CardioSource News SUNDAY

ACC.12
61st Annual Scientific Session & Expo
ACC-i2 with TCT
innovation in intervention

61ST ANNUAL SCIENTIFIC SESSION · CHICAGO · MARCH 24 - 27 2012

Opening Showcase

Transformation serves as overarching theme of ACC.12 session

"Tremendous," said ACC President David Holmes, Jr., MD, as he welcomed attendees to the 61st Annual Scientific Session at Saturday's Opening Showcase.

The standing-room-only crowd attending the session was treated to an inspiring Welcome to Chicago video, tributes to ACC.12 and ACC-i2 with TCT co-chairs and the College's Board of Trustees, and thought-provoking speeches by cardiovascular legend Eugene Braunwald, MD, and Holmes, himself.

Braunwald kicked off the new Legends of Cardiovascular Medicine series with the Simon Dack Lecture, an annual tribute to one of ACC's founders and early presidents. Braunwald, who Holmes noted literally wrote the book on the modern-day treatment of cardiovascular disease, provided not only a look back at early advances in the treatment of acute myocardial infarction (AMI), but a vision for what lies ahead in its second century.

ACC President David Holmes Jr., MD

"It is interesting to look back 100 years … and observe the great advances that have been made," said Braunwald. However, he noted that despite these advances AMI continues to be a major cause of mortality. Braunwald went on to highlight three therapeutic approaches — prevention of lethal myocardial reperfusion injury, post-AMI inhibition of thrombin generation, and post-AMI cell therapy — as examples of future opportunities to improve cardiovascular care.

See **OPENING,** page 22

Welcome to ACC.12 and ACC-i2 with TCT

A sea of humanity rolls into the ACC.12 Annual Scientific Session and Expo Saturday when the exhibition hall opened near the end of the Opening Showcase at McCormick Place.

Antiplatelet agent lowers CV events raises bleeding risk

Results of a secondary prevention trial of a novel antiplatelet agent, vorapaxar, a selective antagonist of protease-activated receptor-1 (PAR-1), found that in stable patients with a history of atherothrombosis, vorapaxar significantly reduced cardiovascular death, myocardial infarction (MI) or stroke when added to standard antiplatelet therapy with aspirin and thienopyridine.

However, the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P): TIMI 50 Trial also found that the agent significantly increases the risk of moderate and severe bleeding, including intracranial hemorrhage, compared with placebo.

Vorapaxar reduced the risk of cardiovascular death, MI or stroke (9.3 versus 10.5 percent at three years, p<0.001), and the reduction was greatest in patients with a prior MI, who showed a 20 percent decline in cardiovascular events (p<0.001), according to David A. Morrow, MD, PhD, who presented the Late-Breaking Clinical Trial (LBCT) results during Saturday's Opening Showcase.

This agent is the first in a new class of investigational PAR-1 thrombin receptor antagonists.

"Our findings indicate a significant reduction in thrombosis adding to standard therapy, including aspirin, for long-term drug therapy in patients with prior MI, unacceptable intracranial hemorrhage risk in patients with prior stroke and uncertain benefit in patients with peripheral arterial disease (PAD)," said Morrow, director of the Samuel A. Levine Cardiac Unit at Brigham and

See **LBCT,** page 21

Providing excellence in cardiac care

The search for excellence in cardiac care is an endless task, but that is no excuse to shirk.

"Excellence, which I define as the pursuit of finding the truth, is probably not achievable,"4

said Magdi Yacoub, MBBch, Imperial College Heart Science Centre, London. "But the pursuit itself is extremely important. Cardiology is the science and the art of applying a surgical specialty to very real people. Even if we never reach the ultimate truth of cardiology, our search will be of tremendous benefit to a great many people."

Yacoub delivered the 43rd annual Bishop Lecture Saturday. His presentation, "The Search for Excellence," was part of the Legends of Cardiovascular Medicine Series.

Cardiovascular disease was directly responsible for 16.7 million deaths in 2002, 60 percent of the total mortality on a global basis, Yacoub said. Fully 80 percent of the CVD toll strikes low- and middle-income countries.

'There has been a tremendous impact

See **YACOUB,** page 23

Magdi Yacoub, MBBch

Inside

Today's schedule

ACC Meet the Experts
8 to 9:30 a.m.
See program for locations of sessions

Late-Breaking Clinical Trials II
8 to 9 a.m.
Joint Main Tent, Hall B, North building

Poster sessions
9:30 to 10:30 a.m.
Hall A, South building

Exhibit Hall open
9:30 a.m. to 4:30 p.m.
Hall A, South building

ACC Meet the Experts
10:45 a.m. to 12:15 p.m.
See program for locations of sessions

Young Investigator Awards Competition
10:45 a.m. to 12:15 p.m.
Room S102b

Poster sessions
11 a.m. to Noon
Hall A, South building

ACC Meet the Experts
12:15 to 1:45 p.m.
See program for locations of sessions

ACC-i2 with TCT Meet the Experts
12:30 to 1:45 p.m.
See program for locations of sessions

ACC-i2 with TCT Live and Taped Cases
2 to 5 p.m.
See program for locations of sessions

ACC Meet the Experts
2 to 3:30 p.m.
See program for locations of sessions

Legend/Dan G. McNamara Lecture
2:15 to 2:45 p.m.
Room N228

Legend/James T. Dove Lecture
4:30 to 5:30 p.m.
Room N247

Clinical Focus Sessions
6:30 to 9 p.m.
Fairmont Hotel

Panelists from the Middle East, North Africa and the U.S. discuss issues relevant to their regions during Friday's International Cardiovascular Conference: Focus on the Middle East.

Middle East symposium highlights importance of international education

Health care professionals from across the Middle East and North Africa gathered at the International Cardiovascular Conference: Focus on the Middle East Friday to discuss cardiology issues.

The fourth annual conference featured representatives from all of the nations of the Middle East and North Africa. Participants came together to discuss issues of patient care that are specific to the region and explore advances made in the diagnosis, treatment and management of cardiovascular disease, with a focus on how these are applied in the context of physician practice in the Middle East.

The program was created under the vision of ACC Past President Douglas Zipes, MD, who gave the inaugural Zipes Lecture, "Sudden Death — What do we Know?" to kick off the program.

This year's program was co-chaired by Ari Kugelmass, MD, and Mohamed Sobhy, MD, governor of the ACC Egypt Chapter. Each session in the program featured two Middle East perspectives and two U.S. per-

See **MIDDLE EAST**, page 22

BRILINTA™ *(ticagrelor)* Tablets

WARNING: BLEEDING RISK
- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

BRIEF SUMMARY of PRESCRIBING INFORMATION:
For full Prescribing Information, see package insert.

INDICATIONS AND USAGE
Acute Coronary Syndromes
BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [*see Clinical Studies (14) in full Prescribing Information*]. BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [*see Warnings and Precautions (5.2)* and *Clinical Studies (14) in full Prescribing Information*].

DOSAGE AND ADMINISTRATION
Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS
History of Intracranial Hemorrhage BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [*see Clinical Studies (14) in full Prescribing Information*].

Active Bleeding BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [*see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1) in full Prescribing Information*].

Severe Hepatic Impairment BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [*see Clinical Pharmacology (12.3) in full Prescribing Information*].

WARNINGS AND PRECAUTIONS
General Risk of Bleeding
Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [*see Adverse Reactions (6.1) in full Prescribing Information*]. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [*see Warnings and Precautions (5.5)* and *Adverse Reactions (6.1) in full Prescribing Information*].

Concomitant Aspirin Maintenance Dose In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [*see Dosage and Administration (2)* and *Clinical Studies (14) in full Prescribing Information*].

Moderate Hepatic Impairment BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [*see Drug Interactions (7.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [*see Drug Interactions (7.2)* and *Clinical Pharmacology (12.3) in full Prescribing Information*].

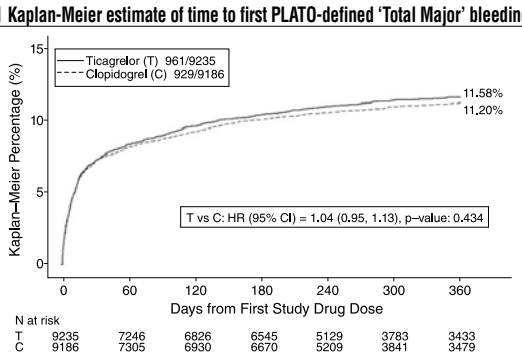
ADVERSE REACTIONS
Clinical Trials Experience
The following adverse reactions are also discussed elsewhere in the labeling:
- Dyspnea [*see Warnings and Precautions (5.4) in full Prescribing Information*]

Because clinical trials are conducted under widely varying conditions, adverse reaction 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. BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding PLATO used the following bleeding severity categorization:
- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

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Braunwald's address, which ended with a standing ovation for his decades of contributions to cardiovascular medicine, was followed by a video tribute to Holmes' presidential year, as well as the official Presidential Address. Holmes' reflected on the past 45 years of success in reducing the number of deaths from heart disease and urged audience members to continue this success through imagination. "We live in interesting times," he said, "but we will continue to lead."

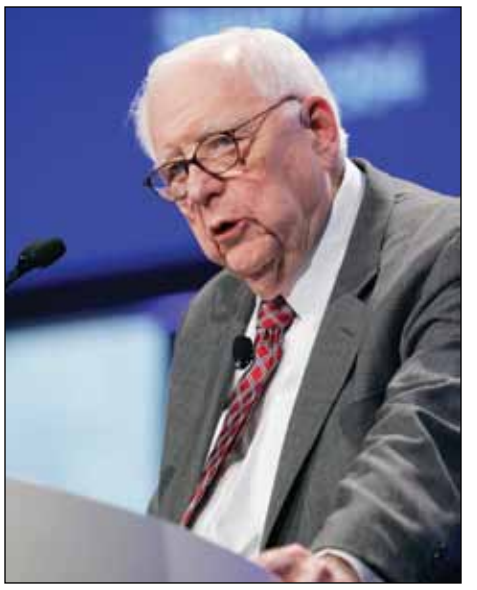
In particular, Holmes said it is important that cardiovascular professionals be agents of transformation in terms of harnessing new technologies, building new relationships and acting on new ideas and approaches. "This is even more important as the U.S. becomes known as the home of the free, the brave and the heavy-set," he said.

He cited the ACC's work with the new public/private Million Hearts initiative, which aims to prevent 1 million strokes and heart attacks over the next five years, as well as efforts already under way with Mended Hearts and Mended Little Hearts to improve awareness of congenital heart disease, as examples of transformational relationships. He also noted the ACC's work with The Society of Thoracic Surgeons, the Food and Drug Administration, the Centers for Medicare and Medicaid Services and other stakeholders to ensure rational dispersion of transaortic valve therapy.

Holmes used the ACC's SMARTCare pilot project in Wisconsin and Florida as an example of a transformational idea. SMARTCare is a collaborative effort of the ACC that brings together local stakeholders, including hospital systems, business, private health plans, patients and state medical specialty societies, around the goal of improving health care delivery and lowering costs.

Holmes closed his session by urging cardiovascular professionals to "make a difference — for you, your family, your patients and your world." ★

For a special video interview with Braunwald, visit the FITs on the Go Blog at CardioSource.org/FIT. Also, stay tuned to Sunday's CardioSourceVideoNews coverage for a special interview with Holmes and ACC President-Elect William Zoghbi, MD, for more insights into the past presidential year and a look ahead at new opportunities.



Eugene Braunwald, MD

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spectives followed by a panel discussion. In particular, the program focused on two main areas: congestive heart failure (CHF) and cardiometabolic syndrome — which are both global epidemics with particular burden in the Middle East.

The CHF Session, chaired by William Zoghbi, MD, president-elect of the ACC, and Hani Najm, MD, governor of the ACC Saudi Arabia Chapter, featured dynamic talks ranging from "Middle East Models for Heart Failure Clinics and Centers," given by Alessandro Salustri, MD, to a thought-provoking talk by Rob Califf, MD, on "Community Wide Management of Heart Failure — The Dangers of Siloed Metrics Focused on Hospitals." There were also a range of other talks followed by panel discussions.

The cardiometabolic syndrome program featured insightful talks concentrating on the burden of the disease, the associated lifestyle aspects, and the specific importance of women and children in combatting cardiometabolic syndrome in the Middle East and worldwide.

The talks were followed by the introduction of the first-ever ACC Cardiovascular Conference on the Middle East Research Project. The project, which focuses on cardiometabolic syndrome, was born out of the ACC Middle East Steering Committee. Chaired by Omar Lattouf, MD, the project will involve all of the countries in the Middle East as well as centers in the U.S.

The chairs of the conference said they were pleased to launch the research project to carry the vision of Zipes moving forward in future years.

"The Middle East program represents the future of ACC education," said Kugelmass. "It's a collaborative future that allows experts from the U.S. and regions around the world to compare successful strategies for treating our global patient base. I am honored to be a part of this future."

ACC's international presence has been expanding over the past few years and now has 17 chapters, including several in the Middle East. The conference was a great start to the array of international activities at ACC.12 and was a testament to the importance of international education in the ACC Annual Scientific Session. ★

Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)

XARELTO® (rivaroxaban) tablets, for oral use
See package insert for full Prescribing Information

WARNINGS: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

A. DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Discontinuing XARELTO places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant *[see Dosage and Administration (2.1) in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO 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**

***[see Warnings and Precautions and Adverse Reactions]*.**

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 for thromboprophylaxis *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation: XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information]*.

CONTRAINDICATIONS

XARELTO is contraindicated in patients with:
- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO *[see Warnings and Precautions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation: Discontinuing XARELTO in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant *[see Dosage and Administration (2.1) and Clinical Studies (14.1) in full Prescribing Information]*.

Risk of Bleeding: XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss. Discontinue XARELTO in patients with active pathological hemorrhage.

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered, but has not been evaluated in clinical trials.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions]*.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

Risk of Pregnancy Related Hemorrhage: XARELTO should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Severe Hypersensitivity Reactions: There were postmarketing cases of anaphylaxis in patients treated with XARELTO to reduce the risk of DVT. Patients who have a history of a severe hypersensitivity reaction to XARELTO should not receive XARELTO *[see Adverse Reactions]*.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction 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 clinical practice.

During clinical development for the approved indications, 11598 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF) and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF study.

Table 1: Bleeding Events in ROCKET AF*

Parameter	XARELTO N = 7111 n (%)	Event Rate (per 100 Pt-yrs)	Warfarin N = 7125 n (%)	Event Rate (per 100 Pt-yrs)
Major bleeding†	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ‡	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥ 2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

* For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.
† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for XARELTO vs. 2.9 per 100 Pt-yrs for warfarin.
‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of rivaroxaban. 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.

Blood and lymphatic system disorders: agranulocytosis
Gastrointestinal disorders: retroperitoneal hemorrhage
Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis
Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock
Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.
- *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Ritonavir (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Clarithromycin (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
- *Erythromycin (combined P-gp and moderate CYP3A4 inhibitor):* Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.
- *Fluconazole (moderate CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 40% and 30%, respectively.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/