HOPE-3
Findings support expanding statin use in intermediate CV risk populations

Chest Pain Choice
Shared decision-making benefits patients in ED, reduces resource utilization

TVT Registry
TAVR clinical outcomes improve with increasing procedure volume

DANAMI 3
Delayed stenting, ischemic postconditioning show negative results

PARTNER 2A | SAPIEN 3
TAVR proves noninferior, superior to surgery in patients with severe aortic stenosis

GAUSS-3
Evolocumab bests ezetimibe for LDL reduction in statin-intolerant patients
Annual ACC Scientific Session steeped in innovation

Nearly 19,000 attendees at the American College of Cardiology 65th Annual Scientific Session learned the latest innovations in CV research and patient management over 3 information-packed days in Chicago, with new data on prevention and treatment approaches poised to change the landscape of patient care.

Interdisciplinary and interactive educational opportunities including several named lectures focusing on front-and-center clinical issues, 2,400 posters and oral presentations featuring cutting-edge science, and two dozen late-breaking clinical trials set the stage for a memorable meeting.

Three reports from the HOPE-3 trial offered clarity to quandaries surrounding the use of therapies to lower BP and cholesterol in populations with intermediate CV risk, while findings from GAUSS-3 shed light on the potential role of PCSK9 inhibitors in patients with statin intolerance.

The Chest Pain Choice trial elucidated the effect of shared-decision making on patients and clinicians, and results from the TVT Registry demonstrated the impact of procedure experience on outcomes. In intervention, promising data from the PARTNER 2A and SAPIEN 3 trials, along with negative findings from DANAMI 3, were welcomed equally as signs of progress.

This CARDIOLOGY TODAY supplement gives a glimpse of the groundbreaking research, with perspectives from key opinion leaders providing context for practice and the future of the field. — The Publishers of CARDIOLOGY TODAY

HOPE-3

Findings support expanding statin use in intermediate CV risk populations

It’s interesting that we have focused a little on primary prevention, in people before they develop any disease or risk factors, and we spend much of our time in cardiology on people who have already had an event, or secondary prevention. What about those people who fall in between? They have risk factors that we know will result in problems later on if we don’t do something. The question is whether or not we could actually treat them and improve their outcome. There were three different aspects of the HOPE-3 trial: treating BP, treating lipids and treating both. The data were quite remarkable. It showed that if you try and treat people without any known disease — just risk factors — with an antihypertensive agent, they actually do much better if their BP is a little high or borderline than if their BP starts off low. Unlike the antihypertensive treatment, the lipid treatment seemed to help just about everyone. It really didn’t matter what their baseline lipids were; they were going to have a decrease in events if they were treated with a statin. When you look at the combined approach portion of the trial, using both pills, a lot of the stories, benefit, which we normally think would result from antihypertensive therapy, was attributed to statins. It appears statins won the day, and antihypertensive therapy should really be reserved for people with elevated BP.

— Kim Allan Williams Sr., MD, FAC

James B. Herrick Professor and Chief, Division of Cardiology
Rush University Medical Center, Chicago
Editorial Board Member, CARDIOLOGY TODAY
Immediate Past President, ACC

Disclosure: Williams reports no relevant financial disclosures.

HOPE-3 BP-Lowering, Cholesterol-Lowering in Intermediate-Risk Individuals without CVD

The trial evaluated antihypertensive therapy, cholesterol lowering therapy and a combination of both in patients at intermediate CV risk.

Design: double-blind, randomized, placebo-controlled, 2-by-2 factorial

Patients: 12,075
Centers: 228
Countries: 21

RESULTS: The first coprimary composite outcome including death from CV causes, nonfatal MI or nonfatal stroke occurred in 260 participants (4.1%) on antihypertensive therapy vs. 279 participants (4.4%) on placebo (HR = 0.94; 95% CI, 0.79-1.10); the second coprimary outcome, additionally including resuscitated cardiac arrest, HF and revascularization, occurred in 312 (4.9%) vs. 328 (5.2%), respectively (HR = 0.9, 95% CI, 0.81-1.13). Further, the first outcome occurred in 235 participants (3.7%) on statin therapy vs. 304 participants (4.8%) on placebo (HR = 0.76; 95% CI, 0.64-0.91) and the second outcome in 277 (4.4%) vs. 363 (5.7%), respectively (HR = 0.75; 95% CI, 0.64-0.88). Finally, the first outcome occurred in 113 participants (3.6%) on combined therapy vs. 157 participants (5.8%) on placebo (HR = 0.71; 95% CI, 0.56-0.9), and the second outcome in 136 (2.1%) vs. 187 (3.0%), respectively (HR = 0.72; 95% CI, 0.57-0.89).


References:


**Involving Patients with Low-Risk Chest Pain in Decision tree**

This clinical trial from the Transcatheter Valve Therapy Registry — comprising more than 40,000 patient records from commercial use in the United States, from 2011 when transcatheter aortic valve replacement was approved to November 2015 — looked at the impact of experience and case volume on outcomes. The researchers showed what we’ve already learned with a lot of procedures in medicine: with improving experience, results improve. As the centers got higher case volume, the acute in-hospital outcomes improve with lower mortality, lower bleeding and lower vascular complications. The findings highlight it is important to concentrate this experience right now in some centers where it is possible to have a reasonable volume. As we grow more experience, we can continue to hope to have improving outcomes with TAVR and continue to move the field forward.

— Amar Krishnaswamy, MD

**Editorial Board Member, Robert and Suzanne Tomsich Department of Cardiovascular Medicine**

**Disclosure:** Krishnaswamy reports no relevant financial disclosures.

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**Clinical outcomes improve with increasing procedure volume**

**PERSPECTIVES**

**Chest Pain Choice**

Shared decision-making benefits patients in ED, reduces resource utilization

**TVT Registry**

TAVR clinical outcomes improve with increasing procedure volume

**The average mortality rate following TAVR, adjusted to account for patient risk**

**4.03%**

**RESULTS:** Among 370 hospitals (total 36,292 procedures) in the TVT Registry during the study period, the site-level annual volume range was 1 to 161 (IQR 22-49; median 32; mean 38). The unadjusted in-hospital mortality rate ranged from 0% to 25%, (IQR 2.5%-5.9%; median 4.6%; mean 4.3%). The average mortality rate following TAVR, adjusted to account for patient risk, was 4.03% (IQR 3.7%-4.4%). Volume-outcome associations were seen for vascular and bleeding complications but not for stroke, which occurred in 2%.

**Disclosure:** Hess reports research support from Edwards Lifesciences and Medtronic; honorary from St. Jude Medical, and a scientific advisory board role for Thombrix Aortic Valve Inc.

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**Chest Pain Choice**

Involving Patients with Low-Risk Chest Pain in Decision tree

The trial determined if shared decision-making using a decision aid increases patient knowledge and decision quality, and safely reduces resource use.

**Results:** Patients demonstrated increased knowledge with the Chest Pain Choice aid compared with standard care (4.23 vs. 3.56, respectively; P < .001) as well as greater engagement (18 vs. 8, respectively; P < .001). There was no difference in MACE between groups. With the aid, fewer patients were admitted to the ED observation unit for stress testing or coronary CT (P < .001), and fewer patients underwent stress testing (P < .013) or coronary CT (P = .12) within 30 days.

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**Clinicians felt the tool helped them in explaining the risks for potential complications**

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**TVT Registry**

Relationship Between TAVR Volume and Outcomes in U.S. Clinical Practice

The researchers evaluate the volume-outcome relationship for all hospitals submitting consecutive cases in the Society of Thoracic Surgeons/AACC TVT Registry from November 2011 to July 2015.

— Susheel Kodali, MD

**Director, Structural Heart and Valve Center**

**NewYork-Presbyterian/Columbia University Medical Center**

**Disclosure:** Kodali reports research support from Edwards Lifesciences and Medtronic; honorary from St. Jude Medical, and a scientific advisory board role for Thombrix Aortic Valve Inc.

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**DISCUSSION**

**TAVR**

This is an interesting study looking at the use of shared decision-making for low-risk chest pain in the emergency department. It sought to determine whether giving a decision-making tool to patients and physicians in the ED could help increase patient knowledge and still be done safely for those coming in with low-risk chest pain and unstable angina. The study investigators randomized almost 1,000 patients to the use of the tool to help communicate their risks for having an adverse event if they were to get testing in the ED in the hospital or if they were to go home and visit their physician for testing soon afterwards. The study essentially showed that while patients felt slightly better and slightly more informed, clinicians felt the tool helped them quite a bit in explaining the risks for potential complications. Overall, the rate of adverse events was basically equivalent in both arms. Ideally, the study would be a lot larger to determine that, because one of the reasons physicians keep people in the ED is they are worried about sending them out too early and them potentially having an event. By transferring some of the decision-making onto the patients and helping them to better understand their risks, we can see if this ought to be established in clinical practice as a way to allow patients to choose — more than just the physicians themselves or the legal system. The field can anticipate more to come from this as a whole.

— Ajay J. Kirtane, MD, SM

**Interventional Cardiologist, NewYork-Presbyterian/Columbia University Medical Center**

**Disclosure:** Kirtane reports no relevant financial disclosures.

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**RESUULTS**

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The DANAMI 3-DEFER trial compared deferred vs. conventional stenting in patients with STEMI. The concept has been of interest in patients with a large thrombus because immediate stenting may lead to distal embolization and microvascular obstruction. The hypothesis is that by performing balloon angioplasty, giving anticoagulation and waiting a few days, much of the thrombus will have dissolved, then stenting will be safer.

The researchers randomized about 1,200 patients to either strategy and saw no difference in the primary outcomes of death, MI, HF and unplanned revascularization. These are important findings because although some small studies looking at surrogate outcomes have suggested this was an effective therapy, this is the largest study performed and does not show any benefit. Several ongoing randomized trials are also investigating deferred stenting; however, these data would suggest the strategy is not likely to be successful, which is important to avoid putting the patient through two procedures rather than a single procedure.

The DANAMI 3-IPost study from the same group randomized a similar number of patients to either standard balloon angioplasty and stenting vs. ischemic post-conditioning – essentially doing prolonged inflations in an attempt to reduce reperfusion injury once the artery is opened. Previous data have suggested it is possible to reduce reperfusion injury by opening and closing the artery with the balloon during primary PCI. This is the largest study that tests the hypothesis, and it shows no reduction in the primary outcome of all-cause mortality and hospitalization for HF in this trial. This is also an extra step for physicians to do; if it’s not effective, we shouldn’t be doing it. Therefore, this was another important study, albeit negative.

In terms of optimizing treatment for patients with ACS in STEMI, neither DANAMI 3-DEFER nor DANAMI 3-IPOST demonstrated findings that advance care in any major way. Deferred stent implantation, or waiting 48 hours rather than treating immediately in the cath lab if the vessel is open, was not beneficial in the DANAMI 3-DEFER trial. Many of us felt fortunate and pleased to see these results because we certainly would prefer to do one procedure instead of two – which is also likely much less expensive.

While there were some glimpses of possible benefits in the DANAMI 3-IPOST trial of postconditioning to reduce reperfusion injury, the major endpoints here were also negative.

These two well-done negative trials emphasize how far the field has come in treating patients with STEMI.

The bottom line is patient outcomes are very good compared to where we were a decade ago before primary PCI was widespread, but we can still make the outcomes of primary PCI better by using optimal pharmacology and devices, and getting patients to the cath lab for appropriate diagnoses and triage to definitive therapy as soon as possible.

— Gregg W. Stone, MD
Director of Cardiovascular Research and Education, Center for Interventional Vascular Therapy
NewYork-Presbyterian Hospital/Columbia University Medical Center
Editorial Board Member, CARDIOLOGY TODAY’S INTERVENTION
Disclosure: Stone reports no relevant financial disclosures.

No reflow happens after balloon angioplasty, but more frequently after stenting. The hope of DANAMI DEFER-3 was to avoid some of that phenomenon with deferred stenting; this is important because no reflow is associated with increased risks for periprocedural MI and mortality.

Attempted solutions for no reflow so far have not worked much — other than intracoronary medications like nicardipine or other similar classes of drugs — and deferring stenting did not show any benefit.

Thrombectomy devices were used almost 60% of the time, and this is a practice interventional cardiologists are actually walking away from. Still, there was no difference between immediate vs. deferred stenting.

Deferred stenting was not really causing much complication or acute vessel closure. There was increased revascularization. But at the end of the day it did not translate into hard clinical endpoints. The other perspective is if an interventional cardiologist does not find it necessary to stent, or avoids stenting immediately during the initial primary PCI, that also has been shown to be safe in this trial.

Likewise, in the iPOST segment of the trial, postconditioning did not work and did not translate into improved clinical endpoints. Most of the focus nowadays is on preconditioning, and although it did decrease MI size, it did not actually translate into clinical difference either. So the jury is still out on that.

At this stage of interventional procedures in primary PCI, we have achieved a lot of progress in terms of skill set, devices and pharmacotherapy. To realize any more advancement is going to take a lot of work and a lot of patients to study to be able to improve on the current state of care for primary PCI.

Part of this could be looking into new fields in terms of initial care, educating patients for early contact and symptom recognition. We must think about global care of MI; in the developed world, about four-fifths of humanity does not have access to this care.

The next thing is to offer the standard of care that we enjoy in the U.S. and Europe to the rest of the world — in Asia, Africa and poorer parts of Europe and South America. This is the next challenge.

— Khaldoon Alaswad, MD, FACC, FSCAI
Director, Cardiac Catherization Laboratory
Edith and Benson Ford Heart & Vascular Institute, Henry Ford Hospital, Detroit
Governor, Michigan Chapter, ACC
Disclosure: Alaswad reports no relevant financial disclosures.
Select IMPORTANT SAFETY INFORMATION (CONT’D)

**WARNING:** SPINAL/EPIDURAL HEMATOMA

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS 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 nonsteroidal 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 ELIQUIS 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.

**CONTRAINDICATIONS**

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

**WARNINGS AND PRECAUTIONS**

- Increased Risk of Thrombotic Events After Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

- Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

  Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.

  – Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients in poor anticoagulation control.

  – There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.

- Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medical products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- Prothrombotic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

- Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

**ADVERSE REACTIONS**

- The most common and serious adverse reactions reported with ELIQUIS were related to bleeding.

**TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS**

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

**DRUG INTERACTIONS**

- **Strong Dual Inhibitors of CYP3A4 and P-gp**: Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.

- **Strong Dual Inducers of CYP3A4 and P-gp**: Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thrombotic events.

- **Anticoagulants and Antiplatelet Agents**: Coadministration of anticoagulants, heparin, aspirin, and chronic NSAID use (e.g., ibuprofen, celecoxib, naproxen) increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

**PREGNANCY CATEGORY B**

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

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**ELIQUIS is the #1 most prescribed oral anticoagulant among cardiologists for new patient starts**

Explore the efficacy and safety data

*Based on IMS SDI VECTOR New-to-brand Prescription Database (NBRx). Oral anticoagulant prescriptions were written by cardiologists and filled by patients who did not have any prescriptions filled for that same oral anticoagulant in the previous 6 months. Claims valid as of 1/1/15 to 9/25/15.

**INDICATIONS**

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

ELIQUIS is indicated for the treatment of DVT and PE, and to reduce the risk of recurrent DVT and PE following initial therapy.

**SELECTED IMPORTANT SAFETY INFORMATION**

**WARNING:** (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

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

Please see additional Important Safety Information, including continued Boxed WARNINGS, on adjacent page.
**ELIQUIS® (apixaban) tablets, for oral use**

**Brief Summary of Prescribing Information.** For complete prescribing information consult official package insert.

**WARNING:** PREMIATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF TIME-RELATED EVENTS

**SPINAL EPIDURAL HEMATOMA**

(A) PREMIATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF TIME-RELATED EVENTS

Procedure discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of time-related events. If anticoagulation is discontinued for a reason other than major orthopedic surgery or completion of a course of therapy, cover with another antiplatelet agent, another anticoagulant or prophylactic dose of an infusion of unfractionated heparin.

(B) SPINAL/EPIDURAL HEMATOMA

Spinal or epidural hematomas, including those without neurologic sequelae, have been reported with the use of ELIQUIS, an oral direct factor Xa inhibitor, in patients undergoing neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in an acute onset of back pain, paraplegia, paraparesis, or bowel/bladder dysfunction. The neurologic deficits may vary from minor and transient to complete, permanent paralysis, and loss of bladder and bowel function.

The risk of these events may be increased by: (1) the performance of neuraxial anesthesia or the concurrent use of another antiplatelet agent, another anticoagulant, and an infusion of another medication used for long-term anticoagulation therapy; (2) inadequate reversal of anticoagulation therapy at the time of neuraxial anesthesia; (3) neuraxial anesthesia or puncture performed after the administration of ELIQUIS for 5 days. If a patient has symptoms consistent with a spinal hematoma, stop ELIQUIS immediately and report the event to Pfizer.

**ANGIOEDEMA**

ELIQUIS is contraindicated in patients with the following conditions:

- Severe hepatic impairment
- Severe renal impairment
- History of anaphylaxis
- History of angioedema
- History of hives or urticaria
- History of a spinal or epidural puncture

**ADVERSE REACTIONS**

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Allergic reactions
- Anaphylaxis
- Angioedema
- Arthralgia
- Asthma
- Blood pressure decrease
- Bruising or bleeding
- Coagulopathy
- Congestive heart failure
- Convulsion
- Coughing
- Dental pain
- Decreased appetite
- Decreased hemoglobin
- Decreased hematocrit
- Decreased red blood cells
- Dehydration
- Diaphoresis
- Dizziness
- Dyspnea
- Ectopic crest
- Edema
- Edema of the legs
- Epistaxis
- Eye pain
- Fatigue
- Fever
- Flushing
- Focal weakness
- Gastric hemorrhage
- Gastrointestinal hemorrhage
- Gastrointestinal perforation
- Gastrointestinal ulcer
- Glomerulonephritis
- Headache
- Hemolytic anemia
- Hiccups
- Hiccups and vomiting
- Hypotension
- Hyperventilation
- Hypomania
- Hypotension
- Hypovolemia
- Hyperglycemia
- Hypothermia
- Hypotension
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Round:

- **endpoint of major bleeding** (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).
- In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).
- The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days.
- **Adverse Reactions:**

  - Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, conjunctival hemorrhage, rectal hemorrhage, incision-site hematoma, operative hemorrhage, and urethral hemorrhage.
  - Hepatobiliary disorders: aminotransferase increased and alanine aminotransferase abnormal.
  - Transaminases increased (including alanine aminotransferase increased).
  - Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery were: menorrhagia, ecchymosis, skin hemorrhage, petechiae.
  - **Common adverse reactions:**

    - **GI lesions:** gastrointestinal ulcer, gastrointestinal perforation, gastrointestinal obstruction, gastrointestinal perforation, gastrointestinal obstruction, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal obstruction, gastrointestinal hemorrhage.
    - **Respiratory system and breast disorders:** mastalgia, childhood (including breast feeding), mastalgia, childhood (including breast feeding).
    - **Musculoskeletal and connective tissue disorders:** subcutaneous tissue necrosis.
    - **Blood and lymphatic system disorders:** hemorrhagic anemia.
    - **Nervous system disorders:** headache.
    - **General disorders and administration-site conditions:** local injection-site reaction.
    - **Reproductive system and breast disorders:** breast pain.
    - **Hematological disorders:** thrombocytopenia (including platelet count decreases).
    - **Conjunctival hemorrhage, rectal hemorrhage, incision-site hematoma, operative hemorrhage, and urethral hemorrhage.
    - **Drug Interactions:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban.

**Table 3: Blinding Results in the AMPLIFY Study**

<table>
<thead>
<tr>
<th>ELIQUIS 2.5 mg bid</th>
<th>ELIQUIS 5 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=840</td>
<td>N=811</td>
<td>N=2689</td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td><strong>Majors</strong></td>
<td><strong>Majors</strong></td>
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</tr>
<tr>
<td><strong>CMR</strong></td>
<td>23 (2.8)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td><strong>CMR + CRNM</strong></td>
<td>27 (3.2)</td>
<td>22 (2.7)</td>
</tr>
<tr>
<td><strong>CMR</strong></td>
<td>75 (8.9)</td>
<td>90 (10.4)</td>
</tr>
<tr>
<td><strong>CMR + CRNM</strong></td>
<td>121 (14.5)</td>
<td>24 (0.7)</td>
</tr>
<tr>
<td><strong>CRNM</strong></td>
<td>54 (6.5)</td>
<td>60 (1.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2676</td>
<td>3359</td>
</tr>
</tbody>
</table>

**Table 4: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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<tr>
<th>ELIQUIS (apixaban)</th>
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**Table 7: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 8: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 10: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 11: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 12: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 13: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 14: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 15: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 16: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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**Table 19: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study**

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</table>
PARTNER 2A, which randomized intermediate-risk patients between TAVR and surgery, and SAPIEN 3, which compared the newest-generation SAPIEN device (Edwards Lifesciences) with a propensity-matched surgical group from PARTNER 2A, were both very exciting trials and important trials in the TAVR literature. The bottom line finding of PARTNER 2A was that TAVR was non-inferior to surgery in the major outcomes of death and stroke, and there was a statistical suggestion in the group who underwent TAVR via trans femoral route, that it may be superior. The SAPIEN 3 data actually demonstrated that the trans femoral approach for TAVR was superior to surgery in intermediate-risk patients for these same outcomes. While the SAPIEN 3 trial data do not theoretically have the statistical rigor of a randomized trial, it does dovetail with the findings from PARTNER 2A. Furthermore, the propensity-matching in SAPIEN 3 was very rigorous; the PARTNER 2A surgical patients were carefully selected, and there was no major difference in surgical techniques or surgical outcomes in terms of the timing of PARTNER 2A and SAPIEN 3 enrollments. It is still a very reasonable comparison, despite the statistical criticisms that will be made about the SAPIEN 3 data.

To date, all of our AVR procedures have been performed for commercial purposes in either high-risk or inoperable patients because those are the patients for whom the procedure is FDA-approved on the basis of clinical trials. Hopefully, the findings of these pivotal trials will result in an expanded indication for TAVR in the intermediate-risk population, but that will require time for the FDA to review the data. It is important to mention that the excellent results achieved with TAVR, and the excellent results demonstrated in PARTNER 2A and SAPIEN 3, are all due to a multidisciplinary heart team approach — meaning patients were assessed by interventional cardiologists, cardiac surgeons and an entire team of nurses and other health extenders. Therefore, it is not to say that for a given patient with intermediate risk, TAVR is always better or surgical AVR is always better, but that we’re able to make a good decision for a specific patient by working together.

— Amar Krishnaswamy, MD
Interventional Cardiologist
Robert and Suzanne Tomsich Department of Cardiovascular Medicine
Cleveland Clinic
Disclosure: Krishna reports no relevant financial disclosures.

GAUSS-3
Evolocumab bests ezetimibe for LDL reduction in statin-intolerant patients

GAUSS-3 asked two separate questions: Is statin intolerance really real? How many patients are truly statin intolerant? It was a very clever double-crossover design. Patients who reported statin intolerance were randomized to placebo or a statin. If they had symptoms on placebo, they could not participate; if they only had statin intolerance, they were randomized. The researchers found that of patients who said they were statin intolerant, 40% of them were truly. That is a much higher number than previously thought; traditionally, it was believed to be around 20 to 30. There has been a perception that statin intolerance is not real, that patients are imagining it or experiencing reactions out-of-proportion with what has been reported. But this study clearly shows that it is real, as we clinicians have been saying for years. The researchers did not look at whether patients who were statin intolerant could tolerate intermittent statins. In outside registries, some patients who are intolerant to two or more statins can take at least once-a-week or twice-a-week statin therapy. Regardless, it’s a great study.

— Leslie Cho, MD
Director, Women’s Cardiovascular Center
Section Head, Preventive Cardiology and Rehabilitation
Robert and Suzanne Tomsich Department of Cardiovascular Medicine
Cleveland Clinic
Disclosure: Cho reports research with Amgen.

Results: For the mean of weeks 22 and 24, LDL with ezetimibe was 183 mg/dL [mean change, −16.7% (95% CI, −20.5% to −12.9%) and with evolocumab was 103.6 mg/dL [mean change, −54.5% (95% CI, −57.2% to −51.8%)]. LDL level at week 24 with ezetimibe was 181.5 mg/dL [mean change, −16.7% (95% CI, −20.8% to −12.9%) and with evolocumab was 104.1 mg/dL [mean change, −52.8% (95% CI, −55.8% to −49.8%)]. For the mean of weeks 22 and 24, between-group difference in LDL was −37.8 mg/dL. For week 24, between-group difference in LDL was −36.1 mg/dL. For week 24, between-group difference in LDL was −36.1 mg/dL. For week 24, between-group difference in LDL was −36.1 mg/dL. For week 24, between-group difference in LDL was −36.1 mg/dL.