Cardioversion, whether pharmacological or electrical, is associated with a risk of thromboembolic events on the order of 5% to 7% within 30 days in nonanticoagulated patients.\textsuperscript{1,2} The risk of thromboembolism is at its highest within the first 7 days after cardioversion (>80% of events), with the greatest risk within the first 2 days (~70% of events).\textsuperscript{3} Thus, the incidence of thromboembolic events within the first week is analogous to the yearly incidence in moderate-risk nonvalvular atrial fibrillation (NVAF) patients who have not undergone cardioversion. This risk can be mitigated to <1% within 30 days with the use of therapeutic anticoagulation before, during, and after cardioversion.\textsuperscript{3} Thromboembolic risk is not negated by a low CHADS\textsubscript{2} (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack), or CHA\textsubscript{2}DS\textsubscript{2}-VASc (adding vascular disease, age 65–74 years, and female sex) score or by a negative transthoracic esophageal echocardiogram (TEE) because of thrombus formation after cardioversion because of left atrial stunning.\textsuperscript{3,4} The single biggest risk factor for thrombus formation is inadequate anticoagulation.\textsuperscript{4}

The conventional approach is to anticoagulate, most commonly with an oral vitamin K antagonist (VKA), for a minimum of 3 weeks before, during, and for a minimum of 4 weeks postcardioversion. The recommendation to anticoagulate for 3 weeks before cardioversion is based on pathophysiologic and observational data, but has not been confirmed by randomized controlled trials.\textsuperscript{5,6} In addition, the retrospective analysis by Gallagher et al demonstrated that thromboembolic events were significantly more common at international normalized ratio (INR) 1.5 to 2.4 versus ≥2.5 (0.93% versus 0%, \(P=0.012\)), reinforcing the importance of establishing therapeutic anticoagulation before cardioversion.\textsuperscript{7} Prior studies evaluating parenteral anticoagulation as a means to expedite time to cardioversion over conventional oral VKA therapy have all ensured “therapeutic anticoagulation” at the time of cardioversion. These studies have shown noninferiority between parenteral anticoagulation and conventional therapy, with cardioversion time ranging from 1 to 3 days versus 21 to 30 days, respectively.\textsuperscript{8,9}

Though the benefits of oral VKAs have long been established in NVAF with respect to stroke reduction, VKAs have the disadvantages of required monitoring and follow-up, complex drug and food interactions, a narrow therapeutic range, and slow onset of action.\textsuperscript{10–14} Since 2010, the US Food and Drug Administration (FDA) has approved the oral direct thrombin inhibitor (DTI) dabigatran (Pradaxa) and 3 oral factor Xa (FXa) inhibitors rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) for prevention of stroke and systemic embolism (SSE) in patients with NVAF.\textsuperscript{15} These agents have all shown either superiority or noninferiority to warfarin in reducing the risk of SSE in this patient population with similar or reduced major bleeding.\textsuperscript{16–19} In these clinical trials, all of these agents have shown a reduction in the risk of intracranial hemorrhage as compared with warfarin.

Oral DTI and oral FXa inhibitors have the potential advantages of a rapid onset, fixed dosing, no required routine monitoring, and fewer drug/food interactions as compared with VKAs. Of particular interest is the rapid onset of action and the potential to avoid parenteral anticoagulation and the delay in action of VKAs, culminating in faster time to cardioversion, improved maintenance of sinus rhythm, and potentially reduced hospitalization days and health-system costs.\textsuperscript{20–23} As such, these agents offer a potential alternative to conventional anticoagulation strategies for cardioversion. However, there is discordance between the major guidelines pertaining to how best to utilize these agents pericardioversion.\textsuperscript{5,20–26}
Given the lack of data, inconsistencies among the guidelines, and the expanding role of oral DTI and oral FXa inhibitor anticoagulants, we reviewed the literature evaluating dabigatran, rivaroxaban, apixaban, and edoxaban in patients requiring cardioversion for atrial fibrillation (AF). Furthermore, we evaluated the pharmacokinetic and pharmacodynamic data for each agent to determine the optimal timing of administration to achieve therapeutic anticoagulation and thus be safely eligible for early cardioversion.

Current Guideline Recommendations

Current AF guidelines all recommend 3 weeks of therapeutic anticoagulation with oral anticoagulation therapy (VKA, DTI, or FXa inhibitors) before cardioversion.5,20,24–26 When early cardioversion is required, all guidelines recommend TEE to exclude the presence of left atrial thrombus. However, when addressing how soon after initiation of anticoagulation cardioversion is safe, ambiguity emerges among the guidelines. The American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), and CHEST guidelines recommend attainment of “therapeutic” parenteral anticoagulation before cardioversion.5,20 The CHEST guidelines suggest that oral DTI and oral FXa inhibitors may be suitable for cardioversion with no recommendation on timing of doses precardioversion other than to state that dabigatran achieves steady state in 2 to 3 days.5 It is important to note that only dabigatran and rivaroxaban were

Table 1. Current Guideline Recommendations

| Feature                                      | 2014 AHA/ACC/HRS20 | 2012 CHEST25 | 2016 EHRA24,25 | 2014 CCS26 |
|----------------------------------------------|--------------------|--------------|----------------|------------|
| Anticoagulation before cardioversion for AF <48 h | IV therapeutic heparin Therapeutic enoxaparin FXa inhibitor, or DTI (Class I, level of evidence C) | IV therapeutic heparin Therapeutic enoxaparin (Grade IIc) | IV therapeutic heparin Therapeutic enoxaparin (Class IIa, level of evidence B) | FXa inhibitor, or DTI preferred over warfarin Bridging to warfarin with therapeutic heparin or enoxaparin (level of evidence moderate) |
| Anticoagulation before cardioversion for AF ≥48 h | Warfarin (INR 2–3) (Class I, level of evidence B) FXa inhibitor, or DTI (Class IIa, level of evidence C) | Warfarin (INR 2–3) DTI (Grade IB) | Warfarin (INR 2–3) FXa inhibitor, or DTI (Class IIa, level of evidence B) | FXa inhibitor, or DTI preferred over warfarin Bridging to warfarin with therapeutic heparin or enoxaparin (level of evidence moderate) |
| Time from first anticoagulation dose to cardioversion in AF <48 h | As soon as possible before or immediately after cardioversion (Class I, level of evidence C) | As soon as possible before presentation to the hospital (Grade IIc) | As soon as possible before cardioversion (Class IIa, level of evidence B) | No immediate initiation of anticoagulation in low-risk patient (level of evidence moderate) After 1 dose of FXa inhibitor or DTI or a dose of therapeutic enoxaparin bridge with warfarin (level of evidence low) |
| Time from first anticoagulation dose to cardioversion in AF ≥48 h | 3 wks (Class I, level of evidence B) As soon as possible for immediate cardioversion (Class I, level of evidence C) | 3 wks (Grade IB) Before cardioversion for immediate cardioversion (Grade IB) | 3 wks (Class I level of evidence B) At least 4 h after FXa inhibitor or DTI* | 3 wks (level of evidence moderate) After 1 dose of FXa inhibitor or DTI or a dose of therapeutic enoxaparin bridge with warfarin (level of evidence low)* |
| Duration of anticoagulation post cardioversion in AF <48 h | May consider not to continue post cardioversion (Class IIIb, level C evidence Long-term pending risk factors (Class I, level of evidence C) | 4 wks (grade IIc) | 4 wks (Class I level of evidence B) | Duration to be determined upon follow-up in clinic in low-risk patient (level of evidence moderate) 4 wks for high-risk patients (level of evidence low) |
| Duration of anticoagulation post cardioversion in AF ≥48 h | 4 wks (Class I, level of evidence C) | 4 wks (grade IB) | 4 wks (Class I, level of evidence B) | 4 wks (level of evidence moderate) |

AF indicates atrial fibrillation; AHA/ACC/HRS, American Heart Association/American College of Cardiology/Heart Rhythm Society; CCS, Canadian Cardiovascular Society; CHEST, American College of Chest Physicians; DTI, direct thrombin inhibitor; EHRA, European Heart Rhythm Association; FXa inhibitor, factor Xa inhibitor; INR, international normalized ratio; IV, intravenous; TEE, transesophageal echocardiogram; wks, weeks.

*TTE is required if plan to proceed with cardioversion 4 h post factor Xa or direct thrombin inhibitor.

*TEE is required before proceeding with cardioversion.
FDA-approved therapies at the time the CHEST guidelines were constructed and these agents were not well studied in the setting of cardioversion. The European Heart Rhythm Association guideline states “anticoagulation with heparin or oral DTI or oral FXa inhibitors should be initiated as soon as possible” without giving a minimum time frame before cardioversion.24 Similarly, the AHA Scientific Statement on Management of oral DTI and FXa inhibitors in the Acute Care and Periprocedural Setting do not provide a minimum time frame or number of doses of anticoagulant before cardioversion.27 Finally, the European Heart Rhythm Association practical guide on the use of oral DTI and FXa inhibitors and Canadian guidelines both recommend a single dose of either a parenteral anticoagulant or oral DTI or oral FXa inhibitor anticoagulant before cardioversion.25,26 The European Heart Rhythm Association recommends the oral DTI/oral FXa inhibitor anticoagulant be administered at least 4 hours before cardioversion, whereas the Canadian guidelines do not specify timeline between administration and cardioversion (Table 1).

Pharmacokinetic Properties

All 4 anticoagulants share similarities, yet subtle differences among their respective pharmacological properties can have important implications for dosing pericardioversion (Table 2).

### Dabigatran

Dabigatran is the only FDA-approved oral DTI currently in use. The time to maximal plasma concentration (Tmax) postdose is 2 hours but can be prolonged until 4 hours if co-administered with food.28 On average, the half-life is 12 to 17 hours but can be substantially prolonged (upwards of 27 hours) depending on the degree of renal impairment.29,30 Steady state is typically obtained in 2 to 3 days.30 When evaluating accumulation over time (single dose versus multidose studies), both the peak concentrations (Cmax) and total concentrations (AUC) are increased. Day 7 compared with a single dose displays a 2- to 2.3-fold higher Cmax and a 1.4- to 1.6-fold higher AUC.28,29 No statistical analyses were provided for these comparisons.

### Rivaroxaban

Rivaroxaban was the first FDA-approved oral FXa inhibitor. The Tmax is 2 to 4 hours after ingestion. The half-life is 5 to 9 hours in younger patients and 11 to 13 hours in elderly patients (≥75 years), with attainment of steady-state concentrations in ≈48 hours.31–33 In single- versus multidose pharmacokinetic studies, rivaroxaban demonstrated no relevant time-dependent accumulation in either AUC (0.85- to 1.13-fold) or estimated Cmax (0.92- to 1.25-fold) from day 1 to day 7.33 No statistical analyses were provided for these comparisons.

### Apixaban

Apixaban has a Tmax of 3 to 4 hours, a half-life of ≈12 hours (range 8–15 hours), and a time to steady state of ≈48 to 72 hours.34,35 In single- versus multidose pharmacokinetic studies, apixaban demonstrated time-dependent accumulation

|                              | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|------------------------------|------------|-------------|----------|----------|
| Tmax, h                      | 2–4        | 2–4         | 3–4      | 1–2      |
| Half-life, h                 | 12–17      | 5–13        | 8–15     | 8–11     |
| Time to steady state, h      | 48–72      | 48          | 48–72    | 48       |
| Cmax accumulation            | Yes (2–2.3×) | No (0.9–1.3×) | Yes (1.3–1.5×) | No (0.9–1.2×) |
| AUC accumulation             | Yes (1.4–1.6×) | No (0.9–1.1×) | Yes (1.3–1.8×) | Yes (1–1.5×) |
| Data to support <3 wks anticoagulation precardioversion | Observational cohort | Prospective RCT, observational cohort | Prospective RCT, observational cohort | Prospective RCT |
| Recommended minimum time on anticoagulant precardioversion | 48–72 h | One dose at least 4 h prior | 48–72 h | One dose at least 2 h prior |
| Data to support loading dose | No | No | RCT 5–10 mg at least 2 h before cardioversion | No |

Pharmacokinetic ratios <1 were considered not to indicate drug accumulation whereas ratios ≥1 were considered to indicate drug accumulation. Anti-Xa indicates anti-factor Xa; AUC, total concentration; Cmax, peak concentration; h, hour; RCT, randomized control trial; Tmax, time to maximal plasma concentration.
with both AUC and Cmax increasing by 1.3- to 1.8- and 1.3- to 1.5-fold from day 1 to day 7, respectively.\textsuperscript{35}

Of note, the Cmax and AUC for 10 mg once daily on day 1 were both higher than the corresponding values for the 5 mg twice daily on day 1 and day 7. No statistical analyses were provided for these comparisons.

### Edoxaban

Edoxaban has a time to maximal plasma concentration of 1 to 2 hours, a half-life of 8 to 11 hours, and a time to steady state of 48 hours.\textsuperscript{36} In single- versus multidose pharmacokinetic studies, edoxaban exposure failed to increase in a time-dependent manner. The Cmax did not increase to any appreciable extent over the range of doses studied, 0.94- to 1.15-fold and AUC accumulated minimally, 1.1- to 1.45-fold, from day 1 to day 10.\textsuperscript{37} Though statistically significant accumulation was noted with twice-daily dosing regimens, “negligible accumulation was observed with daily doses.”\textsuperscript{37}

### Pharmacodynamic Properties

#### Dabigatran

Pharmacodynamic studies indicate a time-dependent prolongation of all coagulation parameters. The activated partial thromboplastin time (aPTT), prothrombin time (PT), reported as INR, thrombin time, and ecarin clotting time are all prolonged by 1.2- to 1.5-, 1.2- to 1.8-, 0.5- to 1.4-, and 1.5- to 1.8-fold, respectively, when evaluating single-dose versus multidose effects.\textsuperscript{28,29} No statistics were provided for these comparisons. Of note, the thrombin time was the only parameter failing to consistently show accumulation over time. One dose (the highest dose) was responsible for this, with all other doses revealing accumulation (1.3- to 1.4-fold). The aPTT and PT are considered more as qualitative measures and thrombin time and ecarin clotting time as quantitative measures of dabigatran activity.\textsuperscript{38}

#### Rivaroxaban

In single- versus multidose pharmacodynamic studies, PT, aPTT, and anti-factor Xa (anti-Xa) levels were the same on day 1 and day 7.\textsuperscript{32,33} No statistical analyses were provided for these comparisons. The PT is considered more of a qualitative measure, with anti-Xa as a quantitative measure and aPTT as an unreliable marker for assessing rivaroxaban activity.\textsuperscript{38}

#### Apixaban

In single- versus multidose pharmacodynamic studies, estimated INR (0.8- to 1.3-fold), aPTT (0.9- to 1.2-fold), and modified prothrombin time (1- to 1.4-fold) were all found to increase in a time-dependent manner with increases most prominent at higher dosages (ie, 10 and 20 mg twice daily) and once steady state was achieved.\textsuperscript{35} No statistical analyses were provided for these comparisons. Similar to rivaroxaban, anti-Xa is considered a quantitative measure, as is modified prothrombin time, but both aPTT and PT are unreliable markers for assessing apixaban activity.\textsuperscript{38}

### Outcome Data

#### Dabigatran

The only randomized prospective trial evaluating cardioversion in patients treated with dabigatran is a post hoc analysis of the RE-LY (Randomized evaluation of long-term anticoagulant therapy: dabigatran vs. warfarin) trial, which evaluated 1270 patients (7% of the 18 113 patients enrolled) allocated to dabigatran versus warfarin for NVAF and found no difference in 30-day outcomes.\textsuperscript{39} For dabigatran 110 mg twice daily, 150 mg twice daily, and dose-adjusted warfarin, SSE were 0.8%, 0.3%, and 0.6%, respectively; dabigatran 110 mg versus warfarin, \( P=0.71 \); dabigatran 150 mg versus warfarin, \( P=0.40 \). Major bleeding occurred in 1.7%, 0.6%, and 0.6%, respectively; dabigatran 110 mg versus warfarin, \( P=0.06 \); dabigatran 150 mg versus warfarin, \( P=0.99 \). Most patients were anticoagulated for 3 weeks before cardioversion, with \( \approx7\% \) anticoagulated <3 weeks. No data were provided on outcomes pertaining to time from anticoagulation to cardioversion (Table 3).
| Study | Number Enrolled (N) | Intervention (N) | AVG CHADS2–VASc or CHADS2 Score | Previous Stroke or TIA (% Patients) | Time From First Anticoagulation Dose to Cardioversion | Duration of Anticoagulation Post Cardioversion | Significant or Serious Bleed | Stroke or Systemic Embolism |
|-------|----------------------|------------------|---------------------------------|-------------------------------------|-----------------------------------------------------|-----------------------------------------------|-----------------------------|-----------------------------|
| Dabigatran | **Cardioversion in Dabigatran** | | | | | | | |
| Nagarakanti, 2011, post hoc analysis of RCT | 1270* | Cardioversion in Dabigatran 150 mg twice daily (672) | CHADS2 2.1±1* | Not reported | Dabigatran 150 mg 20.3 | Majority ≥3 wks ~7% < 3 wks | Not reported | Dabigatran 150 mg 0.6% vs Warfarin 0.6%, RR 0.99, 95% CI (0.25–3.93) |
| | | Cardioversion in Dabigatran 110 mg twice daily (647) | | | Dabigatran 110 mg 19.9 | | | Dabigatran 110 mg 0.77% vs Warfarin 0.6%, RR 1.28, 95% CI (0.35–4.76) |
| | | Cardioversion in Warfarin (664) | | | Warfarin 15 mg 18.5 | | | Dabigatran 150 mg 0.3% vs Warfarin 0.6%, RR 0.49, 95% CI (0.09–2.69) |
| Rivaroxaban | **Rivaroxaban** | | | | | | | |
| ROCKET AF, (Piccini, 2013), post hoc analysis of RCT | 321† | Rivaroxaban 20 mg daily or 15 mg with CrCl 30 to 49 mL/min (160) | CHADS2 3 | Not reported | Rivaroxaban 51.3 | Not reported | Not reported | Rivaroxaban 18.75% vs warfarin 13.04%, P=0.459 |
| X-Vert, (Cappato, 2014), open label | 1504 | Early: Rivaroxaban 20 mg daily or 15 mg with CrCl 30–49 mL/min (585) | CHADS2-VASc ≥2 | Not reported | Early: Rivaroxaban 5.7 | Early: between 1 and 5 d (min 4 h post rivaroxaban dose) | Early: 6 wks | Rivaroxaban 0.61% vs warfarin 0.8%, RR 0.76, 95% CI (0.21–2.67) |
| | | Warfarin (287) | | | Warfarin 7.3 | | | Rivaroxaban 0.51% vs warfarin 1.02%, RR 0.5, 95% CI (0.15–1.73) |
| | | Delayed: Rivaroxaban 20 mg daily or 15 mg with CrCl 30–49 mL/min (417) | | | Delayed: Rivaroxaban 5.8 | Delayed: 3 wks | Delayed: 8 wks | Delayed: Rivaroxaban 0% vs Warfarin 0%, P=0.459 |
| | | Warfarin (215) | | | Warfarin 7.9 | | | Rivaroxaban 0.61% vs warfarin 0.8%, RR 0.76, 95% CI (0.21–2.67) |
| Enomoto, 2016, prospective clinical trial | 91 | Early: Rivaroxaban 15 or 10 mg daily with CrCl 30–50 mL/min (51) | Early: CHADS2-VASc 1.8±1.3 | Early: 1.3±0.9 | Not reported | Early: 2 h | Early: 4 wks | 1 patient reported minor bleeding (HAS-BLED=3) |
| | | Warfarin (40) | | | | | | No thromboembolic events reported |
| | | Delayed: Rivaroxaban 15 or 10 mg daily with CrCl 30–50 mL/min (40) | | | Delayed: 1.2±0.9 | Delayed: 3 wks | Delayed: 4 wks | Delayed: Rivaroxaban 0.51% vs warfarin 1.02%, RR 0.5, 95% CI (0.15–1.73) |
| Apixaban | **Apixaban** | | | | | | | |
| ARISTOTLE, (Flaker, 2014), post hoc analysis of RCT | 540† | Apixaban 5 mg twice daily unless ≥2 of the following were met: age ≥80 years, body weight ≤60 kg, or Scr ≥1.5 mg/dL (265) | CHADS2 1.9±1 | Not reported | Apixaban 12.5 | Apixiban 25±248 days (min 1 day) | Apixaban 0.3% vs Warfarin 0.2%, Warfarin 0% |
| | | Warfarin (275) | | | Warfarin 15.6 | Warfarin 243±231 days (min 4 days) | Warfarin 0% |

Table 3. Randomized Clinical Trials DOAC in Cardioversion
Table 3. Continued

| Study                | Number Enrolled (N) | Intervention (N)                                                                 | AVG CHADS₂-VASc or CHADS₂ Score | AVG HAS-BLED Score | Previous Stroke or TIA (% Patients) | Time From First Anticoagulation Dose to Cardioversion (2.5 doses of apixaban, min 2 h) | Duration of Anticoagulation Post Cardioversion | Significant or Serious Bleed | Stroke or Systemic Embolism |
|----------------------|---------------------|----------------------------------------------------------------------------------|----------------------------------|--------------------|-------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------|-----------------------------|
| EMANATE (Ezekowitz, 2018), RCT, open label | 1500                | Apixaban 5 mg twice daily unless ≥2 of the following were met: age ≥ 80 y, body weight ≤ 60 kg, or SCR ≥ 1.5 mg/dL (753)** Warfarin- heparin (747) | CHADS₂-VASc 2.4 | Not reported | Not reported | 2.5 doses of apixaban, min 2 h)** | 4 weeks | Apixaban 0.41% Warfarin-heparin 0.83%† | Apixaban 0% vs warfarin-heparin 0.83% (P=0.0164) |
| ENGAGE AF-TIMI 48, (Pitt, 2016), post hoc analysis of RCT | 365†‡ | High dose: Edoxaban 60 mg daily, or 30 mg daily for CrCl 15 to 50 mL/min, body weight ≤ 60 kg, or concurrent use of P-glycoprotein inhibitors (140). Low dose§: Edoxaban 30 mg daily, or 15 mg daily for CrCl 15 to 50 mL/min, bodyweight ≤ 60 kg, or concurrent use of P-glycoprotein inhibitors (111) Warfarin (114) | CHADS₂ ≤ 3 | Not reported | Not reported | Median 348 days (IQR 86–526 days) | 4 wks | No major bleeding reported | Warfarin 0% High dose edoxaban 0% Low dose edoxaban 1.81%† |
| ENSURE-AF (Goette, 2016), RCT, open label | 2199                | TEE guided: Edoxaban 60 mg daily or 30 mg for CrCl 15 to 50 mL/min, bodyweight ≤ 60 kg, or concurrent use of P-glycoprotein inhibitors (589) Warfarin- enoxaparin (594) | CHADS₂-VASc 2.6 | Not reported | TEE guided: Edoxaban 7 Warfarin- enoxaparin 8 | TEE guided: 3 days (median 2 days, min 2 h post edoxaban) | 28 days | Edoxaban 1% vs warfarin-enoxaparin 1%, OR 1.48%, 95% CI (0.64–3.55) | Edoxaban <1% vs warfarin-enoxaparin <1%, OR 0.67, 95% CI (0.06–5.88) |

AVG indicates average; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; EMANATE, Eliquis evaluated in acute cardioversion compared to usual treatments for Anticoagulation in subjects with atrial fibrillation; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; ENSURE-AF, Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation; Kg, kilogram; h, hour; IQR, interquartile range; min, minimum; ml/min, milliliter per minute; OR, odds ratio; RCT, randomized controlled trial; RE-LY, randomized evaluation of long-term anticoagulant therapy: dabigatran vs. warfarin; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, risk ratio; SCR, serum creatinine; TEE, transesophageal echocardiography; TIA, transient ischemic attack; wk, weeks; X-VeRT, explore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion.

*Total of 1983 cardioversion in 1270 patients.
†Data from RELY trial.
‡Not clear how many doses of dabigatran patient received.
§Including patients with catheter ablations.
∥No statistical analysis performed.
¶Non US Food and Drug Administration approved dosing.
**Total of 743 cardioversion in 365 patients.
***342 patients received apixaban load (10 mg n=331, 5 mg n=11).
∥∥Min 2 h in patient who received 10 or 5 mg apixaban load.
‡‡Total of 632 cardioversion in 365 patients.
Several retrospective observational studies have been conducted with the majority of patients receiving at least 3 weeks anticoagulation (at FDA-approved dosages) before cardioversion\(^\text{48–54}\) (Table S1). One study required a minimum of 24 hours of anticoagulation before cardioversion\(^\text{55}\) and 1 study did not comment on timeline between dose and cardioversion.\(^\text{56}\) Three of the studies evaluated dabigatran and FXa inhibitors.\(^\text{49,54,55}\) The majority of studies indicated similar SSE and/or major bleeding outcomes between dabigatran compared with warfarin\(^\text{50–56}\) or rivaroxaban\(^\text{49}\) in cardioverted patients. One study did not report on outcomes\(^\text{48}\) and another only evaluated dabigatran without a comparator arm, though event rates were similar to those for warfarin-treated patients documented in the literature.\(^\text{5}\) Femia et al evaluated 284 patients: 109 patients anticoagulated with warfarin and 175 with dabigatran, apixaban, or rivaroxaban.\(^\text{55}\) Of those in the oral DTI and oral FXa inhibitor groups, 54% underwent short-duration anticoagulation, receiving cardioversion within 5 days of initiating anticoagulation (no further information reported on this subset of patients). At 8 weeks of follow-up, the short-duration anticoagulation group demonstrated similar rates of ischemic stroke (0% versus 1.3%, \(P=0.46\)) and major bleeding (1.1% versus 2.5%, \(P=0.59\)) end points compared with patients anticoagulated \(>5\) days before cardioversion (mean duration not reported). A consistent finding among the studies was a faster time to cardioversion (24%–48% reduction in the number of days) with dabigatran use versus warfarin. This is of clinical importance because shorter duration between the onset of AF and cardioversion is associated with improved success of cardioversion.\(^\text{48}\)

Dabigatran has not yet been evaluated in a randomized trial of early versus delayed time to cardioversion.

### Rivaroxaban

In a post hoc analysis of the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, 364 out of the 14 264 patients enrolled in the main trial underwent cardioversion or ablation without a difference in the incidence of SSE at a mean follow-up of 2.1 years (1.88% in rivaroxaban versus 1.86% in the warfarin arm).\(^\text{45}\) Rivaroxaban was dosed at 20 or 15 mg daily in those with creatinine clearance (CrCl) 30 to 49 mL/min versus dose-adjusted warfarin. The incidence of major bleeding or nonmajor clinically relevant bleeding was also similar between the 2 groups (18.75% in rivaroxaban versus 13.04% in the warfarin group), though no statistical analysis was performed given the small number of events. This study investigated outcomes in subjects who went through cardioversion (n=285) and ablation (n=79). Time from first anticoagulation dose to cardioversion was not reported (Table 3).

The use of rivaroxaban in cardioversion was further evaluated in the X-VeRT (explore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion) trial.\(^\text{41}\) In this randomized, prospective, open-label trial, which is the first randomized trial utilizing any of the oral DTI or oral FXa inhibitors in patients undergoing cardioversion, 1504 subjects who had NVAF \(>48\) hours were assigned to rivaroxaban 20 mg daily (15 mg daily with CrCl 30–49 mL/min) or dose-adjusted VKA with or without parenteral anticoagulation before cardioversion until INR goal (2–3) was achieved. Of note, 66.5% of the early cardioversion group received TEE before cardioversion. Parenteral anticoagulation was used for bridging while the INR was subtherapeutic. The primary efficacy end point was the composite of stroke, transient ischemic attack, peripheral embolism, myocardial infarction, and cardiovascular death. The primary safety outcome was major bleeding. Patients underwent either early (1–5 days, 58% of patients) or delayed cardioversion (3–8 weeks, 42% of patients). In the early group, the median time to cardioversion was 1 day (interquartile range 1–2 days). Rivaroxaban was initiated at least 4 hours before cardioversion. At 30-day follow-up, the primary efficacy end point occurred in 0.51% of subjects in the rivaroxaban group and 1.02% in the VKA group (risk ratio 0.50; 95% confidence interval 0.15–1.73). Major bleeding occurred in 0.6% of patients in the rivaroxaban group and in 0.8% of patients in the VKA group (risk ratio 0.76; 95% confidence interval 0.21–2.67). In the early cardioversion group, 4 patients experienced primary outcome in the rivaroxaban group (0.71%) versus 2 patients in the VKA group (1.08%). In the delayed cardioversion group, 1 primary outcome event occurred in the rivaroxaban group (0.24%) versus 2 events in the VKA group (0.93%). Time to cardioversion was shorter for the rivaroxaban group compared with the VKA group: 22 days versus 30 days, respectively, \(P<0.001\). Though no statistical differences were noted in outcomes, there were more thromboembolic events in early versus delayed rivaroxaban groups: 0.71% versus 0.24%, and a lower risk of bleeding: 0.52% versus 0.73% (possibly because of less time on anticoagulation) (Table 3). The small sample size (1504 patients) was underpowered to detect a statistical difference, a theme common among most of these trials, and should be considered with caution because the wide confidence intervals do not eliminate a risk for increased events. It has been estimated that >40 000 patients would be required to achieve adequate power in detecting differences in thromboembolic events—a trial that is unlikely to be conducted.\(^\text{41,44}\) Regardless, both early and delayed strategies reported thromboembolic event rates (0.24%–1.08%)\(^\text{41}\) similar to prior trials of conventional

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anticoagulation (0–1.88%) and an order of magnitude lower than historical trials without the use of anticoagulation (5%–7%) (Table 4).1,2

In the study by Enomoto et al, 91 Japanese subjects with NVAF >48 hours were consecutively allocated to rivaroxaban at least 2 hours before cardioversion (group 1), or rivaroxaban 3 weeks before cardioversion (group 2).42 Dose was determined by CrCl: 15 mg daily if CrCl >50 mL/min; and 10 mg daily for CrCl 30 to 50 mL/min. No thromboembolic or major bleeding events were reported in the study groups at 30 days of follow-up. Time to cardioversion was shorter for group 1 compared with group 2, 3.6 days versus 22.4 days, respectively (no statistical analysis provided). This trial was the smallest of the early cardioversion trials, enrolling a total of 91 patients. Other issues included the nonrandomized nature, use of non-FDA-approved doses, conducted outside of the United States, and the longest time to cardioversion in the early group at an average of 3.6 days, (Table 3).

Table 4. Comparison of Conventional or Delayed Versus Early Cardioversion Trials

| Study          | Drug    | Efficacy Outcome: Stroke or Systemic Embolism, N (%) | Safety Outcome: Major Bleed, N (%) | Death, N (%) |
|---------------|---------|------------------------------------------------------|-----------------------------------|--------------|
| Conventional or delayed cardioversion group |         |                                                      |                                   |              |
| RE-LY post hoc39 | Dabigatran D110: 5/647 (0.77%) D150: 2/672 (0.3%) | D110:11/647 (1.7%) D150: 4/672 (0.60%) | Not reported |
| ROCKET-AF post hoc40 | Rivaroxaban 3/160 (1.88%) | 30/160 (18.75%)† | 3/160 (1.88%) |
| ARISTOTLE post hoc41 | Apixaban 0/331 (0%) | 1/331 (0.30%) | 2/331 (0.60%) |
| ENGAGE AF-TIMI 48 post hoc46 | Edoxaban HDE: 0/140 (0%) LDE: 2/140 (1.43%) | HDE: 0/140 (0%)† LDE: 0/140 (0%)† | HDE: 1/140 (0.71%) LDE: 0/140 (0%) |
| X-VerT41 | Rivaroxaban 0/411 (0%) | 3/411 (0.73%) | 2/411 (0.49%) |
| Enomoto et al42 | Rivaroxaban 0/40 (0%) | 0/40 (0%) | Not reported |
| ENSURE-AF47 | Edoxaban 2/506 (0.40%) | 0/506 (0%) | Not reported |
| Early cardioversion group |         |                                                      |                                   |              |
| X-VerT41 | Rivaroxaban 2/567 (0.35%) | 3/567 (0.53%) | 3/567 (0.53%) |
| Enomoto et al42 | Rivaroxaban 0/51 (0%) | 0/51 (0%) | Not reported |
| EMANATE44,45 | Apixaban 0/753 (0%) | 3/753 (0.40%) | 2/753 (0.27%) |
| ENSURE-AF47 | Edoxaban 1/598 (0.17%) | 3/598 (0.51%) | Not reported |

ARISTOTLE indicates Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; D110, dabigatran 110-mg dose; D150, dabigatran 150-mg dose; EMANATE, Eliquis evaluated in acute cardioversion compared to usual treatments for Anticoagulation in subjects with atrial fibrillation; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48; ENSURE-AF, Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation; HDE, high-dose edoxaban (60 or 30 mg if kidney dysfunction, weight ≤60 kg or P-gp use); LDE, low-dose edoxaban (30 or 15 mg if kidney dysfunction, weight ≤60 kg or P-gp use); RE-LY, randomized evaluation of long-term anticoagulant therapy: dabigatran vs. warfarin; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; X-VerT, explore the efficacy and safety of once-daily oral rivaroxaban for the prevention of cardiovascular events in patients with non-valvular atrial fibrillation scheduled for cardioversion.

*Follow-up 2.1 years, all other trials were 30 days.
†Major and clinically relevant nonmajor bleeding events.

Apixaban

Evidence of chronic apixaban use before cardioversion is limited to a post hoc analysis of the major atrial fibrillation trial [ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation]] which studied apixaban 5 mg twice daily (unless ≥2 of the following were met: age ≥80 years, body weight ≤60 kg, or serum creatinine...
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compared to usual treatments for Anticoagulation in subjects

Warfarin and 251±248 days for the apixaban group. At

rates of other outcomes comparing warfarin versus

from study entry to first cardioversion of 243±231 days for

among groups: myocardial infarction (0.3% versus 0.35%), major bleeding (0.3% versus 0.35%), and death (0.3% versus 0.35%). No statistical analysis

Warfarin and 21 mg given at least 2 hours before cardioversion. This study demonstrated that apixaban was effective in preventing SSE at

follow-up with zero patients in the apixaban group and 6 major bleeds in the warfarin/heparin group. There were no significant differences in the primary efficacy and safety end points among

The study was also limited by an open-label design and similar to the other prospective trials, was a descriptive study without hypothesis testing or power calculations (Table 3).

Edoxaban

In 2016, Plitt et al published a post hoc analysis of the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) trial, looking specifically at differences in SSE events between edoxaban and warfarin in NVAF patients undergoing first electrical cardioversion. There were a total of 632 electrical cardioversion attempts in 365 patients (1.7% of the 21 105 patients enrolled in the overall trial). Patients were chronically anticoagulated with a median time from randomized to first cardioversion of 348 days (interquartile range 86–526 days). In the 30 days postcardioversion, SSE occurred in 2 patients (1.81%) on the lower-dose edoxaban (30 or 15 mg daily). No SSE occurred in patients on warfarin or higher-dose edoxaban (60 or 30 mg daily—FDA-approved dosing regimen for NVAF). Edoxaban dose was reduced by 50% (60 to 30 or 30 to 15 mg) if CrCl was 15 to 50 mL/min, body weight ≤60 kg, or concurrent use of P-glycoprotein inhibitors. There were no major bleeding events in either group and there was 1 death (0.71%) in the 60-mg edoxaban group. There were no significant differences in the primary efficacy and safety end points among the treatment groups (Table 3).

The ENSURE-AF (Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation) trial published in October 2016 was the first multinational, randomized, open-label, prospective trial of an oral FXa inhibitor versus conventional therapy of enoxaparin-warfarin in patients who were undergoing electrical cardioversion. The study population comprised patients with NVAF, the duration of which was no shorter than 48 hours and no longer than 12 months, in whom an electrical cardioversion was planned. A total of 2199 patients were enrolled, the largest published, prospective, randomized trial to date. Patients were stratified into 2 cardioversion approaches—a TEE-guided stratum (1192 patients, 589 on edoxaban) and a non-TEE-guided stratum (1016 patients). Within each stratum patients were randomly assigned to either edoxaban 60 mg

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Similar yet subtle differences in how quickly they reach anticoagulation. The oral DTI and oral FXa inhibitors have decrease the time needed for achievement of therapeutic onset, etc), as well as dosing schemes (ie, loading doses) can decrease the time needed for achievement of therapeutic anticoagulation. The oral DTI and oral FXa inhibitors have similar yet subtle differences in how quickly they reach maximal concentrations postdose (1–4 hours), half-lives (5–17 hours), time to steady state (48–72 hours), and accumulation over time. Based on pharmacokinetic (Cmax, AUC) and pharmacodynamic properties (aPTT, PT, INR, etc) it appears that dabigatran displays the greatest degree of time-dependent accumulation, followed by apixaban and no suggestion of accumulation with rivaroxaban and edoxaban.

Recently, a growing number of prospective, randomized trials have expanded our knowledge on this clinical quandary among AF patients undergoing cardioversion. The results from these trials advocate for the application of early cardioversion with the initiation of oral FXa inhibitors (from single-dose 2–4 hours precardioversion to multidose 48–72 hours of therapy precardioversion) compared with delayed cardioversion (at least 3 weeks of anticoagulation therapy precardioversion) without a difference in efficacy or safety outcomes. No trials have prospectively evaluated dabigatran in this regard. Within the early cardioversion treatment regimen, the minimum number of doses with oral DTI or oral FXa inhibitors before cardioversion remains unanswered. The concept of early cardioversion is of significant interest to optimize maintenance of sinus rhythm, and to reduce hospitalization rates and costs.

Comparison With Prior Knowledge

Phase III NAVF trials comparing oral DTI and oral FXa inhibitors to VKA therapy have consistently shown either superiority or noninferiority in reducing the risk of SSE with similar or reduced major bleeding. Post hoc analyses of these trials in cardioverted patients found no difference in efficacy or safety outcomes, but the number of patients evaluated was small (1.7–7% of the total trial populations). In addition, these studies were conducted primarily in patients on long-term anticoagulation with limited data for patients on <3 weeks’ anticoagulation.

Real-world observation cohort studies of oral DTI and oral FXa inhibitors were affected by similar shortcomings as the post hoc analyses—small sample populations and mainly an evaluation of chronic anticoagulation. These studies also introduced additional confounders in the form of varied patient populations, study design, comparator agents, and outcomes. However, similar SSE and/or major bleeding outcomes were seen in comparison to VKA therapy, and a faster time to cardioversion was also consistently noted.

Though the post hoc analyses and the observational cohort studies seemed to convey efficacy and safety of oral DTI and FXa inhibitors in cardioverted patients, it left many clinicians uncertain about the minimum number of doses required for effective anticoagulation—a concern well validated because inadequate anticoagulation has been reported as the single biggest risk factor for thromboembolism.
Clinical Implications

When used as pretreatment for a minimum of 3 weeks before cardioversion—the conventional or delayed cardioversion strategy—DTI and FXa inhibitors are noninferior VKA therapy in NAVF. When initiated acutely among anticoagulation-naive patients (with or without TEE depending on duration of AF), pharmacologic data and some outcome data provide guidance for safe use. Dabigatran, which displays the greatest accumulation over time and has the least amount of data to support an early cardioversion strategy, should be administered for at least 48 to 72 hours, achieving steady-state concentrations before cardioversion. Rivaroxaban, which displays little to no accumulation over time and has the widest breadth of data to support an early cardioversion strategy, can have cardioversion performed at least 4 hours after the initial dose. Apixaban, which displays modest accumulation over time that appears to be overcome by giving a loading dose, has the most recent data and largest cohort to support an early cardioversion strategy. Apixaban should be administered for at least 48 to 72 hours, achieving steady-state concentrations if the standard dose is utilized before cardioversion or if cardioversion is performed at least 2 hours after a loading dose (10 or 5 mg for those meeting standard requirements for dose adjustment). Finally, edoxaban, which displays little to no accumulation over time and has the largest, randomized, prospective trial to date, can have cardioversion performed at least 2 hours after the initial dose.

Conclusion

There is a growing body of evidence supporting the use of oral DTI and FXa inhibitors in patients requiring cardioversion. Oral DTI and FXa inhibitors offer potential advantages over traditional VKA and parenteral heparins. With standard dosing, it is reasonable to give dabigatran and apixaban for at least 48 to 72 hours before cardioversion, edoxaban at least 2 hours before cardioversion, and rivaroxaban at least 4 hours before cardioversion. With a loading dose, apixaban may be administered at least 2 hours before cardioversion.

Disclosures

None.

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Key Words: anticoagulation • cardioversion • oral direct thrombin inhibitor • oral factor Xa inhibitors • timing
Supplemental Material
| Study                  | Number Enrolled (N) | Intervention (N) | AVG CHADS<sub>2</sub>-VASc or CHADS<sub>2</sub> Score | AVG HAS-BLED Score | Previous stroke or TIA (% patients) | Time from first anticoagulation dose to CV | Duration of anticoagulation post CV | Significant or serious bleed | Stroke or systemic embolism |
|-----------------------|---------------------|------------------|-------------------------------------------------------|-------------------|-----------------------------------|------------------------------------------|-------------------------------|-----------------------------|-----------------------------|
| **DABIGATRAN**        |                     |                  |                                                       |                   |                                   |                                          |                               |                             |                             |
| Choo 2014<sup>1</sup>, retrospective cohort | 242<sup>*</sup> | Dabigatran (62) | Dabigatran CHADS<sub>2</sub>-VASc 1.4±1.5            | Not reported      | Not reported                      | Dabigatran† 45±26.7 days                | Not reported                  | Not reported                | Warfarin 1.8% Dabigatran 1.6%<sup>‡</sup> |
|                        |                     | Warfarin (180)   | Warfarin CHADS<sub>2</sub>-VASc 2.3±1.5              |                   |                                   | Warfarin 67.2 ±44.8 days              |                               |                             |                             |
| Johansson 2015<sup>2</sup>, retrospective cohort | 736                | Dabigatran 150 mg (536) | Dabigatran CHADS<sub>2</sub>-VASc 2±1.5 | Not reported | Dabigatran 7.9 Warfarin (not reported) | 32±15 days                          | Not reported | Dabigatran 0.18% (GI bleed) Warfarin 0%<sup>‡</sup> | Dabigatran 0.53% vs Warfarin 0.6%, 95% CI (0.18-1.54) |
| Study          | N   | Dabigatran | Warfarin | CHADS<sub>2</sub>-VASc | Not reported | Dabigatran 5.9 weeks; IQR (2.9-6.5) | Warfarin 6.9 weeks; IQR (3.9-12.1) | Not reported | Dabigatran 41.6 days (22-148) | Warfarin 78.8 days (32-183) | Not reported | Dabigatran avg 51 days | Warfarin avg 80 days | Not reported | Not reported |
|---------------|-----|------------|----------|-------------------------|-------------|-----------------------------------|-----------------------------------|-------------|--------------------------------|---------------------------------|-------------|----------------------|-------------------|-------------|-------------|
| Pallisgaard   | 1230| Dabigatran (456) | Warfarin (774) | CHADS<sub>2</sub>-VASc 2 | Not reported | Dabigatran 5.9 | Warfarin 5.8 | Not reported | Dabigatran 4 weeks; IQR (2.9-6.5) | Warfarin 6.9 weeks; IQR (3.9-12.1) | Not reported | Dabigatran 0% | Warfarin 0% | Warfarin 0% vs Dabigatran 1%, HR 1.33, 95% CI (0.33-5.42) |
| Basto 2016‡   | 68  | Dabigatran (38) | Warfarin (30) | CHADS<sub>2</sub> 1.76 | Warfarin 2.03 | Dabigatran 2.26 | Warfarin 2 weeks; IQR (2.9-6.5) | Warfarin 6.9 weeks; IQR (3.9-12.1) | Not reported | Dabigatran 0% | Warfarin 0% | Warfarin 0% |
| Benamer 2016‡ | 107 | Dabigatran (54) | Warfarin (42) | CHADS<sub>2</sub>-VASc 1.9±1.8 | Warfarin 2.3±1.8 | Dabigatran 3 | Warfarin 2 | Not reported | Dabigatran avg 51 days | Warfarin avg 80 days | Not reported | Not reported | Not reported | Not reported |

**RIVAROXABAN**
| Study                  | n   | Treatment             | CHADS₂-VASc | Duration | Adverse Events | CRRT | Notes                        |
|------------------------|-----|-----------------------|-------------|----------|----------------|------|------------------------------|
| Camm 2018*, prospective observational | 502 | Rivaroxaban           | 2.7         | 1.7      | Not reported   | Not reported | 0.4%‡                     |
| Russo 2016†, retrospective observational | 78  | Rivaroxaban           | 4±1         | 2.6      | 3±1.4 days     | 4 weeks | Not reported | 1.3% (LAA thrombus) ‡ |
| Serra 2015§, Case Study | 1   | Rivaroxaban           | 4           | 0        | 6 weeks        | Not reported | Not reported | 100% (LAA thrombus) ‡ |

**MIXED TRIALS OF DABIGATRAN, RIVAROXABAN, APIXABAN**

| Study                  | n   | Treatment             | CHADS₂-VASc | Duration | Adverse Events | CRRT | Notes                        |
|------------------------|-----|-----------------------|-------------|----------|----------------|------|------------------------------|
| Kochhäuser, 2014⁰, retrospective cohort | 900 | Dabigatran            | 1.4±1       | 3 weeks  | 0.71%          | Dabigatran 0% |
|                        |     | Rivaroxaban           | 1.3±1       | 4 weeks  | 0.35% vs       | Rivaroxaban 0% |
|                        |     | Warfarin              | 1.6±1       |          | 0.64% P=0.24   | Warfarin 0%   |

Note: ‡ indicates data not reported.
| Study                  | N  | Dabigatran | Rivaroxaban | CHADS2 or CHADS2-VASc | Duration | Exclusions | letters |
|-----------------------|----|------------|-------------|-----------------------|----------|------------|---------|
| Yadlapati 2014\(^{10}\), retrospective cohort | 53 | (30) Dabigatran 1.2±1.1 | Not reported | 3.8       | 21-60 days (AVG: 38±9 days) | Not reported | Dabigatran 0% Rivaroxaban 0%‡ |
| Coquard 2015\(^{11}\), retrospective observational | 50 | (28) Dabigatran 2.2±1.1 | Not reported | Dabigatran 4 Rivaroxaban 23 | Not reported | Not reported | Dabigatran 7.1% (GIB) Rivaroxaban 2% (GIB)‡ |
| Itäinen 2018\(^{12}\), retrospective observational | 1021 | (159) Apixaban 1.8±1.5 | Not reported | 4.2 among all the study groups | Median 38 days (range 10–2535) | 4 weeks | Total 0.5%, 95% CI (0.1–0.9%) Apixaban 0.63% Dabigatran 0.3% Rivaroxaban 0.23% |

\(^{10}\) Yadlapati et al. (2014) Retrospective cohort study.
\(^{11}\) Coquard et al. (2015) Retrospective observational study.
\(^{12}\) Itäinen et al. (2018) Retrospective observational study.
| Study            | N  | Anticoagulant | CHA2DS2-VASc | Follow-up | Closure | Event Rate | Comparison |
|------------------|----|---------------|--------------|-----------|---------|------------|------------|
| Gawalko 2017     | 859| Apixaban (1)  | CHA2DS2-VASc 1±1 | 3 weeks   | Not reported | Not reported | Dabigatran 5.2 vs Rivaroxaban 6.5 (p=0.5607) |
|                  |    | Dabigatran (191) | Rivaroxaban (230) | Warfarin (437) |          |            |            |
|                  |    |               |              |           |         |            |            |
| Femina 2018      | 284| Apixaban (77) | Apixaban CHA2DS2-VASc 3 | Short term = < 5 days (min 24 hrs) | 4 weeks | Warfarin 3.6% vs other anticoagulant (Apixaban, Dabigatran, Rivaroxaban) 1.7% (p=0.4343) | Warfarin 1.8% vs other anticoagulant (Apixaban, Dabigatran, Rivaroxaban) 0.6% (p=0.5607) |
|                  |    | Dabigatran (38) | Dabigatran CHA2DS2-VASc 3 | Rivaroxaban CHA2DS2-VASc 2 | Rivaroxaban CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 |
|                  |    | Rivaroxaban (60) | Rivaroxaban CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 |
|                  |    | Warfarin (109) | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 | Warfarin CHA2DS2-VASc 4 |
|                  |    |               |              |           |         |            |            |
| Study                     | Sample Size | Anticoagulants | CHADS2-VASc | Duration | Comparison  | Median Duration |
|--------------------------|-------------|----------------|-------------|----------|-------------|-----------------|
| Coleman 2015\(^1\), retrospective cohort | 4647 | Apixaban (48) Dabigatran (719) Rivaroxaban (159) Warfarin (3721) | Not reported | Not reported | Apixaban 0 Dabigatran 1.7 Rivaroxaban 0.6 Warfarin 2.7 | 3 weeks | 4 weeks | Warfarin 1.02% vs other anticoagulant (Apixaban 0%, Dabigatran 0.7%, Rivaroxaban 0%) 0.5% (p=0.247) | Warfarin 0.97% vs other anticoagulant (Apixaban 0%, Dabigatran 1.67%, Rivaroxaban 1.89%), 1.62% (p=0.11) |
| Sharif 2017\(^1\), retrospective cohort | 187 | Dabigatran (27) Rivaroxaban (41) Warfarin (119) | Dabigatran CHADS2-VASc 2.1±1.5 Rivaroxaban CHADS2-VASc 2.1±1.4 | Not reported | Dabigatran+ rivaroxaban avg 107.5 days | Not reported | Dabigatran 3.7%, rivaroxaban 2.4% vs warfarin 7.6%, OR | Not reported |
Warfarin
CHADS²-VASC
2.5±1.4

|                |                |                |                |                |                |
|----------------|----------------|----------------|----------------|----------------|----------------|
|                |                |                |                |                | 0.37, 95% CI   |
|                |                |                |                |                | (0.078-1.77)   |

aPTT, activated partial thromboplastin time; AVG, Average; CI Confidence interval; CV, Cardioversion; GI, gastrointestinal; HR, hazard ratio; hrs, hours; IQR, interquartile range; min, minimum; OR, odds ratio; RR, risk ratio; TEE, transesophageal echocardiography; TIA, transient ischemic attack; vs, versus

*242 DCCV in 193 patients
†aPTT was checked prior to DCCV to assure some prolongation
‡No statistical analysis performed
§Includes stroke, death and bleeding
∥Not reported what other anticoagulant were used
#1 patient in dabigatran group had TIA
**Time between referral and CV, not clear when patient started taking anticoagulant
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