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 m²).

ENTRESTO and the ENTRESTO logo are registered trademarks of Novartis AG.

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

Your patient is telling you about her heart failure (HF) symptoms, a sign of increased risk of HF hospitalization and death.1,2
2.8

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 dizziness (6%, 5%) and renal failure/acute renal failure (5%, 5%).

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%), hyperkalaemia (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.

IMPOR TANT SAFETY INFORMATION, CONT’D

Impaired Renal Function, cont’d: 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. These effects are usually reversible. Monitor renal function periodically.

Hyperkalaemia: Hyperkalaemia may occur with ENTRESTO. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalaemia 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.

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

For more information, visit EntrestoHCP.com

CV DEATH OR HF HOSPITALIZATION AS FIRST EVENT

All-Cause Mortality

CV DEATH OR HF HOSPITALIZATION AS FIRST EVENT

(Primary end point)

(Primary end point)

20% ARR
4.7% RRR

16% ARR
2.8% RRR

(RR < 0.0001; HR [95% CI]: 0.80 [0.73, 0.87])

(R = 0.0009; HR [95% CI]: 0.84 [0.76, 0.93])

- Reduced the relative risk of CV death by 20% vs enalapril (3.2% ARR)†§
- Reduced the relative risk of first HF hospitalization by 21% vs enalapril (2.8% ARR)†

When you see symptoms, there’s risk, so it’s time for ENTRESTO.
ENTRESTO™ (sacubitril and valsartan) tablets, for oral use

• When pregnancy is detected, discontinue ENTRESTO as soon as possible (5.1)

<table>
<thead>
<tr>
<th>5.1 Fetal Toxicity</th>
</tr>
</thead>
</table>
| 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 outcomes of drug exposure have not distinguished drugs affecting the renin-angiotensin system from other drugs affecting renal function. In general, perinatal outcomes following the second trimester of pregnancy were similar in U.S. clinical trials for patients receiving renin-angiotensin system inhibitors and for those receiving placebo. Changes in maternal renal function may result in a decrease in the renal function of the fetus. Therefore, fetal outcomes may be similarly altered by other drugs that affect the renin-angiotensin system. When mother and fetus are both exposed, fetal renal dysfunction and hyperkalemia have been observed.

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 large swelling 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.

5.3 Hypotension

ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, e.g., volume- and 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 use of a potassium-sparing diuretic, discontinuation of a concomitant NSAID, or discontinuation of ENTRESTO. 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 treated with the ENTRESTO and enalapril groups reported renal function 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 inhibitors of angiotensin-converting enzyme and angiotensin II receptor antagonists has been associated with oliguria, prerenal azotemia and, rarely, acute renal failure and death. Close monitoring of serum creatinine and down-titrating or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function when compared to baseline treatment [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)]. 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 inhibitors of angiotensin-converting enzyme and angiotensin II receptor antagonists has been associated with oliguria, prerenal azotemia and, rarely, acute renal failure and death. Close monitoring of serum creatinine and down-titrating or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function when compared to baseline treatment [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.

5.6 Hypertension

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 of ENTRESTO.

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, and salt substitutes containing potassium may lead to increases in serum potassium [see Warnings and Precautions (5.3)].

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 drugs affecting renal function. 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 monitor the mother for signs of impending delivery. 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.

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 45% (10.7%) of ENTRESTO treated patients and 516 (12.2%) of patients receiving enalapril. Adverse reactions occurring at an incidence of ≤5% in patients who were treated with ENTRESTO in the double-blind period are shown in Table 1.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENTRESTO (n = 4,203)</th>
<th>Enalapril (n = 4,229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Renal failure/acute renal failure</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Hemoglobin and Hematocrit</th>
<th>Decreases in hemoglobin/hematocrit of &lt;20% were observed in approximately 5% of both ENTRESTO- and enalapril-treated patients in the double-blind period in PARADIGM-HF.</th>
</tr>
</thead>
</table>

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.
ENRESTO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥49 mg sacubitril/51 mg valsartan/kg/day (≥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 ≥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). ENRESTO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at an ENRESTO dose of ≥5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of ENRESTO 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 ENRESTO 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 ENRESTO.

Data
Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [14C] ENRESTO to lactating rats, transfer of LBQ657 into milk was observed. After a single oral administration of 3 mg/kg [14C] 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 (≥65 years) or very elderly (≥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 ENRESTO 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 ENRESTO 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 30 to 60 mL/min/1.73 m²) to moderate (eGFR 10 to 30 mL/min/1.73 m²) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR <10 mL/min/1.73 m²) is 24/26 mg twice daily (see Dosage and Administration (2.3) in the full prescribing information. Warnings and Precautions (3.4) and Clinical Pharmacology (12.3) in the full prescribing information).

18 OVERDOSAGE
Limited data are available with regard to overdose in human subjects with ENRESTO. In healthy volunteers, a single dose of ENRESTO 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 overdose due to the blood pressure lowering effects of ENRESTO. Symptomatic treatment should be provided.

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

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Visit the “Latest in Cardiology” section of ACC.org for a wide variety of perspectives and analysis on recent research and trends. Current hot topics include:

- Highlights From the Updated Peripheral Artery Disease Guidelines
- To Screen or Not to Screen: That’s Not the Only Question
- Shared Decision-Making in Radiation Exposure for Patients and Operators: An Interventional Perspective
- Elderly Loneliness and the Broken Heart

Don’t miss the new “ACC Cardiology Hour,” an expert roundtable discussion of the hottest trials from ACC.17. Valentin Fuster, MD, PhD, MACC, hosts Deepak L. Bhatt, MD, MPH, FACC; Anne B. Curtis, MD, FACC; Kim A. Eagle, MD, MACC; Michael J. Mack, MD, FACC; and Donna M. Mancini, MD, in a lively discussion on FOURIER, SPIRE 1 and SPIRE 2, EBBINGHAUS, SURTAVI, IFR-SWEDHEART, and more. See the video at ACC.org/CardiologyHour.

Check Out Complete ACC.17 Coverage on ACC.org
In case you missed it, the ACC provided coverage of the hottest trials that came out of ACC’s Annual Scientific Session (ACC.17) in Washington, DC. To view all the latest science, check out the ACC.17 Meeting Coverage Page at ACC.org/ACC2017. Also, visit ACC’s YouTube Page to watch daily wrap-up videos highlighting the hottest trials from each day of ACC.17. Check out archived tweets by searching for the official meeting hashtag #ACC17 or scroll through our live coverage of the meeting via Twitter at @ACCcardioEd.

Patient Case Quiz
Check out the following Patient Case Quiz involving valve-in-valve TAVR in aortic homograft failure. Read about the patient, his symptoms and history and answer the following questions by scanning the QR Code.

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Source: IFCC Table of analytical characteristics of commercial cardiac Troponin I and T assay declared by the manufacturer – November 2014 (www.ifcc.org)
ACC.17 In Review: What Have We Learned?

We returned from ACC.17 impressed by the number of clinical trials, the wide array of important clinical studies presented and the impact of many of the trials on the practice of cardiology. Much attention has been focused on the treatment of hyperlipidemia with a monoclonal antibody that blocks PCSK9 and lowers LDL. Previous studies with this class of drug have demonstrated a striking effect on LDL. Now we have data from the FOURIER study that shows lowering LDL with evolocumab translated into a 2 percent lower risk for cardiovascular events in patients with known coronary disease. While statistically significant, the improvement in the event rate is small, and patients may balk at the added cost.

The SPIRE program showed that anti-drug antibodies to another PCSK9 inhibitor, bococizumab, reduced its efficacy in lowering LDL in a substantial number of patients. However, no detrimental effects of bococizumab were found after three years of therapy, and no evidence of cognitive changes were noted from long-term use. Many patients achieve a reasonable LDL goal with a combination of dietary change, statin and in some cases the addition of ezetimibe. Decisions on the use of a PCSK9 inhibitor in practice will be affected by cost and the reluctance of some patients for periodic self-injections.

In the CARAT trial, efforts to raise HDL with the injection of a synthetic HDL failed to reduce atherosclerotic plaque volume and offers yet another failed attempt to reduce atherosclerotic burden by manipulating HDL. Transcatheter aortic valve replacement (TAVR) received more attention at this year’s meeting. We have moved from high-risk elderly patients who were poor surgical candidates for AVR to moderate-risk patients. Data from the SURTAVI trial indicated that intermediate-risk patients have similar outcomes when undergoing TAVR or surgical replacement (SAVR). This information is welcomed news for many intermediate-risk patients who prefer a non-surgical solution to their aortic valve disease. These findings will require further observation as we expand indications for TAVR. Although small and asymptomatic cognitive changes were found in TAVR patients, these were associated with a higher incidence of MRI-documented cerebral microbleeds in the TAVR group.

ACC.17 provided many insights into how to manage patients with a variety of common disorders. Accumulation of thrombus on TAVR valves was examined in the RESOLVE and SAVORY registries. Each registry found significant thrombus on both TAVR valves and surgically implanted bioprosthetic valves, but more thrombus was found on TAVR valves. Anticoagulant therapy, but not antplatelet therapy, prevented thrombus accumulation, and initiation of anticoagulant therapy reversed thrombus accumulation when it was detected. CT appears more sensitive than echocardiography as a detection tool, as it often identifies early valve thrombosis before a significant gradient develops. No long-term consequences were noted with the accumulated thrombus, but the incidence of transient ischemic attacks was higher when thrombus was present on the valve. We’ll continue to monitor data on valve thrombosis that at present does not appear to be a serious concern if patients are treated with anticoagulation therapy.

The perplexing question of the safety and efficacy of long-term, low-dose direct oral anticoagulant (DOAC) therapy for the prevention of recurrent venous thromboembolism (VTE) was addressed by studies presented at ACC.17. EINSTEIN CHOICE provides support for low-dose rivaroxaban for long-term VTE prevention, welcomed news for patients on long-term warfarin. Once again, aspirin seems to be less efficacious and continues to show a higher risk for bleeding. Data last year showed that women with a spontaneous deep vein thrombosis (DVT) could stop anticoagulation after a year with no increase in subsequent DVT risk. These studies provide clinicians with several options in managing long-term care for patients with a DVT. Aspirin seems to be the least efficacious when considering prevention of DVT and risk of bleeding.

Looking at antithrombotic therapy in patients with acute coronary syndrome treated with a P2Y12 inhibitor, GEMINI-ACS-1 found no difference between low-dose rivaroxaban and aspirin for bleeding risk or thrombotic events. In atrial fibrillation (AFib), a secondary analysis of data from the ARISTOTLE trial indicated that digoxin may be associated with increased mortality when the digoxin level is above 1.2 ng/mL.

An alternate solution to stroke risk with AFib – left atrial occlusion – was supported by data from the STS registry that showed a significant reduction in stroke risk for patients with AFib who had the left atrium closed or amputated during mitral or aortic valve surgery or CABG. The improvement was evident in patients who were not treated with anticoagulation after surgery.

There is no end to the analytic potential of an electronic waveform and a digital computer.
A case in point, the iFR-SWEDEHEART group presented data on an alternate measure called the instantaneous wave-free ratio (iFR) to predict the severity of coronary stenosis. The group derived their measure from the aortic pressure wave recorded from the distal pressure catheter inserted to measure fractional flow reserve (FFR) in patients undergoing cardiac catheterization and possible intervention. Their analysis showed a similar predictive value to the FFR, but did not require an intracoronary adenosine injection, eliminating the associated chest discomfort from the vasodilator response. The iFR data were shown to be non-inferior to FFR data, and patients had less discomfort from the IFR procedure.

DEFINE-FLAIR addressed a similar comparison between iFR and FFR with similar results and again raises the question of the real-world application of these clinical trial results. This simpler method of stenosis assessment was shown by both studies to provide similar clinical outcomes when compared with FFR measures. The data are encouraging, particularly because iFR-SWEDEHEART provided real-world registry data. Most interventionalists are likely to persist with FFR measures as both methods still require instrumentation of the coronary artery with two catheters for proximal and distal pressure measurement, and both methods can be done during the intervention with minimal additional procedure time and no added risk.

While we still debate the question of complete revascularization versus culprit-vessel PCI in favor of complete revascularization within 45 days after revascularization for an acute MI. However, it is better to manage a totally occluded artery medically as the outcome is no better compared with doing a PCI and the risk of procedural complications is avoided. Data from the DECISION-CTO trial support the medical approach to management of a CTO.

We continue to be stymied by our inability to achieve substantial improvement in the number of individuals with hypertension who receive either no therapy or inadequate therapy. The REACH trial tried again to improve cardiovascular health with use of improved communication in patients being treated for hypertension. The investigators used e-counseling to encourage patients to maintain their medications and to adhere to lifestyle changes that would lower blood pressure. Both the control group and the intervention group showed some improvement in blood pressure, with the intervention group showing a significantly greater response. The data support the important concept that constant communication between patient and provider is an important component of care for patients with hypertension.

ACC.17 provided many insights into how to manage patients with a variety of common disorders. While many studies did not show positive results that would change practice, many of the negative trials still provided reassurance that our current approach to cardiology care is on track. We look forward to future meetings with similar anticipation of new practice-changing studies, as well as the negative studies that assure us that much of our current therapy is up-to-date.

Alfred A. Bove, MD, PhD, MACC, is professor emeritus of medicine at Temple University School of Medicine in Philadelphia, and a former president of the ACC.

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In Memoriam: ACC Past President Leonard S. Dreifus, MD, MACC

A CC Past President Leonard S. Dreifus, MD, MACC, passed away on March 30 at the age of 92. Dreifus served as president of the ACC from 1978 – 1979. A cardiovascular legend, Dreifus held numerous positions as chief or director of cardiology, and professor of medicine at many institutions throughout his lifetime. His research has been published in over 250 medical journals and books and he has received numerous accolades for his contributions to cardiovascular education and research. He received the Master Teacher Award from the ACC in 1972 and was honored with the Distinguished Fellow title by the ACC.17

“He was of the old guard with Charles Fisch, MD, MACC; Valentin Fuster, MD, PhD, MACC; Borys Surawicz, MD, MACC; and Sylvan Lee Weinberg, MD, MACC,” says Douglas P. Zipes, MD, MACC, a past president of the ACC. “He was a wise man, a wonderful teacher of arrhythmias, expert electrophysiologist and humble about his many talents.”

Dreifus served in the 211th Army Air Force Base Unit during World War II prior to receiving his bachelors from the University of Pennsylvania. He received his medical degree from Hahnemann Medical College and went on to do his internship and residency at Philadelphia General Hospital. After completing his cardiology fellowship at the Cardiovascular Research Institute at the Michael Reese Hospital in Chicago, IL, Dreifus trained at the National Institutes of Health in Maryland.

Dreifus and his wife, Seline, are also well-known for their philanthropic work. The pair helped found the Orlando Philharmonic’s Genius of Youth program, which allows talented musicians from the Juilliard School to perform as soloists with the philharmonic in Orlando. In addition, they are responsible for the “Man Helping Man” sculpture installed at Heart House in Washington, DC.

“As we enter Heart House, we are greeted by the ‘Man Helping Man’ sculpture generously donated by Dr. Dreifus and Seline,” says ACC President Mary Norine Walsh, MD, MACC, “It reminds us not just of the legacy left by Dr. Dreifus, but also our purpose in serving our patients and the public good as clinicians.”

“Both Dr. Dreifus and Seline have served as role models for so many of us over the years,” says ACC Immediate Past President Richard A. Chazal, MD, MACC, “Their intelligence, devotion to the College and love for their fellow man (and for each other) will continue to inspire.”

Valentin Fuster, MD, PhD, MACC, Receives Lifetime Achievement Award

Valentin Fuster, MD, PhD, MACC, was recognized at ACC.17 with the ACC’s Lifetime Achievement Award for his “unwavering dedication to improving cardiovascular medicine worldwide.”

Fuster currently serves as director of the Cardiovascular Institute and Physician-in-Chief at Mount Sinai in New York. He is also general director of the Centro Nacional de Investigaciones Cardiovasculares Carlos III in Madrid, Spain, and is founder and chair of the Science for Health and Education Foundation. He is also editor-in-chief of the Journal of the American College of Cardiology.

He has served as president of the American Heart Association and of the World Heart Federation and is the only cardiologist to have received the highest awards for research from the four leading cardiovascular organizations. He has been named Doctor Honoris Causa by 33 universities around the world and has authored more than 900 scientific articles and six books.

“This is only a selection of his accomplishments,” notes James S. Forrester, MD, FACC. “It should be known his contributions to cardiovascular medicine have had an enormous impact on the treatment of patients with heart disease and the advancement of the specialty.”

In Memoriam: Rolf McMillan Gunnar, MD, MACC

Rolf McMillan Gunnar, MD, MACC, a renowned cardiologist, teacher, scientific author, medical leader, veteran and philanthropist passed away on March 18 at the age of 91. Gunnar attended Northwestern University as a member of the V-12 Navy College Training Program. He completed his medical residency at Cook County Hospital after serving as a U.S. Army Captain and Battalion Surgeon in the Second Infantry Division in Korea, during which he was awarded the Bronze Star with V Device for Valor. Following his residency, he went into private practice in Berwyn, IL, with his father until 1959. Later, he did his cardiology fellowship at Harvard Medical School.

Among his many accomplishments, Gunnar served as director of Adult Cardiology and the Division of Medicine at Cook County Hospital; he was the first Edmund F. Foley Professor of Medicine and Director of the Section of Cardiology at the University of Illinois; professor of medicine, chief of the section of cardiology and later chair of medicine at Loyola University Medical Center. Nationally, he served as chair of the Board of Regents of the American College of Physicians, president of the Association of University Cardiologists and vice president of the ACC. Dr. Gunnar’s research interests included acute myocardial infarction as well as circulatory shock at a time when the discipline of cardiology was relatively new. He and his co-authors published more than 400 scientific papers and abstracts and he co-authored a published book on shock in myocardial infarction.
ACC Welcomes Newest BOT Members

Paul N. Casale, MD, FACC, Robert C. Hendel, MD, FACC, and Cathleen Biga, MSN, RN, became ACC’s newest Board of Trustees members in March. They will serve from 2017 – 2020.

Cacchione to Oversee Ascension Medical Group

Joseph Cacchione, MD, FACC, was recently named president of the Ascension Medical Group, a network of 6,500 employed providers across 16 states.

Cacchione was most recently chair of operations and strategy for the Cleveland Clinic’s Heart and Vascular Institute. Prior to the Cleveland Clinic, he was executive vice president and chief of quality and operations at Saint Vincent Health System in Erie, PA.

Cacchione is also a former member of the ACC’s Board of Trustees.

New Editor of ACC’s EchoSAP 8

Smedar Kort, MD, FACC, has been selected as editor of EchoSAP – the College’s popular self-assessment program on echocardiography. The College is planning to produce a new version of EchoSAP for release in 2018, and in her role as editor, Kort will ensure that users can prepare for the initial or re-certification exam in echocardiography, stay abreast of new advances in the field, teach others and earn Continuing Medical Education credit. Kort is currently clinical professor of medicine at Stony Brook University Medical Center in Stony Brook, NY.

ACC Announces Executive Staff Changes

Cathy Gates, ACC executive vice president (EVP), succeeded Tom Arend as ACC’s chief operating officer, effective March 13. In her new role, Cathy oversees the finance and information technology divisions, in addition to membership, advocacy, operations, human resources and organizational development.

During her more than 20-year tenure at the ACC, Gates has served the College in a variety of roles, including ACC’s “Chief People Officer” and she has worked on a number of significant projects, including spearheading the ACC’s move from its Heart House headquarters in Bethesda, MD, to Washington, DC. Prior to joining ACC, Gates supervised financial and securities and Exchange Commission reporting for three publicly held real estate investment trusts. She also served as a Certified Public Accountant at Ernst and Young, where her client focus was health care and real estate.

Additionally, Brendan Mullen has joined Cathy and Bill Oetgen, MD, FACC, as ACC EVP overseeing communications, business development, marketing, digital and enterprise strategy and international affairs. Prior to this role, Brendan served as ACC vice president of market strategy. Brendan also worked for nearly 10 years as a consultant for the Advisory Board Company and served as vice president of Programs and Strategy at the National Quality Forum.

Scan the QR code for a complete list of Trustees for 2017 – 2018.
ONE CITY, THREE DAYS: ACC.17 BY THE NUMBERS

18,735 TOTAL ATTENDANCE

ABSTRACTS 2,572

23 LATE-BREAKING CLINICAL TRIALS

MEDIA ATTENDEES, WHO GENERATED SOME 1000 ORIGINAL NEWS ARTICLES ON RESEARCH PRESENTED AT ACC.17 338

3 THE NUMBER OF WOMEN WHO HAVE SERVED AS ACC PRESIDENT, INCLUDING ACC’S NEWEST PRESIDENT, MARY NORINE WALSH, MD, FACC

300+ EDUCATION SESSIONS

275+ EXHIBITORS

57,233 TWEETS

17 FEATURED CLINICAL RESEARCH PRESENTATIONS

A WIN FOR DIVERSITY, WITH A DOUBLING OF THE NUMBER OF WOMEN SERVING AS CHAIRS OR PANELISTS IN THE MAIN TENT.

334 DAYS TO ACC.18 IN ORLANDO
We believe this will not only help improve and save lives but that it can ultimately contribute to lower healthcare costs since the earlier adoption of positive health habits can reduce patient clinical risk and potentially eliminate the need for more costly interventions later on,” he said.

**Cardiac Plaque Lipid Content, Fibrous Cap Status To Predict Cardiovascular Outcomes**

In patients with atherosclerotic disease, carotid plaque lipid content and fibrous cap status were strongly associated with systemic cardiovascular outcomes. In the AIM-HIGH trial, Jie Sun, MD, et al., examined 214 patients with acceptable diagnostic image quality. The primary endpoint was fatal and nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome and symptom-driven revascularization.

During the median follow-up of 35.1 months, 18 patients reached the primary endpoint; no significant association was seen between the traditional risk factors or the randomized treatment assignment.

Even though there was a high rate of statin use, calcification, lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH) and thin/ruptured fibrous cap were detected by carotid MRI in 48 percent, 52 percent, 8 percent and 14 percent of the patients, respectively. Patients with thin/ruptured fibrous cap had a 4.31-fold increased risk for the primary endpoint. Plaque lipid content also was significantly associated with the primary endpoint, while the association of plaque calcification content was not statistically significant. The association of IPH with the primary endpoint was positive, but did not reach statistical significance.

“By leveraging the rigorously adjudicated outcome data of a contemporary clinical trial, we evaluated MRI measurements of carotid plaque characteristics as surrogate markers for systemic cardiovascular outcomes,” the authors write. “The observed associations between carotid plaque characteristics and systemic cardiovascular outcomes were not driven by traditional risk factors, plaque burden or AIM-HIGH treatment assignment, which did not significantly predict the primary endpoint by themselves and had little influence on the associations of plaque characteristics with outcomes in multivariate analyses.”

**Noninvasive Imaging Safe and Effective for Most Patients with Chest Pain**

In low- to intermediate-risk patients with acute chest pain, noninvasive imaging is safe and effective in expediting care and reducing hospital admissions. Every year, over eight million patients in the U.S. come to the emergency department for acute chest pain. Nearly 75 percent are diagnosed with non-cardiac or non-ischemic cardiac problems and less than 20 percent of the rest meet criteria for acute coronary syndrome (ACS). Patients at either end of the coronary risk spectrum are easily triaged, but those with low-to-intermediate cardiac risk and no clear evidence of diagnosis present a challenge. Over the last 20 years, cardiac imaging has played an increasing role in helping to diagnose these patients.

In this review, Gilbert I. Raff, MD, FAACC, and colleagues examined trials that evaluated different diagnostic strategies including radionuclide myocardial perfusion imaging (MPI), stress echocardiography, cardiac magnetic resonance (CMR) imaging, coronary computed tomographic angiography (CTA), and high-sensitivity troponin and imaging. Findings from the radionuclide MPI trials included the observation that MPI was safe and unnecessary admissions were lower compared with patients treated with standard-of-care diagnostic strategy, including electrocardiography (ECG). Stress echocardiography was found to have significant clinical and cost benefits compared with a stress ECG.

**Stress echocardiography was found to have significant clinical and cost benefits compared with a stress ECG.**

**Scan the QR code to read the full special issue.**
Greater Radiation Exposure With Radial Versus Femoral PCI

Operators and patients are exposed to more radiation with the radial approach compared with the femoral approach to PCI for acute coronary syndrome, according to the results of a study presented at ACC.17 and simultaneously published in JACC: Interventions. The study—the largest so far on this topic—was conducted in Italy, the Netherlands, Spain and Sweden between October 2011 and November 2014.

In RAD-MATRIX, a sub-study of the MATRIX study, 18 operators wore dosimeters and data were collected on fluoroscopy time and indirectly using a conversion factor of 0.20 mSv per Gy cm². The primary endpoint of the radiation dose at the thorax of the operator was significantly higher with radial access (17 µSv vs. 41 µSv with femoral access; p = 0.02)—and did not differ by right or left radial access. The study did not achieve non-inferiority for the primary hypothesis of the radial access not being associated with a higher operator dose than the femoral access (p value for non-inferiority 0.843).

The difference in the primary endpoint remained significant after normalization of the operator dose by fluoroscopy time or DAP. There was no difference in the radiation dose at the wrist or head of the operator between the two strategies. For patients, the median radiation dose at the thorax of the operator was significantly higher with radial access (64.7 Gy cm² vs. 59.1 Gy cm²; p = 0.0001).

Of note, the incremental increase in the operator’s radiation exposure for a single procedure by radial access versus femoral access is in the range of 1.1 µSv, corresponding to an additive 300 µSv for every 300 procedures—similar to the additive radiation exposure of 17 chest X-rays.


Dose area product (DAP) from a total of 777 procedures performed in 767 patients. Dosimeters were worn on the left wrist, at mid-thorax, and at the head level to measure eye exposure. Patient exposure was measured by radial access… similar to the additive radiation exposure of 17 chest X-rays.

The incremental increase in the operator’s radiation exposure for a single procedure by radial access… similar to the additive radiation exposure of 17 chest X-rays.
Shifts in Eligibility for CRT In Heart Failure Patients Characterized in Analysis of Guideline Criteria

A smaller proportion of patients with heart failure and a left ventricular ejection fraction (LVEF) ≤35 percent were eligible for cardiac resynchronization therapy (CRT) using criteria from the current 2013 ACCF/American Heart Association (AHA) heart failure guidelines compared with those from the 2009 guidelines. The first analysis of the influence of the new CRT criteria on eligibility was presented by Kristin J. Lyons, MDCM, as an oral abstract at ACC.17 and simultaneously published in JACC: Heart Failure.

In a population of 25,102 patients from 238 hospitals, identified in the Get With the Guidelines-HF database, eligibility for CRT was 33.1 percent and 49.1 percent, respectively, based on the 2013 and 2009 criteria (p < 0.0001). Of note, the 2013 guidelines expanded the criteria for CRT to include NYHA Class II patients, but limited the criteria to patients with LVEF ≤35 percent, sinus rhythm, and a left bundle branch block (LBBB) or a non-LBBB and a QRS ≥150 msec.

QRS duration and morphology were the only significant differences in the baseline characteristics of the patients classified as eligible for CRT based on the 2013 and 2009 criteria. In both groups, patients were 73 years old and most were men and white (70 percent each). Their LVEF was 23 percent and 43 percent had atrial fibrillation/flutter; the etiology of heart failure was hypertension for 78 percent and ischemic for 70 percent.

Among the 5,303 patients with a QRS duration of 120-149 msec, only 21.3 percent were eligible with the new criteria versus 78.7 percent with the old criteria. For a QRS ≥150 msec, nearly all patients were eligible for CRT using both criteria. Likewise, nearly all patients with a LBBB were eligible using both criteria. However, using the new criteria, non-LBBB limited eligibility to 56.8 percent versus nearly all patients using the old criteria.

Low adherence to guideline recommendations for CRT was found using both criteria: only 57.8 percent and 54.9 percent of those eligible based on the 2013 and 2009 criteria respectively had a CRT prescribed or placed at the time of hospital discharge. The investigators stated that although there is the potential for health care costs to be reduced because fewer patients are eligible for CRT, improvement is needed in adherence to device therapy for eligible patients with heart failure.

Improvement is needed in adherence to device therapy for eligible patients with heart failure.
More African Americans Qualify for Statin Therapy With ACC/AHA Guidelines

Under the 2013 ACC/American Heart Association (AHA) guidelines on the treatment of blood cholesterol, 25 percent more African Americans qualify for statins compared with the U.S. Preventive Services Task Force (USPSTF) guidelines, according to a study presented at ACC.17 and simultaneously published in JAMA Cardiology.

Ravi V. Shah, MD, et. al., identified 2,812 African Americans without prevalent atherosclerotic cardiovascular disease (ASCVD) and who were not receiving statin treatment. The researchers evaluated statin eligibility in all participants, and 1,743 of these patients also underwent computed tomography (CT) imaging.

The researchers found that 38.1 percent of the patients were statin-eligible by USPSTF Grade B guideline recommendations compared with 49.9 percent by ACC/AHA guidelines. Overall, statin recommendations were consistent for both guidelines in 86.1 percent of patients. While 12.8 percent were statin-eligible based on ACC/AHA guidelines alone, only 1.0 percent was eligible by USPSTF alone, and 25.7 percent of African Americans recommended for statin therapy under the ACC/AHA guidelines were not recommended for statin therapy under the USPSTF guidelines.

Over the median 10-year follow-up, there were 123 incident ASCVD events. The researchers found a 5.0-fold increased hazard of incident ASCVD among statin-eligible participants by the USPSTF guidelines compared with non-eligible participants and a 5.5-fold increased hazard of incident ASCVD among statin-eligible participants by the ACC/AHA guidelines. Those eligible for statins under both guidelines had a higher event rate than those eligible under only the ACC/AHA guidelines.

Finally, the researchers found that while statin-eligible participants under the USPSTF guidelines did not have a significantly higher 10-year ASCVD event rate in the presence of coronary artery calcium (CAC), African American participants not eligible for statins under USPSTF guidelines had a higher ASCVD event rate in the presence of CAC compared with those without CAC.

These data support the use of the ACC/AHA guidelines to identify African American adults likely to benefit from statin therapy.

"Despite debate over the potential cost, risk calibration and metabolic health implications of increasing statin use, these results support a guideline-based approach to statin recommendation, leveraging targeted imaging (or other atherosclerotic measures) in African American individuals to further personalize statin-based prevention programs," the authors conclude.

Mother’s Plasma Folate Levels May Influence Child’s Systolic BP

Higher levels of maternal plasma folate may help counteract the adverse associations of maternal cardiometabolic risk factors on systolic blood pressure (SBP) of the mother’s child, according to research presented at ACC.17 and published March 6 in the American Journal of Hypertension.

Hongjian Wang, MD, and colleagues examined 1,290 mother-child pairs from the Boston Birth Cohort, comprised of predominantly urban, low-income, racial and ethnic minority populations. Of the mothers, 38.2 percent had one or more cardiometabolic risk factors, 14.6 percent had hypertensive disorders, 11.1 percent had diabetes and 25.1 percent had pre-pregnancy obesity. The median for maternal plasma folate levels, taken two to three days after delivery, was 30.32 nmol/L. A total of 28.7 percent of the children had elevated SBP at age three to nine years. These children were more likely to have mothers with pre-pregnancy obesity, hypertensive disorders and diabetes and were also more likely to have lower birth-weight, lower gestational age and higher current body mass index.

Overall, maternal folate levels were not associated with child SBP percentile or elevated SBP. However, the association of maternal folate levels and child SBP was modified by cardiometabolic risk factors of the mother. Children born to mothers with cardiometabolic risk factors and folate levels below the median had a 1.65 to 1.90-fold higher odds of elevated SBP compared with children whose mothers had high median folate levels with no maternal cardiometabolic risk factors. The researchers observed similar associations when only analyzing African American patients. These associations were not found to be explained by gestational age, size at birth, pre-natal folate intake or breastfeeding.

The authors write that the mechanisms underlying the potentially beneficial influence of maternal folate on the SBP of children who have mothers with risk factors are not clear and that future studies are needed to examine this point.

They conclude that “interventions focused on increasing maternal folate intake among mothers with metabolic risk factors may help mitigate the transgenerational association of cardiometabolic diseases.”

NCDR Study Looks at Safety of Vascular Closure Device

Among patients who undergo a PCI procedure with femoral access, the risk of a vascular complication may be higher with the Mynx vascular closure device compared with other vascular closure devices, according to a study published in the New England Journal of Medicine.

The study, led by Frederic S. Resnic, MD, FACC, was designed to assess the postmarketing safety of the Mynx device, and looked at data from 73,124 patients enrolled in ACC’s CathPCI Registry who received the device between Jan. 1, 2011 and Sept. 30, 2013. Results showed that the Mynx device was associated with a “significantly greater risk” of the primary outcome of any vascular complication – a composite of access-site bleeding, access-site hematoma, retroperitoneal bleeding, or any vascular complication requiring intervention – compared with other devices (absolute risk, 1.2 percent vs. 0.8 percent; relative risk, 1.59; 95 percent confidence interval, 1.42 to 1.78; p < 0.001). There was also a “significantly greater risk” of the secondary safety endpoints: access-site bleeding requiring treatment and postprocedural blood transfusion. However, the authors note that the absolute risk differences were small.

The authors add that alerts for the Mynx device were “triggered early, persisted throughout the duration of surveillance, and were present in all subgroups of patients.” In addition, “the primary results were confirmed in an independent, more contemporary cohort of patients.”

In an editorial, Jon Resar, MD, FACC, and Myron L. Weisfeldt, MD, FACC, explain that there may be mitigating factors associated with the use of the Mynx device. “There may have been selective use of this device for arteries that pose a subjectively greater challenge for closure without complications...,” they note. Further, there is a learning curve for using these devices.

They conclude that the study “highlights the value of professional society registries for post-marketing evaluation of device performance in clinical practice and emphasizes the need for the establishment of a National Evaluation System for Health Technology.”

Drones: Future Delivery System for AEDs?

A drone network that was designed with the aid of a novel mathematical model was shown to reduce the time to deliver an automated external defibrillator (AED) to respond to an out-of-hospital cardiac arrest (OHCA), according to recent work by Justin J. Boutilier, BSc, and the Rescu Epistry Investigators.

The authors applied a two-level (optimization and queuing) theoretical model to 53,702 OHCAs that occurred within eight regions (covering about 10,000 square miles) of the Toronto Regional RescuNET emergency medical system between Jan. 1, 2006 and Dec. 31, 2014. The objective of their primary analysis was to determine the size of a drone network needed to deliver an AED at one minute, two minutes or three minutes faster than the historical median 911 response times for each region. A secondary analysis was conducted to determine the size of the reduction in the number of drones required for one large coordinated RescuNET region versus the current eight regions.

Their region-specific primary analysis found that in order to deliver an AED three minutes faster than the median 911 response times, a total of 81 bases and 100 drones would be required. In the most urban region, there was a reduction of six minutes and 43 seconds for the 90th percentile of the AED arrival time relative to historical 911 response times in the region. In the most rural region, this reduction was 10 minutes and 34 seconds.

The investigators determined in their secondary analysis that a single coordinated drone network across all regions would reduce the number of bases required by 39.5 percent and the number of drones by 30.0 percent to achieve similar AED delivery times.

The authors write that prototype drone technology has been developed by several companies and researchers to deliver AEDs to the scene of an OHCA, and that Google has obtained a patent for drone delivery of medical supplies including AEDs. “Although there are technical challenges to overcome, drone-delivered AEDs are a potential transformative innovation in the provision of emergency care to cardiac arrest patients, especially to those who arrest in a private or rural setting,” they state. They also note that the camera on the drone used for navigation also could be employed by the 911 dispatcher to assess the patient visually and provide support for bystander CPR and AED application.

Although there are technical challenges to overcome, drone-delivered AEDs are a potential transformative innovation in the provision of emergency care to cardiac arrest patients.

The much-anticipated results of the FOURIER study at last have provided a look at hard outcomes with a PCSK9 inhibitor. Evolocumab added to statin therapy in patients with clinically evident atherosclerotic cardiovascular disease produced a significant 15 percent reduction in the primary endpoint – a composite of myocardial infarction (MI), stroke, hospitalization for angina, revascularization or cardiovascular death (11.3 percent with placebo, 9.8 percent with evolocumab). For the secondary endpoint of cardiovascular death, MI or stroke, there was a 25 percent reduction after the first year.

Cardiovascular mortality was not reduced, but statistically significant reductions were seen for MI (27 percent) and stroke (21 percent). The reductions in the primary and key secondary endpoints were consistent across all the key subgroups, including dosing regimen of evolocumab and baseline LDL-C levels, including those with the lowest quartile of LDL-C – starting at 74 mg/dL – in whom evolocumab reduced LDL-C down to 22 mg/dL.

FOURIER included 27,564 patients on a moderate- to high-intensity statin regimen followed at 1,272 sites in 49 countries. Most patients (81 percent) had a history of MI, 19 percent had suffered an ischemic stroke and 13 percent had symptomatic peripheral artery disease. The median baseline LDL-C was 92 mg/dL. To be included, patients had an LDL-C ≥70 mg/dL or a non-high density lipoprotein cholesterol ≥100 mg/dL and were on optimized statin therapy. Exclusions included an acute MI or stroke within the previous four weeks, advanced heart failure, uncontrolled heart rhythm disorders, planned cardiac surgery and end-stage kidney disease.

Patients were randomly assigned (1:1) to receive subcutaneous injections of evolocumab (either 140 mg every two weeks or 420 mg every month based on patient preference) or matching placebo. LDL-C was reduced by 59 percent with evolocumab, from a median of 92 to 30 mg/dL, which remained steady throughout the duration of the study.

The rate of adverse events, including allergic reactions, neurocognition, new-onset diabetes and muscle-related problems, were the same in both study arms. Rates of injection site reactions were slightly more common with evolocumab (2.1 vs. 1.6 percent), but most were mild and the overall rates of stopping the study drug due to suspected treatment-related adverse events were low and similar in both groups (1.6 and 1.5 percent). Only 0.3 percent of patients developed antibodies that could bind evolocumab and none interfered with the drug.

Yet, the relatively short follow-up (mean 2.2 years) is a limitation of the study, and PCSK9 inhibitors remain to be studied in other high-risk populations, acknowledged Marc S. Sabatine, MD, FACC, who presented the study.

“FOURIER was an exciting way to kick off ACC.17,” says Seth Martin, MD, FACC. “Given this was a relatively short trial, I fully expect larger benefits to accrue over the long-term. FOURIER provides high-quality evidence that evolocumab works, and I felt fortunate after ACC.17 to bring this information back to my patients in lipid clinic as we work together to optimize their preventive therapy.”

Seth Martin, MD, FACC
“Based on cost-benefit analyses,” Yang says, “importantly to find a sweet spot for insurers to cover this therapy, but more importantly to finding the patients most likely to benefit, but more with statins with or without ezetimibe.”

“An anemic relative risk reduction for the primary endpoint and lack of a cardiovascular mortality benefit will likely raise more questions about the appropriate subset of patients for whom to offer this therapy,” he adds.

A snapshot of access to PCSK9 inhibitors during the first year after their approval by the U.S. Food and Drug Administration has shown that access is limited, with less than a third ever receiving the drug after its prescription, and that rejection rates vary by payer and pharmacy benefit manager.

Ann Marie Navar, MD, PhD, and colleagues examined the fate of the first prescription for PCSK9s in 45,029 patients (median age 66 years, 51 percent women) between August 1, 2015 and July 31, 2016, using a database encompassing 90 percent of retail, 60 percent of mail order and 70 percent of specialty pharmacies. The prescriber was a cardiology practice for 48.2 percent and for 36.9 percent it was a general practice.

The prescription was initially rejected for 79.2 percent of patients. Ultimately, the PCSK9 prescription was approved for nearly half (47.2 percent) of patients – but about a third (34.7 percent) never filled the prescription. The median time to approval was three days. The median time to dispensing was 9.9 days and for 25 percent of patients it was more than a month. Variability in the rates of rejection within payers suggested that factors other than clinical contribute to the decision, said Navar. The rates of rejection ranged from 33.1 to 74.7 percent across pharmacy benefit managers, from 37.9 to 83.5 percent across government-paid insurance programs, and from 33.2 to 77.6 percent across commercial payers.

A prescription by a cardiologist was 60 percent more likely to result in receiving PCSK9 therapy, as was having commercial plus government health insurance and using a mail-order pharmacy. Patients in a coupon program were nearly 17-fold more likely to receive therapy.

Navar noted that the prior authorization processes need to balance cost containment efforts and provider burden, and that the prolonged time to dispensing of the drug could have an impact on utilization and provider willingness to prescribe the drug.

While this study provides some insights into the challenges of obtaining approval for PCSK9 therapy, no data were presented to understand whether the prescribing was for appropriate patients and whether they were being optimally treated with statins with or without ezetimibe.

“A deeper dive into the results of FOURIER is fundamental to identifying the patients most likely to benefit, but more importantly to find a sweet spot for insurers to cover this therapy based on cost-benefit analyses,” Yang says.
ORION-1

A novel approach to lowering LDL-C, with the RNA interference drug inclisiran, provides significant, dose-dependent and sustained reductions at 180 and 240 days in patients at high cardiovascular risk, according to the results of the ORION-1 study presented by Kausik K. Ray, MD, MPhil, FACC.

Six different doses of inclisiran, which interferes with PCSK9 production, were examined in 501 patients (average age 63 years, 35 percent women) in the Phase II double-blind, placebo-controlled trial. About 69 percent of patients had atherosclerotic cardiovascular disease, 24 percent had diabetes, 5 percent had familial hypercholesterolemia and 13 percent were being treated for primary prevention. When they began the study, 73 percent of patients were taking a statin and 31 percent were on ezetimibe.

The primary endpoint of LDL-C reduction at 180 days was reduced by 27.9-41.9 percent with one subcutaneous injection and by 35.5-52.6 percent with two injections (p < 0.001). At 240 days, the reductions in PCSK9 and LDL-C remained significantly lower than at baseline with all the studied doses of inclisiran. Two injections of the 300 mg dose of inclisiran produced the greatest reduction in LDL-C, with 48 percent of patients receiving this dose achieving an LDL-C level ≤50 mg/dL. The average baseline LDL-C level was 128.2 mg/dL and baseline PCSK9 level was 424.3 ng/mL.

The rate of serious adverse events was 11 percent with inclisiran and 8 percent with placebo. Injection site reaction occurred in 5 percent of the patients receiving inclisiran. Injections are given every three or six months.

The results of this study will inform the dose and dosing regimen for the Phase III cardiovascular outcomes study with this drug. The safety profile was excellent, and with the potential to ensure patient adherence via every six month injections, this drug has unique attributes that address several unmet clinical needs. We eagerly await a study of cardiovascular outcomes from the ORION-4 study.

Richard Kovacs, MD, FACC

Tsimane Indians: Low Burden of CAD

The take-home message from a study of Tsimane Indians, a forager-horticulturalist population indigenous to the Bolivian Amazon, is quite strong, says Robert A. Vogel, MD, FACC: “Even in the presence of inflammatory stimuli, the majority of coronary artery disease (CAD) is due to our post-industrialized lifestyle with its consequential high burden of traditional risk factors.” He adds “this study should provide a strong stimulus for helping our patients through teaching better lifestyle patterns.”

The lowest reported levels of vascular ageing for any population studied were found in the Tsimane, with rates of coronary atherosclerosis five-times lower than in the U.S., according to results presented by Randall Thompson, MD, FACC. “The arteries of the Tsimane are 25-30 years younger than the arteries of sedentary urbanites. The data also show that the Tsimane arteries are aging at a much slower rate,” he said.

In the cross-sectional cohort study, researchers visited 85 Tsimane villages between 2014 and 2015 and took non-contrast CT scans of the hearts of 705 adults between the ages of 40 and 94. Based on the CT scans, 85 percent of the Tsimane people had no coronary artery calcium (CAC), 13 percent were at low risk with CAC scores between 1-100 and only 3 percent had moderate or high risk (CAC scores >100). Their mean LDL level was 91 mg/dL and HDL was 39.5 mg/dL.

The lifestyle of the Tsimane Indians is characterized by a diet very low in fat and simple sugar, high in omega-3 and fiber, but not low in salt – and very high levels of physical activity (an average 16,000 steps a day; they were sedentary only about 10 percent of the time). They had few traditional risk factors, but 48 percent had a C-reactive protein level >3 mg/L.

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The lowest reported levels of vascular ageing for any population studied were found in the Tsimane, with rates of coronary atherosclerosis five-times lower than in the U.S., according to results presented by Randall Thompson, MD, FACC. “The arteries of the Tsimane are 25-30 years younger than the arteries of sedentary urbanites. The data also show that the Tsimane arteries are aging at a much slower rate,” he said.

In the cross-sectional cohort study, researchers visited 85 Tsimane villages between 2014 and 2015 and took non-contrast CT scans of the hearts of 705 adults between the ages of 40 and 94. Based on the CT scans, 85 percent of the Tsimane people had no coronary artery calcium (CAC), 13 percent were at low risk with CAC scores between 1-100 and only 3 percent had moderate or high risk (CAC scores >100). Their mean LDL level was 91 mg/dL and HDL was 39.5 mg/dL.

These findings continued into old age, where nearly two-thirds of those over 75 years old had almost no risk of heart disease and only 8 percent had moderate or high risk. By comparison, in a population of 6,814 people ages 45 to 84 in the Multi-Ethnic Study of Atherosclerosis, only 14 percent of Americans had no CAC and 50 percent had a moderate or high risk of CAD.

The lifestyle of the Tsimane Indians is characterized by a diet very low in fat and simple sugar, high in omega-3 and fiber, but not low in salt – and very high levels of physical activity (an average 16,000 steps a day; they were sedentary only about 10 percent of daylight hours). They had few traditional risk factors, but 48 percent had a C-reactive protein level >3 mg/L.
SURTAVI

In the TAVR world, the SURTAVI trial was much-anticipated and it delivered, showing in patients considered to be at intermediate surgical risk that TAVR was non-inferior to surgical aortic valve replacement (SAVR) in patients with symptomatic, severe aortic stenosis.

The primary composite endpoint of all-cause mortality and disabling stroke at 24 months was similar at an estimated 12.6 percent and 14.0 percent in the TAVR and SAVR arms, respectively. “TAVR was just as good as surgery, but it was not statistically superior to it,” said Michael J. Reardon, MD, FACC, who presented the trial. The investigators used a modified intention-to-treat analysis that included patients in whom the procedure for their assigned group was attempted and used a novel Bayesian statistical model.

SURTAVI, conducted at 87 centers in the U.S., Canada, and Europe, is the first study to evaluate outcomes with the self-expanding CoreValve and the new Evolut-R bioprosthesis valves, used in 84 percent and 16 percent of TAVR patients, respectively. To allow for TAVR to be evaluated against real-world surgery, the surgeons performing SAVR could select any biologic valve or whether to enlarge the annulus or base of the valve.

Patients had a mortality risk ≥3 and <15 percent based on The Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) score and overall clinical status including frailty, disability and comorbidity factors. The mean STS PROM score was 4.4 percent. About 60 percent had NYHA Class III/IV heart failure, but those with a SYNTAX score >22 were excluded. Mean patient age was 80 years and 44 percent were women.

Overall, deaths from any cause were similar for TAVR and SAVR: occurring in 2.2 versus 1.7 percent of patients at 30 days, 6.7 versus 6.8 percent at one year and in 11.4 versus 11.6 percent at two years. The rate of major disabling stroke at two years, 2.6 percent for TAVR and 4.5 percent for SAVR, was not statistically significantly different. Although not a primary outcome of the study, researchers noted that the risk of any type of stroke at 30 days was statistically superior for TAVR (3.4 percent vs. 5.6 percent for SAVR).

“We saw the best surgical outcomes we’ve seen yet and TAVR did just as well. This is now the second randomized trial that has met its non-inferiority endpoint and should lead to changes in clinical guidelines that will move the field forward and also benefit our patients,” Reardon said.

Michael J. Reardon, MD, FACC
Indication
• Repatha® is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
• The effect of Repatha® on cardiovascular morbidity and mortality has not been determined.

Important Safety Information
• Contraindication: Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha®.
• Allergic reactions: Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients treated with Repatha®, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha®, treat according to the standard of care, and monitor until signs and symptoms resolve.
• Adverse reactions: The most common adverse reactions (>5% of Repatha®-treated patients and more common than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.
  In a 52-week trial, adverse reactions led to discontinuation of treatment in 2.2% of Repatha®-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to Repatha® treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for Repatha® and placebo, respectively).
• Adverse reactions from a pool of the 52-week trial and seven 12-week trials:
  Local injection site reactions occurred in 3.2% and 3.0% of Repatha®-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection site reactions in Repatha®-treated patients and placebo-treated patients were 0.1% and 0%, respectively.

Allergic reactions occurred in 5.1% and 4.7% of Repatha®-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for Repatha® and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).
Neurocognitive events were reported in less than or equal to 0.2% in Repatha®-treated and placebo-treated patients.

In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1,988 patients treated with Repatha® had at least one LDL-C value < 25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and Repatha® dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by Repatha® are unknown.
Musculoskeletal adverse reactions were reported in 14.3% of Repatha®-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for Repatha® and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).
• Immunogenicity: Repatha® is a human monoclonal antibody. As with all therapeutic proteins, there is a potential for immunogenicity with Repatha®.

Please see Brief Summary of full Prescribing Information on adjacent page.

Table 2. Adverse Reactions Occurring in Greater than 1% of REPATHA-Treated Patients and More Frequently than in Placebo in Pooled 12-Week Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=1224)</th>
<th>REPATHA (N=2052)</th>
<th>Placebo/REPATHA</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy</td>
<td>3.9</td>
<td>4.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.0</td>
<td>4.0</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.6</td>
<td>1.8</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.8</td>
<td>2.1</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>1.2</td>
<td>1.2</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.3</td>
<td>1.2</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>0.7</td>
<td>1.2</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>0.4</td>
<td>1.2</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

In a 52-week, double-blind, randomized, placebo-controlled trial, adverse reactions were reported in patients treated with REPATHA, including some that led to discontinuation of therapy. If signs of serious hypersensitivity reactions occur, discontinue treatment with REPATHA, treat accordingly, and monitor until signs and symptoms resolve.

140 mg every 2 weeks and 420 mg once monthly combined

Adverse Reactions in Eight Pooled Controlled Trials (Seven 12-Week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial (Study 2) and seven 12-week trials. The mean and median exposure duration of REPATHA in this pool of eight trials were 20 weeks and 12 weeks, respectively.

Adverse Reactions in Patients with Hyperlipidemia and in Patients with Familial Hypercholesterolemia

REPATHA is not indicated for use in patients without familial hypercholesterolemia or primary hyperlipidemia (see Indications and Usage (7.1)).

The data described below reflect exposure to REPATHA in 6 placebo-controlled trials that included 2651 patients treated with REPATHA, 5557 exposed to REPATHA plus statins, and 511 exposed for 1 year (median treatment duration of 12 weeks). The mean age of the population was 57 years. 49% of the population were women, 85% White, 6% Black, 6% Asian, and 6% Hispanic. Adverse reactions reported in at least 3% of REPATHA-treated patients, and more frequently than in placebo-treated patients in Study 2, are shown in Table 1. Adverse reactions led to discontinuation of treatment in 2.2% of REPATHA-treated patients and 1% of placebo-treated patients.

The most common adverse reaction that led to REPATHA treatment discontinuation and occurred at a rate greater than placebo was myalgia (1.4% of REPATHA-treated patients, and 0% of placebo-treated patients).

Other adverse reactions that occurred at a rate greater than placebo were back pain (2.2% versus 2.9% for REPATHA and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).

In placebo-treated patients, neurocognitive events were reported in less than 1% in REPATHA-treated patients and 0.6% in placebo-treated patients.

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

- Neurocognitive Events (see Warnings and Precautions (5.1))

1.1 Primary Hyperlipidemia

REPATHA is indicated as an adjunct to diet and maximally tolerated statins for the reduction of LDL-C in adults with homozygous familial hypercholesterolemia (HoFH) (see Indications and Usage (7.1)).

1.2 Homozygous Familial Hypercholesterolemia

REPATHA is indicated as an adjunct to diet and other LDL-lowering therapies (i.e., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

1.3 Limitations of Use

The effect of REPATHA on cardiovascular morbidity and mortality has not been determined.

4. CONTRAINdications

Hyperosensitivity reactions (i.e., rash, urticaria) have been reported in patients treated with REPATHA, including some that led to discontinuation of therapy. If signs of serious hypersensitivity reactions occur, discontinue treatment with REPATHA, treat accordingly, and monitor until signs and symptoms resolve.

4.1怀adverse Reaction Rates Observed in the Clinical Trials of a Drug cannot be extrapolated to all populations, and the general population may not include all subpopulations of patients with the disease studied in the clinical trials. With each new application of a drug, there may be undetected differences in responses between the elderly and younger patients, but greater similarity of some older individuals cannot be ruled out.

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. No data are available in patients with severe hepatic impairment (see Clinical Pharmacology (12.8)).

9. 13. NONCLINICAL TOXICOLOGY

The carcinogenic potential of evolocumab was evaluated in a lifetime study in the hamster of the carcinoembryonic antigen (CEA) assay at 100 mg/kg; the highest dose tested corresponds to 744- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. The monoclonal antibody was not genotoxic. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 25%, respectively.

Reported studies in pregnant monkeys, no effects on embryofetal or perinatal development (up to 6 months of age) were observed when evolocumab was dosed during organogenesis to parturition at 50 mg/kg every 2 weeks to the subcutaneous route at exposures 30- and 12-fold the recommended human doses of 140 mg every 2 weeks and 420 mg once monthly, respectively, based on plasma AUC. No data are available in pregnant women.

This Brief Summary is based on the REPATHA® Prescribing Information as of September 2016.
Impact of Optimal Medical Therapy in the Dual Antiplatelet Therapy Study

Allan S. Jaffe, MD, FACC, interviewed Charles Resor, MD, about an analysis of the impact of optimal medical therapy (OMT) in patients enrolled in the Dual Antiplatelet Therapy (DAPT) study.

Dr. Resor: The DAPT Study randomized approximately 11,000 patients who underwent drug-eluting or bare-metal stent placement and then were free of ischemic or bleeding complications for 12 months to an additional 18 months of continued thienopyridine therapy (standard dose clopidogrel and prasugrel) versus placebo.

How was OMT defined for this analysis?
We defined OMT according to ACC/AHA Class I indications, such that all patients had an indication for a statin, angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) or a beta-blocker.

Did you look at doses or you just whether the patient was on or off therapy at the time of randomization?
We did not have information on medication dosing, so it was just being either on or off those agents at the time of randomization, which was 12 months after the index PCI.

If they came off [these drugs] subsequently, did they change group?
They stayed in the initial group.

What endpoints were you specifically interested in?
We were most interested in major adverse cardiac events (MACE), a composite of myocardial infarction (MI), stroke or death, as well as GUSTO moderate or severe bleeding.

What, in general, did you find?
The primary results of our study were that the use of OMT had no impact on the treatment benefit and risk of continuing a thienopyridine, such that continued thienopyridine use resulted in consistent reductions in ischemic endpoints and consistent increases in bleeding endpoints in this population.

Were the groups the same or were there differences?
There were significant differences between the groups. Patients who were on OMT tended to be younger, and they tended to have lower rates of hypertension, chronic kidney disease and prior PCI or MI.

We would then expect that they would have lower event rates.
That is correct. There were significant differences between the groups. For our comparison of the treatment effect within those two groups, we adjusted our interaction p value for approximately 20 baseline characteristics, procedural characteristics and stent-related factors.

Can you give us some sense of the magnitude of these differences?
There were some significant differences. There was approximately a ten percent higher rate of hypertension in patients who were not on OMT compared with on OMT.

How about the results in terms of MI and MACE?
The hazard ratio for the reduction in MI for patients with continued thienopyridine on OMT was about 0.6, while the hazard ratio in the off-OMT group was about 0.4. While there is some suggestion that the patients off OMT derived a somewhat greater benefit, our interaction analysis showed that the interaction p value did not meet our criteria for significance, suggesting there is a consistent treatment effect between the two groups.

Were the absolute rates different between the OMT and no OMT groups?
There were significant differences in the rates of all three outcomes between the groups.

Was there a cost in terms of bleeding?
For the outcome of GUSTO moderate or severe bleeding, the patients off OMT had higher bleeding rates irrespective of the treatment arm. But, when randomized to continued thienopyridine use, there was no difference in the increase in hazard and bleeding between the on- and off-OMT groups.

Was there a difference between clopidogrel and prasugrel?
Within the primary results of the DAPT Study, there were no differences in ischemic or bleeding outcomes between the two thienopyridines. For this analysis, our results were not different when we adjusted for the particular thienopyridine.

Although you didn't see more detriment, you didn't see more benefit with prasugrel, which is of interest.
We didn't specifically look to compare outcomes by thienopyridine, but we did not see a difference in event rates in our adjusted and unadjusted analyses.

Was there any signal that the various doses of aspirin affected these results?
We didn't specifically look at that in our analysis, but the primary results did not show any significant heterogeneity between the two doses, based on prior reports of the DAPT Study and the supplementary appendix.

A patient could be off OMT because of missing either an ACE inhibitor, ARB, beta-blocker or a statin. Did you see any differences in terms of which drug was not present that defined a patient as off OMT?
When we looked at the treatment benefit of continued thienopyridine across patients who were on or off a statin, beta-blocker, or ACE inhibitor or ARB we did not see any significant differences. [We observed] no significant heterogeneity between the two groups when looking at the treatment benefit of continued thienopyridine.

Were there differences in the absolute rates across the groups?
There were differences in relation to being on or off individual components of OMT. It appeared there was a significant difference in outcomes in patients on or off a statin. Similarly, there was a difference for being on or off a beta-blocker, but less so for the use or not of an ACE inhibitor or ARB. However, the comparison of being on or off the components of OMT was not randomized, so we think there is a significant potential for residual confounding. We feel somewhat less strong about drawing conclusions from those comparisons than we do about saying that there's a consistent treatment benefit across the groups.

Certainly reasonable. Where do we go from here?
The main conclusion of our paper is that the decision to continue DAPT beyond 12 months should be made irrespective of OMT use.

And because the rates were likely somewhat lower in the OMT group regardless of the status of continuing a thienopyridine, you would certainly urge OMT. Absolutely. We would always say your focus should be placed on continuing OMT as much as possible. However, whether or not patients are on OMT should not impact the decision to continue DAPT beyond 12 months.

This interview was edited for print from an interview transcript.

References
Left Atrial Appendage Occlusion in Patients Ineligible for OAC

In this ACCEL interview, Ori Ben-Yehuda, MD, FACC, is interviewed by former JACC Editor-in-Chief Anthony DeMaria, MD, MACC, on the topic of left atrial appendage occlusion (LAAO) in patients not eligible for oral anticoagulation (OAC).

Dr. DeMaria: Please give us the background of your study.

Dr. Ben-Yehuda: There are very few data on patients who may have contraindications for OAC or at least their physicians are worried enough that they don’t place them on OAC for stroke prophylaxis in the setting of atrial fibrillation (AFib). We know the increasing incidence of AFib due to the aging of the population and comorbid conditions is a problem. We wanted to obtain data on the number of such patients and their outcomes. Do they bleed more? Do they have more stroke? What happened if there were not on OAC?

Intuitively I would have thought we knew what happens to people with AFib who have contraindications to OAC, but as you say those data have not been clear. They haven’t been clear because studies that assessed OAC and their efficacy have excluded such patients. We believed also that their incidence is not very high, but they’re out there. This is where big data comes in, by providing databases that collect information on millions of patients. We partnered with an entity called Marketplace, now owned by IBM, that collects insurance claims data on millions of patients. They have 40 million employer-sponsored insurance records, and Medicare supplemental claims data for another 3.4 million. They have information on inpatient and outpatient visits with diagnoses and pharmacy claims, which is very important. We know whether patients were on OAC or whether they filled a prescription.

Tell us about the database and the patient demographics. We looked at a time period between 2010 and 2012 and included patients who had at least one diagnosis code for AFib that was not within 30 days of CABG. We then looked at possible contraindication events, including the most severe (intracranial hemorrhage, intracranial hemorrhage, gastrointestinal hemorrhage), and conditions that would be contraindications that are rarer but recorded in the database, such as untreated (type B) aortic dissection.

We identified 43,000 patients who had these contraindications in the setting of AFib who were not prescribed either OAC or low-molecular-weight heparin.

What did you observe? There was a correlation between the underlying CHADS2 score and CHA2DS2-VASc score and risk of stroke, which increased with increasing scores. We also found these patients, not unexpectedly, had a high bleeding risk even though they’re not on OAC — about 20 percent had another bleeding episode.

I think that’s very important because it justifies their physician’s decision not to place them on OAC. Also, we found a very high risk of ischemic stroke during follow-up in patients with a history of intracranial hemorrhage — independent of the CHADS2 score, but this was limited by the smaller sample size.

In the 20 percent of patients not on OAC who had bleeding, if they had been on an OAC and had bleeding, would it have been attributed to the OAC? Is it possible if everyone had been on an OAC that only about 20 percent would have had bleeds and perhaps they’re the same 20 percent that had bleeding off OAC? In other words, is that finding interesting in terms of whether this group of patients should be given a trial of OAC? It’s a very interesting question. Intuitively, in general, you would think that if a patient has bleeding and then goes on an OAC that the bleeding would be more severe. I think it would be very hard to study this in a controlled manner, as an institutional review board would have a hard time signing on to giving patients who are already at risk a medicine that would increase their risk.

In a large database, we can at least match patients who have similar conditions to those in our study on OAC to see the outcomes. However, beyond the risk scores, physicians have an additional intuitive ability. As we try to develop frailty scores, for example, we see these are not as good as the physician’s assessment. You look at the overall patient and you know whether or not they’re frail. I think that physicians know their patients, and there’ll still be a selection bias, even if we match them on different characteristics.

What did you conclude from your observations? Bleeding was common and ischemic events were fairly prevalent too. There is an overall a correlation between the CHADS2 and CHA2DS2-VASc scores for both ischemic events, for which they were designed to detect risk, and bleeding events. This puts physicians and patients in a quandary. The more you need these medications, the more you’re at risk for side effects (bleeding) of these medications. We definitely showed that [patients who are ineligible and therefore not treated with OAC] is not a rare phenomenon. They tend to have relatively high CHADS2 scores. The vast majority of our patients had a CHADS2 score >1 and a CHA2DS2-VASc score >4. Thus, this is an important group of patients for whom we need to find a solution.

This sets the stage for innovative new therapies that are now approved, such as LAAO to eliminate

These data support the notion that there is a group of patients in whom the risk is sufficient to warrant consideration of these devices. Ori Ben-Yehuda, MD, FACC

There are very few data on patients who may have contraindications for OAC or at least their physicians are worried enough that they don’t place them on OAC for stroke prophylaxis in the setting of atrial fibrillation. Ori Ben-Yehuda, MD, FACC

These patients were evaluated prior to the availability of occlusion devices. How many would qualify today? This is a high-risk group and would qualify. The studies for LAAO and other databases had wider inclusion criteria. An ongoing debate is who really needs these devices. Their cost and availability is an issue, but I think these data support the notion that there is a group of patients in whom the risk is sufficient to warrant consideration of these devices.

Is there a CHADS2 score that helps to define who should have an occlusion device? A CHADS2 score of ≥2 identified patients who were at significant risk. As with our decision to implement OAC, this study suggests that in the absence of the ability to give OAC, the patient should be considered for a closure device.

This interview was edited for print from an interview transcript.

To listen to the ACCEL interview with Ori Ben-Yehuda, MD, FACC, scan the QR code.
Gail Pearson, MD, ScD, FACC, is a pediatric cardiologist, an associate director of the Division of Cardiovascular Sciences and the director of the Adult and Pediatric Cardiac Research Program at the National Heart, Lung, and Blood Institute (NHLBI). Pearson joined the NHLBI in 1997 to oversee and develop the NHLBI’s clinical pediatric cardiovascular research programs. Since 2000, she has occupied several leadership positions within the Institute. Pearson received her medical degree from Johns Hopkins School of Medicine and a doctorate in health policy from Johns Hopkins School of Hygiene and Public Health. Pearson completed her pediatric residency and pediatric cardiology fellowship at the Children’s National Medical Center in Washington, DC, where she continues to teach and provide care for children with congenital heart disease (CHD).

Katlyn Nemani, MD, talked with Pearson about her career, the NHLBI’s investment in pediatric cardiovascular research, programs she has developed and what’s ahead in the next decade.

What inspired your interest in pediatric cardiology, and more specifically in caring for patients with congenital heart disease?

After spending several years in regional health planning and regulation, a change in political winds away from regulation made it clear that I needed to think about career options. Among my friends were two women who were neonatologists, and who encouraged me to think about a career in medicine. I initially dismissed this out of hand, because I didn’t have sufficient undergraduate science courses. I was also single at the time, both parents had passed away, so the prospect of four years of medical school with no visible means of financial support was a bit daunting. Nevertheless, they were persuasive, and so I embarked on a post-baccalaureate pre-med program. I was accepted by Johns Hopkins, which fortunately was interested at the time in students who were not coming directly out of college.

When it came time to think about residency training, pediatrics was a foregone conclusion, in part due to the influence of the two neonatologists who had encouraged me into medical school, and because I liked children and felt there was a great deal of opportunity to make a difference in a child’s life through medicine. Once in pediatrics, I was interested in a sub-specialty that had a critical care component (ironic now, as I am an outpatient pediatric cardiologist), and of those available, only pediatric cardiology provided an opportunity to follow your patients through their lives, which appealed to me greatly. I wanted to help children and their families as they grew up. In addition, during my time at Hopkins, which is one of the birthplaces of pediatric cardiology, I was inspired by that rich history and the opportunities ahead.

Please tell us a bit about the path that led to your career in health policy and leadership position within the NHLBI.

I came to NHLBI through serendipity and a network of women that led me to the position of a pediatric cardiologist when another candidate suddenly changed her mind and left the NHLBI in the lurch. When I took the job, I thought I would be there for maybe 3 years — that was 20 years ago! Over time, I was entrusted with the development of the Pediatric Heart Network (PHN) and other programs, and was promoted into various leadership positions.

Who are the mentors who’ve had the most meaningful impact on your career?

The list is long! I have been fortunate to have had many mentors and a great deal of support throughout my training and career, but I’ll just highlight a few here. First are Billie Short, MD, and Anne Fletcher, MD, the neonatologists and friends who encouraged someone with an undergraduate degree in sociology to go to medical school, and with whom I had the privilege of working on research projects during my residency. While at Hopkins, I had the opportunity to spend time in the Division of Pediatric Cardiology and work with Catherine Neill, MD. Dr. Neill, who passed away at age 84 in 2006, was one of the pioneers in pediatric cardiology, trained by Helen Taussig, MD, FACC, and an extraordinary mentor during research.

Roberta G. Williams, MD, MACC, a pediatric echocardiography pioneer, made a semi-stray comment to me during a break at a conference held by ACC advising me to not reject a position that was not 100 percent clinical, and this came back to me when I was considering my first position at NHLBI.

I would like to give credit also to Michael S. Lauer, MD, FACC, currently Deputy Director of...
the National Institutes of Health, who was my boss for several years at NHLBI. He played a significant role in helping me refine my leadership style, particularly because he embraced the science of management. And my husband of 29 years, Craig Hoffman, MD, whose calm and imperturbable approach to both science and management has been a model I still strive to emulate.

Please tell us about the Pediatric Heart Network, the first program you developed at NHLBI.

The PHN was established in 2001 to improve evidence-based treatment options and standards of care for patients of all ages with CHD and children with acquired heart disease, such as Kawasaki Disease. The PHN is a multi-center clinical research consortium that currently consists of 9 main clinical research sites in the U.S. and Canada, a data coordinating center, and a variable number of auxiliary sites.

Over the past 15 years, the PHN has changed the landscape of pediatric cardiovascular research by providing a vibrant, sustainable, nimble infrastructure for multi-center research. To date, the PHN has conducted more than 20 clinical trials and other studies, which have advanced pediatric cardiovascular science in several areas: surgical care, single ventricle physiology, Marfan syndrome, Kawasaki disease and quality improvement.

The PHN has trained several hundred investigators and study coordinators in the conduct of clinical trials, and enrolled nearly 8,000 children and young adults in our studies. It has developed a robust young investigator program, a productive nursing research program, and the Children and Clinical Studies campaign, which helps patients and families learn about what it means to participate in clinical research. Our success is supported by the US News & World Report’s use of participation in the PHN as a factor in naming the Best Children’s Hospitals.

In 2009 you developed two research efforts to create the Bench to Bassinet Program. What are the goals of the Cardiovascular Development Consortium (CvDC) and the Pediatric Cardiac Genomics Consortium (PCGC)?

NHLBI had funded different programs designed to promote translation of research across the basic to clinical spectrum, and we had learned that you can’t force translation in one 5-year grant program, so we were looking for a novel approach. After a great deal of deliberation and consultation with extramural investigators, the Bench to Bassinet Program was born. The vision for the program was to provide a framework for scientists spanning the domains of basic science, functional genomics, translational biology, and clinical research to collaborate in accelerating progress toward discovery and translation.

The CvDC is a group of four academic institutions conducting basic science research to characterize the molecular networks and pathways that control normal and abnormal heart development. Recent work by the CvDC has enabled the creation of spatiotemporal maps of gene expression at a single cell resolution during heart development, which has revealed cell line-specific gene programs that underlie normal heart development and CHD.

The PCGC is a group of five centers using state-of-the-art genomics tools to identify the genetic causes of CHD and to determine how genes affect treatment outcomes. The PCGC has enrolled more than 10,000 children and adults with CHD, and many of their parents, who have agreed to provide DNA to the PCGC’s CHD Genes study. Recent PCGC studies have uncovered new groups of genes not previously associated with CHD, and have identified a genetic link between CHD and impaired neurodevelopmental outcome.

The CvDC and PCGC were designed to provide a continuum of research that, along with the PHN, would allow focus within the three consortia on their specific scientific strengths, while also encouraging organically, through joint meetings and research projects, translation of findings as they ripen to maturity. For example, we are now using the PCGC’s genomics capabilities and the PHN’s detailed phenotyping data to help us identify genetic and genomic factors that influence outcome. In the future, we hope to add data collection regarding behavioral and environmental risk factors for CHD.

It has been terrific to watch my patients grow up over the years, and watch the grace with which their parents accommodate the challenges of pediatric heart disease. Gail Pearson, MD, ScD, FACC

What goals do you have for the NHLBI in the coming decade?

NHLBI is in the midst of an ongoing Strategic Visioning process designed to anticipate and capitalize on emerging scientific opportunities and identify approaches to overcome new barriers to progress. By way of disclaimer, the comments here reflect my thoughts, and don’t necessarily reflect official NHLBI positions. However, they are consistent with the four NHLBI Strategic Goals and Objectives: Understand Human Biology, Reduce Human Disease, Advance Translational Research, and Develop Workforce and Resources. In fact, the Bench to Bassinet Program is perfectly aligned with these goals.

What aspects of your clinical and research career have been the most rewarding?

The rewards are numerous. The ‘village’ that the PHN has become never ceases to amaze me. It has been nought short of remarkable over the years to watch the selfless energy that the investigators, coordinators and data coordinating center staff pour into the research. The success of our signature programs, the PHN Scholars for young investigators, and the nursing research program also have been extremely gratifying. Every member of the PHN, every day, is pulling together in the same direction – improved outcomes for individuals affected by the conditions we cover.

And then, watching the Bench to Bassinet program mature into a research powerhouse has exceeded all expectations. Who would have thought that the PCGC would so rapidly advance our understanding of the genetics of congenital heart disease and that their inaugural publication would be a Nature paper? I have frequently said in talks, and it remains true, I feel as if I am playing for an All-Star team every day.

I really enjoy interacting with the fellows at Children’s and the early career staff at NHLBI, and helping them to sort out research and other professional issues. Finally, it has been terrific to watch my patients grow up over the years, and watch the grace with which their parents accommodate the challenges of pediatric heart disease. Continuing to practice has significantly informed the programs that I have had the fortune to be able to develop at NIH, and reminds me, every week, why the research we support here at NHLBI is so important. There continue to be so many questions for which we don’t have answers, so it is gratifying to see patients one at a time, and to have the opportunity to design programs to help get the answers.

References
Change, Innovation and the Arts a Focus of ACC.17 Opening Showcase

ACC.17 kicked off with a focus on change, innovation and the importance of the arts. Richard A. Chazal, MD, MACC, welcomed the tens of thousands of attendees to Washington, DC, as part of the Opening Showcase Session.

Chazal paid tribute to all those involved in making ACC.17 happen, including ACC.17 Chair Jeffrey T. Kuvin, MD, FACC, and Co-Chair Andrew M. Kates, MD, FACC. Kuvin, who joined Chazal on stage later in the session, highlighted the many features that made ACC.17 stand out from previous meetings, including 23 Late-Breaking Clinical Trials and 17 Feature Clinical Research presentations; special intensives focused on Palliative Care, Equity in Healthcare and Faculty Development; the more than 275 companies that were part of the ACC.17 Expo; and a highly popular new Personalized Skills Center designed for independent and small group learning. He also noted new opportunities for attendees to earn simultaneous Continuing Medical Education and Maintenance of Certification credit, in addition to credits for nurses, pharmacists and European participants.

Attendees also took a moment of silence to remember ACC Past President Sylvan Lee Weinberg, MD, MACC, who Chazal noted was a role model for an entire generation of clinical cardiologists. “I first met him when he served as a visiting professor at Indiana University in the 1980s,” Chazal said. “His ACC career included a highly successful term as president from 1993 to 1994. He also had a 15-year legacy as editor of ACCEL.”

During his presidential address, Chazal focused on the many changes facing the cardiovascular and broader health care communities, as well as the ACC. Among these changes: new educational requirements and learning styles; a transition from evidence-based medicine to personalized medicine; and a changing health care delivery system in the U.S. Chazal also highlighted changing patient demographics, as well as changes in the cardiovascular workforce and in ACC membership.

“How do we address all of these changes without feeling overwhelmed and frustrated?” Chazal asked. “First, we take a page out of the [Washington, DC] playbook and accept that change is occurring regardless of what we may wish. Next, we prepare to address it.”

Richard A. Chazal, MD, MACC

Chazal challenged attendees not to squander the chance to truly transform cardiovascular care and improve heart health and urged them to take advantage of the changing times to embrace challenges and find new solutions.

“Implementing change is difficult and the transition fraught with anxiety — but few real accomplishments are achieved without angst,” he said. “And, although we cannot control external events, we can control our reactions to these events. We can decide whether to emphasize the inherent challenges or the inherent opportunities presented to us. Today, in a city long accustomed to change, I challenge all of us to meet change head on.”

Following Chazal’s address, David J. Skorton, MD, FACC, secretary of the Smithsonian Institution, delivered the annual Simon Dack Lecture, which focused on “Values: How the Arts and the Humanities Nurture our Careers and our Lives?”

He talked about the many ways the arts and humanities transcend politics and economics and enrich lives. “Arts, humanities and social sciences can help us connect and communicate in a time of division,” he said.

Skorton also discussed the influence of arts and humanities in inspiring technological advance, helping patients recover and providing ethical guidance. He cited examples of using art therapy to help veterans recovering from traumatic brain disease, as well as origami-inspired collapsible stent prototypes.

He closed by touching on the impacts of the arts and humanities on his personal career path, from the musical nature of the hearts rhythms to the color, emotion and imagery of cardiovascular imaging. He called on cardiovascular professionals to champion the arts, humanities and social science as a means of advancing medical science and ethical care.

Read the transcript of Chazal’s Presidential Address at ACC.org/ACC2017.
After three days of expanding knowledge, reaching new heights, rising to challenges and stretching limits, ACC.17 closed with the time-honored tradition of Convocation.

Presided over by outgoing ACC President Richard A. Chazal, MD, MACC, the Convocation Ceremony ushered in 225 new ACC Fellows and nearly 20 new Associates. In addition, the evening recognized recipients of ACC’s Distinguished Awards, as well as recipients of ACC/Merck Research Fellowships, the ACC/William F. Keating, Esq. Endowment Career Development Award, ACC Presidential Career Development Award, the William W. Parmley Young Author Awards for the Journal of the American College of Cardiology (JACC), the Young Author Achievement Awards for JACC Journals, and the ACC Young Investigator Awards.

“Convocation is a time to recognize outstanding leaders in the cardiovascular field – both new and old,” said Chazal. “Congratulations to all of the new Fellows and Associates who have chosen to dedicate their lives to transforming cardiovascular care and improving heart health. These men and women are the future of our profession and of the College.”

During his presidential remarks, Chazal noted that leading the College, particularly during a period of profound change, was the opportunity of a lifetime. He talked about the progress made towards achieving the goals and priorities of ACC’s Strategic Plan, particularly in the areas of Maintenance of Certification, implementation of the Medicare Access and CHIP Reauthorization Act, ACC governance changes and the increasing integration of physicians and the care team with hospitals and systems.

“The progress that we have made in these and other areas of our Strategic Plan is due to the commitment of ACC members and leaders to do what is best for patient care,” said Chazal. “Our value is in our mission statement, which is ultimately all about the patient. Collaboration with each other, as well as with our counterparts in the U.S. and around the world is key to our success.”

The evening also marked the official installation of new ACC leaders, including ACC’s new president, Mary Norine Walsh, MD, FACC. Walsh, ACC’s third female president, is medical director of the heart failure and cardiac transplantation programs and director of nuclear cardiology at St. Vincent Heart Center in Indianapolis, IN, and is also program director of the St. Vincent Advanced Heart Failure and Transplantation Fellowship.

“Convocation offers an opportunity to acknowledge and thank those who are moving our profession forward, as well as recognize those who have helped us reach where we are today,” said Walsh, who focused on the importance of teamwork in her Convocation remarks.

“The delivery of cardiovascular care to our patients is becoming increasingly more complex every day,” said Walsh. “In my own field of advanced heart failure and transplantation, new treatment options and technologies and methods of care are advancing so rapidly that no one physician, surgeon or clinician can successfully care for our patients alone. It takes a team.”

Walsh called on new Fellows and Associates to volunteer with the College and speak up. She also urged them to get to know their colleagues and team members at their hospital, in their practice and/or at the College.

“Be a highly-functioning team. Do what you do best. Expect your teammates to do the same. Our team will be better for your participation and involvement.”

Scan the QR code to read Walsh’s first Leadership Page in the Journal of the American College of Cardiology on the importance of team work.

Convocation Welcomes New FACCs and AACCs to ‘The Team’
Lessons Learned and What’s Next From Million Hearts

Janet S. Wright, MD, FACC, executive director of Million Hearts, a national initiative co-led by the Centers for Disease Control and Prevention (CDC), and the Centers for Medicare and Medicaid Services (CMS), with the goal of preventing 1 million myocardial infarctions and strokes by 2017, gave the 48th Annual Louis F. Bishop Lecture at ACC.17. She spoke with Cardiology editors about her time at Million Hearts and what’s next for the initiative.

What have been some of the biggest Million Hearts accomplishments to date? The accomplishments really belong to our 120+ partners, like the ACC, the American Heart Association, the American Pharmacists Association, the Preventive Cardiovascular Nurses Association, and the American Association of Nurse Practitioners, as well as more than 20 federal agencies and offices. As a result of their collective efforts, millions of patients are now cared for by health systems and practices that have been recognized and rewarded for performance on key cardiovascular disease measures. Additionally, more than 7 million smokers have quit and standardized treatment protocols for hypertension are being implemented across entire systems of care. The first ever pay-for-prevention model is also underway in 48 states to recognize and manage those at high risk for cardiovascular disease.

What have been some of the biggest lessons learned? Implementing what works and doing it at such a large scale is a challenge. Success definitely takes a team with focus and commitment from the top. Even with these assets, however, the wheels of progress turn very slowly. Engaging networks – formal and informal, community-based, health system-based, and best of all, hybrids of these – to focus on a few key strategies can make all the difference in the rate at which our nation’s cardiovascular health and care improve.

How important is the entire care team in achieving Million Hearts’ goals? Team care is essential not only to achieving the aim of a million fewer cardiovascular events in five years but also to good health. We have been particularly committed to disseminating the evidence for pharmacists, community health workers and cardiac rehabilitation teams, among others. While practices and health systems excel in prevention and treatment, teams that bridge the traditional silos of public health and health care are also important for building strong communities that support healthy behaviors.

What are your hopes/goals for Million Hearts moving forward? In order to tip the current flattening of cardiovascular disease mortality rates downward again, we need all-hands-on-deck. Based on modeling, expert interviews, partner feedback, and recent scientific literature, we have designed a new framework for the next five years, Million Hearts 2022. By adding a new focus on physical activity, cardiac rehabilitation and patient engagement, along with very powerful public health and health care actions related to reducing sodium and tobacco and continued improvement in the “ABCS” (Aspirin for those at risk for heart attack and stroke; Blood pressure control; Cholesterol management; and Smoking cessation), we are providing a roadmap to partners for more progress, faster.

ACC Asks Congress for Continued Funding for CV Research

The ACC in March submitted written testimony for the record to the House Appropriations Labor, Health and Human Services, Education and Related Agencies Subcommittee urging continued funding to ensure future medical research advancements in FY ’18 and beyond. The testimony recommends Congress appropriate the following funds towards agencies doing vital work in cardiovascular disease treatment and prevention: $34 billion for the National Institutes of Health (NIH), with $3.3 billion going towards the National Heart, Lung, and Blood Institute and $1.8 billion towards the National Institute of Neurological Disorders and Stroke; $7 billion for the Centers for Disease Control and Prevention (CDC), with $175 million towards the CDC’s Division for Heart Disease and Stroke Prevention to strengthen heart disease prevention efforts at state and local levels, $5 million towards CDC’s Million Hearts initiative, $37 million towards CDC’s WISEWOMAN to help uninsured or under-insured women prevent or control heart disease, $7 million towards CDC congenital heart research to study its effects over the lifespan, and $210 million towards CDC’s Office on Smoking and Health to maintain the program’s cost-effective tobacco control efforts.
Coverage Proposal for PAD Supervised Exercise Therapy

The ACC recently joined with other stakeholders to urge the Centers for Medicare and Medicaid Services (CMS) to move forward with a positive national coverage decision for supervised exercise therapy to treat symptomatic peripheral artery disease. In a joint letter, the ACC and others expressed support for the fundamental proposal, and suggested revisions that would add flexibility and clarity for patients and clinicians. CMS will publish its final decision by May 31, though it could come several weeks before that deadline.

Coding Corner

CMS has announced that practitioners in Florida, Kentucky, Louisiana, Nevada, New Jersey, North Dakota, Ohio, Oregon and Rhode Island are required to report on claims data during the global period of specified procedures using Current Procedural Terminology code 99024, beginning July 1. The specified procedures are those that are furnished by more than 100 practitioners and are either nationally furnished more than 10,000 times annually or have more than $10 million in annual allowed charges. Although reporting is required for global procedures furnished on or after July 1, the ACC encourages all practitioners to begin reporting as soon as possible.

FDA Issues Safety Alert for Absorb GT1 BVS

The U.S. Food and Drug Administration (FDA) has issued a safety alert for the Absorb GT1 Bioresorbable Vascular Scaffold (BVS) by Abbott Vascular due to an increased rate of major adverse cardiac events observed in patients receiving the device. The FDA recommends health care providers follow the instructions included in the FDA-approved BVS physician labeling regarding selecting appropriately-sized heart arteries for BVS implantation and methods to properly implant the device against the vessel wall. The agency also recommends BVS patients be advised to follow dual antiplatelet therapy recommendations prescribed by their health care providers. Additionally, patients experiencing any new cardiac symptoms such as irregular heartbeats, chest pain or shortness of breath should be advised to seek clinical care. Any adverse events related to the BVS should be reported through MedWatch.

HHS Delays Start of Episode Payment Models

The U.S. Department of Health and Human Services (HHS) has delayed the effective date for the final rule for Advancing Care Coordination through Episode Payment Models (EPMs); Cardiac Rehabilitation (CR) Incentive Payment Model; and Changes to the Comprehensive Care for Joint Replacement Model until May 20. This postpones the start date of the EPMs and the CR Incentive Payment Model for three months – from July 1 to Oct. 1. In its statement, HHS noted it is seeking comments on the appropriateness of this delay, as well as a further start date delay until Jan. 1, 2018.

According to HHS, the additional three-month delay “is necessary to allow time for additional review” and to ensure that the agency “has adequate time to undertake notice and comment rulemaking to modify the policy if modifications are warranted, and to ensure that in such a case participants have a clear understanding of the governing rules and are not required to take needless compliance steps due to the rule taking effect for a short duration before any potential modifications are effectuated.”

“Creating value-based payment models for patients with cardiovascular disease is extremely challenging and the ACC has urged the Centers for Medicare and Medicaid Services (CMS) to proceed with great caution in implementing and testing these models in order to ensure that they allow for accurate beneficiary attribution, valid quality and cost measurement, meaningful comparisons and ultimately development of best practices to achieve better health outcomes for patients,” says ACC president Mary Norine Walsh, MD, FACC. “This newest delay provides an opportunity to continue working with CMS to find ways to further refine and improve the effectiveness of the models’ clinical and operational designs. The ACC’s NCDR registries may be helpful in this effort. In the meantime, the College encourages members who are part of the model to continue to prepare for implementation.”

Health Reform Bill Stalled in U.S. House of Representatives

The American Health Care Act (AHCA) was pulled from consideration in the U.S. House of Representatives last month. After much debate, lawmakers could not muster the votes to pass the legislation, which would have repealed and replaced provisions under the Affordable Care Act – a key priority for the new presidential administration and Congress.

The ACC had previously expressed concerns about elements of the AHCA, particularly its impact on patient coverage. “As reflected in CBO’s analysis of the legislation, the estimated impact of the AHCA does not align with ACC’s Principles for Health Policy Reform,” said ACC immediate past president Richard A. Chazal, MD, MACC, in an earlier statement. “We are concerned over the sharp projected increase in the number of uninsured Americans, especially among our most vulnerable populations.”

The College’s principles prioritize improved coverage for – and access to – efficient, high quality care; protection for individuals with pre-existing conditions; and continued national investment in preventive care, medical research and innovations. “Adhering to our Principles for Health Policy Reform, the ACC will continue to work with lawmakers on both sides of the aisle in our efforts to improve coverage for – and access to – efficient, high quality care, particularly for patients with pre-existing conditions like heart disease,” said ACC president Mary Norine Walsh, MD, FACC.
Introducing ACC’s New President: Mary Norine Walsh, MD, FACC

Mary Norine Walsh, MD, FACC

I’m one of the few people who knew from childhood what she wanted to be,” says Mary Norine Walsh, MD, FACC, president of the ACC. The presidential chain was passed on to Walsh by Richard A. Chazal, MD, MACC, at the Convocation ceremony at ACC.17 as he closed out his term as president.

As a child, Walsh grew up as part of a large family in Minneapolis, MN, and when she was seven, she underwent a hospitalization that had an enormous impact on her, planting the seed for her future in medicine. While the dream began with a career aspiration to become a nurse, Walsh’s interests shifted to medicine after she had a few high school science courses under her belt. “The summer I turned 19, I got a job as a nurse’s aide in a community hospital emergency room and that clinched my decision to pursue medical school,” she said. Walsh was initially drawn toward pursuing a residency in emergency medicine, but it was during her third year as a medical student at the University of Minnesota that her cardiology rotation changed her mind.

Walsh went on to complete her internship and residency at the University of Texas Southwestern in Dallas, and her cardiology fellowship at Washington University School of Medicine in St. Louis, MO. She spent a few years working at the Hospital of the University of Pennsylvania before joining what is now St. Vincent Medical Group in Indianapolis, IN where she still practices today. Walsh serves as the medical director of the heart failure and cardiac transplantation programs and director of nuclear cardiology at St. Vincent Heart Center. Additionally, she is program director of the St. Vincent Advanced Heart Failure and Transplantation fellowship.

Walsh’s first involvement with the ACC began by stepping up and reaching out at ACC’s Annual Scientific Session. “I attended a lunchon panel at an ACC Scientific Session sponsored by what was then known as the Women in Cardiology Ad Hoc Task Force,” she recalls. “Marian Limacher, MD, FACC, moderated the session and I approached her after the session was over with an offer of help. I joined the task force and eventually succeeded her as chair.” Walsh’s involvement didn’t end with that chair position. She went on to participate in other committees of the ACC and her state chapter, of which she eventually became chapter president and member of the ACC’s Board of Governors.

“Volunteering as a member of the ACC has been a very important part of my life,” says Walsh. “I realized early on that the mission and vision of the College meshed with my own and I really found a home at the ACC.”

While serving as president of the ACC, Walsh plans to focus on a few primary areas – in addition to and in concert with the College’s strategic plan and priorities. With the health care environment in a constant state of flux, and as it moves from a volume-driven to a value-driven environment, Walsh says that equipping members to most effectively and efficiently function – and thrive – is critical. “Helping practices and institutions make the pivot to payment for value will be a major focus this year,” says Walsh. She adds that the ACC is in a prime position to provide help in this area. “Team-based care has been a passion of mine in my own practice and the College will continue to have a focus on this in the next few years to come. Working in teams will allow us to better serve patients.” Walsh says that another goal of hers throughout her presidential year is to engage more members in ACC’s advocacy efforts. “We need to make our voices heard on Capitol Hill and at our statehouses by advocating for patient access, quality care and even public health issues that result in a decrease in cardiovascular morbidity and mortality,” she says. “Being an advocacy leader can be a goal for all of our members and I hope to help foster that leadership.”

Walsh notes that one of the biggest challenges facing the field of cardiology is the ability of the profession to adapt to the rapidly changing landscape of cardiology and patient care. For example, Walsh notes that many of the procedures that used to be solely in the wheelhouse of cardiovascular surgeons – like coronary bypass and valve surgery – are now completed through less invasive techniques, and in some cases – by cardiologists. “When we see radical shifts in care techniques, our profession must be nimble enough to adapt to the changes,” she says.

“The time for training in both interventional cardiology and electrophysiology has recently been expanded to provide adequate experience for fellows who seek to perform structural procedures and ablations. We will need to continue to make similar course corrections in training as our field evolves.” Additionally, Walsh notes that fellows will need to remain aware of changing market forces as they choose their preferred practice.

We need to make our voices heard on Capitol Hill and at our state houses by advocating for patient access, quality care and even public health issues that result in a decrease in cardiovascular morbidity and mortality. //
Walsh begins her term with the passing of the presidential chain from Richard A. Chazal, MD, MACC.

Team-based care has been a passion of mine in my own practice and the College will continue to have a focus on this in the next few years to come. **Working in teams will allow us to better serve patients.**

Walsh with her two children, Gil and Hanna, and husband, Bob.

In her free time and to stay fit, Walsh is an avid runner.
New Research Explores Success of ACC’s Patient Navigator Program

New research exploring the benefits and best practices of ACC’s Patient Navigator Program was presented during both ACC.17 and NCDR.17. While more data are needed to truly estimate the precise level of benefit of the Patient Navigator Program, the results are encouraging, particularly in the areas of heart failure (HF) education processes, post-discharge phone calls, scheduled follow-up appointments and readmission rates. Highlights include:

Standardizing HF Education and Documentation
Results from a study led by Marit S. Planton, BSN, et al., at St. Vincent’s Medical Center (SVMC) in Bridgeport, CT, found that the ACC Patient Navigator Program helped to successfully identify opportunities for improvement in the HF education process, reduce readmission rates, improve patients’ understanding of HF and encourage compliance among staff.

Over the course of 11 months – from January to November 2016 – SVMC saw its HF education process improve by 112.5 percent, from 32 percent to 68 percent. SVMC plans to expand the new education process to all inpatient hospital units in order to include HF patients who may be in non-cardiac units.

Establishing the P.U.M.P Club
Successful HF readmission reduction at Saint Mary’s Hospital in Waterbury, CT, demonstrated the effect working across institutional silos has on patient outcomes. A study led by Paul Kelly, MD, FACC, et al., found that both short-term and long-term readmission rates declined after establishing its “P.U.M.P Club.”

By creating a multidisciplinary team, holding standardized weekly meetings to review all HF patients and using cardiovascular rehab and pet therapy with patients, the total number of patients readmitted within 150 days of hospital discharge declined from 48 to 31. Moving forward, Saint Mary’s Hospital aims to expand the program and standardize methods across its five-hospital regional health system.

Reducing Hospital Readmissions For AMI and HF Patients
According to a study led by Camille Randol, RN, Jamal M. Brewster, RN, and Richard E. Shaw, PhD, FACC, ACC’s Patient Navigator Program and ACC’s ACTION Registry-GWTG contributed to the reduction of 30-day readmission rates in acute myocardial infarction (AMI) and HF patients between 2014 and 2016.

The 30-day readmission rates for AMI patients at the California Pacific Medical Center in San Francisco, CA, dropped from 12 percent to 8.7 percent, while rates for HF patients dropped by 1.5 percent total. Other results include a 39 percent increase in seven-day follow-up and 82 percent increase in nursing teach back.

Expanding Post-Discharge Phone Calls
Resources from ACC’s Patient Navigator Program helped the University of Utah Hospital and Clinics (UUHC) successfully achieve its goal of improving the number of post-discharge phone calls made, according to a study led by Dawn Young, BSN, et al.

Through the program, UUHC monitored its progress and made adjustments to its processes over the course of a year. The number of phone calls made within 48 hours increased by 57.1 percent, from less than 5 percent in January 2016 to an average of 61 percent by December 2016.

Eliminating Barriers to Follow-Up Appointments
 Scheduled seven-day follow-up appointments are important for HF patients, but they do not guarantee attendance, according to a study led by Lisa Casher, RN. After noticing a drop in attendance at Mercy Hospital in Portland, ME, Casher aimed to help determine the most common barriers HF patients face.

The results found that 46 percent of discharged HF patients were unable to attend their follow-up appointments due to lack of affordable, accessible and reliable transportation. By establishing a source of transportation prior to discharging HF patients, Mercy Hospital increased attendance from 75 percent in Q1 2016 to 86 percent in Q4 2016.

Teaming Up to Improve Care
By applying ACC’s Patient Navigator Program, hospitals may successfully reduce the readmission rate among primary HF patients, according to results from Montefiore Medical Center. A Navigator Team – including a nurse and a pharmacist – provided education, scheduled follow-up and medical therapy recommendations to 51 HF patients from June 2015 to January 2016. Results showed that this patient-tailored approach decreased readmission rates by 81.3 percent, from 25.6 percent to 4.8 percent. In addition, the Patient Navigator Program significantly increased the education available and follow-up offered to patients.

“We are excited to see how our data, especially the early post-discharge appointment, were adopted by the Hospital Readmissions Reduction program at Montefiore Medical Center, across all three campuses in the Bronx,” said Katherine DiPalo, PharmD, et al.

Managing CV Risk in Patients With Type 2 Diabetes
Cardiologists are treating more and more patients with established cardiovascular disease and diabetes. Diabetes, particularly type 2 diabetes, is common in patients with an array of cardiovascular disorders including coronary artery disease, peripheral vascular disease, congestive heart failure and stroke. Over the last decade, studies have shown that patients with diabetes are at greater risk of dying from these cardiovascular diseases than those without diabetes.

Several important randomized trials (i.e., EMPA-REG OUTCOME, SUSTAIN-6 and LEADER) show medical interventions in cardiovascular patients with diabetes can provide protective benefits. Deciphering the findings from these trials was a key component of an ACC.17 session chaired by Christopher Cannon, MD, FACC. The session also offered a closer look at the new therapies and included robust discussion and debate on the cardiologist’s role in managing cardiovascular risk in their diabetic patients.

According to Nathan D. Wong, PhD, FACC, it is critical going forward that cardiologists employ a team-based approach in collaborating with endocrinologists and other providers managing patients with diabetes. As part of ongoing efforts in this area, the ACC, with support from Boehringer Ingelheim Pharmaceuticals Inc. and Eli Lilly and Company, is working to raise awareness and prepare the cardiology community for the coming paradigm shift. Leveraging data from the Diabetes Collaborative Registry, the ACC will identify and capture key learnings from cardiovascular innovators who are managing cardiovascular risk reduction for people with type 2 diabetes. These learnings will be communicated to the wider cardiology community and used to help develop clinician and patient tools.

Learn more at ACC.org/EMPA.

Scan the QR code for a video featuring Christopher Cannon, MD, FACC.
It is time to examine the facts.

IAB Therapy still remains the first-line choice

The facts:

- IAB therapy, with low complication rate, should be considered in early stages of cardiogenic shock.¹
- No clear signal of superior outcome was observed with patients with Impella® CP support when compared with the IABP.²

- Bleeding complications in the IMPRESS™ trial were significantly higher in the Impella arm than the IABP arm (33% vs. 8%).²
- Initiation of therapy prior to primary PCI vs. after PCI decreased mortality in cardiogenic shock from 53% to 25%.²

MORE CHALLENGES, MORE INSIGHTS
Another Dip into ACC.17

BEFORE WE GO THIS MONTH, WE LEAVE YOU WITH A LOOK AT FIVE MORE TRIALS PRESENTED AT ACC.17.

GEMINI-ACS 1: Generates Hypotheses

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor remains the antithrombotic mainstay for patients with an acute coronary syndrome (ACS), regardless of treatment strategy. In previous studies evaluating the addition of an oral anticoagulant (OAC) to antiplatelet therapy in ACS patients (WARIS II and ATLAS ACS-TIMI 51), superior efficacy was offset by a significantly greater risk of major bleeding. In addition, recent trials (WOEST and PIONEER-AF-PCI) comparing dual versus triple antithrombotic treatment regimens in patients with atrial fibrillation (AFib) undergoing PCI now provide support for withholding aspirin, favoring the combination of a P2Y12 inhibitor and an OAC.

Building on these findings, the phase II GEMINI-ACS-1 trial presented at ACC.17 was designed to evaluate the safety of adding aspirin (100 mg daily) versus low-dose rivaroxaban (2.5 mg twice daily) to those already on a P2Y12 inhibitor for an ACS (56 percent received ticagrelor and 44 percent clopidogrel, as selected by the investigator). The study of 3,037 patients was conducted at 371 sites in 21 countries (with 77 percent of patients enrolled in Europe) between April 2015 and October 2016.

Initiation of the study regimen one to 10 days after the index event was associated with no significant difference in the primary endpoint of TIMI non–CABG clinically significant bleeding (5.3 percent for rivaroxaban vs. 4.9 percent for aspirin; p = 0.58). The median duration of treatment was 291 days. TIMI bleeding requiring medical attention was the most common type of bleeding that occurred in the study, at 4 percent in each group. No significant differences were observed for other key secondary bleeding endpoints. Rates of ischemic events were similar in both groups; however, the study was not powered to independently assess them.

The results of the GEMINI-ACS-1 trial add to the growing body of evidence supporting the safety of dual antithrombotic therapy using a P2Y12 inhibitor and an OAC. “Absent another indication for an anticoagulant (i.e., AFib), it is still premature, however, to abandon the standard practice of DAPT in this population,” says Ty Gluckman, MD, FACC. This phase II study has generated hypotheses that would need to be tested in an adequately powered phase III study, he adds, although whether one will be conducted isn’t currently known.

“Another unanswered question is whether a dual antithrombotic regimen that included rivaroxaban would be cost effective, if a phase III study achieved similar results with comparable efficacy and safety,” says Gluckman. Another question is what patient population, beyond those with AFib in need of PCI, might benefit preferentially from a dual antithrombotic regimen that includes a P2Y12 inhibitor and an OAC.

Ty Gluckman, MD, FACC
EINSTEIN CHOICE: Treatment of VTE

Extended treatment with low-dose rivaroxaban provided nearly a three-fold greater reduction in recurrent venous thromboembolism (VTE) than aspirin with a similar rate of bleeding in patients who had completed six to 12 months of anticoagulation in the EINSTEIN CHOICE study.

It is the first study to directly compare low-dose rivaroxaban and aspirin (100 mg) in this population in whom there is equipoise regarding the benefit of continued therapy. The international multicenter study enrolled 3,396 patients. After a median follow-up of 351 days, compared with aspirin (4.4 percent), there was a significant reduction in symptomatic fatal or non-fatal recurrent VTE, with rivaroxaban 10 mg and 20 mg (1.2 percent and 1.5 percent, respectively; p < 0.001).

There was no statistically significant difference in the rates of bleeding between the three treatment groups, which occurred in 0.4 percent of the rivaroxaban 10 mg group, 0.5 percent of the rivaroxaban 20 mg group and 0.3 percent of the aspirin group. There were no differences between groups for any of the secondary efficacy or safety endpoints.

In patients who suffered a provoked VTE, the rate of a recurrent VTE was lower with both doses of rivaroxaban (0.9 percent and 1.4 percent for the 10 and 20 mg doses) versus aspirin (3.6 percent). The number needed to treat to prevent one VTE was 30 with the 10 mg dose of rivaroxaban and 33 with the 20 mg dose of rivaroxaban.

“Combining the results from the EINSTEIN CHOICE and the AMPLIFY EXT studies, the data are convincing now that extending the duration of treatment with rivaroxaban or apixaban can reduce the risk of recurrent VTE without drastically increasing the risk of bleeding,” says Salim Virani, MD, FACC.

Screen to Prevent (S2P): Study For Sports Participation

The single-center S2P study has shown that a protocol consisting of a questionnaire, resting electrocardiogram (ECG), and a screening MRI could be a cost-effective approach to prevent sudden cardiac death (SCD) in young athletes, according to results presented by Paolo E. Angelini, MD.

In the U.S., a basic history and physical remains the predominant screening approach for student athletes, thus the “exact incidence of SCD in population-based studies is not available,” said Angelini. He stated that a list of high-risk cardiovascular conditions (hr-CVC) has not been well defined.

In the S2P study, Angelini and colleagues employed their screening protocol in 5,255 youth ages 11-14 (average age 13 years; 32 percent white, 23 percent black and 19 percent Hispanic) between 2010 and 2017 at the Texas Heart Institute in Houston. They found that symptoms identified in the history and physical and on ECG did not correlate with any hr-CVC and alone were insufficient to identify structural hr-CVCs and their severity.

On MRI screening, the most frequent abnormality was an ECG defect, found in 40 individuals, followed by anomalous origin of the right coronary artery in 23 individuals, and cardiomyopathy in 15 (12 of whom had dilated cardiomyopathy). The investigators also performed quantitative MRI in 1,159 of the participants to help establish parameters for left ventricular mass and left ventricular end-diastolic volume.

The investigators state these data support the use of this protocol to derive prevalence data in the general population, rather than in the SCD population, that can then be used to screen youth for sports or other strenuous activities. “It is safe, accurate, comfortable and likely cost-effective” in high-risk populations to identify those at risk for SCD, Angelini said. The S2P study provides a first step in defining “high risk” by using prevalence data. Further research is needed to explore its potential to prevent SCD in young athletes.
The appropriate amount of exercise for patients with hypertrophic cardiomyopathy (HCM) remains a persistent question. Some concerns are whether exercise could trigger ventricular arrhythmias or induce remodeling. Guideline recommendations continue to be based on expert consensus because of the lack of objective data.

The RESET-HCM study has demonstrated that moderate-intensity aerobic training was safe and effective in patients with HCM, according to results presented by Sara Saberi, MD, MS, in a Featured Clinical Research presentation. The 57 patients randomized to the exercise training group had an increase in the primary endpoint of exercise capacity at 16 weeks compared with the 56 patients in the usual activity group – a mean increase of 1.35 ml/kg/min versus 0.08 ml/kg/min from the mean peak VO₂ at baseline of 22 ml/kg/min (p = 0.02).

The patients in the study were ages 18-80 years, with a mean age of 50, and 42 percent were women. Their history included obstructive HCM in 17 percent, implantable cardioverter-defibrillator (ICD) in 34 percent and sustained ventricular tachycardia or aborted sudden cardiac death in 4 percent. The study period was 2010 to 2015.

In the exercise training group, patients were given a one-hour consultation with a certified exercise physiologist, a tailored exercise program (including cycling, walking, jogging, swimming or using an elliptical trainer) to perform at home and instruction to increase their duration of exercise. In the first week, they were to exercise 20 minutes three times a week at 60 percent of their heart-rate reserve (calculated by their baseline cardio-pulmonary exercise test) and a perceived moderate intensity. For weeks two to four, they were to increase the duration by 5-10 minutes a week, for a maximum of 60 minutes, and exercise four to seven times a week at 70% of their heart-rate reserve and a perceived moderate intensity. This level of exercise was to be maintained through week 16. In the usual activity group, the patients were instructed to continue with their current exercise practice. By 16 weeks, more patients in the exercise training group were exercising regularly, compared with before the study and against the usual activity group (93 percent vs. 28 percent).

No differences were found between the groups for cardiac remodeling or quality of life, based on self-reported questionnaires, other than improvement related to physical function. No major adverse events occurred, including death, aborted sudden cardiac death, appropriate ICD shocks or sustained ventricular tachycardia. Exercise training was not associated with an increase in any non-fatal arrhythmias. They study, however, was not designed to establish long-term safety, stated the investigators.

Further research is required to determine the clinical importance of the improvements in the primary and secondary outcomes in this study, as well as establishing the safety of moderate or higher levels of activity and any potential impact on disease progression.

CVD-REAL: SGLT-2 Inhibitors and Heart Failure

Treatment with a sodium glucose cotransporter-2 inhibitor (SGLT-2i) was associated with a marked reduction in hospitalization for heart failure (HHF) in new users when compared with treatment with other glucose-lowering drugs (oGLD), according to research presented by Mikhail Kosiborod, MD, FACC, in a Featured Clinical Research presentation.

In a large, real-world study across six countries, non-parsimonious propensity scores for SGLT-2i initiation were used to match groups in which a broad population of patients with type 2 diabetes received either SGLT-2i or oGLD treatment. The incidence of HHF was collected via primary care and hospital records in the U.K. and Germany, medical claims and electronic health records in the U.S., and national registries in Sweden, Norway and Denmark. Hazard ratios for HHF were estimated by country and database and pooled in a meta-analysis.

The study included 364,828 patients, evenly divided between each treatment group, with a mean age of 57 years and 44 percent were women. At baseline, 3 percent had HF, 13 percent established cardiovascular disease, and 27 percent had microvascular disease.

For the primary endpoint of HHF, there was a reduction that favored the SGLT-2i in each country. In total, there were 961 HHF during the study period, and the incidence was lower with the SGLT-2i (hazard ratio [HR], 0.61; p < 0.001). The SGLT-2i was also associated with a lower incidence of the secondary endpoint of all-cause death in each country and the total number was 1,334 (HR, 0.49; p < 0.001) and the secondary endpoint of HHF or all-cause death (1,983 events; HR, 0.54; p < 0.001).

In the analysis, there were no signs of significant heterogeneity across the countries, despite the geographic variations in the patient groups receiving SGLT-2i treatment, suggesting the cardiovascular benefits observed are likely class-related, according to the investigators. The results of their analyses align with the findings of the EMPA-REG OUTCOME study, and they think the benefits observed with the SGLT-2i treatment will translate into real-world clinical practice and also may extend to patients with type 2 diabetes at the lower end of the cardiovascular risk spectrum.
Updated AUC Address Coronary Revascularization in SIHD Patients

Updated appropriate use criteria (AUC), developed by the ACC, the Society for Cardiovascular Angiography and Interventions, The Society of Thoracic Surgeons and the American Association for Thoracic Surgery, along with key specialty and subspecialty societies, addresses coronary revascularization in patients with stable ischemic heart disease (SIHD). The new criteria contain several important changes from the original version published in 2012.

Among the biggest changes, the new criteria now use the new terms “appropriate care,” “may be appropriate care,” and “rarely appropriate care” to rate the clinical scenarios, bringing them in line with AUC developed after 2013. In response to comments from stakeholders, the composition of the rating panel was also changed slightly to include five cardiac surgeons, five interventional cardiologists, five cardiologists not directly involved with performing revascularization and one outcomes researcher.

Other changes include replacing prior recommendations mandating two antianginal drugs for medical therapy with a step-wise use of antianginals—an approach more applicable to real-world treatment patterns, according to Gregory J. Dehmer, MD, MACC, writing group member and co-chair of ACC’s AUC Task Force. The use of the Canadian Cardiovascular Society Classification of angina was also replaced with a simplified pattern that groups patients based on whether they have or don’t have ischemic symptoms. Expanded use of fractional flow reserve for lesion assessment is incorporated into the update AUC as well. Lastly, a new table was added to evaluate revascularization in patients being considered for kidney transplantation or percutaneous valve therapies.

In general, the writing group rated revascularization by PCI or CABG surgery as rarely appropriate as a first step in patients with a low burden of coronary disease (e.g., single-vessel disease), low-risk findings on noninvasive testing, and/or no antianginal therapy. However, in patients with two- vessel to three-vessel and left main disease, revascularization by PCI or CABG was rated as may be appropriate care or appropriate care, with CABG consistently rated as appropriate care for intermediate or high disease complexity (SYNTAX ≥22) even in patients with ischemic symptoms who are not on antianginal therapy. The writing group noted that “CABG surgery was consistently rated as appropriate care and PCI as rarely appropriate care for left main bifurcation disease with intermediate or high disease burden in other vessels.” Repeat CABG surgery was also felt to be rarely appropriate in patients with a functional patent internal mammary artery to the left anterior descending in all but one indication, with both PCI and CABG being rated as either may be appropriate or appropriate in the other indications.

“These new AUC are an important advance in the efforts of the partnering societies to improve the quality of cardiovascular care and deliver the right care to the right patients. The document provides a framework for how patients and providers can think about revascularization in the stable setting and will help health systems and medical societies judge quality of care.”

Manesh R. Patel, MD, FACC


AUC for SIHD are a culmination of a two-part revision of the original AUC for coronary revascularization. The first part, AUC addressing revascularization in patients with acute coronary syndrome, was published in December 2016. The new criteria will be integrated soon into ACC’s CathPCI Registry.
INDICATIONS AND USAGE
• PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
• The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined

IMPORTANT SAFETY INFORMATION
• PRALUENT is contraindicated in patients with a history of a serious hypersensitivity reaction to PRALUENT. Reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization
• Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, treat according to the standard of care, and monitor until signs and symptoms resolve
• The most commonly occurring adverse reactions (≥5% of patients treated with PRALUENT and occurring more frequently than with placebo) are nasopharyngitis, injection site reactions, and influenza
• Local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with PRALUENT (7.2% versus 5.1% for PRALUENT and placebo, respectively). Few patients discontinued treatment because of these reactions (0.2% versus 0.4% for PRALUENT and placebo, respectively), but patients receiving PRALUENT had a greater number of injection site reactions, had more reports of associated symptoms, and had reactions of longer average duration than patients receiving placebo
• Neurocognitive events were reported in 0.8% of patients treated with PRALUENT and 0.7% of patients treated with placebo. Confusion or memory impairment were reported more frequently by those treated with PRALUENT (0.2% for each) than in those treated with placebo (<0.1% for each)

*Not actual patients; individual results may vary.
†Patients started on PRALUENT 75 mg Q2W in addition to existing statin therapy: Up-titration to 150 mg Q2W occurred at week 12 in 17% of patients who did not achieve their predefined target LDL-C at week 8.

LDL-C = low-density lipoprotein cholesterol; ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia.
PRALUENT is the only PCSK9 inhibitor that offers 2 doses with 2 levels of efficacy

In COMBO I
44% LDL-C reduction at 24 weeks on top of statins starting with PRALUENT 75 mg

In the LONG TERM Study
58% LDL-C reduction at 24 weeks on top of statins with PRALUENT 150 mg

The recommended starting dose is 75 mg every 2 weeks

CLINICAL STUDIES
COMBO I (Study 2) was a multicenter, double-blind, placebo-controlled trial that compared PRALUENT (n=209) with placebo (n=107). Patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 63 years (range 39-87), 34% were women, 82% were Caucasian, 16% were Black, and 11% were Hispanic/Latino. Mean baseline LDL-C was 102 mg/dL. The primary efficacy endpoint, measured at week 24, was the mean percent change in LDL-C from baseline.

LONG TERM trial (Study 1) was a multicenter, double-blind, placebo-controlled trial that compared PRALUENT 150 mg Q2W (n=1553) with placebo (n=788). The average LDL-C at baseline was 122 mg/dL. The primary efficacy endpoint, measured at week 24, was the mean percent change in LDL-C from baseline.

IMPORTANT SAFETY INFORMATION
- Liver-related disorders (primarily related to abnormalities in liver enzymes) were reported in 2.5% of patients treated with PRALUENT and 1.8% of patients treated with placebo, leading to treatment discontinuation in 0.4% and 0.2% of patients, respectively. Increases in serum transaminases to greater than 3 times the upper limit of normal occurred in 1.7% of patients treated with PRALUENT and 1.4% of patients treated with placebo.
- The most common adverse reactions leading to treatment discontinuation in patients treated with PRALUENT were allergic reactions (0.6% versus 0.2% for PRALUENT and placebo, respectively) and elevated liver enzymes (0.3% versus <0.1%).
- PRALUENT is a human monoclonal antibody. As with all therapeutic proteins, there is a potential for immunogenicity with PRALUENT.

Please see brief summary of Prescribing Information on next page.

Learn more at PraluentHCP.com
PRALUENT® (alirocumab) injection, for subcutaneous use

Brief Summary of Prescribing Information

1 CLINICAL TRIALS AND USAGE

1.1 Primary Hyperlipidemia

PRALUENT® is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

1.2 Limitations of Use

The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined.

2 CONTRAINDICATIONS

PRALUENT is contraindicated in patients with a history of a serious hypersensitivity reaction to PRALUENT. Reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization. See Warnings and Precautions (5.1).

3 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, treat according to the standard of care, and monitor until signs and symptoms resolve [see Contraindications (4)].

6 ADVERSE REACTIONS

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

Allergic Reactions [See Warnings and Precautions (5.1)].

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.

The safety of PRALUENT was evaluated in 9 placebo-controlled trials that included 2476 patients treated with PRALUENT, including 2135 exposed for 4 months and 1999 exposed for more than 1 year. The median treatment duration of 65 weeks. The mean age of the population was 59 years, 40% of the population were women, 90% were Caucasian, 4% were Black or African American, and 3% were Asians. At baseline, 37% of patients had a diagnosis of heterozygous familial hypercholesterolemia and 66% had clinical atherosclerotic cardiovascular disease.

Adverse reactions reported in at least 2% of PRALUENT-treated patients, and more frequently than in placebo-treated patients, are shown in Table 1.

Table 1 Adverse Reactions Occurring in Greater Than or Equal to 2% of PRALUENT-Treated Patients and More Frequently Than with Placebo

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo (N=1276)</th>
<th>PRALUENT® (N=2476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>11.1%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>5.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Influenza</td>
<td>4.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Diarhea</td>
<td>4.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Contusion</td>
<td>1.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1.6%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

75 mg every 2 weeks and 150 mg every 2 weeks combined

Adverse reactions led to discontinuation of treatment in 5.3% of patients treated with PRALUENT and 5.1% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with PRALUENT were allergic reactions (0.6% versus 0.2% for PRALUENT and placebo, respectively) and elevated liver enzymes (0.3% versus <0.1%).

Local Injection Site Reactions

Local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with PRALUENT (7.2% versus 5.1% for PRALUENT and placebo, respectively). Few patients discontinued treatment because of these reactions (0.4% for PRALUENT and placebo, respectively). Patients receiving PRALUENT had a greater number of injection site reactions, had more reports of associated symptoms, and had reactions of longer average duration than patients receiving placebo.

Allergic Reactions

Allergic reactions were reported more frequently in patients treated with PRALUENT than in those treated with placebo (0.6% versus 0.2% for PRALUENT and placebo, respectively). One patient treated with PRALUENT had an allergic reaction associated with a serious event (anaphylaxis) that required hospitalization. See Warnings and Precautions (5.1).

Neurocognitive Events

Neurocognitive events were reported in 0.8% of patients treated with PRALUENT and 0.7% of patients treated with placebo. Confusion or memory impairment were reported more frequently by those treated with PRALUENT (0.2% for each) than in those treated with placebo (<0.1% for each).

Liver Enzyme Abnormalities

Liver-related disorders (primarily related to abnormalities in liver enzymes) were reported in 2.5% of patients treated with PRALUENT and 1.8% of patients treated with placebo, leading to treatment discontinuation in 0.4% and 0.2% of patients, respectively. Increases in serum transaminases to greater than 3 times the upper limit of normal occurred in 1.7% of patients treated with PRALUENT and 1.4% of patients treated with placebo.

Low LDL-C Values

In a pool of both placebo- and active-controlled clinical trials, 796 PRALUENT-treated patients had two consecutive calculated LDL-C values <25 mg/dL, and 288 had two consecutive calculated LDL-C values <15 mg/dL. Changes to background lipid-altering therapies (e.g., maximally tolerated statins) were not made in response to low LDL-C values and PREVIVIA (early dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not identified in clinical trials, the long-term effects of very low levels of LDL-C noted by PRALUENT are unknown.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with PRALUENT. In a pool of placebo- and active-controlled trials, 4.8% of patients treated with PRALUENT had anti-drug antibodies (ADA) newly detected after initiating treatment as compared with 0.6% of patients treated with control.

Adverse reactions due to these antibodies were reported in 1.1% of PRALUENT-treated patients vs. 0.3% of placebo-treated patients. They were similar in nature and severity and led to discontinuation in 0.6% of PRALUENT-treated patients and 0.3% of placebo-treated patients. The antibodies were primarily IgG1 subclass antibodies and were not associated with clinical events. Treatment with PRALUENT was continued in the absence of clinical disease in patients with ADAs.

6.3 Renal Impairment

Mean AUC values were greater in patients with renal impairment than in patients with normal renal function for the total drug and metabolites.

8.6 Renal Impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment. See Precautions (5.8).

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

In controlled studies, 1158 patients treated with PRALUENT, were ≥65 years of age and 241 patients treated with PRALUENT were ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.1 Pregnancy

Risk Summary: There are no available data on use of PRALUENT in pregnant women to inform a risk associated with this drug, in animal reproduction studies, there were no effects on embryonic development when rats were subcutaneously administered alirocumab during organogenesis at dose exposures up to 12-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. No effects on fetal development in rat were observed at doses exposures up to 81-fold the maximum recommended human dose of 150 mg every 2 weeks.

8.2 Lactation

Risk Summary: There is no information regarding the presence of alirocumab in human milk, the effects of alirocumab on the breastfed infant, or the effects on milk production. The development and health benefits of breastfed infants may, in some cases, outweigh the potential benefits of the mother's treatment with PRALUENT. See Precautions (5.8).

8.3 Nursing Mothers

The development and health benefits of breastfed infants may, in some cases, outweigh the potential benefits of the mother's treatment with PRALUENT. See Precautions (5.8).

Data from studies in rats and humans indicate that alirocumab, like other IgG antibodies, crosses the placental barrier. FDA’s experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester. Consider the benefits and risks of PRALUENT and possible risks to the fetus before prescribing PRALUENT to pregnant women.

9 PRECAUTIONS

9.1 Laboratory Tests

No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment. See Clinical Pharmacology (12.3) in the full prescribing information.)

9.2 Therapy of Lipid-Altering Agents

8.7 Hypertensive Reaction

No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment. See Clinical Pharmacology (12.3) in the full prescribing information.)

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Revised: October 2015

ALI-BPLR-SA-OCT15

Reference: 1. PRALUENT® (alirocumab) Prescribing Information.

Sanofi/Regeneron Pharmaceuticals, 2015.
First-Ever Guideline Addresses Evaluation, Management of Syncope

The ACC, with the American Heart Association and the Heart Rhythm Society, released the first guideline for the evaluation and management of patients with syncope. The guideline, published March 9 in the Journal of the American College of Cardiology, aims to provide “contemporary, accessible, and succinct guidance on the management of adult and pediatric patients with suspected syncope.”

Specifically, the guideline includes recommendations on initial evaluation, as well as additional evaluation and diagnosis; management of cardiovascular conditions (i.e., structural, arrhythmic and inheritable conditions); uncommon conditions associated with syncope; and syncope in special populations. Additionally, the guideline addresses quality of life and health care costs of syncope and looks at emerging technologies, evidence gaps and future directions.

Of note, the guideline recommends that if a patient faints, a physician should perform a detailed history and physical examination during the initial evaluation. Using an electrocardiogram during this time may be useful to determine the cause of fainting. People with serious medical conditions that could be related to their fainting should be evaluated and/or treated at a hospital after the initial assessment.

The guideline also explains that certain tests such as routine laboratory testing and routine cardiac imaging may not be useful in evaluating these patients unless the patient has a suspected cardiac issue. Carotid artery or head imaging may not be useful unless there is a specific reason why the patient needs to be evaluated further.

Depending on the reason for fainting, treatment options may include implantable cardioverter-defibrillators, beta-blockers or pacemakers. According to the guideline, patients who faint and who also have certain types of heart issues should restrict their exercise, and athletes who experience fainting should have a heart assessment done by an experienced health care provider or specialist before returning to competitive sports. Heart rhythm monitoring can be a good choice for patients with unexplained fainting who may have intermittent heart rhythm issues that cause fainting.

“Studies show that in the U.S., about one-third to half the population faints at some point in their lifetime,” said Win-Kuang Shen, MD, FACC, chair of the writing group. “Therefore, having these guidelines is not only good for the clinicians using them – but for everyone.”

Win-Kuang Shen, MD, FACC

Training Statement Focuses on Competencies for HF and Transplant Specialists

A new training statement from the ACC and numerous partnering societies addresses the competencies required of sub-subspecialists in Advanced Heart Failure and Transplant Cardiology (AHFTC).

The training statement complements the ACC’s Core Cardiovascular Training Statement (COCATS), and outlines the knowledge, skills and experiences that should result from a 12-month training program in AHFTC and defines the competencies required of these trainees. It also includes detailed recommendations for procedural numbers which trainees, in general, should perform during their fellowship, recognizing that true competency to perform each procedure may exceed or be below this recommendation for any individual trainee.

“The document will serve as a foundation upon which the training of cardiologists entering the field of AHFTC can be based, so that patients with advanced heart failure will be optimally treated by skilled and knowledgeable physicians,” said Mariell Jessup, MD, FACC, chair of the writing committee.

Mariell Jessup, MD, FACC

The document will serve as a foundation upon which the training of cardiologists entering the field of AHFTC can be based, so that patients with advanced heart failure will be optimally treated by skilled and knowledgeable physicians.
Help at the Point of Care: A Review of the ACC’s DAPT Risk Calculator App

In previous columns I’ve reviewed three clinical decision support apps released by the ACC: the ASCVD Risk Estimator, the Guideline Clinical app and the Statin Intolerance app. Having been impressed with both the utility and simplicity of these apps, I was pleased to hear the ACC had released the DAPT Risk Calculator app for guiding dual antiplatelet therapy.

There is a fine balancing act for patients who are receiving DAPT (aspirin plus a P2Y12 inhibitor) that has been the subject of many recent studies. On one hand, prolonged use of DAPT can lead to increased risk of bleeding; conversely, stopping too early can increase the risk of ischemic events. This past fall a joint ACC/American Heart Association Task Force released guidelines in the Journal of the American College of Cardiology related to the duration of DAPT in patients with coronary artery disease. Shortly after, in December 2016, the ACC released the DAPT Risk Calculator, available on iTunes, Google Play, and as web format for convenience.

The application provides clinical decision support for clinicians evaluating the continuation of DAPT therapy for patients at least 12 months post PCI. The DAPT Risk Score is a numerical value between –2 and +9, with a favorable benefit/risk ratio for prolonged DAPT being 2 or more and an unfavorable benefit/risk ratio being less than 2.

Factors used to calculate this score include age (75 or older is ~–2, 65 to 74 is ~1 and under 65 is 0); patient characteristics (current cigarette smoker within the last 2 years, diabetes, myocardial infarction (MI) at presentation, prior PCI or prior MI, each 1 point); and procedural factors (sten diameter <3 mm and paclitaxel-eluting stent each 1 point; congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) <30 percent and saphenous vein graft PCI, each 2 points).

The app provides a simple interface to fill in these characteristics and obtain a DAPT Risk Score with a percent risk for three endpoints: stent thrombosis/MI, major adverse cardiovascular and cerebrovascular event (MACCE) and GUSTO moderate-severe bleeding.

I tried both the iOS and web applications. My hypothetical patient is a 78-year-old (–2 points) smoker within the last 2 years, diabetes, myocardial infarction (MI), each 1 point; and procedural factors (sten diameter <3 mm and paclitaxel-eluting stent each 1 point; congestive heart failure (CHF) or left ventricular ejection fraction (LVEF) <30 percent and saphenous vein graft PCI, each 2 points). The results section provides an easy to understand break down of the change in risk for each of the three endpoints if DAPT is continued versus discontinued (Figure).

One of the elements of the app I like best is the simple toggle function for each of the characteristics that changes the DAPT Risk Score in real time. This provides a visual reminder for contributing factors to DAPT risk. Furthermore, the results page provides a way to email the output to a colleague or the patient, though the app is certainly meant more for clinicians. Unlike the ACC’s Statin Intolerance app which had blood cholesterol and lifestyle recommendations, I wasn’t able to find any patient-facing resources related to DAPT. There are at least six physician-facing resources, however, such as a link to the JAMA article that first published the study of the decision support tool, as well as a DAPT-focused update hub.

By simplifying often complex guidelines into a streamlined decision-support tool, the DAPT Risk Calculator app should help save time at the point of care.

By simplifying often complex guidelines into a streamlined decision-support tool, the DAPT Risk Calculator app should help save time at the point of care. It’s important to note that the app is not a stand-alone decision-support tool and needs to be combined with appropriate clinical judgment to account for differences in patient presentations and needs. The main limitation of the DAPT Risk Score Calculator is not the app itself, but rather the score calculation, which hasn’t yet integrated other important factors because these require validation through research studies. For example, the DAPT Risk Score doesn’t account for baseline variables such as presence of anemia and oral anticoagulant therapy – both important for predicting risk of bleeding while on DAPT.

References
How Does Zika Virus, Marijuana and Erectile Dysfunction Drugs Impact CV Events?

New research exploring Zika-related cardiovascular complications, marijuana’s influence on stroke and heart failure (HF) and erectile dysfunction drugs’ impact on heart attack survivors made headlines in major news outlets during ACC.17.

Zika-Related Cardiovascular Complications
Results from a small case report led by Karina Gonzalez Carta, MD, suggest that the Zika virus may be linked to potentially harmful effects on the heart. The study followed nine patients who reported symptoms and were treated at the Institute of Tropical Medicine in Caracas, Venezuela. Of the nine patients treated, only one reported previous well-controlled high blood pressure, and two thirds were women.

Beginning in July 2016, follow ups were conducted on a six-month basis. Eight of the nine patients with an active Zika infection had arrhythmias and six experienced HF (five with low ejection fraction). Since contracting the infection, the patients have yet to report resolved issues.

The study highlights the need to raise awareness about Zika’s possible link to cardiovascular complications, especially since the data show an average lag time of 10 days from patients’ initial reports of symptoms suggestive of heart problems. “It’s likely that many more people are affected,” Carta said. “We need larger, systematic studies to understand the actual risk of Zika-related cardiac problems and what makes one patient more prone to develop them.”

Marijuana Use and Stroke, HF
Medical and recreational marijuana use may be legal in more than half of U.S. states, but results from a recent study investigating cardiovascular outcomes found that it raises the risk of stroke and HF, even after accounting for demographic factors and additional lifestyle risk factors.

Study investigators found that use was not only associated with a 26 percent increase in the risk of stroke and 10 percent increase in developing HF, it also was linked to obesity, high blood pressure and smoking and alcohol use. Of the 20 million health records of young and middle-aged patients analyzed, marijuana use was diagnosed in 1.5 percent.

“More research will be needed to understand the pathophysiology behind this effect,” said Aditi Kalla, MD, the study’s lead author.

Erectile Dysfunction Drugs After MI
Men 80 years and younger prescribed erectile dysfunction drugs following a myocardial infarction were 33 percent less likely to die and 40 percent less likely to be hospitalized for HF than men who were not.

Study investigators analyzed the records of 43,000 patients from 2007 to 2013 using a Swedish national database. Of the 7 percent of men prescribed an erectile dysfunction drug, 92 filled prescriptions for phosphodiesterase-5 (PDE5) inhibitors, while 8 percent filled prescriptions for alprostadil.

The results came as a surprise for the study’s lead author, Daniel Peter Andersson, MD, PhD, due to previous associations with increased risk of cardiovascular disease in otherwise healthy men. “From the perspective of a doctor, if a patient asks about erectile dysfunction drugs after a [MI] and has no contraindications for PDE5 inhibitors, based on these results you can feel safe about prescribing it,” Andersson concludes.

Note: The editors-in-chief caution there are potential drug-drug interactions with marijuana, including an increase in the anticoagulant effect of warfarin, due to inhibition of its metabolism.
The Legacy of ACC Past Presidents

ACC’s past presidents are critical repositories of the College’s history, serve as invaluable mentors for ACC’s emerging leaders and continue to make important contributions to the ACC long after they have passed on the presidential chain. Ultimately, past presidents represent the continuity and tradition that is the foundation of the College.

I had the privilege of seeing ACC past presidents in action during the Past Presidents’ Forum held during ACC.17 in Washington, DC. Convened by outgoing ACC President Richard A. Chazal, MD, MACC, along with ACC CEO Shali Jacobovitz, the Forum was designed to keep past presidents informed of the College’s strategic direction, to take advantage of their collective wisdom and to gain input to help refine the work of the College in the context of its Strategic Plan.

During the Forum, past presidents were brought up to speed on ACC activities in the areas of Maintenance of Certification, health care reform, hospital accreditation and a broader health system strategy, ACC governance transformation and plans to begin the process for a new Strategic Plan. We were able to share our ideas and discuss the challenges and opportunities that lie ahead – the output of which will be communicated to the ACC’s Board of Trustees.

As the ACC continues to phase in changes to its governance process and structure, the Forum has evolved as a means of keeping past presidents involved in the College and gaining their insights regarding its strategic direction. During my ACC presidential year, I invited ACC’s past presidents to our 2013 ACC Strategic Planning Retreat in Banff, Canada, for them to contribute to the College’s strategic planning process. Fifteen past presidents participated in the Banff strategic planning process, including Forrest Adams, MD, MACC, who at that time was the oldest living past ACC president. I believe our Strategic Plan is stronger because of their participation and I am glad for the opportunities provided by the Forum for similar dialogue and sharing.

This inclusion of past presidents is not a new phenomenon, however. It is part of the ACC’s culture and history to learn from its predecessors, founders and elders. In 1949, Franz Groedel, MD, MACC, and the founders of the ACC envisioned an organization dedicated to providing “professional men and women actively engaged in practice or research relating to diseases of the heart and circulation” with education and other services to improve the quality of cardiovascular care. “We will meet the future not merely by dreams but by concerned action and inextinguishable enthusiasm,” said Groedel.

Since then, the actions and enthusiasm of ACC leaders who followed in Groedel’s footsteps have grown the College into a more than 52,000-member global professional cardiovascular society, serving the entire cardiovascular team including physicians, nurses, nurse practitioners, physician assistants, pharmacists and practice managers. Sixty-eight years later, ACC’s many initiatives in education, science and quality, advocacy and member services have evolved and grown as a result of the vision and leadership of the men and women at the College’s helm.

Bernard of Chartres said that “we are like dwarfs on the shoulders of giants, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size.” Our past presidents are the giants. It’s on their shoulders that ACC leaders both current and future stand.

French writer Antoine de Saint Exupéry said: “As for the future, our task is not to foresee it, but to enable it” and “a rock pile ceases to be a rock pile the moment a single man contemplates it, bearing within him the image of a cathedral.” Over the last nearly seven decades, ACC presidents have enabled the College to move forward and become the professional home for cardiovascular care providers around the world that it is today.

From the Past Presidents’ Forum to Convocation, where past presidents were honored on the dais and ACC’s newest president received the Presidential Chain, ACC.17 was a reminder of the celebration, tradition, transition and renewal that is the ACC presidency. Each and every past ACC president has played a role in the College’s history and each will continue to shape its future.

Franz Groedel, MD, MACC

We will meet the future not merely by dreams but by concerned action and inextinguishable enthusiasm.
INDICATIONS AND USAGE

Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh Class C).

WARNINGS AND PRECAUTIONS

Worsening PAH Symptoms upon Abrupt Withdrawal—Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.

Risk of Bleeding—Orenitram inhibits platelet aggregation and increases the risk of bleeding.

Use in Patients with Blind-end Pouches—The tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum.

ADVERSE REACTIONS

Clinical Trials Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In a 12-week placebo-controlled monotherapy study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included: headache, diarrhea, nausea and flushing. Table 1 lists the adverse reactions that occurred at a rate of Orenitram at least 5% higher than on placebo. Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

Orenitram was studied in a long-term, open-label extension study in which 824 patients were dosed for a mean duration of approximately 2 years. About 70% of patients continued treatment with Orenitram for at least a year. The mean dose was 4.2 mg BID at one year. The adverse reactions were similar to those observed in the placebo-controlled trials.

The safety of Orenitram was also evaluated in an open-label study transitioning patients from Remodulin. The safety profile during this study was similar to that observed in the three pivotal studies.

Table 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Orenitram (N=151)</th>
<th>Placebo (N=77)</th>
<th>Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>63%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>15%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Pain in jaw</td>
<td>11%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>6%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

No treprostinol treatment related effects on labor and delivery were seen in animal studies.

Nursing Mothers—It is not known whether treprostinol is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding.

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

Geriatric Use—Clinical studies of Orenitram did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment—Plasma clearance of treprostinol is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure. Titrate slowly in patients with hepatic insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic function. In patients with mild hepatic impairment (Child Pugh Class A) start at 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. Avoid use of Orenitram in patients with moderate hepatic impairment (Child Pugh Class B). Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C).

Patients with Renal Impairment—No dose adjustments are required in patients with renal impairment. Orenitram is not removed by dialysis.

OVERDOSAGE

Signs and symptoms of overdose with Orenitram during clinical trials reflect its dose-limiting pharmacologic effects and include severe headache, nausea, vomiting, diarrhea, and hypotension. Treat supportively.
**THE ONLY PROSTACYCLIN ANALOGUE IN A TABLET**

As a prostacyclin analogue, Orenitram acts on multiple receptors\(^4\)

**MULTIPLE RECEPTOR ACTIVITY**

<table>
<thead>
<tr>
<th>cAMP</th>
<th>EP2</th>
<th>DP1</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASODILATION</td>
<td>ANTIPLATELET</td>
<td>VASODILATION</td>
<td>ANTIPLATELET</td>
</tr>
<tr>
<td>ANTIPROLIFERATION</td>
<td>ANTIPROLIFERATION</td>
<td>ANTIPROLIFERATION</td>
<td></td>
</tr>
</tbody>
</table>

cAMP=cyclic adenosine monophosphate; DP1=D prostanoid 1 receptor; EP2=prostaglandin E2 receptor 2; IP=prostaglandin I2 receptor; PPAR\(_\gamma\)=peroxisome proliferator-activated receptor-gamma; WHO=World Health Organization.

**INDICATION**

Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

**WARNINGS AND PRECAUTIONS**

- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum

**DRUG INTERACTIONS / SPECIFIC POPULATIONS**

- Concomitant administration of Orenitram with diuretics, antihypertensive agents, or other vasodilators increases the risk of symptomatic hypotension
- Orenitram inhibits platelet aggregation; there is an increased risk of bleeding, particularly among patients receiving anticoagulants
- Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients
- Pregnancy Category C. Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans
- It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding
- Safety and effectiveness in patients under 18 years of age have not been established
- There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients

**ADVERSE REACTIONS**

- In the 12-week placebo-controlled monotherapy study, adverse reactions that occurred at rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and abdominal discomfort

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Please see the brief summary of the full prescribing information for Orenitram on the following page.

For additional information about Orenitram, visit www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

**VISIT ORENITRAM.COM**

FOR ADDITIONAL DOSING, SAFETY, AND EFFICACY INFORMATION