Risk of stroke and other thromboembolic complications after interruption of DOAC therapy compared with warfarin therapy in patients with atrial fibrillation: a retrospective cohort analysis

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ABSTRACT

Direct oral anticoagulants (DOACs) have become the treatment of choice in thromboembolism prophylaxis for non-valvular atrial fibrillation, surpassing warfarin. While interruption of DOAC therapy for various reasons is a common eventuality, the body of data from real-world clinical practice on the implications of such interruptions in different clinical settings is still limited. We assessed complication rates from DOAC (apixaban, rivaroxaban, dabigatran) interruption compared with warfarin in hospitalized patients. We performed a retrospective cohort analysis of electronic records of patients hospitalized in Rabin Medical Center between 2010 and 2017. Incidents of anticoagulation interruptions for various reasons (including unintended interruptions) were collected. DOAC-treated patients were excluded if they reported non-compliance, and warfarin-treated patients were excluded if their international normalized ratio measurement on admission was subtherapeutic. Outcomes included ischemic stroke, systemic thromboembolism, myocardial infarction, and all-cause mortality within 90 days of anticoagulation interruption. The median CHA2DS2-VASc score was 5.0 (IQR 4.0–6.0) in both treatment groups. The associated risk of stroke, thromboembolic complications, myocardial infarction, and all-cause mortality after interruption of anticoagulation was not significantly different between the 2 treatment groups. Selective comparison of patients who were well balanced on warfarin before treatment interruption to DOAC-treated patients did not significantly influence the outcomes. This study did not find a significant difference in the complication rate after interruption of DOAC therapy compared with interruption of warfarin therapy in hospitalized patients with a high risk of thromboembolism.

Significance of this study

What is already known about this subject?

- Direct oral anticoagulants (DOACs) have been replacing vitamin K antagonists for the treatment of non-valvular atrial fibrillation during the last few years.
- Treatment suspension rates due to invasive procedures and other causes are still high and not necessarily reduced compared with warfarin.
- Rates of thromboembolic events after interruption of DOACs compared with warfarin are not clear.

What are the new findings?

- There was no significant difference in a composite outcome of all-cause mortality, stroke, systemic thromboembolism, and myocardial infarction between DOAC and warfarin-treated patients within 90 days of treatment interruption (TI).
- When comparing warfarin-treated patients who were well anticoagulated before the TI to all DOAC-treated patients, there was an increased difference in the risk of thromboembolic complications but this did not reach statistical significance.
- Complications in the DOAC group tended to occur earlier compared with the warfarin group.

How might these results change the focus of research or clinical practice?

- The possibility of a 'rebound' effect following interruption of DOACs is not supported by clear clinical evidence.
- Attention should be focused on the early period following interruption of DOACs in order to detect and possibly prevent complications.

INTRODUCTION

Direct oral anticoagulants (DOACs) have largely surpassed the vitamin K antagonists (mainly warfarin) for thromboembolism prophylaxis in non-valvular atrial fibrillation.[1–3] DOACs offer simpler daily fixed-dose regiments, do not require routine monitoring and have no restriction on dietary consumption of vitamin K-containing foods, thereby providing an opportunity for better treatment compliance.[4]

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Nonetheless, data acquired from several studies indicate that treatment discontinuation rates are still high and not necessarily reduced compared with warfarin.[5] In the RE-LY study, comparing Dabigatran to Warfarin in patients with atrial fibrillation, the rates of discontinuation for dabigatran and warfarin after 2 years were 21% and 16.6%, respectively.[6] In the ARISTOTLE study, a randomized control trail of Apixaban Vs Warfarin, those rates were 21.7% for apixaban and 23.7% for warfarin, when excluding deaths.[7] A retrospective study of a British population found that persistence rates after 12 months of treatment with dabigatran (66.7%), rivaroxaban (73.1%), and apixaban (82.8%) were comparable to vitamin K antagonists (77.8%).[8] A similar study in the USA found that after 2 years only 50.4% of patients treated with rivaroxaban are still adherent to their treatment with even lower number under dabigatran and warfarin (30.6% and 26.5%, respectively).[9]

In addition to treatment discontinuation, treatment suspension due to various indications, mainly invasive procedures, continues to be common with both DOACs and warfarin and is required in 8%–15% of patients each year.[10–14] According to guidelines from the American College of Cardiology, before procedures with low bleed risk when there are no increased patient bleed risk factors, the recommended suspension duration of DOACs is ≥24 hours while warfarin treatment can be continued. Before procedures with high bleed risk, the recommended duration of suspension is ≥48 hours for DOACs (and possibly longer in patients with renal dysfunction) and 5 days for warfarin (longer or shorter periods are recommended according to international normalized ratio (INR) levels).[10] In clinical practice, the suspension duration of DOACs can be longer than recommended. This discrepancy might stem from the relatively limited experience with DOACs and their reversal effect; the possible tendency of clinicians to fear the more immediate and tangible risks of bleeding than long-term thromboembolic events; the language of some guidelines which tend to specify minimal duration of suspension[10 15]; and unplanned delays of invasive procedures. Moreover, the body of data on the implications of treatment interruptions (TI) is still limited in several ways. First, most studies on DOAC TI mainly concern intended interruptions for invasive procedures,[16–20] even though interruptions for other reasons are very common.[21] There are insufficient data about interruptions due to acute changes in the patient's health, such as documented or expected acute

Table 1 Baseline patient characteristics

	Warfarin (n=157)	DOACs (n=144)	All patients
Age (y), median (IQR)	81.0 (75.0–86.0)	80.0 (74.0–87.0)	80.0 (75.0–86.0)
Female, n (%)	98 (62)	73 (51)	171 (57)
BMI (kg/m^2), median (IQR)	27.9 (24.6–31.6)	26.8 (23.9–30.3)	27.3 (23.9–31.2)
Aspirin or P2Y12 receptor blocker, n (%)	54 (34)	27 (19)	81 (27)
Statin, n (%)	97 (62)	101 (70)	197 (66)
Tobacco usage, n (%)			
Never	124 (80)	113 (79)	237 (79)
Current	8 (5)	9 (6)	17 (6)
Past	23 (15)	21 (15)	44 (15)
Total cholesterol (mg/dL), median (IQR)	154 (129–179)	148 (121–173)	149 (124–177)
LDL (mg/dL), median (IQR)	79 (60–99)	77 (61–99)	77 (60–91)
Cockcroft-Gault CrCl (mL/min/1.73 m^2), median (IQR)	50.2 (35.7–70.1)	58.1 (43.3–70.0)	54.2 (38.2–70.0)
MDRD CrCl (mL/min/1.73 m^2), median (IQR)	63.1 (42.7–78.2)	66.3 (51.8–82.6)	64.3 (46.7–80.6)
History of hypertension, n (%)	135 (86)	126 (88)	261 (87)
Any history of thromboembolism, n (%)	90 (57)	89 (62)	179 (59)
History of stroke, n (%)	39 (25)	37 (26)	76 (25)
History of TIA, n (%)	7 (4)	20 (14)	27 (9)
Evidence of vascular damage on imaging, n (%)	19 (12)	18 (13)	37 (12)
History of MI, n (%)	44 (28)	36 (25)	80 (27)
History of systemic thromboembolism, n (%)	7 (4)	6 (4)	13 (4)
Recent thromboembolic event (3 mo), n (%)			
Stroke	4 (3)	3 (2)	7 (2)
MI	4 (3)	4 (3)	8 (3)
CHF, n (%)	76 (48)	62 (43)	138 (46)
PVD, n (%)	26 (17)	20 (14)	46 (15)
DM, n (%)	61 (39)	58 (40)	119 (40)
Charlson score, median (IQR)	6.0 (5.0–7.0)	6.0 (5.0–8.0)	6.0 (5.0–7.0)
CHA2DS2-VASc score, median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–6.0)
CHADS2, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
Subtherapeutic enoxaparin, n (%)	51 (32)	48 (33)	99 (33)
Interruption length (d), median (IQR)	10.0 (5–20)	5.0 (4.0–8.0)	7.0 (4.0–7.0)

BMI, body mass index; CHF, congestive heart failure; CrCl, creatinine clearance; DM, diabetes mellitus; DOACs, direct oral anticoagulants; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischemic attack.

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Table 2 Reasons for anticoagulation interruption according to treatment group

	Warfarin n (%)	DOACs n (%)
Major surgery*	12 (8)	15 (10)
Non-major invasive procedure	49 (31)	61 (42)
Bleeding	31 (20)	25 (17)
Miscellaneous	61 (39)	19 (13)
Subtherapeutic coverage	4 (3)	3 (2)
Acute kidney injury	0 (0)	21 (15)

*Major surgery included open pelvic, abdominal and thoracic surgery, brain surgery, major orthopedic and trauma surgery, and vascular surgery.
DOACs, direct oral anticoagulants.

kidney injury; or about unintended interruptions of treatment. Second, while several studies found that rates of thromboembolic events after interruption of DOACs were comparable to warfarin,[12–14 16] reports from the ARISTOTLE trail and the ROCKET trials, comparing Rivaroxaban treament to Warfarin, showed an increased risk of thromboembolic complications after study drug discontinuation compared with warfarin-treated patients.[12 13] The latter findings were mainly attributed to the transition from the study drug to warfarin. Third, in most studies examining the implication of TIs, the follow-up period for the risk for thromboembolic event was 30–40 days after suspension or termination of DOAC treatment.[12 14 16 17 21] Nonetheless, there is evidence that the period of increased risk is longer. Raunsø *et al*[22] found that an interruption (suspension or termination) of warfarin treatment is associated with a significantly increased risk of death or thromboembolic events within the first 90 days of treatment cessation.[22] While a 30-day postinterruption time frame is in line with the International Society on Thrombosis and Hemostasis recommendations, it was also suggested to consider a longer follow-up of up to 90 days for secondary reporting of outcomes.[23]

Finally, warfarin-treated patients spend a significant proportion of time outside the therapeutic range, as has been reaffirmed in the RE-LY, ARISTOTLE, and ROCKET trials.[6 7 24] Nonetheless, the analysis from those trials of thromboembolic complications after anticoagulation interruption did not differentiate between patients who were well anticoagulated on warfarin and other patients.

Due to the limitation above, we attempted to assess complication rates from interruption of DOACs and warfarin in hospitalized patients.

METHODS

Study design

We conducted a retrospective cohort analysis of patients hospitalized in Rabin Medical Center between the years 2010 and 2017. Data were collected from patient electronic files. Patients were eligible if they were older than 18, diagnosed with atrial fibrillation or flutter before current hospitalization and treated with DOACs (apixaban, dabigatran, or rivaroxaban) or warfarin before current hospitalization. All patients had to have their anticoagulation treatment interrupted (suspended or terminated) during their hospitalization or on discharge. In case a patient had more than 1 episode of TI, each one was collected separately. Pregnant women, patients whose anticoagulation treatment was interrupted due to a hemorrhagic stroke, patients treated with an antidote, DOAC-treated patients who reported non-adherence to treatment on admission and warfarin-treated patients who had subtherapeutic INR measurements on admission were excluded.

Definitions

TI of DOACs was defined as no drug intake for at least 3 days, without full-dose bridging with an alternative anticoagulant. Treatment renewal of DOACs was defined as resumption of drug intake, documented in hospitalization records, or ordered on discharge. TI of warfarin was defined as subtherapeutic INR for at least 3 days or at least 5 days of no warfarin intake without sufficient INR measurements. Treatment renewal of warfarin was defined as the first measurement of INR in the therapeutic range or above it. Ischemic stroke was defined as a new focal neurologic deficit diagnosed by a neurologist as being caused by a stroke. Transient ischemic attack was defined as a new focal neurologic deficit lasting up to 24 hours, without new findings on brain imaging. Well-balanced warfarin treatment was defined as at least 2 INR measurements in the therapeutic range in the 4 weeks prior to TI.

Study outcomes

The primary outcome was a composite of all-cause mortality, stroke, systemic thromboembolism, and

Table 3 Outcomes within 90 d after interruption of anticoagulation according to treatment group

	Warfarin, n (%) (95% CI)	DOACs, n (%) (95% CI)	HR (95% CI) for DOACs versus warfarin
All events	43 (27.4) (20.6 to 35.1)	36 (25.0) (18.2 to 32.9)	0.98 (0.63 to 1.52)
All thromboembolic complications	8 (5.0) (2.2 to 9.8)	10 (6.9) (3.4 to 12.4)	1.40 (0.55 to 3.52)
Death (all cause)	35 (22.3) (16.0 to 29.6)	26 (18.1) (12.12 to 25.3)	0.88 (0.53 to 1.45)
Stroke	3 (1.9)	3 (2.1)	
TIA	1 (0.6)	3 (2.1)	
Systemic thromboembolism	1 (0.6)	1 (0.7)	
MI	3 (1.9)	3 (2.1)	

DOACs, direct oral anticoagulants; MI, myocardial infraction; TIA, transient ischemic attack.

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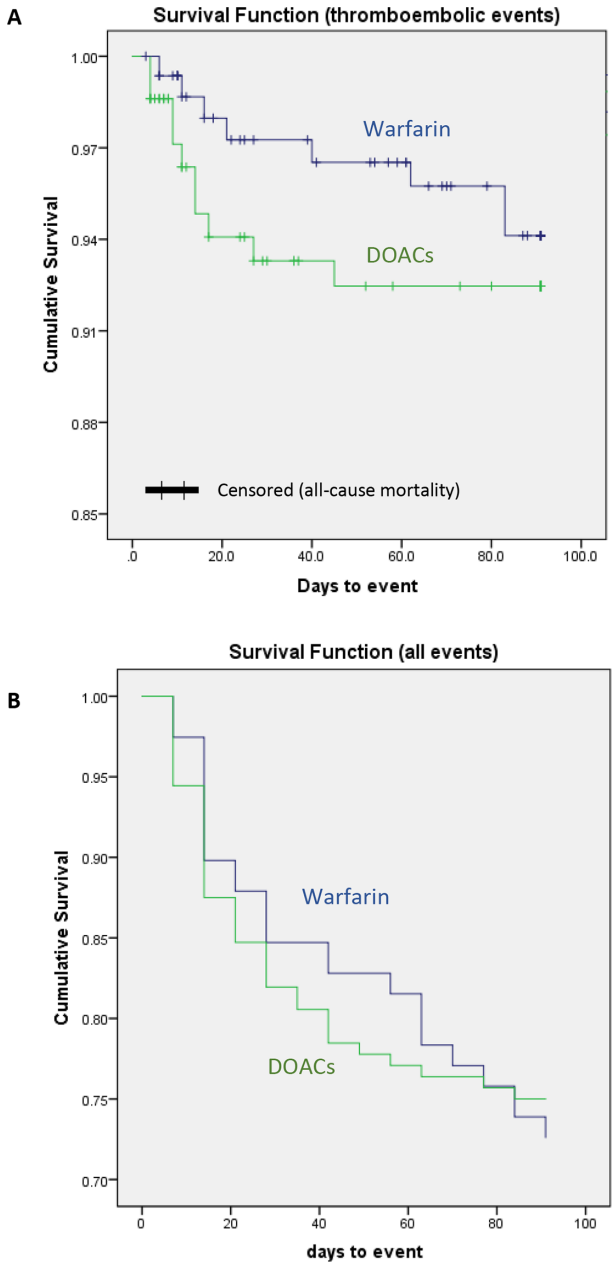

Figure 1 Time to event according to treatment group: (A) thromboembolic complications and (B) thromboembolic complications and all-cause mortality. DOAC, direct oral anticoagulants.

myocardial infarction (MI). The secondary outcomes were (1) a composite of stroke, systemic thromboembolism, and MI; and (2) all-cause mortality.

Statistical analysis

Baseline characteristics are summarized according to treatment groups. Data are shown as absolute values and percentages, or as medians with IQRs, as appropriate. Differences in outcomes were analyzed using Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. 95% CIs for proportions are given according to the Clopper-Pearson method. Survival analyses were performed with proportional hazard regression functions, treating alternative outcomes as competing risks. For every TI, only the first outcome was included in the statistical analysis. A p value <0.05 was regarded as significant.

RESULTS

We collected data from 692 hospital admission records; of those, 391 were excluded for not meeting the study's inclusion criteria.

We included 301 episodes of TI in 296 patients. The warfarin group included 157 episodes and the DOAC group (n=65 for apixaban, n=47 for rivaroxaban, and n=32 for dabigatran) included 144 episodes. As presented in table 1, most baseline characteristics, including CHA2DS2-VASc score (median=5, IQR=4–6) and other cerebrovascular risk factors, were similar between the 2 treatment groups. Patients in the warfarin group were more likely to be female (62.5% vs 51.05%) and treated with an antiplatelet medication (34.4% vs 18.9%) compared with the DOAC group. The TI length in the warfarin group was longer (18.79 vs 9.32 days in the DOAC group).

Interruption characteristics and bridging patterns

The reasons for TI are shown in table 2. In the warfarin group, the most common reasons for TI were invasive procedures (including non-major surgery, endoscopic and endovascular procedures) and bleeding. A significant proportion of TIs in that group were classified as 'miscellaneous'—including logistic error or unknown, apparent failure to maintain therapeutic INR and overcorrection of supratherapeutic INR on admission. In the DOAC group, the most common reasons for TI were invasive procedures, bleeding, and acute kidney injury. As previously noted, we excluded from our research patients who were treated with full-dose parenteral anticoagulation. A third of the patients included in the study were treated with subtherapeutic dosages of parenteral anticoagulation, either as venous thromboembolism prophylaxis or due to the treating physician's decision according to individual risk-benefit assessment.

Outcomes of TIs

Outcomes according to treatment group are shown in table 3 and figure 1. There was no significant difference in our primary and secondary outcomes between DOAC and warfarin-treated patients within 90 days of TI. For all events, HR for DOACs versus warfarin was 0.98 (95% CI 0.63 to 1.52); for all thromboembolic complications and all-cause mortality, HRs were 1.40 (95% CI 0.55 to 3.52) and 0.88 (95% CI 0.53 to 1.45), respectively. Median CHA2DS2-VASc scores of patients who met an outcome were comparable between the 2 treatment groups: 5.0 for all events (warfarin=5.0, DOACs=5.0) and 6.0 for thromboembolic complications (warfarin=6.0, DOACs=5.5). Patients who were well balanced on warfarin before TI (n=53) had no significant difference in baseline characteristics (including median CHA2DS2-VASc score=5, IQR=4–6), discontinuation length, and rate of enoxaparin use compared with the original warfarin cohort. As shown in table 4, a selective comparison of this subgroup to all DOAC patients did not yield a significant difference.

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Table 4 Outcomes of DOAC patients versus selected warfarin patients (well balanced prior to interruption of anticoagulation)

	Warfarin (53), n (%) (95% CI)	DOACs (144), n (%) (95% CI)	HR (95% CI) for DOACs versus warfarin
All events	14 (26.4) (15.3 to 40.3)	36 (25.0) (18.2 to 32.9)	1.01 (0.55 to 1.87)
All thromboembolic complications	1 (1.9) (0 to 10.1)	10 (6.9) (3.4 to 12.4)	3.76 (0.48 to 29.41)
Death (all cause)	13 (24.5) (13.8 to 38.3)	26 (18.1) (12.12 to 25.3)	0.79 (0.41 to 1.54)
Stroke	1 (1.9)	3 (2.1)	
TIA	–	3 (2.1)	
Systemic thromboembolism	–	1 (0.7)	
MI	–	3 (2.1)	

DOACs, direct oral anticoagulants; MI, myocardial infraction; TIA, transient ischemic attack.

DISCUSSION

This study aimed to evaluate the consequences of interrupting anticoagulation treatment, comparing DOACs to warfarin. It demonstrated no significant difference between the two treatment groups in the associated risk of death, stroke, systemic thromboembolism and MI.

The expanding use of DOACs requires physicians to handle an ever more complex decision-making process concerning TIs and their implications in an aging population with ample comorbidities. Reports from phase III DOAC trials found similar complication rates after interruption of DOAC and warfarin therapies.[12–14] Nonetheless, reports from the end of ARISTOTLE and ROCKET trials revealed increased rates of thromboembolic complications after discontinuation of apixaban and rivaroxaban.[25 26] While both reports attributed the excess complication rate to the transition to warfarin, those examples demonstrate the need for more data from different clinical settings.

In the current landscape of publications on this matter, this study is unique in being specifically designed to compare the complication rates following interruptions of DOAC and warfarin therapies in 'real-life' clinical settings; investigating hospitalized patients with high risk of thromboembolism; and measuring complications in an extended period after TI (90 days vs about 30–40 days in most studies). We also explored interruptions for various reasons, including those unrelated to invasive procedures. In order to limit the effect of possible residual anticoagulation, we only included patients with at least 3 days of TI and excluded patients who were treated with a full dose of parenteral anticoagulation.

As could be expected from the study design, patients in our cohort were older and had higher CHA2DS2-VASc scores (median=5.0, IQR=4.0–6.0) compared with other publications.[7–9 11 14 17 22 23] Rates of thromboembolic complications after TI were also higher (30-day rate 2.54% for warfarin and 6.25% for DOACs; 90-day rate 5.0% for warfarin and 6.9% for DOACs) than usually reported.[12–14 16–20] The latter finding might reflect the increased background risk (ie, higher CHA2DS2-VASc scores), or point to an increased risk of complications in hospitalized patients.

When comparing the characteristics of both patient groups, antiplatelet use was more common in the warfarin group. One explanation for this difference could be the fact that in the past antiplatelet drugs were used for primary prevention of cerebrovascular and cardiovascular diseases, but recent research did not support this indication. Another explanation is that current guidelines, updated following the extensive use of DOACs, recommend long-term single therapy with anticoagulation for atrial fibrillation in patients with ischemic heart disease. Despite the difference in antiplatelet use, we found no significant difference in the primary outcome, further supporting the study's conclusion.

Considering that warfarin-treated patients spend a significant proportion of time outside of the therapeutic range and therefore may have 'non-indicated interruptions' of treatment, we performed a post hoc analysis comparing warfarin-treated patients who were well anticoagulated before the TI to all DOAC-treated patients. This comparison demonstrated an increased difference in the risk of thromboembolic complications between the 2 groups but did not reach statistical significance (HR 1.40, 95% CI 0.55 to 3.52 vs HR 3.76, 95% CI 0.48 to 29.41).

The high rate of all-cause mortality in our study led us to ponder the possibility of influence by a large group of terminally ill patients. A review of our data identified only a small number of such patients (n=11), and no further statistical analysis was pursued.

While most events meeting the predetermined outcomes (all-cause death, stroke, systemic thromboembolism, and MI) occurred in the first 30 days after TI in both treatment groups, they were more evenly dispersed in the warfarin group, as shown in figure 1. The latter finding is in line with previous evidence of increased risk in the first 90 days after TI.[22] Complications in the DOAC group tended to occur earlier (7/10 of thromboembolic events occurred in the first 14 days after TI) compared with the warfarin group (2/8 of thromboembolic events occurred in the first 14 days after TI). While such a 'clustering' phenomenon is arguably harder to demonstrate in a 30-day follow-up, clues to its existence were seen in other observational real-life studies,[18 27] but not in the reports from the phase III DOAC trials. A distinction should be made from the long-debated possibility of a 'rebound' effect (ie, an excess risk of thromboembolic complications beyond what would be conferred by background risk factors and acute\subacute insults) following interruption of anticoagulation. This concept is hard to measure and, to date, not supported by clear clinical evidence.

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Our study is mainly limited by its retrospective nature and modest sample size. Comparing the interruption of DOAC therapy to the interruption of warfarin therapy in an observational study is challenging. There are different recommendations concerning indications to interrupt treatment and evolving guidelines concerning the use of bridging therapy; and differences in the length of TI (as was demonstrated in our study). Furthermore, the waning use of warfarin in parallel to the increasing use of DOACs creates a temporal gap between the 2 treatment groups, adding further to the possibility of unaccounted differences. While our sample size did not allow us to perform propensity score matching, we used sequential univariate and multivariate analyses. Nonetheless, unaccounted differences between the 2 treatment groups cannot be ruled out. Finally, our reliance on a cohort derived from a single center and our decision to exclude several groups of patients (non-compliant DOAC patients, warfarin patients with subtherapeutic INR on admission, patients bridged with full-dose parenteral anticoagulation) limit the generalizability of our findings. As our results may indicate a particular clinical problem this cannot be assumed for a broader multiethnical group of patients. Notwithstanding the limitations of the generalizability of our findings, they demonstrate the importance of further studies on selected populations to allow for adequate risk assessment in clinical decision-making.

CONCLUSION

Comparing DOACs to warfarin, this study did not find a significant difference in all-cause mortality and thromboembolic complications after TI in high-risk hospitalized patients. The relatively high complication rate in our cohort compared with published data demonstrates the importance of further studies on selected populations to allow for adequate risk assessment in clinical decision-making concerning interruption of anticoagulation treatment.

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Patient consent for publication Not required.

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REFERENCES

1 López-López JA, Sterne JAC, Thom HHZ, *et al*. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ* 2017;359:j5058.
2 Kimachi M, Furukawa TA, Kimachi K, *et al*. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database Syst Rev* 2017;11:CD011373.
3 Park J, Lee S-R, Choi E-K, *et al*. Effectiveness and safety of direct oral anticoagulant for secondary prevention in Asians with atrial fibrillation. *J Clin Med* 2019;8:e2228:2228.
4 Okumura Y, Yokoyama K, Matsumoto N, *et al*. Patient satisfaction with direct oral anticoagulants and warfarin. *Int Heart J* 2018;59:1266–74.
5 Zielinski GD, Rein N, Teichert M, *et al*. Persistence of oral anticoagulant treatment for atrial fibrillation in the Netherlands: a surveillance study. *Res Pract Thromb Haemost* 2020;4:141–53.
6 Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med Overseas Ed* 2009;361:1139–51.
7 Granger CB, Alexander JH, McMurray JJV, *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
8 Johnson ME, Lefèvre C, Collings S-L, *et al*. Early real-world evidence of persistence on oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a cohort study in UK primary care. *BMJ Open* 2016;6:e011471.
9 Coleman CI, Tangirala M, Evers T. Treatment persistence and discontinuation with rivaroxaban, dabigatran, and warfarin for stroke prevention in patients with Non-Valvular atrial fibrillation in the United States. *PLoS One* 2016;11:e0157769.
10 Doherty JU, Gluckman TJ, Hucker WJ, *et al*. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. *J Am Coll Cardiol* 2017;69:871–98.
11 Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med* 2013;368:2113–24.
12 Garcia D, Alexander JH, Wallentin L, *et al*. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood* 2014;124:3692–8.
13 Healey JS, Eikelboom J, Douketis J, *et al*. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the randomized evaluation of long-term anticoagulation therapy (RE-LY) randomized trial. *Circulation* 2012;126:343–8.
14 Sherwood MW, Douketis JD, Patel MR, *et al*. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (rocket AF). *Circulation* 2014;129:1850–9.
15 Veitch AM, Vanbiervliet G, Gershlick AH, *et al*. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of gastroenterology (Bsg) and European Society of gastrointestinal endoscopy (ESGE) guidelines. *Gut* 2016;65:374–89.
16 Steinberg BA, Peterson ED, Kim S, *et al*. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the outcomes Registry for better informed treatment of atrial fibrillation (ORBIT-AF). *Circulation* 2015;131:488–94.
17 Beyer-Westendorf J, Gelbricht V, Forster K, *et al*. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J* 2014;35:1888–96.
18 Heublein V, Pannach S, Daschkow K, *et al*. Gastrointestinal endoscopy in patients receiving novel direct oral anticoagulants: results from the prospective Dresden NOAC registry. *J Gastroenterol* 2018;53:236–46.
19 Marsh K, Ahuja T, Raco V, *et al*. A retrospective analysis of the periprocedural management of oral anticoagulants in patients undergoing interventional radiology procedures. *J Thromb Thrombolysis* 2018;46:451–60.
20 Shaw JR, Woodfine JD, Douketis J, *et al*. Perioperative interruption of direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Res Pract Thromb Haemost* 2018;2:282–90.
21 Patel MR, Hellkamp AS, Lokhnygina Y, *et al*. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the rocket AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 2013;61:651–8.
22 Raunsø J, Selmer C, Olesen JB, *et al*. Increased short-term risk of thromboembolism or death after interruption of warfarin treatment in patients with atrial fibrillation. *Eur Heart J* 2012;33:1886–92.

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23 Spyropoulos AC, Douketis JD, Gerotziafas G, *et al*. Periprocedural antithrombotic and bridging therapy: recommendations for standardized reporting in patients with arterial indications for chronic oral anticoagulant therapy. *J Thromb Haemost* 2012;10:692–4.
24 Patel MR, Mahaffey KW, Garg J, *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
25 Granger CB, Lopes RD, Hanna M, *et al*. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. *Am Heart J* 2015;169:25–30.
26 Mahaffey KW, Hellkamp AS, Patel MR, *et al*. End of study transition from study drug to open-label vitamin K antagonist therapy: the rocket AF experience. *Circ Cardiovasc Qual Outcomes* 2013;6:470–8.
27 Sakamoto Y, Okubo S, Nito C, *et al*. Ischemic stroke during anticoagulant interruption by healthcare professionals in stroke patients with atrial fibrillation. *J Neurol Sci* 2019;400:113–8.

J Investig Med: first published as 10.1136/jim-2020-001497 on 5 August 2021. Downloaded from file:/ on April 10, 2024 by guest. Protected by copyright.