Periprocedural Anticoagulation Management of Patients With Nonvalvular Atrial Fibrillation

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OBJECTIVE: **To estimate the 3-month cumulative incidence of thromboembolism (TE), bleeding, and death among consecutive patients with nonvalvular atrial fibrillation (AF) who were receiving long-term anticoagulation therapy and were referred to the Thrombophilia Center at Mayo Clinic for periprocedural anticoagulation management.**

PATIENTS AND METHODS: **In a prospective cohort study of consecutive patients receiving long-term anticoagulation therapy who were referred to the Thrombophilia Center for periprocedural anticoagulation management over the 7-year period, January 1, 1997, to December 31, 2003, 345 patients with nonvalvular AF were eligible for inclusion. Warfarin was stopped 4 to 5 days before and was restarted after surgery as soon as hemostasis was assured. The decision to provide bridging therapy with heparin was individualized and based on the estimated risks of TE and bleeding.**

RESULTS: **The 345 patients with AF (mean ± SD age, 74±9 years; 33% women) underwent 386 procedures. Warfarin administration was not interrupted for 44 procedures. Periprocedural heparin was provided for 204 procedures. Patients receiving heparin were more likely to have prior TE (43% vs 24%; *P*<.001) and a higher $CHADS_2$ (*c*ongestive heart failure, *h*ypertension, *a*ge, *d*iabetes, *s*troke) score (2.2 vs 1.9; *P*=.06). Four patients had 6 episodes of TE (3 strokes and 3 acute coronary episodes; TE rate, 1.1%; 95% confidence interval, 0.0%-2.1%). Nine patients had 10 major bleeding events (major bleeding rate, 2.7%; 95% confidence interval, 1.0%-4.4%). There were no deaths. Neither bleeding nor TE rates differed by anticoagulant management strategy.**

CONCLUSION: **The 3-month cumulative incidence of TE and bleeding among patients with AF in whom anticoagulation was temporarily interrupted for an invasive procedure was low and was not significantly influenced by bridging therapy.**

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AF = atrial fibrillation; INR = international normalized ratio; LMWH = low-molecular-weight heparin; TE = thromboembolism; TIA = transient ischemic attack

Atrial fibrillation (AF) is the most common cause of arterial thromboembolism (TE) and is associated with a 5- to 6-fold increased risk of stroke.[1-3] Long-term oral anticoagulation with warfarin reduces the risk of stroke by 68% (range 45%-82%).[4] Approximately two-thirds of patients with AF are at high risk of stroke and should be treated with warfarin.[2-3] Warfarin therapy can be temporarily interrupted so that patients may safely undergo an invasive procedure.[5] Standardizing periprocedural anticoagulation management for patients with AF has been difficult because annual thrombosis risk can vary enormously (0.5%-20%) depending on the presence of other risk factors.[1-6] Moreover, the procedure-specific bleeding risk also varies widely. Several strategies have been proposed, ranging from simple warfarin discontinuation 5 days before surgery with prompt reinitiation postoperatively, to bridging therapy with either intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH).[7-9] In balancing the need for TE prophylaxis and adequate hemostasis, the clinician should take the morbidity and mortality associated with TE and the consequences of postoperative bleeding into account. Although approximately 3% of major postoperative bleeding episodes are fatal, most patients make a full recovery.[10] In contrast, AF-related stroke results in a major neurologic deficit or death in 70% of patients.[3,5,10,11] Consequently, several authorities and consensus groups advocate some form of bridging therapy with a short-acting anticoagulant for most patients with AF.[7,12,13] Even in the absence of anticoagulation, invasive procedures can carry a risk of bleeding for up to 1 week.[5] Therefore, in high-risk patients (particularly those with prior AF-related TE) or when a series of procedures requires interruption of oral anticoagulant therapy for longer than 1 week, the 2006 consensus guidelines of the American College of Cardiology/American Heart Association/European Society of Cardiology Writing Committee recommend that either unfractionated heparin or LMWH be administered intravenously or subcutaneously.[14] Data supporting these recommendations are limited,[15-18] and study patients were not limited to those with nonvalvular AF. To address these limitations, we assessed consecutive patients with nonvalvular AF who were referred to the Thrombophilia Center at

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TABLE 1. **Procedure-Specific Risk of Major Bleeding**

Low risk (<1%)
Outpatient dental procedures
Cataract surgery
Other minor outpatient procedures
High risk (>3%)
Open-heart surgery
Abdominal vascular surgery
Neurosurgery
Major cancer surgery
Urologic procedures

Mayo Clinic for periprocedural anticoagulation management during a 7-year period (January 1, 1997–December 31, 2003) to estimate the 3-month cumulative incidence of TE, bleeding, and all-cause mortality.

PATIENTS AND METHODS

The Thrombophilia Clinic was established in 1997 to facilitate the outpatient delivery of the then newly available anticoagulant, LMWH. Consecutive patients referred to the Thrombophilia Center during the 7-year period, January 1, 1998, to December 31, 1997, who were receiving long-term anticoagulation therapy and had nonvalvular AF were eligible for inclusion; 97% consented to participate. All patients were monitored for 3 months from the date of the Thrombophilia Center consultation. Patients (or family members for deceased patients) who did not return for a clinic visit were mailed a questionnaire or contacted by telephone to determine vital status and to identify any symptoms or signs of TE or bleeding in the 3 months after the Thrombophilia Center consultation.

The study end point adjudication committee reviewed the death certificates and autopsy reports for deceased patients and local medical records of patients who reported TE or bleeding. Two experienced study nurse abstractors reviewed the complete inpatient and outpatient medical records for each patient. The study was approved by the Mayo Clinic Institutional Review Board.

TABLE 2. **Regimens for Bridging Therapy Using Low-Molecular-Weight Heparin (LMWH)**[a]

LMWH (No. of procedures)[b]	Regimen
Ardeparin sodium (n=69)	130 IU anti-Xa/kg subcutaneously every 12 h[c]
Dalteparin sodium (n=91)	100 IU anti-Xa/kg subcutaneously every 12 h[c] or 200 IU anti-Xa/kg subcutaneously every 24 h
Enoxaparin sodium (n=33)	1 mg/kg subcutaneously every 12 h[c] or 1.5 mg/kg subcutaneously every 24 h

[a] No heparin formulations are approved by the Food and Drug Administration for this indication.
[b] Although bridging therapy with LMWH was used for 173 procedures, the total number of procedures in this table is 193 because 20 patients were treated with 2 different kinds of LMWH for the same procedure.
[c] Last dose given on the morning of the day (eg, 24 h) before surgery.

PERIPROCEDURAL ANTICOAGULATION MANAGEMENT

Patients typically were referred to the Thrombophilia Center for periprocedural anticoagulation management recommendations 4 to 7 days before the anticipated procedure. Each patient was evaluated for the patient-specific risk of TE and the procedure-specific risk of major bleeding (Table 1). The decision to provide LMWH bridging therapy was individualized and undertaken at the discretion of the thrombophilia consultant treating each patient. For patients requiring outpatient dental or other minor procedures associated with either a low risk of bleeding or easy access for physical hemostasis, warfarin anticoagulation was reduced to the lower limit of the therapeutic range (international normalized ratio [INR], 2.0).

The risk of stroke was estimated on the basis of age, presence of hypertension, congestive heart failure, prior stroke, transient ischemic attack (TIA) or other cardioembolic event, or known intracardiac thrombus. For patients deemed to be at low risk of stroke, warfarin was stopped 4 to 5 days before surgery and resumed as soon as possible after surgery, starting with the patient's usual daily warfarin dose and without loading doses.

When warfarin was stopped 4 to 5 days before surgery, patients deemed to be at high risk of stroke were either admitted to the hospital and treated with intravenous unfractionated heparin or given bridge therapy with LMWH as outpatients when INR was expected to fall below the lower limit of the therapeutic range. During the 7-year period, 3 successive LMWHs were on the Mayo Clinic formulary and were used for periprocedural anticoagulation therapy; the dose, schedules, and number of procedures for each LMWH are shown in Table 2. To avoid residual effect of heparin at the time of surgery when bridge therapy with LMWH was used,[19] our standard treatment required the last LMWH subcutaneous injection to be given 24 hours before the procedure at 50% of the calculated daily dose. If LMWH therapy was restarted after the procedure, administration of the first dose was usually delayed for at least 24 hours and was delayed even longer if the period of high bleeding risk was prolonged. For patients given bridge therapy with unfractionated heparin, the intravenous infusion was stopped 6 to 8 hours before surgery.

Warfarin was usually restarted immediately after the procedure. Warfarin and LMWH therapy overlapped for at least 5 days and until the INR exceeded the lower limit of the therapeutic range on at least 2 separate measurements performed 24 hours apart. Aspirin and thienopyridine derivative therapy was stopped 1 week before the procedure

and restarted after the procedure when hemostasis was assured.

Definition of Outcomes

The primary efficacy end point was symptomatic arterial or venous TE occurring from 5 days before (the day warfarin therapy was stopped) to 90 days after the procedure or surgery. Arterial TE was defined as ischemic stroke, TIA, amaurosis fugax, unstable angina, myocardial infarction, or other peripheral artery TE. Criteria for unstable angina, myocardial infarction, stroke, and TIA were adapted from those of the American Heart Association.[20] Peripheral artery TE was defined as acute ischemia of an extremity or any organ other than the brain; arterial thromboembolus was confirmed by either embolectomy or direct imaging. Venous TE was defined as deep venous thrombosis or pulmonary embolism as previously described.[21]

The primary safety end point was major bleeding. Major bleeding was defined as overt bleeding plus a hemoglobin decrease of 2 g/dL or more after the procedure or transfusion of 2 units or more of packed red blood cells, or intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or fatal bleeding.[22] Minor bleeding was defined as overt bleeding that did not meet criteria for major bleeding.

All events were judged using a priori study criteria by a committee composed of 4 Thrombophilia Center physicians blinded to patient name and treating physician.

Statistical Analyses

Continuous numerical variables were reported as mean ± SD. Frequencies were reported when appropriate. Continuous variables were compared between the groups treated and not treated with LMWH bridging therapy using the Wilcoxon rank sum test. Categorical factors were compared between these groups using the χ^2 test for independence. The 3-month cumulative incidence rates for first events of TE, major bleeding, and minor bleeding were estimated using the Kaplan-Meier product-limit method.

RESULTS

During the 7-year study period, 345 patients with nonvalvular AF (33% women, mean ± SD age, 74±9 years) were referred to the Thrombophilia Center for periprocedural anticoagulation management of 386 procedures. Twenty-nine patients underwent 2 procedures, 3 patients underwent 3 procedures, and 2 patients underwent 4 procedures. Baseline patient characteristics are shown in Table 3, both overall and by presence or absence of bridging heparin therapy. Of the 345 patients, 271 (79%) had persistent AF, and 118 (34%) had prior TE (stroke, TIA, peripheral artery embolus, or left atrial thrombus). Prevalence of prior TE and coronary artery disease was greater among patients with AF receiving bridging heparin therapy. The $CHADS_2$ score (named for the components of the score: ***c***ongestive heart failure, ***h***ypertension [at least 160/90 mm Hg, past or present], ***a***ge [older than 75 years], ***d***iabetes, and ***s***troke or TIA [past or present]), although slightly higher in this group, did not reach statistical significance. Active cancer and bleeding history were similar in both groups. The distribution of types of surgery and procedures is shown in Table 4. Orthopedic, gastrointestinal, and urological surgeries were the most common procedures.

The timing of warfarin cessation, reinitiation, and the mean duration of warfarin cessation, as well as the timing and duration of bridging heparin therapy are shown in Table 5. Warfarin therapy was continued for 44 procedures, all either dental or ophthalmologic interventions. However, LMWH therapy was administered after 11 of these 44 procedures because of a subtherapeutic INR. For the remaining 342 procedures, warfarin was stopped 5.3±3.0 days before surgery; the total time of warfarin interruption was 6.6±4.6 days. For 25% of patients, warfarin reinitiation was delayed for more than 7 days. Of the total 386 procedures, periprocedural anticoagulation was

TABLE 3. **Baseline Characteristics of 345 Patients With Atrial Fibrillation**[a]

Characteristic	Overall	No bridging heparin	Bridging heparin	*P* value
No. of patients[b]	345	164	181	
Age (y) (mean ± SD)	74±9	74±9	73±9	.22
Women	114 (33)	50 (30)	64 (35)	.34
Atrial fibrillation				
Persistent	271 (79)	135 (82)	136 (76)	
Paroxysmal	74 (21)	29 (18)	45 (24)	.10
$CHADS_2$ index				
Congestive heart failure	85 (25)	34 (21)	51 (28)	.11
Hypertension	206 (62)	101 (62)	105 (58)	.50
Age >75 y	172 (50)	84 (51)	88 (49)	.62
Diabetes mellitus	66 (19)	32 (20)	34 (19)	.86
Stroke/TIA/DTE	118 (34)	40 (24)	78 (43)	<.001
Score (mean ± SD)	2.1±1.4	1.9±1.3	2.2±1.4	.06
Coronary artery disease	131 (38)	46 (28)	85 (47)	<.001
Active cancer	52 (15)	25 (15)	27 (15)	.91
Bleeding history	58 (17)	31 (19)	27 (15)	.32
Renal insufficiency	10 (3)	5 (3)	5 (3)	.87
Aspirin	63 (18)	28 (17)	35 (19)	.59
Ticlopidine/clopidogrel	5 (1)	3 (2)	2 (1)	.57
NSAID	7 (2)	0 (0)	7 (4)	.02
Cyclooxygenase-2 inhibitor	16 (5)	10 (6)	6 (3)	.22

[a] Data are presented as number of patients (percentage of sample) except as noted. DTE = distal thromboembolism (thromboembolic complications at locations other than central nervous system including left atrial thrombus; NSAID = nonsteroidal anti-inflammatory drug; TIA = transient ischemic attack.

[b] To avoid double entry for patients undergoing multiple procedures, this figure represents the demographics for only the first encounter.

TABLE 4. **Distribution of 386 Procedures or Surgeries**[a]

Type of procedure or surgery	No. (%)[b]
Orthopedic	80 (21)
Total hip arthroplasty	34
Total knee arthroplasty	29
Arthroscopic procedures	13
Other	4
Gastroenterologic	78 (20)
Lower endoscopy with polypectomy or biopsy	49
Upper endoscopy with biopsy or stricture dilation	7
Liver or pancreas biopsy	6
Bowel or colon resection	5
Exploratory laparotomy	4
Cholecystectomy	3
Hiatal hernia repair	2
Bariatric surgery	2
Urologic	68 (18)
Cystoscopy with biopsy or urethral stent	20
Prostate biopsy	11
Nephrectomy, cystectomy, or nephrourectomy	9
Prostatectomy	8
Lithotripsy	4
Penile prosthesis	4
Bladder or sphincter repair	3
Other (open biopsies, ablations, brachytherapy)	9
Cardiovascular	54 (14)
Angiography with or without angioplasty or stenting	37
Valve surgery or cardiopulmonary bypass	11
Cardioversion, Maze procedure, AICD or pacemaker	6
Ophthalmologic	20 (5)
Cataract extraction	10
Trabeculectomy	4
Vitreoretinal surgery	3
Blepharoplasty	3
Dental extraction	20 (5)
Vascular	18 (5)
Abdominal aortic aneurysm repair	6
Carotid endarterectomy	6
Revascularization or distal bypass	5
Varicose vein resection	1
Neurologic	14 (4)
Laminectomy with or without tumor resection	6
Myelogram	5
Other	3
Gynecologic	7 (2)
Hysterectomy or salpingo-oophorectomy	4
Vaginal surgeries	3
Other	27 (7)

[a] AICD = automatic implantable cardioverter-defibrillator.
[b] Percentages add to more than 100 because of rounding.

managed with bridging heparin therapy (unfractionated heparin, n=31; LMWH, n=173) for 204 procedures (53%), whereas 182 procedures were managed without bridging heparin therapy. The mean total duration of bridging heparin therapy was 5.9±4.9 days.

THROMBOEMBOLISM

All patients completed the 3-month follow-up for vital status, bleeding, and symptoms of TE. Four patients had 6 TE events after 4 procedures (Table 6). The 3-month cumulative TE incidence was 1.1% (95% CI, 0%-2.1%). Two of the four patients received bridging LMWH therapy. No significant differences in 3-month cumulative TE incidence were noted in patients with AF who had prior vs no prior TE (Figure 1) and low vs high $CHADS_2$ scores (Figure 2).

Of the 4 patients with TE, 1 had a right parasagittal occipital infarct within 72 hours after stopping warfarin and without bridging heparin therapy. A transesophageal echocardiogram showed a large thrombus in the left atrium. Three days later this patient also had an episode of unstable angina. The second patient had a history of stroke and therefore received bridging LMWH therapy for resection of a spinal cord tumor. Two weeks after surgery and with an INR of 3.2, this patient developed right insular infarct. The third patient, who had a history of hypertension and of coronary and peripheral artery disease, underwent an above-knee amputation without bridging therapy, which was complicated by a non–ST-elevation myocardial infarction. The fourth patient had a history of hypertension, coronary artery disease, and chronic heart failure and received bridging LMWH therapy after warfarin was stopped for an automatic intracardiac defibrillator device implantation. This patient developed a large hematoma at the site of

TABLE 5. **Periprocedural Anticoagulation Management of 386 Procedures**[a]

Characteristic	Result
Procedures with warfarin interruption	342 (89)
Warfarin cessation before procedure (d)	5.3±3.0
Warfarin cessation after procedure (d)	1.3±3.4
Periprocedural heparin therapy total	204 (53)
Heparin administered only before procedure	84 (41)
Heparin administered only after procedure	32 (15)
Heparin administered both before and after procedure	88 (44)
Heparin administered before procedure (d)	3.7±1.7
Heparin administered after procedure (d)	6.9±4.5

[a] Categorical data are presented as number of patients (percentage of sample). Continuous data are presented as mean ± SD.

TABLE 6. **Thromboembolism and Bleeding Complications of 386 Procedures**

Complications	No heparin bridging therapy[a] (n=182), No. (%)	Heparin bridging therapy[b] (n=204), No. (%)
Cerebral ischemia	1 (0.6)	2 (1.0)
Acute coronary syndrome	2 (1.2)	1 (0.5)
Bleeding		
Major	4 (2.3)	6 (3.0)
Minor	2 (1.1)	9 (4.6)

[a] Thirty-three patients continued warfarin therapy throughout the procedure or surgery.
[b] Eleven patients who continued warfarin therapy during the procedure or intervention also had low-molecular-weight therapy after procedure because of subtherapeutic international normalized ratio.

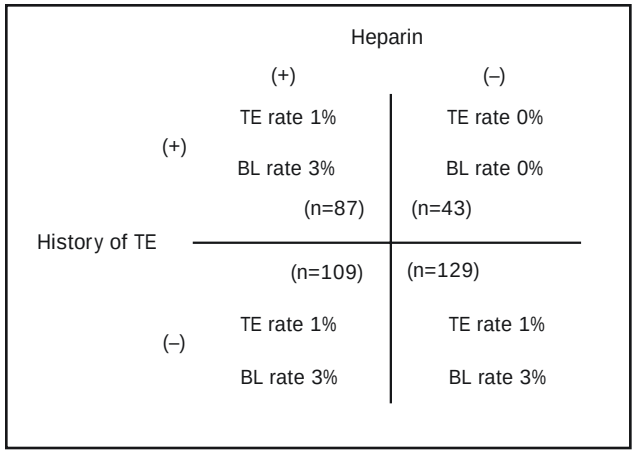

FIGURE 1. Distribution of 3-month thromboembolism (TE) and major bleeding (BL) rates by bridging heparin therapy and prior TE. History of TE included stroke, transient ischemic attack, thromboembolic complications of various location including left atrial thrombus.

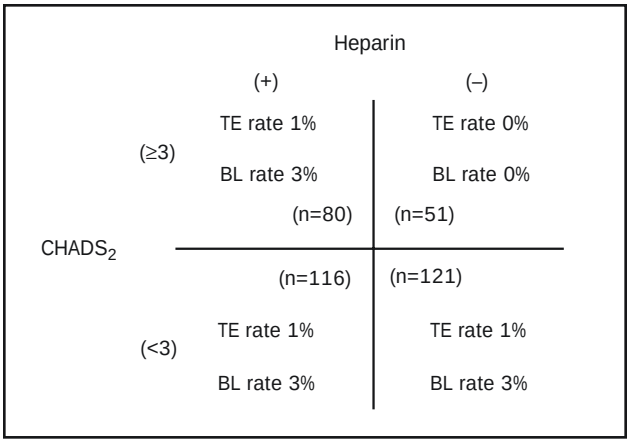

FIGURE 2. Distribution of 3-month thromboembolism (TE) and major bleeding (BL) rates by bridging heparin therapy and $CHADS_2$ score. $CHADS_2$ index is named for the components of the score: ***c***ongestive heart failure, ***h***ypertension (at least 160/90 mm Hg, past or present), ***a***ge (>75 y), ***d***iabetes, and ***s***troke or transient ischemic attack (past or present).

device implantation (classified as minor bleeding) and also was diagnosed at that time with a non–ST-elevation myocardial infarction. Because of the hematoma, both warfarin and LMWH were stopped, but 5 days later the patient had a stroke confirmed by magnetic resonance imaging. Thus, all of the thromboembolic events occurred within 2 weeks of warfarin discontinuation.

Bleeding

Nine patients who underwent 10 procedures (1 patient had rectal polypectomy and several dental extractions in 1 day) experienced 10 major bleeding events (Table 6). The 3-month cumulative major bleeding incidence rate was 2.7% (95% CI, 1.0%-4.4%). Six major bleeding events involved gastrointestinal bleeding, whereas 5 major bleeding events occurred at the surgical site. Two patients had both gastrointestinal hemorrhage and bleeding at the surgical site; one had profuse bleeding during gastrointestinal surgery.

Five of the 9 patients received bridging LMWH heparin therapy. Of the 5 patients who received bridging LMWH, 1 had 2 major bleeding events after inguinal herniorrhaphy, including a large hematoma at the surgical wound site and hematochezia due to sigmoid diverticula occurring 2 weeks later. This patient received only preoperative bridging LMWH. The second of the 5 patients, who received both preoperative and postoperative LMWH, developed gastrointestinal bleeding 5 days after the last LMWH dose and when the INR was supratherapeutic (INR=10.3); the bleeding source was gastropathy confirmed by upper endoscopy and induced by nonsteroidal anti-inflammatory drugs. The third patient received both preoperative and postoperative LMWH and developed bleeding at the surgical site 7 days after the procedure and 24 hours after the last LMWH dose. The fourth patient received only preoperative LMWH and developed bleeding at the surgical site immediately after surgery, and the fifth patient received only preoperative LMWH and developed bleeding 30 days after surgery.

Eleven patients developed 11 minor bleeding events after 11 procedures; the 3-month cumulative minor bleeding incidence was 3.0% (95% CI, 1.2%-4.7%). Of these 11 patients, 10 received bridging LMWH therapy, yet only 5 events occurred in the setting of LMWH.

Of the total cohort, 71 patients (21%) were taking aspirin, nonsteroidal anti-inflammatory drugs, thienopyridine derivatives, or a combination of these drugs. Periprocedural dosing of these medications was managed by surgical services and primary physicians. Aspirin and thienopyridine derivative therapy was stopped 1 week before the procedure and restarted after the procedure when hemostasis was assured.

The rates of TE and bleeding did not differ significantly among those taking 1 or more of these drugs compared with those not receiving such drugs.

DISCUSSION

The major finding of this study is that the 3-month cumulative incidence of TE among patients with nonvalvular AF who required temporary interruption of long-term warfarin therapy for an invasive procedure is quite low. Given the annual risk of stroke in patients with AF who are receiving warfarin prophylaxis, the anticipated daily risk of stroke ranges from 0.001% to 0.023% (3-month risk, 0.09%-

2.07%).[4] The observed cumulative TE incidence in our study was 1.1% (95% CI, 0%-2.1%), well within the anticipated range. The mean duration of warfarin cessation was 6.6 days for our cohort. Yet all of the observed thrombotic events occurred within 2 weeks of warfarin discontinuation. Of the 6 TE events, 3 were acute coronary syndrome events in patients with known coronary artery disease. Although we cannot exclude a cardioembolic cause for these coronary artery events,[23] the more likely etiology is either thrombosis in situ or ischemia caused by low coronary flow due to systemic hypotension. Excluding these acute coronary events, the 3-month cumulative incidence of TE would be 0.8% (95% CI, 0%-1.7%). The TE rates did not differ significantly between those who received bridging heparin compared with those who did not. The group receiving bridging heparin had significantly higher prevalence of prior TE and coronary artery disease, as well as a marginally higher $CHADS_2$ score. Despite not receiving bridging heparin therapy, no patient with prior TE (n=43, Figure 1) or a high $CHADS_2$ score (ie, ≥3; n=51; Figure 2) developed postoperative TE.

Of the 10 episodes of major bleeding, 6 occurred in 5 patients given bridge therapy with LMWH. The observed 3-month cumulative major bleeding incidence of 2.7% (95% CI, 1.0%-4.4%) is comparable to rates previously reported.[19] Five episodes occurred either intraoperatively or soon after surgery and before LMWH therapy was restarted. Because the last preoperative dose of LMWH was reduced to half of the usual daily dose and was given at least 24 hours before surgery, it is unlikely that bridging therapy contributed to these bleeding episodes.[19] Only 1 of these patients had marginal renal function (creatinine 1.8 mg/dL) as a potential contributing factor. If these 5 bleeding events are excluded, then major bleeding potentially related to bridging LMWH is 1.4% (95% CI, 0.2%-2.6%).

This study has several strengths. First, unlike other studies, we reported outcomes from a cohort that was limited to consecutive patients with nonvalvular AF who were receiving long-term anticoagulation therapy while undergoing an invasive diagnostic or therapeutic procedure or surgery. Although others have reported combined outcomes from cohorts of patients with AF, mechanical heart valves, or venous TE who received long-term anticoagulant therapy,[24] the risk of TE and bleeding likely is not uniform across these 3 patient populations. Second, we report follow-up for a full 3 months from the date of the procedure, whereas other cohort studies usually reported follow-up for only 2 to 4 weeks. We chose to expand observation to 3 months because the risk of TE and bleeding is substantially longer than 2 weeks, and we sought to capture the full effect of our periprocedural anticoagulation management protocol. Third, we used standardized a priori definitions of TE and bleeding, and all potential outcomes were centrally adjudicated by a committee blinded to patient name and treating physician.

Several limitations of this study should be noted. First, the delivery of LMWH was not assigned randomly. Careful patient stratification on the basis of perceived risks and benefits of LMWH by attending physicians could have contributed to the low rate of both bleeding and thromboembolic complications observed. Moreover, as this was not designed as an intention-to-treat trial, patient preferences could have also contributed to these outcomes, both favorably and unfavorably. Second, although referral to the Thrombophilia Center was open to all patients with AF, we cannot exclude the possibility of referral bias. For example, patients with AF and a perceived high or low risk of TE might not have been referred to our center, which could have caused an underestimation of the true TE rate or overestimation of the bleeding rate.

At the inception of our cohort study in 1997, LMWH had only recently been marketed in the United States, and there were no studies of bridging heparin therapy for periprocedural management of nonvalvular patients with AF using long-term anticoagulation. Most such patients judged to be at high risk of TE or bleeding were admitted to the hospital for intravenous unfractionated heparin therapy while warfarin anticoagulation was alternately withdrawn and restarted. Given that LMWH and warfarin were effective as both primary prophylaxis and therapy for venous TE, we postulated that they would have similar efficacy and safety as bridging therapy for periprocedural anticoagulation management for patients with nonvalvular AF. Consequently, our initial aim was to estimate the TE and bleeding rates to design a subsequent clinical trial. Although we have faithfully reported all TE and bleeding events and the clinical circumstances around those events so that readers can make their own judgment regarding the likelihood that the event was related to the periprocedural management, we think the true TE and major bleeding rates are closer to 0.8% and 1.4%, respectively. The observed TE rate is sufficiently low as to render a randomized controlled trial impractical. A very large sample would be required to show a clinically important reduction in rate.

CONCLUSION

Our current clinical practice in the Mayo Clinic Thrombophilia Center is to provide LMWH bridging therapy only for those patients at the highest risk of TE (prior stroke; $CHADS_2$ score ≥4), while taking into account the procedure-associated risk of bleeding.

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