs included dabigatran, rivaroxaban, and apixaban. †Dabigatran (mean age: 68, 76, and 79 years in patients with eGFR ≥60, 30-59, and <30 ml/min/1.73 m², respectively; 36%, 53%, and 70% were female in these groups); rivaroxaban (mean age: 67, 76, and 80 years in patients with eGFR ≥60, 30-59, and <30 ml/min/1.73 m²; 39%, 53%, and 64% were female in these groups); apixaban (mean age: 70, 78, and 78 years in patients with eGFR ≥60, 30-59, and <30 ml/min/1.73 m²; 44%, 56%, and 57% were female in these groups).
CI = confidence interval; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; HR = hazard ratio.

among those with eGFR <30 ml/min/1.73 m² (HR: 1.31; 95% CI: 0.81 to 2.13; p = 0.271).

Data comparing the renal adverse effect of DOACs versus that of warfarin are limited, particularly among patients with pre-existing moderate-to-severe kidney dysfunction. This study, conducted in a large U.S. community-based cohort across the spectrum of eGFR, showed that DOACs were associated with a lower risk of AKI but mainly among patients with relatively preserved kidney function (eGFR >60 ml/min/1.73 m²). Among patients with eGFR 30 to 59 ml/min/1.73 m², only dabigatran was associated with a lower risk of AKI compared with warfarin, and there was a trend toward higher AKI risk among all DOAC users compared with warfarin users with eGFR <30 ml/min/1.73 m². Coupled with case reports of fatal bleeding events in patients with severe renal impairment who were taking dabigatran (4,5), caution may be needed when DOACs are prescribed in patients with advanced chronic kidney disease.

Jung-Im Shin, MD, PhD
Shengyuan Luo, MBBS
G. Caleb Alexander, MD, MS
Lesley A. Inker, MD, MS
Josef Coresh, MD, PhD
Alex R. Chang, MD, MS
*Morgan E. Grams, MD, PhD

*Welch Center for Prevention, Epidemiology, and Clinical Research

Johns Hopkins University
2024 East Monument Street
Suite 2-600 (Room 2-638)
Baltimore, Maryland 21205
E-mail: mgrams2@jhmi.edu

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Persistent Survival Benefit From Remote Ischemic Pre-Conditioning in Patients Undergoing Coronary Artery Bypass Surgery



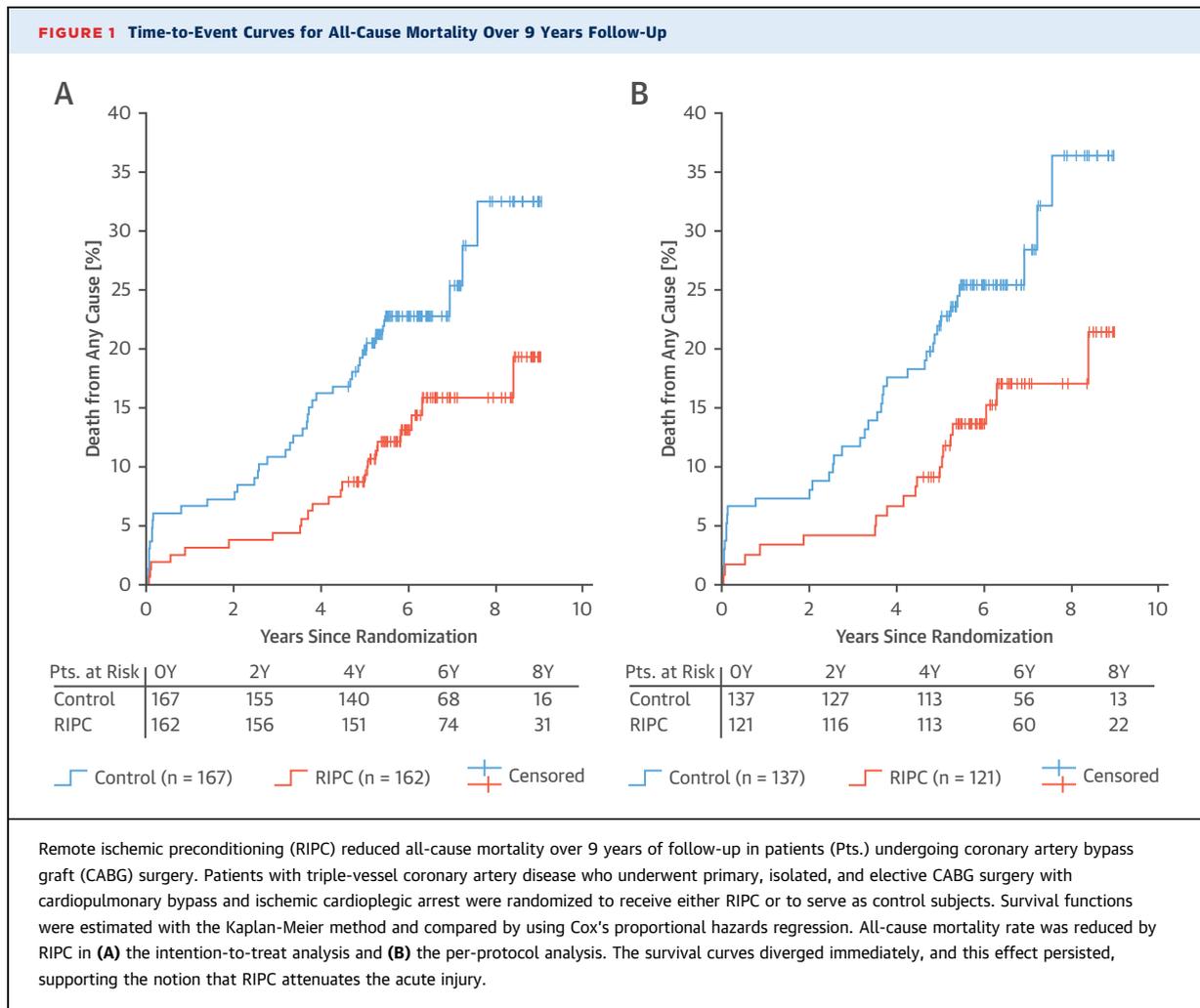
Our single-center, randomized, double-blind, controlled trial included patients undergoing coronary artery bypass graft (CABG) surgery under cardiopulmonary bypass and ischemic cardioplegic arrest. Remote ischemic preconditioning (RIPC) by 3 cycles of 5-min blood pressure cuff inflation and 5-min deflation on the left upper arm reduced myocardial injury, as reflected by troponin release, and improved short-term outcome (i.e., reduced all-cause mortality, major adverse cardiac and cerebrovascular events, and repeat revascularization) over a mean follow-up of 1.54 ± 1.22 years (1).

Short-term and more long-term protection by RIPC in patients undergoing cardiovascular surgery was confirmed in a retrospective analysis of several, but not all, studies. Two prospective, large Phase III trials (ERICCA [Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Surgery] and RIPHeart [Remote Ischemic Preconditioning for Heart Surgery]) of RIPC in patients undergoing cardiovascular surgery were neutral for troponin release and outcome after 1 year (2). In both studies, however, patients were anesthetized with propofol, and propofol abrogates the protection by RIPC (3,4). In our trial, in contrast, propofol was not used; anesthesia was induced with the opioid sufentanil and etomidate, and it was maintained with isoflurane (1). The number of events in our follow-up analysis was small (all-cause mortality: 3 for RIPC vs. 11 for control), and thus the protection by RIPC could have been a false-positive

finding. We have therefore now repeated a follow-up analysis after an additional 5 years.

This follow-up was performed between August 14, 2017, and August 24, 2017, by telephone call and written request to the patients or the local resident registration offices, respectively; the response rate was 100%. Survival functions were estimated with the Kaplan-Meier method and compared by using Cox's proportional hazards regression. After a follow-up of 5.82 ± 1.93 years, all-cause mortality in the intention-to-treat cohort was still lower in the RIPC group (n = 23; 14.2%) than in the control group (n = 39; 23.4%) (p = 0.028) (Figure 1A). A separate per-protocol analysis was performed without protocol violators, as done in the initial analysis (1), and a sustained better long-term survival after RIPC was confirmed (Figure 1B).

To the best of our knowledge, the present single-center, randomized, double-blind, controlled trial is



the first to show that RIPC under opioid/isoflurane anesthesia provides prognostic benefit for up to 9 years of follow-up in patients undergoing CABG surgery. In fact, a survival benefit persisted for so long after the procedure that the all-cause mortality rate in our control group was comparable to that in a contemporary CABG cohort (5). The survival curves diverged immediately, and this effect persisted, supporting the notion that RIPC attenuates the acute injury.

Our study has limitations. It was a retrospective analysis of a single-center trial that was powered only for the primary endpoint of the area under the curve of troponin I as a surrogate marker for cardioprotection. Due to the retrospective nature of our analysis and the long time between the procedure and follow-up, there were no reliable data on the causes of death, and we therefore report only all-cause mortality.

Petra Kleinbongard, PhD

Jürgen Peters, MD

Heinz Jakob, MD

Gerd Heusch, MD

*Matthias Thielmann, MD

*Department of Thoracic and Cardiovascular Surgery

West German Heart and Vascular Center Essen

University of Essen Medical School

Hufelandstrasse 55

45122 Essen

Germany

E-mail: matthias.thielmann@uni-due.de

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Functional Contribution of Circumferential Versus Longitudinal Strain



Different Concepts Suggest Conflicting Results

The study by Stokke et al. (1) notes that circumferential strain contributes more than twice as much as longitudinal strain to left ventricular ejection fraction, but previous research has shown that 60% of stroke volume is generated by left ventricular longitudinal function (2). The different interpretations stem from alternative physiological conceptual frameworks and methods. Although at first glance these differences seem to be in conflict, they are both valid and compatible.

Alternative perspectives of cardiac pumping include the ventricular perspective or the reciprocating, integrated atrioventricular (AV) volume perspective. Stokke et al. (1) uses strain as a local, directional, wall-motion measure. Because fiber angle varies continuously from the epicardium to the endocardium (longitudinal to circumferential to longitudinal), a convenient simplification is to express global function in longitudinal or circumferential components. Radial strain and fractional shortening are due to conservation of myocardial mass and longitudinal shortening influenced by wall thickness. Longitudinal and circumferential function must be coupled. Consider a thought experiment of a left ventricle having only longitudinally arranged fibers. Longitudinal contraction (with zero or minimal epicardial inward displacement) alone must generate concentric wall thickening (radial strain). A midwall circumferential line should, due to concentric wall thickening (3), shorten in systole. Thus, there ought to be finite circumferential strain despite the exclusively longitudinally oriented fibers. Hence, circumferential systolic strain cannot be ascribed to a separate “circumferential fiber function” but instead is generated by all fibers having varying orientation, including longitudinally oriented fibers.

The results of Stokke et al. (1) are not in conflict with the higher values attributed to longitudinal function obtained in studies using the reciprocating, integrated AV volume perspective. In this perspective, motion and AV reciprocating volume pumping is viewed from the outside. It does not involve fiber orientation or strain. Longitudinal shortening is described and measured in terms of apically directed AV plane (piston-like) displacement with