

EDITORIAL

Discontinuing Oral Anticoagulation Therapy

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The initiation and interruption of oral anticoagulation therapy (OAT) is challenging, as it may be associated with a significant hazard for thromboembolic and bleeding complications (1). Since OAT with coumarins was first established some 60 years ago (2), we are aware of a certain risk of therapy-associated complications, especially in case of overdosage (3,4). Only recently have we learned that the stability of OAT, rather than its intensity, is the major factor to avoid such complications (5,6).

Due to their pharmacokinetics, vitamin K antagonists (VKAs) have a very narrow therapeutic index (7). Moreover, although different among acenocoumarol, phenprocoumon and sodium warfarin, the half-life of VKAs shows great inter-patient variation due to genetic factors, liver function, age, and the underlying procoagulatory disorder (8-10). Finally, when the International Normalized Ratio (INR) is within the therapeutic range, more than 98% of the administered VKA is bound to the plasma albumin, and any displacement from the binding sites increases drug sensitivity (11).

With respect to the initiation or discontinuation of OAT, one should consider the following:

- When starting OAT, there is a delay in the onset of any anticoagulatory effect. This delay is dependent on the clearance rate of the fully carboxylated clotting factors and the time required for the undercarboxylated factors to reach a steady state (12). On the other hand, there is an immediate and dose-dependent influence of the VKA on the concentration of plasma protein C, a very potent anticoagulatory factor. If, after the initiation of OAT, anticoagulant-effective protein C levels are decreasing faster than those of the procoagulatory vitamin K-dependent clotting factors, the result is a hyper- rather than a hypocoag-

ulable state (13). In order to avoid rapidly decreasing protein C levels when commencing OAT, oral anticoagulation should be started with moderate doses of VKAs not exceeding 10 mg, especially in patients aged over 60 years (14) (Fig. 1).

- The opposite occurs when OAT is more or less abruptly discontinued. The concentration of vitamin K-dependent clotting factors increases only slowly, while protein C levels recover promptly; this results in a hypocoagulable state with an increased risk for bleeding complications. An inappropriate discontinuation of OAT may therefore result in a significant bleeding risk, exactly in a situation where it is believed that everything has been done to reduce hemorrhagic complications (15).

Current guidelines

With respect to OAT discontinuation, statements have been issued by the American College of Chest

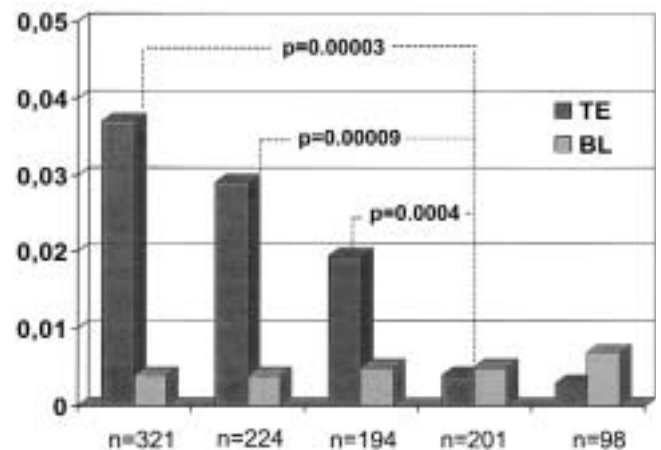


Figure 1: Initiation of oral anticoagulation therapy. Influence of initial doses of phenprocoumon (mg given in the first 2 days) on the incidence (within 50 days) of clinically relevant thromboembolic (TE) and bleeding complications (BL) in 1,038 patients with first ever initiation of oral anticoagulant therapy (1984-1988).

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Physicians (ACCP) (16,17), the American College of Cardiology/American Heart Association (ACC/AHA) (18) and, most recently, by the European Society of Cardiology (ESC) (19). The ACC/AHA and ESC guidelines focus on patients with mechanical valve prostheses, whereas the recommendations of the ACCP apply to all patients receiving VKAs. As a general consensus among the three practice guidelines, the management of periprocedural anticoagulation must be individualized on the basis of the patient's risk for thromboembolic events and anticoagulation-related and/or procedure-related bleedings. If hemorrhage is unlikely, or may be easily controlled, then interruption of OAT is unnecessary and the procedure can be performed safely after adjustment of the INR to the lower end of the therapeutic corridor (usually 2.0-2.2) (16-19).

The level of evidence for most recommendations is low, because so far no prospective randomized studies have been conducted to compare different treatment regimens in a conclusive way. Hammerstingl and co-workers are therefore to be congratulated for the results of their BRAVE registry published in this issue of *The Journal of Heart Valve Disease* (20). However, the design and results of the BRAVE study raise several questions that require comment.

An INR ≥ 1.8 has been shown as the lowest value to be effective in preventing thromboembolic events among patients with a moderate to significant hazard for intracardiac thrombosis and consequent emboli (single aortic or mitral valve replacement with a bileaflet prosthesis) (5). To allow for a safety margin, most guidelines consider an INR ≥ 2.0 to be sufficient to prevent thromboembolic complications in the majority of indications (18).

Recent guidelines do not recommend an overlapping treatment with heparin for patients with low thrombogenic heart valve prostheses, at least in the aortic position, if OAT is stopped for < 72 h to allow the INR to fall below 1.5 (18) (class I recommendation, level of evidence B).

Only in high-risk patients or in those carrying older mitral valve prostheses, is overlapping heparin recommended when the INR falls below 2.0. This is a first step to 'liberalize' the former very strict regimens, although at present there are no more data available for this moderate approach than for the previous strict regimen of overlapping heparin therapy.

It is very likely that patients with mechanical heart valve prostheses but not on point-of-care systems are, for at least 10 to 20% of their time, below their target therapeutic INR, without presenting with prosthetic valve thrombosis or cardioembolic events (5,21). The strict regulation of how to control oral anticoagulation when a patient is hospitalized is therefore less of a clinically relevant problem than a forensic one. It is at least

questionable whether we do harm to the patient by an overlapping heparin therapy.

In literal terms, who has ever seen a patient with a cardiac valve prosthesis and stable anticoagulation develop a valve thrombosis after cessation of OAT for 72 h? Clinicians should be encouraged to study this aspect more intensively, not only to broaden the database but also to provide guideline committees with appropriate data.

According to older recommendations, patients included in the BRAVE registry received overlapping heparin in 60% of cases for endoscopic procedures (31%) or cardiac catheterization (29%).

For many reasons, most high-volume centers (including ours, with 1,600 valve procedures each year) never adhere to these recommendations, but allow the INR to fall to ≤ 2.2 and then perform interventions with a low or moderate bleeding risks (e.g., cardiac catheterization, endoscopy, dental extraction) during moderate but still effective OAT. Although we have very good experiences (low costs, low complications, shorter in-hospital stays), this approach is in a gray zone. Fortunately, recent guidelines on the management of valvular heart disease published by the ESC (19) state that the interruption of oral anticoagulation is not required in many minor surgical procedures (including dental extraction) where bleeding is easily controlled. What cardiologists demand from dentists (extractions) should go without saying for their own procedures (e.g., cardiac catheterization), and also for endoscopies with and without biopsy. In patients at high risk for local bleeding complications (e.g., diabetes, severe peripheral artery disease, renal failure) and undergoing cardiac catheterization, one should consider a non-femoral access (e.g., radial artery) rather than utilize an overlapping heparin therapy (22,23).

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