

**Periprocedural Bridging Anticoagulation in Patients with Venous Thromboembolism: A  
Registry-based Cohort Study**

Geoffrey D Barnes, MD, MSc<sup>1</sup>

Yun Li, PhD<sup>2</sup>

Xiaokui Gu, MD, MA<sup>1</sup>

Brian Haymart, RN, MS<sup>1</sup>

Eva Kline-Rogers, MS, RN, NP<sup>1</sup>

Mona A Ali, PharmD<sup>3</sup>

Jay Kozlowski, MD<sup>4</sup>

Gregory Krol, MD<sup>5</sup>

James B Froehlich, MD, MPH<sup>1</sup>

Scott Kaatz, DO, MSc<sup>6</sup>

1 – Department of Internal Medicine, Frankel Cardiovascular Center, University of Michigan, Ann Arbor, MI

2 – School of Public Health, University of Michigan, Ann Arbor, MI

3 – Department of Pharmacy, Beaumont Hospital, Royal Oak, MI

4 – Department of Internal Medicine, Huron Valley Sinai Hospital, Commerce Township, MI

5 – Department of Internal Medicine, Henry Ford Health System, Detroit, MI

6 – Division of Hospital Medicine, Henry Ford Hospital, Detroit, MI

**Corresponding Author:**

Geoffrey D Barnes, MD, MSc

2800 Plymouth Rd, B14 G214

Ann Arbor, MI 48109-2800

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734-763-0047 (phone)

734-647-3301 (fax)

[gbarnes@umich.edu](mailto:gbarnes@umich.edu)

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**Abstract**

**Background:** Use of bridging anticoagulation increases a patient's bleeding risk without clear evidence of thrombotic prevention among warfarin-treated patients with atrial fibrillation. Contemporary use of bridging anticoagulation among warfarin-treated patients with venous thromboembolism (VTE) have not been studied.

**Methods:** We identified warfarin-treated patients with VTE who temporarily stopped warfarin for a surgical procedure between 2010 and 2018 at six health systems. Using the 2012 American College of Chest Physicians (ACCP) guideline, we assessed use of periprocedural

bridging anticoagulation based on recurrent VTE risk. Recurrent VTE risk and 30-day outcomes (bleeding, thromboembolism, emergency department visit) were each assessed using logistic regression adjusted for multiple procedures per patient.

**Results:** During the study period, 789 warfarin-treated patients with VTE underwent 1529 procedures (median 2, IQR 1-4). Unadjusted use of bridging anticoagulation was more common in patients at high-risk for VTE recurrence (99/171, 57.9%) than for patients at moderate (515/1078, 47.8%) or low risk of recurrence (134/280, 47.86%). Bridging anticoagulation use was higher in high-risk patients compared to low- or moderate-risk patients in both unadjusted ( $p=0.013$ ) and patient-level cluster-adjusted analyses ( $p=0.031$ ). Adherence to ACCP guidelines in high- and low-risk patients did not change during the study period (OR 0.98 per year, 95% CI 0.91-1.05). Adverse events were rare and not statistically different between the two treatment groups.

**Conclusions:** Bridging anticoagulation was commonly overused among low-risk patients and underused among high-risk patients treated with warfarin for VTE. Adverse events were rare and not different between the two treatment groups.

**Abstract: 244/250 words**

**Essentials:**

- Peri-procedural bridging anticoagulation has unclear benefit for warfarin-treated patients with venous thromboembolism
- Between 2010-2018, 789 warfarin-treated patients with venous thromboembolism scheduled for surgical procedures were identified at six health centers
- Use of bridging anticoagulation was more common for patients at high thromboembolic risk than low or moderate risk

- There was no meaningful change in the use of guideline-concordant bridging anticoagulation during the study period

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## **Background**

Vitamin K antagonists, such as warfarin, remain a leading treatment option world-wide for patients with venous thromboembolism (VTE). While some patients require only short 3- or 6-month courses of treatment, an increasing proportion of patients with VTE are treated with oral anticoagulant medications indefinitely to prevent recurrence.[1, 2] These patients frequently require temporary interruption of anticoagulation therapy for elective invasive or surgical procedures, such as colonoscopy and orthopedic surgery. Given the relatively long period of time while warfarin's anticoagulant effect wears off before surgery or builds back up after surgery, many clinicians have historically used shorter acting "bridging" anticoagulants, like low molecular weight heparins (LMWH), to help reduce the risk of VTE recurrence. However, the efficacy of bridging anticoagulation has been questioned in a recently published analyses of patients with VTE.[3, 4] However, both of these analysis largely included patients treated up to a decade ago. A contemporary, multi-center analysis of bridging LMWH use in patients with VTE has not been performed. This is particular importance given recent efforts to reduce the overall use of bridging anticoagulation among patients with atrial fibrillation, based largely on the BRIDGE trial published in 2015.[5]

We used a multi-center collaborative of anticoagulation clinics to explore the use of bridging anticoagulation among patients with VTE treated with warfarin. We assessed the association between VTE risk and use of bridging anticoagulation, based on the 2012 American College of Chest Physicians (ACCP) guidelines. We also describe rates of adverse events in patients who did and did not receive bridging anticoagulation.

## **Methods**

### *Data Source*

We used the Michigan Anticoagulation Quality Improvement Initiative (MAQI<sup>2</sup>) registry to explore the use of bridging anticoagulation (primarily with LMWH) among chronic warfarin-treated patients with VTE between July 2010 and December 2018. This six-center registry of warfarin-treated patients managed in anticoagulation clinics across the state of Michigan is sponsored by Blue Cross-Blue Shield/Blue Care Network of Michigan.[6] Patients newly initiating warfarin at one of the participating health care centers and managed longitudinally in the anticoagulation clinic are randomly selected to be enrolled and followed in the MAQI<sup>2</sup> registry through retrospective data collection. Enrollment in the registry has no impact on clinical care (including periprocedural), which is directed by the individual patient's providers. No MAQI<sup>2</sup>-led quality initiatives targeted at bridging anticoagulation use were underway during the study period. Patients are followed until warfarin therapy is discontinued or the patient is no longer followed by the anticoagulation clinic. Trained abstractors perform data abstraction manually using standardized data forms with pre-specified data dictionaries. Data abstractors examined the medical record for adverse events resulting in care at their particular health center as well as any that was reported to the anticoagulation clinic but may have occurred at an outside hospital or clinic. Random audits are performed by the MAQI<sup>2</sup> coordinating center to ensure data abstraction accuracy. IRB approval was obtained at each participating site and at the coordinating center (University of Michigan).

#### *Patient Selection*

To be included in the study, patients had to be receiving warfarin therapy, followed by one of the six participating health centers, and have VTE as their only indication for warfarin therapy. Patients with multiple indications (e.g. atrial fibrillation and VTE) for anticoagulation were excluded. Patients were required to have at least 30 days of continuous warfarin use both prior to and immediately following a temporary interruption for a surgical or other invasive procedure (e.g. colonoscopy) and had a temporary interruption of warfarin therapy between July 2010 and December 2018.

#### *Outcomes*

The primary outcome was the use of bridging anticoagulation, defined as the use of therapeutic doses of intravenous unfractionated heparin, subcutaneous LMWH, or subcutaneous fondaparinux at any time during the 5 days prior to and/or following surgery or procedure (subsequently referred to as “bridging anticoagulation”). Prophylactic doses of anticoagulants were not included in the outcome measure. Adverse events within 30-days of the index procedure were manually chart abstracted as any bleeding, major bleeding as defined by the International Society on Thrombosis and Haemostasis, any emergency department visit, stroke, or recurrent VTE.[7]

Our primary analysis compared the rate of bridging anticoagulation based on the 2012 American College of Chest Physicians (ACCP) guideline for perioperative management.[8] Specifically, patients at high-risk for recurrent VTE were those with their index VTE event < 3 months prior to their procedure date or patients with the antiphospholipid antibody syndrome. Patients at moderate-risk for recurrent VTE were those whose index VTE event was 3-12 months prior to their procedure date, had a history of cancer, had a history of recurrent VTE, or had a known thrombophilia other than antiphospholipid antibody syndrome. Patients with an index VTE event >12 months prior to the procedure and without any above comorbidities were considered low-risk for recurrent VTE. According to the ACCP guidelines, bridging anticoagulation is recommended for patients at high-risk for recurrent VTE and not recommended for patients at low-risk for recurrent VTE (Grade 2C). Since patients with moderate risk of recurrent VTE do not have a guideline-recommended strategy, analysis of guideline-congruent bridging use focused only on patient with low- or high-risk of recurrent VTE.

#### *Statistical Analysis*

A linear regression analysis was performed to assess for changes in bridging anticoagulation use over time. This trend analysis was performed for all patients as well as individually for low- and high-risk patients. Association between level of recurrent VTE risk and use of bridging anticoagulation was first assessed using chi-squared analysis. We then performed logistic

regression adjusting for multiple procedures per patient. Next, we assessed for guideline compliance in the use of bridging anticoagulation. Another logistic regression model was developed to predict guideline-congruence over time, adjusted for multiple procedures per patient. In sensitivity analysis, we compared use of bridging anticoagulation and guideline-congruence for patients with deep vein thrombosis (DVT) only separately from patients with pulmonary embolism (PE) with or without DVT.

To assess for rates of adverse events, we examined for any reported bleeding or thromboembolic event as well as any emergency department visit that occurred within 30-days following the procedure and was documented in the medical record. Differences in adverse event rates were compared using chi-squared analyses.

Statistical significance was set at an alpha of 0.05. Statistical analyses were performed using Stata version 15.1 (College Station, TX).

## Results

Between July 2015 and December 2018, 791 warfarin-treated patients with VTE experienced 1529 temporary interruptions for surgical or invasive procedures (median 2.0 procedures per patient, inter-quartile range 1-4). Patient demographics and comorbidities are summarized in Table 1 and show important differences in age (66.5 vs 61.4 years), male (52.0% vs. 46.5%), prior VTE (38.0% vs. 44.4%), provoked VTE (31.7% vs. 19.5%), and number of comorbidities between patients who did not and those who did receive bridging anticoagulation. Most patient were on warfarin therapy for more than one year at the time of their procedural interruption (mean 997 [SD 1302] days). Bridging was used in 748/1529 (48.9%) of all procedures. Procedure type by bridging anticoagulation use is shown in the online appendix.

### *Bridging Anticoagulation by VTE Risk*

Bridging anticoagulation was used more commonly in patients at high-risk for recurrent VTE than in patients at low- or moderate-risk (57.9% vs. 47.8%,  $p=0.013$ , Table 2). After adjusting for

multiple procedures per patient, bridging anticoagulation was more common among high-risk patient (OR 1.50, 95% CI 1.04-2.17,  $p=0.031$ ). Use of bridging anticoagulation was numerically, but not statistically significantly, higher among patients VTE in the past 90 days (88/158, 55.7%) as compared to 90-364 days (198/420, 47.1%) or  $\geq 365$  days (462/951, 48.6%;  $p=0.234$ ). Use of bridging anticoagulation was higher among patients with antiphospholipid antibody syndrome (12/14, 85.7%) as compared to those without (736/1520, 48.4%;  $p=0.006$ ). Bridging anticoagulation use by various VTE risk elements are shown in the supplemental appendix.

Among patients with either low- or high-risk for recurrent VTE, guideline-congruent use of bridging anticoagulation ranges from 48.1% to 68.2% of patients between 2010 and 2018 ( $p_{\text{trend}}=0.597$ , Figure). In sensitivity analysis, use of bridging anticoagulation was more common among high-risk patients with DVT only (57.7% vs. 44.4%,  $p=0.005$ ) but not among patients with PE (56.5% vs. 51.5%,  $p=0.456$ ). There was no change in guideline-congruent bridging anticoagulation use during the study period for both low- ( $p_{\text{trend}}=0.766$ ) and high-risk patients ( $p_{\text{trend}}=0.760$ ; supplemental appendix).

### *Adverse Events*

Rates of 30-day adverse events were low among all patients (Table 2). Any bleeding occurred in fewer than 3% of patients in both the bridging and non-bridging anticoagulation groups while major bleeding rates, stroke rates and recurrent VTE rates were similarly low. Overall, fewer than 4% of each cohort required an emergency department visit within 30 days following their procedure.

### **Discussion**

Our study demonstrates that contemporary use of bridging anticoagulation among warfarin-treated patients with VTE is often not congruent with ACCP guideline recommendations and has not changed significantly over the 9-year study period. Specifically, there is significant overuse of bridging anticoagulation among patients at low-risk for recurrent VTE. Patients at



high-risk for recurrent VTE are frequently not receiving bridging anticoagulation. Overall, rates of adverse events are low in both patients who did and did not receive bridging anticoagulation.

Overuse of bridging anticoagulation among patients at low-risk for recurrent VTE is of particular concern. There have been numerous publications suggesting a lack of significant benefit with bridging therapy for these low-risk patients. First, Clark and colleagues reported no significant reduction in VTE recurrence risk among a single-center cohort of 1178 warfarin-treated patients with VTE who did or did not receive bridging LMWH.[3] This study also demonstrated a significant increase in the rate of clinically relevant bleeding (2.7% vs. 0.2%,  $p=0.01$ ) with bridging anticoagulation use. Of note, the vast majority of patients in this analysis were considered low-risk for VTE recurrence. However, this study analyzed patients managed largely before the 2012 ACCP guidelines were published. Similar results were seen in a nation-wide analysis by Sjögren and colleagues from Sweden.[4] Examining patients managed between 2006 and 2011, they found higher rates of bleeding among those treated with VTE receiving bridging anticoagulation as compared to those without any bridging anticoagulation (10.4% vs. 2.1%). They also reported higher rates of thrombotic complications among the patients receiving bridging anticoagulation (10.3% vs 5.3%). Rates of bleeding and thromboembolism in this cohort were similar to those reported by Clark and colleagues.

A recent meta-analysis of observational studies confirmed the increased rate of bleeding without a reduction in thromboembolism events for patients with VTE who received periprocedural bridging LMWH as compared to those who did not.[9] However, that meta-analysis was limited in its ability to distinguish between patients at high- and low-risk of thromboembolism. Nearly all studies in that meta-analysis included patients enrolled before the 2012 ACCP guidelines were published.

Potential under-use of bridging anticoagulation is also a concern among high-risk patients. While none of the studies noted above had significant numbers of high-risk patients, the meta-analysis demonstrated very low incidence rates of recurrent VTE both in the overall analysis and

in the subgroup of patients at high-thromboembolic risk.[9] A randomized trial of bridging is probably warranted in high-risk populations, including those with recent VTE and/or higher-risk thrombophilia. Further research is also needed to address optimal peri-procedural management of direct oral anticoagulants (DOAC) in patients with VTE. The recently published PAUSE trial only enrolled patients with atrial fibrillation, limiting its ability to inform peri-procedural management for patients with VTE treated with DOAC medications.[10]

Our study enrolled a cohort of patients of whom most had been taking warfarin for >12 months since their VTE event. Therefore, our ability to completely explore for potential bridging anticoagulation practice changes among patients with higher VTE recurrence risk (those with <3 months of warfarin therapy or with high-risk thrombophilia) was somewhat limited.

Deciding on appropriate use of bridging anticoagulation remains a challenge for patients with other thrombotic cardiac conditions, including atrial fibrillation and mechanical heart valves. We previously have shown significant reductions in the use of bridging anticoagulation for patients with atrial fibrillation following the publication of the BRIDGE trial in 2015.[11, 12] Of note, the overall use of bridging anticoagulation among patients with atrial fibrillation was similar between the Michigan collaborative and nation-wide data analyses (13.6% and 13.0% in November 2017).

Our study has a number of important strengths, including the use of manually abstracted clinical data from multiple, diverse clinical sites. We also include the most contemporary data on bridging anticoagulation use among warfarin-treated VTE patients. However, we acknowledge several limitations. First, while our data represents six diverse health systems, these health systems are located in one geographic area and may not be generalizable to other populations or locations. As such, we are subject to potential selection bias given that these patients were all managed by anticoagulation clinics. And despite their diverse settings, some predominately manage cardiology patients while others manage patients with a wide variety of indications for anticoagulation. Second, as with any observational study, we are unable to adjust for any unmeasured confounders. Third, our data did not collect procedural details until

2016. Therefore, we are unable to report on the types of procedures for all patients. However, data from 2016-2018 (online appendix) demonstrate a wide range of procedure types. Fourth, while bridging anticoagulation was defined in our data collection form as therapeutic doses of parenteral anticoagulants further details about the specific medication, dose, or administration was not collected. Therefore, we cannot comment on differences in pre- versus post-procedure use of bridging anticoagulation. Finally, since use of bridging anticoagulation is determined by individual clinicians and not standardized across each health system, we are unable to associate any center-level differences to specific protocols or practices.

In summary, we demonstrate frequent use of bridging anticoagulation among patients with VTE that is not congruent with ACCP guideline recommendations. Specifically, overuse of bridging anticoagulation remains common for low-risk patients while many high-risk patients do not receive bridging anticoagulation during a temporary warfarin interruption. Efforts to align bridging anticoagulation use with guideline- and evidence-based strategies are needed.

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**Author Contributions:** GDB, YL, XG, and SK designed the research methods; GDB, BH, EKR, MAA, JK, GK, JBF, SK helped with data collection; GDB and XG performed statistical analyses; GDB, XG, SK made significant contributions to the initial manuscript draft; GDB, YL, XG, BH, EKR, MAA, JK, GK, JBF, SK made critical revisions to the manuscript.

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**Figure – Guideline-congruent Bridging Anticoagulation Use in Low- and High-risk Patients with VTE**

Yearly use of guideline-congruent bridging anticoagulation, defined as use among patients at high-risk for VTE recurrence and no use among patients at low-risk for VTE recurrence according to 2012 American College of Chest Physicians.[8]

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**Table 1 – Demographics and Comorbidities of Warfarin-Treated Patients Undergoing Surgical Procedures**

	All (n=1,534)	Bridging Anticoagulation (n=748)	No Bridging Anticoagulation (n=781)	P Value
Mean age (SD)	64.0 (13.9)	61.4 (13.8)	66.5 (13.5)	<0.001
Male	754 (49.3%)	348 (46.5%)	406 (52.0%)	0.033
Race				0.597
- White	1162 (76.0%)	563 (75.3%)	599 (76.7%)	
- Black	247 (16.2%)	128 (17.1%)	119 (15.2%)	
- Other	120 (7.8%)	57 (7.6%)	63 (8.1%)	
Heart Failure	151 (9.9%)	50 (6.7%)	101 (12.9%)	<0.001
Hypertension	1020 (66.7%)	451 (60.3%)	569 (72.9%)	<0.001
Diabetes	398 (26.0%)	155 (20.7%)	243 (31.1%)	<0.001
Prior Stroke/TIA	164 (10.7%)	64 (8.6%)	100 (12.8%)	0.007
Prior Myocardial Infarction	108 (7.1%)	34 (4.6%)	74 (9.5%)	<0.001
Peripheral Artery Disease	148 (9.7%)	45 (6.0%)	103 (13.2%)	<0.001
Recurrent VTE	629 (41.1%)	332 (44.4%)	297 (38.0%)	0.012
Provoked VTE	264 (26.1%)	91 (19.5%)	173 (31.7%)	<0.001
Known Thrombophilia	180 (11.8%)	105 (14.0%)	75 (9.6%)	0.007
Antiphospholipid Antibody Syndrome	14 (0.9%)	12 (1.6%)	2 (0.3%)	0.006
Cancer	556 (36.4%)	230 (30.8%)	326 (41.7%)	<0.001
Chronic Kidney Disease	278 (18.2%)	93 (12.4%)	185 (23.7%)	<0.001

Chronic Liver Disease	71 (4.6%)	29 (3.9%)	42 (5.4%)	0.163
Prior Bleeding	1010 (66.1%)	477 (63.8%)	533 (68.3%)	0.065
Heavy Alcohol Use	120 (7.9%)	50 (6.7%)	70 (9.0%)	0.098
Antiplatelet Medications	505 (33.0%)	235 (31.4%)	270 (34.6%)	0.190
NSAID Medications	140 (9.2%)	87 (11.6%)	53 (6.8%)	0.001
Mean HAS-BLED (SD)	3.1 (1.5)	2.9 (1.5)	3.4 (1.5)	<0.001
Mean Days on Warfarin (SD)	997 (1302)	971 (1245)	1022 (1353)	0.443
<90 days	158 (10.3%)	88 (11.8%)	70 (9.0%)	0.176
90-364 days	420 (27.5%)	198 (26.5%)	222 (28.4%)	
≥365 days	951 (62.2%)	462 (61.8%)	489 (62.6%)	

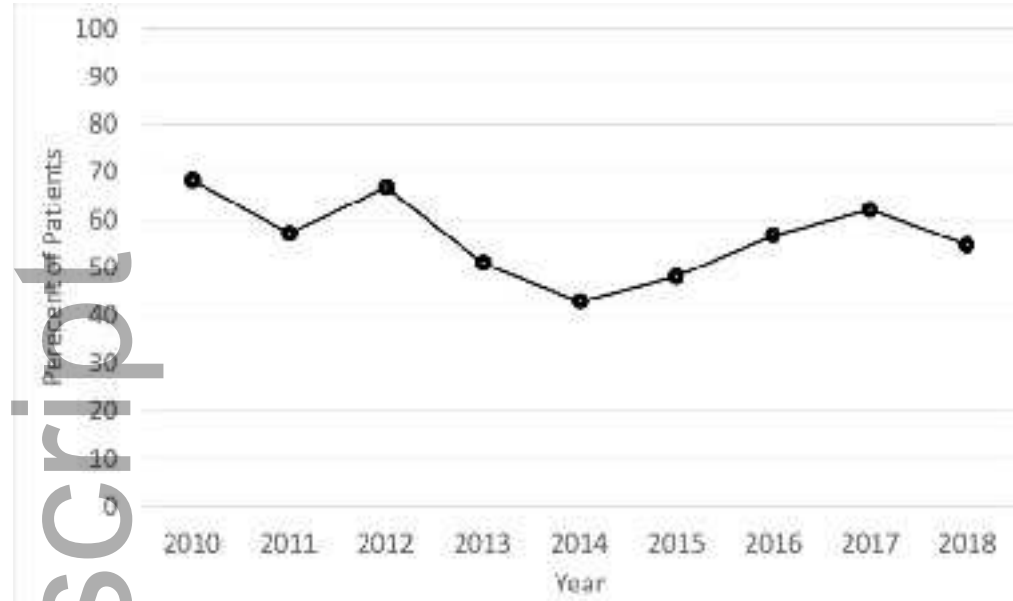
SD – standard deviation, TIA – transient ischemic attack, NSAID – non-steroidal anti-inflammatory drug



**Table 2 – Use of Bridging Anticoagulation by VTE Recurrent Risk**

		Bridging Anticoagulation (n=748)	No Bridging Anticoagulation (n=781)
VTE Risk Category	Low Risk (n=280)	134 (47.9%)	146 (52.1%)
	Moderate Risk (n=1078)	515 (47.8%)	563 (52.2%)
	High Risk (n=171)	99 (57.9%)	72 (42.1%)
30-day Outcomes	Any bleeding	22 (2.9%)	22 (2.8%)
	Major Bleeding	5 (0.7%)	7 (0.9%)
	Stroke	1 (0.1%)	1 (0.1%)
	Recurrent VTE	2 (0.3%)	0
	Any Emergency Department Visit	28 (3.7%)	25 (3.2%)

Use of bridging anticoagulation and associated 30-day adverse event rates by the American College of Chest Physicians 2012 guideline VTE recurrence risk category. Percentages represent rows for VTE risk category and columns for 30-day outcomes. Major bleeding defined by the International Society on Thrombosis and Haemostasis.<sup>7</sup> VTE – venous thromboembolism.



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