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

VOL. 65, NO. 23, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.04.017

Long-Term Safety of Drug-Eluting and Bare-Metal Stents

Evidence From a Comprehensive Network Meta-Analysis

Tullio Palmerini, MD,* Umberto Benedetto, MD,† Giuseppe Biondi-Zoccai, MD,‡ Diego Della Riva, MD,* Letizia Bacchi-Reggiani, MSTAT,* Pieter C. Smits, MD, PHD,§ Georgios J. Vlachojannis, MD, PHD,§ Lisette Okkels Jensen, MD,‖ Evald H. Christiansen, MD, PHD,¶ Klára Berencsi, MSTAT,‖ Marco Valgimigli, MD,# Carlotta Orlandi, MD,* Mario Petrou, MD,† Claudio Rapezzi, MD,* Gregg W. Stone, MD**

ABSTRACT

BACKGROUND Previous meta-analyses have investigated the relative safety and efficacy profiles of different types of drug-eluting stents (DES) and bare-metal stents (BMS); however, most prior trials in these meta-analyses reported follow-up to only 1 year, and as such, the relative long-term safety and efficacy of these devices are unknown. Many recent studies have now reported extended follow-up data.

OBJECTIVES This study sought to investigate the long-term safety and efficacy of durable polymer-based DES, bioabsorbable polymer-based biolimus-eluting stents (BES), and BMS by means of network meta-analysis.

METHODS Randomized controlled trials comparing DES to each other or to BMS were searched through MEDLINE, EMBASE, and Cochrane databases and proceedings of international meetings. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted.

RESULTS Fifty-one trials that included a total of 52,158 randomized patients with follow-up duration ≥3 years were analyzed. At a median follow-up of 3.8 years, cobalt-chromium everolimus-eluting stents (EES) were associated with lower rates of mortality, definite stent thrombosis (ST), and myocardial infarction than BMS, paclitaxel-eluting stents (PES), and sirolimus-eluting stents (SES) and less ST than BES. Phosphorylcholine-based zotarolimus-eluting stents had lower rates of definite ST than SES and lower rates of myocardial infarction than BMS and PES. The late rates of target-vessel revascularization were reduced with all DES compared with BMS, with cobalt-chromium EES, platinum chromium-EES, SES, and BES also having lower target-vessel revascularization rates than PES.

CONCLUSIONS After a median follow-up of 3.8 years, all DES demonstrated superior efficacy compared with BMS. Among DES, second-generation devices have substantially improved long-term safety and efficacy outcomes compared with first-generation devices. (J Am Coll Cardiol 2015;65:2496–507) © 2015 by the American College of Cardiology Foundation.

From the *Unità Operativa di Cardiologia, Policlinico S. Orsola, Bologna, Italy; †Oxford Heart Center; Oxford University, Oxford, England; ‡Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; §Department of Cardiology, Maasstad Ziekenhuis, Rotterdam, the Netherlands; ‖Department of Cardiology, Odense University Hospital, Odense, Denmark; ¶Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; #Erasmus Medical Center, Thoraxcenter, Rotterdam, the Netherlands; and the **Columbia University Medical Center/New York-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, New York. Dr. Palmerini has received speaker fees from Abbott Vascular. Dr. Biondi-Zoccai has lectured, consulted, and served on advisory boards for Bayer; has consulted for DirectFLow Medical, SICI-GISE, Novartis, and Abbott Vascular; has lectured for Abbott Vascular, AstraZeneca, WebMD, and St. Jude Medical; and has consulted and lectured for Boston Scientific, Cordis, and Medtronic. Dr. Smits has received speaker fees from Abbott Vascular; and institutional research grants from Abbott Vascular, Terumo, and St. Jude Medical. Dr. Vlachojannis has received speaker fees from Abbott Vascular. Dr. Jensen has received research grants from Terumo, St. Jude Medical, Biosensors, and Biotronik; and honoraria from Abbott Vascular, AstraZeneca, St. Jude Medical, Biotronik, and Amgen. Dr. Valgimigli has received personal fees and nonfinancial support from The Medicines Company, AstraZeneca, and Terumo; and personal fees from Abbott Vascular outside the scope of the submitted work. Dr. Stone has been a consultant to Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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

Manuscript received January 16, 2015; revised manuscript received April 2, 2015, accepted April 7, 2015.

Although first-generation sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Miami Lakes, Florida) and paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts) significantly reduced the risk of restenosis and ischemia-driven target-vessel revascularization (TVR) compared with bare-metal stents (BMS) (1,2), an ongoing propensity for very late stent thrombosis (ST) and adverse events emerged with both types of stent (3). To mitigate these risks, newer devices were developed that used novel stent materials, platforms, and delivery systems, with more biocompatible polymers (both durable and bioresorbable) than their predecessors. Several randomized controlled trials (RCTs) and meta-analyses have suggested that these newer devices may have a better safety profile not only compared with first-generation drug-eluting stents (DES) but also when compared with BMS (4,5); however, most of these studies had a limited follow-up of 1 year, with very few reporting data beyond 2 years. The long-term relative safety and efficacy of second-generation DES have therefore not been investigated in depth.

SEE PAGE 2508

An example of the importance of extended follow-up may be seen from the PROTECT trial (Patient-Related Outcomes With Endeavor Versus Cypher Stenting Trial), in which reduced rates of ST with phosphorylcholine-based zotarolimus-eluting stents (PC-ZES) (Medtronic, Santa Rosa, California) compared with SES emerged only at 4 years of follow-up (6). Similarly, any advantages of bioabsorbable polymer-based DES compared with permanent polymer-based DES might only be expected to be present at long-term follow-up.

Since the publication of the most recent meta-analysis comparing different types of DES with each other or with BMS (7), several RCTs have significantly extended their period of surveillance, reporting data at 3 to 6 years after stent implantation (8–20). For this reason, to examine the long-term relative safety and efficacy of different DES and BMS, we performed an updated network meta-analysis including only trials with a follow-up duration of at least 3 years.

METHODS

OBJECTIVES, DEFINITIONS, AND STUDY DESIGN. The primary endpoint of this network meta-analysis was the long-term rate of definite ST defined according to the Academic Research Consortium criteria (21). Only RCTs investigating currently U.S. Food and Drug Administration (FDA)-approved DES and BMS with a follow-up duration of ≥3 years were included in the meta-analysis. In addition, we also included studies with biolimus-eluting stents (BES) (BioMatrix, Biosensors, Newport Beach, California; and Nobori, Terumo Clinical Supply, Kakamigahara, Japan), because these devices have been investigated extensively in several large-scale RCTs (22–26) and are the most widely used bioabsorbable polymer-based DES outside the United States. Thus, the DES studied in the present report were SES, PES, cobalt-chromium everolimus-eluting stents (CoCr-EES) (Abbott Vascular, Santa Clara, California), platinum-chromium EES (PtCr-EES) (Boston Scientific), PC-ZES, Resolute ZES (Re-ZES) (Medtronic), and BES.

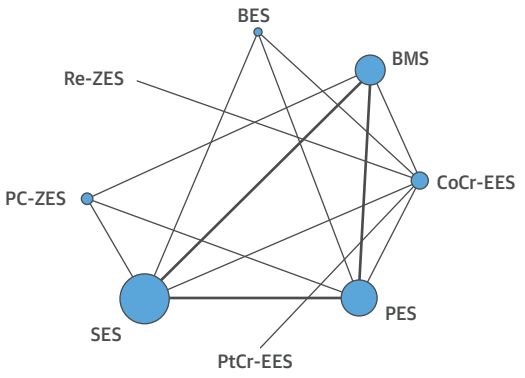
Secondary pre-specified endpoints included long-term rates of Academic Research Consortium definite/probable ST and very late (>1 year) definite and definite/probable ST, as well as death, cardiac death, myocardial infarction (MI), and TVR. This review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statements.

DATA SOURCE AND STUDY SELECTION. Relevant RCTs to include in this meta-analysis were searched through MEDLINE, the Cochrane database, the EMBASE database, the Transcatheter Cardiovascular

ABBREVIATIONS AND ACRONYMS

BES = biolimus-eluting stent(s)
BMS = bare-metal stent(s)
CI = credible interval
CoCr-EES = cobalt-chromium everolimus-eluting stent(s)
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PC-ZES = phosphorylcholine-based zotarolimus-eluting stent(s)
PES = paclitaxel-eluting stent(s)
PtCr-EES = platinum chromium everolimus-eluting stent(s)
RCT = randomized controlled trial
Re-ZES = Resolute zotarolimus-eluting stent(s)
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TVR = target-vessel revascularization

FIGURE 1 Evidence Network Between Stents Included in Meta-Analysis



BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); PC-ZES = phosphorylcholine polymer–based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PtCr-EES = platinum-chromium everolimus-eluting stent(s); Re-ZES = Resolute zotarolimus-eluting stent(s); SES = sirolimus-eluting stent(s).