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BRIEF REPORT

Dabigatran Versus Warfarin for Direct Current Cardioversion in Atrial Fibrillation

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ABSTRACT

Introduction: Direct current cardioversion (DCCV) is considered as the most effective treatment for atrial fibrillation (AF). AF is associated with an increased risk of thromboembolism, and DCCV may increase this risk. The current recommendation is, therefore, to anticoagulate for at least 3 weeks before DCCV and 4 weeks after the procedure.

Methods: A retrospective study of patients referred for elective DCCV as treatment for AF in Hampshire Hospitals NHS Foundation Trust was performed to compare the safety and efficacy of dabigatran with warfarin in this setting.

Results: During a 12-month period, 129 patients were referred for DCCV for the treatment of AF and 107 patients received DCCV. Fifty-four patients were anticoagulated with dabigatran, 42 patients with warfarin, and 11 patients with other direct oral anticoagulants (DOACs) with choice of agent determined following an informed discussion with the patient. The average number of days between the date of referral for DCCV and the date of DCCV for patients who were on dabigatran was 51 days, while for warfarin, this was 82 ($P = 0.001$). The proportion of cancelation and rescheduling for warfarin patients was 21.4%, while for dabigatran, this was 5.5%. Patients were reviewed 6–20 weeks after DCCV; the success rate of DCCV for dabigatran patients was 61%, whilst for warfarin patients, this was 52%. The success rate went up to 69% for patients who received DCCV within 45 days of referral ($P = 0.165$).

Conclusion: This retrospective study supports clinical experience that DCCV is more likely to be successful when there is a shorter duration between the onset of AF and the date of DCCV, and shows that the use of dabigatran in comparison with warfarin facilitates earlier DCCV.

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INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia affecting 1% of the general population increasing to 18% for those over 80 years old [1]. AF can cause turbulence in the blood flow within the heart resulting in clot formation. Clots can then migrate to the peripheral circulation resulting in stroke or limb thromboembolism [2–4]. This risk ranges from 5 to 7% in non-anticoagulated patients and is affected by other factors reflected in the CHA_2DS_2–VASc risk score: congestive heart failure, hypertension, age, diabetes mellitus, previous stroke, vascular disease history, and gender [5, 6, 10].

Cardioversion with restoration of sinus rhythm can be achieved either pharmacologically or electrically. The most effective treatment for AF is direct current cardioversion (DCCV) [1]. However, this procedure can increase the risk of thromboembolism. The current recommendation is, therefore, to anticoagulate for at least 3 weeks before cardioversion and 4 weeks after the procedure to minimize the risk of embolization [7–11]. The risk of thromboembolism with adequate anticoagulation is as low as 0.7–0.8% [9]. Traditionally, the vitamin K antagonist, warfarin, has been used; however, this agent has considerable limitations as it can take time to get patients into target international randomized ratio (INR) range, and they run the risk of having DCCV canceled if their INR is out of range. The rate of success of DCCV in AF is largely affected by the duration of the AF; a shorter duration of AF is associated with a higher rate of success of DCCV and less relapse [15]. The use of DOACs in this setting to achieve rapid stable anticoagulation is, therefore, an attractive option.

The availability of the direct oral anticoagulants (DOACs) has dramatically changed the anticoagulation landscape. Dabigatran was the first DOAC approved for stroke prevention in AF. Dabigatran is a direct thrombin inhibitor (DTI) that has several advantages over warfarin. Dabigatran has rapid onset of action with peak plasma concentration within 60 min and a half-life between 12 and 17 h [12]. Dabigatran has a stable pharmacokinetic profile, and there is, therefore, no need to monitor use with blood tests in most patients [12]. This study aimed to compare the safety and efficacy of dabigatran and warfarin around DCCV in terms of stroke prevention, time taken to get to DCCV, and the success of cardioversion in achieving sinus rhythm.

METHODS

A retrospective study of sequential patients referred for elective DCCV to Basingstoke and North Hampshire Hospital over 12 months running from September 2013 to September 2014. Patients were divided into two cohorts; Cohort A received dabigatran, while Cohort B was managed with warfarin. All patients with non-valvular AF planned for DCCV were included in the study. Patients managed with chemical cardioversion and those with mechanical valves and severe valvular heart disease were excluded from the study. Patients who started on anticoagulation with warfarin or dabigatran for DCCV were eligible for the study. The choice of agent determined following an informed discussion with the patient. Risks and

benefits of oral anticoagulant have been discussed. Those already on warfarin or dabigatran for another indication (pulmonary embolism) were also included.

Patients who were on warfarin received variable dosing according to their INR. Their INR was checked weekly until the time of DCCV with target INR of 2–3. In line with normal practice, if the INR was not within the therapeutic range, the procedure was canceled pending adjustment of the dose of warfarin until the INR within the therapeutic range. Patients who were on dabigatran had baseline screening blood tests with coagulation profile, urea and electrolyte (U&Es) and liver function tests (LFT) with no further blood tests if results were normal/stable. Only patients with stable renal function and creatinine clearance above 30 mL/min commenced on dabigatran. Dabigatran was initiated at a dose of 110 mg twice daily for people over 75 years old and 150 mg twice daily for people less than 75 years old. On the date of the procedure, a written consent obtained from the patient after a discussion with risks and benefits of DCCV. In addition, the duration of dabigatran therapy was reviewed ensuring that a full course of 3 weeks had been taken, and if more than two doses had been missed, the procedure was canceled and rescheduled for another date.

The following data were collected: patient diagnosis, patient demographics, comorbidities, including cardiovascular risk factors (CHA_2DS_2–VASc), time between the referral for AF and the date of DCCV, the rate of cancelation and rescheduling of DCCV, and the success rate of DCCV in restoring sinus rhythm. Complications of oral anticoagulant with DCCV were monitored for whole number of patients. Clinical outcomes, including cerebrovascular accident, transient ischemic attack, and peripheral arterial embolism, and bleeding events, were evaluated during 6–8 weeks of post-procedure follow-up.

Data were analyzed using the SPSS Statistics (SPSS Inc., Chicago, IL, USA) version 17.0. Differences between categorical values were analyzed using Pearson's Chi-square test and Fisher's exact test, while the Mann–Whitney *U* test was used for continuous values. A *P* value less than 0.050 was considered statistically significant.

This article is based on previously conducted procedures and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS AND DISCUSSION

During the period of 12 months from September 2013 to September 2014, 129 patients were referred for elective DCCV for the treatment of AF with 107 patients actually receiving DCCV. The majority of referred patients 98.1% (105 out of 107) was newly started on oral anticoagulants, and only two (1.9%) patients were already receiving anticoagulants for the indication of pulmonary embolism. Fifty-four patients who received DCCV were on dabigatran (50.5%; Cohort A), 42 patients were on warfarin (39.2%; Cohort B), and 11 patients were on another DOAC (10.2%).

Twenty-two patients were canceled for various reasons; 4 patients with low INR (18%), 4 patients (18%) returned spontaneously to sinus rhythm, while the remaining cancelations were either because the patient was too unwell to receive DCCV or because they had been referred for ablation.

The majority of the referred patients (96 patients; 89.7%) had a low CHA_2DS_2–VASc score of between 0 and 3, while only 10.3% (11 out of 107) had a CHA_2DS_2–VASc score of between 4

and 9. For patients receiving dabigatran, the average CHA_2DS_2–VASc was 1.9 ± 1.8, while for warfarin, the average was 2.3 ± 1.3 with no statistical significance ($P = 0.291$).

The average age of included patients was 65.45 years, and there was no statistical significance in age between those on dabigatran and those on warfarin. The total number of male patients was 70, and the total number of females was 26, a ratio of 2.7:1. In terms of comorbidities in the total number of patients: 38 had congestive heart failure, 36 had hypertension, 11 had diabetes, 14 had a history of vascular disease, and 5 had previous cerebrovascular disease. There was no statistical difference in comorbidities with CHA_2DS_2–VASc between Cohort A and Cohort B (Table 1).

The average number of days between the date of referral for DCCV and the date of DCCV for patients who were on dabigatran was 51 days, while for patients on warfarin, this was 80 days ($P = 0.001$); for those who were on another DOAC, this was 50 days (Table 1).

The proportion of cancelation and rescheduling to a later date because of suboptimal INR for warfarin patients was 21.4% (9 out of 42 patients). In contrast, those who received dabigatran had a low rate of rescheduling with only three patients (5.5%) having DCCV postponed due to missing doses (Table 1).

The percentage of immediate success of DCCV with achievement of sinus rhythm was 86%. The majority of the patients (73%) received one DCCV; 16% and 11% required 2

Table 1 Background data and outcome: Cohort A versus Cohort B

Category	Dabigatran (Cohort A)	Warfarin (Cohort B)	*P* value
Number of patients, *n*	54	42	–
Mean age ± SD (range), years	64.0 ± 10.9 (25–82)	66.9 ± 8.0 (45–84)	0.124[a]
Gender, *n*			0.772[b]
Male	40	30	
Female	14	12	
Heart failure, *n*	20	18	0.563[b]
Hypertension, *n*	23	13	0.795[b]
Diabetes mellitus, *n*	4	7	0.158[c]
Vascular disease, *n*	7	7	0.610[c]
Cerebrovascular accident, *n*	3	2	0.862[c]
Mean CHA_2DS_2–VASc score ± SD	1.9 ± 1.8	2.3 ± 1.3	0.291[a]
Interval between referral and DCCV (days)	51	80	0.001[a]
Cancelation and rescheduling of DCCV	3	9	0.219[c]
DCCV with successful outcome	33	22	0.391[b]

DCCV direct current cardioversion, *SD* standard deviation

[a] Mann–Whitney *U* test

[b] Pearson's Chi-square test

[c] Fisher's exact test

and 3 DCCV, respectively. At 6–20 week review following DCCV, the overall success rate was 57% (61 patients out of 107), and the proportion of patients who failed to maintain sinus rhythm was 46 out of 107 (43%). For those patients on dabigatran, the success rate was 61% (33 out of 54), and the failure rate was 39% (21 patients out of 54; Table 1). In comparison, the success rate for patients on warfarin was 52% (22 patients out of 42; Table 1), and the failure rate were 48% (20 out of 42). Six patients who received other DOACs had successful DCCV. There were no reported cases of cerebrovascular accident, transient ischemic attack, and peripheral arterial embolism or bleeding events in patients who received dabigatran, warfarin, or other DOACs. In addition, no discontinuation of any of the drugs was reported.

As previous studies have shown that shorter duration of AF associated with higher success rate of DCCV and less relapse [15], analysis was made for those patients who had AF duration of ≤45 days. Review of patients with time between referral and date of DCCV ≤45 days included 32 patients out of 107 (30%). Twenty-one patients were on dabigatran, 7 patients were on warfarin, and 4 patients were on another DOAC. At 6–20 week review post-DCCV, the overall success of DCCV in restoring sinus rhythm was 22 patients out of 32 (69%; $P = 0.165$; Table 2) reflecting a higher success rate in this cohort. This finding was not statistically significant due to the relatively small number of patients. There were a high number of dabigatran patients receiving DCCV within 45 days compared to warfarin, which indicates that dabigatran can be associated with more rapid DCCV and a shorter AF.

Patients with heart failure represented a large group of 38 (39.8% of the total). Twenty of these patients received dabigatran, while 18 patients had warfarin. The total success rate was 73.7% (28 patients; $P = 0.009$). The percentage of the success of DCCV for heart failure who received dabigatran was 85% (17 patients; $P = 0.006$), while for warfarin patients, this was 61% (11 patients; $P = 0.327$; Table 2).

Table 2 Analysis of patients who received direct current cardioversion within 45 days and outcome; patients with background of heart failure and outcome

Category	Number of patients	Success rate	*P* value
Number of patients with ≤45 days referral			
Total	32	22 (69%)	0.165
Cohort A (dabigatran)	21	–	–
Cohort B (warfarin)	7	–	–
Heart failure patients			
Total	38	28 (73.7%)	0.009
Cohort A (dabigatran)	20	17 (85%)	0.006
Cohort B (warfarin)	18	11 (61%)	0.327

One of the limitations of this study is the relatively small number of patients in this single-center study; however, the data are comparable with other published studies [1]. The relatively higher cost of dabigatran (£75.60 per month) may limit its use in comparison with warfarin (£0.86–1.67 per month but with additional monitoring costs) [13]. In the UK, it is estimated that the overall cost for outpatient DCCV is approximately £722 [14], and this cost is predicted to be higher with cancelation and rescheduling. Dabigatran may, therefore, be a more cost-effective approach for DCCV.

CONCLUSIONS

Shorter duration between the onset of AF and the date of DCCV is associated with a higher probability of successful DCCV. The use of dabigatran in comparison with warfarin facilitated earlier DCCV with a lower probability of rescheduling due to inadequate anticoagulation. Dabigatran was, therefore, associated with greater success from DCCV in our study. This is more convenient for patients and staff.

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Compliance with Ethics Guidelines. This article is based on previously conducted procedures and does not involve any new studies of human or animal subjects performed by any of the authors.

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