

## A Retrospective Cohort Study to Compare the Efficacy and Safety of the New Direct Oral Anticoagulants versus Warfarin for Elective Cardioversion in Patients with Non-Valvular AF

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### Abstract

**Introduction:** Currently Direct Oral Anticoagulants (DOACs) are recommended as an alternative to Warfarin for long term anticoagulation in patients with non-valvular Atrial Fibrillation (AF), but Warfarin is recommended pericardioversion although never validated in controlled clinical trials. In spite of that, DOACs have been increasingly used pericardioversion because of their proven efficacy and safety in long term anticoagulation and the advantage of not needing any blood checks.

**Objectives:** Our research hypothesis was that the use of DOACs instead of Warfarin for stroke prevention in elective AF cardioversion can reduce the waiting time to cardioversion, cancellations, and cost while being as effective and safe as Warfarin in preventing stroke and thromboembolic complications.

**Methods and Results:** In our study we compared the time to cardioversion, cancellations, cost, and complications at 1 month for patients post AF cardioversion on Warfarin and DOACs from January 2014 to December 2015. During this period a total number 152 cardioversions were performed on 128 patients (3 patients had 3 cardioversions and 18 patients had 2 cardioversions), of which 77 (50.6%) were on Warfarin and 75 (49.2%) on DOACs (Dabigatran 31 (41.3%), Apixaban 35 (46.6%), Rivaroxaban 9 (12%). The cardioversion was successful in 136 cases (89.4%), of which 68 were on Warfarin (88.3%) and 68 were on DOACs (90.6%) ( $P = 0.79$ ). 44 patients of the Warfarin group remained in sinus rhythm at 1 month (57%) compared to 39 patients in DOAC group (52%) ( $P = 0.62$ ). Eight procedures out of 77 on Warfarin were postponed due to sub therapeutic INR (10.4%).

The average waiting time to cardioversion from the date of pre assessment clinic was 6.2 weeks in Warfarin group compared to 4.5 weeks in DOACs group ( $p < 0.005$ ). For a single patient, the use of a DOAC instead of Warfarin for elective AF cardioversion saved 27.85 £. There were no embolic or bleeding complications observed in the DOAC group at 1 month follow up while in Warfarin group there were three minor bleeding cases (3.8%) and no embolic complications.

**Conclusion:** The use of DOACs for elective cardioversion reduced the cancellations, cost, and the waiting time to cardioversion significantly with no complications. The patient compliance is the main issue when using DOAC for cardioversion as there is no routine blood test to check it. Further clinical trials are required to statistically prove the efficacy of DOACs in preventing stroke and embolic complications during elective cardioversion for non-valvular AF.

**Keywords:** Direct Oral Anticoagulants (DOACs); Atrial Fibrillation (AF); Warfarin

### Introduction

Atrial Fibrillation (AF) is the most common type of cardiac arrhythmias. AF symptoms include palpitations, chest pain, breathlessness, dizziness, or even loss of consciousness in severe cases [1]. Those symptoms can considerably affect the patient quality of life [2]. In about 33% of cases it may occur without symptoms [3].

AF affects about one in every 25 adults above 60 years of age and one in every 10 above 80 years [4]. It is estimated prevalence in Europe and USA in 2014 is 2 - 3% [5]. In UK the incidence of atrial fibrillation has increased from 5.9/1000 person-years in 2001 to 6.9/1000 person-years in 2013 with exponential increase by age and higher incidence in males of all ages [6].

AF is classified into three main types according to its duration and response to cardioversion [7]:

- Paroxysmal AF
- Persistent AF
- Permanent AF

Lone AF is the term used to describe AF in the absence of cardiovascular or other causes [1].

Non-valvular AF is the term used to describe AF in the absence of significant rheumatic mitral stenosis or prosthetic heart valve [1].

Atrial fibrillation results in turbulent blood flow and stasis of blood in the atria which lead to formation of intra atrial thrombus, particularly in the left atrial appendage, that can embolize from left atrium and block a distal artery causing thromboembolic complications, mainly stroke or limb ischemia. AF increases the risk of stroke by five folds [8] and the stroke associated with AF is usually more severe than ischemic stroke caused by other causes [9] and result in higher mortality [10].

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All patients with AF should be assessed for one year stroke risk using CHA2DS2-VASc score [7]: (Congestive heart failure/left ventricular dysfunction, Hypertension, Age  $\geq 75$  [doubled], Diabetes, Stroke [doubled] - Vascular disease, Age 65 - 74, and Sex category [female] [11]. The minimum score is 0 and the maximum score is 9. It estimates the annual risk of stroke and thromboembolism in patients with non-valvular AF.

In AF patients with a CHA2DS2-VASc score of 2 or more, oral anticoagulation with adjusted-dose Warfarin (INR 2 - 3); or a direct thrombin inhibitor (Dabigatran); or an oral factor Xa inhibitor (e.g. Rivaroxaban, Apixaban, Edoxaban) is recommended for life [7], after assessing the patient bleeding risk and considering patient preference. The current guidelines recommend new oral anticoagulants as an alternative to Warfarin for stroke prevention in non-valvular AF patients.

Electrical cardioversion of AF was first described by Lown in 1963 [12]. It involves delivering a synchronized direct current electrical shock. Cardioversion of AF carries a high risk of dislodging a preformed thrombus in the left atrium and leading to systemic embolization or stroke. This risk is particularly high if AF has started more than 48 hours before cardioversion. In patients who are not anticoagulated the risk of stroke associated with cardioversion is 5 - 7% [13]. Warfarin reduces the peri-procedural incidence of thromboembolic events to between 0.5 and 1.6% [14]. Therefore, all AF patients who are planned for cardioversion should either have transesophageal echocardiography to exclude left atrial thrombus if facilities and experienced staff are available, or they should be anticoagulated for at least three weeks prior to cardioversion and four weeks after except in the case of haemodynamically unstable patients who need urgent electrical cardioversion.

The current guidelines recommend that before elective cardioversion AF patients should be on therapeutic anticoagulation with warfarin (INR range 2.0 to 3.0) rather than DOAC for at least 3 weeks if onset of AF is  $> 48$  hours [7]. After successful cardioversion, anticoagulants should be continued for at least 4 weeks as the atria will be stunted and the risk of thrombus formation is still high, or for life in patients with a high risk of AF recurrence or CHA2DS2 VASc score of  $\geq 2$  [7].

Although the DOACs are currently recommended as an alternative to Warfarin for long term anticoagulation in patients with non-valvular AF, but Warfarin is preferred pericardioversion although never validated in controlled clinical trials [15]. The reason is that the evidence is not strong for the efficacy of the use of DOACs during this period. In spite of that, DOACs have been increasingly used pericardioversion because of their proven efficacy and safety in long term anticoagulation and the advantage of not needing any blood checks.

## **Methods and Results**

In our hospital we set up a nurse-led elective outpatient cardioversion service in 2011. We have started using the DOACs prior to cardioversion since 2014. We conducted a retrospective cohort study to compare the waiting time to cardioversion, cancellations, and complications at 1 month for patients post AF cardioversion on Warfarin and DOACs from January 2014 to December 2015. We also estimated and compared the cost of elective AF cardioversion when using Warfarin and DOACs to see the effect of cancellations. Our research hypothesis was that the use of DOACs instead of Warfarin for stroke prevention in elective AF cardioversion would reduce the waiting time to cardioversion, cancellations, and cost while being as effective and safe as Warfarin in preventing stroke and thromboembolic complications.

All AF patients who had elective cardioversion on Warfarin or a DOAC during the study period were included. Random sampling was not used because of the small number of patients.

**Inclusion Criteria:** AF patients who were:

- Adults >18 years of age
- Persistent or chronic atrial fibrillation
- Referred for outpatient elective cardioversion
- Electrically cardioverted in the period from January 2014 to December 2015
- On Warfarin or a NOAC (Dabigatran, Apixaban, Rivaroxaban).

**Exclusion Criteria:** AF patients who were:

- Paroxysmal Atrial fibrillation
- Spontaneously cardioverted
- Chemically cardioverted
- Urgent cardioversion due to hemodynamic instability
- Anticoagulation contraindication.

The data were collected from online clinic letters from the pre assessment and one-month follow up clinics. The data source was a computer programme called Cardiology Prism which contained all clinics' and procedures' letters of cardiology patients. Statistical Package for Social sciences (SPSS) version 22.00 programme was used for data analysis. We used Pearson's CHI squared test to compare the categorical variables and Independent t-test for parametric continuous variables comparison with 95% confidence interval. P value of 0.05 is considered as a cut-off point to determine the significance of an observed difference. P value of < 0.05 indicates that there is less than 5% chance that the difference is a matter of chance which means a statistically significant difference (i.e. rejection of null hypothesis).

During this period a total number 152 cardioversions were performed on 128 patients (3 patients (2.3%) had 3 cardioversions and 18 patients (14%) had 2 cardioversions). Seventy-seven patients (50.6%) were on Warfarin and 75 patients (49.2%) were on DOACs (of which Dabigatran 31 (20.3%), Apixaban 35 (23%), Rivaroxaban 9 (5.9%) (Figure 1).

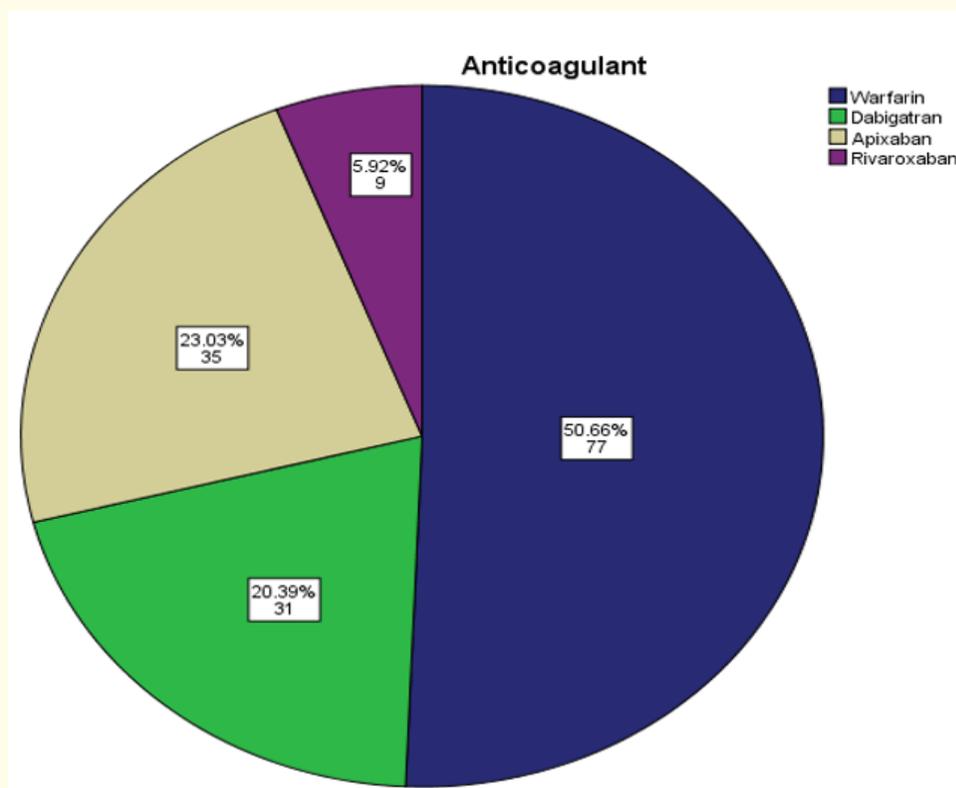


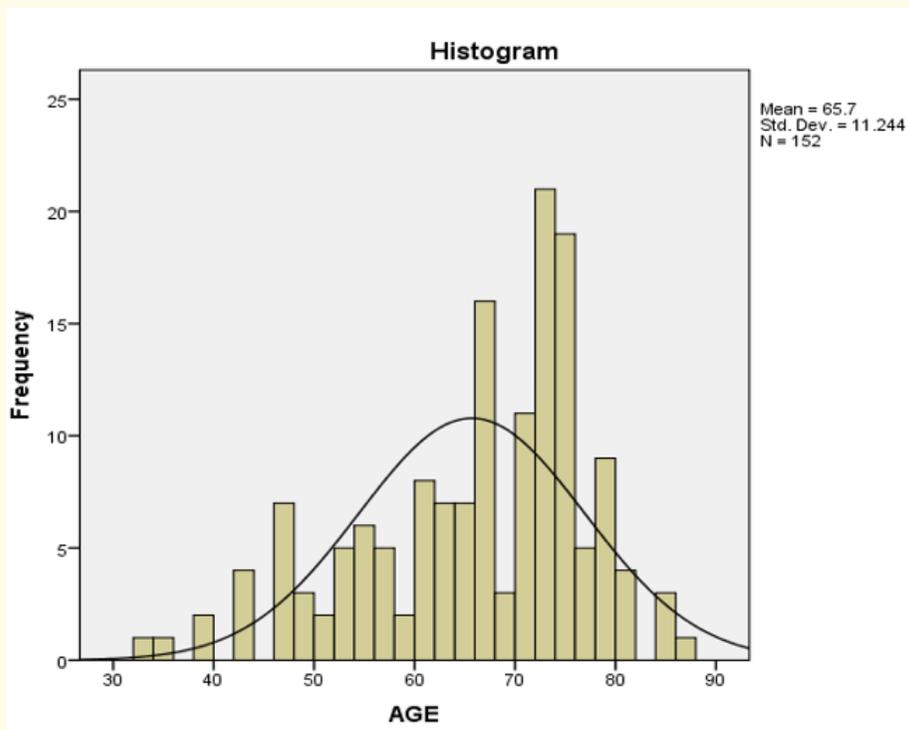
Figure 1: Percentages of anticoagulant use.

Males represented the majority of cases (117, 76.9%). They were 60 in warfarin group (77.9%) and 57 in DOAC group (76%) with no significant difference between the groups (P = 0.77) (Table 1).

Patient gender						
Anticoagulation			Frequency	Percent	Valid Percent	Cumulative Percent
Warfarin	Valid	Male	60	77.9	77.9	77.9
		Female	17	22.1	22.1	100.0
		Total	77	100.0	100.0	
DOAC	Valid	Male	57	76.0	76.0	76.0
		Female	18	24.0	24.0	100.0
		Total	75	100.0	100.0	

Table 1: Patients' gender distribution.

The mean age of all patients was  $65.7 \pm 11.2$  years (Figure 2). There was a significant difference in the mean age between Warfarin and DOAC groups ( $68.3 \pm 8.9$ ,  $62.9 \pm 12.6$  respectively, 95% CI,  $P = 0.003$ ). There were more patients in DOAC group below the age of fifty (15, 20%) compared to Warfarin group (3, 3.8%), and more patients in Warfarin group above the age of 70 (43, 55.8%) compared to DOAC group (30, 40%).



**Figure 2:** Age distribution.

There were no significant differences between the two study groups when comparing the proportions of patients with diabetes mellitus, hypertension, Cerebrovascular accident (CVA) or transient Ischemic attacks (TIA), Ischemic heart disease (IHD), and Peripheral vascular disease (PVD). Diabetic patients represented 18.2% (no = 14) of the warfarin group and 9.3% (no = 7) of the DOAC group ( $P = 0.11$ ). Patients with hypertension were 55.8% (no = 43) in Warfarin group and 50.7% (no = 38) in DOAC group ( $P = 0.52$ ). Patients with previous history of CVA or TIA were 11.7% (no = 9) and 8% (no = 6) in the Warfarin and NOAC groups respectively ( $P = 0.44$ ). Patients with history of IHD or PVD represented 35.1% (no = 27) of Warfarin group and 29.3% (no = 22) of the DOAC group ( $P = 0.45$ ) (Table 2).

About half of the patients in each group had normal left ventricular systolic function (49.4% in warfarin group, 53.3% in DOAC group) but there were more patients with severe left ventricular dysfunction in the DOAC group (13.3%) compared to Warfarin group (2.6%). Therefore, there was a slightly significant difference between the groups ( $P = 0.03$ ) (Table 2).

CHA2DS2 VASc score was used to assess the risk of stroke for patients pre cardioversion and to determine the need for life long anticoagulation. The components of the score were compared between the groups. As mentioned above, only age and left ventricular function

showed significant differences. The mean score for Warfarin group was  $2.9 \pm 1.3$  compared to  $2.5 \pm 1.5$  in DOAC group ( $P = 0.06$ ), indicating no significant difference (Table 2).

	<b>Warfarin no = 77</b>	<b>DOAC no = 75</b>	<b>P value</b>
Diabetes mellitus	Yes 14 (18.2%) No 63 (81.8%)	Yes 7 (9.3%) No 68 (90.7%)	0.11
Hypertension	Yes 43 (55.8%) No 34 (44.2%)	Yes 38 (50.7%) No 37 (49.3%)	0.52
CVA/TIA	Yes 9 (11.7%) No 68 (88.3%)	Yes 6 (8%) No 69 (92%)	0.44
IHD/PVD	Yes 27 (35.1%) No 50 (64.9%)	Yes 22 (29.3%) No 53 (70.7%)	0.45
LV function	Normal 38 (49.4%) Mild 23 (29.9%) Mod 14 (18.2%) Severe 2 (2.6%)	Normal 40 (53.3%) Mild 12 (16%) Mod 13 (17.3%) Severe 10 (13.3%)	0.03
CHA2DS2 VAS score	Mean $2.9 \pm 1.3$	Mean $2.5 \pm 1.5$	0.06

**Table 2:** Risk factors for stroke and CHA2DS2 VASc score comparison.

The cardioversion was successful in restoring sinus rhythm in 68 patients out of 77 on Warfarin group (88.3%, success rate) and 68 out of 75 on DOAC group (90.7% success rate). There was no significant difference in the success rate between the groups ( $P = 0.63$ ). After one month, those who remained in sinus rhythm in Warfarin group were 57.1% (no = 44), compared to 52% in DOAC group (no = 39) with no significant difference ( $P = 0.52$ ).

One of the main research questions was about the effect of using DOAC on reducing the waiting time for cardioversion. The results showed that the mean waiting time for cardioversion from the pre assessment clinic date was significantly shorter in DOAC group compared to warfarin group ( $4.87 \pm 1.77$  weeks vs  $6.21 \pm 2.42$ , 95% CI,  $P < 0.005$ ).

The other important research question was about the difference in cancellations and rescheduling. Eight patients in the Warfarin group were cancelled and rescheduled during the study period due to inadequate INR results (10.4%). There were no procedure cancellations in the DOAC study group and we concluded that the use of DOACs significantly reduced cancellations for AF cardioversion compared to Warfarin ( $P = 0.004$ ).

The secondary research question was about the difference in complications rate at one month follow up. There was no incidence of CVA/TIA in both groups. There were 3 cases of minor bleeding in the Warfarin group (3.9%) which required holding of Warfarin temporarily but no cases of bleeding in DOAC group. The difference was not statistically significant ( $P = 0.08$ ).

To estimate the total cost of cardioversion in each group we included multiple components:

1. The cost of the drug therapy in UK: it was taken from NICE guidelines for atrial fibrillation management costing template which was published in June 2014 [16]. We took the cost of Warfarin 4.5mg as the average cost for patient on Warfarin group and multiplied it by the mean waiting time for cardioversion (6.2 weeks). For the DOAC group, the cost each of the three drugs (Dabigatran, Rivaroxaban, Apixaban) was multiplied by the mean waiting time (4.8 weeks) (Table 3). The average cost of the DOACs was then calculated.
2. The cost of the INR test for patients in Warfarin group: we got the cost of a single non-consultant anticoagulation clinic from the National Schedule of Reference Costs Year: 2014-15 [17] which was £15.98 and multiplied it by the mean waiting time in weeks as a weekly INR was required before cardioversion to ensure adequate anticoagulation. The total cost for a single patient was £95.88.
3. The cost of cardioversion procedure: The NICE Atrial fibrillation: clinical guideline methods, evidence and recommendations 2014 report stated that “Direct current cardioversion (X501) and external cardioversion electrical cardioversion (X502) are not coded separately as a HRG, and therefore the day case unit cost for Arrhythmia or Conduction Disorders (EB07) is the closest proxy, which has a weighted cost of £835 taking comorbidities and or complications into account” [16]. Therefore, we took this cost estimation for calculating the total cost of cardioversion in our study.
4. For cancelled and rescheduled cases in Warfarin group, we added the cost of extra 4 weeks of drug therapy (£3.08) and INR checks (£63.92) in addition to the cost of an extra cardioversion procedure.

Drug Name	Daily dose	Cost per day £ [16]	Total Cost per patient £
Warfarin	4.5 mg	0.11	4.77
Dabigatran	300 mg	2.20	73.92
Rivaroxaban	20 mg	2.10	70.56
Apixaban	10 mg	2.20	73.92

**Table 3: Cost of Anticoagulants.**

	Patient on Warfarin	Patient on DOAC
Cost of drug therapy £	4.77	72.8 (average)
Anticoagulation clinic	95.88	NA
Cardioversion	835	835
Total cost £	935.65	907.8

**Table 4: Cost comparison.**

For a single patient, the use of a DOAC instead of Warfarin for elective AF cardioversion would save £27.85, and when multiplied by the number of patients who had cardioversion on Warfarin in our study (no = 77) the total cost saving would be £2144.45. In addition, the costs of the eight cancelled and rescheduled patients were calculated. The cost of extra four weeks of Warfarin was £30.4; the cost of extra anticoagulation clinics was £511.36; and the cost of cardioversions was £6680, which brought the total cost of cancellation and re-scheduling to £7221.76. Therefore, the total cost saving if a DOAC was used instead of Warfarin for elective AF cardioversion in our study would be £9366.21 over two years.

## Discussion

The use of DOACs for a short period prior to electrical cardioversion of AF has not been adequately validated in large clinical trials. In spite of that, they have been increasingly used for this indication over the last few years. Several observational studies have shown their efficacy and safety in this setting without significant complications. We investigated in this study the effect of using DOACs for elective AF cardioversion service in our hospital on the waiting time for cardioversion, cancellation and rescheduling, and cost. We also compared the incidence of complications between patients on DOACs and Warfarin.

The total number of patients was only 152 cases over the two years' period following the start of using DOACs for stroke prevention prior to AF cardioversion. This represents the major limitation of this study.

Comparing the patients' characteristics between the two groups showed a significant difference in the mean age (Warfarin:  $68.3 \pm 8.9$ , DOAC:  $62.9 \pm 12.6$ ,  $P = 0.003$ ). That made age a confounding factor in our study which might be another study limitation. The higher age in the Warfarin group might had an effect on maintaining therapeutic INR and hence higher number of cancellations and rescheduling of cardioversion procedures. An observational study on the impact of age on anticoagulation with Warfarin was published in 2016 by Abohelaika, *et al* [18]. They found that the frequency of Warfarin dose changes and INR checks increased by age after the age of 67, with significantly lower time in therapeutic range (TTR < 65%) in elderly patients. This actually support our research hypothesis as DOACs do not require blood tests and their anticoagulant effect is predictable as long as the patient is compliant with the medication, hence their use for stroke prevention in AF cardioversion would reduce cancellations and rescheduling particularly in elderly patients.

Another significant difference between the two groups is the left ventricular systolic function. Although about half of the patients in each group had normal LV systolic function (49.4% in warfarin group, 53.3% in DOAC group), but there were more patients with severe LV systolic dysfunction in DOAC group which made the difference statistically significant. That difference did not have any effect on either the primary or secondary study outcomes.

The results of the study showed significantly shorter waiting time for cardioversion when DOACs were used for anticoagulation. This can help in reducing the waiting list for elective cardioversion and improving patients' satisfaction by earlier relieve of AF symptoms. It might also help in maintaining sinus rhythm for longer duration post cardioversion as some studies showed that early cardioversion of persistent AF improves the outcome and maintenance of sinus rhythm [19]. This might be due to less atrial remodeling, fibrosis, and dilatation with short period of AF and therefore less substrate to maintain AF circuits.

Another benefit of using DOACs for anticoagulation prior to cardioversion in our study was the significant reduction in cancellations and rescheduling. The only reason for cancellations of cardioversion procedures in Warfarin group was sub therapeutic INR, a test which is not required to check adequate anticoagulation for patients' on DOACs prior to cardioversion. Cancellations in our study meant at least further 4 weeks on Warfarin with therapeutic INR (2-3) before another appointment for cardioversion could be arranged which caused significant delay and extra costs with prolongation of patients' suffering and anxiety. Some argue that it is better to have a test to check adequate anticoagulation before cardioversion, even though that might delay the procedure, rather than depending on patients' compliance. In spite of this issue of compliance, studies have not shown till now any significant increased risk of embolic complications with the use of DOACs. Actually, the current tendency towards patient-centered approach in healthcare systems entails involving the patients in the process of decision making about their management plan. Therefore, patients have the responsibility to adhere to the medical recommendations which they agreed upon. Ensuring patient's compliance with DOACs is of paramount importance before cardioversion and every effort should be done to emphasize this point to the patient. That is involve explaining the medical information in simple terms, saying the important information first and repeating them, categorizing information and giving them in small pieces, and providing simple written information for the patient to take home.

Calculations of the cost of uncomplicated elective AF cardioversion procedures in our study showed that using DOACs has reduced the cost in spite of their high prices in comparison to Warfarin. That was mainly due to the required frequent INR checks for patients on Warfarin and their longer mean waiting time. In addition to that, cancellations and rescheduling in Warfarin group have added extra costs which could have been saved if DOACs were used instead of Warfarin. The rate of cancellations in our study in warfarin group was 10.4% which was considerably low when compared to rate of cancellations in previous studies which reached up to 64% in X-Vert trial [20]. When considering the annual total number of elective AF cardioversions in UK and the extra costs of the cancelled and rescheduled procedures due to sub therapeutic INR, a significant amount of money will be saved by using DOACs.

The thromboembolic and bleeding complications were low in our study. There was no any case of stroke or peripheral embolism either immediately post cardioversion or after one month in both groups. The number of bleeding complications was numerically higher in the warfarin group but did not reach statistical significance. This supports the efficacy and safety of DOACs as an alternative to Warfarin for anticoagulation prior to AF cardioversion.

## **Conclusion**

The new direct oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban) have been increasingly used instead of Warfarin for anticoagulation in non-valvular AF and venous thromboembolism. Their efficacy and safety in real world practice was established via several clinical and observational studies. Their use for anticoagulation prior to elective AF cardioversion lacks a strong evidence. Till now, only four randomized clinical trials were done to evaluate their efficiency in this setting, three of those were post hoc analyses of the three major original trials which were not specifically designed to test their use prior to cardioversion.

In this a small observational study we showed the efficacy of using DOACs for a nurse-led elective AF cardioversion in terms of reducing the waiting time to the procedure, reducing cancellations and rescheduling due to inadequate anticoagulation, and saving cost in comparison to warfarin. We also showed that the use of DOACs to be as effective and safe as Warfarin in regard to embolic and bleeding complications if not better, at least numerically.

We recommend further large randomized clinical trials to compare DOACs vs Warfarin for anticoagulation prior to elective cardioversion of non-valvular AF. We also encourage using DOACs in this setting as they proved to be safe and effective and significantly reduced the cost of cardioversion.

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