need of prolonged dual antiplatelet therapy with aspirin and clopidogrel. We agree that the subject is complex, but physicians should acknowledge that current guidelines are based on Level of Evidence: C (2,3). In our opinion, there is no evidence to suggest that dual antiplatelet therapy is necessary in patients who receive oral anticoagulation, which itself offers coronary protection (4). Our registry-based study and 1 randomized study support the use of clopidogrel in addition to vitamin K antagonist (without aspirin) in patients with atrial fibrillation who are discharged after myocardial infarction or percutaneous coronary intervention (5). Although most stents implanted in recent years are drug-eluting stents, we acknowledge the important limitation of our data that no information on stent type was available. However, there is no indication that stent type should affect the risk of bleeding. Dr. Aytürk and colleagues wisely highlight that it is a multifaceted challenge when prescribing numerous antithrombotic drugs, and we would like to add to the ongoing and important discussion that bleeding risk merits serious attention. A bleeding event, per se, is associated with increased mortality, blood transfusion is associated with poorer prognosis, and minor bleedings could result in discontinuation of life-saving antithrombotic therapies (6). This is emphasized by the use of bleeding as a primary endpoint in many contemporary trials of antiplatelet use following stent implantation.

Until more randomized trial data are available, careful assessment of bleeding risk and recognizing current (although sparse) evidence is crucial when individualizing antithrombotic therapy in patients with atrial fibrillation who experience an acute coronary event with or without stent implantation (7). Due to bleeding complications, interventionists should carefully consider the need for a drug-eluting stent compared with a bare-metal stent and carefully consider the indication for stent implantation.

*Morten Lamberts, MD, PhD
Gunnar H. Gislason, MD, PhD
Jonas Bjerring Olesen, MD, PhD
Søren Lund Kristensen, MD
Anne-Marie Schjerning Olsen, MD
Anders Mikkelsen, MB
Christine Benn Christensen, MD
Gregory Y. H. Lip, MD
Lars Køber, MD, DMSc
Christian Torp-Pedersen, MD, DMSc
Morten Lock Hansen, MD, PhD

*Department of Cardiology-Post 635
Copenhagen University Hospital Gentofte
Niels Andersens Vej 65
2900 Hellerup
Denmark
E-mail: mortenlamberts@gmail.com

http://dx.doi.org/10.1016/j.jacc.2013.11.049

REFERENCES

1. Lamberts M, Gislason GH, Olesen JB, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol 2013;62:981–9.

2. Huber K, Lip GY. Differences between ACC/AHA and ESC guidelines on antiplatelet therapy in patients with acute coronary syndromes. Thromb Haemost 2013;110:11–3.

3. Faxon DP, Eikelboom JW, Berger PB, et al. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. Thromb Haemost 2011;106:572–84.

4. Hurlen M, Abdelnoor M, Smith P, Eriksson J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969–74.

5. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381:1107–15.

6. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2011;32:1854–64.

7. Marin F, Huber K, Lip GYH. Antithrombotic therapy in atrial fibrillation and stent implantation: treatment or threats by the use of triple or dual antithrombotic therapy. Thromb Haemost 2013;110:623–5.

Baroreflex Sensitivity

A Reliable Predictor of Response to Renal Denervation?

We read the paper by Zuern et al. (1), demonstrating that cardiac baroreflex sensitivity (BRS) may predict the blood pressure (BP) response to renal denervation (RDN) in patients with treatment-resistant hypertension, with great interest. These findings appear to be of major clinical importance if indeed patient groups that may particularly benefit from RDN can be identified. However, there are several issues that will have to be addressed to fully understand the relevance of these findings.

It is surprising that the authors did not measure BRS function at some stage after RDN, which would have been important to understand whether or not RDN actually alters BRS as such and therefore provide information on relevant mechanisms potentially underlying improved BP control after successful RDN. Furthermore, given that half of the patients from this study cohort were classified as

"responders," defined as a reduction in ambulatory systolic blood pressure (SBP) of >10 mm Hg, it appears crucial to ascertain whether the BP reduction following RDN parallels BRS improvement in these patients. This is even more important in view of recent findings demonstrating that baroreflex function consistently improves after RDN in hypertensive rats and humans, even if BP is not improved (2). In this context, it is noteworthy that similar to previous studies (3,4), baseline BP also emerged as an important determinant of the BP response to RDN in this analysis.

The methodology applied by the authors may raise some concern. In contrast to the commonly used application of the sequence method for the assessment of BRS described by Parati et al. (5), spontaneous sequence of BRS in this study was estimated only during the progressive increase of SBP over 3 or more consecutive beats in which RR intervals are simultaneously prolonged, but not when SBP progressively falls and cardiac intervals are progressively shortened. Additionally, assessment of baroreflex control of heart rate is to a large extent driven by vagal influences, not necessarily by the sympathetic nervous system, although the opposite is frequently quoted in the literature (6). Nevertheless, our own findings from more than 100 patients with resistant hypertension indicate that these patients are typically characterized by very high levels of muscle sympathetic nerve activity, with RDN resulting in sympathetic inhibition in most. In this context, it will be important to assess whether spontaneous arterial baroreflex control of muscle sympathetic nerve activity may be an even better predictor of the BP response to RDN. It should also be noted that, although established hypertension is associated with impaired baroreflex function, the role of baroreflex control in long-term regulation of BP is more disputable and has not yet been fully elucidated.

Dagmara Hering, MD, PhD
Murray D. Esler, MBBS, PhD
***Markus P. Schlaich, MD**

*Baker IDI Heart and Diabetes Institute
Neurovascular Hypertension &
Kidney Disease Laboratory
75 Commercial Road
Melbourne, Victoria 8008
Australia
E-mail: Markus.Schlaich@bakeridi.edu.au

http://dx.doi.org/10.1016/j.jacc.2013.10.088

Please note: Drs. Schlaich and Esler are supported by career fellowships from the NHMRC, and are investigators in studies sponsored by Medtronic. The laboratories of Drs. Schlaich and Esler currently receive research funding from Medtronic, Abbott Pharmaceuticals, Servier Australia, and Allergan. Prof. Esler serves on scientific advisory boards of Abbott (formerly Solvay) Pharmaceuticals and Medtronic. Professor Schlaich serves on scientific advisory boards for Abbott (formerly Solvay) Pharmaceuticals, Boehringer-Ingelheim, Novartis Pharmaceuticals, and Medtronic; and has received honoraria and travel support from Abbott, Boehringer-Ingelheim, Servier, Novartis, and Medtronic. Dr. Hering is a clinical research fellow from Medical Univeristy of Gdansk, Poland, and was awarded a research fellowship from Polish Foundation for Science (KOLUMB 2010-1).

REFERENCES

1. Zuern CS, Eick C, Rizas KD, et al. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. J Am Coll Cardiol 2013;62:2124–30.

2. Hart EC, McBryde FD, Burchell AE, et al. Translational examination of changes in baroreflex function after renal denervation in hypertensive rats and humans. Hypertension 2013;62:533–41.

3. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 2011;57:911–7.

4. Esler MD, Krum H, Schlaich M, Schmieder RE, Bohm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation 2012;126:2976–82.

5. Parati G, Frattola A, Di Rienzo M, Castiglioni P, Pedotti A, Mancia G. Effects of aging on 24-h dynamic baroreceptor control of heart rate in ambulant subjects. Am J Physiol 1995;268:H1606–12.

6. Esler M, Lambert E. Reduced HRV and baroreflex sensitivity as universally applicable cardiovascular "risk factors": waiting for the bubble to burst. Clin Auton Res 2003;13:170–2.

REPLY: Baroreflex Sensitivity: A Reliable Predictor of Response to Renal Denervation?

We appreciate the interest in our paper (1) and the opportunity to reply to the thoughtful comments by Dr. Hering and colleagues.

We agree that testing the effect of renal sympathetic denervation (RDN) on cardiac baroreflex sensitivity (BRS) would provide important insights into the mechanistic basis of RDN. However, this was not the objective of our study (1). The primary goal of our clinical study was to prospectively identify patients with resistant hypertension who would eventually benefit from RDN. We showed in 50 hypertensive patients that impaired cardiac BRS was a strong and independent predictor of blood pressure (BP) reduction after RDN.

Dr. Hering and colleagues speculated that RDN should lead to BRS improvement only in patients who benefit from RDN in terms of BP reduction. Their interesting hypothesis was on the basis of physiological considerations as well as on a recent study in 7 hypertensive rats and 8 hypertensive human patients, which investigated the effects of RDN on BP, muscle sympathetic nerve activity (MSNA), and BRS (2). In that study, rats consistently showed significant reductions of BP and MSNA as well as improvements of BRS, whereas in humans, no significant effects