*Hans Gustav Hørsted Thyregod, MD
Daniel Andreas Steinbrüchel, MD, DMSc
Lars Søndergaard, MD, DMSc

*Department of Cardiothoracic Surgery
The Heart Centre, Rigshospitalet
Copenhagen University Hospital
Blegdamsvej 9, DK-2100
Copenhagen, Denmark
E-mail: hans.gustav.thyregod@regionh.dk

http://dx.doi.org/10.1016/j.jacc.2015.06.1345

Please note: Dr. Søndergaard is a proctor for Medtronic, Inc; he has been involved in research contracts with St. Jude Medical, Inc.; and he received speakers fees from Medtronic, Inc. Drs. Søndergaard and Steinbrüchel have been involved in research contracts with Medtronic, Inc. Dr. Thyregod has reported that he has no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Thyregod HG, Steinbruchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the All-Comers NOTION Randomized Clinical Trial. J Am Coll Cardiol 2015;65:2184–94.

2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

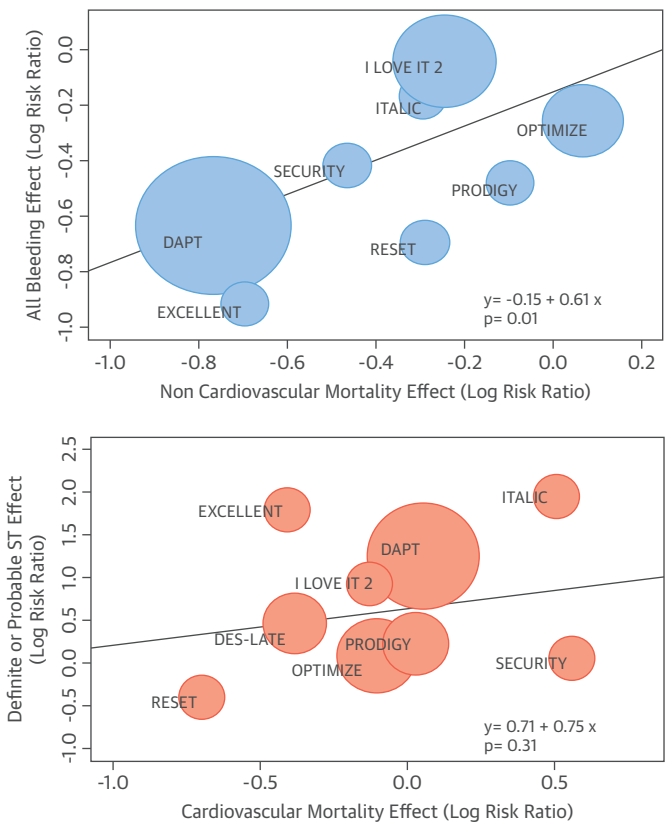
3. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

Meta-Analyses of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation

Do Bleeding and Stent Thrombosis Weigh Similar on Mortality?

We read with interest the meta-analyses of Giustino et al. (1) and Palmerini et al. (2) recently published in the *Journal*. These studies add meaningfully to the ongoing debate on dual antiplatelet therapy (DAPT) duration, but their conclusions on mortality are conflicting, with Giustino et al. (1) concluding that prolonging DAPT increases all-cause mortality and Palmerini et al. (2) demonstrating no significant effect on this endpoint. Indeed, addressing the net benefit of extended DAPT requires preliminary clarification of the relative weights of stent thrombosis (ST) and bleeding on mortality, an issue that has not been explored by any trial or meta-analysis of DAPT duration. We hypothesized that in the contemporary era of drug-eluting stents, ST and bleeding have a different impact on mortality. To explore this hypothesis, we performed a meta-regression of the effects sizes of ST and bleeding on mortality in trials of DAPT duration, including the recently presented I-LOVE-IT (Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary) 2 randomized substudy (China Interventional Therapeutics, March 19, 2015, Beijing, China). Trials were excluded if the outcomes of interest were not available. Risk ratios for treatment effects in individual trials were log-transformed before being used as independent variables in linear meta-regression analyses. Statistical analyses were performed using the open-source R Software (R Foundation for Statistical Computing, Vienna, Austria). We found a significant association between all bleeding and noncardiovascular mortality across individual studies (8 trials; intercept value [IV]: -0.15; slope estimate [SE]: 0.61; $p = 0.01$) (**Figure 1**, top graph), while there was no evidence of a significant correlation of all bleeding with both cardiovascular (8 trials; IV: -0.46; SE: -0.17; $p = 0.69$) and all-cause mortality (10 trials; IV: -0.33; SE: 0.75; $p = 0.18$). On the other hand, no significant associations were found between ST and both cardiovascular (9 trials; IV: 0.75;

FIGURE 1 Association Between Log-Transformed Risk of All Bleeding and ST With Noncardiovascular and Cardiovascular Mortality, Respectively



The **size of each circle** represents the precision of each estimate (the inverse variance of the log relative risk in the trial), and the line is the best fit for the metaregression model.

SE: 0.71; p = 0.31) (**Figure 1**, bottom graph) and all-cause mortality (11 trials; IV: 0.52; SE: -0.86; p = 0.42).

The observed significant link between bleeding and noncardiovascular mortality is consistent with a pattern already noted in the DAPT trial, where bleeding-related, trauma-related, and cancer-related causes primarily contributed to the observed higher risk of all-cause mortality with prolonged DAPT (3). Conversely, we did not find the risk of ST across DAPT trials to be significantly associated with cardiovascular mortality. Indeed, it has been suggested that the association between ST and mortality depends on timing, with late ST less likely to present with fatal outcomes (4).

The observational nature of meta-regressions carries major unavoidable limitations, including the risk of incorrect conclusions caused by ecological fallacy (i.e., when inferences about individuals are made on the basis of aggregate statistics). To account for 2 other potential limitations of this regression approach: 1) effect size in the analysis is treated as a fixed regressor ignoring the degree of variance of the variable entered in the model; and 2) the unknown covariance among effect sizes determined by the presence of a within-study correlation among different reported outcomes—we also used a multivariate meta-analytic approach (5) to explore the consistency of our findings and confirmed a moderate-to-strong relationship between the log odds ratios for all bleeding and noncardiovascular mortality (rho coefficient = 0.52), whereas only a weak association was demonstrated between the log odds ratio for ST and cardiovascular mortality (rho coefficient = 0.24).

In conclusion, in drug-eluting stent trials of DAPT duration, bleeding seems to be significantly associated with noncardiovascular mortality, whereas ST does not seem to be significantly associated with cardiovascular mortality. Therefore, DAPT prolongation over current recommendations should only be undertaken after careful consideration of the benefit-risk balance.

*Davide Capodanno, MD, PhD
Giuseppe Gargiulo, MD
Sergio Buccheri, MD
Daniele Giacoppo, MD
Piera Capranzano, MD
Corrado Tamburino, MD, PhD
*Division of Cardiology
Ferrarotto Hospital
University of Catania, Italy
Citelli 1
Catania 95124
Italy
E-mail: dcapodanno@gmail.com

http://dx.doi.org/10.1016/j.jacc.2015.05.085

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Sanjay Kaul, MD, served as Guest Editor for this paper.

REFERENCES

1. Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2015;65:1298–310.

2. Palmerini T, Sangiorgi D, Valgimigli M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation. An individual patient data pairwise and network meta-analysis. J Am Coll Cardiol 2015;65:1092–102.

3. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

4. Secemsky EA, Matteau A, Yeh RW, et al. Comparison of short- and long-term cardiac mortality in early versus late stent thrombosis (from Pooled PROTECT Trials). Am J Cardiol 2015;115:1678–84.

5. Wei Y, Higgins JP. Estimating within-study covariances in multivariate meta-analysis with multiple outcomes. Stat Med 2013;32:1191–205.