1st Annual
Future Leaders in Heart Failure
Turnberry Isle Miami
www.hfsa.org
The Heart Failure Society of America (HFSA) is committed to dedicating time and resources to support cardiology fellows, nurses, and pharmacists who are early in their respective careers and are committed to a career in heart failure.

This intensive two-day symposium is specifically designed to both educate and facilitate the various pathways these future leaders will encounter as they embark on a career in heart failure.

HFSA wishes to express its gratitude to the following companies who, through their generosity, have helped to make this symposium possible:

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Medstar Heart and Vascular Institute

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Baylor College of Medicine

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Clinical Nurse Specialist, Palliative Care Medicine
University of Vermont Medical Center

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Patricia Uber, PharmD
Clinical Pharmacy Specialist, Advanced Heart Failure and Transplant VCU Health System

Payman Zamani, MD, FHFSA
Assistant Professor of Medicine
Hospital of the University of Pennsylvania
Agenda

Friday, May 5th

3:00 PM – 5:30 PM | GRAND BALLROOM FOYER
Registration Opens

5:30 PM – 5:40 PM | BALLROOM III
Welcome / Opening Remarks
  Welcome
  Program Overview
  Acknowledgements

Moderators:
Jonathan Rich, MD, FHFSA – Chair, Program Planning Committee
Mandeep Mehra, MD, FHFSA – HFSA President

5:40 PM – 6:00 PM | BALLROOM III
Getting to the Heart of the Matter:
A Conversation with a Patient

Moderator:
Jonathan Rich, MD, FHFSA

Patient Representative:
Cynthia Chauhan – AdHoc Patient Representative – HFSA Board of Directors

History of HFSA Video

6:00 PM – 7:00 PM | BALLROOM III
Career Pathways Panel Discussion:
How did you get here? Revealing the inner truths about heart failure faculty and their careers

Moderator:
Jonathan Rich, MD, FHFSA
Payman Zamani, MD, FHFSA

Faculty:
Cindy Bither, ACNP, ANP
Jim Fang, MD, FHFSA
Barry Greenberg, MD, FHFSA
Mariell Jessup, MD
Douglas Mann, MD, FHFSA
Herb Patterson, PharmD, FHFSA

7:00 PM – 7:15 PM | BALLROOM III
Let’s Have Some Fun This Weekend
Tell us one thing about you that nobody will know (don’t hold back!).

Moderator:
Leo Buckley, PharmD

7:15 PM | MAGNOLIA COURTYARD
Dinner Reception
Agenda
Saturday, May 6th

7:00 AM – 8:00 AM | MAGNOLIA COURTYARD
Breakfast & Networking

8:00 AM – 9:30 AM | BALLROOM III
Pursuing Our Evidence Group: Defining the Problems and Unmet Needs

Moderators:
Biykem Bozkurt, MD, PhD, FHFSAn, FACC, FAHA
Paul Mather, MD, FHFSAn
Robert Page III, PharmD, FHFSAn

A. Acute Heart Failure
   i. Therapeutics – Why are we failing?
   ii. Is remote monitoring the answer to reducing admissions?

   Faculty:
   Lynne Stevenson, MD

B. HFpEF – Why is it so challenging?
   i. Phenotyping
   ii. Therapeutics

   Faculty:
   Ken Margulies, MD, FHFSAn

C. HFrEF – From Pills to Pumps
   i. Sacubitril/valsartan, is it the new big thing or just the next step?
   ii. Heartmate 3/HVAD; what will “LVAD 4.0” look like? What does it “need” to look like?

   Faculty:
   Mandeep Mehra, MD, FHFSAn

D. Prevention of Heart Failure:
   i. Can it be accomplished?
   ii. Changing behaviors- is it possible?

   Faculty:
   Christopher Lee, RN, PhD, FHFSAn, FAHA, FAAN

9:30 AM – 10:00 AM
30-Minute Break

10:00 AM – 11:45 AM | BALLROOM III
Guidelines/Research/Quality Improvement and Implementation: How Do We Solve the Problems?

Moderators:
Jim Fang, MD, FHFSAn
Patricia Uber, PharmD
Payman Zamani, MD, FHFSAn

A. Guideline – Worth all the trouble?
   i. Where is all of the evidence when you need it?
   ii. When to “get” with the guidelines and when to “ignore” the guidelines

   Faculty:
   Biykem Bozkurt, MD, PhD, FHFSAn, FACC, FAHA

B. Research – Where is the future of HF research?
   i. Basic discovery: small molecules? Small devices?

   Faculty:
   Doug Mann, MD, FHFSAn

   ii. Are observational data useful? How do registries help?

   Faculty:
   Barry Greenberg, MD, FHFSAn

   iii. Future of HF clinical trials and/or use of Big Data

   Faculty:
   Larry Allen, MD, MHS, FHFSAn

(continued on next page)
C. Implementation of the last dance: How to establish (and implement) an effective palliative care team

Faculty:
Ann Laramee, MS, ANP-BC, ACNS-BC, CHFN, ACHPN, FHFSA

11:45 AM – 12:45 PM  |  VERANDA EAST & WEST
Lunch & Networking

12:45 PM – 1:30 PM  |  BALLROOM III
The Economics of Heart Failure

A. What is Happening to Healthcare Reform?
   i. Affordable Care Act vs. American Health Care Act?
   ii. HF is increasing, the budget is decreasing: Doesn’t something have to give?

Faculty:
Marvin Konstam, MD, FHFSA

B. Cracking the nut on readmissions
   i. Is it a real illness or a milestone?
   ii. Reducing mortality, reducing readmissions: Are these competing outcomes?

Faculty:
Larry Allen, MD, MHS, FHFSA

2:30 PM – 3:00 PM
30-Minute Break

3:00 PM – 3:45 PM  |  BALLROOM III
The New UNOS Transplant Status Criteria

A. Part I
   i. The what and why of the new criteria
   ii. Key implications (pros vs cons) and future controversies

Faculty:
Jim Fang, MD, FHFSA

B. Part II
   i. Impact on durable MCS
   ii. But how do we solve the problem of wasted organs?

Faculty:
Lynne Stevenson, MD

1:30 PM – 2:30 PM  |  BALLROOM III
The Perils and Future of Heart Failure

Moderators:
Mariel Jessup, MD
Marvin Konstam, MD, FHFSA

Panel Discussion:
Karol Harshaw-Ellis, DNP, FHFSA
John Chin, MD, FHFSA
Mandeep Mehra, MD, FHFSA
Lynne Stevenson, MD
Herb Patterson, PharmD, FHFSA

A. Earning potential: Value based vs Fee for service: Implications for the HF provider
   i. Understanding the RVU; What is the value of HF certification/AAHFN certification

B. Navigating cost containment vs new expensive drugs/devices
   i. Role of PharmDs in the hospital?

C. Role of lobbying and Policy/Advocacy opportunities
   i. New HF subspecialty designation and recognition
Afternoon Breakout Sessions

A. Salons V/VI - Physicians
   (Roundtables Rotate every 15 minutes)

   i. Managing the stress of a heart failure career
      1. Work-life balance

      Faculty:
      Paul Mather, MD, FHFSA – Lead Discussant
      Larry Allen, MD, MHS, FHFSA
      Jonathan Rich, MD, FHSA
      Lynne Stevenson, MD

   ii. Playing well with industry
      1. Pros/cons
      2. Careers in industry?

      Faculty:
      Marvin Konstam, MD, FHFSA – Lead Discussant
      Barry Greenberg, MD, FHFSA

   iii. Finding/succeeding in a clinical job
      1. Academic and/or private/hybrid

      Faculty:
      John Chin, MD, FHFSIA – Lead Discussant
      Biykem Bozkurt, MD, PhD, FHFSIA, FACC, FAHA
      Mariell Jessup, MD

   iv. Finding/succeeding in an academic job
      1. Funding
      2. Mentor-Mentee relationships

      Faculty:
      Jim Fang, MD, FHFSIA – Lead Discussant
      Doug Mann, MD, FHFSIA
      Ken Margulies, MD, FHFSIA
      Payman Zamani, MD, FHFSIA

B. Salon II - Nurses
   (Group Discussion – 15 minutes per topic)

   Considering the below roles:
   i. Community Hospital Clinician

   Faculty:
   Ann Laramee, MS, ANP-BC, ACNS-BC, CHFN, ACHPN, FHFSA

   ii. Academic Medical Center Clinician

   Faculty:
   Karol Harshaw-Ellis, DNP, FHFSA

   iii. Nurse Scientist

   Faculty:
   Christopher Lee, RN, PhD, FHFSIA, FAHA, FAAN

   iv. Nurse Executive

   Faculty:
   Cindy Bither, ACNP, ANP

C. Salon III - PharmDs
   (Group Discussion – 15 minutes per topic)

   i. Career Opportunities in Heart Failure:
      What does it take to be a successful HF pharmacist?

      1. Patient care

      Faculty:
      Patricia Uber, PharmD

      2. Research

      Faculty:
      Herb Patterson, PharmD, FHFSIA

(continued on next page)
Agenda
Saturday, May 6th (continued)

3. Service

Faculty: Robert Page, PharmD, FHFSA

ii. Cultivating mentor-mentee relationships

Faculty: Leo Buckley, PharmD

4:45 PM – 5:00 PM
Recap / Announcements

5:00 PM – 7:00 PM
Personal Networking / Free Time

7:00 PM | VERANDA EAST & WEST
Reception & Dinner

A. Cocktails
B. Announcement of “Top 10 List”

Faculty: Leo Buckley, PharmD

C. Keynote Speaker
   “Implementation Science: How do we actually do this?”

Faculty: Mandeep Mehra, MD, FHFSA

D. Dessert / Nightcap
Agenda
Sunday, May 7th

8:00 AM – 9:00 AM | Veranda East & West
Breakfast & Networking

9:00 AM – 9:30 AM
Faculty Words of Wisdom

A. What HFSA means to me and what it should mean to you
B. Sage parting advice in a “one-liner”

9:30 AM | BALLROOM III
Concluding Remarks

Moderators:
Jonathan Rich, MD, FHFSA
Mandeep Mehra, MD, FHFSA
Michele Blair – HFSA CEO
Turnberry Isle Miami Floorplans
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 m²).

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 (5.3)].

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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

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

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

8.7 Renal Impairment
No dose adjustment is required in patients with mild to moderate renal impairment (eGFR 60 to 90 mL/min/1.73 m²). However, ENTRESTO should be used with caution in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) due to the potential for serious adverse reactions which may result in worsening of renal function, including possible acute renal failure. If necessary, reduce the dose or discontinue ENTRESTO based on the severity of renal impairment [see Dosage and Administration (2.3) in the full prescribing information, Warnings and Precautions (5.4) and Clinical Pharmacology (12.3) in the full prescribing information].

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

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

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

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ENTRESTO is a trademark of Novartis AG
Issued: July/2015
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 therapy to 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, 16% 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, hypoadosteronism, 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%), hyperkalemia (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 430 (10.7%) of ENTRESTO treated patients and 516 (12.2%) of patients receiving enalapril.

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

<table>
<thead>
<tr>
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<th>ENTRESTO (n = 4,203)</th>
<th>Enalapril (n = 4,229)</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
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<tr>
<td>Hypotension</td>
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<tr>
<td>Hyperkalemia</td>
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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 of PARADIGM-HF, 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)].

Orithostasis 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 1.3% of patients treated with ENTRESTO compared to 1.3% of patients treated with enalapril.
ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

INDICATION

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

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

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

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

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

ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 ml/min/1.73 m²) 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.

References:
4. ENTRESTO (prescribing Information). East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015.

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These effects are usually reversible. Monitor renal function periodically.

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

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

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

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

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

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

STUDY DESIGN: PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO to enalapril in symptomatic (NYHA class II–IV) adult HFpEF 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 for 27 months, and patients were treated for up to 4.3 years. At the primary end point, the first event in the composite of CV death or first HF hospitalization, ENTRESTO was superior to enalapril, P < 0.0001. ACC = American College of Cardiology, AHA = American Heart Association, HF = heart failure, NYHA = New York Heart Association, HFpEF = heart failure with reduced ejection fraction, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.

ENTRESTO® reduced the risk of CV death or HF hospitalization as first event vs enalapril.

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: FETAL TOXICITY

• When pregnancy is detected, discontinue ENTRESTO as soon as possible

• Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

ENTRESTO is contraindicated in patients with hypertension 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.

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

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FOR MORE INFORMATION, VISIT EntrestoHCP.com

ENTRESTO® reduced the risk of CV death or HF hospitalization as first event vs enalapril.

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

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

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