Original Investigation

Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures

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IMPORTANCE The risk of bleeding and recurrent venous thromboembolism (VTE) among patients receiving long-term warfarin sodium therapy for secondary VTE prevention who require temporary interruption of anticoagulant therapy for surgery or invasive diagnostic procedures has not been adequately described.

OBJECTIVE To describe the rates of clinically relevant bleeding and recurrent VTE among patients in whom warfarin therapy is interrupted for invasive procedures and compare these rates among patients who did and did not receive bridge therapy.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted at Kaiser Permanente Colorado, an integrated health care delivery system. Patients in whom warfarin therapy was interrupted for invasive diagnostic or surgical procedures between January 1, 2006, and March 31, 2012, were identified via queries of administrative data sets. A total of 1812 procedures in 1178 patients met inclusion criteria. Data on outcomes and exposures were collected between June 1, 2005, and April 30, 2012.

EXPOSURES Use of bridge therapy vs no bridge therapy during warfarin interruption.

MAIN OUTCOMES AND MEASURES Thirty-day clinically relevant bleeding, recurrent VTE, and all-cause mortality. Outcomes were verified via manual review of medical records.

RESULTS Among the 1178 patients, the mean (SD) age was 66.1 (12.7) years, 830 procedures (45.8%) were in men, and the most common indication for warfarin therapy was deep vein thrombosis (56.3%). Most patients were considered to be at low risk for VTE recurrence at the time of warfarin interruption (1431 procedures [79.0%]) according to the consensus guidelines of the American College of Chest Physicians. Clinically relevant bleeding within 30 days after the procedure in the bridge therapy and non–bridge therapy groups occurred in 15 patients (2.7%) and 2 patients (0.2%), respectively (hazard ratio, 17.2; 95% CI, 3.9-75.1). There was no significant difference in the rate of recurrent VTE between the bridge and non–bridge therapy groups (0 vs 3; $P = .56$). No deaths occurred in either group.

CONCLUSIONS AND RELEVANCE Bridge therapy was associated with an increased risk of bleeding during warfarin therapy interruption for invasive procedures in patients receiving treatment for a history of VTE and is likely unnecessary for most of these patients. Further research is needed to identify patient- and procedure-related characteristics associated with a high risk of perioperative VTE recurrence during warfarin therapy interruption.

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Invited Commentary

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Patients who are receiving warfarin sodium for the secondary prevention of venous thromboembolism (VTE) and require interruption of anticoagulant therapy for an invasive diagnostic or surgical procedure present a common dilemma for clinicians. Optimally, the balance between procedure-related bleeding and recurrent VTE should be assessed. If the risk of bleeding is low, warfarin use may be continued throughout the procedure.[1] Warfarin interruption is required for several days before the procedure when the risk of bleeding is high or moderate. When paired with the delayed onset of anticoagulation after resumption of treatment with warfarin, the risk of recurrent VTE in the perioperative period may increase.

The use of a short-acting anticoagulant, typically low-molecular-weight heparin, during the periprocedural period has been suggested[1] for patients at high risk of VTE recurrence to minimize this risk. This strategy, commonly referred to as *bridge therapy*, reduces exposure to subtherapeutic anticoagulation for 3 or 4 days during warfarin therapy withdrawal before the procedure and 5 or more days after the procedure during warfarin therapy reinitiation. Risk estimates for bleeding and VTE associated with bridge therapy in real-world patients with VTE who are receiving anticoagulant therapy are lacking.[2] Cohort studies[1,3-7] have largely focused on patients at risk for stroke due to atrial fibrillation or thrombosis related to mechanical heart valves.

Deciding which patients with VTE should receive bridge therapy depends primarily on the estimated risk of recurrent VTE in the periprocedural period. The *Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition* (*AT9*) guidelines[2] classify periprocedural risk as high (>10% per year), moderate (5%-10% per year), and low (<5% per year) depending on the annual risk of recurrence without anticoagulant therapy. However, this risk stratification scheme is based on indirect evidence from studies outside of the perioperative setting and receives a 2C grade (ie, weak recommendation with low quality evidence from observational studies or case series).

Providing real-world rates of bleeding and VTE in this population has the potential to clarify risk-benefit analysis of bridge therapy and identify patients in whom warfarin therapy may be safely interrupted without bridge therapy. The aim of the present study was to provide and compare real-world rates of clinically relevant bleeding and recurrent VTE among patients receiving warfarin for a prior VTE in whom treatment was interrupted for invasive procedures and either did or did not receive bridge therapy.

Methods

Study Design and Setting

This retrospective cohort study was conducted at Kaiser Permanente Colorado (KPCO), an integrated health care delivery system providing care to more than 540 000 members. Each year approximately 2400 procedures requiring coordination of periprocedural warfarin therapy are performed at KPCO. Anticoagulation services at KPCO are provided by the centralized, telephone-based Clinical Pharmacy Anticoagulation and Anemia Service (CPAAS).[8] Periprocedural warfarin therapy plans are developed by CPAAS pharmacists using a collaborative drug therapy management guideline and approved by referring physicians. Detailed information regarding each periprocedural plan is recorded in an electronic patient tracking tool (DAWN AC, 4S Information Systems, Ltd) and the electronic medical record. All study activities were approved by the KPCO institutional review board. Because of the retrospective, data-only nature of the study and with approval from the KPCO institutional review board, patient informed consent was not obtained.

Table 1. Recurrent Venous Thromboembolism Risk Stratification

AT9 Risk Category	Criteria
High	Acute VTE within past 3 mo; severe thrombophilia (deficiency of protein C, protein S, or antithrombin; antiphospholipid antibody syndrome; or multiple abnormalities)
Medium	Acute VTE within past 3-12 mo; nonsevere thrombophilia (heterozygous factor V Leiden, prothrombin 20210 mutation, increased factor VIII activity); recurrent VTE; or active cancer
Low	Acute VTE >12 mo previously; no other risk factors

Abbreviations: *AT9*, *Antithrombotic Therapy and Prevention of Thrombosis, Ninth Edition*; VTE, venous thromboembolism.

Study Population

This study included consecutive patients who underwent an invasive diagnostic or surgical procedure (index procedure) between January 1, 2006, and March 31, 2012, and who (1) were at least aged 18 years at the time of the index procedure, (2) were monitored by the CPAAS, (3) were receiving warfarin therapy for secondary prevention of VTE (defined as deep vein thrombosis of the upper or lower extremity and/or pulmonary embolism), (4) had an international normalized ratio of 1.5 or lower on the day of or the day before the index procedure, (5) had at least 180 consecutive days of Kaiser Foundation Health Plan membership before the procedure, (6) resumed warfarin therapy within 30 days after the procedure, and (7) did not have another procedure-related interruption of warfarin therapy within 90 days after the index procedure date. Patients with an indication for warfarin other than VTE (eg, atrial fibrillation and mechanical heart valve) were excluded. Patients were stratified (high, moderate, or low) according to their underlying risk for recurrent VTE in accordance with the *AT9* guidelines (**Table 1**).[2]

Study Outcomes

The primary outcome of the study was clinically relevant bleeding (defined as any clinically overt bleeding, regardless of severity, resulting in hospitalization or an emergency department visit or that complicated the procedure) occurring up to 30 days following the index procedure. Secondary outcomes included major bleeding, recurrent VTE, and all-cause mortality occurring up to 30 days following the index procedure. Thirty-day rates were chosen because it has been suggested[9] that this time may best predict procedure-related events. Major bleeding was a subset of the clinically relevant bleeding events that also met the criteria for major bleeding set forth

by the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[10]

Data Collection

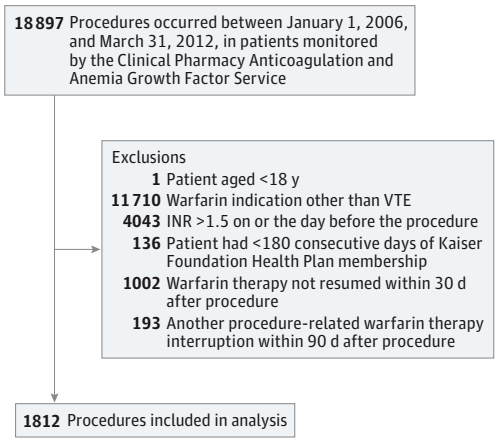
Potential study patients were identified using KPCO electronic administrative data sets supplemented by manual reviews of medical records using a structured data abstraction form. The KPCO membership database was used to confirm health plan membership eligibility and identify deaths during the follow-up period. Information pertaining to the type of invasive procedure necessitating interruption of warfarin therapy (gastrointestinal tract endoscopy; spinal or intracranial; orthopedic; dermatologic; abdominal or thoracic [major and non-major]; urologic; dental; vascular; ears, eyes, nose, and throat; and pacemaker or implantable cardiac defibrillator procedures, as well as other procedure types) was gathered from DAWN AC. Bleeding and recurrent VTE events were identified administratively using predefined *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes and confirmed via manual review of the medical records by 2 study team members (N.P.C. and L.E.D. or E.M.S.) using a standardized abstraction form, with disagreements resolved by a third reviewer (D.M.W.). Recurrent thromboembolism required objective confirmation of new thrombosis or thrombus extension on duplex ultrasonography, ventilation or perfusion scanning, or computed tomographic angiography.

Comorbidities (eg, alcoholism, stroke or systemic embolism, diabetes mellitus, heart failure, hypertension, and renal insufficiency) present in the 180 days before the index procedure were identified administratively using predefined *ICD-9* codes. Patients with cancer were identified administratively from queries of the KPCO Tumor Registry. *Active cancer* was defined as the reception of chemotherapy or other cancer-related treatment (eg, hormonal therapy), cancer-related surgery, or cancer-related radiotherapy during the 180 days before the index procedure. The presence of thrombophilia was identified administratively using DAWN AC and KPCO laboratory records and was verified via manual review of the medical records when necessary. The use of bridge therapy was determined by identifying purchases of parenteral anticoagulants recorded in the KPCO pharmacy database and manual review of periprocedural plans recorded in DAWN AC.

Statistical Analysis

Data on outcomes and exposures were collected between June 1, 2005, and April 30, 2012. All procedures meeting inclusion criteria were included in the analysis, and multiple procedures in the same patient could be included provided that each met the inclusion criteria and was separated from the other procedures by at least 90 days. No formal power calculation was performed because all procedures fitting inclusion and exclusion criteria were analyzed. Patient characteristics were summarized using descriptive statistics. Thirty-day bleeding and thromboembolic rates were calculated by dividing the counts of each event by the total number of included procedures and multiplying by 100. Rates are reported as percentages with 95% CIs. Because multiple procedures were included for some patients, conditional unadjusted logistic analyses and linear regression analyses were used to compare categorical and continuous variables, respectively. Unadjusted Cox proportional hazards regression modeling was used to determine the hazard ratio of 30-day bleeding and its 95% CI. Patients were censored on the date of bleeding or 30 days after their procedure, whichever came first. Because of the low rate of outcome events, adjustment for potential confounders was not possible. Subanalyses were performed by assessing the bleeding outcome using only a patient's first procedure during the study period and between patients who received a therapeutic vs prophylactic bridging dose. Statistical analysis was performed using SAS, version 9.2 (SAS Institute Inc), and Stata, version 9.2 (StataCorp).

Figure. Patient Algorithm



INR indicates international normalized ratio; VTE, venous thromboembolism. Warfarin was given as warfarin sodium.

Results

There were 1812 procedures in 1178 patients who met the inclusion criteria (**Figure**). The mean (SD) age of the overall cohort was 66.1 (12.7) years; 830 procedures (45.8%) were in men; 1021 (56.3%) and 791 (43.7%) were receiving warfarin treatment for deep vein thrombosis (upper or lower extremity) and pulmonary embolism, respectively, and 175 (9.7%) had confirmed thrombophilia (**Table 2**). Warfarin therapy was interrupted most commonly for gastrointestinal tract endoscopic procedures (673 [37.1%]), followed by orthopedic (247 [13.6%]), spinal or intracranial (175 [9.7%]), and nonmajor abdominal or thoracic (155 [8.6%]) procedures. When stratified by the *ATA* guideline for recurrent VTE risk classification, 1431 (79.0%) procedures were in low-risk, 324 (17.9%) in moderate-risk, and 57 (3.1%) in high-risk patients. Bridge therapy was administered in 410 of 1431 (28.7%), 109 of 324 (33.6%), and 36 of 57 (63.2%) procedures performed in low-, moderate-, and high-risk patients, respectively. Of the 555 bridge therapy plans, 401 plans (72.5%) and 154 plans (27.8%) used therapeutic and prophylactic doses, respectively.

Table 2. Patient and Procedure Characteristics by Bridging Status

Characteristic	No. (%) Overall (N = 1812)	Bridge Therapy (n = 555)	No Bridge Therapy (n = 1257)	*P* Value
Patient				
Age, mean (SD), y	66.1 (12.7)	62.5 (13.3)	67.7 (12.1)	<.001
Male sex	830 (45.8)	262 (47.2)	568 (45.2)	.43
Indication				
DVT LE	930 (51.3)	267 (48.1)	663 (52.7)	.15
DVT UE	91 (5.0)	27 (4.9)	64 (5.1)	
PE	791 (43.7)	261 (47.0)	530 (42.2)	
Comorbidity diagnosis				
Hypertension	853 (47.1)	243 (43.8)	610 (48.5)	.06
Diabetes mellitus	305 (16.8)	88 (15.9)	217 (17.3)	.46
Renal insufficiency	192 (10.6)	51 (9.2)	141 (11.2)	.20
Heart failure	16 (0.9)	6 (1.1)	10 (0.8)	.55
Alcoholism	31 (1.7)	9 (1.6)	22 (1.8)	.85
VTE proximity to procedure, mo				
<3	24 (1.3)	18 (3.2)	6 (0.5)	<.001
3-12	51 (2.8)	21 (3.8)	30 (2.4)	.10
>12	1737 (95.9)	516 (93.0)	1221 (97.1)	<.001
Recurrent VTE	195 (10.8)	81 (14.6)	114 (9.1)	<.001
Active cancer	53 (2.9)	19 (3.4)	34 (2.7)	.40
Positive thrombophilia test				
Severe[a]	33 (1.8)	18 (3.2)	15 (1.2)	.003
Nonsevere[b]	142 (7.8)	53 (9.5)	89 (7.1)	.07
Recurrent VTE risk category[c]				
High	57 (3.1)	36 (6.5)	21 (1.7)	<.001
Medium	324 (17.9)	109 (19.6)	215 (17.1)	.22
Low	1431 (79.0)	410 (73.9)	1021 (81.2)	<.001
Procedure				
Type				
Gastrointestinal endoscopy	673 (37.1)	187 (33.7)	486 (38.7)	.04
Orthopedic	247 (13.6)	118 (21.3)	129 (10.3)	<.001
Spinal or intracranial	175 (9.7)	24 (4.3)	151 (12.0)	<.001
Nonmajor abdominal or thoracic	155 (8.6)	81 (14.6)	74 (5.9)	<.001
Dermatologic	111 (6.1)	21 (3.8)	90 (7.2)	.006
Urologic or bladder	102 (5.6)	26 (4.7)	76 (6.1)	.25
Vascular	74 (4.1)	25 (4.5)	49 (3.9)	.55
Dental	61 (3.4)	5 (0.9)	56 (4.5)	<.001
EENT	53 (2.9)	14 (2.5)	39 (3.1)	.50
Major abdominal or thoracic	35 (1.9)	17 (3.1)	18 (1.4)	.02
Pacemaker or ICD	11 (0.6)	4 (0.7)	7 (0.6)	.75
Other	115 (6.4)	33 (5.9)	82 (6.5)	.64

Abbreviations: DVT, deep vein thrombosis; EENT, ears, eyes, nose, and throat; EGD, esophagogastroduodenoscopy; ICD, implanted cardioverter/defibrillator; LE, lower extremity; PE, pulmonary embolism; UE, upper extremity; VTE, venous thromboembolism.

[a] Includes protein C, protein S, or antithrombin deficiency; antiphospholipid antibodies; homozygous factor V Leiden; homozygous prothrombin 20210 mutation; or multiple thrombophilic traits.

[b] Includes heterozygous factor V Leiden or heterozygous prothrombin 20210 mutation.[2]

[c] See Table 1 for risk factors.

Primary Outcome

The 30-day rates of clinically relevant bleeding among the bridge and non-bridge therapy groups were 2.7% (15 events; 95% CI, 1.5%-4.4%) and 0.2% (2 events; 95% CI, 0.02%-0.6%), respectively (hazard ratio, 17.2; 95% CI, 3.9-75.1) (**Table 3**). Subanalysis using only the first procedure for each patient provided similar results (30-day rates of clinically relevant bleeding among the bridge and non-bridge therapy groups were 3.0% and 0.3%, respectively; $P < .001$). There were 9 (2.2%) and 6 (3.9%) 30-day clinically relevant bleeding events among patients who received a therapeutic or prophylactic dose of a bridge anticoagulant, respectively ($P = .28$). Of the 15 bleeding events occurring in the bridge cohort, 9 (52.9%) were procedure complications and 5 (33.3%) were directly related to bridging agent injections (eg, rectus sheath hematoma). Bleeding complications occurred most frequently in pacemaker or implantable cardiac defibrillator (n = 11), urologic (n = 102), and vascular (n = 74) procedures (1 [9.1%], 3 [2.9%], and 2 [2.7%] complications, respectively).

Secondary Outcomes

Recurrent VTE complication rates were not significantly different between bridging status groups or across *AT9* guide-

Table 3. Outcomes at 30 Days Overall and by Bridging Status and VTE Risk Category[a]

Outcome	No./Total No. (%)			*P* Value
	Overall (N = 1812)	Bridge Therapy (n = 555)	No Bridge Therapy (n = 1257)	
Clinically Relevant Bleeding				
Risk				
High	3/57 (5.3)	2/36 (5.6)	1/21 (4.8)	.90
Moderate	5/324 (1.5)	5/109 (4.6)	0/215	.004
Low	9/1431 (0.6)	8/410 (2.0)	1/1021 (0.1)	<.001
Overall	17/1812 (0.9)	15/555 (2.7)	2/1257 (0.2)	.01
Recurrent VTE				
Risk				
High	0/57	0/36	0/21	>.99
Moderate	1/324 (0.3)	0/109	1/215 (0.5)	.48
Low	2/1431 (0.1)	0/410	2/1021 (0.2)	.37
Overall	3/1812 (0.2)	0/555	3/1257 (0.2)	.56

Abbreviation: VTE, venous thromboembolism.

[a] Risk categorized as high (>10% per year), moderate (5%-10% per year), and low (<5% per year) depending on the annual risk of recurrence without anticoagulant therapy.

line risk categories (*P* = .56) (Table 3). No recurrent VTE events occurred in high-risk patients. No 30-day deaths occurred in either group. Of the 17 clinically relevant bleeding events in the cohort, 14 met the definition of major bleeding (0.8% of all procedures). Major bleeding occurred in 12 bridge therapy procedures (2.2%) and 2 of the non-bridge therapy procedures (0.2%) (*P* < .001).

Discussion

The use of a bridge agent among patients receiving long-term anticoagulation therapy for a history of VTE was associated with a 17-fold higher risk of bleeding without a significant difference in the rate of recurrent VTE. Bleeding rates in patients in the bridge therapy group who experienced clinically relevant bleeding did not differ significantly between those receiving therapeutic and prophylactic doses of the bridge therapy agent. Bleeding was either directly attributed to the administration of the bridging agent or a complication of the procedure in most cases. Conversely, recurrent VTE events were rare in both the bridge and non-bridge therapy groups, including within the non-bridge therapy high-risk subgroup. Thus, the risk of bleeding associated with bridge therapy appeared to outweigh the potential benefits in our study population. Our results highlight the need for further research to identify patient- or procedure-related characteristics that predict a high risk of VTE recurrence during interruption of warfarin therapy.

The rates of bleeding and recurrent thrombosis observed in our study are similar to those reported elsewhere. A retrospective cohort study[11] compared rates of recurrent VTE and major bleeding during periprocedural management stratified by the acuity of the original VTE event. A higher rate of major bleeding was observed among low-risk bridge therapy compared with nonbridge therapy (2.5% vs 0.9%, respectively) and a low rate of recurrent VTE across all risk groups. A second retrospective cohort study[12] of patients with a history of VTE in whom warfarin therapy was interrupted periprocedurally reported 30-day major bleeding and VTE rates of 1.26% (95% CI, 0.64%-2.47%) and 0.3% (95% CI, 0.1%-1.1%), respectively. Approximately one-fourth (24.6%) of the cohort received bridge therapy, but no significant difference was found in the risk of recurrent VTE between the bridge and nonbridge groups. As a result, the authors concluded that a nonbridged periprocedural approach was promising for patients who were receiving anticoagulant therapy for a history of VTE. Finally, a recent systematic review and meta-analysis[13] analyzed outcomes of periprocedural anticoagulation management in studies in which approximately 22% of the patients were receiving warfarin therapy for a prior VTE. Their analysis reinforces a low overall rate of recurrent thromboembolism among patients with a history of VTE who received bridge therapy compared with those who did not (0.6% vs 0.9%; odds ratio [OR], 0.80; 95% CI, 0.42-1.54). In contrast, use of bridge therapy was associated with an increased risk for major bleeding (OR, 3.60; 95% CI, 1.52-8.50), although the affect was not as pronounced as in our analysis. The authors[13] concluded that bridge therapy may be avoided in patients not deemed to be at high risk for recurrent VTE.

Our results confirm and strengthen the findings of those previous studies and highlight the need for a risk categorization scheme that identifies patients at highest risk for recurrent VTE who may benefit from bridge therapy. In addition, our results suggest that the *AT9* guideline moderate and low recurrent VTE risk categories could be combined since there appears to be little, if any, risk difference between them. It is also noteworthy that most of our bridge cohort was categorized as being at low risk for recurrent VTE. It is possible that other patient- and procedure-specific factors not captured by the *AT9* guideline recommendations influenced the decision to use bridge therapy in such patients, including VTE recurrence during a previous interruption of warfarin therapy, high procedure-related VTE risk (eg, joint replacement surgery), and patient or provider preference.

There are several limitations inherent in our retrospective study design. First, the use of administratively collected data may have resulted in omitted or misclassified procedures and outcomes. We performed manual checks to mitigate this risk and ensure that data were categorized as accu-

rately as possible, but we cannot exclude the possibility that some patients may have received bridge therapy without our knowledge, especially during procedures requiring hospitalization. However, proceduralists approve CPAAS plans for anticoagulation management a priori, thereby limiting the possibility of unknown use of bridge therapy. Second, owing to the overall low event rates, especially among the high-risk subgroup, we were unable to adjust the outcomes for potential confounding. In addition, we identified only a small number of patients at high risk for VTE who did not receive bridge therapy. Most of the patients included in this analysis had received long-term (>12 months) anticoagulation for VTE before the procedure. Most of these patients likely had idiopathic VTE, but we were unable to definitively categorize patients' VTE history according to provoked vs idiopathic status. However, we believe our results offer a unique perspective of real-world outcomes in patients receiving warfarin for secondary VTE prevention, many of whom would have received bridge therapy in other health care systems.

Conclusions

Bridge therapy was associated with an increased risk of bleeding during interruption of warfarin therapy for invasive procedures in patients with a history of VTE and is likely unnecessary for most of these patients. Further research is needed to identify patient- and procedure-related characteristics associated with a high risk of perioperative VTE recurrence during interruption of warfarin therapy.

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Study concept and design: Clark, Witt, Davies, Saito, McCool, Douketis, Delate.
Acquisition, analysis, or interpretation of data: Witt, Davies, Saito, Douketis, Metz, Delate.
Drafting of the manuscript: Clark, Witt, Davies, Saito, Douketis, Metz.
Critical revision of the manuscript for important intellectual content: Clark, Witt, Davies, Saito, McCool, Douketis, Delate.
Statistical analysis: Witt, Saito, Delate.
Administrative, technical, or material support: Metz, Delate.
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Conflict of Interest Disclosures: Dr Douketis reports being a consultant for Boerhinger-Ingelheim and serving as a consultant during 4 advisory board meetings (Astra-Zeneca, Boehringer-Ingelheim, Pfizer, and Sanofi) relating to the development and clinical use of novel, but not approved for clinical use, antiplatelet drugs (ticagrelor) and anticoagulant drugs (apixaban, dabigatran, and semuloparin). No other disclosures were reported.

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