Thrombosis is the leading cause of acute coronary syndromes, stroke, and venous thromboembolism. Accordingly, anticoagulants have been successfully used in each of these settings. Since the discovery of unfractionated heparin in the early 1900s, the number of anticoagulant choices has increased at an accelerating rate. For treatment of acute coronary syndromes, these include low-molecular weight heparins, fondaparinux, as well as direct thrombin inhibitors such as bivalirudin. While warfarin and other vitamin K antagonists have long been the dominant oral anticoagulants, novel oral agents such as dabigatran, rivaroxaban, and apixaban have expanded the number of therapeutic options.

All of these agents have potential pros and cons. For example, unfractionated heparin is relatively inexpensive and easily monitored. However, it may increase bleeding compared with direct thrombin inhibitors such as bivalirudin. Analogously, for patients with atrial fibrillation, warfarin is inexpensive and has a long track record of preventing thromboembolic events; however, it is subject to multiple potential food and drug interactions and requires close monitoring to maintain optimal time in therapeutic range. In contrast, the novel oral anticoagulants have been shown to be noninferior compared with warfarin for stroke prevention in atrial fibrillation, rivaroxaban, and apixaban expanded the number of therapeutic options.

Given the increasing scope of anticoagulant therapy and the introduction of multiple novel agents in recent years with unique efficacy and safety profiles, we have chosen to dedicate this series introduction of multiple novel agents in recent years with unique efficacy and safety profiles, we have chosen to dedicate this series to the topic of therapeutic anticoagulation. We have included articles on topics such as the efficacy, safety, and cost-effectiveness of bivalirudin in acute coronary syndromes, outcomes associated with discontinuation and variable monitoring of vitamin K antagonist therapy, and indirect comparison of the clinical utility and cost-effectiveness of the novel oral anticoagulants.

**Parenteral Anticoagulants**

Intravenous unfractionated heparin (UFH) and bivalirudin are 2 of the most commonly used parenteral anticoagulants in patients with acute coronary syndromes who undergo percutaneous coronary intervention. UFH was discovered more than 90 years ago and is one of the oldest drugs still in widespread clinical use. It has been shown to improve outcomes in patients with venous thromboembolism and acute coronary syndromes. To its advantage, UFH is inexpensive and can be rapidly reversed using intravenous protamine sulfate. However, UFH may have variable pharmacokinetics, as it requires a cofactor for its anticoagulant activity, is heterogeneous in molecular size, and has variable affinity for endothelial cells, macrophages, and multiple plasma proteins; this variability may contribute to excessive anticoagulation and major bleeding.

In contrast to indirect anticoagulants such as UFH, direct thrombin inhibitors such as hirudin and bivalirudin directly bind to thrombin and block its enzymatic activity. Hirudin was the first direct thrombin inhibitor to come into common use after its isolation from the salivary glands of the medicinal leech, Hirudo medicinalis. However, concerns about its immunogenicity led to the development of additional direct thrombin inhibitors, including bivalirudin. On the basis of landmark clinical trials in patients with acute coronary syndromes, bivalirudin has been licensed as an alternative to UFH in patients undergoing percutaneous coronary intervention for both ST-elevation myocardial infarction and non–ST-elevation myocardial infarction/ unstable angina. Both clinical trial data and early real-world experience have shown that bivalirudin-treated patients are less likely to suffer major bleeding complications.

The following summaries concern multiple topics pertinent to anticoagulation with UFH or bivalirudin including optimal anticoagulation levels in patients undergoing peripheral vascular interventions, differences in bleeding complications with UFH relative to bivalirudin, and cost-effectiveness of both agents in patients undergoing percutaneous coronary intervention.

**Bivalirudin Therapy is Associated With Improved Clinical and Economic Outcomes in ST-Elevation Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention: Results From an Observational Database**

**Summary:** The authors’ objective was to compare clinical and economic outcomes in a real-world population of ST-elevation myocardial infarction...
patients undergoing primary percutaneous coronary intervention using bivalirudin or a combination of heparin+glycoprotein IIb/IIIa inhibitors. They analyzed 21,316 ST-elevation myocardial infarction admissions from 2004 through 2008 in the Premier Perspective database. Patients receiving bivalirudin were compared with those receiving heparin+glycoprotein IIb/IIIa inhibitors and propensity matching was used to account for imbalances in the baseline characteristics of the 2 groups. The primary outcome was in-hospital death, and secondary outcomes included rates of bleeding, transfusion, length of stay, and in-hospital cost. Compared with patients receiving heparin+glycoprotein IIb/IIIa inhibitors, patients receiving bivalirudin had fewer in-hospital deaths (3.2% versus 4.0%; \(P = 0.01\)), less clinically apparent bleeding (6.9% versus 10.5%; \(P < 0.0001\)), and less transfusion (5.9% versus 7.6%; \(P = 0.0001\)). Patients receiving bivalirudin also had shorter average length of stay (4.3 versus 4.5 days; \(P < 0.0001\)) and lower average in-hospital costs ($18,640 versus $19,967; \(P = 0.0001\)). Sensitivity analyses found that mortality and length of stay differences were the outcomes most sensitive to small unmeasured confounding.

**Conclusion:** This real-world analysis of a large nationally representative dataset provides findings that are consistent with the landmark Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. In both studies, bivalirudin was associated with reduced bleeding rates and better survival in ST-elevation myocardial infarction patients. A reduction in bleeding rates may also explain the shorter average length of stay and hospital costs associated with bivalirudin use in the current Pinto et al study. It is important to note that mortality differences between bivalirudin and heparin+glycoprotein IIb/IIIa inhibitors groups were very sensitive to assumptions related to unmeasured confounding and that the study was supported by the maker of bivalirudin.

### Bleeding Risk Comparing Targeted Low-Dose Heparin With Bivalirudin in Patients Undergoing Percutaneous Coronary Intervention: Results From a Propensity Score-Matched Analysis of the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) Registry

**Summary:** Randomized trials of patients undergoing percutaneous coronary intervention have shown that bivalirudin is associated with reduced bleeding compared with unfractionated heparin (UFH). Yet given the high UFH doses that were administered in some of these studies, it is unknown whether bleeding differences were driven by excessive anticoagulation. To address this question, the authors analyzed over 6,500 patients in the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. Patients were divided into 3 groups on the basis of the antithrombotic drug used during percutaneous coronary intervention: (1) UFH only, (2) UFH+glycoprotein IIb/IIIa inhibitor, and (3) bivalirudin only. Propensity score matching was used to adjust for 89 measured covariates. Using guideline definitions, UFH-treated groups were stratified based on the activated clotting time (ACT) achieved (low ACT, optimal ACT, and high ACT). The primary outcome was a composite bleeding outcome including access-site bleeding, thrombolysis in myocardial infarction major or minor bleeding, and transfusion. The authors also tracked acute and chronic ischemic outcomes (in-hospital death/myocardial infarction and 12-month death/myocardial infarction/unplanned revascularization, respectively). The authors consistently found that bivalirudin use was associated with decreased bleeding relative to UFH or UFH+glycoprotein IIb/IIIa inhibitor regardless of the level of ACT achieved. In addition, both acute and chronic ischemic outcomes were similar between bivalirudin-treated and UFH or UFH+glycoprotein IIb/IIIa inhibitor patients without regard to the ACT.

**Conclusion:** Using real-world data, the authors found that relative to a bivalirudin-based strategy, UFH-based anticoagulation results in greater bleeding without improved ischemic outcomes in patients undergoing percutaneous coronary intervention regardless of the ACT. These findings provide convincing evidence that the favorable bleeding profile of bivalirudin in randomized controlled trials of percutaneous coronary intervention is not an artifact of excessive UFH dosing. Additional analyses demonstrating the interaction between anticoagulation strategy, ACT, and periprocedural bleeding risk would have provided further clinically useful information.

### Defining the Optimal Degree of Heparin Anticoagulation for Peripheral Vascular Interventions: Insight From a Large, Regional, Multicenter Registry

**Summary:** Although unfractionated heparin (UFH) is the most commonly used antithrombotic agent in percutaneous peripheral vascular interventions (PVIs), the optimal level of anticoagulation is unknown. The authors sought to correlate total UFH dose and peak procedural activated clotting time with postprocedural outcomes in patients undergoing PVI. They examined 4,743 patient records from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium PVI Quality Improvement Initiative registry, a prospective multicenter registry of patients undergoing PVI. Carotid and aortic interventions were excluded, as were patients who received glycoprotein IIb/IIIa inhibitors. Over 75% of interventions involved the lower extremity. Periprocedural and in-hospital outcomes were compared between patients who received a total UFH dose < or ≥ 260 U/kg and between patients who had a peak procedural activated clotting time < or ≥ 225 seconds. Through the use of a variety of propensity-matched, multivariate models with and without hierarchical modeling for the specific physician performing the PVI and the hospital site of care, the authors found that both postprocedural hemoglobin drop ≥ 3 g/dL and transfusion rate were positively associated with a total UFH dose ≥ 260 U/kg and a peak procedural activated clotting time ≥ 225 seconds. Neither procedural success nor in-hospital major adverse cardiac events were associated with the degree of anticoagulation.

**Conclusion:** Evidence-based anticoagulation targets are lacking for PVI, and this was the first large-scale study to evaluate optimal degrees of anticoagulation using UFH. Although higher degrees of anticoagulation were unsurprisingly linked to excess bleeding, they were not associated with reduced in-hospital major adverse cardiac events. One can thereby question the logic of using more intense anticoagulation. Study findings also suggest the value of targeting not only activated clotting time as is often done currently, but also total UFH dose, which is rarely considered.

### Cost-Effectiveness of Targeting Patients Undergoing Percutaneous Coronary Intervention for Therapy With Bivalirudin Versus Heparin Monotherapy According to Predicted Risk of Bleeding

**Summary:** Bivalirudin has been shown to reduce the incidence of major bleeding compared with unfractionated heparin (UFH) in patients undergoing percutaneous coronary intervention. The authors studied the cost-effectiveness of substituting bivalirudin for UFH monotherapy in 81,628 patients from the 2004 to 2006 National Cardiovascular Data Registry (NCDR) CathPCI Registry. First, a model was used to predict major bleeding among patients receiving UFH only. Bivalirudin treatment was assumed to decrease this risk of major bleeding by 33% compared with UFH alone. Costs were tallied using wholesale drug acquisition costs plus the costs associated with complications. A decision analytic Markov model was then created to estimate lost life expectancy associated with a major bleed, which was predicted to occur in 2.2% of patients. With these assumptions, bivalirudin treatment was estimated to increase costs by $571 per patient, yielding cost-effectiveness ratios of $287,473 per bleeding event averted and $1,173,360 per quality-adjusted life-year gained. At willingness-to-pay thresholds of $50,000 and $100,000 per quality-adjusted life-year gained, bivalirudin was cost-effective for patients with a bleeding risk ≥ 8% (2.5% of patients) and ≥ 5% (7.9% of patients).
patients), respectively. Bivalirudin was cost saving only for patients with a >20% risk of major bleeding (0.16% of CathPCI population). Notably, the initial bleeding risk model had only moderate ability to predict major bleeding (c-index 0.69), and cost-effectiveness estimates were sensitive to bivalirudin’s predicted efficacy in reducing major bleeding.

Conclusion: Routine use of bivalirudin in place of UFH monotherapy in patients undergoing percutaneous coronary intervention will increase costs for virtually all patients. However, cost-effectiveness is achieved in substantially more patients at traditional willingness-to-pay thresholds of $50,000 and $100,000 per quality-adjusted life-year gained. This approach can help payers develop informed guidelines for the use of expensive therapies. Unfortunately, the estimates from this article are hindered by a use of a bleeding model with only moderate ability to predict major bleeding. In addition, the sensitivity of cost-effectiveness to the efficacy of bivalirudin raises the question as to whether alternative bleeding avoidance strategies such as radial access and closure devices may be more cost-effective.1,24

Warfarin

Since its rise from humble beginnings as a rodenticide through its initial approval by the Food and Drug Administration in 1954 as an anticoagulant, warfarin has been the gold standard for anticoagulation to prevent morbidity and mortality in patients with atrial fibrillation or venous thromboembolism.3,10,11 In recent years, however, this supremacy has been challenged by novel oral anticoagulants with potentially improved safety profiles and lower monitoring needs.6–8 Yet, warfarin still remains the dominant agent in use given its excellent efficacy when optimally managed, cost advantage (≈$/month), and extensive evidence based regarding its benefits and harms. Increasingly, metrics are being developed to quantify interinstitutional variation in anticoagulation control and spur the achievement of increased therapeutic efficacy and reduced harm from bleeding.25 The following articles describe multiple topics pertinent to anticoagulation with warfarin including the use of different monitoring intervals of the international normalized ratio and time in therapeutic range, the effect of periprocedural interruptions in warfarin therapy, as well as the impact of cognitive decline on anticoagulation control.

Net Clinical Benefit of Warfarin in Patients With Atrial Fibrillation: A Report From the Swedish Atrial Fibrillation Cohort Study

Summary: In patients with atrial fibrillation (AF), risk factors for bleeding after anticoagulant treatment are largely similar to those that predict thromboembolic events. In this context, the authors sought to investigate the net clinical benefit of warfarin therapy among 182,678 patients included in the Swedish Hospital Discharge Register. The net clinical benefit was defined as number of avoided ischemic strokes with anticoagulation minus the number of excess intracranial bleedings. All patients were followed up for ≥1.5 years and stratified according to risk scores based on the diagnostic codes in the register. The CHA2DS2-VASc score was used to measure the stroke risk and the HAS-BLED score was used to calculate the bleeding risk. Assuming a weight of 1.5 to compensate for the generally more severe outcomes with intracranial bleeding, net clinical benefit favored anticoagulation for almost all AF patients. The exceptions were patients at very low risk of ischemic stroke with a CHA2DS2-VASc score of 0 and those with moderately elevated bleeding risk. The results were broadly similar when using the CHADS2 score, except for patients with very low embolic risk. The CHA2DS2-VASc was able to identify those patients (n=6205, 3.9% of all patients) who had no net clinical benefit or even some disadvantage from anticoagulant treatment.

Conclusion: In this study, the authors demonstrate the superiority of CHA2DS2-VASc score when compared with CHADS2, as CHADS2 may assign a low risk to many AF patients who are not truly low risk. When using CHA2DS2-VASc, results show that the risk of developing ischemic stroke in AF patients without anticoagulation therapy exceeds that of developing intracranial bleeding with treatment in almost all patients. The vast majority of patients with AF should therefore be offered effective thromboprophylaxis.26

Admission International Normalized Ratio Levels, Early Treatment Strategies, and Major Bleeding Risk Among Non–ST-Segment-Elevation Myocardial Infarction Patients on Home Warfarin Therapy: Insights From the National Cardiovascular Data Registry

Summary: The decision to administer antithrombotic therapy to patients on home warfarin who present with non–ST-segment-elevation myocardial infarction can be complicated by the level of anticoagulation. Using data from the Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines (ACTION Registry-GWTG), the authors stratified 5787 non–ST-segment-elevation myocardial infarction patients according to their admission international normalized ratio (INR) levels. Among these patients, 46%, 35%, and 19% had subtherapeutic (INR <2), therapeutic (INR, 2–3), and supratherapeutic (INR >3) INR levels, respectively. Of those patients with INR ≥2 at admission, 45% were treated with early heparin in the first 24 hours of hospitalization, 35% and 14% were respectively prescribed early clopidogrel and glycoprotein IIb/IIIa inhibitors, and 36% received an early invasive strategy. Higher risk of major bleeding was noted among patients with therapeutic INR (15%; adjusted odds ratio: 1.25; 95% confidence interval [CI], 1.03–1.50) and supratherapeutic INR (22%; odds ratio: 1.60; 95% CI, 1.30–1.97) levels compared with patients who had subtherapeutic INR levels (12%). Early use of antipatelet and antithrombin therapy was associated with increased bleeding risk (odds ratio: 1.40 [95% CI, 1.14–1.72] for heparin; 1.50 [95% CI, 1.22–1.84] for clopidogrel; and 1.82 [95% CI, 1.43–2.32] for glycoprotein IIb/IIIa inhibitors). INR level at admission was not significantly related with the use of heparin, clopidogrel, or glycoprotein IIb/IIIa inhibitors early therapy and was not associated with the use of these antithrombotic drugs and bleeding events.

Conclusion: This study reports discrepancies between current treatment practices and guideline recommendations regarding early use of antipatelet treatment in patients on home warfarin who present with non–ST-segment-elevation myocardial infarction. Results demonstrated that the early use of antipatelet and antithrombin therapy was associated with increased bleeding risk regardless of admission INR level. In addition, the study demonstrated that higher INR on admission was associated with increased risk of bleeding. Although this study was able to characterize the relative harms of antithrombotic therapy in the setting of oral anticoagulation, it was limited by its lack of characterization of its relative benefits. This information will be required to understand the net clinical benefit of various antithrombotic therapies in this population.27

Ablation of Atrial Fibrillation Under Therapeutic Warfarin Reduces Periprocedural Complications: Evidence From a Meta-Analysis

Summary: Periprocedural thromboembolic and hemorrhagic events are among the most important and insidious complications of radiofrequency catheter ablation of atrial fibrillation. Although adequate anticoagulation management during the procedure is required to reduce thromboembolic risks, the optimal anticoagulation strategies remain undefined. Recent studies suggest that radiofrequency catheter ablation of atrial fibrillation performed under continuous warfarin (CW) may reduce the risk of thromboembolic events as compared with warfarin discontinuation and periprocedural heparin bridging. In this systematic review, the authors evaluated
the impact of CW compared with warfarin discontinuation on the periprocedural complications of atrial fibrillation catheter ablation. From the 9 identified studies, a total of 27,402 patients were included in the analysis (6,400 undergoing ablation with CW). Analysis showed that CW was associated with a striking decrease of thromboembolic complications (odds ratio, 0.10; 95% CI, 0.05–0.23; P<0.001) and in minor bleeding complications (odds ratio, 0.38; 95% confidence interval, 0.21–0.71; P=0.002) compared with warfarin discontinuation. CW also did not increase the risk of major bleeding (odds ratio, 0.67; 95% confidence interval, 0.31–1.43; P=0.30), including cardiac tamponade (odds ratio, 0.69; 95% confidence interval, 0.19–2.47; P=0.57).

Conclusion: In the absence of properly designed randomized trials, this meta-analysis provides an estimate of bleeding complications related to 2 commonly used anticoagulation strategies for patients undergoing radiofrequency catheter ablation of atrial fibrillation and lends support to continued warfarin anticoagulation. These findings raise questions about the potential risks and benefits of bridging anticoagulation strategies in other settings; perioperative changes in anticoagulation may introduce more harm than is commonly assumed.

Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment: Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centers for Anticoagulation

Summary: Vitamin K antagonist therapy is being widely used to prevent venous thromboembolism and stroke in patients with atrial fibrillation. As both venous thromboembolism and stroke risk as well as the risk for bleeding increase with age, the use of vitamin K antagonist therapy among the elderly is particularly challenging. In this large multicenter prospective observational study, the authors sought to evaluate the quality of anticoagulation therapy and incidence of bleeding in patients >80 years. This study enrolled 4093 patients aged >80 years with a total follow-up of 9603 patient-years. The median age at the beginning of follow-up was 84 years (range, 80–102 years). Among the bleeding events, 179 (1.87 per 100 patient-years) were major bleeds and 26 (0.27 per 100 patient-years) were fatal bleeds. Results show that men and patients >85 presented with higher bleeding rates compared with women and younger patients (relative risk: 1.4; 95% confidence interval: 1.12–1.72; and relative risk: 1.3; 95% confidence interval: 1.0–1.65). History of bleeding, active cancer, and history of falls were independently associated with bleeding risk in Cox regression analysis.

Conclusion: In this large study of very old patients on vitamin K antagonist treatment, the rate of major bleeding events was low. Therefore, age alone should not be a contraindication to treatment with vitamin K antagonist. To evaluate the quality of anticoagulation in this study as well as its generalizability to other settings, it would have been helpful to know patients’ anticoagulation time in therapeutic range as well as the overall therapeutic range at the study sites.

The Business Case for Quality Improvement: Oral Anticoagulation for Atrial Fibrillation

Summary: The authors’ objective was to demonstrate the potential cost savings from improved international normalized ratio control among 67,077 Veterans Health Administration patients anticoagulated with warfarin for atrial fibrillation. A simulation model was created that calculated the number of ischemic strokes, major bleeds, and deaths based on the percentage of time the international normalized ratio was in a therapeutic range of 2 to 3. Patients were at high risk of adverse thrombotic events, as almost 50% had a CHADS2 score ≥3. Improving the time in therapeutic range by 5% prevented 1141 adverse events and reduced costs by $15.9 million over 2 years. Improving the time in therapeutic range by 10% prevented 2087 events and saved $29.7 million. In sensitivity testing, cost savings were most sensitive to estimated stroke risk and the estimated stroke reduction from improved international normalized ratio control.

Conclusion: This study describes an opportunity to simultaneously save money and improve patient outcomes. A quality improvement program to enhance anticoagulation control in atrial fibrillation can be cost saving for the payer, even if only modestly effective in improving international normalized ratio control. A system such as the Veterans Health Administration may be able to leverage economies of scale to create low-cost interventions that improve anticoagulation control and reap the cost savings of decreased morbidity and mortality from stroke. Other smaller systems may find this approach more challenging.

Warfarin Discontinuation After Starting Warfarin for Atrial Fibrillation

Summary: Appropriate use of warfarin reduces the risk of ischemic stroke for many patients with atrial fibrillation. However, there are several reasons that may lead to warfarin discontinuation. Using the data from Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) registry, the authors determined the independent predictors of prolonged (≥180 days) warfarin discontinuation. Overall, 4188 patients had new initiation of warfarin therapy (mean age: 71.8 years). Within 1 year after initiation, 26.3% of patients discontinued therapy. Discontinuation rates were lower for subsequent years (additional 8% during year 2 and 3.6% during year 3). There were 263 hospitalizations with incident hemorrhage, the majority of which (65%) resulted in warfarin discontinuation. Among patients without incident bleeding, multivariable Cox regression found the following as independent predictors of discontinuation: age <65 years (adjusted hazard ratio [95% confidence interval]: 1.33 [1.03–1.72]), a shorter period of time in the therapeutic range for international normalized ratio (hazard ratio [95% confidence interval]: 1.46 [1.42–1.49]) and lower CHADS2 risk of stroke (hazard ratio [95% confidence interval]: 2.54 [1.86–3.47] comparing 0 versus 4–6).

Conclusion: In this study, warfarin discontinuation was common, even among patients without incident hospitalization for bleeding. The greater rate of discontinuation among low-risk patients (ie, younger patients and those with lower CHADS2 scores) may reflect clinical decision making relating to the risk versus benefit of warfarin therapy. Discontinuation among patients with poor international normalized ratio control is more concerning and may be correctable if greater attention is given to improving drug adherence or reducing drug–drug and drug–food interactions. Novel anticoagulants may be also used as alternatives given their fewer interactions. Study findings were limited by the data fields captured by the ATRIA registry and therefore did not fully incorporate socioeconomic factors, concomitantly prescribed medications, and other factors that could affect treatment adherence.

Prompt Repeat Testing After Out-of-Range INR Values: A Quality Indicator for Anticoagulation Care

Summary: The authors examined whether the time between an out-of-range international normalized ratio (INR) value and repeat INR testing (the follow-up interval) is a potential measure of the quality of anticoagulation. They studied the records of 104,451 patients attending anticoagulation clinics in the Veterans Health Administration. For each site of care, the authors computed the average follow-up interval after low (≤1.5) or high (>4.0) INR results as well as average time in therapeutic range for patients at this location. They found that 57% and 36% of patients had at least 1 low or high INR, respectively. The site mean follow-up times after a low INR ranged from 10 to 24 days and from 6 to 18 days after a high INR. Longer follow-up intervals were associated with worse site-level anticoagulation control after low INR (1.04% worse anticoagulation control for each additional day until retesting,
Atrial fibrillation is an important comorbidity in the aging population, in whom cognitive dysfunction is common and may impair appropriate anticoagulation. Using the data from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) trial, the authors tested the association between cognitive dysfunction, appropriate anticoagulation, and ensuing outcomes. Cognitive function was assessed by the Mini-Mental Status Examination (MMSE), with values <26 being suggestive of cognitive impairment. Appropriateness of anticoagulation was assessed using the time in
therapeutic range (TTR). Among 2510 participants receiving oral anticoagulation who had complete data, 171 (6.8%) patients had a MMSE score <24 and 194 (7.7%) had a score ≤26. Over a follow-up period of 1.3 years, the median TTR was 65% in the overall cohort and 58% in the group with MMSE ≤25. On multivariate analysis, a MMSE score ≤26 was an independent predictor of lower TTR. Moreover, both vascular events and bleeding were less common among patients with MMSE scores ≥26 compared with patients with MMSE≤26 (hazard ratio, 0.46; 95% confidence interval, 0.27–0.78; P=0.002 and hazard ratio, 0.56; 95% confidence interval, 0.37–0.85; P=0.04, respectively). After adjustment for TTR, the MMSE score was no longer a predictor of bleeding events.

Conclusion: The authors demonstrate that suboptimal time in TTR may mediate the relationship between cognitive dysfunction and increased vascular and bleeding events in patients taking warfarin for atrial fibrillation. Therefore, when anticoagulation is initiated in patients with cognitive dysfunction, extra care, such as enrollment in anticoagulation clinics, involvement of caregivers, and simplified medication instructions may be warranted to improve anticoagulation control. Alternatively, if safety remains a concern, novel oral anticoagulants that have a better safety profile and less need for monitoring may be considered; however, many of these agents must be taken twice daily and raise the overall pill burden.66

Novel Oral Anticoagulants

The search for safer alternatives to warfarin has been the focus of research for decades. Despite being effective at preventing thromboembolic complications, warfarin has several limitations including interactions with food and medications as well as the need for frequent laboratory monitoring. These limitations have prompted the introduction of newer anticoagulants that target thrombin and factor Xa, key enzymes in the coagulation pathway. The initial development of these drugs was slowed after ximelagatran, a direct thrombin inhibitor licensed briefly in Europe, was shown to cause fatal hepatotoxicity.39 However, safer agents such as dabigatran, rivaroxaban, and apixaban have been introduced in recent years, and shown to have promising advantages over warfarin including lower risk of intracranial bleeding, no clear interactions with food, fewer interactions with medications, and no need for frequent laboratory monitoring and dose adjustment.37,38

Although some of these drugs have been approved by the Food and Drug Administration for prophylaxis of venous thromboembolism and prevention of strokes in patient with nonvalvular atrial fibrillation, they have been shown to be efficacious in other settings as well.40,41

Despite the associated optimism, transition from warfarin to newer anticoagulants will likely be gradual given the challenges posed by these agents in the clinical setting. Because of lack of availability of antidotes and tests to determine the anticoagulant effect of these agents, concerns exist about management in patients who bleed while taking these drugs. Moreover, further information is needed on optimal methods to transition from warfarin to one of these agents, protocols for periprocedural interruption of anticoagulation, management strategies for patients requiring urgent procedures, and dosing in settings of chronic disease including renal failure. Higher cost may also be an obstacle to use. Eventually, comparative efficacy of these agents with long-term use will be needed.

The following section contains summaries pertaining to issues concerning novel oral anticoagulants including associated periprocedural bleeding, anticoagulation during cardioversion, cost-effectiveness, and comparative efficacy.

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared to Warfarin: Results From the RE-LY Randomized Trial

Summary: In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran was shown to be noninferior to warfarin in patients with nonvalvular atrial fibrillation. This subanalysis was undertaken to compare the peri-procedural bleeding risk of patients treated with dabigatran 110 mg (D110), dabigatran 150 mg (D150), or warfarin, as the lack of an effective antidote to dabigatran could lead to increased peri-procedural bleeding. Bleeding rates were evaluated from 7 days prior until 30 days after invasive procedures, considering only the first procedure for each patient. A total of 4591 patients underwent at least 1 invasive procedure: 24.7% of patients receiving D110; 25.4% receiving D150; and 25.9% receiving warfarin (P=0.34). Among patients assigned to either dabigatran dose, the study drug was taken an average of 49 (interquartile range 35–85) hours before the procedure as compared with 114 (interquartile range 87–144) hours in patients receiving warfarin (P=0.001). There was no significant difference in the rates of peri-procedural major bleeding between patients receiving D110 (3.8%), D150 (5.1%), or warfarin (4.6%); (D110 versus warfarin: relative risk [RR]=0.83, 95% confidence interval [CI]: 0.59–1.17; D150 versus warfarin: RR=1.09, 95% CI: 0.80–1.49). Among patients having urgent surgery, major bleeding occurred in 17.8% with D110, 17.7% with D150, and 21.6% with warfarin (D110 versus warfarin: RR=0.82, 95% CI: 0.48–1.41; D150 versus warfarin: RR=0.82, 95% CI: 0.50–1.35, P=0.44). There was no significant difference in the composite rate of peri-procedural cardiovascular death, ischemic stroke, and pulmonary embolism between patients receiving D110 (1.2%), D150 (1.5%), or warfarin (1.2%); (D110 versus warfarin: RR=1.05, 95% CI: 0.55–2.01; D150 versus warfarin: RR=1.29, 95% CI: 0.70–2.38).

Conclusion: In this subgroup analysis of RE-LY, the authors demonstrated that dabigatran was not associated with higher rates of major peri-procedural bleeding as compared with warfarin despite being interrupted much closer to the actual procedure time. Results were similar even when urgent surgery was required and planned drug interruption was not always possible. However, as exclusion criteria for RE-LY comprised patients with severe renal impairment and valvular impairment, patients in whom dabigatran has been prescribed in the real world,42 peri-procedural bleeding may be more common in typical practice and will require rigorous evaluation. Also, measurement of bleeding in the warfarin arm may be confounded by a low use of vitamin K and fresh-frozen plasma in this subgroup, given the open-label nature of this trial.43

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation: An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

Summary: Twice daily dabigatran 150 mg and 110 mg (D150 and D110 respectively) were shown in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial to be effective treatment strategies for nonvalvular atrial fibrillation. The purpose of this RE-LY substudy was to report safety results of both doses of dabigatran compared with warfarin while considering both patient age and different types of major bleeding. The study cohort included 18 113 patients who were followed for a median of 2 years. Compared with warfarin, twice daily D110 was associated with a lower risk of major bleeding (2.87% versus 3.57%; P=0.002), whereas twice daily D150 was associated with a similar risk of major bleeding (3.31% versus 3.57%; P=0.32). There was a significant treatment-by-age interaction, such that twice daily D110 compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% versus 3.04%; P<0.001) and a similar risk in those aged ≥75 years (4.43% versus 4.37%; P=0.89; P for interaction <0.001), whereas twice daily D150 compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; P=0.001) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; P=0.07; P for interaction <0.001). The interaction with age was evident for intracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age.
Conclusion: Data from these subanalyses of the RE-LY trial indicate an age-by-treatment interaction for bleeding in patients with atrial fibrillation at risk of stroke. Although both doses of dabigatran were associated with lower risk of major bleeding in patients aged <75 years, an increased risk of extracranial bleeding was noted with the higher dose of dabigatran (150 mg) in patients aged >75 years; though rates of thromboembolic events were not reported in these age groups. Given that elderly patients may have various associated risk factors for bleeding including polypharmacy and renal failure, this finding underscores the added importance of tailoring dabigatran dosing to bleeding risk in this age group. The Food and Drug Administration’s decision to favor dabigatran 150 mg even in patients >75 years under the premise that the morbidity of stroke outweighs that of other nonfatal bleeding may need to be revisited, provided the efficacy end points of treatment with these agents are known.46

Dabigatran Versus Warfarin in Patients With Atrial Fibrillation: An Analysis of Patients Undergoing Cardioversion

Summary: Given the increased risk of thromboembolic events during cardioversion in patients with nonvalvular atrial fibrillation, the authors of this post hoc analysis from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial sought to investigate outcomes associated with cardioversion for patients on different anticoagulation regimens. Among 18,113 patients with atrial fibrillation randomized to receive twice daily dabigatran 110 mg (D110), twice daily dabigatran 150 mg (D150), or warfarin, a total of 1983 cardioversions were performed in 1270 patients (647, 672, and 664 in the D110, D150, and warfarin groups, respectively). Precedardioversion transesophageal echocardiography was encouraged, particularly in dabigatran-assigned patients. Data from before, during, and 30 days after cardioversion were analyzed. For patients on D110, D150, or warfarin, transesophageal echocardiography was performed before cardioversion in 25.5%, 24.1%, and 13.3% of patients, of which 1.8%, 1.2%, and 1.1% were positive for left atrial thrombi. Continuous treatment with study drug for ≥3 weeks before cardioversion was lower in D110 (76.4%) and D150 (79.2%) compared with warfarin (85.5%; P=0.01 for both comparisons). Respective stroke and systemic embolism rates at 30 days were similar at 0.8%, 0.3%, and 0.6% (D110 versus warfarin, P=0.71; D150 versus warfarin, P=0.40). Rates of stroke and systemic embolism were also similar in patients who did and did not undergo transesophageal echocardiography. Major bleeding rates were respectively 1.7%, 0.6%, and 0.6% (D110 versus warfarin, P=0.06; D150 versus warfarin, P=0.99).

Conclusion: Cardioversion of patients with nonvalvular atrial fibrillation in the RE-LY trial appears to be comparably safe and efficacious whether patients were receiving dabigatran or warfarin. This study was also the largest cardioversion study to date, and therefore provides good estimates of thromboembolic complications associated with the cardioversion procedure. As dabigatran use increases with time, care must be taken not to apply this study to patients with valvular atrial fibrillation, for whom novel oral anticoagulants have not been approved already taking warfarin with excellent international normalized ratio control may have little to gain by switching to dabigatran.49,50

Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

Summary: In this substudy of Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), the authors report rates of myocardial infarction (MI), unstable angina, cardiac arrest, cardiac death, and the prespecified “net clinical benefit” of dabigatran versus warfarin. “Net clinical benefit” was defined as the combination of stroke, systemic embolism, MI, major bleeding, and all-cause death. MI occurred at annual rates of 0.82% and 0.81% with twice daily dabigatran 110 mg or 150 mg (D110 and D150, respectively) compared with 0.64% with warfarin (hazard ratio [HR] 1.29, 95% confidence interval [CI] 0.96–1.75 for D110; HR 1.27, 95% CI 0.94–1.71 for D150). Annual rates of a composite of MI, unstable angina, cardiac arrest, and cardiac death were 3.16% per year with D110, 3.33% per year with D150, and 3.41% per year with warfarin (HR 0.93 for D110 versus warfarin, 95% CI 0.80–1.06 and HR 0.98 for D150 versus warfarin, 95% CI 0.85–1.12). Events prespecified as net clinical benefit occurred at a rate of 7.34% per year with D110, 7.11% per year with D150, and 7.91% per year with warfarin (HR 0.92 for D110 versus warfarin, 95% CI 0.84–1.01 and HR 0.90 for D150 versus warfarin, 95% CI 0.82–0.99). The relative effects of dabigatran versus warfarin on myocardial ischemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.

Conclusion: These data indicate that there may be a nonsignificantly higher risk of MI with prescription of dabigatran compared with warfarin in patients with nonvalvular atrial fibrillation. These findings are particularly concerning as RE-LY was not powered to identify differences in ischemic outcomes between study arms. Further study45 has demonstrated a significant risk of myocardial ischemic events with dabigatran administration. We will need adequately powered studies to determine whether the net clinical benefit in favor of dabigatran as shown here truly exists, especially in patients with a previous history of MI or coronary artery disease.45

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Summary: Using results from Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) and other trials, the authors developed a Markov decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies in a hypothetical cohort of 70-year-old patients with atrial fibrillation. The cost-effectiveness threshold was set at $50,000 per quality-adjusted life year. Assuming the annual costs of warfarin and dabigatran are $545 and $3240, respectively, and that the average risk of major bleeding is 3% per year, the most cost-effective therapy depended on stroke risk. Only aspirin was cost-effective for persons with a CHADS2 score of 0. Warfarin was cost-effective for persons with a CHADS2 score of 1 or 2 unless bleeding risk was high or anticoagulation control was poor. Dabigatran 150 mg twice daily was cost-effective unless anticoagulation control was excellent. Neither dabigatran 110 mg twice daily nor dual antiplatelet therapy was ever cost-effective.

Conclusion: Although a previous study48 has shown dabigatran to be a cost-effective choice in the setting of nonvalvular atrial fibrillation, the current study provides a more detailed analysis by also considering risk of stroke, risk of bleeding, and adequacy of anticoagulation control. However, true cost-effectiveness needs to be assessed in the context of everyday practice, where adherence to dabigatran may be compromised by its relatively high cost compared with warfarin. As per updated ACC/AHA guidelines for the management of atrial fibrillation, patients already taking warfarin with excellent international normalized ratio control may have little to gain by switching to dabigatran.49,50

Dabigatran and Warfarin in Vitamin K Antagonist-Naive and -Experienced Cohorts With Atrial Fibrillation

Summary: Observational and post hoc analyses suggest that patients who have previously used vitamin K antagonists are more likely to find a personalized dose that keeps international normalized ratio in the therapeutic range and minimizes complications. Therefore,
in a prespecified substudy, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) investigators determined whether an interaction existed between previous use of vitamin K antagonists and outcomes in the main treatment arms. Among patients naïve to vitamin K antagonists, the annual event rates for stroke or systemic embolism were 1.69%, 1.57%, and 1.07% for warfarin, dabigatran 110 mg twice daily, and dabigatran 150 mg twice daily, respectively. Corresponding event rates in vitamin K-experienced patients were 1.74%, 1.51%, and 1.15%. Similarly, there was no interaction between previous vitamin K experience and bleeding events. Major bleeding rates were comparable between warfarin and dabigatran 150 mg twice daily arms, but were lower for the dabigatran 110 mg twice daily arm. In all subgroups, rates of intracranial bleeding were lower with dabigatran compared with warfarin.

Conclusion: Previous experience with a vitamin K antagonist did not influence the benefits of dabigatran relative to warfarin among subjects in the RE-LY study. Higher dabigatran doses consistently had greater efficacy in preventing stroke and systemic embolism, and lower doses had less major bleeding relative to warfarin. Yet, it is unknown whether study findings are applicable to real-world practice, as clinical trial subjects would be expected to be more adherent and capable of medication management than the general population. In addition, findings should be interpreted with caution in patient subgroups that were underrepresented in RE-LY, such as those at high risk of stroke.

Cost-Effectiveness of Apixaban Compared With Aspirin for Stroke Prevention in Atrial Fibrillation Among Patients Unsuitable for Warfarin

Summary: The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin-K Antagonist Treatment (AVERROES) trial showed that apixaban (5 mg twice daily) was superior to aspirin (81–324 mg daily) for reduction of stroke or systemic embolism without an increase in rates of major bleeding in patients for whom vitamin K antagonists were unsuitable. The authors used Markov modeling to determine the associated costs and quality-adjusted life-years with treatment due to apixaban versus aspirin. The model was constructed for a base case of a 70-year-old patient with a CHADS2 score of 2 and low risk of bleeding. The authors found that 1-year and 10-year total costs per patient were $3454 and $44 232 for apixaban, and $1805 and $50 066 for aspirin. One-year and 10-year quality-adjusted life-years were 0.96 and 6.87 for apixaban, and 0.96 and 6.51 for aspirin. Besides time, the results were sensitive to several other assumptions including baseline stroke risk and the monthly costs for management of major stroke.

Conclusion: For atrial fibrillation patients unsuitable for warfarin therapy, alternatives include aspirin, aspirin plus a thienopyridine, or apixaban. In this cost-effectiveness analysis, apixaban was inferior to aspirin at 1 year but was dominant at 10 years among patients unsuitable for warfarin. The improved cost-effectiveness of apixaban at 10 years reflects in part the cumulative benefit of stroke reduction on quality of life and reduction of costs for management of stroke. The study has several limitations. First, the authors assigned a cost to apixaban based on that of other novel oral anticoagulants in the United States. However, this cost may be too high based on estimates from Europe where the drug is already approved. In addition, as the authors have highlighted, the long-term cost-effectiveness of apixaban should be interpreted with caution, since AVERROES was terminated with a median follow-up of 1.1 years and long-term efficacy of apixaban remains unknown.

Enoxaparin Versus Dabigatran or Rivaroxaban for Thromboprophylaxis After Hip or Knee Arthroplasty: Results of Separate Pooled Analyses of Phase III Multicenter Randomized Trials

Summary: Oral anticoagulants are more convenient to use compared with injectable formulations. Several phase III randomized trials assessed the efficacy and safety of dabigatran (150–220 mg once daily) and rivaroxaban (10 mg once daily) for prevention of venous thromboembolism (VTE) after hip or knee arthroplasty. In this study, the authors conducted a pooled analysis of these trials, comparing their safety and efficacy with the use of enoxaparin treatment (30 mg twice daily or 40 mg once daily) for an equal duration of time. Compared with dabigatran, there was a trend toward better efficacy for enoxaparin (odds ratio [95% confidence interval]: 0.76 [0.44–1.31]; P=0.02 for heterogeneity). After excluding one of the studies, efficacy in favor of enoxaparin became statistically significant and heterogeneity was reduced (odds ratio [95% confidence interval]: 0.49 [0.26–0.94]; P=0.19 for heterogeneity). Bleeding (a composite of major and clinically relevant nonmajor bleeding) was similar in the 2 groups (odds ratio [95% confidence interval]: 0.90 [0.71–1.15]). Compared with rivaroxaban, the rate of symptomatic VTE was higher in patients receiving enoxaparin (odds ratio [95% confidence interval]: 2.04 [1.32–3.17]), However, patients receiving enoxaparin had a lower rate of bleeding (odds ratio [95% confidence interval]: 0.79 [0.62–0.99]). There was little evidence suggestive of publication bias.

Conclusion: Novel oral anticoagulants are approved or are in the process of approval for VTE prophylaxis in several countries. Head-to-head comparative effectiveness studies for novel anticoagulants are unlikely to be conducted in the near future. Therefore, findings of this study have important implications regarding the choice of pharmacoprophylaxis in patients undergoing joint arthroplasty based on the patient’s risks for VTE versus bleeding. Lack of studies comparing the safety and efficacy of novel oral anticoagulants versus warfarin for VTE prevention remains a limitation.

Comparative Efficacy and Safety of New Oral Anticoagulants in Patients With Atrial Fibrillation

Summary: Dabigatran, rivaroxaban, and apixaban are 3 novel oral anticoagulants that were tested against warfarin in 3 large trials for stroke prevention in atrial fibrillation: Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE). The authors provided an indirect comparison between these new agents with regard to the reduction of stroke or systemic embolism, and major bleeding. All of the novel anticoagulants showed numerically superior efficacy for the prevention of stroke or systemic embolism compared with warfarin, but the difference reached statistical significance only for dabigatran (150 mg twice daily) and apixaban (hazard ratio [95% confidence interval]: 0.88 [0.75–1.05], 0.66 [0.52–0.81] and 0.79 [0.66–0.95], for rivaroxaban, dabigatran, and apixaban, respectively). To explain these findings of differential benefit, the authors point out that the patients in the ROCKET-AF trial were more medically complex with higher CHADS2 scores, and higher control-arm event rates as compared with patients in RE-LY and ARISTOTLE. Accordingly, a separate comparison of all high-risk patients in the 3 trials was conducted that showed numerically superior efficacy for apixaban and dabigatran compared with rivaroxaban without clear statistical differences. In all analyses, apixaban showed significantly lower rates of major bleeding compared with rivaroxaban and dabigatran.
Conclusion: This study showed comparable efficacy for dabigatran, rivaroxaban, and apixaban for stroke prevention in atrial fibrillation patients, while suggesting a better safety profile for bleeding for apixaban. Three recent analyses reported slightly better efficacy with dabigatran compared with rivaroxaban. However, as the preembolism risk of stroke was higher among the rivaroxaban-treated patients in the ROCKET-AF trial, one would expect higher event rates in this population. This study was therefore unique in comparing outcomes across a similarly high-risk subset of patients in ROCKET-AF, RE-LY, and ARISTOTLE. Mega-trials comparing the efficacy of new anticoagulants are unlikely to be conducted in the near future. Accordingly, indirect comparisons such as this study, individual patient meta-analysis of data, as well as long-term follow-up of patients in the 3 trials, may be helpful.

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