ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

ABSTRACT

BACKGROUND

It is uncertain whether bridging anticoagulation is necessary for patients with atrial fibrillation who need an interruption in warfarin treatment for an elective operation or other elective invasive procedure. We hypothesized that forgoing bridging anticoagulation would be noninferior to bridging with low-molecular-weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with respect to major bleeding.

METHODS

We performed a randomized, double-blind, placebo-controlled trial in which, after perioperative interruption of warfarin therapy, patients were randomly assigned to receive bridging anticoagulation therapy with low-molecular-weight heparin (100 IU of dalteparin per kilogram of body weight) or matching placebo administered subcutaneously twice daily, from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure. Follow-up of patients continued for 30 days after the procedure. The primary outcomes were arterial thromboembolism (stroke, systemic embolism, or transient ischemic attack) and major bleeding.

RESULTS

In total, 1884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (risk difference, 0.1 percentage points; 95% confidence interval [CI], −0.6 to 0.8; P=0.01 for noninferiority). The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005 for superiority).

CONCLUSIONS

In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health; BRIDGE ClinicalTrials.gov number, NCT00786474.)

From St. Joseph's Healthcare Hamilton (J.D.D.) and the Department of Medicine (J.D.D.) and Hamilton Health Science Center (S.S., A.G.G.T.), McMaster University, Hamilton, ON, Canada; Hofstra North Shore–Long Island Jewish School of Medicine, Manhasset (A.C.S.), and Mount Sinai Medical Center, New York (A.S.D.) — both in New York; Hurley Medical Center, Flint, MI (S.K.); University of Cincinnati College of Medicine, Cincinnati (R.C.B.); NorthShore University HealthSystem, Evanston (J.A.C.), and Rush University Medical Center, Chicago (A.K.J.) — both in Illinois; University of Washington Medical Center, Seattle (D.A.G.); Veterans Affairs Loma Linda Healthcare System, Loma Linda, CA (A.J.); and Duke Clinical Research Institute (D.F.K., V.H.) and Department of Medicine (T.L.O.), Duke University Medical Center, Durham, NC. Address reprint requests to Dr. Ortel at Duke University Medical Center, Box 3422, Durham, NC, 27710, or at thomas.ortel@duke.edu.

*A complete list of investigators in the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) study is provided in the Supplementary Appendix, available at NEJM.org.

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For patients with atrial fibrillation who are receiving warfarin and require an elective operation or other elective invasive procedure, the need for bridging anticoagulation during perioperative interruption of warfarin treatment has long been uncertain.[1-3] Each year, this common clinical scenario affects approximately one in six warfarin-treated patients with atrial fibrillation.[4,5] Warfarin treatment is typically stopped 5 days before an elective procedure to allow its anticoagulant effect to wane; it is resumed after the procedure, when hemostasis is secured, at which point 5 to 10 days of treatment is required to attain therapeutic anticoagulation.[6,7] During the interruption of warfarin treatment, bridging anticoagulation therapy, typically with low-molecular-weight heparin, can be given to minimize the time that patients do not have an adequate level of anticoagulation, with the intent of minimizing the risk of perioperative arterial thromboembolism, such as stroke.[6]

Multiple observational studies have assessed the timing and dosing of perioperative bridging with low-molecular-weight heparin.[8-15] However, the fundamental question of whether bridging anticoagulation is necessary during perioperative warfarin interruption has remained unanswered.[16-18] Because of the lack of evidence, practice guidelines have provided weak and inconsistent recommendations regarding the need for bridging anticoagulation.[19-21]

Against this background, the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial was designed to address a simple question: in patients with atrial fibrillation, is heparin bridging needed during interruption of warfarin therapy before and after an operation or other invasive procedure? We hypothesized that forgoing bridging altogether would be noninferior to bridging with low-molecular-weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with regard to the outcome of major bleeding.

Methods

Study Design and Oversight

The BRIDGE trial was a randomized, double-blind, placebo-controlled trial. The protocol (available with the full text of this article at NEJM.org) was designed by the steering committee (see the Supplementary Appendix, available at NEJM.org, for a full list of trial personnel) and approved by the institutional review board at each participating clinical center. The Duke Clinical Research Institute managed the study. The clinical coordinating center was responsible for study coordination, randomization, and distribution of the study drug. The data coordinating center was responsible for maintenance of the study database, data validation, and analyses. Eisai donated the dalteparin, and University of Iowa Pharmaceuticals prepared the matching placebo. Eisai had no role in the design or conduct of the study, the analysis of the data, or the preparation of the manuscript. The steering committee vouches for the completeness and accuracy of the data and analyses and for the fidelity of this report to the trial protocol.

Patients

Patients were eligible to participate in the trial if they were 18 years of age or older; had chronic (permanent or paroxysmal) atrial fibrillation or flutter, confirmed by means of previous electrocardiography or pacemaker interrogation (patients with atrial fibrillation associated with valvular disease, including mitral valve disease, were eligible); had received warfarin therapy for 3 months or longer, with an international normalized ratio (INR) therapeutic range of 2.0 to 3.0; were undergoing an elective operation or other elective invasive procedure that required interruption of warfarin therapy; and had at least one of the following $CHADS_2$ stroke risk factors: congestive heart failure or left ventricular dysfunction, hypertension, age of 75 years or older, diabetes mellitus, or previous ischemic stroke, systemic embolism, or transient ischemic attack. Patients were not eligible if they had one or more of the following: a mechanical heart valve; stroke, systemic embolism, or transient ischemic attack within the previous 12 weeks; major bleeding within the previous 6 weeks; creatinine clearance of less than 30 ml per minute; platelet count of less than 100×10^3 per cubic millimeter; or planned cardiac, intracranial, or intraspinal surgery. A complete list of the trial inclusion and exclusion criteria is provided in the Supplementary Appendix. All participants provided written informed consent.

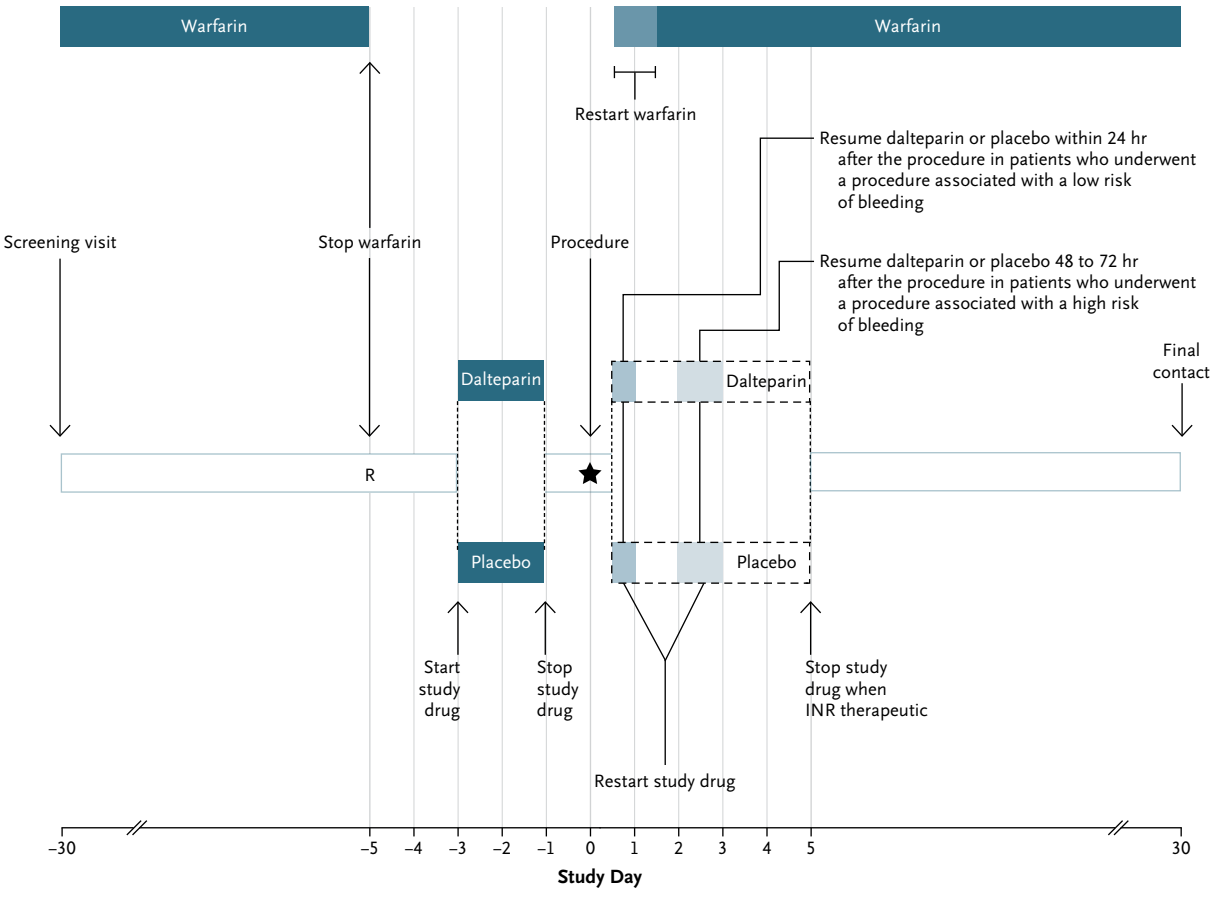

Figure 1. BRIDGE Study Design.

Screening visits occurred between 30 days and 5 days before the planned procedure, and randomization (R) occurred 5 days before the procedure. Warfarin treatment was discontinued 5 days before the procedure, and administration of the study drug was initiated 3 days before the procedure. It was recommended that the international normalized ratio (INR) be measured 1 day before the procedure; if the INR was greater than 1.8, oral vitamin K (1.0 to 2.5 mg) was recommended; if the INR was 1.5 to 1.8, oral vitamin K was optional. If the procedure or surgery was delayed up to 3 days, administration of the study drug was continued until 24 hours before the procedure. Warfarin treatment was restarted on the evening of or the day after the procedure, and the study drug was restarted 12 to 24 hours after a minor (or low-bleeding-risk) procedure and 48 to 72 hours after a major (or high-bleeding-risk) procedure. Administration of the study drug was continued after the procedure until the INR was 2.0 or higher on one occasion. The final patient follow-up occurred 30 days after the procedure. LMWH denotes low-molecular-weight heparin.

PROCEDURES

Patients were randomly assigned to receive bridging anticoagulation therapy with dalteparin sodium (100 IU per kilogram of body weight administered subcutaneously twice daily) or to receive no bridging therapy (i.e., a matching subcutaneous placebo) from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Randomization was stratified according to study center either with the use of an interactive voice-response system with a toll-free telephone number and access codes or through the Internet. The study drugs were provided in identical vials.

The administration of study drug followed a standardized perioperative management protocol (Fig. 1). Warfarin treatment was stopped 5 days before the procedure, and administration of the study drug (dalteparin or matching placebo) was started 3 days before the procedure. The last preprocedure dose of dalteparin or placebo was given in the morning approximately 24 hours

before the procedure.[22,23] Warfarin treatment was restarted on the evening of or the day after the procedure, at the patient's usual dose. Administration of dalteparin or placebo was resumed 12 to 24 hours after a minor (or low-bleeding-risk) procedure and 48 to 72 hours after a major (or high-bleeding-risk) procedure.[8,10] The designation of a procedure as having a low or high bleeding risk was guided by means of a classification scheme (see Table S1 in the Supplementary Appendix), but the final determination of risk was left to the investigator's discretion. The patient continued to take the study drug after the procedure until the INR was 2 or higher on one occasion. Patients had follow-up encounters by telephone weekly, with the final encounter 30 to 37 days after the procedure. Perioperative management of antiplatelet therapy was left to the site investigator's discretion.

STUDY OUTCOMES

All study outcomes were assessed by 37 days after the procedure. The primary efficacy outcome was arterial thromboembolism, including stroke (ischemic or hemorrhagic), transient ischemic attack, and systemic embolism, and the primary safety outcome was major bleeding. The secondary efficacy outcomes were acute myocardial infarction, deep-vein thrombosis, pulmonary embolism, and death, and the secondary safety outcome was minor bleeding. The definitions of the outcomes are provided in the Supplementary Appendix. All study outcomes were independently and blindly adjudicated.

STATISTICAL ANALYSIS

The primary efficacy outcome was arterial thromboembolism at 30 days. The initial sample-size estimates for arterial thromboembolism were based on the results of contemporaneous cohort studies, which suggested that the rate in the bridging group would be 1.0%.[8-10,24,25] We also assumed that the rate in the no-bridging group would be 1.0%. The primary analysis of efficacy was a noninferiority analysis with a one-sided test at the 0.025 level. The noninferiority margin was set at 1.0%. We determined that the hypothesis of inferiority would be rejected if the upper boundary of the 95% confidence interval for the difference in rates would be less than 1.0 percentage point. We prespecified that the 95% confidence interval for the difference in event rates would be calculated with the use of methods based on Barnard's test,[26] because this test permits the calculation of confidence intervals in analyses with small sample sizes. The confidence interval values were calculated with the use of StatXact software, version 9 (Cytel).[27]

The primary safety outcome was major bleeding at 30 days after the procedure. The null hypothesis of no difference in the incidence of major bleeding was tested with a two-sided test at the 0.05 level. The expected bleeding rates were 1.0% in the no-bridging arm and 3.0% in the bridging arm. The P value was calculated with the use of Fisher's mid-P test, as implemented in SAS software, version 9.3 (SAS Institute), and the 95% confidence interval was a likelihood-ratio confidence interval calculated with the same version of SAS.

We calculated that a sample of 1641 patients per group would give the study 80% power to detect the noninferiority of no bridging therapy, assuming a rate of arterial thromboembolism of 1.0% in each group and a noninferiority margin of 1.0%, at a one-sided alpha level of 0.025 for arterial thromboembolism and a two-sided alpha level of 0.05 for bleeding. With a 10% allowance for patients withdrawing from the study, the required sample size was 1813 per group. We calculated that this sample size would also give the study more than 99% power to detect the expected difference in bleeding rates.

After approximately 850 patients had been enrolled, it was clear that the rate of arterial thromboembolism, as assessed by investigators who were unaware of the study-group assignments, was less than 0.5%, and we determined that a revised sample size of 2526 would provide at least 90% power for each primary end point. After 1720 patients were enrolled, the rate of arterial thromboembolism was 0.46%, and the bleeding rate was 2.3% in the entire population. A revised sample size of 1882 was calculated on the basis of the estimate that this would provide nearly 90% power for the two primary end points.

RESULTS

PATIENTS

As shown in Figure 2, we recruited 1884 patients during the period from July 2009 through December 2014 at 108 sites in the United States and Canada; 950 patients were assigned to the placebo

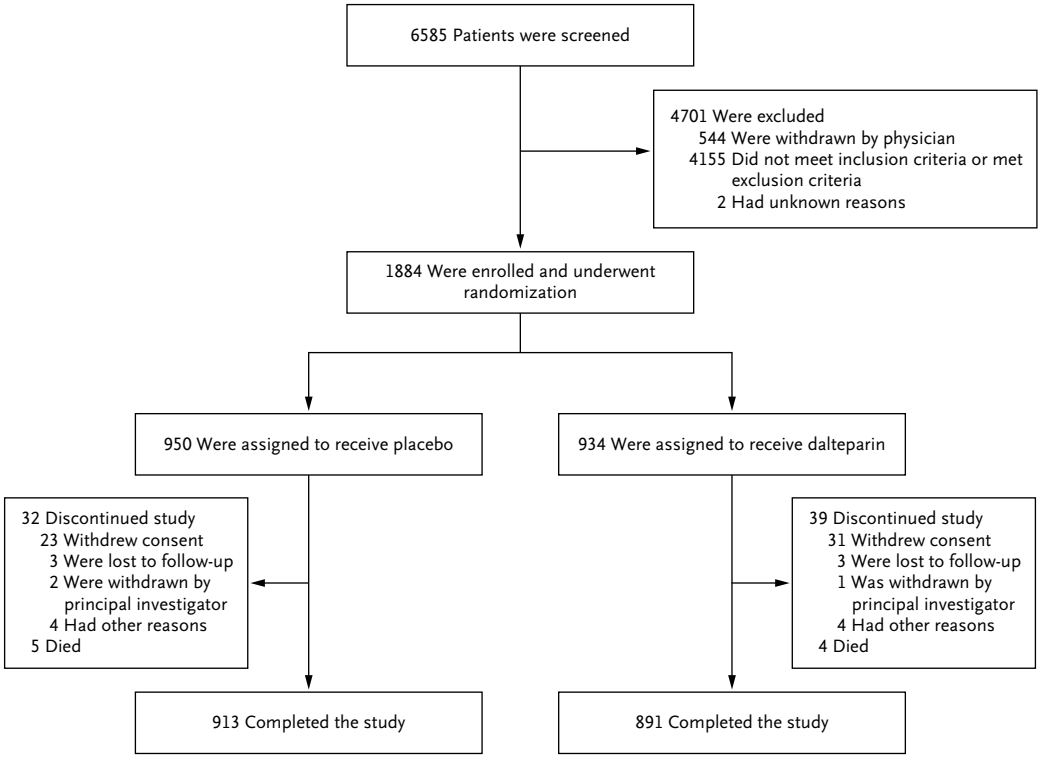

Figure 2. Screening, Randomization, and Follow-up.

(no-bridging) group, and 934 patients were assigned to receive bridging treatment with dalteparin (bridging group). Table 1 shows the characteristics of the patients at baseline. The mean age of the patients was 71.7 years, and 73.4% of patients were male; the mean body weight was 95.8 kg. The mean $CHADS_2$ score ($CHADS_2$ scores range from 1 to 6, with higher scores indicating a greater risk of stroke) was 2.3; 38.3% of patients had a $CHADS_2$ score of 3 or higher. A total of 34.7% of the patients were taking aspirin, and 7.2% were taking another antiplatelet drug.

Of the 1884 patients enrolled in the trial, 1722 actually underwent the anticipated procedure (as-treated group), and 162 did not. The categories and types of operations and procedures that the participants underwent are shown in Table S2 in the Supplementary Appendix. The most common procedures were gastrointestinal (44.0%), cardiothoracic (17.2%), and orthopedic (9.2%). Overall, 89.4% of patients underwent a procedure that was classified as minor (low bleeding risk) according to the prespecified classification; however, 69.1% were treated as having a low bleeding risk by the site investigator.

PERIOPERATIVE ANTICOAGULANT MANAGEMENT

The mean (±SD) number of doses of study drug administered was 5.0±1.1 before the procedure and 16.0±7.9 after the procedure (Table 2). The mean dose of dalteparin administered was 9093±2240 IU subcutaneously twice daily. Adherence to the study-drug protocol, defined as administration of 100% of protocol-specified doses of study drug, was 86.5% before the procedure and 96.5% after the procedure.

STUDY OUTCOMES

Of the 1884 patients enrolled in the trial, 71 discontinued participation and did not provide outcome data; therefore, data from 1813 patients were available for the analysis (Fig. 2). At 30 days after the procedure, the incidence of arterial thromboembolism was 0.4% (four events among 918 patients) in the no-bridging group and 0.3% (three events among 895 patients) in the bridging

Table 1. Baseline Characteristics of the Patients.*

Characteristic	No Bridging (N=950)	Bridging (N=934)
Age — yr	71.8±8.74	71.6±8.88
Male sex — no. (%)	696 (73.3)	686 (73.4)
Race — no. (%)†		
White	860 (90.5)	849 (90.9)
Nonwhite	88 (9.3)	82 (8.8)
Unknown	2 (0.2)	3 (0.3)
Weight — kg	96.2±24.87	95.4±23.50
$CHADS_2$ score‡		
Mean	2.3±1.03	2.4±1.07
Distribution — no. (%)		
0	1 (0.1)	1 (0.1)
1	216 (22.7)	212 (22.7)
2	382 (40.2)	351 (37.6)
3	229 (24.1)	232 (24.8)
4	96 (10.1)	106 (11.3)
5	23 (2.4)	27 (2.9)
6	3 (0.3)	5 (0.5)
CHF or left ventricular dysfunction — no. (%)	289 (30.4)	310 (33.2)
Hypertension — no. (%)	833 (87.7)	806 (86.3)
Diabetes mellitus — no. (%)	390 (41.1)	382 (40.9)
Stroke — no. (%)	79 (8.3)	99 (10.6)
Transient ischemic attack — no. (%)	79 (8.3)	77 (8.2)
Mitral valve disease — no. (%)	165 (17.4)	142 (15.2)
Stenosis	19 (2.0)	10 (1.1)
Regurgitation	142 (14.9)	133 (14.2)
Prolapse	13 (1.4)	5 (0.5)
Myocardial infarction — no. (%)	138 (14.5)	155 (16.6)
Renal disease — no. (%)	108 (11.4)	92 (9.9)
Solid malignant disease — no. (%)	68 (7.2)	52 (5.6)
Laboratory values		
Hemoglobin — g/dl	13.8±1.67	13.8±1.62
Platelet count — thrombocytes/mm^3	209,300±592,900	209,200±580,500
INR	2.4±0.57	2.4±0.57
Serum creatinine — mg/dl	1.1±0.32	1.1±0.32
Creatinine clearance — ml/min	88.1±39.50	87.6±40.14
Medication use — no. (%)		
Aspirin	324 (34.1)	329 (35.2)
Clopidogrel	30 (3.2)	21 (2.2)
Nonsteroidal antiinflammatory drug	34 (3.6)	25 (2.7)
COX-2 inhibitor	8 (0.8)	13 (1.4)

* Plus–minus values are means ±SD. There were no significant differences between the groups ($P<0.05$). CHF denotes congestive heart failure, COX-2 cyclooxygenase type 2, and INR international normalized ratio.
† Race was self-reported. The patients for whom data were unknown are those who chose not to provide information.
‡ $CHADS_2$ is a score used to estimate the risk of stroke in patients with atrial fibrillation. The score ranges from 1 to 6; 1 point each is assigned for congestive heart failure, hypertension, age of 75 years or older, and diabetes mellitus, and 2 points are assigned for stroke or transient ischemic attack.

Table 2. Perioperative Anticoagulant Management.

Variable	No Bridging (N=950)	Bridging (N=934)	P Value
Warfarin treatment			
Preprocedure time not taking warfarin			0.28
No. of patients with data	872	839	
Mean — days	5.2±1.4	5.3±1.8	
Time to first postprocedure warfarin dose			0.40
No. of patients with data	735	696	
Mean — days	1.5±1.3	1.4±1.0	
Low-molecular-weight heparin or placebo			
Preprocedure dose			0.61
No. of patients with data	796	768	
Mean no. of doses	5.0±0.7	5.0±1.4	
Patients in whom the last dose was taken on the morning of the day before the procedure — no./total no. (%)	778/796 (97.7)	734/768 (95.6)	0.02
Time to first postprocedure dose			
Major surgery or procedure (high bleeding risk)			0.74
No. of patients with data	235	223	
Mean — hr	53.3±31.6	51.3±27.9	
Minor surgery or procedure (low bleeding risk)			0.74
No. of patients with data	526	497	
Mean — hr	21.1±2.3	21.0±2.4	
Postprocedure dose			0.47
No. of patients with data	764	721	
Mean no. of doses	15.7±7.4	16.1±8.4	
Aspirin treatment — no./total no. (%)			0.53
Interruption ≥7 days before procedure	92/324 (28.4)	92/329 (28.0)	
Interruption <7 days before procedure	41/324 (12.7)	33/329 (10.0)	
No interruption	191/324 (59.0)	204/329 (62.0)	

group (mean between-group difference, 0.1 percentage points; 95% confidence interval [CI], −0.6 to 0.8; P=0.01 for noninferiority; P=0.73 for superiority) (Table 3). In an as-treated analysis, the rates of arterial thromboembolism were 0.3% (three events among 875 patients) in the no-bridging group and 0.4% (three events among 847 patients) in the bridging group (mean between-group difference, 0.0 percentage points; 95% CI, −0.7 to 0.7; P=0.006 for noninferiority). Patients in whom arterial thromboembolism occurred had a mean $CHADS_2$ score of 2.6 (range, 1 to 4), and five of the seven events occurred after a minor procedure. The median time to an arterial thromboembolism event after the procedure was 19.0 days (interquartile range, 6.0 to 23.0).

Major bleeding occurred in 1.3% of the patients (12 of 918) in the no-bridging group and in 3.2% (29 of 895) in the bridging group, which indicated that no bridging was superior to bridging with regard to major bleeding (relative risk, 0.41; 95% CI, 0.20 to 0.78; P=0.005). None of the instances of major bleeding were fatal. Forgoing bridging was associated with a risk of minor bleeding that was significantly lower than the risk associated with bridging (12.0% vs. 20.9%, P<0.001). The median time to a major bleeding outcome after the procedure was 7.0 days (interquartile range, 4.0 to 18.0).

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

There was no significant difference between the groups in the rates of acute myocardial infarction, deep-vein thrombosis, pulmonary embolism, or death. Information on the causes of death and times to death is provided in Table S3 in the Supplementary Appendix.

DISCUSSION

We found that in patients with atrial fibrillation who require perioperative interruption of warfarin treatment for an elective procedure, a strategy of discontinuing warfarin treatment without the use of bridging anticoagulation was noninferior to the use of bridging anticoagulation for the prevention of arterial thromboembolism; in addition, bridging conferred a risk of major bleeding that was nearly triple the risk associated with no bridging. There was also less minor bleeding without bridging than there was with bridging, and there was no significant difference between the groups with regard to myocardial infarction, venous thromboembolism, or death. Taken together, these findings show that there is a net clinical benefit in favor of a strategy of forgoing bridging, as compared with perioperative bridging with low-molecular-weight heparin.

The findings in our trial are consistent with those from nonrandomized comparisons of these strategies. A meta-analysis of observational studies involving a total of 12,278 patients with atrial fibrillation or mechanical heart valves who received or did not receive bridging with low-molecular-weight heparin showed no significant difference in the rate of arterial thromboembolism (odds ratio with bridging, 0.80; 95% CI, 0.42 to 1.54) but a higher rate of major bleeding (odds ratio, 3.60; 95% CI, 1.52 to 8.50) in association with bridging.[28] In a substudy of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY),[29] in which patients with atrial fibrillation were randomly assigned to receive warfarin or dabigatran in an open-label manner, bridging anticoagulation was associated with a rate of major bleeding that was higher than that associated with no bridging (6.8% vs. 1.6%, P<0.001) among 1424 warfarin-treated patients who had treatment interruption for an elective procedure, and there was no significant effect on arterial thromboembolism (0.5% vs. 0.2%, P=0.32).[30] The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation study (ORBIT-AF), which involved 2200 patients with atrial fibrillation who required an elective procedure, also showed a higher rate of bleeding if bridging anticoagulation therapy was used during perioperative interruption of warfarin treatment.[31]

The rationale for the use of bridging anticoagulation therapy has been anchored on the premise that the associated higher bleeding risk was clinically acceptable because it would be offset by a lower risk of perioperative arterial thromboembolism.[32] The findings from the BRIDGE trial as well as from nonrandomized studies suggest that the perioperative risk of arterial thromboembolism in patients with atrial fibrillation during interruption of warfarin treatment may have been overstated and may not be mitigated by bridging anticoagulation. Indeed, the mechanisms of perioperative arterial thromboembolism may be more closely related to factors such as the type of procedure[33] and to intraoperative alterations in blood pressure.[34] The premise that warfarin interruption leads to rebound hypercoagulability and that the milieu of the procedure confers a prothrombotic state, which in turn leads to arterial thromboembolism, is not supported by the results of this trial.[35-37]

There are potential limitations of the BRIDGE trial. First, although we aimed to recruit a representative sample of patients with atrial fibrillation

for whom bridging anticoagulation is normally considered, certain groups were underrepresented. Few patients had a $CHADS_2$ score of 5 or 6, although the mean score of 2.3 is similar to that among patients with atrial fibrillation who were assessed in recent trials and patient registries, in which the mean scores were between 2.1 and 2.8.[29,38-40] Patients undergoing major surgical procedures associated with high rates of arterial thromboembolism and bleeding (e.g., carotid endarterectomy, major cancer surgery, cardiac surgery, or neurosurgery)[19,33] were not represented in the trial, although the procedures performed were representative of the most common interventions patients undergo during an interruption of therapeutic anticoagulation, the majority of which are low-risk procedures, such as colonoscopy or ambulatory surgery.[4,5,41] In addition, the findings should not be applied to patients with mechanical heart valves, who were specifically not included in the trial.

Second, the overall rate of arterial thromboembolism was lower than expected, which potentially affected the power of the trial to detect a benefit associated with bridging. Although we had expected perioperative arterial thromboembolism rates to be approximately 1.0%,[8,9,12,24] the observed rate (0.4%) is similar to rates in recent studies involving patients who had perioperative interruption of warfarin treatment.[4,5,31,42] In addition, the noninferiority margin we selected turned out to be large in relation to the actual observed event rate; it reflected the original estimate of the event rate as specified in the trial protocol.

Third, the observed rate of major bleeding in the bridging group (3.2%, with no instances of fatal bleeding) may be considered to be modest. However, our bridging protocol was designed to minimize bleeding, and the higher rates of bleeding reported in other studies of bridging anticoagulation probably reflect resumption of bridging therapy too soon after operations with a high bleeding risk[10,43] or a lack of standardized bridging protocols.[28,30]

Fourth, the reduction in the study sample size may raise concerns. This reduction was driven by the lower rate of arterial thromboembolism overall, with the proviso that power was maintained to address the primary study hypotheses. Although extending the trial was considered, this was not done because the added statistical power would have been negligible and because recruitment had been challenging throughout the course of the trial.

Finally, one may contend that the trial findings have diminished relevance because of the decreasing use of warfarin in the treatment of patients with atrial fibrillation, given the availability of the newer direct oral anticoagulants.[6] However, warfarin remains widely used among patients with atrial fibrillation.[44-46] Furthermore, the trial findings may also apply to the newer agents. In the substudy of the RE-LY trial discussed above, dabigatran-treated patients who had treatment interruption for an elective procedure had more major bleeding with bridging therapy than without bridging therapy, and there was no significant effect on arterial thromboembolism.[30]

In conclusion, in the BRIDGE trial, we found that for patients with atrial fibrillation who require temporary interruption of warfarin treatment for an elective operation or other elective invasive procedure, a strategy of forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism. The strategy of forgoing bridging treatment also decreased the risk of major bleeding.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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THE AUTHORS REPLY: Santos-Gallego and Badimon hypothesize that patients who underwent PCI reperfusion within the first 120 minutes after the onset of ischemia might benefit from the protection afforded by cyclosporine. To our knowledge, there is no experimental evidence that cyclosporine might be more effective after a short period of ischemia. In our study, cyclosporine did not salvage myocardial tissue, regardless of the duration of ischemia, including in the 12.5% of patients with less than 2 hours of ischemia. The 87.5% of patients with 2 hours of ischemia or more, in whom larger infarcts developed and who had a worse clinical outcome, would certainly have had the most benefit from any protection against reperfusion injury.

Pottecher et al. suggest that confounders, including preexisting angina, coronary collateral vessels, or diabetes may explain the lack of a protective effect of cyclosporine. Previous phase 2 trials have shown that postconditioning angioplasty reduces infarct size, although some patients might have had preexisting angina.[1,2] A per-protocol analysis showed that exclusion of patients with coronary collateral vessels did not modify the CIRCUS results. Experimental data suggest that hyperglycemic (but not diabetic) animals may be resistant to postconditioning induced by brief episodes of ischemia and reperfusion but not by cyclosporine. Transient hyperglycemia in patients with acute myocardial infarction may be indicative of a sympathetic system activation but not of diabetes. To our knowledge, there is no evidence so far that diabetes might prevent any cyclosporine-induced protection.

Zografos and Katritsis hypothesize that clopidogrel might have interfered with the pharmacokinetic properties of cyclosporine and prevented its protective effect. Only 2.7% of the patients in our trial received clopidogrel, whereas 63.2% received prasugrel and 34.1% received ticagrelor. We have no evidence that clopidogrel had any effect on cardiovascular events.

Bernardi and Di Lisa propose that after its binding to cyclophilin D, cyclosporine delays, but does not fully inhibit, the PTP, which might explain the lack of effect in patients with acute myocardial infarction. However, pharmacologic or genetic inhibition of cyclophilin D is sufficient in most animal models to significantly reduce infarct size.[3] Prolonged administration of cyclosporine may certainly be detrimental after acute myocardial infarction, mainly because it might facilitate adverse left ventricular remodeling.[4] However, a single intravenous injection of cyclosporine was used in this trial, and we did not observe any related increase in left ventricular remodeling. We agree that the results of CIRCUS do not challenge the concept of reperfusion injury.

Nathan Mewton, M.D., Ph.D.
Cyrille Bergerot, M.D.
Michel Ovize, M.D., Ph.D.
Hospices Civils de Lyon
Lyon, France
michel.ovize@chu-lyon.fr

Since publication of their article, the authors report no further potential conflict of interest.

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Bridging Anticoagulation in Patients with Atrial Fibrillation

TO THE EDITOR: Douketis et al. (Aug. 27 issue)[1] report on the results of the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial. They conclude that in patients with atrial fibrillation who required an operation or procedure, a strategy of discontinuing warfarin treatment without

the use of bridging anticoagulation was noninferior to the use of bridging anticoagulation for the prevention of arterial thromboembolism.

However, in the study methods, they did not take into account silent stroke. Silent stroke is defined as the evidence of infarction on brain imaging without a clinical finding of acute neurologic deficit related to that lesion. The prevalence of silent stroke is much higher than the prevalence of stroke with neurologic deficit,[2] especially among patients with atrial fibrillation[3] and those who are undergoing high-risk procedures,[4] and it is associated with long-term complications (e.g., neurocognitive dysfunction and psychiatric disorders).[5]

We think this is an important study that will improve care for selected patients who receive anticoagulation therapy yet need procedures that require temporary discontinuation of this therapy. However, we think there is a need for caution until future studies include an assessment of silent stroke and its effect on function.

Andrea Duca, M.D.
Ospedale San Raffaele
Milan, Italy
duca.andrea@hsr.it

Andy Jagoda, M.D.
Mount Sinai Hospital
New York, NY

Dr. Jagoda reports being a member of Brain Attack Coalition and serving on advisory boards for Pfizer, Boehringer Ingelheim, and AstraZeneca. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The central question about the BRIDGE trial is whether it investigated the right target population of patients who were undergoing the relevant target procedures. First, most of the patients were classified as having a low risk of thromboembolism. The mean $CHADS_2$ score ($CHADS_2$ scores range from 1 to 6, with higher scores indicating a greater risk of stroke) of the patients was 2.3, and patients with high $CHADS_2$ scores (5 or 6) composed only 3% of the study population. Among these latter patients, annual stroke rates range from 12 to 18%.[1] This high risk of stroke probably exceeds the risk of major bleeding; therefore, this group of patients might benefit from bridging therapy.

Second, the majority of the patients underwent procedures such as gastrointestinal endoscopy (including biopsies) that are associated with a low risk of bleeding. There is general consensus that these procedures can be performed while the patient is continuing to receive anticoagulation therapy.[2] Data are lacking from a trial that compares forgoing bridging with bridging with low-molecular-weight heparin in patients who have a moderate-to-high risk of arterial thromboembolism and a $CHADS_2$ score of 5 or 6 and who are undergoing major surgery such as carotid endarterectomy and major surgery for cancer.

Roel Vink, M.D., Ph.D.
Tergooi Hospital
Hilversum, the Netherlands
rovink@tergooi.nl

Maaike Sohne, M.D., Ph.D.
St. Antonius Hospital
Nieuwegein, the Netherlands

Menno V. Huisman, M.D., Ph.D.
Leiden University Medical Center
Leiden, the Netherlands

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the BRIDGE trial, bridging with low-molecular-weight heparin significantly increased the risk of major bleeding without decreasing the risk of thromboembolism among patients with atrial fibrillation who were deemed to require interruption of vitamin K antagonists for invasive procedures. It was surprising that the rate of myocardial infarction was not significantly higher in the bridging group than in the no-bridging group (1.6% vs. 0.8%), although fatal

myocardial infarctions were observed only in the no-bridging group (two of seven patients with myocardial infarction died). It would be useful to know whether these events were due to ischemic imbalance related to major bleeding (myocardial infarction type 2)[1] rather than to thrombotic events.

Temporary discontinuation of vitamin K antagonists and non–vitamin K antagonist oral anticoagulants leads to a similar thromboembolic risk[2,3] and, as with vitamin K antagonists, a higher bleeding risk occurs with bridging during discontinuation of non–vitamin K antagonist oral anticoagulant therapy.[2] Because of the pharmacologic properties of non–vitamin K antagonist oral anticoagulants, caution is needed in applying the results of the BRIDGE trial to patients with atrial fibrillation who receive these agents. The usefulness of low-molecular-weight heparin may be limited to patients with immobility who require early postoperative venous thromboprophylactic anticoagulation, with deferred resumption of full-dose anticoagulation.[4] To our knowledge, the use of non–vitamin K antagonist oral anticoagulants at a reduced or thromboprophylactic dose in patients with atrial fibrillation has not yet been studied.[4]

Daniel Caldeira, M.D.
Joao Costa, M.D., Ph.D.
University of Lisbon
Lisbon, Portugal
dgcaldeira@hotmail.com
Joaquim J. Ferreira, M.D., Ph.D.
Instituto de Medicina Molecular
Lisbon, Portugal

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We think that the study reported by Douketis et al. is highly relevant, since every year, nearly 250,000 North Americans require interruption of an oral anticoagulant for invasive procedures.[1] The question of "to bridge or not to bridge" poses a conundrum for many providers.

There are two issues that we think, if expanded on, would allow better applicability of the findings of the trial. First, the authors do not provide specific reasons why 544 patients were withdrawn from enrollment by their physicians. Since clinicians need to use their judgment in weighing the risks and benefits of anticoagulant bridging, further information about patients who were deemed to be too high risk for study inclusion would be useful.

Second, it would be helpful to evaluate the association between bleeding prediction formulas (e.g., the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly [>65 years], Drugs/Alcohol Concomitantly [HAS-BLED] score) and the risk of periprocedural bleeding in both trial groups, since this information may help determine whether these scores predict which patients may benefit from a specific strategy. Although this study is timely, we think that the additional information we suggest would help providers use a more targeted, patient-specific approach in clinical practice.

Boris Arbit, M.D.
Jennifer Padwal, B.S.
Jonathan Hsu, M.D.
University of California, San Diego
San Diego, CA
jonathan.hsu@ucsd.edu

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1513255

TO THE EDITOR: I would like to call attention to one issue of concern in the article by Douketis et al. As stated in the Discussion section, choosing a noninferiority margin of 1.0%, not depending on the actual rate of thromboembolic events (absolute risk), increases the relative risk that is considered acceptable if the actual event rate is lower than expected.

If, as planned in the protocol, the rate of thromboembolic events had been 1.0% in the

bridging group, the relative risk that would be considered acceptable for noninferiority would have been 2.0 (calculated as the sum of 1.0% plus 1.0% divided by 1.0%). Doubling the risk would have been considered an acceptable increase in the risk of thromboembolic events in the no-bridging group.

However, since the actual risk in the bridging group is only 0.3%, the relative risk considered to be acceptable is 4.3 (the sum of 1.0% plus 0.3% divided by 0.3%). The acceptable risk with respect to the rate of thromboembolic events is thus increased by a factor of 4. I am not sure this risk should be considered to be acceptable. In practice, I think that patients for whom a no-bridging strategy will be proposed should be told that the risk of thromboembolic events will probably not be increased by more than a factor of 4.

Alexis Clapin, M.D.
11 rue Treilhard
Paris, France
etudesetbiasis@gmail.com

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Duca and Jagoda infer that detection of silent stroke would have been an important outcome to measure. This would have necessitated routine imaging to detect subclinical events, adding cost and complexity to the intentionally simple study design. Moreover, data are lacking on the incidence and clinical significance of perioperative silent stroke among patients who are undergoing types of surgery that are associated with an increased risk of stroke.[1]

Vink and colleagues question whether the findings of the BRIDGE trial are applicable to patients who have atrial fibrillation and a $CHADS_2$ score of 5 or 6 and those undergoing high-risk operations. Patients with a $CHADS_2$ score of 5 or 6 constituted 3% of the study population, but such patients are infrequently observed in clinical practice. The types of operations or procedures observed in our trial reflected those described in other studies involving patients who were assessed for bridging.[2] Overall, we interpret the results as being applicable to most patients with atrial fibrillation who are assessed for periprocedural management of anticoagulant therapy.

With regard to the comments of Caldeira et al.: because of the small number of events, we did not assess determinants that might explain the higher number of myocardial infarctions in the bridging group than in the no-bridging group. We agree that caution is needed when extrapolating the findings of our trial to patients who require interruption of a direct oral anticoagulant for an operation or a procedure.

Arbit and colleagues raise concern that 544 screened patients were deemed ineligible by their physicians. However, this number constituted only 12% of patients who were excluded for reasons other than that they might have been deemed to be too high risk to participate in the trial. A study is under way to assess predictors of perioperative bleeding in our trial and the usefulness of bleeding prediction scores, including HAS-BLED.[3]

In reply to Clapin: the use of a relative-risk measure for rare events is potentially problematic.[4] The BRIDGE trial was designed so that there was not a large difference between the rates of thromboembolic events in the no-bridging group and the bridging group. A consensus determination by clinicians was that an absolute difference of 1.0% should be ruled out to ensure that result. This was part of the original trial protocol, but it was not incorporated into the informed-consent documents. The BRIDGE steering committee was aware of the implications of the noninferiority margin on the observed lower-than-expected rate of thromboembolism but determined that it was acceptable, given the low absolute event rate and the need to adhere to the prespecified analysis plan.

James D. Douketis, M.D.
McMaster University
Hamilton, ON, Canada

Vic Hasselblad, Ph.D.
Duke Clinical Research Institute
Durham, NC

Thomas L. Ortel, M.D., Ph.D.
Duke University Medical Center
Durham, NC
thomas.ortel@duke.edu

Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1513255

Cannabinoids in the Treatment of Epilepsy

TO THE EDITOR: The need for effective antiseizure drugs in addition to available compounds is obvious. The review article by Friedman and Devinsky (Sept. 10 issue)[1] highlights experimental data that suggest antiseizure effects of cannabinoids. However, the overview of studies indicating that cannabinoids can also provoke seizures seems incomplete, since studies examining the effects of recreational use of cannabis and other studies suggest serious adverse effects, including clinically significant drug–drug interactions, in patients who have epilepsy with or without underlying conditions.[2-5]

I agree that data are lacking from well-controlled clinical trials on the antiseizure properties of cannabinoids. However, it is well documented that cannabinoids can also provoke seizures, depending on the content of the cannabidiol and Δ^9-tetrahydrocannabinol (Δ^9-THC), the ratio of these two agents in the products used, and the underlying conditions in the patient. Thus, the authors' suggestion regarding relaxation of the regulatory status of cannabis-derived drugs seems less applicable to the treatment of epilepsy than to the treatment of other conditions in which the therapeutic application of cannabinoids has been considered. Trials should be performed cautiously, with carefully planned safety monitoring and early interim analyses by independent boards, in order to not overlook subgroups of patients who may have an undesirable increase in epileptic activity.

Joep Killestein, M.D., Ph.D.
VU University Medical Center
Amsterdam, the Netherlands
j.killestein@vumc.nl

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We agree with the assessment by Killestein. Studies showing that Δ^9-THC or synthetic cannabinoid agonists can provoke or exacerbate seizures or interact with other drugs suggest that caution should be used when studying and administering medications containing these compounds. In our article, we noted anecdotal reports of seizures that were provoked by cannabis use,[1] and we noted that cannabidiol can increase the levels of the N-desmethyl metabolite of clobazam and increase the antiseizure and toxic effects of this drug.[2]

However, although some currently marketed antiseizure medications are associated with clinically significant drug–drug interactions or may rarely provoke seizures in some patients, these side effects do not outweigh the overall benefit of the drugs. At this time, we think that the weight of the limited evidence suggests that there may be a benefit associated with some cannabinoids in the treatment of epilepsy and little solid scientific evidence that cannabis that contains various mixtures of cannabidiol and Δ^9-THC can provoke seizures. Therefore, we support the relaxation of restrictions to allow further scientific study. We do not yet know the overall risks and benefits of cannabinoids in the treatment of epilepsy, but we hope that randomized, controlled studies will answer these questions soon.

Daniel Friedman, M.D.
Orrin Devinsky, M.D.
New York University Langone School of Medicine
New York, NY
daniel.friedman@nyumc.org

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