



Use of Novel Oral Anticoagulants Post-cardioversion in Atrial Fibrillation: A Safety Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author MGC suggested the topic. Authors SM and PP did the literature research. Author SM prepared the manuscript. Authors CBM and MGC edited the manuscript and made necessary changes to the document.

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Review Article

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ABSTRACT

Atrial fibrillation is considered the most common sustained arrhythmia worldwide, especially in geriatric population and is associated with significant morbidity and mortality. Arterial embolization is the most serious complication of atrial fibrillation. Vitamin K antagonists were the only form of oral anticoagulant medication approved for long-term use since 1940s, till the advent of three novel oral anticoagulants- dabigatran, rivaroxaban and apixaban. The new anticoagulants are more convenient to administer than warfarin. Pivotal trials of these drugs showed that they are not only as effective as warfarin, but also cause less intracranial bleeding. There is data emerging regarding the safety of these agents in the context of cardioversion. The purpose of this review is to examine the current published safety data for the use of novel oral anticoagulants around the time of cardioversion.

Keywords: *New oral anticoagulants; non-valvular atrial fibrillation; genetic, polymorphism; mutations; cardioversion; echocardiogram; transesophageal; thromboembolic; intracranial; bleeding.*

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1. INTRODUCTION

Atrial fibrillation (AF) is considered the most common sustained arrhythmia worldwide, especially in geriatric population and is associated with significant morbidity and mortality. The prevalence of atrial fibrillation in United States was estimated to be in the range of 2.7 to 6.1 million in 2010. Atrial fibrillation is associated with electrical and structural remodeling of the atria, which perpetuates arrhythmia recurrence and maintenance. Shortening of the atrial refractory period has been found to be contributing to persistence of atrial fibrillation. Brundel et al. [2] reported that persistent AF is accompanied by reductions in mRNA and protein levels of several potassium channels. Researchers have demonstrated a functional role for small non-coding RNAs in the atrial remodeling process involved in pathogenesis of AF [1,3-6].

A genetic component to development of AF has been suggested by recent studies and genome-wide association studies (GWAS) have indicated that common single-nucleotide polymorphisms (SNPs) have a role in the development of AF. The association between mutations in KCNQ1 gene encoding the pore-forming α -subunit of potassium channel I_{ks} and familial AF was identified by Chen et al. Darbar et al. identified rare variants in SCN5A gene that encodes the α -subunit of cardiac sodium channel in familial forms of AF. Zhang et al. identified NUP155, an AF locus on chromosome 5q13 in a large AF family with an autosomal recessive inheritance pattern. Many other genetic mutations have been also reported to be associated with pathogenesis of AF. However, they account for familial or sporadic cases only [7-10].

Arterial embolization is the most serious complication of AF, with ischemic stroke being the most clinically evident event and peripheral embolization representing less than 10% of overall cases. Penado S, et al. found that patients with AF not on anticoagulation had a 2.1-fold increased risk for recurrent stroke and 2.4-fold increased risk for severe recurrent stroke [11-12]. The risk of thromboembolism has been shown to be reduced in all cases of AF by anti-thrombotic therapy. Vitamin K antagonists (VKAs) were the only form of oral anticoagulant medication approved for long-term use since their inception into clinical practice in the 1940s. However VKAs have been associated with limitations including slow onset of action, variable

dose requirements related to common genetic polymorphisms influencing their metabolism, varying amounts of dietary intake of vitamin K and interactions with other drugs being used concomitantly [13-15].

The last few years have seen the advent of three new oral anticoagulants (NOACs)- dabigatran, rivaroxaban and apixaban. The NOACs have several advantages over warfarin, including less dietary interference with their metabolism, fewer drug interactions and a more predictable anticoagulant effect that allows for administration of NOACs in fixed doses without the need for routine coagulation laboratory monitoring. Consequently, the new anticoagulants are more convenient to administer than warfarin. In addition, the pivotal trials that led to the FDA approval of the NOACs showed that not only are they as effective as warfarin, but the new agents also cause less intracranial bleeding [16-18]. The purpose of this review is to examine the current published safety data for the use of novel oral anticoagulants around the time of cardioversion.

2. OBSERVATIONS

The European Society of Cardiology has recommended that in patients with non-valvular AF of more than 48 h duration or unknown duration undergoing cardioversion, oral anticoagulation should have been given for at least 3 weeks prior to cardioversion, or transesophageal echocardiography should be performed to rule out left atrial thrombi. After cardioversion, continuous oral anticoagulation is recommended for another 4 weeks [19-21].

We performed a literature search for all studies with use of NOAC drugs in electrical cardioversion. Observational data from the RE-LY, ROCKET-AF and ARISTOTLE trials did not show any difference in the number of strokes or systemic embolisms with use of NOACs and that the stroke rate was comparable with that in prior trials with other forms of anticoagulation, with or without transesophageal echocardiogram guidance.

Ernest H. Law and Wendy Gordon performed a literature search for published studies evaluating the NOACs as alternatives to warfarin for the prevention of thromboembolic events before and after cardioversion for AF. Three out of the four identified articles presented the results of retrospective analyses of data on NOAC use in relatively small cohorts of patients with AF who

underwent cardioversion procedures during large clinical trials. However these clinical trials were not specifically designed to assess outcomes with NOAC use compared to warfarin [22].

Nagarakanti et al. [23] evaluated the data on all patients from the RE-LY trial who underwent cardioversion and were anticoagulated with either dabigatran or warfarin. 1,983 cardioversions were performed in 1,270 patients with non-valvular AF, with more than 80% of patients receiving electrical cardioversion. More patients had TEE before cardioversion in the two dabigatran groups (25.5% and 24.1% in the 110- and 150 mg groups, respectively) relative to the warfarin group (13.3%). The numbers of patients with a left atrial thrombus on a pre-procedure TEE were similar in the three treatment groups. Low rates of stroke and systemic embolism 30 days after cardioversion were observed in all patient groups irrespective of pre-cardioversion TEE (cumulative rate, 0.8% with dabigatran etexilate 110 mg [p = 0.71] versus warfarin, 0.3% with dabigatran etexilate 150 mg [p = 0.4] versus warfarin, and 0.6% with warfarin use). Moreover, the rates of major bleeding in this post hoc subgroup analysis were low across all treatment groups (1.7% and 0.6% in the groups receiving dabigatran etexilate 110 and 150 mg, respectively, and 0.6% in the warfarin group). There were no statistically significant differences in the rates of stroke, embolism, and major bleeding in all groups.

A post hoc analysis of data from the ROCKET AF study evaluated covariates associated with 364 patients receiving electrical or pharmacological cardioversion or catheter ablation, out of which 143 received electrical cardioversion, 142 received pharmacological cardioversion and 79 received catheter ablation. The patients' mean age was 69 years, with 41.3% being males. Approximately half were classified as having persistent AF and the other half as having paroxysmal AF, with a small percentage (approximately 2%) experiencing first-episode AF. Patients in the ROCKET AF study were reported to have a mean CHADS score of 3. Rates of stroke and systemic embolism in this post hoc analysis were very similar at 30 days in both rivaroxaban and warfarin arms (1.88% versus 1.86%). The cumulative rate of specified types of bleeding (major and nonmajor but clinically relevant) was numerically higher in the rivaroxaban group at 30 days (18.75%) compared with the warfarin group (13.04%). [24].

Kennedy et al. [25] reported a study involving 43 patients who received dabigatran for a minimum of four weeks prior to the TEE-guided electrical cardioversion for AF. Endpoints reported included left appendage assessments for thrombus, left atrial appendage velocities by pulse wave Doppler and coagulation indexes. No patients experienced any adverse clinical neurologic events at six weeks after cardioversion.

Another post hoc study cohort reviewed 540 patients from the ARISTOTLE trial who underwent cardioversion. The primary endpoint of thromboembolic events (stroke, systemic embolism, and myocardial infarction) at 30 days after cardioversion was evaluated in these patients receiving apixaban or warfarin. The mean age in this group of patients was 67.2 years and predominately comprised men with a history of hypertension (88.1%), diabetes (26.7%), congestive heart failure (23%), and stroke or TIA (14.1%, with a mean CHADS score of approximately 2. The results of the analysis revealed that among the 540 patients who underwent a total of 743 cardioversions, no stroke or systemic embolic events occurred. One major bleeding event occurred in each group. [26].

The Recently published X-VERT (Explore the Efficacy and Safety of Once-daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion) study is the first prospective study, which compared rivaroxaban to dose-adjusted VKA therapy in patients with atrial fibrillation undergoing elective cardioversion. The primary end point examined was the composite of stroke, transient ischemic attack, non-central nervous system systemic embolism, myocardial infarction and cardiovascular death. Of the 978 patients receiving rivaroxaban therapy, only 6 (1.06%) had a primary outcome event compared to 5 out of 492 patients (1.81%) receiving VKA therapy. As far as safety outcomes are concerned, major bleeding occurred in 6 out of 988 patients (0.61%) receiving rivaroxaban therapy compared to 4 out of 499 patients (0.80%) receiving VKA therapy. The study concluded that rivaroxaban was as effective and safe as VKA therapy in patients with atrial fibrillation undergoing elective cardioversion [27].

3. CONCLUSION

NOAC drugs have revolutionized anticoagulation therapy for patients undergoing cardioversion by providing options in a clinical scenario previously dominated by warfarin therapy. Although the studies reviewed are underpowered, there is no signal that NOACs are less safe than warfarin for cardioversion. The absence of the need for routine monitoring, paucity of food or drug interactions and predictable anticoagulant effect make them convenient choices in appropriate clinical scenarios. However the lack of an antidote in case of bleeding is a safety concern for use of NOACs, especially in high-risk patients. There is a need for large scale prospective trials to study the safety profile of the other NOACs as recently published for rivaroxaban, for use in patients post-cardioversion.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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