American Heart Association | American Stroke Association

Use of Direct Oral Anticoagulants Among Patients Undergoing Cardioversion: The Importance of Timing Before Cardioversion

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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.[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).[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.[3] Thromboembolic risk is not negated by a low $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack), or CHA_2DS_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.[3,4] The single biggest risk factor for thrombus formation is inadequate anticoagulation.[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.[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.[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.[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.[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.[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.[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.[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.[5,20,24–26]

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010854

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J Am Heart Assoc. 2018;7:e010854. DOI: 10.1161/JAHA.118.010854.

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/HRS[20]	2012 CHEST[5]	2016 EHRA[24,25]	2014 CCS[26]
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 2C)	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) Therapeutic enoxaparin DTI (Grade 1B)	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 presentation to the hospital (Grade 2C)	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 1B) Before cardioversion for immediate cardioversion (Grade 1B)	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 IIb, level C evidence Long-term pending risk factors (Class I, level of evidence C)	4 wks (grade 2C)	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 1B)	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.

*TEE 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

Table 2. Clinical Comparison of FXa Inhibitors and DTI

	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.[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.[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.[37] Though statistically significant accumulation was noted with twice-daily dosing regimens, "negligible accumulation was observed with daily doses."[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.[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.[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.[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.[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.[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.[38]

Edoxaban

In single- versus multidose pharmacodynamic studies, aPTT, PT, and anti-Xa levels failed to reveal a time-dependent accumulation. There was no statistically significant difference in maximal aPTT (0.96-fold change), 1.27-fold increases for maximal PT and 0.84- to 1.08-fold change for maximal anti-Xa levels (no statistics provided for the latter 2 values) between day 1 and 10 for single daily doses.[37] Similar to apixaban, anti-Xa is considered a quantitative measure, but both aPTT and PT are unreliable markers for assessing edoxaban activity.[38]

The concern with pharmacokinetic/pharmacodynamic studies surrounds the testing of non-FDA-approved dosing regimens. When comparing these nonstandard doses, regimens displaying total daily doses similar to the FDA-approved doses were selected (ie, dabigatran 100 mg three times daily, total daily dose of 300 mg daily, analogous to 150 mg twice daily). Also, the pharmacokinetic data utilized 24-hour concentrations of BID dosing for apixaban but single-dose values for dabigatran, edoxaban, and rivaroxaban. Thus we are left attempting to interpret imperfect comparisons.

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.[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 ≈7% anticoagulated <3 weeks. No data were provided on outcomes pertaining to time from anticoagulation to cardioversion (Table 3).

Table 3. Randomized Clinical Trials DOAC in Cardioversion

Study	Number Enrolled (N)	Intervention (N)	AVG $CHADS_2$-VASc or $CHADS_2$ Score	AVG HAS-BLED 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									
Nagarakanti, 2011,[39] post hoc analysis of RCT	1270*	Cardioversion in Dabigatran 150 mg twice daily (672) Cardioversion in Dabigatran 110 mg twice daily (647) Cardioversion in Warfarin (664)	$CHADS_2$ 2.1±1†	Not reported	Dabigatran 150 mg 20.3 Dabigatran 110 mg 19.9 Warfarin 19.5†	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) Dabigatran 110 mg 1.7% vs Warfarin 0.6%, RR 2.82, 95% CI (0.9–8.82) Dabigatran 150 mg 0.6% vs Dabigatran 110 mg 1.7%, RR 0.35, 95% CI (0.11–1.09)	Dabigatran 150 mg 0.3% vs Warfarin 0.6%, RR 0.49, 95% CI (0.09–2.69) Dabigatran 110 mg 0.77% vs Warfarin 0.6%, RR 1.28, 95% CI (0.35–4.76) Dabigatran 150 mg 0.3% vs Dabigatran 110 mg 0.77%, RR 0.39, 95% CI (0.07–1.98)
Rivaroxaban									
ROCKET AF, (Piccini, 2013),[40] post hoc analysis of RCT	321§	Rivaroxaban 20 mg daily or 15 mg with CrCl 30 to 49 mL/min (160) Warfarin (161)	$CHADS_2$ 3	Not reported	Rivaroxaban 51.3 Warfarin 54	Not reported	Not reported	Rivaroxaban 18.75% vs warfarin 13.04% *P*=0.459	Rivaroxaban 1.88% Warfarin 1.86%‖
X-VeRT, (Cappato, 2014),[41] RCT, open label	1504	Early: Rivaroxaban 20 mg daily or 15 mg with CrCl 30–49 mL/min (585) Warfarin (287)	$CHADS_2$-VASc ≥2	Not reported	Early: Rivaroxaban 5.7 Warfarin 7.3	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)	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) Warfarin (215)			Delayed: Rivaroxaban 5.8 Warfarin 7.9	Delayed: 3 wks	Delayed: 8 wks		
Enomoto, 2016,[42] prospective clinical trial	91	Early: Rivaroxaban 15 or 10 mg daily with CrCl 30–50 mL/min (51)¶	Early: $CHADS_2$-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)‖	No thromboembolic events reported‖
		Delayed: Rivaroxaban 15 or 10 mg daily with CrCl 30–50 mL/min (40)¶	Delayed: $CHADS_2$-VASc 1.6±1.4	Delayed: 1.2±0.9		Delayed: 3 wks	Delayed: 4 wks		
Apixaban									
ARISTOTLE, (Flaker, 2014),[43] 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) Warfarin (275)	$CHADS_2$ 1.9±1	Not reported	Apixaban 12.5 Warfarin 15.6	Apixaban 251±248 days (min 1 day) Warfarin 243±231 days (min 4 days)	4 wks	Apixaban 0.3% Warfarin 0.2%‖	Apixaban 0% Warfarin 0%‖

Continued

DOI: 10.1161/JAHA.118.010854

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Table 3. Continued

Study	Number Enrolled (N)	Intervention (N)	AVG $CHADS_2$-VASc or $CHADS_2$ Score	AVG HAS-BLED 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
EMANATE (Ezekowitz, 2018),[44,45] 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 days (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)
Edoxaban									
ENGAGE AF-TIMI 48, (Plitt, 2016),[46] 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)	$CHADS_2$ ≤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),[47] 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)	$CHADS_2$ 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[48–54] (Table S1). One study required a minimum of 24 hours of anticoagulation before cardioversion[55] and 1 study did not comment on timeline between dose and cardioversion.[56] Three of the studies evaluated dabigatran and FXa inhibitors.[49,54,55] The majority of studies indicated similar SSE and/or major bleeding outcomes between dabigatran compared with warfarin[50–56] or rivaroxaban[49] in cardioverted patients. One study did not report on outcomes[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.[6] Femia et al evaluated 284 patients: 109 patients anticoagulated with warfarin and 175 with dabigatran, apixaban, or rivaroxaban.[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.[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).[40] 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.[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.[41,44] Regardless, both early and delayed strategies reported thromboembolic event rates (0.24%–1.08%)[41] similar to prior trials of conventional

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 hoc[39]	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 hoc[40]*	Rivaroxaban	3/160 (1.88%)	30/160 (18.75%)†	3/160 (1.88%)
ARISTOTLE post hoc[43]	Apixaban	0/331 (0%)	1/331 (0.30%)	2/331 (0.60%)
ENGAGE AF-TIMI 48 post hoc[46]	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-VeRT[41]	Rivaroxaban	0/411 (0%)	3/411 (0.73%)	2/411 (0.49%)
Enomoto et al[42]	Rivaroxaban	0/40 (0%)	0/40 (0%)	Not reported
ENSURE-AF[47]	Edoxaban	2/506 (0.40%)	0/506 (0%)	Not reported
Early cardioversion group				
X-VeRT[41]	Rivaroxaban	2/567 (0.35%)	3/567 (0.53%)	3/567 (0.53%)
Enomoto et al[42]	Rivaroxaban	0/51 (0%)	0/51 (0%)	Not reported
EMANATE[44,45]	Apixaban	0/753 (0%)	3/753 (0.40%)	2/753 (0.27%)
ENSURE-AF[47]	Edoxaban	1/589 (0.17%)	3/589 (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.

anticoagulation (0–1.88%)[39,40,43,46] 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 among 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).

Several retrospective cohort studies have evaluated rivaroxaban at FDA-approved doses for cardioversion (Table S1). The majority of patients received anticoagulation for at least 3 weeks before cardioversion.[49,51,54,57,58] The requirements for anticoagulation before cardioversion ranged from at least 24 hours to 10 days in 3 studies[55,59,60] with no discussion of requirements in 2 studies.[56,61] The studies comparing rivaroxaban and dabigatran to warfarin found similar SSE and/or major bleeding outcomes.[50,54,55] Rivaroxaban was compared with dabigatran and apixaban in 2 studies and indicated similar SSE outcome.[58,60] Of note, 1 study had only 1 patient on apixaban,[58] and the other study included 159 patients on apixaban.[60] Two studies evaluated rivaroxaban without a comparator arm.[59,61] The SEE outcome reported was similar to warfarin-treated patients reported in the literature.[41] A 2015 case report investigated left atrial appendage that occurred after 6 weeks of anticoagulation with rivaroxaban. Of note, this patient was concurrently taking oxcarbazepine, which can decrease the effectiveness of rivaroxaban.[62]

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

≥1.5 mg/dL) versus dose-adjusted warfarin in patients with NVAF.[43] Out of a total of 18 201 patients enrolled in the ARISTOTLE trial, 743 cardioversions were performed in 540 patients. The minimum duration of therapy before cardioversion (percentages not available) was 4 days for warfarin and 1 day for apixaban. However, the vast majority of patients in the trial had been chronically anticoagulated with a mean time from study entry to first cardioversion of 243±231 days for warfarin and 251±248 days for the apixaban group. At 30 days postcardioversion, no SSE occurred in either treatment group, though the overall event rate in ARISTOTLE was low. Rates of other outcomes comparing warfarin versus apixaban were low and similar 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 was performed given the small number of events (Table 3).

The EMANATE (Eliquis evaluated in acute cardioversion compared to usual treatments for Anticoagulation in subjects with atrial fibrillation) trial is a randomized, prospective, open-label trial evaluating apixaban versus usual care with heparin plus VKA during elective cardioversion for new-onset NVAF (diagnosed within 3 months before randomization) in 1500 patients who are anticoagulation-naïve (<48 hours of parenteral and/or oral anticoagulation).[44,45] The study has notable exclusion criteria including severely hemodynamically unstable patients requiring emergent cardioversion, other conditions requiring anticoagulation, dual antiplatelet therapy use, and valvular heart disease (including mitral stenosis, mechanical and prosthetic valves, and valve repair). The study required 5 doses of apixaban before cardioversion, allowing for a single 10-mg dose (or 5 mg for patients meeting standard criteria for dose adjustment) if urgent cardioversion is planned at a minimum of 2 hours before cardioversion. For patients in the usual-care arm, similar timing was allowed after administration of heparin. Of note, 55% of the apixaban group received TEE before cardioversion. This study demonstrated that apixaban was effective in preventing SSE at 30-day (with cardioversion) or 90-day (without cardioversion) follow-up with zero patients in the apixaban group and 6 patients in the warfarin/heparin group experiencing SSE (5 ischemic strokes, 1 hemorrhagic stroke, and zero systemic embolic events), P=0.015. Bleeding risk was also similar, with 3 major bleeds in the apixaban group and 6 major bleeds in the warfarin/heparin group (P=0.338). Roughly half of the patients in the apixaban group (342 out of 753) received a loading dose. The mean time from apixaban loading dose to cardioversion was 3.3 days (standard deviation 8.8 days) in patients with imaging and 4.1 days (standard deviation 9.5 days) in patients without imaging. In this loading-dose group, there were zero SSE, 1 major bleed, and 1 death. The mean time to cardioversion in patients not receiving an apixaban loading dose was 21.7 days (standard deviation 14.6 days) with imaging and 32.5 days (standard deviation 21.2 days) without imaging. The mean time to cardioversion in the heparin plus VKA group was 17.8 days. The EMANATE trial represents the largest sample size to date for evaluation of an early cardioversion group. This was also the only trial to utilize a loading dose (10 or 5 mg for patients meeting standard criteria for dose adjustment) given at least 2 hours before cardioversion, which appears appropriate based on its pharmacokinetic evaluation where AUC and Cmax after 1 dose of 10 mg was higher than 7 days of the standard dose of 5 mg twice daily. 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.[46] 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 SEE 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.[47] 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

daily (30 mg for CrCl 15–50 mL/min, body weight ≤60 kg, or concurrent use of P-glycoprotein inhibitors) or enoxaparin-dose-adjusted warfarin with warfarin dose adjusted to maintain an INR of 2 to 3. In the TEE-guided stratum, a TEE and electrical cardioversion had to be performed within 3 days of randomization; patients with an INR <2 were given a minimum of 1 dose of enoxaparin and warfarin before cardioversion and patients assigned to edoxaban were given a minimum of 1 dose at least 2 hours before cardioversion. In both groups, anticoagulation was continued for 28 days postcardioversion. Of note, 100% of patients in the early cardioversion group had TEE performed. In the non-TEE-guided stratum, patients were anticoagulated with warfarin (with the addition of enoxaparin for patients with an INR <2 until INR was therapeutic) or edoxaban for a minimum of 21 days before electrical cardioversion. Median time to cardioversion was 2 days in the TEE stratum and 23 days in the non-TEE stratum. The primary efficacy outcome was the composite end point of SSE, myocardial infarction, and cardiovascular death and the primary safety outcome was the composite end point of major and clinically relevant nonmajor bleeding—both assessed 30 days after cardioversion. The combined primary efficacy end point in the overall population (TEE guided and non-TEE guided groups) was not different between the edoxaban group and the enoxaparin-warfarin group (0.46% versus 1%, odds ratio 0.46, 95% confidence interval 0.12–1.43). The combined primary safety end point in the overall population was not different between the edoxaban group and the enoxaparin-warfarin group (1.5% versus 1.02%, odds ratio 1.48, 95% confidence interval 0.64–3.55). End points were evenly distributed in the TEE-guided stratum and non-TEE-guided stratum groups. Unlike trials of oral DTI and other oral FXa inhibitors, the ENSURE-AF did not reduce time to cardioversion compared with warfarin. Similar to other prospective trials, the ENSURE-AF was limited by an open-label design (Table 3).

Summary of Findings

Limited and heterogeneous data exist evaluating the optimal timing of oral DTI and oral FXa inhibitors pre-cardioversion. In the absence of high-quality data, a critical appraisal of the pharmacological properties of a medication can lend important clinical insight. It is commonly accepted that at least 5 half-lives of a medication are required to obtain steady full-state plasma concentrations. However, certain pharmacokinetic properties (ie, more complete absorption, faster time to 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.[16–19] 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.[39,40,43,46]

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.[4]

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-naïve 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

Table S1. Retrospective Cohort Trials of DOACs in Cardioversion.

Study	Number Enrolled (N)	Intervention (N)	AVG $CHADS_2$-VASc or $CHADS_2$ 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[1], retrospective cohort	242*	Dabigatran (62) Warfarin (180)	Dabigatran $CHADS_2$-VASc 1.4±1.5 Warfarin $CHADS_2$-VASc 2.3±1.5	Not reported	Not reported	Dabigatran† 45±26.7 days Warfarin 67.2 ±44.8 days	Not reported	Not reported	Warfarin 1.8% Dabigatran 1.6%‡
Johansson 2015[2], retrospective cohort	736	Dabigatran 150 mg (536) Dabigatran 110 mg (34) Warfarin (166)	Dabigatran $CHADS_2$-VASc 2±1.5 Warfarin $CHADS_2$-VASc 2.5	Not reported	Dabigatran 7.9 Warfarin (not reported)	32±15 days	Not reported	Dabigatran 0.18% (GI bleed) Warfarin 0%‡	Dabigatran 0.53% vs Warfarin 0.6%, 95% CI (0.18-1.54)

Pallisgaard 2015[3], retrospective cohort	1230	Dabigatran (456) Warfarin (774)	$CHADS_2$-VASc 2	Not reported	Dabigatran 5.9 Warfarin 5.8	Dabigatran 4 weeks; IQR (2.9-6.5) Warfarin 6.9 weeks; IQR (3.9-12.1)	Not reported	Dabigatran 0% Warfarin 0%‡	Warfarin 2% vs Dabigatran 1%, HR 1.33, 95% CI (0.33-5.42) §
Basto 2016[4], retrospective observational	68	Dabigatran (38) Warfarin (30)	Dabigatran $CHADS_2$ 1.76 Warfarin $CHADS_2$ 1.67	Dabigatran 2.26 Warfarin 2.03	Not reported	Dabigatran 41.6 days (22-148) Warfarin 78.8 days (32-183)	Not reported	Dabigatran 0% Warfarin 3.3% (hematuria) ‡	Dabigatran 0% Warfarin 0%‡
Benamer 2016[5], retrospective Cohort	107	Dabigatran (54) Warfarin (42) Other anticoagulant (11)‖	Dabigatran $CHADS_2$-VASc 1.9±1.8 Warfarin $CHADS_2$-VASc 2.3 ±1.8	Not reported	Dabigatran 3 Warfarin 2	Dabigatran avg 51 days Warfarin avg 80 days	Not reported	Not reported	Not reported
RIVAROXABAN									

Camm 2018[6], prospective observational	502	Rivaroxaban (502)	$CHADS_2$-VASc 2.7	1.7	9.4	Not reported	Not reported	0.4%‡	0.6%‡
Russo 2016[7], retrospective observational	78	Rivaroxaban (78)	$CHADS_2$-VASc 4±1	Not reported	2.6	3±1.4 days	4 weeks	Not reported	1.3% (LAA thrombus) ‡
Serra 2015[8], Case Study	1	Rivaroxaban (1)	$CHADS_2$-VASc 4	Not reported	0	6 weeks	Not reported	Not reported	100% (LAA thrombus) ‡
MIXED TRIALS OF DABIGATRAN, RIVAROXABAN, APIXABAN									
Kochhäuser, 2014[9], retrospective cohort	900	Dabigatran (288) Rivaroxaban (141) Warfarin (471)	Dabigatran $CHADS_2$-VASc 2.4±1.4 Rivaroxaban $CHADS_2$-VASc 2.3±1.4 Warfarin $CHADS_2$-VASc 2.7±1.5	Dabigatran 1.4±1 Rivaroxaban1.3±1 Warfarin 1.6±1	Not reported	3 weeks	4 weeks	Rivaroxaban 0.71%, Dabigatran 0.35% vs Warfarin 0.64% P=0.24	Dabigatran 0% Rivaroxaban 0% Warfarin 0% P=0.99**

Yadlapati 2014[10], retrospective cohort	53	Dabigatran (30) Rivaroxaban (23)	$CHADS_2$ 1.2±1.1	Not reported	3.8	21-60 days (AVG: 38±9 days)	Not reported	Dabigatran 0% Rivaroxaban 0%‡	Dabigatran 0% Rivaroxaban 0%‡
Coquard 2015[11], retrospective observational	50	Dabigatran (28) Rivaroxaban (22)	$CHADS_2$-VASc 3±1.8	2.2±1.1	Dabigatran 4 Rivaroxaban 23	Not reported	Not reported	Dabigatran 7.1% (GIB) Rivaroxaban 2% (GIB) ‡	Dabigatran 0% Rivaroxaban 0%‡
Itäinen 2018[12], retrospective observational	1021	Apixaban (159) Dabigatran (680) Rivaroxaban (431)	CHA2DS2-VASc 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 0.7%	Total 0.2%, 95% CI (0.04–0.44%) Apixaban 0% Dabigatran 0.3% Rivaroxaban 0.23%

Gawalko 2017[13], retrospective observational	859	Apixaban (1) Dabigatran (191) Rivaroxaban (230) Warfarin (437)	CHA2DS2-VASc 1 ±1	1±1	Dabigatran 5.2 Rivaroxaban 6.5 Warfarin 6	3 weeks	Not reported	Not reported	Dabigatran 6.8% Rivaroxaban 4.4% Warfarin 6.9% (LAA thrombus) (p=0.29, Dabigatran vs Rivaroxaban)
Femia 2018[14], retrospective cohort	284	Apixaban (77) Dabigatran (38) Rivaroxaban (60) Warfarin (109)	Apixaban CHA2DS2-VASc 3 Dabigatran CHA2DS2-VASc 3 Rivaroxaban CHA2DS2-VASc 2 Warfarin CHA2DS2-VASc 4	Not reported	Apixaban 3.9 Dabigatran 2.6 Rivaroxaban 3.3 Warfarin 9.2	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)
						Long term = >5 days		Long term 2.5% vs Short term 1.1%	Long term 1.3% vs short term 0% (p=0.4571)

								(p=0.5932)	
Coleman 2015[15], 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[16], retrospective cohort	187	Dabigatran (27) Rivaroxaban (41) Warfarin (119)	Dabigatran $CHADS_2$-VASc 2.1±1.5 Rivaroxaban $CHADS_2$-VASc 2.1±1.4	Not reported	Not reported	Dabigatran+ rivaroxaban avg 107.5 days Warfarin avg 144.2 days**	Not reported	Dabigatran 3.7%, rivaroxaban 2.4% vs warfarin 7.6%, OR	Not reported

			Warfarin $CHADS_2$-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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