ORIGINAL RESEARCH

Short-Term Risk of Bleeding During Heparin Bridging at Initiation of Vitamin K Antagonist Therapy in More Than 90 000 Patients With Nonvalvular Atrial Fibrillation Managed in Outpatient Care

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***Background*—**Several studies have recently examined the risks of bleeding and of ischemic stroke and systemic embolism associated with perioperative heparin bridging anticoagulation in patients with nonvalvular atrial fibrillation. However, few studies have investigated bridging risks during vitamin K antagonist initiation in outpatient settings.

***Methods and Results*—**A retrospective cohort study was conducted on individuals starting oral anticoagulation between January 2010 and November 2014 for nonvalvular atrial fibrillation managed in outpatient care and identified from French healthcare insurance. Bleeding and ischemic stroke and systemic embolism events were identified from the hospitalization database. Adjusted hazard ratios with 95% CI were estimated using Cox models during the first and 2 following months of anticoagulation. Of 90 826 individuals, 30% had bridging therapy. A total of 318 (0.35%) cases of bleeding and 151 (0.17%) ischemic stroke and systemic embolism cases were identified during the first month of follow-up and 231 (0.31%) and 122 (0.16%) during the 2 following months, respectively. At 1 month of follow-up, the incidence of bleeding was higher in the bridged group compared with the nonbridged group (0.47% versus 0.30%; $P<0.001$), and this increased risk persisted after adjustment for covariates (hazard ratio=1.60; 95% CI, 1.28–2.01). This difference disappeared after the first month of treatment (0.93; 0.70–1.23). No significant difference in the occurrence of ischemic stroke and systemic embolism was observed either at 1 month of follow-up or later.

***Conclusions*—**At vitamin K antagonist initiation for nonvalvular atrial fibrillation managed in ambulatory settings, bridging therapy is associated with a higher risk of bleeding and a similar risk of arterial thromboembolism compared with no bridging therapy. **(*J Am Heart Assoc*. 2016;5:e004065 doi: 10.1161/JAHA.116.004065)**

Key Words: anticoagulant • arterial thrombosis • bleeding • heparin bridging • nonvalvular atrial fibrillation • vitamin K antagonist

Nonvalvular atrial fibrillation (NVAF), a treatable risk factor for ischemic stroke, is considered a worldwide epidemic predicted to increase in the coming decades. Indeed, in 2010, the estimated global prevalence of AF was 33.5 million.[1] Oral anticoagulation is the cornerstone treatment for NVAF patients with a moderate or high risk of thromboembolic complication.[2]

Although direct oral anticoagulants (dabigatran, rivaroxaban, apixaban) have been on the market since 2010, vitamin K antagonists (VKAs: warfarin, acenocoumarol, fluindione) remain a standard treatment in the management of NVAF.

Recently, several studies have examined the risks of bleeding and of ischemic stroke and systemic embolism (IS/SE) associated with perioperative heparin bridging

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anticoagulation in patients with NVAF.[3–6] However, no studies have investigated bridging risks during VKA initiation in outpatient settings.

It has been shown that the bleeding risk is highest during the first month of VKA initiation.[7] This risk may be greatest when a VKA is combined with another antithrombotic agent, particularly in patients for whom a bridging therapy is indicated. Bridging therapy at the initiation of VKA therapy consists of transitioning a bridging agent (low-molecular-weight heparin [LMWH] or other pentasaccharide, eg, fondaparinux and unfractionated heparin) to a VKA.

There is an overall consensus in favor of a bridging therapy prior to urgent cardioversion in patients with life-threatening hemodynamic instability caused by new-onset NVAF.[8–13] The recommendation in guidelines[9,10,12] and summaries of product characteristics[14,15] is less clear for those with stable NVAF who do not require rapid anticoagulation. In real-life conditions, a bridging regimen is commonly used in those with a low stroke risk.[16–19] This practice is not supported by evidence.

VKA use has declined recently in favor of direct oral anticoagulants; however, the latest available results have shown that they are still more widely used than direct oral anticoagulants.[20–24] Since millions of patients worldwide may be at risk of being unnecessarily exposed to bridging therapy, adverse health outcomes associated with management of VKA still warrant investigation.

Therefore, the purpose of this cohort study was to assess the safety and effectiveness of a bridging regimen during the initiation of VKA therapy in NVAF patients in outpatient care.

Methods

Data Sources

A nationwide and retrospective cohort study was carried out using a French national health insurance database (SNIIRAM).[25–31] This database contains anonymous individual data on all reimbursements for patient health expenditure, including medicinal products and outpatient medical and nursing care, prescribed or provided by healthcare professionals. The SNIIRAM database does not provide any direct information about the medical indication of each reimbursement, but it does contain the patient's status with respect to full reimbursement of care for a severe and costly long-term condition listed in the International Classification of Diseases, 10th edition (ICD-10).[32]

Information from the SNIIRAM database has been cross-referenced with the French hospital discharge database (PMSI), which provides medical information on all patients admitted into the hospital in France, including discharge diagnoses coded in the ICD-10.[33]

This study was approved by the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*). Since the study was observational and used anonymous data, informed consent from participants was not required.

Study Population

This study included individuals aged 18 years or over who had their first VKA (warfarin, fluindione, or acenocoumarol) dispensed between January 1, 2010 and November 30, 2014 for NVAF (inclusion date). A previously used algorithm was applied to identify NVAF individuals managed on an outpatient basis.[25,26] The study consisted of identifying individuals with a nonhospitalized long-term AF condition (ICD-10 code I48) fully covered by insurance, having used a Holter monitor or antiarrhythmic drug before or within 3 months after the start of the VKA therapy. Individuals with a history of heart valve disease or surgery, cancer, dialysis for renal failure, any lesion or condition posing a high risk of major bleeding such as anemia, hepatic impairment or liver disease, current or recent gastroduodenal ulceration, dementia, and recent lower limb surgery were excluded. Individuals with a prevalent event related to outcomes of interest were also excluded (IS/SE, transient ischemic attack, ischemic heart disease, and bleeding).

Exposure

Bridging therapy was defined as the receipt of a subcutaneous heparin—LMWH (tinzaparin, enoxaparin, nadroparin, and dalteparin) and fondaparinux, or an unfractionated heparin (heparin calcium)—7 days before or after VKA treatment. In order to attribute the use of heparins in the context of bridging therapy in outpatient care, individuals who had a history of heparin use within the year prior to VKA initiation were not included.

Outcomes

These were identified using previously used algorithms[25,26] from the hospitalization database, which contains discharge diagnoses.

The primary outcome was bleeding (ICD-10 codes for intracranial bleeding: I60, I61, I62, S06.3, S06.4, S06.5, S06.6; gastrointestinal bleeding: K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K92.0, K92.1, K92.2, I85.0, K62.5; and other: N02, R31, D62, R58, J94.2, R04.0, R04.1, R04.2, R04.8, R04.9, K66.1, M25.0, N92.0, N92.1, N92.4, N93.8, N93.9, N92.0, N95.0, H11.3, H35.6, H43.1, H45.0, H92.2, I32.2).

Secondary outcomes were ischemic stroke (IS; ICD-10 code: I63 [cerebral infarction except I63.6]) or systemic embolism (SE; ICD-10 code: I74).

Covariates

Social deprivation index is a measure of an area's level of deprivation based on the following: the median household income, the percentage of high school graduates in the population aged 15 years and older, the percentage of blue-collar workers in the active population, and the unemployment rate. This index has been divided into quintiles: the lower quintile (Q1) represents the least deprived and the highest quintile (Q5) the most deprived.[34]

VKA prescribers were categorized as general practitioner, private practice cardiologist, other private practice specialist, and practitioner in a private institution.

Occurrence of the following comorbidities before initiation of a VKA was considered: heart failure, diabetes mellitus, high blood pressure, chronic kidney disease, chronic hepatitis, peripheral arterial disease, and alcohol- and smoking-related hospitalization and consultation.

The CHA2DS2-VASc score evaluates the risk of IS/SE in patients with AF[35] and the HAS-BLED score evaluates the risk of bleeding in patients on oral anticoagulation.[36] Both scores include some modified items that were originally created from clinical examinations and laboratory tests. These modified scores are described in Tables S1 and S2.

Using a drug claims database, concomitant medications were defined as a drug of interest dispensed at least once in the 4 months prior to VKA initiation, namely, antiarrhythmic agents or digitalis glycosides, lipid-lowering agents, nonsteroidal anti-inflammatory drugs, oral corticosteroids, gastroprotective agents, benzodiazepines, antiplatelet agents, and antihypertensive agents.

Statistical Analysis

Bivariate association was examined between bridging status and covariates using χ^2 and Fisher's exact tests for categorical variables, a Cochran–Mantel–Haenszel trend test for ordered variables, and a *t* test and ANOVA for continuous variables. Association between outcomes and bridging status was studied during the first and 2 following months of anticoagulation: for crude analysis, a log-rank test was used to examine differences between bridged and nonbridged groups in the occurrence of events of interest; for multivariate analysis, a Cox proportional hazards regression model[37] was used to estimate hazard ratios (HR) and their 95% CI for bleeding and IS/SE. Regarding bleeding risk, individuals experiencing this event were followed up from date of inclusion to date of the outcome. Those without such an event were censored on the date of the following events, whichever came first: IS/SE (the other end point), death, switch from initial VKA to another oral anticoagulant, up to 3 months of follow-up, or December 2014. The same was carried out for IS/SE and for each type of outcome of interest (intracranial, gastrointestinal, and other type of bleeding, and ischemic stroke and systemic embolism) (eg, for intracranial bleeding, censored events also included gastrointestinal and other types of bleeding).

The following covariates were used in the adjusted models: sex, age, social deprivation index, type of VKA therapy, type of VKA prescribers, comorbidities, and concomitant medications. Three models were studied: model 1 containing no covariate; model 2, which is adjusted for sex and age; and model 3, which is further adjusted for all covariates.

The main analysis consisted of examining bleeding events occurring within 1 month of follow-up to be in line with short-term exposure to a bridging therapy, which is recommended for 5 days on average, and the bleeding risk is highest during this period.[7,38] The proportional hazards assumption was assessed graphically. In addition, a sensitivity analysis was conducted after adjustment for the propensity score for bridging use, built with a logistic regression model including all covariates.[39]

Interactions between bridging status and bleeding events according to sex, age, and modified CHA2DS2-VASc and HAS-BLED scores were tested. Since evidence of interaction was found between bridging status and sex for bleeding (P=0.049), analyses were also performed with stratification according to sex. In addition, to test whether bleeding risk associated with bridging therapy depended on time, we fitted Cox proportional hazards regression models with cubic spline functions with four knots at 7, 14, 21, and 28 days.[40,41]

A further analysis was conducted to examine the relationship between the risks of IS/SE and bridging therapy.

All analyses were performed with SAS software, version 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

Between January 2010 and November 2014, 163 840 individuals were identified with nonhospitalized NVAF who had a first dispensing of VKA. After excluding those who did not meet the inclusion criteria, our study sample was composed of 90 826 individuals, 27 147 (30%) of whom had bridging therapy at VKA initiation (Figure 1). In the bridging group, 87.8% had a bridging agent and a VKA dispensed on the same day; LMWH represented 80.0%, fondaparinux 16.7%, and heparin calcium 3.6% (the total percentage does not add up to 100%, as 0.3% were dispensed 2 types of heparin). Four types of LMWH were used: tinzaparin (45.2%), enoxaparin (29.6%),

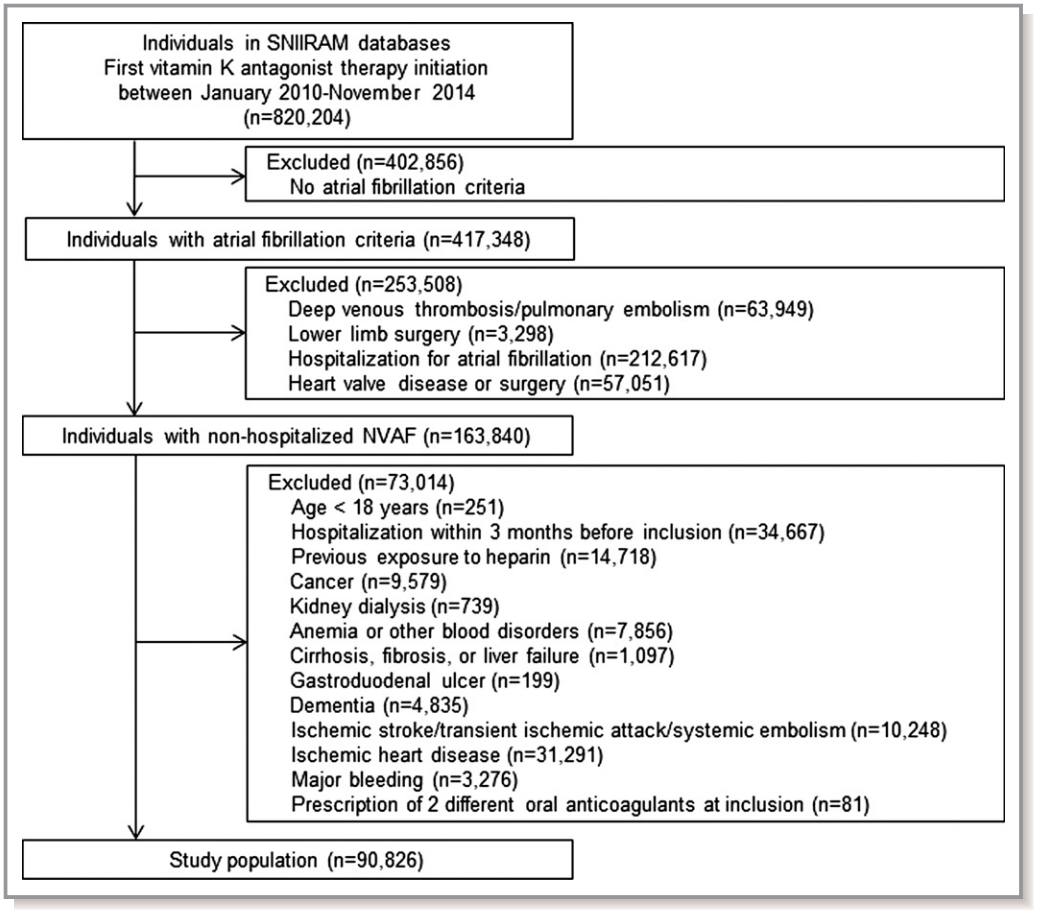

Figure 1. Flow diagram of study population. NVAF indicates nonvalvular atrial fibrillation.

nadroparin (5.1%), and dalteparin (0.2%). Further details on the bridging agents are reported in Table S3.

Table 1 compares bridged and nonbridged individuals for the baseline characteristics. The mean age of the study population was 72.3 years (SD=11.7). Half of them were female (49.9%). Bridged individuals were more likely to be younger, female, on fluindione, and have had a first VKA prescribed by a cardiologist than their nonbridged counterparts. They were more likely to have heart failure and high blood pressure, and less likely to have chronic renal impairment, chronic hepatitis, and peripheral arterial disease. The bridged group had a slightly lower risk of IS/SE (mean modified CHA2DS2-VASc score=2.74 [SD=1.50] versus 2.83 [SD=1.40]) than the nonbridged group, but the same risk of bleeding (mean modified HAS-BLED score=1.86 [SD=1.00]). Overall, bridged individuals were less likely to be using concomitant medications, particularly antiplatelet agents, but had higher use of nonsteroidal anti-inflammatory agents and oral corticosteroids.

Outcomes

A total of 318 (0.35%) cases of bleeding (57 intracranial, 99 gastrointestinal, and 162 other) and 151 (0.17%) IS/SE cases were identified during the first month of follow-up and 231 (0.31%) cases of bleeding (59 intracranial, 57 gastrointestinal, and 115 other) and 122 (0.16%) IS/SE cases were identified during the 2 following months (Table 2 and Table S4).

During 1 month of follow-up, the incidence of bleeding was higher in the bridged group than the nonbridged group (0.47% [n=127] versus 0.30% [n=191], $P<0.001$); this difference was due to gastrointestinal and other types of bleeding. The association with intracranial bleeding was not significant. Moreover, no significant difference was observed for IS/SE (0.16% [n=44] versus 0.17% [n=107], $P=0.840$).

During the 2 following months, no difference was found between bridged and nonbridged groups for any of the events of interest (Table 2).

In multivariate analyses, different strategies of adjustment for confounding factors (models 1–3) generated similar HRs for bleeding (Table 3).

After adjustment for all confounding factors (model 3), a 60% increased risk was observed in the bridged group compared with the nonbridged counterpart during the first month of follow-up (HR=1.60; 95% CI, 1.28–2.01). Adjustment for the propensity score did not modify HR estimates (HR=1.60; 95% CI, 1.27–2.01). The 1-month bleeding risk

Table 1. Demographic and Clinical Characteristics of the Study Population

	All	No Heparin Bridging	Heparin Bridging	
	N=90 826	N=63 679 (70.1%)	N=27 147 (29.9%)	*P* Value
Age, mean (SD), y	72.3 (11.7)	72.6 (11.9)	71.5 (11.4)	<0.001*
Women, n (%)	45 316 (49.9)	32 702 (51.4)	12 614 (46.5)	<0.001†
Social deprivation index (quintiles), n (%)				
1	15 484 (17.9)	10 873 (17.9)	4611 (17.8)	0.110†
2	17 295 (20.0)	12 036 (19.8)	5259 (20.3)	
3	17 399 (20.1)	12 210 (20.1)	5189 (20.0)	
4	18 121 (20.9)	12 633 (20.8)	5488 (21.2)	
5	18 330 (21.2)	12 973 (21.4)	5357 (20.7)	
Missing data	4197 (4.6)	2954 (4.6)	1243 (4.6)	0.693†
Type of VKA, n (%)				
Acenocoumarol	6220 (6.8)	4932 (7.7)	1288 (4.7)	<0.001†
Fluindione	75 192 (82.8)	51 857 (81.4)	23 335 (86.0)	
Warfarin	9414 (10.4)	6890 (10.8)	2524 (9.3)	
Type of VKA prescriber, n (%)				
General practitioner	48 080 (52.9)	35 620 (55.9)	12 460 (45.9)	<0.001†
Private practice cardiologist	41 049 (45.2)	26 890 (42.2)	14 159 (52.2)	
Other private practice specialist	1467 (1.6)	1014 (1.6)	453 (1.7)	
Practitioner in private institution	230 (0.3)	155 (0.2)	75 (0.3)	
Comorbidities, n (%)				
Heart failure	20 827 (22.9)	14 477 (22.7)	6350 (23.4)	0.031†
Diabetes mellitus	15 133 (16.7)	10 677 (16.8)	4456 (16.4)	0.192†
Hypertension	57 233 (63.0)	39 269 (61.7)	17 964 (66.2)	<0.001†
Chronic renal impairment	879 (1.0)	671 (1.1)	208 (0.8)	<0.001†
Chronic hepatitis	236 (0.3)	181 (0.3)	55 (0.2)	0.027†
Peripheral arterial disease	2678 (2.9)	1950 (3.1)	728 (2.7)	0.002†
Alcohol-related conditions, n (%)	411 (0.5)	286 (0.4)	125 (0.5)	0.816†
Smoking-related conditions, n (%)	959 (1.1)	680 (1.1)	279 (1.0)	0.588†
Modified CHA2DS2-VASc score, mean (SD)	2.8 (1.5)	2.83 (1.4)	2.74 (1.5)	<0.001*
Modified CHA2DS2-VASc score, n (%)				
Low (0–2)	36 105 (39.8)	24 596 (38.6)	11 509 (42.4)	<0.001‡
Intermediate (3)	23 667 (26.0)	17 247 (27.1)	6420 (23.6)	
High (4–7)	31 054 (34.2)	21 836 (34.3)	9218 (34.0)	
Modified HAS-BLED score, mean (SD)	1.86 (1.0)	1.86 (1.0)	1.86 (1.0)	0.848*
Modified HAS-BLED score, n (%)				
Low (0–1)	31 679 (34.9)	22 551 (35.4)	9128 (33.6)	0.297‡
Intermediate (2)	32 127 (35.3)	21 959 (34.5)	10 168 (37.5)	
High (3–5)	27 020 (29.8)	19 169 (30.1)	7851 (28.9)	

Continued

Table 1. Continued

	All	No Heparin Bridging	Heparin Bridging	
	N=90 826	N=63 679 (70.1%)	N=27 147 (29.9%)	*P* Value
Concomitant medications, n (%)				
Antiarrhythmic agents	63 642 (70.1)	44 662 (70.1)	18 980 (69.9)	0.507†
Lipid-lowering agents	33 974 (37.4)	24 201 (38.0)	9773 (36.0)	<0.001†
Nonsteroidal anti-inflammatory agents	15 369 (16.9)	10 056 (15.8)	5313 (19.6)	<0.001†
Oral corticosteroids	10 085 (11.1)	6595 (10.4)	3490 (12.9)	<0.001†
Gastroprotective agents	27 159 (29.9)	19 415 (30.5)	7744 (28.5)	<0.001†
Benzodiazepines	23 497 (25.9)	16 665 (26.2)	6832 (25.2)	0.002†
Antiplatelet agents	33 844 (37.3)	24 724 (38.8)	9120 (33.6)	<0.001†
Antihypertensive agents	73 973 (81.4)	52 290 (82.1)	21 683 (79.9)	<0.001†

VKA indicates vitamin K antagonist.
*t test.
†Chi-square test.
‡Cochran-Armitage trend test.

also increased with bridging duration: when it lasted 7 days or less, the HR was 1.29 (95% CI: 0.95–1.76) and for 8 days or more, it was 1.93 (95% CI: 1.47–2.52). Moreover, the 1-month bleeding risk appeared to be similar according to types of heparin (Table S5). However, our study is not sufficiently powered to thoroughly examine differences in bleeding risk between heparins. The 1-month bleeding risk was also studied in subgroups defined according to the prescriber's specialty: in patients managed by cardiologists, this risk was 43% higher in the bridged group compared with the nonbridged group (HR=1.43; 95% CI: 1.05–1.95) and 76% higher in those managed by general practitioners (HR=1.76; 95% CI: 1.25–2.47). HRs in these subgroups were not statistically different (*P*-value for interaction=0.455).

When the risk was studied according to type of bleeding, a HR of 1.43 (95% CI, 0.82–2.47) was found for intracranial,

Table 2. Number of Events According to Duration of Follow-Up

	All, n (%)	No Heparin Bridging, n (%)	Heparin Bridging, n (%)	*P* Value*
From 0 to 1 month of follow-up				
Bleeding	318 (0.35)	191 (0.30)	127 (0.47)	<0.001
Intracranial	57 (0.06)	37 (0.06)	20 (0.07)	0.389
Gastrointestinal	99 (0.11)	57 (0.09)	42 (0.15)	0.006
Other	162 (0.18)	97 (0.15)	65 (0.24)	0.004
Ischemic stroke plus systemic embolism	151 (0.17)	107 (0.17)	44 (0.16)	0.840
Ischemic stroke	124 (0.14)	94 (0.15)	30 (0.11)	0.165
Systemic embolism	27 (0.03)	13 (0.02)	14 (0.05)	0.013
From 2 to 3 months of follow-up				
Bleeding	231 (0.31)	162 (0.32)	69 (0.29)	0.555
Intracranial	59 (0.08)	38 (0.07)	21 (0.09)	0.521
Gastrointestinal	57 (0.08)	41 (0.08)	16 (0.07)	0.558
Other	115 (0.15)	83 (0.16)	32 (0.13)	0.374
Ischemic stroke plus systemic embolism	122 (0.16)	84 (0.16)	38 (0.16)	0.899
Ischemic stroke	83 (0.11)	59 (0.11)	24 (0.10)	0.587
Systemic embolism	40 (0.05)	26 (0.05)	14 (0.06)	0.652

*Log-rank test.

Table 3. Bleeding and Arterial Thromboembolism Risks According to Duration of Follow-Up

	n (Events)/N Total	HR*	95% CI	*P* Value	HR†	95% CI	*P* Value	HR‡	95% CI	*P* Value
From 0 to 1 month of follow-up										
Bleeding										
Heparin bridging										
No	191/63 679	1			1			1		
Yes	127/27 147	1.56	1.25 to 1.95	<0.001	1.61	1.28 to 2.01	<0.001	1.60	1.28 to 2.01	<0.001
Ischemic stroke plus systemic embolism										
Heparin bridging										
No	107/63 679	1			1			1		
Yes	44/27 147	0.97	0.68 to 1.37	0.841	1.00	0.70 to 1.42	0.999	1.00	0.70 to 1.42	0.998
From 2 to 3 months of follow-up										
Bleeding										
Heparin bridging										
No	162/51 379	1			1			1		
Yes	69/23 867	0.92	0.69 to 1.22	0.556	0.93	0.70 to 1.24	0.627	0.93	0.70 to 1.23	0.593
Ischemic stroke plus systemic embolism										
Heparin bridging										
No	84/51 430	1			1			1		
Yes	38/23 914	0.98	0.67 to 1.43	0.899	1.02	0.70 to 1.50	0.917	1.11	0.76 to 1.64	0.594

HR indicates hazard ratio.
*No adjustment.
†Adjustment for age and sex.
‡Adjustment for age, sex, comorbidities (heart failure, diabetes mellitus, high blood pressure, chronic kidney disease, chronic hepatitis, peripheral arterial disease, alcohol- and smoking-related hospitalization and consultation), and comedications (antiarrhythmic agents or digitalis glycosides, lipid-lowering agents, nonsteroidal anti-inflammatory drugs, oral corticosteroids, gastroprotective agents, benzodiazepines, antiplatelet agents, and antihypertensive agents).

1.80 (95% CI, 1.20–2.69) for gastrointestinal, and 1.56 (95% CI, 1.14–2.15) for other types of bleeding.

In addition, to test whether the risk of bleeding associated with bridging therapy depended on time, we fitted Cox models with cubic spline functions.[40,41] The HR was highest within the first week after the start of VKA and decreased towards 1 around the third week (Figure S1).

Although no significant interaction was observed between bridging status and bleeding according to modified CHA2DS2-VASc or HAS-BLED scores (Table S6), effect modification was, however, found for sex (*P* value for interaction=0.049): the risk was twice as high in women (HR=2.04; 95% CI, 1.49–2.80) (Figure 2 and Table S4). Overall, women had a higher baseline risk profile than men: they were 5 years older, had a lower social deprivation index, were less likely to consult a cardiologist, and had higher modified CHA2DS2-VASc and HAS-BLED scores (Tables S7 and S8).

The bleeding risk was similar in both groups (HR=0.93; 95% CI, 0.70–1.23) when the risk was studied during the second and third months of follow-up (Table 3).

Regarding the risk of IS/SE, no significant difference was observed between the bridged and nonbridged groups either at 1 month or later (Table 3). Moreover, these results did not vary according to modified CHA2DS2-VASc or HAS-BLED scores (*P* values for interaction of 0.320 and 0.486, respectively; Table S9).

Discussion

In patients with NVAF managed in an outpatient care setting at the time of VKA initiation, a 60% increase in bleeding risk was found among those who were on a bridging regimen in the first month of oral anticoagulation compared with those who had VKA therapy alone. The difference in risk between both groups disappeared in the following month. Women with bridging therapy were also shown to be particularly exposed to this risk since it was doubled compared with nonbridged counterparts. Moreover, a similar risk was observed between these groups with regard to IS/SE.

To our knowledge, this large study represents the first of its kind to examine effectiveness and safety outcomes in NVAF individuals managed in outpatient care who received bridging therapy at the initiation of oral anticoagulation.

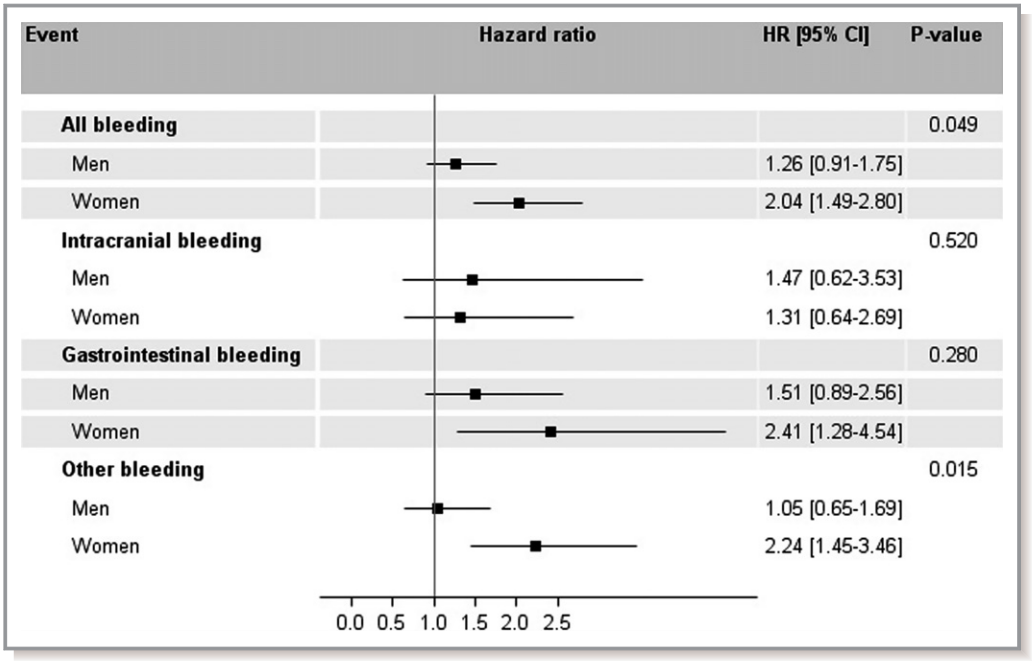

Figure 2. Study of the interaction between heparin bridging and sex at 1 month of follow-up (N=90 826). The *P*-value is from the test statistic for testing the interaction between bridging status and sex after adjustment for age, comorbidities (heart failure, diabetes mellitus, high blood pressure, chronic kidney disease, chronic hepatitis, peripheral arterial disease, alcohol- and smoking-related hospitalization and consultation) and comedications (antiarrhythmic agents or digitalis glycosides, lipid-lowering agents, nonsteroidal anti-inflammatory drugs, oral corticosteroids, gastroprotective agents, benzodiazepines, antiplatelet agents, and antihypertensive agents). Other bleeding includes the following: acute posthemorrhagic anemia, conjunctival hemorrhage, hemothorax, hemoperitoneum, hemarthrosis, hematuria, postmenopausal bleeding (women), epistaxis, hemoptysis, hemorrhage from other sites in respiratory passages, hemorrhage not classified elsewhere. HR indicates hazard ratio.

In this study, the bridging therapy was initiated in 30% of the analytic sample, and the stroke and bleeding risk profile at baseline was similar in the bridged and nonbridged groups. In the literature, incidence of bridging therapy at initiation of VKA therapy has rarely been estimated. Two publications were found, reporting that bridging anticoagulation was used in 62% of patients managed in outpatient settings[19] and in 19% of hospitalized patients with low stroke risk.[16] These results, along with ours, support that bridging therapy is common in clinical practice.

Several reasons may explain this. First, recommendations in guidelines[9,10,12] and summaries of product characteristics[14,15] do not strongly advise against bridging therapy. Indeed, several health professionals have criticized the lack of clarity of these guidelines.[17–19,42,43]

Second, it may be possible that some physicians continue to believe in the theoretical possibility of a transient hypercoagulable state when starting VKA therapy due to the difference in plasma half-life between vitamin K–dependent coagulation factors (II, VII, IX, and X) and proteins C and S, which are important components in coagulation inhibition. A rapid decrease in protein C and S levels may lead to thrombotic occlusions of the microvasculature resulting in necrosis, particularly of the skin.[44] Unlike our study, results from a nested case–control study conducted on AF patients using the UK Clinical Practice Research Datalink supported this theory, since Azoulay et al found a 71% increased risk of stroke in the first 30 days of warfarin use compared with nonuse, whereas a decreased risk was observed after 30 days of use.[45] However, this theory does not justify the routine use of bridging therapy since VKA-induced skin necrosis occurs mostly in patients with inherited or acquired thrombophilia, such as protein C or S deficiencies,[44] and several case studies have also reported that LMWH can also lead to skin necrosis.[46,47] Lastly, there is insufficient evidence justifying systematic use of bridging therapy. This study showed that bridging therapy was associated with an increased risk of bleeding without any beneficial effect, and only 1 study conducted on 5327 patients in hospital settings was found that could put our results into perspective.[16] Kim et al reported bleeding and stroke rates of 1.0% and 0.3%, while in our study they were 0.35% to 0.17%, respectively. The lower rates here may lie in the difference between the study settings, (ie, our analytic sample managed in outpatient care

may be healthier than hospitalized patients). Despite the different incidence rates, Kim et al[16] found results similar to ours for bleeding and stroke risks: they observed an increased bleeding risk associated with bridging therapy (odds ratio 4.44, 95% CI 1.68–11.72) and a comparable stroke risk between bridged and nonbridged groups.

A statistically significant bridging status–sex interaction on 1-month bleeding risk was also observed. A subgroup analysis according to sex showed that bleeding risk was higher in bridged women than in nonbridged women, whereas in men no difference was observed. To our knowledge, this finding has not been previously reported. This result may be partially due to differences in pharmacokinetics and pharmacodynamics existing between men and women.[48] In addition, sex difference was studied in relation to 1-month bleeding risk in the bridged and nonbridged groups: consistent with ATRIA and SPAF studies,[49] women did not have a statistically significant higher bleeding risk than men either as a whole or in bridged and nonbridged groups (data available on request).

This study has several limitations. Since the study population consisted of French healthcare insurance beneficiaries with no history of hospitalization for NVAF or of cerebrovascular accident/transient ischemic attack or ischemic heart disease, our results cannot extend to individuals who initiated their oral anticoagulation in the hospital or to those with a high baseline risk of arterial thromboembolism.

In order to examine outcomes of interest in stable NVAF patients managed in outpatient settings, we selected those who had no history of hospitalization 3 months before the date of first VKA dispensing from a community pharmacy. In doing so, we selected those for whom bridging therapy is not indicated. Indeed, bridged and nonbridged groups were quite similar in terms of baseline thromboembolism risk (mean modified CHA2DS2-VASc score of 2.7 and 2.8, respectively). However, we could have included patients for whom bridging therapy was necessary: a small number of patients were hospitalized within 1 month following the first VKA dispensing for electrical cardioversion (2.3% in bridged and 1.0% in nonbridged groups). The HR for 1-month bleeding risk associated with bridging therapy remained unchanged (HR=1.60; 95% CI: 1.27–2.01) after excluding these patients.

In addition to this sensitivity analysis, we also estimated 1-month bleeding risk in patients with only confirmed AF with an ICD-10 code of I48 (68%): the risk was still 39% higher in the bridged group compared to the nonbridged group (HR=1.39; 95% CI: 1.09–1.77).

Like other health insurance databases, the SNIIRAM database does not capture certain clinical and laboratory data such as international normalized ratio (INR) values. Although INR value is an important covariate, we do not believe our results were significantly affected by the lack of this information since the same target INR range (2–3) is recommended for bridged and not bridged patients and heparins do not modify INR values.

In this study, we could not specifically calculate the sensitivity and specificity of the ICD-10 diagnoses for outcomes defined from the hospitalization database (PMSI) as compared to medical record review. Although these measures are not available, information on hospital stay, in particular the cause of hospitalization, is accurate and precise as it is used to allocate budget to both public and private hospitals; therefore, the quality of diagnosis codes from these data is regularly checked against patients' medical records. Importantly, as SNIIRAM and PMSI are independent databases, we believe that diagnostic bias is not differential between bridged and not bridged individuals. Indeed, crude incidence rates and risk estimates for bleeding and ischemic stroke or systemic embolism calculated here were consistent with those from other studies.[16,25]

Other variables defined using administrative data, such as NVAF, IS/SE, other comorbidities, alcohol- and tobacco-related hospitalization, and modified CHA2DS2-VASc and HAS-BLED scores may be questionable. However, the same algorithms used in a recently published study[25,26] were applied and it was found that incidence rates for bleeding and stroke are close to those reported in a study conducted in hospital settings.[16] Moreover, expected findings were observed with these derived variables: (1) after 1 month of follow-up, no bleeding risk difference was observed between bridged and nonbridged individuals, which is consistent with short-term exposure to a bridging therapy, which usually lasts 5 days[38]; (2) modified CHA2DS2-VASc score was strongly associated with ischemic stroke and systemic embolism, and modified HAS-BLED score with bleeding events.

A causal relationship between bridging anticoagulation and studied outcomes cannot be confirmed as these findings are based on an observational study. Lastly, although as many confounding factors as possible were taken into account, such as comorbidities and concomitant medications, the confounding effect of unmeasured and/or unknown factors cannot be ruled out. However, our results should not be affected by diagnostic biases since databases to define bridging status and end points are completely independent.

Conclusions

Bridging therapy was widely used at the initiation of oral anticoagulation in a stable NVAF population. This practice did not decrease the IS/SE risk but increased the bleeding risk. These findings do not support the use of routine bridging in this population.

Author Contributions

Bouillon and Zureik wrote the first and successive drafts of this paper. Bouillon carried out all the statistical analyses. All authors contributed to interpretation of the results and the paper's revision and approved its final version. Bouillon and Zureik are its guarantors. All the authors are employees of public institutions (Bouillon, Dray-Spira, Bertrand, Boudali, Zureik: French National Agency for Medicines and Health Products Safety [ANSM]; Ducimetière: French Institute of Health and Medical Research [Inserm]). There was no funding source for this study. Bouillon and Zureik had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Disclosures

None.

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