

## Drug Class Review: Target Specific Oral Anticoagulants Dabigatran (Pradaxa), Rivaroxaban (Xarelto), and Apixaban (Eliquis) September 2013

VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

### OBJECTIVE

The purpose of this review is to compare the three target specific oral anticoagulants (TSOAC) and warfarin.

**Table 1. Oral Anticoagulants Available in the US**

Generic Name	Brand (Manufacturer)	MOA	Strengths (mg)	FDA Approval
Dabigatran	Pradaxa (Boehringer Ingelheim)	Direct thrombin inhibitor	150, 75	10/2010
Rivaroxaban	Xarelto (Janssen Ortho, Bayer)	Factor Xa inhibitor	10, 15, 20	11/2011
Apixaban	Eliquis (Bristol Myers Squibb/Pfizer)	Factor Xa inhibitor	5, 2.5	12/2012
Warfarin	Coumadin (Bristol Myers Squibb), several generics	Vitamin K antagonist	1, 2, 2.5, 3, 4, 5, 6, 7.5, 10	6/1954

### FDA-APPROVED INDICATIONS<sup>1,2,3,4</sup>

Dabigatran, rivaroxaban, and apixaban are indicated for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation (AF). In addition, rivaroxaban and apixaban are approved for the prevention of venous thromboembolism (VTE) in patients undergoing knee or hip replacement surgery. Rivaroxaban, dabigatran, and apixaban are approved for the treatment of acute VTE and prevention of recurrent events). Warfarin has been the standard of care for over 50 years and carries several indications. (Table 2)

**Table 2. FDA Approved Indications**

	Stroke prevention in nonvalvular AF	VTE prophylaxis	VTE treatment	Thromboembolism prevention in heart valve replacement	Post myocardial infarction
<b>Dabigatran</b>	X		X		
<b>Rivaroxaban</b>	X	X	X		
<b>Apixaban</b>	X	X	X		
<b>Warfarin</b>	X	X	X	X	X

### Phase 3 Outcome Studies and Off Label Uses

Dabigatran, rivaroxaban, and apixaban have been studied in phase 3 trials for various indications. (Table 3)

**Table 3. Summary of TSOAC Phase 3 Trials**

	Stroke Prevention in Nonvalvular AF	VTE prophylaxis in TKR	VTE prophylaxis in THR	Acute VTE treatment	Extended VTE treatment	ACS	DVT Prophylaxis in medically ill
<b>Dabigatran</b>	<b>RE-LY</b>	RE-MOBILIZE RE-MODEL	RE-NOVATE RE-NOVATE II	<b>RE-COVER</b> <b>RE-COVER II</b>	<b>RE-MEDY</b> <b>RE-SONATE</b>	RE-DEEM*	--
<b>Rivaroxaban</b>	<b>ROCKET AF</b>	<b>RECORD-3</b> <b>RECORD-4</b>	<b>RECORD-1</b> <b>RECORD-2</b>	<b>ENSTEIN DVT</b> <b>ENSTEIN PE</b>	<b>ENSTEIN Continued Treatment</b>	ATLAS-TIMI 51	MAGELLAN
<b>Apixaban</b>	<b>ARISTOTLE</b> <b>AVERROES</b>	<b>ADVANCE-1</b> <b>ADVANCE-2</b>	<b>ADVANCE-3</b>	<b>AMPLIFY</b>	<b>AMPLIFY-EXT</b>	APPRAISE-2	ADOPT

Non-bolded studies are for off-label indications

\*RE-DEEM was a phase 2 study

### METHODS

This review is limited to the three TSOACs currently approved in the U.S.: apixaban, dabigatran, and rivaroxaban. Investigational agents not approved by FDA for use in the U.S. are not included in this review. Also excluded were trials conducted solely in Asian populations. Published phase 3 clinical trials were primarily used for this review. In cases where a trial determined necessary to this review has not yet been published, abstracts or the FDA briefing documents were used. A literature search was performed on PubMed using the search using apixaban, dabigatran, and rivaroxaban through April 2013 (VTE treatment, VTE prophylaxis, and Peri-Cardioversion sections updated September 2014). Discussion of dabigatran 110 mg dose for the AF indication was generally excluded, as this dose was not approved in the U.S.

**PHARMACOLOGY**<sup>1,2,3,4</sup>

Rivaroxaban and apixaban are oral, selective factor Xa inhibitors that block the active site of Xa and do not require a co-factor. Dabigatran is an oral direct thrombin inhibitor that prevents the formation of thrombin by inhibiting the thrombin-dependent conversion of fibrinogen to fibrin. Dabigatran, rivaroxaban, and apixaban inhibit both free and clot-bound fibrin and indirectly inhibit thrombin-induced platelet aggregation. Warfarin is a vitamin K antagonist that inhibits the synthesis of vitamin K-dependent clotting factors including Factors II, VII, IX, and X, and the anticoagulant proteins C and S.

**PHARMACOKINETICS**<sup>1,2,3,4</sup>

Compared to warfarin, the TSOACs exhibit a rapid onset of action and short half-life. The three TSOACs share a similar onset of action and duration of effect but differ notably in their metabolism and elimination. Dabigatran etexilate is formulated for oral administration as a prodrug that is rapidly absorbed and converted to the active moiety dabigatran by esterase-catalyzed hydrolysis in the liver. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes but is susceptible to drug interactions via the efflux transporter P-glycoprotein (P-gp). Rivaroxaban and apixaban are metabolized by CYP3A4 and other CYP450 enzymes. The majority of dabigatran is removed by the kidneys, where a lesser portion of rivaroxaban undergoes renal elimination. Only about a quarter of a dose of apixaban is removed by the kidneys. Dabigatran’s low protein binding and renal elimination potentially allow for removal of the drug by dialysis in cases of overdose, although clinical data are limited.

**Table 4. Pharmacokinetic Parameters**<sup>1,2,3,4</sup>

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
<b>Bioavailability</b>	3-7%	10 mg dose: 80-100% 20 mg dose: 66% (fasting; increased with food)	50%; prolonged absorption	~100%
<b>Time to maximum concentration (Tmax)</b>	1-2 hrs	2-4 hrs	3 – 4 hrs	4 hrs (peak anticoagulant effect delayed 72-96 hrs)
<b>Protein binding</b>	35%	92-95%	87%	99%
<b>Volume of distribution</b>	50-70 L	50 L	21 L	0.14L/kg
<b>Metabolism</b>	Conjugation	CYP3A4/5, CYP2J2, hydrolysis	CYP3A4 (major); CYP1A2, 2C8, 2C19, 2J2 (all minor)	CYP2C9, 2C19, 2C8, 2C18, 1A2, 3A4
<b>Elimination</b>	Renal (80%)	Renal (66%; 36% as unchanged drug)	Renal (27%); fecal	Hepatic metabolism
<b>Half-life</b>	12-17 hrs	5-9 hrs*	12 hrs	~40 hrs

\*Half-life is increased to 11-13 hrs in the elderly

**PHARMACODYNAMICS**

- Dabigatran produces predictable, dose-dependent prolongation in clotting times, as measured by changes in ecarin clotting time (ECT), thrombin clotting time (TT), and activated partial thromboplastin time (aPTT).<sup>1,5</sup> The aPTT test is readily available and may be used to provide a qualitative estimate of presence of anticoagulant; however, the aPTT is less sensitive at higher concentrations of dabigatran. The TT test is a very sensitive test for dabigatran but may not be widely available. The ECT test is also sensitive for dabigatran but is not typically available for use outside of a research setting.

- Rivaroxaban produces dose-dependent inhibition of factor Xa activity and prolongation of the Neoplastin PT (prothrombin), aPTT and HepTest.<sup>2,6</sup> Though the effects are significantly influenced by reagent type, the PT test is considered appropriate to qualitatively detect the presence of anticoagulant effect of rivaroxaban. Anti-factor Xa activity testing may be considered as an alternative to PT testing. Drug specific anti-Xa assays are being investigated.
- Apixaban produces a dose-dependent inhibition of factor Xa as measured by the anti-Xa chromogenic assay. The changes in PT, INR, and aPTT are small and highly variable.<sup>7</sup>
- INR is calibrated to vitamin K antagonists only and is not useful to measure the effects or estimate presence or absence of the TSOACs; however, dabigatran, apixaban, and rivaroxaban may affect INR.
- Because of their predictable pharmacokinetics, routine monitoring of the anticoagulant effects of the TSOACs is not needed. However, there may be certain situations where an estimate of anticoagulant activity is desired (e.g., acute bleed or need for urgent invasive procedure). Quantitative tests (i.e., supra-, sub-, or therapeutic concentrations) for the TSOACs have not been established. Qualitative indication of the presence or absence of anticoagulant activity may be estimated using the following:
  - Dabigatran – aPTT, TT
  - Rivaroxaban – PT, anti-Factor Xa
  - Apixaban – anti-Factor Xa
- There is currently no reversal agent for the TSOACs. Because of their short half-lives, it is expected that bleeding events can often be managed by discontinuing the drug and providing supportive care. Activated charcoal may be used to reduce the absorption of the TSOACs in cases of suspected overdose, though the drugs are rapidly absorbed within a few hours after administration. Hemodialysis can remove dabigatran; however, clinical data are limited. Preliminary study in healthy volunteers found that a 4-factor prothrombin complex concentrate (PCC) product reversed the laboratory parameters of individuals receiving rivaroxaban.<sup>8</sup> It is not known whether PCC would be safe and effective in patients on rivaroxaban or other TSOACs with serious, life-threatening bleeding events.

#### **DOSING AND ADMINISTRATION**<sup>1,2,3,4</sup> (updated September 2014)

- Even though the onset and duration of effect of all three TSOACs are similar, rivaroxaban was studied and subsequently approved as a once daily drug (for maintenance doses), and dabigatran and apixaban were studied and approved as twice daily medications (rivaroxaban is dosed twice daily only for the first three weeks following acute VTE).
- Apixaban and dabigatran may be taken with or without food. Rivaroxaban exhibits dose dependent bioavailability. Higher doses (e.g., 15 mg and 20 mg strengths used for VTE treatment and AF) should be taken with the evening meal to enhance absorption.
- Dosage adjustments of the TSOACs are recommended in renal impairment, high risk patients, and patients on certain types of interacting medications. Lower doses of rivaroxaban and apixaban have been studied in pivotal clinical trials in AF for use in special populations; however, the lower dose of dabigatran approved in the U.S. for use in patients with AF and renal impairment was approved based on pharmacokinetic modeling only and has not been studied clinically. (Tables 5 and 6)
  - A reduced dose of apixaban 2.5 mg twice daily is recommended for patients with AF and two or more of the following: age  $\geq 80$  yrs; weight  $\leq 60$  kg; or serum creatinine (SCr)  $\geq 1.5$  mg/dL. This dose was studied clinically (in the ARISTOTLE and AVERROES trials). For patients on strong dual inhibitors of CYP3A4 and P-gp and receiving doses greater than 2.5 mg twice daily, a 50% dose reduction is recommended. For patients already on 2.5 mg twice daily receiving a concomitant strong dual inhibitor of CYP3A4 and P-gp, apixaban should be avoided.
  - A reduced dose of dabigatran 75 mg twice daily is recommended for patients with AF, moderate renal impairment (CrCl 30-50 ml/min) AND who are on dronedarone or systemic ketoconazole.

For patients with AF, severe renal impairment (CrCl 15-30 ml/min) AND on dronedarone or systemic ketoconazole, dabigatran should be avoided. These manufacturer’s recommendations are based on pharmacokinetic modeling only and have not been studied clinically.

- A reduced dose of rivaroxaban 15 mg once daily is recommended for patients with AF and estimated CrCl of 15-50 ml/min. This dose was studied clinically in patients with CrCl 30-50 ml/min. Full dose rivaroxaban (20 mg daily) is recommended for patients with VTE and an estimated CrCl of 30 ml/min or greater. Rivaroxaban should be avoided in patients with VTE and an estimated CrCl <30 ml/min.

**Table 5: Dosing and Administration of TSOACs and Warfarin**<sup>1,2,3,4</sup>

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
<b>Usual dose</b>	<u>AF</u> : 150 mg twice daily <u>VTE tx</u> : 150 mg twice daily (after 5-10 days with parenteral agent)	<u>AF</u> : 20 mg once daily <u>VTE tx</u> : 15 mg twice daily x21 days, then 20 mg once daily <u>VTE ppv</u> : 10 mg once daily	<u>AF</u> : 5 mg twice daily <u>VTE tx</u> : 10 mg twice daily x7 days, then 5 mg twice daily. After at least 6 mos of tx, 2.5 mg twice daily <u>VTE ppv</u> : 2.5 mg twice daily	<u>AF</u> : once daily, titrate to INR 2-3
<b>Special dosing</b>	Renal Drug interactions	Renal	High risk patients Drug interactions	Variable dosing
<b>Routine anticoagulant monitoring</b>	No	No	No	Yes
<b>Split, crush, chew</b>	No; increased exposure	OK to crush and mix with water or applesauce immediately prior to use;  Cannot be administered via feeding tubes placed distal to the stomach due to decreased absorption	Preliminary info suggests OK	OK
<b>Reversal agent</b>	No	No	No	Yes
<b>Dietary considerations</b>	No	Yes, take doses >10 mg with evening meal	No	Yes; consistency with vitamin K containing foods
<b>Storage considerations</b>	Yes; store caps in original bottle to protect against moisture; discard 4 mos after opening	No	No	No

**Table 6: Special Dosing of TSOACs According to Indication**<sup>1,2,3</sup>

TSOAC		Moderate Renal Impairment	Severe Renal Impairment
<b>Dabigatran (AF)</b>	Prescribing info	CrCl 30-50 ml/min AND on dronedarone or ketoconazole  75 mg twice daily	CrCl 15-30 ml/min  75 mg twice daily
	RE-LY Criteria	No adjustment	CrCl <30 ml/min excluded
<b>Dabigatran (VTE tx)</b>	Prescribing info	CrCl <50 ml/min AND on P-gp inhibitor  Avoid use	CrCl <30 ml/min - Dosing recs cannot be provided
	RE-COVER Criteria	No adjustment	CrCl <30 ml/min excluded

<b>Rivaroxaban (AF)</b>	Prescribing info	CrCl 30-50 ml/min 15 mg once daily	CrCl 15-30 ml/min 15 mg once daily
	ROCKET AF Criteria	CrCl 30-49 ml/min 15 mg once daily	CrCl <30 ml/min excluded
<b>Rivaroxaban (VTE tx)</b>	Prescribing info	No adjustment	CrCl <30 ml/min Avoid use
	EINSTEIN Criteria	No adjustment	CrCl <30 ml/min excluded
<b>Rivaroxaban (VTE ppv)</b>	Prescribing info	No adjustment	CrCl <30 ml/min Avoid use
	RECORD Criteria	No adjustment	CrCl <30 ml/min excluded
<b>Apixaban (AF)</b>	Prescribing info	SCr $\geq$ 1.5 mg/dL plus at least one of the following: Age $\geq$ 80 yrs, wt $\leq$ 60 kg 2.5 mg twice daily	ESRD and on hemodialysis: 5 mg twice daily. If age $\geq$ 80 or wt $\leq$ 60 kg, 2.5 mg twice daily
	ARISTOTLE Criteria	SCr $\geq$ 1.5 mg/dL plus at least one of the following: Age $\geq$ 80 yrs, wt $\leq$ 60 kg 2.5 mg twice daily	CrCl <25 ml/min or SCr >2.5 mg/dL excluded
<b>Apixaban (VTE ppv)</b>	Prescribing info	No adjustment	No adjustment
	ADVANCE Criteria	No adjustment	CrCl <30 ml/min
<b>Apixaban (VTE tx)</b>	Prescribing info	No adjustment	No adjustment
	AMPLIFY Criteria	No adjustment	SCr >2.5 mg/dL or CrCl <25 ml/min excluded

## EFFICACY

### I. NONVALVULAR AF

No head to head studies comparing the TSOACs have been conducted. Each of the three pivotal phase 3 trials included for efficacy were large, published, multinational, randomized controlled, noninferiority, industry-sponsored studies that compared a TSOAC to adjusted dose warfarin in patients with nonvalvular AF and at increased risk for stroke. Two of the studies were double-blinded, and one was open label. A fourth phase 3 study evaluating the use of apixaban vs. aspirin in patients considered unsuitable for warfarin provides supportive information. If noninferiority was established, superiority testing was done. Studies differed in design and patient populations but evaluated the same primary composite efficacy outcome of stroke (ischemic, hemorrhagic, or uncertain) or systemic embolism and similar secondary outcomes. Patients were followed for about 2 years.

#### *Dabigatran*

In the phase 3, prospective, randomized, open-label, blinded outcomes (PROBE design), noninferiority RE-LY trial, 18,113 patients with nonvalvular AF plus at least one additional risk factor for stroke were randomized to receive open-label warfarin (INR of 2 to 3) or blinded dabigatran at a dose of 110 mg or 150 mg given twice daily.<sup>9</sup> Patients were well balanced between treatment arms and had an overall mean CHADS<sub>2</sub> score of 2.1 and age of 71 years. For the primary composite endpoint of all stroke (ischemic, hemorrhagic, or unspecified) or systemic embolism, the FDA approved dose of dabigatran 150 mg was shown to be noninferior and superior to warfarin as well as superior to the 110 mg dose of dabigatran (not approved for use in the U.S). In looking at the individual outcomes, dabigatran 150 mg was superior to warfarin in preventing both ischemic and hemorrhagic stroke. A favorable trend in all-cause mortality approached statistical significance for dabigatran 150 mg vs. warfarin. The rate of myocardial infarction was numerically higher with dabigatran. (Tables 9, 10, 11)

In the RELY-ABLE observational extension study, about half of the patients who received dabigatran in RE-LY were followed for an additional 2.3 years, continuing on their randomized dose of dabigatran.<sup>10</sup> Annual, adjudicated event rates for the endpoint of stroke and systemic embolism with both doses of dabigatran were somewhat higher during the observational extension period than during the RE-LY trial, though rates were no higher than in the warfarin arm of RE-LY. Of note, the 150 mg dabigatran dose was no longer statistically superior to the 110 mg dabigatran dose for the reduction in stroke and systemic embolism. Rates of hemorrhagic stroke and myocardial infarction remained low and similar to results from RE-LY.

### **Rivaroxaban**

In the phase 3, double-blinded ROCKET-AF trial, 14,264 moderate-to-high risk patients with nonvalvular AF and prior stroke or two additional risk factors for stroke were randomized to rivaroxaban 20 mg once daily or adjusted dose warfarin.<sup>11</sup> A reduced dose of rivaroxaban 15 mg once daily was given to patients with a CrCl of 30-49 ml/min). The study population had a median age of 73 years and a mean CHADS<sub>2</sub> score of 3.5. Over half of the patients had a prior TIA/stroke. The mean time in therapeutic range (TTR) was 55%, which is lower than TTRs reported in other major, contemporary trials. Rivaroxaban was found to be non-inferior to warfarin for the primary composite endpoint of all stroke or systemic embolism in the primary analysis of the per-protocol population and in analyses conducted of other prespecified populations. Superiority of rivaroxaban over warfarin was not established. Compared to warfarin, rivaroxaban was associated with a significant reduction in the individual outcome of hemorrhagic stroke but not ischemic stroke. No excess of MI was noted with rivaroxaban. There was a favorable trend in mortality with rivaroxaban compared to warfarin but the difference was not statistically significant. (Tables 9, 10, 11)

### **Apixaban**

In the phase 3, double-blinded ARISTOTLE trial, 18,201 patients with nonvalvular AF and at least one additional risk factor for stroke were randomized to receive apixaban 5 mg twice daily or adjusted dose warfarin.<sup>12</sup> A reduced dose of apixaban 2.5 mg twice daily was given to patients with two or more of the following: age of 80 years or more, weight of 60 kg or less, or SCr of 1.5 mg/dL or greater. The study population had a mean age of 70 years and a mean CHADS<sub>2</sub> score of 2.1. For the primary composite endpoint of stroke or systemic embolism, apixaban was found to be noninferior and superior to warfarin. The difference in the rate for the primary endpoint was driven primarily by a significant reduction in hemorrhagic stroke with apixaban, with no difference in the rate of ischemic stroke between groups. Based on prespecified, sequential testing of additional endpoints, apixaban was found to be superior to warfarin for major bleeding, and there was a borderline statistically significant mortality benefit with apixaban. (Tables 9, 10, 11)

In the similarly designed phase 3, double-blinded, superiority AVERROES trial, 5599 patients with nonvalvular AF plus at least one additional risk factor for stroke who were considered unsuitable for warfarin were randomized to receive apixaban 5 mg twice daily (reduced to 2.5 mg twice daily in high risk patients as in ARISTOTLE) or aspirin 81 to 324 mg daily.<sup>13</sup> The study population had a mean age of 70 years and a baseline CHADS<sub>2</sub> score of 2. The study was terminated early when results from the planned interim analyses showed a clear benefit, providing a mean duration of follow-up of 1.1 years. For the primary composite endpoint of stroke or systemic embolism, apixaban was superior to aspirin with annual event rates of 1.6% vs. 3.7% (HR 0.45; 95% CI 0.32-0.62; p <0.001), driven primarily by a reduction in ischemic stroke with no significant excess in major bleeding.

### **Subgroup analyses**

The treatment effect of dabigatran, rivaroxaban, and apixaban compared to warfarin in each of their respective pivotal trials appeared to be consistent overall across multiple subgroups with no significant interactions noted among any of the subgroups tested.<sup>9,11,12,14</sup> Specifically, treatment effects were consistent in patients with renal impairment and in patients 75 years of age and older for all three agents. There were negative trends with rivaroxaban vs. warfarin only in the small number of patients with CHADS<sub>2</sub> score of 6 and in apixaban vs. warfarin in patients less than 65 years old.

### **Outcomes based on INR control**

Subanalyses of the three pivotal TSOAC vs. warfarin trials have been conducted to evaluate outcomes based on the center's INR control. The mean time in therapeutic range (TTR) in ROCKET AF with rivaroxaban vs. warfarin was 55% and lower than in other contemporary, major clinical trials including RELY (mean TTR 64%) and ARISTOTLE (mean TTR 62%) with dabigatran and apixaban, respectively. In all of the trials, there was a

substantial range of TTRs across different centers and countries. Significant limitations exist with the analyses, as they were based on post randomization data. Individual TTRs within a center’s TTR may vary significantly, and factors in addition to TTR may influence a center’s care and likelihood of outcomes.

- *Dabigatran*: The advantage of dabigatran over warfarin for the risk of stroke and systemic embolism appeared to be less in the setting of good INR control. In contrast, rates of intracranial bleeding remained lower with dabigatran vs. warfarin regardless of the center’s INR control.<sup>15</sup>
- *Rivaroxaban*: Findings from the published ROCKET AF study suggested that the treatment effect of rivaroxaban remained favorable compared to warfarin in the highest quartile of the center’s TTR reflecting the best INR control.<sup>11</sup> However, in a separate analysis conducted by the FDA using different methods to calculate the center’s TTR, the treatment effect of rivaroxaban was less favorable when the center’s TTR was about 68% or higher.<sup>16,17</sup> In total, it remains unclear how rivaroxaban compares to warfarin that is better controlled (e.g., higher TTR).
- *Apixaban*: Findings from the published subanalysis of the ARISTOTLE trial and FDA review suggested that the overall effects for apixaban on the primary composite endpoint of reduction in stroke and systemic embolism were fairly consistent across a wide range of center TTR quartiles.<sup>18,19</sup> In the FDA analysis but not the published substudy, the advantage of apixaban over warfarin for the outcome of all-cause death was most apparent at centers with lower TTR.

**TSOACs as a Class**

Three systematic reviews that compare TSOACs as a class to warfarin are summarized. A systematic review conducted on behalf of the VA Evidence-Based Synthesis Project (ESP) compared the effectiveness of the TSOACs to warfarin for the AF and VTE indications using data from six phase 3 trials available at the time.<sup>20</sup> For the AF indication, data from the three pivotal AF studies (RE-LY, ROCKET-AF, and ARISTOTLE) including over 44,000 patients were used to compare dabigatran 150 mg, rivaroxaban, and apixaban as a class to warfarin. The TSOACs were associated with a significantly lower risk of all-cause mortality and hemorrhagic stroke compared to warfarin. The risk of ischemic stroke favored the TSOACs but the difference was not significant. Lip et al. conducted an indirect comparison between the TSOACs (discussed below) but included a weighted average effects table of the TSOACs vs. warfarin using data from the same three pivotal AF studies as the VA ESP analysis.<sup>21</sup> Results were very consistent with the VA ESP findings. In addition, the Lip et al. study showed that the TSOACs were associated with a reduction in the composite endpoint of stroke and systemic embolism. Dentali et al. conducted a systematic review and meta-analysis of 12 phase 2 and 3 trials including dabigatran, rivaroxaban, apixaban, and edoxaban (not approved in the U.S.) in AF.<sup>22</sup> Overall, they reported similar findings to the VA ESP and Lip analyses. Limitations of these analyses include the small number of studies evaluated (in two of the three reviews) and the inclusion of a combination of drugs with different mechanisms of action, both of which could limit the ability to detect important differences in outcomes.

**Table 7. Systematic reviews of TSOACs vs. WARF in AF: Efficacy Outcomes**

Review	Drugs	# of Trials	Stroke/SE	Ischemic stroke	Hemorrhagic stroke	All-cause death
Adam et al. <sup>20</sup>	D150 RIVA APIX	3	--	0.89 (0.78-1.02)	<b>0.48 (0.36-0.62)</b>	<b>0.88 (0.82-0.96)</b>
Lip et al. <sup>21</sup>	D150 RIVA APIX	3	<b>0.79 (0.71-0.88)</b>	0.88 (0.77-1)	<b>0.47 (0.36-0.62)</b>	<b>0.88 (0.82-0.95)</b>
Dentali et al. <sup>22</sup>	DABI RIVA APIX EDOX	12	<b>0.77 (0.7-0.86)</b>	0.92 (0.81-1.04)	--	<b>0.89 (0.83-0.96)</b>

Bolded values are statistically significant

In the absence of head-to-head study, indirect comparisons between the TSOACs have been conducted and published. Lip and colleagues evaluated the comparative effectiveness between dabigatran, rivaroxaban, and apixaban based on data from the phase 3 pivotal trials for AF.<sup>21</sup> No significant differences in efficacy endpoints

including mortality were noted between apixaban and rivaroxaban or dabigatran (either dose). Dabigatran 150 mg was associated with lower rates of certain stroke endpoints compared to rivaroxaban. Apixaban was generally associated with less bleeding. In a separate analysis by Mantha et al. of the same 3 pivotal trials, overall similar findings were reported.<sup>23</sup> Rasmussen et al. conducted an indirect comparative analysis of dabigatran, rivaroxaban, and apixaban with data from the three pivotal AF trials (RE-LY, ROCKET-AF, ARISTOTLE) to evaluate the comparative efficacy and safety in primary and secondary stroke prevention between the TSOACs.<sup>24</sup> For the secondary prevention of stroke (in patients with previous TIA/stroke), no significant differences in safety and efficacy between dabigatran 150 mg, rivaroxaban, and apixaban were found except for a higher rate of MI with dabigatran. For the primary prevention of stroke (in patients with no history of TIA/stroke), there were some differences between the agents. Dabigatran 150 mg was associated with lower risk of stroke than apixaban. Apixaban was overall associated with less bleeding. Given the limitations of indirect comparisons including differences in study design, patient population, definitions of outcomes, the results do not establish superiority of one TSOAC over another. The authors of all of the analyses state that the results are hypothesis generating only.

**Table 8. Indirect comparisons of the TSOACs for Efficacy Outcomes**<sup>21,23</sup>

		APIX vs. D150	APIX vs. RIVA	D150 vs. RIVA	RIVA vs. D150
Stroke/SE	Mantha et al.	1.22 (0.91-1.62)	0.9 (0.71-1.16)	-	<b>1.35 (1.02-1.78)</b>
	Lip et al.	1.22 (0.91-1.62)	0.9 (0.71-1.13)	<b>0.74 (0.56-0.97)</b>	-
Ischemic Stroke	Mantha et al.	1.2 (0.86-1.67)	1.02 (0.75-1.38)	-	1.19 (0.85-1.65)
	Lip et al.	1.21 (0.88-1.67)	0.98 (0.72-1.33)	0.81 (0.58-1.13)	-
Hemorrhagic Stroke	Mantha et al.	1.93 (0.92-4.07)	0.88 (0.48-1.59)	-	2.2 (1-4.84)
	Lip et al.	1.96 (0.94-4.08)	0.86 (0.48-1.57)	<b>0.44 (0.2-0.96)</b>	-
Myocardial infarction	Mantha et al.	0.68 (0.45-1.03)	1.1 (0.74-1.62)	-	<b>0.62 (0.42-0.93)</b>
	Lip et al.	0.69 (0.46-1.05)	1.09 (0.74-1.6)	<b>1.57 (1.05-2.33)</b>	-
All-cause death	Mantha et al.	1.01 (0.85-1.2)	0.97 (0.83-1.15)	-	1.04 (0.87-1.24)
	Lip et al.	1.01 (0.85-1.2)	1.05 (0.84-1.3)	1.04 (0.82-1.3)	-

Bolded values are statistically significant; Results not intended to be comparative as study conditions differed

**Guidelines**

- The 2012 American College of Chest Physicians (ACCP) CHEST Guidelines provide a weak preference (Grade 2B) for dabigatran over adjusted dose vitamin K antagonist (VKA) therapy for patients with AF/paroxysmal AF who are at intermediate risk or higher risk of stroke (CHADS<sub>2</sub> score of ≥1).<sup>25</sup> At the time the guidelines were written, only dabigatran was approved for AF. Situations where dabigatran over VKA for stroke prevention in AF is not suggested: rheumatic mitral valve disease (including mitral stenosis), stable coronary artery disease, following intracoronary stent placement, or ACS with medical management.
- The 2012 American Heart Association (AHA)/American Stroke Association (ASA) Science Advisory on Oral Antithrombotic Agents in Nonvalvular AF provide similar recommendations for dabigatran and apixaban (Class I; Level of Evidence B) as an efficacious alternative to warfarin in patients with nonvalvular AF plus at least one additional risk factor for stroke.<sup>26</sup> Rivaroxaban is recommended as a reasonable alternative to warfarin (Grade IIb; Level of Evidence C).

**Summary:**

- Dabigatran, rivaroxaban, and apixaban have been shown to be noninferior to adjusted dose warfarin in the reduction of stroke and systemic embolism in patients with nonvalvular AF based on results from three large clinical trials. Further, dabigatran 150 mg and apixaban were found to be superior to warfarin for the composite primary endpoint. Only dabigatran 150 mg was associated with a reduction in ischemic stroke compared to warfarin, while all three TSOACs were associated with a consistent and significant reduction of 40% or greater in the risk of hemorrhagic stroke compared to warfarin.
- Favorable trends in mortality were seen with all three TSOACs compared to warfarin, but the difference reached borderline statistical significance only with apixaban.

- The data evaluating the influence of TTR on efficacy endpoints with the TSOACs vs. warfarin have significant limitations and show some inconsistencies. However, the data in total suggest that the advantages of the TSOACs over warfarin may be more apparent when INR control is suboptimal.
- Compared to warfarin, systematic reviews of the TSOACs as a class suggest that the TSOACs have a favorable impact on hemorrhagic stroke and all-cause mortality with a similar effect on the risk of ischemic stroke.
- No head to head studies between the TSOACs have been conducted, so superiority of one TSOAC over another cannot be determined. Differences in study design and patient populations between the pivotal trials limit the ability of making indirect comparisons between the TSOACs.

**Table 9. Phase 3 Pivotal AF Study Design**<sup>9,11,12</sup>

	<b>APIX vs. WARF ARISTOTLE</b>	<b>DABI vs. WARF RELY</b>	<b>RIVA vs. WARF ROCKET AF</b>
<b>Design</b>	Multinational, prospective, randomized, double-blind, noninferiority Efficacy analysis based on ITT	Multinational, prospective, randomized, open-label, blinded outcomes, non-inferiority Analysis based on ITT	Multinational, prospective, double-blind, noninferiority Primary analysis based on per-protocol
<b>Treatment Arms</b>	APIX 5 BID WARF (INR 2-3)	DABI 110 BID DABI 150 BID WARF (INR 2-3)	RIVA 20 daily WARF (INR 2-3)
<b>Key Inclusion</b>	Nonvalvular AF with ≥1 additional risk factors for stroke	Nonvalvular AF with increased risk of stroke	Nonvalvular AF with prior stroke or ≥2 additional risk factors for stroke
<b>Key Exclusion</b>	<ul style="list-style-type: none"> <li>▪ Moderate or severe mitral stenosis</li> <li>▪ Conditions other than AF that required anticoagulation (e.g., prosthetic heart valve)</li> <li>▪ Active infective endocarditis</li> <li>▪ Conditions associated with increased bleeding risk</li> <li>▪ Planned ablation</li> <li>▪ Stroke in past 7 days</li> <li>▪ Active liver disease</li> <li>▪ SCr &gt;2.5 mg/dL or CrCl &lt;25 ml/min</li> </ul>	<ul style="list-style-type: none"> <li>▪ History of heart valve disorder (e.g., prosthetic valve or hemodynamically relevant valve disease)</li> <li>▪ Active infective endocarditis</li> <li>▪ Conditions with increased bleeding risk</li> <li>▪ Plan for ablation or surgical cure of AF</li> <li>▪ Severe stroke in past 6 mos or any stroke in past 14 days</li> <li>▪ Active liver disease</li> <li>▪ CrCl ≤30 ml/min</li> </ul>	<ul style="list-style-type: none"> <li>▪ Prosthetic heart valve</li> <li>▪ Hemodynamically significant mitral stenosis</li> <li>▪ Active endocarditis</li> <li>▪ Condition with increased bleeding risk</li> <li>▪ Planned cardioversion</li> <li>▪ Known atrial myxoma or left ventricular thrombus</li> <li>▪ Severe stroke in past 3 mos or any stroke in past 14 days; TIA in past 3 days</li> <li>▪ Active liver disease</li> <li>▪ CrCl &lt;30 ml/min</li> </ul>
<b>Concomitant antiplatelet therapy</b>	<u>Exclusions:</u> ASA >165 mg/day or ASA+thienopyridine	<u>Discouraged:</u> ASA OTC meds, chronic use of corticosteroids, NSAIDs  <u>Permitted:</u> ASA ≤100 mg/day, clopidogrel, ticlopidine, dipyridamole, ASA/dipyridamole	<u>Exclusions:</u> combo ASA+thienopyridine, chronic NSAIDs  <u>Permitted:</u> ASA ≤100 mg/day OR thienopyridine

**Table 10. AF Pivotal Studies Baseline Characteristics**<sup>9,11,12</sup>

	<b>APIX vs. WARF ARISTOTLE</b>	<b>DABI vs. WARF RELY</b>	<b>RIVA vs. WARF ROCKET AF</b>
Average Age†	70 yrs	71 yrs	73 yrs
Patients ≥75 yrs	31%	40%	44%
CHADS <sub>2</sub> score (mean)	2.1	2.1	3.5
0-1	34%	32%	-
2	36%	36%	13%
3-6	30%	32%	87%
Prior VKA use	57%	50%	62%
Prior TIA/stroke	19%	20%	55%
Baseline ASA	31%	40%	36%
Mean TTR	62%	64%	55%
Median follow-up	1.8 yrs	2 yrs	1.9 yrs

†Age reported as mean for ARISTOTLE and RELY and median for ROCKET AF

**Table 11. AF Pivotal Studies 1° Outcomes and Selected 2° Outcomes**<sup>9,11,12</sup>

	<b>APIX vs. WARF (ARISTOTLE)</b> N <sub>R</sub> =18,201			<b>DABI vs. WARF (RELY)</b> N <sub>R</sub> =18,113			<b>RIVA vs. WARF (ROCKET AF)</b> N <sub>R</sub> =14,264		
	<b>APIX % per yr</b>	<b>WARF % per yr</b>	<b>HR (95% CI)</b>	<b>D150 % per yr</b>	<b>WARF % per yr</b>	<b>RR (95% CI)</b>	<b>RIVA % per yr</b>	<b>WARF % per yr</b>	<b>HR (95% CI)</b>
<b>1° Endpt: all stroke/SE</b>	1.27 <sup>a</sup> *	1.6	0.79 (0.66-0.95)	1.11 <sup>a</sup> *	1.69	0.66 (0.53-0.82)	2.1 <sup>c</sup>	2.4	0.88 (0.75-1.03)
<b>Ischemic stroke (or unspecified)</b>	0.97	1.05	0.92 (0.74-1.13)	0.92*	1.2	0.76 (0.6-0.98)	1.34	1.42	0.94 (0.75-1.17)
<b>Hemorrhagic stroke</b>	0.24*	0.47	0.51 (0.35-0.75)	0.1*	0.38	0.26 (0.14-0.49)	0.26*	0.44	0.59 (0.37-0.93)
<b>Myocardial infarction</b>	0.53	0.61	0.88 (0.66-1.17)	0.74*	0.53	1.38 (1-1.91)	0.91	1.12	0.81 (0.63-1.06)
<b>All-cause death</b>	3.52*	3.94	0.89 (0.8-0.998)	3.64	4.13	0.88 (0.77-1)	1.87	2.21	0.85 (0.7-1.02)

\*p <0.05 for difference between groups; <sup>a</sup>p <0.05 for noninferiority and superiority; <sup>c</sup>p <0.05 for noninferiority in per-protocol population (superiority not met in intention to treat population); Results not intended to be comparative as study conditions differed

## II. PERI-CARDIOVERSION ANTICOAGULANT USE IN AF (updated September 2014)

Peri-cardioversion anticoagulation is a standard recommendation in clinical practice based primarily on observational studies that demonstrates a substantial reduction in the risk of stroke and systemic embolism compared to the use of no anticoagulation; however, there is an increased risk of clinically important bleeding. CHEST Guidelines recommend at minimum three weeks of therapeutic anticoagulation before procedure (or transesophageal echocardiogram [TEE] guided approach with abbreviated anticoagulation) and at least four weeks after cardioversion in patients with AF of unknown or greater than 48 hours' duration (with long term continuation of anticoagulation a separate issue).<sup>25</sup> With conventional warfarin treatment (goal INR 2.5), the estimated risks of death, nonfatal stroke, and major (nonintracranial) bleeding are 1%, 0.3%, and 1.5% respectively over the 8 week peri-cardioversion period.<sup>25,27</sup> Evidence available on the use of TSOACs as an alternative to warfarin during the peri-cardioversion period includes one prospective, randomized, open label trial comparing rivaroxaban to VKAs, three post-hoc analyses from the pivotal AF trials for dabigatran, rivaroxaban, and apixaban, a retrospective cohort study evaluating dabigatran and rivaroxaban, and several case reports describing experiences with dabigatran.

A prospective, randomized, open-label, multinational, industry-sponsored study explored the efficacy and safety of rivaroxaban vs. VKA in patients with hemodynamically stable nonvalvular atrial fibrillation undergoing elective cardioversion (X-VerT trial)<sup>28,29</sup> A total of 1,504 patients were randomized in a 2:1 ratio to receive rivaroxaban 20 mg orally once daily (or 15 mg for patients with CrCl 30-49 ml/min) or VKA (goal INR 2.5; range 2-3). A strategy of early cardioversion (within 1-5 days of randomization) or delayed cardioversion (within 3-8 weeks of randomization) was determined by the provider prior to randomization. The primary endpoint was a composite of stroke, transient ischemic attack, peripheral embolism, MI, and cardiovascular death within 30 days after cardioversion. A total of 10 primary outcome events was observed for a cumulative risk of 0.51% (5/978) in the rivaroxaban group and 1.02% (5/492) in the VKA group (rivaroxaban vs. warfarin RR 0.50; 95% CI 0.15-1.73). Rates of major bleeding were similar and low between rivaroxaban (0.61%) and warfarin (0.80%) groups and included three intracerebral bleeds and three fatal bleeds. Cardioversion procedures were more frequently delayed in the warfarin group compared to the rivaroxaban group, mainly due to inadequate anticoagulation. Of note, this study was not powered to detect statistically significant differences between treatment groups and results are considered exploratory.

A post-hoc analysis of patients who underwent cardioversion during the RE-LY trial comparing dabigatran and warfarin was conducted and is published.<sup>30</sup> According to the RE-LY study protocol, cardioversion was permitted, and continuation of study drug during cardioversion was recommended. TEE was encouraged, and cardioversion was not recommended in patients with left atrial thrombus. A total of 7% (n=1270) of patients underwent 1983 cardioversion procedures during the trial. Rates of stroke and systemic embolism as well as major bleeding within the 30 days after cardioversion were low and appeared to be similar between treatment arms, though the study was not powered to detect a difference.

A post-hoc analysis of patients who underwent cardioversion or ablation during the ROCKET-AF trial comparing rivaroxaban and warfarin was conducted and is published.<sup>31</sup> Per the ROCKET-AF study protocol, patients who planned to undergo elective cardioversion were excluded. As a result, only a small number of patients in ROCKET-AF underwent cardioversion or an AF ablation procedures (n=321 patients and 460 procedures). Of the total 321 patients, 285 patients underwent 375 electrical or pharmacologic cardioversion. These patients represented a higher risk population given the higher baseline risk and large portion of persistent AF in the ROCKET-AF trial. Most patients undergoing cardioversion continued study drug on the day of procedure, while about half of the patients undergoing ablation were taking study drug on the day of the procedure. There was an increase in the number of stroke/systemic embolic events and death in the 30 days following a cardioversion or ablation procedure, but no apparent difference between treatment with rivaroxaban vs. warfarin was noted. A 2-fold increased risk of hospitalization and 50% increased risk of clinically relevant bleeding in the 30 days following cardioversion or ablation was observed with no apparent differences between study drug treatments.

A post-hoc subgroup analysis of patients in the ARISTOTLE trial who underwent cardioversion with apixaban was conducted and is published.<sup>32</sup> According to the ARISTOTLE protocol, cardioversion was permitted. Continuation of randomized therapy before and after the procedure was recommended, though suspension of study medication to use open-label warfarin was allowed. A total of 540 patients (3% of the study population) underwent 743 cardioversion procedures. In the 30 days following cardioversion, there were no strokes or systemic embolic events in either the apixaban or warfarin group. Rates of other outcomes including MI, major bleeding, and death were low

and appeared similar between groups. Results from a separate analysis of patients who continued study medication for cardioversion procedures (451 of 540 patients; 83%) confirmed low and similar rates of outcomes between apixaban and warfarin treated patients.

A single center, retrospective cohort study was conducted that evaluated all patients (n=53) who underwent successful direct-current cardioversion and were anticoagulated with dabigatran or rivaroxaban for 21 to 60 days prior to the procedure.<sup>33</sup> Patients had a median age of 66 years and a mean CHADS2 score of 1.2. No thromboembolic or major bleeding events were observed within 60 days of cardioversion.

Multiple case reports of embolic events following the use of dabigatran for cardioversion have been published, including two cases reported in a non-English language.<sup>34,35, 36,37</sup> Successful resolution of a left atrial appendage thrombus with dabigatran has also been reported.<sup>38</sup>

Preliminary data were presented at the November 2013 AHA meeting evaluating the presence of left atrial appendage thrombus (LAA) with dabigatran, rivaroxaban, and warfarin in 487 consecutive patients scheduled to undergo cardioversion or ablation procedures.<sup>39</sup> Patients were anticoagulated for at least 30 days before the pre-procedural TEE was performed. Anticoagulation with dabigatran was associated with a significantly higher prevalence of LAA thrombus (6.7%) detected by TEE compared to warfarin (0.96%) and rivaroxaban (0.78%). In contrast, post-hoc subanalysis of patients who underwent cardioversion from the pivotal RE-LY trial did not show an increased risk of adverse outcomes (e.g., stroke and systemic embolism) at 30 days with dabigatran 150 mg vs. warfarin. In the 25% of patients treated with dabigatran 150 mg who underwent TEE prior to cardioversion, 1.8% had left atrial thrombi detected vs. 1.1% in warfarin group (13% of warfarin CV patients underwent TEE).

**Guidelines**

CHEST 2012 Guidelines for patients with AF for greater than 48 hours’ duration undergoing elective cardioversion recommend warfarin (INR 2-3), therapeutic dose LMWH, or dabigatran (Grade 1B) for at least 3 weeks prior and 4 weeks following the procedure.<sup>25</sup> The 2014 ACCF/AHA Guidelines on the management of AF recommend therapeutic anticoagulation with warfarin for the same duration around the peri-cardioversion period (Class I; LOE B) but state that the use of dabigatran, rivaroxaban, and apixaban is reasonable (Class IIa; LOE B).<sup>40</sup>

**Table 12. Outcomes During Cardioversion with TSOACs and Baseline Estimates with Conventional WARF**<sup>25,27,30,31</sup>  
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	WARF-CONV Tx ACUTE	DABI 150 vs. WARF RELY		RIVA vs. WARF ROCKET AF		RIVA vs. WARF X-VeRT		APIX vs. WARF ARISTOTLE	
<b>Procedure</b>	CV	CV		CV and AF ablation		CV		CV	
<b>Timeframe</b>	8 wks (4 wks pre-post)	30 days post		Study duration		30 days		30 days post	
<b>Treatment</b>	<b>WARF</b>	<b>DABI 150</b>	<b>WARF</b>	<b>RIVA</b>	<b>WARF</b>	<b>RIVA</b>	<b>WARF</b>	<b>APIX</b>	<b>WARF</b>
<b>N</b>	603	672†	664†	160	161	978	492	331	412
<b>Stroke/SE</b>	0.3%	0.3%	0.6%	1.9%	1.9%	0.2%	0.4%	0	0
<b>Major bleed</b>	1.5%	0.6%	0.6%	18.8%*	13%*	0.6%†	0.8%†	0.3%	0.2%
<b>Death</b>	-	-	-	1.9%	3.7%	0.5%	0.6%	0.6%	0.5%

\*Reported as clinically relevant bleeding – includes major bleeding plus clinically relevant nonmajor bleeding;

†Safety population included additional patients (everyone who received study drug)

Results not intended to be comparative as study conditions differed

Summary:

- Evidence for the use of a TSOAC as an alternative to warfarin during the peri-cardioversion period (three to four weeks before and four weeks after the procedure) is of low quality and based on one prospective, randomized, open label trial, three published post-hoc analyses, , one retrospective cohort study, and several case reports. Unpublished data looking at the presence of LAA thrombus with dabigatran vs. warfarin is preliminary but concerning.
- Based on the currently available evidence, the TSOACs do not appear to be associated with worse outcomes (e.g., stroke, systemic embolism, major bleeding) than warfarin in patients undergoing

cardioversion. The number of outcome events overall was small, and the only prospective, randomized trial with rivaroxaban vs. warfarin was not powered to detect a difference between treatments.

- Further study is needed to better establish whether differences in outcomes exist between the TSOACs and warfarin in patients undergoing cardioversion.

### III. PERI-PROCEDURAL USE OF ANTICOAGULANTS IN AF ABLATION

Similar to the recommendations for the peri-cardioversion procedure, the general recommendations in patients with AF who are undergoing ablation are to maintain therapeutic anticoagulation for at least three weeks prior (or TEE guided approach) and two months post procedure (with long term anticoagulation a separate issue).<sup>41</sup> With warfarin treatment in this setting, the historical approach has been to discontinue warfarin and bridge patients pre- and post-procedure with heparin or LMWH, which was based largely on expert opinion. However, more recent evidence from observational data and meta-analyses supports the use of uninterrupted warfarin throughout the peri-procedural period.<sup>42</sup> A third alternative for peri-procedural anticoagulation in AF ablation is the use of a TSOAC. All three strategies are discussed in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.<sup>41</sup> Data on the use of TSOACs during AF ablation is limited. Planned AF ablation procedure was an exclusion from the pivotal trials evaluating dabigatran and apixaban.

Dabigatran has been evaluated for use during the peri-procedural period of AF ablation procedures in several nonrandomized studies using varying anticoagulation protocols. Most of the studies found similar rates of thromboembolic and bleeding outcomes with dabigatran vs. standard of care.<sup>43,44,45</sup> In contrast, a larger multicenter, prospective registry study with matched controls receiving uninterrupted warfarin showed a higher rate of bleeding and thromboembolic events with dabigatran when it was stopped the morning of the procedure and restarted 3 hours after hemostasis was achieved.<sup>46</sup>

A post-hoc analysis of patients who underwent cardioversion or AF ablation during the ROCKET-AF trial comparing rivaroxaban and warfarin was conducted and has been published.<sup>31</sup> In the small number of patients who underwent cardioversion (n=321 patients and 460 procedures) or ablation procedures (n=79 patients and 85 procedures), there were no apparent differences between rivaroxaban and warfarin treatment.

#### Summary:

- Evidence for the use of a TSOAC as an alternative to warfarin during the peri-procedural period around AF ablation (at least three weeks before and two months after) is limited to a small post-hoc analysis of rivaroxaban from the pivotal ROCKET AF trial and several nonrandomized studies using dabigatran in a variety of protocols.
- Of the TSOACs, dabigatran has been evaluated in the largest number of patients and procedures. While most of the studies have not detected a difference in thromboembolic or bleeding outcomes with dabigatran vs. the standard of care (warfarin or warfarin/LMWH), one larger, multicenter, nonrandomized study identified a higher number of bleeding and thromboembolic events with the use of dabigatran.

### IV. TREATMENT OF ACUTE VTE (updated September 2014)

The three TSOACs approved for use in the U.S. have been studied in randomized, phase 3, noninferiority trials and compared to standard treatment (parenteral anticoagulant followed by adjusted dose VKA) for the prevention of recurrent VTE in patients presenting with acute VTE. Rivaroxaban, was the first TSOAC indicated for use by the FDA, but dabigatran and apixaban have subsequently been granted FDA approval. There are no head-to-head studies comparing the TSOACs. Results from two rivaroxaban studies, two dabigatran studies, and one apixaban study are available and published. The studies differed significantly in design but evaluated a similar primary composite endpoint of symptomatic, recurrent VTE and similar secondary endpoints. If noninferiority was determined, superiority testing was done. Across the five studies, patients tended to be younger (mid-late 50s) with good renal function. Certain subgroups of patients (e.g., cancer, recurrent VTE) represented small portions of the

study populations. (Tables 14 and 15) Extended treatment beyond the initial 3, 6, or 12 months following an acute VTE event is discussed separately. Edoxaban is not approved in the U.S. at this time but was included in some of the systematic reviews summarized below.

### ***Dabigatran***

Dabigatran has been evaluated in two nearly identically designed, double-blind, noninferiority, phase 3 acute VTE treatment studies, RECOVER I and II.<sup>47,48</sup> Patients assigned to both dabigatran and warfarin treatment arms were treated initially with a parenteral anticoagulant followed by either dabigatran (150 mg twice daily) or warfarin (goal INR 2-3) for a duration of 6 months. For the primary composite endpoint of recurrent symptomatic VTE or VTE-related death, dabigatran was found to be noninferior but not superior to warfarin (goal INR 2-3) in both individual studies as well as in a pooled analysis of RECOVER I and II (2.4% dabigatran vs. 2.2% warfarin; HR=1.09; 95% CI 0.76-1.57). For the secondary endpoints, there was a trend of more symptomatic, nonfatal PE events in RECOVER I and more symptomatic DVT events in RECOVER II with dabigatran. Other secondary endpoints including bleeding were numerically similar or lower with dabigatran compared to warfarin. When age was analyzed as a continuous variable, there was a trend of reduced efficacy with dabigatran vs. warfarin in younger patients, though the difference was not statistically significant. (Table 15)

### ***Rivaroxaban***

Rivaroxaban has been evaluated in two published, open label, event-driven, noninferiority, phase 3 acute VTE treatment studies and compared to standard treatment with adjusted dose VKA as part of the EINSTEIN clinical development program.<sup>49,50</sup> In the Acute DVT and Acute PE studies, rivaroxaban was found to be noninferior to standard treatment with enoxaparin followed by VKA (goal INR 2-3) for the reduction of recurrent VTE, with similar or lower rates major or clinically relevant bleeding. Though a favorable efficacy trend for rivaroxaban was observed in the Acute DVT study, superiority was not established. In both studies, rivaroxaban was shown to be effective when taken in a higher dose (15 mg twice daily) for the first 3 weeks followed by a lower maintenance dose (20 mg once daily) without the need for bridge therapy using an injectable anticoagulant. (Table 15)

### ***Apixaban***

Apixaban has been evaluated in the randomized, double-blind, non-inferiority AMPLIFY trial, where apixaban was compared to conventional treatment with enoxaparin followed by warfarin (goal INR 2-3) for a duration of 6 months.<sup>51</sup> For the prevention of VTE and VTE-related death, apixaban was shown to be noninferior to conventional therapy with significantly lower rates of major bleeding. Except for a numerical excess of nonfatal PE with apixaban (27 vs. 23 events), other secondary endpoints were numerically similar or lower with apixaban. Apixaban was shown to be effective when taken in a higher dose (10 mg twice daily) for the first 7 days followed by a lower maintenance dose (5 mg twice daily) without the need for bridge therapy using an injectable anticoagulant. (Table 15)

### ***Patients with Cancer***

Patients with cancer are at higher risk for thromboembolism (and death following VTE) and tend to experience more anticoagulant related bleeding. LMWHs have been shown to be superior to VKAs for the treatment of cancer-associated VTE and are preferred by professional guidelines. Studies of the TSOACs for VTE treatment included only small numbers of patients with cancer. Further, the pivotal TSOAC clinical trials used VKAs as the comparator, which has been shown to be inferior in cancer-associated VTE. Subgroup analyses have been performed but are of limited value given the small number of patients and events. A preliminary phase 2 study has been conducted in patients with metastatic cancer for the primary prevention of VTE that supports additional investigation. Further study is needed to establish safety and efficacy of TSOACs in the cancer population.

### ***TSOACs as a class***

Several systematic reviews and meta-analyses have been conducted evaluating the TSOACs to warfarin and are summarized. In 2014, Gomez-Outes et al. evaluated six trials including over 21,000 patients comparing the TSOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) to warfarin in the treatment of acute VTE.<sup>52</sup> As a class, TSOACs were found to be comparable to warfarin in preventing recurrent VTE, with a significantly lower risk of major bleeding and clinically relevant bleeding and no differences in death. Kakkos and colleagues describe similar findings in their 2014 systematic review and meta-analysis of the TSOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) using data from clinical trials in the acute VTE setting (n=6) and the long term, secondary prevention

setting (n=3).<sup>53</sup> In addition to the comparable risk of recurrent VTE and lower risk of major bleeding and clinically relevant bleeding with TSOACs vs. warfarin in the acute VTE setting, a trend of more fatal PE was observed. TSOACs were associated with a favorable overall net clinical benefit. In a separate 2014 analysis conducted by van der Hulle et al., five phase 3 studies of dabigatran, rivaroxaban, apixaban, and edoxaban were evaluated (prior to RE-COVER II publication with dabigatran).<sup>54</sup> Consistent with the more recent analyses, van der Hulle et al. also found that TSOACs had comparable efficacy to warfarin with less bleeding than VKAs. In a 2014 more broad review and meta-analyses of over 45,000 patients conducted to evaluate a wide range acute VTE treatment regimens, Castellucci and colleagues did not identify significant differences in recurrent thromboembolism between TSOAC- and VKA-containing regimens. Rivaroxaban and apixaban appeared to have a more favorable bleeding risk than other treatment regimens.<sup>55</sup> A systematic review conducted in 2012 on behalf of the VA Evidence-Based Synthesis Project (ESP) compared the effectiveness of the TSOACs to warfarin for the AF and VTE indications using data from six phase 3 trials available at the time.<sup>20</sup> For the VTE indication, data from three pivotal studies (EINSTEIN-DVT, EINSTEIN-PE, and RE-COVER) including over 10,000 patients were used to compare dabigatran and rivaroxaban as a class to warfarin. No differences in VTE recurrence or mortality with the TSOACs compared to warfarin were found.<sup>20</sup> In looking at major bleeding and fatal bleeding in the AF and VTE study populations combined, there was an overall lower risk of bleeding with the TSOACs vs. warfarin (RR 0.80; 95% CI 0.63-1.01 for major bleeding; RR 0.6; 95% CI 0.46-0.77 for fatal bleeding), though GI bleeding tended to be higher (RR 1.3; 95% CI 0.97-1.73). A 2012 systematic review and meta-analysis of 9 trials (including phase 2 and 3 studies) evaluating apixaban, dabigatran, rivaroxaban, and ximelagatran was conducted by Fox and colleagues to evaluate the risk of recurrent VTE and bleeding with the TSOACs compared to the standard of care (VKA therapy) and each other.<sup>56</sup> There was no significant difference in the risk of recurrent VTE or all-cause mortality with the TSOACs vs. VKA as stratified by drug. There was a trend of less major bleeding with the TSOACs compared to warfarin, but only rivaroxaban was associated with a significantly lower risk of major bleeding. Based on indirect comparisons, no difference was detected between the risk/benefit profile of dabigatran or rivaroxaban, though the strength of such analysis is limited. (Table 13)

**Table 13. Systematic reviews of TSOACs vs. WARF in Acute VTE Treatment: Efficacy Outcomes**

Review	Drugs	# of Trials	Recurrent VTE	VTE/PE death	All-cause death
Adam et al. <sup>20</sup> 2012	DABI RIVA	3	0.95 (0.71-1.27)	1.00 (0.48-2.10)	0.97 (0.72-1.3)
Kakkos et al. <sup>53</sup> 2014	DABI RIVA APIX EDOX	9	0.89 (0.75-1.05)	1.30 (0.57-2.96)	0.98 (0.84-1.14)
van der Hulle et al. <sup>54</sup>	DABI RIVA APIX EDOX	5	0.88 (0.74-1.05)	1.02 (0.39-5.96)	0.97 (0.83-1.14)
Gomez-Outes et al. <sup>52</sup>	DABI RIVA APIX EDOX	6	0.91 (0.79-1.06)	0.98 (0.67-1.44)	0.98 (0.84-1.14)

**Guidelines**

The 2012 ACCP CHEST Guidelines provide a weak preference (Grade 2C) for VKA over rivaroxaban or dabigatran in the acute and long term treatment of VTE (in patients with no cancer), stating that the evidence with each agent is of moderate quality because of imprecision for each outcome.<sup>57</sup> The guidelines were written before the AMPLIFY study with apixaban was completed. The American Society of Clinical Oncology (ASCO) 2013 VTE Guidelines recommend that TSOACs not be used at this time for the prevention or treatment of VTE in patients with cancer due to insufficient evidence.<sup>58</sup> Similarly, the National Comprehensive Cancer Network (NCCN) 2014 Guidelines on VTE disease do not recommend the use of TSOACs for prophylactic or therapeutic anticoagulation in patients with cancer.<sup>59</sup>

**Summary:**

- The TSOACs dabigatran, rivaroxaban, and apixaban have been shown to be noninferior to adjusted dose VKA therapy in the prevention of recurrent VTE in patients presenting with acute VTE (3, 6, or 12 month duration).
- Compared with adjusted dose VKA therapy, major bleeding rates were similar with dabigatran and tended to be lower with rivaroxaban and apixaban.
- Study populations tended to be younger (50s) with good renal function, and certain subgroups of patients including the elderly, patients with cancer, or patients with recurrent VTE represented small portions of the study groups.
- Results from systematic reviews of the TSOACs as a class suggest that the TSOACs are comparable to adjusted dose VKAs in preventing recurrent VTE with a tendency of less bleeding and no difference in mortality.

**Table 14. Study Design Pivotal Acute VTE Treatment Studies (3, 6, or 12 months duration)**

Study	DABI RECOVER I <sup>47</sup> N <sub>R</sub> =2564	DABI RECOVER II <sup>48</sup> N <sub>R</sub> =2589	RIVA EINSTEIN ACUTE DVT <sup>49</sup> N <sub>R</sub> =3449	RIVA EINSTEIN ACUTE PE <sup>50</sup> N <sub>R</sub> =4832	APIX AMPLIFY <sup>51</sup> N <sub>R</sub> =5395
<b>Design</b>	Multinational, prospective, randomized, double-blind, non-inferiority Primary analysis based on modified intention to treat (received study drug)		Multinational, prospective, open-label, noninferiority, event-driven Primary analysis based on intention to treat	Multinational, prospective, open-label, noninferiority, event-driven Primary analysis based on intention to treat	Multinational, prospective, double-blind, noninferiority study Primary analysis based on intention to treat in pts whose 6 mo outcome was known
<b>Treatment Arms</b>	<u>Initial tx:</u> (mean duration 9-10 days) All pts - parenteral agent for ≥5 days AND therapeutic INR  <u>Maintenance tx</u> (6 mos) DABI 150 BID WARF (INR 2-3)		<u>Initial tx:</u> RIVA 15 BID x21 days ENOX 1 mg/kg BID plus VKA for ≥5 days AND therapeutic INR  <u>Maintenance tx</u> (3, 6, or 12 mos as per prescriber) RIVA 20 mg daily VKA (INR 2-3)	<u>Initial tx:</u> RIVA 15 BID x21 days ENOX 1 mg/kg BID plus VKA for ≥5 days AND therapeutic INR  <u>Maintenance tx</u> (3, 6, or 12 mos as per prescriber) RIVA 20 mg daily VKA (INR 2-3)	<u>Initial tx:</u> APIX 10 BID x7 days ENOX 1 mg BID plus WARF for ≥5 days AND therapeutic INR  <u>Maintenance tx</u> (6 mos) APIX 5 BID WARF (INR 2-3)
<b>Key Inclusion</b>	Acute, symptomatic, objectively confirmed proximal DVT of the legs or PE in whom 6 mos of treatment was appropriate		Acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE	Acute, symptomatic, objectively confirmed PE with or without symptomatic DVT	Acute, symptomatic, objectively confirmed DVT or PE (with or without DVT)
<b>Key Exclusion</b>	<ul style="list-style-type: none"> <li>▪ Symptoms for &gt;14 days</li> <li>▪ PE with hemodynamic instability</li> <li>▪ PE requiring thrombolytic tx</li> <li>▪ Recent unstable cardiovascular disease</li> <li>▪ High bleeding risk</li> <li>▪ CrCl &lt;30 ml/min</li> <li>▪ Liver disease with aminotransferase level &gt;2-3x ULN</li> <li>▪ Additional indication for warfarin</li> <li>▪ Pregnancy or at risk for pregnancy</li> <li>▪ Need for long term antiplatelet tx (except ASA ≤100 mg daily)</li> </ul>		<ul style="list-style-type: none"> <li>▪ CrCl &lt;30 ml/min</li> <li>▪ Clinically significant liver disease or alanine aminotransferase &gt;3x ULN</li> <li>▪ Bacterial endocarditis</li> <li>▪ Active bleeding or at high risk</li> <li>▪ SBP &gt;180 or DBP &gt;110 mmHg</li> <li>▪ Pregnant or breast feeding</li> <li>▪ Childbearing potential without contraception</li> <li>▪ Concomitant use of strong CYP3A4 inhibitors or inducers</li> <li>▪ Additional indication for anticoagulation</li> <li>▪ Discouraged antiplatelet and non-steroidal anti-inflammatory drugs but ASA ≤100 mg daily, clopidogrel 75 mg daily, or both were allowed</li> </ul>	<ul style="list-style-type: none"> <li>▪ Thrombectomy</li> <li>▪ IVC filter placement</li> <li>▪ Treatment with fibrinolytic</li> <li>▪ CrCl &lt;30 ml/min</li> <li>▪ Clinically significant liver disease or alanine aminotransferase &gt;3x ULN</li> <li>▪ Bacterial endocarditis</li> <li>▪ Active bleeding or high risk</li> <li>▪ SBP &gt;180 or DBP &gt;110 mm Hg</li> <li>▪ Pregnant or breastfeeding</li> <li>▪ Childbearing potential without contraception</li> <li>▪ Concomitant use of strong CYP3A4 inhibitor or inducer</li> <li>▪ Additional indication for anticoagulant</li> <li>▪ Discouraged antiplatelet and non-steroidal anti-inflammatory drugs but ASA ≤100 mg daily, clopidogrel 75 mg daily, or both were allowed</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cancer with plan for long term LMWH</li> <li>▪ Active bleeding or at high risk</li> <li>▪ Provoked VTE in absence of risk factor for recurrence</li> <li>▪ Planned treatment &lt;6 mos</li> <li>▪ Additional indication for anticoagulation</li> <li>▪ Dual antiplatelet therapy</li> <li>▪ ASA &gt;165 mg daily</li> <li>▪ Concomitant use of potent CYP3A4 inhibitors</li> <li>▪ Hemoglobin &lt;9 g/dL</li> <li>▪ Platelet &lt;100K /mm<sup>3</sup></li> <li>▪ SCr &gt;2.5 mg/dL or CrCl &lt;25 ml/min</li> </ul>

**Table 15. Phase 3 Acute VTE Treatment Studies (3, 6 or 12 mos duration)**

	DABI			DABI			RIVA			RIVA			APIX		
Study	RECOVER I			RECOVER II			EINSTEIN Acute DVT			EINSTEIN Acute PE			AMPLIFY		
Baseline	N <sub>R</sub> =2564			N <sub>R</sub> =2589			N <sub>R</sub> =3449			N <sub>R</sub> =4832			N <sub>R</sub> =5395		
TTR	60%			57%			58%			63%			61%		
Mean age	55 yrs			55 yrs			56 yrs			58 yrs			57 yrs		
Male	58%			61%			57%			53%			58%		
Unprovoked	Not stated			Not stated			62%			64%			90%		
Cancer	5%			4%			6%			5%			3%		
Prior VTE	26%			18% <sup>§</sup>			19%			20%			16%		
Results	DABI	WARF	HR (95% CI)	DABI	WARF	HR (95% CI)	RIVA	VKA	HR (95% CI)	RIVA	VKA	HR	APIX	WARF	HR (95% CI)
1 <sup>o</sup> Endpt: Sx VTE <sup>a</sup>	2.4%	2.1%	1.1 (0.65-1.84)	2.3%	2.2%	1.08 (0.64-1.80)	2.1%	3%	0.68 (0.44-1.04)	2.1%	1.8%	1.12 (0.75-1.68)	2.3%	2.7%	0.84 (0.6-1.18)
Sx DVT	1.3%	1.4%	0.87 (0.44-1.71)	2%	1.3%	1.48 (0.8-2.74)	0.8%	1.6%	-	0.7%	0.7%	-	0.8%	1.3%	-
Sx nonfatal PE	1%	0.6%	1.85 (0.74-4.64)	0.5%	1%	0.54 (0.21-1.35)	1.2%	1.1%	-	0.9%	0.9%	-	1%	0.9%	-
VTE-death <sup>b</sup>	0.1%	0.2%	0.33 (0.03-3.15)	0.2%	0	-	0.2%	0.4%	-	0.4%	0.3%	-	0.5%	0.6%	-
Major bleed	1.6%	1.9%	0.82 (0.45-1.48)	1.2%	1.7%	0.69 (0.36-1.32)	0.8%	1.2%	0.65 (0.33-1.3)	1.1%*	2.2%	0.49 (0.31-0.79)	0.6%*	1.8%	0.31 (0.17-0.55)
All-cause death	1.6%	1.7%	0.98 (0.53-1.79)	2%	1.9%	0.98 (0.56-1.71)	2.2%	2.9%	0.6 (0.44-1.02)	2.4	2.1	1.13 (0.77-1.65)	1.5%	1.9%	0.79 (0.53-1.19)

DB=double-blind; RCT=randomized controlled trial; VKA=vitamin K antagonist

<sup>§</sup>Baseline difference between groups was statistically different (19% DABI vs. 16% WARF)

<sup>a</sup>Primary endpoint was defined slightly differently between trials: EINSTEIN Acute DVT and Acute PE – composite of DVT, nonfatal or fatal PE; RECOVER and AMPLIFY – composite of symptomatic VTE or VTE-death;

<sup>b</sup>VTE death – AMPLIFY, EINSTEIN PE, EINSTEIN DVT – endpoint included fatal PE and deaths where PE could not be ruled out.

\*p ≤0.05 for difference between treatment groups

Results not intended to be comparative as study conditions differed

## V. EXTENDED TREATMENT OF VTE (updated September 2014)

The three TSOACs have been evaluated in published, randomized, phase 3, industry sponsored, double-blinded trials and compared to warfarin or placebo for the extended treatment of VTE following the initial 3, 6, or 12 months of treatment following an acute VTE event. There are no direct studies comparing one TSOAC to another. Rivaroxaban was the first TSOAC indicated for VTE treatment and secondary prevention in the U.S., but dabigatran and most recently apixaban have also been granted FDA approval. Dabigatran has been studied in two studies, an active control and placebo-controlled trial. Rivaroxaban and apixaban were each studied in single placebo-controlled trials. There were differences in the study design between the trials. Each of the four trials examined a primary composite outcome of symptomatic, recurrent VTE, though definitions varied on the inclusion of VTE-related death or all-cause death. (Table 16)

### *Rivaroxaban*

Rivaroxaban was evaluated for the extended treatment of VTE in the double-blind, placebo controlled EINSTEIN-Continued Treatment study where 1,196 patients with clinical equipoise for continuing anticoagulation beyond their initial 6 to 12 months of treatment were randomized to receive ongoing treatment with rivaroxaban 20 mg once daily or placebo.<sup>49</sup> For the primary endpoint of symptomatic, recurrent VTE, rivaroxaban was found to be superior to placebo; however, there was a significantly increased risk of clinically relevant bleeding. The number of major bleeding events was low but occurred more frequently with rivaroxaban.

### *Dabigatran*

Dabigatran has been evaluated for the extended treatment of VTE in two double-blinded, phase 3 studies: an active control noninferiority study (REMEDY) and a placebo-controlled superiority study (RESONATE).<sup>60</sup> In the REMEDY trial, patients who were considered at increased risk of thromboembolism and who had completed at least 3 months of anticoagulation for VTE treatment prior to study entry were randomized to dabigatran 150 mg twice daily or adjusted dose warfarin (INR 2-3) for a duration of 6 to 36 months. For the primary endpoint of recurrent VTE or VTE-related death, dabigatran was deemed noninferior to warfarin, though event rates were numerically higher with dabigatran. Dabigatran was associated with lower or similar rates of bleeding, but there was a significant increase in the rate of ACS with dabigatran vs. warfarin.

In the RESONATE study, patients who had completed 6 to 18 months of anticoagulation treatment for VTE prior to study entry were randomized to dabigatran 150 mg twice daily or placebo for 6 months and then followed for 12 months after completing treatment. Dabigatran was superior to placebo in the risk of recurrent VTE or VTE related death (or unexplained death), though there was a nearly 3-fold increased risk of major or clinically relevant nonmajor bleeding. Major bleeding rates in both groups were low and similar. No excess of ACS with dabigatran was observed. In both REMEDY and RESONATE, the investigators observed no significant differences in efficacy among subgroup analyses.

### *Apixaban*

Apixaban was evaluated for the extended treatment of VTE in the industry sponsored, placebo controlled, phase 3 AMPLIFY-EXT trial.<sup>61</sup> A total of 2486 patients who completed 6 to 12 months of treatment for acute VTE and with clinical equipoise for continuation of anticoagulation were randomized to one of three arms: 1) apixaban 2.5 mg twice daily; 2) apixaban 5 mg twice daily; 3) placebo for 12 months. For the primary composite endpoint of recurrent VTE or all-cause death, both doses of apixaban were superior to placebo. Similarly for the outcome of recurrent VTE or VTE related death, apixaban was superior. Major bleeding rates were low and similar between groups, though there was a nonsignificant trend of more clinically relevant bleeding with both doses of apixaban.

### *TSOACs as a Class*

A systematic review and meta-analysis was conducted by Kakkos and colleagues and included three placebo controlled trials on secondary prevention of VTE (the RE-MEDY trial that compared dabigatran to warfarin was excluded).<sup>53</sup> Compared to placebo, TSOACs significantly reduced the risk of recurrent VTE (RR 0.17; 95% CI 0.12-0.24), including reductions in DVT and PE, at the expense of increased clinically relevant bleeding (RR 2.35; 95% CI 1.65-3.35). The overall net clinical benefit favored the TSOACs.

### *Guidelines*

The 2012 ACCP CHEST Guidelines were published before the results of the dabigatran and apixaban extended treatment trials were available. The decision to continue treatment beyond the initial 3 months depends on the

patient’s baseline risk for recurrent thromboembolism and bleeding as well as the patient’s preference (e.g., long term use of injections, need for laboratory monitoring, treatment costs, etc.). In situations where the decision has been made to continue anticoagulant treatment, the 2012 CHEST Guidelines suggest VKA or LMWH as first or second line treatment depending on the presence of cancer followed by dabigatran or rivaroxaban as third line choices (Grade 2C).

**Summary:**

- Dabigatran, rivaroxaban, and apixaban have each been shown to be superior to placebo in preventing recurrent VTE when used as extended treatment beyond the initial 3, 6, or 12 months of acute treatment. Major bleeding rates were low overall. Clinically relevant bleeding rates with the TSOACs were similar (apixaban) or higher (dabigatran and rivaroxaban) compared to placebo.
- In addition, dabigatran was deemed noninferior to warfarin for the extended treatment of VTE; however, recurrent VTE event rates as well as ACS rates were higher with dabigatran. Bleeding events were lower with dabigatran.
- The extended treatment studies provide additional information on the use of the TSOACs for durations of up to a mean of 16 months with dabigatran and about 6 to 12 months for rivaroxaban and dabigatran. Study populations tended to be younger (50’s) with good renal function, and certain subgroups of patients including the elderly and patients with cancer represented small portions of the study groups.

**Table 16. Extended VTE Treatment Phase 3 Studies**

Study	DABI REMEDY <sup>60</sup> N <sub>R</sub> =2866			DABI RESONATE <sup>60</sup> N <sub>R</sub> =1353			RIVA EINSTEIN Cont’d Tx <sup>49</sup> N <sub>R</sub> =1196			APIX AMPLIFY-EXT <sup>61</sup> N <sub>R</sub> =2486		
	Design	DB, noninferiority, active-control	DB, PC, superiority									
Required Tx Prior to Enrollment	3-12 mos prior tx for VTE Considered at increased risk of VTE	6-18 mos prior tx for VTE No clear need for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	6-12 mos prior tx for VTE Clinical equipoise for cont’d anticoag	
Treatment	DABI 150 BID WARF (INR 2-3)	DABI 150 BID PBO	DABI 150 BID PBO	RIVA 20 daily PBO	APIX 2.5 BID APIX 5 BID PBO	APIX 2.5 BID APIX 5 BID PBO						
Tx duration	~16 mos (range 6-36 mos)	6 mos (plus 12 mos f/u)	6 mos (plus 12 mos f/u)	~9 mos (6 or 12 mos)	12 mos (plus 1 mo f/u)	12 mos (plus 1 mo f/u)						
<b>Baseline</b>												
TTR	65%			NA			NA			NA		
Mean age	55 yrs			56 yrs			58 yrs			57 yrs		
Male	39%			44%			58%			57%		
Pts enrolled from Acute VTE study	40% (RECOVER and RECOVER II)			2% (RECOVER and RECOVER II)			53% (EINSTEIN DVT and PE)			33% (AMPLIFY)		
Cancer	4%			0			5%			2%		
Unprovoked	Not stated			Not stated			74%			92%		
Known hypercoag	18%			11%			8%			4%		
<b>Results</b>	<b>D %</b>	<b>W %</b>	<b>HR (95% CI)</b>	<b>D %</b>	<b>P %</b>	<b>HR (95% CI)</b>	<b>R %</b>	<b>P %</b>	<b>HR (95% CI)</b>	<b>A %</b>	<b>P %</b>	<b>HR (95% CI)</b>
1° Endpt: Sx, recurrent VTE/VTE-death	1.8†	1.3	1.44 (0.78-2.64)	0.4*	5.6	0.08 (0.02-0.25)	1.3*	7.1	0.18 (0.09-0.39)	2.5mg-1.7* 5mg-1.7*	8.8	0.19 (0.11-0.33) 0.2 (0.11-0.34)
Major bleed	0.9	1.8	0.52 (0.27-1.02)	0.3	0	Not estimable	4	0	NA	2.5mg: 0.2 5mg: 0.1	0.5	0.49 (0.09-2.64) 0.25 (0.03-2.24)
Major or CRNMB	5.6*	10.2	0.54 (0.41-0.71)	5.3*	1.8	2.92 (1.52-5.6)	6*	1.2	5.19 (2.3-11.7)	2.5mg: 3.2 5mg: 4.3	2.7	1.2 (0.69-2.1) 1.62 (0.96-2.73)

\*p <0.05 for difference between groups; †p <0.05 for noninferiority; Results not intended to be comparative as study conditions differed

## **VI. VTE PROPHYLAXIS IN TKR AND THR (updated September 2014)**

For the primary prevention of VTE in patients undergoing TKR and THR surgery, all three TSOACs have been studied in randomized, double-blind, noninferiority, phase 3 trials of similar design and compared to enoxaparin. Rivaroxaban was the first approved TSOAC in the U.S. for the indication, but apixaban has also been granted FDA approval. There are no head-to-head trials of the TSOACs. The primary endpoint in all of the trials was the composite of total VTE (any DVT or nonfatal PE) and all-cause mortality, and the primary safety endpoint was major bleeding, which was defined somewhat differently across the studies. As a secondary endpoint, the composite of major VTE was evaluated and defined as proximal DVT, non-fatal PE, or VTE related death in most of the trials. If noninferiority was determined, superiority testing was done. Between about 25% and 40% of randomized patients were not evaluable for the primary efficacy analysis across the trials, mostly due to inability to obtain or adequately assess for VTE by venography. There were differences in the study design and patient populations across the trials (e.g., timing of initiation of study drug treatment, timeframe for inclusion of outcome events, definition of major bleeding, etc.) that limit the ability to make comparisons between the studies of different drugs. (Table 18)

### ***Rivaroxaban***

Rivaroxaban was evaluated in four phase 3 studies.<sup>62,63,64,65</sup> The duration of treatment between groups within each study was the same except in RECORD-2, where short term treatment with enoxaparin (10-14 days) was compared to long term treatment with rivaroxaban (31-39 days). In all four trials, rivaroxaban was found to be superior to enoxaparin 40 mg once daily and 30 mg twice daily in patients undergoing TKR or THR for the primary composite endpoint. For the secondary endpoint of major VTE, rivaroxaban was superior to enoxaparin 40 mg once daily but not 30 mg twice daily. Major bleeding was not statistically different between treatment groups in any of the studies, though there was a tendency for more major bleeding events with rivaroxaban. Of note, the FDA did not include the RECORD 4 trial in support of the VTE prophylaxis indication for rivaroxaban because of significant concerns with study conduct, oversight, and data collection.<sup>66</sup> (Table 16)

### ***Dabigatran***

Dabigatran was evaluated in four phase 3 studies.<sup>67,68,69,70</sup> In three of the trials, dabigatran was shown to be noninferior to enoxaparin 40 mg once daily in patients undergoing TKR or THR for the primary endpoint. Similar or lower rates of clinically significant VTE and similar rates of major bleeding were observed. In contrast, dabigatran was inferior to a higher dose of enoxaparin (30 mg twice daily), the U.S. FDA approved dose in patients undergoing TKR, in the RE-MOBILIZE trial. Clinically significant VTE and major bleeding were not statistically different between treatment groups. (Table 16)

### ***Apixaban***

Apixaban was evaluated in three phase 3 studies.<sup>71,72,73</sup> In two of the trials, apixaban was found to be noninferior and superior to enoxaparin 40 mg once daily in patients undergoing TKR or THR for the primary endpoint and secondary endpoint of major VTE with similar rates of major bleeding. Compared to the higher enoxaparin dose of 30 mg twice daily in a TKR population, apixaban was inferior to enoxaparin for the primary endpoint; however, apixaban was associated with less major bleeding. An excess of PE events were observed in two of the three apixaban clinical trials, though the clinical significance of the finding is unclear. (Table 18)

### ***TSOACs as a class***

A systematic review and meta-analysis of 16 trials (including phase 3 and 2b studies) with the TSOACs was conducted to evaluate the risk of symptomatic VTE and clinically relevant bleeding (included major bleeding plus nonmajor clinically relevant bleeding) with the TSOACs compared to enoxaparin and each other.<sup>74</sup> (Table 17) Compared to enoxaparin, rivaroxaban was associated with a significantly lower risk of symptomatic VTE (RR 0.48; 95% CI 0.31-0.75; p=0.001) at the expense of an increased risk of clinically relevant bleeding (RR 1.25; 95% CI 1.05-1.49; p=0.001). Dabigatran and apixaban were associated with similar risk of symptomatic VTE compared to enoxaparin (RR 0.71; 95% CI 0.23-2.12 for dabigatran vs. enoxaparin and RR 0.82; 95% CI 0.41-1.64 for apixaban vs. enoxaparin). Both doses of dabigatran (150 mg and 220 mg) were associated with a similar clinically relevant bleeding risk as enoxaparin, while apixaban was associated with a significantly lower risk of bleeding vs. enoxaparin (RR 0.82; 95% CI 0.69-0.98; p=0.03). The net clinical benefit (including symptomatic VTE, major bleeding, and death) was not statistically different between the TSOACs and enoxaparin. Based on indirect

comparisons between the TSOACs, there was a trend of lower VTE risk with rivaroxaban but higher risk of bleeding, whereas apixaban appeared to be associated with a lower risk of bleeding. No difference in net clinical benefit between the TSOACs was noted. (Table 17)

**Guidelines**

The 2012 ACCP CHEST Guidelines provide a weak preference (Grade 2B) for LMWH over the TSOACs in the prevention of VTE in patients undergoing TKR or THR, given the well-established efficacy, safety, and long-term experience with LMWH coupled with the lack of long term safety data with the TSOACs.<sup>75</sup>

The 2011 Guidelines from the American Academy of Orthopedic Surgeons (AAOS) do not provide a preference for one agent over another for VTE prophylaxis in patients undergoing TKR or THR.<sup>76</sup>

Summary:

- The TSOACs have been shown to be at least as effective as enoxaparin 40 mg once daily for VTE prophylaxis in patients undergoing TKR and THR.
- Compared to the higher U.S. dose of enoxaparin 30 mg twice daily for VTE prophylaxis in TKR, dabigatran and apixaban were found to be inferior, while rivaroxaban maintained an efficacy advantage over enoxaparin.
- Major bleeding rates were low and generally similar between enoxaparin and the TSOACs in the clinical trials; however, there was a tendency for more bleeding with rivaroxaban and less bleeding with apixaban in some of the trials and per meta-analysis and systematic review.

**Table 17. Risk Differences for TSOACs vs. Enoxaparin (Direct) and for TSOAC vs. TSOAC (Indirect) for Primary VTE Prophylaxis in TKR and THR per Systematic Review<sup>74</sup>**

	Absolute Difference in events per 1000 patients treated (95% CI)		
	Symptomatic VTE	Clinically Relevant Bleeding	Major Bleeding
<b>Direct Comparisons</b>			
RIVA vs. ENOX	-5 (-9 to -1)*	9 (2 to 17)*	4 (-0.4 to 8)
DABI vs. ENOX	-2 (-9 to 5)	5 (-4 to 13)	-1 (-6 to 5)
APIX vs. ENOX	-1 (-4 to 2)	-8 (-15 to -1)*	-1 (-7 to 5)
<b>Indirect Comparisons</b>			
RIVA vs. DABI	-3 (-11 to 4)	5 (-7 to 16)	4 (-2 to 11)
RIVA vs. APIX	-4 (-9 to 1)	18 (7 to 28)*	5 (-2 to 12)
APIX vs. DABI	1 (-7 to 8)	-13 (-24 to -2)*	0 (-8 to 7)

Random effects model of events during treatment; \*denotes significant differences between treatments

**Table 18. Phase 3 Studies of Primary VTE prophylaxis in patients undergoing TKR and THR**<sup>62,63,64,65,66,67,68,69,70,71,72,73</sup>

Study	Type	N <sub>R</sub>	Treatment	Total VTE + any death (%)	Major VTE (%)	Major Bleed	Summary/Conclusions	
DABI	RE-MOBILIZE 12-15 days 73% eff anal	TKR	2,596	DABI 150 daily	33.7	3	0.6	<ul style="list-style-type: none"> <li>▪ DABI inferior ENOX <u>BID</u></li> <li>▪ Clinically significant VTE rates similar</li> <li>▪ Major bleeding not statistically different</li> </ul>
				DABI 220 daily	31.1	3.4	0.6	
				ENOX 30 BID	25.3	2.2	1.4	
	RE-MODEL 6-10 days 74% eff anal	TKR	2,076	DABI 150 daily	40.5	3.8	1.3	<ul style="list-style-type: none"> <li>▪ DABI non-inferior to ENOX daily</li> <li>▪ Clinically significant VTE rates similar</li> <li>▪ Major bleeding similar</li> </ul>
				DABI 220 daily	36.4	2.6	1.5	
				ENOX 40 daily	37.7	3.5	1.3	
	RE-NOVATE 28-35 days 77% eff anal	THR	3,463	DABI 150 daily	8.6	4.3	1.3	<ul style="list-style-type: none"> <li>▪ DABI non-inferior to ENOX daily</li> <li>▪ Clinically significant VTE rates similar</li> <li>▪ Major bleeding similar</li> </ul>
				DABI 220 daily	6	3.1	2	
RE-NOVATE II 28-35 days 77% eff anal	THR	2,055	DABI 220 daily	7.7	2.2	1.4	<ul style="list-style-type: none"> <li>▪ DABI non-inferior to ENOX daily</li> <li>▪ Clinically significant VTE rates lower w/ DABI</li> <li>▪ Major bleeding similar</li> </ul>	
			ENOX 40 daily	8.8	4.2	0.9		
RIVA	RECORD-1 31-39 days 69% eff anal	THR	4,541	RIVA 10 daily	1.1	0.2	0.3	<ul style="list-style-type: none"> <li>▪ RIVA superior to ENOX daily for efficacy</li> <li>▪ Primary endpt driven by lower rates of any DVT with RIVA</li> <li>▪ Major bleeding not statistically different</li> </ul>
				ENOX 40 daily	3.7	2	0.1	
	RECORD-2 RIVA 31-39 days ENOX 10-14 days 69% eff anal	THR	2,509	EXT-RIVA 10 daily	2	0.6	<0.1	<ul style="list-style-type: none"> <li>▪ EXT-RIVA superior to ST-ENOX for efficacy, including major VTE</li> <li>▪ Low and similar rates of major bleeds; nonmajor bleeds slightly higher with RIVA (observation only)</li> </ul>
				ST-ENOX 40 daily	9.3	5.1	<0.1	
	RECORD-3 10-14 days 67% eff anal	TKR	2,531	RIVA 10 daily	9.6	1	0.6	<ul style="list-style-type: none"> <li>▪ RIVA superior ENOX daily (Euro TKR dose), including major VTE</li> <li>▪ Low and similar rates of major and nonmajor bleeds</li> </ul>
				ENOX 40 daily	18.9	2.6	0.5	
	RECORD-4 10-14 days 61% eff anal	TKR	3,148	RIVA 10 daily	6.9	1.1	0.7	<ul style="list-style-type: none"> <li>▪ RIVA superior to ENOX <u>BID</u></li> <li>▪ No difference in major or symptomatic VTE</li> <li>▪ Slightly higher rates of major and nonmajor bleeds (not statistically different)</li> </ul>
				ENOX 30 BID	10.1	1.5	0.3	
APIX	ADVANCE-1 10-14 days 68% eff anal	TKR	3,195	APIX 2.5 BID	9	2	0.7	<ul style="list-style-type: none"> <li>▪ APIX inferior to ENOX <u>BID</u> for efficacy</li> <li>▪ Excess of PE events with APIX</li> <li>▪ Less major bleeding with APIX</li> </ul>
				ENOX 30 BID	8.8	1.6 (+any death)	1.4	
	ADVANCE-2 10-14 days 65% eff anal	TKR	3,057	APIX 2.5 BID	15.1	1.1	0.6	<ul style="list-style-type: none"> <li>▪ APIX superior to ENOX daily for efficacy</li> <li>▪ Excess of PE events with APIX</li> <li>▪ Major bleeding similar</li> </ul>
ENOX 40 daily				24.4	2.2	0.9		
ADVANCE-3 32-38 days 71% eff anal	THR	5,407	APIX 2.5 BID	1.4	0.5	0.8	<ul style="list-style-type: none"> <li>▪ APIX superior to ENOX daily for efficacy</li> <li>▪ Major bleeding similar</li> </ul>	
			ENOX 40 daily	3.9	1.1	0.7		

Results not intended to be comparative as study conditions differed

Major VTE=proximal DVT, nonfatal PE, VTE-related death (for dabi); Major VTE=proximal DVT, nonfatal or fatal PE, and all cause death (for apix)

Major bleeding: Hgb drop with riva and apix (ADVANCE 2 and ADVANCE 3) used postop Hgb level rather than pre-op, which may underestimate major bleeding; RIVA trials did not include surgical site bleeding in their definition unless it required reoperation.

## VII. ACS (OFF-LABEL)

None of the TSOACs carries an FDA indication for use in patients with ACS. Rivaroxaban and apixaban were each evaluated in a phase 3, double-blind, multicenter, randomized, placebo-controlled trial to examine the efficacy and safety of the addition of a TSOAC to the standard of care (aspirin alone or in combination with a thienopyridine). Both studies evaluated a similar primary composite endpoint of cardiovascular death, MI, or stroke. Dabigatran has not been studied in a phase 3 trial for ACS and was found to be associated with a dose dependent increase in bleeding in the phase 2 RE-DEEM trial evaluating safety.

### ***Rivaroxaban***

In ATLAS-TIMI 51, low doses of rivaroxaban (2.5 mg or 5 mg twice daily) were added to the standard of care (aspirin plus thienopyridine) in patients with recent ACS (and stabilized).<sup>77</sup> A total of 15,526 patients were randomized to receive rivaroxaban or placebo. For the index event, 50% of patients presented with STEMI, 26% with NSTEMI, and 24% with unstable angina. The mean age was 62 years and mean duration of follow-up was 13 months. For the primary composite endpoint of cardiovascular death, myocardial infarction (MI), or stroke, rivaroxaban was found to be superior to placebo (8.9% vs. 10.7% [placebo]; HR 0.84; 95% CI 0.74-0.96; p=0.008). The rates of the individual components of cardiovascular death and MI were significantly lower with rivaroxaban, though there was no benefit with regard to stroke. Subgroup analyses were overall consistently favorable with rivaroxaban, except in patients with previous TIA/stroke, where there was a nonsignificant trend favoring placebo. Of note, patients with prior TIA/stroke were excluded from the study. The superior efficacy of rivaroxaban was accompanied by a nearly 4-fold increased risk in TIMI major bleeding not associated with coronary artery bypass graft (CABG) surgery (2.1% vs. 0.6%; HR 3.96; 95% CI 2.46-6.38; p <0.001), including increased intracranial hemorrhage (0.6% vs. 0.2%; HR 3.28; 95% CI 1.28-8.42). When the results were examined by rivaroxaban dose, both the 2.5 mg and 5 mg dose were associated with significant improvements compared to placebo for the primary efficacy endpoint, and the 2.5 mg dose was associated with a trend of less bleeding compared to the 5 mg dose. Rivaroxaban has been granted approval for ACS in Europe and is under review by FDA.

### ***Apixaban***

In the APPRAISE-2 study, full dose apixaban (5 mg twice daily) was added to aspirin or aspirin plus thienopyridine in high risk patients with recent ACS.<sup>Error! Bookmark not defined.</sup><sup>78</sup> The study was terminated early when about 7,400 patients out of the planned 10,800 patients were enrolled due to a significant increase in bleeding without a reduction in recurrent ischemic events. Nearly all patients were on aspirin (97%) plus a P2Y12-receptor antagonist (81%), mostly clopidogrel. For the primary composite endpoint of cardiovascular death, MI, or ischemic stroke, apixaban was not shown to be superior to placebo, with annual event rates of 13.2% with apixaban compared to 14% with placebo (HR 0.95; 95% CI 0.8-1.11). The risk of TIMI (Thrombolysis in MI) major bleeding was increased significantly in apixaban treated patients, with annual rates of 2.4% vs. 0.9% with placebo (HR 2.59; 95% CI 1.5-4.46). Further, apixaban increased the risk of intracranial hemorrhage (0.6% per year vs. 0.2% per year; HR 4.1; 95% CI 1.15-14.38).

### ***Dabigatran***

Dabigatran was evaluated in a phase 2, dose escalation trial in 1,861 patients with recent ACS and on dual antiplatelet therapy.<sup>79</sup> There was a dose dependent increase in bleeding outcomes with dabigatran along with a reduction in D-dimer concentrations.

**Summary:** Of the three TSOACs, only rivaroxaban has been shown to reduce the primary composite endpoint of cardiovascular death, MI, and stroke when added to the standard of care (aspirin plus thienopyridine) in patients with recent ACS. Even though a lower dose was used, rivaroxaban was associated with a significant increase in bleeding.

## VIII. VTE PROPHYLAXIS IN MEDICALLY ILL PATIENTS (OFF-LABEL)

Rivaroxaban and apixaban were each evaluated in a single, randomized, multicenter, double-blinded, active comparator, phase 3 published trial for the prevention of VTE in acutely ill medical patients. No studies evaluating dabigatran in this setting were located. Extended treatment with rivaroxaban or apixaban was compared to short term treatment with enoxaparin. The studies differed somewhat in design and evaluated similar primary and

secondary outcomes. In both studies, approximately 30% of randomized patients were not evaluated, mainly due to inadequate assessment of VTE (similar to the DVT prophylaxis studies in orthopedic patients). Compared to the VTE prophylaxis studies in the orthopedic population, patients in the MAGELLAN and ADOPT studies of acutely medically ill populations tended to be older (67 to 71 years of age) and had a variety of medical illnesses.

**Rivaroxaban**

Patients in the MAGELLAN study were randomized to receive extended treatment with rivaroxaban 10 mg once daily for 35 +/- 4 days or enoxaparin SC 40 mg once daily for 10 +/- 4 days.<sup>80</sup> Patients had a mean age of 71 years and were well matched according to baseline characteristics. For the primary composite endpoint of DVT (asymptomatic or symptomatic), nonfatal PE, and VTE-related death, rivaroxaban was found to be noninferior to enoxaparin at 10 days (2.7% in each group; RR 0.97; 95% CI 0.71-1.31; p=0.0025 for noninferiority) and superior to enoxaparin followed by placebo at 35 days (4.4% vs. 5.7%; RR 0.77 [95%CI 0.77 [0.62-0.96]; p=0.02 for superiority). Rivaroxaban was associated with a significantly increased risk in the primary safety endpoint of clinically relevant bleeding (including major plus nonmajor clinically relevant bleeding) for the entire study period (2.8% vs. 1.2% for days 1-10; RR 2.3; 95% CI 1.63-3.17; 4.1% vs. 1.7% for days 1-35; RR 2.5; 95% CI 1.85-3.25; p <0.0001 for both comparisons). Major bleeding was similarly increased with rivaroxaban, and there were more fatal bleeds (7 events vs. 1 event; p not given). The net clinical benefit, considering efficacy and bleeding, significantly favored enoxaparin at day 10 and day 35.

**Apixaban**

Extended treatment with apixaban was compared to short term treatment with enoxaparin for the prevention of VTE in acutely ill medical patients in the phase 3, double-blinded, multicenter, randomized, controlled ADOPT study.<sup>81</sup> Patients were randomized to receive apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg subcutaneous once daily for 6-14 days. For the primary composite endpoint of asymptomatic proximal vein thrombosis, symptomatic DVT, nonfatal PE, and VTE related death during the treatment period, apixaban was not shown to be superior to short term enoxaparin for the primary endpoint (2.7% vs. 3.1%; RR 0.87 95% CI 0.62-1.23) and was associated with a 2.5 fold increase in major bleeding (0.47% vs. 0.19%; RR 2.58; 95% CI 1.02-7.24). Nonmajor clinically relevant bleeding rates were similar between treatment groups. In examining the post-enoxaparin treatment phase (i.e., apixaban vs. placebo), apixaban was associated with a positive trend of reduced primary endpoint events, though the between group difference did not reach statistical significance. The authors conclude that while extended prophylaxis shows promise, further study is needed to identify which medically ill patients may benefit from treatment.

**Summary:** For the prevention of VTE in acutely ill medical patients, rivaroxaban and apixaban have been shown to be noninferior to enoxaparin in efficacy but are associated with a significant excess in bleeding. The net clinical benefit considering efficacy and bleeding was evaluated with rivaroxaban vs. enoxaparin and favored enoxaparin.

**SAFETY AND TOLERABILITY**

**I. OVERALL ADVERSE EVENTS**

**Table 19. Phase 3 Pivotal AF Studies: Overall Incidence of Adverse Events**<sup>1,2,3,14,17,19</sup>

	ARISTOTLE N <sub>R</sub> =18,201		RELY N <sub>R</sub> =18,113		ROCKET AF N <sub>R</sub> =14,264	
Duration	1.8 yrs		2 yrs		1.9 yrs	
	APIX	WARF	D150	WARF	RIVA	WARF
Any adverse event (%)	81.5	83.1	78	76	81.4	81.5
Adverse event leading to DC (%)	7.6	8.4	21*	16	15.7	15.2
Serious adverse event (%)	35	36.5	21	23	35	36.5

\*Difference noted as significant (p <0.05);

Rates not intended to be comparative as study conditions and methods differed

**II. DEATHS**

In each of the phase 3 AF studies with the TSOACs, a favorable trend in vascular death and all cause death was observed compared to warfarin.<sup>9,11,12</sup> The mortality benefit in ARISTOTLE with apixaban vs. warfarin reached borderline statistical significance. In the VTE treatment studies with dabigatran and rivaroxaban, all-cause death was similar between TSOAC and comparator arms (warfarin or placebo).<sup>47,49,50</sup> In the pooled data from the rivaroxaban DVT prophylaxis studies (RECORD 1-4), a favorable trend was observed for rivaroxaban vs. enoxaparin for all-cause deaths. The trend remained favorable when RECORD 4 data were excluded.<sup>94,82</sup>

### III. OTHER SERIOUS ADVERSE EVENTS

- *Dabigatran*: Types and frequencies of serious adverse events with dabigatran vs. warfarin occurred similarly were not notably different in the AF population of the RE-LY trial (about 21% of patients in each arm).<sup>83</sup>
- *Rivaroxaban*: In ROCKET AF, serious adverse events were reported in 35% of rivaroxaban patients and 36% of warfarin patients. Anemia, GI bleeding, and syncope were reported more frequently in rivaroxaban-treated patients.<sup>17</sup> In pooled analyses of the RECORD 1-4 VTE prophylaxis studies, serious adverse events were reported with slightly lower frequency with rivaroxaban compared to enoxaparin (6.6% vs. 8.5%).<sup>65,94</sup>
- *Apixaban*: Serious adverse events occurred in the ARISTOTLE AF population with similar frequencies in the apixaban and warfarin groups (35% apixaban and 37% warfarin). Syncope and dizziness were reported more frequently with apixaban compared to warfarin, though occurred in less than 1% of patients.<sup>19</sup>

### IV. COMMON NON-BLEEDING ADVERSE EVENTS

With the exception of higher rates of dyspepsia and gastritis reported with dabigatran, frequencies and types of common non-bleeding adverse events were similar with each of the TSOACs compared to warfarin based on results from the individual pivotal AF studies.<sup>17,83,94</sup>

### V. OTHER ADVERSE EVENTS

#### **Bleeding**

The major risk of TSOAC treatment is bleeding. Bleeding complications were commonly reported with dabigatran (the frequency of GI adverse events exceeded bleeding events) and were the most commonly reported adverse events with rivaroxaban and apixaban. A summary of bleeding events by indication is provided below.

#### *Atrial Fibrillation*

Bleeding endpoints were defined similarly across the three pivotal trials evaluating a TSOAC vs. warfarin. Compared to warfarin, each of the TSOACs were associated with statistically similar or lower risk of major bleeding in the individual trials. All three TSOACs were consistently associated with about a 50% reduction in the risk of intracranial hemorrhage. Apixaban was found to be superior to warfarin for major bleeding. There was no excess of fatal or life threatening bleeding with any of the TSOACs compared to warfarin; however, there was a significantly higher risk of GI bleeding with dabigatran and rivaroxaban vs. warfarin.

Compared to aspirin in the AVERROES trial, apixaban was associated with a similar rate of major bleeding with no excess of intracranial, gastrointestinal, or fatal bleeding, though minor bleeding was significantly higher.

In the observational extension study of the RE-LY trial, about half of the patients from RE-LY continued their randomized dabigatran treatment and were followed for an additional median of 2.3 years.<sup>10</sup> Annual, adjudicated event rates for major bleeding during the extension period were somewhat higher with dabigatran (3.7% per year with dabigatran 150 mg) compared to rates seen in RE-LY (3.1% per year with dabigatran 150 mg), though no statistical comparisons were provided. Intracranial bleeding rates remained low.

**Table 20. Selected Bleeding Outcomes for TSOACs vs. Warfarin in AF from Individual Pivotal Phase 3 Trials**<sup>9,11,12</sup>

	APIX vs. WARF (ARISTOTLE) N <sub>R</sub> =18,201			DABI vs. WARF (RELY) N <sub>R</sub> =18,113			RIVA vs. WARF (ROCKET AF) N <sub>R</sub> =14,264		
	APIX % / yr	WARF % / yr	HR (95% CI)	D150 % / yr	WARF % / yr	RR (95% CI)	RIVA % / yr	WARF % / yr	HR (95% CI)
<b>Major bleed†</b>	2.1*	3.1	0.69 (0.6-0.8)	3.1	3.4	0.93 (0.81-1.07)	5.6	5.4	1.04 (0.9-1.2)
<b>Intracranial bleed</b>	0.3*	0.8	0.42 (0.3-0.58)	0.3*	0.7	0.4 (0.27-0.6)	0.5*	0.7	0.67 (0.47-0.93)
<b>GI bleed</b>	0.8	0.9	0.89 (0.7-1.15)	1.5*	1	1.5 (1.19-1.89)	3.2*	2.2	Not given
<b>Major or CRNMB<sup>§</sup></b>	4.1*	6	0.68 (0.61-0.75)	-	-	-	14.9	14.5	1.03 (0.96-1.11)

\*p <0.05 between treatment groups

†Primary safety point for ARISTOTLE and RELY; <sup>§</sup>Primary safety endpoint for ROCKET AF; CRNMB=clinically relevant nonmajor bleed; Rates not intended to be comparative as study conditions and methods differed

*TSOACs as a class:* Bleeding outcomes from three systematic reviews are summarized in Table 21.<sup>20,21,22</sup> (See the Efficacy section, Nonvalvular AF, TSOACs as a class for additional information on the reviews). The TSOACs were associated with a lower risk of fatal bleeding and a favorable trend in the risk of major bleeding compared to warfarin. In contrast, there was a trend of a higher risk of GI bleeding with the TSOACs vs. warfarin. Indirect comparisons between the TSOACs (dabigatran, rivaroxaban, and apixaban) suggest an overall lower risk of bleeding with apixaban.<sup>21,23</sup>

**Table 21. Systematic Reviews of TSOACs vs. WARF: Bleeding Outcomes**

Review	Drugs	Indications	# of Trials	Major bleed	Intracranial bleed	GI bleed	Fatal bleed
Adam et al. <sup>20</sup>	D150 RIVA APIX	AF VTE tx	6 (Phase 3)	0.8 (0.63-1.01)	--	1.3 (0.97-1.73)	<b>0.6 (0.46-0.77)</b>
Lip et al. <sup>21</sup>	D150 RIVA APIX	AF	3 (Phase 3)	<b>0.88 (0.81-0.95)</b>	<b>0.49 (0.4-0.6)</b>	--	--
Dentali et al. <sup>22</sup>	DABI RIVA APIX EDOX	AF	12 (Phase 2 and 3)	<b>0.86 (0.8-0.93)</b>	<b>0.46 (0.39-0.56)</b>	--	--

Bolded values are significant; Adam et al. included data from AF and VTE treatment populations in safety analysis

*Outcomes based on INR control:* Assessment of bleeding outcomes based on the center’s INR control has been conducted as part of sub-analysis from the pivotal AF trials for dabigatran and apixaban (a similar analysis of bleeding events from ROCKET AF with rivaroxaban vs. warfarin was not identified). In the RELY trial, rates of major bleeding and GI bleeding with dabigatran vs. warfarin were influenced by the quality of the center’s INR control.<sup>15</sup> As the center’s INR control improved, major and GI bleeding rates for warfarin decreased. Consequently, hazard ratios with dabigatran vs. warfarin appeared less favorable in the setting of better INR control. Apixaban was associated with lower rates of major bleeding compared to warfarin regardless of the quality of INR control, though the effect appeared to be less when TTR was higher.<sup>18</sup>

*Bleeding outcomes based on age:*

- *Dabigatran:* The risk of bleeding by age was examined in a subgroup analysis of the pivotal RE-LY trial, where 40% of patients were 75 years of age and older.<sup>84</sup> A significant interaction between age and treatment was found. In patients 75 years of age and older, the 150 mg dose of dabigatran was associated with significantly higher rates of GI bleeding and extracranial bleeding and a trend of more major bleeding compared to warfarin. In contrast, patients younger than 75 years experienced significantly less extracranial bleeding and major bleeding on dabigatran vs. warfarin. Dabigatran was associated with a consistently lower risk of intracranial hemorrhage, regardless of age.

**Table 22. Risk of bleeding by age with dabigatran vs. warfarin from RE-LY<sup>84</sup>**

	DABI 150 % per yr	WARF % per yr	RR (95% CI)
<b>Major bleed</b>			

<75 yrs	2.12*	3.04	0.7 (0.57-0.86)
≥75 yrs	5.1	4.37	1.18 (0.98-1.42)
<b>Extracranial bleed</b>			
<75 yrs	1.91*	2.44	0.78 (0.63-0.98)
≥75 yrs	4.68*	3.44	1.39 (1.13-1.70)
<b>GI bleed</b>			
<75 yrs	1.22	1.03	1.19 (0.87-1.63)
≥75 yrs	2.8*	1.59	1.79 (1.35-2.37)
<b>Intracranial bleed</b>			
<75 yrs	0.26*	0.61	0.43 (0.25-0.74)
≥75 yrs	0.41*	1	0.42 (0.25-0.7)

p < 0.05 for difference between groups

- **Rivaroxaban:** The risk of bleeding according to multiple subgroups including age was examined as part of the ROCKET AF trial, where about 44% of patients were 75 years of age or older.<sup>11</sup> A significant interaction between treatment and age was not found. In patients greater than 75 years of age, rivaroxaban was associated with a trend of an increased risk of bleeding as measured by the composite endpoint of major and clinically relevant nonmajor bleeds. Patients 75 years of age and younger experienced similar rates of major bleeding compared to warfarin.

**Table 23. Risk of Bleeding by Age with Rivaroxaban vs. Warfarin from ROCKET AF<sup>11</sup>**

	RIVA % per yr	WARF % per yr	RR (95% CI)
<b>Major and clinically relevant nonmajor bleed</b>			
<65 yrs	14.6	15.8	0.93 (0.78-1.11)
65-75 yrs	19.5	20	0.98 (0.87-1.1)
>75 yrs	25.8	23.4	1.12 (1-1.25)

- **Apixaban:** The risk of bleeding according to multiple subgroups including age was examined as part of the ARISTOTLE trial, where 31% of patients were 75 years of age and older.<sup>12</sup> There were no significant interactions based on age and treatment. The risk of bleeding remained lower with apixaban vs. warfarin in patients 75 years of age and older.
- **Summary:** The risk of bleeding increases with age. Subgroup analyses based on age were conducted in the pivotal trials comparing TSOACs to warfarin for AF. Compared to warfarin, dabigatran was associated with an increased risk of GI bleeding and extracranial bleeding in patients 75 years and older, though intracranial bleeding remained lower regardless of age. There was a trend of higher bleeding rates found with rivaroxaban compared to warfarin in the elderly. With apixaban, bleeding in the elderly subgroup remained lower than warfarin.

Acute treatment of VTE (updated September 2014)

Bleeding endpoints were similarly defined across the pivotal trials evaluating a TSOAC vs. warfarin, though there were some notable differences (e.g., inclusion of all bleeding events or only first event, length of time bleeding events were counted after stopping study drug, etc.). Compared with adjusted dose VKA therapy, major bleeding rates were similar with dabigatran, lower with apixaban, and tended to be lower with rivaroxaban.<sup>47,48,49,50,51</sup> When all clinically relevant bleeding was considered (major bleeding plus nonmajor clinically relevant bleeding), dabigatran and apixaban were superior to warfarin. There was no excess in fatal bleeding with any of the TSOACs vs. warfarin, and the number of intracranial bleeds was similar or lower with TSOACs. GI bleeding was reported more frequently with dabigatran and less frequently with apixaban compared to warfarin.

**Table 24. Major and clinically relevant bleeding with TSOACs vs. Warfarin from Pivotal Acute VTE Trials<sup>47,48,49,50,51</sup>**

Study	DABI RECOVER N <sub>R</sub> =2564			DABI RECOVER II N <sub>R</sub> =2589			RIVA EINSTEIN ACUTE DVT N <sub>R</sub> =3449			RIVA EINSTEIN ACUTE PE N <sub>R</sub> =4833			APIX AMPLIFY N <sub>R</sub> =5395		
	D	W	HR	D	W	HR	R	VKA	HR	R	VKA	HR	A	W	HR
Results															

	%	%	(95% CI)	%	%	(95% CI)	%		(95% CI)			(95% CI)			(95% CI)
Major bleed	1.6	1.9	0.82 (0.45-1.48)	1.2	1.7	0.69 (0.36-1.32)	0.8	1.2	0.65 (0.33-1.3)	1.1*	2.2	0.49 (0.31-0.79)	0.6*	1.8	0.31 (0.17-0.55)
Major+ CRNM bleed	5.6*	8.8	0.63 (0.47-0.84)	5*	7.9	0.62 (0.45-0.84)	8.1	8.1	0.97 (0.76-1.22)	10.3	11.4	0.90 (0.76-1.07)	4.3*	9.7	0.44 (0.36-0.55)

\*p <0.05 for difference between groups; CRNMB=clinically relevant nonmajor bleeding; clinically relevant bleeding defined as major plus clinically relevant nonmajor bleeding

*TSOACs as a class:*

Bleeding outcomes from four systematic reviews are summarized in Table 25. (See the Efficacy section, Treatment of Acute VTE, TSOACs as a class for additional information on the reviews). Overall, the TSOACs were associated with a lower risk of bleeding compared to warfarin.

**Table 25. Systematic Reviews of TSOACS vs. WARF: Bleeding Outcomes**

Review	Drugs	Indications	# of Trials	Major bleed	Intracranial bleed	GI bleed	Fatal bleed
Adam et al. <sup>20</sup>	DABI RIVA APIX	AF VTE tx	6 (Phase 3)	0.8 (0.63-1.01)	-	1.3 (0.97-1.73)	<b>0.6 (0.46-0.77)</b>
van der Hulle et al. <sup>54</sup>	DABI RIVA APIX EDOX	Acute VTE tx	5	<b>0.6 (0.41-0.88)</b>	<b>0.39 (0.16-0.94)</b>	0.68 (0.36-1.30)	<b>0.36 (0.15-0.87)</b>
Gomez-Outes et al. <sup>52</sup>	DABI RIVA APIX EDOX	Acute VTE tx	6	<b>0.62 (0.45-0.85)</b>	<b>0.34 (0.17-0.69)</b>	--	<b>0.36 (0.15-0.84)</b>
Kakkos et al. <sup>53</sup>	DABI RIVA APIX EDOX	Acute VTE tx	10 (6 Acute VTE)	<b>0.63 (0.51-0.77)</b>	-	-	0.51 (0.26-1.01)

Bolded values are significant; Adam et al. included data from AF and VTE treatment populations in safety analysis; Kakkos et al. analysis of acute VTE tx only

*Bleeding outcomes based on age or other factors:*

- *Dabigatran:* Subgroup analysis of pooled data from RECOVER I and II did not identify a signal for increased bleeding risk with dabigatran vs. warfarin in patients with an age greater than 75 years, CrCl between 30-50 ml/min, or history of bleeding events. When clinically relevant bleeding (major bleeding plus clinically relevant nonmajor bleeding) was examined using age as a continuous variable, dabigatran maintained a favorable risk profile compared to warfarin until about 85 years of age.<sup>48</sup>
- *TSOACs as a class:* Based on pooled analyses of data from the rivaroxaban clinical trials (EINSTEIN DVT and EINSTEIN PE) and the edoxaban study, an increased risk of major plus clinically relevant nonmajor bleeding in subgroups of patients with cancer, age of 75 years or older, or CrCl <50 ml/min was not apparent.<sup>52</sup>

Extended Treatment of VTE

The risk of bleeding in the extended treatment of VTE (following the initial 3, 6, or 12 months of anticoagulation treatment for an acute VTE event) was evaluated in each of the individual trials with the TSOACs compared to placebo (apixaban, dabigatran, and rivaroxaban) and warfarin (dabigatran).<sup>49,60,61</sup> Compared to placebo, the risk of clinically relevant bleeding (major plus clinically relevant nonmajor bleeding) was slightly higher with apixaban (not statistically significant) and significantly higher with dabigatran and rivaroxaban. Major bleeding events were low overall. Compared to warfarin, dabigatran was associated with about 50% reduction in major bleeding and clinically relevant bleeding.

**Table 26. Bleeding Outcomes with TSOACs vs. Comparator from Pivotal Extended VTE Trials<sup>49,60,61</sup>**

	DABI vs. WARF	DABI vs. PBO	RIVA vs. PBO	APIX vs. PBO
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Study	REMEDY			RESONATE			EINSTEIN Cont'd Tx			AMPLIFY-EXT		
Treatment	DABI 150 BID WARF (INR 2-3)			DABI 150 BID PBO			RIVA 20 daily PBO			APIX 2.5 BID APIX 5 BID PBO		
Tx duration	~16 mos (range 6-36 mos)			6 mos (plus 12 mos f/u)			~9 mos (6 or 12 mos)			12 mos (plus 1 mo f/u)		
Results	D %	W %	HR (95% CI)	D %	P %	HR (95% CI)	R %	P %	HR (95% CI)	A %	P %	HR (95% CI)
Major bleed	0.9*	1.8	0.52 (0.27-1.02)	0.3	0	Not estimable	4	0	NA	2.5mg: 0.2 5mg: 0.1	0.5	0.49 (0.09-2.64) 0.25 (0.03-2.24)
Major or CRNMB	5.6*	10.2	0.54 (0.41-0.71)	5.3*	1.8	2.92 (1.52-5.6)	6*	1.2	5.19 (2.3-11.7)	2.5mg: 3.2 5mg: 4.3	2.7	1.2 (0.69-2.1) 1.62 (0.96-2.73)

\*p <0.05 for difference between groups; CRMB=clinically relevant nonmajor bleeding

VTE Prophylaxis in TKR and THR

All of the phase 3 studies included in the review compared a TSOAC to enoxaparin. Bleeding definitions differed somewhat between the trials. Overall, rates of major bleeding across all studies were low with TSOAC and enoxaparin treatment; however, there was a tendency for more clinically relevant bleeding (major bleeding plus clinically relevant nonmajor bleeding) with rivaroxaban and less bleeding with apixaban compared to enoxaparin in some of the trials and per meta-analysis and systematic review. Dabigatran and enoxaparin were associated with a similar risk of clinically relevant bleeding (See Table 18 – VTE prophylaxis in patients undergoing TKR and THR under Efficacy section)

**Table 27. Meta-analysis of Clinically Relevant Bleeding with TSOACs vs. Enoxaparin for VTE prophylaxis in TKR and THR<sup>74</sup>**

TSOAC	RR compared to ENOX	95% CI
Dabigatran	1.12	0.94-1.35
Rivaroxaban	1.25*	1.05-1.49
Apixaban	0.82*	0.69-0.98

\*p <0.05 for difference between groups

ACS

Rivaroxaban and apixaban were each evaluated in a phase 3, placebo-controlled trial where the TSOAC was added to the standard of care (primarily aspirin plus clopidogrel). Full dose apixaban (5 mg twice daily) was studied in APPRAISE-2, and low dose rivaroxaban (2.5 or 5 mg twice daily) was evaluated in ATLAS-TIMI 51. The addition of TSOAC to standard of care (i.e., triple antithrombotic therapy) was associated with a significant increase in bleeding outcomes. In ATLAS-TIMI 51, the increased bleeding was accompanied by an improvement in the composite primary efficacy endpoint of cardiovascular death, MI, and stroke with rivaroxaban vs. placebo. In contrast, the APPRAISE-2 study with apixaban was terminated early because of an increased risk of bleeding without a significant reduction in recurrent ischemic events. The risk of TIMI (Thrombolysis in MI) major bleeding was increased significantly in apixaban treated patients, with annual rates of 2.4% vs. 0.9% with placebo (HR 2.59; 95% CI 1.5-4.46). Further, apixaban increased the risk of intracranial hemorrhage (0.6% per year vs. 0.2% per year; HR 4.1; 95% CI 1.15-14.38).

**Table 28. Bleeding Outcomes from Phase 3 ACS ATLAS TIMI-51: Low-dose Rivaroxaban vs. Placebo<sup>77</sup>**

Study	RIVA				
	ATLAS-TIMI 51 N <sub>R</sub> =15,526				
Results	RIVA 5	RIVA 2.5	PBO	HR (95% CI) RIVA 5 vs. PBO	HR (95% CI) RIVA 2.5 vs. PBO
TIMI Major bleed not assoc w/ CABG	2.4*	1.8*	0.6	4.47 (2.71-7.36)	3.46 (2.08-5.77)
Intracranial bleed	0.7*	0.4*	0.2	3.74 (1.39-10.07)	2.83 (1.02-7.86)
Fatal bleed	0.4	0.1	0.2	1.72 (0.75-3.92)	0.67 (0.24-1.89)

\*p <0.05 between rivaroxaban treatment and placebo

**Outcome Events After Discontinuation**

Dabigatran, rivaroxaban, and apixaban contain boxed warnings in the prescribing information that discontinuing the TSOAC places patients at increased risk of thrombotic events.<sup>1,2,3</sup> A published analysis is available summarizing

outcomes in patients discontinuing rivaroxaban vs. warfarin from ROCKET AF.<sup>85</sup> Data for apixaban is limited to the FDA Medical Review and an oral presentation.<sup>19,86</sup>

*Study completers:* About 92% of patients from ROCKET AF and 85% of patients from ARISTOTLE transitioned to open label VKA after the end of the trials. A 4-fold increase in the risk of stroke or systemic embolic events occurred within the 30 days following discontinuation of rivaroxaban or apixaban at the end of the studies, mostly between 3 and 30 days. When outcome event rates in patients transitioning to VKA from rivaroxaban or apixaban at the end of the studies were compared to event rates in VKA naïve patients at the beginning of the studies, outcome rates were similar. Major bleeds also appeared to be higher in the 30 days following completion of the study in patients who received rivaroxaban or apixaban during the study. More strokes also occurred in apixaban study-completers compared to aspirin in the 30 days after stopping study drug in the AVERROES trial.<sup>19</sup> This finding is notable since most of the AVERROES study completers were not transitioning to warfarin.

*Early discontinuation:* There was no significant increase in outcome events between warfarin and TSOAC (rivaroxaban or apixaban) arms observed in patients who permanently discontinued study drug early, though overall outcome events occurred more frequently in this population.

**Table 29. Outcome Events in Patients Discontinuing Treatment from ROCKET AF and ARISTOTLE<sup>11,12</sup>**

	ROCKET AF			ARISTOTLE		
	RIVA N (% per yr)	WARF N (% per yr)	HR (95% CI)	APIX N (% per yr)	WARF N (% per yr)	HR (95% CI)
<b>Study Completers (N)</b>	4587	4652		6791	6569	
Stroke/SEE	22 (6.42)	6 (1.73)	3.72 (1.51-9.16)	21 (4.02)	5 (0.99)	4.07 (1.54-10.81)
Major bleed	25 (7.29)	7 (2.01)	3.62 (1.56-8.36)	26 (4.97)	10 (1.97)	Not given
<b>Early Discontinuation</b>	2470	2425		1841	2028	
Stroke/SEE	42 (25.6)	36 (23.28)	1.1 (0.71-1.72)	52 (40)	67 (47)	0.86 (0.6-1.24)
Major bleed	21 (12.71)	33 (21.29)	0.6 (0.35-1.04)	Not given	Not given	Not given

Note: events were counted from day 3 to 30 for ROCKET and day 1 to 30 for ARISTOTLE. Most events occurred between days 3 and 30.

*Temporary Interruptions in TSOAC therapy:* Because of the excess in primary outcome events identified when apixaban or rivaroxaban was discontinued, further analysis describing outcomes in patients who had temporary interruptions in treatment is of interest and described in publication (rivaroxaban) and in the FDA medical reviews (dabigatran and apixaban).<sup>14,19,85</sup> In patients who had interruptions in therapy for more than 30 days in ARISTOTLE, there was a trend of more primary outcome events in the apixaban vs. warfarin arms, with about 1 more event per 100 patient-years (approximately 5 vs. 4 events per 100 patient-years). The FDA noted that these event rates were not importantly different from event rates in study completers during the 30 days following discontinuation of therapy. A similar trend was noted with rivaroxaban vs. warfarin in the ROCKET-AF trial. Per the FDA Medical Review for dabigatran, outcome events (both thromboembolic and bleeding) in patients who had temporary lapses in therapy in RE-LY were infrequent and appeared similar between dabigatran and warfarin treatment groups.<sup>14</sup>

### Hepatotoxicity

Due to the severe hepatotoxicity associated with the direct thrombin inhibitor ximelagatran, the clinical development program for each of the TSOACs included intensive investigation for signals of similar effects. With ximelagatran, hepatotoxicity was evident during the clinical trials. Data for the hepatic safety of the TSOACs for FDA approval was based primarily on the pivotal AF trials with dabigatran and apixaban and on the AF and VTE treatment trials for rivaroxaban.<sup>19,83,94</sup> Drug exposure was about 2 years for the AF trials. Proportions of patients experiencing transaminase elevations were similar or lower in patients receiving dabigatran, rivaroxaban, or apixaban vs. the comparator (warfarin, enoxaparin, or aspirin). Potential Hy's law cases, a more specific indicator of drug induced liver injury defined as elevated aspartate aminotransferase/alanine aminotransferase (AST/ALT) >3x ULN and total bilirubin >2x ULN, were infrequent and balanced between the TSOAC and comparator treatments. In total, the FDA concluded that the data do not suggest a significant risk of drug induced liver injury with dabigatran, rivaroxaban, or apixaban.<sup>19,83,94</sup> A systematic review that examined the comparative effectiveness and safety of the TSOACs (dabigatran, rivaroxaban, and apixaban) as a class compared to warfarin in 6 pivotal phase 3 trials for AF and VTE treatment indications likewise found no evidence of an increased risk of significant transaminase elevations.<sup>20</sup>

### Prosthetic Heart Valve-related Adverse Events

Dabigatran was associated with a higher risk of adverse outcomes (valve thrombosis, stroke, MI, bleeding) in patients with mechanical prosthetic heart valves in the RE-ALIGN trial.<sup>87,88,89</sup> The trial was stopped early, and FDA issued a safety communication and required package label updates contraindicating the use of dabigatran in patients with mechanical prosthetic heart valves. Further, revised labeling includes the statement that the use of dabigatran in patients with AF in the setting of other forms of valvular heart disease (including presence of a bioprosthetic heart valve) has not been studied and is not recommended.<sup>1</sup>

Patients with prosthetic heart valves requiring anticoagulation were excluded from the pivotal phase 3 AF trials with dabigatran, rivaroxaban, and apixaban. Significant valvular disorders were also exclusions in the studies. In the presence of data demonstrating harm with one of the agents and in the absence of additional data demonstrating efficacy and safety, use of the TSOACs in patients with prosthetic heart valves is not recommended.

### Myocardial Infarction

A higher number of adjudicated MIs were found with dabigatran vs. warfarin in the RE-LY trial, a difference that was statistically significant with dabigatran 150 mg in the original published investigation.<sup>9</sup> An updated analysis that included previously unidentified events confirmed an excess number of MIs with dabigatran, though the between-group difference was no longer statistically significant.<sup>90</sup> In a post-hoc subgroup evaluation of myocardial ischemic events in RE-LY, investigators showed a nonsignificant increase in MI with dabigatran but no excess in the composite endpoint of ischemic coronary events (MI, unstable angina, cardiac arrest, and cardiac death).<sup>91</sup> There was no significant difference in treatment effect in patients with and without coronary artery disease (CAD). There appears to be no dose-response relationship, and the imbalance of MI events was evident both on and off study drug treatment. In a pooled analysis of the acute VTE treatment trials RECOVER I and II, a nonsignificant excess of MI was noted with dabigatran vs. warfarin.<sup>48</sup> A meta-analysis investigating seven RCTs with dabigatran (for AF, VTE, and ACS indications) found that dabigatran was associated with a significant increase in the risk of MI or ACS vs. comparator (warfarin, enoxaparin or placebo).<sup>92</sup> In total, there appears to be a small but consistently elevated risk of MI/ACS with dabigatran. There appears to be about a 30% relative increase in MI/ACS with dabigatran that translates into about a 0.2-0.3% per year absolute increase in events.

**Table 30. MI Events with Dabigatran from RE-LY<sup>9,90</sup>**

	DABI 150 N (%/yr)	WARF N (%/yr)	DABI 150 vs. WARF RR (95% CI)	P
RE-LY	89 (0.74)	63 (0.53)	1.38 (1-1.91)	0.04
RE-LY updated	97 (0.81)	75 (0.64)	1.27 (0.94-1.71)	0.12

There was no excess in MI found with rivaroxaban or apixaban vs. warfarin in the pivotal phase 3 AF studies ROCKET AF and ARISTOTLE, respectively.<sup>11,12</sup> In a systematic review evaluating phase 3 studies of the TSOACs for AF and VTE treatment indications, an increased risk of MI with dabigatran was found, but there was not a significant increased risk of MI found with the class of factor Xa inhibitors including apixaban or rivaroxaban.<sup>20</sup>

### GI Adverse Events

Gastrointestinal adverse events occurred more frequently (35% vs. 24%) and were more likely to result in treatment discontinuation with dabigatran vs. warfarin in the AF patient population studied in RE-LY.<sup>9</sup> Specifically, dyspepsia-like symptoms and gastritis-like symptoms were more often reported with dabigatran. Most of the disparity in the discontinuation rates between dabigatran and warfarin occurred in the first 3-4 months of treatment, after which the rates of discontinuation between treatment groups were similar.<sup>93</sup> Similarly, there was significantly more dyspepsia reported with dabigatran vs. warfarin in the acute VTE population in RECOVER I (3.1% vs. 0.7%; p <0.001) and RECOVER II (1% vs. 0.2%; p <0.05).

### Tolerability

Per systematic review of 6 pivotal AF and VTE treatment studies of the TSOACs (dabigatran, rivaroxaban, and apixaban), there was a higher rate of drug discontinuation with the TSOACs compared to warfarin. Within the TSOACs, dabigatran was associated with a higher risk for discontinuation compared to rivaroxaban and apixaban.<sup>20</sup>

- *Dabigatran*: Significantly more patients receiving dabigatran for AF compared to warfarin discontinued study drug due to adverse events in RELY (21% dabigatran 150 mg vs. 16% warfarin).<sup>9</sup> Gastrointestinal adverse events (e.g., dyspepsia, gastrointestinal hemorrhage, nausea) occurred more frequently with dabigatran and were the most frequently reported adverse events resulting in treatment discontinuation. In patients with acute VTE treated for 6 months, more patients in the dabigatran arm discontinued treatment due to an adverse event compared to warfarin in RE-COVER I (9% vs. 6.8%; p=0.05) but not in RECOVER II.<sup>47,48</sup> Dabigatran was not associated with an excess of treatment discontinuations due to adverse events compared to placebo or warfarin in the RESONATE and REMEDY study populations for the extended treatment of VTE.<sup>60</sup>
- *Rivaroxaban*: Permanent discontinuation rates of study medication due to adverse events in the AF study population from ROCKET AF were similar between rivaroxaban and warfarin groups (15.7% vs. 15.2%), with more patients discontinuing rivaroxaban due to mucosal bleeding (hematuria, gastrointestinal, gingival, nose).<sup>94</sup> In a pooled analysis of the DVT prophylaxis studies (RECORD 1-3), there was no excess of discontinuations due to adverse events with rivaroxaban vs. enoxaparin (3.7% vs. 4.7%).<sup>94</sup> Similarly, rates of early withdrawals due to adverse events were similar in the Acute VTE studies between rivaroxaban and warfarin (about 4%). In contrast, more rivaroxaban patients stopped study drug due to an adverse event compared to placebo in the VTE extension study compared to placebo (6.5% vs. 3%).
- *Apixaban*: In the AF patient population studied in the ARISTOTLE trial, 7.6% of apixaban-treated patients compared to 8.4% of warfarin-treated patients stopped study drug early due to adverse events.<sup>12</sup> Compared to aspirin in the AVERROES trial, less patients treated with apixaban discontinued therapy due to adverse events (17.9% per year vs. 20.5% per year; p=0.03).<sup>13</sup> Early withdrawals due to adverse events were lower with apixaban compared to placebo in the AMPLIFY-EXT VTE extension trial (8% vs. 16%).

## DRUG INTERACTIONS

### Pharmacodynamic interactions

The combined use of oral anticoagulants with medications that affect hemostasis increases the risk of bleeding.

*Aspirin*: When aspirin is combined with anticoagulants, there is an increased risk of bleeding. Baseline aspirin use during the phase 3 AF trials ranged between 30-40%. Based on information in the published trials and FDA briefing documents, concomitant use of aspirin plus an anticoagulant (dabigatran, rivaroxaban, apixaban, and warfarin) was associated with a 1.4 to 2 fold increased risk of major bleeding. There did not appear to be a difference in the magnitude of increased risk between the TSOAC and warfarin.<sup>9,11,12,17,83,84</sup>

*Thienopyridine*: Based on the small number of patients receiving thienopyridine with a TSOAC or warfarin from the pivotal AF studies (about 5% in RE-LY and ROCKET AF), there appeared to be an increased risk of bleeding. No differences were noted between the magnitude of increased risk between warfarin and TSOAC.<sup>17,83</sup> No specific information was identified with apixaban plus thienopyridine use from ARISTOTLE.

*Combination aspirin plus thienopyridine*: Patients on combination therapy with aspirin and thienopyridine were excluded from 2 of the 3 pivotal AF studies, ROCKET (rivaroxaban) and ARISTOTLE (apixaban), and only a small number of patients were on dual antiplatelet therapy in RE-LY. In phase 3 studies of ACS populations where dual antiplatelet therapy was used in addition to a TSOAC, significant increases in major bleeding were found. (See Safety section on bleeding).

### Non-pharmacodynamic interactions

- *Warfarin*: There are multiple drug interactions with warfarin via several pathways including changes in plasma protein binding, enzyme induction, and enzyme inhibition (CYP450 interactions via CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4). There have also been reports of INR changes with the addition or discontinuation of antibiotics, antifungals, and herbal products.<sup>4</sup> The majority of non-pharmacodynamic

interactions with warfarin can be managed through INR monitoring and dose adjustments as needed, particularly when the use of the interacting medication is chronic.

- **TSOACs:** Though there are some similarities, many drug interactions between the TSOACs differ. The clinical significance of drug interactions with the TSOACs has not been fully realized.
  - In patients on a drug that increases TSOAC exposure and who have renal impairment, both pathways of elimination are affected. Dabigatran and rivaroxaban undergo significant renal elimination.
  - It is unknown whether patients on multiple medications that increase TSOAC levels have a greater magnitude of elevation than those on a single interacting medication. (The possibility of additive effects may be considered when selecting drug therapy.)
  - Pharmacokinetic and pharmacodynamic studies have been conducted for multiple medications with the TSOACs; however, consideration should be given to medications not specifically studied with the potential for similar interactions.
  - The inability to readily measure (and interpret) the anticoagulant effect of the TSOACs complicates the clinical management of patients on interaction medications.

**Table 31. Drug Interactions with TSOACs**<sup>1,2,3</sup>

	<b>APIX</b>	<b>DABI</b>	<b>RIVA</b>
PK considerations	Primarily CYP3A4 metabolism Substrate of CYP3A4, P-gp	Prodrug is substrate of P-gp	CYP metabolism Substrate of CYP3A4, P-gp
P-gp inducers (e.g., rifampin)		Reduced dabig levels; AVOID	
P-gp inhibitors (e.g., dronedarone, ketoconazole)		Increased dabig levels; CAUTION If renal impairment, reduced dose or AVOID	
Combined CYP3A4 and P-gp inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's Wort)	AVOID		AVOID
Combined strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole, itraconazole, ritonavir and ritonavir combinations)	Increased apix levels; Reduced dose 2.5 mg twice daily In pts on reduced dose, AVOID		Increased riva levels; AVOID
Combined weak and moderate CYP3A4 and P-gp inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, , ranolazine, erythromycin, felodipine, azithromycin, dronedarone)	No info/no specific recs		If renal impairment, CAUTION

**SPECIAL POPULATIONS**

**Geriatric Use:** In the pivotal phase 3 AF studies, the percent of patients that were 75 and older were 40%, 44%, and 31% for dabigatran, rivaroxaban, and apixaban, respectively.<sup>1,2,3</sup> While stroke/SE occur more frequently with increasing age, the treatment effect was maintained with all three agents in the elderly vs. younger patients. Bleeding risk also increases with age. With dabigatran 150 mg, patients 75 years of age and older experienced significantly more bleeding compared to warfarin (See Safety section on bleeding).<sup>84</sup> In contrast, the lower risk of major bleeding with apixaban found in the overall study population in ARISTOTLE was maintained in patients 75 years and older.<sup>12</sup> With rivaroxaban, there was a trend of increased bleeding with rivaroxaban vs. warfarin in patients 75 years and older.<sup>11</sup> The treatment effect and safety endpoints appear to be maintained with rivaroxaban in patients 75 years and older for the DVT treatment and DVT prophylaxis indications based on subgroup analyses from the phase 3 trials.

**Pregnancy and Nursing Mothers:** Dabigatran and rivaroxaban are classified as Pregnancy Category C drugs, and apixaban is classified as a Pregnancy Category B drug based on animal data. There are no studies in pregnant women. All three drugs carry the risk of pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. It is not known if these drugs are excreted in human breast milk. Because many drugs are excreted into breast milk and because of the potential for serious adverse reactions in nursing infants exposed to these agents, caution should be used if administering to a nursing mother. Consider discontinuing drug or breastfeeding, weighing the importance of the drug vs. nursing to the mother.<sup>1,2,3</sup>

## CONCLUSIONS (updated September 2014)

- **Atrial fibrillation:** Dabigatran, rivaroxaban, and apixaban have been shown to be at least as effective as adjusted dose warfarin for the prevention of all stroke and systemic embolism accompanied by similar or lower rates of major bleeding in controlled clinical trial settings. The TSOACs as a class have been associated with a significant and consistent reduction in hemorrhagic stroke and intracranial bleeding, though only dabigatran was found to further reduce the risk of ischemic stroke beyond the reduction seen with warfarin. TTR with warfarin tended to influence the advantage of TSOACs over warfarin observed in clinical trials. Compared to warfarin, dabigatran and rivaroxaban were associated with higher rates of GI bleeding and a tendency of higher bleeding risk in patients 75 years of age and older. **(FDA Approval: dabigatran, rivaroxaban, apixaban)**
- **VTE treatment:** Dabigatran, rivaroxaban, and apixaban have been shown to be noninferior to adjusted dose VKA therapy in the prevention of recurrent VTE following acute VTE (for the first 3, 6, or 12 months after an event), with a similar to lower risk of major bleeding. Rivaroxaban and apixaban were studied without the use of LMWH at the initiation of therapy, whereas dabigatran treatment was preceded by 5 to 10 days of parenteral anticoagulant therapy. In the extended treatment setting, the TSOACs as a class have been shown to be more effective than placebo with low major bleeding rates overall. Clinically relevant bleeding (including major plus non major clinically relevant bleeding) occurred more frequently with TSOACs vs. placebo, though the difference between apixaban and placebo did not reach statistical significance. Certain patient groups (e.g., elderly, active cancer) represented small portions of the study population in the acute and extended treatment settings. **(FDA Approval: rivaroxaban, dabigatran, apixaban)**
- **VTE prophylaxis in TKR and THR:** The TSOACs have been shown to be at least as effective as enoxaparin 40 mg once daily for VTE prophylaxis in patients undergoing TKR and THR. Compared to the 30 mg twice daily enoxaparin dose (U.S. approved TKR dose), only rivaroxaban maintained an efficacy advantage. Major bleeding rates with all of the agents were low and generally similar between treatment groups. In total, there was a tendency of more bleeding with rivaroxaban and less bleeding with apixaban. **(FDA Approval: rivaroxaban, apixaban)**
- **Safety:** None of the TSOACs should be used in patients with prosthetic heart valves in the absence of favorable safety and efficacy data, given the information from RE-ALIGN where dabigatran was associated with adverse thromboembolic and bleeding outcomes in patients with mechanical prosthetic heart valves. Dabigatran appears to be associated with about a 30% relative increase but small absolute increase risk of MI/ACS (0.2-0.3% per year) compared to warfarin. Data in total do not indicate a signal for drug induced liver injury with the TSOACs (dabigatran, rivaroxaban, and apixaban) as was found with ximelagatran.

- Compared to warfarin, TSOACs offer patients advantages of predictable dosing, convenience of no INR monitoring, and less dietary restrictions. In contrast, long-term data with the TSOACs are lacking, and data in certain patient populations and for certain indications is not available. The TSOACs have a shorter half-life than warfarin, but the optimal management of acute, severe bleeding in the setting of anticoagulation on a TSOAC (and without an antidote) is unclear. The impact of adherence on outcomes with TSOACs, given their shorter half-life than warfarin, outside of a controlled trial setting is unclear. Although no routine anticoagulant monitoring is needed with the TSOACs, periodic renal function assessment is necessary. Further, if a measure of a patient's anticoagulant status is needed urgently (e.g., bleeding, need for urgent procedure), the most effective laboratory tests to qualitatively measure the presence or absence of anticoagulant has not been well established or may not be readily available. If quantitative measures of the TSOACs are desired (e.g., to assess for the impact of drug interactions or renal impairment), laboratory testing has not yet been established.
- Since no head-to-head studies have been conducted, one cannot conclude whether important differences exist between the efficacy and safety of the TSOACs exist. There are significant differences between the TSOACs in their pharmacokinetics, administration, drug interactions, side effect profile, areas of completed study, and indications for regulatory approval.

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**CONSIDERATIONS IN CHOICE OF AGENT FOR AF**

	DABI	RIVA	APIX	WARF
<b>Pivotal study TSOAC vs. warfarin (INR 2-3)</b>	RE-LY Open-label	ROCKET-AF Double-blind	ARISTOTLE Double-blind	(Comparator)
<b>Mean CHADS2 score</b>	2.1	3.5	2.1	-
<b>Mean TTR</b>	64%	55%	62%	-
<b>Efficacy Reduction in all stroke, systemic embolism</b>	Superior	Non-inferior	Superior	-
<b>Safety Major bleeding</b>	Similar	Similar	Superior	-
<b>Mortality</b>	Favorable trend	Favorable trend	Superior	-
<b>Dosing</b>	150 mg BID	20 mg once daily	5 mg BID	Variable dose; once daily
<b>Special considerations</b>	Caps cannot be crushed or opened	Cannot be administered via feeding tube placed distal to stomach	None	None
<b>Renal impairment</b>	Primarily renal elimination	Significant renal elimination	Minor renal elimination	Minimal renal elimination
<i>Note: The VA PBM recommendations for renal dosing are based on evidence from the pivotal clinical trials and may differ from information provided in the package label.</i>	<b>PBM recommendations:</b> Avoid if CrCl <30 ml/min (not studied)  Avoid if CrCl ≤50 ml/min and if on concomitant dronedarone or systemic ketoconazole	<b>PBM recommendations:</b> Avoid if CrCl <30 ml/min (not studied)  Reduced dose of 15 mg once daily for patients with CrCl 30-50 ml/min (studied and FDA approved)	<b>PBM recommendations:</b> Avoid if SCr >2.5 mg/dL or CrCl <25 ml/min (not studied)  Reduced dose of 2.5 mg BID if patients have 2 or more: ▪ SCr ≥1.5 mg/dL ▪ ≥80 yrs ▪ wt ≤60 kg (studied and FDA approved)	n/a
	<b>Package Labeling:</b> Reduced dose of 75 mg BID if CrCl 15-30 ml/min  Reduced dose of 75 mg BID if CrCl 30-50 ml/min AND on concomitant dronedarone or systemic ketoconazole.  No recommendations for CrCl <15 ml/min or dialysis	<b>Package Labeling:</b> Reduced dose of 15 mg once daily if CrCl 15-50 ml/min  Avoid if CrCl <15 ml/min	<b>Package Labeling:</b> Reduced dose of 2.5 mg BID if patients have 2 or more: ▪ Age ≥80 yrs ▪ Wt ≤60 kg ▪ Serum creatinine ≥1.5 mg/dL  End stage renal disease and on stable hemodialysis: ▪ 5 mg BID if age <80 yrs and wt >60 kg ▪ 2.5 mg BID if age ≥80 yrs or wt ≤60 kg	n/a
<b>Geriatric Patients</b>	Increased bleeding vs. warfarin in pts ≥75 yrs and older	Trend of increased bleeding in pts >75 yrs	No increase bleeds vs. warfarin  Reduce dose of 2.5 mg BID available if ≥2 high risk factors present: age ≥80 yr, wt ≤60 kg, SCr ≥1.5 mg/dL	No overall differences noted.  Consider lower initiation dose and greater sensitivity to dose/INR response in elderly
<b>PUD/GI issues</b>	Increased risk of GIB vs. warfarin  Increased GI adverse effects (e.g., dyspepsia, gastritis), more treatment discontinuations due to adverse effects, particularly in beginning of treatment	Increased risk of GIB vs. warfarin	None	None

(Cont'd)	DABI	RIVA	APIX	WARF
<b>Dietary considerations</b>	Take with full glass of water	Must take with meal for adequate absorption	None	Steady intake of Vitamin K containing foods
<b>CAD considerations</b>	Numerical increase in MI vs. warfarin  30% relative increased risk; 0.2-0.3% per yr absolute increase in MI/ACS events	None	None	None
<b>Drug interactions</b>	Prodrug is substrate of P-gp  AVOID use P-gp inducers (e.g., rifampin, phenytoin, St. John's Wort)- reduced dabigatran effect  Caution with P-gp inhibitors (e.g., dronedarone, ketoconazole); AVOID if concurrent renal impairment	CYP3A4, P-gp substrate  AVOID use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) – reduced rivaroxaban effect  AVOID use with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir and ritonavir combinations)- increased rivaroxaban effect	CYP3A4, P-gp substrate  AVOID use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin) – reduced apixaban effect  Reduced dose of apixaban 2.5 mg BID available for use with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, and ritonavir combinations) – increased apixaban effect	Alterations in plasma protein binding; CYP2C9, 1A2, 3A4 induction or inhibition; antibiotics, antifungals, herbals
<b>ASA/thienopyridine concomitant use</b>	Increased bleeding  Little data on ASA+thienopyridine in AF;  Increased bleed with unknown benefit in Phase 2 study of ACS pts	Increased bleeding  No data on ASA+thienopyridine in AF;  Increased bleed with benefit in ACS pts (low dose rivaroxaban)	Increased bleeding  No data on ASA+thienopyridine in AF;  Increased bleed without benefit in ACS pts	Increased bleeding
<b>Cardioversion</b>	Moderate data; post-hoc, retrospective analysis; appears no worse than warfarin for thromboembolic and bleeding outcomes	Limited data; post-hoc, published combined analysis of cardioversion and ablation pts; no difference in outcomes with RIVA vs. WARF in small number of pts	Limited data; abstract only; small number of outcomes in both APIX and WARF groups; no apparent differences between treatments	Good data; standard of care
<b>Ablation</b>	Low quality data; most but not all studies suggest similar thromboembolic/bleeding risk	Very limited data; published combined analysis of cardioversion and ablation pts; no difference in outcomes with RIVA vs. WARF in very small number of pts	No data	Good data; standard of care
<b>Prosthetic Heart Valve</b>	Data showing increased adverse outcomes in mechanical prosthetic valves; contraindicated; not recommended for other valvular disease	Not studied and not recommended	Not studied and not recommended	OK
<b>Additional indications for anticoagulation</b>	FDA approved for: • VTE treatment	FDA approved for: ▪ VTE treatment ▪ VTE prophylaxis in	FDA approved for: ▪ VTE treatment ▪ VTE prophylaxis in	Several indications for use

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		orthopedic surgery	orthopedic surgery	
<b>Anticoagulant Lab testing</b>	None routinely recommended; if urgently needed, aPTT, TT (qualitative estimate; presence or absence)	None routinely recommended; if urgently needed, PT, anti-Factor Xa (qualitative estimate; presence or absence)	None routinely recommended; if urgently needed, anti-Factor Xa (qualitative estimate; presence or absence)	INR

## REFERENCES

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1. Dabigatran (Pradaxa) Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. April 2014.
2. Rivaroxaban (Xarelto) Prescribing Information. Janssen Pharmaceuticals, Inc. Titusville, NJ. March 2014.
3. Apixaban (Eliquis) Prescribing Information. Bristol-Myers Squibb, Princeton NJ and Pfizer Inc. New York, NY. August 2014.
4. Warfarin (Coumadin) Prescribing Information. Bristol-Myers Squibb Company. Princeton, NJ. October 2011.
5. Boehringer Ingelheim Pharmaceuticals, Inc. Monitoring the anticoagulant activity of dabigatran. Drug Information Letter. December 29, 2010.
6. Janssen Scientific Affairs, LLC. Xarelto: Coagulation Monitoring. Medical Information Letter. March 12, 2012.
7. Bristol Myers Squibb. Monitoring of anticoagulant activity of apixaban. Medical Information Letter. February 12, 2013.
8. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. *Circulation*. 2011;124: 1573-1579.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). *N Engl J Med*. 2009;361:1139-51.
10. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) Study. *Circulation*. 2013;128:237-43.
11. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation (ROCKET AF). *N Engl J Med*. 2011; Sep 8;365(10):883-91.
12. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-92.
13. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation (AVERROES). *N Engl J Med*. 2011;364:806-17.
14. FDA Medical Review for dabigatran. Accessed at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022512Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000MedR.pdf) (Accessed on May 28, 2013)..
15. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376:975-83.
16. Rosenstein R, Parra D. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; Dec 15;365(24):2334; letter.
17. FDA Rivaroxaban Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm270796.pdf> (Accessed May 25, 2013).
18. Wallentin L, Lopes RD, Hanna M, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted INR control for stroke prevention in atrial fibrillation. *Circulation*. 2013; epub ahead of print (DOI: 10.1161/CIRCULATIONAHA.112.142158).
19. FDA Medical Review for Regulatory Action for Apixaban. Accessed at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/202155Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf). (Accessed on March 20, 2013).
20. Adam SS, McDuffie JR, Ortel TL, et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism. *Ann Intern Med*. 2012;157:796-807.
21. Lip GYH, Larsen TB, Skjoth F, et al. Indirect comparisons of new oral anticoagulants for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2012;60:8:738-46.
22. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation. *Circulation*. 2012;126:2381-91.
23. Mantha S and Ansell J. An indirect comparison of dabigatran, rivaroxaban, and apixaban for atrial fibrillation. *Thromb Haemost*. 2012;108:476-84.
24. Rasmussen LH, Larsen TB, Graungaard T, et al. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. *BMJ*. 2012;345: e7097. doi: 10.1136/bmj.e7097.

25. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation. *CHEST*. 2012;141(2)(Suppl):e531S-75S.
26. Furie KL, Goldstein LB, Albers GW, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:3442-53.
27. Klein AL, Grimm RA, Murray RD, et al. Assessment of cardioversion using transesophageal echocardiography investigators (ACUTE). Use of transesophageal echocardiography to guide cardioversion I patients with atrial fibrillation. *N Engl J Med*. 2001;344(9):1411-20.
28. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;doi:10.1093/eurheartj/ehu367.
29. Ezekowitz MD, Cappato R, Klein AL, et al. Rationale and design of the eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of cardiovascular events in patients with nonvalvular aTrial fibrillation scheduled for cardioversion trial: a comparison of oral rivaroxaban once daily with dose adjusted vitamin K antagonists in patients with nonvalvular atrial fibrillation undergoing elective cardioversion. *Am Heart J*. 2014;167:646-52.
30. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. An analysis of patients undergoing cardioversion. *Circulation*. 2011;123:131-36.
31. Piccini JP, Stevens SR, Lokhnygina Y, et al. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET-AF trial. *J Am Coll Cardiol*. 2013;61:1998-2006.
32. Flaker G, Lopes RD, Al-Khatib S, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation. *J Am Coll Cardiol*. 2014;63:1082-87.
33. Yadlapati A, Groh C, Passman R, et al. Safety of short-term use of dabigatran or rivaroxaban for direct-current cardioversion in patients with atrial fibrillation or atrial flutter. *Am J Cardiol*. 2014;113(8):1362-3.
34. Faust AC, Smith MB, Kawalsky D. Acute ischemic stroke following cardioversion in a patient receiving dabigatran. *Ann Pharmacother*. 2013;47(10):1368-71.
35. Gagliardi L, Guerbaai RA, Marliere S, et al. Coronary embolization following electrical cardioversion in a patient treated with dabigatran. *Int J Cardiol*. 2014;175(3):571-2.
36. Amara W, Guedeny P, Iusuf A. [Ischemic stroke after cardioversion and atrial flutter ablation in a patient taking dabigatran]. *Ann Cardiol Angeiol (Paris)*. 2013;62(5):358-60.
37. Buch TN, Holm J, Munck LK. [Extensive thromboembolism after cardioversion in a patient treated with dabigatran]. *Ugeskr Laeger*. 2013;175(6):333-4. Danish
38. Vidal A, Vanerio G. Dabigatran and left atrial appendage thrombus. *J Thromb Thrombolysis*. 2012;34(4):545-7.
39. Di Biase L, Burkhardt JD, Gilbert G, et al. Dabigatran has a higher risk of left atrial appendage thrombus formation in patients with AF when compared to warfarin and rivaroxaban. Oral abstract presented at AHA meeting on November 18, 2013.
40. January CT, Wan S, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;129 (pub ahead of print).
41. Calkins H, Kuck KH, Cappato R, et al. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. 2012 HRS/EHRA/ECAS Expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Heart Rhythm*. 2012;9:632-96.
42. Passman R. Radiofrequency catheter ablation to prevent atrial fibrillation. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013.
43. Winkle RA, Mead HR, Engel G, et al. The use of dabigatran immediately after atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2012;23:264-68.

44. Bassiouny M, Saliba W, Rickard J, et al. use of dabigatran for peri-procedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2013; Apr 13 [e-pub ahead of print].
45. Kim JS, She F, Jongnarangsin K, et al. Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm*. 2013;10(4):483-89.
46. Lakkireddy D, Reddy YM, DiBiase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation. *J Am Coll Cardiol*. 2012;59(13):1168-74.
47. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism (RE-COVER). *N Engl J Med*. 2009;361:2342-52.
48. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. (RECOVER-II). *Circulation*. 2014;129:764-772.
49. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism (EINSTEIN). *N Engl J Med*. 2010;363:2499-510.
50. Buller HR, Prins MH, Lensing AWA, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism (EINSTEIN PE). *N Engl J Med*. 2012; 366:1287-97.
51. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism (AMPLIFY). *N Engl J Med*. 2013;369(9):799-808.
52. Gomez-Outes A, Terleira-Fernandez, Lecumberri R, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. *Thromb Res*. 2014; <http://dx.doi.org/10.1016/j.thromres.2014.06.020>.
53. Kakkos SK, Kirkilesis GI, Tsolakis IA. Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg*. 2014;<http://dx.doi.org/10.1016/j.ejvs.2014.05.001>.
54. van der Hulle T, Kooiman J, Den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:320-8.
55. Castellucci LA, Cameron C, Gregoire LG, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism. *JAMA*. 2014;312(11):1122-35.
56. Fox BD, Kahn SR, Langleben D, et al. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomized controlled trials. *BMJ*. 2012;345:e7498 doi: 10.1136/bmj.e7498.
57. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease. *CHEST*. 2012;141(2)(Suppl):e419S-e494S.
58. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2013;31:2189-2204.
59. Streiff MB, Bockenstedt PL, Cataland SR, Chesney C, Eby C, Fanikos J, Fogerty AE, Gao S, Goldhaber SZ, Hassoun H, Hendrie P, Holmstrom B, Kuderer N, Lee JT, Millenson MM, Neff AT, Ortel TL, Siddiqi T, Smith JL, Yee GC, Zakarija A, McMillian N, Naganuma M. Cancer Associated Venous Thromboembolic Disease. National Comprehensive Cancer Network (NCCN) Guidelines. Version 1.2014. Online. Accessed on 8/22/2014.
60. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709-18.
61. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708.
62. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. (RECORD-1). *N Engl J Med*. 2008;358:2765-75.

63. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty (RECORD-2). *Lancet*. 2008;372:31-39.
64. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358:2776-86.
65. Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD-4): a randomized trial. *Lancet*. 2009;373:1673-80.
66. FDA Summary Review for Regulatory Action for Rivaroxaban at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2011/022406Orig1s000SumR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000SumR.pdf) . (Accessed on May 20, 2013).
67. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC et al. Oral thrombin inhibitor dabigatran etexilate vs. North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty*. 2009;24(1):1-9.
68. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 2007;5:2718-85.
69. Eriksson BI, Dahl OE, Rosencher N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial (RE-NOVATE). *Lancet*. 2007;370:949-56.
70. Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RENOVATE II). *Thromb Haemost*. 2011;105:721-29.
71. Lassen MR, Raskob GE, Gallus A, et al. Apixaban or enoxaparin thromboprophylaxis after knee replacement. *ADVANCE-1*. *N Engl J Med*. 2009;361:594-604.
72. Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double blind trial. *Lancet*. 2010;375:807-15.
73. Lassen MR, Gallus A, Raskob GE, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. (ADVANCE-3). *N Engl J Med*. 2010;363:2487-98.
74. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, et al. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ*. 2012;344:e3675.
75. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients. *CHEST*. 2012;141(2)(Suppl):e278S-325S.
76. American Academy of Orthopedic Surgeons (AAOS). Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Summary of Recommendations. September 24, 2011. Accessed at: [http://www.aaos.org/Research/guidelines/VTE/VTE\\_summary\\_of\\_recs.pdf](http://www.aaos.org/Research/guidelines/VTE/VTE_summary_of_recs.pdf) (Accessed on May 21, 2013).
77. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome (ATLAS TIMI-51). *N Engl J Med*. 2012;366(1):9-19.
78. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome (APPRAISE-2). *N Engl J Med*. 2011;365:699-708.
79. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J*. 2011;32(22):2781-9.
80. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513-23.
81. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. apixaban versus enoxaparin for thromboprophylaxis in medically ill patients (ADOPT). *N Engl J Med*. 2011;365:2167-77.
82. Turpie AGG, Lassen MR, Erikson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty: pooled analysis of four studies (RECORD 1-4). *Thromb Haemost*. 2011;105(3):444-53.
83. Dabigatran Etexilate, Boehringer Ingelheim Briefing Information for the FDA Cardiovascular and Renal Drugs Advisory Committee Briefing Document. August 27, 2010. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226009.pdf> (accessed May 29, 2013).
84. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. *Circulation*. 2011;123:2363-72.

85. Patel MR, Hellkamp AS, Lokhnygina Y, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2013;61:651-58.
86. Granger C, Alexander J, Hanna M, et al. Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial. Oral presentation at: European Society of Cardiology Congress; August 25-29, 2012;Munich, Germany.
87. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J*. 2012;163:931-37.
88. FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. Accessed at: <http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm> . Accessed on June 1, 2013.
89. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013. DOI: 10.1056/NEJMoa1300615.
90. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363:1875-76.
91. Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY trial. *Circulation*. 2012;125:669-76.
92. Uchino K, Hernandez AV, et al. Dabigatran association with higher risk of acute coronary events. Meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med*. 2012;172(5):397-402.
93. Pradaxa (dabigatran etexilate) Product Dossier. Boehringer Ingelheim Pharmaceuticals, Inc. October 2010.
94. FDA Medical Review for Regulatory Action for Rivaroxaban at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2011/022406Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000MedR.pdf) . (Accessed on May 29, 2013).