SM Online
Scientific Resources

SM Journal of Hematology and Oncology

Article Information

Received date: Jul 29, 2016
Accepted date: Aug 01, 2016
Published date: Aug 03, 2016

*Corresponding author

Visweshwar Nathan, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA, Email: nviswesh@health.usf.edu

Editorial

Is Warfarin Obsolete?

Visweshwar N[1]*, Malachowski S[1], Jaglal M[2] and Laber D[2]

[1]*Morsani College of Medicine, University of South Florida, Tampa, Florida, USA*
[2]*Moffitt Cancer Center, Tampa, Florida, USA*

Warfarin, the vitamin K antagonist, was the only one oral anticoagulant available over the last six decades for clinical use. Recently, though there has been an introduction of Newer Oral Anti Coagulants (NOACs) such as dabigatron, rivaraxoban, apixaban and edoxaban. These NOACs have changed the landscape for prophylaxis and treatment of Venous Thrombo Embolism (VTE) and non valvular atrial fibrillation.

Clinicians generally prefer NOACs over warfarin, because warfarin bears increase risks of food and drug interactions, has longer half-life, has complicated induction and interruption, and requires frequent PT-INR monitoring [1,2]. The ACCP published guidelines in 2016, will likely further this preference, because the guidelines endorse the use of NOACs over warfarin for prophylaxis and treatment of pulmonary embolism and DVT in patients without cancer [3]. The NOACs were approved after large randomized trials corroborated non-inferiority of these agents over warfarin. In RE-LY trial administering dabigatran to patients was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage when compared to warfarin [4]. In the randomized, double-blind ARISTOTLE clinical trial apixaban was superior to warfarin in the prevention of stroke or systemic embolism, in the reduction of bleeding, and in the reduction of mortality in patients with atrial fibrillation [5]. In the ROCKET-AF double-blind clinical trial for patients with atrial fibrillation, it is concluded that rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group [6]. Major bleeding complications in these multicenter trials were between 2.5-3% but risk of intracranial bleeding was 52 % lower with NOACs than with warfarin [7]. However, these trials excluded patients that were pregnant, over the age of 80, or had cancer or lupus anticoagulant syndrome.

Warfarin is preferred over NOACs in cases of renal failure because NOACs are renally excreted, and therefore, they are not oral anticoagulant of choice in renal failure. Dose modification is advised according to the creatinine clearance for certain NOACs such as apixaban. Patients taking the NOACs, dabigatron specifically, may have GI symptoms secondary to the astringent moiety used in the preparation of this agent. However, major symptoms such as GI bleeding, can occur with any of the NOACs in cases where patients have pre-existing abnormalities in the GI tract, including AV malformation of the small and large bowel. The elderly are especially prone for bleeding with NOACs, as these are active molecules when they pass through the GI tract [8]. Warfarin might be a beneficial alternative in this population, as warfarin is not locally active and needs to synthesize proteins in the absence of vitamin K (II, VII, IX and X) for its anticoagulant effect [9].

The FDA has approved idarucizumab, a humanized antibody, an antidote for dabigatron. The agent andexenet is currently in phase III trials for counteracting the effect of Rivaroxaban. In the context of Life threatening complications including intracranial hemorrhage (the incidence was less with NOACs) the role of antidotes for NOACs and warfarin is questionable. The mortality rate is very high (about 60%) with warfarin overdose. There is no data available for NOACs in this setting.

Warfarin is the drug of choice for patients with lupus anticoagulant syndrome, valvular atrial fibrillation and in renal impairment. However, in the context of cancer patient with VTE, low molecular weight heparin is preferred over warfarin and NOACs. Monitoring therapy with warfarin is still debated, as there are no guidelines for INR testing for patients on long-term warfarin therapy. For patients receiving a long-term warfarin treatment, once a steady state is achieved, constant dose is maintained, but these patients are advised to take caution whenever there is a change in the drug or dietary habits. Warfarin education by trained health care personnel should be emphasized, so that patients are made aware of the drug interaction with prescription medication/over-the-counter medication and the need for consistent fiber intake with fruits and green leafy vegetables to avoid obesity.

Authors of the new VTE guidelines (ACCP guidelines -10th edition) clearly state that these guidelines are not based on level I evidence. NOACs appear to have some utility based on trials, but reversibility is still questionable with most of these agents. Warfarin has a long history of use providing much more information regarding the risk and benefit profile, with minimal end organ

damage when compared to NOACs. However the NOACs may have some benefit, but we do not know the risks very well. Warfarin should still be strongly considered in many situations because we understand its risk/benefit profile, and have ways that are well tested in the event that we need to reverse it. Of course with global cost constraint in the healthcare industry, it is always prudent to use the NOACs judiciously. There is no need to switch from warfarin to NOACs for therapeutically stable patients, unless there is a definite clinical indication.

References

1. Kokubo Y. New Oral Anticoagulants (NOAC) Studies in the Ideal and the Real World - Needs of Prospective Observational Studies. Circ J. 2015; 79: 962-963.
2. Leong-Sit P, Healey JS. Is It Time to Systematically Replace Warfarin With a New Oral Anticoagulant for Higher-Risk Patients With Nonvalvular Atrial Fibrillation? Can J Cardiol. 2016.
3. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016; 149: 315-352.
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361: 1139-1151.
5. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-992.
6. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365: 883-891.
7. Verdecchia P, Angeli F, Aita A, Bartolini C, Reboldi G. Why switch from warfarin to NOACs? Intern Emerg Med. 2016; 11: 289-293.
8. Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology. 2015; 149: 586-595.
9. Zareh M, Davis A, Henderson S. Reversal of warfarin-induced hemorrhage in the emergency department. West J Emerg Med. 2011; 12: 386-392.