What The Vascular Specialist Need To Know About The Newer Oral Anticoagulants, Their Pitfalls And How To Use Them.

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The Washington Post reports: New bloodthinners thicken the drug market Monday, November 22, 2010. “Warfarin, is one of the most effective therapies in all of medicine, but it also can be hard to manage and poses serious risks of uncontrolled and potentially fatal bleeding”

Background:
Patients with peripheral arterial disease (PAD) have generalized atherosclerosis; coronary, cerebral, abdominal en peripheral vascular disease (1). Compared to patients without PAD, the incidence of MI (myocardial infarction (MI)) or stroke during follow-up is three times increased. Despite antiplatelet therapy, up to 10–20% of these patients still have cardiovascular events, indicating that the underlying atherothrombotic activity is not optimally controlled by antiplatelet agents. For more than 50 years, warfarin, a vitamin K antagonist (VKA), had been the only available oral anticoagulant used in patients with PAD. However, its narrow therapeutic index and multiple drug and diet interactions affected its safety, compliance, and efficacy. A meta-analysis revealed that 44% of bleeding complications with warfarin were associated with supratherapeutic international normalized ratios and that 48% of thromboembolic events occurred with subtherapeutic readings (2). Difficulties in achieving optimal anticoagulation with warfarin therapy are attributed to its slow onset of action, variable pharmacologic effects, and numerous food and drug interactions. These shortcomings have prompted the development of New Oral AntiCoagulants (NOACs) that target key coagulation factors, such as factors Xa and IIa (thrombin).

Additional value of vitamin K antagonists in peripheral arterial obstructive disease: The WAVE (Warfarin Antiplatelet Vascular Evaluation) trial randomized 2161 patients with PAD to receive antiplatelet therapy (primarily aspirin) either with or without an oral vitamin-K antagonist (VKA) (primarily warfarin) (3,4). No significant difference was seen in the primary end point of MI, stroke, or CV (cardiovascular (CV)) death over a follow-up averaging 35 months, nor in a second primary composite end point that consisted of the first one or severe ischemia in the coronary or peripheral arterial beds. However, the combined therapy showed a significant increase in hemorrhagic strokes with combination therapy.

Comparison with vitamin K antagonists:
In comparison to oral Vitamin K antagonist (VKA), the NOACs; either direct inhibitors (direct inhibitors) of thrombin or Factors (Factor) Xa have overall favorable pharmacological effects. The NOACs were developed with the limitations of standard heparin and warfarin in mind, examples of these are dabigatran (IIa), rivaroxaban (Xa and apixaban (Xa). In common with these novel anticoagulants is the convenience of use with no requirement for laboratory monitoring and limited drug interactions, which may provide multifaceted treatment options for atherosclerosis and anticoagulation in the future (5).
The relative benefit of any new agents was compared to warfarin, by Lip et al. This latter approach is similar to pooling or meta-analysis of all the studies, and provides a reasonable overview of the “class effect.” For all the new oral anticoagulants, they found that this class as a whole significantly reduced the risk of: 1) stroke or systemic embolism by 21% (p < 0.001); 2) stroke by 23% (p < 0.001); 3) hemorrhagic stroke by 53% (p < 0.001); and 4) all-cause mortality by 12% (p < 0.001). In addition, major bleeding was lower for any new oral anticoagulant by 13% (p < 0.001) compared with warfarin (6).

For the indirect comparisons between individual agents, however, the picture remains a bit confusing. A “significantly lower risk of stroke or systemic embolism (by 26%) for dabigatran 150 mg twice daily compared with rivaroxaban.” On the other hand, they conclude “we found no profound significant differences in efficacy between apixaban, and dabigatran (both doses) or rivaroxaban.” They also report no significant difference in MI event rates among the 3 agents. Yet, within the individual trials, the rate of MI was definitely higher with dabigatran, but not with either of the factor Xa inhibitors (6). These conflicting results lend support to the conclusion that such methods for indirect comparisons may not be the most accurate due to several sources of confounding.

Addition to antiplatelet therapy: The addition of NOACs to antiplatelet treatment was evaluated in patients with an acute coronary syndrome. The hypothesis was this might reduce ischaemic events but increase bleeding risk. In a meta-analysis, studying 30,866 patients the efficacy and safety of adding NOACs to single (aspirin) or dual (aspirin and clopidogrel) antiplatelet therapy was evaluated (7). The study included 4135 (13.4%) on single, and 26,731 (86.6%) on dual antiplatelet therapy. Major adverse cardiovascular events (MACEs) as the composite of all-cause mortality, MI, or stroke and all clinically significant bleeding were compared. When compared with aspirin alone the combination of an oral anticoagulant and aspirin reduced the incidence of MACE with 30%, but the incidence of bleedings was increased to 79%. Compared with dual antiplatelet therapy with aspirin and clopidogrel, adding an oral anticoagulant decreased the incidence of MACE modestly with 13%, but more than doubled the bleeding to 134%. In patients with a recent acute coronary syndrome (ACS), the addition of a new oral anticoagulant to antiplatelet therapy results in a modest reduction in cardiovascular events but a substantial increase in bleeding, most pronounced when new oral anticoagulants are combined with dual antiplatelet therapy. The use of two antiplatelet agents, as prescribed early after coronary stent placement, is a major drawback for the comparison for patients with PAD.

Choosing an Oral Anticoagulant:
When identifying a long-term oral anticoagulant for a patient, it is important to adopt a personalized approach. The NOACs are not all superior in terms of efficacy compared with warfarin; hence, patients who are stable with warfarin therapy with acceptable/minimal complications will not benefit from switching to an NOAC. Warfarin remains the standard of care for the management of patients with known valvular AF or mechanical heart valves until further safety and efficacy data regarding the use of NOAs (NOACs) in these situations is available. However, for patients with new-onset AF the European Society of Cardiology recommends the prescription of NOACs. Patients with hepatic dysfunction or associated coagulopathies or impaired renal function (CrCl <30 mL/min per 1.73 m2) are not good candidates for NOACs owing to their hepatic metabolism and renal excretion. If compliance is
an issue, rivaroxaban, with its once-daily administration, might be a better choice than dabigatran or apixaban. Dabigatran is best avoided in patients with ulcer/nonulcer dyspepsia given its tartaric acid core and described associations with GI adverse effects. In patients with a recent history of GI bleeding, apixaban may be a better choice as it has a lower incidence of GI bleeding (compared to warfarin) than dabigatran and rivaroxaban (in comparison with warfarin). Given the recent association of dabigatran with a trend toward an increase in the incidence of MI, rivaroxaban or apixaban should possibly be considered when selecting an NOAC in this subset of patients. On the other hand, in patients with a history of ischemic strokes while taking warfarin, dabigatran and apixaban may be suitable alternatives as they are the only NOACs with a lower rate of ischemic stroke than warfarin.

Management of Bleeding Complications/Overdose:
Lack of specific agents that reverse the anticoagulant effect complicates the management of NOACs-associated bleeding events or the periprocedural reversal of anticoagulation (9). Management of minor bleeding, eg, epistaxis, consists of addressing the potential anatomical defects, eg, cauterization or nasal packing. The decision to hold the next dose of drug will hinge on the comorbidities and assessment of risks of drug discontinuation. Given the relatively short half-lives of the NOAs in patients with normal renal function, most of the anticoagulant effect should dissolve within 48 hours (8).

Administration of oral activated charcoal retards absorption of recently ingested drug, eg, within a couple hours of presentation. Given that only 35% of dabigatran is bound to plasma proteins, hemodialysis typically removes 60% of dabigatran and should be considered, especially in patients with impaired renal function. However, given the extensive volume of distribution (50-70 L) of dabigatran, a “rebound” increase in dabigatran plasma levels may occur after hemodialysis. Although there are no data, dialysis is unlikely to be effective for rivaroxaban and apixaban as they are more than 85% to 90% protein bound.

Recombinant Factor VIIa: This agent has been used in clinical practice to help reverse life-threatening bleeds caused by NOACs. It decreases the bleeding time in animal models but does not reverse the anticoagulation effect on most other laboratory coagulation tests. Unfortunately, other than case reports, there are no randomized controlled studies confirming its benefit in these situations. One must keep in mind the potential serious adverse effects of recombinant factor VIIa, including disseminated intravascular coagulation and systemic thrombosis.

Prothrombin Complex Concentrates: A randomized controlled study using a nonactivated 4-factor PCC showed normalization of the PT alone in patients taking rivaroxaban but not dabigatran (10). No studies have evaluated PCCs in patients receiving the NOACs with clinical bleeding; however, its use seems reasonable in the setting of serious bleeding.

Unsolved issues: "As there are no readily available and validated tests for measuring the anticoagulant effect of the newer oral anticoagulants, routine clinical monitoring of all patients on anticoagulant therapy is still essential, regardless of which type they are using.”
"And while the new oral anticoagulants don't require monitoring with a blood test, there is significant risk for the patient because there is no readily-available antidote to reverse bleeding should it occur when using these newer agents."

“The issue of the cost, a daily of Pradaxa costs $6.75. In contrast to warfarin, which is almost for free. However, the NOACs may be a cost-effective alternative to warfarin because it won't require regular blood testing, which can cost up to $250 a month” (11)

Potential use of new oral anticoagulants in peripheral arterial disease: Combined anti-thrombotic treatment, the combination of antiplatelet (antiplatelet) therapy and warfarin, has the potential to improve outcome in POAD (PAD) patients. However, the combined treatment has narrow therapeutic windows, need for frequent laboratory monitoring, higher risk for food and drug interactions. How to combine the best of both worlds? The development of NOACs, as an alternative for warfarin has potential major advantages. The take home message of the NOACs findings in patients with acute coronary syndromes was that higher doses, as expected, were associated with an increased bleeding risk during follow-up, counteract the benefit of a reduction of MACE. This might be associated with the frequent use of dual-antiplatelet therapy mandatory after coronary stent placement. The ideal NOAC in POAD (PAD) patients would have the following properties: a reduced incidence of bleeding events compared to warfarin, a non-inferior effect on MACE compared to warfarin, and compatible with aspirin. A low-dose rivaroxaban, 2.5 mg twice daily in combination with aspirin might be an alternative. Similar to the outcome of the WAVE trial this needs to be confirmed, as PAOD is not a substitute for coronary artery disease. The COMPASS study, a randomized, 3-arm trial, patients will be randomized to receive rivaroxaban (2.5 mg bid) plus ASA (100 mg od), rivaroxaban (5.0 mg bid), or ASA (100 mg od). This study might provide the answer if a NOAC replace warfarin in PAD patients.

References:


