Hsp70 preventing thrombosis: benefit without burden?

Daniel Duerschmied and Christoph Bode*

Department of Cardiology and Angiology I, Heart Center, University of Freiburg, Freiburg, Germany

Online publish-ahead-of-print 20 April 2016

This editorial refers to ‘Hsp70 protects from stroke in atrial fibrillation patients by preventing thrombosis without increased bleeding risk’ by M. Allende et al., pp. 309–318.

Thromboembolism is a major killer worldwide and is also involved in debilitating chronic ischaemic disease of heart and brain. Most cases of myocardial infarction, stroke, and pulmonary embolism are caused by a thrombus that contains fibrin and activated platelets. Antithrombotic therapy targets both the coagulation process of fibrin formation and platelet activation. However, any antithrombotic agent that effectively prevents thrombus formation increases the risk for bleeding, because both coagulation and platelets are required for haemostasis. Clinicians generally accept this paradigm as an unavoidable trade-off. Many researchers however refuse to accept this and have tried to develop antithrombotics without impact on bleeding—unfortunately futile in most cases.

Cardiovascular and haematological scientists in collaboration with genomics and small molecule discovery experts from the Universities of Navarra and Murcia in Spain have now chosen an appealing approach in the quest for an antithrombotic without side effects: Allende et al. compared patients at risk for thromboembolism—patients with permanent atrial fibrillation—who had suffered from a thrombo-embolic event to patients at comparable risk who had not suffered from stroke. Both groups were treated with a vitamin K antagonist (VKA). A microarray gene analysis yielded one particularly interesting gene that was down-regulated in stroke patients: HSPA1B, which encodes for heat shock protein 70 kDa (Hsp70). This finding in itself is surprising, because Hsp70 has not been on the list of most thrombosis researchers.

This finding was derived from a small discovery cohort (n = 8 in each group) and had to be confirmed in a larger cohort with 200 patients. The result was even more surprising this time, especially concerning its magnitude: compared with the quartile with lowest Hsp70 expression, relative stroke risk was reduced by almost 80% in the quartile with highest Hsp70 expression. The authors hence speculated that Hsp70 induction may prevent embolic stroke.

This hypothesis was tested in animal models, first using HSPA1A/B knock-out mice that do not express Hsp70. These mice were prone to thromboembolism—but tail bleeding and coagulation tests were unchanged. The next logical—and clinically relevant—step was to treat wild-type mice with Hsp70 inducers. Two Hsp70 inducers were tested, and both prevented thromboembolism without affecting tail bleeding. Permit us to direct the reader’s attention directly to Figure 4G of the paper, which shows the results of a clinically relevant experiment: The Hsp70 inducer also left aspirin-boosted tail bleeding unchanged. This experimental design is elegant, because it confirms previous findings from several preclinical and clinical studies and puts the effect of a novel agent into an important context. Especially antithrombotic combination therapy (anticoagulant + platelet inhibitors) increases the risk for bleeding and novel approaches are needed.

The reader should consider several limitations of the study by Allende et al. Both discovery and validation cohorts were relatively small. Bleeding tendency was only tested in vitro and in one general bleeding assay (tail bleeding), although this precludes general conclusions. One important finding of the large Phase III trials and current registry data of direct oral anticoagulants (DOACs) was that not all bleeding complications are equally relevant. While devastating intracranial haemorrhage was consistently reduced by DOACs compared with VKA, non-life-threatening Gastrointestinal bleeding was increased.

In the present study, no true murine stroke model was used. Most importantly, mechanistic data are far from comprehensive. The only mechanistic explanation provided by the authors is that Hsp70 induction increased thrombomodulin and activated protein C.

The above considerations do not devaluate the present study but should stimulate further research. The interesting effects of Hsp70 induction need to be reproduced. The mechanism needs to be deciphered. At this stage, it is not even clear which cell type increases Hsp70 production (endothelial cells and a general leucocyte population were tested). If these questions can be answered and if the hypotheses brought forward by Allende et al. can be translated into clinical meaning, Hsp70 may become a clinically very important link between thrombosis and immunity. Other preclinical studies have indicated that the paradigm that links bleeding and antithrombotic efficacy may be broken, and Hsp70 induction is a promising strategy.

References


---

**Corrigendum**

doi:10.1093/cvr/cvw063

**Corrigendum to:** A glimpse of Cre-mediated controversies in epicardial signalling [Cardiovasc Res 2013; 100 (3): 347–349]

The authors wish to acknowledge the following funding information which was omitted from the above article:
This work was supported by the National Institutes of Health, The National Institute of Arthritis and Musculoskeletal and Skin Diseases” [A.F. R01 AR061392]; the National Institutes of Health, The National Heart, Lung, and Blood Institute” [A.F. R01 HL120920]; and the National Institutes of Health, The National Heart, Lung, and Blood Institute” [W. S. R01 HL81092].

The authors apologize for this omission.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2016. For permissions please email: journals.permissions@oup.com.