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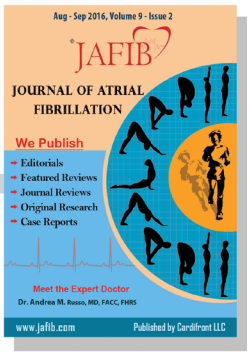

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A Comparison Between NOACs and Warfarin on Time to Elective Cardioversion

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Abstract

Cardioversion of atrial fibrillation is a procedure that has been commonly performed for over half a century. There is known to be an elevated risk of thromboembolism around the time of cardioversion, which has been shown to be drastically reduced with oral anticoagulation. The consistency of therapeutic anticoagulation in the weeks leading up to elective cardioversion is an important factor in the safety of the procedure. Until recently, the only option for oral anti-coagulation was Warfarin. The challenges of dosing Warfarin to achieve a therapeutic INR are well documented. In recent years, novel oral anticoagulant medications have been developed, which are thought to provide a consistent intensity of anticoagulation and do not require routine monitoring or dose adjustment. The purpose of this review is to examine the literature pertaining to a comparison of Warfarin versus novel oral anti-coagulants with respect to time of elective cardioversion.

Introduction

Atrial Fibrillation is the most common cardiac arrhythmia in the general population.[1] Cardioversion (electrical or pharmacological) is performed in patients with AF to restore sinus rhythm in the appropriate clinical setting.[2] Cardioversion was first performed and described in this population in the mid-1950s.[3] Cardioversion in patients with AF is associated with an increased risk (5-7%) of thromboembolic events without anticoagulation.[4] The risk of thromboembolism is magnified around the time of cardioversion, due to atrial stunning which occurs immediately post-cardioversion and persists for several weeks.[5,6] This peri-procedural stroke risk is reduced with the use of anticoagulant drugs prior to cardioversion. In one of the first studies (conducted during the mid-1960s) examining the effect of anticoagulation on thromboembolic episodes after electrical cardioversion, 437 patients were enrolled; 228 patients received anticoagulant therapy and 209 control patients did not. The atrial arrhythmia was successfully converted to sinus rhythm in 348 patients. Embolic episodes occurred in 2 patients (0.8 percent) in the anticoagulant group and in 11 patients (5.3 percent) in the control group. This difference was statistically significant. This early study paved the way for modern anti-coagulation guidelines pertaining to cardioversion of AF.[7]

Guidelines recommend that 3 weeks of therapeutic international normalized ratio (INR) are achieved before cardioversion; additionally, the oral anticoagulant should be continued for a minimum of 4 weeks post cardioversion.[1] The cut-offs of 3 weeks of anticoagulation prior to cardioversion and 4 weeks of anticoagulation post-cardioversion are based on data from non-randomized observational and retrospective studies; clinical guideline documents acknowledge the arbitrary nature of these cut-offs.[5,8] Importantly, cardioversion can be safely performed with less than 3 weeks of anticoagulation if guided by trans-esophageal echocardiography.[9]

Until recently, the only available oral anticoagulant was Warfarin. Over the past few years, newer anticoagulant drugs (NOACs) have been approved for prevention of stroke in patients with AF; these agents have all proved to be non-inferior to Warfarin with respect to rates of stroke and embolism. In the most recent ACC/AHA/HRS guidelines, anticoagulation with Dabigatran, Rivaroxaban or Apixaban at least 3 weeks before and 4 weeks after cardioversion is considered reasonable.(Class IIa – Level of evidence: C)[1]

In this review, we examine the evidence relating to the relative efficacy of NOACs compared to Warfarin with respect to the prevention of thromboembolism around the time of cardioversion.[10] We focus on the limited available data related to "time to cardioversion" comparisons between NOACs and Warfarin. The majority of the available literature regarding NOAC use in this regard focuses on Dabigatran.

Cardioversion and Dabigatran Efficacy

In a small single center study of the general efficacy of NOAC therapy prior to cardioversion in relatively low risk patients, a cohort of patients with a mean $CHADS_2$ score of 1.2±1.1 were treated with

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Rivaroxaban or Dabigatran prior to DCCV. Average anticoagulant treatment time pre-cardioversion was 38±9 days. Roughly 20% of patients underwent TEE prior to DCCV. Of the 30 patients that were treated with Dabigatran, no patients experienced any adverse clinical neurologic events or major bleeding events at 60 days post-cardioversion.[11]

The safety of using Dabigatran in converting persistent atrial arrhythmias to sinus rhythm without transesophageal echocardiography was studied by Cozma et al; 82 patients (of which 45 had persistent atrial fibrillation and 37 had atrial flutter) were included. Dabigatran was used for 3 weeks before and 6 months after cardioversion. Mean age was 63.1±10.4 years. Forty-nine patients underwent uncomplicated electric cardioversion and 11 patients were pharmacologically cardioverted. The mean CHA_2DS_2-VASc score was 3.0 ± 1.4. No major cardiac or neurologic events occurred during the follow up period of 19.4 ± 9.5 months.[12]

Dabigatran and Time to Cardioversion

A post hoc analysis of the landmark RE-LY trial was performed with special focus on cardioversion. A total of 1983 cardioversions performed in 1270 patients were considered (647 on Dabigatran 110mg BID, 672 on Dabigatran 150mg BID and 664 on Warfarin). Cardioversions performed on protocol assigned drug taken for more than 3 weeks were 76.4% in the D110 group, 79.2% in the D150 group, and 85.5% in the Warfarin group. Such "delays" in cardioversion were statistically more frequent in the Warfarin group; however, it should be noted that the rate of TEE-guided cardioversion was higher in the Dabigatran group (25.5% in D110, 24.1% in D150 and 13.3% in Warfarin). Stroke and systemic embolism rates at 30 days were 0.8%, 0.3% and 0.6% in the D110 group, the D150 group, and the Warfarin group respectively (these differences were not statistically significant); there was no significant difference in thromboembolic event rate in patients with and without transesophageal echocardiography.[13]

In a retrospective analysis, the adequacy of 1 month of Dabigatran therapy prior to cardioversion in preventing thromboembolic episodes was studied in 631 patients. Of the cohort, 570 were oral anticoagulant naïve when Dabigatran was initiated. A Warfarin control group consisted of 166 patients. The mean age was 64.2± 11.2 and the majority of patients were male (68.4%). The average CHA_2DS_2-VASc score was 2.0 ± 1.5 and the mean creatinine was 88.1± 32.4mL/min. The dose of Dabigatran was 150mg BID. In the Warfarin control group, the mean age was 71 and the average CHA_2DS_2-VASc score was 2.5. A total of 705 cardioversions were performed; 121 patients underwent more than one cardioversion. The median time from initiation of Dabigatran to first cardioversion was 32 days. Sinus rhythm was established in 91.1 % after cardioversion. In the Warfarin control group, 166 patients underwent 172 cardioversions. The median time from initiation of Warfarin to first cardioversion was 74 days. In the 570 patients who were anticoagulant naïve, there were three events of thromboembolism within 30 days after cardioversion, an incidence of 0.53%. In the Warfarin comparison group, one transient ischemic attack occurred within 30 days, an incidence of 0.60%.[14]

Anticoagulant naïve patients with a first time discharge diagnosis of non valvular atrial fibrillation and plans for elective cardioversion on anticoagulation were included in a study using data from the nationwide Danish registries. Authors compared the proportion of patients undergoing cardioversion within the first 4 weeks of starting anticoagulation on Warfarin versus Dabigatran. In this study, a composite end point of stroke, major bleeding and death within 30 weeks after cardioversion was employed. A total of 1230 patients were included with 37% in the Dabigatran group (n=456) and 63% in the Warfarin group (n=774). The study population consisted of mostly men. Of note, patients prescribed Warfarin were slightly older and had a higher prevalence of chronic heart failure (D 11.0% vs W 19.1%, p<0.001), ischemic heart disease (D 8.3% vs W 13.8%, p = 0.005), and hypertension (D 63.8% vs W 70.5%, p = 0.017). The median time to cardioversion was 4 weeks (IQR 2.9-6.5) in the Dabigatran group and 6.9 weeks (IQR 3.9-12.1) in the Warfarin group. The adjusted odds ratio of cardioversion within the first 4 weeks was 2.3 (95% CI 1.7-3.1, p<0.005) in favor of Dabigatran treatment. TEE was performed prior to cardioversion in 6% of patients in the Dabigatran group and 5% of patients in the Warfarin group. The composite endpoint of stroke, major bleeding or death within 30 weeks after cardioversion occurred in 3 patients (0.7%: bleed 0, stroke 1, death 2) in the Dabigatran group and in 13 patients (1.4%: bleed 0, stroke 1, death 12) in the Warfarin group. The time dependent Cox regression analysis found a non-significant difference [hazard ratio 1.33; 95% CI 0.33 to 5.42) for the composite endpoint in the Warfarin group compared to the Dabigatran group.[15]

Dabigatran Dosing

There have been case reports of thromboembolic episodes after cardioversion of patients taking inappropriate doses of uninterrupted Dabigatran. A recently published case report described a 66 year-old male taking the 110mg BID dose of Dabigatran for new onset atrial fibrillation experiencing a ST elevation myocardial infarction from a thromboembolic coronary occlusion 48 hours after elective DCCV. The patient had been on Dabigatran for 23 days prior to cardioversion. This patient was on a lower dose of Dabigatran (110mg, not approved for use in US) despite his young age and normal renal function.[16]

In a retrospective survey of the incidence and fate of left atrial thrombus during Dabigatran therapy in patients with AF, a total of 198 patients underwent TEE to rule out the presence of left atrial thrombus before cardioversion. Dabigatran 150mg BID and 110mg BID were given to 98 and 100 patients respectively. Dabigatran was administered for <3 weeks in 21%, for 3-6 weeks in 24% and for ≥ 6 weeks in 55% of patients prior to TEE. Left atrial thrombus was found in eight patients (4%); these individuals tended to be older, had higher $CHADS_2$ score and had a higher prevalence of prior stroke or transient ischemic attack. One patient had been on Dabigatran 150mg BID for ≥ 3 weeks while the remaining seven were on 110mg BID. A second TEE was performed in six of the eight patients; these studies revealed complete resolution of the thrombus in five patients with the earliest resolution within 23 days after the first TEE. Of these five patients, one was receiving a prolonged 150mg BID dose, two had an increase in dosage from 110mg to 150mg BID and the remaining two were switched to Warfarin. Two patients (1%) had a stroke at days 3 and 15 after cardioversion while on Dabigatran 110mg BID, despite the fact that LA thrombus was not detected before cardioversion.[17]

Rivaroxaban and Apixaban – Efficacy and Time to Cardioversion

In the X-VeRT trial , an exploratory prospective randomized trial in patients undergoing elective cardioversion,1504 patients

were assigned to Rivaroxaban or VKA therapy in a 2:1 ratio; 1002 patients were assigned to Rivaroxaban and 502 to VKA. Patients were scheduled to undergo early (1-5 days) or delayed (21-25 days) cardioversion. TEE was performed in 564 of 872 (Rivaroxaban: 377; VKA:187) patients scheduled to undergo early cardioversion and in 64 of 632 (Rivaroxaban:33; VKA:31) patients scheduled for delayed cardioversion. The decision to perform a TEE and the timing of TEE was at the investigator's discretion, but the intention to perform a TEE was declared before randomization. The primary efficacy outcome (which included composite of stroke, TIA, peripheral embolism, MI and cardiovascular death) occurred in 5 of 978 patients (0.51%) in the Rivaroxaban group and in 5 of 492 patients (1.02%) in the VKA group (risk ratio 0.50; 95% CI 0.15 – 1.73). The primary safety outcome was major bleeding, which occurred in 6 patients (0.6%) in the Rivaroxaban group and 4 patients (0.8%) in the VKA group (RR 0.76; 95% CI 0.21-2.67). The patients randomized to the early cardioversion arm had a target of receiving cardioversion within 5 days of enrollment; the target for patients in the delayed cardioversion arm was 21-25 day post enrollment. In the delayed group (where most patients did not have a TEE), Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs (median 22 days vs. 30 days; P<0.001).[18,19]

Other published work supports the assertion that Rivaroxaban is safe and effective for use in patients with AF prior to cardioversion.[11]

There is limited data available comparing Apixaban to VKAs prior to cardioversion. In a comparison of 743 cardioversions in 540 patients (265 on Apixaban and 275 on Warfarin) from the ARISTOTLE trial, no stroke or systemic emboli occurred in the 30-day follow up period. Major bleeding occurred in 1 patient (0.2%) receiving Warfarin and 2 patients receiving Apixaban (0.6%).20

Summary

Though there are no prospective randomized controlled trials comparing the efficacy of anticoagulation and time to cardioversion with Dabigatran compared to Warfarin, it appears from the above evidence that anticoagulation with Dabigatran for at least 3 weeks prior to cardioversion is associated with similar thromboembolic risks as compared to Warfarin.[2,10] The pharmacology of Dabigatran, allowing for therapeutic anticoagulation 2 hours after the first dose, would explain the shorter times from anticoagulant initiation to cardioversion noted with Dabigatran as compared to Warfarin, which requires the achievement of a therapeutic INR with subsequent maintenance in the therapeutic range for 3-4 consecutive weeks. It should be noted that left atrial thrombus has been noted in patients on reduced doses of Dabigatran and a TEE prior to cardioversion might be reasonable in these patients. Furthermore, inappropriate dose reduction of Dabigatran is well described in the literature and may be a risk factor for thromboembolism.

The newer NOACs (Rivaroxaban, Apixaban, and Edoxaban) have limited data with respect to safety/efficacy related to the cardioversion of AF. Data is even more sparse regarding time from initiation of these medications to cardioversion. Existing data suggest that the use of Rivaroxaban and Apixaban peri-cardioversion is safe and that Rivaroxaban is associated with shorter times to cardioversion than Warfarin, particularly when TEE guidance is not used.

A prospective randomized trial comparing cardioversion with Edoxaban versus Warfarin – the ENSURE-AF study – is currently underway.[21]

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