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Rationalizing Cardiology Care in an Era of Hospital Consolidation

The health care landscape has dramatically changed during the past few years—and will continue to do so—as hospitals consolidate into larger entities. For many organizations, mergers and acquisitions present opportunities for greater geographic reach, enhanced clinical capacity, increased care coordination, and economies of scale. When it comes to the cardiovascular (CV) service line, consolidation can enable greater subspecialization for services (e.g., congenital heart disease, TAVR, transplant) that typically have limited volume but are critical to comprehensive patient care. However, consolidation can also create a crowded clinical environment in which newly consolidated hospitals provide overlapping services; and while subspecialty care and patient access are key priorities of the CV service line, redundancies are not.

Enter *rationalization*, the third installment in our series on the five key attributes of a thriving value-based enterprise. To mitigate the potential clutter of consolidation, systems are evaluating the (re)distribution of cardiology services and centralizing or colocating similar service offerings within a particular market. The intent is to contain costs and optimize resource utilization while also providing high-quality care. Yet the decision to rationalize services, although increasingly necessary, can be highly complex. This article highlights the common challenges organizations may face and offers

guidance for determining the appropriate level of rationalization.

YES, RATIONALIZATION IS COMPLICATED

I am currently working with several hospital systems that are managing multiple CV surgery programs within close proximity to each other. While volumes may have justified this service duplication

To mitigate the potential clutter of consolidation, systems are evaluating the (re)distribution of cardiology services and centralizing or colocating similar service offerings within a particular market.

5 or 10 years ago, the practicality and benefits of having two programs are now much more difficult to explain. Most agree that clinical cardiology services (e.g., clinical consults, routine testing) need to be readily available and in close proximity to where people live and work. Conversely, heart transplantation and VAD implants should be centralized on a regional or multiregional basis.

The ideal distribution of subspecialty and surgical services generally lies somewhere in between these two options. Questions regarding the number and location of open-heart programs are obviously important and need to be addressed. From a quality perspective, having a high-volume open-heart program is more advantageous than one with a lower case volume; however, many patients and providers are hesitant to remove on-site surgical backup from their local facilities. Similarly, some systems opt to limit the number of cath labs available for diagnostic interventional procedures and instead, focus on enhancing their processes for transferring STEMI cases from local facilities to a regional cath lab facility. While there are a number of benefits to these rationalization efforts, many health care systems are reluctant to venture down this path for fear of the strategic, financial, operational, and cultural and political considerations that accompany such endeavors.

Even though challenges exist and can be difficult to overcome, systems cannot afford to tip-toe around tough discussions given the steadily growing emphasis on value-based care—particularly for CV services—that continues to be at the forefront of CMS' reimbursement initiatives. Successfully managing the complexities of rationalization strategies requires systems to establish a carefully constructed framework for identifying, evaluating, and prioritizing their options. More importantly, it requires a collaborative process that brings both physicians and administrators to the table to ask the important questions and engage in a logical, unprejudiced assessment of the benefits and risks.

RATIONALIZATION FRAMEWORK

Rationalizing services requires careful analysis, a

TABLE Example Considerations for CV Service Line Rationalization

Strategic	Operational	Financial	Cultural and Political
<ul style="list-style-type: none"> • Patient/provider loyalty and retention when services are relocated • Degree of competitive response and potential local market shifts • Anticipated on-site CV offerings in the long term (that might necessitate a short-term service) 	<ul style="list-style-type: none"> • Potential to improve outcomes through volume consolidation of high-risk procedures • Downstream implications (e.g., impact on cardiac imaging studies, lab tests) • Proximity to related services (e.g., cardiac rehab, SNFs) • Equipment/space under- or over-capacity 	<ul style="list-style-type: none"> • Impact of lost revenue streams and associated contribution margin • Implications of value-based reimbursement and other cost/financial factors • Hospital and CEO performance incentive structures • Capital initiative funding at the local level 	<ul style="list-style-type: none"> • Reactions of medical staff and hospital leadership • Shift in mind-set from silo to system orientation • Previous promises/agreements made to boards, communities, local governments, and donors regarding the types and level of services provided by the facility

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well-defined strategy, and the ability to cultivate influential champions for change. There should ultimately be a compelling case for why service redistribution is necessary, as well as how services will be distributed to best support the strategic and financial success of the system.

Regardless of how services are redistributed, there are several other critical elements that need to be factored into a framework for rationalization.

» **Establish clear ground rules and transparent decision-making criteria.** Providing a clear decision-making path and precise criteria to be followed helps organizations communicate an unbiased, stakeholder-inclusive, and transparent approach to service distribution.

» **Engage stakeholders throughout the decision-making process.** Reactions to rationalization efforts vary and often depend on whether a community perceives it will be losing or gaining services. Engaging stakeholders in the discussion increases the opportunity

to address questions and concerns early on while creating win-win scenarios for those who are directly impacted.

» **Enlist local and/or regional provider input into system initiatives.** If a decision is made to consolidate

a particular service at the system level, ensure that local stakeholders still have venues to provide system-wide guidance and feedback. For example, the implementation of regional, multi-organizational committees for programs like TAVR can provide a strong means to co-

ordinate care pathways across the system and, in the process, secure broad provider support at the local level.

» **Start with services that have the greatest potential for improving quality and cost.** Take manage-

There should ultimately be a compelling case for why service redistribution is necessary, as well as how services are distributed to best support the strategic and financial success of the system.

Pradaxa® (dabigatran etexilate mesylate) capsules for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information.

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see Warnings and Precautions].

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of PRADAXA and neuraxial procedures is not known [see Warnings and Precautions].

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary [see Warnings and Precautions].

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated [see Warnings and Precautions].

INDICATIONS AND USAGE: Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation: PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. **Treatment of Deep Venous Thrombosis and Pulmonary Embolism:** PRADAXA is indicated for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days. **Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism:** PRADAXA is indicated to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated.

CONTRAINDICATIONS: PRADAXA is contraindicated in patients with: Active pathological bleeding [see Warnings and Precautions and Adverse Reactions]. History of a serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock) [see Adverse Reactions]. Mechanical prosthetic heart valve [see Warnings and Precautions].

WARNINGS AND PRECAUTIONS: Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant. **Risk of Bleeding:** PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding. Risk factors for bleeding include the concomitant use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment. **Reversal of Anticoagulant Effect:** A specific reversal agent for dabigatran is not available. Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited [see Overdosage]. Activated prothrombin complex concentrates (aPCCs, e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis [see Boxed Warning]. To reduce the potential risk of bleeding associated with the concurrent use of dabigatran and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae. **Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves:** The safety and efficacy of PRADAXA in patients with bileaflet mechanical prosthetic heart valves was evaluated in the RE-ALIGN trial, in which patients with bileaflet mechanical prosthetic heart valves (recently implanted or implanted more than three months prior to enrollment) were randomized to dose adjusted warfarin or 150, 220, or 300 mg of PRADAXA twice a day. RE-ALIGN was terminated early due to the occurrence of significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding (predominantly post-operative pericardial effusions requiring intervention for hemodynamic compromise) in the PRADAXA treatment arm as compared to the warfarin treatment arm. These bleeding and thromboembolic events were seen both in patients who were initiated on PRADAXA post-operatively within three days of mechanical bileaflet valve implantation, as well as in patients whose valves had been implanted more than three months prior to enrollment. Therefore, the use of PRADAXA is contraindicated in patients with mechanical prosthetic valves [see Contraindications]. The use of PRADAXA for the prophylaxis of thromboembolic events in patients with atrial fibrillation in the setting of other forms of valvular heart disease, including the presence of a bioprosthetic heart valve, has not been studied and is not recommended. **Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure:** The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone. **Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation:** Consider reducing the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) [see Drug Interactions and Use in Specific Populations]. **Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism:** Avoid use of PRADAXA and concomitant P-gp inhibitors in patients with CrCl <50 mL/min [see Drug Interactions].

ADVERSE REACTIONS: The most serious adverse reactions reported with PRADAXA were related to bleeding [see Warnings and Precautions]. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation:** The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study provided safety information on the use of two doses of PRADAXA and warfarin. The numbers of patients and their exposures are described in Table 1. Limited information is presented on the 110 mg dosing arm because this dose is not approved.

Table 1 Summary of Treatment Exposure in RE-LY

	PRADAXA 110 mg twice daily	PRADAXA 150 mg twice daily	Warfarin
Total number treated	5983	6059	5998
Exposure			
> 12 months	4936	4939	5193
> 24 months	2387	2405	2470
Mean exposure (months)	20.5	20.3	21.3
Total patient-years	10,242	10,261	10,659

Drug Discontinuation in RE-LY: The rates of adverse reactions leading to treatment discontinuation were 21% for PRADAXA 150 mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal events (i.e., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea). **Bleeding [see Warnings and Precautions]:** Table 2 shows the number of patients experiencing serious bleeding during the treatment period in the RE-LY study, with the bleeding rate per 100 patient-years (%). Major bleeds fulfilled one or more of the following criteria: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding). A life-threatening bleed met one or more of the following criteria: fatal, symptomatic intracranial bleed, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 2 Bleeding Events* (per 100 Patient-Years)

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI**)
Randomized patients	6076	6022	
Patient-years	12,033	11,794	
Intracranial hemorrhage	39 (0.3)	91 (0.8)	0.42 (0.29, 0.61)
Life-threatening bleed	183 (1.5)	221 (1.9)	0.81 (0.67, 0.99)
Major bleed	409 (3.4)	426 (3.6)	0.94 (0.82, 1.08)
Any bleed	1997 (16.6)	2169 (18.4)	0.91 (0.85, 0.96)

*Patients contributed multiple events and events were counted in multiple categories.

**Confidence interval

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (hazard ratio 1.2, 95% CI: 1.0 to 1.4) for patients ≥75 years of age. There was a higher rate of major gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (5.7% vs. 3.9%, respectively). **Gastrointestinal Adverse Reactions:** Patients on PRADAXA 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer). **Hypersensitivity Reactions:** In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving PRADAXA. **Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism:** PRADAXA was studied in 4387 patients in 4 pivotal, parallel, randomized, double-blind trials. Three of these trials were active-controlled (warfarin) (RE-COVER, RE-COVER II, and RE-MEDY), and one study (RE-SONATE) was placebo-controlled. The demographic characteristics were similar among the 4 pivotal studies and between the treatment groups within these studies. Approximately 60% of the treated patients were male, with a mean age of 55.1 years. The majority of the patients were white (87.7%), 10.3% were Asian, and 1.9% were black with a mean CrCl of 105.6 mL/min. Bleeding events for the 4 pivotal studies were classified as major bleeding events if at least one of the following criteria applied: fatal bleeding, symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding), bleeding causing a fall in hemoglobin level of 2.0 g/dL (1.24 mmol/L or more, or leading to transfusion of 2 or more units of whole blood or red cells). RE-COVER and RE-COVER II studies compared PRADAXA 150 mg twice daily and warfarin for the treatment of deep vein thrombosis and pulmonary embolism. Patients received 5-10 days of an approved parenteral anticoagulant therapy followed by 6 months, with mean exposure of 164 days, of oral only treatment; warfarin was overlapped with parenteral therapy. Table 3 shows the number of patients experiencing bleeding events in the pooled analysis of RE-COVER and RE-COVER II studies during the full treatment including parenteral and oral only treatment periods after randomization.

able steps toward rationalization by focusing on initiatives that will improve overall patient care as well as the system's bottom line. For example, begin by transitioning low-volume and/or high-acuity cases to a particular hospital as a way to monitor and garner trust in the

new arrangement before incorporating more sweeping changes.

DIFFICULT BUT OFTEN NECESSARY

Rationalization approaches are often met by internal—and sometimes external (e.g., boards, patient communi-

ty)—resistance, and thus are utilized infrequently. Yet with the continued trend toward consolidation, systems are facing overlapping CV services, diminishing volumes, overcapacity, and increasing costs. Though difficult to work through, a thoughtful strategy for rationalizing services

can represent the means to better manage costs and care delivery in the wake of value-based reform. ■

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Table 3 Bleeding Events in RE-COVER and RE-COVER II Treated Patients

	Bleeding Events-Full Treatment Period Including Parenteral Treatment		
	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI) ^c
Patients	N=2553	N=2554	
Major bleeding event ^a	37 (1.4)	51 (2.0)	0.73 (0.48, 1.11)
Fatal bleeding	1 (0.04)	2 (0.1)	
Bleeding in a critical area or organ	7 (0.3)	15 (0.6)	
Fall in hemoglobin ≥ 2 g/dL or transfusion ≥ 2 units of whole blood or packed red blood cells	32 (1.3)	38 (1.5)	
Bleeding sites for MBE ^b			
Intracranial	2 (0.1)	5 (0.2)	
Retroperitoneal	2 (0.1)	1 (0.04)	
Intraarticular	2 (0.1)	4 (0.2)	
Intramuscular	2 (0.1)	6 (0.2)	
Gastrointestinal	15 (0.6)	14 (0.5)	
Urogenital	7 (0.3)	14 (0.5)	
Other	8 (0.3)	8 (0.3)	
Clinically relevant non-major bleeding	101 (4.0)	170 (6.7)	0.58 (0.46, 0.75)
Any bleeding	411 (16.1)	567 (22.7)	0.70 (0.61, 0.79)

Note: MBE can belong to more than one criterion.

^aPatients with at least one MBE.

^bBleeding site based on investigator assessment. Patients can have more than one site of bleeding.

^cConfidence interval

The rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg in the full treatment period was 3.1% (2.4% on warfarin). The RE-MEDY and RE-SONATE studies provided safety information on the use of PRADAXA for the reduction in the risk of recurrence of deep vein thrombosis and pulmonary embolism. RE-MEDY was an active-controlled study (warfarin) in which 1430 patients received PRADAXA 150 mg twice daily following 3 to 12 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-MEDY study had a combined treatment duration of up to more than 3 years, with mean exposure of 473 days. Table 4 shows the number of patients experiencing bleeding events in the study.

Table 4 Bleeding Events in RE-MEDY Treated Patients

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI) ^c
	Patients	N=1430	N=1426
Major bleeding event ^a	13 (0.9)	25 (1.8)	0.54 (0.25, 1.16)
Fatal bleeding	0	1 (0.1)	
Bleeding in a critical area or organ	7 (0.5)	11 (0.8)	
Fall in hemoglobin ≥ 2 g/dL or transfusion ≥ 2 units of whole blood or packed red blood cells	7 (0.5)	16 (1.1)	
Bleeding sites for MBE ^b			
Intracranial	2 (0.1)	4 (0.3)	
Intraocular	4 (0.3)	2 (0.1)	
Retroperitoneal	0	1 (0.1)	
Intraarticular	0	2 (0.1)	
Intramuscular	0	4 (0.3)	
Gastrointestinal	4 (0.3)	8 (0.6)	
Urogenital	1 (0.1)	1 (0.1)	
Other	2 (0.1)	4 (0.3)	
Clinically relevant non-major bleeding	71 (5.0)	125 (8.8)	0.56 (0.42, 0.75)
Any bleeding	278 (19.4)	373 (26.2)	0.71 (0.61, 0.83)

Note: MBE can belong to more than one criterion.

^aPatients with at least one MBE.

^bBleeding site based on investigator assessment. Patients can have more than one site of bleeding.

^cConfidence interval

In the RE-MEDY study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg was 3.1% (2.2% on

warfarin). RE-SONATE was a placebo-controlled study in which 684 patients received PRADAXA 150 mg twice daily following 6 to 18 months of oral anticoagulant regimen. Patients in the treatment studies who rolled over into the RE-SONATE study had combined treatment duration up to 9 months, with mean exposure of 165 days. Table 5 shows the number of patients experiencing bleeding events in the study.

Table 5 Bleeding Events in RE-SONATE Treated Patients

	PRADAXA 150 mg twice daily N (%)	Placebo N (%)	Hazard Ratio (95% CI) ^c
	Patients	N=684	N=659
Major bleeding event ^a	2 (0.3)	0	
Bleeding in a critical area or organ	0	0	
Gastrointestinal ^b	2 (0.3)	0	
Clinically relevant non-major bleeding	34 (5.0)	13 (2.0)	2.54 (1.34, 4.82)
Any bleeding	72 (10.5)	40 (6.1)	1.77 (1.20, 2.61)

Note: MBE can belong to more than one criterion.

^aPatients with at least one MBE.

^bBleeding site based on investigator assessment. Patients can have more than one site of bleeding.

^cConfidence interval

In the RE-SONATE study, the rate of any gastrointestinal bleeds in patients receiving PRADAXA 150 mg was 0.7% (0.3% on placebo). **Clinical Myocardial Infarction Events:** In the active-controlled VTE studies, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA [20 (0.66 per 100 patient-years)] than in those who received warfarin [5 (0.17 per 100 patient-years)]. In the placebo-controlled study, a similar rate of non-fatal and fatal clinical myocardial infarction was reported in patients who received PRADAXA [1 (0.32 per 100 patient-years)] and in those who received placebo [1 (0.34 per 100 patient-years)]. **Gastrointestinal Adverse Reactions:** In the four pivotal studies, patients on PRADAXA 150 mg had a similar incidence of gastrointestinal adverse reactions (24.7% vs. 22.7% on warfarin). Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA in 7.5% vs. 5.5% on warfarin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 3.0% vs. 1.7%, respectively. **Hypersensitivity Reactions:** In the 4 pivotal studies, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in 0.1% of patients receiving PRADAXA. **Postmarketing Experience:** The following adverse reactions have been identified during post approval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of PRADAXA: angioedema, thrombocytopenia, esophageal ulcer.

In RE-LY, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA (0.7 per 100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

DRUG INTERACTIONS: Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation: The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone. In patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitors dronedarone or systemic ketoconazole. The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors [see Warnings and Precautions and Use in Specific Populations]. The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided [see Warnings and Precautions and Use in Specific Populations]. **Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism:** Avoid use of PRADAXA and P-gp inhibitors in patients with CrCl <50 mL/min [see Warnings and Precautions and Use in Specific Populations].

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at maximum recommended human dose [MRHD] of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation

(gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits. **Labor and Delivery:** Safety and effectiveness of PRADAXA during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using PRADAXA in this setting [see Warnings and Precautions]. Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons). **Nursing Mothers:** It is not known whether dabigatran is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PRADAXA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness of PRADAXA in pediatric patients have not been established. **Geriatric Use:** Of the total number of patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups [see Warnings and Precautions and Adverse Reactions]. **Renal Impairment: Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation:** No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min). Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot be provided. Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors [see Warnings and Precautions and Drug Interactions]. **Treatment and Reduction in the Risk of Recurrence of Deep Venous Thrombosis and Pulmonary Embolism:** Patients with severe renal impairment (CrCl ≤ 30 mL/min) were excluded from RE-COVER. Dosing recommendations for patients with CrCl ≤ 30 mL/min or on dialysis cannot be provided. Avoid use of PRADAXA with concomitant P-gp inhibitors in patients with CrCl <50 mL/min [see Warnings and Precautions and Drug Interactions].

OVERDOSAGE: Accidental overdose may lead to hemorrhagic complications. There is no reversal agent for dabigatran. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy [see Warnings and Precautions].

Rx only

Revised: January 2015

PXD-BS (1-15)

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PC-PXD-0021-PROF

