Off-Label Use of New Oral Anticoagulants
A One-Way Ticket to Nowhere
Carlos A. Molina, MD, PhD; Magdy H. Selim, MD, PhD

More than 40 years ago, the rudimentary train of secondary stroke prevention reached a milestone station: the demonstration in several randomized controlled trials that oral vitamin K antagonists reduce the risk of recurrent ischemic event in patients with stroke and nonvalvular atrial fibrillation (AF). Warfarin rapidly became an evidence-based standard of care. This stroke prevention paradigm was then easily translated, and blessed by the church of the evidence-based medicine, into recommendations for adding other non-AF cardioembolic wagons in the train of oral anticoagulation (OAC). Recently, large randomized controlled trials have shown that new oral anticoagulants (NOACs) are an alternative for vitamin K antagonists to prevent stroke in patients with AF. This novel milestone led not only to a rapid implementation of NOACs in AF population but also encouraged its off-label use in several non-AF cardioembolic strokes where OAC is indicated. However, given the complexity of contemporary evidence-based stroke care, the off-label use of NOACs represents heavy wagons that may derail the train of stroke prevention in the uncertainty station.

Drs Choi and Hill like long trains. They consider that given the safety benefit of NOACs in AF trials, it would be reasonable to translate and apply the favorable NOACs profile to our patient with low ventricular ejection fraction and sinus rhythm. Conversely, Dr Donnan prefers a short but strong engine train. He warns us of the risk of getting lost in translation from the results of AF trials to non-AF conditions. He argues that there is no evidence to support the safety and efficacy of adding a NOAC to antiplatelet therapy and that this combination is unlikely to provide benefit over a dual antiplatelet therapy.

Does our patient require OAC? If after complete workup including long-term ECG monitoring a paroxysmal AF is detected, then OAC should be considered. However, the decision making on OAC in our patient needs to balance between the risk of stent thrombosis, embolic stroke, and major bleeding. Several phase II trials have shown a definite increase in the incidence of bleeding with the combination of OAC and dual antiplatelet therapy. Recent evidence indicates that single rather than dual antiplatelet therapy may be adequate when an OAC is used in a patient with a recent coronary stent. If long-term cardiac monitoring is negative and echocardiographic assessment does not show any alternate source of cardioembolism (large aortic arch plaque, anteroseptal akinesia, intracardiac thrombus, and so on) and a low ventricular ejection fraction remains the only potential mechanism of stroke, then OAC should not be prescribed. The Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial was a large, double-blinded randomized controlled trial that tested whether warfarin or aspirin was superior for stroke or systemic embolism prevention among subjects with low ventricular ejection fraction but in sinus rhythm. There was no significant overall difference in the primary composite end point of stroke and all-cause mortality between the 2 treatment groups. Although warfarin was effective in preventing ischemic strokes, it increased in 2-fold the risk of major bleeding compared with aspirin.

Given that the potential benefit of warfarin in WARCEF was negated by the associated increase in bleeding complications and the more favorable safety profile of NOACs compared with vitamin K antagonists in AF trials, should an NOAC be added to antiplatelet therapy in our patient? Although this therapeutic option is attractive, there is no evidence supporting the use NOACs for secondary prevention in non-AF patients with stroke. The more favorable pharmacokinetics and pharmaco-dynamics, as well as higher safety of NOACs in AF trials, does not ensure a smooth landing in other non-AF conditions. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxelate in Patients After Heart Valve Replacement (RE-ALIGN) trial, using dabigatran for anticoagulation for patients with prosthetic heart valves, was prematurely terminated because of both increased embolic events and increased bleeding. RE-ALIGN represents a call for caution when translating results of NOACs in new scenarios of OAC in stroke prevention. In patients with acute coronary syndrome, a phase III study with apixaban in addition to antiplatelet therapy was also terminated prematurely because of increased bleeding without evidence for efficacy. Similarly, a phase III study with rivaroxaban on background antiplatelet therapy, in doses lower than evaluated for stroke prevention, reached a milestone station: the uncertainty station.
prevention in AF, showed significant reductions in the composite of death, myocardial infarction, and stroke overall and at each dose and reductions in mortality but also an increased rate of major bleeding compared with antiplatelet therapy alone. In a meta-analysis of patients with recent acute coronary syndrome, the addition of an NOAC to antiplatelet therapy led to a modest reduction in cardiovascular events but a substantial increase in bleeding, most pronounced in patients receiving dual antiplatelet therapy. Although the reduction of ischemic events by NOACs was most promising when added to single antiplatelet therapy with aspirin, the risk of stent thrombosis remains in the absence of dual antiplatelet therapy. Thus, the overall benefit–risk profile of adding an NOAC to antiplatelet treatment after acute coronary syndrome is unknown.

An off-label treatment is usually considered as an exceptional measure when no other evidence-based and approved therapeutic option is available. Although in certain clinical situations the off-label use of NOACs seems a reasonable alternative, it may unnecessarily increase the risk of major bleeding, and the benefit is uncertain. Moreover, data collected from off-label use of drugs represent not only biased and confusing information for physicians but also an expensive 1-way ticket to nowhere. The introduction of NOACs and their preferential profile compared with warfarin opens the door to possible new applications and generates multiple important hypotheses to be tested. Therefore, randomized controlled trials of NOACs in conditions such as cryptogenic stroke, stroke patients with low ventricular ejection fraction, stroke related to an underlying hypercoagulability, or dissection are needed. Such trials should take into account the complexity of contemporary treatment regimens in cardiovascular diseases including potential combination with dual and new antiplatelet agents (ticagrelor and prasugrel) and second-generation coronary stents with a lower risk of late stent thrombosis. Until then, keeping our patient on dual antiplatelet seems to be the more reasonable, safer, and evidence-based decision.

Disclosures

None.

References

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