ORIGINAL RESEARCH

Comparison of claims vs patient-reported adherence measures and associated outcomes among patients with nonvalvular atrial fibrillation using oral anticoagulant therapy

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Objective: To compare oral anticoagulant (OAC) adherence among patients with nonvalvular atrial fibrillation (NVAF) using patient-reported and claims-based measures, and to evaluate the effect of OAC adherence on health care costs and patient satisfaction with OAC therapy.

Methods: This was a hybrid US observational study consisting of a longitudinal cohort survey followed by linkage and analysis of respondents' administrative claims data. Patients with NVAF receiving warfarin, dabigatran, rivaroxaban, or apixaban completed an initial survey and follow-up surveys at 4, 8, and 12 months. Patient-reported adherence was measured at each survey by Morisky Medication Adherence Scale (MMAS-8) and pharmacy claims-determined adherence by the proportion of days covered (PDC) for the 12-month period following the initial survey date; adherence was defined as MMAS-8 score =8 and PDC $\geq$80%. Patient satisfaction with OAC therapy was assessed by the Duke Anticoagulation Satisfaction Scale (DASS).

Results: Overall, 675 patients completed at least the initial survey (warfarin, n=271; dabigatran, n=266; rivaroxaban, n=128; apixaban, n=10). Fewer than half (47.9%) were PDC adherent, 37.2% were MMAS-8 adherent, and 19.4% were adherent by both measures. Total medical costs of PDC-adherent patients were significantly lower vs PDC-nonadherent patients (US$640 vs $993 per-patient per-month, respectively, $p<0.05$). MMAS-8-adherent patients reported higher treatment satisfaction; total DASS score was significantly lower among MMAS-8-adherent than MMAS-8-nonadherent patients (37.3 vs 42.9, respectively, $p<0.001$).

Conclusion: Using claims-based or patient-reported methods to measure OAC adherence may lead to different results when assessing impact on health care costs and satisfaction with anticoagulation medication. These results underscore the importance of considering both claims-based and patient-reported measures when evaluating treatment adherence in real-world settings.

Keywords: adherence, atrial fibrillation, OAC, health care costs

Introduction

Oral anticoagulants (OACs) have long been recommended for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in the absence of elevated bleeding risk or contraindications.[1] The introduction of non-vitamin K antagonist OACs (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, enabled effective anticoagulation without the inconvenience associated with warfarin.[2–6] Patients with NVAF require sustained OAC therapy, but maintaining adherence on a long-term basis can be challenging.[3,7–12] Nonadherence to OACs may result in increased health care costs, more inpatient admissions and emergency department (ED) visits,

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and higher risk of stroke,[7,9–11,13–15] compared with patients who take their OACs as prescribed.

Studies aimed at evaluating OAC adherence in everyday clinical practice have commonly measured adherence using either prescription fill data or patient self-reports, each of which is subject to limitations. Patient self-reports are subjective and may be influenced by errors in recall,[16–18] whereas objective claims-based prescription fill data may contain coding errors, and documentation of a prescription fill is not proof that the patient took the medication as prescribed.[3,10,11,19,20] To our knowledge, no studies have assessed OAC adherence using both prescription claims and patient-reported data. To fill this research gap, the current study compared OAC adherence in patients with NVAF using both prescription fill data obtained from administrative claims and patient self-reports collected in a series of surveys. Additionally, the effect of OAC adherence on health care costs and patient satisfaction with OAC therapy was evaluated.

Methods
Study design and patients
This was a hybrid US observational study consisting of a longitudinal cohort survey of adults with NVAF who were treated with warfarin, dabigatran, rivaroxaban, or apixaban followed by linkage and analysis of respondents' survey and administrative claims data.

The patient survey sample was identified from medical and pharmacy claims in the HealthCore Integrated Research Database (HIRD). The HIRD contains a broad, clinically rich and geographically diverse spectrum of longitudinal administrative claims from 14 geographically dispersed health plans in the US. The HIRD is generally representative of the US Census population, although patients aged 65 years and older are underrepresented.[21] Patients were selected for the survey based on claims submitted between October 2011 and June 2014 (the patient sample list identification period). Currently active, survey-eligible patients (18 years of age or older) had at least one medical claim for atrial fibrillation (International Classification of Diseases, Version 9, Clinical Modification [ICD-9-CM] code 427.31) and at least one pharmacy claim for warfarin, dabigatran, rivaroxaban, or apixaban during the patient sample identification period.

Patients' initial OAC cohort assignment was based on the OAC drug (ie, index drug) associated with the date of the last prescription fill for warfarin, dabigatran, rivaroxaban, or apixaban (ie, index fill date) in the patient sample identification period and confirmed at the time of the initial survey. Patients' final OAC cohort assignment was based on patients'

self-report of the OAC they were currently taking. Patients remained classified according to OAC treatment use at the time of initial survey throughout the 12-month follow-up period. However, current OAC treatment was assessed at each follow-up survey (ie, 4-, 8-, and 12-month surveys) in order to determine if and when switching or discontinuation occurred.

All patients were active members of a commercial (employer-provided) or Medicare Advantage health insurance plan at the time of the initial survey. Patients were required to have at least 6 months continuous enrollment prior to the index fill date to allow for identification of the survey-eligible population. Patients were excluded if they had one or more medical claims for valvular heart disease, valve replacement, cardiovascular surgery, or hyperthyroidism in the 6 months prior to the index fill date.

Eligible patients received a pre-notification letter with opt-out/opt-in telephone numbers ~2 weeks prior to the initial survey. After the 2-week window had elapsed, patients who had neither opted-in nor opted-out were contacted by telephone by professional interviewers, presented with a brief description of the study, and invited to participate in the study. Consenting patients who qualified for the study were surveyed regarding their experiences with anticoagulant treatment over a 12-month period. Survey participation consisted of completing a maximum of four surveys either with an interviewer over the phone or via the internet. The follow-up surveys were conducted at 4, 8, and 12 months after the initial survey (Figure 1). While completion of the initial survey was necessary for study participation, patients were not required to complete all three follow-up surveys. That is, if patients could not be contacted within the time window for a specific follow-up survey, an attempt was made to contact them at the next follow-up time point rather than exclude them from further surveys. Thus, it was possible for patients to complete 1 to 4 surveys.

The protocol and all survey-related materials were approved by the New England Institutional Review Board and all patient data were handled in compliance with the regulations of the US Insurance Portability and Accountability Act of 1996.

Using the date of the initial survey as the survey index date, a study database consisting of the medical and pharmacy claims of survey respondents was extracted from the HIRD for the 12-month periods prior to and after the initial survey from which a patient-level analytic file was developed and linked with respondents' survey data. The combined survey and claims analytic file was used to examine medication
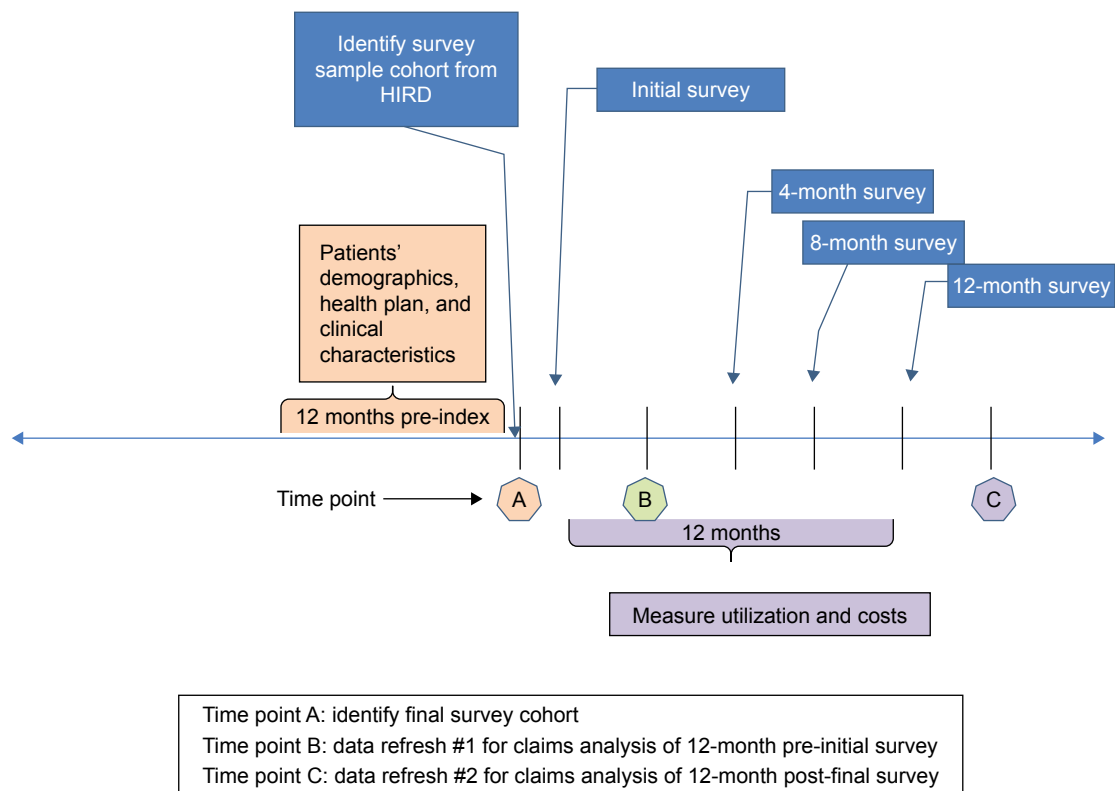
Figure 1 Overall study design diagram.
Abbreviation: HIRD, HealthCore Integrated Research Database.

adherence, patient-reported outcomes, health care resource utilization (HCRU), and costs of care. Patients were grouped into one of four OAC cohorts (ie, warfarin, dabigatran, rivaroxaban, or apixaban) based on their OAC treatment at the time of the initial survey.

Adherence measures

Adherence for the 12-month period following the initial survey was assessed in two ways: patient self-report and pharmacy claims data. Patient-reported adherence was determined using the eight-item Morisky Medication Adherence Scale (MMAS-8), a validated patient-reported questionnaire that measures medication-taking behavior and explores the circumstances influencing adherence, such as difficulty in remembering to take medications. The MMAS-8 is composed of eight questions based on four themes: forgetfulness, negligence, interruption of drug intake after clinical improvement, and restart of drug intake when symptoms worsen.[22] The total MMAS-8 score ranges from 0 to 8, with higher scores indicating better medication adherence. The MMAS-8 was administered at all four survey time points (initial survey and 4-, 8-, and 12-month follow-up surveys). For each patient, an average MMAS-8 score was calculated from the patient's

MMAS-8 scores for each time point, depending on the number of surveys the patient had completed.

The proportion of days covered (PDC) used pharmacy claims data to determine the 12-month NOAC PDC over the 12-month period following the initial survey. PDC was calculated by dividing the number of days covered by the index OAC prescription fill by 365 (ie, the number of days in the follow-up period), then multiplying the result by 100%.

Warfarin adherence was determined using a modified Go et al algorithm involving the combination of prescription fills from pharmacy claims and a proxy measure for international normalized ratio (INR) testing.[23] The date of INR testing recorded in medical claims (current procedural code 85610) was used instead of INR laboratory results because INR test results are only available for a subset of HIRD patients.

Other measures

HCRU and costs were estimated during the 12-month follow-up period. HCRU was calculated for inpatient hospitalizations, ED visits, outpatient physician office visits, and prescription fills and was reported as proportions. Costs were presented as per-member per-month because although costs were analyzed for the 12-month period after the initial survey, not all

patients remained enrolled for the entire period. Bleeding/stroke-related utilization was calculated for services with an ICD-9-CM diagnosis code for bleeding/stroke event.

All-cause, stroke-related, and bleeding-related total health care costs were calculated for overall total medical costs, inpatient hospitalizations, ED visits, and physician office visits and other outpatient services. Pharmacy costs were not included in total costs because of substantial price differentials between the generic warfarin and the proprietary NOACs. All costs were adjusted using the 2015 annual medical care component of the Consumer Price Index. All HCRU costs were presented on a per-member per-month basis.

Patient demographic and clinical characteristics were compared among OAC treatment cohorts during the 12-month baseline period prior to the initial survey. Baseline comorbid conditions were identified by ICD-9-CM codes associated with medical claims at any position during the pre-index period. Overall pre-index comorbidity burden was assessed using the Deyo-Charlson Comorbidity Index[24] (DCI). The $CHADS_2$ stroke risk score, based on the presence of congestive heart failure, hypertension, diabetes, prior stroke or transient ischemic attack (TIA), and age 75 years or older, was calculated during the pre-index period.[25,26] Bleeding risk was assessed using two alternative bleeding score schemes: the $HEMORR_2AGES$ score[27] (based on the presence of prior bleed, hepatic or renal disease, alcohol abuse, malignancy, reduced platelet count or function, hypertension, anemia, excessive falls, prior stroke, and age older than 75 years) and the ATRIA bleeding score[7] (based on the presence of anemia, severe renal disease [estimated glomerular filtration rate less than 30 mL/min or dialysis dependent], age 75 years or older, any prior hemorrhage diagnosis, and hypertension). The $CHADS_2$ and bleeding risk scores were determined from claims data. Other clinical outcomes included stroke or TIA requiring inpatient hospitalizations or ED visits and bleeding events requiring inpatient hospitalizations or ED or outpatient visits during the follow-up period.

OAC treatment satisfaction was assessed using the Duke Anticoagulation Satisfaction Scale[28] (DASS), which was administered at all four survey time points. The DASS was developed to measure the quality of life (QOL) and satisfaction among patients receiving OAC treatment. It consists of 25 items that address both the negative (ie, limitations, hassles, and burdens) and positive (ie, confidence, reassurance, and satisfaction) impacts of anticoagulation. Each item has seven responses: 1) not at all, 2) a little, 3) somewhat, 4) moderately, 5) quite a bit, 6) a lot, and 7) very much. Three domain scores and a total score can be calculated. The limitations domain consists of nine items pertaining to limitations on such things as physical activities due to fear of bleeding and dietary restrictions; item responses are summed with scores ranging from 9 to 63. The hassles/burdens domain consists of eight items dealing with both daily hassles such as remembering to take the medication and occasional hassles such as having to wait while visiting a provider for blood testing with scores ranging from 8 to 56. The psychological impact domain also consists of eight items dealing with such things as reassurance because of OAC treatment with scores ranging from 8 to 56; the total score is calculated by summing the responses to the 25 items with scores ranging from 25 to 175. Six items were reverse-coded before scores were calculated. Lower scores indicate greater satisfaction with the use of OAC medication, fewer hassles and burdens, and less psychological impact. Individual domain and total DASS scores were determined at each survey and an average total DASS score was calculated depending on the number of follow-up surveys completed by the survey respondent.

Statistical analysis

Descriptive analyses were performed and the descriptive results were analyzed separately using PDC- and MMAS-8-adherent and nonadherent groups. A two-sample t-test was used to test differences for continuous variables and the χ^2 test was used for categorical variables. The Wilcoxon rank-sum test was used for non-normal continuous variables (eg, cost variables). Comparisons were made within each OAC cohort as changes from the initial survey to each survey time point rather than across OAC cohorts. Results were reported as mean percentages (SD, median) for continuous variables and as relative frequencies for categorical variables.

A generalized linear model with log-link and gamma distribution was used to compare total all-cause and stroke- or bleeding-related medical costs between adherent and nonadherent groups. The model was adjusted for patient age, gender, commercial vs Medicare Advantage health plan type, region of residence, self-reported dosing schedule, DCI score, and pre-index $CHADS_2$ stroke and $HEMORR_2AGES$ and ATRIA bleeding risk scores. A conventional alpha of 0.05 and two-tailed level of significance was used. All data analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata version 12 (StataCorp LP, College Station, TX, USA).

Results
Patient characteristics

Overall, 795 patients completed the initial survey: 321 (40.4%) were in the warfarin cohort, 319 (40.1%) in the

dabigatran cohort, 141 (17.7%) in the rivaroxaban cohort, and 14 (1.8%) in the apixaban cohort. After merging the survey data of the 795 respondents with their claims data for the 12-month periods prior to and following the initial survey date, 676 respondents had complete claims data for at least 12 months prior to and following the initial survey date. Of these, 675 respondents had an overall mean MMAS score and they comprised the study population: 271 (40.1%) patients in the warfarin cohort, 266 (39.4%) in the dabigatran cohort, 128 (19.0%) in the rivaroxaban cohort, and 10 (1.5%) in the apixaban cohort (Table 1). While commercial health insurance was most common in all treatment groups, a higher proportion of patients in the NOAC groups had Medicare Advantage health plans than in the warfarin group.

The majority of patients in the warfarin (99.6%) and dabigatran cohorts (63.2%) completed the initial survey in 2012, whereas the majority in the rivaroxaban group (51.6%) completed the initial survey in 2013. All of the patients in the apixaban group completed the initial survey in 2014.

Patients in the warfarin cohort were slightly younger (mean 56.0 years) when diagnosed with atrial fibrillation compared with the NOAC cohorts (mean 62.3 years) and had a longer mean duration of atrial fibrillation (8 years warfarin vs 4 years NOAC; Table 2). As expected, self-reported duration of current therapy reflected the order in which each medication entered the market: 53.9% of the warfarin group were on current therapy for longer than 5 years; 52.6% of the dabigatran group were on current therapy for

Table 1 Demographic characteristics overall and by OAC cohort at initial survey

Characteristics	All patients (N=675)	Warfarin (n=271)	Dabigatran (n=266)	Rivaroxaban (n=128)	Apixaban (n=10)
Male, n (%)	409 (60.6)	156 (57.6)	172 (64.7)	76 (59.4)	5 (50.0)
Age categories, years, n (%)					
<55	73 (10.8)	35 (12.9)	23 (8.6)	14 (10.9)	1 (10.0)
55–64	306 (45.3)	131 (48.3)	122 (45.9)	50 (39.1)	3 (30.0)
≥65	296 (43.9)	105 (38.7)	121 (45.5)	64 (50.0)	6 (60.0)
Age, years, mean (SD)[a]	65 (10)	64 (10)	66 (9.6)	67 (10.5)	66 (12)
Type of health insurance, n (%)[b]					
Commercial	510 (75.6)	232 (85.6)	194 (72.9)	79 (61.7)	5 (50.0)
Medicare Advantage	165 (24.4)	39 (14.4)	72 (27.1)	49 (38.3)	5 (50.0)
Region of patient residence, n (%)[b]					
Midwest	251 (37.2)	101 (37.3)	93 (35.0)	55 (43)	2 (20.0)
South	153 (22.7)	68 (25.1)	58 (21.8)	23 (18)	4 (40.0)
Northeast	142 (21.0)	67 (24.7)	56 (21.1)	17 (13.3)	2 (20.0)
West	129 (19.1)	35 (12.9)	59 (22.2)	33 (25.8)	2 (20.0)
Year of initial survey, n (%)					
2012	458 (67.9)	270 (99.6)	168 (63.2)	20 (15.6)	0 (0)
2013	164 (24.3)	1 (0.4)	97 (36.5)	66 (51.6)	0 (0)
2014	53 (7.9)	0 (0)	1 (0.4)	42 (32.8)	10 (100)
Race/ethnicity, n (%)					
White, non-Hispanic	636 (94.2)	260 (95.9)	250 (94)	116 (90.6)	10 (100)
Other	23 (3.4)	5 (1.8)	12 (4.5)	6 (4.7)	0 (0)
Refused/missing	1 (0.1)	0 (0)	0 (0)	1 (0.8)	0 (0)
Married, n (%)	453 (67.1)	180 (66.4)	182 (68.4)	81 (63.3)	10 (100)
Education level, n (%)					
High school or less	176 (26.1)	72 (26.6)	67 (25.2)	36 (28.1)	1 (10.0)
At least some college	498 (73.8)	199 (73.4)	198 (74.4)	92 (71.9)	9 (90.0)
Refused/missing	1 (0.1)	0 (0)	1 (0.4)	0 (0)	0 (0)
Employment status, n (%)					
Employed	378 (56)	165 (60.9)	145 (54.5)	64 (50.0)	4 (40.0)
Disabled/retired	287 (42.5)	100 (36.9)	117 (44.0)	64 (50.0)	6 (60.0)
Other	7 (1.0)	4 (1.5)	3 (1.1)	0 (0)	0 (0)
Do not know/refused/missing	3 (0.4)	2 (0.7)	1 (0.4)	0 (0)	0 (0)
Household income (US dollars), n (%)					
<$50,000	238 (35.3)	103 (38.0)	88 (33.1)	43 (33.6)	4 (40.0)
$50,000–$99,999	222 (32.9)	88 (32.5)	85 (32)	45 (35.2)	4 (40.0)
≥$100,00	134 (19.9)	47 (17.3)	62 (23.3)	25 (19.5)	0 (0)
Do not know	81 (12.0)	33 (12.2)	31 (11.7)	15 (11.7)	2 (20.0)

Notes: [a]Age was determined on the initial survey date; [b]information was obtained from claims data.
Abbreviation: OAC, oral anticoagulants.

Table 2 Clinical characteristics overall and by OAC cohort at initial survey

Characteristics	All patients (N=675)	Warfarin (n=271)	Dabigatran (n=266)	Rivaroxaban (n=128)	Apixaban (n=10)
Age diagnosed with AF, years, mean (SD)	59 (12.0)	56 (11.3)	61 (12.0)	63 (12.0)	63 (13.2)
Duration of AF, years, mean (SD)	6 (6.6)	8 (6.9)	5 (6.6)	4 (5.2)	3 (3.4)
Specialty of doctor who "originally" prescribed current OAC, n (%)					
Cardiologist	559 (82.8)	204 (75.3)	237 (89.1)	110 (85.9)	8 (80.0)
Primary care provider	89 (13.2)	54 (19.9)	22 (8.3)	11 (8.6)	2 (20.0)
Other	20 (3.0)	10 (3.7)	5 (1.9)	5 (3.9)	0 (0)
Do not know/refused	7 (1.0)	3 (1.1)	2 (0.8)	2 (1.6)	0 (0)
Specialty of doctor who "currently" prescribes current OAC, n (%)					
Cardiologist	475 (70.4)	157 (57.9)	209 (78.6)	100 (78.1)	9 (90.0)
Primary care provider	175 (25.9)	100 (36.9)	49 (18.4)	25 (19.5)	1 (10)
Other	21 (3.1)	12 (4.4)	7 (2.7)	2 (1.6)	0 (0)
Do not know/refused	4 (0.6)	2 (0.7)	1 (0.4)	1 (0.8)	0 (0)
Duration of current OAC, n (%)					
<1 year	252 (37.3)	21 (7.7)	123 (46.2)	98 (76.6)	10 (100)
1–5 years	271 (40.1)	103 (38)	140 (52.6)	28 (21.9)	0 (0)
>5 years	147 (21.8)	146 (53.9)	1 (0.4)	0 (0)	0 (0)
Do not know/refused	5 (0.7)	1 (0.4)	2 (0.8)	2 (1.6)	0 (0)
Used ≥1 OAC other than current OAC, n (%)	444 (65.8)	116 (42.8)	217 (81.6)	102 (79.7)	9 (90.0)

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulant.

1 to 5 years; and 76.6% of the rivaroxaban and 100% of the apixaban groups were on current therapy for less than 1 year. A higher proportion of patients in the NOAC groups (81.6% dabigatran, 79.7% rivaroxaban, 90.0% apixaban) reported using at least one OAC other than their current medication, compared with 42.8% in the warfarin group. Across all treatment groups, cardiologists were most likely the initial and current prescribers of OAC treatment, although the proportion of primary care providers currently prescribing OACs was greater than initial prescribers.

Overall, DCI, stroke risk, and bleeding risk scores were similar among all four treatment groups (Table 3). During the baseline period, a higher proportion of patients in the rivaroxaban and apixaban treatment groups had medical claims for coronary artery disease, cardiomyopathy, stroke or TIA event, and bleeding events compared with the warfarin and dabigatran treatment groups.

Adherence

Patients had the opportunity to report their adherence in an initial survey plus up to three follow-up surveys 4, 8, and 12 months later. Overall, 156 patients (23.1%) completed all four surveys (ie, the initial plus three follow-up surveys), 143 patients (21.2%) completed three surveys, 126 (18.7%) completed two surveys, and 250 (37.0%) completed only the initial survey (Table 4). Across the treatment cohorts, the proportions of patients completing the surveys roughly followed the overall pattern.

The mean MMAS-8 scores changed little among the initial and follow-up surveys, both for the overall study population as well as for each treatment cohort (Table 4). The mean overall MMAS-8 score was 7.2, beginning at a high of 7.3 at the initial survey before dipping slightly to 7.2 at the 4- and 8-month surveys and 7.1 at the 12-month survey. The overall mean MMAS-8 score by treatment cohort was 7.3 for all cohorts except dabigatran, which was 7.1. The apixaban cohort reported both the highest (7.5) and lowest (6.8) mean MMAS-8 scores, likely due to the small sample size of that cohort.

Slightly less than half of all patients were adherent according to the claims-based PDC measure (Table 5). Using the self-reported MMAS-8 scores, slightly more than a third of patients were considered adherent. Fewer than one in five patients were considered adherent by both PDC and MMAS.

Health care utilization

Among PDC-adherent patients, a significantly lower proportion had inpatient hospitalizations and ED visits compared with patients considered PDC-nonadherent (Figure 2). However, a greater proportion of PDC-adherent patients had outpatient office visits compared with the PDC-nonadherent patients. These differences were largely eliminated when adherence was measured using MMAS-8 scores (Figure 3). No significant differences were found in terms of inpatient hospitalizations or outpatient visits, but a significant difference was maintained in terms of ED visits.

Table 3 Claims-determined comorbidities, stroke, and bleeding risk scores overall and by OAC cohort for the 12-month period before the initial survey

	All patients (N=675)	Warfarin (n=271)	Dabigatran (n=266)	Rivaroxaban (n=128)	Apixaban (n=10)
Comorbidity scores					
DCI score, mean (SD)	2 (1.9)	1 (1.8)	2 (1.8)	2 (2.3)	1 (1.5)
Stroke risk scores					
CHADS$_2$,[a] mean (SD)	2 (1.2)	2 (1.1)	2 (1.2)	2 (1.2)	2 (1.4)
CHA$_2$DS$_2$-VASc,[b] mean (SD)	3 (1.6)	3 (1.6)	3 (1.6)	3 (1.6)	3 (1.8)
Bleeding risk scores					
ATRIA,[c] mean (SD)	2 (2.1)	2 (1.9)	2 (2.0)	2 (2.3)	2 (2.1)
HEMORR$_2$HAGES,[d] mean (SD)	2 (1.7)	2 (1.6)	2 (1.6)	2 (1.9)	3 (1.7)
Pre-index comorbid conditions, n (%)					
Hypertension	521 (77.2)	198 (73.1)	212 (79.7)	105 (82.0)	6 (60.0)
Hyperlipidemia	468 (69.3)	187 (69.0)	183 (68.8)	89 (69.5)	9 (90.0)
Coronary artery disease	228 (33.8)	84 (31.0)	82 (30.8)	58 (45.3)	4 (40.0)
Diabetes	206 (30.5)	79 (29.2)	90 (33.8)	36 (28.1)	1 (10.0)
Heart failure	151 (22.4)	57 (21.0)	58 (21.8)	34 (26.6)	2 (20.0)
Renal disease	108 (16.0)	36 (13.3)	43 (16.2)	29 (22.7)	0 (0.0)
Cardiomyopathy	102 (15.1)	39 (14.4)	38 (14.3)	23 (18.0)	2 (20.0)
Peripheral artery disease	62 (9.2)	29 (10.7)	24 (9.0)	8 (6.3)	1 (10.0)
Any stroke/TIA event,[e] n (%)	87 (12.9)	32 (11.8)	33 (12.4)	20 (15.6)	2 (20.0)
Any bleeding event,[f] n (%)	110 (16.3)	43 (15.9)	40 (15.0)	23 (18.0)	4 (40.0)

Notes: [a]The CHADS$_2$ stroke risk score was calculated by adding 1 point each for congestive heart failure, hypertension, diabetes, and age >75 years and 2 points for prior stroke or TIA[25]; [b]the CHA$_2$DS$_2$-VASc stroke risk was calculated by adding 1 point each for congestive heart failure/left ventricle dysfunction, hypertension, diabetes, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age between 65 and 74 years, female gender, and 2 points each for age >75 years and prior stroke or TIA[37]; [c]the HEMORR$_2$HAGES score was calculated by adding 2 points for prior bleed and 1 point each for age >75 years, hepatic or renal disease, alcohol abuse, malignancy, reduced platelet count or function, hypertension, anemia, excessive falls, genetic risk factor (not available), and prior stroke[27]; [d]the ATRIA bleeding score was calculated by adding 3 points for anemia, 3 points for severe renal disease (estimated glomerular filtration rate <30 mL/min or dialysis dependent), 2 points for age ≥75 years, 1 point each for any prior hemorrhage diagnosis, and 1 point for hypertension[7]; [e]stroke/TIA events included ischemic stroke, hemorrhagic stroke, and TIA events; [f]bleeding events included those requiring hospitalization, emergency department visits, or outpatient visits.
Abbreviations: DCI, Deyo-Charlson Comorbidity Index; OAC, oral anticoagulants; TIA, transient ischemic attack.

Medical costs

Total medical costs were significantly lower in the PDC-adherent than the PDC-nonadherent cohort (Figure 4). Unadjusted stroke-related medical costs were similar between the two groups but significantly lower for unadjusted bleeding-related medical costs in the PDC-adherent vs PDC-nonadherent cohort. The adjusted stroke-related total medical costs were 86% lower for PDC-adherent vs PDC-nonadherent cohort, and bleeding-related total medical costs were 75% lower for PDC-adherent vs PDC-nonadherent cohort.

When adherence was measured using the MMAS-8, between-group differences in total medical, stroke-related, and bleeding-related medical costs did not reach statistical significance (Figure 5).

Outpatient medical costs made up the largest proportion of total costs in both PDC- and MMAS-8-adherent cohorts (Figure 6). While they were significantly lower for adherent patients than nonadherent patients defined by PDC, they were not significant between MMAS-8 cohorts. Inpatient hospitalization costs were significantly lower for PDC-adherent than PDC-nonadherent cohorts, but were similar between the MMAS-8-adherent and -nonadherent cohorts.

ED costs made up the smallest proportion of total costs and were similar between the adherent and nonadherent cohorts for both PDC and MMAS-8 scores.

Treatment satisfaction

The mean DASS total scores were lower for the dabigatran and rivaroxaban cohorts, indicating greater treatment satisfaction, than for the warfarin and apixaban cohorts, as well as for the overall mean DASS total score (Table 4). This pattern was also seen for the DASS domains of limitations, treatment inconvenience, and psychological impact.

Treatment satisfaction, as measured by the DASS, was slightly higher in the PDC-adherent compared with the PDC-nonadherent cohort (Figure 7); however, the difference was not statistically significant. In contrast, the total DASS score was significantly lower in the MMAS-8-adherent than the MMAS-8-nonadherent cohort, indicating higher treatment satisfaction among MMAS-8-adherent patients. The individual domain scores for limitations, treatment inconvenience, and psychological impact also trended lower among the MMAS-8-adherent cohort compared with the MMAS-8-nonadherent cohort, indicating greater satisfaction,

Table 4 Number of surveys completed per respondent and mean MMAS-8 and DASS scores by survey and OAC cohort for the 12-month period including and following the initial survey

	All patients (N=675)	Warfarin (n=271)	Dabigatran (n=266)	Rivaroxaban (n=128)	Apixaban (n=10)
Number of surveys completed per respondent, n (%)					
Initial survey only	250 (37.0)	90 (33.2)	111 (41.7)	45 (35.2)	4 (40.0)
Two surveys (initial +1)	126 (18.7)	52 (19.2)	47 (17.7)	26 (20.3)	1 (10.0)
Three surveys (initial +2)	143 (21.2)	56 (20.7)	51 (19.2)	34 (26.6)	2 (20.0)
Four surveys (initial +3)	156 (23.1)	73 (26.9)	57 (21.4)	23 (18.0)	3 (30.0)
MMAS-8[a] scores, mean (SD)					
Initial survey	7.3 (1.0)	7.4 (0.8)	7.1 (1.1)	7.4 (1.0)	7.4 (0.7)
4-month	7.2 (1.0)	7.3 (0.9)	7.1 (1.2)	7.3 (0.9)	6.8 (1.2)
8-month	7.2 (1.0)	7.2 (1.0)	7.0 (1.1)	7.3 (1.0)	7.2 (1.1)
12-month	7.1 (1.1)	7.1 (1.1)	7.0 (1.2)	7.4 (1.2)	7.5 (0.9)
Overall[b]	7.2 (0.9)	7.3 (0.8)	7.1 (1.0)	7.3 (0.9)	7.3 (0.7)
DASS total scores, mean (SD)					
Initial survey	41.6 (13.3)	45.4 (13.4)	39.0 (12.5)	38.6 (12.5)	43.2 (15.4)
4-month	39.7 (13.8)	42.5 (14.4)	38.0 (12.5)	36.7 (13.7)	36.8 (8.6)
8-month	40.5 (14.1)	44.8 (15.2)	37.2 (12.9)	36.3 (10.3)	36.3 (11.3)
12-month	40.6 (14.4)	45.3 (15.4)	36.7 (12.5)	38.0 (13.2)	33.8 (7.1)
Overall[b]	40.9 (12.6)	44.6 (13.1)	38.4 (11.4)	38.2 (11.7)	40.5 (14.0)
DASS limitations scores, mean (SD)					
Initial survey	12.6 (4.9)	14.0 (5.3)	11.7 (4.4)	11.7 (4.4)	13.0 (4.1)
4-month	12.6 (4.9)	13.7 (4.8)	11.7 (5.3)	12.0 (3.9)	10.3 (1.9)
8-month	13.0 (5.6)	14.5 (6.1)	12.0 (5.3)	11.6 (3.7)	10.5 (1.7)
12-month	13.0 (5.3)	14.5 (5.4)	11.4 (4.9)	12.4 (5.1)	12.2 (3.9)
Overall[b]	12.5 (4.5)	13.9 (4.8)	11.5 (3.9)	11.8 (4.2)	12.4 (3.5)
DASS treatment inconvenience scores, mean (SD)					
Initial survey	11.6 (4.7)	12.7 (5.2)	11.0 (4.3)	10.5 (3.5)	12.2 (6.6)
4-month	11.2 (4.6)	12.3 (5.5)	10.5 (3.5)	10.2 (3.9)	9.3 (1.9)
8-month	11.5 (4.8)	12.8 (5.3)	10.4 (4.2)	10.6 (3.9)	10.5 (3.0)
12-month	11.6 (4.8)	12.9 (5.5)	10.7 (4.2)	10.7 (3.9)	8.8 (1.6)
Overall[b]	11.5 (4.2)	12.6 (4.9)	10.8 (3.4)	10.5 (3.2)	11.5 (6.3)
DASS psychological impact scores, mean (SD)					
Initial survey	17.3 (7.1)	18.6 (6.9)	16.3 (7.0)	16.6 (7.5)	18.0 (7.6)
4-month	15.8 (7.1)	16.5 (7.1)	15.7 (6.7)	14.3 (7.7)	17.3 (5.9)
8-month	15.9 (6.6)	17.4 (6.8)	15.1 (6.3)	14.0 (6.2)	15.3 (8.5)
12-month	15.9 (6.9)	17.7 (7.4)	14.3 (5.9)	14.9 (6.8)	12.8 (6.9)
Overall[b]	16.9 (6.6)	18.0 (6.3)	16.1 (6.6)	16.0 (7.0)	16.7 (5.1)

Notes: [a]Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA; [b]the overall score was calculated by taking the mean of the individual scores based on the number of surveys the respondent completed.
Abbreviations: OAC, oral anticoagulant; MMAS-8, Morisky Medication Adherence Scale 8-item; DASS, Duke Anticoagulant Satisfaction Scale.

Table 5 Comparison of adherence measured using PDC and the mean MMAS scores among NVAF patients with OAC therapy for the 12-month period including and after the initial survey

MMAS (patient survey)	PDC (claims data)		Total	p-value[a]
	PDC ≥80%	PDC <80%		
MMAS =8	131	120	251	
MMAS <8	192	232	424	
Total	323	352	675	<0.001

Notes: [a]p-value was estimated using McNemar test. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.
Abbreviations: PDC, proportion of days covered; MMAS, Morisky Medication Adherence Scale; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant.

but were statistically similar among the PDC-adherent and PDC-nonadherent cohort patients.

Discussion

This real-world study assessed OAC adherence among patients with NVAF using two alternative methods: the claims-based PDC and the patient-reported MMAS-8. Each measure represents a different perspective: while the PDC provides a broad view of adherence over a 12-month period, the MMAS-8 gives a snapshot of the specific time point at which the questionnaire is completed. Regardless of the measure used, fewer than half of patients with NVAF adhered
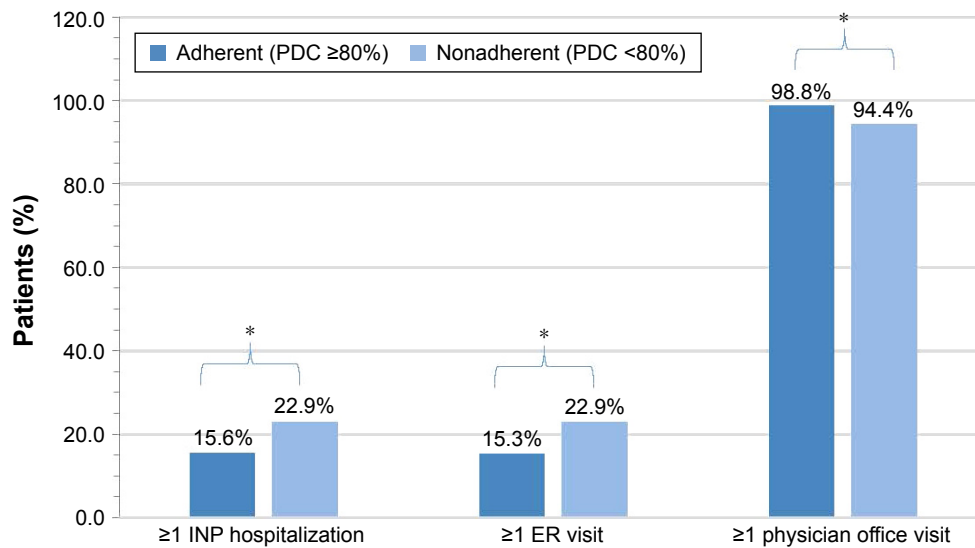
Figure 2 All-cause health care resource utilization[a] between adherent and nonadherent patients using PDC calculated from claims for the 12-month period including and after the initial survey.
Notes: [a]Unadjusted results; *$p<0.05$; PDC$_{Adherent}$ n=323, PDC$_{Nonadherent}$ n=352.
Abbreviations: PDC, proportion of days covered; INP, inpatient; ER, emergency room.

to their OAC regimen. Adherence rates were higher when measured using PDC rather than MMAS-8 (47.9% PDC vs 37.2% MMAS-8), but only one in five patients (19.4%) were adherent according to both measures.

Our findings in general are consistent with previous results that showed adherence with OAC therapy was associated with reduced health care utilization and lower total health care costs.[16] However, the type of HCRU significantly

reduced by adherence varied by the criteria used to define adherent behavior. Research in a variety of therapeutic areas, including hypertension and depression as well as atrial fibrillation, has supported the positive relationship between treatment satisfaction and adherence.[29–33] While the relationship between treatment satisfaction and adherence may be evident, a literature review highlighted the lack of consistent definitions and measures of adherence and satisfaction.[33] The
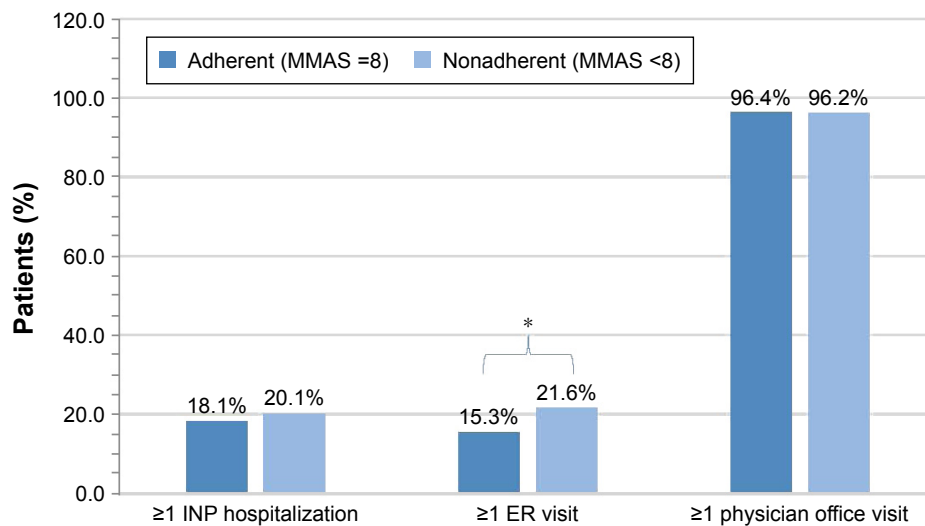
Figure 3 All-cause health care resource utilization[a] between adherent and nonadherent patients using mean MMAS-8 scores determined from patient self-report for the 12-month period including and after the initial survey.
Notes: [a]Unadjusted results; *$p<0.05$; MMAS$_{Adherent}$ n=251, MMAS$_{Nonadherent}$ n=424. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.
Abbreviations: MMAS-8, Morisky Medication Adherence Scale 8-item; INP, inpatient; ER, emergency room.
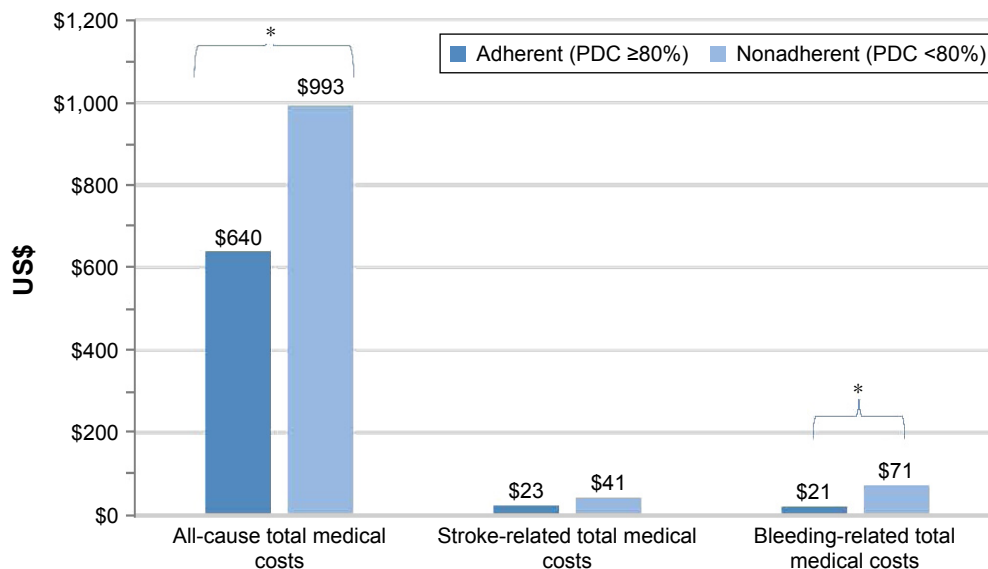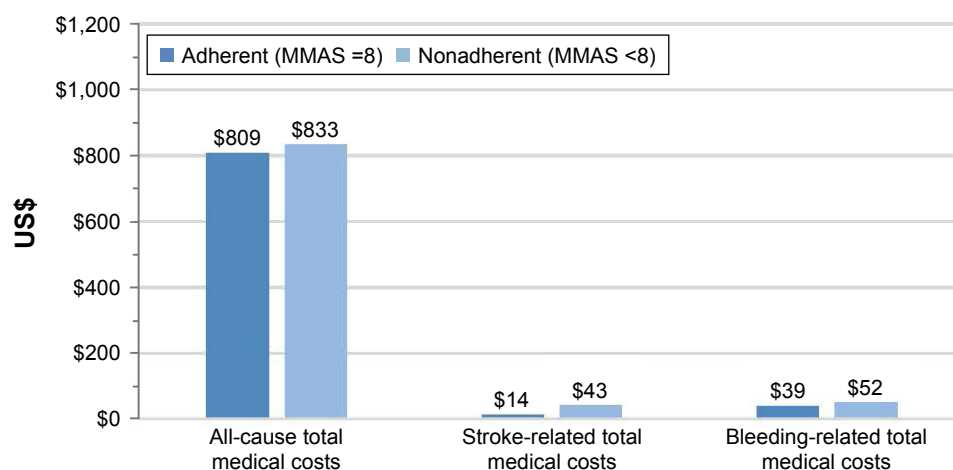
Figure 4 Comparison of all-cause, stroke-related, and bleeding-related total medical costs[a] between adherent and nonadherent patients using PDC calculated from claims for the 12-month period including and after the initial survey.
Notes: [a]Unadjusted results; *$p<0.05$; $PDC_{Adherent}$ n=323, $PDC_{Nonadherent}$ n=352.
Abbreviation: PDC, proportion of days covered.

differences between claims-based and patient-reported adherence in the current study further underscores the need for a "gold standard" for measuring adherence and satisfaction.

Overall, patients who were nonadherent according to PDC had significantly higher utilization of inpatient and ED services than patients who were adherent, but only ED use was significantly different between the adherent and nonadherent cohorts according to MMAS-8 scores. On the other hand, MMAS-8-defined adherent patients had greater satisfaction with anticoagulant treatment than MMAS-8-

nonadherent patients, but DASS scores were not different between PDC-adherent and PDC-nonadherent cohorts. Although our results support PDC as a more sensitive measure in predicting economic outcomes, it may be less predictive of long-term adherence behavior than the MMAS-8, considering treatment satisfaction is an important factor for maintaining adherence of chronic medications.[34] Further research is warranted.

To our knowledge, this is the first study comparing both claims-based and patient-reported adherence measures and

Figure 5 Comparison of all-cause, stroke-related, and bleeding-related total medical costs[a] between adherent and nonadherent patients using mean MMAS-8 scores determined from patient self-report for the 12-month period including and following the initial survey.
Notes: [a]Unadjusted results; $MMAS_{Adherent}$ n=251, $MMAS_{Nonadherent}$ n=424. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.
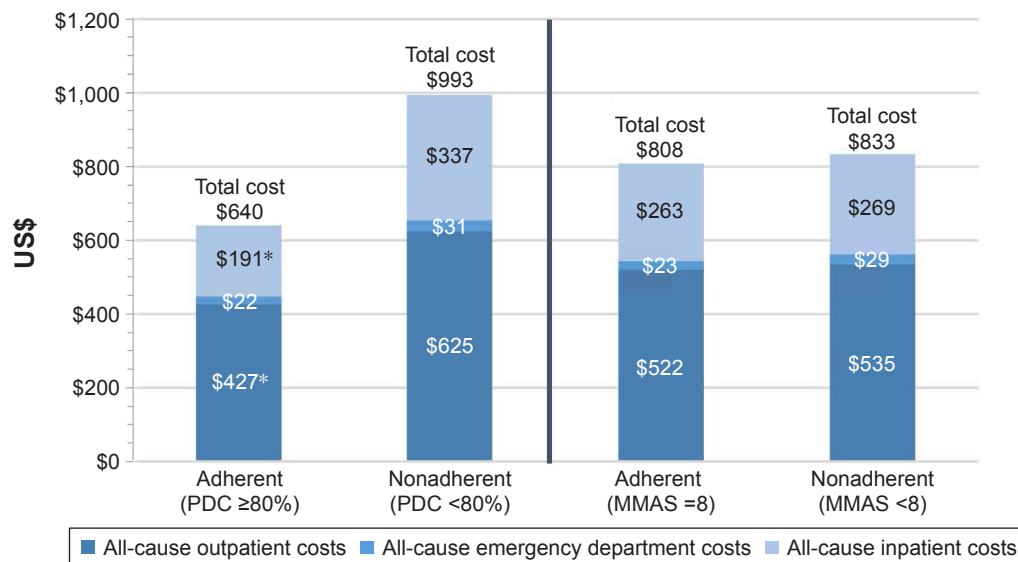**Abbreviation:** MMAS-8, Morisky Medication Adherence Scale 8-item.

Figure 6 Comparison of all-cause total medical costs by type of services between adherent and nonadherent patients using PDC and mean overall MMAS-8 scores for the 12-month period including and following the initial survey.
Notes: *p<0.05 vs nonadherent PDC cohort; PDC$_{Adherent}$ n=323, PDC$_{Nonadherent}$ n=352, MMAS$_{Adherent}$ n=251, MMAS$_{Nonadherent}$ n=424. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.
Abbreviations: PDC, proportion of days covered; MMAS-8, Morisky Medication Adherence Scale 8-item.

their impact on economic burden in patients with NVAF receiving OAC therapy. Strengths of this study included the use of a large administrative claims database as a sampling frame to identify eligible patients to survey and the unique ability to link patients' medical and pharmacy claims data

with their survey data. Our findings suggested that prescription refill patterns and MMAS-8 assess different aspects of adherence that are complementary to each other. While the claims-based PDC may be a more sensitive measure than self-reported adherence in predicting economic outcomes,
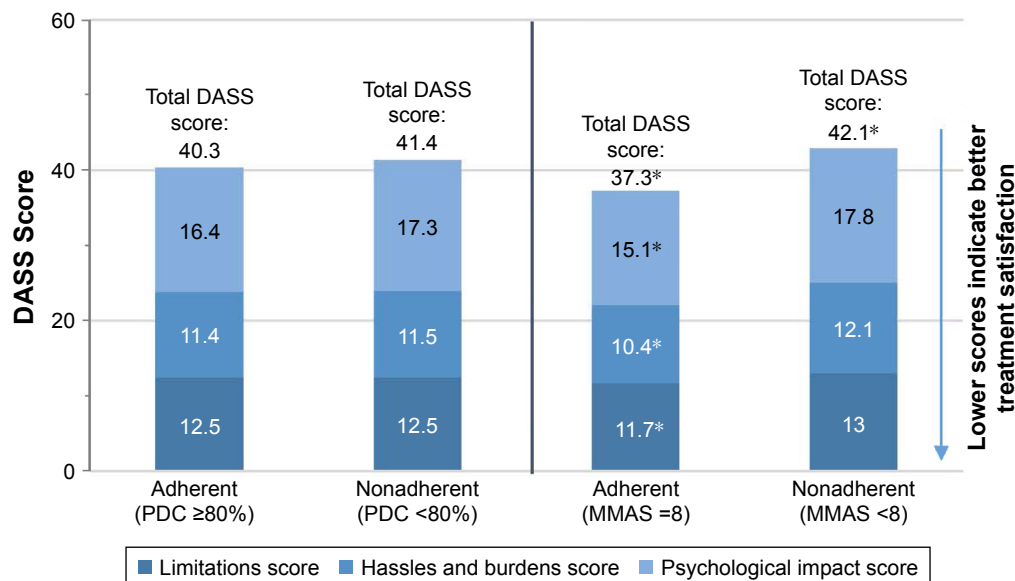
Figure 7 Comparison of Duke Anticoagulation Satisfaction Scale (DASS) mean scores between adherent and nonadherent patients using PDC and mean overall MMAS-8 scores for the 12-month period including and following the initial survey.
Notes: *p<0.05 vs MMAS nonadherent cohort; PDC$_{Adherent}$ n=323, PDC$_{Nonadherent}$ n=352, MMAS$_{Adherent}$ n=251, MMAS$_{Nonadherent}$ n=424. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, USA.
Abbreviations: PDC, proportion of days covered; MMAS-8, Morisky Medication Adherence Scale 8-item.

the MMAS-8 provided supplemental insights in terms of how patients took their OAC on a day-to-day basis. Potential factors that may contribute to adherence – such as lack of patients' knowledge about OAC use and treating physicians' compliance with guidelines[35] and their role in individualizing treatment management[36] – remain subjects for future research.

Our findings should be viewed in light of several limitations. First, the study analyzed data between October 2011 and June 2014. Given that apixaban was approved for stroke prevention in December 2012, the number of patients using apixaban in the study was much smaller than those using other NOACs and particularly those using warfarin. Patients using warfarin tended to have lived with an atrial fibrillation diagnosis longer and had a considerably longer duration of therapy than those using NOACs, which may have affected adherence and the generalizability of the study findings. Second, the study population was identified from the HIRD administrative claims database, which primarily consists of patients with commercial insurance. Therefore, the results may not be generalizable to other populations, such as individuals without insurance, those with government-sponsored insurance (eg, Medicaid), or those living outside the US. Third, PDC was estimated using prescription claims records. We were unable to assess whether patients took the medication as prescribed, and adherence may have been confounded by unobserved patient characteristics that could not be controlled for in our analysis. Lastly, the self-reported patient survey data collected by the MMAS-8 and DASS could not be validated and may have been subject to recall biases. Also, the $CHADS_2$ and bleeding risk scores were determined from claims data. Claims data may have contained undetected coding errors that may have affected the stroke and bleeding risk scores.

Conclusion

Findings from this study showed that using a claims-based or patient self-reported method to measure OAC adherence in patients with NVAF may yield different results when assessing treatment impact on HCRU and costs. Patients who self-reported higher adherence to treatment reported greater treatment satisfaction, which may influence daily prescription-taking behavior. These results underscore the importance of considering both claims-based and patient-reported measures when evaluating treatment adherence in a real-world setting.

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