

Monitoring of Antithrombotic Therapy

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Antithrombotic therapy is a fundamental treatment of atherothrombotic diseases. Although more potent antithrombotic therapy might reduce cardiovascular events, recent clinical trials often fail to show that potent antithrombotic therapy is superior to conventional therapy because the efficacy is offset by the increase in bleeding events. Appropriate antithrombotic therapy in individual patients, which can prevent ischemic events without causing major bleeding, is an important issue. To realize personalized antithrombotic therapy, it has been desired to be able to assess the risk benefit balance of antithrombotic therapy by laboratory monitoring of antithrombotic drugs, as well as risk stratification and genetic analysis.

Concerning vitamin K antagonists (warfarin), targeted prothrombin time (PT)-international normalized ratio is established and widely used in clinical practice to minimize both ischemic and hemorrhagic events. However, there are no similarly established laboratory tests to monitor the other antithrombotic drugs. PT or activated partial thromboplastin time is useful to some extent in estimating the concentration of direct oral anticoagulants (DOACs) and is often measured for the evaluation of perioperative bleeding risk or for the control of major bleeding. The development of more sensitive and convenient methods and their standardization are great concerns in the evaluation of intensity of anticoagulation and thrombogenicity under treatment. As for antiplatelet agents, inhibition of platelet function has been measured using various methodologies such as light transmittance aggregometry, VerifyNow, flow cytometry, and urinary metabolites. It has been shown that high on-treatment platelet reactivity is associated with recurrent ischemic events¹. However, in most interventional clinical trials, selection of P2Y₁₂ antagonists according to the assessment of platelet function has

not been shown to improve the efficacy of antiplatelet therapy. Therefore, platelet function tests are not recommended for routine clinical practice.

On the other hand, antithrombotic therapy has recently become more complicated. Antithrombotic drugs are administered to patients those who are at high risk of both thrombosis and bleeding such as elderly or cancer-bearing patients. Combinations of antiplatelet agents and anticoagulants are required for some patients with atrial fibrillation and those undergoing percutaneous coronary intervention. It is often necessary to make careful decisions about the use of antithrombotic drugs in patients with major bleeding. Due to the uncertainty associated with antithrombotic therapy in various clinical situations, there is growing interest in the laboratory monitoring of antithrombotic therapy to aid the improvement of treatment strategy.

Total Thrombus-Formation Analysis System (T-TAS, Fujimori Kogyo Co., Tokyo, Japan) is a newly developed automated microchip-based flow-chamber system for the quantitative analysis of thrombus formation in whole blood². Thrombus formation on collagen-coated surface under arterial shear flow reflects platelet thrombus formation (platelet chip: PL), and thrombus formation on a collagen and tissue thromboplastin-coated surface under low shear rate reflects mixed (platelet and fibrin) thrombus formation (atheroma chip: AR). The unique characteristic of T-TAS is that it may reflect physiological thrombogenicity better than most conventional methods because it measures thrombus formation on collagen (and tissue factor) surface stimulated with shear stress without exogenous agonists in whole blood. Moreover, the measurement of T-TAS is simple and rapid and requires only a small volume of blood. The parameters obtained by T-TAS showed only weak correlation with those obtained by the other laboratory tests³. Although T-TAS does not reflect specific action of antithrombotic drugs, previous studies have shown

that PL is useful to assess the effects of antiplatelet agents⁴⁻⁶, and AR is useful to assess the effects of anticoagulants⁷. In addition, AR has shown to be useful for the monitoring of bleeding during cardiac surgery^{8,9}. Concerning cardiac surgery, although there is little evidence, viscoelastic measurements such as ROTEM is recommended for the management of hemostasis to reduce blood loss and transfusion. ROTEM reflects decrease in coagulation factors, decrease in platelet count, or increase in fibrinolytic activity, but ROTEM is measured without flow and is relatively insensitive for platelet function.

In *J Atheroscler Thromb*, Tatsuro Mitsuse and colleagues report that AR level could be a significant predictor of 1-year bleeding events in patients with coronary artery disease (CAD) treated with various antithrombotic therapies, including antiplatelet agents and anticoagulants¹⁰. The authors previously reported that PL level is a potentially useful predictor of periprocedural bleeding events in patients with CAD undergoing elective PCI¹¹, and AR level is a predictor of periprocedural bleeding events in patients undergoing catheter ablation for atrial fibrillation treated with anticoagulants¹². These results should be interpreted carefully, because T-TAS parameters just before bleeding events might not be equal to those at recruitment and clinical conditions at bleeding were unclear. Bleeding events in the chronic phase of cardiovascular disease are different in nature from periprocedural bleedings. Periprocedural bleedings comparatively depend on the intensity of antithrombotic therapy, which can be assessed by laboratory tests. However, long-term bleeding risks depend on the intensity of antithrombotic therapy¹³, as well as on various factors¹⁴ such as comorbidities, control of the risk factors of bleeding, and severity of arteriosclerosis. T-TAS may help to evaluate the long-term bleeding risks by assessing not only the intensity of antithrombotic therapy but also the global thrombogenicity of individuals. If so, the combination of T-TAS reflecting global thrombogenicity and other laboratory tests reflecting specific antithrombotic actions may allow more detailed evaluation. Additional studies are needed to confirm whether using T-TAS or a combination of T-TAS with other laboratory tests for monitoring of antithrombotic therapy can be beneficial for clinical practice.

Conflict of Interest

None.

References

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