



PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/88811>

Please be advised that this information was generated on 2017-12-06 and may be subject to change.

CORRESPONDENCE



Duration of Clopidogrel Therapy with Drug-Eluting Stents

TO THE EDITOR: In their article about the duration of dual antiplatelet therapy after implantation of drug-eluting stents, Park and colleagues (April 15 issue)¹ report that the use of extended dual antiplatelet therapy in patients who had received drug-eluting stents was not significantly more effective than aspirin monotherapy in reducing the rate of myocardial infarction or death from cardiac causes. Yet the rate of a composite of myocardial infarction, stroke, or death from any cause was nearly significantly higher in patients receiving extended dual antiplatelet therapy than in those receiving aspirin alone. These results are unpredictable and thus are difficult to interpret, although the authors commented that the results seem most likely to be due to chance. Stent length is a known predictor of stent thrombosis and thus myocardial infarction after treatment with a drug-eluting stent.² Did the trend toward the use of longer stents in patients receiving extended dual antiplatelet therapy as compared with patients receiving aspirin ($P=0.07$) affect the higher incidence of myocardial infarction, stroke, or death from any cause? Furthermore, several medications (cilostazol,³ metformin,⁴ pio-

glitazone,⁵ and angiotensin-receptor blockers) have been reported to decrease the incidence of death or myocardial infarction. Is it possible that differences in the use of these medications affect the results?

Hiroyuki Okura, M.D.

Kawasaki Medical School Hospital
Kurashiki, Japan
hokura@fides.dti.ne.jp

No potential conflict of interest relevant to this letter was reported.

1. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 2010;362:1374-82.
2. Moreno R, Fernández C, Hernández R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol* 2005;45:954-9.
3. Lee SW, Park SW, Yun SC, et al. Triple antiplatelet therapy reduces ischemic events after drug-eluting stent implantation: Drug-Eluting stenting followed by Cilostazol treatment REduces Adverse Serious cardiac Events (DECREASE registry). *Am Heart J* 2010;159(2):284.e1-291.e1.
4. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROACTIVE Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-89.
5. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

THIS WEEK'S LETTERS

- 488 Duration of Clopidogrel Therapy with Drug-Eluting Stents
- 491 Physician Cost Profiling
- 493 Outpatient Management of Severe COPD
- 495 What's Keeping Us So Busy in Primary Care?
- 496 PLA2R Autoantibodies and Recurrent Membranous Nephropathy after Transplantation

TO THE EDITOR: On reading the article by Park and colleagues comparing aspirin alone and dual therapy with clopidogrel and aspirin to decrease adverse events 12 months after cardiac stenting, we are surprised that, given the failure to show a benefit, the obvious trend toward harm with dual therapy was not analyzed further, since the outcome of myocardial infarction, stroke, or death from cardiac causes showed a trend toward a worse outcome with dual therapy. The inclusion of major bleeding events to this composite outcome

would have resulted in the difference between the two groups reaching significance ($P=0.03$).

This is not dissimilar to the findings for potent anticoagulants by Sharrock and colleagues,¹ who examined anticoagulation strategies to reduce mortality from any cause following joint arthroplasty. The use of potent anticoagulants not only failed to reduce the rate of thromboembolic events but increased the rate of death from any cause.

We conclude that newer anticoagulants must undergo more stringent evaluation as evidence emerges that they not only fail to achieve their primary purpose but also may increase the risk of complications.

Stavros G. Memtsoudis, M.D., Ph.D.

Nigel E. Sharrock, M.B., Ch.B.

Hospital for Special Surgery
New York, NY
memtsoudiss@hss.edu

No potential conflict of interest relevant to this letter was reported.

1. Sharrock NE, Gonzalez Della Valle A, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res* 2008;466:714-21.

TO THE EDITOR: Park and colleagues did not find a beneficial effect when dual antiplatelet therapy was continued beyond 12 months in patients with drug-eluting stents. Although they describe several limitations of their study, an important limitation is missing, especially if we consider that the participants were Korean. A recent study showed that up to 51% of the Korean population (as compared with 24.5% of whites) have specific alleles on CYP2C19 that are associated with poor metabolism of some drugs.¹ Indeed, several studies have shown increased resistance to clopidogrel and worse outcomes in patients with poor metabolism of clopidogrel prescribed for acute coronary syndromes² and after elective stent procedures.³

In the study described by Park and colleagues, no information is given on the distribution of the CYP2C19 polymorphism among the participants. Therefore, it is unclear whether the negative results are due to clopidogrel resistance in the studied population or to lack of efficacy beyond 12 months of treatment. We believe that genetic variation is an additional reason to be conservative with the extrapolation of these findings to other parts of the world.

Alexander J.M. Rennings, M.D.

Bas J.J.W. Schouwenberg, M.D.

Hein A.W. van Onzenoort, Pharm.D.

Radboud University Nijmegen Medical Center
Nijmegen, the Netherlands
a.rennings@pharmtox.umcn.nl

No potential conflict of interest relevant to this letter was reported.

1. Man M, Farmen M, Dumaul C, et al. Genetic variation in metabolizing enzyme and transporter genes: comprehensive assessment in 3 major East Asian subpopulations with comparison to Caucasians and Africans. *J Clin Pharmacol* 2010 February 19 (Epub ahead of print).

2. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009; 360:354-62.

3. Harmsze A, van Werkum JW, Bouman HJ, et al. Besides CYP2C19*2, the variant allele CYP2C9*3 is associated with higher on-clopidogrel platelet reactivity in patients on dual antiplatelet therapy undergoing elective coronary stent implantation. *Pharmacogenet Genomics* 2010;20:18-25.

TO THE EDITOR: The article by Park and colleagues is an important contribution to further defining the optimal antiplatelet therapy in patients receiving drug-eluting stents. Currently available data, on which present guidelines are based, were collected mostly in North America and Western Europe.¹ The article by Park and colleagues adds important information about a large Asian population.

Marked lifestyle differences and possible genetic heterogeneity translate into a relatively low prevalence and incidence of coronary artery disease in relation to cerebrovascular disease in Asia, as compared with Western countries.² This may be the reason why the study by Park and coworkers was not sufficiently powered with regard to the primary and secondary end points. Substantial evidence indicates that Asian patients tend to require lower doses of anticoagulation therapy — including warfarin,³ tissue plasminogen activators,⁴ and even antiplatelet treatment² — than do Western patients.

These differences show that guidelines developed in Western countries cannot easily be transferred globally. The reverse restriction also applies: the transfer of the conclusions drawn by Park and colleagues in Asian patients to non-Asian populations necessitates considerable caution.

Christoph Knosalla, M.D., Ph.D.

Michael Dandel, M.D., Ph.D.

Roland Hetzer, M.D., Ph.D.

Deutsches Herzzentrum Berlin
Berlin, Germany
knosalla@dhzb.de

No potential conflict of interest relevant to this letter was reported.

1. King SB III, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 Focused update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, writing on behalf of the 2005 Writing Committee. *Circulation* 2008;117:261-95.
2. Goto S, Toda E. Antiplatelet therapy after coronary intervention in Asia and Japan: the Asian perspective of antiplatelet intervention. *Hamostaseologie* 2009;29:321-5.
3. Cheng TO. Maintenance doses of warfarin in Chinese patients. *QJM* 1996;89:557.
4. Ross AM, Gao R, Coyne KS, et al. A randomized trial confirming the efficacy of reduced dose recombinant tissue plasminogen activator in a Chinese myocardial infarction population and demonstrating superiority to usual dose urokinase: the TUCC trial. *Am Heart J* 2001;142:244-7.

THE AUTHORS REPLY: Regarding the comments of Okura: Owing to lower-than-expected rates of outcomes, our study was underpowered to detect a clinically significant difference between the two groups. Although the confidence interval of the relative treatment effect was wide, the results rule out all but a modest benefit of continued dual antiplatelet therapy and raise the possibility that prolonged dual antiplatelet therapy would be harmful. Thus, we believe that our results could be clinically directive. Adjustment of significant covariates, including stent length, in a multivariable Cox regression model did not substantially alter the estimate of the relative risks of the outcomes. Furthermore, the use of other cardioactive medications at discharge and during follow-up was well balanced between the two groups; therefore, it might not affect the results.

Regarding the comments of Memtsoudis and Sharrock: In our study, the rates of the two composite outcomes (myocardial infarction or stroke or either death from any cause or death from cardiac causes) were not significantly greater with dual therapy than with aspirin monotherapy, but a trend prompting concern was noted. Due to low numbers of events and inherent limitations of secondary-outcomes analysis, these findings should be interpreted with caution, and it does not appear that the type of treatment adequately explains the observed difference in the rates of serious composite outcomes. So the related findings are due to chance, or — it could be specu-

lated in clinically stable patients representing a crude proxy for patients with reduced basal platelet activity — a provocative, harmful effect of long-term clopidogrel use might exist.¹

Regarding the comments of Rennings and colleagues: The considerable variation in responsiveness and resistance to clopidogrel suggests² that long-term clopidogrel use does not always ensure a consistent protective effect in recipients of drug-eluting stents. We also believe that markedly different gene variants among ethnic groups might affect the results of clopidogrel use worldwide.³ Therefore, further studies of individualized antiplatelet therapy that involve genotyping should be conducted, for purposes of optimal antiplatelet treatment.⁴

Regarding the comments of Knosalla and colleagues: We acknowledge that relatively lower rates of clinical outcomes in our study, as compared with rates in Western studies, might be partly due to differences in the populations of patients, lesion characteristics, interventional practices, or ethnic or genetic diversity,⁵ potentially limiting the reproducibility of our results in other settings. However, an unexpected and detrimental effect of long-term clopidogrel use was also seen in a low-risk group of Western subjects, and our findings should therefore be reconfirmed or refuted through large clinical trials conducted in other ethnic groups.

Seung-Jung Park, M.D.

Duk-Woo Park, M.D.

Asan Medical Center
Seoul, Korea
sjpark@amc.seoul.kr

Since publication of their article, the authors report no further potential conflict of interest.

1. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
2. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007;49:1505-16.
3. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009;302:849-57.
4. Damani SB, Topol EJ. The case for routine genotyping in dual-antiplatelet therapy. *J Am Coll Cardiol* 2010 May 5 (Epub ahead of print).
5. Park DW, Yun SC, Lee JY, et al. C-reactive protein and the risk of stent thrombosis and cardiovascular events after drug-eluting stent implantation. *Circulation* 2009;120:1987-95.