Direct anticoagulation therapy

Pan-Arab Meeting & Saudi Society of Hematology
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• Oral direct anticoagulants
• Parenteral anticoagulant
What we will discuss today

• Indications for (Direct oral anticoagulants) DOAC use and the evidence for it
• Special situations.
• Management of bleeding from DOACs
• Management of patients on DOACs preoperatively.
Direct oral anticoagulants

• 2 types:
  • Direct Thrombin inhibitor only one available which Dabigatran.
  • Inhibits thrombin

• Direct Factor X inhibitors:
  • Rivaroxaban
  • Apixaban
  • Edoxaban.
  • Betrixaban
Benefits of Direct oral Anticoagulants

• Lower bleeding risks compared to warfarin especially intracerebral bleeds.
• No need for laboratory monitoring
• Little effect of diet on the pharmacokinetics of the drugs
Postoperative Venous Thromboprophylaxis

• Dabigatran:
  • In patients undergoing **total knee replacement** surgery (the REMODEL study) oral dabigatran 150 mg or 220 mg daily was compared with enoxaparin 40 mg daily starting 12 hours pre-operatively.
  • This trial was designed as a non-inferiority study and achieved non-inferiority compared with enoxaparin for the prevention of total VTE and reduction of all-cause mortality. There was no difference in the incidence of symptomatic VTE.
Postoperative Venous Thromboprophylaxis

• Dabigatran:

• The RENOVATE trial in patients undergoing total hip replacement surgery compared oral dabigatran 150 mg/day or 220 mg/day starting within one to four hours postoperatively with enoxaparin 40 mg once daily starting 12 hours pre-operatively.

• For the composite endpoint of total VTE and all-cause mortality, both arms of the dabigatran study showed non-inferiority to enoxaparin, with similar bleeding rates and with most major bleeding events being at the surgical site.
Postoperative Venous Thromboprophylaxis

• Dabigatran:
• The REMOBILIZE trial was carried out in patients undergoing total knee replacement surgery.
• In this study, dabigatran etexilate 150 mg/day or 220 mg/day starting with a dose of either 75 or 110 mg 6 to 12 hours postoperatively, respectively in the two groups, was compared with enoxaparin 30 mg twice daily, starting 12 to 24 hours postoperatively.
• Among 1896 patients, dabigatran 220 and 110 mg showed inferior efficacy to enoxaparin (venous thromboembolism rates of 31% [P = .02 vs enoxaparin], 34% [P < .001 vs enoxaparin], and 25%, respectively).
Postoperative Thromboprophylaxis

• Rivaroxaban:
• Total Hip replacement in RECORD 1, rivaroxaban (10mg od 35 days) showed superiority to enoxaparin (40mg od 35 days) for the reduction of total VTE, with no difference in major bleeding events.
• Total hip replacement RECORD 2 showed superiority of rivaroxaban (10mg od 35 days) Vs Enoxaparin 40mg od for 12 days in the incidence of total VTE, major VTE, and proximal or distal DVT, and notably in the incidence of symptomatic VTE.
Postoperative Venous Thromboprophylaxis

• Rivaroxiban:
• In patients undergoing total knee replacement (RECORD 3), rivaroxaban 10 mg orally once daily was compared with enoxaparin 40 mg subcutaneously daily starting 12 hours preoperatively, with either agent continued for 12 ± 2 days.
• In this study, rivaroxaban was superior to enoxaparin in the reduction of total VTE, major VTE and distal DVT, and significantly reduced the incidence of symptomatic VTE.
Postoperative Venous Thromboprophylaxis

• In patients undergoing total knee replacement RECORD 4 study, were randomly assigned to receive either rivaroxaban 10 mg daily PO or enoxaparin 30 mg twice daily starting 12 to 24 hours postoperatively, with both given for 12 ± 4 days.

• There was a significant decrease in total VTE with rivaroxaban, but the difference in the incidence of major VTE and symptomatic VTE did not reach statistical significance.

• Authors interpretation it is non inferior to enoxaparin at that dose.
Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

Michael Iud Lessen, Gary E Raskob, Alexander Gallus, Graham Pinero, Daile Chen, Philip Horack, and the ADVANCE-2 investigators

Summary
Background: Low-molecular-weight heparins such as enoxaparin are preferred for prevention of venous thromboembolism after major joint replacement. Apixaban, an orally active factor Xa inhibitor, might be as effective, have lower bleeding risk, and be easier to use than is enoxaparin. We assessed efficacy and safety of these drugs after elective total knee replacement.

Methods: In ADVANCE-2, a multicentre, randomised, double-blind phase 3 study, patients undergoing elective unilateral or bilateral total knee replacement were randomly allocated through an interactive central telephone system to receive oral apixaban 2.5 mg twice daily (n=1528) or subcutaneous enoxaparin 40 mg once daily (1529). The randomisation schedule was generated by the Bristol-Myers Squibb randomisation centre and stratified by study site and by unilateral or bilateral surgery with a block size of four. Investigators, patients, statisticians, adjudicators, and steering committee were masked to allocation. Apixaban was started 12–24 h after wound closure and enoxaparin 12 h before surgery; both drugs were continued for 10–14 days, when bilateral ascending venography was scheduled. Primary outcome was the composite of asymptomatic and symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death during treatment. The statistical plan required non-inferiority of apixaban before testing for superiority. Analysis was by intention to treat for non-inferiority testing. The study is registered at ClinicalTrials.gov, number NCT00452530.

Findings: 1973 of 3057 patients allocated to treatment (1528 apixaban, 1529 enoxaparin) were eligible for primary efficacy analysis. The primary outcome was reported in 147 (15%) of 976 apixaban patients and 243 (24%) of 997 enoxaparin patients (relative risk 0.62 [95% CI 0.51–0.74]; p=0.00; absolute risk reduction 9.3% [5.8–12.7%]). Major or clinically relevant non-major bleeding occurred in 53 (4%) of 1501 patients receiving apixaban and 72 (5%) of 1508 treated with enoxaparin (p=0.09).

Interpretation: Apixaban 2.5 mg twice daily, starting on the morning after total knee replacement, offers a convenient and more effective orally administered alternative to 40 mg per day enoxaparin, without increased bleeding.

Funding: Bristol-Myers Squibb; Pfizer.
• In ADVANCE-2, a multicentre, randomised, double-blind phase 3 study, patients undergoing elective unilateral or bilateral total knee replacement were randomly allocated through an interactive central telephone system to receive oral apixaban 2·5 mg twice daily (n=1528) or subcutaneous enoxaparin 40 mg once daily (1529).

• 1973 of 3057 patients allocated to treatment (1528 apixaban, 1529 enoxaparin) were eligible for primary efficacy analysis. The primary outcome was reported in 147 (15%) of 976 apixaban patients and 243 (24%) of 997 enoxaparin patients (relative risk 0·62 [95% CI 0·51–0·74]; p<0·0001; absolute risk reduction 9·3% [5·8–12·7]).
Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement

Michael Rud Lassen, M.D., Gary E. Raskob, Ph.D., Alexander Gallus, M.D., Graham Pineo, M.D., Dulei Chen, Ph.D., and Ronald J. Portman, M.D.

ABSTRACT

BACKGROUND

The optimal strategy for thromboprophylaxis after major joint replacement has not been established. Low-molecular-weight heparins such as enoxaparin may be the target factor Xa but to some extent also inhibit thrombin. Apixaban, a specific factor Xa inhibitor, may provide effective thromboprophylaxis with a low risk of bleeding and improved ease of use.

METHODS

In a double-blind, double-dummy study, we randomly assigned patients undergoing total knee replacement to receive 2.5 mg of apixaban orally twice daily or 30 mg of enoxaparin subcutaneously every 12 hours. Both medications were started 12 to 24 hours after surgery and continued for 10 to 14 days. Bilateral venography was then performed. The primary efficacy outcome was a composite of asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause during treatment. Patients were followed for 60 days after anticoagulation therapy was stopped.

RESULTS

A total of 3195 patients underwent randomization, with 1599 assigned to the apixaban group and 1596 to the enoxaparin group. 908 subjects were not eligible for the efficacy analysis. The overall rate of primary events was much lower than anticipated. The rate of the primary efficacy outcome was 9.0% with apixaban as compared with 8.8% with enoxaparin (relative risk, 1.02; 95% confidence interval, 0.78 to 1.32). The composite incidence of major bleeding and clinically relevant nonmajor bleeding
Postoperative Venous Thromboprophylaxis

- Apixaban:

- One group of patients received 2.5 mg of Apixaban orally twice daily as well as an injection of placebo that mimicked injection with enoxaparin. The other group received 30 mg of enoxaparin subcutaneously every 12 hours along with placebo tablets that were identical in appearance to Apixaban tablets.
Postoperative Venous Thromboprophylaxis

• Apixaban:

  • The rate of the primary efficacy outcome was 9.0% with Apixaban as compared with 8.8% with enoxaparin (relative risk, 1.02; 95% confidence interval, 0.78 to 1.32).

  • The composite incidence of major bleeding and clinically relevant nonmajor bleeding was 2.9% with apixaban and 4.3% with enoxaparin (P=0.03).

  • As compared with enoxaparin for efficacy of thromboprophylaxis after knee replacement, apixaban did not meet the prespecified statistical criteria for noninferiority.
Edoxaban:

STARS E-3 and STARS J-5 compared edoxaban with the low molecular weight heparin enoxaparin.

A pooled analysis of the results showed that when compared with enoxaparin, Edoxaban was associated with a lower incidence of DVT and PE (5.1 versus 10.7 percent) and a similar safety profile.
Treatment of Venous thromboembolism
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

BACKGROUND
Rivaroxaban, an oral factor Xa inhibitor, may provide a simple, fixed-dose regimen for treating acute deep-vein thrombosis (DVT) and for continued treatment, without the need for laboratory monitoring.

METHODS
We conducted an open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT. In parallel, we carried out a double-blind, randomized, event-driven superiority study that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism. The primary efficacy outcome for both studies was recurrent venous thromboembolism. The principal safety outcome was major bleeding or clinically relevant nonmajor bleeding in the initial-treatment study and major bleeding in the continued-treatment study.

RESULTS
The study of rivaroxaban for acute DVT included 3449 patients: 1731 given rivaroxaban and 1718 given enoxaparin plus a vitamin K antagonist. Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%], vs. 51 events with enoxaparin–vitamin K antagonist [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P=0.001). The principal safety outcome occurred in 8.1% of the patients in each group. In the continued-treatment study, which included 602 patients, the rate of major bleeding was lower with rivaroxaban (1.2%) than with placebo (2.0%) (P=0.03).

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*The investigators participating in the EINSTEIN–DVT and EINSTEIN–Extension Studies are listed in the Supplementary Appendix, available at NEJM.org.

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VTE therapy

• Einstein: open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT.

• Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%], vs. 51 events with enoxaparin–vitamin K antagonist [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001).
Oral Apixaban for the Treatment of Acute Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY Investigators

BACKGROUND

Apixaban, an oral factor Xa inhibitor administered in fixed doses, may simplify the treatment of venous thromboembolism.

METHODS

In this randomized, double-blind study, we compared apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute venous thromboembolism. The primary efficacy outcome was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding.

RESULTS

The primary efficacy outcome occurred in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18; difference in risk [apixaban minus conventional therapy], −0.4 percentage points; 95% CI, −1.3 to 0.4). Apixaban was noninferior to conventional therapy (P<0.001) for predefined upper limits of the 95% confidence intervals for both relative risk (≤1.80) and difference from the Internal and Cardiovascular Medicine–Stroke Unit, University of Perugia, Perugia, Italy (G.A.); the Department of Vascular Medicine, Academic Medical Center, Amsterdam (H.R.B.); King’s College Hospital, London (A.C.); Pfizer, Groton, CT (M.C., M.J., U.M., R.P., J.T.); the Department of Haematology, Flinders Medical Centre and Flinders University, Adelaide, SA, Australia (A.S.G.); the University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City (G.E.R.); and the Departments of Medicine and Biochemistry and Biomedical Sciences, McMaster University, and Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada (J.I.W.). Address reprint requests to Dr. Agnelli at the University of Perugia, Piazzale Menghini 1, 06100 Perugia, Italy, or at agnellig@unipg.it.

Investigators in the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial are...
In this randomized, double-blind study, that compared apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute venous thromboembolism.
• The primary efficacy outcome occurred in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18.

• Apixaban was noninferior to conventional therapy (P<0.001) for predefined upper limits of the 95% confidence intervals for both relative risk (<1.80) and difference in risk (<3.5 percentage points).
Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators

ABSTRACT

BACKGROUND
Whether the oral factor Xa inhibitor edoxaban can be an alternative to warfarin in patients with venous thromboembolism is unclear.

METHODS
In a randomized, double-blind, noninferiority study, we randomly assigned patients with acute venous thromboembolism, who had initially received heparin, to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or to receive warfarin. Patients received the study drug for 3 to 12 months. The primary efficacy outcome was recurrent symptomatic venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS
A total of 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism. Among patients receiving warfarin, the time in the therapeutic range was 63.5%. Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.70 to 1.13; P=0.001 for noninferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority). The rates of other adverse events were similar in the two groups. A total of 938 patients with pulmonary embolism had right ventricular dysfunction, as assessed by measurement of N-terminal pro-brain natriuretic peptide levels; the rate of recurrent symptomatic venous thromboembolism did not differ significantly between the two treatment groups.
• In a randomized, double-blind, noninferiority study, we randomly assigned patients with acute venous thromboembolism, who had initially received heparin, to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or to receive warfarin.
A total of 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism.

Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.70 to 1.13; P<0.001 for noninferiority).
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D.,
Patrick Misini, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D.,
David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D.,
for the RE-COVER Study Group

ABSTRACT

BACKGROUND
The direct oral thrombin inhibitor dabigatran has a predictable anticoagulant effect and may be an alternative therapy to warfarin for patients who have acute venous thromboembolism.

METHODS
In a randomized, double-blind, noninferiority trial involving patients with acute venous thromboembolism who were initially given parenteral anticoagulation therapy for a median of 9 days (interquartile range, 8 to 11), we compared oral dabigatran, administered at a dose of 150 mg twice daily, with warfarin that was dose-adjusted to achieve an international normalized ratio of 2.0 to 3.0. The primary outcome was the 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Safety end points included bleeding events, acute coronary syndromes, other adverse events, and results of liver-function tests.

RESULTS
A total of 30 of the 1274 patients randomly assigned to receive dabigatran (2.4%), as compared with 27 of the 1265 patients randomly assigned to warfarin (2.1%), had recurrent venous thromboembolism; the difference in risk was 0.4 percentage points (95% confidence interval [CI], 0.0 to 1.6; P<0.001 for the prespecified non-inferiority margin). The hazard ratio with dabigatran was 1.10 (95% CI, 0.65 to 1.84). Major bleeding episodes occurred in 20 patients assigned to dabigatran and 11 assigned to warfarin; the risk of major bleeding was 0.5 percentage points higher with dabigatran (95% CI, 0.0 to 1.5; P=0.007).

The results of the RE-COVER study are compatible with those of a large randomized trial comparing dabigatran with warfarin for the prevention of recurrent VTE in the setting of an initial episode of VTE. In patients who had acute VTE, the RE-COVER study suggests that dabigatran may offer a safe and effective alternative to warfarin as monotherapy.
In a randomized, double-blind, noninferiority trial involving patients with acute venous thromboembolism who were initially given parenteral anticoagulation therapy for a median of 9 days (interquartile range, 8 to 11), we compared oral dabigatran, administered at a dose of 150 mg twice daily, with warfarin that was dose-adjusted to achieve an international normalized ratio of 2.0 to 3.0.
A total of 30 of the 1274 patients randomly assigned to receive dabigatran (2.4%), as compared with 27 of the 1265 patients randomly assigned to warfarin (2.1%), had recurrent venous thromboembolism; the difference in risk was 0.4 percentage points (95% confidence interval [CI], -0.8 to 1.5; P<0.001 for the prespecified noninferiority margin). The hazard ratio with dabigatran was 1.10 (95% CI, 0.65 to 1.84).
DOACs in Atrial fibrillation
## Trials of warfarin versus newer anticoagulants in AF

<table>
<thead>
<tr>
<th>Study drug and dose</th>
<th>Mean CHADS\textsubscript{2} score</th>
<th>Percent on aspirin</th>
<th>Primary outcome</th>
<th>Major bleeding definition</th>
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</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 110 mg twice per day 150 mg twice per day</td>
<td>2.1</td>
<td>40</td>
<td>All stroke and systemic embolism</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20 mg once per day</td>
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<td>36</td>
<td>All stroke and systemic embolism</td>
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<td>ARISTOTLE</td>
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<td>Death</td>
<td>Stroke (nH)</td>
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<tr>
<td><strong>RE-LEY</strong></td>
<td>110 mg</td>
<td>1.53/1.69 (A)</td>
<td>2.71/3.36 (C)</td>
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<td></td>
<td>150 mg</td>
<td>1.11/1.69 (B)</td>
<td>3.11/3.36</td>
<td>3.64/4.13</td>
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<tr>
<td><strong>ROCKET-AF</strong></td>
<td>As treated analysis</td>
<td>1.70/2.20 (A)</td>
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<tr>
<td></td>
<td>Intention to treat analysis</td>
<td>2.10/2.40 (A)</td>
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<td>4.50/4.90</td>
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<tr>
<td></td>
<td><strong>ARISTOTLE</strong></td>
<td>1.27/1.60 (B)</td>
<td>2.13/3.09 (B)</td>
<td>3.52/3.94 (B)</td>
</tr>
</tbody>
</table>

CHADS²: estimate of stroke risk; (A): statistically significant for noninferiority; (B): statistically significant for superiority; (C): statistically significant.

* Target INR 2.0 to 3.0 in each study.

† Mean follow-up of approximately two years in each study.

△ Dose of rivaroxaban adjusted to 15 mg per day for renal insufficiency (creatinine clearance 30 to 49 mL/minute [0.5 to 0.82 mL/second]).

○ Dose of apixaban adjusted to 2.5 mg twice per day with two or more of: age ≥ 80 years, body weight ≤ 60 kg, or renal insufficiency (serum creatinine level ≥ 1.5 mg/dL [133 μmol/L]).

References:
EDOXABAN VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION


ABSTRACT

BACKGROUND

Edoxaban is a direct oral factor Xα inhibitor with proven antithrombotic effects. The long-term efficacy and safety of edoxaban as compared with warfarin in patients with atrial fibrillation is not known.

METHODS

We conducted a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk atrial fibrillation (median follow-up, 2.8 years). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. The principal safety end point was major bleeding.

RESULTS

The annualized rate of the primary end point during treatment was 1.50% with warfarin (median time in the therapeutic range, 68.4%), as compared with 1.18% with high-dose edoxaban (hazard ratio, 0.79; 97.5% confidence interval [CI], 0.63 to 0.99; P<0.001 for noninferiority) and 1.60% with low-dose edoxaban (hazard ratio, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiority). In the intention-to-treat analysis, there was a trend favoring high-dose edoxaban versus warfarin (hazard ratio, 0.87; 97.5% CI, 0.73 to 1.04; P=0.08) and an unfavorable trend with low-dose edoxaban versus warfarin (hazard ratio, 1.13; 97.5% CI, 0.96 to 1.34; P=0.10). The annualized rate of major bleeding was 1.0% with warfarin versus 1.7% with high-dose edoxaban (hazard ratio, 1.73; 97.5% CI, 1.09 to 2.76; P=0.02) and 1.2% with low-dose edoxaban (hazard ratio, 1.26; 97.5% CI, 0.83 to 1.91; P=0.28). The bleeding rates were similar in patients with high-risk and low-risk atrial fibrillation.

From Brigham and Women’s Hospital and Harvard Medical School, Boston (R.P.G., C.T.R., E.B., S.A.M., S.D.W., L.T.G., E.M.A.); Mount Sinai Medical Center, New York (J.L.H.); University Hospitals Case Medical Center, Cleveland (A.L.W.); Thomas Jefferson Medical College, Philadelphia (M.D.E.); McMaster University, Hamilton, ON, Canada (J.W.); University Hospital, Jihlava, Brno, Czech Republic (J.S.); Institute of Cardiology, Warsaw, Poland (W.R.); Cardiology Research Center, Moscow (M.R.); National Hospital Organization, Osaka National Hospital, Osaka, Japan (Y.K.); Quintiles, Durham, NC (J.B., S.P.P., and Daiichi Sankyo Pharma Development, Edison, NJ (M.S., I.P., J.J.H., M.M.)). Address reprint requests to Dr. Giugliano at the Division of Cardiovascular Medicine, Brigham and Women’s Hospital, TIMI Study Group, 350 Longwood Ave., 1st Flr, Boston, MA 02115, or at rggiugliano@partners.org.

Drs. Giugliano and Ruff contributed equally to this article.
• The high-dose edoxaban group received 60 mg, and the low-dose group 30 mg.
• For patients in either group, the dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated creatinine clearance of 30 to 50 ml per minute, a body weight of 60 kg or less, or the concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors).
• Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.
## Standard dosing of direct oral anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Nonvalvular AF–stroke prophylaxis</th>
<th>VTE treatment</th>
<th>VTE primary prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>150 mg twice daily</td>
<td>Parenteral anticoagulation for 5 to 10 days; then dabigatran 150 mg twice daily</td>
<td>110 mg for the first day, then 220 mg once daily</td>
</tr>
<tr>
<td>Apixaban (Elliquis)</td>
<td>5 mg twice daily</td>
<td>10 mg twice daily for one week, then 5 mg twice daily</td>
<td>2.5 mg twice daily</td>
</tr>
<tr>
<td>Betrixaban (Bevyxxa)</td>
<td></td>
<td></td>
<td>160 mg on the first day, followed by 80 mg once daily, with food</td>
</tr>
<tr>
<td>Edoxaban (Savaysa, Lixiana)</td>
<td>60 mg once daily</td>
<td>Parenteral anticoagulation for 5 to 10 days; then edoxaban 60 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>20 mg once daily with the evening meal</td>
<td>15 mg twice daily with food for three weeks; then 20 mg once daily with food</td>
<td>10 mg once daily, with or without food</td>
</tr>
</tbody>
</table>

This is a simplified table that lists the most common dosing in individuals with normal renal function, normal weight, and lack of concomitant interacting medications (e.g., P-glycoprotein inhibitors or inducers). Refer to UpToDate topics on AF, VTE treatment, VTE prophylaxis, and DOAC dosing for possible changes based on impaired renal function or extremes of weight. Other factors may influence dosing in individual patients.

AF: atrial fibrillation; VTE: venous thromboembolism, includes deep vein thrombosis and pulmonary embolism; DOAC: direct oral anticoagulant.

* Dosing may be reduced for certain drugs in certain settings (e.g., use of dabigatran 110 mg twice daily for individuals who are at increased risk of bleeding; refer to UpToDate topic on anticoagulation for atrial fibrillation for other examples)

† Treatment for acute VTE typically refers to the first three to six months of administration; continued treatment beyond six months may be done with a lower dose for some anticoagulants (e.g., apixaban, rivaroxaban); the dose is not lowered when therapy is continued using dabigatran or edoxaban. Refer to the latest prescribing information for each individual anticoagulant.

Δ Prophylaxis refers to primary prophylaxis in settings such as after knee or hip surgery.
Clinical areas whereby a conventional anticoagulant is still drug of Choice

• Patients with Prosthetic valves
• Pregnant ladies with an indication for anticoagulation.
• Patients with severe renal impairment
• Patients with Antiphospholipid syndrome
• Patients who are on warfarin for a long time with a stable INR.
• Cancer associated thrombosis????
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mecurri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Bütler, M.D., for the Hokusai VTE Cancer Investigators

ABSTRACT

BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients

From the University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City (G.E.R.); the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam (N.E., H.R.B.), and ITREAS, Academic Research Organization (A.S.)—both in Amsterdam; the Department of Vascular Medicine and Hemostasis, University Hospital Leuven, Leuven, Belgium (P.V.); Ottawa Hospital Research Institute, Ottawa (M.C.); London Health Sciences Centre-Victoria Hospital, London, ON (M.J.K.); University Health Network, University of Toronto, Toronto (E.Y.), and McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON (J.J.W.)—all in Canada; the Department of Medicine and Aging Sciences, University G. D'Annunzio, Chieti, Italy (M.D.N.); the Department of Medicine, Division of Hematology, University of Washington, Seattle (D.G.), Daiichi Sankyo Pharma Development, Parsippany, NJ (M.A.G., M.F.M., M.S., G.Z.); Thrombosis Research Institute and University College London, London (A.R.K.); the Department of Respiratory Disease, Hôpital Européen Georges-Pompidou, Assistance Publique–Hôpitaux de Paris, Paris (G.M.); the Department of Internal Medi-
• Randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral Edoxaban at a dose of 60 mg once daily (edoxaban group) or

• Subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group).

• Treatment was given for at least 6 months and up to 12 months.
• A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for noninferiority; P=0.87 for superiority).

• Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).
Special situations
Renal excretion of DOACs

- **Dabigatran** – Excretion is approximately 80 to 85 percent renal.
- **Rivaroxaban** – Excretion is approximately 35 percent renal; severe hepatic impairment could result in bio-accumulation.
- **Apixaban** – Excretion is approximately 25 percent renal; severe hepatic impairment could result in bio-accumulation.
- **Edoxaban** – Excretion is approximately 35 percent renal; severe hepatic impairment could result in bio-accumulation.
- **Betrixaban** – Excretion is approximately 11 percent renal, not recommended in hepatic impairment.
Renal impairment

• Using the Cockcroft-Gault equation with creatinine values measured by most laboratories in the United States today will result in a 10 to 40 percent overestimate of creatinine clearance.

• Safest is Apixaban can be used upto Cr/Cl of 25mls/min.

• Dabigatran is the DOAC with the highest element of renal excretion.

• Caution and avoidance in patients who are 80 years of age (preferably avoid).

• Example 88 year old with creatinine of 111 umol/l and weight of 60 kg Cr/Cl would be 29mls/min.
Dyspepsia is a common side effect of dabigatran, with an incidence from 12 to 33 percent in some studies. In the RE-LY trial, which randomized 18,113 individuals with AF to dabigatran or warfarin, non-bleeding gastrointestinal events (eg, dyspepsia, dysmotility, gastrointestinal reflux) were twice as common in those who received dabigatran (16.9 versus 9.4 percent; relative risk [RR] 1.81; 95% CI 1.66-1.97 percent)
Management of major bleeding from DOACs

• Serious/major bleeding is defined as bleeding that is potentially associated with significant blood loss requiring blood transfusion or,
• Bleeding into a critical closed space (eg, intracranial bleeding, compartment syndrome).
• Major bleeding may also include bleeding requiring an intervention for management (eg, surgery, interventional radiology procedures, endoscopic treatments).
Management of bleeding from DOACs

- **Five half lives**: is when 97% of the drug is excreted.
- **Dabigatran** – 12 to 17 hours; five half-lives will have elapsed by day 2.5 to 3.5 after the last dose.
- **Rivaroxaban** – 5 to 9 hours; five half-lives will have elapsed by day 1 to 2 after the last dose.
- **Apixaban** – 8 to 15 hours; five half-lives will have elapsed by day 1.5 to 3 after the last dose.
- **Edoxaban** – 6 to 11 hours; five half-lives will have elapsed by day 1.3 to 2 after the last dose.
- **Betrixaban** – 19 to 27 hours; five half-lives will have elapsed by day 4 to 5.5 after the last dose.
### Direct oral anticoagulant-associated bleeding reversal strategies

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>Agent</th>
<th>Possible interventions</th>
</tr>
</thead>
</table>
| Major bleeding (eg, intracranial, retroperitoneal, compartment syndrome, massive gastrointestinal) | Dabigatran (Pradaxa)                       | • Idarucizumab pronounced "I-dare-you-cizumab"  
• Activated PCC* (eg, FEIBA)  
• Antifibrinolytic agent (eg, tranexamic acid, epsilon-aminocaproic acid)  
• Anticoagulant discontinuation  
• Oral activated charcoal (if last dose within prior two hours)  
• Hemodialysis  
• RBC transfusions if needed for anemia  
• Platelet transfusions if needed for thrombocytopenia or impaired platelet function (eg, due to aspirin)  
• Surgical/endooscopic intervention if appropriate |
|                                                                                  | Rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana), betrixaban (Bevyxxa) | • 4-factor unactivated PCC* (eg, Kcentra)  
• Antifibrinolytic agent (eg, tranexamic acid, epsilon-aminocaproic acid)  
• Anticoagulant discontinuation  
• Oral activated charcoal (if last dose recent enough)  
• RBC transfusions if needed for anemia  
• Platelet transfusions if needed for thrombocytopenia or impaired platelet function (eg, due to aspirin)  
• Surgical/endooscopic intervention if appropriate |
Preoperative management of patients on DOACs
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Renal function and dose</th>
<th>Interval between last dose and procedure</th>
<th>Resumption after procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>NOTE: No anticoagulant is administered the day of the procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt; 50 ml/minute; Dose 150 mg twice daily</td>
<td>Give last dose three days before procedure (i.e., skip four doses on the two days before the procedure)</td>
<td>Give last dose two days before procedure (i.e., skip two doses on the day before the procedure)</td>
</tr>
<tr>
<td></td>
<td>CrCl 30 to 50 ml/minute; Dose 150 mg twice daily</td>
<td>Give last dose five days before procedure (i.e., skip eight doses on the four days before the procedure)</td>
<td>Give last dose three days before procedure (i.e., skip four doses on the two days before the procedure)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt; 50 ml/minute; Dose 20 mg once daily</td>
<td>Give last dose three days before procedure (i.e., skip two doses on the two days before the procedure)</td>
<td>Give last dose two days before procedure (i.e., skip one dose on the day before the procedure)</td>
</tr>
<tr>
<td></td>
<td>CrCl 30 to 50 ml/minute; Dose 15 mg once daily</td>
<td>Give last dose three days before procedure (i.e., skip two doses on the two days before the procedure)</td>
<td></td>
</tr>
</tbody>
</table>
## Perioperative management of oral direct thrombin inhibitors and factor Xa inhibitors

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Renal function and dose</th>
<th>Interval between last dose and procedure</th>
<th>Resumption after procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>NOTE: No anticoagulant is administered the day of the procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt;50 mL/minute</td>
<td>Give last dose three days before procedure (ie, skip two doses on the two days before the procedure)</td>
<td>Resume 48 to 72 hours after surgery (ie, postoperative day 2 to 3)</td>
</tr>
<tr>
<td></td>
<td>Dose 20 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 30 to 50 mL/minute</td>
<td>Give last dose two days before procedure (ie, skip one dose on the day before the procedure)</td>
<td>Resume 24 hours after surgery (ie, postoperative day 1)</td>
</tr>
<tr>
<td></td>
<td>Dose 15 mg once daily</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>CrCl &gt;50 mL/minute</td>
<td>Give last dose three days before procedure (ie, skip four doses on the two days before the procedure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose 5 mg twice daily</td>
<td>Give last dose two days before procedure (ie, skip two doses on the day before the procedure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl ≤50 mL/minute</td>
<td>Give the last dose three days before the procedure (ie, skip two doses on the two days before the procedure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose 2.5 mg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>CrCl 50 to 95 mL/minute</td>
<td>Give the last dose two days before the procedure (ie, skip one dose on the day before the procedure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose 60 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl ≤50 mL/minute*</td>
<td>Give the last dose two days before the procedure (ie, skip two doses on the two days before the procedure)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose 30 mg once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Management of perioperative patients requiring Neuraxial anesthesia on DOACs

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of days to stop medication in normal renal function patients (&gt;50 ml/min)</th>
<th>No. of days to stop the medication renal impaired patients (Creatinine clearance of 30-50mls/min)</th>
<th>Resumption of a DOAC postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (American Heart association)</td>
<td>5 days preoperatively</td>
<td>7 days</td>
<td>1-day</td>
</tr>
<tr>
<td>Rivaroxaban (European Society of Anaesthesiology)</td>
<td>22hrs-26hrs</td>
<td>No advice</td>
<td>4-6 hrs</td>
</tr>
<tr>
<td>Rivaroxaban (American heart association)</td>
<td>3 days</td>
<td>5 days</td>
<td>1 day</td>
</tr>
<tr>
<td>Rivaroxaban (FDA) 20-45 years of age</td>
<td>18 hrs</td>
<td>No advice</td>
<td>No advice</td>
</tr>
<tr>
<td>Rivaroxaban (FDA) 60-76 yrs of age</td>
<td>26hrs</td>
<td>No advice</td>
<td>No Advice</td>
</tr>
</tbody>
</table>
American Society of Regional Anesthesia and Pain Medicine  ASRA
While work continues on the full 4th Edition of this Practice Advisory, we are publishing the draft recommended time intervals before and after neuraxial block or catheter removal:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time before puncture/catheter manipulation or removal</th>
<th>Time after puncture/catheter manipulation or removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>5 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>3 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>7-10 days</td>
<td>6 hours</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>5-7 days</td>
<td>6 hours</td>
</tr>
</tbody>
</table>

*Developed at 4th ASRA Practice Advisory for Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy

Draft recommended time intervals
Conclusion

• DOACs have been found to be efficacious on VTE prophylaxis post operatively and in treatment of VTE and in treatment of patients with Atrial fibrillation
• If you are to use choose to use a DOAC at your institution choose one to avoid confusion in doses
• Avoid its use in patient above age of 80 and patient with creatinine clearance of <30mls/min.
• Have a protocol that deals with how to treat patients presenting with major bleed and preoperative management.
Thank you for your attention
Thrombin structure showing active site

References: