Nation-Wide Use of Periprocedural Bridging Anticoagulation in Patients With Atrial Fibrillation

Geoffrey D. Barnes, MD, MSc[a,b,*], Kristian Seiler, BS[b], Patrick Brady, MHA[b], and Neil Kamdar, MA[b,c,d,e,f]

The randomized, controlled BRIDGE trial established a lack of efficacy for use of bridging anticoagulation in warfarin-treated patients who underwent surgical procedures. A large nation-wide insurance claims database was used to perform a retrospective interrupted time series cohort study of adult patients with atrial fibrillation treated with warfarin who underwent surgical procedures. Patients were assessed for the use of low-molecular-weight heparin (LMWH) use as a periprocedural bridging anticoagulant between July 2015 and November 2017. The interrupted time series regression model was used to estimate the reduction in use of bridging LMWH following the publication of the BRIDGE trial in July 2015. The cohort consisted of 9,278 warfarin-treated patients with atrial fibrillation. Use of bridging LMWH declined by an estimated 6.7% (95% confidence interval [CI] 2.1% to 11.3%) to 13.0% following publication of the BRIDGE trial. The decline in bridging LMWH use was numerically larger for patients with a moderate- or high risk of stroke (8.9% decline, 95% CI 0.4% to 17.4%) than for patients at low risk for stroke (6.2% decline, 95% CI 0.7% to 11.5%). Significant predictors of bridging LMWH use include younger age and no co-morbid diabetes. In conclusion, this nation-wide, claims-based study identified a significant reduction in the use of bridging LMWH following the publication of the BRIDGE trial for warfarin-treated patients with AF. **(Am J Cardiol 2019;124:1549−1553)**

Warfarin, used for decades to reduce atrial fibrillation (AF)-related stroke risk, remains a leading treatment strategy to reduce the risk of stroke and systemic embolism for the approximately 6 million Americans with prevalent AF.[1,2] Given warfarin's relatively long effective half-life, it must be stopped 5 to 7 days preprocedure to safely perform the surgery without an increased risk of bleeding. During that time period without warfarin anticoagulation, many patients are given "bridging anticoagulation" with short acting unfractionated heparin or low-molecular-weight heparin (LMWH) as there is a theoretical increased risk of stroke. However, in 2015, the landmark Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE) trial demonstrated no difference in the rate of postprocedure stroke but an increased risk of bleeding in the patients randomized to bridging LMWH compared with patients randomized to placebo.[3] We sought to use a large administrative claims database to examine if use of bridging anticoagulation declined following this publication and to identify current predictors of bridging LMWH use in the post-BRIDGE trial period.

Methods

We performed a retrospective cohort study of adults who underwent procedures for cholecystectomy, orthopedic hip and/or knee replacement, cystectomy, prostatectomy, colectomy, and/or hysterectomy, with a diagnosis of AF in any patient care setting using a national, private insurance claims database. The Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN) is a de-identified claims database capturing all emergency department (ED), outpatient, and inpatient encounters of over 79 million adults and children with both medical and pharmacy coverage who are commercially insured by a single, large US private payer. The study was deemed exempt by the Institutional Review Board (IRB) at the University of Michigan.

Using all private payer claims, we identified all adults with age ≥18 years from July 2010 to November 2017 with International Classification of Diseases, 9th/10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) or Current Procedural Terminology (CPT) Fourth Edition (CPT-4) procedure codes for cholecystectomy, hip and knee replacement, cystectomy, prostatectomy, colectomy, and/or hysterectomy, and diagnosis codes for AF between July 1, 2010 and November 30, 2017 (Supplemental Appendix). We required that patients had at least 12 months of continuous enrollment before the index procedure and at least 1-month enrollment following the index procedure. These patients were also required to have use of warfarin (identified using National Drug Codes) in the 30 days before the index procedure and in the postoperative day 14 to 30 window (Supplemental Appendix).

[a]Department of Internal Medicine, Frankel Cardiovascular Center, University of Michigan, Ann Arbor, Michigan; [b]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan; [c]Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan; [d]Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan; [e]Department of Surgery, University of Michigan, Ann Arbor, Michigan; and [f]Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, Michigan. Manuscript received May 21, 2019; revised manuscript received and accepted August 6, 2019.

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*Corresponding author: Tel: (734) 763-0047.

E-mail address: gbarnes@umich.edu (G.D. Barnes).

@GBarnesMD (twitter).

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All adults meeting inclusion criteria for the previously mentioned surgical procedure groups with a diagnosis of AF were identified if they received bridging LMWH, defined as any use of enoxaparin during the 14 days preoperative period. Enoxaparin use was identified from National Drug Codes (Supplemental Appendix). Only the first procedure of any type for each patient was included in the analysis.

Consistent with previous claims-based analyses, we identified patient co-morbidities during the ≥12 months of consecutive enrollment before the surgical procedure using ICD-9-CM and ICD-10-CM codes with at least 1 inpatient or 2 outpatient service dates (Supplemental Appendix).[4–6] Previous bleeding requires at least 1 inpatient service date to limit this to be more consistent with a clinically relevant "major" bleeding event. From these co-morbidities, we calculated the CHA_2DS_2-VASc score to estimate AF-related stroke risk.[7]

We used a quasiexperimental study design by implementing a multiple group interrupted time series analysis to estimate the impact of a nonrandomized intervention. This statistical method estimated the time-dependent trend of bridging LMWH use both before and following the publication of the BRIDGE trial in July 2015. This study design had 2 periods: the "pre-BRIDGE trial" period (July 2010 to June 2015) and the "post-BRIDGE trial" period (July 2015 to November 2017).

We presented patient demographics, co-morbidities, and unadjusted use of bridging LMWH in relation to the BRIDGE trial publication using descriptive statistics. We then developed a logistic regression model to predict the use of bridging LMWH in a similar approach as was done previously.[8] This model included an indicator variable for the BRIDGE trial publication (pre vs post) and a full factorial interaction between the surgical procedure date and this indicator variable.

We next assessed the use of bridging anticoagulation graphically using an estimated percentage over 2-month intervals (e.g., January to February 2015). We used a 2-month interval to increase the number of procedures per unit time. We fitted linear regression lines using Ordinary Least Squares estimation for the percentage of patients receiving bridging anticoagulation in each of the 2 study periods (pre-BRIDGE trial and post-BRIDGE trial).

We performed 3 steps to estimate the impact of the BRIDGE trial on bridging LMWH use: (1) we estimated trends in bridging LMWH use in the pre-BRIDGE trial period from the interrupted time series model, (2) we extrapolated from the pre-BRIDGE trial best-fit line to the end of the study period (November 2017) to estimate the expected percentage of patients receiving bridging LMWH if the BRIDGE trial had *not* been conducted and published (i.e., the counterfactual), and (3) we estimated the difference between the predicted counterfactual and actual percentage of bridging LMWH use at the end of the study period (November 2017). The difference is an estimate of the impact the BRIDGE trial had on bridging LMWH use.

To assess for differences in bridging LMWH use based on key patient characteristics, we conducted 3 subanalyses. The first was stratified by age categories (<65, 65 to 74, ≥75 years). The second was stratified by stroke risk, as determined by the 2017 American College of Cardiology (ACC) Expert Consensus Pathway (low or moderate/high stroke risk).[9] The third was stratified by a history of preprocedure stroke.

To identify predictors of bridging LMWH use in the post-BRIDGE trial period, we performed multivariable logistic regression analyses on various stroke-related risk factors, all of which adjusted for procedure type. Each of these models was limited to patients who had a recent bleeding event (within 12 months of the surgical procedure) as similar patients were excluded from the BRIDGE trial.[3] The first model assessed for the association between preprocedure stroke history and use of bridging LMWH. The second model assessed for each of the individual elements of the CHA_2DS_2-VASc score (heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke, vascular disease, age 65 to 74 years, and female gender). The third model compared patients with low stroke risk compared with moderate or high stroke risk according to the 2017 ACC Expert Consensus Pathway.[9] Model discrimination was estimated using the C statistic and goodness of fit was described using the Hosmer-Lemeshow p value with 10 groupings. Statistical analysis was performed using Stata version 14.2 (StataCorp, Cary, NC). A two-sided p value of <0.05 was set as the significance threshold.

Results

Our cohort consisted of 9,278 warfarin-treated patients with AF who underwent a surgical procedure between 2010 and 2017. Although the patients were largely older age with hypertension, the majority were categorized at low risk of stroke (Table 1).

Bimonthly use of bridging LMWH with model estimates pre- and post-BRIDGE trial is shown in Figure 1. Before the publication of the BRIDGE trial, there was a small increase in the odds of receiving bridging LMWH (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.00 to 1.02, $p = 0.004$). The predicted probability of bridging LMWH use from the hypothetical situation without the BRIDGE trial publication was 21.1% (95% CI 17.2% to 25.1%) in November 2017. However, with the publication of the BRIDGE trial in 2015, the predicted probability of bridging LMWH use was 14.4% (95% CI 12.0% to 16.8%), a reduction of 6.7% (95% CI 2.1% to 11.3%, $p = 0.004$).

As shown in Table 2, predicted use of bridging LMWH declined more in patients at lower risk for stroke than those at intermediate or high stroke risk. The use of bridging LMWH similarly declined for patients age 75+ years and for those with no previous preprocedural stroke (Table 2).

As shown in Table 3, in patients without a recent history of bleeding, the use of LMWH bridging declined as the overall stroke risk increased, as assessed by the CHA_2DS_2-VASc score. There was no difference in the use of bridging LMWH based on a history of previous stroke. Bridging LMWH was less common among older patients and among patients with a history of diabetes after controlling for other elements of the CHA_2DS_2-VASc score. The use of bridging LMWH was not different between patients at low versus moderate or high risk of stroke. All predictive models showed modest discrimination and good overall fit.

Discussion

This nation-wide, claims-based study identified a significant reduction in the use of bridging LMWH following the

Table 1
Patient demographics and co-morbidities

Variable	All (n = 9,278)	Pre-BRIDGE trial (n = 6,234)	Post-BRIDGE trial (n = 3,217)
Mean (SD) age (y)	74.3 (8.6)	74.0 (8.7)	74.9 (8.5)
<65	1,212 (13.1%)	881 (14.2%)	331 (10.7%)
65 to 74	3,082 (33.2%)	2023 (32.7%)	1059 (34.3%)
75+	4,984 (53.7%)	3287 (53.1%)	1697 (55.0%)
Men	4,958 (53.4%)	3252 (52.5%)	1706 (55.3%)
Heart failure	2,348 (25.3%)	1478 (23.9%)	870 (28.2%)
Hypertension	7,523 (81.2%)	4992 (80.6%)	2540 (82.3%)
Diabetes mellitus	3,025 (32.6%)	1927 (31.1%)	1098 (35.6%)
Stroke (with ICH)	418 (4.5%)	305 (4.9%)	113 (3.7%)
Stroke (without ICH)	415 (4.5%)	304 (4.9%)	111 (3.6%)
Vascular disease	3,289 (35.5%)	2621 (42.3%)	668 (21.6%)
Mean CHA_2DS_2-VASc (SD)	3.8 (1.5)	3.8 (1.5)	3.7 (1.4)
Low stroke risk	6,489 (68.7%)	4198 (67.3%)	2291 (71.2%)
Prior bleeding	879 (9.5%)	451 (7.3%)	428 (13.9%)

ICH = intracranial hemorrhage; SD = standard deviation.
Low stroke risk assessed according to 2017 Expert Consensus Document.[10]

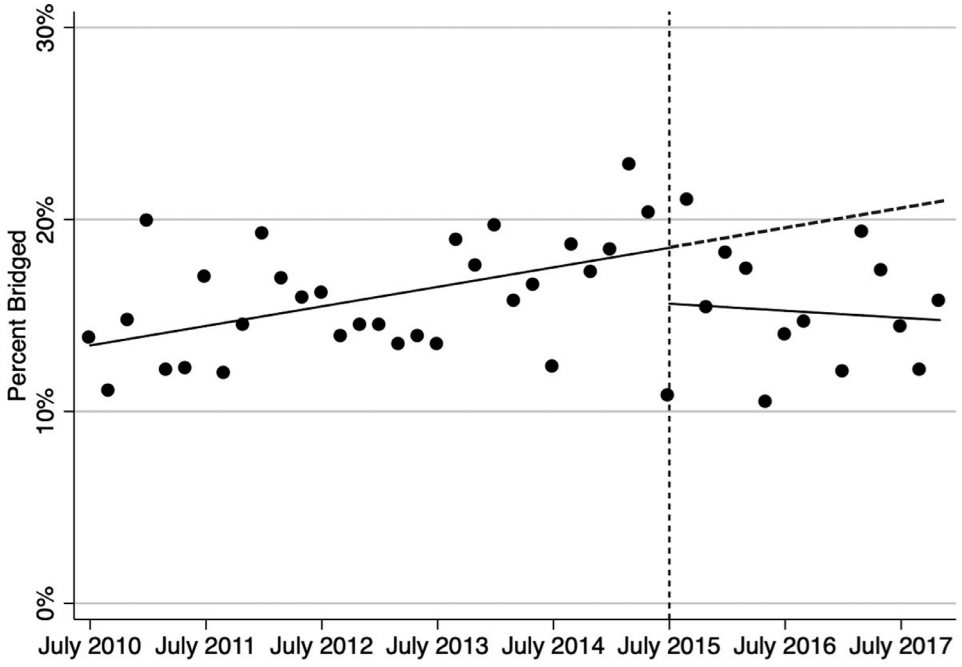

Figure 1. Bimonthly use of bridging LMWH for warfarin-treated patients with atrial fibrillation. Unadjusted bimonthly rates of bridging low-molecular-weight heparin (LMWH) use among warfarin-treated patients with atrial fibrillation. The vertical line separates the time before and after the publication of the BRIDGE trial.[3] The dotted line represents the "counterfactual" estimate of bridging LMWH use after July 2015 if the BRIDGE trial had not been published.

publication of the BRIDGE trial for warfarin-treated patients with AF. These results replicate the findings from a single-state quality collaborative in a larger and more diverse population of patients.[8]

Although the overall trend toward less bridging LMWH use was seen in both the previous quality collaborative study and this nation-wide study, there are some important differences.[8] In the quality collaborative, patients with previous stroke were more often using bridging LMWH in post-BRIDGE trial period (26.0%, 95% CI 12.8% to 39.2%) compared with this nation-wide claims-based analysis (15.7%, 95% CI 0.1% to 31.6%). This could reflect the inherent limitations of a claims-based analysis for identifying less common risk factors (e.g., previous stroke) or risk factors that occurred before the claims-based lookback period. Uncertainly remains in many clinicians and expert consensus documents about forgoing bridging LMWH in patients with a previous stroke.[9] Further studies (both quantitative and qualitative) should explore this pattern of physician decision-making. Second, overall reductions in bridging LMWH use were larger in the quality collaborative (14.2%, 95% CI 5.7% to 22.6%) than this nation-wide, claims-based analysis (6.7%, 95% CI 2.1% to 11.3%). Nonetheless, important similarities between the 2 studies exist. These include overall similarly predicted rates of bridging LMWH use in November 2017 (13.6% in the quality collaborative and 14.4% in

Table 2
Average change in predicted use of bridging LMWH

	Without BRIDGE trial effect	With BRIDGE trial effect	Predicted reduction in bridging LMWH Use	p Value
Atrial fibrillation (all, n = 9,278)	21.1% (17.2%-25.1%)	14.3% (12.0%-16.8%)	−6.7%	0.004
Atrial fibrillation subgroups				
Age <65 (n = 1,212)	25.1% (14.1%-36.2%)	15.9% (7.8%-23.9%)	−9.3%	0.183
Age 65 to 74 (n = 3,082)	22.7% (15.6%-29.8%)	17.4% (13.0%-21.7%)	−5.3%	0.210
Age 75+ (n = 4,984)	20.4% (14.9%-25.9%)	12.5% (9.4%-15.6%)	−7.9%	0.014
Low stroke risk (n = 6,489)	20.9% (16.2%-25.5%)	14.7% (11.9%-17.5%)	−6.2%	0.027
Not low stroke risk (n = 2,789)	21.9% (14.5%-29.2%)	13.0% (8.6%-17.4%)	−8.9%	0.041
No prior stroke (n = 8,860)	21.2% (17.2%-25.3%)	14.3% (11.9%-16.7%)	−6.9%	0.004
Prior stroke (n = 418)	18.6% (1.7%-35.5%)	15.7% (0.1%-31.6%)	−2.9%	0.805

LMWH = low-molecular-weight heparin.

Predicted use of LMWH bridging (95% confidence interval) is presented with and without the effect of the BRIDGE trial in November 2017. Estimates based on bimonthly data.

Table 3
Predictors of LMWH bridging

Model		Odds ratio	C statistic	Hosmer-Lemeshow p value
1	CHA_2DS_2-VASc Score	0.86 (0.78-0.93)	0.642	0.407
2	Prior stroke	1.03 (0.48-2.20)	0.617	0.934
3	Prior stroke	1.03 (0.49-2.19)	0.664	0.867
	Heart failure	0.92 (0.70-1.20)		
	Hypertension	1.01 (0.77-1.33)		
	Age 65 to 74 vs <65	0.70 (0.50-0.97)		
	Age ≥75 vs <65	0.42 (0.30-0.58)		
	Diabetes mellitus	0.72 (0.56-0.91)		
	Vascular disease	0.88 (0.63-1.19)		
	Female	1.00 (0.80-1.25)		
4	Low vs moderate/high stroke risk	1.16 (0.90-1.49)	0.621	0.757

LMWH = low-molecular-weight heparin.

Four logistic regression models to predict LMWH bridging in the post-BRIDGE trial period. Analysis performed on patients without bleeding events in the 12 months before their surgical procedure. Stroke risk groups estimated using the 2017 American College of Cardiology Expert Consensus Pathway.[10]

this study) and reductions in both the low and moderate or high stroke risk subgroups.

Since the BRIDGE trial primarily enrolled patients at low-risk for stroke, one might expect that lower stroke risk patients may be less likely to receive bridging LMWH following that trial's publication. However, there was no difference in the odds of receiving bridging LMWH between patients at low risk and patients at moderate or high risk of stroke in the post-BRIDGE period. In light of the more commonly used CHA_2DS_2-VASc score in clinical practice compared with the $CHADS_2$ score used to describe stroke risk in the BRIDGE trial, many clinicians may rely more heavily on previous stroke rather than stroke risk to make bridging LMWH decisions.

Our analysis has many important strengths including the large sample size from a nation-wide population of patients. However, important limitations must also be acknowledged. As with all retrospective analyses, we can only assess for association and not causation. Similarly, claims-based analyses may not capture all aspects of clinical care and certain data (e.g., medication dosing and administration) are not directly measured. Third, we were unable to assess the use of bridging LMWH among all surgical procedures in this analysis. However, the findings from the broadly selected surgical procedures in this analysis largely match those seen in previous studies that included all potential surgical procedures.[8] We chose not to include more commonly performed procedures, such as colonoscopy, as warfarin is not always interrupted for these procedures and therefore an assessment of bridging LMWH use is not as reliable.[10] Fourth, while the mean age in this cohort was 74.3 years, this largely represents a select group of Medicare patients with Medicare Advantage. These patients may differ from other traditional Medicare patients. Few patients were at high stroke risk ($CHADS_2$ of 5 or 6), limiting our ability to do a subgroup analysis in this population that was underrepresented in the BRIDGE trial. Finally, although this analysis suggests lower rates of bridging LMWH use in November 2017 than would have been predicted based on pre-BRIDGE trial publication trends, this difference is a hypothetical comparison and future studies will be needed to see how bridging LMWH use continues to change in the future. These may include future population-based observational studies along with the ongoing PERIOP 2 randomized trial (NCT00432796).

In summary, this nation-wide analysis of warfarin-treated patients with AF who underwent surgical procedures demonstrates a reduction in the use of bridging LMWH therapy following the publication of the BRIDGE trial in 2015. These results demonstrate that earlier findings of reduced bridging LMWH use in smaller quality

collaboratives are being realized more broadly across the United States. How this change in bridging LMWH use will impact rates of bleeding and thromboembolic events in a nonrandomized population remains to be explored.

Disclosures

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Supplementary materials

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