

Adherence to Oral Anticoagulant Medications

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ABSTRACT **Background:** Oral anticoagulants (OAC) reduce the risk for stroke and death from all causes in patients with non-valvular atrial fibrillation (NVAF)

Objective: To explore adherence rates of OAC among patients with NVAF in long-term use in a real-world setting and to examine patient characteristics associated with good adherence.

Methods: We conducted a population-based cohort study with members of Clalit Health Services, Israel. All patients aged ≥ 30 years with a diagnosis of NVAF before 2016 who were treated with OAC were included. We included patients who filled at least one prescription per year in the three consecutive years 2016–2018. We analyzed all prescriptions that were filled for the medications from 1 January 2017 to 31 December 2017. We considered purchasing of at least nine monthly prescriptions during 2017 as good medication adherence.

Results: We identified 26,029 patients with NVAF who were treated with OAC; 10,284 (39.5%) were treated with apixaban, 6321 (24.3%) with warfarin, 6290 (24.1%) with rivaroxaban, and 3134 (12.0%) with dabigatran. Rates of good medication adherence were 88.9% for rivaroxaban, 84.9% for apixaban, 83.6% for dabigatran, and 55.8% for warfarin ($P < 0.0001$). Advanced age was associated with higher adherence rates ($P < 0.001$). Socio-economic status was not associated with medication adherence. Good adherence with OAC was associated with lower low density lipoprotein (LDL) cholesterol and glucose levels.

Conclusions: Adherence rates to OAC in chronic use among patients with chronic NVAF are high. Investing in OAC adherence may have a wider health impact than expected.

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KEY WORDS: direct oral anticoagulants (DOAC), medication adherence, non-valvular atrial fibrillation (NVAF), primary care, warfarin

Good medication adherence is a key factor in chronic disease management and is associated with a long-term decrease in healthcare expenditures [2]. Adherence of over 80% to prescribed medications is associated with 8–26% fewer hospitalizations, 3–12% fewer emergency department visits, and up to 15% fewer outpatient visits among patients with various chronic diseases [2]. Poor adherence is associated with adverse outcomes and higher healthcare costs, which is of growing concern to clinicians and healthcare systems [3].

Good adherence is important for patients with NVAF since the risk reduction of stroke and death reported with DOAC therapy is eliminated on discontinuation of DOAC therapy [4].

Primary non-adherence to OAC has been found to be low [5]. However we found no studies relating to long-term head-to-head adherence to OAC.

The aim of this study was to explore adherence rates of long-term use of oral anticoagulant medications among patients with NVAF in long-term use in a real world setting, and to investigate patient characteristics associated with good adherence to OAC.

PATIENTS AND METHODS

SETTING

The study was conducted by Clalit Health Services (CHS) in Israel and was approved by the local ethics committee. Since 1995, every Israeli citizen and permanent resident receives health care provided by one of four health maintenance organizations (HMO). CHS is the largest HMO in Israel, serving over 52% of the population nationwide. Patient medical records have been fully computerized for two decades and an extensive healthcare database has been created. The demographic data are updated directly from the population registry of the ministry of interior. All laboratory tests are free of charge, and results are recorded automatically in patient electronic medical files and reported directly to the primary care physician. All community pharmacies used by CHS are computerized and report to one central repository. CHS issues medications and requires nominal co-payments of US\$5–25 per medication per month. This system ensures that all filled prescriptions are documented.

Oral anticoagulants (OAC) reduce the risk for stroke and death from all causes in patients with non-valvular atrial fibrillation (NVAF) [1]. Both warfarin and direct acting oral anticoagulants (DOAC) are superior to no therapy or to aspirin treatment in NVAF patients. DOAC therapy was found to be superior to warfarin for stroke prevention, with reduced risk of major bleeding [1]. DOAC therapy has been associated with a 30% lower risk of stroke and death from any cause compared with patients who did not receive any oral anticoagulation therapy.

STUDY POPULATION

All patients 30 years of age and older with a diagnosis of NVAF before 2016 who were treated by the same family physician during 2016–2018 and were treated with OAC were included. Patients who died during the study period 2016–2018) were excluded. We included patients who filled at least one prescription per year of OAC in the three consecutive years 2016–2018. This approach was used to ensure medication use before and after 2017, to exclude patients who stopped treatment for any reason during the study period, and to ensure that the same medication was prescribed through the entire year of 2017.

The following OACs were included: warfarin, apixaban, dabigatran, and rivaroxaban, which are the most common OACs used in Israel.

We analyzed all prescriptions that were filled for the medications from 1 January 2017 to 31 December 2017 as pharmacy filled prescriptions, which has been shown to be an accurate and inexpensive data collection method [6,7].

We considered purchasing at least 9 monthly prescriptions during 2017, equal to at least 75% adherence, as good medication adherence compared to lower adherence (purchasing of fewer than 9 prescriptions during 2017). This method is close to the commonly used 80% cutoff [7,8].

Since warfarin dosage may change considerably according to the international normalized ratio (INR) we also considered patients who had more than 8 INR measures during 2017, in which at least 70% of the results were within therapeutic range, as adherent to warfarin [9].

Demographic information collected included: age, gender and socioeconomic status (SES). Patients with low SES were defined as those exempt from healthcare payments based on their income by the National Insurance Institute of Israel. These patients pay reduced co-payments on chronic medications and these co-payments are capped at US\$75 per month. We also extracted data about body mass index (BMI) and other chronic diagnoses recorded in the central database for chronic diseases on 1 January 2017, including lab results of the average fasting glucose levels and low density lipoprotein (LDL) cholesterol during 2017. We included INR measures during 2017. We calculated the percentage of measures that were in the therapeutic range of $2 \leq \text{INR} \leq 3$ out of the total recorded measurements in 2017.

STATISTICAL ANALYSIS

We calculated adherence rates for each medication separately. For each medication we used logistic regression models to calculate the odds ratio and to examine associations among medication adherence and age, sex, SES, BMI, and presentation of chronic diseases.

STATA 8.0 statistical software (Stata Corp. College Station, TX, USA) was used for statistical analysis.

RESULTS

The study included 26,029 individuals with NVAF who were treated with anticoagulant medication during the study period. Of those, 10,284 (39.5%) were treated with apixaban, 6321 (24.3%) with warfarin, 6290 (24.1%) with rivaroxaban, and 3134 (12.0%) with dabigatran during the study period.

Table 1 shows baseline characteristics of the patients. CHAD score was greater than 1 in 75.0% of the patients.

Rates of good medication adherence were 88.9% for rivaroxaban, 84.9% for apixaban, 83.6% for dabigatran, and 55.8% for warfarin [Figure 1], based on filled prescriptions ($P < 0.0001$) for all between groups comparisons with warfarin.

Table 1. Characteristics of the 28,536 study patients (2017)

Age in years, mean \pm SD (range)	75.8 \pm 9.7(30–95)
Gender (% men)	47.1%
Low socioeconomic status	49.0%
BMI (kg/m ²) mean \pm SD (range)	29.6 \pm 5.7 (13.3–78.7)
Hypertension	83.6%
Hyperlipidemia	88.9%
Diabetes mellitus	43.0%
s/p MI	26.7%
Congestive heart failure	28.5%
s/p TIA	10.7%
s/p CVA	23.3%
Glucose mean \pm SD (range)	115.1 \pm 33.3 (50–583)
LDL cholesterol (mg/dl) mean \pm SD (range)	86.5 \pm 28.4 (20–254)
Creatinine mean \pm SD (range)	1.05 \pm 0.5 (0.2–12.3)

BMI = body mass index, CVA = cerebrovascular accident, LDL = low density lipoprotein, MI = myocardial infarction. SD = standard deviation, s/p = status post, TIA = transient ischemic attack

Figure 1. Rates of good medication adherence to oral anticoagulants

*Adherence rate for warfarin, including purchasing of at least nine monthly prescriptions or patients who had more than 8 INR measures during 2017, in which at least 70% of the results were within therapeutic range

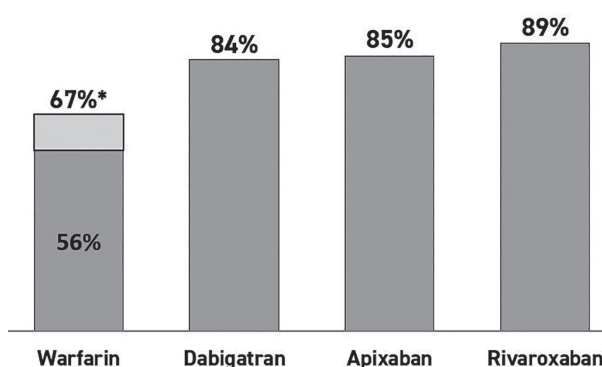


Table 2. Blood glucose and LDL cholesterol (mg%) levels among patients with high adherence rate compare to low adherence rate

	Fasting glucose			LDL		
	High adherence (mean ± SD)	Low adherence (mean ± SD)	P value	Low adherence (mean ± SD)	High adherence (mean ± SD)	P value
Apixaban	120.9 ± 41.4	115.5 ± 32.6	< 0.0001	91.6 ± 29.9	84.5 ± 28.1	< 0.0001
Dabigatran	118.4 ± 41.0	114.8 ± 32.2	0.02	91.6 ± 30.7	82.9 ± 26.8	< 0.0001
Rivaroxaban	120.5 ± 43.7	116.9 ± 32.7	0.01	93.9 ± 30.2	85.1 ± 27.0	< 0.0001
Warfarin	111.2 ± 31.5	110.8 ± 30.1	0.68	90.9 ± 29.1	89.1 ± 29.2	0.03

LDL = low density lipoprotein, SD = standard deviation

Table 3 Odds ratio with 95% confidence interval for good adherence to medications according to basic characteristics

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Age	1.03 (1.02–1.04)	1.02 (1.006–1.03)	1.03 (1.02–1.04)	1.01 (1.003–1.013)
Sex	1.01 (0.82–1.16)	1.04 (0.82–1.31)	1.25 (1.03–1.52)	0.99 (0.88–1.11)
Low SES	1.00 (0.90–1.12)	0.98 (0.81–1.120)	0.90 (0.76– 1.06)	1.23 (1.11–1.36)
Charlson score	0.98 (0.96–1.01)	0.99 (0.95–1.04)	0.99 (0.95–1.02)	0.98 (0.96–1.002)
CHAD score	1.03 (0.95–1.11)	1.07 (0.94–1.23)	0.97 (0.86–1.09)	1.07 (1.002–1.03)
Body mass index	1.00 (0.99–1.01)	0.99 (0.97–1.01)	1.01 (0.99–1.03)	1.02 (1.01–1.02)

SES = socioeconomic status

Bold signifies confounders that were significant

When we considered patients who had more than 8 INR measures during 2017, in which 70% of the results were within therapeutic range as adherent to warfarin, adherence rate for warfarin was 66.9% ($P < 0.0001$ for all between-group comparisons).

Good adherence with OAC medications was found to be associated with lower LDL cholesterol and lower fasting glucose levels [Table 2].

In multivariate analysis [Table 3], advanced age was associated with higher adherence rates for all medications tested ($P < 0.001$). SES was not associated with medication adherence.

DISCUSSION

We found adherence rates to chronic OAC among patients with NVAf in a real-world setting are high. Adherence to DOAC was higher than adherence to warfarin.

Previous studies reported a high adherence rate to OAC based on self-reported adherence by patients [10,11]. Another study reported an adherence rate to DOAC of 78% at 6 months and 73% adherence at 12 months in naïve patients for OAC [12]. Adherence to rivaroxaban, which is taken once daily, was slightly higher compared to other DOAC [13,14]. We found higher adherence rates to DOAC compared to warfarin. In a systematic review of patients who were prescribed DOAC, patients presented higher scores in Health Related Quality of Life (HRQoL) questionnaire that was attributed to lack of blood monitoring associated with the use of warfarin [15].

The adherence rates to DOAC are higher than adherence rate to oral medications in other chronic diseases, including patients with diabetes [16] and patients with hypertension [17]. This finding may be due to lower adverse effects of DOAC compared to anti-hypertensives and diabetic medications or to different self-health perceptions in patients with NVAf; however, studies have demonstrated less than half of the Israeli patients with NVAf receive OAC treatment [18,19].

Age was the only factor associated with adherence to OAC treatment. Older age was associated with better adherence rates. This finding has been reported before [13,20].

SES was not associated with adherence to DOAC, despite their cost, which is approximately 3 times more than warfarin.

Better adherence to OACs was associated with lower glucose and LDL levels. The relationship between better medication adherence and better glucose and LDL levels has also been noted in treating diabetes [16] and hypertension [17]. OACs have no effect on glucose or LDL levels. The lower level of glucose and LDL may represent better adherence to other medications or life style intervention, which influence patient outcome.

LIMITATIONS

We used medication purchasing as a proxy for medication adherence. However, this does not necessarily reflect medication utilization. We had no information about medication side effects, patient support systems, or patient–physician relationships, which

influence medication adherence. We had no direct information as to whether medications were discontinued for a period by a physician, which would result in an underestimation of adherence. This limitation is a special concern regarding warfarin, as it has no fixed dose regimen, causing difficulty in the estimation of adherence.

However, the large population and the completeness of the data acquisition likely enable a good estimate of medication adherence. Since purchase of each medication the year before and the year after the analysis was a study inclusion criterion, we assume that no major changes were made in treatment regimens. Since NVAF requires long-term treatment, we can assume that medications that were given for at least 3 years reflect real life adherence. As for warfarin, we used INR tests and INR results as another proxy for adherence. It did not change the difference in adherence rate between warfarin and DOAC.

CONCLUSIONS

Adherence rates to DOAC among patients with NVAF in a real world setting are high. DOAC have higher adherence rates to treatment when compared to warfarin. Better adherence to OAC is associated with better glucose and LDL levels. Investing in OAC adherence may have a wider health impact than expected.

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Capsule

Precision blockade of inflammatory IL-6

The cytokine interleukin-6 (IL-6) has critical functions in various tissues but is also implicated in autoimmune disease. Precisely targeting only the pathway by which IL-6 induces inflammatory immune cell activation would be desirable. Heise and co-authors developed a chimeric molecule that bound to and trapped an IL-6 trans-signaling protein complex. Compared with

a previously developed molecule that targets this complex, the authors' molecule was more selective for the IL-6 complex than a similar IL-11 complex and more effectively inhibited the IL-6-induced inflammatory activation of cultured T cells.

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