ORIGINAL RESEARCH ARTICLE

Direct oral anticoagulation and mortality in moderate to high-risk atrial fibrillation

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ABSTRACT

Objective Although direct oral anticoagulants (DOAC) are the recommended antithrombotic therapy for patients with non-valvular atrial fibrillation (NVAF), anticoagulation in patients with NVAF is still inadequate. The effect of withholding DOAC therapy on patient survival is unknown. Therefore, our objective was to compare all-cause mortality rates between DOAC-treated patients with NVAF and similar patients receiving no anticoagulation.

Methods We performed a retrospective cohort study analysing Clalit Health Services' extensive electronic database, regarding all newly diagnosed, anticoagulant-naïve patients with NVAF who were eligible for DOAC therapy from 1 January 2011 to 31 December 2016. Patients who received DOAC therapy were matched by propensity scoring to patients receiving no anticoagulation. The primary outcome was all-cause mortality. Final patient follow-up date was 15 May 2017.

Results 18 901 eligible patients were identified. 8298 received treatment with a DOAC and 10 603 received no anticoagulation therapy. Of those, 5657 patients who received DOAC therapy were matched with 5657 patients who did not receive any anticoagulant. Death occurred in 715 patients in the DOAC-treated group (7.6% per year) and in 2075 patients in the non-anticoagulated patient group (11.1% per year). DOAC therapy was associated with significantly lower risk for all-cause mortality (HR=0.69, 95% CI 0.63 to 0.75, p<0.001). The benefit of DOAC therapy was demonstrated across all subgroups analysed.

Conclusions In this cohort of newly diagnosed patients with NVAF, DOAC therapy was associated with a significantly lower risk of death compared with no oral anticoagulation. Our findings provide further evidence for the importance of providing DOAC anticoagulation in patients with NVAF.

INTRODUCTION

Anticoagulation with vitamin K antagonists (VKA) is associated with a significant reduction in stroke and all-cause mortality rates in patients with atrial fibrillation (AF).[1] Direct oral anticoagulants (DOAC) have equivalent or superior efficacy compared with VKAs in reducing the rate of stroke and systemic embolism in patients with non-valvular AF (NVAF).[2–4] Their predictable anticoagulant effect allows fixed dose administration without the need for routine coagulation monitoring or dietary modifications, thereby simplifying treatment and potentially improving utilisation and adherence. This has led to a process where physicians have increasingly adopted the DOACs in preference to VKAs.[5] Nevertheless, DOAC use remains suboptimal in many healthcare systems and many patients with NVAF still do not receive any anticoagulant[6 7] often without a clear reason.[8]

There is little information available regarding the effect of anticoagulation on overall mortality among patients with AF, and no randomised controlled clinical trial (RCT) with this endpoint has been performed. Since DOACs are the standard of care, given their efficacy in reducing stroke and systemic embolism, a prospective randomised study examining the overall mortality benefit of DOACs versus no anticoagulation cannot be considered ethical. Therefore, we performed this observational cohort study to evaluate rates of overall mortality in patients with AF receiving DOAC therapy compared with similar patients receiving no anticoagulation.

METHODS

Data source

Clalit Health Services' (CHS) comprehensive computerised patient register was the data source for this retrospective cohort study. CHS is the largest healthcare maintenance organisation in Israel, with approximately 4.5 million insured members (52% of the total population). The annual turnover in CHS is <1%, thus very few patients are lost to follow-up. CHS's information is maintained in a central computerised data warehouse that includes demographic, clinical, hospitalisation, laboratory and all dispensed medication data.[9]

Study population

We identified all patients with a diagnosis of AF from 1 January 2011 until 31 December 2016. Patients were identified on the basis of physician-assigned diagnoses of AF on either hospital discharge, hospital outpatient clinic or primary care physician visits. To minimise selection and channelling bias, we included in the current study only VKA-naïve, newly diagnosed patients. Although CHA_2DS_2-VASc score is currently the standard for estimating AF stroke risk,[10] eligibility for DOAC therapy reimbursement in Israel during the study period was limited to patients at moderate to high risk for stroke and systemic embolism, as defined according to the $CHADS_2$ score with a value of 2 or greater.[11] Therefore, key exclusion criteria were previous treatment with VKAs, AF diagnosis before 2011, missing medication data, or missing data

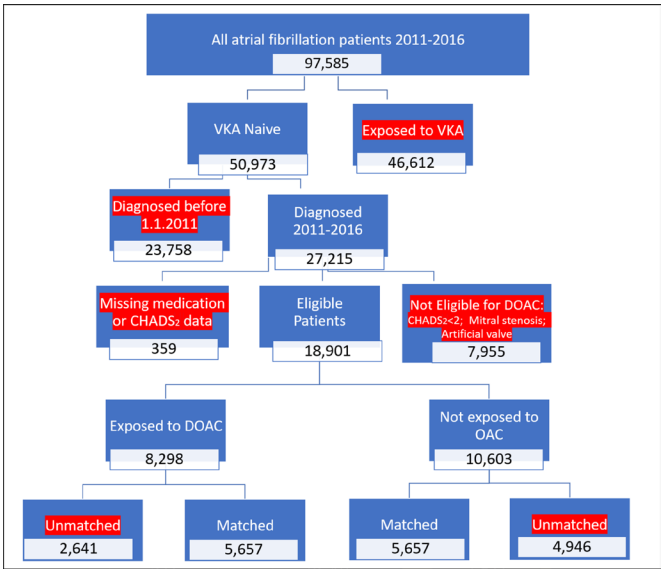

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the patient cohort. DOAC, direct oral anticoagulants; OAC, oral anticoagulants; VKA, vitamin K antagonists.

needed to calculate the $CHADS_2$ score. Patients were followed until 15 May 2017 or death.

Study outcomes

The primary effectiveness endpoint was all-cause mortality. Secondary endpoints were ischaemic stroke (including transient ischaemic attack), acute myocardial infarction and major bleeding events that required hospitalisation. Detailed definitions of the endpoint events are provided in online supplementary table 1.

DOAC initiation and adherence

Patient's initiation of DOAC therapy and long-term adherence were determined based on CHS's electronic dispensing records. Patients were considered to be 'on DOAC therapy' up to 30 days after their last filled prescription. Patients were defined as 'discontinued DOAC therapy' if they stopped treatment for any reason, more than 30 days prior to the end of the follow-up period.

Propensity score matching

We created a matched cohort (DOAC treatment vs no anticoagulant) using 1:1 propensity score matching (PSM), without replacement and using a calliper of 0.1. Propensity scores were estimated using logistic regression, which included information on 22 sociodemographic and clinical characteristics and concurrent medications. The results of the PSM are detailed in online supplementary table 2. Multivariate regression on all patients who met the study criteria, including the unmatched patients, was used for sensitivity analysis.

Statistical analysis

Cox proportional hazards regression was used to compare mortality outcomes in the matched cohort. The proportional hazards assumptions of the Cox model were verified by visual examination of the Kaplan-Meier graphs for each variable. In order to minimise immortal time bias, the regression incorporated a time-dependent analysis[12] by classifying the DOAC-treated patients as unexposed until they become exposed. The regression model included the treatment (DOAC or no anticoagulation) and was controlled for 24 baseline characteristics as the independent variables and all-cause mortality as the dependent variable. The Charlson Comorbidity Index score was used to account for other major diseases influencing mortality such as myocardial infarction, cancer, HIV infection, chronic obstructive pulmonary disease and liver disease.[13] Kaplan-Meier survival curves were used to demonstrate cumulative hazard rates for the primary outcome of death using R statistical software V.3.4.4.

A second Cox proportional hazards regression model was constructed to evaluate separately HRs for all-cause mortality in patients 'on DOAC therapy' and the HR for all-cause mortality in patients who permanently discontinued DOAC treatment, both versus the 'no-anticoagulation' group as the reference. The regression model was controlled for all 24 baseline characteristics as the independent variables and mortality as the dependent variable.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, V.24. P values <0.05 determined statistical significance in all analyses.

Subgroup analysis

Subgroup analysis was performed on various subgroups, including gender, age, comorbidities and concurrent medications. HRs in the sensitivity analysis were adjusted for immortal time bias. Forest plots were generated using the SAS software, V.9.4 (SAS Institute).

Compliance to guidelines and ethical approvals

The study was designed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement, as detailed in the online supplementary table 3. The study was approved by CHS's data extraction committee and ethical approval was provided by the Institutional Review Board of CHS.

RESULTS

Study population

A total of 97 585 patients with a diagnosis of AF between 2011 and 2016 were identified in the CHS database. Of those, 46 612 patients were excluded because of previous treatment with VKAs. Another 23 758 patients who were diagnosed before 2011 (7955 patients with $CHADS_2$ score <2 or with mitral stenosis or an artificial valve and 359 patients with missing medication and/or $CHADS_2$ data) were also excluded. Of the remaining 18 901 patients, 8298 started DOAC therapy and 10 603 received no anticoagulation. A total of 11 314 patients were matched 1:1 by propensity scoring (Consolidated Standards of Reporting Trials diagram is presented in figure 1).

Propensity score matching

Matched patients' key clinical characteristics are presented in table 1. There were no significant differences in any of the characteristics between the two groups after matching, except for previous myocardial infarction and beta blocker therapy, which were not included in the PSM.

Mortality during follow-up

The mean follow-up time was 30.3 months (median 28.5; IQR 17.3, 41.6). Cumulative survival of the DOAC-treated and the non-anticoagulated patients during the study period is presented in figure 2. Death occurred in 715 patients in the DOAC-treated group (7.6% per year) and in 2075 patients in the non-anticoagulated patient group (11.1% per year, after adjustment for

Table 1 Baseline characteristics of the propensity-matched patient groups

Patient characteristics	DOAC treated n=5657	No anticoagulant n=5657
Age (years; mean, SD)	78 (11)	78 (11)
Age >75 years (n [%])	3658 (64.7)	3602 (63.7)
Female Sex (n [%])	2704 (47.8)	2682 (47.4)
BMI, kg/m^2 (mean)	29.1	29.1
Socioeconomic status (mean)	5.46	5.46
Creatinine clearance (mean)	1.03	1.03
Estimated glomerular filtration rate (mL/min/1.73 m^2) (mean)	66.24	66.47
Charlson Comorbidity Index	3.34	3.36
CHA_2DS_2-VASc (mean)	4.74	4.70
$CHADS_2$ (mean)	3.14	3.12
Concomitant illnesses (n [%])		
Congestive heart failure	1613 (28.5)	1600 (28.3)
Hypertension	5371 (94.9)	5365 (94.8)
Peripheral vascular disease	1039 (18.4)	1010 (17.9)
Diabetes mellitus	3194 (56.5)	3171 (56.1)
Chronic renal failure	1339 (23.7)	1363 (24.1)
Cerebrovascular incident	1813 (32.0)	1792 (31.7)
Previous myocardial infarction	745 (13.2)	647 (11.4)
Concomitant medications at baseline (n [%])*		
Platelet aggregation inhibitors (Aspirin, P2Y12 inhibitors)	3474 (61.4)	3526 (62.3)
Cardiac glycosides	215 (3.8)	207 (3.7)
Antiarrhythmics	1268 (22.4)	1220 (21.6)
Low ceiling diuretics	2503 (44.2)	2442 (43.2)
High ceiling diuretics	703 (12.4)	702 (12.4)
Angiotensin receptor blockers	1882 (33.3)	1871 (33.1)
Lipid-modifying agents	3943 (69.7)	3887 (68.7)
ACE inhibitors	2863 (50.6)	2824 (49.9)
Non-steroidal anti-inflammatories	2382 (42.1)	2348 (41.5)
Beta blockers	4823 (85.3)	3960 (70.0)

*Anatomical Therapeutic Chemical (ATC) coding is detailed in online supplementary table 7.
BMI, body mass index; DOAC, direct oral anticoagulants.

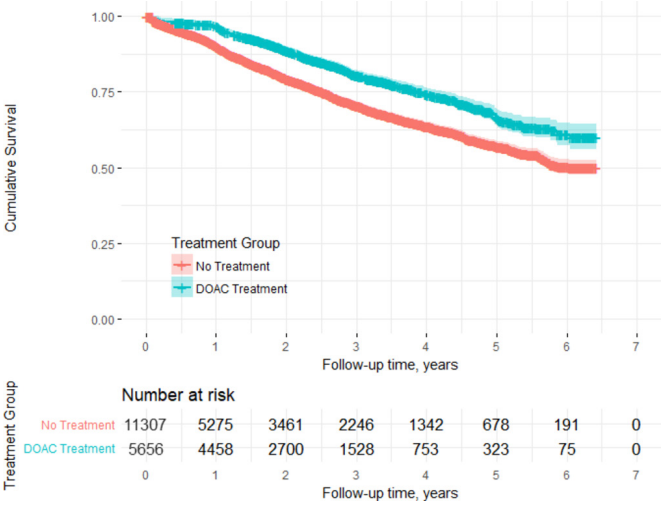

Figure 2 Cumulative survival of the DOAC-treated and the non-anticoagulated patients. DOAC, direct oral anticoagulants.

immortality time bias), as detailed in table 2. The adjusted HR for death in DOAC-treated patients was 0.69 (95% CI 0.63 to 0.75). The Cox proportional hazards regression model is detailed in the online supplementary table 4.

A multivariate regression model of all 18 901 eligible patients (online supplementary table 5) demonstrated comparable results to the PSM model: adjusted HR 0.66 (95% CI 0.61 to 0.71). The mortality benefit of DOAC therapy was significant across all subgroups (figure 3) and in all concomitant drugs (online supplementary figure 1).

'On DOAC therapy' versus 'discontinued DOAC treatment'

Of the 715 deaths in the DOAC group, 336 occurred in patients on DOAC therapy (5.3 per 100 patient-years, adjusted HR for death in patients on DOAC therapy was 0.47 [95% CI 0.42 to 0.53]). A total of 379 patients died after permanent discontinuation of DOAC therapy (12.1 per 100 patient-years, adjusted HR=0.95 [95% CI 0.85 to 1.07, NS]) (table 2). Results of the regression model are presented in the online supplementary table 6. Cumulative survival of patients receiving DOAC therapy continuously versus DOAC therapy that was discontinued versus non-anticoagulated patients is presented in figure 4.

Secondary outcomes

During the follow-up period, major cardiac events occurred in 96 patients in the DOAC group and in 327 patients in the non-anticoagulated group ([1.0 and 2.5/100 patient-years, respectively]; adjusted HR=0.33 [95% CI 0.27 to 0.41, p<0.001]).

Cerebrovascular events occurred in 151 patients in the DOAC group and in 267 of the non-anticoagulated patients ([1.6 and 2.0/100 patient-years, respectively]; adjusted HR=0.67 [95% CI 0.55 to 0.82; p<0.001]). There were 140 major bleeding requiring hospitalisation among the DOAC-treated versus 215 events in the non-anticoagulated patients ([1.5 and 1.6/100 patient-years, respectively]; HR=0.82 [95% CI 0.66 to 1.02], p=0.074, NS).

DISCUSSION

In this cohort of newly diagnosed patients with moderate to high-risk NVAF treated in routine clinical practice, DOAC therapy was associated with a 31% reduction in all-cause mortality rate compared with no oral anticoagulation.

To our knowledge, the current study is the first to demonstrate reduced mortality in DOAC-treated patients with NVAF compared with patients receiving no anticoagulation in a relatively long follow-up period (mean of 30.3 months). A strength of the current study is that the patient cohort was well defined and consisted only of patients diagnosed with NVAF during the study period, thus avoiding bias of including previously diagnosed and non-anticoagulated patients with AF. Another strength of this study is that patients were extensively characterised and well matched by propensity scoring allowing for reliable comparison between the groups. Using propensity matching in this large observational study provides a more valid estimate of treatment effects because it compares patients with similar observed characteristics, all of whom were potential candidates for DOAC therapy.[14] Although we were able to match most of the eligible patients, 40% of the patients did not meet the matching criteria and were thus excluded from the analysis which may have introduced a selection bias. However, multivariate regression modelling that included all valid patients was performed as a sensitivity analysis and demonstrated comparable results, with a slightly higher association with mortality (HR 0.66 vs 0.69).

Table 2 Primary outcome—rates of all-cause mortality

	DOAC			No anticoagulant				
Population	Patients (n)	Deaths (n)	Deaths/100 patient-years	Patients (n)	Deaths (n)	Deaths/100 patient-years	Adjusted HR (95% CI)	P value
All patients	5657	715	7.6	5657	2075	11.1	0.69 (0.63 to 075)	<0.001
Continuous treatment	3801	336	5.3	5657	2075	11.1	0.47* (0.42 to 0.53)	<0.001
Discontinued treatment	1856	379	12.1	5657	2075	11.1	0.95† (0.85 to 1.07)	0.60

'Continuous treatment' denotes those patients receiving DOACs until the end of study follow-up.
'Discontinued treatment' denotes patients who received DOACs in whom treatment was permanently discontinued prior to end of follow-up.
*HR refers to 'Continuous treatment' compared with 'no anticoagulant'.
†HR refers to 'Discontinued treatment' compared with 'no anticoagulant'.
DOAC, direct oral anticoagulant.

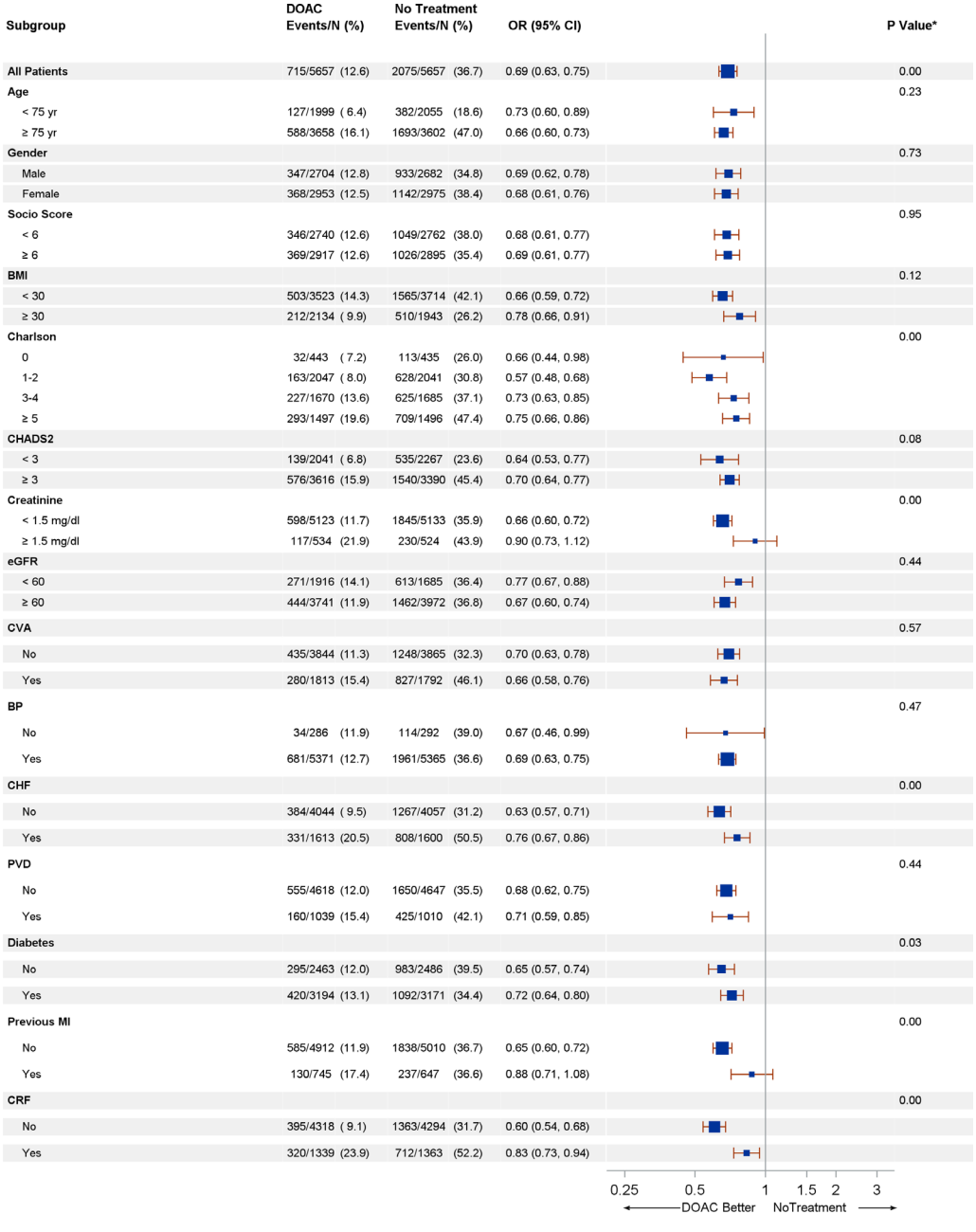

Figure 3 Relative risk of death in major patient subgroups. BMI, body mass index; BP, blood pressure; CHF, congestive heart failure; CRF, chronic renal failure; CVA, cerebrovascular accident; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PVD, peripheral vascular disease.

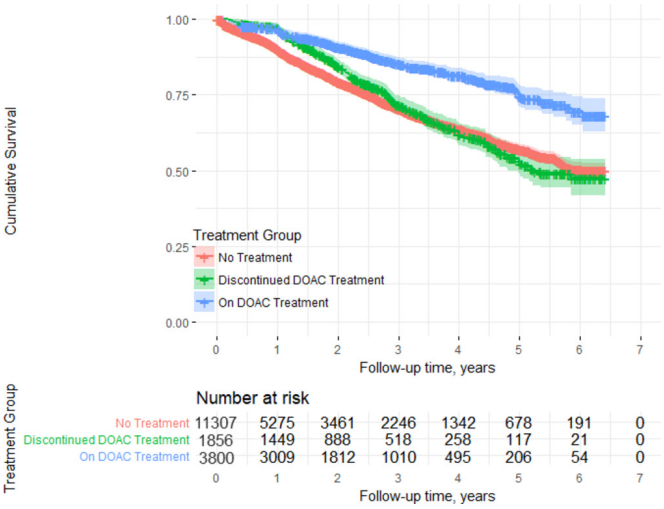

Figure 4 Cumulative survival of patients receiving DOAC therapy continuously versus DOAC therapy that was discontinued versus non-anticoagulated patients. *DOAC-treated patients are classified as unexposed ('No treatment') until they become exposed in order to minimise immortal time bias. DOAC, direct oral anticoagulants.

It should be emphasised that our study has a few other limitations that are common for retrospective database analyses. First, our primary outcome measure was all-cause mortality. We were unable to assess cardiovascular mortality separately, since we could not ascertain the specific causes of death, which are not recorded in the CHS database. Further, while propensity matching is an effective method to ensure similarity between patient groups in retrospective studies, there may be biases that were unrecognised and not included in the terms used for matching.

A meta-analysis of 29 trials comparing anticoagulation to no anticoagulation in patients with AF performed more than two decades ago demonstrated a reduction in all-cause mortality of 26% among patients with AF receiving VKAs (95% CI 3% to 43%).[15] A recent meta-analysis of RCTs comparing DOACs to VKAs[16] demonstrated a 10% reduction in all-cause mortality. If we assume a cumulative effect of these two studies, it is reasonable to expect a 30% reduction in mortality of DOAC versus no anticoagulation, as was demonstrated in our study. The all-cause mortality rate of patients in our current study is significantly higher than that observed in RCTs, but this is to be expected from a real-world study,[17] in which patients are usually older and have more comorbidities.

While the precise reason for the reduction in overall mortality observed in patients with AF who receive anticoagulants is unclear, some possible explanations may be proposed. First, anticoagulation together with antiplatelet therapy has re-emerged as effective treatment for avoiding ischaemic coronary events[18] and therefore may reduce cardiac mortality resulting from myocardial ischaemia. Second, anticoagulation may reduce the incidence of fatal stroke.[19] Third, patients receiving anticoagulants may be more closely monitored and may receive better overall medical care, and finally, patients receiving anticoagulants may be healthier than those who are not, since increasing numbers of comorbidities and overall poor health are known to deter physicians from prescribing anticoagulants.[20 21]

Despite their proven efficacy in AF, anticoagulants are still underused for various reasons.[6] Recently, the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) investigators have demonstrated that in their prospective worldwide registry of over 50 000 patients with AF with an indication for anticoagulation, only 66.2% received anticoagulant therapy.[22] While this study could not determine the reasons for underuse of anticoagulation in patients with AF, it was able to identify a significant overuse of antiplatelet monotherapy among the patients. Potential reasons for this phenomenon were concern for an increased risk of intracranial haemorrhage in certain populations, and both physician and patient concern of exposure to serious bleeding. This rate of anticoagulant use in GARFIELD-AF is similar to that in our cohort in which only 62.4% of the patients received an anticoagulant.

The study demonstrates that two factors have a significant impact on overall mortality rates in NVAF: lack of prescription of any anticoagulant for eligible patients, and second is the discontinuation of therapy in patients who have already initiated DOAC therapy. We do not have data to explain the reasons for patients not receiving or discontinuing therapy. Future studies should attempt to reveal the reasons for these practices at the individual patient level.

It can be hypothesised that OAC in general and DOACs in particular have a strong impact on the risk of death by preventing major venous thromboembolic complications.[18 19] This hypothesis is strengthened by the results of our secondary outcomes, which demonstrate a 67% reduction in such events. Future research with validated causes of death should be performed to further evaluate this premise.

CONCLUSIONS

In this large study of patients with NVAF managed routinely, overall mortality rates were significantly lower among those receiving DOAC therapy. Our findings provide further evidence for the importance of DOAC therapy in patients with NVAF.

Key messages

What is already known on this subject?

- Direct oral anticoagulants (DOAC) are currently standard of care therapy for patients with non-valvular atrial fibrillation (NVAF) for preventing stroke and systemic embolism. However, anticoagulation therapy is still provided inadequately in many healthcare systems and many patients with NVAF still do not receive neither vitamin K antagonists nor DOACs.

What might this study add?

- This study is the first to demonstrate an association of long-term DOAC therapy with reduced mortality, when compared with providing no anticoagulation in patients with NVAF.

How might this impact on clinical practice?

- Our findings provide further evidence for the major significance of DOAC therapy in patients with NVAF.

Contributors RA: conception of the research; drafting the manuscript for critically important intellectual content; interpretation of data. RS: data analysis; revising the manuscript for critically important intellectual content. AH: conception of the research; acquisition of data; drafting the manuscript for critically important intellectual content; interpretation of data. SDG: conception of the research; revising the manuscript for critically important intellectual content. EB: conception of the research; acquisition of data. OA and MHE: interpretation of data; revising the manuscript for critically important intellectual content. DG: conception of the research; securing the funding for the research; revising the manuscript for critically important intellectual content.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by Clalit Health Services's (CHS) data extraction committee and ethical approval was provided by the Institutional Review Board of CHS.

Provenance and peer review Not commissioned; externally peer reviewed.

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