

# CLEVELAND CLINIC JOURNAL OF MEDICINE

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## Cardiovascular disease: Innovations in devices and techniques

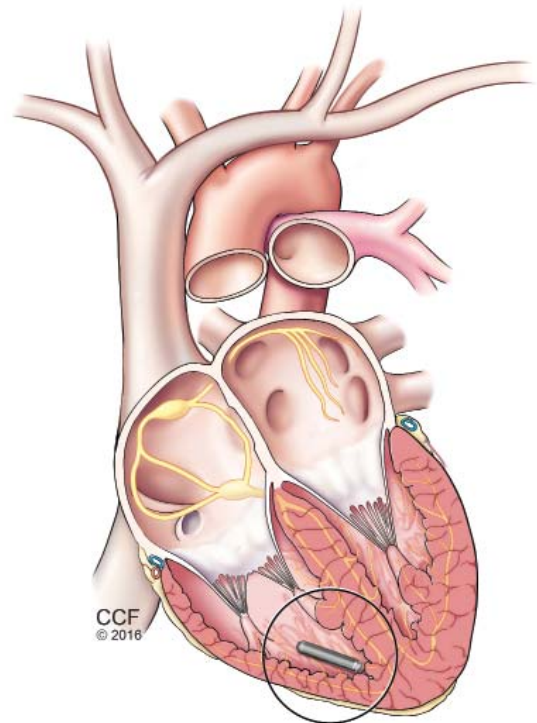
Transcatheter mitral valve replacement

Bioresorbable stents

Leadless cardiac pacing

PCSK9 inhibition

Fibromuscular dysplasia



Implanted leadless pacemaker

Supplement Editor

Maan A. Fares, MD

**SUPPLEMENT**

#1 PRESCRIBED  
NOAC IN THE US\*<sup>1</sup>

20,000 PATIENTS<sup>†2-16</sup>  
AND COUNTING...

BEYOND EXTENSIVE RANDOMIZED CLINICAL TRIALS,  
PUBLISHED SAFETY OUTCOMES FROM OBSERVATIONAL STUDIES  
OF REAL-WORLD PATIENTS<sup>†2-16</sup>

NOAC = non-vitamin K antagonist oral anticoagulant.

\*Among Factor Xa inhibitors and direct thrombin inhibitors.

<sup>†</sup>Based on the following registries, claims databases, and studies: Optum Labs=16,253; IMS Health LifeLink=1649; Truven Health=5563; Danish registry=1303; XAMOS=8778; Symphony=3654; ORTHO-TEP=1043; Japanese registry=1035; Dresden NOAC=1776; XALIA=2505; DoD database=27,467; XANTUS=6784; RELIEF=1039; SWIVTER=417; REVISIT-US=11,411.

## IMPORTANT SAFETY INFORMATION

### **WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA**

#### **A. Premature discontinuation of XARELTO® increases the risk of thrombotic events**

Premature discontinuation of any oral anticoagulant, including XARELTO®, increases the risk of thrombotic events. If anticoagulation with XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

#### **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, see Drug Interactions
- ◆ A history of traumatic or repeated epidural or spinal punctures
- ◆ A history of spinal deformity or spinal surgery
- ◆ Optimal timing between the administration of XARELTO® and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Please see Important Safety Information throughout.

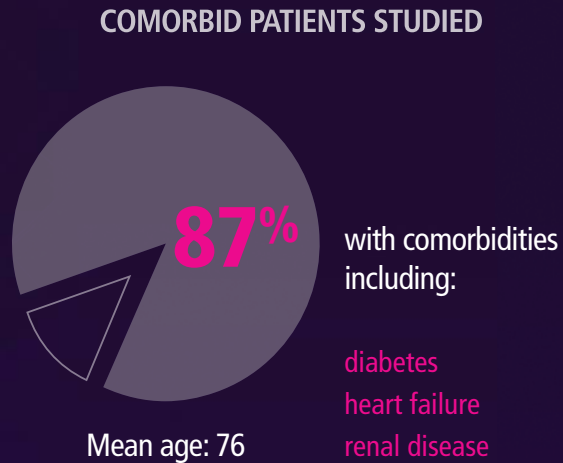
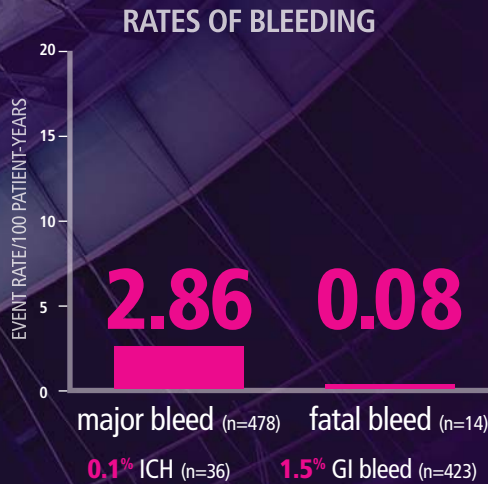
Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit [www.XareltoHCP.com/PI](http://www.XareltoHCP.com/PI).

 **Xarelto®**  
rivaroxaban tablets

# Real-world safety outcomes from one ongoing US study of 27,467 nonvalvular AF patients<sup>13</sup>



Results based on 15 months of data from an ongoing, 5-year postmarketing safety surveillance study to evaluate major bleeding in patients receiving XARELTO® in a real-world clinical setting. Cases of major bleeding were identified through electronic health records from the US Department of Defense database, from January 1, 2013, to March 31, 2014.



RESULTS ARE NOT INTENDED FOR DIRECT COMPARISON WITH CLINICAL TRIALS

A validated computer database algorithm developed by Cunningham et al, which identifies bleeding-related hospitalizations from a primary discharge diagnosis, was used to identify major bleeding events in this study. The definition of major bleeding is not an exact match with the ROCKET AF trial.

**LIMITATIONS:** This is a retrospective study and there is no comparator arm in the trial. Differences in study design, patient populations, definition of safety outcomes, and data collection methods make it difficult to make comparisons with clinical trials.<sup>13</sup>

## RATES OF BLEEDING IN ROCKET AF (N=7111)\*<sup>17</sup>:

- ♦ The event rate per 100 patient-years was 3.6 (n=395) for major bleed and 0.20 (n=27) for fatal bleed<sup>†</sup>
  - 0.8% of patients experienced an ICH (n=55) and 3.1% of patients experienced a GI bleed (n=221)

AF = atrial fibrillation; GI = gastrointestinal; ICH = intracranial hemorrhage.

\*XARELTO® was evaluated versus dose-adjusted warfarin in more than 14,000 patients with nonvalvular AF at moderate to high risk for stroke in a rigorously designed, multicenter, randomized, double-blind, double-dummy, event-driven phase III trial. XARELTO® demonstrated effective reduction in the risk of stroke and non-CNS systemic embolism in patients with prior stroke or multiple comorbidities.<sup>17</sup>

<sup>†</sup>Major bleeding from ROCKET AF study was defined as clinically overt bleeding associated with a decrease in hemoglobin of  $\geq 2$  g/dL, transfusion of  $\geq 2$  units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.<sup>17</sup>

## SIX INDICATIONS STRONG

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). 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
- For the treatment of deep vein thrombosis (DVT)
- For the treatment of pulmonary embolism (PE)
- For the reduction in the risk of recurrence of DVT and of PE following initial 6 months treatment for DVT and/or PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee replacement surgery
- For the prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery

## IMPORTANT SAFETY INFORMATION (cont'd)

### CONTRAINDICATIONS

- ♦ Active pathological bleeding
- ♦ Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

### WARNINGS AND PRECAUTIONS

- ♦ **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including 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® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.



## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

- ♦ **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. 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.
  - Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y<sub>12</sub> platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
- ♦ **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. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next XARELTO® dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. 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), or 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.
- ♦ **Use in Patients With Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation of XARELTO® in patients who develop acute renal failure while on XARELTO®.
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.
- ♦ **Use in Patients With Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- ♦ **Use With P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with combined P-gp and strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Avoid concomitant use of XARELTO® with drugs that are P-gp and strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort).
- ♦ **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used 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 and is not readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- ♦ **Patients With Prosthetic Heart Valves:** The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.
- ♦ **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

### DRUG INTERACTIONS

- ♦ Avoid concomitant use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

Please see Important Safety Information throughout.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit [www.XareltoHCP.com/PI](http://www.XareltoHCP.com/PI).

## IMPORTANT SAFETY INFORMATION (cont'd)

### DRUG INTERACTIONS (cont'd)

- ♦ XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (eg, diltiazem, verapamil, dronedarone, and erythromycin) unless the potential benefit justifies the potential risk.

### USE IN SPECIFIC POPULATIONS

- ♦ **Pregnancy Category C:** XARELTO® should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus. There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing.
- ♦ **Labor and Delivery:** Safety and effectiveness of XARELTO® during labor and delivery have not been studied in clinical trials.

- ♦ **Nursing Mothers:** It is not known if rivaroxaban is excreted in human milk.
- ♦ **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- ♦ **Females of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

### OVERDOSAGE

- ♦ Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable.

### ADVERSE REACTIONS IN CLINICAL STUDIES

- ♦ The most common adverse reactions with XARELTO® were bleeding complications.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit [www.XareltoHCP.com/PI](http://www.XareltoHCP.com/PI).

**References:** 1. Data on file. Janssen Pharmaceuticals, Inc. Based on IMS Health, NPA Weekly, July 2016. 2. Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood*. 2014;124(6):955-962. 3. Beyer-Westendorf J, Lützner J, Donath L, et al. Efficacy and safety of thromboprophylaxis with low-molecular-weight heparin or rivaroxaban in hip and knee replacement surgery. Findings from the ORTHO-TEP registry. *Thromb Haemost*. 2013;109(1):154-163. 4. Ogawa S, Ikeda T, Kitazono T, et al; on behalf of the Rivaroxaban Postmarketing Surveillance Registry Investigators. Present profiles of novel anticoagulant use in Japanese patients with atrial fibrillation: insights from the rivaroxaban postmarketing surveillance registry. *J Stroke Cerebrovasc Dis*. 2014;23(10):2520-2526. 5. Laliberté F, Cloutier M, Nelson WW, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin*. 2014;30(7):1317-1325. 6. Turpie AGG, Haas S, Kreutz R, et al. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *Thromb Haemost*. 2014;111(1):94-102. 7. Abraham NS, Singh S, Alexander CG, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ*. 2015;350:h1857. 8. Chang H-Y, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ*. 2015;350:h1585. 9. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. *Am J Cardiol*. 2015;115(8):1095-1101. 10. Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace*. 2015;17(2):187-193. 11. Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol*. 2016;3(1):e12-21. 12. Camm AJ, Amarencu P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Euro Heart J*. 2016;37(14):1145-1153. 13. Tamayo S, Peacock WF, Patel M, et al. Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27,467 patients taking rivaroxaban. *Clin Cardiol*. 2015;38(2):63-68. 14. Coleman CI, Antz M, Ehken B, Evers T. REal-Life Evidence of stroke prevention in patients with atrial fibrillation — The RELIEF study. *Int J Cardiol*. 2016;203:882-884. 15. Kucher N, Aujesky D, Beer JH, et al. Rivaroxaban for the treatment of venous thromboembolism: the SWIIs Venous ThromboEmbolic Registry (SWIVTER). *Thromb Haemost*. 2016;116(3). [Published online ahead of print June 23, 2016]. DOI:10.1160/TH16-03-0209. 16. Coleman CI, Antz M, Bowrin K, et al. Real-world Evidence of Stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US Study. *Curr Med Res Opin*. 2016;15:1-23. 17. Patel MR, Mahaffey KW, Garg J, et al; and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

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Janssen Pharmaceuticals, Inc.



Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)

**XARELTO®** (rivaroxaban) tablets, for oral use

See package insert for full Prescribing Information

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

**A. Premature discontinuation of XARELTO increases the risk of thrombotic events**

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see *Dosage and Administration (2.3, 2.7) 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
- optimal timing between the administration of XARELTO and neuraxial procedures is not known

[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 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*].

**Treatment of Deep Vein Thrombosis:** XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

**Treatment of Pulmonary Embolism:** XARELTO is indicated for the treatment of pulmonary embolism (PE).

**Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism:** XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

**Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

**CONTRAINDICATIONS**

XARELTO is contraindicated in patients with:

- active pathological bleeding [see *Warnings and Precautions*]
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) [see *Adverse Reactions*]

**WARNINGS AND PRECAUTIONS**

**Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including 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 is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see *Dosage and Administration (2.3, 2.7) 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 and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

**XARELTO® (rivaroxaban) tablets**

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y<sub>12</sub> platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) [see *Drug Interactions*], selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.

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*].

**Reversal of Anticoagulant Effect:** 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. Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

**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*].

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban [see *Clinical Pharmacology (12.3) in full Prescribing Information*]. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO [see *Clinical Pharmacology (12.3) in full Prescribing Information*]. The next XARELTO dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO for 24 hours.

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.

**Use in Patients with Renal Impairment: Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly [see *Dosage and Administration (2.4) in full Prescribing Information*]. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO [see *Use in Specific Populations*].

**Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population [see *Use in Specific Populations*].

**Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment [see *Use in Specific Populations*].

**Use in Patients with Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased [see *Use in Specific Populations*].

**Use with P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan) [see *Drug Interactions*].

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) [see *Drug Interactions*].

**Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO should be used 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).

**Patients with Prosthetic Heart Valves:** The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

**Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

**ADVERSE REACTIONS**

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation [see *Boxed Warning and Warnings and Precautions*]
- Bleeding risk [see *Warnings and Precautions*]
- Spinal/epidural hematoma [see *Boxed Warning and Warnings and Precautions*]

**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, 16326 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); 4728 patients who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of PE; 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 trial.

**Table 1: Bleeding Events in ROCKET AF\*- On Treatment Plus 2 Days**

Parameter	XARELTO N=7111 n (%/year)	Warfarin N=7125 n (%/year)	XARELTO vs. Warfarin HR (95% CI)
Major Bleeding†	395 (3.6)	386 (3.5)	1.04 (0.90, 1.20)
Intracranial Hemorrhage (ICH)‡	55 (0.5)	84 (0.7)	0.67 (0.47, 0.93)
Hemorrhagic Stroke§	36 (0.3)	58 (0.5)	0.63 (0.42, 0.96)
Other ICH	19 (0.2)	26 (0.2)	0.74 (0.41, 1.34)
Gastrointestinal (GI)¶	221 (2.0)	140 (1.2)	1.61 (1.30, 1.99)
Fatal Bleeding#	27 (0.2)	55 (0.5)	0.50 (0.31, 0.79)
ICH	24 (0.2)	42 (0.4)	0.58 (0.35, 0.96)
Non-intracranial	3 (0.0)	13 (0.1)	0.23 (0.07, 0.82)

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

\* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

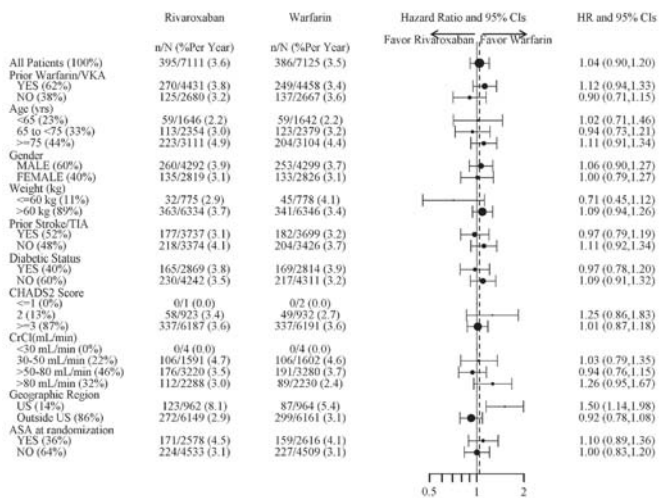
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

# Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

**Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days**



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

**Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of PE:** EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

**Table 2: Bleeding Events\* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies**

Parameter	XARELTO† N=4130 n (%)	Enoxaparin/ VKA† N=4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2 g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

\* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

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EINSTEIN Extension Study: In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.

**Table 3: Bleeding Events\* in EINSTEIN Extension Study**

Parameter	XARELTO <sup>†</sup> 20 mg N=598 n (%)	Placebo <sup>‡</sup> N=590 n (%)
Major bleeding event <sup>‡</sup>	4 (0.7)	0
Decrease in Hb ≥2 g/dL	4 (0.7)	0
Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.3)	0
Gastrointestinal	3 (0.5)	0
Menorrhagia	1 (0.2)	0
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)
Any bleeding	104 (17.4)	63 (10.7)

\* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

<sup>†</sup> Treatment schedule: XARELTO 20 mg once daily; matched placebo once daily

<sup>‡</sup> There were no fatal or critical organ bleeding events.

*Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:* In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

**Table 4: Bleeding Events\* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)**

	XARELTO 10 mg N=4487 n (%)	Enoxaparin <sup>†</sup> N=4524 n (%)
<b>Total treated patients</b>	<b>N=4487 n (%)</b>	<b>N=4524 n (%)</b>
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event <sup>‡</sup>	261 (5.8)	251 (5.6)
<b>Hip Surgery Studies</b>	<b>N=3281 n (%)</b>	<b>N=3298 n (%)</b>
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event <sup>‡</sup>	201 (6.1)	191 (5.8)
<b>Knee Surgery Study</b>	<b>N=1206 n (%)</b>	<b>N=1226 n (%)</b>
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event <sup>‡</sup>	60 (5.0)	60 (4.9)

\* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

<sup>†</sup> Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

<sup>‡</sup> Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN Extension study are shown in Table 5.

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**Table 5: Other Adverse Reactions\* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study**

System Organ Class Preferred Term	XARELTO N=598 n (%)	Placebo N=590 n (%)
<b>Gastrointestinal disorders</b>		
Abdominal pain upper	10 (1.7)	1 (0.2)
Dyspepsia	8 (1.3)	4 (0.7)
Toothache	6 (1.0)	0
<b>General disorders and administration site conditions</b>		
Fatigue	6 (1.0)	3 (0.5)
<b>Infections and infestations</b>		
Sinusitis	7 (1.2)	3 (0.5)
Urinary tract infection	7 (1.2)	3 (0.5)
<b>Musculoskeletal and connective tissue disorders</b>		
Back pain	22 (3.7)	7 (1.2)
Osteoarthritis	10 (1.7)	5 (0.8)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Oropharyngeal pain	6 (1.0)	2 (0.3)

\* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

**Table 6: Other Adverse Drug Reactions\* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies**

System/Organ Class Adverse Reaction	XARELTO 10 mg N=4487 n (%)	Enoxaparin <sup>†</sup> N=4524 n (%)
<b>Injury, poisoning and procedural complications</b>		
Wound secretion	125 (2.8)	89 (2.0)
<b>Musculoskeletal and connective tissue disorders</b>		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
<b>Nervous system disorders</b>		
Syncope	55 (1.2)	32 (0.7)
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

\* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication

<sup>†</sup> Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

*Other clinical trial experience:* In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

**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, thrombocytopenia

*Gastrointestinal disorders:* retroperitoneal hemorrhage

*Hepatobiliary disorders:* jaundice, cholestasis, hepatitis (including hepatocellular injury)

*Immune system disorders:* hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

*Nervous system disorders:* cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

*Skin and subcutaneous tissue disorders:* Stevens-Johnson syndrome

**DRUG INTERACTIONS**

**General Inhibition and Induction Properties:** 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, conducted in subjects with normal renal function, evaluating the concomitant use with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir), increases in rivaroxaban



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exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors [see *Warnings and Precautions*].

**Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems:** Results from drug interaction studies and population PK analyses from clinical studies indicate coadministration of XARELTO with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) [see *Warnings and Precautions*].

**Anticoagulants and NSAIDs/Aspirin:** Single doses of enoxaparin and XARELTO given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and XARELTO resulted in an additive effect on factor Xa (FXa) inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Coadministration of the platelet aggregation inhibitor clopidogrel and XARELTO resulted in an increase in bleeding time for some subjects [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs [see *Warnings and Precautions*].

**Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems:** Results from a pharmacokinetic trial with erythromycin indicated that patients with renal impairment coadministered XARELTO with drugs classified as combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) have increased exposure compared with patients with normal renal function and no inhibitor use. Significant increases in rivaroxaban exposure may increase bleeding risk.

While increases in rivaroxaban exposure can be expected under such conditions, results from an analysis in the ROCKET AF trial, which allowed concomitant use with combined P-gp and either weak (e.g., amiodarone) or moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, and erythromycin), did not show an increase in bleeding in patients with CrCl 30 to <50 mL/min [Hazard Ratio (95% CI): 1.05 (0.77, 1.42)] [see *Use in Specific Populations*].

XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) unless the potential benefit justifies the potential risk [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** Pregnancy Category C: There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus [see *Warnings and Precautions*].

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of  $\geq 10$  mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

**Labor and Delivery:** Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

**Nursing Mothers:** It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were

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>75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups [see *Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information*].

**Females of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

**Renal Impairment:** In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

**Nonvalvular Atrial Fibrillation:** In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in full Prescribing Information*].

**Patients with End-Stage Renal Disease on Dialysis:** Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study [see *Clinical Pharmacology (12.2, 12.3) in full Prescribing Information*]. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

**Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE:** In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

**Prophylaxis of DVT Following Hip or Knee Replacement Surgery:** The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

**Hepatic Impairment:** In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated [see *Clinical Pharmacology (12.3) in full Prescribing Information*].

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

### OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdose occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable [see *Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information*]. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products.

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# Cardiovascular disease: Innovations in devices and techniques:

## Supplement Editor

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# Cardiovascular disease: Innovations in devices and techniques

Innovations are dominating the early part of the 21st century and the impact on cardiovascular medicine has been especially remarkable. Keeping up and evaluating the relevance of these innovations and the role in patient care is a constant challenge and opportunity for providers and scientists alike.

This *Cleveland Clinic Journal of Medicine* supplement on cardiovascular disease presents healthcare providers with evidenced-based reviews of important innovations and a glimpse into their potential for an exciting future.

In this supplement, Amar Krishnaswamy, MD, and colleagues look to new frontiers in valve replacement therapies. The success of transcatheter aortic valve replacement has led to extending the technique to the mitral valve. While technical challenges exist with transcatheter mitral valve replacement, methods to overcome these challenges are feasible. The authors review the various valve devices currently under development and examine their potential implications in practice.

The introduction of stents in percutaneous coronary interventions has been one of the most revolutionary innovations in cardiovascular medicine, resulting in impressive outcomes during the past few decades. Despite the dramatic advancement, persistent rates of restenosis and thrombosis continue to cause substantial morbidity and mortality. Stephen Ellis, MD, and Haris Riaz, MD, discuss the evolution of stent design from bare-metal stents through drug-eluting stents and their impact on outcomes. The evolution continues with the development of bioresorbable polymers and stents without polymers. The authors consider the promise of these innovations, especially bioresorbable stents, to further reduce restenosis and stent thrombosis.

Erich Kiehl, MD, and Daniel Cantillon, MD,

present information about the latest innovation in cardiac pacing—leadless pacemakers. The first leadless pacemaker was approved earlier this year. In over 50 years of use of transvenous pacemakers, long-term complications have primarily involved the endovascular leads and surgical pocket. The authors discuss the promise of leadless cardiac pacing using catheter-based delivery of a self-contained device in the right ventricle to favorably reduce these complications, as well the current limitation of single-chamber pacing and possible future directions.

Innovations in monoclonal antibody therapy have resulted in a new class of biologic drugs to lower low-density-lipoprotein (LDL) in the blood—PCSK9 inhibitors. These new biologics target the overexpression of the PCSK9 protein in the liver, thereby increasing LDL receptors available to metabolize and remove LDL from the blood. Khendi White, MD, Chaitra Mohan, MD, and Michael Rocco, MD, discuss potential candidates for recently approved PCSK9 inhibitor therapy.

Ellen Brinza, MS, and Heather Gornik, MD, discuss new findings in our understanding of fibromuscular dysplasia (FMD). This uncommon nonatherosclerotic disease leads to narrowing, dissection, or aneurysm of medium-sized arteries. FMD is caused by abnormal development of the arterial cell wall and can cause symptoms if narrowing or a tear decreases blood flow through the artery. The authors discuss evaluation, management, and surveillance strategies as well as important lifestyle modifications and appropriate treatment of symptoms.

We hope this presentation of recent innovations in cardiovascular medicine is useful and informative to you and your clinical practice.



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# Transcatheter mitral valve replacement: A frontier in cardiac intervention

## ■ ABSTRACT

As transcatheter aortic valve replacement (TAVR) has become routine, device manufacturers and investigational cardiologists have set their sights on the mitral valve. Although transcatheter mitral valve replacement (TMVR) poses several technical challenges, they appear to be surmountable, and work is proceeding. Here we review the various devices being developed and preliminary results of trials in humans.

## ■ KEY POINTS

Most TMVR procedures are performed by either a retrograde transapical approach or an antegrade transseptal approach.

In the small number of patients who have undergone TMVR for native mitral valve regurgitation to date, mortality rates at 30 days have been high, reflecting the seriousness of illness in these patients.

At present, none of the new devices for TMVR in patients with native mitral valve regurgitation are approved for general use, although some of them are being tested in phase 1 clinical trials that are enrolling patients.

Valves made for TAVR have been used for TMVR in patients with degenerative mitral stenosis or failure of mitral bioprostheses; however, these are off-label uses of these devices.

In the last 10 years, we have seen a revolution in transcatheter therapies for structural heart disease. The most widely embraced, transcatheter aortic valve replacement (TAVR) was originally intended for patients in whom surgery was considered impossible, but it has now been established as an excellent alternative to surgical aortic valve replacement in patients at high or intermediate risk.<sup>1-3</sup> As TAVR has become established, with well-designed devices and acceptable safety and efficacy, it has inspired operators and inventors to push the envelope of innovation to transcatheter mitral valve replacement (TMVR).

This review summarizes the newest data available for the TMVR devices currently being tested in patients with native mitral regurgitation, bioprosthetic degeneration, and degenerative mitral stenosis.

## ■ THE MITRAL VALVE: THE NEW FRONTIER

Whereas the pathologic mechanisms of aortic stenosis generally all result in the same anatomic consequence (ie, calcification of the valve leaflets and commissures resulting in reduced mobility), mitral valve regurgitation is much more heterogeneous. Primary (degenerative) mitral regurgitation is caused by intrinsic valve pathology such as myxomatous degeneration, chordal detachment, fibroelastic deficiency, endocarditis, and other conditions that prevent the leaflets from coapting properly. In contrast, in secondary or functional mitral regurgitation, the leaflets are normal but do

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**TABLE 1**  
**Percutaneous mitral valve repair devices**

Type of repair	Device	Technique	Status
Edge-to-edge repair	MitraClip	V-shaped clip applied via femoral vein	FDA approval for patients with degenerative mitral regurgitation COAPT trial for patients with functional mitral regurgitation CE Mark approval for all mitral regurgitation
Indirect annuloplasty	Carillon	Nitinol wire placed in the coronary sinus via the internal jugular vein	US trial being planned CE Mark approval
Direct annuloplasty	Mitralign	Anchors placed in the posterior annulus via femoral artery	Feasibility trial published
	Valtech Cardioband	Anchors placed in the posterior annulus via the femoral vein	Feasibility trial published
Chordal repair	NeoChord	Transapical approach	CE Mark approval
Valve spacer	Mitra-Spacer	Balloon placed in the mitral valve to reduce regurgitant orifice and improve coaptation, transfemoral and transapical delivery	First-in-man completed <sup>9</sup> Technology licensed for possible tricuspid valve use
Chamber remodelling	Basal annuloplasty of the cardia externally (BACE)	Silicone band placed externally at the atrioventricular groove and inflated	First-in-man completed <sup>10</sup>

FDA = US Food and Drug Administration

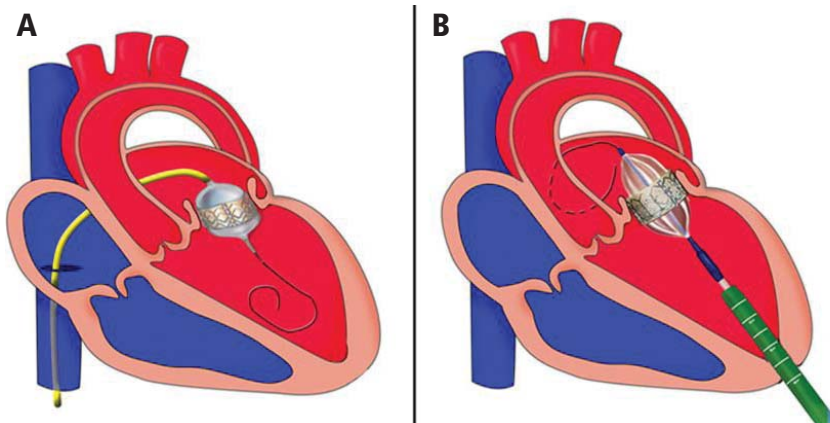
not coapt properly because of apical tethering to a dilated left ventricle, reduced closing forces with left ventricular dysfunction, or annular dilation as the result of either left ventricular or left atrial dilation.

Surgical mitral valve repair is safe and effective in patients with degenerative mitral regurgitation caused by leaflet prolapse and flail. However, some patients cannot undergo surgery because they have comorbid conditions that place them at extreme risk.<sup>4</sup> For example, most patients with functional mitral regurgitation due to ischemic or dilated cardiomyopathy have significant surgical risk and multiple comorbidities, and in this group surgical repair has limited efficacy.<sup>5</sup> A sizeable proportion of patients with mitral regurgitation may not be offered surgery because their risk is too high.<sup>6</sup> Therefore, alternatives to the current surgical treatments have the potential to benefit a large number of patients.

Similarly, many patients with degenerative mitral stenosis caused by calcification of the mitral annulus also cannot undergo cardiac surgery because of prohibitively high risk. While rheumatic disease is the most common cause of mitral stenosis worldwide,

degenerative mitral stenosis may be the cause in up to one-fourth of patients overall and up to 60% of patients older than 80 years.<sup>7</sup> In the latter group, not only do old age and comorbidities such as diabetes mellitus and chronic kidney disease pose surgical risks, the technical challenge of surgically implanting a prosthetic mitral valve in the setting of a calcified annulus may be significant.<sup>8</sup>

The mitral valve is, therefore, the perfect new frontier for percutaneous valve replacement therapies, and TMVR is emerging as a potential option for patients with mitral regurgitation and degenerative mitral stenosis. The currently available percutaneous treatment options for mitral regurgitation include edge-to-edge leaflet repair, direct and indirect annuloplasty, spacers, and left ventricular remodeling devices (Table 1).<sup>9,10</sup> As surgical mitral valve repair is strongly preferred over mitral valve replacement, the percutaneous procedures and the devices that are used are engineered to approximate the current standard surgical techniques. However, given the complex pathologies involved, surgical repair often requires the use of multiple repair techniques in the



**FIGURE 1.** Routes of transcatheter mitral valve replacement: (A) transseptal antegrade via the femoral vein; (B) transapical retrograde via direct left ventricular access.

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same patient. Therefore, percutaneous repair may also require more than one type of device in the same patient and may not be anatomically feasible in many patients. Replacing the entire valve may obviate some of these challenges.

Compared with the aortic valve, the mitral valve poses a greater challenge to percutaneous treatment due to its structure and dynamic relationship with the left ventricle. Some specific challenges facing the development of TMVR are that the mitral valve is large, it is difficult to access, it is asymmetrical, it lacks an anatomically well-defined annulus to which to anchor the replacement valve, its geometry changes throughout the cardiac cycle, and placing a replacement valve in it entails the risk of left ventricular outflow tract obstruction. Despite these challenges, a number of devices are undergoing preclinical testing, a few are in phase 1 clinical trials, and registries are being kept. Depending on the specific device, an antegrade transseptal approach to the mitral valve (via the femoral vein) or a retrograde transapical approach (via direct left ventricular access) may be used (Figure 1).

### ■ NATIVE MITRAL VALVE REGURGITATION

For degenerative mitral regurgitation, the standard of care is cardiac surgery at a hospital experienced with mitral valve repair, and with very low rates of mortality and morbidity. For patients in whom the surgical risk is prohibitive, percutaneous edge-to-edge leaflet repair using the MitraClip (Abbott Vascular, Minneapolis, MN) is the best option if the anatomy permits. If the mitral valve pathology is not amenable to MitraClip repair, the patient may be evaluated for TMVR under a clinical trial protocol.

For functional mitral regurgitation, the decisions are more complex. If the patient has chronic atrial fibrillation, electrical cardioversion and antiarrhythmic drug therapy may restore and maintain sinus rhythm, though if the left atrium is large, sinus rhythm may not be possible. If the patient has left ventricular dysfunction, guideline-directed medical therapy should be optimized; this reduces the risk of exacerbations, hospitalizations, and death and may also reduce the degree of regurgitation. If the patient has severe left ventricular dysfunction and a wide QRS duration, cardiac resynchronization

therapy (biventricular pacing) may also be beneficial and reduce functional mitral regurgitation. If symptoms and severe functional mitral regurgitation persist despite these measures and the patient's surgical risk is deemed to be extreme, options include MitraClip placement as part of the randomized Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy (COAPT) trial, which compares guideline-directed medical therapy with guideline-directed therapy plus MitraClip. Another option is enrollment in a clinical trial or registry of TMVR.

At this writing, six TMVR devices have been implanted in humans:

- Fortis (Edwards Lifesciences, Irvine, CA)
- Tendyne (Tendyne Holding Inc, Roseville, MN)
- NaviGate (NaviGate Cardiac Structures, Inc, Lake Forest, CA)
- Intrepid (Medtronic, Minneapolis, MN)
- CardiAQ (Edwards Lifesciences, Irvine, CA)
- Tiara (Neovasc Inc, Richmond, BC).

Most of the early experience with these valves has not yet been published, but some data have been presented at national and international meetings.

#### The Fortis valve

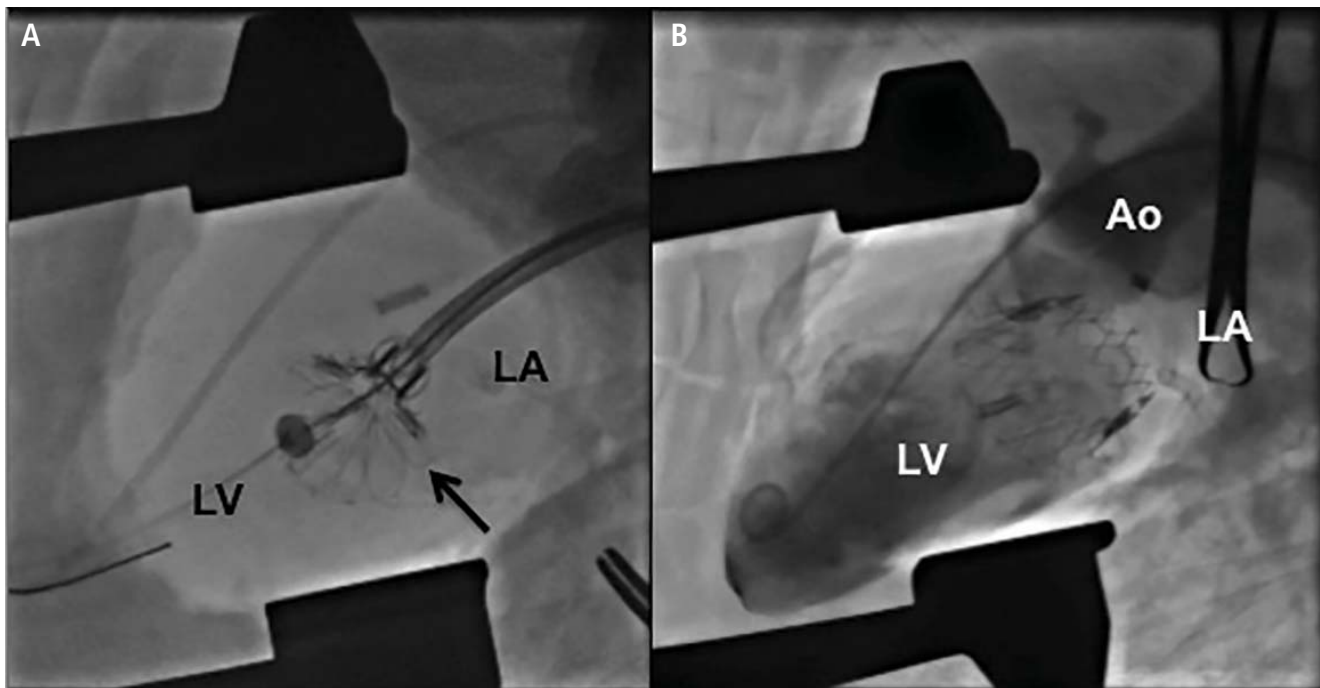
The Fortis valve consists of a self-expanding nitinol frame and leaflets made of bovine pericardium and is implanted via a transapical approach.

The device was successfully implanted in three patients in Quebec City, Canada, and at 6 months, all had improved signifi-



**Fortis valve**  
Courtesy of Edwards Lifesciences.





**FIGURE 2.** Transatrial implantation of the NaviGate transcatheter mitral valve replacement prosthesis. (A) Initial unsheathing of the valve (arrow) via the left atrium (LA); (B) no residual mitral regurgitation on left ventriculography (LV). Ao = ascending aorta

cantly in functional class and none had needed to be hospitalized.<sup>11</sup> Echocardiographic assessment demonstrated trace or less mitral regurgitation and a mean transvalvular gradient less than 4 mm Hg in all.

Bapat and colleagues<sup>12</sup> attempted to implant the device in 13 patients in Europe and Canada. The average left ventricular ejection fraction was 34%, and 12 of 13 patients (92%) had functional mitral regurgitation. Procedural success was achieved in 10 patients, but five patients died within 30 days. While the deaths were due to nonvalvular issues (multiorgan failure, septic shock, intestinal ischemia after failed valve implantation and conversion to open surgery, malnutrition leading to respiratory failure, and valve thrombosis), the trial is currently on hold as more data are collected and reviewed. Among the eight patients who survived the first month, all were still alive at 6 months, and echocardiography demonstrated no or trivial mitral regurgitation in six patients (80%) and mild regurgitation in two patients (20%); the average mitral gradient was 4 mm Hg, and there was no change in mean left ventricular ejection fraction.

### The Tendyne valve

The Tendyne valve is a self-expanding prosthesis with porcine pericardial leaflets. It is delivered transapically and is held in place by a tether from the valve to the left ventricular apex.

In the first 12 patients enrolled in an early feasibility trial,<sup>13</sup> the average left ventricular ejection fraction was 40%, and 11 of the 12 patients had functional mitral regurgitation. The device was successfully implanted in 11 patients, while one patient developed left ventricular out-flow tract obstruction and the device was uneventfully removed. All patients were still alive at 30 days, and the 11 patients who still had a prosthetic valve did not have any residual mitral regurgitation.

As of this writing, almost 80 patients have received the device, though the data have not yet been presented. Patients are being enrolled in phase 1 trials.

### The NaviGate valve

The NaviGate valve consists of a trileaflet subassembly fabricated from bovine pericardium, mounted on a self-expanding nitinol stent, and is only implanted transatrially.



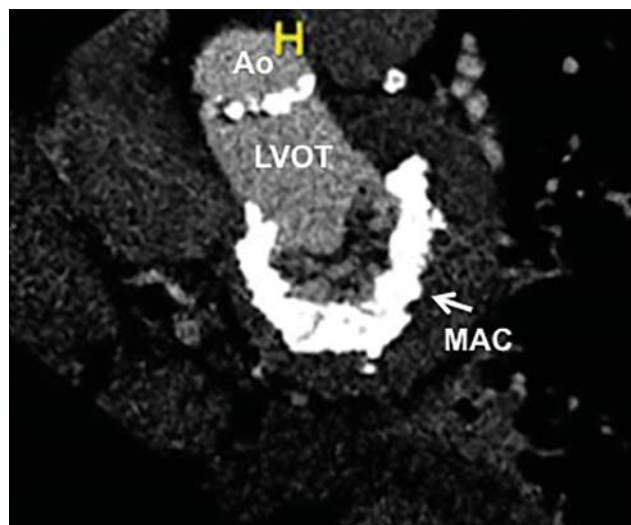
**Tendyne valve**

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**NaviGate valve**

Courtesy of Jose Navia.



**FIGURE 3.** Mitral annular calcification (MAC) provides a “frame” for transcatheter mitral valve replacement prosthesis implantation in the mitral position for degenerative mitral stenosis. Ao = aorta; LVOT = left ventricular outflow tract

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NaviGate valves were successfully implanted in two patients via a transatrial approach (Figure 2). Both patients had excellent valve performance without residual mitral regurgitation or left ventricular outflow tract obstruction. The first patient showed significant improvement in functional class and freedom from hospitalization at 6 months, but the second patient died within a week of the implant due to advanced heart failure.<sup>14</sup> A US clinical trial is expected soon.

### The Intrepid valve



**Intrepid valve**  
Courtesy of Medtronic.

The Intrepid valve consists of an outer stent to provide fixation to the annulus and an inner stent that houses a bovine pericardial valve. The device is a self-expanding system that is delivered transapically.

In a series of 15 patients, 11 had functional mitral regurgitation (with an average left ventricular ejection fraction of 35%) and four had degenerative mitral regurgitation (with an average left ventricular ejection fraction of 57%).<sup>15</sup> The device was successfully implanted in 14 patients, after which the average mitral valve gradient was 4 mm Hg. All patients but one were left with no regurgitation (the other patient had 1+ regurgitation).

A trial is currently under way in Europe.

### The CardiAQ valve

The CardiAQ is constructed of bovine pericardium and can be delivered by the transseptal or transapical route.

Of 12 patients treated under compassionate use,<sup>16</sup> two-thirds (eight patients) had functional mitral regurgitation. Two patients died during the procedure, three died of noncardiac complications within 30 days, and one more died of sepsis shortly after 30 days. This early experience demonstrates the importance of careful patient selection and postprocedural management in the feasibility assessment of these new technologies.

Patients are being enrolled in phase 1 trials.



**CardiAQ valve**  
Courtesy of Edwards Lifesciences.

### The Tiara valve

The Tiara valve, a self-expanding prosthesis with bovine pericardial leaflets, is delivered by the transapical route.

Eleven patients underwent Tiara implantation as part of either a Canadian special access registry or an international feasibility trial. Their average Society of Thoracic Surgeons score (ie, their calculated risk of major morbidity or operative mortality) was 15.6%, and their average left ventricular ejection fraction was 29%. Only two patients had degenerative mitral regurgitation. Nine patients had uneventful procedures and demonstrated no residual mitral regurgitation and no left ventricular outflow tract obstruction. The procedure was converted to open surgery in two patients owing to valve malpositioning, and both of them died within 30 days. One patient in whom the procedure was successful suffered erosion of the septum and died on day 4.<sup>17</sup>

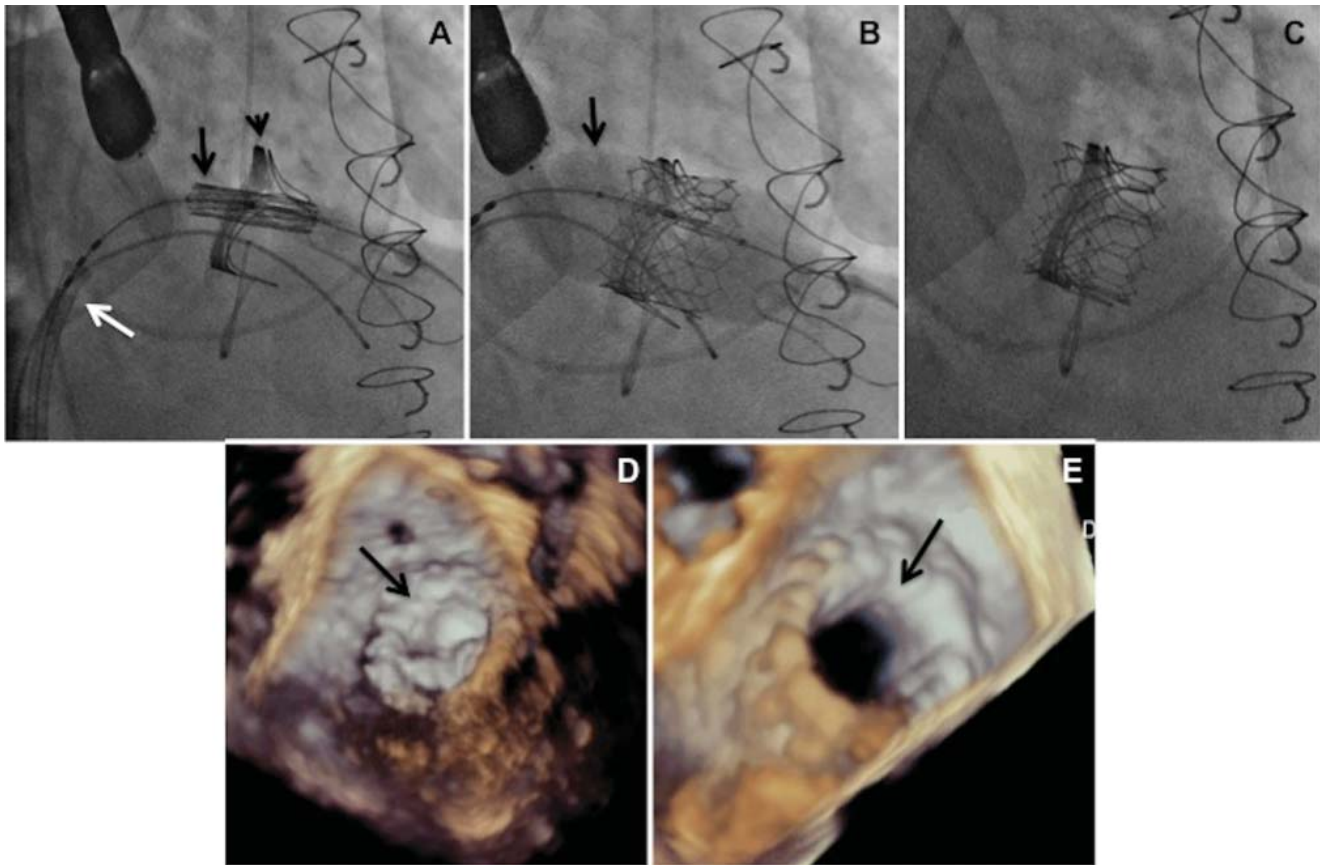
Patients are being enrolled in phase 1 trials.



**Tiara valve**  
Reprinted from *EuroIntervention* (Cheung A, et al. Transcatheter mitral valve implantation with Tiara bioprosthesis. *EuroIntervention* 2014; 10:U115-U119.) © 2014 with permission from Europa Digital & Publishing.

## DEGENERATIVE MITRAL STENOSIS

In patients with degenerative mitral stenosis, extensive mitral annular calcification may provide an adequate “frame” to hold a transcatheter valve prosthesis (Figure 3). Exploiting this feature, numerous investigators have successfully deployed prosthetic valves designed for TAVR in the calcified mitral annulus via the retrograde transapical and antegrade transseptal routes.



**FIGURE 4.** Transfemoral mitral valve-in-valve placement of a balloon-expandable valve. (A) Catheter via femoral vein (white arrow) and crossing the interatrial septum with unexpanded valve in place (black arrow) within the mitral prosthesis (arrowhead); (B) balloon inflation of the TAVR prosthesis (black arrow); (C) fully expanded valve in place; (D) 3D transesophageal echocardiographic view from the left atrium of the stenosed mitral valve (arrow); (E) mitral valve open (arrow) after valve-in-valve placement.

Guerrero and colleagues presented results from the first global registry of TMVR in mitral annular calcification at the 2016 EuroPCR Congress.<sup>18</sup> Of 104 patients analyzed, almost all received an Edwards' Sapien balloon-expandable valve (first-generation, Sapien XT, or Sapien 3); the others received Boston Scientific's Lotus or Direct Flow Medical (Direct Flow Medical, Santa Clara, CA) valves. With an average age of 73 years and a high prevalence of comorbidities such as diabetes, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease, and prior cardiac surgery, the group presented extreme surgical risk, with an average Society of Thoracic Surgeons risk score of 14.4%. Slightly more than 40% of the patients underwent transapical implantation, slightly less than 40% underwent transfemoral or transeptal implantation, and just under 20% had a direct atrial approach.

The implantation was technically successful in 78 of 104 patients (75%); 13 patients (12.5%) required

a second mitral valve to be placed, 11 patients (10.5%) had left ventricular outflow tract obstruction, four patients (4%) had valve embolization, and two patients (2%) had left ventricular perforation. At 30 days, 11 of 104 patients (10.6%) had died of cardiac causes and 15 patients (14.4%) had died of noncardiac causes. When divided roughly into three equal groups by chronological order, the last third of patients, compared with the first third of patients, enjoyed greater technical success (80%,  $n = 32/40$  vs 62.5%,  $n = 20/32$ ), better 30-day survival (85%,  $n = 34/40$  vs 62.5%,  $n = 20/32$ ), and no conversion to open surgery (0 vs 12.5%,  $n = 4/32$ ), likely demonstrating both improved patient selection and lessons learned from shared experience. At 1 year, almost 90% of patients had New York Heart Association class I or II symptoms. Prior to the procedure, 91.5% had New York Heart Association class III or IV symptoms.

At present, TMVR in mitral annular calcification is not approved in the United States or elsewhere.



However, multiple registries are currently enrolling patients or are in formative stages to push the frontier of the currently available technologies until better, dedicated devices are available for this group of patients.

### ■ BIOPROSTHETIC VALVE OR VALVE RING FAILURE

Implantation of a TAVR prosthetic inside a degenerated bioprosthetic mitral valve (valve-in-valve) and mitral valve ring (valve-in-ring) is generally limited to case series with short-term results using the Edwards Sapien series, Boston Scientific Lotus, Medtronic Melody (Medtronic, Minneapolis, MN), and Direct Flow Medical valves (Figure 4).<sup>19–23</sup>

The largest collective experience was presented in the Valve-in-Valve International Data (VIVID) registry, which included 349 patients who had mitral valve-in-valve placement and 88 patients who had mitral valve-in-ring procedures. Their average age was 74 and the mean Society of Thoracic Surgeons score was 12.9% in both groups.<sup>24</sup> Of the 437 patients, 345 patients (78.9%) underwent transapical implantation, and 391 patients (89.5%) received a Sapien XT or Sapien 3 valve. In the valve-in-valve group, 41% of the patients had regurgitation, 25% had stenosis, and 34% had both. In the valve-in-ring group, 60% of the patients had regurgitation, 17% had stenosis, and 23% had both.

Valve placement was successful in most patients. The rate of stroke was low (2.9% with valve-in-valve placement, 1.1% with valve-in-ring placement), though the rate of moderate or greater residual mitral regurgitation was significantly higher in patients undergoing valve-in-ring procedures (14.8% vs 2.6%,  $P < .001$ ), as was the rate of left ventricular outflow tract obstruction (8% vs 2.6%,  $P = .03$ ). There was also a trend toward worse 30-day mortality in the valve-in-ring group (11.4% vs 7.7%,  $P = .15$ ). As with aortic valve-in-valve procedures, small surgical mitral valves ( $\leq 25$  mm) were associated with higher postprocedural gradients.

Eleid and colleagues<sup>25</sup> published their experience with antegrade transseptal TMVR in 48 patients with an average Society of Thoracic Surgeons score of 13.2%, 33 of whom underwent valve-in-valve procedures and nine of whom underwent valve-in-ring procedures. (The other six patients underwent mitral valve implantation for severe mitral annular calcification.) In the valve-in-valve group, 31 patients successfully underwent implant procedures, but two patients died during the procedure from left ventricular perforation. Of the nine valve-in-ring patients,

two had acute embolization of the valve and were converted to open surgery. Among the seven patients in whom implantation was successful, two developed significant left ventricular outflow tract obstruction; one was treated with surgical resection of the anterior mitral valve leaflet and the other was medically managed.

### ■ CONCLUSION

Transcatheter mitral valve replacement in regurgitant mitral valves, failing mitral valve bioprosthetics and rings, and calcified mitral annuli has been effectively conducted in a number of patients who had no surgical options due to prohibitive surgical risk. International registries and our experience have demonstrated that the valve-in-valve procedure using a TAVR prosthesis carries the greatest likelihood of success, given the rigid frame of the surgical bioprosthetic that allows stable valve deployment. While approved in Europe for this indication, use of these devices for this application in the United States is considered “off label” and is performed only in clinically extenuating circumstances. Implantation of TAVR prosthetics in patients with prior mitral ring repair or for native mitral stenosis also has been performed successfully, although left ventricular outflow tract obstruction is a significant risk in this early experience.

Devices designed specifically for TMVR are in their clinical infancy and have been implanted successfully in only small numbers of patients, most of whom had functional mitral regurgitation. Despite reasonable technical success, most of these trials have been plagued by high mortality rates at 30 days in large part due to the extreme risk of the patients in whom these procedures have been conducted. At present, enrollment in TMVR trials for patients with degenerative or functional mitral regurgitation is limited to those without a surgical option and who conform to very specific anatomic criteria.

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# Bioresorbable stents: The future of interventional cardiology?

## ABSTRACT

The introduction of stents has drastically reduced target-lesion restenosis rates associated with percutaneous coronary angioplasty. Bare-metal stents were the first introduced, followed by drug-eluting stents, both of which had significant impacts on the complication rates. Stents, however, have resulted in the emergence of stent thrombosis and stent restenosis, which can cause life-threatening cardiac complications. Three new technological approaches are being investigated to overcome these complications: stents coated with bioresorbable polymers, stents without polymers, and completely bioresorbable stents. Initial results are encouraging, but more data are needed to ascertain their implications for clinical practice.

## KEY POINTS

Stents have dramatically improved outcomes associated with percutaneous coronary angioplasty.

Bare-metal stents were the first stents developed, followed by first- and second-generation drug-eluting stents, which have progressively reduced complication rates.

Despite the improvements with conventional stents, persistent rates of restenosis and stent thrombosis remain, which can lead to increased coronary morbidity and mortality.

New stent technologies include stents coated with bioresorbable polymers, stents without polymers, and completely bioresorbable stents.

Interventional cardiology has made great strides in the last few decades. Percutaneous coronary intervention (PCI) is among the most commonly performed medical procedures globally.<sup>1</sup> At the time of inception, PCI was plagued by high complication rates—balloon catheters had a 50% target-lesion restenosis rate at 6 months and required emergency bypass surgery in up to 6% patients.<sup>2</sup> With passage of time, the complication rate of PCI has markedly decreased.

The introduction of stents had a dramatic impact on lowering the complication rates. Initially, the bare-metal stents (BMS) reduced the stent restenosis rate to 10% to 15%. Drug-eluting stents (DES) have further revolutionized the field (Figure 1), significantly lowering rates of stent thrombosis (less than 0.5% in 1 year) and risk of restenosis (less than 5% in 1 year).<sup>3-6</sup> The second-generation DES widely used in contemporary practice have made even more reductions owing to their improved designs and metallic and polymer composition; and concurrent advancements in the medical management, including use of antithrombotic and antiproliferative drugs, have further contributed to improved rates.

What, then, is to be hoped for? Unfortunately, with the advent of stents, complications such as stent thrombosis and stent restenosis also emerged. These complications can be life-threatening in the form of post-procedural or late myocardial infarction and cardiac death. Thus, although the US Food and Drug Administration (FDA) assesses target-lesion failure (defined as a composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target vessel revascularization) at 1 year, patients can have complications for the remainder of their lives. Despite the advancements attained by the second-generation DES over their predecessors, the issue of stent thrombosis and restenosis continues to plague second-generation DES with a 2% to 2.5% increased rate of target-lesion failure each year, seemingly forever (Figure 2).<sup>7,8</sup>

This article will briefly discuss the stent design and pathophysiology driving stent thrombosis and restenosis along with potential strategies to mitigate

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the problem. It pays special emphasis to bioresorbable stents, given their increasing interest among interventional cardiologists and patients, and given their potential to transform the practice of PCI.

### STENT DESIGN

Contemporary DES essentially consist of three components:

- A metallic alloy with a mesh-like design serves as the platform for the stent.
- This framework is coated with a multi-layered polymer that holds and releases the active drug in a controlled manner so that its effects can be extended.
- An antiproliferative drug (absent in the bioresorbable stents) that inhibits the smooth muscle proliferation and neointimal hyperplastic response: sirolimus or paclitaxel in first-generation DES; everolimus or zotarolimus in second-generation DES (Figure 3).

### WHAT CAUSES STENT THROMBOSIS AND RESTENOSIS?

Several theories and pathophysiological mechanisms have been proposed to explain these late adverse events (Table 1). However, our overall understanding of the cause remains modest at best. The major factor seems to be persistent presence of polymer on the stent and the ensuing inflammation. The second issue appears to be related to neoatherosclerosis that is generally defined as lipid or calcified neointima. Neoatherosclerosis is especially problematic for the second-generation DES. Neoatherosclerosis eventually predisposes to the development of thin cap fibroadenoma, and the rupture of thin cap leads to stent thrombosis and restenosis.

Autopsy studies suggest that approximately 50% of first- and second-generation DES start developing neoatherosclerosis within 1 to 3 years of implantation.<sup>9</sup> Turbulence created by thick strutted stents or incomplete impaction of stents to the vessel

wall predisposes the stents to platelet aggregation and fibrinogen deposition, thereby increasing the risk of neoatherosclerosis. Despite these pathologic insights, no treatment strategy has been shown to attenuate the problem, with the exception of high-dose statins.

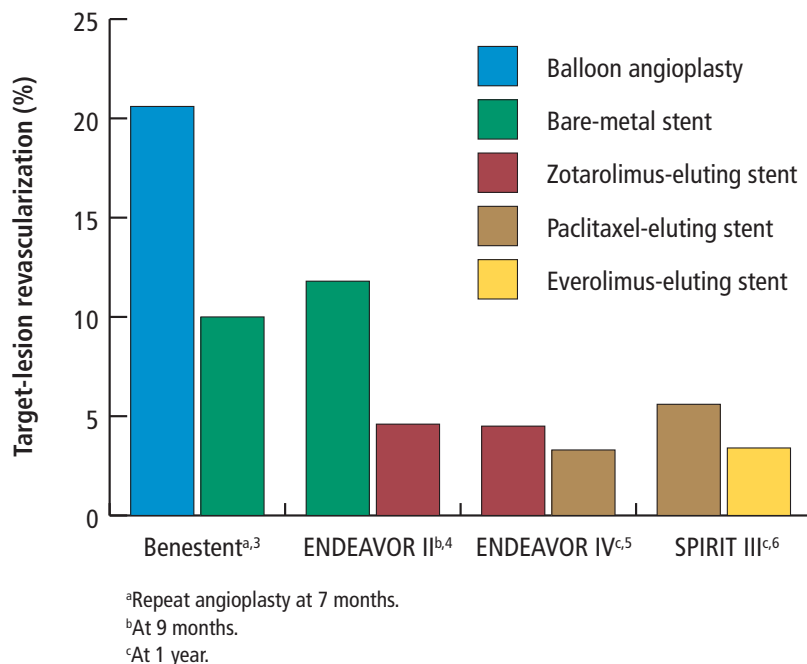


FIGURE 1. Reduction of restenosis rates by stent type.

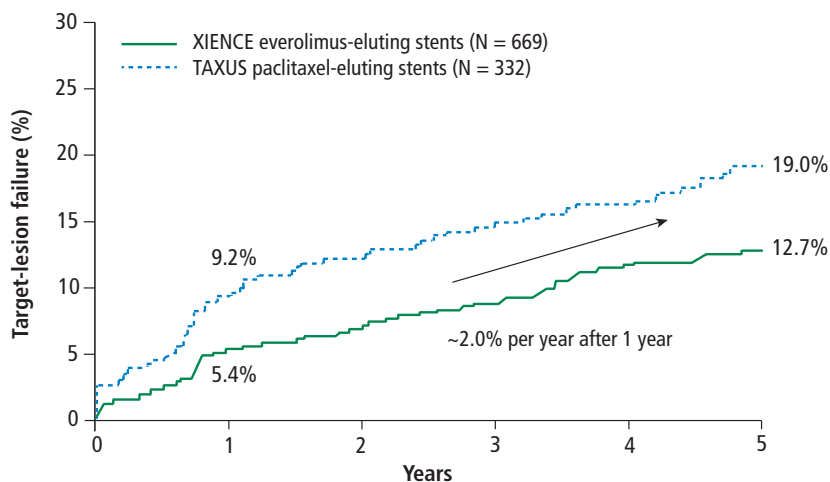
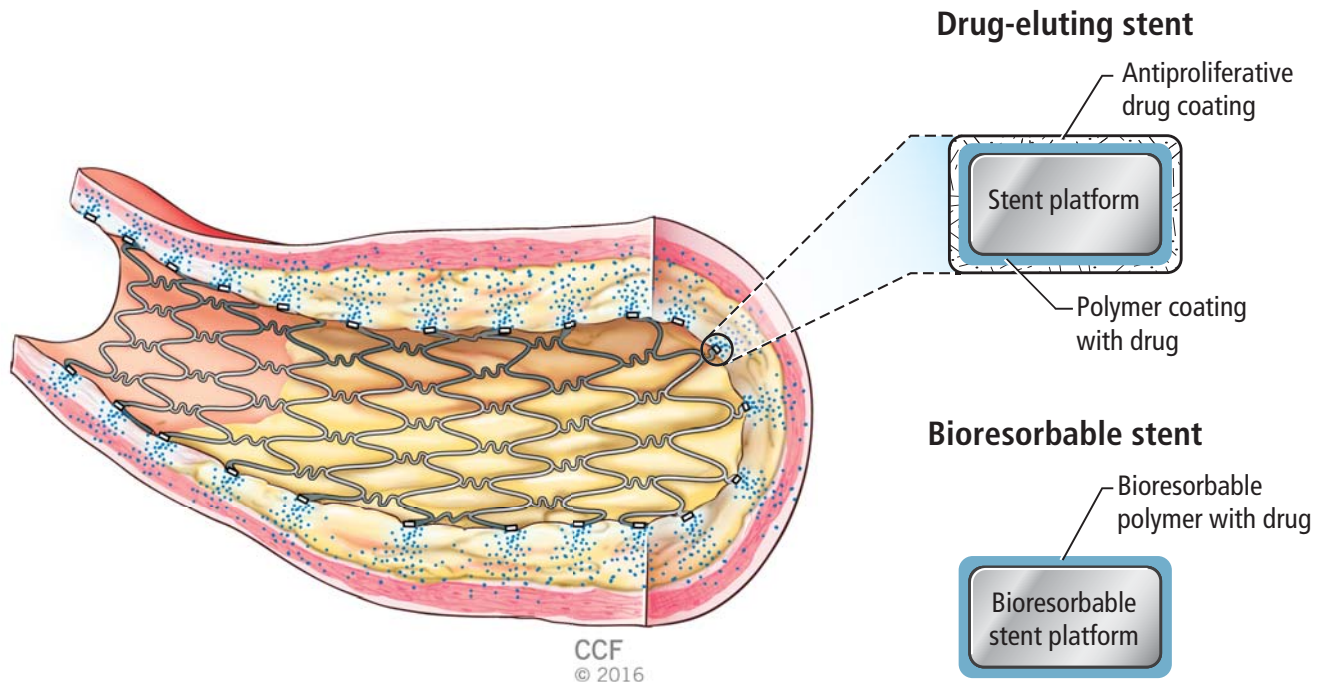


FIGURE 2. Second- vs first-generation drug-eluting stents.

Reprinted from *JACC: Cardiovascular Interventions* (Gada H, et al. 5-Year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC: Cardiovasc Interv* 2013; 6:1263–1266) with permission from Elsevier. © The American College of Cardiology Foundation. <http://www.sciencedirect.com/science/journal/19368798>



**FIGURE 3.** Components of drug-eluting and bioresorbable stents.

**■ CAN WE SOLVE THE PROBLEM?**

Three technological approaches have been proposed to overcome stent thrombosis and restenosis:

- Stents coated with bioresorbable polymers that quickly degrade
- Stents without polymers
- Stents that are completely resorbed.

**■ STENTS WITH BIORESORBABLE POLYMERS**

As described above, the presence of a polymer on the stent predisposes it to inflammation. Therefore, it would be logical to hypothesize that a bioresorbable polymer would reduce the inflammation. This approach is typified by the second-generation paclitaxel-eluting stent (Synergy, Boston Scientific). It has a biodegradable coating that resorbs within 4 months and releases everolimus in a dose intensity similar to that seen with the contemporary second-generation DES.

The largest trial of this device to date, the Evolve II study, randomly assigned 1,684 patients to the bio-stable-polymer, everolimus-eluting chromium stent (Promus, Boston Scientific) or the paclitaxel-eluting stent (Synergy, Boston Scientific).<sup>10</sup> Two-year follow-up data suggest that the rate of target-lesion failure was 9.4% in the paclitaxel-eluting stent patients vs 8.5% in the everolimus-eluting stent patients.

Notably, no definite stent thrombosis was seen in the Synergy-treated patients 24 hours after the initial device implantation.

**■ STENTS WITHOUT POLYMERS**

If polymers predispose to inflammation, stents without polymers should mitigate the risk. Such stent types are exemplified by the BioFreedom (Biosensors International) stainless steel stent, a polymer-free urolium (also known as biolimus A9)-eluting stent. These stents have a microstructured surface that holds the drug without a polymer and releases the active drug over a few months.

The LEADERS FREE clinical trial studied this stent in 2,466 patients at high risk of bleeding.<sup>11</sup> The patients were randomized to receive either a BMS or the polymer-free stent. All patients were required to receive dual antiplatelet therapy for only 1 month. At 1 year, the composite risk of cardiac death, myocardial infarction, and stent thrombosis was 9.4% in patients with BioFreedom stents vs 12.9% in BMS patients. Of note, the primary end point did not include stent restenosis, thereby not disadvantaging the BMS.

Medtronic’s polymer-free, sirolimus-eluting stent is currently under investigation in the RevElution clinical trial.<sup>12</sup> It has a cylindrical structure with the

core replaced by the active drug sirolimus. Abluminal holes in the stent allow controlled release of the drug. A pharmacokinetic analysis show that 90% of the medication is released within the first 90 days and that tissue concentrations are maintained in the therapeutic range until at least that time.<sup>13</sup> This actually exceeds that of the second-generation everolimus-eluting DES.

### ■ BIORESORBABLE STENTS

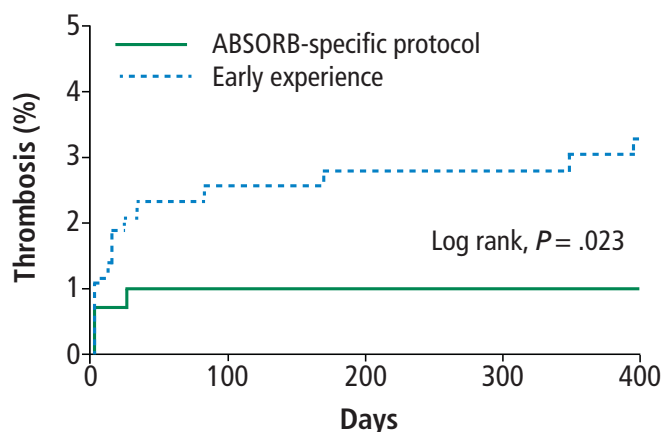
Bioresorbable scaffolds or stents disappear entirely over time and have drawn considerable attention in the interventional cardiology community. The FDA recently approved Abbott's Poly-L-Lactic Acid (PLLA) everolimus-eluting stent (Absorb). The rate of bioresorption of this device can be controlled by modulating the respective contribution of amorphous and crystalline PLLA backbone. The advantage of bioresorbable stents appears to stem from the fact that with bioresorbable devices, the vessel may actually expand and the purported nidus for inflammation goes away. This has been demonstrated by serial intravascular ultrasound-based studies.<sup>14</sup>

The return of pulsatility also appears to modulate the transition of smooth muscles from proliferative back to their contractile phenotype. This has been hypothesized to reduce the risk of neoatherosclerosis and, consequently, stent restenosis. The limitation of this device is the large strut size (157 micron for Absorb vs 81 microns for Xience). Dissolving metallic scaffolds also tend to have thicker struts than the current DES (120 vs approximately 80 microns).

The Absorb III trial was a pivotal noninferiority US trial that led to the device approval.<sup>15</sup> In this trial, 2,008 patients were randomized to receive the Absorb bioresorbable, everolimus-eluting stent or the DES Xience. The primary study end point was target-lesion failure at 1 year. As is often the case with US landmark studies, patient and lesion complexities were limited. Patients with acute

**TABLE 1**  
Construction of first- and second-generation drug-eluting stents (DES) and proposed pathophysiological mechanism of late adverse events

	Construction	Mechanism
First-generation DES	Thick struts Uneven polymer distribution with poor integrity and thick coating of durable polymers High drug dose	Uncovered struts Hypersensitivity Malapposition from fibrin deposition Stent fracture Neoatherosclerosis (especially for second-generation DES)
Second-generation DES	Thinner struts More biocompatible polymer (durable) Reduced drug dose	



Patients (N)					
Early experience	369	369	369	369	369
ABSORB-specific	292	292	281	217	155

**FIGURE 4.** ABSORB learnings: MICAT. Pre-dilation with noncompliant balloon sized 1:1 to normal vessel with complete balloon expansion; post-dilation at 14–16 atmospheres.

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coronary syndrome, elevated cardiac enzymes, high-risk anatomic lesions such as bifurcation lesions, and chronic total occlusion were excluded. Patients with diabetes comprised less than one-third of the patients, and lesions were relatively short at 13 ± 6 mm.

Device success per lesion was lower with Absorb than with Xience (94.3% vs 99.3%;  $P < .0001$ ). This

**TABLE 2**  
**Key elements of technique with the Absorb scaffold**

Properly choose the lesion

- Definitely  $\geq 2.5$ – $3.75$  mm in diameter (if in doubt, check intravascular ultrasound or optical coherence tomography)
- No excessive tortuosity or calcium proximal

Prepare the lesion by 1:1 predilation and confirm  $< 40\%$  diameter residual stenosis

Post-dilate with 1:1 noncompliant balloon at  $\geq 14$  atmospheres

Pay attention to expansion limits

- Oversizing the scaffold by a balloon  $> 0.5$  mm the scaffold diameter risks strut fracture

Prescribe dual antiplatelet therapy

is likely due to the larger strut size. Absorb III did meet the prespecified primary end point for noninferiority ( $P = .007$ ), although the rate of adverse events was somewhat higher (7.8% vs 6.1%). A subgroup analysis reveals that 19% of all lesions were smaller than what was originally intended, and in these patients, the Absorb device performed poorly with a 4.6% risk of device thrombosis. When limited to patients with the intended reference vessel sizes, the results of target-lesion failure and stent thrombosis were similar (6.6% vs 5.5% and 0.8% vs 0.5%, respectively).<sup>15</sup>

The implantation technique also seems to have influenced the results, with increased use of post-dilation as the study evolved. Recent observations from the MICAT group have shown that the use of high pressure post-dilation and other procedural advancements may considerably reduce adverse outcomes associated with Absorb (**Figure 4**).<sup>16</sup> Thus, while the pooled analysis in the form of a meta-analysis has suggested an increased risk of device thrombosis,<sup>17</sup> the difference is attenuated by selecting lesions of appropriate size, high-pressure post-dilation, and procedural advancements (**Table 2**).

**CONCLUSION AND THE WAY FORWARD**

Current first-generation bioresorbable stents can achieve results similar to those of second-generation DES, provided that they are used in patients with noncomplicated coronary lesions and the implant techniques are optimized. We do not know the outcomes of bioresorbable stents in patients with complex lesions. Current experience suggests that other changes in technique would be needed. For example,

minimizing scaffold overlap in long and bifurcating lesions. Whether that would translate into diminishing the rate of late adverse events remains to be determined. As of now, we only have data on approximately 100 highly selected patients beyond 3 years (no adverse events 2.5 to 5 years after implantation).

Several investigational second-generation bioresorbable stents, including Elixir’s Dissolve PLLA, Boston Scientific’s FAST, and a newer version of Absorb, are in early clinical trials. Smaller strut thickness holds the promise of attenuating the risk of stent thrombosis. Since the polymer persists, no reduction in dual antiplatelet therapy duration is likely to be achieved.

Results from long-term follow-up of Absorb III and on-going trials are eagerly awaited to ascertain whether the rate of late complications of DES can be mitigated. It would not be surprising if the second-generation bioresorbable stents make DES a thing of the past within the next decade.

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# Leadless cardiac pacing: What primary care providers and non-EP cardiologists should know

## ■ ABSTRACT

Over the last 50 years, the use of transvenous pacemakers has been constrained by long-term complications that affect more than 1 in 10 patients, largely attributable to the endovascular leads and surgical pocket. Leadless cardiac pacing involves a self-contained pacemaker deployed directly into the heart without a lead or incisional access. The procedure has shown promise, eliminating pocket-related complications. Other advantages include postprocedural shoulder mobility and the ability to drive, shower, and bathe. Current devices are limited to single-chamber ventricular pacing. Future advances may allow atrial and dual-chamber pacing and combination with a subcutaneous defibrillator to deliver antitachycardia pacing and provide bradycardia backup.

## ■ KEY POINTS

Leadless cardiac pacing has emerged as a safe and effective alternative involving catheter-based delivery of a self-contained device directly into the right ventricle without incisional access, leads, or a surgical pocket. The procedure typically can be performed in 30 minutes or less, with fewer postprocedure restrictions.

Leadless pacing is showing promising results, but it is currently limited to single-chamber pacing.

Future directions include atrial and dual-chamber pacing and combining the procedure with a subcutaneous implantable cardioverter-defibrillator.

## ■ WHY LEADLESS PACING?

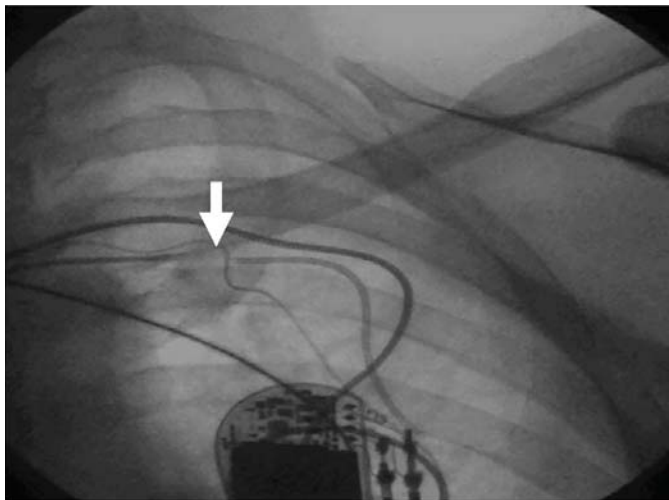
The first clinical implantation of a cardiac pacemaker was performed surgically in 1958 by Drs. Elmvist and Senning via thoracotomy and direct attachment of electrodes to the myocardium. Transvenous pacing was introduced in 1962 by Drs. Lagergren, Parsonnet, and Welti.<sup>1,2</sup> The general configuration of transvenous leads connected to a pulse generator situated in a surgical pocket has remained the standard of care ever since. Despite almost 60 years of technological innovation, contemporary permanent transvenous pacing continues to carry significant short- and long-term morbidity. Long-term composite complication rates are estimated at over 10%,<sup>3</sup> further stratified as 12% in the 2 months post-implant (short-term) and 9% thereafter (long-term).<sup>4</sup> Transvenous pacing complications are associated with an increase in both hospitalization days (hazard ratio 2.3) and unique hospitalizations (hazard ratio 4.4).<sup>5</sup>

### Short-term complications

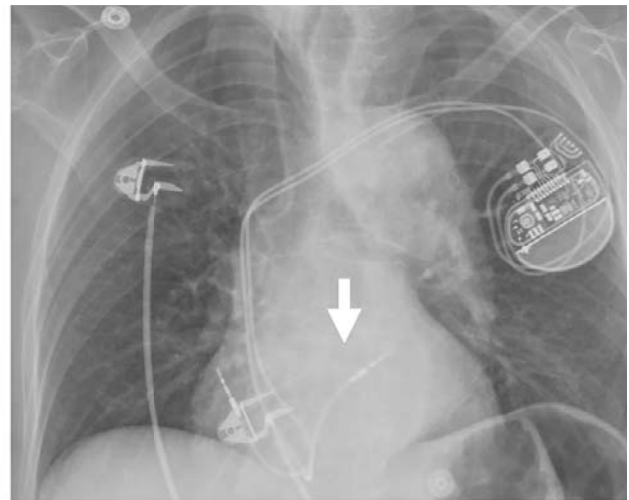
Short-term complications include lead dislodgment, pocket hematoma, pericardial effusion, and pneumothorax (**Figure 1**). Pocket hematomas are common with concurrent antiplatelet or anticoagulant administration, with incidence estimates varying from 5% to 33% depending on the definition.<sup>6</sup> Morbidity associated with pocket hematoma include prolonged hospitalization, need for re-operation,<sup>7</sup> and an almost eightfold increase in the rate of device infection over the long term compared with patients without pocket hematoma.<sup>8</sup> New pericardial effusions after implant may affect up to 10% of patients; they are generally small, including 90% attributable to pericarditis or contained microperforation not requiring intervention. Overt lead perforation resulting in cardiac tamponade occurs in about 1% of transvenous pacemaker implants, of which 10% (0.1% overall) require open chest surgery, with the remainder treated with percutaneous drainage.<sup>9</sup>

Dr. Kiehl reported no financial interests or relationships that pose a potential conflict of interest with this article. Dr. Cantillon reported consulting for Boston Scientific Corporation and St. Jude Medical; membership on advisory committees for Boston Scientific Corporation and St. Jude Medical; and teaching/speaking for Boston Scientific Corporation.

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Lead fracture



Lead dislodgment



Pocket infection



Hematoma

**FIGURE 1.** Common transvenous pacemaker lead and pocket-related complications.

Source: Lead fracture and pocket infection images courtesy of Dr. Mohamed Kanj. Hematoma image courtesy of Dr. John Rickard.

### Long-term complications

Long-term complications are predominantly lead and pocket-related but also include venous occlusive disease and tricuspid valve pathology.<sup>4</sup> The development of primary lead failure due to insulation defects, conductor fracture, or dislodgment has been associated with major adverse events in 16% of patients, and an additional 6% if transvenous lead extraction is needed, which can rarely lead to hemorrhagic death by vascular tears involving the heart or superior vena cava.<sup>10</sup> Fibrous tissue growth around the indwelling vascular leads can result in venous obstruction present in up to 14% of patients by 6 months after implant.<sup>11</sup>

This increases to 26% by the time of device replacement or upgrade, which is typically 5 to 10 years after the original implant, including 17% of patients with a complete venous occlusion.<sup>12</sup> In addition, worsened tricuspid regurgitation due to lead impingement on the valve is seen in 7% to 40% of patients depending on definitions,<sup>13</sup> with post-implant severe tricuspid regurgitation independently associated with increased mortality risk.<sup>14</sup> The rate of device infection is 1% to 2% at 1 year,<sup>8,15</sup> and 3% over the lifetime of the initial transvenous system; this increases to more than 10% after generator replacement.<sup>16</sup>

*Continued on page S29*

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**Reference:** 1. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol.* 2014;64:1-12.

## **WATCHMAN™ Left Atrial Appendage Closure Device with Delivery System and WATCHMAN Access System**

### **INDICATIONS FOR USE**

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The WATCHMAN Access System is intended to provide vascular and transseptal access for all WATCHMAN Left Atrial Appendage Closure Devices with Delivery Systems.

### **CONTRAINDICATIONS**

Do not use the WATCHMAN Device if:

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a device. See **Table 46** in the DFU.
- Any of the customary contraindications for other percutaneous catheterization procedures (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
- There are contraindications to the use of warfarin, aspirin, or clopidogrel.
- The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description section) such that the use of the WATCHMAN Device is contraindicated.

### **WARNINGS**

- Device selection should be based on accurate LAA measurements obtained using fluoro and ultrasound guidance (TEE recommended) in multiple angles (e.g., 0°, 45°, 90°, 135°).
- Do not release the WATCHMAN Device from the core wire if the device does not meet all release criteria.
- If thrombus is observed on the device, warfarin therapy is recommended until resolution of thrombus is demonstrated by TEE.
- The potential for device embolization exists with cardioversion <30 days following device implantation. Verify device position post-cardioversion during this period.
- Administer appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.
- For single use only. Do not reuse, reprocess, or resterilize.

### **PRECAUTIONS**

- The safety and effectiveness (and benefit-risk profile) of the WATCHMAN Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
- The LAA is a thin-walled structure. Use caution when accessing the LAA and deploying the device.
- Use caution when introducing the WATCHMAN Access System to prevent damage to cardiac structures.
- Use caution when introducing the Delivery System to prevent damage to cardiac structures.
- To prevent damage to the Delivery Catheter or device, do not allow the WATCHMAN Device to protrude beyond the distal tip of the Delivery Catheter when inserting the Delivery System into the Access Sheath.
- If using a power injector, the maximum pressure **should not** exceed 100 psi.
- In view of the concerns that were raised by the RE-ALIGN<sup>1</sup> study of dabigatran in the presence of prosthetic mechanical heart valves, caution should be used when prescribing oral anticoagulants other than warfarin in patients treated with the WATCHMAN Device. The WATCHMAN Device has only been evaluated with the use of warfarin post-device implantation.

### **ADVERSE EVENTS**

Potential adverse events (in alphabetical order) which may be associated with the use of a left atrial appendage closure device or implantation procedure include but are not limited to:

Air embolism, Airway trauma, Allergic reaction to contrast media/medications or device materials, Altered mental status, Anemia requiring transfusion, Anesthesia risks, Angina, Anoxic encephalopathy, Arrhythmias, Atrial septal defect, AV fistula, Bruising, hematoma or seroma, Cardiac perforation, Chest pain/discomfort, Confusion post procedure, Congestive heart failure, Contrast related nephropathy, Cranial bleed, Decreased hemoglobin, Deep vein thrombosis, Death, Device embolism, Device fracture, Device thrombosis, Edema, Excessive bleeding, Fever, Groin pain, Groin puncture bleed, Hematuria, Hemoptysis, Hypotension, Hypoxia, Improper wound healing, Inability to reposition, recapture, or retrieve the device, Infection / pneumonia, Interatrial septum thrombus, Intratracheal bleeding, Major bleeding requiring transfusion, Misplacement of the device / improper seal of the appendage / movement of device from appendage wall, Myocardia erosion, Nausea, Oral bleeding, Pericardial effusion / tamponade, Pleural effusion, Prolonged bleeding from a laceration, Pseudoaneurysm, Pulmonary edema, Renal failure, Respiratory insufficiency / failure, Surgical removal of the device, Stroke – Ischemic, Stroke – Hemorrhagic, Systemic embolism, TEE complications (throat pain, bleeding, esophageal trauma), Thrombocytopenia, Thrombosis, Transient ischemic attack (TIA), Valvular damage, Vasovagal reactions

There may be other potential adverse events that are unforeseen at this time.

**CAUTION:** Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only.

Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.

<sup>1</sup>Eikelboom JW, Connolly SJ, Brueckmann M, et al. *N Engl J Med.* 2013;369:1206-14.

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**FIGURE 2.** Leadless pacemakers (A) Nanostim and (B) Micra.

### LEADLESS PACING TECHNOLOGY

The principal goal of leadless pacing is to reduce short- and long-term pacemaker complications by eliminating the two most common sources of problems: the transvenous leads and the surgical pocket. Discussion of leadless pacing strategies began as early as 1970.<sup>17</sup> Although several preclinical studies demonstrated efficacy with leadless prototypes,<sup>18–20</sup> clinical implementation of fully leadless technology did not occur until recently. As shown in **Figure 2**, there are now two commercially available leadless pacing devices: Nanostim (St. Jude Medical Inc., St. Paul, MN) and Micra (Medtronic Inc., Dublin, Ireland). At the time of this writing, both have commercial approval in Europe. In the United States, Micra received commercial approval from the US Food and Drug Administration on April 6, 2016, with a similar decision expected on Nanostim. The current approved indications for leadless pacing are chronic atrial tachyarrhythmia with advanced atrioventricular (AV) block; advanced AV block with low level of physical activity or short expected lifespan; and infrequent pauses or unexplained syncope with abnormal findings at electrophysiologic study. Although differ-

**TABLE 1**

**Overview of leadless pacemakers Nanostim and Micra based on completed human trials**

	Nanostim	Micra
Manufacturer	St. Jude Medical	Medtronic
Size (height × width)	42.0 × 6.0 mm	25.9 × 6.7 mm
Volume	1.0 mL	0.8 mL
Mass	2 g	2 g
Delivery sheath size	18 F	23 F
Primary fixation mechanism	Helix	Tines
Projected battery life <sup>a</sup>	15.0 years	12.5 years
Remote monitoring	No	Yes
Rate-responsive pacing	Yes, temperature-based	Yes, accelerometer-based
Retrieval system	Yes	No

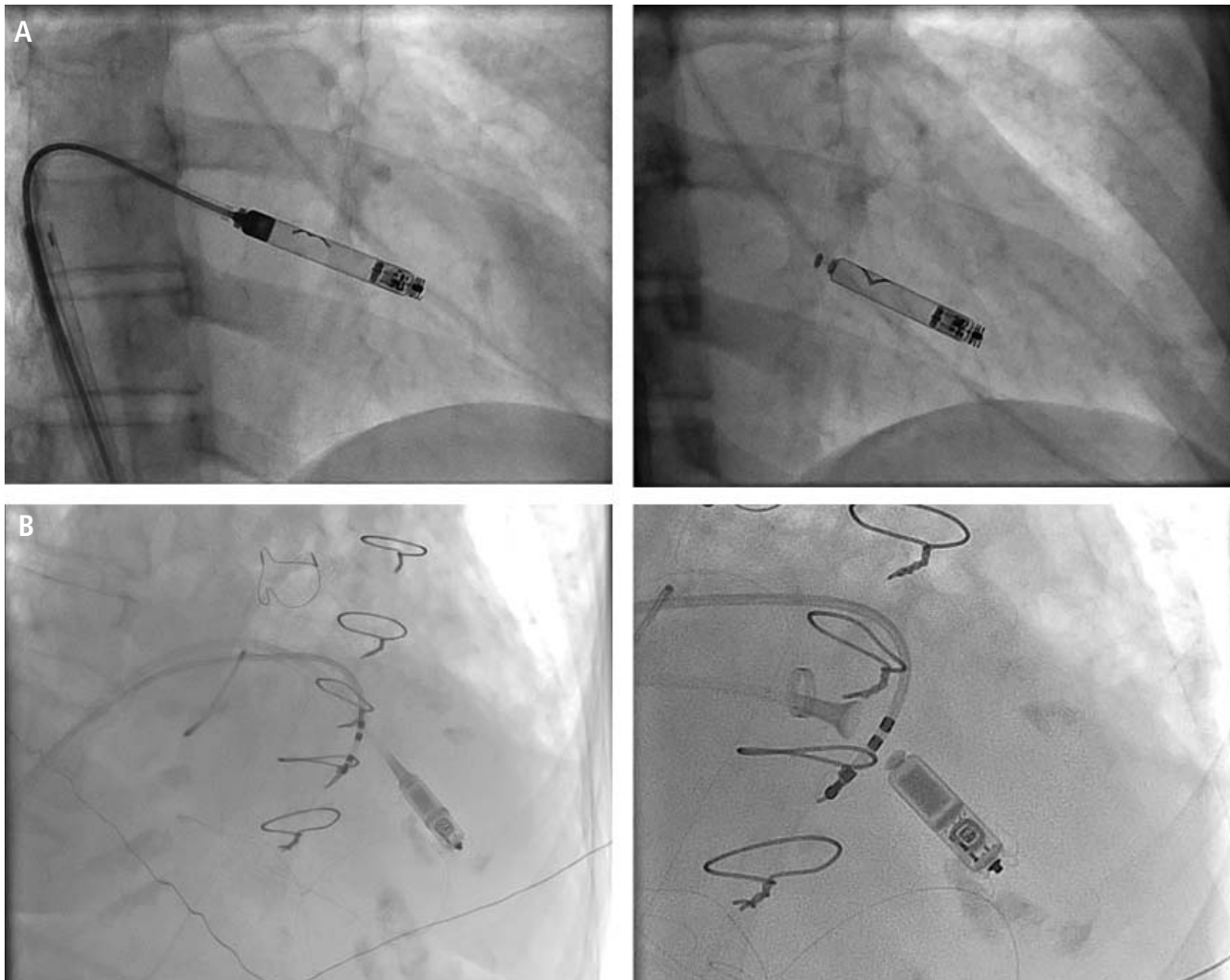
<sup>a</sup>Based on reported projections at 3 months. Data from references 21–27.

ences exist between Nanostim and Micra, as shown in **Table 1**,<sup>21–27</sup> there are fundamental similarities. Both are single-unit designs encapsulating the electrodes and pulse generator with rate-adaptive functionality. Both are delivered via an endovascular femoral venous approach without the need for incisional access, transvenous leads, or surgical pocket (**Figures 3 and 4**).<sup>21–27</sup>

### Nanostim: Landmark trials

As the world's first-in-man leadless pacemaker, Nanostim was evaluated in two prospective, non-randomized, multicenter, single-arm trials abbreviated LEADLESS<sup>22</sup> and LEADLESS II.<sup>24</sup> The first human feasibility study, LEADLESS, enrolled 33 patients with approved indications for ventricular-only pacing while excluding patients with expected pacemaker dependency. The most common indication was bradycardia in the presence of persistent atrial arrhythmias, thereby obviating the need for atrial pacing. The primary outcome was freedom from serious complications at 90 days. The secondary outcomes were implant success rate and device performance at 3 months. The results demonstrated 94% composite safety (31 of 33 patients) at 3 months. There was one cardiac perforation leading to tamponade and eventually death after prolonged hospitalization, and one inadvertent deployment into the left





**FIGURE 3.** Fluoroscopic images depicting catheter-based deployment and subsequent release for the (A) Nanostim and (B) Micra.

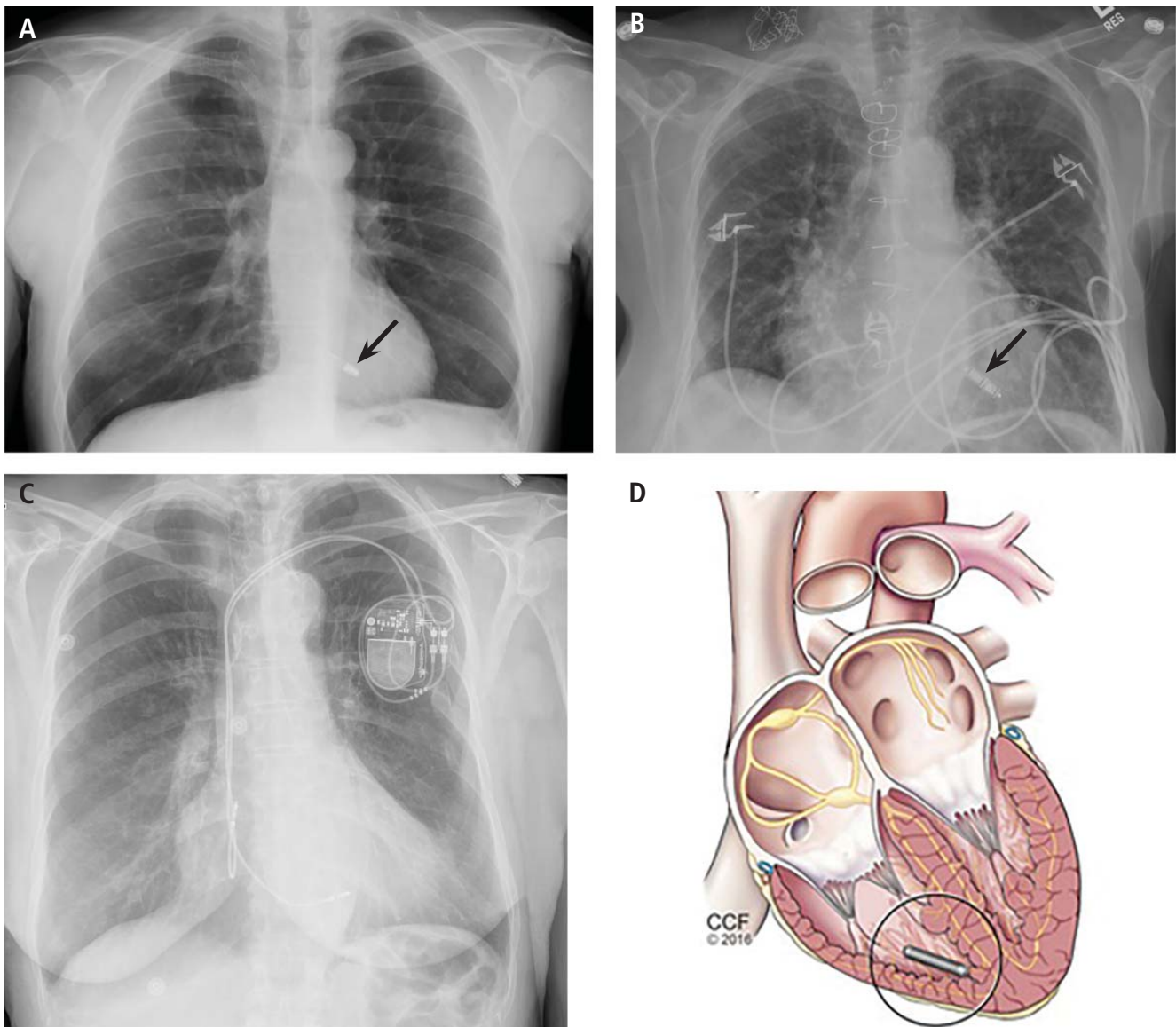
ventricle via patent foramen ovale that was successfully retrieved and redeployed without complication. The implant success rate was 97%, and the electrical parameters involving sensing, pacing thresholds, and impedance were as expected at 3 months. Results of 1-year follow-up were published for the LEADLESS cohort,<sup>25</sup> revealing no additional complications from 3 to 12 months, no adverse changes in electrical performance parameters, and 100% effectiveness of rate-responsive programming.

The subsequent LEADLESS II trial enrolled 526 patients but did not exclude patients with expected pacemaker dependency, and its results were reported in a preplanned interim analysis when 300 patients had reached 6 months of follow-up (mean follow-up  $6.9 \pm 4.2$  months).<sup>24</sup> The primary efficacy end point involved

electrical performance including capture thresholds and sensing. Initial deployment success was 96% with expected electrical parameters at implant that were stable at 6 months of follow-up. The rate of freedom from serious adverse events was 93%, with complications including device dislodgment (1.7%, mean  $8 \pm 6$  days after implant), perforation (1.3%), performance deficiency requiring device retrieval and replacement (1.3%), and groin complications (1.3%). There were no device-related deaths, and all device dislodgments were successfully treated percutaneously.

There was no prospective control arm involving transvenous pacing in either the LEADLESS or LEADLESS II trial. Thus, in an effort to compare Nanostim ( $n = 718$ ) vs transvenous pacing, complication rates were calculated for a propensity-matched





**FIGURE 4.** Frontal-plane radiographs showing implanted Nanostim (A) and Micra (B) leadless pacing devices and a traditional dual-chamber pacemaker (C). Panel D depicts cardiac deployment.

registry cohort of 10,521 transvenous patients, and differences were reported.<sup>26</sup> At 1 month, the composite complication rate was 5.8% for Nanostim (1.5% pericardial effusion, 1% dislodgment) and 12.7% for transvenous pacing (7.6% lead-related, 3.9% thoracic trauma, infection 1.9%) ( $P < .001$ ). Between 1 month and 2 years, complication rates were only 0.6% for Nanostim vs 5.4% for transvenous pacing ( $P < .001$ ). This lower complication rate at 2 years was driven almost entirely by a 2.6% infection rate and 2.4% lead-complication rate in the transvenous pacemaker group, nonexistent in the leadless group.

#### Micra: Landmark trials

Micra was evaluated in a prospective, nonrandomized, multicenter, single-arm trial, enrolling 725 patients with indications for ventricular-only pacing; approximately two-thirds of the cohort had bradycardia in the presence of persistent atrial arrhythmias, similar to the Nanostim cohort.<sup>27</sup> The efficacy end point was stable capture threshold at 6 months. The safety end point was freedom from major complications resulting in new or prolonged hospitalization at 6 months. The implant success rate was 99%, and 98% of patients met the primary efficacy end point.

The safety end point was met in 96% of patients. Complications included perforation or pericardial effusion (1.6%), groin complication (0.7%), elevated threshold (0.3%), venous thromboembolism (0.3%), and others (1.7%). No dislodgments were reported. There was no prospective, randomized control arm to compare Micra and transvenous pacing. A post hoc analysis was performed comparing major complication rates in this study with an unmatched 2,667-patient meta-analysis control cohort.<sup>27</sup> The hazard ratio for the leadless pacing strategy was calculated at 0.49 (95% confidence interval 0.33 to 0.75,  $P = .001$ ) with absolute risk reduction 3.4% at 6 months resulting in a number needed to treat of 29.4 patients. Further broken down, Micra patients compared with the control cohort had reduced rates of both subsequent hospitalizations (3.9% to 2.3%) and device revisions (3.5% to 0.4%).

### ■ ADVANTAGES OF LEADLESS PACING

As discussed above, the major observed benefit with both Nanostim and Micra compared with transvenous cohorts is the elimination of lead and pocket-related complications.<sup>25,27</sup> Leadless pacing introduces a new 1% to 2% groin complication rate for both devices not present with transvenous pacing, and also a 1% device dislodgment rate in the case of Nanostim (all dislodgments were treated percutaneously). Data from both clinical trials suggest that the complication rates are largely compressed acutely. In contrast, there are considerable mid-term and long-term complications for transvenous systems.<sup>3-5</sup> Indeed, the mid- to long-term window is where leadless pacing is expected to have the most favorable impact. As with any new disruptive technology, operator experience may be important, as evidenced by a near halving of the complication rate observed in the LEADLESS II trial after gaining the experience of 10 implants.<sup>25</sup>

Other benefits of leadless pacing include a generally quick procedure (average implant time was 30 minutes in LEADLESS and LEADLESS II)<sup>22,25</sup> and full shoulder mobility afterwards, so that patients can resume driving once groin soreness has subsided, typically within a few days. (Current studies are investigating whether immediate shoulder mobility with leadless pacing is beneficial to older patients suffering from arthritis.) The lack of an incision allows patients to bathe and shower as soon as they desire, whereas after transvenous pacemaker implant, motion in the affected shoulder is usually restricted for several weeks to avoid lead dislodgment, and showering and

bathing are restricted to avoid contamination of the incision with nonsterile tap water. (In some cases, a tightly adherent waterproof dressing can be used.) The leadless systems were designed for compatibility with magnetic resonance imaging (MRI), whereas not all transvenous pacemaker generators and leads are MRI compatible.

Leadless devices are not expected to span the tricuspid valve to create incident or worsening tricuspid regurgitation. In a recent small study of 22 patients undergoing Micra implant, there were no new cases of severe tricuspid regurgitation after the procedure, with only a 9% increase in mild and 5% increase in moderate tricuspid regurgitation,<sup>28</sup> vs a rate of 40% of worsening tricuspid regurgitation and 10% of new severe tricuspid regurgitation with transvenous pacing.<sup>13,14</sup>

Transvenous pacemaker implant requires surgery for pulse generator exchange at a mean of 7 years, a procedure carrying significant risk of short- and long-term complications.<sup>10</sup>

### ■ END-OF-SERVICE QUESTIONS: ATTEMPT RETRIEVAL OR NOT?

Both leadless systems have favorable projected in-service battery life: a reported 15.0 years for Nanostim<sup>25</sup> and mean 12.5 years for Micra.<sup>27</sup> The inevitable question is what to do then. The Nanostim system was designed to be retrievable using a dedicated catheter system. Micra was not designed with an accompanying retrieval system. Pathologic examinations of leadless devices at autopsy or after explant have revealed a range of device endothelialization, from partial at 19 months to full at 4 months.<sup>29,30</sup>

As of this writing, no extraction complications have been observed with Nanostim explants up to 506 days after implant ( $n = 12$ , mean 197 days after implant).<sup>31</sup> Needless to say, there is not yet enough experience worldwide with either system to know what the end-of-service will look like in 10 to 15 years. One strategy could involve first attempting percutaneous retrieval and replacement, if retrieval is not possible, abandoning the old device while implanting a new device alongside. Another strategy would be to forgo a retrieval attempt altogether. In the LEADLESS II study,<sup>24</sup> the mean patient age was 75. In this cohort, forgoing elective retrieval for those who live to reach the end of pacemaker service between the age of 85 and 90 would seem reasonable assuming the next device provides similar longevity. For younger patients, careful consideration of long-term strategies is needed. It is not known what the replacement technology will look like in another decade with respect

to device size or battery longevity. Preclinical studies using swine and human cadaver hearts have demonstrated the feasibility of multiple right-ventricular Micra implants without affecting cardiac function.<sup>32,33</sup>

### ■ OTHER LIMITATIONS AND CAUTIONARY NOTES

At present, leadless pacing is approved for single-chamber right-ventricular pacing. In the developed world, single right-ventricular pacing modes account for only 20% to 30% of new pacemaker implants, which total more than 1 million per year worldwide.<sup>34,35</sup> As with any new technology, the up-front cost of leadless pacemaker implant is expected to be significantly higher than transvenous systems, which at this point remains poorly defined, as the field has not caught up in terms of charges, reimbursement, and billing codes. While those concerns fall outside the scope of this review, it is not known if the expected reductions in mid- and long-term complications will make up for an up-front cost difference. However, a cost-efficacy study reported that one complication of a transvenous pacemaker system was more expensive than the initial implant itself.<sup>36</sup> The longest-term follow-up data currently available are with Nanostim, showing an absolute complication reduction of 11.7% at 2 years,<sup>24</sup> a disparity only expected to widen with prolonged follow-up, particularly after transvenous generator exchange, when complication rates rapidly escalate.

### ■ FUTURE DIRECTIONS

The next horizon of leadless technology will be for right-atrial and dual-chamber pacing to treat the far more pervasive pacing indication of sinus node dysfunction with or without AV block. In the latter application, the two devices will communicate. Prototypes and early nonhuman evaluations are ongoing for both. Leadless pacing is also being investigated for use in tachycardia. Tjong et al<sup>37</sup> reported on the safety and feasibility of an entirely leadless pacemaker plus an implantable cardioverter-defibrillator (ICD) system in two sheep and one human using both Nanostim and subcutaneous ICD. Currently, two important limitations of subcutaneous ICD are its inability to provide backup bradycardia and antitachycardia pacing (it provides only defibrillation). The EMBLEM PACE study will enroll 250 patients to receive a leadless pacemaker and Emblem subcutaneous ICD (Boston Scientific, Boston, MA), with patients subsequently receiving commanded antitachycardia pacing for ventricular arrhythmias and bradycardia pacing provided by the leadless device as indicated.

### ■ CONCLUSIONS

Leadless cardiac pacing is a safe and efficacious alternative to standard transvenous pacing systems. Although long-term data are limited, available short- and mid-term data show that the elimination of transvenous leads and the surgical pocket results in significant reductions in complication rates. Currently, leadless pacing is approved only for right-ventricular pacing, but investigation of right-atrial, dual-chamber, and fully leadless pacemaker-defibrillator hybrid systems is ongoing.

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# PCSK9 inhibition: A promise fulfilled?

## ■ ABSTRACT

The association of reduced proprotein convertase subtilisin/kexin type 9 (PCSK9) activity with reduced cardiovascular disease (CVD) events—and the need for add-ons to statin therapy to achieve treatment goals—has led to the rapid development and US Food and Drug Administration (FDA) approval of monoclonal antibody therapies to inhibit PCSK9. Now that PCSK9 inhibitors are approved by the FDA for use in certain patients, data from ongoing long-term clinical trials addressing tolerability, safety, and proof of additional reduction in CVD events are eagerly awaited

## ■ KEY POINTS

Potential candidates for PCSK9 inhibitor therapy are patients with familial hypercholesterolemia with a lifetime burden of elevated low-density-lipoprotein cholesterol (LDL-C) and thus a low likelihood of optimal control on current therapies; patients with complete or partial statin intolerance, with high-intensity statin dosing limited by adverse effects; and patients at high CVD risk with LDL-C goals not achieved with current therapies.

Subcutaneously administered monoclonal antibodies targeting PCSK9 are currently the only PCSK9 inhibitors with FDA approval.

PCSK9 inhibitors under study include agents with more durable effect and that require less frequent injections, RNA-interference therapies, vaccinations, antisense therapies, and oral formulations.

**S** tatin therapy has been shown to substantially reduce adverse events associated with low-density-lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD). Statins alone are often not adequate to achieve treatment goals, and residual CVD risk remains high. Combination therapies of statins with ezetimibe and resins to further lower LDL-C, fibrates and omega 3 fatty acids to lower triglycerides, and niacin to lower both and raise high-density-lipoprotein cholesterol are available, but additional risk reduction has not been consistently demonstrated in clinical trials.

The link between atherogenic lipoproteins and CVD is strong, and the need to develop therapies in addition to statins to substantially and safely reduce LDL-C is a priority. The association of reduced proprotein convertase subtilisin/kexin type 9 (PCSK9) activity with reduced LDL-C and CVD events has led to the rapid development and approval of monoclonal antibody therapies to inhibit PCSK9.

In this review, we discuss trials of these therapies that have shown durable reductions in LDL-C of more than 50%, with acceptable tolerability. Now that PCSK9 inhibitors are approved by the US Food and Drug Administration (FDA), extended data are needed as to long-term tolerability, safety, and efficacy of these agents and, most importantly, demonstration of additional reduction in CVD events.

## ■ A CASE FOR ADDITIONAL THERAPIES

CVD is the leading cause of morbidity and death in the United States, responsible for one in four deaths. Hyperlipidemia and, specifically, elevated LDL-C have been found to be important drivers of atherosclerosis and, in turn, adverse cardiovascular (CV) events. Likewise, numerous observational and clinical trials have shown that reducing LDL-C, particularly with statins, decreases CVD events.<sup>1-4</sup> More aggressive lowering with higher doses or more intensive statin therapy further reduces rates of adverse outcomes.<sup>3,4</sup> In addition, the pleiotropic effects of statins imply that not all of their benefits are derived from LDL-C lowering alone.<sup>5</sup> Consequently, it is now

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standard practice to use statins at the highest tolerable dose to reach target LDL-C levels and prevent CV events in high-risk patients with CVD or multiple coronary artery disease risk factors, regardless of the LDL-C levels.<sup>6,7</sup>

The American College of Cardiology (ACC) and the American Heart Association released cholesterol guidelines in 2013 that recommend a risk-based approach for statin therapy rather than targeting specific LDL-C levels.<sup>6</sup> Although this evidence-based approach may better conform to clinical trials, the debate that lower LDL-C targets will further prevent CVD continues.

Indeed, it appears that lower is better, as demonstrated by the IMPROVE-IT trial.<sup>8</sup> Although the control group receiving simvastatin monotherapy had low LDL-C levels (mean, 69.9 mg/dL; 1.8 mmol/L), the experimental group receiving simvastatin plus ezetimibe achieved even lower levels (mean, 53.2 mg/dL; 1.4 mmol/L) after 1 year of therapy and had a significantly lower composite primary end point of CV death, major coronary event, or nonfatal stroke at 7 years (34.7% for simvastatin monotherapy vs 32.7% for combined therapy).<sup>9</sup> Furthermore, the event-rate reduction with the addition of ezetimibe was the same as the average predicted by the Cholesterol Treatment Trialists' meta-analysis: an LDL-C reduction of 1 mmol/L (38.6 mg/dL) yields a 23% risk reduction in major coronary events over 5 years.<sup>10</sup> Although only a modest absolute reduction in outcomes, it supports the notion that further reduction of LDL-C levels by more potent therapies may offer greater benefit.

There is strong evidence that statin therapy reduces the risk of developing CVD in patients with or without a previous atherosclerotic event; however, residual CVD risk remains even for those on therapy. A contributing factor to this residual risk is that many statin-treated patients have insufficient response or intolerance and do not achieve adequate LDL-C reductions.

There are three clinically important patient populations who are inadequately managed with current therapies and remain at high risk of subsequent CV events; these are patients who would benefit from additional therapies.

**1. Patients with familial hypercholesterolemia (FH).** This is the most common genetic disorder in the world, yet it is frequently undiagnosed and untreated. Due to high baseline cholesterol levels, achieving LDL-C treatment goals is challenging.

- The prevalence may be closer to 1:200 to 1:250 rather than the often quoted 1:500.<sup>11</sup>

- Fewer than 12% of patients with heterozygous FH achieve the LDL-C goal of < 100 mg/dL with maximal statin treatment alone or with a second agent.<sup>12</sup>

**2. Patients with hyperlipidemia not due to FH who are at elevated CV risk and undertreated.**

In US and European surveys, between 50% and 60% of patients receiving statins with or without other therapies failed to reach LDL-C reduction goals.<sup>13</sup>

- Variation in response to statin treatment between individuals may be considerable.
- Poor adherence to statin therapy is common.

**3. Patients with side effects to statins, particularly muscle symptoms that prevent statin use or substantially limit the dose.**

- Although the incidence of myopathy is low (< 0.1%) and rhabdomyolysis is even less common, observational studies suggest that 10% to 20% of patients may limit statin use due to muscle-associated complaints including muscle aching, cramps, or weakness.<sup>14</sup>
- Side effects may be dose-dependent, limiting the use of the high-intensity statin doses that are frequently necessary to achieve LDL-C goals.

Consequently, there is great interest in developing therapies beyond statins that may further reduce CV events. However, treatments other than ezetimibe for further management of hyperlipidemia and risk reduction have failed to demonstrate consistent benefit when added to statin therapy.<sup>15-19</sup> The largest studies were with niacin and fibrates. Unfortunately, most trials demonstrated no overall outcomes benefit or only benefits in subgroup analyses, leaving the door open to other pharmacologic interventions.

Studies with the cholesterol ester transfer protein (CETP) inhibitor torcetrapib, in combination with statin therapy, actually demonstrated an overall increase in all-cause mortality in the treatment group.<sup>20</sup> Two large outcome trials of the CETP inhibitors dalcetrapib and evacetrapib were stopped after interim analysis predicted no benefit. Although drugs such as lomitapide (a microsomal triglyceride transfer protein inhibitor) and mipomersen (an antisense oligonucleotide inhibitor of ApoB-100 synthesis) can lower LDL-C by reducing ApoB synthesis,<sup>21</sup> they are approved only in the small population of individuals with homozygous FH and liver toxicity and side effects are a concern.

Accordingly, current cholesterol management guidelines continue to offer LDL-C as the main target of lipid-modifying therapy, with statins as the primary



**TABLE 1**  
Gain-of-function and loss-of-function PCSK9 mutations

Gain-of-function mutations			
PCSK9 variant	Population	Clinical characteristics	
D374Y	British, Norwegian, families; 1 Utah family	Premature CVD, tendon xanthomas, severe hypercholesterolemia	
S127R	French, South African, Norwegian families	Tendon xanthomas, CVD, early MI, stroke	
R215H	Norwegian family	Brother died at 31 from MI; strong family history of CVD	
Loss-of-function mutations			
PCSK9 variant	Population	LDL-C	CVD risk
R46L	ARIC, DHS	↓ 15%	↓ 47%
Y142X or C679X	ARIC, DHS	↓ 28%–40%	↓ 88%
R46L	CGPS	↓ 11%	↓ 46%

ARIC = Atherosclerotic Risk in Communities study; CGPS = Copenhagen General Population Study; CVD = cardiovascular disease; DHS = Dallas Heart Study; MI = myocardial infarction  
Data from references 25–29.

treatment choice. The desire to build on statin therapy to prevent further progression of atherosclerosis and clinical CVD has encouraged continued focus on strategies to lower LDL-C to even greater extents.

Fortunately for practitioners, for the first time since lovastatin was approved in 1987, there is a new therapy approved by the FDA that significantly lowers LDL-C and, potentially, improves CV outcomes—the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. This review will focus on the PCSK9 inhibitors, a novel therapeutic class that reduces LDL-C through increased hepatic clearance. These drugs are rapidly emerging as an ideal adjunctive therapy to statins for patients at the highest risk and as a highly efficacious alternate therapy in patients intolerant of statins.

**■ PCSK9 INHIBITORS: DISCOVERY, MECHANISM, AND THERAPEUTIC INTERVENTIONS**

Two PCSK9 inhibitors have received FDA approval: alirocumab (Praluent) and evolocumab (Repatha). Among new molecular entities for clinical use, PCSK9

inhibitor therapies had one of the shortest durations from discovery to development and approval.

Mutations in the PCSK9 gene associated with autosomal dominant hypercholesterolemia were first identified in 2003 in a French family.<sup>22</sup> The PCSK9 protein is now known to be a secreted enzymatic serine protease that is primarily synthesized in the liver and binds to the LDL receptor (LDL-R)/LDL-C complex on the surface of hepatocytes, marking the receptor for lysosomal degradation rather than recycling to the cell surface. Thus, it reduces the quantity of LDL-R that is available to remove LDL-C from circulation.<sup>23</sup> As a result, higher levels of PCSK9 are associated with higher levels of plasma LDL-C.

The clinical importance of PCSK9 in regulating LDL-C is supported by observed mutations and polymorphisms. Gain-of-function mutations that increase the activity of PCSK9 have been shown to be associated with elevated LDL-C, premature CVD, and myocardial infarction (MI).<sup>24</sup> Conversely, loss-of-function mutations (heterozygotes found in 1% to 3% of the population) result in decreased activity of PCSK9, lower LDL-C, and lower incidence of CVD (Table 1).<sup>25–29</sup> These observations, combined with data showing that homozygote loss-of-function individuals with very low LDL-C were generally very healthy, sparked interest in developing inhibition of PCSK9 activity as a therapeutic strategy for hyperlipidemia.

Multiple pharmacologic developments are aimed at inhibiting PCSK9, with many compounds in clinical trials. The approaches include gene silencing with loss-of-function mutations, synthetic peptides, oral small molecules, and monoclonal antibodies. Gene silencing was first observed in 2007 when administration of antisense oligonucleotides targeted to selectively inhibit PCSK9 mRNA was found to up-regulate LDL-R, thereby decreasing serum levels of LDL-C.<sup>30</sup>

The first study to establish the role of synthetic peptides in PCSK9 inhibition was performed in 2008. In this study, the epidermal growth factor-like A synthetic peptide blocked the interaction between PCSK9 and LDL-R, thereby decreasing the degradation of LDL-R and preserving LDL uptake.<sup>31</sup> Although studies are limited, synthetic peptides remain an area of great interest given their promising effects on lipid metabolism. Recently, a synthetic PCSK9-binding adnectin derived from the human fibronectin known as BMS-962476, had favorable results in a phase 1 clinical trial. An RNA interference molecule, subcutaneous ALN-PSC, inhibits PCSK9 gene expression by causing destruction of messenger RNA, thus inhibiting PCSK9 synthesis (Table 2).<sup>32</sup>



## ■ PCSK9 INHIBITORS: CLINICAL TRIALS

Subcutaneously administered monoclonal antibodies targeting PCSK9 currently are the only PCSK9 inhibitors FDA-approved for clinical use. The first study to demonstrate efficacy in enhancing uptake of serum LDL-C was performed in 2009.<sup>33</sup> Multiple phase 1 and 2 studies soon followed, demonstrating acceptable safety and 50% to 70% reductions in LDL-C at upper-dose titrations.<sup>34</sup> Additionally, there were significant reductions in total cholesterol, ApoB, triglycerides, and lipoprotein(a).

These early developments paved the way for larger phase 3 trials (Table 3).<sup>35-48</sup> The PCSK9 inhibitors evolocumab and alirocumab have been shown in multiple phase 3 clinical trials to achieve a consistent dose-dependent 50% to 60% reduction in LDL-C across a broad range of CVD risk, pretreatment LDL-C levels, and background therapy: monotherapy (MENDEL-2, ODYSSEY COMBO I),<sup>35,44</sup> added to statin therapy (LAPLACE-2, ODYSSEY CHOICE I),<sup>38,46</sup> and in individuals with heterozygous FH (RUTHERFORD-2, ODYSSEY-FH).<sup>37,42</sup> Trials with bococizumab are under way.

The GAUSS-2 clinical trial (Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2) demonstrated similar efficacy in reducing LDL-C in patients with clinically assessed statin intolerance due to muscle-related adverse symptoms.<sup>39</sup> In GAUSS-3, patients were first identified as being statin intolerant secondary to muscle-associated symptoms based on a randomized, crossover trial of atorvastatin vs placebo.<sup>40</sup> The 43% of participants who experienced intolerable muscle-related symptoms on the statin but not on placebo were then randomized to evolocumab vs ezetimibe. Results showed significant reduction in LDL-C in the evolocumab group (52.8%) compared with the ezetimibe group (16.7%). Additionally, among patients with muscle symptoms on statin therapy, PCSK9 therapy was discontinued for muscle symptoms in only 0.7% of evolocumab recipients and 6.8% of ezetimibe recipients.

Overall, the PCSK9 inhibitors are generally well tolerated with injection site reactions being the most common side effect. A meta-analysis published in 2015 of 25 trials including more than 12,000 patients treated with evolocumab and alirocumab reported no significant difference in adverse events or safety outcomes vs placebo or ezetimibe.<sup>49</sup> Antidrug binding or neutralizing antibody production to these agents, thus far, has not been shown to be an issue. Additional analyses have not indicated an adverse effect

**TABLE 2**  
Studies of PCSK9-inhibitor therapies

Drug	Sponsor	Stage of development	FDA approval
<u>Monoclonal antibodies</u>			
Alirocumab (SAR236553, REGN727)	Sanofi, Regeneron	Phase 3	July 2015
Evolocumab (AMG145)	Amgen	Phase 3	August 2015
Bococizumab (PF0499614, RN316)	Pfizer	Phase 3	No
LY3015014	Lilly	Phase 2	No
<u>PCSK9-binding adnectin</u>			
BMS-962476	Bristol-Meyers Squibb	Phase 1	No
<u>siRNA</u>			
ALN-PCS	Alnylam Pharmaceuticals	Phase 1	No

Data from reference 32.

on gonadal hormone levels or increased incidence of new-onset diabetes.

Two studies published in 2015 offer insight into longer term durability and safety as well as potential CVD outcome benefit (Table 4)<sup>50,51</sup>:

- OSLER-1 and 2: Open-Label Study of Long-Term Evaluation against LDL-Cholesterol (OSLER) trials—evolocumab trial,<sup>50</sup>
- ODYSSEY long term: Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy—alirocumab trial.<sup>51</sup>

The OSLER trials reported durable LDL-C reductions of 61% and the ODYSSEY trial reported a LDL-C reduction of 62%.<sup>50,51</sup> In both studies, the overall occurrence of adverse events was similar to placebo, but both reported a higher rate of neurocognitive effects in the active treatment groups (evolocumab 0.9% vs 0.3% for standard therapy; alirocumab 1.2% vs 0.5% for placebo). It must be noted that although the absolute rate of neurocognitive adverse events is low, it is unclear if these events were related to the drugs themselves or to extreme lowering of LDL-C. Nevertheless, the FDA has raised concerns about neurocognitive events. A sub-study of the ongoing FOURIER

**TABLE 3**  
Clinical trials of PCSK9 inhibitors

Study	Drug	Description	No. patients	Weeks	Baseline LDL	Mean % LDL lowering
<b>Phase 3 efficacy trials</b>						
MENDEL-2 <sup>35</sup>	Evolocumab	Monotherapy vs ezetimibe and placebo	614	12	140–144	55–57
DESCARTES <sup>36</sup>	Evolocumab	Long-term tolerability/ efficacy atorvastatin 10–80 ± ezetimibe	901	52	104 (95–120)	55–57
RUTHERFORD-2 <sup>37</sup>	Evolocumab	LDL-C goal achievement in HeFH on statin	331	12	151–161	59–61
LAPLACE-2 <sup>38</sup>	Evolocumab	Combined with different statins vs ezetimibe and placebo	2,067	12	108	55–76
GAUSS-2 <sup>39</sup>	Evolocumab	Statin intolerant vs ezetimibe	307	12	192–195	53–56
GAUSS-3 <sup>40</sup>	Evolocumab	Statin intolerant vs ezetimibe	511	24	212–219	53
TAUSSIG <sup>41</sup>	Evolocumab	Homozygous FH statin ± ezetimibe, open label	94	12	321	20.9
ODYSSEY FH I <sup>42</sup>	Alirocumab	HeFH vs ezetimibe	486	24	145	58
ODYSSEY FH II <sup>42</sup>	Alirocumab	HeFH vs ezetimibe	249	24	135	51
ODYSSEY-High FH <sup>43</sup>	Alirocumab	HeFH on statin vs placebo	106	24	196–201	46
ODYSSEY-COMBO I <sup>44</sup>	Alirocumab	Hypercholesterol vs placebo	316	24	95–100	48
ODYSSEY-COMBO II <sup>45</sup>	Alirocumab	High CVD risk with ezetimibe vs placebo/ezetimibe	707	24	105–109	51
ODYSSEY CHOICE I <sup>46</sup>	Alirocumab	Maximum statin or statin intolerant vs placebo	803	24	112–148	52 (no statin) 59 (+ statin)
ODYSSEY CHOICE II <sup>47</sup>	Alirocumab	Combined with ezetimibe or fenofibrate or as monotherapy vs placebo	233	24	154–164	56
<b>Phase 2 trials</b>						
NCT01592240 <sup>48</sup>	Bococizumab	Dose ranging, added to statins	250	24	105–118	34–53

CVD = cardiovascular disease; **DESCARTES** = Durable Effect of PCSK9 Antibody Compared With Placebo Study; **GAUSS-2** = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2; **GAUSS-3** = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3; HeFH = heterozygous familial hypercholesterolemia; **LAPLACE-2** = LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; LDL-C = low-density lipoprotein cholesterol; **MENDEL-2** = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2; **ODYSSEY CHOICE I** = Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab (REGN727/ SAR236553) in Patients With Primary Hypercholesterolemia; **ODYSSEY CHOICE II** = Phase III Study To Evaluate Alirocumab in Patients With Hypercholesterolemia Not Treated With a Statin; **ODYSSEY COMBO I** = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; **ODYSSEY COMBO II** = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia; **ODYSSEY FH** = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy; **ODYSSEY-High FH** = Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; **RUTHERFORD-2** = Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2; **TAUSSIG** = Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders

trial with evolocumab—EBBINGHAUS—is expected to address this concern.

In addition, analyses of CV events showed that the PCSK9 inhibitors effectively cut the CV rate in half in both studies (Figure 1).<sup>50,51</sup> In the OSLER trials,<sup>50</sup> evolocumab recipients had 53% reduction in major CV events (0.95% vs 2.18% in the standard

therapy group;  $P = .003$ ). In ODYSSEY,<sup>51</sup> alirocumab recipients had a 48% reduction in major CV events (1.7% vs 3.3% for placebo;  $P = .02$ ). Furthermore, a 2015 meta-analysis of 24 phase 2 and 3 trials reported a statistically significant 55% reduction in all-cause mortality and 50% reduction in CV mortality with PCSK9 inhibitors.<sup>52</sup>

For many reasons including short length of follow-up, study design, and small numbers of outcome events, the OSLER and ODYSSEY studies, although enticing, are exploratory and hypothesis-generating only and results need to be interpreted with caution. Nevertheless, they have set the stage for ongoing prospective randomized outcome trials that are studying the CV effects and tolerability of PCSK9 inhibitors over a longer time frame. These include the following trials.

- The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) is an ongoing trial with the primary end point of CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization in high-risk patients receiving evolocumab or placebo.<sup>53</sup>
- The ODYSSEY trial is examining the effect of alirocumab vs placebo on the composite primary endpoint of coronary heart disease death, non-fatal MI, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalization in patients who have had an acute coronary syndrome event during the previous 4 to 52 weeks.<sup>54</sup>
- The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE) trials are investigating the effect of bococizumab, a third PCSK9 “humanized” monoclonal antibody, vs placebo in reducing death, MI, stroke, or unstable angina in patients at high-risk of CVD who are receiving standard lipid-lowering therapy with LDL-C > 70 mg/dL (1.8 mmol/L) (SPIRE-1) or > 100 mg/dL (2.6 mmol/L) (SPIRE-2).<sup>55,56</sup>

Because these outcome trials are attempting to enroll more than 70,000 patients and are event driven, it is difficult to predict when they will be completed (Table 5).<sup>53–56</sup> However, recent estimates indicate completion of at least one trial by the end of 2016 or early 2017, with interim analyses of others expected at that time. It is hoped that they will answer the all-important question of whether PCSK9 inhibitors are associated with further CV event reduction benefit.

**TABLE 4**  
Outcome and safety data of evolocumab and alirocumab trials

	Pooled OSLER-1, OSLER-2 <sup>50</sup> evolocumab	ODYSSEY LONG TERM <sup>51</sup> alirocumab
No. patients	4,465	2,341
Follow-up	11.1 months	78 weeks
Study type	Open-label, randomized evolocumab and standard care (n = 2,976) vs standard care (n = 1,489)	Randomized, alirocumab (n = 1,553) vs placebo (n = 788) (post hoc events)
% Reduction LDL-C (median mg/dL)	61 (120 to 48)	61.9 (122 to 48)
CV events	CV death, MI, CVA, UA revascularization, CHF	CV death, MI, CVA, UA
Rate CV events (HR)	0.95% vs 2.18% (0.47)	1.7% vs 3.3% (0.52)
Other adverse events, % of patients		
Severe adverse events	7.5 vs 7.5	18.7 vs 19.5
Liver function tests	1.0 vs 1.2	1.8 vs 2.1
Creatine phosphokinase	0.6 vs 1.1	3.7 vs 4.9
Musculoskeletal	6.4 vs 6.0	5.4 vs 2.9
Neurocognitive	0.9 vs 0.6	1.2 vs 0.5

CHF = congestive heart failure; CV = cardiovascular; CVA = cerebral vascular accident; HR = hazard ratio; LDL-C = low-density-lipoprotein cholesterol; MI = myocardial infarction; OSLER-1, OSLER-2 = Open-Label Study of Long-Term Evaluation Against LDL-Cholesterol 1, 2; ODYSSEY LONG TERM = Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy; UA = unstable angina

**■ CURRENT FDA INDICATIONS AND GUIDELINES**

The two PCSK9 inhibitors approved by the FDA—alirocumab (subcutaneous 75 mg every 2 weeks up titrated to 150 mg) and evolocumab (subcutaneous 140 mg every 2 weeks or 420 mg every 4 weeks)—are both indicated for use with statins in patients with heterozygous FH or known atherosclerotic CVD who require further reduction in LDL-C levels despite lifestyle interventions and use of maximally tolerated statins. Evolocumab has also been approved for use in patients with homozygous FH.

Although PCSK9 inhibitors are not specifically approved for patients unable to tolerate statins, the results of GAUSS-3, which documented that statin intolerance is a real, definable entity and very responsive to PCSK9 inhibition, makes these drugs promising agents for patients intolerant of statins and, thus, unable to benefit from high-intensity statin therapy.

In April 2016, the ACC released a clinical consensus update to their 2013 cholesterol guidelines, which

is their first recommendation specifically addressing the use of non-statin therapies, including the newer PCSK9 inhibitors.<sup>57</sup> For high-risk patients with clinical atherosclerotic CVD or LDL-C > 190 and failure to achieve at least a 50% reduction in LDL-C on maximally tolerated statin, non-statin may be considered. Ezetimibe, given its safety and tolerability, should be the first additional medication added. Bile acid sequestrants may be used as a second-line therapy if ezetimibe is not tolerated and triglycerides are not elevated. If therapy goals are not met on maximally tolerated statin and ezetimibe, either approved PCSK9 inhibitor can be added or used to replace ezetimibe. The document also specifies that given the lack of long-term safety and efficacy data on the PCSK9 inhibitors, they are not recommended for use in primary prevention patients in the absence of FH.

CONCLUSION

Although statin therapy has been shown to substantially reduce LDL-C and CVD adverse events, there remains a high rate of inadequate goal achievement and residual CVD risk in patients receiving statins. Combination therapies with ezetimibe and resins to further lower LDL-C, fibrates and omega 3 fatty acids to lower triglycerides, and niacin to lower both and raise high-density-lipoprotein cholesterol are available, even though additional CV risk reduction is minimal or elusive when these drugs are added to statin therapy.

The link between atherogenic lipoproteins and CVD is strong, and the need to develop therapies in addition to statins to substantially and safely reduce LDL-C remains a priority. The association of reduced PCSK9 activity with reduced LDL-C and CV events has led to rapid development and approval of monoclonal antibody therapies to inhibit PCSK9. In trials, these therapies have shown substantial and durable reductions in LDL-C of more than 50%, with acceptable tolerability. Now that PCSK9 inhibitors are approved by the FDA, extended data about long-term tolerability, safety, and efficacy and, most importantly, demonstration of additional reduction in CVD events are needed. It is hoped that the long-term ongoing trials will provide these data.

For the immediate future, statin therapy will continue to be the cornerstone of lipid and CVD risk management based on their low generic cost, proven CVD risk reduction, and clinicians' comfort with their use. However, the reliable efficacy of PCSK9 inhibitors and the fact that statin therapy itself increases PCSK9

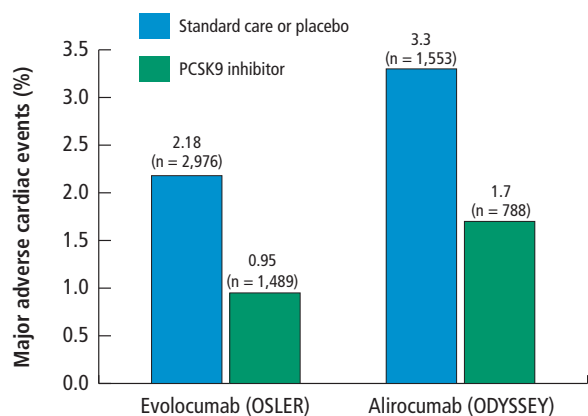


FIGURE 1. Effect of PCSK9 inhibitors on cardiovascular events.<sup>50,51</sup>

TABLE 5  
Ongoing trials of PCSK9 inhibitors

Trial	Drug	Primary outcome	No. patients	Expected completion	LDL-C on background therapy (mg/dL)
FOURIER <sup>53</sup>	Evolocumab	Time to CV death, MI, hospitalization for UA, stroke, or coronary revascularization	27,500	2016–2017	> 70
ODYSSEY <sup>54</sup>	Alirocumab	Time to CV death, nonfatal MI, hospitalization for UA, stroke	18,000	2017	> 70
SPIRE-1, <sup>55</sup> SPIRE-2 <sup>56</sup>	Bococizumab	Time to composite major CV event (CV death, nonfatal MI, nonfatal stroke, and hospitalization for UA)	26,000	2017–2018	70–99 SPIRE-1 > 100 SPIRE-2

CV = cardiovascular; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C = low-density-lipoprotein cholesterol; MI = myocardial infarction; ODYSSEY OUTCOMES = Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; SPIRE-1, SPIRE-2 = The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects; UA = unstable angina



activity makes the addition of PCSK9 inhibitors to statins an attractive approach in high-risk patients failing to reach LDL-C treatment goals.

Although current indications are limited, there are patients at high CVD risk who would be appropriate candidates for these therapies. These include patients with the following:

- FH with lifetime burden of elevated LDL-C and associated low likelihood of achieving optimal LDL-C control on current available therapies
- Complete or partial statin intolerance with high-intensity statin dosing limited by side effects
- High CV risk who are not at LDL-C goal on current therapies.

Now that the first therapies are available, practitioners can expect newer approaches to tackle PCSK9-mediated LDL-C reduction. Bococizumab is lagging in phase 3 trials, but the SPIRE program is moving forward with special population studies expected to conclude in 2016 and simultaneous long-term outcomes trials. Other PCSK9 inhibitors being investigated include agents with more durable effect requiring less frequent injections, RNA-interference therapies, vaccinations, antisense therapies, and oral formulations.

The PCSK9 inhibitors hold promise as an adjunct to statin therapy. Their eventual clinical role will depend on a balance between substantial LDL-C reductions, long-term safety, tolerability, and reduction in CVD events vs the cost (estimated at \$14,000 a year), access from payers, acceptance of injectable therapies, and magnitude of incremental benefit when added to current therapies. Nevertheless, initial clinical trial data are encouraging and these drugs may be an important addition to the therapeutic armamentarium against CVD.

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# Fibromuscular dysplasia: Advances in understanding and management

## ■ ABSTRACT

Several key findings in recent years have reshaped our understanding of fibromuscular dysplasia (FMD), an uncommon nonatherosclerotic disease of medium-sized arteries that affects mainly women. While the true prevalence of this disease remains unknown, studies suggest that more people may be affected than previously reported. Better understanding of the clinical manifestations and natural history of FMD and advances in diagnostic imaging have altered the clinical approach to managing patients with this uncommon vascular disease. Although there are a multitude of unanswered questions regarding FMD, this review highlights recent insights and how this information has modified clinical care for those affected.

## ■ KEY POINTS

There is no cure for FMD. Management focuses on thorough evaluation and surveillance, lifestyle modification, and treatment of symptoms. Vascular procedures, such as angioplasty or treatment of aneurysms, are required for some patients.

The overwhelming majority (> 90%) of patients with FMD are women. But men seem to have a more aggressive course, with a rate of aneurysm or dissection two times higher than that in women.

The disease can affect medium-sized vessels throughout the body. In addition to the typical “string-of-beads” appearance or focal lesions, manifestations include arterial tortuosity, aneurysm, and dissection.

**F**ibromuscular dysplasia (FMD) is an uncommon vascular disease that leads to narrowing (with either a beaded appearance or, less commonly, focal stenosis), dissection, or aneurysm of medium-sized arteries. Awareness of FMD within the medical community has rapidly expanded during the past decade owing to heightened interest among clinicians, multicenter coordinated research initiatives, and patient advocacy efforts.

In addition, a better understanding of the clinical manifestations and natural history of the disease along with advances in diagnostic imaging have altered the clinical approach to management. There are many unanswered questions regarding FMD, but this review highlights recent insights and how this information has modified clinical care for those affected.

## ■ DISTINCT FROM ATHEROSCLEROSIS

FMD results from abnormal development of the arterial cell wall, most commonly the vessel media and less commonly the vessel intima (**Figure 1**).<sup>1,2</sup> Distinct from atherosclerotic processes, FMD shares few typical cardiovascular risk factors aside from an association with tobacco smoking.<sup>3,4</sup>

The most common variant of FMD is the multifocal type, with the affected arteries resembling a string of beads due to alternating regions of stenosis and dilation.<sup>1,5</sup> FMD can also cause a singular stenosis (focal type FMD) and has more recently been associated with findings of arterial tortuosity, aneurysm, and dissection.<sup>6,7</sup>

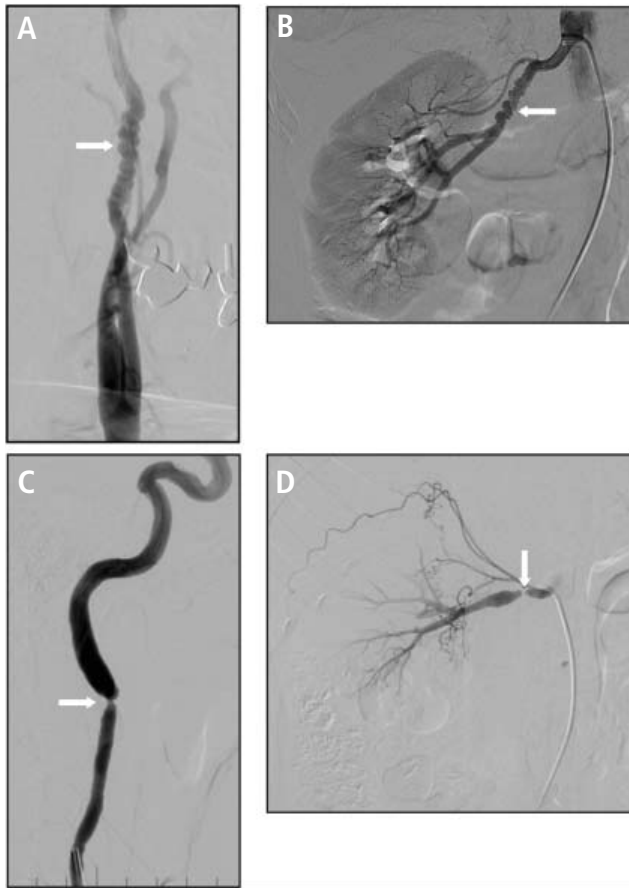
Though the disease typically affects the renal and extracranial carotid arteries, it has been noted in most medium-sized arteries throughout the body, most commonly the mesenteric, external iliac, and brachial arteries.<sup>1</sup> The location of diseased segments determines symptoms, which commonly include hypertension, headache, and pulsatile tinnitus.<sup>8</sup> The overwhelming majority of people affected (> 90%) are women.<sup>8</sup>

The diagnosis of FMD should be suspected in the case of young or middle-aged women presenting with

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**FIGURE 1.** Multifocal fibromuscular dysplasia (FMD) involving the internal carotid artery (A) and a renal artery (B) with a “string-of-beads” appearance. The less common type, focal FMD, involving the internal carotid artery (C) and a renal artery (D).

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migraine headaches, pulsatile tinnitus, or hypertension and for women with cervical bruits without typical risk factors for atherosclerotic disease. The diagnosis should also be suspected among patients who have suffered an arterial dissection or who are found to have a cerebral, carotid, or renal aneurysm.

■ **THE US REGISTRY FOR FMD**

Since it began enrolling patients in 2009, the US Registry for Fibromuscular Dysplasia has grown to include 13 active centers. It collects longitudinal data on the clinical characteristics, presentation, vascular bed involvement, vascular procedures, and clinical outcomes of patients with FMD.<sup>8,9</sup> **Table 1** highlights key findings and lessons learned from registry publications, many of which have altered previous concepts of this disease.<sup>3,7,8,10–12</sup>

■ **EPIDEMIOLOGY AND PATHOPHYSIOLOGY**

**Prevalence**

Although FMD is considered a rare disease (and recognized as such by the National Organization of Rare Diseases), the exact prevalence is unknown. A review of 8 studies conducted from 1963 to 2011 found the prevalence of FMD ranged from 2.0% (3 of 150) to 6.6% (47 of 716) among healthy renal transplant donors for a mean prevalence of 3.3% (268 of 8,029) among all donors.<sup>13–21</sup> Findings from the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, which studied the effectiveness of medical therapy alone vs medical therapy and stenting for treatment of significant renal artery stenosis and hypertension, found that 5.8% (58 of 997) of participants who underwent angiography had concomitant renal FMD.<sup>22</sup> Importantly, patients with FMD were supposed to have been excluded from the trial, suggesting that FMD is often overlooked or underdiagnosed. A review published in 2010 reported the prevalence of cerebrovascular FMD to be 0.3% to 3.2% in patients undergoing cerebral angiography, but it noted significant heterogeneity in patient populations and definitions of FMD across published studies.<sup>23</sup>

**Risk factors for FMD:**

**Female sex and tobacco smoking**

The mechanisms underlying the pathogenesis of FMD are still poorly understood, and its development is likely related to a combination of genetic and environmental factors. There seems to be a hormonal component to the pathogenesis of FMD, as most patients with this condition are women: approximately 91.5% of patients enrolled in the US Registry.<sup>10</sup> Men with FMD, however, seem to have a more aggressive course with a rate of aneurysm or dissection two times higher than that in women with FMD.<sup>7</sup>

Studies have reported an increased risk of FMD in patients with a history of tobacco smoking.<sup>3,24</sup> A US Registry report notes that FMD patients with a history of smoking had a statistically significant higher rate of aneurysm than those who had never smoked (24.8% vs 18.9%), and there was a trend toward increased prevalence of major vascular events in smokers, including subarachnoid hemorrhage, transient ischemic attack, stroke, mesenteric ischemia, renal infarction, and major coronary event.<sup>3</sup> This study also found that patients with FMD who were smokers were more likely to have claudication symptoms (15.1% vs 7.4%) or to have undergone a vascular procedure (45.9% vs 36.7%).<sup>3</sup> Further research is



**TABLE 1**  
**Key findings of publications from the US Registry for Fibromuscular Dysplasia**

Olin et al <sup>8</sup> (2012)	<ul style="list-style-type: none"> <li>• First publication from the US Registry</li> <li>• Extracranial carotid FMD is as common as renal FMD</li> <li>• Defined common symptoms, including hypertension, headache, and pulsatile tinnitus</li> </ul>
Kim et al <sup>10</sup> (2013)	<ul style="list-style-type: none"> <li>• Only 8.5% of registrants were male</li> <li>• Renal involvement was higher in men than in women (89.7% vs 74.1%); extracranial involvement was more common in women than in men (74.9% vs 44.1%)</li> <li>• Compared with women, men were twice as likely to have an aneurysm (40.8% vs 20.4%) or dissection (39.6% vs 20.0%)</li> <li>• Renal artery dissection with flank pain and infarction was a pattern of disease presentation in men with FMD</li> </ul>
Weinberg et al <sup>11</sup> (2015)	<ul style="list-style-type: none"> <li>• High rate of antiplatelet and antihypertensive therapy among registrants</li> <li>• 72.9% of FMD patients were on antiplatelet therapy (58.8% on aspirin alone, 4.6% on clopidogrel only)</li> <li>• 71.7% of patients were on antihypertensive medications, with 21.5% on three or more</li> </ul>
Green et al <sup>12</sup> (2016)	<ul style="list-style-type: none"> <li>• Mean age at the time of diagnosis in pediatric patients was 8.4 ± 4.8 years</li> <li>• Significantly more male patients in the pediatric FMD population vs the adult FMD population (42.2% vs 6.0%)</li> <li>• Compared with adults, pediatric patients more likely to have renal artery involvement (97% vs 69.7%) and mesenteric artery involvement (38.9% vs 16.2%)</li> <li>• More pediatric FMD patients than adult FMD patients reported having a family member with FMD (17.2% vs 4.7%)</li> </ul>
Kadian-Dodov et al <sup>7</sup> (2016)	<ul style="list-style-type: none"> <li>• 21.7% of patients in the registry had an aneurysm, 25.7% had a dissection, and 41.7% had an aneurysm or dissection</li> <li>• Roughly one-third of patients with aneurysm required intervention, most commonly for those found in the extracranial carotid, renal, and intracranial arteries</li> </ul>
O'Connor et al <sup>3</sup> (2016)	<ul style="list-style-type: none"> <li>• 34.5% of patients in the registry were current or former smokers</li> <li>• Smoking history was associated with worse outcomes than in nonsmokers, including an increased need for revascularization (45.9% vs 36.7%), and a higher likelihood of aneurysm (24.8% vs 18.9%) and adverse symptoms such as claudication (15.1% vs 7.4%)</li> </ul>

FMD = fibromuscular dysplasia  
 Data from references 3, 7, 8, 10–12.

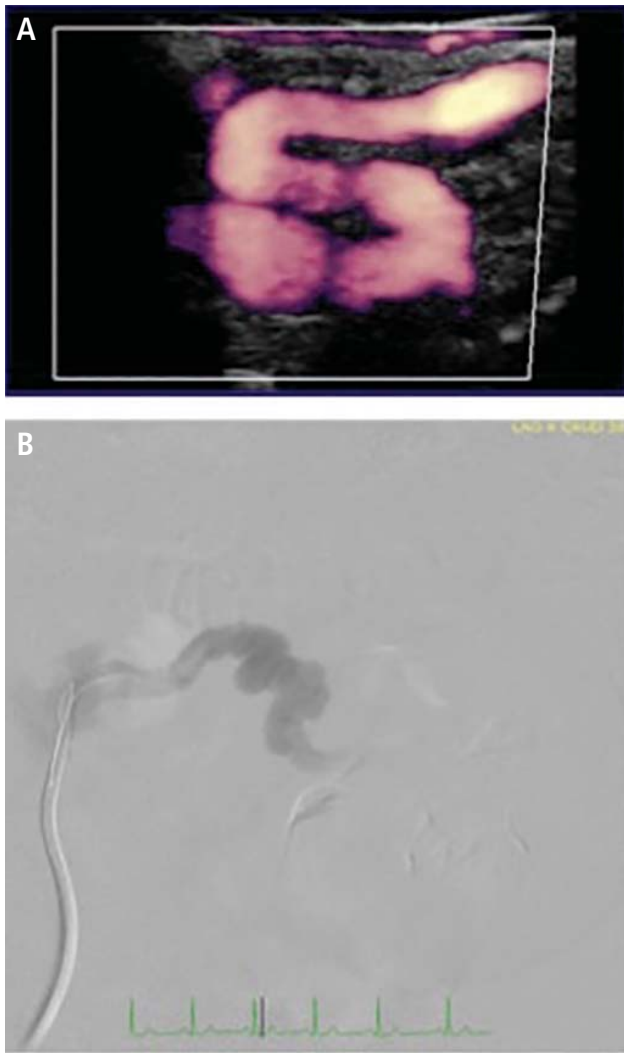
needed to fully understand the relationship between smoking and its interaction with other environmental, hormonal, and genetic factors.

### FMD and connective tissue features

While studies have suggested a genetic component to the development of FMD, the specific genetic mechanisms are unknown.<sup>1</sup> Studies have explored the potential relationship between FMD and genetic connective tissue disorders that can present with vascular manifestations, such as Loeys-Dietz, Marfan, and Ehlers-Danlos syndromes, and isolated case reports have noted concomitant FMD lesions in patients with these classical genetic disorders.<sup>25–31</sup> In a series of patients with FMD from Cleveland Clinic who underwent genetic testing for selected connective tissue disorders, including Ehlers-Danlos syndrome and Loeys-Dietz syndrome, the overall yield of these tests was low.<sup>31</sup> These studies suggest some overlap of FMD

and other vascular connective tissue disorders, as well as the likelihood that the arterial manifestations of FMD may develop through multiple potential genetic pathways.

A series of 47 patients with FMD seen at the National Institutes of Health found a high incidence of connective tissue features on physical examination, with 95.7% of patients exhibiting at least four features of connective tissue disease, including marked hypermobility, scoliosis, craniofacial abnormalities, and pes planus (flat foot deformity).<sup>32</sup> A study of a larger cohort of female patients seen at Cleveland Clinic did not find classical connective tissue features (such as pectus deformity, hypermobility, atrophic scarring, and club foot deformity) to a greater extent than what is reported in the general population, but it did find a significant prevalence of severe myopia (near sightedness), high-arched palate, dental crowding, and early-onset arthritis.<sup>33</sup> Additional studies are



**FIGURE 2.** (A) Duplex ultrasonography with color power angiography in a patient with fibromuscular dysplasia shows arterial tortuosity (the “S curve”) in the internal carotid artery and areas of beading. This feature can also be seen in renal arteries, as shown on angiography (B).

needed to clarify the potential relationship between the spectrum of connective tissue disorders and FMD.

■ **A BROADER SCOPE OF ARTERIAL MANIFESTATIONS**

Since FMD was first described in the 1930s,<sup>34</sup> most case reports have focused on its renal artery manifestations. In 1964, extrarenal involvement was first reported, which included carotid, iliac, and visceral arteries.<sup>35</sup> The medical community has since recognized that the disease can affect medium-sized vessels throughout the body and, more recently, that it is a multifaceted disease with varying arterial manifesta-

tions outside of the typical string-of-beads appearance or focal FMD lesions.<sup>1</sup> In addition to multifocal or focal narrowings, arterial manifestations of FMD include arterial tortuosity, aneurysm, and dissection.

**Arterial tortuosity**

Tortuosity or redundancy of the arteries, particularly the internal carotid arteries, has recently been reported in association with FMD.<sup>6</sup> A study based on vascular ultrasonography findings identified this anatomic variant (described as having the appearance of an S-curvature of the internal carotid artery) in 31.9% (37 of 116) of FMD patients.<sup>6</sup> This rate of tortuosity is higher than that in the general population, especially when compared with patients of similar age (under age 70). Arterial tortuosity is a common finding in FMD and may be seen in other arterial segments (Figure 2).

**Aneurysm and dissection**

Both arterial aneurysm and arterial dissection are recognized as manifestations of FMD. A US Registry report published in 2016 found a high prevalence of aneurysm and dissection in the FMD population.<sup>7</sup> Of the 921 patients included in this analysis, 21.6% had an aneurysm, 25.7% had an arterial dissection, and 41.7% had either aneurysm or dissection. The most common locations for aneurysm were the extracranial carotid, renal, and intracranial arteries, whereas dissection commonly occurred in the extracranial carotid, vertebral, renal, and coronary arteries. The authors noted that these data may be an underestimation, because the entire cohort did not undergo comprehensive screening for asymptomatic aneurysm or dissection. Patients with aneurysm were more likely to have a history of smoking and subarachnoid hemorrhage, while those with dissection were younger and more likely to have headache, neck pain, and end-organ ischemia, including stroke, renal infarction, or myocardial infarction.

**FMD of the coronary arteries**

The association between FMD and spontaneous coronary artery dissection (SCAD) has recently been discovered (Figure 3). SCAD typically presents as troponin-positive acute coronary syndrome.<sup>36</sup> FMD has been identified as a predisposing condition for SCAD in two case series from Vancouver General Hospital<sup>37</sup> and Mayo Clinic.<sup>38</sup> The case series from Mayo Clinic found that 45% of SCAD patients had FMD in the extracoronary vessels; the case series from Vancouver General Hospital found that 72% had FMD. A more recent study found that there seems to

be other manifestations of FMD in the coronary arteries aside from SCAD.<sup>39</sup> In this series, 32 patients with multifocal FMD (in the renal, external iliac, or cerebrovascular arteries) who underwent coronary angiography for suspected symptomatic coronary artery disease (either acute coronary syndrome or stable angina) were found to have coronary artery lesions different from those of atherosclerotic disease. In addition to coronary lesions of dissection (SCAD), the most common findings were marked coronary arterial tortuosity (the “S curve”), followed by areas of atypical-appearing irregular or smooth stenosis. More than half of patients in the series had segments of coronary artery ectasia (enlargement).

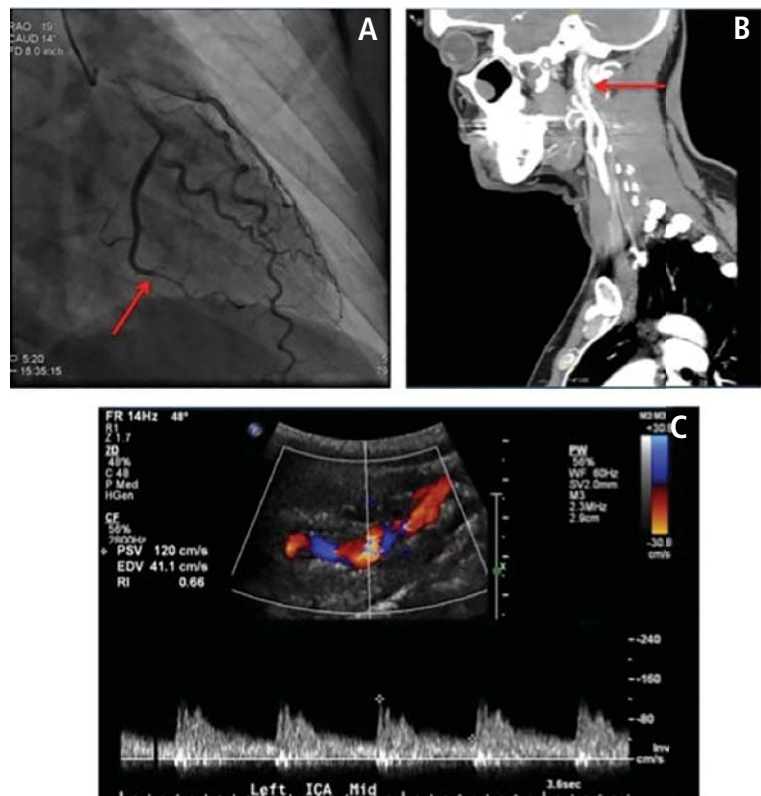
### ■ APPROACH TO MANAGEMENT

There is no cure for FMD, and thus management strategies focus on thorough evaluation and surveillance, lifestyle modification, and treatment of symptoms. Vascular procedures, such as angioplasty or treatment of aneurysms, are required for some patients. Because patients with FMD present with a diverse set of symptoms, consultation with a specialist who has experience with FMD and who works closely with an interdisciplinary team of experts is recommended.<sup>1</sup> The interdisciplinary FMD care team may include a vascular medicine physician, cardiologist, nephrologist, neurologist, neurosurgeon, vascular surgeon, and vascular interventionalist (interventional cardiologist and radiologist).

### Imaging and screening the vasculature in FMD patients

Because of the variability in location and manifestations of FMD and the high prevalence of aneurysm and dissection, all patients should undergo comprehensive one-time head-to-pelvis screening during the workup for FMD.<sup>1,7</sup> Although the technical standard of diagnostic imaging is catheter angiography, noninvasive imaging—computed tomographic angiography (CTA), magnetic resonance angiography (MRA), duplex ultrasonography—is more commonly used to diagnose and monitor the disease.

A study from our group at Cleveland Clinic assessed the utility of a specialized CTA protocol of the chest, abdomen, and pelvis to image and diagnose manifes-



**FIGURE 3.** Spontaneous coronary artery dissection (SCAD) in a 42-year-old woman with fibromuscular dysplasia (FMD) who presented with chest pain and nausea and non-ST-segment elevation myocardial infarction. She was found with coronary angiography to have SCAD of the left circumflex coronary (A, red arrow). Computed tomographic angiography showed a string-of-beads appearance of the left internal carotid artery (B, red arrow). Duplex ultrasonography showed turbulence and tortuosity in the mid to distal left internal carotid artery, consistent with a diagnosis of multifocal carotid FMD (C).

tations of FMD outside of the cerebrovasculature.<sup>40</sup> Incremental findings on imaging included areas of beading or focal narrowing in a new vascular territory and previously undiagnosed arterial aneurysm or dissection. These findings were seen in a variety of vascular beds, including the renal, iliac, and mesenteric arteries, although aortic abnormalities were rare. This study supports the diagnostic value of CTA for FMD to detect asymptomatic aneurysms and areas of arterial dissection, but it also suggests that routine vascular imaging of the thorax may not be necessary.<sup>40</sup> In cases of SCAD, on-table renal and iliac angiography (performed after coronary angiography) can assist in diagnosis of FMD as an underlying cause.<sup>36</sup> The cerebrovascular arteries (carotid, vertebral, and intracranial vessels) can be imaged later with noninvasive imaging (CTA, MRA).

As a general strategy, once patients with FMD undergo comprehensive imaging, a surveillance

program is customized for the patient based on the anatomic location of the disease and the nature of the imaging findings. For example, renal and internal carotid artery FMD may be followed with annual duplex ultrasonography, whereas cerebral and renal or visceral aneurysms require periodic CTA or MRA.

### Medical therapies

The medical regimen for patients with FMD varies based on disease location and symptoms, though there are no definitive treatment guidelines because of limited data. A study from the US Registry found that 72.9% of registrants were treated with antiplatelet medications,<sup>11</sup> and this is a standard approach in our clinical practice for prevention of thromboembolic events. Antiplatelet drug therapy was more common in elderly patients, patients with a history of coronary artery disease or vascular intervention for FMD, and patients with isolated cerebrovascular FMD.<sup>11</sup> Blood pressure management is also important in the medical therapy of patients with FMD who have hypertension. For patients with renal artery involvement, treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker has been suggested.<sup>1</sup>

### Vascular intervention

The need for vascular intervention (eg, angioplasty or endovascular or surgical aneurysm treatment) is determined primarily by symptoms, with renal artery angioplasty for hypertension the most common FMD-related procedure. It is uncommon for vascular intervention to be performed for cerebrovascular FMD in the absence of recurrent transient ischemic attack or stroke despite antiplatelet therapy, arterial dissection that has failed medical management, or sizable aneurysm that requires treatment to prevent rupture.

When considering intervention for renal artery FMD, it is important to note that the appearance of multifocal FMD (beading) on angiography or non-invasive imaging does not reflect the hemodynamic severity of disease: translesional pressure gradients should be measured across the affected artery to determine if there is actually hemodynamic stenosis caused by an area of beading and to select patients for balloon angioplasty.<sup>1</sup> Repeat pressure gradient assessment is done after angioplasty to confirm hemodynamic success.<sup>1</sup> Surgical intervention for renal FMD is uncommon. It is generally reserved for complex cases in which endovascular techniques have failed.<sup>1</sup>

Asymptomatic patients with cerebral, visceral, or arterial aneurysm may require endovascular or surgical treatment. If surgery is indicated, the treatment approach (coiling, stenting, or open surgery)

is determined by the size and location of the aneurysm, patient-related factors that may influence the risk of rupture (eg, uncontrolled hypertension, family history of ruptured aneurysm), the anatomic characteristics of the aneurysm, and the feasibility of endovascular vs open surgical repair. A US Registry study of 200 patients with an aneurysm reported that 31.5% underwent intervention to treat the aneurysm.<sup>7</sup> Aneurysms requiring intervention were most commonly noted in the extracranial carotid, renal, and intracranial arteries.<sup>7</sup>

### CONCLUSION

Awareness and understanding of FMD have substantially improved in recent years, and this has translated into better care for many patients with FMD. Important advancements have included the recognition of the variability of manifestations of this disease—ranging from an arterial string-of-beads appearance to aneurysm, dissection, and tortuosity—and establishing the need for comprehensive vascular imaging screening in FMD patients. Establishing the association of FMD with SCAD has led to better care for patients with SCAD and presents the opportunity to optimize management of these patients to prevent further vascular events. Research initiatives and heightened awareness have provided valuable insight into this disease, but further work is needed to determine the causal mechanisms of FMD and to continue to develop better management strategies.

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**ENTRESTO™ (sacubitril and valsartan) tablets, for oral use**  
**Initial U.S. Approval: 2015**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

**WARNING: FETAL TOXICITY**

- **When pregnancy is detected, discontinue ENTRESTO as soon as possible (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.1)**

**1 INDICATIONS AND USAGE**

**1.1 Heart Failure**

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

**4 CONTRAINDICATIONS**

ENTRESTO is contraindicated:

- in patients with hypersensitivity to any component
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy [see *Warnings and Precautions (5.2)*]
- with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor [see *Drug Interactions (7.1)*]
- with concomitant use of aliskiren in patients with diabetes [see *Drug Interactions (7.1)*].

**5 WARNINGS AND PRECAUTIONS**

**5.1 Fetal Toxicity**

ENTRESTO can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue ENTRESTO. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus [see *Use in Specific Populations (8.1)*].

**5.2 Angioedema**

ENTRESTO may cause angioedema. In the double-blind period of PARADIGM-HF, 0.5% of patients treated with ENTRESTO and 0.2% of patients treated with enalapril had angioedema [see *Adverse Reactions (6.1)*]. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

ENTRESTO has been associated with a higher rate of angioedema in Black than in non-Black patients.

Patients with a prior history of angioedema may be at increased risk of angioedema with ENTRESTO [see *Adverse Reactions (6.1)*]. ENTRESTO should not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy [see *Contraindications (4)*].

**5.3 Hypotension**

ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. In the double-blind period of PARADIGM-HF, 18% of patients treated with ENTRESTO and 12% of patients treated with enalapril reported hypotension as an adverse event [see *Adverse Reactions (6.1)*], with hypotension reported as a serious adverse event in approximately 1.5% of patients in both treatment arms. Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue ENTRESTO. Permanent discontinuation of therapy is usually not required.

**5.4 Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO. In the double-blind period of PARADIGM-HF, 5% of patients in both the ENTRESTO and enalapril groups

reported renal failure as an adverse event [see *Adverse Reactions (6.1)*]. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)* in the full prescribing information].

As with all drugs that affect the RAAS, ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

**5.5 Hyperkalemia**

Through its actions on the RAAS, hyperkalemia may occur with ENTRESTO. In the double-blind period of PARADIGM-HF, 12% of patients treated with ENTRESTO and 14% of patients treated with enalapril reported hyperkalemia as an adverse event [see *Adverse Reactions (6.1)*]. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of ENTRESTO may be required [see *Dosage and Administration (2.1)* in the full prescribing information].

**6 ADVERSE REACTIONS**

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Angioedema [see *Warnings and Precautions (5.2)*]
- Hypotension [see *Warnings and Precautions (5.3)*]
- Impaired Renal Function [see *Warnings and Precautions (5.4)*]
- Hyperkalemia [see *Warnings and Precautions (5.5)*]

**6.1 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 practice.

In the PARADIGM-HF trial, subjects were required to complete sequential enalapril and ENTRESTO run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized double-blind period comparing ENTRESTO and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the ENTRESTO run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice.

In the double-blind period, safety was evaluated in 4,203 patients treated with ENTRESTO and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to ENTRESTO received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of ENTRESTO treated patients and 516 (12.2%) of patients receiving enalapril.

Adverse reactions occurring at an incidence of  $\geq 5\%$  in patients who were treated with ENTRESTO in the double-blind period are shown in Table 1.

**Table 1: Adverse Reactions Reported in  $\geq 5\%$  of Patients Treated with ENTRESTO in the Double-Blind Period**

	<b>ENTRESTO (n = 4,203) %</b>	<b>Enalapril (n = 4,229) %</b>
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

In the PARADIGM-HF trial, the incidence of angioedema was 0.1% in both the enalapril and ENTRESTO run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with ENTRESTO than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with ENTRESTO and 0.5% with enalapril [see *Warnings and Precautions (5.2)*].

Orthostasis was reported in 2.1% of patients treated with ENTRESTO compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with ENTRESTO compared to 1.3% of patients treated with enalapril.

### Laboratory Abnormalities

#### Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of >20% were observed in approximately 5% of both ENTRESTO- and enalapril-treated patients in the double-blind period in PARADIGM-HF.

#### Serum Creatinine

Increases in serum creatinine of >50% were observed in 1.4% of patients in the enalapril run-in period and 2.2% of patients in the ENTRESTO run-in period. During the double-blind period, approximately 16% of both ENTRESTO- and enalapril-treated patients had increases in serum creatinine of >50%.

#### Serum Potassium

Potassium concentrations >5.5 mEq/L were observed in approximately 4% of patients in both the enalapril and ENTRESTO run-in periods. During the double-blind period, approximately 16% of both ENTRESTO- and enalapril-treated patients had potassium concentrations >5.5 mEq/L.

## **7 DRUG INTERACTIONS**

### **7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System**

Concomitant use of ENTRESTO with an ACE inhibitor is contraindicated because of the increased risk of angioedema [see *Contraindications (4)*].

Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan.

The concomitant use of ENTRESTO with aliskiren is contraindicated in patients with diabetes [see *Contraindications (4)*]. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m<sup>2</sup>).

### **7.2 Potassium-Sparing Diuretics**

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium [see *Warnings and Precautions (5.5)*].

### **7.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)**

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

### **7.4 Lithium**

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

ENTRESTO can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, ENTRESTO treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits. When pregnancy is detected, consider alternative drug treatment and discontinue ENTRESTO. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

##### Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to ENTRESTO for hypotension, oliguria, and hyperkalemia. In neonates with a history of

*in utero* exposure to ENTRESTO, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

#### Data

##### Animal Data

ENTRESTO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses  $\geq$  49 mg sacubitril/51 mg valsartan/kg/day ( $\leq$  0.14 [LBQ657, the active metabolite] and 1.5 [valsartan]-fold the maximum recommended human dose [MRHD] of 97/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses  $\geq$  5 mg sacubitril/5 mg valsartan/kg/day (4-fold and 0.06-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). ENTRESTO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at an ENTRESTO dose of  $\geq$  5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of ENTRESTO are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (4.5-fold the MRHD on the basis of LBQ657 AUC) and valsartan at doses up to 600 mg/kg/day (0.86-fold the MRHD on the basis of AUC) indicate that treatment with ENTRESTO during organogenesis, gestation and lactation may affect pup development and survival.

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with ENTRESTO.

#### Data

Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [<sup>14</sup>C] ENTRESTO to lactating rats, transfer of LBQ657 into milk was observed. After a single oral administration of 3 mg/kg [<sup>14</sup>C] valsartan to lactating rats, transfer of valsartan into milk was observed.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **8.5 Geriatric Use**

No relevant pharmacokinetic differences have been observed in elderly ( $\geq$ 65 years) or very elderly ( $\geq$ 75 years) patients compared to the overall population [see *Clinical Pharmacology (12.3) in the full prescribing information*].

### **8.6 Hepatic Impairment**

No dose adjustment is required when administering ENTRESTO to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patients with moderate hepatic impairment (Child-Pugh B classification) is 24/26 mg twice daily. The use of ENTRESTO in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients [see *Dosage and Administration (2.4) in the full prescribing information, Clinical Pharmacology (12.3) in the full prescribing information*].

### **8.7 Renal Impairment**

No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m<sup>2</sup>) to moderate (eGFR 30 to 60 mL/min/1.73 m<sup>2</sup>) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR <30 mL/min/1.73 m<sup>2</sup>) is 24/26 mg twice daily [see *Dosage and Administration (2.3) in the full prescribing information, Warnings and Precautions (5.4) and Clinical Pharmacology (12.3) in the full prescribing information*].

## **10 OVERDOSAGE**

Limited data are available with regard to overdosage in human subjects with ENTRESTO. In healthy volunteers, a single dose of ENTRESTO 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of ENTRESTO. Symptomatic treatment should be provided.

ENTRESTO is unlikely to be removed by hemodialysis because of high protein binding.

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"NOW I CAN ONLY MAKE IT HALFWAY UP BEFORE I HAVE TO CATCH MY BREATH."

Your patient is telling you about her heart failure symptoms, a sign of increased risk of HF hospitalization and death.<sup>1,2</sup>

ACC/AHA/HFSA  
GUIDELINE  
RECOMMENDED  
**CLASS I**<sup>3</sup>  
LEVEL OF EVIDENCE B-R



**Entresto**<sup>®</sup>  
(sacubitril/valsartan) tablets

24/26mg • 49/51mg • 97/103mg

ENTRESTO<sup>®</sup> reduced the risk of CV death or HF hospitalization as first event vs enalapril<sup>4</sup>

When you see symptoms, there's risk, so it's time for **ENTRESTO**.

#### INDICATION

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

#### IMPORTANT SAFETY INFORMATION

##### WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue ENTRESTO as soon as possible
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

ENTRESTO is contraindicated in patients with hypersensitivity to any component. ENTRESTO is contraindicated in patients with a history of angioedema related to previous angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy.

ENTRESTO is contraindicated with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor. ENTRESTO is contraindicated with concomitant use of aliskiren in patients with diabetes.

**Angioedema:** ENTRESTO may cause angioedema. Angioedema associated with laryngeal edema may be fatal. ENTRESTO has been associated with a higher rate of angioedema in Black patients and in patients with a prior history of angioedema. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered.

**Hypotension:** ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose. If hypotension persists despite dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia) reduce the dosage or temporarily discontinue ENTRESTO. Permanent discontinuation of therapy is usually not required.

**Impaired Renal Function:** Decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function.

ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m<sup>2</sup>).

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure.

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These effects are usually reversible. Monitor renal function periodically.

**Hyperkalemia:** Hyperkalemia may occur with ENTRESTO. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of ENTRESTO may be required.

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

**ARBs:** Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan.

**Lithium:** Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

**Common Adverse Events:** In a clinical trial, the most commonly observed adverse events with ENTRESTO vs enalapril, occurring at a frequency of at least 5% in either group, were hypotension (18%, 12%), hyperkalemia (12%, 14%), cough (9%, 13%) dizziness (6%, 5%) and renal failure/acute renal failure (5%, 5%).

**Please see Brief Summary of Prescribing Information, including Boxed WARNING, on following pages.**

**STUDY DESIGN:** PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO to enalapril in symptomatic (NYHA class II-IV) adult HF/EF patients (left ventricular ejection fraction ≤40%). After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice daily, followed by ENTRESTO 100 mg (49/51 mg) twice daily, increasing to 200 mg (97/103 mg) twice daily. Patients were then randomized to receive either ENTRESTO 200 mg (97/103 mg) (n=4209) twice daily or enalapril 10 mg (n=4233) twice daily. The median follow-up duration was 27 months, and patients were treated for up to 4.3 years. At the primary end point, the first event in the composite of CV death or first HF hospitalization, ENTRESTO was superior to enalapril,  $P < 0.0001$ .<sup>4</sup>

ACC=American College of Cardiology; AHA=American Heart Association; HFSA=Heart Failure Society of America; B-R=Class of Recommendation B, randomized trial; CV=cardiovascular; HF=heart failure; NYHA=New York Heart Association; HF/EF=heart failure with reduced ejection fraction; ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker.

For more information, visit [EntrestoHCP.com](http://EntrestoHCP.com)