ORIGINAL ARTICLE

DOACs vs warfarin - comparison of efficacy and bleeding risk in patients with non valvular atrial fibrillation

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Abstract: **Objectives –** Direct oral anticoagulants (DOACs) have been analysed in clinical trials and real world data studies as their use in clinical practice has increased over the recent years. This study aimed to compare DOACs and warfarin in patients with non valvular atrial fibrillation (NVAF) focusing particularly on stroke prevention efficacy and side effects. **Methods –** We reviewed 150 patients' notes from a single Scottish medical practice between October 2015- October 2017. The statistical methods were cox regression analysis and Chi square test. **Results –** The mean CHA_2DS_2-VASc score was 1.89 for DOACs group and 2.05 for warfarin group. Ischaemic stroke while on anticoagulants occurred in one patient in DOACs group compared to five patients in the warfarin group (p=0.291). Side effects such as minor bleeding occurred in 11 patients in the DOACs group contrasting 29 cases in the warfarin group (p=0.024). Major bleeding was reported in three patients in each anticoagulant group (p=0.711). **Conclusion –** Minor bleeding events were significantly lower in DOACs group compared to warfarin group. In this real-world sample of NVAF patients, effectiveness and risks of DOACs versus warfarin were similar in regard to ischaemic stroke and major bleeding.
Keywords: bleeding, direct oral anticoagulants, non valvular atrial fibrillation, stroke prevention, warfarin.

Rezumat: **Obiective –** Anticoagulantele orale directe (DOACs) au fost analizate în numeroase trialuri și studii clinice. Utilizarea acestora în medicină a crescut substanțial în ultimii ani. Acest studiu are ca obiectiv principal compararea eficacității și a efectelor adverse dintre DOACs și warfarină la pacienții cu fibrilație atrială non valvulară. **Metode –** S-au analizat anonim fișele medicale a 150 de pacienți dintr-un centru medical din Scoția între octombrie 2015- octombrie 2017. Metodele statistice folosite au fost regresia cox și testul Chi pătrat. **Rezultate –** Media scorului CHA_2DS_2-VASc a fost 1,89 la grupul DOACs și 2,05 la grupul warfarină. Un pacient din grupul DOAC a suferit accident cerebral ischemic comparativ cu cinci pacienți din grupul warfarină (p=0,291). 11 pacienți din grupul DOAC contrastând cu 29 de cazuri din grupul warfarină (p=0,024) au prezentat efecte adverse precum hemoragie minoră. Hemoragia majoră a fost raportată la trei pacienți în fiecare grup (p=0,711). **Concluzie –** Hemoragiile minore au fost raportate într-un număr mai redus în grupul DOAC comparativ cu grupul warfarină. Din punct de vedere al prevenției accidentului vascular cerebral, riscurile și eficacitatea clinică a anticoagulantelor orale a fost similară în ambele grupuri.
Cuvinte cheie: hemoragie, anticoagulante orale directe, fibrilația atrială non valvulară, prevenția accidentului vascular cerebral, warfarină.

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INTRODUCTION

Atrial fibrillation (AF) remains one of the most prevalent sustained heart rhythm disorder, affecting an estimated 2% of the world population and poses a significant risk factor for stroke, heart failure, sudden death and cardiovascular morbidity worldwide[1,2]. Oral anticoagulation was underused in patients with atrial fibrillation but this was improved by educational intervention and clinical guidelines[3]. Understandably, major work has been done by medical professionals worldwide to improve stroke prevention therapy with an ultimate goal to save many lives. Therefore, therapy with oral anticoagulants was developed and numerous studies have demonstrated that these can prevent the majority of ischaemic strokes in AF patients therefore prolong life[4-6]. For NVAF patients taking oral anticoagulants, the net clinical benefit is significantly positive with the exception of those at very low stroke risk which was shown in meta-analysis and observational studies[4,6]. Side effects such as minor or major bleeding and monitoring vitamin K antagonists therapy are among the most common reasons for withholding or interrupting completely oral anticoagulants[7,8].

Although Warfarin has been the dominant anticoagulant treatment for AF for many years, DOACs are being increasingly used for this common medical condition. The four DOACs have proven their safety and effectiveness in double-blind, randomized clinical trials (RCTs) of patients with NVAF at increased risk for stroke but also in real world data studies published in recent years[9-12]. The emergence of several DOACs has offered potential advantages over warfarin, such as predictable and stable pharmacokinetic profile and less interactions with food or other drugs[14]. Large randomised trials have demonstrated the relative safety and efficacy of these agents versus Warfarin, but in selected patients with NVAF[9-12] and subsequent observational data have provided conflicting results.

Conclusion of RCTs are that DOACs are an effective treatment in stroke prevention but their use is also associated with a higher risk of bleeding either minor or major[14]. When medical professionals prescribe anticoagulants they should select the most appropriate one, taking into consideration patient's risk factors, patient's preference, cost, tolerability, drug interactions and time in the INR time in the therapeutic range (TTR) if the patient is on warfarin.

The aim of this study was to compare DOACs with warfarin in patients with NVAF considering mainly their efficacy and side effects in a real-world setting.

MATERIAL AND METHODS

Based on data availability from a Scottish medical practice we retrieved 150 anonymized patients' notes with a diagnosis of NVAF. This study represented a single centre retrospective observational cohort study performed between october 2015 - october 2017. Inclusion criteria was represented by all patients diagnosed with NVAF taking an oral anticoagulant. We have excluded patients who have been diagnosed with valvular AF, had absolute contraindications to oral anticoagulants and patients treated with antiplatelet therapy (aspirin or clopidogrel). The following information was collected for the observation period: comorbidities, possible contraindications to anticoagulation, previous stroke, type of medication, side effects of medication, CHADS, CHA_2DS_2-VASC score, HAS-BLED score and demographic characteristics (age and sex). To reduce the selection bias, we matched the demographic data for patients from the two anticoagulant groups (DOACs vs warfarin). Ethical approval was obtained from the institution review board, all data being anonymised before the review of medical notes.

Statistical analysis

The baseline characteristics of the cohort were compared using Chi-squared test for categorical data. Statistically significant was defined as p-value <0.05. For comparison and outcome, cross tabulation table was used with number of cases and percentages. Hazard ratio were estimated using Cox proportional hazard regression analysis models. Statistical analysis was carried out using IBM SPSS software version 22 and Numbers for iOS 2016.

RESULTS

Baseline characteristics

The DOACs group was comprised of 65 patients (43%) whereas warfarin group had 85 patients (57%). Demographically, DOACs group consisted of 71% males and 29% females and warfarin group was represented by 69% males and 31% females. Age mean was 74.78 (SD, 8.45) in the DOACs group and 74.06 (SD, 8.21) in the warfarin group. DOACs users had CHA2DS2-VASC score mean of 1.89 compared to 2.05 in the warfarin group (Figure 1). The mean HAS-BLED score was approximately 2.5 in both DOACs and warfarin users. The patients in the warfarin group had overall suffered from a higher number of comorbidities (Table 1, Figure 2).

Table 1. Patients' baseline characteristics

Total patients with AF (n=150)	DOACs (n=65)	Warfarin (n=85)
Age, years	74.78±8.45	74.06±8.21
Female	19 (29%)	27 (31%)
Male	46 (71%)	58 (69%)
Body weight	83.41	85.95
eGFR	>60 (n=50); 46 (n=15)	>60 (n=50); 45 (n=25)
Heart failure	13 (20%)	21 (24.70)
Hypertension	31 (47.69%)	51 (60%)
Diabetes mellitus	14 (21.53%)	23 (27.05%)
Previous stroke/TIA	10 (15.38%)	14 (16.47%)
Coronary artery disease	17 (26.15%)	28 (32.94%)
Required cardioversion	10 (15.38%)	18 (21.17%)
Cardiology review	44 (67.69%)	69 (81.17%)
Obesity	7 (10.76%)	12 (14.11%)
Malignancy	11 (16.92%)	7 (8.23%)
Psychosis	3 (4.61%)	2 (2.35%)
Epilepsy	3 (4.61%)	1 (1.17%)
Previous GI bleed	0	4 (4.70%)
GI ulcer	4 (6.15%)	5 (5.88%)
CHA_2DS_2-VASc score overall	1.89	2.05

The values are expressed as n (%) or mean. AF=atrial fibrillation; eGFR=estimated glomerular filtration rate; DOACs=direct oral anticoagulants; TIA=transient ischaemic attack; GI=gastrointestinal, CHA_2DS_2-VASc=congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years (doubled), diabetes, previous stroke/TIA/thromboembolism (doubled), vascular disease, age 65-74 years, female sex.

Ischaemic stroke

A total of six patients suffered an ischaemic stroke while on anticoagulants. Hence, one patient was on DOAC therapy and five patients were on warfarin. Patients were admitted to hospital, so INR was not documented at the time of stroke. In the Cox proportional hazard regression analysis for ischaemic stroke events, the hazard ratio (HR) was 3.183 (CI), 0.372-27.263 with p value of 0.291 (Table 2).

Side effects

Three cases in the DOACs group and three cases in the warfarin group suffered from a major gastrointestinal hemorrhage (p 0.711) (Table 3). Throughout the study period there were no hemorrhagic strokes reported. Minor bleeding occurred in 11 patients in the DOACs group contrasting with 29 cases in the warfarin group (Cramer's value=0.185, p value 0.024) (Table 4). Based on the type of minor bleeding presented in these groups, there were five patients with epistaxis, five patients with lower gastrointestinal bleeding and one patient with haematuria in the DOACs group. In the warfarin group there were 29 patients with minor bleeding. Consequently, 12 patients had

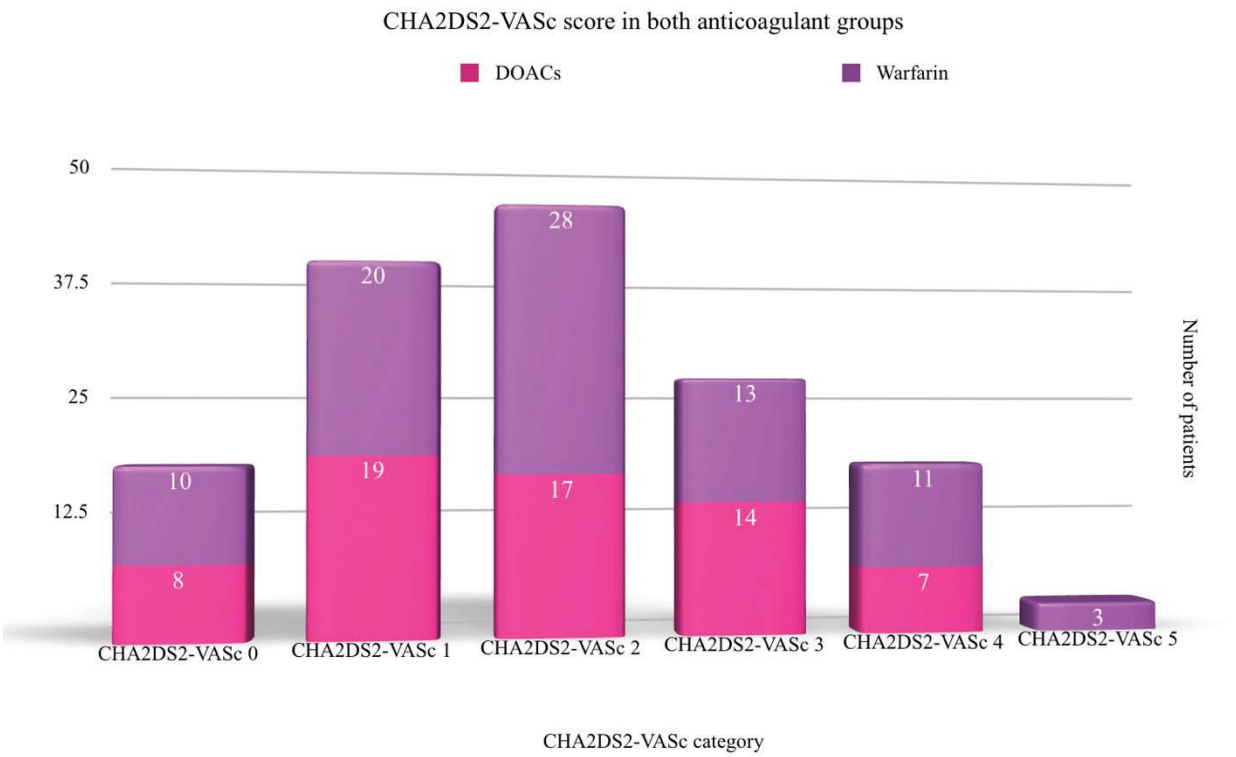

Figure 1. CHA_2DS_2-VASc score in both anticoagulant groups.

Table 2. Cox regression analysis DOACs vs Warfarin and ischaemic stroke events

Cox regression analysis (n=150)	WARFARIN (n=85)	DOACs (n=65)	HR	p value
Ischaemic stroke 6 events (4.1%)	5 (3.4%)	1(0.7%)	3.183 (0.372-27.263)	0.291

Tabel 3. Chi square test DOACs vs warfarin in major bleeding events

Chi-Square Tests- Major Bleeding	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.137a	1	0.711		
Continuity Correctionb	0.000	1	1.000		
Likelihood Ratio	0.136	1	0.712		
Fisher's Exact Test				0.701	0.512
Linear-by-Linear Association	0.136	1	0.712		
N of Valid Cases	150				
Symmetric Measures					
	Value		Approximate Significance		
Nominal by Nominal	Phi		0.030	0.711	
	Cramer's V		0.030	0.711	
N of Valid Cases	150				

epistaxis, 9 patients had lower gastrointestinal bleeding, 4 patients had vaginal bleeding, 3 patients had haematuria and one patient had haemoptisis.

DISCUSSION

Taking into account the general characteristics of the study's population and comparing the number of patients in both groups, the warfarin group had more pa-

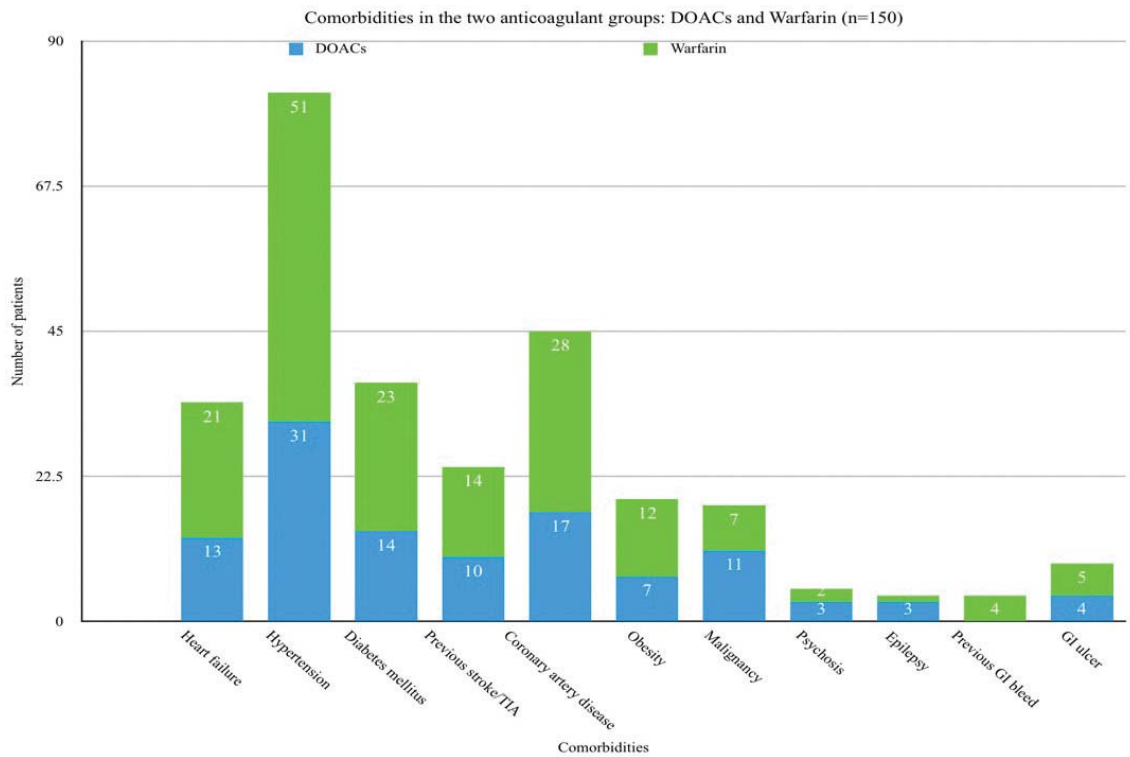

Figure 2. Comorbidities in the two anticoagulant groups: DOACs and Warfarin (n=150).

Table 4. Chi square test DOACs vs warfarin in minor bleeding events

Chi-Square Tests- Minor bleeding	Value	df	Asymptotic Significance (2-sided)	Exact Sig (2-sided)	Exact Sig (1-sided)
Pearson Chi-Square	5.129a	1	0.024		
Continuity Correctionb	4.319	1	0.038		
Likelihood Ratio	5.305	1	0.021		
Fisher's Exact Test				0.026	0.018
Linear-by-Linear Association	5.095	1	0.024		
N of Valid Cases	150				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 17.07 b. Computed only for a 2x2 table					
Symmetric Measures	Value		Approximate Significance		
Nominal by Nominal	Phi		-0.185	0.024	
	Cramer'sV		0.185	0.024	
N of Valid Cases	150				

tients than the DOACs group. Demographically (sex, age), DOACs and warfarin groups were almost identical in characteristics with an average age of 74 years and less females compared to males. This result was similar to the large RCTs that compared each DOAC with warfarin[9-12]. CHA_2DS_2-VASC score was slightly lower in the DOACs group compared to warfarin group (Figure 1). The mean HAS-BLED score was similar in both groups. The patients in the warfarin group had suffered from a higher number of comorbidities except epilepsy, malignancy and psychosis.

Ischaemic stroke

A total of six patients suffered an ischaemic stroke: one patient was on a DOAC and five patients were on Warfarin. The HR was 3.183 which showed that the risk of having an ischaemic stroke while taking warfarin was three times higher compared to taking DOACs. However, p=0.291 result was not statistically significant. The above results showed similarities with many real world data studies and clinical trials in regard to stroke prevention meaning that warfarin and DOACs have similar efficacy in preventing stroke[15,16]. A similar conclusion was reported in Hart et al study[4] where DOACs had a non-inferior efficacy to warfarin and a reduced ischaemic stroke by two-thirds compared with placebo. This study showed no difference between DOACs compared with warfarin in terms of the risk of having an ischemic stroke or systemic embolism.

In contrast, XANTUS study[17] described the use of DOACs for stroke prevention in a broad NVAF patient population which showed better outcomes for DOACs compared to warfarin.

Side effects

In this study, major gastrointestinal bleeding requiring admission to hospital was equally distributed in both groups, three patients were admitted to hospital from each group. The p value of 0.711 for major bleeding events accepted the null hypothesis that there was no statistically significant differences between the two groups of patients on warfarin vs DOACs anticoagulants.

In contrast to the above findings, Sterne et al.18 demonstrated advantages for taking DOACs because these were associated with lower risk of major bleeding, and mortality compared with warfarin in the largest real-world practice in patients with non valvular atrial fibrillation. Other studies such as Sjogren et al.[15] showed that DOACs are as effective for stroke prevention as well-managed warfarin but cause fewer major bleedings.

In this study there was a higher prevalence of minor bleeding events reported in the warfarin group (Cramer's value=0.185, p value 0.024). These results suggest that there was a small correlation between the type of anticoagulant and minor bleeding. Minor bleeding events in this study illustrated that patients taking warfarin had an increased risk for minor bleeding compared with patients taking DOACs. Likewise, Yap et al[19] shows that dabigatran had fewer reported minor bleeding compared to warfarin.

This study's findings were similar compared with studies such as Patel et al and Granger et al[10,11] which found decreased bleeding in apixaban and rivaroxaban (DOACs) compared with warfarin.

Sjogren et al[15] found that the risks for all-cause stroke or systemic embolism were similar in both

groups of oral anticoagulants (DOACs vs warfarin), but DOACs were associated with significantly lower risks of all-cause mortality, major bleeding and intracranial haemorrhage but higher risk of gastrointestinal bleeding[15].

DOACs have advantages over warfarin in patients with AF, but Sterne et al found no strong evidence that DOACs should replace warfarin or low molecular weight heparin (LMWH) in primary prevention, treatment or secondary prevention of venous thromboembolism (VTE)[18].

All DOACs seem to be safe and effective alternatives to warfarin in a routine care setting[20]. Pandya et al. demonstrated that the risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran etexilate compared with warfarin[20]. The above conclusions were similar with most large observational real world data studies around the world concluding that DOACs were showing similar efficacy compared with warfarin for stroke prevention but may possibly have better outcomes in reduced risk of bleeding[21-24].

Hanley et al[21] goes beyond and states that it can be difficult to understand why a prescriber would start warfarin in a new patient without a contraindication to a DOAC[25]. In addition, Hanley et al[21] stated that switching to a newer agent may not be necessary for the patient in whom the INR has been well controlled with warfarin and concluded that the decision to use a DOAC versus warfarin must be an individual one[21]. Similarly to Hanley et al[21], we recommend the use of up-to-date guidelines for oral anticoagulants and that warfarin is a very effective treatment and should be continued in patients who have good TTR but patients should be aware that they can have slightly increased risk of bleeding compared to DOACs. Finally, DOACs have showed to be effective in stroke prevention for patients with NVAF and have fewer bleeding events compared to warfarin[17].

CONCLUSION

Overall minor bleeding events were significantly lower in the DOACs group compared to warfarin group. In this real-world sample of NVAF patients, effectiveness and risks of DOACs versus warfarin were similar in regard to ischaemic stroke and major bleeding. Future studies should ideally focus on different subgroups of patients and have a larger number of patients such as a national database.

LIMITATIONS

As with all retrospective observational single centre studies, the accuracy of data depend on the quality of notes taking by medical professionals. Some minor side effects may not be reported by patients or documented by the clinician as they were deemed not life threatening.

Abbreviations

aF= Atrial Fibrillation; CAD=coronary artery disease; CHA_2DS_2-VASc=congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years (doubled), diabetes, previous stroke/TIA/thromboembolism (doubled), vascular disease, age 65–74 years, female sex; CHF=congestive heart failure; CI=confidence intervals; DOACs=direct oral anticoagulants; GI= gastrointestinal; HAS-BLED=Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol; INR=International Normalised Ratio; NVAF=non valvular Atrial Fibrillation; HR=hazard ratio; RCTs=randomised clinical trials; TTR=Time in Therapeutic Range

Conflict of interest: None declared.

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