

## Changing the scope of preventative and therapeutic approaches in atherothrombosis

Karlheinz Peter<sup>1</sup>; Gregory Y. H. Lip<sup>2</sup>

<sup>1</sup>Baker Heart Research Institute, Centre for Thrombosis & Myocardial Infarction, Melbourne, Victoria, Australia; <sup>2</sup>Haemostasis, Thrombosis & Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

Major recent advances in the development of preventative and therapeutic approaches in atherothrombotic disease has prompted this Theme Issue of *Thrombosis and Haemostasis*. We are currently witnessing a fascinating introduction of novel antithrombotic agents into clinical practice, which will probably result in the disappearance of some drugs, which generations of physicians and patients have learned to live with, including all their advantages and disadvantages.

Indeed, warfarin has been synonymous with oral anticoagulation as is heparin for intravenous anticoagulation. Hopefully, both may soon be replaced by new agents – broadly the oral direct thrombin inhibitors or oral factor Xa inhibitors – that provide major benefits for patients. Also anti-platelet therapy will change with the availability of a plethora of different agents already approved or currently in clinical trials or in development, including prasugrel or ticagrelor. Finally, the therapeutic potential of stem cell therapy (see upcoming Theme Issue by Guest Editor H. F. Tse) for the clinical consequences of atherothrombosis, myocardial infarction, has attracted major interest but also major controversy.

Freudenberger et al. start off this Theme Issue with a systematic assessment of the clinical data available for anticoagulation therapy in patients with heart failure (1). The latter is commonly seen in clinical

practice, and many complications associated with heart failure can be thrombosis-related.

Oral anticoagulation with warfarin or other vitamin K antagonists are associated with a high rate of bleeding complications as well as therapeutic failures. For decades, these shortcomings have initiated major drug development programs in the pharmaceutical industry. However, only recently advances in the understanding of serine protease biology and sophisticated drug development tools have resulted in long sought-after successful drug development programs. Of the drugs in development, the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban are amongst those most advanced. In this issue, Ufer et al. provide a thorough comparison of these agents (2).

One of the most fascinating drug developments in the field of anticoagulation is the generation of nucleic acid aptamers as described in a detailed review by Becker et al. (3). Specific three-dimensional structures of small RNA or DNA single-stranded molecules allow the blockade of enzyme function. Using a powerful screening technology, nucleic acid combinatorial libraries are incubated with the coagulation protease to be targeted. High-affinity blockers are then amplified by repeated screening rounds. The first aptamer developed for humans targets factor IXa and indeed this aptamer has successfully passed a phase 1 trial and overall looks promising. One of the biggest advantages of the aptamer technology is the technology-inherent availability of an antidote, which is composed of the antisense strand of the respective DNA or RNA sequence. In this, the aptamer technology is clearly superior to other drug developments in the field of anticoagulation or anti-platelet therapy where an antidote is typically not available.

Personalised pharmacotherapy has long been discussed but rarely performed in

clinical practice. Indeed, ADP P<sub>2</sub>Y<sub>12</sub> receptor blockade seems to be an example where patients might benefit from personalised medicine. In this Theme Issue, Zürn et al. describe how genetic factors (various cytochrome P450 isoforms), co-medication with statins or proton pump inhibitors can interfere with the efficacy of ADP receptor blockers, in particular clopidogrel (4). The authors discuss the laboratory methods available to assess the individual clopidogrel response and how this response may indeed determine clinical outcome such as stent thrombosis. Gurbel et al. (5) elegantly discuss how reversible P<sub>2</sub>Y<sub>12</sub> receptor blockade versus irreversible ADP receptor blockade may be associated with a wider therapeutic window, providing strong anti-platelet effects with less bleeding complications. The availability of a whole set of P<sub>2</sub>Y<sub>12</sub> receptor blockers with oral versus intravenous administration, reversible versus irreversible binding and blocking mechanisms, and more or less drug-specific response variation will allow a personalised platelet inhibition that will hopefully provide maximal benefit to each individual patient in each individual clinical setting.

Personalised medicine may also benefit patients on aspirin treatment, where rates of aspirin non-responders of up to 30–40% have even been reported. It remains to be determined, which method of platelet activity tests are best to be used and also whether an increase in doses may overcome so-called “aspirin resistance”. Brambilla et al. address this clinical dilemma and show that an increase in aspirin dose in patients after coronary bypass surgery is clearly beneficial (6). This effect is not seen in all of the platelet activity assays used, including the classical light transmission aggregometry.

The current theme issue also includes a report of an interesting alternative anti-coagulative approach. Henry et al. describe low-molecular-weight lignins, which

### Correspondence to:

Prof. Karlheinz Peter  
Baker Heart Research Institute  
Centre for Thrombosis & Myocardial Infarction  
PO Box 6492, St Kilda Road  
Melbourne, 8008 Victoria, Australia  
Fax: +61 3 8532 1160  
E-mail: Karlheinz.Peter@bakeridi.edu.au

Received: January 26, 2010

Accepted: January 26, 2010

Prepublished online: February 2, 2010

doi:10.1160/TH10-01-0063

Thromb Haemost 2010; 103: 487–488

Thrombosis and Haemostasis 103.3/2010

mimic the biological activities of heparin and heparan sulfate in their inhibition of thrombin, factor Xa and plasmin (7).

Finally, if preventative and therapeutic measures fail and patients suffer loss of myocardial cells in atherothrombotic events, regenerative cell therapy represents a promising therapeutic approach. Although the initial enthusiasm is clearly dampened, clinical trials have shown a modest, but significant improvement in left ventricular ejection fraction and clinical status of patients after cell transplantation. Nevertheless, the initial premise of stem cell homing, engraftment and integration into the host myocardium remain vexing issues. Also the optimal time point after myocardial infarction and the best mode of application have yet to be determined. In the current Theme Issue, Charwat et al. describe a typical study addressing the question of delivery of stem cells (8). Whilst attracting major research interest and increasing publications, regenerative cell therapy still needs more research to be ready for routine application, in contrast to the pharmacological innovations addressed above.

This selection of articles above represents a flavour of the breath of coverage in this Theme Issue. Clearly, this builds and extends on the many themes recently pub-

lished in *Thrombosis and Haemostasis* on thrombosis-related topics in cardiovascular diseases. For example, we have highlighted the controversies around prasugrel (9, 10) and how this agent weighs up against ticagrelor (11). Sharing the enthusiasm with the new oral anticoagulants, we have highlighted new developments with dabigatran (12) and rivaroxaban (13), as well as new oral antiplatelet agents (14). The list is endless, and we are likely to see even more over the next few years, which would be very exciting.

## References

1. Freudenberger RS, Schumaecker MM, Homma S. What is the appropriate approach to prevention of thromboembolism in heart failure? *Thromb Haemost* 2010; 103: 489-495.
2. Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. *Thromb Haemost* 2010; 103: 572-585.
3. Becker RC, Povsic T, Cohen MG, et al. Nucleic acid aptamers as antithrombotic agents opportunities in extracellular therapeutics. *Thromb Haemost* 2010; 103: 586-595.
4. Zürn C, Geisler T, Gawaz M. ADP-receptor blockade A case for personalised pharmacotherapy? *Thromb Haemost* 2010; 103: 496-506.
5. Becker RC, Gurbel PA. Platelet P2Y12 receptor antagonist pharmacokinetics and pharmacodynamics: A foundation for distinguishing mechanisms of bleeding and anticipated risk for platelet-directed therapies. *Thromb Haemost* 2010; 103: 535-544.
6. Brambilla M, Parolari A, Camera M, et al. Effect of two doses of aspirin on thromboxane biosynthesis and platelet function in patients undergoing coronary surgery. *Thromb Haemost* 2010; 103: 516-524.
7. Henry B, Abdel Aziz M, Qibing Z, et al. Sulfated, low molecular weight lignins are potent inhibitors of plasmin in addition to thrombin and factor XA: Novel opportunity for controlling complex pathologies. *Thromb Haemost* 2010; 103: 507-515.
8. Charwat C, Lang I, Dettke M, et al. Effect of intramyocardial delivery of autologous bone marrow mononuclear stem cells on the regional myocardial perfusion: NOGA-guided subanalysis of the MYSTAR prospective randomised study. *Thromb Haemost* 2010; 103: 564-571.
9. Serebruany V, Shalito I, Kopyleva O. Prasugrel development – claims and achievements. *Thromb Haemost* 2009; 101: 14-22.
10. Calatzis A. Another view on prasugrel. *Thromb Haemost* 2009; 101: 12-13.
11. Serebruany VL. The TRITON versus PLATO trials: Differences beyond platelet inhibition. *Thromb Haemost* 2010; 103: 259-261.
12. Wolowacz SE, Roskell NS, Plumb JM, et al. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost* 2009; 101: 77-85.
13. Mueck W, Borris LC, Dahl OE, et al. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Haemost* 2008; 100: 453-461.
14. Gachet C. P2 receptors, platelet function and pharmacological implications. *Thromb Haemost* 2008; 99: 466-472.