Geriatric Nursing 40 (2019) 212–213

Contents lists available at ScienceDirect

Geriatric Nursing

journal homepage: www.gnjournal.com

Pharmacy Column

William Simonson,
PharmD, BCGP, FASCP

Should anticoagulants be prescribed with Aspirin?

William Simonson, PharmD, BCGP, FASCP

Oregon State University, Corvallis, OR, United States

Keywords:
Novel oral anticoagulant
Aspirin
Bleeding
Combination therapy
Drug interaction

In my practice as a consultant pharmacist in a skilled nursing facility I have observed a striking lack of consistency when it comes to concurrent use of aspirin (ASA) and oral anticoagulants (OAC). Some prescribers avoid ASA in their patients who are taking anticoagulants while some prescribe 81 mg, 162 mg or 325 mg, usually by mouth, once daily, along with the OAC.

There is a reason for this discrepancy – in spite of the frequency of combined use, at present we don't have clear evidence-based guidelines defining whether ASA should be added to OAC therapy and, if so, when it should be added. Keeping in mind that most therapies are not cast in stone and must be tailored to the individual so a universal formula for combining ASA and OACs likely does not exist.

The purpose of this column is to take a quick look at some of the information that might eventually help us answer the question whether the antiplatelet agent aspirin (ASA) should be prescribed to individuals who are also taking an OAC. This is a topic that would best be addressed as a massive review article but, due to space limitations I will focus on the vitamin K antagonist anticoagulant warfarin which I will refer to as VKA, as well as the four direct oral anticoagulants (DOAC) currently available in the US: dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Savaysa®). Some readers may be familiar with the term novel oral anticoagulant or "NOAC" but DOAC is now the preferred acronym. The reader is referred to reference #1 below for an explanation.[1] In this article the antiplatelet agent that I primarily address is ASA and not the other antiplatelet medications clopidogrel (Plavix®), prasugrel (Effient®) or ticagrelor (Brilinta®).

First, I would like to remind the reader that in geriatric drug therapy it is paramount to weigh the risk v. benefit of any medication including combinations such as the one we are discussing. The benefits of adding ASA to a therapy that already includes an OAC is the possibility of achieving improved efficacy from ASA's antiplatelet effect which the OACs do not possess. The potential risk is excessive bleeding which is a real concern since the major adverse effect of all anticoagulants is bleeding. As well, bleeding is a potential adverse side effect of ASA due to its antiplatelet effect and also its ability to cause GI bleeding which could be exacerbated when taken with an anticoagulant.

We know that this combination has associated risk. The complete prescribing information (also referred to as the package insert or the

E-mail address: wsimonsonpharmd@gmail.com

https://doi.org/10.1016/j.gerinurse.2019.03.007
0197-4572/$ – see front matter

"PI") for the five OAC's being discussed point out that the risk of bleeding increases when anticoagulants are used with ASA (as well as other medications that may cause bleeding). None of these anticoagulant PIs recommends for or against concurrent ASA use.

The drug interaction screen of the online drug compendial resource "Micromedex" states that the concurrent use of these OAC's with antiplatelet agents, including ASA, is a drug interaction of major significance which may result in increased risk of bleeding.[2]

Numerous studies evaluating the DOACs compared to warfarin have included subjects that were also taking ASA in combination with the anticoagulants. This enabled has researchers to at least indirectly look at the safety and efficacy of the combination of an OAC and ASA.

In the Rocket-AF study concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding when taken with rivaroxaban.[3]

The ARISTOTLE study found that concomitant use of ASA increased the risk of bleeding on apixaban from 1.8% per year to 3.4% and the bleeding risk on warfarin from 2.7% per year to 4.6% per year.[4]

The AMPLIFY trial evaluated the safety and efficacy of low molecule weight heparin and the OAC apixaban with or without ASA. Rates of venous thromboembolism (VTE) or VTE-related death were similar whether apixaban patients were taking or not taking antiplatelet therapy, 92% of which consisted of low dose (not greater than 165 mg daily) ASA while major bleeding rates were threefold higher in those taking versus not taking antiplatelet agents.[5]

A 2018 meta-analysis of published randomized controlled trials was performed to assess the efficacy and safety of DOACs compared with VKAs in patients with atrial fibrillation and concomitant ASA therapy. The study did not answer whether and how to use DOACs in patients also taking ASA but did demonstrate that the combination of a DOAC and ASA may be safer and more effective than combined therapy with VKA and ASA.[6] To me this finding is particularly interesting because as more clinicians switch from warfarin to the DOACs bleeding may decrease even in the face of concomitant therapy with ASA.

A major factor contributing to the confusion of risk v benefit of anticoagulant therapy, with or without antiplatelet therapy, is the fact that, until recently, there had not been a randomized controlled trial evaluating these two groups. In January, 2019 the results of the "OAC-ALONE" study were published but unfortunately, the study failed to enroll a sufficient number of subjects and results were inconclusive.[7] There is still a need for such a head-to-head study.

While the authoritative "Chest" guidelines on antithrombotic therapy are not standards of practice they do provide valuable perspective. The most recent guidelines provide a strong recommendation based on moderate quality evidence in favor of DOACs over VKA for stroke prevention in patients with atrial fibrillation (a fib). They also provide a strong recommendation against antiplatelet therapy alone for afib. They define antiplatelet therapy as clopidogrel monotherapy or dual therapy with clopidogrel and ASA. If an antiplatelet drug is used with an OAC they suggest the use of clopidogrel, not ASA. The Chest guidelines also address combined DOAC-ASA use by providing two recommendations that they classify as "weak with low quality evidence." The first is that if ASA is used concomitantly with an anticoagulant, it be given at a dosage of 75–100 mg daily with concomitant use of a PPI to minimize gastrointestinal bleeding. The second recommendation is that in patients with AF and stable CAD anticoagulation be accomplished with either a DOAC or warfarin rather than the combination of an OAC and ASA.[8]

It seems reasonable to adopt the risk-benefit approach to the issue of combined OAC and ASA. This combination or other anticoagulant combinations may be preferred for patients at high risk of ischemic events (post-acute coronary syndrome, DM, or complex percutaneous coronary intervention) and low risk of bleeding. Conversely, as noted by the Chest guidelines above, patients with AF and stable CAD may more appropriately be treated with a VKA or, more appropriately, a NOAC.

This discussion would be incomplete without at least a brief discussion of triple antithrombotic therapy which is concurrent use of an OAC as well as ASA and additional antiplatelet medication. While the rationale for such therapy has been described, a recent study of data from a prescription database in Denmark demonstrated that triple therapy resulted in a high rate of major bleeding in all age groups studied. The authors recommended if triple therapy is used, the duration of therapy should be as short as possible. They further opined that the bleeding risk is unacceptably high in patients >90 year of age if risk factors or history of bleeding are present.[9]

My interpretation of the data above is that the combination of an OAC and ASA is somewhat safer than combining ASA with warfarin but either combination is associated with increased bleeding risk. Whether any OAC/ASA combination has significantly greater efficacy is questionable. One of the clearest points is that if ASA is used it should at a dosage that is somewhat less than 325 mg daily, which is the strength of a standard ASA tablet in the US. After that it is a balance of risk v benefit. We would likely want to avoid ASA in someone who is experiencing active bleeding while a patient with serious risk of clotting may require more intensive therapy up to and including triple drug therapy. I look forward to seeing a head-to-head study to give us a clearer picture of the safety and efficacy of combined OAC/ASA.

References

1. Kane S. NOAC, DOAC, or TSOAC: what should we call novel oral anticoagulants? *Pharmacy Times*. September 19, 2016. Available at: https://www.pharmacytimes.com/contributor/sean-kane-pharmd/2016/09/noac-doac-or-tsoac-what-should-we-call-novel-oral-anticoagulants. Accessed 6 February, 2019.
2. Drug Interactions. *Micromedex Solutions*. Ann Arbor, MI: Truvem Health Analytics, Inc; 2019. Available at: http://www.micromedexsolutions.com. Accessed 6 February, 2019.
3. Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891.
4. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *NEJM*. 2011;365:981–992.
5. Cohen AT, Agnelli G, Buller HR, et al. Characteristics and outcomes in patients with venous thromboembolism taking concomitant anti-platelet agents and anticoagulants in the Amplify Trial. *Thromb Haemost*. 2019. https://doi.org/10.1055/s-0038-1676983. PMID30650446.
6. Bennaghmouch N, de Veer AJWM, Bode K, et al. *Circulation*. 2018;137:1117–1129.
7. Matsumura-Nakano Y, et al. Open-label randomize trial comparing oral anticoagulation with and without single antiplatelet therapy in patients with atrial fibrillation and stable coronary artery disease beyond 1 year after coronary stent implantation. *Circulation*. 2019;139:604–616.
8. Lip GYH, Banerjee A, Borani G, et al. Antithrombotic therapy for atrial fibrillation. *Chest*. 2018;154:1121–1201.
9. Van Rein N, Heide-Jorgensen U, Lijfering WM, et al. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation*. 2019;139:775–786.