

Heparin bridge is associated with more post-polypectomy bleeding and emergency department visits among anticoagulated patients

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Abstract

Background Among patients undergoing colonoscopy, anticoagulants are usually stopped and are sometimes substituted by a heparin bridge (hep-bridge). We aimed to assess adverse events associated with hep-bridge compared to temporary cessation of anticoagulants (no-bridge).

Methods This was a single-center, retrospective cohort study that included anticoagulated patients undergoing colonoscopy between 2013 and 2016 at a Veterans Affairs Medical Center. In the no-bridge cohort, warfarin was stopped for 5 days and novel anticoagulants for 2 days pre-procedure. In the hep-bridge cohort, anticoagulants were stopped and were substituted by subcutaneous enoxaparin. The primary outcome was post-polypectomy bleeding. Secondary outcomes included cardiovascular events, all-cause adverse events and emergency department or unscheduled ambulatory office visits within 30 days. The predictive values of the HAS-BLED and CHADS₂ scores were evaluated.

Results A total of 662 patients were included, of whom 551 underwent polypectomy (mean age 68.6 years; 97.6% male). Four hundred seventy colonoscopies were performed with no-bridge and 192 with hep-bridge. Post-polypectomy bleeding occurred in 6.0% of procedures: 5.7% in the no-bridge cohort compared to 13.0% of hep-bridge procedures (P=0.0038). Cardiovascular or thrombotic events occurred after 2.6% of the no-bridge and 5.2% of the hep-bridge procedures (P=0.1176). Emergency department or unscheduled office visits within 30 days were reported after 18.7% of the no-bridge procedures and 29.7% of the hep-bridge procedures (P<0.0001). Neither CHADS₂ nor HASBLED scores predicted bleeding.

Conclusion The use of hep-bridge was associated with a greater incidence of post-polypectomy bleeding and more emergency department and unscheduled office visits compared with cessation of all anticoagulants.

Keywords Colonoscopy, bleeding, polypectomy, anticoagulation, bridge therapy, CHADS₂

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Introduction

Colonoscopy remains the preferred method for prevention of colorectal cancer, serving as both a screening and a therapeutic modality. With an estimated 22.4 million colonoscopies performed annually in the United States and another 11 million individuals estimated to be taking anticoagulant therapy, gastroenterologists will increasingly need to be familiar with these medications and understand the associated adverse events [1,2]. It is essential for clinicians to understand, and more importantly reduce, procedure-associated adverse events, including the most common post-polypectomy bleeding [3,4]. Reported to occur in approximately 0.3-10% of cases overall, the incidence of post-polypectomy bleeding related specifically to a population of patients on anticoagulants is less well defined [4,5].

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Patients using anticoagulation therapy present a unique and common clinical dilemma for the gastroenterologist: balancing the risk of anticoagulation cessation against the risk of procedure-associated hemorrhage [6]. Additional concerns that must be factored into this decision include the risk of thromboembolic events, reported to be as high as 3% when anticoagulation is withheld [7,8]. To reduce this risk of thromboembolic events, high-risk patients have traditionally been switched from warfarin to a shorter-acting bridge anticoagulation therapy (i.e., unfractionated or low-molecular-weight heparin [LMWH]) [4,6,9]. Despite current guidelines from national societies regarding the management of periprocedural anticoagulants, it remains unclear whether stopping anticoagulants temporarily and substituting them with LMWH as a temporary anticoagulant bridge therapy will result in more post-colonoscopy bleeding and a smaller number of thromboembolic events compared to complete anticoagulant interruption [10-12].

Thus, the aim of this study was to evaluate both the bleeding adverse events and thromboembolic events in patients undergoing colonoscopy who usually take anticoagulants, comparing those using a heparin bridge (hep-bridge) with those who temporarily stop all anticoagulation medications.

Patients and methods

Study design

This was a single-center, retrospective cohort study conducted at the Providence Veterans Affairs (VA) Medical Center in Rhode Island, using data extracted from the Veterans Affairs Computerized Patient Record System (CPRS). The study was approved by the Institutional Review Board at the Providence VA Medical Center on December 1, 2016. All patients who underwent outpatient and inpatient colonoscopy between January 2013 and November 2016 and had been prescribed anticoagulation therapy at the time of the procedure were identified. A systematic chart review was then performed to collect the relevant data, including demographics, periprocedural anticoagulation strategy and postprocedural outcomes. Colonoscopies were performed either by a trainee under the direct supervision of an experienced, board-certified gastroenterologist, or by the gastroenterologist themselves. Multiple colonoscopies in the same patient were included only if they occurred more than one year apart.

Cohort selection and anticoagulation strategy

Patient records were reviewed and categorized into 2 specific cohorts: a temporary anticoagulation cessation group (“no-bridge”) and a bridging group (“hep-bridge”). The choice of periprocedural anticoagulation strategy was based upon patient-specific risk factors and was made by a clinical pharmacist in the hospital’s anti-coagulation clinic, where all patients were managed using a standardized Providence VA

protocol. In this protocol, patients with atrial fibrillation and CHADS₂ scores of 1 to 2 were not prescribed hep-bridge [13,14]. Patients with atrial fibrillation and CHADS₂ scores of 3 to 4 were not prescribed a bridge unless the patient had a history of cerebrovascular accident. For those with atrial fibrillation and a CHADS₂ score of 5 to 6, hep-bridge was prescribed. Additionally, any patient with a mechanical cardiac valve was prescribed hep-bridge.

For patients in the no-bridge cohort, warfarin was stopped 5 days pre-procedure and reinitiated immediately following colonoscopy, as per standard protocol. In the hep-bridge cohort, warfarin was held and subcutaneous enoxaparin (1 mg/kg b.i.d.) was started 5 days prior to the procedure. Enoxaparin was stopped on the day of the colonoscopy and warfarin was restarted immediately post-procedure and continued until the target international normalized ratio (INR) was reached. Enoxaparin was typically continued with warfarin for 5 days post-procedure in the hep-bridge cohort. Other oral anticoagulants (apixaban, rivaroxaban) were stopped 2 days pre-procedure, without any hep-bridge, and reinitiated immediately following colonoscopy, as per hospital protocol.

Clinical characteristics and covariates

Demographic information including sex, age, and race/ethnicity was recorded. Additional patient-specific characteristics, including specific risk factors for bleeding (i.e. end-stage renal disease or cirrhosis), type of anticoagulant and indication for use, platelet count at time of procedure and INR, were also documented. CHADS₂ and HAS-BLED scores were calculated regardless of the indication for anticoagulation, not only in patients with documented atrial fibrillation [13-16]. Procedure-related measures collected included indication for colonoscopy, whether polypectomy was performed, method of endoscopic polyp resection (cold/hot biopsy or cold/hot snare), polyp location, size of largest polyp, number of polyps identified, and whether placement of an endoscopic clip was performed. These data were collected based on previous reports that documented factors associated with post-polypectomy bleeding [5,17-19].

Adverse events and post-polypectomy bleeding definition

Any complication occurring within 30 days after the procedure was determined by chart review. Immediate procedural bleeding was included if an additional intervention such as a clip was required during the procedure for hemostasis. Meaningful delayed post-procedural bleeding was defined as either rectal bleeding on gross examination of stool that led the patient to visit the physician or emergency department, or direct visualization on repeat colonoscopy within 30 days of the initial procedure. The severity of gastrointestinal bleeding was determined by the need for transfusion. Non-gastrointestinal related adverse events included any confirmed thromboembolic event (deep venous thrombosis, pulmonary embolism,

myocardial ischemia/infarction, cerebrovascular accident, peripheral arterial thrombosis, and any non-gastrointestinal complication that resulted in an emergency department visit, hospital admission, or unscheduled outpatient primary care visit within 30 days of the colonoscopy. The records of such events were reviewed to determine any possible relationship to colonoscopy, anticoagulation, or thromboembolic etiology.

Measured outcomes

The primary outcome measure in this study was the incidence of post-polypectomy bleeding. Secondary outcomes included cardiovascular events, defined as thrombotic events, all-cause adverse events, emergency department or unscheduled ambulatory office visits within 30 days of the procedure, and predictive values of the CHADS₂ and HAS-BLED scores for adverse events.

Statistical analysis

Patient characteristics and outcomes were compared using univariate *t*-tests for continuous variables. SAS version 9.4 (The SAS Institute, Cary, NC) was used for multiple regression analyses. Multiple regression was used to model the probabilities of dichotomous outcomes as a function of bleed risk severity (CHADS₂ or HAS-BLED) and whether or not a bridge was used, along with their interaction. Alpha per comparison was set to 0.05 (i.e. without adjustment) owing to the likely correlated nature of the multiple hypotheses being tested and a desire to be liberal in detecting a differential risk for clinical reasons. Classical sandwich estimation was used to adjust for any model misspecification.

Results

Demographic and clinical characteristics

A total of 662 colonoscopy procedures in 610 patients were identified during the predetermined study period, based on the above inclusion and exclusion criteria. Among these 662 procedures, 470 procedures were documented to have been performed without bridge anticoagulation and 192 procedures with enoxaparin bridge therapy. The mean age of the patients was 68.6 years and 97.6% were male. The most common indication for anticoagulation was atrial fibrillation or atrial flutter, noted in 341 procedures (51.5%), followed by a history of deep venous thrombosis or pulmonary embolism, in 204 procedures (30.8%) (Fig. 1). The most common indication for colonoscopy was polyp surveillance in 369 patients (55.7%), followed by colorectal cancer screening in 137 patients (20.7%) (Fig. 2). Polypectomy was performed in a total of 551 procedures (83.2%) and included 498 cold biopsy polypectomies and 87 snare polypectomies (Fig. 3). Additional

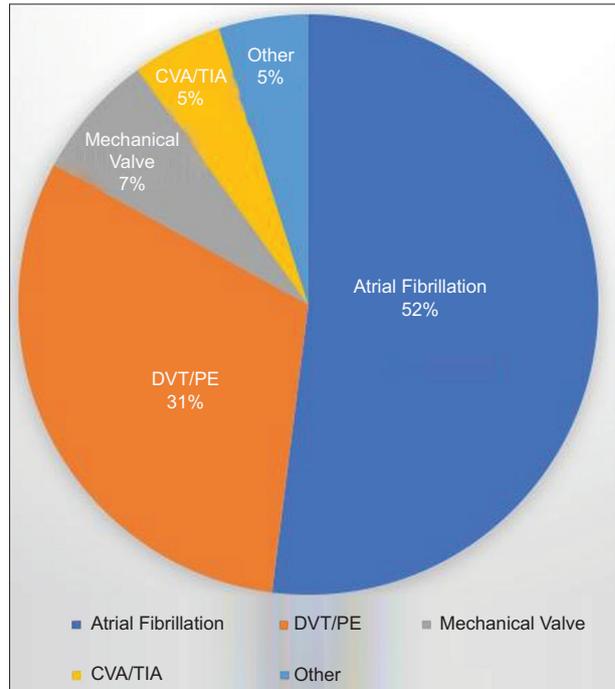


Figure 1 Indications for anticoagulation among veterans CVA/TIA, cerebrovascular accident/transient ischemic attack; DVT/PE, deep vein thrombosis/pulmonary embolism

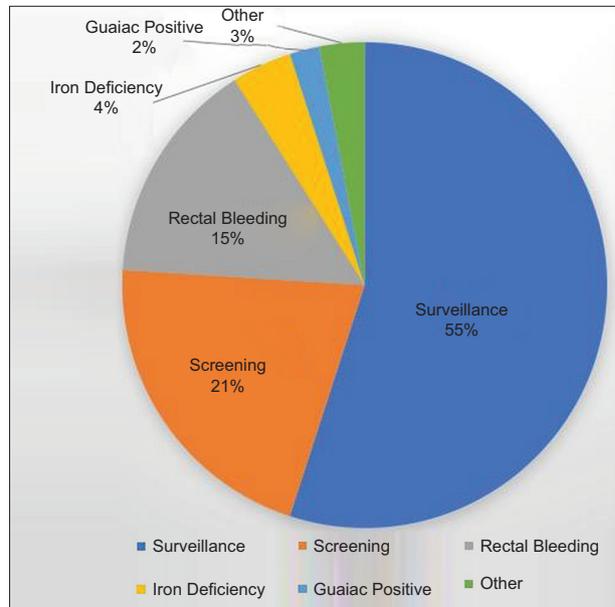


Figure 2 Indications for colonoscopy among veterans

demographic information, including patient and procedure characteristics, is summarized in Table 1.

Post-polypectomy bleeding was observed in 7.85% of total procedures (n=52). Subdividing this by cohort, there was a statistically significant difference in post-polypectomy bleeding: 5.7% of non-bridge procedures (n=27) and 13.0% (n=25) of hep-bridge procedures (P=0.0038). When the data were further stratified according to polypectomy method,

there was no significant difference in post-polypectomy bleeding between non-bridge and hep-bridge groups, whether snare cautery—74% (n=20) vs. 80% (n=20), respectively; $P=0.8549$ —or cold biopsy—1.5% (n=7) vs. 2.6%, respectively (n=5); $P=0.6123$ —was used. Adverse cardiovascular or thromboembolic events occurred in 3.9% of the total

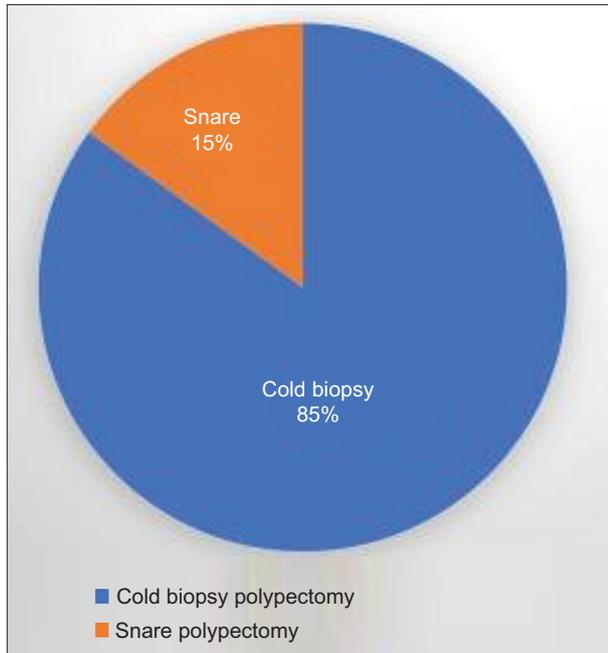


Figure 3 Type of polypectomy method during colonoscopy

procedures (n=26): 2.6% of the no-bridge and 5.2% of the hep-bridge procedures ($P=0.1176$). The incidence of post-procedure hospitalization, and emergency department and unscheduled ambulatory visits differed significantly between the 2 groups: 88 non-bridge procedures (18.7%) and 57 bridge procedures (29.7%) ($P<0.0001$). The most common chief complaints associated with these unscheduled emergency department and ambulatory visits were orthostatic (n=19 for non-bridge, n=11 for hep-bridge), urinary (n=9 for non-bridge, n=4 for hep-bridge), or musculoskeletal symptoms (n=4 for non-bridge, n=9 for hep-bridge). Thirty-day outcomes post-colonoscopy are shown in Table 2.

Multivariate analysis

Multivariate logistic regression was also performed to evaluate CHADS₂ and HAS-BLED scores as predictors of 30-day unscheduled visits and gastrointestinal adverse events. Neither CHADS₂ nor HAS-BLED scores were predictive of adverse events.

Discussion

As the frequency and utilization of both colonoscopies and anticoagulation continues to rise, endoscopists will encounter an increasing number of patients taking anticoagulant medications [1,20]. Therefore, examination of these therapeutic

Table 1 Baseline characteristics of veterans who received heparin bridge compared to those in whom anticoagulation was interrupted

Baseline characteristics	No-bridge cohort (n=470)	Bridge cohort (n=192)	P-value
Mean age (years)	69.3	67.1	<0.0001
Sex			0.9713
Male	460 (98.0%)	199 (97.9%)	
Female	10 (2.1%)	4 (2.1%)	
Race/Ethnicity			0.1032
Caucasian	444 (94.5%)	187 (97.4%)	
Other	26 (5.5%)	5 (2.6%)	
Type of anticoagulation			0.0003
Warfarin	401 (85.3%)	183 (95.3%)	
Direct-acting oral anticoagulant	69 (4.7%)	9 (4.7%)	
Cold biopsy polypectomy	400 (85.1%)	151 (78.6%)	0.5383
Snare polypectomy	78 (16.6%)	36 (18.8%)	0.5771
Clip placement required	95 (20.2%)	29 (15.1%)	0.2017

Table 2 Thirty-day outcomes among veterans with heparin bridge therapy compared to those in whom anticoagulation was interrupted

30-Day adverse events	No-bridge cohort (n=470)	Bridge cohort (n=192)	P-value
Post-polypectomy bleeding	27 (5.7%)	25 (13.0%)	0.0038
Blood transfusion required	9 (1.9%)	3 (1.6%)	0.7618
Emergency department or ambulatory visit	88 (18.7%)	57 (29.7%)	<0.0001
Cardiovascular or thromboembolic event	12 (2.6%)	10 (5.2%)	0.1176

agents and associated management decisions—whether to stop anticoagulant therapy entirely or use hep-bridge—remain critical for improving patient outcomes and reducing overall healthcare-related costs. The results of this study demonstrated that continued anticoagulation (i.e. hep-bridge therapy) is associated with higher rates of post-polypectomy bleeding, as well as other periprocedural adverse events, compared with temporary anticoagulation cessation.

Antithrombotic therapy has been proven to reduce the risk of thromboembolic events in patients at high risk for this complication, but it increases the risk of post-polypectomy bleeding in patients undergoing colonoscopy [4,5,18,21]. Because the temporary cessation of warfarin increases the risk of thromboembolic events, hep-bridge therapy is often prescribed as a compromise between the competing health risks of bleeding after polypectomy and precipitation of a potentially life-threatening thromboembolic event [4,6,10]. Our study provides real-world estimates of the rates of post-polypectomy bleeding and non-gastrointestinal adverse events following colonoscopy and polypectomy in patients who discontinue their anticoagulants completely versus those who receive a hep-bridge.

Given these findings, it is also important to understand the mechanism of anticoagulation and relation to post-polypectomy bleeding. The ability to form a clot post-polypectomy relies on primary and secondary hemostasis. Unlike aspirin and other anti-platelet agents, such as clopidogrel, the use of hep-bridge will inhibit the formation of insoluble, cross-linked fibrin and the activation of thrombin. Interestingly, previous studies have also shown anticoagulants to be associated with a higher risk of post-polypectomy bleeding, but not in direct relation to antiplatelet agents, perhaps because of the impact on secondary, rather than primary hemostasis [22-26]. Post-polypectomy bleeding was observed in 7.85% of cases in this study (5.7% of non-bridge procedures and 13.0% of bridging procedures). While initially these rates appear to be higher than those previously reported (bleeding in approximately 1-2% of post-polypectomy cases), other studies have demonstrated delayed bleeding rates as high as 34% among patients with anticoagulant use [18,21,27,28].

Many risk factors have been associated with post-polypectomy bleeding, including age greater than 75 years, polyp size greater than 1 cm, location and morphology of the polyp, resection technique, and notably anticoagulation, with a 3- to 5-fold greater incidence of procedure-related bleeding in patients taking anticoagulants [4-6,17-19]. Rates of thromboembolic events in the setting of temporary cessation of anticoagulation for endoscopy have been reported to be as high as 3%, with an absolute risk of 1% for patients who interrupt anticoagulation for ≤ 5 days [7,8]. Guidelines from the American College of Chest Physicians regarding anticoagulation management in patients with non-valvular atrial fibrillation in the periprocedural period recommend considering stopping vitamin K antagonists, based on the risk of thromboembolism and bleeding, and assessing CHADS₂ scores to determine the need for bridge therapy [11].

Current guidelines from both the European and American Gastroenterology Associations regarding the management of

anticoagulation and the use of bridge therapy, specifically in high-risk patients undergoing endoscopy, are largely based on low-quality evidence and expert opinion [6,12]. The guidelines from the British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy classify colonoscopy with polypectomy as a high-risk procedure for post-procedural bleeding, and suggest that pre-procedural bridge therapy should be used for patients on warfarin who are at high risk for thromboembolic events. These high-risk patients include those with atrial fibrillation and mitral stenosis, patients with a prosthetic metal heart valve in the mitral position, a prosthetic heart valve and atrial fibrillation, and patients within 3 months of a venous thromboembolism. The American Society for Gastrointestinal Endoscopy specifically recommends bridge therapy for high-risk patients with atrial fibrillation on warfarin who have mechanical valves, a history of a stroke, and a CHADS₂ score ≥ 2 . The Society also recommends bridge therapy for patients with a mechanical aortic valve, any thromboembolic risk factor, and older-generation and mechanical mitral valve replacements in those with valvular heart disease [6]. However, these societal guidelines from experts are based on very limited data. Previously published studies have compared bridge therapy to temporary cessation of anticoagulation with regard to post-polypectomy bleeding; however, they generally comprised small numbers of patients, while in one of them important thromboembolic event outcomes were not reported [23,29].

A retrospective study showed a high incidence of post-polypectomy bleeding with hep-bridge therapy (8.3%) for antiplatelet agents, compared with an even higher 24.2% with hep-bridge therapy for warfarin [23]. Similar results were noted in a large meta-analysis, which reported that patients receiving periprocedural hep-bridge were at increased risk of overall bleeding (>5 -fold increased risk) and major bleeding (>3 -fold increased risk), whereas the risk of thromboembolic events was similar to that of non-bridged patients [24]. A prospective study evaluated the incidence of gastrointestinal bleeding in patients on warfarin or hep-bridge therapy and found that the use of enoxaparin therapy was not significantly associated with a risk of postprocedural hemorrhage [30]. Likewise, another study concluded that hep-bridge therapy was associated with a low risk of thromboembolic and major bleeding events in high-risk patients who required temporary interruption of warfarin before undergoing nonsurgical invasive procedures, such as gastrointestinal endoscopy or cardiac catheterization [31]. In one randomized controlled trial comparing bridge therapy to a no-bridge strategy in patients undergoing a variety of elective surgical and other invasive procedures, the use of hep-bridge resulted in more major bleeding, without a significant benefit in terms of preventing arterial thrombosis [32].

In our study, the use of hep-bridge was associated with a greater incidence of gastrointestinal bleeding, as well as more visits to the emergency department and other unscheduled ambulatory office visits within 30 days of the colonoscopy. The most common complaints prompting these visits were orthostatic symptoms, urinary complaints or musculoskeletal symptoms, though these symptoms cannot be easily attributed to the hep-bridge alone. Moreover, the HAS-BLED score had

Summary Box

What is already known:

- Colonoscopies in patients receiving anticoagulation therapy have become increasingly common for gastroenterologists
- There is a need to balance the risk of anticoagulation cessation against the risk of procedure-associated hemorrhage so as to make these procedures as safe and effective as possible
- At the time of colonoscopy, anticoagulants may be stopped and substituted by a heparin bridge (hep-bridge), although there are limited data describing the adverse events of this practice

What the new findings are:

- Among a population of veterans, the use of hep-bridge was associated with a greater incidence of post-polypectomy bleeding
- The hep-bridge strategy was associated with more emergency department and unscheduled office visits compared to the cessation of all anticoagulants

no predictive value for such visits. In addition, the predictive value of this score for post-polypectomy bleeding risk appears to be inconsistent. In a recent prospective, observational, multi-center registry study of patients with a history of venous thromboembolism who started anticoagulation with a HAS-BLED score of ≥ 3 , the score had good specificity and negative predictive value but lacked sensitivity when predicting bleeding events in the first 6 months of anticoagulation therapy [33].

Our study is one of the largest studies in the United States to evaluate the use of bridge therapy exclusively in the setting of colonoscopy, the most common endoscopic procedure performed in the United States. Since our patients were all from a VA hospital, with a relatively homogenous, largely male and Caucasian population and with a high frequency of polypectomy, the results may not be generalizable to other populations. Furthermore, there was a significant difference in age between the 2 groups, suggesting that the 2 cohorts may not be totally comparable. Another limitation is that our study was not controlled, but rather a single-center retrospective analysis of current practice. In this study, patients with atrial fibrillation and CHADS₂ scores of 1 to 4 were not prescribed hep-bridge, in accordance with our VA protocol. For those with atrial fibrillation and a CHADS₂ score of 5 to 6, hep-bridge therapy was prescribed. It is possible some patients may have developed rebleeding and presented to another institution or were lost to follow up so that any events were not recorded.

In conclusion, our results clearly indicate that hep-bridge, prescribed to patients with the highest risk of cardiovascular

morbidity, is nevertheless associated with higher rates of both post-polypectomy bleeding and other periprocedural adverse events compared to the temporary cessation of anticoagulation. Since neither the CHADS₂ nor the HAS-BLED scores was predictive of adverse events, 30-day unscheduled visits or 30-day hospital admissions, this suggests that there is a need for a better scoring system that will enable practitioners to estimate the likelihood of adverse events after colonoscopy in anticoagulated patients, whether or not they receive hep-bridge.

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