Direct thrombin inhibitors in patients with mechanical heart valves: Ready for clinical trials?

Hans-Jürgen Rupprecht
II. Medizinische Klinik, GPR Klinikum Rüsselsheim, Rüsselsheim, Germany

Unfractionated heparin (UFH) as continuous infusion or the subcutaneous administration of low-molecular-weight heparin (LMWH) is considered to be the gold-standard for "bridging" of oral anticoagulation in patients at high risk for thromboembolic events such as those with mechanical heart valves. Due to their potential to cause heparin-induced thrombocytopenia (HIT) heparins may not be utilised universally and alternative anticoagulation strategies are needed.

Clinical data on non-heparin anticoagulants in such a scenario is scarce and limited to a few case reports. There is no randomised trial, not even observational data on the use of newer non-heparin anticoagulants in a significant number of patients with mechanical heart valves. In a small series of five patients with temporary total artificial heart bivalirudin has been used over a mean of 15 days without overt thrombosis or major bleeding complications (1). In other clinical settings like percutaneous coronary intervention (PCI) or bypass-surgery, replacement of heparins with direct thrombin-inhibitors (DTI) due to HIT revealed promising results (2–5), but these data cannot simply be translated to the high-risk situation of patients with mechanical heart valves. Therefore, the problem of bridging oral anticoagulants in high-risk patients with contraindication for heparins is still a matter of debate.

In this issue of *Thrombosis and Haemostasis* Maegdefessel et al. (6) may shed a first glimpse on the potential role of newer anticoagulants, especially DTI, in the setting of artificial heart valves. They compared thrombus formation on mechanical valves using an in-vitro flow model and blood from healthy volunteers. The latter was anticoagulated by either UFH given as a bolus only, or the DTI argatroban or bivalirudin (each bolus only or bolus + infusion). After a total exposure time of 60 minutes (min) in their thrombosis tester the amount of thrombus on the mechanical valve was weighed in the respective treatment groups and electron microscopy was performed. Argatroban and bivalirudin, when given as bolus + continuous infusion, were equally effective as UFH-bolus in the prevention of thrombus formation on mechanical heart valves. This was also reflected by sufficient and comparable ACT- and aPTT-levels in the three groups at the start of their experiment. The bolus-only strategy with the DTI was not sufficient to inhibit clot-formation to the same degree as with the heparin-bolus. Accordingly lower ACT- and aPTT-values in the DTI bolus groups were measured during the later stage of the experiment. In addition, a qualitative comparison of electron microscopic analyses revealed no obvious difference between the heparin-bolus and the DTI-(bolus+infusion) groups, only inadequate inhibition of thrombus formation with a DTI-bolus.

The lack of efficacy in the DTI-bolus groups may at least be partly explained by the reversible nature of thrombin binding. Both substances are selective, direct and reversible thrombin inhibitors with plasma half-lives in vivo of 25 min for bivalirudin and 45 min for argatroban. Thrombin may regain activity also in the in vitro setting once DTI are detached from thrombin. Bivalirudin in addition is eliminated predominantly by other proteases, presumably contributing to the loss of its inhibitory effect also in vitro. Moreover, a portion of the substance might have been attached to the in-vitro test system, thus lowering the effect, when given as a bolus only, although the authors did not find visible thrombus formation after the experiment on their test system (7).

The data confirm what is already clinical practice in approved indications of both drugs. Argatroban as well as bivalirudin have to be given continuously in the clinical setting anyway and despite the somewhat longer half-life UFH has to be administered as continuous infusion in vivo as well.

However, a word of caution is appropriate: There are data from in-vitro tests, not including mechanical valves, where DTI were not equally effective in the inhibition of thrombus formation as compared to UFH despite similar clotting test results (8, 9). The potential of UFH to inhibit both factor Xa and thrombin may be of relevance especially in the setting of artificial surfaces like mechanical heart valves. Therefore, equivalence between UFH and DTI has not consistently been demonstrated in vitro. Moreover, in-vitro results may not necessarily be translated into equivalent clinical situations.

Preceding a transition into clinical practice with timing and dosing requirements, the balance between efficacy of inhibition...
and bleeding risk has to be considered. Drug selection should be based on pharmacokinetics and -dynamics as well as patient-related factors, the availability/approval-status and the physician’s experience. While bivalirudin is eliminated predominantly by proteolysis (80%) and in part by renal excretion (20%), argatroban is hepatically metabolised, with corresponding restrictions of use in patients with renal failure (bivalirudin) and in patients with liver disease in the latter substance (argatroban). Argatroban substantially increases the international normalised ratio, which may be problematic in the transition phase from argatroban to coumadines. Registries and finally prospective randomised trials are needed to further clarify the role of such DTI in the clinical arena.

It is the merit of Maegdefessel et al. to provide solid in-vitro data, indicating equivalent efficacy of DTI as compared to UFH in the high risk surrounding of artificial heart valves. This may open an avenue for further clinical evaluation of alternative anticoagulant regimens in patients who need bridging anticoagulation and in whom heparin use is restricted.

Conflict of interest
The author gives lectures and/or is a member of the advisory boards of GSK, CVT, Berlin-Chemie, Sanofi-Aventis, BMS, Lilly and is married to an employee of THE MEDICINES COMPANY.

References