ACC.16 Daily
65TH ANNUAL SCIENTIFIC SESSION & EXPO
APRIL 3, 2016 | CHICAGO
SUNDAY

EXPO DAILY & MAP
INCLUDED INSIDE!

ACC.16 Kicks Off With Focus on Population Health, Prevention

ACC President **Kim Allan Williams, MD, FACC**, welcomed thousands of cardiovascular professionals to his hometown of Chicago for the College's 65th Annual Scientific Session as part of the Opening Showcase Session on Saturday.

"Chicago has experienced the intersection of history and change countless times over the years and has carved its own roads into the history of the U.S.," Williams said. "I can't think of a better place to host a meeting that is occurring at a time where as a profession we are experiencing an intersection of science and change. Chicago by its very nature sparks innovation and I hope we can all capture a bit of that spark and carry it with us when we leave."

As part of the session, Williams paid tribute to all those involved in making ACC.16 happen, including ACC.16 Chair **Athena Poppas, MD, FACC**, and Co-Chair **Jeffrey Kuvin, MD, FACC**. Poppas, who joined Williams on stage later in the session, highlighted the many new features that make ACC.16 stand out from previous meetings, including an enhanced poster area, special intensives focused on hot topics in cardiovascular care, the more

See OPENING SHOWCASE, page 6

HOPE-3 Trial Supports Broader Use of Statins in Intermediate-Risk Populations

Statins may significantly reduce adverse cardiovascular events in people with average cholesterol and blood pressure (BP) levels who are considered to be at intermediate risk for cardiovascular disease, while the use of BP-lowering medications may be beneficial only in hypertensive patients, according to three separate reports from the HOPE-3 trial presented yesterday during the joint ACC/ *Journal of the American College of Cardiology* Late-Breaking Clinical Trial Session and simultaneously published in the *New England Journal of Medicine*.

> "Our approach, which used a **combination of moderate doses of two BP-lowering drugs plus a statin**, appears to produce the biggest 'bang,' in terms of **reducing events with few side effects.**"
>
> *Salim Yusuf, MBBS, DPhil, FACC*

Eva M. Lonn, MD, FACC, Jackie Bosch, PhD and **Salim Yusuf, MBBS, DPhil, FACC**, examined 12,705 subjects with at least one known cardiovascular risk factor, but who had not been diagnosed with cardiovascular disease. Participants were randomly assigned one of four groups:

See HOPE-3 TRIAL, page 8

PARTNER 2A Shows Rates of Death Similar For High-Risk Patients Undergoing TAVR or Surgical Aortic Valve Replacement

Transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement resulted in similar rates of death from disabling stroke or any cause in high-risk patients with aortic stenosis, according to results from the PARTNER 2A trial presented yesterday during the joint ACC/ *Journal of the American College of Cardiology* Late-Breaking Clinical Trial Session and simultaneously published in the *New England Journal of Medicine (NEJM)*.

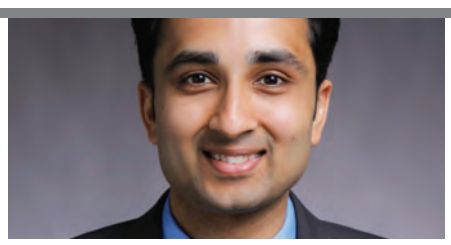
The trial, led by **Martin B. Leon, MD, FACC**, et al., looked at data from 2,032 intermediate-risk patients at 57 sites across the U.S. and Canada. In the previous PARTNER 1 trial, TAVR was shown to be superior to standard therapy in patients with symptomatic severe aortic stenosis who were not candidates for surgery. This result was equivalent to that of surgery in high-risk patients. However, experiences with first-generation TAVR systems resulted in recurrent peri-procedural complications. For PARTNER 2A, the authors set out to compare the

See PARTNER 2A, page 24

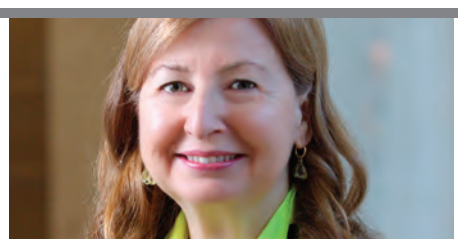
Download the free **ACC.16 eMeeting Planner mobile app** for the most up-to-date information.

INSIDE

11 MASERI-FLORIO LECTURE
Jagat Narula, DM, MD, PhD, MACC, will address the burden of cardiovascular disease and share insights from his research during the 15th Annual Maseri-Florio International Lecture.



14 ZIPES LECTURE
The role of contemporary stents will be discussed by Sripal Bangalore, MBBS, MHA, FACC, in today's Douglas P. Zipes, MD, MACC, Distinguished Young Scientist Lecture.



28 BISHOP LECTURE
Lifelong challenges of Adult Congenital Heart Disease was the focus of the 47th Annual Louis F. Bishop Lecture presented by Carole A. Warnes, MD, FACC.

MORE

When maximally tolerated statins and diet aren't enough to get patients with clinical ASCVD or HeFH to their LDL-C goal...

ADD PRALUENT® (alirocumab): POWER LIKE NEVER BEFORE...

Larry: Has ASCVD and achieved LDL-C reduction beyond statins[1]*

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.[1]

LDL-C = low-density lipoprotein cholesterol; **ASCVD =** atherosclerotic cardiovascular disease; **HeFH =** heterozygous familial hypercholesterolemia.

...AND MORE POWER IF YOU NEED IT

Stephanie: Has ASCVD and achieved LDL-C reduction beyond statins[1]*

PRALUENT offers 2 doses with 2 levels of efficacy[1]

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[1]

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.[1]

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.[1]

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 75mg/mL 150mg/mL

Redefining Possible

PRALUENT® **Rx Only**

(alirocumab) injection, for subcutaneous use

Brief Summary of Prescribing Information

1 INDICATIONS 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.

4 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)*]

5 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 6 months and 1999 exposed for more than 1 year (median treatment duration of 65 weeks). The mean age of the population was 59 years, 40% of the population were women, 90% were Caucasians, 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

Adverse Reactions	Placebo (N=1276)	PRALUENT* (N=2476)
Nasopharyngitis	11.1%	11.3%
Injection site reactions†	5.1%	7.2%
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%
Diarrhea	4.4%	4.7%
Bronchitis	3.8%	4.3%
Myalgia	3.4%	4.2%
Muscle spasms	2.4%	3.1%
Sinusitis	2.7%	3.0%
Cough	2.3%	2.5%
Contusion	1.3%	2.1%
Musculoskeletal pain	1.6%	2.1%

*75 mg every 2 weeks and 150 mg every 2 weeks combined
†includes erythema/redness, itching, swelling, pain/tenderness

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 (0.2% 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.

Allergic Reactions

Allergic reactions were reported more frequently in patients treated with PRALUENT than in those treated with placebo (8.6% versus 7.8%). The proportion of patients who discontinued treatment due to allergic reactions was higher among those treated with PRALUENT (0.6% versus 0.2%). Serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported in patients using PRALUENT in controlled clinical trials [*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 therapy (e.g., maximally tolerated statins) were not made in response to low LDL-C values, and PRALUENT 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 PRALUENT are unknown.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with PRALUENT. In a pool of ten 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.

Patients who developed ADA had a higher incidence of injection site reactions compared with patients who did not develop ADA (10.2% vs 5.9%).

A total of 1.2% of patients treated with PRALUENT developed neutralizing antibodies (NAb) on at least one occasion as compared with no patients treated with control, and 0.3% of patients both tested positive for NAb and exhibited transient or prolonged loss of efficacy. The long-term consequences of continuing PRALUENT treatment in the presence of persistent NAb are unknown.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay as well as other factors. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PRALUENT with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: There are no available data on use of PRALUENT in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on embryo-fetal 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. In monkeys, suppression of the humoral immune response was observed in infant monkeys when alirocumab was dosed during organogenesis to parturition at dose exposures 13-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. No additional effects on pregnancy or neonatal/infant development were observed at dose exposures up to 81-fold the maximum recommended human dose of 150 mg every two weeks. Measurable alirocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating 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.

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.

Data; *Animal Data* - In Sprague Dawley rats, no effects on embryo-fetal development were observed when alirocumab was dosed at up to 75 mg/kg/dose by the subcutaneous route on gestation days 6 and 12 at exposures 12-fold the maximum recommended human dose of 150 mg every two weeks, based on serum AUC.

In cynomolgus monkeys, suppression of the humoral immune response to keyhole limpet hemocyanin (KLH) antigen was observed in infant monkeys at 4 to 6 months of age when alirocumab was dosed during organogenesis to parturition at 15 mg/kg/week and 75 mg/kg/week by the subcutaneous route, corresponding to 13- and 81-fold the human exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC. The lowest dose tested in the monkey resulted in humoral immune suppression; therefore it is unknown if this effect would be observed at clinical exposure. No study designed to challenge the immune system of infant monkeys was conducted. No additional embryo-fetal, prenatal or postnatal effects were observed in infant monkeys, and no maternal effects were observed, when alirocumab was dosed at up to 75 mg/kg/week by the subcutaneous route, corresponding to maternal exposure of 81-fold the exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC.

8.2 Lactation

Risk Summary: There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for PRALUENT and any potential adverse effects on the breastfed infant from PRALUENT or from the underlying maternal condition. Human IgG is present in human milk, but published data suggest that breastmilk IgG antibodies do not enter the neonatal and infant circulation in substantial amounts.

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.

8.6 Renal Impairment

No dose adjustment is needed for patients with mild or moderately impaired renal function. No data are available in patients with severe renal impairment. [*See Clinical Pharmacology (12.3) in the full prescribing information.*]

8.7 Hepatic 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 Clinical Pharmacology (12.3) in the full prescribing information.*]

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SANOFI REGENERON

01/2016 US-PRB-1513 US.ALI.16.01.008

Reference: 1. PRALUENT® (alirocumab) Prescribing Information. Sanofi/Regeneron Pharmaceuticals, 2015.

Today's Schedule:
SUNDAY, APRIL 3

Joint ACC/*Journal of the American Medical Association* Late-Breaking Clinical Trials
8:00 – 9:15 a.m.
Main Tent (North Hall B1)

Women and Cardiovascular Disease: The "Special" Population Intensive
8:00 a.m. – 1:45 p.m.
Grand Ballroom S100bc

Cardiovascular Update For the Clinician: A Symposium by Valentin Fuster, MD, PhD, MACC
8:00 a.m. – 6:00 p.m.
Room S406a

International Sessions
8:00 a.m. – 6:00 p.m.
Rooms N427ab and N427cd

Expo Hall Open
9:30 a.m. – 4:45 p.m.

Poster Sessions
9:30 a.m. – 12:30 p.m.
South Hall A

Joint ACC/TCT Late-Breaking Clinical Trials
10:45 a.m. – Noon
Main Tent (North Hall B1)

Professional Enhancement and the Nonclinical Competencies: Leadership, Communication and Quality Intensive
12:30 – 6:00 p.m.
Grand Ballroom S100a

ACC.i2 Live Case Session IV, V and VI
12:30 – 6:00 p.m.
Main Tent (North Hall B1)

Poster Sessions
1:30 – 4:30 p.m.
South Hall A

15th Annual Maseri-Florio International Lecture
2:00 – 3:30 p.m.
Room S502

Douglas P. Zipes, MD, MACC, Distinguished Young Scientist Awardee Lecture
4:45 – 6:00 p.m.
Room S103cd

ACC Clinical Focus Sessions
6:00 – 8:30 p.m.
Room S102 and Grand Ballroom S100bc

Visit the **ACC.16 App** for additional session details.

FIT Jeopardy: Battle of the State Chapters Competition

Yesterday, 28 state chapter teams competed in the preliminary rounds of the inaugural FIT Jeopardy: Battle of the State Chapters Competition. Don't miss the final round today from 2:15 – 3:15 p.m. in the Engage@ACC.16 Studio (Expo, #6098). Follow **@ACCCardioEd** on Twitter to get a glimpse of the FIT Jeopardy action and use the hashtag **#ACCFITJeopardy** to cheer on your team!

DON'T MISS TODAY'S LATE-BREAKING CLINICAL TRIALS

Joint ACC/*Journal of the American Medical Association* Late-Breaking Clinical Trials

- ACCELERATE
- GAUSS-3
- LDL-C, FH Mutation Status and Risk For CAD
- The Stepathlon CV Health Study
- Involving Patients With Low-Risk Chest Pain in Discharge Decisions

Session 404
8:00 – 9:15 a.m.
Main Tent (North Hall B1)

Joint ACC/TCT Late-Breaking Clinical Trials

- DANAMI 3-DEFER
- DANAMI 3-iPOST
- EARLY-BAMI
- PARTNER II: Sapien 3 TAVR vs. Surgery in Intermediate-Risk Patients With Severe AS
- Relationship Between Procedure Volume and Outcome For TAVR in U.S. Clinical Practice: Insights From the STS/ACC TVT Registry

Session 405
10:45 a.m. – Noon
Main Tent (North Hall B1)

View complete news coverage at *ACC.org/ACC2016*

ACC.16 Daily
SUNDAY

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ACC.org

OPENING SHOWCASE from page 1

than 270 companies making up the ACC.16 Expo, opportunities to obtain simultaneous continuing medical education and Maintenance of Certification credit, and increased interactive opportunities both on and off the Expo floor.

Attendees also had the chance to hear a special taped welcome address from First Lady Michelle Obama, who highlighted the *Let's Move* campaign and thanked the ACC and attendees for focusing on lifestyle changes that can prevent cardiovascular disease.

During his presidential address, Williams highlighted the significant gains over the last six decades in reducing cardiovascular mortality and preventing and treating the disease. However, he noted that cardiovascular disease continues to be the number one cause of death around the world – a position it has held since the influenza epidemic from 1918-1919. "I think it is time to finally cede this position," he said. "The goal of becoming #2 is well within our grasp – more so than ever before."

According to Williams, success in this area will depend on the ability of the health care community to make the most out of the opportunities afforded by the rapid advances in technologies and treatments over the last several decades. He urged an expanded focus on primary prevention and health promotion and noted that the ACC is uniquely poised to lead in this area with its more than 52,000 members worldwide, a growing network of domestic and international chapters, and strong partnerships with government agencies and other medical specialty societies.

"We must own our actions and we must be visible to the public and our patients in positive ways that affect their lives," he said. "We must turn off the faucet instead of just mopping the floor."

> "We must own our actions and **we must be visible to the public and our patients** in positive ways that affect their lives."
>
> *Kim Allan Williams, MD, FACC*

David B. Nash, MD, MBA, presented the 2016 Simon Dack Lecture during the Opening Showcase Session.

Following his address, attendees took a moment of silence to remember **Borys Surawicz, MD, MACC**, who served the College as president from 1979-1980. **David B. Nash, MD, MBA**, founding dean of the Jefferson School of Population Health, then provided the annual Simon Dack Lecture, which focused on "Population Health: Is it the Secret Sauce?"

Nash highlighted some of the challenges posed by the current health care environment, including confusion by patients around treatment options; the need for better evidence at the bedside; the current balancing act between fee-for-service compensation and value-based payment; $1.2 trillion in wasteful health care spending annually; and the approximately 40 percent of the public who are at risk of heart disease as a result of smoking, unhealthy eating, lack of exercise and/or alcohol consumption.

He applauded the ACC for recognizing these challenges and "pivoting" towards value-based payment and population health management. He urged a change in culture that includes practice based on evidence, decreases in clinical variation and engagement with patients across the continuum of care. He also stressed the need for aligning physician and executive compensation with population health management.

He closed by calling on attendees to come together around population health management. "If we don't take initiative, others will take over for us," he said.

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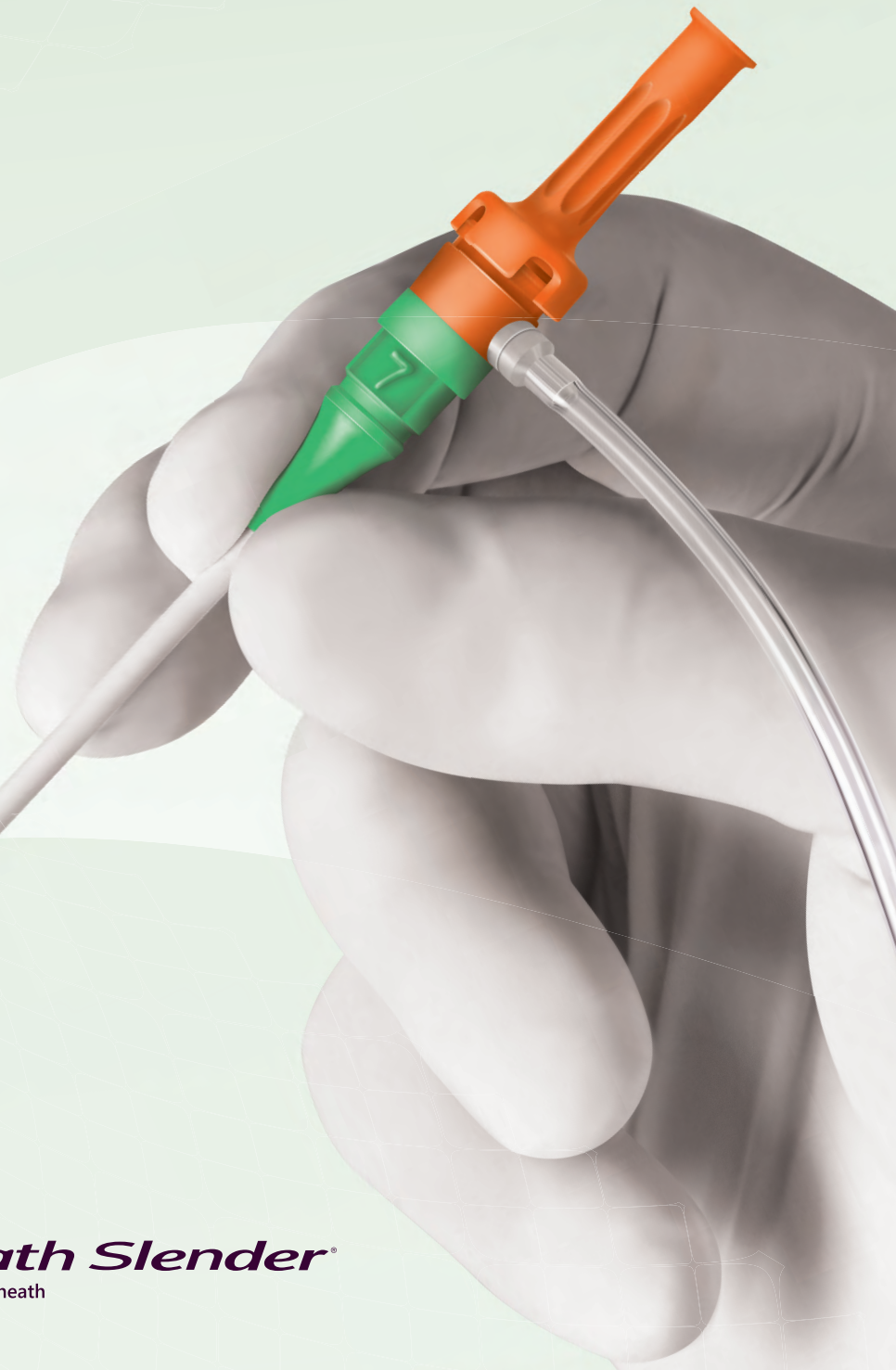

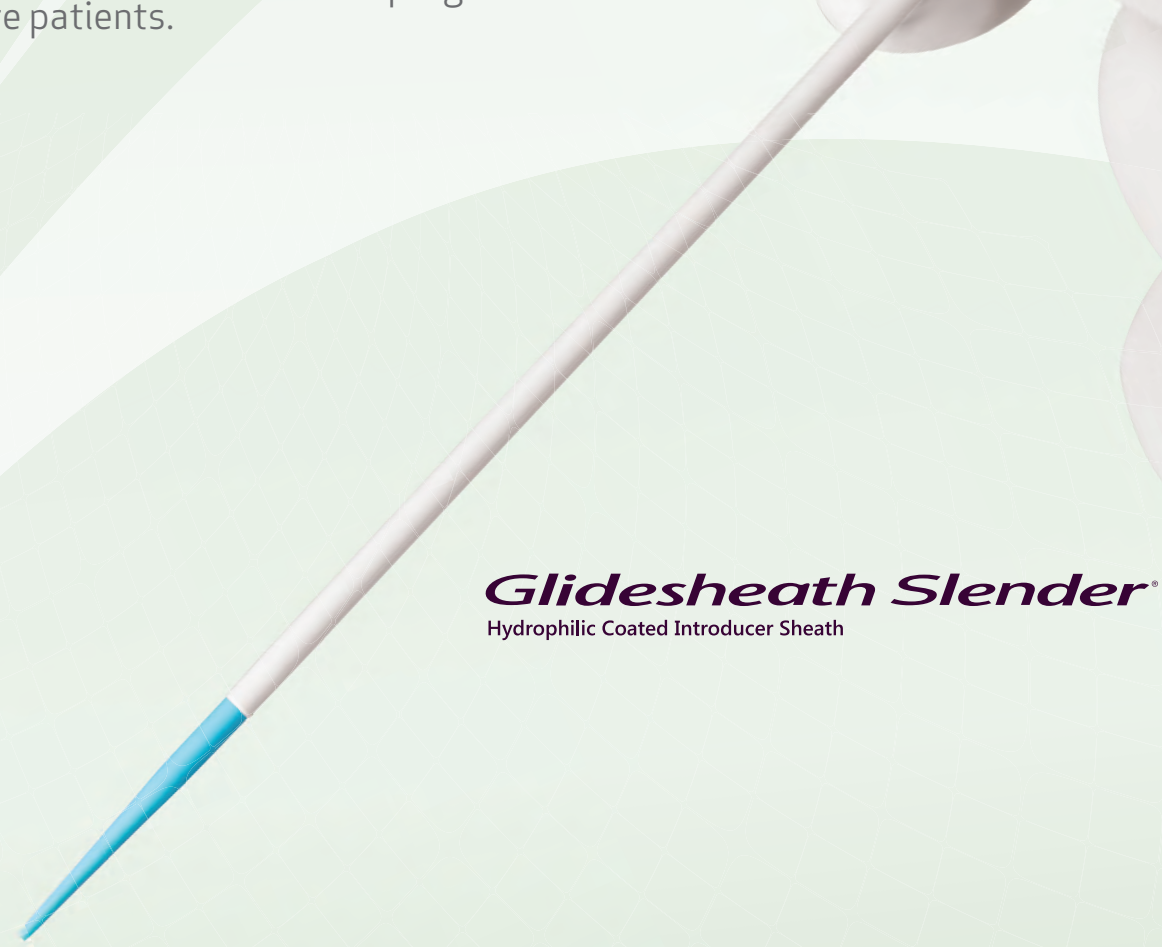

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TERUMO INTERVENTIONAL SYSTEMS

#Cardiology Ontology:
Using Hashtags to Improve #CVD Care

Cardiology now has a hashtag ontology page dedicated to facilitating social media use as a way to assemble and disseminate hashtags pertinent to cardiovascular diseases. This enables health care professionals, patients and family members to organize discussions surrounding cardiovascular medicine in an effort to keep the interest of the patient foremost. The hashtag ontology also allows patients and providers to search information related to such topics as #CVDPrev, #AFib, #cvHCM (hypertrophic cardiomyopathy), #Statin, and #vhdAS (aortic stenosis), among others.

According to the members of the Cardiovascular Symplur Ontology Project, led by **R. Jay Widmer, MD, PhD**, a fellow in training at Mayo Clinic, the ontology will "provide a comfortable basis for those with an interest in cardiovascular disease to easily join and subsequently navigate the Twitterverse. Moreover, this will provide commonality for those across the globe to share thoughts and ideas regarding cardiology topics both novel and dogmatic."

Scan the QR code to read more about the cardiology ontology project on the *ACC in Touch Blog*.

LBCT-HOPE 3 from page 1

rosuvastatin 10mg plus a combination pill of candesartan 16mg and hydrocholothiazide 12.5mg daily, rosuvastatin 10mg plus a placebo daily, a placebo plus the combination pill daily, or two placebo pills daily. Over 5.6 years of follow-up, cardiovascular death, myocardial infarction or stroke occurred in 3.5 percent of patients receiving both drugs and in 5 percent of patients receiving only placebo. The relative risk reduction in those taking both drugs was 30 percent overall, 40 percent in those with hypertension and 20 percent in those without hypertension.

A second HOPE-3 trial analysis led by Bosch, et al., focused only on the use of statins and found that 3.7 percent of those taking a statin experienced the first co-primary endpoint – a composite of cardiovascular deaths, myocardial infarction and stroke – compared with 4.8 percent of patients taking a placebo. Additionally, 4.4 percent of the statin group experienced the second co-primary endpoint – a composite of the events in the first co-primary endpoint plus heart failure, resuscitated cardiac arrest and revascularization procedures – compared with 5.7 percent of the placebo group. After 12 months, patients taking statins experienced, on average, a 25 percent reduction in low-density lipoprotein cholesterol.

A third analysis, led by Lonn, et al., examined only BP lowering drugs and found no significant improvements overall compared to placebo. However, among those patients with BP over 143.5 mm Hg prior to therapy, 4.8 percent experienced the first co-primary endpoint and 5.7 percent experienced the second co-primary endpoint, significantly lower than 6.5 and 7.5 percent, respectively, among patients taking placebo.

The trial, designed to focus on preventing cardiovascular disease before it starts, is the first to assess outcomes of preventative treatment with cholesterol and BP-lowering drugs in a large, globally diverse population at intermediate risk for developing cardiovascular disease.

According to the authors, the findings point to the value of a more simplified approach, which places more emphasis on statins in the general population and adds low doses of combination BP medications to the statins in patients with mild hypertension. Participants will be tracked for an additional three to five years. The researchers will continue to conduct additional analyses examining the effects on cognitive decline, erectile dysfunction and vision, along with detailed analyses of potential differences among ethnic groups and geographic regions.

"Most of the hypertension guidelines right now focus on what agents to use and what BP to aim for, and there has been very little emphasis on the importance of statins in treating patients with hypertension," Yusuf said. "Our approach, which used a combination of moderate doses of two BP-lowering drugs plus a statin, appears to produce the biggest 'bang,' in terms of reducing events with few side effects."

Transcatheter Aortic Valve Replacement (TAVR)

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*Includes all valves from the Edwards SAPIEN transcatheter heart valve platform.

See adjacent page for Important Safety Information.

CAUTION: Federal (United States) law restricts these devices to sale by or on the order of a physician.

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IMPORTANT SAFETY INFORMATION

EDWARDS SAPIEN 3 TRANSCATHETER HEART VALVE WITH THE EDWARDS COMMANDER DELIVERY SYSTEM

Indications: The Edwards SAPIEN 3 transcatheter heart valve (THV), model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

Contraindications: The THV and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

Warnings: Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation. There is an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments. The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices**. There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing. Incorrect sizing of the THV may lead to paravalvular leak, migration, embolization, and/or annular rupture. Accelerated deterioration of the THV may occur in patients with an altered calcium metabolism. Prior to delivery, the THV must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. THV leaflets mishandled or damaged during any part of the procedure will require replacement of the THV. Caution should be exercised in implanting a THV in patients with clinically significant coronary artery disease. Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the THV to ensure proper THV positioning and deployment. Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g., kinked or stretched), or if the expiration date has elapsed. Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored. Patient injury could occur if the delivery system is not un-flexed prior to removal. Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials. The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting. THV recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without anticoagulation.

Precautions: Long-term durability has not been established for the THV. Regular medical follow-up is advised to evaluate THV performance. Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon. Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis. Safety, effectiveness, and durability have not been established for valve-in-valve procedures. Safety and effectiveness have not been established for patients with the following characteristics/comorbidities: non-calcified aortic annulus; severe ventricular dysfunction with ejection fraction < 20%; congenital unicuspid or congenital bicuspid aortic valve; mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+); pre-existing prosthetic heart valve or prosthetic ring in any position; severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome; blood dyscrasias defined as leukopenia (WBC < 3000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy; hypertrophic cardiomyopathy with or without obstruction (HOCM); echocardiographic evidence of intracardiac mass, thrombus, or vegetation; a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated; significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater, marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta; access characteristics that would preclude safe placement of 14F or 16F Edwards eSheath introducer set, such as severe obstructive calcification, severe tortuosity, or diameter less than 5.5 mm or 6 mm, respectively; or bulky calcified aortic valve leaflets in close proximity to coronary ostia.

Potential Adverse Events: Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography: death; stroke/transient ischemic attack, clusters, or neurological deficit; paralysis; permanent disability; respiratory insufficiency or respiratory failure; hemorrhage requiring transfusion or intervention; cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention; pericardial effusion or cardiac tamponade; embolization including air, calcific valve material, or thrombus; infection including septicemia and endocarditis; heart failure; myocardial infarction; renal insufficiency or renal failure; conduction system defect which may require a permanent pacemaker; arrhythmia; retroperitoneal bleed; AV fistula or pseudoaneurysm; reoperation; ischemia or nerve injury; restenosis; pulmonary edema; pleural effusion; bleeding; anemia; abnormal lab values (including electrolyte imbalance); hypertension or hypotension; allergic reaction to anesthesia, contrast media, or device materials; hematoma; syncope; pain or changes at the access site; exercise intolerance or weakness; inflammation; angina; heart murmur; and fever. Additional potential risks associated with the use of the THV, delivery system, and/or accessories include: cardiac arrest; cardiogenic shock; emergency cardiac surgery; cardiac failure or low cardiac output; coronary flow obstruction/transvalvular flow disturbance; device thrombosis requiring intervention; valve thrombosis; device embolization; device migration or malposition requiring intervention; valve deployment in unintended location; valve stenosis; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis); device degeneration; paravalvular or transvalvular leak; valve regurgitation; hemolysis; device explants; nonstructural dysfunction; mechanical failure of delivery system and/or accessories; and non-emergent reoperation.

EDWARDS CRIMPER

Indications: The Edwards Crimper is indicated for use in preparing the Edwards SAPIEN 3 transcatheter heart valve for implantation.

Contraindications: There are no known contraindications.

Warnings: The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices**. There is no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.

Precautions: For special considerations associated with the use of the Edwards Crimper prior to transcatheter heart valve implantation, refer to the Edwards SAPIEN 3 transcatheter heart valve Instructions for Use.

Potential Adverse Events: There are no known potential adverse events associated with the Edwards Crimper.

CAUTION: Federal (United States) law restricts this device to sale by or on the order of a physician.

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Promotion of Global CV Health

Focus of 15th Annual Maseri-Florio International Lecture

Anthropology and archeology meet preventive cardiology today in the 15th Annual Maseri-Florio International Lecture. Featured speaker **Jagat Narula, DM, MD, PhD, MACC**, will address the burden of cardiovascular disease and share insights from his research, including imaging studies in mummies and special populations, that could inform strategies for the promotion of cardiovascular health worldwide.

Cardiovascular disease is the leading noncommunicable disease (NCD) and remains the leading cause of death globally, contributing nearly half of the NCD-related deaths in 2012, according to estimates from the World Health Organization. Of the 17.5 million deaths that year, 7.4 million were estimated to be caused by coronary heart disease. Many of these deaths are premature, before the age of 60 years.

More often than not, the first manifestation of coronary heart disease is an acute coronary syndrome event, either a myocardial infarction or sudden cardiac death. Cardiovascular imaging modalities are capable of identifying the high-risk, vulnerable plaque, and one must focus on the high-risk patients and not continue to chase individual plaques, says Narula, who is editor-in-chief of *JACC: Cardiovascular Imaging*, the Philip J. and Harriet L. Goodhart Chair in cardiology, chair of the departments of cardiology at Mount Sinai West and St. Luke's Hospitals, director of cardiovascular imaging at Mount Sinai Health System, as well as associate dean at the Arnhold Institute of Global Health at Mount Sinai.

> "I am grateful to the Maseri-Florio Foundation for their **contribution to the important cause of promoting cardiovascular health globally**, particularly in low- and middle-income countries."
>
> *Jagat Narula, DM, MD, PhD, MACC*

Atherosclerosis is a diffuse disease. In a decade of follow-up, about one-half of the acute coronary events occur from the high-risk plaques and the other half come from non-high-risk plaques. This has shifted the focus from the vulnerable plaque to the vulnerable patient, and the need to identify patients with this dynamic disease process.

The large-scale, observational INTERHEART study, conducted in 27,000 patients across 52 countries, has demonstrated that more than 90 percent of atherosclerotic disease is attributed to risk factors. The imaging of the mummies by the Horus Group from four different geographic regions and cultures found further evidence that even 4,000 years ago the disease occurred due to the same risk factors.

In his Maseri-Florio lecture, Narula will focus on the use of cardiovascular imaging strategies for better understanding the atherosclerotic disease process. He will touch on the role of risk factors, the interplay between genes and the environment and the impact on the development of coronary heart disease, and the role of infection and inflammation. He will make a case for promoting global cardiovascular wellness, with strategies to address modifiable risk factors, public health screening of risk factors and education.

"I am grateful to the Maseri-Florio Foundation for their contribution to the important cause of promoting cardiovascular health globally, particularly in low- and middle-income countries," says Narula.

The **15th Annual Maseri-Florio International Lecture** will take place today from **2:00 – 3:30 p.m.** in **room S502**.

ACC Professional Life Survey Shows Female Cardiologists Remain Underrepresented, Face More Work-Life Challenges

Female cardiologists remain underrepresented in the field, comprising less than 20 percent of cardiologists who see adult patients. Additionally, women may be less likely than their male counterparts to get married and have children and may be more likely to face challenges related to child care, family leave policies, and professional discrimination, according to results from ACC's third professional life survey presented yesterday during a poster session.

The study, led by **Sandra Lewis, MD, FACC**, chair of ACC's Women in Cardiology Section, looked at results from ACC's 2015 professional life survey – which examined cardiologists' career decisions, family life and satisfaction by gender – and compared data to two previous surveys that were conducted in 1996 and 2006.

Out of the more than 2,000 cardiologists who completed the 2015 survey, results showed that women make up half of all medical school graduates and nearly half of internal medicine specialists, yet they represent less than one-fifth of adult cardiologists.

In addition, 15 percent of female cardiologists are single vs. 5 percent of male cardiologists. These proportions have not changed significantly since the first survey in 1996. However, 72 percent of female cardiologists report having children, a proportion that is significantly up from 63 percent in 1996. Even so, this is significantly lower than their male counterparts, of whom 86 percent report having children in the 2015 survey.

Further, men are far more likely to report having a spouse that provides child care at home, at 57 percent as compared to 13 percent among women. Nearly half of women report needing additional child care for nights and on-call rotations, as compared to a quarter of men.

One area of improvement for both women and men is that around one in 10 report no official family leave policy at their workplace. This proportion is significantly down from rates seen in past surveys and suggests that more workplaces have adopted such policies.

> **"Twenty years ago, we acknowledged a need to increase the number of women in cardiology, and 10 years ago we saw an increase, but we've hit a wall. We need to understand the barriers to women entering cardiology and work toward breaking down those barriers."**
>
> *Sandra Lewis, MD, FACC*

The survey also sheds light on career satisfaction and professional challenges. Although about seven out of eight cardiologists of both genders report overall satisfaction with their careers, women are more likely to say their level of professional advancement is lower than their peers.

Sixty-three percent of women report experiencing past discrimination, such as receiving a lower salary than others in their cohort or being passed up for promotion. That proportion is significantly down from 71 percent and 69 percent in 1996 and 2006, respectively, but still substantially higher than the rates reported by men, which remain flat at around 22 percent in all three surveys.

"I'm very concerned that we haven't seen much growth in the number of women in adult cardiology," says Lewis. "Twenty years ago, we acknowledged a need to increase the number of women in cardiology, and 10 years ago we saw an increase, but we've hit a wall. We need to understand the barriers to women entering cardiology and work toward breaking down those barriers."

A Professional Enhancement and the Nonclinical Competencies: Leadership, Communication and Quality Intensive will take place today from **12:30 – 6:00 p.m.** in the **Grand Ballroom S100a.**

Lounge & Learn Pavilion the Center of Activity

Attendees visit the Lounge & Learn Pavilion in North Hall B1, home to the Fellows in Training, Early Career, Women in Cardiology, Cardiovascular Teams and International Lounges at ACC.16.

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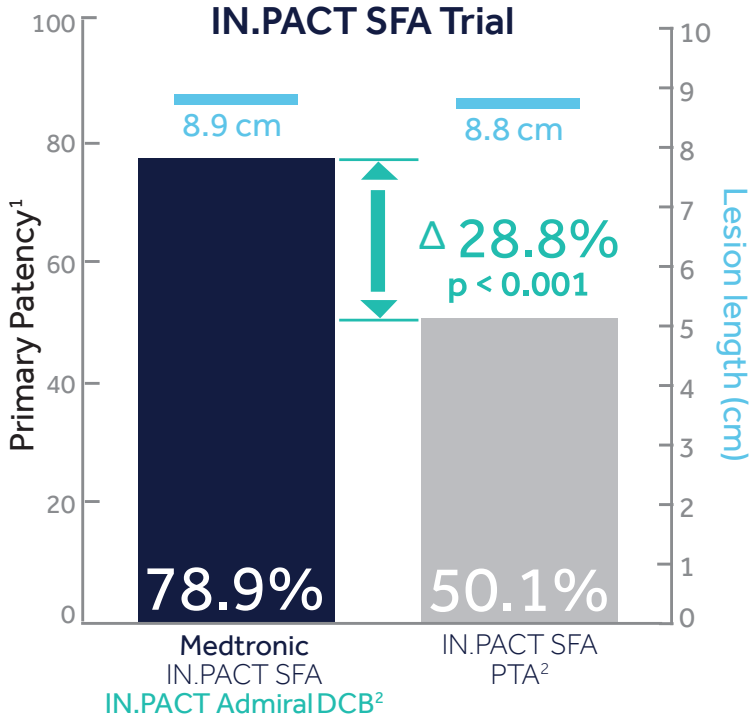

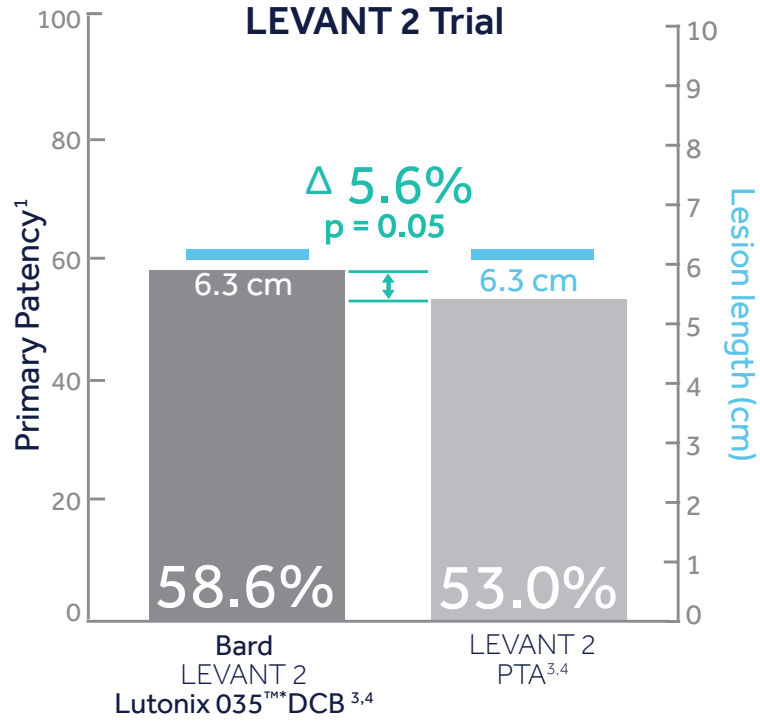

Note: Primary patency rates are not directly comparable: chart is for illustration only.
*Based on 2-year primary patency outcomes from FDA pivotal trials.

[1] Primary patency rates and mean lesion lengths may be calculated differently, and therefore may not be directly comparable; chart is for illustration only.
[2] IN.PACT SFA Trial values represent IN.PACT™ Admiral™ DCB arm as evaluated by 720-day Kaplan-Meier, primary patency defined as PSVR ≤ 2.4 and freedom from clinically-driven TLR; Laird J, et al. 24-Month Results from the IN.PACT SFA Trial. J Am Coll Cardiol. 2015;66(21):2329-2338. doi:10.1016/j.jacc.2015.09.063
[3] LEVANT 2 values represent Lutonix 035 as evaluated by 730-day Kaplan Meier, primary patency defined as PSVR < 2.5 and freedom from TLR; Presented by Laurich C, SVS Chicago 2015.
[4] LEVANT 2 mean lesion lengths presented in appendix of Rosenfield K, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. NEJM 2015:373:145-53.

Medtronic
Further, Together

Contemporary Stents Focus of Review in Zipes Lecture

In the four decades since percutaneous coronary intervention (PCI) was introduced, coronary stents have become integral to the management of patients with coronary artery disease requiring revascularization in the majority of patients. Reduction of coronary risk factors and aggressive medical therapy remain cornerstones of treatment for these patients.

Advances in PCI techniques and stent technology over the last three decades have reduced periprocedural complications and improved patient outcomes with this revascularization strategy. Procedural success rates are in the 93 to 99 percent range, adverse event rates are 4.53 percent, and the mortality rate for elective procedures is 0.2 percent, according to data from ACC's CathPCI Registry from January 2010 to June 2011. In 2010, an estimated 954,000 patients underwent PCI in the U.S.

"Even though we have newer generation stents, with what appears to be improvements in their coatings and design, we must thoroughly understand the data to determine the best treatment strategy for each patient, whether that is medical therapy, surgery, or PCI."

Sripal Bangalore, MBBS, MHA, FACC

The development of drug-eluting stents (DES) has been a major contributor to the improved outcomes, by addressing the in-stent restenosis seen with bare-metal stents, which has been a substantial complication after PCI.

The role of more contemporary DES, including those with bioresorbable polymers and permanent polymers, and their impact on patient outcomes will be discussed by **Sripal Bangalore, MBBS, MHA, FACC**, of New York University Langone Medical Center, in this year's Douglas P. Zipes, MD, MACC, Distinguished Young Scientist Lecture.

In his lecture, Bangalore will review outcomes with the bioresorbable polymers, durable polymer stents, and the older-generation DES and bare-metal stents. Bangalore will try to answer the question of whether the latest generation of DES reduce death or myocardial infarction (MI) compared with older generation stents. Prior randomized trials of PCI versus medical therapy in patients with stable coronary artery disease have failed to show a reduction in death or MI with PCI. Similarly, trials of PCI versus coronary artery bypass graft (CABG) surgery have shown superiority of CABG for hard outcomes. However, both of these sets of trials compared PCI using older generation stents. Whether newer generation stents have superior outcomes will dictate whether the results from the trials with older stents are still relevant and how they contribute to current clinical decision making.

Bangalore is the principal investigator of the National Heart, Lung, and Blood Institute-sponsored ISCHEMIA-CKD trial, and along with its parent ISCHEMIA trial, it is amongst the trials that are eagerly awaited to provide evidence comparing optimal medical therapy alone with that of revascularization in patients with stable ischemic heart disease. The trials will compare the best of contemporary medical therapy alone versus the addition of optimal revascularization therapy using the current generation of stents.

"Even though we have newer generation stents, with what appears to be improvements in their coatings and design, we must thoroughly understand the data to determine the best treatment strategy for each patient, whether that is medical therapy, surgery, or PCI," says Bangalore. "Along with the other presentations in this session, I hope my lecture provides a basis for these clinical decisions."

The **Douglas P. Zipes, MD, MACC, Distinguished Young Scientist Awardee Lecture** will take place today from **4:45 – 6:00 p.m.** in **room S103cd**.

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ACTELION

Women's Studies Find Sex-Specific Approaches Needed For CAD Evaluation; Women Experience Differences in Advice, Treatment and Outcomes

Gender may affect the way risk of coronary artery disease (CAD) is factored, and there is a need for gender-specific approaches to CAD evaluation, according to a study which will be presented today and simultaneously published in *JACC: Cardiovascular Imaging*. These findings will be included in tomorrow's special issue of *JACC: Cardiovascular Imaging* focused on imaging in women.

Kshipra Hemal, et al., looked at 10,003 men and women enrolled in the PROMISE trial – comprised of low- to intermediate-risk, stable outpatients with symptoms suggested of CAD – and found that compared to men, women had a greater number of cardiac risk factors, but were more likely to be characterized as lower risk – not only by providers, but also by risk scores. In addition, risk factors for cardiovascular disease more commonly found in women than men – depression, sedentary lifestyle, and family history of early-onset cardiovascular disease – were found to be excluded from most risk-assessment questionnaires. The authors further found that chest pain and shortness of breath were the most common symptoms reported by both men and women with suspected cardiovascular disease.

"This study shows the importance of taking into account the differences between women and men throughout the entire diagnostic process for suspected heart disease," says Hemal. "The next step in this research will be to examine whether and how the differences we have identified between women and men influence outcomes."

> "This study shows the **importance of taking into account the differences between women and men** throughout the entire diagnostic process for suspected heart disease."
>
> *Kshipra Hemal*

Meanwhile, a separate study which will be presented in a poster session tomorrow by **C. Noel Bairey Merz, MD, FACC**, et al., found that many women are aware of cardiovascular disease risk factors, yet few are advised of risk.

The study looked at 1,011 U.S. women ages 25 to 60, and found that 74 percent reported one or more risk factors, yet only 16 percent were told they were at risk. In addition, 76 percent reported rarely or never discussing cardiovascular health with family and friends. The report also found that 34 percent of women were told to lose weight and 45 percent said that they would cancel or postpone a health appointment until losing weight.

The authors conclude that "social stigma regarding body weight may contribute to women not discussing heart health," and suggest that moving forward, communication and outreach are needed to counter lack of awareness and stigma.

Women also experience differences in treatment and outcomes. According to a study led by **Edina Cenko, MD**, et al., admission delays in primary percutaneous coronary intervention (PCI) of more than two hours are significantly more frequent in women than in men, and women have a higher risk of short-term mortality than men.

The study, which will be presented in a poster session tomorrow, analyzed 6,679 patients with ST-segment elevation myocardial infarction (STEMI) who had a primary PCI within 24 hours of symptom onset. Results showed that hospital admissions of less than two hours were associated with a lower risk of death. According to the authors, "after multivariable adjustment, women remained significantly associated with a higher risk of death."

Delays also can be significant in door-to-balloon (DTB) times for women compared to men, according to a separate study by **Mostafa El-Refai, MD**, et al. which will also be presented tomorrow in a poster session.

The study looked at 193 STEMI patients, of which 21 percent were women, and found a "substantial difference" in DTB time between women and men. Further, women had more after-hours presentations and lower maximum ST elevation on ECG compared to men.

The authors conclude that the delays were associated with both clinical- and system-related factors, and that a delay in cath lab activation "disproportionately affects women."

C. Noel Bairey Merz, MD, FACC, co-chair of ACC's Cardiovascular Disease in Women Committee, and **Martha Gulati, MD, MS, FACC,** editor-in-chief of ACC's CardioSmart, will co-chair a **Women and Cardiovascular Disease: The 'Special' Population Intensive** today from **8:00 a.m. – 1:45 p.m. in Grand Ballroom S100bc.**

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Use ENTRESTO™ in place of ACEis and ARBs for HF*r*EF patients[1]

ENTRESTO was studied in the largest HF trial ever conducted[2]

- Trial stopped early due to finding of significantly reduced risk of CV death and the primary end point being met[3]

ENTRESTO has been proven superior to enalapril, a current standard-of-care[4] medication[1]

- Superiority vs enalapril, a standard-of-care ACEi therapy, across a range of NYHA class II–IV patients with chronic HF and reduced ejection fraction

20% REDUCED RISK OF CV DEATH OR FIRST HF HOSPITALIZATION vs ENALAPRIL[1]

P<0.0001 HR (95% CI): 0.80 (0.73, 0.87)

4.7% ABSOLUTE RISK REDUCTION[1]

REDEFINE EXPECTATIONS IN HEART FAILURE

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

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.

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

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

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

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

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

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

STUDY DESIGN: PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO to enalapril in 8442 symptomatic (NYHA class II–IV) adult HF*r*EF patients (left ventricular ejection fraction ≤40%). After discontinuing their existing ACEi or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice daily, followed by ENTRESTO 100 mg (49/51 mg) twice daily, increasing to 200 mg (97/103 mg) twice daily. Patients were then randomized to receive either ENTRESTO 200 mg (97/103 mg) (n=4209) twice daily or enalapril 10 mg (n=4233) twice daily. The median follow-up duration was 27 months, and patients were treated for up to 4.3 years. The primary end point was the first event in the composite of CV death or first HF hospitalization.[1]

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HF*r*EF = heart failure with reduced ejection fraction; CV = cardiovascular; NYHA = New York Heart Association; HF=heart failure.

For more information, visit **EntrestoHCP.com**

References: 1. ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015. **2.** McMurray JJV, Packer M, Desai AS, et al. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014;16(7):817-825. **3.** McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. **4.** Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128(16):e240-e327.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

12/15 ETR-1321798

NOVARTIS PHARMACEUTICALS

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

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

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

1 INDICATIONS AND USAGE

1.1 Heart Failure

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

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

5.2 Angioedema

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

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

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

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

5.3 Hypotension

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

5.4 Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO. In the double-blind period of PARADIGM-HF, 5% of patients in both the ENTRESTO and enalapril groups reported renal failure as an adverse event *[see Adverse Reactions (6.1)]*. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3) in the full prescribing information]*.

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

5.5 Hyperkalemia

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

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:
- Angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Impaired Renal Function *[see Warnings and Precautions (5.4)]*
- Hyperkalemia *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

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

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

Table 1: Adverse Reactions Reported in ≥5% of Patients Treated with ENTRESTO in the Double-Blind Period

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

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

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

Laboratory Abnormalities

Hemoglobin and Hematocrit

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

Serum Creatinine

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

Serum Potassium

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

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

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

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

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

7.2 Potassium-Sparing Diuretics

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

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

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

7.4 Lithium

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to ENTRESTO for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to ENTRESTO, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Focused Update on the Use of DAPT Released

Updated guidelines for the use of dual antiplatelet therapy (DAPT) – aspirin plus a $P2Y_{12}$ inhibitor – in patients with coronary artery disease, were released March 29 by the ACC and the American Heart Association and published in the *Journal of the American College of Cardiology*.

The document updates recommendations on duration of DAPT across six previously published guidelines: percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, stable ischemic heart disease (SIHD), ST-elevation myocardial infarction, non-ST-elevation acute coronary syndromes (ACS) and perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery.

These recommendations are based on findings of recent studies of the length of time patients with coronary artery disease – specifically those with myocardial infarction and those receiving a stent – should be treated with DAPT. The new recommendations are also based on the use of newer stents that have a lower risk of clotting than some older stents. Studies examining shorter duration (three to six months) of DAPT compared with a standard 12 months of therapy in select, mostly lower-risk patients did not find any increased risk of stent thrombosis and, in some cases, found less bleeding. Other studies of prolonged or extended DAPT for an additional 18 or 36 months found a decrease in the risk of myocardial infarction and stent thrombosis at the expense of an increase in bleeding risk.

"Treatment with more intensive antiplatelet therapy and treatment for a longer duration of time with antiplatelet medicines in general involves a **fundamental tradeoff between a decreased risk of future heart attack and an increased risk of bleeding complications."**

Glenn N. Levine, MD, FACC

In the update, recommendations for DAPT generally consist of a Class I recommendation of "should be given" for a minimum time period of time (usually six to 12 months), and a Class IIb recommendation of "may be considered" for continuation beyond that time. Shorter duration of DAPT is recommended for patients at lower ischemic risk with high bleeding risk, whereas a longer duration of treatment may be reasonable for patients at higher ischemic risk with lower bleeding risk. These recommendations apply to newer-generation stents and, in general, only to those not treated with oral anticoagulant therapy. A dose of 81 mg daily (range 75 – 100 mg) is now recommended in patients treated with DAPT.

The document also addresses DAPT after CABG and issues regarding the timing of non-cardiac surgery in patients treated with PCI and DAPT. The writing committee notes that decisions about the timing of surgery and whether to discontinue DAPT after stent implantation should be individualized, and involve weighing the particular surgical procedure and the risks of delaying the procedure, the risks of ischemia and stent thrombosis, and the risk and consequences of bleeding.

"Treatment with more intensive antiplatelet therapy and treatment for a longer duration of time with antiplatelet medicines in general involves a fundamental tradeoff between a decreased risk of future heart attack and an increased risk of bleeding complications," explains **Glenn N. Levine, MD, FACC**, chair of the writing committee for the document.

To accompany the DAPT Update, the ACC has developed a DAPT After PCI Overview Tool that provides clinicians with guidance when treating SIHD and ACS patients undergoing PCI. The tool, the first in a new DAPT Update Toolkit, highlights that 81 mg of aspirin daily should be used in all SIHD and ACS patients as the gold standard. In addition to outlining the recommendations for these patients, the tool also utilizes the treatment algorithm for all clinicians to use when treating patients with SIHD and ACS who have undergone PCI.

Visit **ACC's DAPT Focused Update Hub** at ***ACC.org/DAPT,*** to access the full DAPT Update, all of the available ACC resources, expert commentary, a poll and more. Join the conversations on **Twitter** using the hashtag **#DAPT.**

Perspective: Life After MI For an Athlete

By Michael Scott Emery, MD, FACC

Many athletes have the misconception that, because they are "fit and athletic," heart disease cannot strike them. Unfortunately, while exercise does lower the risk of heart disease, it does not make you immune. An acute bout of exercise can raise a person's risk of a cardiac event while they are exercising, though this risk is greater in newer exercisers than in habitual exercisers. That being said, the benefits of regular physical activity certainly outweigh the increased relative risk of triggering a coronary event during the exercise session, and habitual exercise diminishes the risk of sudden cardiac death during vigorous exercise.

The positive benefits of regular physical activity are largely associated with moderate-intensity activity whereas the potentially negative effects of exercise are predominately related to high-intensity activity. The risk of a subsequent exercise-related event increases with the extent of disease, left ventricular dysfunction, inducible ischemia and electrical instability.

Aggressive and intense medical therapy, particularly with statin medications, is also very important. The key ingredient may be time, and that time may be longer than most patient athletes may like. In general, we recommend putting a damper on competitive activities for two years, as we think it takes about that long for statin therapy to stabilize those potentially vulnerable plaques.

"One of the early questions often asked is, 'When can I go back to doing what I was doing before?' That can be a difficult discussion as the data on returning to higher levels of exercise after a MI are scarce."

Michael Scott Emery, MD, FACC

Many patient athletes utilize exercise not only for health benefits, but as a means for them to process their day-to-day stressors. One of the early questions often asked is, "When can I go back to doing what I was doing before?" That can be a difficult discussion as the data on returning to higher levels of exercise after a myocardial infarction (MI) are scarce.

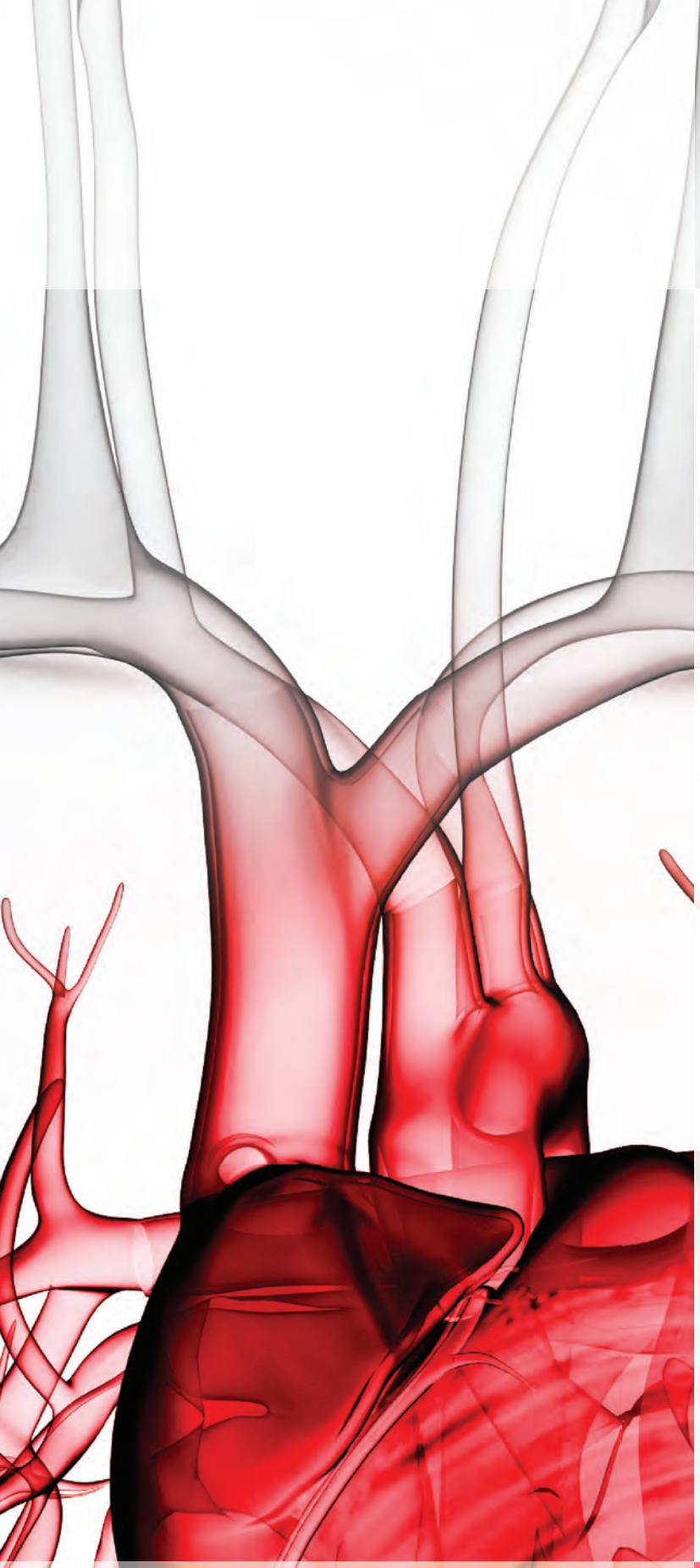
The first step is cardiac rehab, the benefits of which cannot be denied. Unfortunately, most athletic individuals quickly outpace the standard protocols and may need some coaching and modifications in order to complete it. Once cardiac rehab is completed, things can become difficult for both the patient athlete and the physician. It is at this point in this process where I have long, frank discussions with my patient athletes. We discuss their risk factors and how aggressively we can control them, which can be difficult, as most patient athletes do not want to take medications. We use exercise testing – particularly cardiopulmonary exercise testing – as a guide for exercise prescription and intensity. Controlling intensity, which may be a crucial aspect to reducing risk, especially early in the recovery phase, can be difficult for them as they are used to going at full pace.

When discussing "competition," we have to gauge what that means for each patient athlete. For many older athletes, the competition is not about signing up for an event to get a medal, it is about the friendly competition with their peers. In other words, who can get up the next hill first or a final sprint after a run or car ride. Risk increases with intensity of the competitive sport and intensity of the participant's effort.

I generally do not tell my athletes not to do something; rather, I try to educate them to make the ultimate decision. While it is generally safer to refrain from doing intense exercise, in the end, that is a choice for the patient athlete and their family. My duty, as their physician, is try to help them understand their risks.

Emery is a speaker in today's session, **"Life After MI for an Athlete – Debate,"** from **4:45 – 6:00 p.m. in room S505.** The session will include a case presentation on a patient who is 50 years old and is a high-intensity athlete who ends up with anterior wall MI and ejection fraction of 45 percent. An aggressive and conservative approach will be debated.

Search the **ACC.16 App** for additional **Sports Cardiology** sessions.



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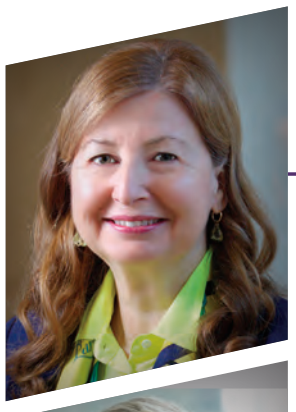

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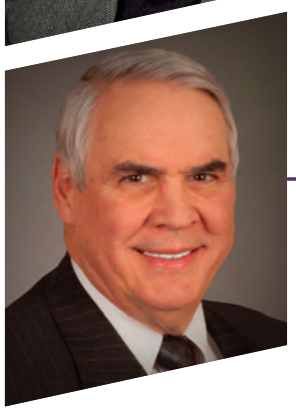

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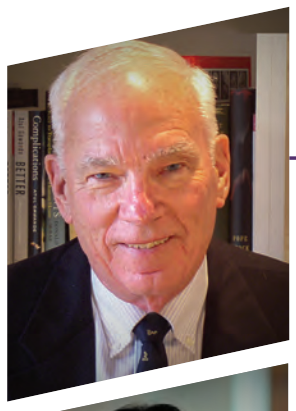

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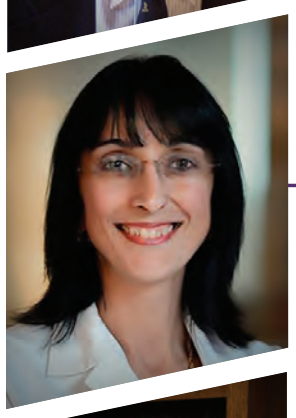

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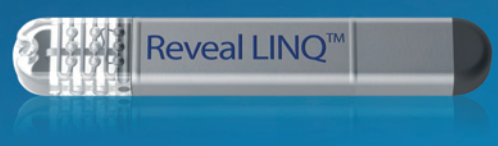

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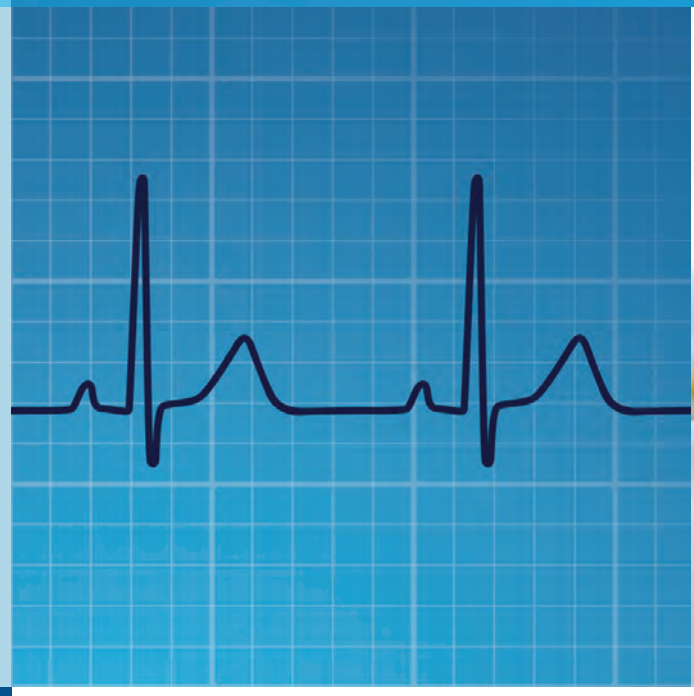

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ACC Working to Reaffirm Importance of Professionalism

While the concept of medical professionalism can be traced back to the guild system of medieval Europe, Thomas Percival's *Medical Ethics* from the early 1900s was the first to describe medicine as a "profession" and as a "public trust." Public response to this concept has varied over the centuries – from distrust to acceptance. However, given recent concerns over declining public trust in health care as a whole, there has been a push by many in the medical profession, including the ACC, to reaffirm their dedication to professionalism.

"We are facing several challenges: rapidly changing health care delivery and payment systems; calls for new levels of accountability; migration from volume to value; new requirements for maintaining certification; new parameters for relationships with industry and conflicts of interest; and new norms defining patient- and family-centered practice," wrote **Patrick T. O'Gara, MD, MACC, John Gordon Harold, MD, MACC**, and **Deborah Ness, MS**, in a Leadership Page in the *Journal of the American College of Cardiology*. "What better time than the present to pause and review the fundamental principles by which we all aspire to conduct ourselves?"

> "What better time than the present to pause and review the fundamental principles by which we all aspire to conduct ourselves?"
>
> *Deborah Ness, MS*

> "Based on the Physician Charter on Professionalism, the MOC module is being considered for use by more than 20 specialties."
>
> *William Oetgen, MD, FACC*

Over the last several years the ACC has unanimously ratified and approved the adoption of the "Medical Professionalism in the New Millennium: A Physician Charter." This charter, originally published in *The Lancet* and *Annals of Internal Medicine* in 2002, is the standard for a document expressing the tenets of medical professionalism, and has been adopted by more than 100 medical societies and medical specialty societies around the world. Additionally, the College has developed mentoring and leadership programs aimed at educating the next generation of cardiovascular professionals about the importance of professionalism. Ongoing development of Appropriate Use Criteria also continues to ensure appropriate use of tests and procedures based on the latest science and evidence.

Most recently, ACC's 2016 ACC Lifelong Learning Competencies for General Cardiologists, defines the knowledge, skills, and behaviors expected of practicing clinical cardiologists based on the six competency domains, including professionalism, developed by the Accreditation Council for Graduate Medical Education and American Board of Medical Specialties, and endorsed by the American Board of Internal Medicine.

The College's new Medical Professionalism Maintenance of Certification (MOC) module is also gaining traction both among ACC members, as well as externally with other medical specialty societies. The free, online module allows participants to earn 10 MOC points by answering 30 multiple-choice questions on the topic of medical professionalism, including integrity and accountability, fair and ethical use of health care resources, self-regulation and commitment to excellence.

"Based on the Physician Charter on Professionalism, the MOC module is being considered for use by more than 20 specialties," said ACC Executive Vice President for Science, Quality and Education **William Oetgen, MD, FACC**. "We are excited about the opportunity to come together with the broader house of medicine to ensure our responsibilities to our patients and our profession are recognized."

Visit ***ACC.org/MedProf*** to access ACC's Medical Professionalism MOC Module.

PARTNER 2A, from page 1

safety and effectiveness of the second-generation SAPIEN XT TAVR system.

The patients in the PARTNER 2A trial were placed into two cohorts: 76.3 percent were entered into the transfemoral-access cohort and 23.7 percent were entered into the transthoracic-access cohort. The patients were randomly assigned to undergo either TAVR with a second-generation valve system (1,011 patients) or surgical replacement (1,021 patients). The study's authors hypothesized that TAVR would not be inferior to surgical replacement. The primary endpoint was mortality from any cause or disabling stroke at two years.

Results showed that the rate of death from the primary endpoint was similar in the TAVR group and the surgery group. In the transfemoral-access cohort, TAVR resulted in a lower risk of death or disabling stroke than surgery. In the transthoracic-access cohort, the outcomes were similar in both groups. At two years, the rate of death from any cause was 16.7 percent after TAVR and 18 percent after surgery. The rate of disabling stroke was 6.2 percent after TAVR and 6.4 percent after surgery.

Data also showed that major vascular complications were more frequent in the TAVR group than in the surgery group at 30 days. But complications such as life-threatening bleeding, acute kidney injury, and new-onset atrial fibrillation were less frequent in the TAVR group.

Although long-term durability assessments of transcatheter bioprosthetic valves need further clinical investigation, the authors of PARTNER 2A affirm that the results of the study support the use of TAVR as an alternative to surgery in intermediate risk patients.

In an accompanying editorial published in *NEJM*, **Neil E. Moat, MB, BS**, notes the importance of the decreased rates of acute kidney injury and atrial fibrillation, along with shorter hospital stays reported in the TAVR group. "These are very important findings and reinforce the fact that TAVR is less invasive than conventional surgery." In addition, Moat states that "the results published in the *Journal* seem to confirm that TAVR is the treatment of choice in most patients with aortic stenosis who are at high risk for early death and major complications from conventional surgery."

SUDDEN CARDIAC DEATH

post-PCI and post-MI

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BOTTOM LINE

1 in 10 high-risk post-PCI patients **die in the first 3 months,**

with about

60% of this mortality due to

SUDDEN CARDIAC DEATH.[1,2]

SOURCES: 1. Halkin A et al. Prediction of Mortality After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: CADILLAC Risk Score. JACC 2005;45:1397–1405. 2. Stone G et al. Prevention of Sudden Cardiac Arrest Post PTCA in High-Risk Patients. http://www.theheart.org/article/1202823.do (April 2011).

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Written on the Wall

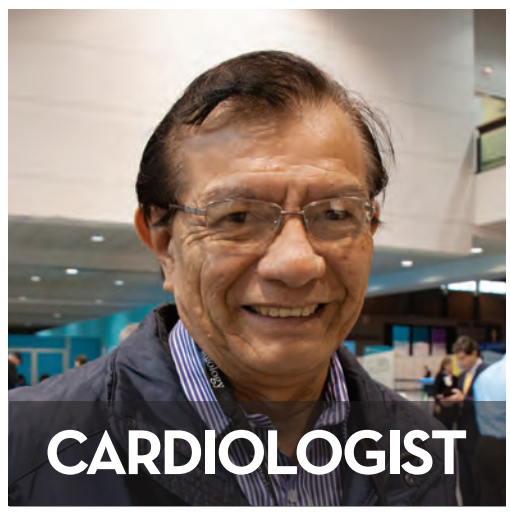
IF I DIDN'T CHOOSE CARDIOLOGY, I WOULD HAVE BEEN A...

Praveen Kanaparti, MBBS, FACC
Jacksonville, FL

"If I weren't a physician, I would have loved to fly planes. I love traveling and seeing new places and being a pilot would have offered me that. Plus, it's such a great feeling of freedom when you fly."

Eri Kato, MD
Tokyo, Japan

"As a child, I was often sick and I spent some time in the hospital. This inspired me to become a cardiologist. At first, I didn't think I was ready so I started out as a banker but then I realized you only live once and you have to do what you love so I switched careers and became a cardiologist."



Evert Torrejon Carbajal, MD
Lima, Peru

"I always wanted to be a cardiologist and there is no other profession I would have chosen instead. My mother was my inspiration in choosing this profession and always spoke so highly of doctors. I always wanted to help people and over time I decided cardiology is one of the best professions to do so."

Stop by the **Lounge & Learn Pavilion** to answer this question and others on the interactive question walls.

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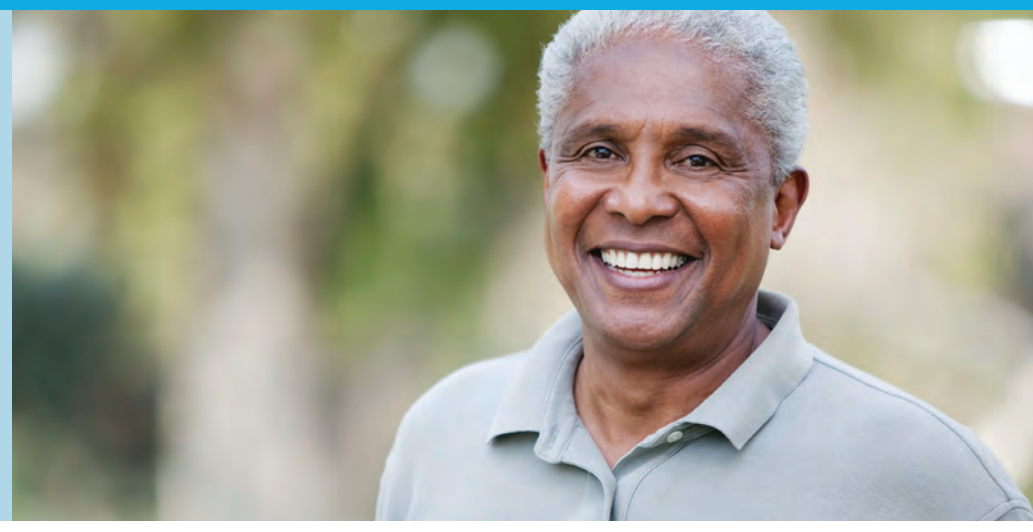

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Further, Together

Lifelong Challenges of ACHD Focus of 47th Annual Louis F. Bishop Lecture

Adult congenital heart disease (ACHD) was the topic of the 47th Annual Louis F. Bishop Lecture presented Saturday by **Carole A. Warnes, MD, FACC**, of the Mayo Clinic.

Her lecture, "Adult Congenital Heart Disease: the Challenge of a Lifetime," highlighted the challenges faced by surgeons, cardiologists and ACHD patients and the need for advanced education and training resources for all three of these groups.

More than one million U.S. adults have congenital heart disease (CHD), noted Warnes, and the population is growing. Cardiologists are seeing more ACHD patients in their practices, but often have very little training or education about the disease. ACHD patients are rarely referred to specialists in a timely manner.

One of the greatest challenges ACHD patients face, noted Warnes, is the fact that they believe they were "cured" in childhood – and many regular cardiologists may believe that too.

In the 1940s and 1950s, 25 percent of babies born with CHD would die as newborns, 60 percent would die in their first year and 15 percent would not survive past puberty. As the surgeries improved, along with anesthesia, intensive care, and noninvasive diagnosis, the mortality rate decreased, "and this is why we have so many adults with CHD today," said Warnes.

While many ACHD patients believe that because they had successful surgeries as children, they are "fixed." According to Warnes, that is rarely the case. "When a reoperation is needed, it comes as a huge surprise," she said. "They may need a fourth or fifth operation when they thought they were cured by the first." ACHD patients over the age of 40 face the same health issues that all people over 40 face – with added complications like arrhythmia, which, said Warnes, "skyrockets" in ACHD patients over 40. "General cardiologists may not realize that a patient's arrhythmia comes from CHD," she noted, which means the patient may not receive the appropriate treatment. Additional complications include endocarditis, pulmonary vascular disease and ventricular dysfunction.

"These patients are extraordinarily courageous – but they don't have good advice or education so sometimes they just don't know."

Carole A. Warnes, MD, FACC

The biggest challenge facing surgeons today is reoperation, which is often impeded by complications like progression of trivial lesions, degeneration of valve replacements and conduits and calcification of abnormal valves.

Many ACHD patients face the challenge of being "unaware, uninformed and uneducated," said Warnes. "These patients are extraordinarily courageous – but they don't have good advice or education so sometimes they just don't know. They have to be their own advocates but they are not prepared."

In addition to dealing with complications from CHD, patients face huge insurance obstacles. Doctors have to spend a lot of time writing letters on behalf of their patients to insurance companies, workplaces, and a number of other entities.

The priority today, Warnes asserted, is to educate cardiologists and patients about the continuing challenges of ACHD. "We must bridge the gap between pediatric and ACHD physicians," she explained. General cardiologists need to understand the complexities of CHD. "Cardiologists must work together to create an open exchange of information," and commit to tracking and measuring results. She added that it needs to be easier for cardiologists to refer CHD patients.

Warnes closed by noting that many ACHD patients feel that their condition has been a positive force in their lives, giving them the gifts of resilience, compassion and empathy, a sense of what's important, and a sense of the value of life.

Learn more about ACC's Adult Congenital and Pediatric Cardiology Section at *ACC.org/ACPC*.

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*Source: 2015–2016 US News & World Report Ranking of Top 50 Adult Cardiology & Heart Surgery Hospitals.

ACC Publishes Guidance For Non-Statin Therapies

A new expert consensus document regarding the use of non-statin therapies to lower cholesterol in high-risk patients published April 1 in the *Journal of the American College of Cardiology*. This document is the first expert consensus decision pathway from the ACC and provides practical guidance for clinicians and patients in situations not covered by the *2013 ACC/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults*.

Since the publication of the 2013 cholesterol guideline, the U.S. Food and Drug Administration has approved proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors for certain patients and the recent publication of the HPS2-THRIVE and IMPROVE-IT trials have provided new evidence about adding non-statin therapies to statins as combination therapy. The writing committee supports consideration of adding ezetimibe 10 mg daily as the first non-statin agent for many higher-risk patient groups. However, they do not recommend niacin as an additional non-statin therapy for the situations discussed in the document. Consistent with the 2013 guideline, this new document recommends looking first at lifestyle issues, including diet, exercise and smoking, followed by statin therapy.

> "This consensus pathway document is the first in a new format, where we offer **guidance to clinicians in an easy-to-understand algorithm** approach framed in a data supported fashion."
>
> *James L. Januzzi Jr., MD, FACC*

The algorithms in the document provide a suggested clinical workflow for consideration of the addition of non-statin therapies to evidence-based statin therapy, and assume that patients are in one of the four evidence-based statin benefit groups identified in the 2013 guideline. The writing committee explains that for other groups of patients, care should be individualized.

Defining thresholds of low-density lipoprotein cholesterol (LDL-C), in terms of percentage reduction and absolute values, for consideration of net atherosclerotic cardiovascular disease (ASCVD) risk-reduction benefit, is critical to helping determine use of additional non-statin therapies in selected high-risk patients. The writing committee emphasizes that these are not firm triggers for adding medication but factors that may be considered within the broader context of an individual patient's clinical situation.

Additional considerations for the initiation of non-statin therapies include the extent of available scientific evidence for safety and tolerability, potential for drug-drug interactions, efficacy of additional LDL-C lowering in ASCVD event reduction, cost, convenience and medication storage, pill burden, route of administration, potential to jeopardize adherence to evidence-based therapies, and importantly, patient preferences.

"This consensus pathway document is the first in a new format, where we offer guidance to clinicians in an easy-to-understand algorithm approach framed in a data supported fashion," says **James L. Januzzi Jr., MD, FACC**, chair of ACC's Task Force on Clinical Expert Consensus Documents. "While like any consensus document before it, this effort contains abundant useful information, the ACC recognizes the importance of providing useful decision support to busy clinicians as well. I feel the authors threaded the needle perfectly with this pathway, providing a useful resource for understanding the appropriate use of non-statin therapies while simultaneously guiding clinicians for such use."

To access the full expert consensus document, visit *ACC.org*.

Check out the following **Prevention Sessions** taking place today:

Contemporary Issues in Preventive Cardiology II
9:30 a.m. – 12:30 p.m.
Poster Area, South Hall A1

Severe Hypertriglyceridemia – When to Consider Going Beyond LDL-C
12:30 – 1:45 p.m.
Room S404

Preventive Cardiology Potpourri
1:30 – 4:30 p.m.
Poster Area, South Hall A1

Search the **ACC.16 App** for additional Prevention Learning Pathway Sessions.

INDICATIONS The Medtronic CoreValve and CoreValve Evolut R systems are indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (ie, Society of Thoracic Surgeons predicted risk of operative mortality score ≥8% or at a ≥15% risk of mortality at 30 days).

CONTRAINDICATIONS The CoreValve and CoreValve Evolut R systems are contraindicated for patients presenting with any of the following conditions: known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated; ongoing sepsis, including active endocarditis; preexisting mechanical heart valve in aortic position.

WARNINGS *General* Implantation of the CoreValve and CoreValve Evolut R systems should be performed only by physicians who have received Medtronic CoreValve training. This procedure should only be performed where emergency aortic valve surgery can be performed promptly. Mechanical failure of the delivery catheter system and/or accessories may result in patient complications. Transcatheter Aortic Valve (Bioprosthesis) Accelerated deterioration of the bioprosthesis may occur in patients presenting with an altered calcium metabolism.

PRECAUTIONS *General* The safety and effectiveness of the CoreValve and CoreValve Evolut R systems have not been evaluated in the pediatric population. The safety and effectiveness of the bioprosthesis for aortic valve replacement have not been evaluated in the following patient populations: patients who do not meet the criteria for symptomatic sever native aortic stenosis as defined: (1) symptomatic severe high gradient aortic stenosis – aortic valve area ≤1.0cm^2 or aortic valve area index ≤0.6 cm^2/m^2, a mean aortic valve gradient ≥40 mmHg; or a peak aortic-jet velocity ≥4.0 m/s, (2) symptomatic severe low-flow/low-gradient aortic stenosis – aortic valve area ≤1.0cm^2 or aortic valve area index ≤0.6 cm^2/m^2, a mean aortic valve gradient <40 mmHg; and a peak aortic-jet velocity <4.0 m/s ; who are at moderate or low surgical risk (predicted perioperative mortality risk of <15%); with untreated, clinically significant coronary artery disease requiring revascularization; with a preexisting prosthetic heart valve with a rigid support structure in either the mitral or pulmonic position if either the preexisting prosthetic heart valve could affect the implantation or function of the bioprosthesis or the implantation of the bioprosthesis could affect the function of the preexisting prosthetic heart valve; with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support. The safety and effectiveness of a CoreValve or CoreValve Evolut R bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis has not been demonstrated. Implanting a CoreValve or CoreValve Evolut R bioprosthesis in a degenerated surgical bioprosthesis [transcatheter aortic valve in surgical aortic valve (TAV in SAV)] should be avoided in the following conditions. The degenerated surgical bioprosthesis presents with a: significant concomitant perivalvular leak (between the prosthesis and the native annulus), is not securely fixed in the native annulus, or is not structurally intact (eg, wireform frame fracture); partially detached leaflet that in the aortic position may obstruct a coronary ostium; stent frame with a manufacturer's labeled inner diameter <17 mm. The safety and effectiveness of the bioprosthesis for aortic valve replacement have not been evaluated in patient populations presenting with the following: blood dyscrasias as defined: leukopenia (WBC <1000 cells/mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states; congenital bicuspid or unicuspid valve; mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation [3-4+]); moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation; hypertrophic obstructive cardiomyopathy; new or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation; native aortic annulus size <18 mm or >29 mm for CoreValve and <18 mm or >26 mm for CoreValve Evolut R per the baseline diagnostic imaging or surgical bioprosthetic aortic annulus size <17 mm or >29 mm for CoreValve and <17 mm or >26 mm for CoreValve Evolut R; transarterial access not able to accommodate an 18-Fr sheath or the 14-Fr equivalent EnVeo R InLine sheath; sinus of valsalva anatomy that would prevent adequate coronary perfusion; moderate to severe mitral stenosis; severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20%;; symptomatic carotid or vertebral artery disease; severe basal septal hypertrophy with an outflow gradient.

Prior to Use Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors. Damage may result from forceful handling of the catheter. Prevent kinking of the catheter when removing it from the packaging. This device was designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death. The bioprosthesis size must be appropriate to fit the patient's anatomy. Proper sizing of the device is the responsibility of the physician. Refer to Instructions for Use for available sizes. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed below. Patients must present with access vessel diameters of ≥6 mm for the CoreValve system and ≥5 mm for the CoreValve Evolut R system or an ascending aortic (direct aortic) access site ≥60 mm from the basal plane for both systems. Implantation of the bioprosthesis should be avoided in patients with aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) of >30° for right subclavian/axillary access or >70° for femoral and left subclavian/axillary access. Use caution when using the subclavian/axillary approach in patients with a patent LIMA graft or patent RIMA graft. For direct aortic access, ensure the access site and trajectory are free of patent RIMA or a preexisting patent RIMA graft.

During Use For direct aortic and subclavian access procedures, care must be exercised when using the tip-retrieval mechanism to ensure adequate clearance to avoid advancement of the catheter tip through the bioprosthesis leaflets during device closure. For direct aortic access procedures, use a separate introducer sheath; do not use the EnVeo R InLine sheath. Adequate rinsing of the bioprosthesis with sterile saline, as described in the Instructions for Use, is mandatory before implantation. During rinsing, do not touch the leaflets or squeeze the bioprosthesis. If a capsule becomes damaged during loading or the capsule fails to close, replace the entire system (bioprosthesis, catheter, and CLS). Do not use a catheter with a damaged capsule. After a bioprosthesis has been inserted into a patient, do not attempt to reload that bioprosthesis on the same or any other catheter. AccuTrak DCS Only: During implantation, if resistance to deployment is encountered (e.g., the micro knob starts clicking or is tight or stuck), apply upward pressure to the macro slider while turning the micro knob. If the bioprosthesis still does not deploy, remove it from the patient and use another system. AccuTrak DCS Only: Once deployment is initiated, retrieval of the bioprosthesis from the patient (e.g., use of the catheter) is not recommended. Retrieval of a partially deployed valve using the catheter may cause mechanical failure of the delivery catheter system, aortic root damage, coronary artery damage, myocardial damage, vascular complications, prosthetic valve dysfunction (including device malposition), embolization, stroke, and/or emergent surgery. AccuTrak DCS Only: During deployment, the bioprosthesis can be advanced or withdrawn as long as annular contact has not been made. Once annular contact is made, the bioprosthesis cannot be advanced in the retrograde direction; if necessary, and the frame has only been deployed ≤2/3 of its length, the bioprosthesis can be withdrawn (repositioned) in the antegrade direction. However, use caution when moving the bioprosthesis in the antegrade direction. EnVeo R DCS Only: If a misload is detected, unsheath the bioprosthesis and examine the bioprosthesis for damage (for example, permanent frame deformation, frayed sutures, or valve damage). Do not attempt to reload a damaged bioprosthesis. Do not load the bioprosthesis onto the catheter more than 2 times or after it has been inserted into a patient. EnVeo R DCS Only: Use the deployment knob to deploy and recapture the bioprosthesis. Do not use the trigger for deploying or recapturing because it could cause inaccurate placement of the bioprosthesis. EnVeo R DCS Only: Once the radiopaque capsule marker band reaches the distal end of the radiopaque paddle attachment (point of no recapture), retrieval of the bioprosthesis from the patient is not recommended. Retrieval after the point of no recapture may cause mechanical failure of the delivery catheter system, aortic root damage, coronary artery damage, myocardial damage, vascular complications, prosthetic valve dysfunction (including device malposition), embolization, stroke, and/or emergent surgery. EnVeo R DCS Only: During deployment, the bioprosthesis can be advanced or withdrawn as long as annular contact has not been made. Once annular contact is made, the bioprosthesis cannot be advanced in the retrograde direction; recapture until the bioprosthesis is free from annular contact, and then reposition in the retrograde direction. If necessary, and the radiopaque capsule marker band has not yet reached the distal end of the radiopaque paddle attachment, the bioprosthesis can be withdrawn (repositioned) in the antegrade direction. However, use caution when moving the bioprosthesis in the antegrade direction. While the catheter is in the patient, ensure the guidewire is extending from the tip. Do not remove the guidewire from the catheter while the catheter is inserted in the patient. Use the handle of the delivery system to reposition the bioprosthesis. Do not use the outer catheter sheath. Once deployment is complete, repositioning of the bioprosthesis (e.g., use of a snare and/or forceps) is not recommended. Repositioning of a deployed valve may cause aortic root damage, coronary artery damage, myocardial damage, vascular complications, prosthetic valve dysfunction (including device malposition), embolization, stroke, and/or emergent surgery. Do not attempt to retrieve or to recapture (EnVeo DCS only) a bioprosthesis if any one of the outflow struts is protruding from the capsule. If any one of the outflow struts has deployed from the capsule, the bioprosthesis must be released from the catheter before the catheter can be withdrawn. Ensure the capsule is closed before catheter removal. When using a separate introducer sheath, if increased resistance is encountered when removing the catheter through the introducer sheath, do not force passage. Increased resistance may indicate a problem and forced passage may result in damage to the device and/or harm to the patient. If the cause of resistance cannot be determined or corrected, remove the catheter and introducer sheath as a single unit over the guidewire, and inspect the catheter and confirm that it is complete. Clinical long-term durability has not been established for the bioprosthesis. Evaluate bioprosthesis performance as needed during patient follow-up. Postprocedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. Postprocedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment. Excessive contrast media may cause renal failure. Preprocedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage. Conduct the procedure under fluoroscopy. The safety and efficacy of a CoreValve or CoreValve Evolut R bioprosthesis implanted within the initial transcatheter bioprosthesis have not been demonstrated. However, in the event that a CoreValve or CoreValve Evolut R bioprosthesis must be implanted within the initial transcatheter bioprosthesis to improve valve function, valve size and patient anatomy must be considered before implantation of the bioprosthesis to ensure patient safety (for example, to avoid coronary obstruction). In the event that valve function or sealing is impaired due to excessive calcification or incomplete expansion, a postimplant balloon dilatation of the bioprosthesis may improve valve function and sealing. To ensure patient safety, valve size and patient anatomy must be considered when selecting the size of the balloon used for dilatation. The balloon size chosen for dilatation should not exceed the diameter of the native aortic annulus or, for surgical bioprosthetic valves, the manufacturer's labeled inner diameter. Refer to the specific balloon catheter manufacturer's labeling for proper instruction on the use of balloon catheter devices. Note: Bench testing has only been conducted to confirm compatibility with NuMED Z-MED IITM Balloon Aortic Valvuloplasty catheters where CoreValve or CoreValve Evolut R bioprosthesis device performance was maintained after dilation. Data on File.

POTENTIAL ADVERSE EVENTS Potential risks associated with the implantation of the CoreValve or CoreValve Evolut R transcatheter aortic valve may include, but are not limited to, the following: • death • myocardial infarction, cardiac arrest, cardiogenic shock, cardiac tamponade • coronary occlusion, obstruction, or vessel spasm (including acute coronary closure) • cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may require intervention) • emergent surgical or transcatheter intervention (for example, coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty) • prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement • prosthetic valve migration/embolization • prosthetic valve endocarditis • prosthetic valve thrombosis • delivery catheter system malfunction resulting in the need for additional re-crossing of the aortic valve and prolonged procedural time • delivery catheter system component migration/embolization • stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits • heart failure • cardiac failure or low cardiac output • ancillary device embolization • individual organ (for example, cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure • major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding) • vascular access-related complications (eg, dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis) • mitral valve regurgitation or injury • conduction system disturbances (for example, atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker • infection (including septicemia) • hypotension or hypertension • hemolysis • peripheral ischemia • bowel ischemia • abnormal lab values (including electrolyte imbalance) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to radiation through fluoroscopy and angiography • permanent disability.

Please reference the CoreValve and CoreValve Evolut R Instructions for Use for more information regarding indications, warnings, precautions and potential adverse events.

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

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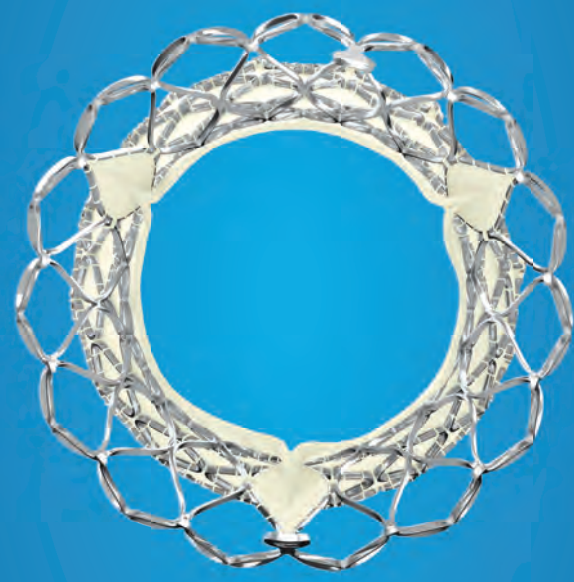

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