

# Anticoagulant Use, the Prevalence of Bridging, and Relation to Length of Stay among Hospitalized Patients with Non-Valvular Atrial Fibrillation

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## Abstract

**Objective:** The objectives of this study were to describe inpatient anticoagulation and bridging in patients with non-valvular atrial fibrillation (NVAF) and to identify whether differences exist in length of stay (LOS) among bridged versus non-bridged NVAF patients.

**Design:** Administrative claims data were used to select patients  $\geq 18$  years with a primary or secondary discharge diagnosis of NVAF and inpatient warfarin use from 1 July 2004 to 30 September 2009. Patients with valvular or transient causes of NVAF or pregnancy were excluded. Inpatient bridging was defined as receipt of an anticoagulant in addition to warfarin during the hospitalization. LOS was reported for non-bridged patients (warfarin only) and compared with three bridging regimens: low molecular weight heparin/pentasaccharide (LMWH/PS); unfractionated heparin (UFH); and two-agent bridging (LMWH/PS and UFH). Multivariate analyses were performed to evaluate the association between bridging and LOS, adjusting for demographic and clinical variables.

**Results:** Of 6340 NVAF patients, 48% received inpatient warfarin (mean LOS 5.5 days); among them, 64% received bridging therapy (mean LOS 6.3 days) [LMWH/PS 45% (mean LOS 5.6 days), UFH 36% (mean LOS 6.0 days), two-agent bridging 18% (mean LOS 8.4 days)]. Following multivariate analysis, relative to patients who received inpatient warfarin only, LOS was significantly higher for patients with UFH (19.3%) and patients with two-agent bridging (45.1%). Patients with pre-period warfarin, cancer, or diabetes mellitus who received bridging agents had significantly longer LOS than patients with those conditions who were not bridged.

**Conclusion:** LOS was longer for bridged than non-bridged patients. Further studies are needed to identify predictors of bridging and to explain why bridged NVAF patients had longer LOS.

## Introduction

Atrial fibrillation (AF) is a frequently occurring cardiac arrhythmia and a significant risk factor for ischemic stroke.<sup>[1-4]</sup> Prevalence in the US is estimated at 3 million persons and increases with age, occurring in approximately 9% of the population aged 80–89 years.<sup>[5,6]</sup> Over a third of AF patients are hospitalized each year, with hospitalization costs accounting for \$US2.3 billion of the \$US6 billion annual incremental AF-specific costs.<sup>[1]</sup> Anticoagulation (AC) has proven effective in the prevention of stroke in patients with AF,<sup>[7-10]</sup> yet approximately 55% of patients are untreated, resulting in total direct costs from

stroke to Medicare of \$US4.8 billion.<sup>[6]</sup> Guidelines from the American Heart Association/American Stroke Association (AHA/ASA) for the primary prevention of stroke recommend use of warfarin in non-valvular AF (NVAF) patients at high risk for stroke and also for patients at moderate risk if they can be safely treated.<sup>[9]</sup> There are occasions when patients require AC but when warfarin, due to its relatively slow onset and long half-life, may need to be temporarily discontinued, delayed, or supplemented with a faster onset parenteral AC agent until it takes effect. In these cases, bridging therapy may be used.

Bridging therapy is the transition of one AC agent to another and has two major applications. Bridging therapy most commonly

describes peri-procedural AC in patients maintained on warfarin therapy but who need to transition from warfarin to a parenteral AC agent (typically low molecular weight heparin [LMWH] or unfractionated heparin [UFH]) to maintain thromboprophylaxis while reducing the risk of bleeding during surgery.<sup>[11-13]</sup> The second bridging therapy application is acute AC with a rapid onset, parenteral AC as a short-term transition to either *de novo* warfarin therapy or when resuming interrupted long-term warfarin therapy.<sup>[14,15]</sup> Transition phases can include the time period around the initiation of warfarin, when it may be necessary to quickly achieve a therapeutic international normalized ratio (INR) in patients at risk for embolic events, and the time period surrounding planned or unplanned surgical or other invasive procedures, when it may be necessary to interrupt existing warfarin therapy to reduce bleeding risk. AHA/ASA guidelines on prevention of stroke in AF patients with stroke or transient ischemic attack (TIA) consider use of LMWH as bridging therapy 'reasonable' to fill the gap in AC in high-risk AF patients who must interrupt AC therapy.<sup>[10]</sup> The American College of Chest Physicians (ACCP) 2008 practice guidelines suggest that AF patients at high or moderate risk for thromboembolism receive therapeutic dose subcutaneous (SC) LMWH (preferred) or intravenous (IV) UFH as bridging therapy in patients requiring temporary peri-operative interruption of warfarin.<sup>[11]</sup> Despite these guidelines, there is a lack of consensus among clinicians on an appropriate bridging therapy strategy, which tends to be based on the clinical judgment as well as personal opinion of the attending physician.<sup>[13]</sup> Available data do not adequately address the benefits and risks of bridging therapy, and questions remain on indications for its use and the choice, dosing, and timing of bridging agents.<sup>[16-18]</sup>

The objectives of the current study are to describe AC treatment in the inpatient setting in patients hospitalized with NVAf, to determine the prevalence of inpatient bridging therapy, and to identify whether differences exist in length of stay (LOS) among bridged versus non-bridged NVAf patients, after controlling for demographic and clinical differences between the two groups. In this study, a broad definition of bridging was used, identified by evidence of receipt in the inpatient setting of both warfarin and a parenteral agent, without regard for timing of bridging agents or bridging indication.

## Design

### Data Sources

Three Truven Health Analytics MarketScan<sup>®</sup> databases were used in this study: the Hospital Drug Database (HDD), the

Commercial Claims and Encounters (Commercial) Database, and the Medicare Supplemental and Coordination of Benefits (Medicare) Database. The HDD is derived primarily from the hospital billing systems of 584 hospitals. Data elements include admission and discharge dates, primary and secondary diagnoses and procedures, patient demographics, drug utilization, and supplies.

The Commercial database contains the healthcare experience of privately insured individuals covered under a variety of fee-for-service, fully capitated, and partially capitated health plans. The database is constructed from claims and enrollment data provided by large employer-sponsored health plans from across the USA. Approximately 35 million individuals are included annually in the database, encompassing employees, their spouses, and dependents. The Medicare database contains the healthcare experience of approximately 2.5 million individuals annually with Medicare Supplemental insurance paid for by employers.

The Commercial and Medicare data include medical claims for healthcare services performed in both the inpatient and outpatient settings and enrollment data including member demographic information and eligibility and benefits data. The medical claims files include service dates, provider reimbursement amounts, and patient co-payment and deductible amounts. Within the Medicare database, both the Medicare-covered portion of payment (represented as the coordination of benefits amount) and the employer-paid portion are included, as well as any out-of-pocket patient expenses. The medical care claims are linked to complete outpatient prescription drug claims, including claims for mail order prescriptions and specialty pharmacy, which fully capture prescription fills from all locations. These databases include persons from all US States and are de-identified and fully compliant with the Health Insurance Portability and Accountability Act of 1996. MarketScan data quality has been assessed and the comprehensiveness of the data has been confirmed through frequent audits of the data. There are more than 400 publications using MarketScan data.

Because this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval was not required.

### Patient Selection

Patients  $\geq 18$  years of age with a primary or secondary discharge diagnosis of AF [International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) diagnosis code 427.31] from 1 July 2004 through 30 September 2009 (enrollment window) were selected from the HDD. The subset of HDD AF patients also included in the Commercial and Medicare

databases was identified. Patients were required to have a minimum of 6 months of continuous medical and pharmacy coverage prior to the admission date of the first AF admission (index admission) in the enrollment window and a minimum of 30 days of coverage subsequent to the discharge date of the index admission, as well as complete data for all study variables. For patients with multiple AF admissions, only the index admission was evaluated. Index admissions were required to have both admission and discharge dates. Since there is no diagnosis for NVAF, patients were excluded if claims for a valvular cause or transient cause of AF were present during the index admission, specifically pulmonary embolism, cardiac surgery, or hyperthyroidism, to limit AF admissions to those most representative of patients with NVAF. Patients with evidence of hyperthyroidism in the 6-month pre-index period were also excluded, as were patients with pregnancy at any time in the study window, defined as the 6-month pre-index period through the 30-day post-index period. All study patients were required to have evidence of warfarin use during the index admission to be included in the bridging analysis.

### Outcomes

The number and percentage of NVAF patients with anticoagulant use during the index admission were quantified, overall and by specific agent. AC was reported for the entire NVAF group, and also stratified by presence/absence of inpatient bridging therapy. Bridging therapy was defined as receipt of a second anticoagulant (bridging agent) in addition to warfarin during the index admission. Three bridging agent regimens were evaluated: LMWH or other pentasaccharide (e.g. fondaparinux) [LMWH/PS]; unfractionated heparin (UFH) [excluding UFH used for line flushing]; and two-agent bridging (LMWH/PS and UFH).

LOS for the index admission was measured and reported for patients on warfarin alone and for patients with inpatient bridging therapy by bridging agent.

### Variables

Demographic, utilization, and cost variables measured in the 6 months prior to the index admission and reported by bridging therapy status included mean age, age group, sex, payer type (commercial, Medicare), plan type (fee-for-service, managed care, other/unknown), population density (urban, rural, unknown), geographic region (Northeast, North Central, South, West, unknown), concomitant medications of interest (including warfarin), previous hospitalization, and mean and median total

pre-period healthcare payments (inflation adjusted to 2009 dollars based on the Medical Care Consumer Price Index). Specific co-morbid conditions were measured in the 6-month pre-period as well as during the index admission. The Charlson Comorbidity Index (Deyo version) [CCI],<sup>[19]</sup> based on the presence or absence of specific ICD-9-CM diagnosis codes consistent with 19 conditions, was also measured, as was the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, a predictor of the clinical risk of stroke and thromboembolism in patients with AF.<sup>[20]</sup>

### Statistical Analyses

Descriptive statistics were reported by inpatient bridged/non-bridged categories for demographic and clinical variables in the pre-hospitalization period as well as by inpatient medications for patients receiving inpatient warfarin. Because LOS is a skewed variable, multivariate analysis was performed using a generalized linear model (GLM) with a log link and gamma error distribution to evaluate the association between bridging therapy and LOS, adjusting for demographic and clinical variables. All model fitting was done using PROC GENMOD in SAS version 9.2 (SAS, Cary, NC, USA).

For ease of understanding the modeled relation between study variables and LOS, results were presented as ‘percentage change’ relative to a reference LOS for a ‘low risk’ NVAF patient, as well as total days hospitalized during the index admission. The reference patient was defined as a 73-year-old male who received inpatient warfarin without a bridge agent, not from the Western region, with total 6-month pre-period costs of \$US8800 and all other variables equal to ‘No.’ In addition to calculating the parameter estimates and confidence intervals, PROC GENMOD also produced the predicted LOS associated with a change in one variable (e.g. ‘no’ to ‘yes’), for a patient with one particular characteristic and all other factors the same as the reference. To estimate the percent change in LOS and days LOS for patients with both a bridge agent and an additional condition (e.g. cancer and LWMH/PS bridging), the calculations were more complex and included contributions to LOS identified by the model for both main effects and the interaction effect. The interactions include the extra effects, either synergistic or antagonistic, that occur when both factors are present, whether over and above (synergistic) or under and below (antagonistic) those of the two factors being present on their own.

The models were used to compare estimated LOS in the low risk NVAF reference group (e.g. none of the pre-selected comorbid conditions) that did not receive bridging therapy to three types of NVAF patients: (i) those who were also low risk but received inpatient bridging therapy; (ii) those with selected

conditions (e.g. cancer or diabetes mellitus) who did not receive bridging therapy; and (iii) those with a selected co-morbidity who received bridging therapy. This method controlled for the demographic and clinical variables described above and reported in tables I and II.

**Table I.** Demographic characteristics of NVAF patients by bridging therapy

Characteristic	NVAF patients on warfarin				p-Value
	Bridged <sup>a</sup> (N= 1944)		Non-bridged <sup>b</sup> (N= 1093)		
	n/mean	%/SD	n/mean	%/SD	
Age (years)	72.3	10.8	75.3	9.8	<0.001
Age group (years)					<0.001
18–24	1	0.1%	0	0.0%	
25–34	3	0.2%	0	0.0%	
35–44	23	1.2%	4	0.4%	
45–54	102	5.2%	35	3.2%	
55–64	304	15.6%	116	10.6%	
65+	1511	77.7%	938	85.8%	
Sex					0.426
Male	1098	56.5%	601	55.0%	
Female	846	43.5%	492	45.0%	
Payer					<0.001
Commercial	426	21.9%	152	13.9%	
Medicare	1518	78.1%	941	86.1%	
Insurance plan type					<0.001
Fee-for-service	905	46.6%	585	53.5%	
Managed care	997	51.3%	495	45.3%	
Other/unknown	42	2.2%	13	1.2%	
Population density					0.719
Urban	1606	82.6%	909	83.2%	
Rural	334	17.2%	183	16.7%	
Unknown	4	0.2%	1	0.1%	
Geographic region					0.569
Northeast	40	2.1%	15	1.4%	
North central	500	25.7%	296	27.1%	
South	1364	70.2%	762	69.7%	
West	36	1.9%	19	1.7%	
Unknown	4	0.2%	1	0.1%	

a Bridged=inpatient warfarin with inpatient LMWH/PS and/or with UFH.

b Non-bridged=inpatient warfarin without inpatient LMWH/PS or UFH.

**LMWH/PS**=low molecular weight heparin/pentasaccharide; **N**=number of patients in database sample meeting study selection criteria; **n**=number of patients in database sample meeting study selection criteria with specified demographic characteristic; **NVAF**=non-valvular atrial fibrillation; **UFH**=unfractionated heparin.

## Results

### Non-Valvular Atrial Fibrillation (NVAF) Patients, Inpatient Anticoagulant Use, and Length of Stay

A total of 6340 patients had a hospitalization for NVAF from 1 July 2004 through 30 September 2009 and met the selection criteria for age, eligibility, and exclusionary diagnoses (figure 1). Seventy percent of NVAF hospitalizations were medical admissions; 30% were surgical admissions.

Of the 6340 NVAF patients, 76% received inpatient warfarin, LMWH/PS, or UFH (figure 2). Another 9% received an antiplatelet or an AC other than warfarin, LMWH/PS, or UFH. Fifteen percent of NVAF patients received no AC. Among the 48% (n= 3037) of patients who received inpatient warfarin, 64% (n= 1944) received bridging therapy. LMWH/PS accounted for 45% of bridging therapy, UFH for 36%, and two-agent bridging therapy for 18%. The descriptive tables and multivariate analyses were confined to the 3037 patients that received inpatient warfarin, stratified by receipt of inpatient bridging therapy versus inpatient warfarin alone.

The mean LOS for the 6340 NVAF patients was 5.2 days (SD 5.5 days); median LOS was 4 days. Of the 3037 NVAF patients receiving inpatient warfarin (alone or in combination with a bridging agent), mean and median LOS were 5.5 days (SD 5.2 days) and 4 days. Among NVAF patients not receiving inpatient warfarin, mean LOS was 5.0 days (SD 5.7 days), with a median LOS of 3 days.

### NVAF Patients: Bridged versus Non-Bridged

Bridged patients were younger (table I), and were more likely to be covered under a commercial payer and to have a managed care health plan than non-bridged patients receiving warfarin alone. No differences by sex, urban/rural location, or region were observed (table I). Bridged patients also were slightly healthier, as indicated by lower CCI, CHA<sub>2</sub>DS<sub>2</sub>-VAsC [(i) Congestive heart failure or left ventricular dysfunction, 1 pt, (ii) Hypertension, 1 pt, (iii) Age ≥75 years, 2 pts, (iv) Diabetes mellitus, 1 pt, (v) Stroke, transient ischemic attack, or thromboembolism, 2 pts, (vi) Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque), 1 pt, (vii) 65≤Age<75, 1 pt, (viii) Sex category, 1 pt if female)] score, and pre-period inpatient utilization and healthcare costs, than non-bridged patients (table II). There were some differences in co-morbid conditions assessed in the pre-period, with higher rates of acute myocardial infarction (AMI), atrial flutter, and ischemic stroke/TIA/cerebrovascular disease in bridged patients than non-bridged patients.

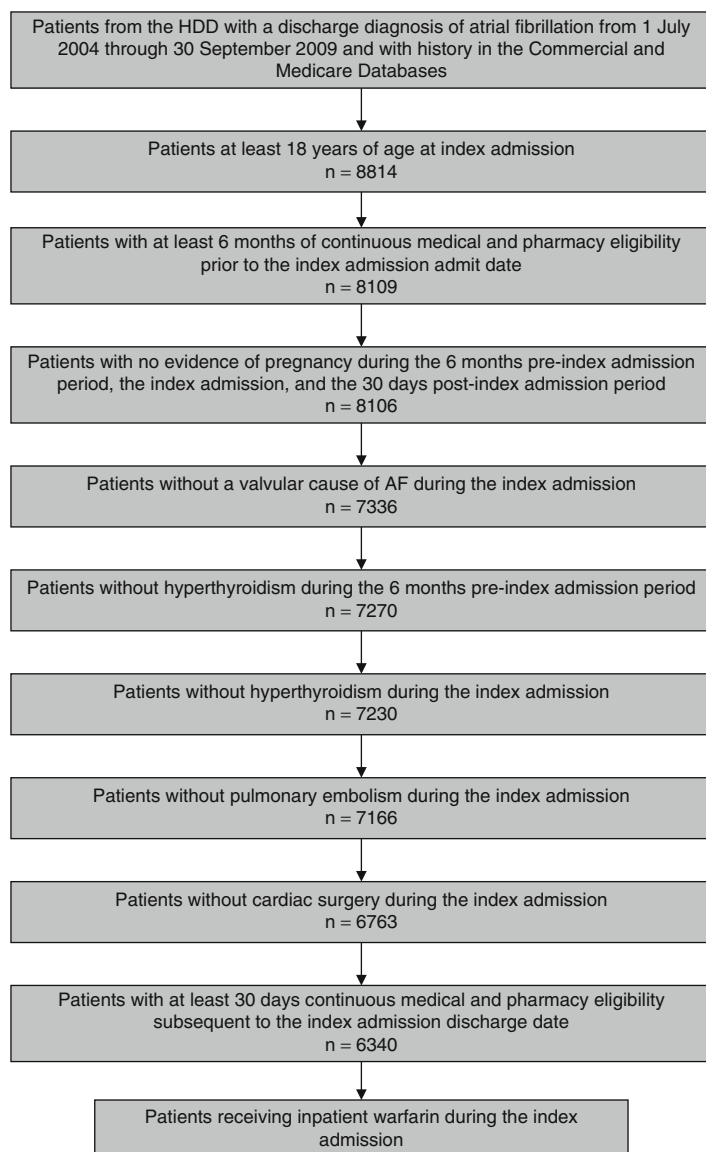
**Table II.** Clinical characteristics of NVAF patients in the 6-month pre-period and during the index hospitalization

Characteristic	NVAF patients on warfarin				p-Value
	Bridged <sup>a</sup> (N= 1944)		Non-bridged <sup>b</sup> (N= 1093)		
	n/mean	%/SD	n/mean	%/SD	
<b>Co-morbidity/risk indicators</b>					
Charlson-Deyo Comorbidity Index	1.1	1.5	1.3	1.6	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	3.5	1.7	3.8	1.5	<0.001
<b>Co-morbid conditions</b>					
Cancer	171	8.8%	81	7.4%	0.184
Rheumatoid arthritis	37	1.9%	22	2.0%	0.834
Multiple sclerosis	1	0.1%	3	0.3%	0.104
Coronary artery disease	793	40.8%	493	45.1%	0.021
Acute myocardial infarction	73	3.8%	20	1.8%	0.003
Cardiomyopathy	200	10.3%	122	11.2%	0.453
Ischemic stroke/TIA/cerebrovascular disease	175	9.0%	73	6.7%	0.025
Heart failure	555	28.5%	391	35.8%	<0.001
Atrial flutter	225	11.6%	69	6.3%	<0.001
Hypertension	1396	71.8%	787	72.0%	0.91
Peripheral artery disease	193	9.9%	95	8.7%	0.264
Liver disease	28	1.4%	21	1.9%	0.313
Renal disease	379	19.5%	225	20.6%	0.47
COPD/emphysema	404	20.8%	238	21.8%	0.52
Hypothyroidism	285	14.7%	183	16.7%	0.127
Diabetes mellitus	552	28.4%	304	27.8%	0.732
Peptic ulcer/GERD	305	15.7%	152	13.9%	0.187
VTE	71	3.7%	28	2.6%	0.104
<b>Concomitant medications of interest (pre-period only)</b>					
ARB or ACE inhibitor (including combinations)	952	49.0%	606	55.4%	<0.001
β-adrenoceptor antagonist	905	46.6%	600	54.9%	<0.001
Amiodarone	103	5.3%	110	10.1%	<0.001
Clopidogrel	173	8.9%	68	6.2%	0.009
Statin	789	40.6%	452	41.4%	0.68
Proton-pump inhibitor	493	25.4%	295	27.0%	0.325
H <sub>2</sub> -receptor antagonist	85	4.4%	44	4.0%	0.649
Warfarin	713	36.7%	881	80.6%	<0.001
<b>Utilization and expenditures (pre-period only)</b>					
Inpatient hospitalization	207	10.6%	145	13.3%	0.031
Medical costs, \$US	8239	19 464	9754	20 710	0.044

a Bridged=inpatient warfarin with inpatient LMWH/PS and/or with UFH.

b Non-bridged=inpatient warfarin without inpatient LMWH/PS or UFH.

**ACE**=angiotensin converting enzyme; **ARB**=angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); **CHA<sub>2</sub>DS<sub>2</sub>-VASc score**=(i) Congestive heart failure or left ventricular dysfunction, 1 pt, (ii) Hypertension, 1 pt, (iii) Age ≥75 years, 2 pts, (iv) Diabetes mellitus, 1 pt, (v) Stroke, transient ischemic attack, or thromboembolism, 2 pts, (vi) Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque), 1 pt, (vii) 65≤Age<75, 1 pt, (viii) Sex category, 1 pt if female; **COPD**=chronic obstructive pulmonary disease; **GERD**=gastroesophageal reflux disease; **LMWH/PS**=low molecular weight heparin/pentasaccharide; **N**=number of patients in database sample meeting study selection criteria; **n**=number of patients in database sample meeting study selection criteria with specified demographic characteristic; **NVAF**=non-valvular atrial fibrillation; **TIA**=transient ischemic attack; **UFH**=unfractionated heparin; **VTE**=venous thromboembolism.



**Fig. 1.** Study attrition table of NVAF patients. **AF** = atrial fibrillation; **HDD** = Hospital Drug Database; **NVAF** = non-valvular atrial fibrillation.

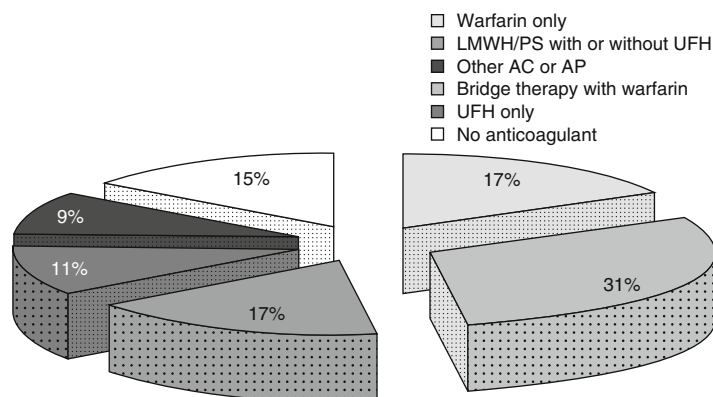
Among bridged patients, only 36.7% had received warfarin in the 6 months prior to the index admission, compared with 80.6% of non-bridged patients ( $p < 0.001$ ) [table II]. Bridged patients were more likely to have a primary discharge diagnosis of AF than non-bridged patients (37.9% vs 20.8%,  $p < 0.001$ ) [table III]. Although inpatient mortality was low regardless of bridging status, death occurred in 14 (0.7%) of the 1944 bridged patients versus none of the 1093 non-bridged patients ( $p = 0.005$ ).

Overall, LOS was longer in bridged patients (mean 6.3, SD 5.9, median 5 days) than in those receiving warfarin alone (mean 4.2, SD 3.1, median 3 days). Patients receiving LMWH/PS as the bridging agent had the shortest LOS (mean 5.6, SD

5.3, median 4 days) of the bridging regimens, while those receiving two-agent bridging had the longest LOS (mean 8.4, SD 8.4, median 6 days).

#### Multivariate Analysis

Multivariate analysis estimated that compared with patients who were on warfarin only, patients with a bridging regimen had an 18.2% higher LOS ( $p = 0.0017$ , data not shown). Multivariate analysis was also used to investigate the change in LOS associated with each of the bridging regimens, controlling for demographic and clinical characteristics. Results are presented for the change in one variable from the reference population, with the exception of the bridge agent interactions, which report the change in LOS for two variables compared with the reference (table IV). The predicted LOS for the warfarin-only reference group was 3.74 days. Compared with the reference LOS, patients receiving inpatient warfarin and UFH had a 19.3% increase in LOS ( $p = 0.0030$ ), while those receiving inpatient warfarin and two-agent bridging had a 45.1% increase in LOS ( $p < 0.0001$ ). Although patients bridged with LMWH/PS had an increase in LOS of 8.3%, it was not significant ( $p = 0.1577$ ). To put the differences in LOS among bridged patients in perspective, LOS was reported for non-bridged patients in comparison with the non-bridged reference patient for selected conditions. Female patients had a 6% shorter LOS than the reference male patient ( $p = 0.0133$ ). Every increase of 1 year in age above 73 years resulted in a 1.2% increase in LOS ( $p < 0.0001$ ). Patients receiving warfarin in the pre-period had an 8.5% shorter LOS than the reference patient who received warfarin during the inpatient stay only, although the difference was not significant at the 0.05 level ( $p = 0.0814$ ).



**Fig. 2.** Anticoagulant (AC)/antiplatelet (AP) use for NVAF patients during index hospitalization ( $n = 6340$ ). **LMWH/PS** = low molecular weight heparin/pentasaccharide; **NVAF** = non-valvular atrial fibrillation; **UFH** = unfractionated heparin.

**Table III.** Index admission status and drug use

Status or drug use	NVAF patients on warfarin				p-Value
	Bridged <sup>a</sup> (N = 1944)		Non-bridged <sup>b</sup> (N = 1093)		
	n	%	n	%	
In-hospital mortality	14	0.7	0	0	0.005
AF principal discharge diagnosis	737	37.9	227	20.8	<0.001
Admitted from emergency room	1113	57.3	604	55.3	0.288
Inpatient anticoagulant use					
Warfarin	1944	100.0	1093	100.0	n/a
LMWH	1226	63.1	0	0.0	<0.001
UFH	1062	54.6	0	0.0	<0.001
Fondaparinux (PS)	15	0.8	0	0.0	0.004
Argatroban	1	0.1	1	0.1	0.68
Bivalirudin	24	1.2	4	0.4	0.016
Lepirudin	0	0.0	0	0.0	n/a
Aspirin (acetylsalicylic acid)	829	42.6	265	24.2	<0.001
Clopidogrel	207	10.6	62	5.7	<0.001
Aspirin + clopidogrel	136	7.0	29	2.7	<0.001
Rate control medications	1805	92.8	943	86.3	<0.001
Antiarrhythmic medications	1142	58.7	486	44.5	<0.001

a Bridged=inpatient warfarin with inpatient LMWH/PS and/or with UFH.

b Non-bridged=inpatient warfarin without inpatient LMWH/PS or UFH.

**AF**= atrial fibrillation; **LMWH**= low molecular weight heparin; **LMWH/PS**=LMWH/pentasaccharide; **N**= number of patients in database sample meeting study selection criteria; **n**= number of patients in database sample meeting study selection criteria with specified demographic characteristic; **n/a**= not applicable; **NVAF**= non-valvular atrial fibrillation; **PS**= pentasaccharide; **UFH**= unfractionated heparin.

There were no significant changes in predicted LOS from the reference population for individual variables of pre-period warfarin use or occurrence of cancer or diabetes. Thus among NVAF patients not receiving bridging therapy, there was no difference in LOS for those with cancer versus those without cancer. However, significant increases in predicted LOS were observed for NVAF patients with cancer who received bridging therapy compared with the reference NVAF group without cancer and without bridging therapy. Similarly, among non-bridged groups, the models did not predict differences in LOS for NVAF patients with pre-period warfarin use or diabetes as compared with the reference NVAF group. As with cancer, estimated LOS was higher for patients with pre-period warfarin use or with diabetes in conjunction with inpatient bridging therapy. The greatest increase in LOS (101.2%,  $p=0.0107$ ) was found for patients with cancer who received two-agent (LMWH/PS and UFH) bridging with inpatient warfarin. Predicted LOS for these patients was 7.53 days, compared with the reference LOS of 3.74 days (no cancer and no bridging therapy) and the predicted LOS for cancer and no bridging therapy of 4.05 days

(figure 3). Similarly, patients with diabetes who also received bridging had a 24.5% increase in LOS with LMWH/PS, 21.1% higher with UFH, and 54.4% higher with both bridging agents than the reference LOS of 3.74 days for a non-diabetic AF patient receiving inpatient warfarin (table IV). For the three clinical variables shown here, no differences were predicted in LOS as compared with the reference group, but the addition of bridging therapy resulted in longer predicted LOS for each variable.

## Discussion

The current study found that less than half of NVAF patients received warfarin while hospitalized. Among patients receiving inpatient warfarin, nearly two-thirds also received inpatient bridging therapy. LMWH/PS was the most common bridging agent, followed by UFH. Only 18% of patients with bridging therapy received both LMWH/PS and UFH. Patients receiving bridging therapy were younger and generally in better health, with slightly lower CCI and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores,

lower rates of previous hospitalization, and lower pre-period healthcare costs. Bridged patients had higher rates of atrial flutter, ischemic stroke/TIA/cerebrovascular disease, and acute myocardial infarction (AMI), conditions associated with higher thrombotic risk, but only 36.7% of bridged patients had evidence of warfarin use in the 6 months before hospitalization. The study used observational data to describe rather than predict receipt of bridging therapy and thus the reasons for bridging are unknown. However, the results suggest that patients without

evidence of warfarin in the pre-period who received bridging would likely have received rapid onset parenteral agents along with initiation of warfarin, for long-term use. The higher rates among the bridged group of patients with AF as a principal discharge diagnosis, as well with evidence of AMI, stroke, and atrial flutter, also suggest that the majority of the observed bridging was for rapidly establishing effective AC by using a parenteral agent in association with initiation of warfarin. Subsequent research, incorporating clinical data in addition to that available in administrative claims, is needed to understand clinical decision-making regarding inpatient bridging in NVAF patients.

A longer LOS was found in patients bridged during hospitalization (mean 6.3 days, median 5 days) compared with the LOS for patients receiving inpatient warfarin alone (mean 4.2 days, median 3 days). Significant increases in LOS remained for UFH and two-agent bridging after adjustment for demographic and clinical variables including diabetes and cancer. While the NVAF patients in the current study were not limited to those with surgical indications for bridging, the LOS results are nevertheless consistent with studies of patients with periprocedural bridging. Tolosana et al.<sup>[21]</sup> found a median of 5 days for bridged versus 2 days for non-bridged patients at high risk for thromboembolism and requiring implant or replacement of a pacemaker or implantable cardiac defibrillator. As in the current study, where patients receiving LMWH/PS alone as the bridging agent had the shortest LOS compared with either UFH alone or UFH with LMWH/PS, Spyropoulos et al.<sup>[22]</sup> found that LOS was decreased in patients bridged in the hospital with LMWH versus UFH (4.6 vs 10.3 days). Of the 901 patients requiring bridging for elective surgery or procedures in Spyropoulos et al.,<sup>[22]</sup> 74.5% were receiving oral AC for arterial indications, while 25.5% had venous indications. AF (without mechanical heart valves) accounted for 38.7% of the 901 patients. The ACCP recommends SC LMWH over UFH for bridging therapy,<sup>[23]</sup> and bridging with UFH requires longer LOS than bridging with SC LMWH, which, unlike IV UFH, can be home-administered.<sup>[24]</sup>

Given that in the current study, bridged patients were somewhat younger and healthier than non-bridged patients, it would not have been unreasonable to expect a shorter LOS in these patients if bridging had no effect on LOS. Yet, following multivariate analysis, LOS was significantly longer for patients bridged with UFH or two-agent bridging. Also, although the rate (0.7%) and number of inpatient deaths was small, all 14 deaths were among patients receiving bridging therapy. This finding is contrary to Billet et al.<sup>[15]</sup> who found model-adjusted mortality rates to be lower among bridged patients, and thus

**Table IV.** Predicted change in length of stay

Variables	NVAF Patients treated with warfarin (N=3037)	
	% Change in length of stay relative to reference <sup>a</sup>	p-Value
Bridge: LMWH/PS	8.3	0.1577
Bridge: UFH	19.3	0.0030
Bridge: two-agent	45.1	<0.0001
Age above 73 years <sup>b</sup>	1.2	<0.0001
Female	-6.0	0.0133
Pre-period warfarin	-8.5	0.0814
Bridge therapy: LMWH/PS and pre-period warfarin <sup>c</sup>	20.8	0.0047
Bridge therapy: UFH and pre-period warfarin <sup>c</sup>	21.7	0.0066
Bridge therapy: two-agent and pre-period warfarin <sup>c</sup>	30.6	0.0089
Cancer	8.3	0.2941
Bridge therapy: LMWH/PS and cancer <sup>c</sup>	36.7	0.0148
Bridge therapy: UFH and cancer <sup>c</sup>	55.2	0.0013
Bridge therapy: two-agent and cancer <sup>c</sup>	101.2	0.0107
Diabetes mellitus	1.1	0.8017
Bridge therapy: LMWH/PS and diabetes <sup>c</sup>	24.5	0.0025
Bridge therapy: UFH and diabetes <sup>c</sup>	21.1	0.0237
Bridge therapy: two-agent and diabetes <sup>c</sup>	54.4	0.0004

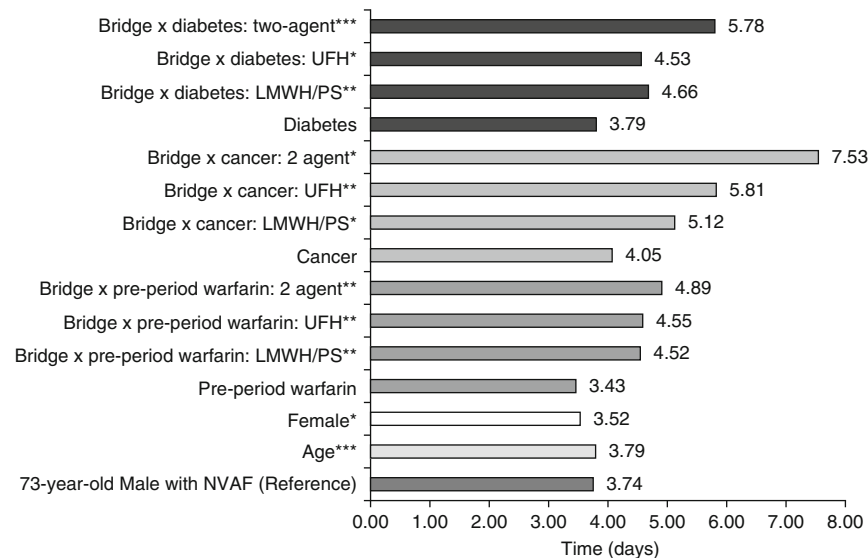
a The reference LOS = 3.74 days for Age 73 years, Male, Not West, Total Payments of 8.8 (thousands of \$US), and all other variables 'No.'

b For the continuous variable Age, the percentage change is for an increase of 1 year.

c The percentage change for the interactions reflects the value of the synergistic effects above those of bridge therapy and pre-period warfarin, cancer, or diabetes on their own.

**LMWH/PS** = low molecular weight heparin/pentasaccharide; **LOS** = length of stay; **NVAF** = non-valvular atrial fibrillation; **UFH** = unfractionated heparin.





**Fig. 3.** Estimated LOS during Index hospitalization by bridging regimen and selected variables. The reference LOS is 3.74 days for male aged 73 years, not from the Western region, with total 6-month pre-period costs of \$US8800 and all other variables equal to 'No'. Calculation of LOS reported for interaction terms (e.g. bridge×cancer: LMWH/PS) includes main effects and interaction effects. **LOS**=length of stay; **LMWH/PS**=low molecular weight heparin/pentasaccharide; **NVAF**=non-valvular atrial fibrillation; **UFH**=unfractionated heparin. \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  vs reference.

our mortality results may not be robust to adjustment. The discrepancy in mortality results, as well as the increased LOS among bridged patients, suggests that the benefits versus risks of bridging therapy, as well as possible alternatives, are worth further assessment.

Due to the limitations of observational data, the reason for longer LOS in NVAF patients receiving inpatient bridging could not be ascertained. One hypothesis is that the bridging procedure itself may delay an invasive procedure or discharge until therapeutic levels of AC are established. An alternate hypothesis is that bridging could be a marker of patient complexity not evident in the co-morbidity indicators investigated here, and thus both the decision to bridge and the observed longer LOS may be caused by unobservable factors requiring closer monitoring or additional care. Subsequent research is needed that is designed to identify and evaluate both the causes for bridging and for the longer LOS observed in patients receiving bridging therapy.

Unexpected findings of this study were that, although patients bridged with LMWH/PS did not have statistically significant longer stays than a similar reference group, those with diabetes or cancer who were bridged with LMWH/PS (as well as with UFH or both agents) had longer LOS than the non-bridged reference patients without these conditions. However, non-bridged patients with cancer or with diabetes did not have longer LOS than the non-bridged reference group without these conditions. Bridging is associated with longer LOS for a range of co-morbid conditions and may interact with selected con-

ditions, resulting in longer LOS than for bridged patients without these conditions. Since both cancer and diabetes are complex, it is possible that the bridged group with these conditions had a higher level of severity, unobservable in claims data, which may have resulted in both longer LOS and a higher likelihood to receive bridging therapy. The reasons for this finding cannot be assessed from our study design but are intriguing questions for subsequent analyses. Previous research has suggested that a range of co-morbidities, including certain types of cancer, may affect the expected therapeutic effect of warfarin and that AC may confer survival advantages to patients with solid tumors.<sup>[11]</sup>

This study adds to the existing evidence that bridging therapy results in an increased LOS compared with inpatient receipt of warfarin alone, and that these increases in LOS associated with bridging are greater for patients with a range of co-morbidities such as cancer and diabetes. Given this outcome, it is clearly important to weigh the clinical benefits against the risks of bridging as a means of managing AC in the NVAF patient during hospitalization. While the average risk of stroke in NVAF patients not treated with AC is reported to be 4.5%,<sup>[22]</sup> risk varies considerably depending on age and selected co-morbidities such as diabetes, congestive heart failure, hypertension, and prior stroke or TIA.<sup>[25,26]</sup> Determining when the risk of thromboembolism is sufficiently high to require bridging during warfarin initiation, during periods of subtherapeutic AC in patients already treated with warfarin, or during interruption of warfarin peri-operatively, is challenging. Two recent reviews,

focused on patients undergoing surgery or procedures, have attempted to sort through the available data and to provide guidance to physicians faced with this decision.<sup>[25,26]</sup> Kaatz and Paje<sup>[25]</sup> cite a 30-day risk of stroke in AF patients with discontinuation of AC and without bridging of 0.6–1.8%, increasing to greater than 3% in patients undergoing more complex surgery. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score provides a means for assessing thromboembolic risk.<sup>[20]</sup> Various approaches have been used, including type and length of the surgical procedure, the significance of the potential bleed, and subjective determination by the physician.<sup>[25,26]</sup> The HAS-BLED bleeding risk score, which incorporates diagnostic as well as laboratory data such as INR values shows promise,<sup>[27]</sup> although HAS-BLED cannot readily be applied in studies such as ours, which use administrative claims data. Future research should include factors such as bleeding and thrombosis to better understand clinical decision-making regarding bridging therapy and why it results in longer LOS.

Several limitations to the study should be noted. First, this was a retrospective, observational study based on administrative claims data and therefore the reasons for patient receipt of inpatient bridging or explanation for longer LOS among bridged than non-bridged patients could not be determined. Another limitation of this type of study is that the selection of patients with NVAf is limited by completeness and accuracy of medical coding. However, as selection was based on hospitalization discharge diagnosis codes, concern over inclusion of patients based on rule-out diagnoses in the outpatient setting or admission diagnoses in the inpatient setting would not be an issue. Third, so as to provide a broad view of bridging therapy in the inpatient setting, medical and surgical admissions were not differentiated. Fourth, factors impacting LOS were identified from demographic and clinical variables that could be defined using administrative claims data. The relation to LOS for variables not captured in these data but which might have influenced LOS, such as bleeding risk as identified by HAS-BLED scoring, cannot be determined from this study. Fifth, differences in LOS from the reference group were shown for one variable at a time and for the interaction of bridging agents with pre-period warfarin, cancer, and diabetes, as well as other co-morbidities not reported here. Interactions with other drugs and inpatient procedures were not evaluated, and LOS was not evaluated for multiple combinations of demographic or clinical conditions different to the reference population. Sixth, the current study defined bridging as inpatient receipt of warfarin in addition to LMWH/PS, UFH, or two-agent bridging, without regard to the timing of the agents. Thus bridging that occurred in the outpatient setting, including peri-operative

bridging pre-admission or post-discharge, was not captured. In addition, LMWH use prior to the index admission and procedures performed during the index hospitalization were not tracked, and, therefore, their impact on observed LOS could not be determined. Finally, the study population was comprised of commercially insured patients and patients with employer-paid supplemental Medicare coverage, and results may not be representative of all patients with NVAf, especially the uninsured or those covered by Medicaid.

## Conclusion

This retrospective observational study found that, in patients hospitalized with NVAf, inpatient bridging therapy was common among those under warfarin therapy, and more common in patients who had no previous warfarin use and had thrombotic risk. Bridging therapy was also found to be associated with a longer LOS. Patients receiving inpatient warfarin only had shorter LOS than those receiving warfarin in conjunction with inpatient LMWH/PS, UFH, or both types of bridging agents. Additional research is needed to identify predictors of inpatient bridging therapy as well as to explain why, even after controlling for demographic and clinical characteristics, NVAf patients receiving inpatient bridging therapy had longer LOS than those who were not bridged.

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