Personalized antithrombotic treatment in high-risk patients with coronary artery disease

Impact paragraph

In this thesis, we explored a number of scientific questions related to clinical problems that are encountered in everyday management of high-risk patients with antithrombotic therapy after percutaneous coronary intervention (PCI). We aimed to explore ways to identify patients at highest risk for bleeding while on dual/triple antithrombotic therapy. In this chapter, the relevance of the results described in this thesis and their scientific and societal impact will be discussed.

Prescribing the optimal combination of antithrombotic agents for each individual patient is a growing challenge for physicians. Not only do we treat more complex patients with more comorbidities, also the spectrum of antithrombotic drugs has been expanded during the last decennia, making the best selection of (a combination of) these treatment options a complex decision. Common characteristic for all antithrombotic drugs is that they reduce the risk for (recurrent) thrombosis, however, always at the price of increased bleeding risk. Indeed, with current generations of very potent antithrombotic medication, bleeding is the main adverse effect, particularly given its association with mortality[1]. Balancing these risks and benefits is the cornerstone for successful antithrombotic treatment.

With this in mind, an outpatient clinic for high-risk patients was initiated within the Thrombosis Expertise Center in the Maastricht University Medical Center in 2014 with the purpose of: 1) close monitoring of the high-risk patients during their 6-12 month treatment period on dual antiplatelet therapy 2) personalizing treatment regimens with the goal of optimizing efficacy and safety outcome in the individual patient, and 3) increasing the knowledge on the value of platelet function testing (PFT) and other laboratory assays to predict bleeding and to guide treatment decisions. Close collaboration between the department of Internal Medicine, department of Cardiology, Central Diagnostic Laboratory and the Cardiovascular Research Institute Maastricht (CARIM) has led to a well-organized outpatient clinic with affiliated scientific research that formed the basis for this thesis.

Bleeding complications have major impact on patients' health and well-being, since they can cause additional monitoring or hospital visits, extra diagnostic procedures, blood transfusion, hospitalization, or even death. But also, the minimal bleedings (BARC type 1), which are often not monitored nor reported in large clinical trials, have impact on patients' quality of life[2]. These minimal bleedings are often neglected and thought to be 'part of the game', however with an incidence of 30.9% within our cohort, we

believe that they do not only have impact on the quality of life, but also affect adherence, and might be a prediction of future clinically relevant bleeding[3]. Identifying these patients at risk for bleeding is a first important step towards prevention of bleeding. When these patients have been identified, they can be monitored closely with adjustment of therapy when indicated. Besides close monitoring, extra laboratory tests could help to predict bleeding and identify patients at highest risk.

For patients, we believe that this close monitoring could lead to safer prescription of dual/triple antithrombotic therapy, although no comparative cohort is available to serve as a control group for the cohort described in this thesis. A safer treatment will result in a reduction in healthcare costs and an increase in quality of life. Reduction in bleeding episodes could eventually lead to decreased hospitalization, decreased use of transfusion products, with accompanied economic and social benefits. However, such an economic evaluation of cost-effectiveness on our data has not been performed yet. Moreover, the close monitoring of these patients learned us that during follow-up they encounter several other issues that need to be addressed, such as evaluation of (iron-deficiency) anaemia, reduced kidney function, and drug-drug interactions. Unpublished data from our cohort, beyond the focus of this thesis, indicate that in ± 25% of our patients there is potential gain in improving safety by tackling these additional risk factors. We take these experiences with us when modifying the outpatient clinic for the whole spectrum of high-risk patients on antithrombotic medication in the near future.

This thesis also evaluated the use of established and new laboratory tests regarding the identification of patients at risk for bleeding. Current guidelines recommend risk stratification for tailoring individual treatment in high-risk patients post-PCI[4,5]. Both platelet function testing (PFT) and genotyping can provide useful prognostic insights, but previous trials evaluating treatment strategies based on these tests have produced mixed results[6]. Moreover, a multitude of PFTs is available and correlation of these tests is only slight to moderate[7]. We showed that the correlation to genetic background of the patient partly explains the poor correlation of these PFTs[8]. This is relevant for local laboratories without the opportunity of genetic testing, or that need to decide which test from the range of available PFTs to implement. Pharmacogenomic testing is expected to become more common soon. Recent studies have already shown that pharmacogenomic-based prescription of P2Y12 inhibitors is a cost-effective strategy and improves quality of life[9,10]. This thesis also proposed several new laboratory tests regarding the identification of patients at risk for bleeding. The results of chapter 5 and 6 indicated that it is of interest to measure thrombin generation and (tPA-) ROTEM to predict future bleeding episodes in patients on dual antithrombotic therapy[11,12].

However, substantial overlap in data between patients with and without bleeding make it still difficult to position any of these assays in the routine laboratory workup. Finally, in chapter 7 we provided real-world data on patients with atrial fibrillation undergoing PCI[13]. Our findings suggest that physicians did not use a 'one size fits all' strategy, but were capable to choose the optimal combination of antithrombotic drugs for different patients, which underlines the importance of monitoring high-risk patients and tailoring individual therapy.

All studies described in this thesis have been published in international peer review journals. The findings of this thesis were presented at the scientific meetings of the International Society of Thrombosis and Haemostasis (ISTH) and the European Society of Cardiology (ESC), and at several national congresses. In this way, our results are shared with a broad audience of both basic researchers in this field, and physicians (cardiologists, internists) treating patients on antithrombotic therapy. Together, we hope that we can further improve the care for high-risk post-PCI patients, so that the future care for these patients goes beyond prescribing 'standard' antithrombotic therapy.

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