JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 25, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.10.003

# Bivalirudin Versus Heparin Anticoagulation in Transcatheter Aortic Valve Replacement

## The Randomized BRAVO-3 Trial

George D. Dangas, MD, PhD,* Thierry Lefèvre, MD,† Christian Kupatt, MD,‡ Didier Tchetche, MD,§ Ulrich Schäfer, MD,‖ Nicolas Dumonteil, MD,¶ John G. Webb, MD,# Antonio Colombo, MD,** Stephan Windecker, MD,†† Jurriën M. ten Berg, MD, PhD,‡‡ David Hildick-Smith, MD,§§ Roxana Mehran, MD,* Peter Boekstegers, MD,‖‖ Axel Linke, MD,¶¶ Christophe Tron, MD,## Eric Van Belle, MD, PhD,*** Anita W. Asgar, MD,††† Andreas Fach, MD,‡‡‡ Raban Jeger, MD,§§§ Gennaro Sardella, MD,‖‖‖ Hans Ulrich Hink, MD,¶¶¶ Oliver Husser, MD, PhD,### Eberhard Grube, MD,**** Efthymios N. Deliargyris, MD,†††† Ilknur Lechthaler,‡‡‡‡ Debra Bernstein, PhD,†††† Peter Wijngaard, PhD,‡‡‡‡ Prodromos Anthopoulos, MD,‡‡‡‡ Christian Hengstenberg, MD,§§§§ for the BRAVO-3 Investigators

## ABSTRACT

**BACKGROUND** Anticoagulation is required during transcatheter aortic valve replacement (TAVR) procedures. Although an optimal regimen has not been determined, heparin is mainly used. Direct thrombin inhibition with bivalirudin may be an effective alternative to heparin as the procedural anticoagulant agent in this setting.

**OBJECTIVES** The goal of this study was to determine whether bivalirudin offers an alternative to heparin as the procedural anticoagulant agent in patients undergoing TAVR.

**METHODS** A total of 802 patients with aortic stenosis were randomized to undergo transfemoral TAVR with bivalirudin versus unfractionated heparin during the procedure. The 2 primary endpoints were major bleeding within 48 h or before hospital discharge (whichever occurred first) and 30-day net adverse clinical events, defined as the combination of major adverse cardiovascular events (all-cause mortality, myocardial infarction, or stroke) and major bleeding.

**RESULTS** Anticoagulation with bivalirudin versus heparin did not meet superiority because it did not result in significantly lower rates of major bleeding at 48 h (6.9% vs. 9.0%; relative risk: 0.77; 95% confidence interval [CI]: 0.48 to 1.23; $p = 0.27$) or net adverse cardiovascular events at 30 days (14.4% vs. 16.1%; relative risk: 0.89; 95% CI: 0.64 to 1.24; risk difference: -1.72; 95% CI: -6.70 to 3.25; $p = 0.50$); regarding the latter, the prespecified noninferiority hypothesis was met ($p_{noninferiority} < 0.01$). Rates of major adverse cardiovascular events at 48 h were not significantly different (3.5% vs. 4.8%; relative risk: 0.73; 95% CI: 0.37 to 1.43; $p = 0.35$). At 48 h, the bivalirudin group had significantly fewer myocardial infarctions but more acute kidney injury events than the heparin group; at 30 days, these differences were no longer significant.

**CONCLUSIONS** In this randomized trial of TAVR procedural pharmacotherapy, bivalirudin did not reduce rates of major bleeding at 48 h or net adverse cardiovascular events within 30 days compared with heparin. Although superiority was not shown, the noninferiority hypothesis was met with respect to the latter factor. Given the lower cost, heparin should remain the standard of care, and bivalirudin can be an alternative anticoagulant option in patients unable to receive heparin in TAVR. (International, Multi-center, Open-label, Randomized Controlled Trial in Patients Undergoing TAVR to Determine the Treatment Effect [Both Safety and Efficacy] of Using Bivalirudin Instead of UFH [BRAVO-2/3]; NCT01651780) (J Am Coll Cardiol 2015;66:2860–8) © 2015 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From *The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; †Institut Cardio Vasculaire Paris Sud, Hôpital Privé Jacques Cartier, Massy, France; ‡LMU Munich, Munich, Germany; §Clinique Pasteur, Toulouse, France; ‖University Heart Center, Hamburg, Germany, and Asklepios Clinics St. Georg, Hamburg, Germany; ¶CHU Rangueil, Toulouse, France; #St. Paul's Hospital, Vancouver, British Columbia, Canada; **San Raffaele Hospital, Milan, Italy; ††Department of Cardiology, Bern University Hospital, Bern, Switzerland; ‡‡St. Antonius Ziekenhuis, Nieuwegein, the Netherlands; §§Sussex Cardiac Centre-Brighton & Sussex University Hospitals NHS Trust, Brighton, East Sussex, United Kingdom;

Aortic stenosis affects 1% to 4% of the general population, with a higher incidence among elderly subjects (1). Although surgical aortic valve replacement has been the mainstay of treatment, transcatheter aortic valve replacement (TAVR) was introduced for patients deemed inoperable or at high surgical risk (2). TAVR has rates of major cardiovascular events comparable to open surgery and is superior to conservative treatment (3–6), but it still has significant complications. In randomized trials and daily practice, unfractionated heparin has been the standard empiric procedural anticoagulation regimen for TAVR. Although partial or complete reversal of heparin with protamine can be used, practice patterns vary, with guideline statements based on expert consensus rather than on evidence from randomized trials (2). The rapid expansion of TAVR procedures worldwide necessitates dedicated clinical investigation in the field of periprocedural pharmacology, with the goal of building a robust evidence base, deriving appropriate practice guidelines, and further improving clinical outcomes.

SEE PAGE 2869

Bivalirudin is a reversible direct thrombin inhibitor with a half-life of 25 min; it reduces major bleeding while providing stable effective anticoagulation in the setting of percutaneous coronary interventions compared with other regimens (7–12). The goal of the present prospective study was to examine whether bivalirudin offers an alternative to heparin as a procedural anticoagulant agent in patients undergoing TAVR as tested in retrospective studies (13,14).

## METHODS

The BRAVO-3 (Effect of Bivalirudin on Aortic Valve Intervention Outcomes-3) trial was an open-label, randomized controlled trial comparing bivalirudin with unfractionated heparin in high-risk or inoperable patients undergoing TAVR, conducted in 31 European and North American sites (15). Clinical follow-up was performed on days 1 and 2, on the day of hospital discharge, and 30 days post-procedure.

The executive committee governed all aspects of the clinical trial. The Icahn School of Medicine at Mount Sinai clinical coordinating center was responsible for the study design; the identification, education, and training of participating sites, in close collaboration with the sponsor; study management; and organization and conduct of the study committees (Online Appendix). The study sponsor was responsible for funding; protocol development in collaboration with the executive committee and the clinical coordinating center; on-site monitoring and safety surveillance; statistical analyses; and data management. The institutional review board at each site approved the study protocol and activities. An independent clinical events committee reviewed and adjudicated all major clinical events. An independent data safety monitoring board was responsible for study oversight and the final sample size recommendation (adaptive study design).

**STUDY POPULATION.** Patients with aortic stenosis who were ≥18 years of age, at high surgical risk (defined as a European System for Cardiac Operative Risk Evaluation score of ≥18, or deemed inoperable), and scheduled for TAVR via transfemoral access were eligible for enrollment. The main exclusion criteria were planned surgical cutdown access; presence of a previous mechanical or mitral bioprosthetic valve; severe left ventricular dysfunction (ejection fraction <15%); minimal luminal diameter <6.5 mm for the common femoral artery; severe aortic or mitral regurgitation; concurrent percutaneous coronary intervention; recent bleeding or neurological event; and dialysis dependence. The full lists of inclusion and exclusion criteria are provided in the Online Appendix. All patients provided written informed consent.

**ABBREVIATIONS AND ACRONYMS**

**BARC** = Bleeding Academic Research Consortium

**CI** = confidence interval

**TAVR** = transcatheter aortic valve replacement

‖‖Helios Heart Center Siegburg, Siegburg, Germany; ¶¶Universität Leipzig, Herzzentrum, Leipzig, Germany; ##CHU de Rouen, Rouen, France; ***Department of Cardiology and INSERM UMR 1011, University Hospital, and CHRU Lille, Lille, France; †††Institut de Cardiologie de Montreal, Montreal, Quebec, Canada; ‡‡‡Klinikum links der Weser Bremen, Bremen, Germany; §§§Cardiology University Hospital Basel, Basel, Switzerland; ‖‖‖Policlinico Umberto I, Rome, Italy; ¶¶¶Universitätsmedizin Mainz, Mainz, Germany; ###Deutsches Herzzentrum München, Technische Universität München, Germany; ****Universitaetsklinikum Bonn, Bonn, Germany; ††††The Medicines Company, Parsippany, New Jersey; ‡‡‡‡The Medicines Company, Zurich, Switzerland; and the §§§§DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany, and Deutsches Herzzentrum München, Technische Universität München, Munich, Germany. Supported by The Medicines Company. Drs. Dangas, Mehran, and Fach have received grants from The Medicines Company (modest level). Dr. ten Berg has received personal fees from The Medicines Company. Dr. Windecker has received research grants (to the institution) from The Medicines Company. Drs. Anthopoulos, Bernstein, Deliargyris, and Wijngaard and Mrs. Lechthaler are employees of The Medicines Company. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Deepak Bhatt, MD, served as Guest Editor for this paper.

Manuscript received October 4, 2015; accepted October 5, 2015.