EuroIntervention

Bleeding after coronary stenting in patients on oral anticoagulation: who is guilty?

Andrea Rubboli[1]*, MD, FESC; Axel Schlitt[2], MD; K.E. Juhani Airaksinen[3], MD, FESC; Gregory Y.H. Lip[4], MD, FESC, FACC

1. Division of Cardiology & Cardiac Catheterization Laboratory, Maggiore Hospital, Bologna, Italy; 2. Department of Medicine III, Martin Luther University, Halle, Germany; 3. Department of Medicine, Turku University Hospital, Turku, Finland; 4. University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom

The authors have no conflict of interest to declare.

Dear Editor,

The interesting paper by Hälg et al[1] adds further data to the complex issues related to the optimal management of patients requiring oral anticoagulation (OAC) who undergo coronary artery stent implantation. The available evidence to guide management is limited as well as of poor quality, and current recommendations are essentially derived from experts' consensus[2-4]. In summary, the triple therapy of OAC, aspirin and clopidogrel is recommended as the most effective antithrombotic combination for the prevention of both thromboembolism and stent thrombosis, although a relevant incidence of major bleeding, which increases as treatment prolongs, is to be expected during the follow-up period[2,3]. Also, the implantation of drug eluting stents should be avoided, because of the prolonged need for clopidogrel (and therefore triple therapy) with such stents[2,3].

The data presented by Hälg et al are consistent with this. Nonetheless, triple therapy of OAC, aspirin and clopidogrel cannot be completely guilty of the significantly higher incidence of late bleeding. Only four out of the eight OAC patients experiencing late bleeding were on triple therapy at the time of the event, whereas the remaining four were receiving the combination of OAC and aspirin. On univariate and multivariate analysis, it is the OAC treatment in itself, rather than its association with either one or two antiplatelet agents, which was predictive of late haemorrhagic complications. Apart from exposing patients to wide fluctuation, including overshoots, of the intensity of anticoagulation (as shown by INR values widely above the therapeutic range in two of the four patients on triple therapy and in one of the four patients on the combination of OAC and aspirin who experienced a late bleeding event), an indication for OAC may just identify a subgroup of more fragile patients being at higher risk of both thromboembolic and haemorrhagic complications. Indeed, both thromboembolism and bleeding appear to share many risk factors in common[5].

While having confirmed that early (i.e., in-hospital) bleeding is relevant and related more to procedural variables, such as vascular approach and glycoprotein IIb/IIIa administration, rather than to concurrent OAC treatment, Hälg et al still fail to answer the question whether or not prolonged triple therapy is indeed associated with an increase in major bleeding, and whether or not drug eluting stents should ever be used in this patient subset.

Large prospective studies, where treatment durations and ongoing antithrombotic therapies at the time of either bleeding or thromboembolic complications are recorded, need to be carried out. The Atrial Fibrillation and Coronary Artery Stenting (AFCAS) Registry, which is currently ongoing in several European countries, where 1,000 patients with atrial fibrillation undergoing coronary stent implantation will be prospectively enrolled, may help in answering, among several others, these important questions.

References

1. Hälg C, Brunner-La Rocca HP, Kaiser C, Jeger R, Osswald S, Pfisterer M, Hoffmann A, for the BASKET investigators. Early and late increased bleeding rates after angioplasty and stenting due to combined antiplatelet and anticoagulant therapy. *EuroIntervention* 2009;5:425-31.

* *Corresponding author: Division of Cardiology & Cardiac Catheterization Laboratory, Maggiore Hospital, Largo Nigrisoli 2, 40133 Bologna, Italy*
E-mail: andrearubboli@libero.it

2. Rubboli A, Halperin JL, Airaksinen KE, Buerke M, Eeckhout E, Freedman SB, Gershlick AH, Schlitt A, Tse HF, Verheugt FW, Lip GY. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. *Ann Med* 2008;40:428-436.

3. Holmes DR Jr, Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. *J Am Coll Cardiol* 2009;54:95-109.

4. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen KJ, Cuisset T, Kirchhof P, Marín F. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting. A Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Thromb Haemost* 2009;in press.

5. Iijima R, Ndrepepa G, Mehilli J, Byrne RA, Schulz S, Neumann FJ, Richardt G, Berger PB, Schömig A, Kastrati A. Profile of bleeding and ischaemic complications with bivalirudin and unfractionated heparin after percutaneous coronary intervention. *Eur Heart J* 2009;30:290-6.

Triple therapy: the future or from the past?

Willem Dewilde[1]*, MD; Nicolien Breet[2], MD; Jurriën Ten Berg[2], MD, PhD, FACC

1. Catharina Hospital, Eindhoven,The Netherlands; 2. Sint Antonius Hospital, Nieuwegein, The Netherlands

The authors have no conflict of interest to declare.

We read the article by Hälg et al[1] with great interest. We learned that patients on triple antithrombotic therapy have an elevated bleeding risk after stent implantation. Hälg et al state that the potential risk of embolic complications must be carefully balanced against the risk of major bleeding in this patient population. Unfortunately, Hälg et al only describe the elevated bleeding risk in their patient population on triple therapy.

We are also interested in whether the use of triple therapy has any influence on thromboembolic risk in the BASKET patient population. We would also like to know the rates of stent thrombosis, reinfarction, stroke and target vessel revascularisation. We believe that these rates could provide us very useful information. We agree that prospective clinical trials are needed in order to evaluate the best treatment strategy for patients on oral anticoagulant therapy (OAC) who undergo percutaneous coronary interventions (PCI). Unfortunately, all present recommendations are not based on randomised trials, but on expert opinion. In patients with the indication for chronic oral anticoagulation who need to undergo PCI, there are many possibilities, but the combinations of OAC + aspirin and aspirin + clopidogrel are unsafe because of elevated risk of stent thrombosis and stroke respectively[2]. Triple therapy, which is currently recommended, is known to elevate bleeding risk.

A last possibility is the combination of clopidogrel and OAC, which seems to be promising[2]. Therefore, a first randomised international multicentre open label trial was started on December 1, 2008 to assess the hypothesis that after PCI with stent implantation in patients on oral anticoagulant therapy, the combination of oral anticoagulation therapy & clopidogrel 75 mg/day is superior to triple therapy treatment because of the reduced risk of bleeding[3]. The primary outcome is the combination of TIMI and GUSTO minor and major bleeding up to 30 days and one year. The secondary outcomes are major adverse cardiac events (myocardial infarction, stent thrombosis, target vessel revascularisation, stroke). The sample size is 496. Because, to date, no randomised study has yet addressed this issue, the WOEST (What is the Optimal antiplatElet & anticoagulant therapy in patients with oral anticoagulation and coronary StenTing; clinical trials.gov:NCT00769938) trial will help to define new guidelines for patients with indication for long-term anticoagulation who need coronary stenting.

References

1. Hälg C, Brunner-La Rocca HP, Kaiser C, Jeger R, Osswald S, Pfisterer M, Hoffmann A; BASKET investigators. Early and late increased bleeding rates after angioplasty and stenting due to combined antiplatelet and anticoagulant therapy. *EuroIntervention*. 2009;5:425-31.

2. Rubboli A, Halperin JL, Airaksinen KE, Buerke M, Eeckhout E, Freedman SB, Gershlick AH, Schlitt A, Tse HF, Verheugt FW, Lip GY. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. *Ann Med*. 2008;40:428-36.

3. Dewilde W., Ten Berg JM, Trial design: WOEST Trial: What is the Optimal antiplatElet & anticoagulant therapy in patients with oral anticoagulation and coronary StenTing: *Am Heart J*. 2009;158:713-8.

** Corresponding author: Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands*
E-mail: willemdewilde@yahoo.com

Reply

Andreas Hoffmann[1], MD, FESC; Hans-Peter Brunner-La Rocca[2], MD, FESC

1. University Hospital, Basel, Switzerland; 2. Maastricht University Medical Centre, Maastricht, The Netherlands

The authors have no conflict of interest to declare.

Drs Dewilde et al enquire about some additional endpoints in the group on oral anticoagulants in comparison to those without. They are summarised in the following table. Despite some trends in increased mortality, there were no significant differences found.

Endpoint at 36 months follow-up	APT, no OAC (N=769)	APT+OAC (N=44)	p-value
Stroke	8 (1%)	1 (2%)	0.40
MACE	167 (22%)	11 (25%)	0.58
TVR	121 (16%)	8 (18%)	0.67
Stent thrombosis*	41 (5%)	3 (6%)	0.76
Myocardial infarction	64 (8%)	2 (5%)	0.57
Cardiac death	29 (4%)	4 (9%)	0.10

MACE: major adverse cardiac events as defined in (1); TVR: target vessel revascularisation; APT: antiplatelet therapy; OAC: oral anticoagulation.
* definite or probable.

We agree that a dual combination of oral anticoagulation and clopidogrel might be an alternative to triple therapy, a hypothesis to be tested. Thus, we are looking forward to results of the WOEST study[2].

Drs. Rubboli et al are correct in their remark concerning our paper when they point out that oral anticoagulation may merely be a marker of a higher bleeding risk, rather than the actual cause. Our data, in a strict sense, indeed show that the combination of oral anticoagulants with either single or dual antiplatelet therapy are associated with an increased late bleeding rate.

While the BASKET study was not intended to address the issue of bleeding, it offered a unique opportunity to study this important question in an unselected cohort of all-comers with a complete long-term follow-up. By using multivariate analysis, we tried to eliminate confounding factors as much as possible. Although some confounders may be unknown, the strong independent association of anticoagulants with late bleeding suggests an independent contribution. This is also in agreement with most studies on antithrombotic therapy, independent of underlying disease and agents used, showing that the stronger the antithrombotic therapy, the higher the bleeding risk[3].

The risk in our study might have been even greater if all patients had remained on triple therapy throughout the entire follow-up period. We agree that post hoc analyses as our own, and even prospective registries, do not provide a final conclusion on the bleeding risk of triple antithrombotic therapy. A randomised controlled trial would be needed, but it is unlikely that such a trial will be done. Thus, data such as ours help to assess the risks involved with interventions and associated drug therapies.

The conclusions drawn in our paper are valid and in agreement with current guidelines[4]. They are not altered by the reflections made by Rubboli et al. Accordingly, indications for oral anticoagulation should be critically reviewed in patients undergoing PCI and stent therapy. Patients with strong indications for oral anticoagulants (which may be questioned in many cases of atrial fibrillation with intermediate risk[5]) should preferably not be treated with drug eluting stents as the lower rate of restenosis may be outweighed by a higher rate of bleeding –and even mortality– due to anticoagulant and prolonged aggressive antiplatelet therapy. It seems wise to reduce potentially harmful therapies to a minimum.

References

1. Brunner-LaRocca H, Kaiser C, Pfisterer M. Targeted stent use in clinical practice based on evidence from the BAsel Stent Cost Effectiveness Trial (BASKET). *Eur Heart J* 2007;28:719-716.

2. Dewilde W., Ten Berg JM, Trial design: WOEST Trial: What is the Optimal antiplatElet & anticoagulant therapy in patients with oral anticoagulation and coronary StenTing: *Am Heart J*. 2009;158:713-718.

3. Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians.. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:257S-298S.

4. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M; ESC Committee for Practice Guidelines (CPG), Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Silber S, Aguirre FV, Al-Attar N, Alegria E, Andreotti F, Benzer W, Breithardt O, Danchin N, Di Mario C, Dudek D, Gulba D, Halvorsen S, Kaufmann P, Kornowski R, Lip GY, Rutten F. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2008;29:2909-2945.

5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864-2870.

** Corresponding author: Department of Cardiology, University Hospital, Lange Gasse 78, Basel, Switzerland, CH 4052, Basel, Switzerland*
E-mail: andreas.hoffmann@unibas.ch