Postoperative Strokes and Intracranial Bleeds in Patients With Atrial Fibrillation: The FibStroke Study

Antti Palomäki, MD; Tuomas Kiviniemi, MD, PhD; Juha E.K. Hartikainen, MD, PhD; Pirjo Mustonen, MD, PhD; Antti Ylitalo, MD, PhD; Ilpo Nuotio, MD, PhD; Päivi Hartikainen, MD, PhD; Jussi Jaakkola, BM; Riho Luute, MD; K.E. Juhani Airaksinen, MD, PhD

Heart Center (Palomäki, Kiviniemi, Jaakkola, Airaksinen), Turku University Hospital and University of Turku, Turku, Finland; Heart Center (Hartikainen, Luute), Kuopio University Hospital, Kuopio, Finland; Department of Medicine (Mustonen), Keski-Suomi Central Hospital, Jyväskylä, Finland; Heart Center (Ylitalo), Satakunta Central Hospital, Pori, Finland; Department of Medicine (Nuotio), Turku University Hospital and University of Turku, Turku, Finland; NeuroCenter, Neurology Department (Hartikainen), Kuopio University Hospital, Kuopio, Finland

ABSTRACT

Background: Patients with atrial fibrillation (AF) frequently undergo invasive procedures. Optimal perioperative use of oral anticoagulation (OAC) and heparin bridging is not well defined.

Hypothesis: Discontinuation of OAC for minor procedures/operations places AF patients at risk for thromboembolism.

Methods: In this study, we assessed perioperative antithrombotic treatment in patients with AF who suffered a postoperative stroke or intracranial bleeding. The FibStroke Study includes AF patients with an ischemic stroke or intracranial bleed identified from the discharge registries of 4 Finnish hospitals. In total, 3632 consecutive patients developed 3252 ischemic strokes and 794 intracranial bleeds. All invasive procedures during the 30 days preceding the stroke or intracranial bleed were identified.

Results: A total of 194/3252 (6.0%) ischemic strokes and 23/794 (2.9%) intracranial bleeds were preceded by a procedure. Altogether, 69% of the patients were on OAC prior to index procedure, OAC was interrupted in 81.2% of the procedures preceding a stroke, and heparin bridging was used in 27.8% of interruptions. Of the procedures leading to stroke, 42.3% were low-bleeding-risk procedures, and OAC was interrupted in 84.7% of these procedures. The median time from procedure to stroke was 4 days. Heparin bridging was used in 54.5% of OAC interruptions preceding intracranial bleeding and combination of anticoagulation with antiplatelet therapy by 43.5% of patients with postoperative intracranial bleeding.

Conclusions: Perioperative interruption of OAC is common in patients who suffer a postoperative stroke, even in patients with low-bleeding-risk procedures. Postoperative intracranial bleeding is frequently preceded by perioperative heparin bridging.

Dr. Palomäki has given a lecture for Bayer. Dr. Mustonen has given lectures for Orion, Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, Sanofi-Aventis, and Leo Pharma and has been a member of the advisory boards for Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, and Leo Pharma. Dr. Juha Hartikainen has received research grants from the Finnish Foundation for Cardiovascular Research and the European Union Seventh Framework Programme, has given lectures for Cardiome, St. Jude Medical, and Biotronic, and has been member of the advisory boards for AstraZeneca, Amgen, and Bayer. Dr. Kiviniemi has given lectures for Bayer, Boehringer Ingelheim, Medicines Company, AstraZeneca, and St. Jude Medical and received research grants from the Finnish Foundation for Cardiovascular Research and the Finnish Cardiac Society. Dr. Päivi Hartikainen has received honoraria from Genzyme, Novartis, Biogen Idec, and TEVA and given lectures for Sanofi-Aventis. Dr. Luute has received honoraria from Webster-Biosense, Biotronic, Bayer, and St. Jude Medical and given lectures for Bristol-Myers Squibb. Dr. Airaksinen has received research grants from the Finnish Foundation for Cardiovascular Research, has given lectures for Bayer, Cardiome, Novartis, and Boehringer Ingelheim, and has been a member of the advisory boards for Bayer, AstraZeneca, and Boston Scientific.

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Additional Supporting Information may be found in the online version of this article.

Introduction

Treatment with oral anticoagulation (OAC) significantly reduces the risk of stroke and improves survival in patients with atrial fibrillation (AF).¹ However, >10% of patients with AF undergo invasive procedures each year, leading often to OAC interruptions.^{2–5} Although continuous antithrombotic medication predisposes to perioperative bleeding, interruption of OAC may carry an increased risk of thromboembolic complications. On the other hand, the risk of bleeding is increased when heparin bridging is used.^{5–7} There is only limited data concerning the magnitude of postoperative strokes in the total stroke burden of patients with AF. Similarly, the characteristics and perioperative antithrombotic therapy in patients with perioperative stroke or intracranial bleed remain largely unknown. In this study we identified patients with ischemic stroke or intracranial bleed preceded by an operation or invasive procedure in a large population of patients with a previously diagnosed AF who suffered an ischemic stroke or intracranial bleed from 2003 to 2012.

Methods

The Atrial Fibrillation as a Cause of Stroke and Intracranial Hemorrhage Study (FibStroke; <http://www.ClinicalTrials.gov/NCT02146040>) is part of a larger protocol in progress to assess thrombotic and bleeding complications related to AF in Finland.^{8–11}

The FibStroke registry included all consecutive patients with a previously diagnosed AF who suffered an ischemic stroke or intracranial bleeding during the study period.^{12,13} Data for the study were collected from 2 university hospitals and 2 central hospitals in Finland. The initial screening was conducted by identifying all patients from the hospital discharge records with the following criteria: (1) the patient had been diagnosed with AF or atrial flutter, and (2) the patient had been diagnosed with ischemic stroke, transient ischemic attack (TIA) or intracranial bleed between 2003 and 2012 (in one central hospital from 2006 to 2012). A comprehensive list of the *International Classification of Diseases, Tenth Revision* (ICD-10) codes used for the screening has been published earlier (for the list, see Supporting Information, Methods, in the online version of this article).^{12,13} After the initial screening, all patient files were reviewed individually by the investigators, and all procedures and cardioversions performed during the 30 days preceding the stroke, TIA, or intracranial bleeding were identified. Data were collected in structured electronic case-report forms.

A total of 3632 patients had a history of AF; after the diagnosis of AF, they developed a total of 3252 ischemic strokes and 794 intracranial bleeds during the study period. For this prespecified analysis, we chose the patients in whom an operation or invasive procedure was performed during the 30 days preceding the stroke or intracranial bleed. Two patients developed 2 events after the same procedure; only the first event for both patients was included in the analysis.

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. Informed consent was not required because of

Table 1. Demographics of AF Patients With Postoperative Ischemic Stroke or Intracranial Bleed

	Ischemic Stroke, n = 191	Intracranial Bleed, n = 23	P Value
Female sex	108 (56.5)	6 (26.1)	0.006
Age, y, mean $\pm$ SD	78.0 $\pm$ 9.1	75.9 $\pm$ 8.8	0.29
CHA ₂ DS ₂ -VASc score	4.0 (3.0–5.0)	5.0 (3.0–6.0)	0.55
CHA ₂ DS ₂ -VASc score $\geq$ 2	183 (94.3)	22 (95.7)	0.79
CHADS ₂ score	2.0 (1.0–3.0)	3.0 (1.0–4.0)	0.58
CHADS ₂ score $\geq$ 2	139 (71.6)	16 (69.6)	0.83
HAS-BLED score	2.0 (2.0–3.0)	3.0 (2.0–4.0)	0.009
HAS-BLED score $\geq$ 3	82 (42.9)	16 (69.6)	0.015
HTN	127 (66.5)	16 (69.6)	0.77
DM	40 (20.9)	9 (39.1)	0.05
CAD	72 (37.7)	15 (65.2)	0.011
Previous MI	30 (15.7)	10 (43.5)	0.003
Previous stroke or TIA	47 (24.7)	5 (21.7)	0.75
History of HF	56 (29.3)	7 (30.4)	0.91
Mechanical heart valve	6 (3.1)	1 (4.3)	0.554
Pacemaker	27 (14.1)	6 (26.1)	0.136

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHADS₂, congestive HF, HTN, age $\geq$ 75 y, DM, prior stroke/TIA/TE; CHA₂DS₂-VASc, congestive HF, HTN, age $\geq$ 75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (women); DM, diabetes mellitus; HAS-BLED, HTN, abnormal renal/liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; HF, heart failure; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; MI, myocardial infarction; SD, standard deviation; TE, thromboembolism; TIA, transient ischemic attack.

Nominal variables are reported as n (%) and continuous variables are reported as median (IQR), unless otherwise noted.

Three patients had 2 strokes after 2 different procedures. Characteristics at the time of first event are predicted.

the registry nature of the study. The study conforms to the Declaration of Helsinki.

Diagnosis of AF was confirmed by 12-lead electrocardiogram according to the standard criteria. The diagnoses of stroke and intracranial bleed were confirmed from the patient records, as diagnosed by the treating neurologist. Only strokes and intracranial bleeds considered as definite by the treating physician were included in our study. All patients were imaged by computed tomography or magnetic resonance imaging. Bridging therapy was defined as any dose of low-molecular-weight heparin (LMWH) administered during the interruption of OAC.

Low-bleeding-risk procedures were identified according to previously published expert-opinion review articles.^{14,15}

Statistical Analysis

Continuous variables were reported as mean $\pm$ SD if they were normally distributed and as median (interquartile

range [IQR]) if they were skewed, unless stated otherwise. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between study subgroups were performed with the Mann-Whitney test for continuous and χ^2 test or Fisher exact test, as appropriate, for categorical variables. All tests were 2-sided, and statistical significance was set at 5%. Statistical analysis was performed using SPSS Statistics software, version 22.0 (IBM Corp., Armonk, NY).

Results

We identified a total of 194 ischemic strokes that developed within 30 days after an operation or an invasive procedure, accounting for 6.0% of the 3252 ischemic strokes that occurred during the study period. Three patients developed 2 ischemic strokes after 2 separate procedures, which were 2 years, 4 years, and 10 months apart, respectively. The delays from the procedure to the event are depicted in the Figure 1. The median time from the procedure to stroke was 4 days (IQR, 1–12 days). Sixty-five percent of the strokes occurred during the first week after the procedure, and 81% occurred during the first 2 weeks.

Characteristics of the patients who developed an ischemic stroke after operation or invasive procedure are depicted in Table 1. Most patients (94.3%) had an increased estimated risk of AF-related thromboembolism, characterized by CHA₂DS₂-VASC (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/TIA, vascular disease, age 65–74 years, sex category [women]) score ≥ 2 .

Characteristics of the operations and invasive procedures preceding the stroke are depicted in Tables 2 and 3. The majority (62%) of the procedures were elective, and 69% of the patients were on OAC prior to procedure. Oral anticoagulation was interrupted in 108 (81%) of the procedures, and LMWH bridging therapy was used in 30 (28%) of the interruptions.

Of all the procedures leading to ischemic stroke, 82 (42.3%) were classified as low-bleeding-risk procedures. Of these patients, 59 (72.0%) were using OAC, which was interrupted in 50 (84.7%) patients. Many of the endoscopies were performed because of anemia or bleeding. If endoscopies were excluded, 61/168 (36.3%) of the operations were classified as low bleeding risk. (For a list of the low-bleeding-risk procedures, see Supporting Information, Table, in the online version of this article.)

Of the 794 intracranial bleeds, 23 (2.9%) were preceded by an operation or invasive procedure. The median delay from the procedure to intracranial bleed was 4 days (IQR, 2–21 days). Patients who developed an intracranial bleed had a higher HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding, labile international normalized ratio, elderly age, drugs or alcohol) score and more often had a history of diabetes mellitus, coronary artery disease, and previous myocardial infarction (Table 1). The procedures were more often urgent than the procedures preceding ischemic strokes, and use of antiplatelet agents was significantly more common among patients who developed an intracranial bleed after the procedure (Table 2). Sixteen (69.6%) patients were on OAC prior to the procedure, and it was interrupted in 11 (68.8%) patients, whereas

Table 2. Perioperative Characteristics of Patients With Postoperative Strokes and Intracranial Bleeds

	Ischemic Stroke, n = 194	Intracranial Bleed, n = 23	P Value
Urgent/emergency procedure	74 (38.1)	16 (69.6)	0.004
OAC prior to procedure	133 (68.6)	16 (69.6)	0.92
Warfarin	130/133 (97.8)	16 (100)	
Dabigatran	3/133 (2.2)	0 (0)	
OAC interrupted	108/133 (81.2)	11/16 (68.8)	0.24
LMWH bridging	30/108 (27.8)	6/11 (54.5)	0.066
Any periprocedural LMWH (regardless of previous anticoagulation)	64/194 (33.0)	11/23 (47.8)	0.157
Antiplatelet drug (ASA or clopidogrel)	55 (28.4)	12 (52.2)	0.019
Antiplatelet with anticoagulation at the time of stroke or bleed	33 (17.1)	10 (43.5)	0.01
Death within 30 days after event	33 (17.0)	9 (39.1)	0.011

Abbreviations: ASA, aspirin; LMWH, low-molecular-weight heparin; OAC, oral anticoagulation.
Data are reported as n (%).
Three patients had 2 ischemic strokes after 2 different procedures.

bridging therapy was applied in 6 patients (54.5% of interruptions). Combination of anticoagulation (OAC or LMWH) with an antiplatelet agent was significantly more common in the patients suffering an intracranial bleed than ischemic stroke (43.5% vs 17.0%; $P = 0.01$). Bridging with LMWH was more common in patients with intracranial bleed but failed to reach statistical significance (54.5% vs 33.0%; $P = 0.066$). Intracranial bleeds were significantly more often fatal than ischemic strokes (39.1% vs 17.0%; $P = 0.011$). The characteristics and perioperative anticoagulation of the procedures preceding intracranial bleeds are depicted in Table 4.

Discussion

This study showed that an invasive procedure or operation preceded 6% of ischemic strokes and 2.9% of intracranial bleeds in patients with previously diagnosed AF. Importantly, strokes were often preceded by interruption of OAC due to low-bleeding-risk operations or procedures. Bridging therapy with LMWH was used in more than half of the operations leading to intracranial bleeding. The median time from operation to an ischemic stroke or intracranial bleed was 4 days.

There are only limited data concerning optimal perioperative management of antithrombotic treatments in patients with AF and the current recommendations are based mainly on experts' opinions and consensus. In a meta-analysis, heparin bridging was associated with an increased risk for bleeding, whereas no difference in the rate of thromboembolic

Table 3. Perioperative Anticoagulation in 194 Procedures Preceding an Ischemic Stroke in Patients With a Previously Diagnosed AF

Procedure	N	OAC Preoperatively	OAC Interrupted	LMWH Bridging	Low Bleeding Risk
Endoscopy	26	16 (61.5)	15 (93.8)	3 (20.0)	21 (80.8)
Coronary angiography with/without PCI	23	9 (39.1)	2 (22.2)	1 (50.0)	0 (0)
GI surgery	22	20 (90.9)	18 (90.0)	7 (38.9)	10 (45.5)
Orthopedic/trauma surgery	20	12 (60.0)	11 (91.7)	6 (54.5)	8 (40.0)
Vascular surgery	16	11 (68.8)	9 (81.8)	6 (66.7)	0 (0)
Plastic/general surgery	15	12 (80.0)	10 (83.3)	2 (20.0)	9 (60.0)
Peripheral angiography with/without PTA	14	11 (78.6)	10 (90.9)	3 (30.0)	12 (85.7)
Urologic surgery	12	10 (83.3)	10 (100)	0 (0)	0 (0)
Pacemaker implantation	11	8 (72.7)	5 (62.5)	1 (20.0)	11 (100)
CABG/heart valve surgery	9	3 (33.3)	1 (33.3)	0 (0)	0 (0)
Ophthalmologic surgery	8	7 (87.5)	5 (71.4)	0 (0)	8 (100.0)
Head and neck surgery	4	3 (75.0)	2 (66.7)	0 (0)	0 (0)
Thoracocentesis	4	4 (100)	3 (75.0)	1 (33.3)	0 (0)
Gynecologic surgery	3	2 (66.7)	2 (100)	0 (0)	1 (33.3)
Neurosurgery	3	2 (66.7)	2 (100)	0 (0)	0 (0)
Dental procedure	2	2 (100)	2 (100)	0 (0)	2 (100.0)
AF ablation	1	1 (100)	1 (100)	0 (0)	0 (0)
Paracentesis	1	0 (0)	0 (0)	0 (0)	0 (0)
Total	194	133 (68.6)	108/133 (81.2)	30/108 (27.8)	82 (42.3)

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; GI, gastrointestinal; LMWH, low-molecular-weight heparin; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty.
Data are reported as n (%).

events could be observed.⁶ In the prospective registry study Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), bridging was also associated with a higher risk of bleeding and adverse events, without any benefit regarding thromboembolic complications.⁵ The most convincing data of the lack of benefit from bridging therapy in patients with AF was presented in the randomized Effectiveness of Bridging Anticoagulation for Surgery (BRIDGE) trial, where no benefit could be observed in the patients randomized to LMWH, although the risk of bleeding was markedly increased.⁷ Thus, it seems that routine use of bridging therapy with LMWH is not the optimal solution for anticoagulation during the perioperative period.

There is increasing evidence to support the safety of uninterrupted OAC during many cardiologic procedures when compared with heparin bridging. The uninterrupted OAC approach seems to be equally safe or even superior to bridging therapy in pacemaker implantation,^{10,16} coronary angiography, percutaneous coronary intervention,^{17–19} and coronary bypass operations.⁹ For example, in the randomized trial on pacemaker implantations, the risk for device-pocket hematoma was 16.0% in patients receiving heparin bridging compared with 3.5% in patients continuing

warfarin, with no difference in the thromboembolic or surgical complications.¹⁶

It is worth noting that certain procedures carry such a low risk for major bleeding that it is generally recommended to proceed without interrupting OAC. These procedures include most dental procedures and simple dental extractions²⁰; diagnostic upper or lower gastrointestinal endoscopy, including biopsy²¹; most eye surgery (including cataract surgery)²²; and most cutaneous procedures. In our study, we observed that OAC was interrupted in the great majority of procedures leading to ischemic stroke, including endoscopies, plastic/general surgery, pacemaker implantation, and ophthalmologic surgery, even in patients with high CHA₂DS₂-VASc score. Although the need for OAC interruption must always be decided by the operator according to the clinical judgment, it is likely that many of these procedures could have been performed safely with uninterrupted OAC. In addition, the uninterrupted approach eliminates the extra costs and bleeding risks associated with bridging therapy. Endoscopies were preceded by a seemingly high rate of OAC discontinuation, but many of these procedures were done because of bleeding or anemia.

Table 4. Perioperative Anticoagulation in 23 Procedures Preceding an Intracranial Bleed in Patients With a Previously Diagnosed AF

Procedure	N	OAC Preoperatively	OAC Interrupted	LMWH Bridging
Coronary angiography with/without PCI	5	4 (80.0)	1 (25.0)	1 (100.0)
Peripheral angiography with/without PTA	5	2 (40.0)	2 (100)	0 (0)
Pacemaker implantation	3	3 (100)	2 (66.7)	1 (50.0)
Endoscopy	3	2 (66.7)	2 (100)	1 (50.0)
Urologic surgery	2	2 (100)	1 (50.0)	0 (0)
Plastic/general surgery	2	0 (0)	0 (0)	0 (0)
Vascular surgery	1	1 (100)	1 (100)	1 (100)
Orthopedic/trauma surgery	1	1 (100)	1 (100)	1 (100)
Thoracocentesis	1	1 (100)	1 (100)	1 (100)

Abbreviations: AF, atrial fibrillation; LMWH, low-molecular-weight heparin; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty.
Data are reported as n (%).

Figure 1. Timing of postoperative strokes and intracranial bleeds in patients with previously diagnosed AF. Abbreviations: AF, atrial fibrillation.

The mechanisms of postoperative stroke are likely multifactorial. Common reasons include OAC discontinuation prior to operation. Moreover, any surgery activates hemostatic cascade, and vitamin K antagonist re-initiation also induces a transient prothrombotic state. It is also possible that perioperative stress may induce paroxysmal AF. Irrespective of the exact mechanism, it seems that optimization of anticoagulation could improve the safety of invasive procedures in patients with AF. In case of procedures with low bleeding risk, the uninterrupted approach has been shown to be safe. In patients with high bleeding risk and interrupted OAC, there are no data to support any benefit of heparin bridging.

Study Limitations

The retrospective design of the study carries all the inherent limitations of an observational study, including individual risk-based decision-making in treatment choices. There was a wide variation of dosing and timing of bridging therapy, which reflects the paucity of solid data to support any specific

approach to perioperative anticoagulation. The strengths of the study include the identification of all consecutive stroke and TIA patients with a diagnosis of AF from reliable hospital discharge records and the thorough individual case-by-case review of the electronic patient charts. Thus, we believe that our data present a comprehensive real-world view of postoperative strokes in patients with AF.

Conclusion

Strokes in patients with AF who are undergoing operation or invasive procedures were often preceded by interrupted OAC. A significant proportion were low-bleeding-risk procedures, and interruption of OAC was common also in these procedures. Identifying the procedures that can be safely performed with uninterrupted OAC could reduce the risk of postoperative strokes. Heparin bridging and antiplatelet therapy were common in patients with postoperative intracranial bleed, and avoiding unnecessary use of LMWH in this setting might improve the safety of invasive procedures in patients with AF.

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