A TEAM APPROACH TO TREATING STROKES

The stroke response team at Mayo Clinic in Jacksonville, FL, is skilled in rapid diagnosis and treatment of stroke, brain hemorrhage and other cerebrovascular and brain disorders.

So whether your patients need a proactive screening, a second opinion or emergency surgery, Mayo Clinic is your partner in delivering the best possible care when it's needed most. For immediate referrals, call us at 800-634-1417.

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- Complete diagnostic radiology services
- Dedicated Neuro ICU
- NIH-funded clinical trials
- Telestroke network
- Post-stroke care, case management and rehabilitation services

Certified as a Comprehensive Stroke Center by the Joint Commission and by the State of Florida.
“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

ENTRESTO® (sacubitril/valsartan) tablets 24/128 mg - 68/512 mg - 97/105 mg

ENTRESTO® reduced the risk of CV death or HF hospitalization as first event vs enalapril³

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

HYPTENSION: ENTRESTO lowers blood pressure and may cause symptomatic hypotension. Patients with an advanced renal-angiotensin system, such as volume- 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/or treatment of other causes of hypotension (e.g., hypovolemia) reduce the dose 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 (GFR < 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.

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, hypoadrenalism, 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 hypertension (15%, 22%), hyperkalemia (12%, 14%), cough (9%, 13%) dizziness (8%, 5%) and renal failure/pre-eclampsia (5%, 1%).

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

STUDY DESIGN: PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO to enalapril in symptomatic (NYHA class II-IV) adult HF/EF patients (left ventricular ejection fraction <40%). After discontinuing their existing ACE 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 (49/65 mg) twice daily, increasing to 200 mg (97/103 mg) twice daily. Patients were then randomized to receive either ENTRESTO 210 mg (97/103 mg) (n=2097) twice daily or enalapril 10 mg (n=2233) twice daily. The median follow-up duration was 27 months, and patients were treated for up to 4.3 years. At the primary end point, the first event in the composite of CV death or first HF hospitalization, ENTRESTO was superior to enalapril, P=0.0011. ACC—American College of Cardiology; AHA—American Heart Association; HFA—Heart Failure Association of Europe; B-6—Class of Recommendation; B6—randomized trial; CV—cardiovascular; HF—heart failure; NYHA—New York Heart Association; HREF—heart failure with reduced ejection fraction; ACEI—angiotensin-converting enzyme inhibitor; ARB—angiotensin II receptor blocker.

For more information, visit EntrestoHCP.com

References:
4. ENTRESTO (prescribing information). East Hanover, N.J.: Novartis Pharmaceuticals Corp; August 2015.

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ENTRESTO™ (saquinavir and ralsuranil) 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 (6.2))
- 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 alikiren 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, 19% 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 constrictive 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 downward 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 area 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, hypoadrenergism, 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, 5.5% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.2%) 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 adverse event during the double-blind period occurred in 456 (16.7%) 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>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>13</td>
<td>12</td>
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<tr>
<td>Hyperkalemia</td>
<td>12</td>
<td>14</td>
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<tr>
<td>Cough</td>
<td>9</td>
<td>13</td>
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<tr>
<td>Dizziness</td>
<td>6</td>
<td>5</td>
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<td>Renal failure/acute renal failure</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, the incidence of angioedema was higher in patients treated with ENTRESTO than enalapril (0.3% 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)).

Orthostatic 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 alikiren is contraindicated in patients with diabetes [see Contraindications (4)]. Avoid use with alikiren 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 (5.5)].

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 concurrent 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 hypotenion, 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 transfusion 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 15 [valsartan]-fold the maximum recommended human dose [MRHD] of 57/103 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 breast-feeding 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 (eGFR 60 to 90 mL/min/1.73 m²) to moderate (eGFR 30 to 60 mL/min/1.73 m²) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) is 24/26 mg twice daily [see Dosage and Administration (2.3) in the full prescribing information, Warnings and Precautions (5.4) and Clinical Pharmacology (12.3) in the full prescribing information].

10 OVERDOSE

Limited data are available with regard to overdose in human subjects with ENTRESTO. In healthy volunteers, a single dose of ENTRESTO 583 mg sacubitril/517 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

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

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

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Issued: July/2015
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Prevention of Medical Errors and Patient Safety
By Linda Edwards, MD, Francys Calle Martin, Esq., LHRM, and Kari Aasheim, JD

Following a number of studies on the high incidence of medical errors and increasing efforts to improve patient safety, the prevention and reduction of medical errors has become a priority for federal and state regulatory agencies and healthcare providers across the nation. It is important for physicians to understand how federal, state, and independent regulatory agencies have shaped the patient safety movement and have provided an organized structure for identifying the causes of medical errors and the manner in which they can best be prevented. Based on national reports of patient safety events and malpractice data, federal, state, and independent regulatory agencies have established patient safety goals for the prevention of medical errors.

Features

Heart Failure, A Historic Perspective
By Dmitry Yaranov, MD, Khadeeja Esmail, MD, and Alan Miller, MD

Challenges of Development and Management of an Outpatient Heart Failure Disease Management Program
By Stacey Manning, DNP, ACNP, Erica Fetner, MSN, FNP, Mary Leen, DNP, ACNP, and Simone Nader, MD, FACC

Left Ventricular Assist Device Therapy for Advanced Heart Failure
By Parag Patel, MD, Mariella Velez-Martinez, MD, Kevin Landolfo, MD, and Daniel Yip, MD

New Pharmacologic Therapies for Heart Failure
By Oludamilola Olueye, MD, MBBS, Yahaira Ortiz Gonzalez, MD, and Mohamad H. Yamani, MD

Implantable PA Pressure Monitoring for Heart Failure Management: A Single Center Experience
By Sumant Lamba, MD, FACC

Also in this Issue

Three, Two, One: A Look at Crohn’s Disease Diagnosis
By Mark R. Fleisher, MD
The role of a physician in day to day practice continues to change rapidly. When I got into practice, I hoped that I would be spending the majority of my time caring for patients, talking to families, and always expanding my knowledge with time to read journals and attend CME conferences. Though these things do happen, I have found myself mired in the world of EMRs, physician scut work and feeling like a glorified scribe.

For all the great promises and hype of the electronic medical record, all physicians can agree that those lofty goals have fallen way short. We spend the majority of the day, in the office and in the hospital, typing, scrolling, and cursing the EMR. We click on boxes and think less. We hunt through the hospital EMR trying to find the elusive and accurate I/O’s, walking pulse oximetry tests, microbiology and pathology reports. The deluge of order sets that order more tests than needed seem to be the only way to admit or discharge a patient. The dangerous and often wrong admission and discharge medication reconciliation, in my opinion, has caused more confusion and even harm. Templated and cookie cutter physical exams litter the long forgotten SOAP note. Office and hospital notes are a vast landscape of cut and pasted labs, medications, nursing notes, and meaningless data rather than a clear, concise, and meaningful thought process of a physician. When trying to create the diagnosis list, ICD 10 now had 10-20 codes for what was a simple diagnosis. With our heads buried in the EMR, the most valuable interaction between patients and physicians, observation and conversation, has become a lost art. Unfortunately, physicians were not as engaged and involved in the EMR process since inception so what could have been better, is now just thrust/shoved down our throats.

In the last few years, I have noticed my clinical judgement and decision making called in to question. I am not challenged by fellow physicians for better patient care, but rather by insurance companies and the benefit managers who doubt my clinical acumen. When I think it is best for a nuclear stress test (a patient who cannot walk on a treadmill), I am met with denial and delay. When I think a patient can benefit from the newest heart failure medication, I am told to try a generic and that reduced mortality and hospitalization are not good enough reasons for my patient. I am told to call yet another 1-800 number, press 3-4 different cues, and enter 24 digit codes to only talk to a nurse who has the gall to tell me I need to order a stress test first instead of a left heart catheterization on a patient who has classical exertional angina. Our decision making is being overridden in the name of protocols and profit. In an odd sense of irony, I am told at times that my EMR documentation is not sufficient enough to support the initiation of a drug or the ordering of a procedure. In our state, the Florida Medical Association, along with the Duval County Medical Society, is working hard to pass legislation to end fail first protocols and cut prior authorization red tape.

Finally, every day is spent picking a code and a charge that match up and make some sense. The change to ICD 10 has added precious minutes to each patient visit every day. As a cardiologist, I find it important to document that a patient has type 2 diabetes. It used to be simple, but now I have to know if the diabetes has a complication, with or without the use of insulin, or if the patient’s cat also has the disease. I used to be a cardiologist dealing with coronary disease. In 2017, I am a cardiologist dealing with coronary disease, in the native vessel, with or without angina, that could be the initial or subsequent visit, or in a transplanted heart. It would seem logical that a patient with chest pain and two or more cardiovascular risk factors would be a reasonable candidate for a stress test. No, not any more. According to Medicare, having chest pain with cardiac risk factors is not a valid reason to get a stress test. I have to officially give someone angina pectoris to walk them on a treadmill. Going from 14,000 codes in ICD 9 to 69,000 codes in ICD 10 will make me a better physician and somehow make sure I am giving better care to my patients.

Now with MIPS, MACRA, 30 day readmissions, bundled payments, patient satisfaction scores, and “quality metrics” cluttering my day, I don’t know what I would do with the 15 minutes I spend with my patients.

Ruple Galani, MD
Editor-in-Chief
Northeast Florida Medicine

Ongoing Physician Scut Work
Physician Health and Wellness: Reclaim your Passion for Medicine

I love being a doctor! I am often asked, “when did you decide to become a doctor?” My mom would tell you that I was committed to it since preschool. But I can specifically recall when it became the path I was determined to take. I remember it so well because it was a tragic day. I was in elementary school. Those innocent years when all you should have to worry about is if the ice cream man will come today or if you will have enough people to play freeze tag with. It appeared to be a routine day at HollyBrook Homes apartments, the housing projects where I was living. The adults watched from their porches or steps as the children ran freely playing. The sound of laughter and glee quickly changed to screams of disbelief and distress. In an instant one of the dilapidated walls that separated one building from the other had fallen over and a little boy was being crushed underneath it. Neighbors worked furiously to remove the concrete rubble. The paramedics arrived and the boy was rushed to the neighborhood hospital. Everyone stood around in shock at what had just occurred. They spoke with a hopefulness that the quick recapturing and maintaining the initial joy we embraced when we decided that medicine was our calling. The Duval County Medical Society and Duval County Medical Society Foundation have designed a program that provides a confidential and voluntary resource to help you maneuver through those emotionally challenging days. Through a 24-7 confidential hotline and direct online access, free counseling and coaching services are available to all the DCMS members. These resources are available by calling our hotline at (904) 631-1446 or visiting us online at dcmsonline.org/physician_wellness.

We also encourage all entities that employ physicians to develop programs that can provide more long-term support. Furthermore, the DCMS understands that mental health issues are a global problem and that before we can properly treat it, we must be able to correctly identify those who are suffering. This has led to our partnership with the Mental Health First Aid Collaboration in Jacksonville. The goal is to train citizens to recognize mental health crises and provide appropriate responses. You can register at jaxmentalhealth.org. We hope that this collaboration is exactly what it takes to improve the overall health of physicians and the community as a whole.

Visiting us online at dcmsonline.org/physician_wellness.
“Helping Physicians Care for the Health of Our Community”

When an epidemic of yellow fever threatened young Jacksonville back in 1853, local doctors came together to form a strategic alliance; together, they would combat this public health epidemic. Since that fateful day 164 years ago, the Duval County Medical Society has been “helping physicians care for the health of our community.”

It’s more than our mission statement; it’s a statement of purpose. Jacksonville has one of the highest quality networks of medical care in the country. In the often high-stakes competitive world of medicine, Jacksonville’s institutions stand out again and again for excellence. That excellence is due in large part to one of the most qualified communities of physicians anywhere, all dedicated to improving the health of the community.

Today, it is time for the society to truly come to the aid of physicians. Across the country, we are seeing an epidemic of burnout in the physician community. According to the Medscape Physician Lifestyle Report of 2017, 51% of physicians report suffering from burnout. That’s up 25% from 2013. Burnout is listed as the number one reason a physician will stop practicing medicine before retirement age.

The reasons for physician burnout are myriad. Long work hours, increased bureaucratic paperwork, proliferation of EHRs, low reimbursement rates and lack of overall sense of purpose top the lists of reasons given for burnout. There is no lack of resources available for physicians to handle these stressors, but utilization rates remain low.

As a physician, you understand that you work in a highly-regulated environment. It is reasonable that questions regarding treatment for mental health are a part of the Medical Licensure process. However, the questions often lack the nuance to appropriately assess the severity, or lack thereof, of the problem. For that reason, there can be a reluctance to seek treatment which creates a medical record.

Most hospitals and large facilities have an Employee Assistance Program available to those who need help. Utilization data shows that, for whatever reason, physician utilization of these internal programs is very low.

Unfortunately, we are aware that there is a problem in the physician community of self-medication. The PRN, Professional’s Resource Network, is a fantastic resource for physicians who have drug or alcohol addiction problems. This is a proven and effective way to help restore physicians to their primary mission of helping their patients.

There is a step missing in this process. After the stress or burnout gets to be a real problem, and before self-medication, early retirement, or worse, there may be an opportunity to help physicians who need some help from a professional mental health counselor, but don’t know or don’t trust where to go.

That is why the Duval County Medical Society Foundation has created the Physician Wellness Program. This is a free and confidential resource for any DCMS member. If you are in need of help, you can have up to six free sessions with a Certified Counselor. These sessions are pre-clinical and will not create a medical record. They are confidential, and the cost is completely covered by the DCMS Foundation.

We believe that the Physician Wellness Program is the next step in fulfilling our mission to help physicians care for the health of our community. By helping physicians in their time of need, we will ensure that our city continues to have the best and brightest physicians, performing at their very best in their mission to help their patients each and every day.

To learn more visit dcmsonline.org/physician_wellness.
Residents’ Corner: University of Florida Jacksonville Orthopaedic Residency

A Legacy Continues: University of Florida Jacksonville Orthopaedic Residency Program

About Our Program

The University of Florida Jacksonville Orthopaedic Residency Program carries a rich history of camaraderie and resilience steeped in a tradition of humanitarianism. The division of orthopaedics was first established in 1962 at Duval Medical Center under the leadership of Dr. Hugh Haston. The Jacksonville Health Education Program (JHEP), a cooperative teaching initiative among the local hospitals at that time, officially began the orthopaedic residency on July 1st of that same year with Dr. George Fipp, a proud Notre Dame graduate, as the first trainee. During that year of training Dr. Fipp participated in the first total hip operation to ever be performed in Jacksonville.

Since that time, the residency program has proliferated to include several area campuses with official University of Florida affiliation taking place in 1984. Starting in 2003, under the leadership of former Chair and Program Director Dr. B. Hudson Berrey, the number of residents per class expanded to four. The most recent addition to the leadership staff is Chairman Dr. Paul Dougherty, who plans to continue strengthening the existing foundation and expand upon the plethora of research opportunities.

The residency mission statement is to provide the foundation for a lifetime of learning and practice of orthopaedic surgery, and to produce graduates who exemplify the highest ideals of our profession. It is our purpose to excel in research, education and clinical service, while maintaining the highest ethical standards and providing compassionate healthcare services.

To accomplish these goals the orthopaedic program has partnered with multiple local institutions to ensure a quality, comprehensive education.

Residents receive their primary orthopaedic trauma training at UF Health Jacksonville, a 695-bed hospital and the only level-I trauma center serving northeast Florida and southeast Georgia. Trainees have also benefited from partnerships with the Mayo Clinic Jacksonville and Nemours Children’s Health System which provide exceptional models of specialized patient care in orthopaedic oncology, foot and ankle, joint reconstruction, hand and pediatric orthopaedic surgery. To round out the training experience, residents rotate with large group practices, including Jacksonville Orthopaedic Institute (JOI) and Southeast Orthopaedics, which provide exposure to the private practice model in adult joint reconstruction, adult spine and orthopaedic sports medicine. These rotations are further enhanced as many of the program alumni have returned to the area after completing their fellowship training and now serve as attending faculty. These include Dr. Marielle Amoli at Nemours (class of 2015), Dr. Anthony Bell at UF Health Jax (class of 2014), Dr. Brett Frykberg at JOI (class of 2013), and Dr. Aaron Bates (class of 2008) and Dr. Brett Puckett (class of 2003) of Southeast Orthopaedics.

A Legacy Continues: University of Florida Jacksonville Orthopaedic Residency Program

Dr. George Fipp was the first trainee of the University of Florida Jacksonville Orthopaedic Residency Program

Dr. Fipp began traveling to Haiti in 1982 to provide care to the underserved. The legacy continues today.
Dedication to Research

Residents have been well represented at the local, state and national level for their research endeavors that include poster and podium presentations as well as peer-reviewed journal publications. Since 2003, three months of the resident’s second year of training are dedicated exclusively to research. Research interests cover a vast range of subject areas and have included the following topics:

- Dynamic MRI for diagnosis of pathologic extensor carpi ulnaris tendon instability
- Low energy open ankle fractures in the elderly
- MRI prevalence of anterolateral ligament in the knee
- Use of tumor prothesis in non-oncologic salvage procedures of the distal femur
- Patient outcomes after arthroscopic superior capsular reconstruction for irreparable rotator cuff tears
- The effects on a Level 1 Trauma Center by a Level 2 Trauma Center in close proximity

Continuing a Legacy

Dr. Fipp’s legacy lives on at UF Health Jacksonville’s Orthopaedic Program through the scholarship established in his honor in 2014. He first began traveling to Haiti in 1982 to provide care to the underserved. As the trip became more established and ties were formalized with a local hospital, Hôpital Sacré Coeur, and the overseeing organization, The CRUDEM Foundation, Dr. Fipp recognized the excellent opportunity to involve the residents. The week long trip to Milot, Haiti has now become a tradition for the residents and continues to provide an essential complement to the overall orthopaedic residency education as it gets the residents out of their comfort zone and allows them to understand firsthand the professional and personal blessings of being a surgeon-in-training in the United States. Following Dr. Fipp’s passing in 2006, Dr. John Lovejoy Jr., a longtime friend of Dr. Fipp and professor emeritus of the residency program, carried on the torch and expanded upon Dr. Fipp’s original work; his greatest contribution came through the provision of care to devastated Haitians after the 2010 earthquake. For this reason, Dr. Lovejoy was awarded the American Academy of Orthopaedic Surgeons Humanitarian Award in 2015.

Inspired by the legacy of our predecessors, as residents, we take great pride in being a part of the University of Florida Jacksonville Orthopaedic Residency family and look forward to furthering the awesome accomplishments of those who came before us.

The University of Florida Jacksonville Orthopaedic Residency Program has grown since its inception in 1962. Pictured here are the graduating classes of 1975 and 2016.
Approximately 5.7 million adult Americans currently have a diagnosis of heart failure, with 915,000 new heart failure cases annually.\(^1\) This prevalence is expected to increase 46 percent by 2030, resulting in over eight million adults with heart failure.\(^2\) This disease process produces a large economic burden nationally with an annual estimated cost of $30.7 billion,\(^2\) which is projected to increase to $69.7 billion by 2030.\(^2\)

Over the past two decades, there has been a decline in heart failure mortality due to implementation of several evidence-based therapies including beta blockers, ACE inhibitors, aldosterone antagonists, automatic implantable cardioverter-defibrillators (AICD) and cardiac resynchronization therapies (CRT). Quality improvement programs including Get with the Guidelines, government mandated CMS performance measures, and increased educational programs have improved practitioner implementation of these therapies.\(^3\) Although heart failure mortality rates have declined, one year (29.6 percent)\(^4\) and five year mortality rates (52.6 percent)\(^5\) remain unacceptably high. It is evident that more needs to be done to combat this disease process.

Fortunately, treatment options for heart failure with reduced ejection fraction (HFrEF) have expanded considerably over the past five years. Recently, two new pharmacologic agents, valsartan/sacubitril and ivabradine, have been FDA approved for the management of HFrEF and implemented in the heart failure guidelines.\(^6\) Technological innovations have further widened the scope of heart failure therapies as novel implantable sensors for heart failure are being utilized to assist in the management and prevention of congestion, leading to a decline in heart failure admission rates. Disease management strategies and the development of heart failure clinics have aimed to reduce heart failure readmissions and mortality on a community level by providing standardized expert care. Advanced therapies for end stage heart failure, including left ventricular assist devices and cardiac transplant, have markedly improved mortality for those with an expected survival of less than two years. With these advances, there is more hope than ever for patients with heart failure.

With over one million hospital discharges and nearly 1.8 million outpatient physician visits for heart failure per year, internists and non-cardiac specialists are certainly expected to become familiar with the novel heart failure management strategies available. In this edition of *Northeast Florida Medicine*, our focus on heart failure will address transformations in the entire spectrum of this disease process by providing an in-depth review of several of the advances described above. Northeast Florida is certainly privileged to have an extensive list of experts who dedicate a majority of their time in managing heart failure patients.

The articles that follow were developed by expert faculty, fellows, and nurse practitioners from four different centers, thereby highlighting the multidisciplinary, wide-ranging, integrative approach involved in heart failure management:

**Drs. Dmitry Yaranov, Khadeeja Esmail and Alan Miller** from the Division of Cardiology, Department of Medicine at University of Florida, Jacksonville discuss historical changes in the management of heart failure from the 1600s to today. They highlight the involvement of several neurohormonal pathways implicated in the progression of heart failure and medical therapies aimed at reducing adverse remodeling. The growing intersection of device therapy and advanced heart failure management is also described.

**Challenging, Time Consuming, and Costly: Heart Failure**

Parag Patel, MD  
Guest Editor

Ruple Galani, MD  
Guest Editor
Nurse Practitioners Stacey Manning, Erica Fetner and Mary Leen and Dr. Simone Nader from Baptist Heart Specialists systematically illustrate the challenges involved in the development and management of an outpatient heart failure disease management program. In a pilot study aimed at decreasing 30 day rehospitalization rates, they demonstrate that a thorough multidisciplinary dynamic approach to heart failure management can lead to impressive reductions in heart failure readmissions.

Drs. Mariella Velez-Martinez, Kevin Landolfo, Daniel Yip and I outline data supporting the utilization of left ventricular assist device therapy in the management of end stage heart failure. We depict the basic components of the left ventricular assist devices, indications for implantation, and clinical challenges associated with long term therapy.

Drs. Oludamilola Oluleye, Yahaira Ortiz Gonzalez and Mohamad Yamani from Mayo Clinic Florida give an in-depth assessment of the two newest therapies aimed at improving heart failure outcomes: valsartan/sacubitril and ivabradine. In this article, clinical data supporting medication use, information regarding medication titration, and detailed descriptions of potential side-effects are provided.

Dr. Sumant Lamba from First Coast Cardiovascular Institute highlights the interplay between technological advances in device therapy and outpatient management of heart failure. He describes data supporting utilization of invasive PA pressure monitoring to minimize heart failure readmissions and improve volume management. He further highlights a single center “real-life” implementation of this technology, describing both outcomes and challenges.

The contributions of these authors clinically, and to this edition of Northeast Florida Medicine, have been invaluable. It has truly been an honor and privilege to work with this group on the Heart Failure edition as we try to improve heart failure outcomes in our patients. We hope that this journal will provide a solid foundation for the recent advances in the Heart Failure field and thereby enhance the management of the heart failure population within our community.

References:
Unmatched
A full spectrum of specialized cardiac care dedicated to improving lives.

Comprehensive Heart Failure Program
Congestive heart failure (CHF) is a major public health concern across the nation and here in our local community. Backed by the unmatched resources of the area’s only dedicated heart hospital, the Baptist Heart Failure Program is designed to meet the challenge of caring for this growing population using the innovative approaches to effective management such as our HeartConnect telehealth service. Our CHF Clinics, located at all five Baptist Medical Centers, focus on improving patient quality of life through a comprehensive program of medical treatment, care coordination, rehabilitation and support services.

With seven locations (and growing), our team of more than 30 board-certified cardiologists is dedicated to delivering full-service, high-quality heart and vascular care close to home.

Services provided include:

- Specialized medical care
- Nursing care coordination
- Medication, diet and lifestyle education
- Exercise and cardiac rehabilitation
- Outpatient IV inotropic medications
- Evaluation for advanced surgical treatment options
- Assistance in affording expensive medications
- Access to research studies

BaptistHeartSpecialists.com
Heart Failure, A Historic Perspective

By Dmitry Yaranov, MD, Khadeeja Esmail, MD, and Alan Miller, MD
Division of Cardiology, Department of Medicine, University of Florida, Jacksonville, Florida

Introduction:

Despite pharmacotherapy advances in patients with heart failure (HF), overall morbidity and mortality rates remain high. Five year mortality rates range from 10 percent in asymptomatic patients with heart failure with reduced ejection fraction (HFrEF) to as high as 40 percent in advanced HF patients. HF is the primary diagnosis for > 1 million admissions in the United States.1-2 This paper reviews the history of HF treatment approaches with a focus on clinical trials.

Historical Perspective:

The first descriptions of HF come from ancient Greece, with minimal understanding of the pathophysiology and the use of foxglove for treatment.3 The development of morphology, pathology and attempts to characterize hemodynamics in patients with HF, led to lifestyle modifications such as limitation of activities and fluid restriction. The early key research observations that catalyzed the emergence and subsequent rapid growth of heart failure are summarized in Table 1. The use of digitalis and diuretics were the main treatment modalities of HF up to the 1980s.

Heart failure with reduced ejection fraction:

Advances in our understanding of the pathophysiology of HF have been essential for innovations in the field over the last 30 years. Clinical trials beginning in the late 1970s and early 1980s targeted HFrEF. Left ventricular dysfunction and the fall in cardiac output with subsequent activation of several neurohormonal compensatory mechanisms became major targets for HF clinical trials. This led to the beginning of the pharmacotherapy era in HF.

In the 1980s, The Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure (V-Heft) trial was the first major trial powered to assess mortality. It studied the combination of isosorbide dinitrate (ISDN) as a venous dilator and hydralazine as an arterial dilator versus standard therapy with digitalis and diuretics. The vasodilator drugs showed a 22 percent relative risk reduction in mortality, with borderline significance.4,5 The FDA did not approve the drug combination at that time. This era continued with the frequent use of positive inotropes, venous vasodilators, and hydralazine, in addition to standard therapies with diuretics and digitalis.

In the late 1980s, activation and alterations in neurohormonal systems, particularly the renin-angiotensin-aldosterone system and sympathetic nervous system, were proven to play a fundamental role in the development and subsequent progression of chronic heart failure. Drs. Jay Cohn and Milton Packer helped focus on neurohormonal axis intervention. The use of angiotensin converting enzyme inhibitors (ACEI), beta blockers, and spironolactone were shown to alter the natural history of disease progression.

Renin-Angiotensin-Aldosterone System

Effects of Enalapril on Mortality in Severe Congestive Heart Failure (CONSENSUS) was the first trial to demonstrate the mortality benefits of ACE inhibitors in NYHA class IV patients.6

Table 1: Major Developments in Heart Failure in the Pre-pharmacologic Era

<table>
<thead>
<tr>
<th>Date</th>
<th>Investigator</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>1628</td>
<td>William Harvey</td>
<td>First description of circulation</td>
</tr>
<tr>
<td>1785</td>
<td>William Withering</td>
<td>Work on medical use of digitalis</td>
</tr>
<tr>
<td>1819</td>
<td>René Laennec</td>
<td>Invention of the stethoscope</td>
</tr>
<tr>
<td>1895</td>
<td>Wilhelm Röntgen</td>
<td>Discovery of X-rays</td>
</tr>
<tr>
<td>1929</td>
<td>Werner Forssman</td>
<td>Performs first catheterization</td>
</tr>
<tr>
<td>1954</td>
<td>Inge Edler and Hellmuth Hertz</td>
<td>Ultrasound use for cardiac structures detection</td>
</tr>
<tr>
<td>1967</td>
<td>Christiaan Barnard</td>
<td>First cardiac transplantation performed</td>
</tr>
</tbody>
</table>
It was followed by Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure (SOLVD), which confirmed the effects of ACE inhibitors in NYHA class II–III with LVEF < 35 percent. The mortality benefit in the latter appeared to be driven largely by the prevention of HF progression. ACEI became standard of care for HF patients (Table 2).

Renin-angiotensin-aldosterone system intervention was revisited in early 2000, with the idea of angiotensin receptor blockers (ARB) use in addition to ACEI; however, major trials (Val-HeFT, CHARM-Added) were negative. Subgroup analysis suggested increased mortality, and the combination of ACEI and ARB was not recommended. However, the use of an ARB in ACEI intolerant patients was found to be effective. Trials with direct renin inhibitors, endothelin receptor antagonists, vasopeptidase inhibitors, antagonists of cytokines, dihydropyridine calcium channel blockers, and oral phosphodiesterase inhibitors failed to show any benefit in mortality compared to standard care.

Beta Blockers

The sympathetic nervous system is activated in heart failure, as an early compensatory mechanism to provide inotropic support and maintain cardiac output. The effects of chronic sympathetic stimulation precipitate further deterioration in cardiac function. The first benefit of beta blockers in chronic HF was reported in the mid-1970s, and initial observations of improved survival were made in 1979. The US Carvedilol Heart Failure Study Group trial was the first trial to demonstrate a benefit of beta blockers in patients with HF and to show safety and dose response. However, the trial was not powered for mortality. Later trials, primarily CIBIS II, COPERNICUS and MERIT-HF, firmly established beta-blockers (in addition to ACEI) as the cornerstone of treatment of HFrEF (Table 3).

Aldosterone Antagonists

Investigators noted that despite the use of ACEI, aldosterone levels often remain elevated in patients with HF, and increased levels are associated with increased mortality. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure (RALES) and Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction (EPHESUS) trials, which evaluated aldosterone receptor blockade in patients with HFrEF, led to wide use of spironolactone in patients with severe HF. Those trials were followed by Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF), showing improved mortality in patients with mild HF symptoms.

Heart Failure with Preserved Ejection Fraction:

Despite the advances in pharmacotherapy in patients with HFrEF, the use of the same therapies in HF with preserved ejection fraction failed to show improvements in mortality or morbidity (Table 4). The incidence and contribution of diastolic dysfunction remains controversial, although it has been estimated that 30-50 percent of patients with HF have normal ventricular systolic function.
systolic contraction. However, knowledge of diastolic dysfunction has little effect on management of most patients with chronic heart failure, as there are still many uncertainties over its optimal management strategies.

**Newer Therapies:**

Clinical research focusing on neurohormonal activation continues with newer therapies. Recent guideline updates recommend two new oral agents for the management of patients with HFrEF. The new drug combination (Valsartan/Sacubitril) was shown to improve mortality in Angiotensin-Nephrilysin Inhibition versus Enalapril in the Heart Failure (PARADIGM-HF) trial. The Ivabradine and Outcomes in Chronic Heart failure (SHIFT): a randomized placebo-controlled study (SHIFT) showed benefit with a new drug class (sinoatrial node blocking agent) on clinical outcomes to reduce hospitalizations in patients with HF and it confirmed the important role of heart rate in the pathophysiology of this disorder.

**Cardiac Devices:**

The introduction of cardiac devices in the management of heart failure with reduced EF represents a major milestone in the history of heart failure. The initial skepticism of cardiac devices, including the implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT) and ventricular assist device (VAD), led to a burst of clinical trials which revealed multiple benefits of these devices. As a result of these trials cardiac devices are a mainstay in the treatment of HFrEF.

**Implantable Cardioverter Defibrillators**

By the mid 20th century, it was well known that ventricular arrhythmias were the mechanism of death in a large proportion of patients with cardiac disease. Sudden cardiac death (SCD) is the initial presentation of cardiac disease in 15 percent of patients, and more than 50 percent of all such deaths occur outside the hospital. SCD associated with ventricular arrhythmias was the primary mode of death in patients with chronic heart failure and reduced EF. Dr. Michel Mirowski was one of the first clinicians to recognize this problem and come up with a solution. Implantable cardioverter defibrillators (ICDs) have revolutionized the management of patients with high-risk ventricular arrhythmias.

**Table 3: Major Beta Blockers Trials**

<table>
<thead>
<tr>
<th>Beta blocker trials</th>
<th>Inclusion Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Carvedilol Heart Failure Study Group (Carvedilol vs. placebo)</td>
<td>LVEF ≤ 35%, symptoms of HF 3 for at least 3 months, on treatment with ACEI and diuretics</td>
<td>65% relative risk reduction of death, but not powered for mortality</td>
</tr>
<tr>
<td>CIBIS-II (Bisoprolol vs. placebo)</td>
<td>LVEF ≤ 35%, NYHA III-IV, on treatment with ACEI, diuretics, vasodilators</td>
<td>34% risk reduction in annual mortality. The greatest benefit appeared to be in the reduction sudden cardiac death.</td>
</tr>
<tr>
<td>MERIT-HF (Metoprolol succinate CR/XL vs. placebo)</td>
<td>LVEF ≤ 40%, NYHA II-IV, on treatment with ACEI and diuretics</td>
<td>34% reduction in all-cause mortality</td>
</tr>
<tr>
<td>CAPRICORN (Carvedilol vs. placebo)</td>
<td>LVEF ≤ 40%, stable, definite MI 3-21 days before randomization, on treatment with ACEI</td>
<td>Negative for co-primary endpoints of all-cause mortality or CV hospital admission, possible 23% reduction in the mortality</td>
</tr>
<tr>
<td>COPERNICUS (Carvedilol vs. placebo)</td>
<td>LVEF &lt;25%, severe symptomatic chronic HF</td>
<td>35% relative risk reduction in all-cause mortality</td>
</tr>
</tbody>
</table>

**Table 4: Major Heart Failure with Preserved Ejection Fraction**

<table>
<thead>
<tr>
<th>HF with preserved ejection fraction trials</th>
<th>Inclusion criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM – Preserved (Candesartan vs. placebo)</td>
<td>LVEF &gt; 40%, NYHA II-IV, history of hospitalization for cardiac reasons</td>
<td>10% relative risk reduction of CV death or hospital admission, not statistically</td>
</tr>
<tr>
<td>I-PRESERVE (Irbesartan vs. placebo)</td>
<td>LVEF ≥ 45%, NYHA II-IV, history of hospitalization for HF in previous 6 months</td>
<td>No statistically significant benefit</td>
</tr>
<tr>
<td>TOPCAT (Spironolactone vs. placebo)</td>
<td>LVEF ≥ 45%</td>
<td>No significant reduction in mortality in overall trial.</td>
</tr>
</tbody>
</table>
cardioverter defibrillators (ICD) were pioneered at Sinai Hospital in Baltimore by a team including Dr. Mirowski and Dr. Morton Mower in 1969. The first device was implanted in humans in February 1980 at Johns Hopkins by Dr. Levi Watkins Jr. The FDA approved ICDs in 1985.24

**Chronic Resynchronization Therapy**

After the ICD, CRT or biventricular pacing was a major contributor to the management of heart failure with reduced EF. CRT involves synchronized pacing of left and right ventricle. An estimated 20-30 percent of patients with heart failure and reduced EF have intraventricular conduction delay which is associated with increased morbidity and mortality.25 CRT started in the late 1980s with animal studies. Results from multiple clinical trials revealed CRT improved quality of life, increased ejection fraction, reduced mortality, decreased mitral regurgitation, and caused reverse remodeling of the heart.26

**Implantable Remote Hemodynamic Monitoring**

Despite advances in heart failure therapy, patients with heart failure suffer from repeated hospitalizations and it is estimated over one million hospitalizations per year cost more than $40 billion dollars.27 This has resulted in increased research in reducing heart failure hospitalization as well as new therapies to treat acute decompensated heart failure. The CardioMEMS device is the only FDA approved implantable remote hemodynamic monitoring system for heart failure. The device monitors pulmonary artery pressure based on the known fact that elevation in LV filling pressures precedes weight gain and symptoms of heart failure decompensation. The CHAMPION trial showed a 37 percent reduction in heart failure admissions. Devices, such as CardioMEMS, are the future of heart failure management and many clinical trials are ongoing to develop monitoring devices which will allow early recognition of heart decompensation.28

**Table 5: ICD Trials**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT I Prior MI, NSVT on monitor, EF≤35%, inducible sustained monomorphic VT during EPS and after procainamide</td>
<td>Significant reduction in overall mortality, cardiac mortality and arrhythmia death in ICD group vs pharmacologic group, 11 cardiac deaths vs 27</td>
</tr>
<tr>
<td>MADIT II Prior MI &gt;30 days prior to enrollment, EF ≤30%</td>
<td>ICD group with 14.2% all cause mortality vs 19.8% in conventional medical therapy group</td>
</tr>
<tr>
<td>CABG PATCH Severe CAD requiring surgery, EF&lt;36%, abnormal signal averaged EKG, no history of sustained VT or syncope</td>
<td>No difference in overall mortality between ICD group and conventional medical therapy group</td>
</tr>
<tr>
<td>MUSTT Prior MI(4 days to &gt;3 years prior to enrollment), asymptomatic NSVT at least 4 days post MI or post revascularization but within 6 months of enrollment, EF ≤40%, induced sustained VT during EPS</td>
<td>Primary endpoint(arrhythmic death or SCD) was 9% in ICD group vs 37% in antiarrhythmic drug group</td>
</tr>
<tr>
<td>SCD-HEFT NYHA II/III, EF≤35%, CHF for 3 months prior with treatment with ACEI and Beta blocker if tolerated</td>
<td>All cause mortality was 29% in ICD group vs 36% in placebo</td>
</tr>
<tr>
<td>DINAMIT MI 6-40 days prior, EF ≤35%, decreased heart rate variability or elevated heart rate ≥80bpm</td>
<td>No difference in all cause mortality between ICD and standard therapy group</td>
</tr>
<tr>
<td>IRIS EF ≤40, resting heart rate ≥90bpm, NSVT ≥150bpm</td>
<td>No difference in all cause mortality between ICD and standard therapy group</td>
</tr>
<tr>
<td>CAT Recent onset ≤9 months, EF ≤30%</td>
<td>No significant difference in all cause mortality between ICD and standard therapy</td>
</tr>
<tr>
<td>AMIOVIRT EF ≤35%, NYHA I, II, III, asymptomatic NSVT</td>
<td>No significant difference in all cause mortality between ICD and admiodarone</td>
</tr>
<tr>
<td>DEFINITE EF ≤35%, ventricular premature beats or NSVT</td>
<td>Significant reduction in all cause mortality, 7.9% in ICD group vs 14.1% in medical therapy group</td>
</tr>
<tr>
<td>SCD-HEFT NYHA II/III, EF≤35%, CHF for 3 months prior with treatment with ACEI and Beta blocker if tolerated</td>
<td>All cause mortality was 29% in ICD group vs 36% in placebo</td>
</tr>
</tbody>
</table>
Left Ventricular Assist Devices

Medical therapy, ICDs and CRT have improved mortality in many patients with heart failure but there is a large group of end stage heart failure patients with NYHA class IV, stage D. The amount of donor hearts is insufficient for this large population and there was a need for a device which could provide mechanical circulatory support. The first clinical application of a pneumatically driven ventricular assist device (VAD) was attributed to DeBakey in 1966 when a 37 year-old woman was successfully supported for 10 days with a paracorporeal circuit after complex cardiac surgery. The first long term VAD was developed in 1988 by Dr. William F. Bernhard of Boston Children's Hospital. The first generation VADs were introduced in the 1990s and approved by the FDA in 1994. Initially, VADs were created as bridge to transplant. However, among those with advanced heart failure many are ineligible and approximately 50,000 to 100,000 patients per year may benefit from a VAD as destination therapy. In 2000, the FDA granted premarket approval for the Thoratec HeartMate XVE LVAD for destination therapy based on the REMATCH trial.

Conclusion:
The development of any subspecialty in medicine is associated with a better understanding of pathophysiology of the process, new approaches, and techniques in diagnosis and management, as well as rapidly developing pharmacologic and device aspects of treatment. Current research, concentrating on manipulation of molecular mechanisms in HF, is ongoing. ♦

Table 6: CRT Trials

<table>
<thead>
<tr>
<th></th>
<th>Inclusion Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPANION</td>
<td>NYHA III, IV, QRS ≥120ms, EF ≤35%</td>
<td>Decreased all cause mortality with CRT vs medical therapy, 56% vs 68%</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>NYHA III, IV, EF ≤35%, QRS prolongation</td>
<td>Decreased all cause mortality in CRT+medication group vs medication along, 20% vs 30%</td>
</tr>
<tr>
<td>ECHO CRT</td>
<td>NYHA III, IV, EF ≤35%, QRS &lt;130</td>
<td>Increased mortality in CRT group vs control group, 11.1% vs 6.4%</td>
</tr>
<tr>
<td>MADIT CRT</td>
<td>NYHA I/II, EF ≤30%, QRS ≥130</td>
<td>Decreased mortality in CRT-D group vs ICD, 17% vs 25%</td>
</tr>
<tr>
<td>RAFT</td>
<td>NYHA II/III, EF ≤30%, QRS ≥120</td>
<td>Decreased mortality in CRT-D vs ICD, 33% vs 40%</td>
</tr>
</tbody>
</table>

References


Challenges of Development and Management of an Outpatient Heart Failure Disease Management Program

By Stacey Manning, DNP, ACNP, Erica Fetner, MSN, FNP, Mary Leen, DNP, ACNP, and Simone Nader, MD, FACC
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Abstract: In the United States, heart failure readmissions cost approximately $17.4 billion annually. In view of declining reimbursement and increased health care costs, a community hospital in the southeastern United States started a heart failure disease management pilot program in an effort to reduce hospital readmissions within thirty days of discharge. Challenges of implementation included staffing, clinic space, physician and hospital buy-in, financial considerations, and patient compliance. Success of the pilot program resulted in a permanent program starting at the largest of the hospital campuses. A second heart failure disease management program started in late summer of 2016 at the second largest of the hospitals. The 30 day hospital readmission rate at the beginning of the heart failure disease management program was 16.7 percent compared to 0 percent 12 months later. Additionally, the rate of 30 day hospitalizations for non-enrollees at the end of the first 12 months was 20.7 percent compared to 0 percent for enrollees.

Introduction

Heart Failure (HF) affects 6.5 million adults in the United States and, due to longer survival rates, incidence is predicted to increase 25 percent by the year 2030. Combined with heart disease, it is the leading cause of death in the United States. Symptoms can include shortness of breath at rest and on exertion, orthopnea, weight gain, peripheral edema, and abdominal swelling, fatigue, and generalized weakness. It could be called the “Oncology of Cardiology.” HF is the primary cause of more than one million hospital admissions each year. Of those one million admissions, approximately 24 percent will be readmitted to the hospital within thirty days. Total costs associated with caring for HF patients exceed $30 billion dollars annually. These costs include medications, healthcare services, and lost productivity.

The Medicare Payment Advisory Commission estimates that unplanned readmissions for HF cost $17.4 billion annually. The Centers for Medicare and Medicaid Services (CMS) tracks HF readmissions within 30 days of hospital discharge. Penalties or payment reductions of up to three percent of Medicare payments can be charged for inpatient prospective payment system (IPPS) hospitals with excess readmissions. With declining reimbursement and increased health care costs, hospitals are trying various interventions to decrease length of stay and reduce hospital readmissions within 30 days of discharge. While there are multiple strategies to reduce HF readmissions, this article focuses on an outpatient, multidisciplinary HF disease management program (DMP) and the challenges associated with its development and management.

Pilot Program Development

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines include a recommendation that HF patients be followed after hospital discharge in a multidisciplinary disease-management program (DMP). The goal is to provide care for patients at high risk of hospital readmission, to facilitate the implementation of guideline directed medical therapy, to address barriers to behavior modification, and to reduce the risk of re-hospitalization. With this in mind, efforts to develop a multidisciplinary HF DMP began in early 2013 at a 500-bed nonprofit community hospital in the southeastern United States. The focus was to develop a program consisting of a cardiologist, nurse practitioner, pharmacist, and dietitian.

Challenges to implementation included physician buy-in and hospital support in providing services of the pharmacist and dietitian who were also tasked with other duties in their respective departments. Over a 10 month period of time, evidence based practice guidelines, current practice, and HF readmission data were shared at the hospital cardiology service line meetings. Finally, consensus was achieved to begin a six month pilot program in January 2014.

The HF DMP was located at the on-campus cardiology practice. There were space constraints and numerous issues related to patient flow which had to be resolved. In addition, the initial staffing plan did not include medical assistants (MA’s) to assist with the clinics. As patient volume increased, a MA was added to the team to assist with vital signs, six minute walk tests, administration of the Minnesota Living with Heart Failure questionnaire, and follow-up on laboratory tests. An office triage nurse was available to provide intravenous access and administration of intravenous diuretics as needed. A nurse practitioner provided the majority of

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care delivered to the patients according to a protocol developed and approved by the cardiology service. There was a cardiologist available at all times to assist with collaboration as needed.

One major challenge of the program was obtaining laboratory test results in a timely fashion to enable titration of diuretic and other medical therapies while the patient was at the clinic. The fact that the cardiology service and the health system laboratory service utilized disparate electronic medical records exacerbated the problem. Over time, a system was developed to alert the laboratory to the nature of the tests and the importance of obtaining results within a two hour time frame. Other challenges included seeing patients for hospital follow-up with a lack of documentation and paucity of patient education. The time allotted for the pharmacist to perform medication reconciliation was increased, as well as the time for the nurse practitioner to provide education and encourage adherence to the therapeutic regimen. Patients with HF often have comorbid medical conditions that require coordination of care among other medical specialists. This care coordination was initially difficult but improved when the other specialists were educated about the program and collaboration progressed relatively quickly.

**Pilot Program Outcomes**

At the end of the six month pilot, approximately 70 patients were actively enrolled in the program. Data was analyzed from a cohort of patients in the program to compare utilization data for a four month period of time before and after starting the program. The results of the analysis demonstrated a 76 percent reduction in hospital admissions, 70 percent reduction in total hospital days, and 100 percent reduction in 30 day re-admissions (n=21). Based on this data and the improvement in quality of life scores as rated by the patients, the decision was made to continue the program and eventually expand it to other hospitals in the health system.

**Ongoing Challenges of Patient Engagement**

Management and treatment of HF consists of a complex regimen of diet, exercise, medications, and self-monitoring, which increases the risk for patient non-adherence and the need for a multi-disciplinary approach. Patient engagement and compliance with treatment is often a challenge. Non-adherent behavior is associated with 15-42 percent of decompensated and exacerbated HF, leading to preventable re-hospitalization and premature mortality. Despite treatment challenges, HF DMP’s have demonstrated effectiveness in reducing all-cause mortality by 29-40 percent, all cause hospitalizations by 12 percent, and HF specific hospitalizations by 25-27 percent. Feldman et al,10 studied six multidisciplinary DMP’s, and found improvement in the six minute walk test, and a decrease in emergency department visits and hospitalizations. Given the evidence of individual studies supporting the positive outcomes of HF DMP’s, it is essential to consider all possible factors that may lead to non-adherence when developing and initiating a collaborative plan of care.

**Patient Adherence**

Because of the complexity of HF, patients are tasked with understanding new medications, signs and symptoms of worsening HF, as well as dietary modifications. A variety of factors can affect patient adherence including education level, literacy, socioeconomic status, cognitive function, physical function, depression, anxiety, fatigue, prior hospitalizations, age, and co-morbid conditions. Cognitive impairment can be found in as many as 75 percent of HF patients given most are typically older. Because HF can have such a profound impact on patients’ lives, clinical depression is common. Depression is estimated to affect one in five HF patients making them less likely than their non-depressed counterparts to adhere to regimens. Factors such as depression and lack of social support also resulted in less than two thirds of patients taking their prescribed medications. Additionally non-adherence rates ranging from 3-50 percent were found for diet restrictions, and from 12-75 percent for daily monitoring of blood pressure and weight.

A study of an 84 bed Veterans Hospital showed only 35 percent of Veterans with HF weighed themselves daily and 71 percent followed the prescribed diet. Forty three percent of those veterans needed help with transportation and follow-up appointments due to factors such as age, immobility, co-morbidities, and HF symptomology. All of these factors have to be considered by DMP team members when caring for HF patients when compliance issues are noted.

**Lack of Referrals**

Lack of patient referrals to the HF DMP and coordination of transition from the hospital into the DMP are additional ongoing challenges. The ideal HF DMP patient is referred early and learns about the disease process and lifestyle modifications early rather than in response to acute hospitalization. Unfortunately, the bulk of referrals seem to be triggered by hospitalization. A study of 57,969 patients found that only 19.2 percent of hospitalized patients were referred to a HF DMP. When a hospital has an on-site DMP, patients are eight times more likely to be referred. Of those patients, over 90 percent were also referred to other disciplines, helping to achieve utilization of necessary services and overall optimal patient care. Methods to improve these referral challenges are continually being tested and education of healthcare partners and hospitalists of the HF DMP benefits are ongoing.
Heart Failure

Palliative Care

Given the complexity, unpredictable illness trajectory, and high rates of morbidity and mortality with HF, referrals to palliative care should always be a consideration when appropriate. Although palliative care should be considered and sometimes implemented earlier in the disease process, it usually tends to be implemented later toward end of life. This can result in missed opportunities that may have benefited the patient earlier. A longitudinal study to examine health care providers and care givers view of palliative care found that palliative care was viewed as terminal, which influenced less use. Another study found that clinicians are hesitant to discuss poor prognosis with patients in order to avoid causing fear or hopelessness and therefore palliative care was found to be rarely utilized. A retrospective medical record review by Bekelman looked at fifty patients over a 3.5 year time period, to show that within one year of the initial palliative care visit, advanced care planning was discussed with 48 percent of patients, future fears and concerns 34 percent, care coordination with other healthcare providers 58 percent, referrals made to social work 26 percent, and physical therapy 28 percent. This study demonstrates the importance of involving palliative care services in HF DMP’s.

Financial Barriers

While patient compliance, treatment challenges, and care coordination pose difficulties in both the development and success of any DMP, one of the greatest obstacles of DMP implementation is the financial barriers to stakeholders. There is a vast amount of knowledge published on the benefits of DMP’s, but there is little published on the costs absorbed by those providing the care. Considering that DMP’s utilize services of other specialists including a nutritionist, pharmacist, physical therapist, and social worker on a regular basis, programs need to consider that the time spent away from hospital duties while working in these DMP’s is typically not reimbursed by third-party payers. The average HF DMP appointment is billed at a level 4 service which is only reimbursed on an average of $108 by Medicare. With this in mind, understandably, physician practices, integrated health systems, and hospitals are hesitant to start DMP’s despite improved patient outcomes and reduced readmissions. There are currently limited financial incentives in place for healthcare providers and hospitals to initiate these programs which poses a moral dilemma if the needs of the patients come first.

With evidence supporting that DMPs reduce hospital readmissions and decrease healthcare costs for third party payers, there is a need for new payment models to incentivize programs to provide evidence based care and provide care coordination. Some health plans actually reward providers who meet nationally recognized quality guidelines with a small financial bonus. In addition, Medicare has established a Shared Savings Program (SSP) in response to section 3022 of the Affordable Care Act. The SSP was created to facilitate coordination and cooperation among providers to improve quality of care for Medicare beneficiaries and reduce costs. To participate in this program, providers, hospitals and

Figure 1. Readmission Rate of Disease Management Program Enrollees October 1, 2014 – September 30, 2015
suppliers must create an Accountable Care Organization (ACO) which are a group of health care providers who voluntarily work with Medicare to provide high quality service to Fee-for-Service beneficiaries. While all of these incentives are a step in the right direction, the fact remains that a HF DMP program remains a financial burden for medical institutions.

Conclusion

It is well established that DMPs increase coordination and quality of care, as well as decrease costs, for third-party payers. As Medicare and third-party payers demand quality matrix to drive payment incentives, DMPs will become more commonplace. In the case of the HF DMP discussed in this article, it has been a dynamic work in progress and changes continue to be made based on lessons learned. Due to program success, a second heart failure disease management program opened in late summer of 2016 at the second largest of the hospitals.

Thus far, 301 patients have been served in the HF DMP program, of which 245 remain active. For fiscal year 2015, the peak rate of 30-day readmissions was in the first month of the new HF DMP (16.7 percent) compared to 12 months later (0 percent) (Figure 1). HF DMP enrollees consistently had a lower 30-day readmission rate than non-enrollees. In October of 2015, after one full year in operation, the HF DMP 30-day readmission rate was 0 percent compared to 20.7 percent for non-enrollees (Figure 2). The mortality rate of patients enrolled in the DMP is less than 3 percent.

The cost of caring for patients with HF will only continue to increase because of longer survival rates. With the HF population predicted to increase 25 percent by 2030, strategies to improve the quality, access, efficiency, and equity of HF multidisciplinary management are needed to meet the needs of this population. Integrating primary care with cardiology services is the most likely model to successfully decrease the burden that this disease poses to both the individuals as well as our society. Finally, more reporting of HF DMP data in a consistent format is needed in the literature. Currently there is a vast body of evidence reported in literature with individual program successes, but due to heterogeneity of the programs and what they report, there is little strong evidence in the form of systematic reviews and meta-analyses to report to Medicare and third-party payers which would strengthen the argument for increased financial incentives for HF DMP’s.

Figure 2. Readmission Rate Comparison of DMP Enrollees and Non-enrollees October 1, 2014 – September 30, 2015


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Heart Failure

Left Ventricular Assist Device Therapy for Advanced Heart Failure

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Abstract: Therapies for heart failure have significantly improved survival for heart failure patients. This has led to an increase in the number of patients surviving to end stage heart failure. Left Ventricular Assist Device (LVAD) therapies have become a viable option for destination therapy or a bridge to transplant for this population of patients. Given increased implementation of LVADs, more internists and non-cardiac specialists are expected to manage these patients.

Introduction

Approximately 60,000 Americans with end stage heart failure are refractory to medical therapy.¹ Although cardiac transplantation remains the gold standard, it is a scarce option with approximately 2,300 heart transplants performed yearly in the U.S.² This supply-demand mismatch has fueled the development of alternative treatment options including mechanical circulatory support (MCS).

The utilization of left ventricular assist devices (LVADs) has increased over the past two decades.³ Hence, it is important for internists and non-cardiac specialists to become familiar with LVADs as it is increasingly likely they will encounter them in the clinical setting. This review provides an overview of LVADs, defines indications for referral to heart failure specialists for consideration of advanced therapies and discusses common LVAD complications and management.

Device Overview

The failure of cardiac transplantation to provide long term survival in the 1960s and 70s provided a strong stimulus for the development of LVADs. In 1975, the clinical VAD program was developed by the National Heart, Lung, and Blood Institute and a pump was proposed that could provide support for up to two years without external venting.⁴ Since then, newer generation LVADs have been developed and now are a viable therapy in transplant candidates and non-candidates with end-stage heart failure. To date, over 15,000 LVADs have been implanted in the US.⁵

Second generation devices are the most commonly utilized pumps in the U.S. and provide axial flow, imparting continuous unloading of the left ventricle. The pump pulls blood from the heart via an inflow cannula and pushes it out the ascending aorta via an outflow cannula. It is supported by an electrical system that connects to the pump through a percutaneous driveline, tunneled subcutaneously to exit the body near the right iliac crest. These percutaneous wires are connected to a system controller which is either supported by batteries or uses a power base unit attached to an electrical outlet (Figure 1A). The axial flow design allows for a significant reduction in device size and weight due to the elimination of a filling reservoir and it allows for nearly silent operation. Patients occasionally do not have a pulse and mean arterial blood pressures can be assessed. In addition, peripheral

Figure 1A: External equipment of an LVAD including the anatomical location of the pump in-situ. The electrical system that connects to the device is through a percutaneous driveline tunneled subcutaneously to exit the body above the right iliac crest. The driveline is connected to a system controller which is supported by batteries or has a power base unit attached. Reprinted with the permission of Thoratec Corporation.

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oxygen monitoring is occasionally unreliable in these patients due to lack of pulsatility.

Currently, the HeartMate II (St. Jude Medical, St. Paul, MN) is a second generation pump approved for bridge to transplantation and the only pump approved for destination therapy in the U.S. Parameters, such as speed, power, flow, and pulsatility index (PI), are controlled and measured and displayed in the device system controller/display module (Figure 1B). The speed denotes how fast the motor is spinning, measured in rotations per minute, and is selected by the clinician. The power signifies the amount of energy required to maintain the set speed of the pump and is directly measured by the device. Flow is an estimate of cardiac output derived from pump speed and pump power. The PI is a calculated variable that indicates the amount of native heart pumping function. A higher PI implies greater native LV contractile function and lower LVAD contribution. The HeartMate II can operate at a speed of 6,000-15,000 rpm, providing flows of up to 10 L/minute. The advantage of this second generation design is that the pump rotor is the only moving part which allows for improved durability. The weight (290g) and driveline is much smaller compared to the first generation LVAD and the lithium-ion batteries also provide 8-12 hours of support.

The HeartWare HVAD (HeartWare, Framingham, MA) is a third generation pump that has been approved for bridge to transplant. It is a centrifugal flow pump with a magnetically levitated impeller (Figure 2). The pump is directly inserted into the left ventricle and sits within the pericardial space. Theoretically, the bearingless design of this device has long term durability (>10 years). The pump size (140g) and driveline size (5.3 mm) is smaller than the second generation pumps. The size and design of the pump allows for operation at a lower speed of 1,800-4,000 rpm and flows of up to 10 L/minute. The system controller and module display parameters are fairly similar to the HeartMate II.

Clinical Data
Supporting Utilization of LVADs

The clinical indications for placement of an LVAD have evolved over the past two decades. To date, there are two indications for LVAD placement:

1. Bridge to Transplantation
2. Destination Therapy

Bridge to Transplantation (BTT)

The paucity of hearts, extended waiting times and diminished survival while on a transplant list, led to the strategy of BTT. LVAD implantation as a bridge allows patients awaiting cardiac transplant to stabilize their renal function, optimize their nutritional status, and achieve physical therapy goals prior to undergoing transplantation. Additionally, for patients with progressive cardiogenic shock, BTT can be a lifesaving intervention.

The first pivotal trial evaluating the safety and efficacy of a continuous flow pump for BTT was published in 2007. One hundred thirty-three patients were enrolled and received an LVAD. Of these, 25 died, five were ineligible, and three were withdrawn from the study. Of the remaining 100 patients, 56 percent were successfully transplanted, 43 percent were stable with LVAD in place and 1 percent achieved cardiac recovery and underwent device explanation within 180 days. Overall actuarial survival was 89 percent at one month and 68 percent at 12 months which was markedly better compared to historical controls that received medical therapy alone (25 percent 12 month survival). The HeartMate II was approved in 2008 for BTT and the HeartWare HVAD was approved in 2012 after demonstrating similar outcomes in its pivotal trial. Based on registry data from 2014,
Heart Failure

Survival has since improved with 86 percent of BTT patients either undergoing transplant, stable with an LVAD, or achieving cardiac recovery within one year. Given these results, BTT use increased significantly and comprises approximately 42 percent of patients waiting for transplant.

Destination Therapy (DT)

As the devices have continued to improve, the possibility of utilizing LVADs as an alternative to transplantation has become a reality. The only second generation device to receive FDA approval for destination therapy in the U.S. to date is the HeartMate II. The actuarial survival at one and two years for the HeartMate II pivotal trial (68 percent and 58 percent) was better compared with the HeartMate XVE (55 percent and 24 percent) and historical controls that received medical therapy alone (25 percent and 8 percent). There were no primary-pump failures at two years in the HeartMate II pivotal trial, demonstrating improved device durability. There was also significant improvement in measures of functional status and quality of life in patients with the HeartMate II. The FDA approved the HeartMate II for destination therapy in January 2010. With a post-approval one year survival of 80 percent and two year survival of 70 percent, LVADs are now considered a viable alternative for transplantation.

Due to device specific improvements in survival with DT, a subset of destination therapy patients are bridged with the hopes of ultimately achieving transplant candidacy, previously termed “bridge to decision.” Traditionally, obese patients, patients with elevated pulmonary pressures secondary to heart failure, patients with recent cancers in remission, and patients who were actively using tobacco were not considered transplant candidates. However, MCS promotes improvement in functional status allowing for exercise and weight loss, provides reduction in pulmonary pressures for patients with pulmonary hypertension secondary to heart failure, patients with recent cancers in remission, and patients who were actively using tobacco were not considered transplant candidates. However, MCS promotes improvement in functional status allowing for exercise and weight loss, provides reduction in pulmonary pressures for patients with pulmonary hypertension secondary to heart failure, and allows for survival until a patient is deemed low risk for cancer recurrence, and gives patients an opportunity to undergo smoking cessation.

Patient Referral and Eligibility for LVAD Support

With the improvement of MCS and the increasing utilization of LVADs for BTT and DT, heart failure specialists are relying on appropriate referral of end-stage heart failure patients that may be eligible for these advanced therapies. Therefore, the internist has to be aware of the indications and appropriate timing of referral to the heart failure cardiologist. Clinical indicators for referral for potential LVAD support are described in Table 1. Patients with poor functional status, recurrent heart failure hospitalizations despite compliance, inability to uptitrate cardiac medications, and those who are on high dose diuretics or refractory to diuretics should be referred to an LVAD/Transplant center. It is important that patients are referred early in the process of heart failure so that there is time to optimize therapies, teach patients and their family about MCS, and solidify care giver plans. Models that predict survival, such as the Seattle Heart Failure Model and the Heart Failure Survival Score, may also be helpful in guiding primary care physicians with their referral practices by potentially identifying high-risk heart failure patients for LVAD implantation and transplantation.

Once the patient is referred for advanced therapies such as LVAD or transplantation, a thorough evaluation is undertaken by the referral center to determine candidacy. This evaluation includes an assessment of 1) heart failure severity, 2) non-cardiac considerations, and 3) cardiac considerations.

Clinical Assessment of Heart Failure Severity

Clinical assessment of heart failure severity requires a thorough evaluation of clinical presentation, hemodynamic studies, and functional studies. It is crucial to consider LVAD implantation prior to the development of end-organ failure or occurrence of irreversible injury due to comorbidities.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a national registry for patients receiving

<table>
<thead>
<tr>
<th>Table 1: Clinical Indications for Referral for Potential LVAD Support</th>
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<tbody>
<tr>
<td><strong>More than two admissions for heart failure in the past year</strong></td>
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<tr>
<td><strong>Cardiac cachexia</strong></td>
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<tr>
<td><strong>Continued NYHA IV symptoms</strong></td>
</tr>
<tr>
<td><strong>Worsening renal function</strong></td>
</tr>
<tr>
<td><strong>Diuretic resistance (Furosemide &gt; 80 mg daily, Bumetanide &gt; 2 mg daily, or frequent metolazone use.)</strong></td>
</tr>
<tr>
<td><strong>Intractable ventricular arrhythmias</strong></td>
</tr>
<tr>
<td><strong>Inability to tolerate or uptitrate blockers or angiotensin converting enzyme inhibitors</strong></td>
</tr>
<tr>
<td><strong>Failure to remodel with cardiac resynchronization therapy</strong></td>
</tr>
</tbody>
</table>
mechanical support, derived a scale to classify the clinical severity of ambulatory and hospitalized patients with stage D heart failure and NYHA Class III and IV symptoms (Table 2). Given that inotrope dependence is associated with < 50 percent six-month survival, LVADs should be considered for INTERMACS Level 1-3. In the REMATCH Study, most of the survival benefit was with patients on inotropes at the time of implant. Survival for patients on inotropes versus for patients on optimal medical management at six months was 60 percent versus 39 percent. With several studies citing poorer overall post-surgical outcomes in INTERMACS 1-2 patients compared to less severe levels, many are proposing LVAD implantation for patients earlier in the spectrum of heart failure (e.g., INTERMACS 4-7). The ROADMAP study, a prospective observational study of patients with advanced ambulatory HF, demonstrated improved survival and functional status in LVAD patients when compared with patients with optimal medical management. However, adverse events tended to be higher in the LVAD group. Further studies, including REVIVE-IT, are underway to help determine whether LVAD therapies can be considered in less sick patients.

It is necessary to look at both non-cardiac and cardiac considerations for LVAD eligibility (Table 3). Cardiac and non-cardiac factors that play a role in decision making rarely occur in isolation. Patient selection is very difficult in this practice and should be left to the LVAD implanting center given the center’s expertise in putting together the whole picture when determining which patients would benefit from LVAD therapy.

**Non-cardiac Considerations for LVAD Eligibility**

**General Considerations:**

In general, patients with life-limiting comorbidities, including advanced pulmonary disease, irreversible end stage chronic kidney disease, incurable cancer, advanced peripheral vascular disease or limiting stroke, are not considered LVAD candidates.

**Age:**

Compared to chronological age, physiologic age is an important consideration for LVAD eligibility. LVAD support is much more challenging physically, psychologically, and emotionally for elderly patients compared to younger patients. While age is a

<table>
<thead>
<tr>
<th>INTERMACS Level</th>
<th>Hemodynamic status</th>
<th>Time to MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 “Crashing and burning”</td>
<td>Critical cardiogenic shock despite escalating inotropes and IABP</td>
<td>Within Hours</td>
</tr>
<tr>
<td>2 “Progressive decline”</td>
<td>IV inotropes with deterioration in nutrition, renal function, or fluid retention.</td>
<td>Within a Few Days</td>
</tr>
<tr>
<td>3 “Stable but inotrope dependent”</td>
<td>Stable but dependent on mild-moderate inotrope dose (hospitalized or at home)</td>
<td>Within a Few Weeks</td>
</tr>
<tr>
<td>4 “Resting symptoms home on oral therapies”</td>
<td>Patient experiences daily symptoms of congestion at rest or during ADL</td>
<td>Within weeks to months</td>
</tr>
<tr>
<td>5 “Exertion intolerant”</td>
<td>Severe limited tolerance for activity but comfortable at rest</td>
<td>Variable</td>
</tr>
<tr>
<td>6 “Exertion limited”</td>
<td>Completes mild activity but fatigued within minutes of exertion</td>
<td>Variable</td>
</tr>
<tr>
<td>7 “Advanced NYHA III”</td>
<td>Clinically stable, completes reasonable activity without recent decompensation</td>
<td>Not an MCS Candidate</td>
</tr>
</tbody>
</table>


**Table 3: Considerations for LVAD Eligibility**

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Non-cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular failure</td>
<td>Age</td>
</tr>
<tr>
<td>Significant valvular insufficiency</td>
<td>Renal function</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Hepatic function</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>Nutritional status</td>
</tr>
<tr>
<td>Neurological/Psychological function</td>
<td>Cancer</td>
</tr>
<tr>
<td>Inability to tolerate anticoagulation</td>
<td>Social support</td>
</tr>
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risk factor for LVAD implantation, MCS can be safely utilized in patients > 70 years of age. The two year survival was 63 percent compared to a survival of 70 percent for patients enrolled in the INTERMACS registry.25 It is important to note patient selection of relatively healthier septuagenarians with the ability to succeed after LVAD placement was important to attain these results.

**Renal Function:**

Although renal dysfunction secondary to reduced cardiac output is reversible, it has been associated with adverse outcomes in patients supported with an LVAD.26 During the evaluation process for a VAD it is important to determine if renal insufficiency is irreversible. Patients with a creatinine level persistently > 2.5 mg/dL, BUN > 40 mg/dL, or on chronic dialysis are at greatest risk for adverse outcomes and these patients may need a renal biopsy for further assessment.27

**Hepatic Function:**

Hepatic dysfunction is associated with adverse outcomes after LVAD implant, primarily due to increased risk of bleeding.28 Increased transfusions due to perioperative bleeding can result in worsening right heart failure, often requiring placement of right ventricular assist device (RVAD). It is important to differentiate between hepatic congestion due to heart failure versus cirrhosis prior to LVAD placement, given that patients with primary portal hypertension or moderate cirrhosis are not candidates for LVAD support.

**Nutrition:**

Due to the metabolic deficiencies in patients with advanced heart failure,29 patients must undergo evaluation and optimization of nutritional status. Malnutrition increases patient risks for infection, decreases the likelihood of postoperative recovery, and may be associated with poor outcomes.30 Pre-albumin levels of <15 mg/dL, at two weeks of VAD implantation,31 cachexia (BMI < 21 in males or 19 in females), low albumin, and low total protein32 are associated with high risk of dying before discharge. An enteral feeding tube may be needed to provide support prior to LVAD placement.

**Neurological / Psychosocial Function:**

Given the complex management involved with LVAD care, patients with a neurologic disease that compromises their ability to care for the device are poor candidates for MCS. Patients with history of TIA or stroke should undergo CT or MRI scanning and undergo formal evaluation by a neurologist and psychiatrist. Patients with psychiatric disorders, history of drug abuse, and other psychosocial issues need to be assessed for ability to manage the device and comply with care instructions. Active drug users are typically not appropriate candidates for LVAD therapy. Current smokers who demonstrate an interest in cessation can undergo bridge to candidacy with the understanding that transplantation will only be offered after abstinence for three to six months.33 Strong family support is crucial for success. Many centers consider lack of family support an absolute contraindication for LVAD placement.

**Patient/Family/Physician Expectations:**

It is important that patients and their physicians have realistic expectations and full understanding of goals when considering mechanical support. Because of the strong desire of physicians to “save” their patients, maintaining objectivity to avoid futile situations is crucial.34 Not maintaining objectivity may create situations in which emotions influence patient selection. Caution is particularly important in situations where the patient is young, the heart failure is an acute process, and when physicians feel they have invested in a good amount of patient care.34 Because patients with LVADs can have stable hemodynamics despite unanticipated complications such as stroke or progression of renal failure, there is a possibility for patients to have ongoing, prolonged suffering. Patients should undergo formal discussions about other options besides MCS, including hospice. Palliative care physicians are invaluable in these discussions.35,36

**Cardiac Considerations for LVAD Eligibility:**

**Right Ventricular Failure:**

The primary cardiac structural abnormality that influences the efficacy of device placement involves right ventricular (RV) failure. Acute unloading of the left ventricle after LVAD placement leads to decompression of the left ventricle causing the interventricular septum to be pulled towards the LV, such that the septum bulges away from the right ventricle. This septal shift, in addition to increased venous return after LVAD placement, can adversely alter RV shape, size, and contractility.37

The RV is a major determinant of early post-implantation outcomes because there are no current durable outpatient biventricular support devices. Biventricular support often requires inpatient stay with a paracorporeal right ventricular support device. Approximately 20-35 percent of patients who undergo LVAD implantation develop RV failure and require prolonged inotropic support or RVAD.38,39
Valve Competency:

Significant valvular abnormalities can lead to important adverse events in patients undergoing LVAD therapy and may require repair or replacement. Moderate to severe aortic insufficiency can markedly impact the hemodynamics of the pump. Left ventricular decompression after placement of an LVAD results in decreased LV pressures and an increased gradient across the aortic valve. This leads to increased aortic insufficiency that can progress over time. This recirculation leads to increasing pump work, decreasing effective forward blood flow, and decreasing systemic perfusion. In this case, the flow registered by the device may artificially be 1.5-2 L/min higher than the true cardiac output.

Mitral regurgitation usually improves after MCS due to left ventricular decompression and usually is not a concern prior to LVAD placement. On the other hand patients with baseline tricuspid regurgitation (TR) may develop worsened regurgitation post-operatively due to increased RV dysfunction in the setting of RV morphological changes after LVAD initiation. Worsening TR can impair forward blood flow from the right to the left side of the heart leading to signs and symptoms of right sided heart failure. Both tricuspid regurgitation and aortic insufficiency can be surgically corrected during LVAD implantation in the operating room.

Arrhythmias:

Both atrial and ventricular arrhythmias are common in patients with cardiogenic shock and advanced cardiomyopathies. Often, these arrhythmias improve after support with the LVAD due to LV decompression and withdrawal of inotropes. Ventricular arrhythmias after LVAD implantation are generally well tolerated, have not been associated with worsening hemodynamics or clinical deterioration and, in fact, the hemodynamic support offered by the LVAD can be life-saving in the setting of ventricular arrhythmias. Thus, LVAD therapy is considered a viable option for support in patients with refractory ventricular arrhythmias.

Postoperative Complications and Management

The benefits of MCS must be tempered by the risks of device placement and postoperative complications. Registry data demonstrate that the major complications that occurred after three months of LVAD implantation include stroke (14 percent), LVAD-related infections (16 percent), bleeding (23 percent), arrhythmias (11 percent), respiratory failure (6 percent), renal failure (5 percent), and rehospitalizations (64 percent). RV failure leading to death was seen in 4 percent of this group.

Right Ventricular Failure

Development of RV failure has been associated with increased morbidity and mortality after LVAD placement. Myocardial stunning, ischemia, arrhythmias, and increased pulmonary vascular resistance are other factors that may affect the RV. If needed, RV function can be supported after surgery with inotropes, pulmonary vasodilators, such as inhaled nitric oxide or sildenafil, and/or temporary placement of an RVAD. RV failure requiring the extended use of postoperative inotropes ranges from 20-27 percent and support requiring a RVAD is less than 5 percent.

Stroke/Thromboembolism:

Stroke and thromboembolic complications are a primary concern for most physicians during and after placement of the LVAD. They occur because contact between the pump surface and the patient’s blood activates coagulation pathways and attracts platelets and complement, initiating clot formation. In order to limit clot formation, all second and third generation LVADs require anticoagulation with warfarin and antiplatelet medications.

Thromboembolism and hemolysis may also be associated with pump thrombosis, which typically manifests as increased power consumption and flow in second generation pumps. Labs frequently demonstrate an increase in LDH, plasma free hemoglobin, and indirect bilirubin which frequently predates changes in device parameters. Patients occasionally develop hematuria and “Coca-Cola” urine during episodes of pump thrombosis. Pump thrombosis rates have occurred in up to eight percent of continuous flow devices. Utilization of antiplatelet agents, such as clopidogrel or thrombolytics, have been reported; however, pump thrombosis more often requires surgical replacement of the pump. Both approaches are associated with high mortality.

Anticoagulation during LVAD support is required to avoid thrombotic complications. Warfarin is used to maintain international normalized ratio goal of 2-3. Antiplatelet therapy with aspirin is also part of the antithrombotic regimen. Data suggests that tight BP control in LVAD patients with a goal MAP of 60-80 mmHg decreases the risk of stroke and thromboembolism as well. It is imperative that the cardiologist and primary care provider utilize antihypertensive agents when needed to achieve these goals. Utilization of evidence based heart failure therapies including ACE inhibitors and beta blockers are preferred antihypertensives.
GI bleeding

GI bleeding has also become more of a concern with the utilization of continuous-flow devices. Based on several reports, approximately 13-30 percent of patients with continuous-flow devices have GI bleeding. Proposed mechanisms for bleeding include 1) warfarin use, 2) arteriovenous malformation in the setting of nonpulsatility, in a mechanism similar to that of Heyde’s syndrome, and 3) development of acquired von Willebrand disease, possibly due to increased shear stress involved with axial flow pumps. If GI bleeding occurs after LVAD implantation, anticoagulation is typically held, the dose is decreased, minimally invasive endoscopy strategies are employed, or octreotide is considered. Major GI surgery (e.g. partial colectomy) may be needed if GI bleeding persists.

Infection

Infection is the leading comorbidity and a significant cause of death in patients undergoing LVAD therapy. The types of infections may be non-VAD related (pneumonia, urinary tract infection, line sepsis) or device related (driveline infection, pump pocket infection, surgical site infection and endocarditis). The high rate of infection in LVAD patients is likely related to the preoperative malnourished state as well as the externalization of the driveline.

The two primary organisms that cause VAD related infections are Staphylococcus epidermidis and Staphylococcus aureus. Driveline infections are the most common types of device related infection with rates ranging from 18-52 percent. They often remain localized and can be successfully treated with antibiotic treatment and appropriate wound care; however, relapse is common. Patients who have recurrent device infections or septicemia often require chronic suppressive antibiotic therapy until a heart transplant can be performed or a new device can be implanted.

Device Malfunction

Although LVAD failure was the second leading cause of death in the REMATCH trial which evaluated first generation devices, there were no reported pump failures in the HeartMate II DT study or the HeartWare BTT study.

Psychosocial Problems

Although LVAD placement has been associated with improved functional status and quality of life, these devices introduce new stressors to patients and caregivers, especially in patients undergoing DT. Caregivers have been shown to experience significantly more psychological distress compared to their loved ones. Early involvement from social workers, palliative care, psychiatry, and support groups is important to provide patients and their families a fulfilling life.

Future of VAD Therapy

Adverse events and device durability have limited the widespread use of MCS. Third generation ventricular assist devices, such as the MVAD Pump (HeartWare, Inc.), Levacor (World Heart Corp), HeartMate III (Thoratec Corp), Berlin Heart Incor (Berlin Heart AG) and DuraHeart (Terumo Somerset), have attempted to improve upon these issues and some have entered clinical trials in the United States. Further research has also focused on the development of a fully implantable system. The LionHeart LVAS (Arrow International) was one of the first devices to be a fully implantable system by using a transcutaneous energy transmission system (TETS). Similar technology that could revolutionize this field in the future is the research focus of many device companies today.

Conclusion

LVAD therapy is effective for the management of end stage heart failure as a bridge to transplantation and destination therapy. With an increasing LVAD population, primary care physicians, specialists and other health care personnel will encounter these patients more frequently in the community. It is imperative that such health care providers have a basic understanding of the indications, functionality, limitations, and complications associated with these devices.

References


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Prevention of Medical Errors and Patient Safety

Background:
The Duval County Medical Society (DCMS) is proud to provide its members with free continuing medical education (CME) opportunities in subject areas mandated and suggested by the State of Florida Board of Medicine to obtain and retain medical licensure. The DCMS would like to thank the St. Vincent's Healthcare Committee on CME for reviewing and accrediting this activity in compliance with the Accreditation Council on Continuing Medical Education (ACCME).

This issue of Northeast Florida Medicine includes an article, “Prevention of Medical Errors and Patient Safety” authored by Linda Edwards, MD, Francys Calle Martin, Esq., and Kari Aasheim, JD, which has been approved for 2 AMA PRA Category 1 credits. For a full description of CME requirements for Florida physicians, please visit www.dcmsonline.org.

Faculty/Credentials:
Linda Edwards, MD is the Senior Associate Dean for Educational Affairs, University of Florida College of Medicine, Jacksonville, FL. Francys Calle Martin, Esq. is the Senior Loss Prevention Attorney and Vice President of Florida Academic Healthcare Patient Safety Organization. Kari Aasheim, JD is the Deputy Administrator for the University of Florida J. Hillis Miller Health Center Self Insurance Program.

Objectives:
1. Define medical error and discuss the multiple factors propelling medical error prevention and patient safety efforts.
2. Review The Joint Commission and state agency standards, regulations relating to sentinel and adverse events, and the process of root cause analysis.
3. Review the Board of Medicine’s most misdiagnosed conditions and provide examples of each and the consequences for both the patient and the healthcare provider.

Date of release: March 1, 2017 Date Credit Expires: March 1, 2019 Estimated Completion Time: 2 hours

How to Earn this CME Credit:
1. Read the “Prevention of Medical Errors and Patient Safety” article.
2. Complete the posttest. Scan and email your test to Kristy Wolski at kristy@dcmsonline.org or mail it to 1301 Riverplace Blvd., Suite 1638, Jacksonville, FL 32207.
3. You can also go to www.dcmsonline.org/NEFMCMED to read the article and take the CME test online.
4. All non-members must submit payment for their CME before their test can be graded.

CME Credit Eligibility:
A minimum passing grade of 70% must be achieved. Only one re-take opportunity will be granted. If you take your test online, a certificate of credit/completion will be automatically downloaded to your DCMS member profile. If you submit your test by mail, a certificate of credit/completion will be emailed within four weeks of submission. If you have any questions, please contact Kristy Wolski at 904.355.6561 or kristy@dcmsonline.org.

Faculty Disclosure:
Linda Edwards, MD, Francys Calle Martin, Esq., and Kari Aasheim, JD report no significant relations to disclose, financial or otherwise with any commercial supporter or product manufacturer associated with this activity.

Disclosure of Conflicts of Interest:
St. Vincent's Healthcare (SVHC) requires speakers, faculty, CME Committee and other individuals who are in a position to control the content of this education activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly evaluated by SVHC for fair balance, scientific objectivity of studies mentioned in the presentation and educational materials used as basis for content, and appropriateness of patient care recommendations.
Prevention of Medical Errors and Patient Safety

By Linda Edwards, MD, Francys Calle Martin, Esq., LHRM, and Kari Aasheim, JD

Abstract: Following a number of studies on the high incidence of medical errors and increasing efforts to improve patient safety, the prevention and reduction of medical errors has become a priority for federal and state regulatory agencies and healthcare providers across the nation. It is important for physicians to understand how federal, state, and independent regulatory agencies have shaped the patient safety movement and have provided an organized structure for identifying the causes of medical errors and the manner in which they can best be prevented. Based on national reports of patient safety events and malpractice data, federal, state, and independent regulatory agencies have established patient safety goals for the prevention of medical errors.

Introduction

The Health and Medicine Division, formerly known as the Institute of Medicine (IOM), is a division of the National Academies of Sciences, Engineering, and Medicine focused on improving health and healthcare in our nation and throughout the world. This team issues recommendations and reports to foster discussion and critical thinking, such as the oft-cited 1999 report To Err Is Human, in which a medical error is defined as, “the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim.” The IOM estimates as many as 98,000 people die every year as a result of preventable medical errors. A recently released study published by Johns Hopkins University researchers in the British Medical Journal claims that 251,000 lives are lost every year as a result of medical errors. If correct, this statistic places medical error third among leading causes of death in the United States, behind heart disease and cancer. Medical error prevention is, therefore, an urgent public health concern requiring close examination of contributing factors and prompt identification of appropriate strategies to reduce risks to patients.

Error Reduction and Prevention

To control increasing government costs resulting from pervasive medical error in the United States, Congress passed the Deficit Reduction Act (DRA) in 2006, which required the Centers for Medicare and Medicaid Services (CMS) to compile a list of conditions that, in part, result in high costs and can reasonably be prevented. CMS developed a list of Hospital Acquired Conditions (HACs) and implemented policies denying or limiting payment by CMS for treatment made necessary by HACs. The current list of HACs is lengthy, but some notable examples include falls, catheter-associated urinary tract infections, unplanned retained foreign objects after surgery, and significant pressure ulcers. While these HACs may not be the result of an error or negligent care, the reimbursement consequences have raised the stakes significantly in medical error prevention.

At the state level, the Florida Board of Medicine has prescribed a range of disciplinary actions for a variety of medical errors, such as wrong site surgery, unplanned retained foreign objects, practicing beyond the scope permitted, and gross or repeated malpractice. In addition, Florida’s statutes require hospitals, ambulatory surgical centers, nursing homes, and physician offices to report certain adverse events to the Florida Agency for Health Care Administration (AHCA) and risk management, as governed by 395.0197, Florida Statutes. Under Florida law, an adverse event is defined as, “an event over which healthcare personnel could exercise control and which is associated in whole or in part with medical intervention, rather than the condition for which such intervention occurred,” and results in one of a number of injuries including death, brain damage, additional medical or surgical intervention, or transfer to a higher level of care. Each facility must submit an annual report of these occurrences to AHCA. A subset of adverse incidents that meet the foregoing criteria and result in one of the injuries listed, must be reported to AHCA within 15 days of the occurrence, hence the name “Code 15” report. This report includes a description of the circumstances surrounding the event, as well as analysis and interventions taken to correct and prevent recurrence. License numbers of personnel who were directly involved in, or witnessed, an adverse event are also required on Code 15 reports.
Physician providers are also required to report certain adverse incidents occurring in their office to the Florida Department of Health (DOH), rather than AHCA. Adverse events that are required to be reported by physician offices are similar to those reported by hospitals to AHCA.\(^6\) AHCA routinely forwards Code 15 reports to DOH to determine whether they should initiate a practitioner investigation. AHCA also maintains an annual report of malpractice claims reported statewide.

**Root Cause Analysis (RCA)**

The Joint Commission (TJC) is an independent, not-for-profit organization that accredits and certifies over 21,000 healthcare organizations across the nation and has become a symbol of patient safety given its commitment to the highest quality performance standards. TJC defines a sentinel event as a patient safety event that reaches a patient and results in death, permanent harm, or severe temporary harm and intervention required to sustain life.\(^7\) When a sentinel event occurs, TJC requires a RCA be completed within 45 days, though many facilities complete them sooner while the details of the event are fresh in everyone’s minds. While in Florida AHCA’s definition of an adverse event is not necessarily synonymous with TJC’s Sentinel Event, most adverse events undergo a RCA. They are called “sentinel” because they signal the need for immediate investigation and response.

The first step involved in a RCA is gathering the information and circumstances surrounding the event by using a multidisciplinary team that includes leadership and all those involved in the event. The causal factors identified drive the corrective action plan, and specific individuals and departments are identified as responsible for the corrective actions. Once solutions to the patient safety event are identified and implemented, it is important to close the loop by following up in a timely fashion to ensure that actions taken were effective.

Not all sentinel events occur because of a medical error, and not all medical errors result in a sentinel event. Hospital reporting of sentinel events to TJC is voluntary. Therefore, the most reported RCA events per year represent only a small proportion of actual events occurring between 2005 and 2016. Presently, the top ten sentinel events reported to TJC are wrong patient/site/procedure, unintended retention of a foreign body, delays in treatment, suicide, operative or post-operative complications, falls, other unanticipated event, medication error, criminal event, and perinatal death/injury.\(^8\) Of the sentinel events reported to TJC through RCA, human factors, leadership, and communication continue to be the top three root causes for the past several years. Since 1998, TJC has published “Sentinel Event Alerts” which address root causes and risk reduction strategies of sentinel events. Many of the strategies and recommendations have since become TJC hospital standards of accreditation.

The proactive counterpart to RCAs, Failure Mode and Effect Analysis (FMEA), is a method for evaluating processes before an adverse event occurs by identifying where and how failures might occur. A FMEA team, comprised of individuals involved in the process, reviews the steps in the process to identify and evaluate those parts of the process most in need of change. Prioritizing is important to ensure systems and processes with the highest likelihood of patient or staff harm are addressed first.

In 2015, the National Patient Safety Foundation (NPSF), an independent, not-for-profit organization, published “RCA²: Improving Root Cause Analyses and Actions to Prevent Harm.”\(^9\)

Recognizing the value of the RCA process, but noting its inconsistent success, RCA² sought to create methods and techniques to identify how and why the patient safety event occurred, but then also take positive action to prevent its recurrence. “The most important step in the RCA² process is the identification of actions to eliminate or control system hazards or vulnerabilities identified in the causal statements.” Once identified, the focus turns to the development of strong action plans with support of facility leadership. Numerous patient safety organizations, including TJC, have endorsed the use of RCA².

**Patient Safety**

In 2005, Congress passed the Patient Safety and Quality Improvement Act (PSQIA) which established federal privileges and confidentiality for patient safety work product reported to a Patient Safety Organization (PSO).\(^10,11\) As of January 2017, there are 52 listed PSOs serving Florida.\(^12\) The legal protections of the PSQIA have significantly enhanced provider willingness to share patient safety and performance improvement information to facilitate development and dissemination of preventive measures and best practices.

In 2002, TJC established its National Patient Safety Goals program to help accredited organizations focus on specific areas of patient safety concern. For 2017, TJC has identified the following National Patient Safety Goals:\(^13\)

1. Identify patients correctly
2. Improve staff communication
3. Use medicines safely
4. Use alarms safely
5. Prevent infection
6. Identify patient safety risks
7. Prevent mistakes in surgery
The first goal addresses the issue of reliably identifying the patient for whom service or treatment is intended and matches the service or treatment to that patient using acceptable identifiers. Acceptable patient identifiers include their name, identification number, or telephone number. Two identifiers must be used when administering medications or blood products.

The second goal is to improve the effectiveness of communication among caregivers. The rationale is to ensure that critical test results are promptly communicated to the appropriate caregiver so that indicated treatment can be started immediately. TJC proposes the development and implementation of written procedures for managing the results of critical tests and diagnostic procedures.

The third National Patient Safety Goal promotes reducing or eliminating errors involving medication administration. Since 2005, there have been more than 460 sentinel events related to medication error.8

The fourth goal is the safe use of critical alarms which addresses issues such as overuse of alarms. Overuse of alarms may confuse or desensitize staff to critical alerts. The Joint Commission requires hospitals to establish alarms as an organizational priority and identify the most important alarms to manage, based on their own internal situations.

The fifth goal is to reduce infections in healthcare facilities, including post-operative infections, central line infections, and urinary tract infections from the use of catheters. Prevention and control strategies must be tailored to the specific needs of each hospital, based on their own risk assessment.

The sixth goal is to identify patient safety risks, including patient assessments for suicide risk, which is a frequently reported sentinel event. Between 2005 and 2016, there were 972 sentinel events reported to TJC involving suicide.4 Identification of individuals at risk for suicide while under the care of, or following discharge from, a healthcare organization is an important step in protecting at-risk individuals.

The seventh National Patient Safety Goal is the prevention of mistakes during surgery. There were 1,225 wrong patient, wrong site, or wrong procedure surgeries voluntarily reported to TJC from 2005 through the second quarter of 2016.9 This is the leading reported sentinel event and the figure nearly doubled from 2014, when there were 73 sentinel events reported, to 2015 with 121 reported. Having a pre-procedure verification process and performing a time-out with the operating room team before anesthesia is administered to ensure the correct procedure, for the correct patient, at the correct site, is a recognized standard of practice. Marking the location of the surgery is also recommended.

Patient safety is also a Florida statutory requirement. Under Florida Statute 395.1012,14 each licensed facility is required to adopt a patient safety plan implementing the requirements of the Conditions of Participation for hospitals receiving reimbursement from CMS.15 This statute further requires that all licensed facilities appoint a patient safety officer and a patient safety committee, which will include at least one person who is neither employed by nor practicing in the facility,14 to promote the health and safety of patients by evaluating patient safety measures of the facility and implementing the patient safety plan.14

Diagnostic Errors

Diagnosis is the foundation upon which all healthcare services and treatment rest. It is through correct diagnosis that subsequent healthcare decisions are made. Building upon To Err Is Human, IOM published Improving Diagnosis in Healthcare in 2015, revealing the occurrence of diagnostic errors had been largely underestimated and that most patients would suffer at least one diagnostic error in their lifetime.

Noting numerous conflicting definitions of diagnostic error in the healthcare industry, IOM endorses a patient-centered definition: “failure to (a) establish an accurate and timely explanation of the patient’s health problem(s) or (b) communicate that explanation to the patient.”16 Taking some inspiration from TJC National Patient Safety Goals, the IOM outlined eight goals to reduce diagnostic error and improve diagnosis.16

- Facilitate more effective teamwork in the diagnostic process among healthcare professionals, patients, and their families.
- Enhance healthcare professional education and training in the diagnostic process.
- Ensure that health information technologies support patients and healthcare professionals in the diagnostic process.
- Develop approaches to identify, learn from, and reduce diagnostic errors and near misses in clinical practice.
- Establish a work system and culture that supports the diagnostic process and improvements in diagnostic performance.
- Develop a reporting environment and medical liability system that facilitates improved diagnosis through learning from diagnostic errors and near misses.
• Design a payment and care delivery environment that supports the diagnostic process.

• Provide dedicated funding for research on the diagnostic process and diagnostic errors.

According to that IOM study, diagnostic errors cause harm by preventing or delaying the appropriate treatment or providing unnecessary or harmful treatment. In the outpatient setting, it is estimated that each year five percent of adults will experience a diagnostic error. In the hospital setting, diagnostic errors are estimated to account for 6 to 17 percent of adverse incidents each year.16

Diagnostic errors are also the leading type of paid medical malpractice claims and are twice as likely to have caused the patient’s death. In a recent study analyzing 25 years of data submitted to the National Practitioner Data Bank,17 diagnostic errors were the highest claim type at 28.6 percent and accounted for 35.2 percent of total payments, which was also the highest proportion. Diagnostic errors were the leading cause of claims-associated death and disability. After adjusting for inflation, diagnosis-related payments totaled $38.8 billion.16

Misdiagnosed Conditions

The timely and accurate diagnosis of medical conditions is of significant importance to the Florida Board of Medicine, so much so that continuing education requirements include mandatory discussion of the five most misdiagnosed conditions.18 As of the date of this publication, those conditions include cancer related issues, neurological/spine related issues, cardiac/stroke related issues, infectious/communicable diseases, and pulmonary related issues.18 It is important to look at each condition and actual Board of Medicine case scenarios.

Cancer Related Issues

In 2016, the American Cancer Society estimated 1,685,210 new cancer cases were diagnosed, and 595,690 deaths were attributed to cancer in the United States.19 Florida had one of the highest state diagnosis rates at 121,240. The top three most diagnosed cancers in Florida were lung and bronchus, female breast, and prostate cancer.19

Misdiagnosis of cancer, includes missed diagnosis, wrong diagnosis, and delayed diagnosis. In one case presented to the Board of Medicine, the patient underwent an x-ray of the chest that revealed a focal area of increased density in her lung. The physician documented the findings, as well as the patient’s reluctance to undergo a CT scan citing lack of insurance. Six years later, new diagnostic studies revealed a small infiltrate of her lung and radiographic follow-up was recommended. The physician documented a plan to follow up, but failed to do so, and failed to order additional studies. Over a year later, the patient presented to another physician who ordered a CT of the chest which revealed a malignant appearing mass in the right lung, and a biopsy later revealed adenocarcinoma.

The Board of Medicine found that the physician failed to practice medicine with that level of care, skill, and treatment which, in light of all relevant surrounding circumstances, is recognized as acceptable and appropriate by a reasonably prudent similar health-care provider. The physician was also cited for keeping illegible records, not documenting tests ordered, radiographic follow up, or crucial conversations with the patient, as well as not maintaining a concise ongoing problem list.

Neurological/Spine Related Issues

A retrospective study of diagnostic errors in neurological emergencies found that these incidents can be classified into three categories: knowledge gaps, cognitive errors, and systems-based errors.20 Misdiagnosis of cerebellar lesions and erroneous radiology resident interpretations of neuroimaging were the most common mistakes nationwide.

In a related incident before the Board of Medicine, a patient presented with complaints of severe headaches, confusion, and dizziness and a history of previous shunt insertion for hydrocephalus. A CT scan revealed hydrocephalus with shunt catheter in place and no signs of acute intracranial hemorrhage. The patient was diagnosed with a malfunctioning shunt and was taken to the operating room where the old shunt was removed and a new shunt placed. A left frontal burr hole was also made. The physician documented in the operative report that he had evacuated blood from the patient’s head and informed the patient of it. Post-operatively, the patient was found to be obtunded and having seizures, requiring ventilator-assistance. The investigation revealed the physician performed an unnecessary procedure by drilling a burr hole that was not indicated and deceptively documented that a hematoma was evacuated.

Cardiac/Stroke Related Issues

There has been much publicity recently regarding the failure to diagnose heart disease, particularly in women, and the historical and cultural reasons for this disparity.21 According to the Centers for Disease Control, heart disease is the leading cause of death
for women in the United States.

Almost 64 percent of women who die suddenly from heart disease have no previous symptoms, making it more difficult to diagnose.

The Board of Medicine reviewed an incident of a patient who presented to the emergency room with unstable vital signs and complaints of left arm, side, and knee pain subsequent to a fall. Her history was positive for myocardial infarction, coronary artery bypass grafts, hypertension, and myelofibrosis. The emergency department physician incorrectly interpreted the chest x-ray, despite the radiology report indicating pleural effusion and left lower lobe atelectasis and an abnormal electrocardiogram showing tachycardia. The only treatment rendered was a 500mL bolus of normal saline. Without further evaluation or timely intervention, the patient continued to deteriorate, coded, and expired.

The Board of Medicine determined that the physician failed to meet the standard of care by failing to properly diagnose and treat the patient, failing to correctly interpret the chest x-ray, failing to address the abnormal electrocardiogram, and failing to recognize a hemothorax in a patient with left sided chest trauma with hypotension and tachycardia.

Infectious/Communicable Diseases

The misdiagnosis of infectious or communicable diseases is concerning not only for the patient involved, who will likely have a delay in the initiation of care, but for other patients and healthcare workers who may also be exposed. In this next scenario, the patient arrived in the emergency room with a temperature of 102°F and altered mental state and was diagnosed with transient ischemic attack. A consulting neurologist diagnosed encephalitis and recommended a lumbar puncture, but this recommendation was not acted upon. A CT scan of the head did not show hemorrhagic or thrombotic infarct, and the presence of fever suggested a differential diagnosis of herpes or toxoplasma infection. Accordingly, an infectious disease consultation was requested. The infectious disease physician was found to have failed to meet the standard of care by having his P.A. perform the exam, failing to reference herpes simplex encephalitis in the differential, failing to order a spinal tap, failing to order an MRI, and failing to immediately start the patient on acyclovir antiviral therapy. The patient suffered seizures, further deterioration, and was placed on a ventilator. Ultimately, the failure resulted in severe irreversible brain injury caused by untreated herpes encephalitis and the patient remained in a state of total dependency.

Pulmonary Related Issues

In one retrospective study of pulmonary embolism, over 30 percent of patients presenting to the emergency department had a delayed diagnosis. Patients were often sent home or admitted to the hospital with an incorrect diagnosis depending on their clinical presentation or other chronic, coexisting medical conditions.

The Board of Medicine reviewed the treatment of a patient who arrived to the emergency room from her physician’s office with shortness of breath and chest pain and to be ruled out for pulmonary embolism. The emergency room physician utilized a shortness of breath template and recorded no new vital signs. After ordering essentially non-diagnostic studies, the ER physician ordered antibiotics and potassium chloride to treat the diagnosis of cough and hypokalemia and discharged the patient. One week later, the patient died from a saddle pulmonary embolism. The physician was found to have practiced below the standard of care by failing to perform a proper history and physical, failing to order appropriate diagnostic studies, and failing to rule out pulmonary embolism.

Medical Error Reduction: In Conclusion

Medical errors will never be completely eliminated, but by utilizing available patient safety data, adhering to National Patient Safety Goals, and utilizing tools such as RCA to identify those areas of greatest patient safety concern, medical errors can be reduced. As the preceding examples have illustrated, commonly encountered challenges with the stages of the diagnostic process can be minimized by consistently performing a thorough history and physical, promptly following up on diagnostic tests, and communicating findings to the patient. Medical record documentation is also extremely important to the practice of medicine and the communication between multiple services and healthcare providers involved in a patient’s care. Failure to keep appropriate written records is also a frequent cause of Board of Medicine disciplinary action and a hindrance to the provision of appropriate care. As more and more healthcare organizations transition to the electronic health record, the benefits of this technology, such as diagnostic decision support, clinical reminders, and system alerts, will help avert the risk of diagnostic missteps.
References:

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18. 2016 Florida Administrative Code, Florida Department of State. Department of Health: Board of Medicine- License Renewal and Reactivation; Continuing Education. F.A.C. 64B8-13.005.


Prevention of Medical Errors & Patient Safety Quiz

CME Questions & Answers (circle one answer)/Free to DCMS Members/$55.00 charge non-members*

(Return by March 1, 2019 BY MAIL: 1301 Riverplace Blvd. Suite 1638, Jacksonville, FL 32207 or ONLINE: www.dcmsonline.org/NEFMCME)

1. To Err is Human, the 1999 study by the Institute of Medicine, estimated that as many as 98,000 patients die in hospitals every year as a result of preventable medical errors.
   a. True
   b. False

2. The federal Patient Safety and Quality Improvement Act (PSQIA):
   a. Establishes federal privilege and confidentiality protections for patient safety information.
   b. Seeks to improve patient safety standards.
   c. Allows healthcare providers to identify and learn from errors through voluntary reporting systems.
   d. All of the above.

3. Most patient safety events are not the result of individual carelessness, but system failures.
   a. True
   b. False

4. What are factors propelling medical error prevention?
   a. Malpractice suits
   b. Media coverage of error, reimbursement denials for preventable hospital acquired conditions, state, federal and professional licensure requirements
   c. Computerized medical records
   d. Mortality rate

5. Per The Joint Commission, when must a root cause analysis be completed for a Sentinel Event?
   a. Within 45 days
   b. As soon as possible
   c. Within 15 days
   d. When you can get a team together

6. What is the current number one sentinel event reported to The Joint Commission?
   a. Medical errors
   b. Equipment defects
   c. Wrong patient surgery, wrong site surgery, wrong procedure surgery
   d. Infection

7. Human factors, leadership, and communication continue to be the top 3 root causes of The Joint Commission reported events.
   a. True
   b. False

8. What is the primary focus of the RCA team?
   a. Meet the Joint Commission requirements
   b. Identify weaknesses and failures in systems and processes and take effective action that will result in sustained improvement
   c. Terminate those involved in the event
   d. Report the event to the Department of Health

9. Certain adverse events have to be reported to Florida's Agency for Health Care Administration (AHCA) within 15 days.
   a. True
   b. False

10. What are the Florida Board of Medicine's most misdiagnosed conditions this biennium?
    a. Sepsis, cardiovascular disease, urologic disease, cancer, fetal distress
    b. Meningitis, Zika, Tuberculosis, neurological conditions
    c. Cancer, neurological, cardiac, infectious disease, and pulmonary
    d. Brain injury, fractures, surgical complications, appendicitis, blood dysplasia, Leukemia

Evaluation questions & CME Credit Information

(Please evaluate this article. Circle one number using this scale: 1= Strongly Agree to 5= Strongly Disagree)

The articles met the stated objectives: ____________

The articles were appropriate to my practice: ____________

The topics were current and well presented: ____________

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New Pharmacologic Therapies for Heart Failure

By Oludamilola Oluleye, MD, MBBS, Yahaira Ortiz Gonzalez, MD, and Mohamad H. Yamani, MD
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Abstract: Heart failure (HF) continues to be a life threatening condition that often results in recurrent hospitalizations and increased costs for the patient and health care system. The development of novel therapies, which improve morbidity and mortality, appears to be the dawn of a new era. Ivabradine (Corlanor) and Sacubitril/Valsartan (Entresto) were both approved by the FDA in 2015 to curb the burden of heart failure in the United States. Ivabradine targets the If current channel inhibiting the sinoatrial (SA) node which results in a decreased heart rate thereby suppressing the abnormally increased sympathetic activity in patients with heart failure. Sacubitril targets nephrilysin which results in diuresis and vasodilatation. Valsartan inhibits the angiotensin receptor leading to suppression of the overactive Renin-Angiotensin-Aldosterone System (RAAS). Both of these new drug therapies have been proven to reduce hospitalizations and mortality in patients with HF reduced ejection fraction and are currently included in the guidelines for HF therapy.

Introduction:

The epidemic of HF has become a major burden on health care costs. The estimated prevalence is more than 5.8 million in the United States with a survival of 50 percent at 5 years and 10 percent at 10 years. Reduction of readmission rates has become a major quality metric in most hospitals, primarily driven by the Hospital Readmission Reduction Program established by Medicare and Medicaid which inflicts a reimbursement penalty on institutions with multiple readmissions. Improvements in the morbidity and mortality of HF have been associated with medical therapies such as the institution of β-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone blockade which are known as goal directed medical therapies (GDMT). The original fundamental understanding of the neurohormonal dysregulation that takes place in patients with HF has subsequently facilitated the development of novel therapies to target the RAAS and adrenergic system.

In 2015, two new drugs were approved by the FDA within four months of each other for the treatment of heart failure: Ivabradine (Corlanor) and Sacubitril/Valsartan (Entresto).

Ivabradine

Under normal conditions, the sympathetic and parasympathetic nervous systems work in synchrony to regulate the cardiovascular system. In the setting of HF there is dysregulation of the compensatory mechanisms, resulting in decreased parasympathetic activity and increased sympathetic activity. The overly active and less inhibited sympathetic nervous system causes increased norepinephrine release resulting in increased activity of β1 receptor (increased heart rate) and α1 receptor (vasoconstriction), decreased nitric oxide, and increased activation of RAAS. An elevated resting heart rate has been associated with increased cardiovascular risks and adverse prognosis. For this reason, targeting the adrenergic nervous system with β-blockers has been the mainstay of therapy for HF. Trials such as CIBIS II, MERIT-HF and COMET, have shown improvements in heart rate and survival. In a meta-analysis by McAlister et al, the relative risk reduction for death is decreased by 18 percent with every five beats per minute (bpm) reduction in heart rate with β-blocker. Some of the limitations for achieving target doses of β-blockers recommended by the 2013 ACCF/AHA Guidelines for the Management of Heart Failure include COPD, hypotension, asthma, and acute heart failure decompensation. This has led to the development of new therapies, such as Ivabradine, which have been shown to reduce adverse cardiovascular outcomes in patients with HF without some of the side effects noted with β-blockers.

Ivabradine was approved by the FDA on April 15, 2015 for stable symptomatic chronic HF patients with reduced left ventricular ejection fraction (LVEF) ≤ 35 percent, who are in sinus rhythm with resting heart rate ≥ 70 bpm and are on maximally tolerated β-blockers doses or have a contraindication to β-blockers. Contraindications for the use of Ivabradine include blood pressure < 90/50 mmHg, sick sinus syndrome, sinoatrial block or complete heart block (unless the patient has a permanent pacemaker), resting heart rate < 60 bpm, severe hepatic impairment, heart rate solely maintained by the pacemaker, and patients taking a CYP3A4 inhibitor.
Ivabradine acts by inhibiting the I$_f$ current channel, specifically at the SA node. Since depolarization of the action potential for the SA node is dependent on the I$_f$ current, its blockade results in decreased spontaneous firing of the SA node and subsequent reduction in the heart rate.$^{23,24}$ The selective antagonist action of Ivabradine on the I$_f$ current allows it to be very useful, as it has no impact on the T- or L-Type calcium channels or on the delayed rectifier potassium channel avoiding QT prolongation or QRS widening.$^{23}$ The major adverse effects of Ivabradine include bradycardia, hypertension, atrial fibrillation and a phenomenon called phosphenes. Phosphene is a visual disturbance associated with enhanced brightness, halos, and image disturbance. The recommended starting dose is 5mg twice a day to achieve a target heart rate between 50-60 beats per minute. Patient should be reassessed in two weeks. If target heart rate has not been achieved, the dose can be increased by 2.5mg twice a day for a maximum dose of 7.5mg twice a day. No renal dose adjustment required. The drug is metabolized in the liver by CYP3A4 with a half-life of six hours.

The Systolic Heart Failure treatment with I$_f$ inhibitor Ivabradine trial (SHIFT) was a large multinational randomized, double blind, placebo-controlled trial of 6,506 patients with symptomatic HF and LVEF of <35 percent. Results showed that HF patients with reduced left ventricular function who are on β-blockers and have not achieved target heart rates < 70 bpm benefit from the addition of Ivabradine.$^{25}$ More than 70 percent of patients achieved a resting heart rate lower than 70 bpm after a month of treatment. Median follow-up was 22.9 months. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening HF. Analysis was by intention to treat. The addition of Ivabradine significantly reduced the combined outcome of hospitalizations from HF and cardiovascular death (24 percent versus 29 percent for placebo) (HR 0.82, 95 percent CI 0.75–0.90, p<0.0001). The number needed to treat [NNT] for two years was 26. The effects were driven mainly by hospital admissions for worsening HF (21 percent placebo versus 16 percent Ivabradine; HR 0.74, 95 percent CI 0.66-0.83; p<0.0001) and deaths due to HF (5 percent versus 3 percent); HR 0.74, 95 percent CI 0.58–0.94, p=0.014). However, there was no significant difference in cardiovascular death or all-cause mortality.$^{25}$ The impact of Ivabradine on the combined cardiovascular events in relation to heart rate has been well illustrated.

The unloading effect of Ivabradine on the left ventricle was studied in a subgroup of patients from the SHIFT trial who were evaluated with echocardiography at baseline and after eight months of therapy with Ivabradine compared to the placebo group.$^{26}$ As demonstrated in the SHIFT trial there was a significant decrease in heart rate in Ivabradine group of -11 ± 13 bpm vs -2 ± 12 bpm (p < 0.0001). Since stroke volume is equal to cardiac output divided by heart rate, the decrease in heart rate resulted in higher stroke volume. There was also a decrease in arterial elastance (Ea) -0.26 ± 0.68 mmHg/ml for Ivabradine versus 0.10 ± 0.58 mmHg/ml for placebo (p < 0.0001), which is a measure of the arterial vascular load on the heart. The ventricular-arterial coupling ratio (Ea/Ees) was also reduced -0.13 ±0.46 for Ivabradine versus 0.11 ±0.43 for placebo (p = 0.02), where Ees represents LV end systolic elastance which is a measurement of ventricular contractility.$^{26}$ The reduction in the Ea/Ees ratio demonstrates the ventricular unloading advantages of heart rate reduction, as well as improved contractility with the use of Ivabradine.

The appropriateness and effectiveness of Ivabradine in acute heart failure was evaluated in the ETHIC-AHF trial,$^{27}$ which was a prospective, randomized, non-blinded, and single center study. The study consisted of 71 patients with acute heart failure of irreversible etiology, left ventricular dysfunction with EF < 40 percent, with sinus rhythm with HR > 70 bpm who were randomized within the first 24-48 hours to placebo (N=38) or Ivabradine (N=33). After 28 days Ivabradine could be added to the control group. All patients were on GDMT. The primary outcome of the study was the heart rate at 28 days and the secondary outcomes were heart rate at four months, adverse effects, and combined events of all-cause mortality, and hospital admission for HF or cardiovascular cause. Heart rate at 28 days was lower on the Ivabradine group with an average of 64.3 ± 7.5 bpm versus 70.3 ± 9.3 bpm (p = 0.01) in the placebo group and at four months it was 60.6 ± 7.5 bpm for Ivabradine versus 67.8 ± 8 bpm for placebo (p = 0.004). No statistically significant differences were noted on all-cause mortality or hospital admission.$^{27}$

The cost of Ivabradine is $375/month which amounts to $4,500/year. In a 10 year cost effectiveness analysis,28 the estimated total cost of Ivabradine including hospitalization, adverse effects, and drug acquisition was $369,762 compared to $378,356 with GDMT, which estimates a total cost savings of $8,594. The high cost of drug acquisition is outweighed by the reduction in hospitalizations resulting in incremental savings compared to GDMT, as well as increment improvements in quality adjusted years (QALYs) of 4.02 versus 3.78 favoring Ivabradine.$^{28}$
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Sacubitril/Valsartan (Entresto)

The dysregulation on RAAS in patients with HF has encouraged numerous studies evaluating the benefits of blocking different pathways of the cascade. Angiotensin converting enzyme inhibitors (ACEI) were introduced in 1991 and their use is associated with a decrease in HF mortality by 16-28 percent while angiotensin receptor blockers (ARB) have inconsistent reduction in mortality and are used in patients intolerant to ACEI.29,30,31,32 The introduction of β-blockers in 1995 and aldosterone-receptor antagonist in 1999 resulted in an additional 34 percent and 15 percent decrease in mortality; respectively when added to ACEI.9,33,34,35

Angiotensin receptor-neprilysin inhibitor (ARNI) in the form of Entresto (LCZ696, sacubitil/valsartan) was approved in the United States in July 2015. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial36 compared Entresto versus Enalapril. ARNI reduced HF mortality by 16 percent, cardiovascular death by 20 percent and HF hospitalization by 21 percent.36 In fact, Entresto was noted to decrease heart failure hospitalization by 40 percent within the first 30 days from randomization, with a 23 percent reduction in cumulative number of hospitalizations for heart failure exacerbation, when compared to Enalapril.37

Patients with HF usually develop compensatory mechanisms that involve activation of the renin angiotensin and natriuretic peptide systems. This leads to vasoconstriction, hypertension, elevated aldosterone levels, increased sympathetic tone, increased fibrosis and ventricular hypertrophy, which over time lead to worsening heart failure.38 Interestingly, Entresto targets the two

![Figure 1: Mechanism of Action of Entresto](image-url)
Entresto is a combination of Sacubitril, a neprilysin inhibitor and Valsartan, an ARB. The prodrug sacubitril is converted to active neprilysin inhibitor LBQ657 which inhibits neprilysin, the enzyme which degrades vasoactive substances such as atrial natriuretic peptide (ANP), brain natriuretic peptide, C-type natriuretic peptide (CNP), adrenomedullin, angiotensin II, bradykinin and substance P. Of note, N-terminal pro-BNP (NT-proBNP) is not a substrate for neprilysin. Inhibition of neprilysin results in higher levels of natriuretic peptides, which results in diuresis, natriuresis, vasodilatation as well as decreased renin release. In a pilot study of 350 patients, it was noted that higher levels of soluble neprilysin (greater than 0.67 ng/ml) were associated with increased risk of cardiovascular death or heart failure hospitalization with a hazard ratio of 1.87 (95 percent CI 1.11-3.16, p = 0.02) at two months and 1.59 (95 percent CI 1.16-2.19, p = 0.004) at end of follow up. In addition, with an increased number of patients to 1069, higher concentration of soluble neprilysin above a median of 0.642 ng/ml was associated with increased risk of cardiovascular death or heart failure hospitalization with a hazard ratio of 1.37 (95 percent CI 1.11-1.69, p = 0.003) and cardiovascular death with a hazard ratio of 1.59 (95 percent CI 1.16-2.19, p = 0.004). The addition of Valsartan to sacubitril allows for blockade of the angiotensin type 1 (AT1) receptor thereby inhibiting the RAAS, targeting an additional pathway of disequilibrium in HF patients.

Entresto is approved for use in HF patients with reduced ejection fraction (HFrEF) and chronic heart failure with New York Heart Association (NYHA) class II-III. It should be used in addition to other GDMT therapies and in place of an ACEI or single agent ARB. It is contraindicated in patients with simultaneous use of ACEI/ARB, aliskiren in diabetics, previous history of angioedema to ACEI or ARB, or hypersensitivity reaction to neprilysin inhibitor or ARB.

Entresto is orally administered with ≥ 60 percent bioavailability for sacubitril. The peak plasma concentrations of sacubitril, neprilysin and valsartan are reached in 0.5 hours, 2 hours and 1.5 hours respectively with a steady state reached after three days in twice daily dosing. It is 94-97 percent highly bound to plasma protein with a half-life elimination of 1.4 hours, 11.5 hours and 9.9 hours for sacubitril, LBQ657 and valsartan, respectively. Metabolites of Entresto are excreted in both urine and feces.

Recommended starting dose of Entresto (sacubitril/valsartan) is 24/26mg twice a day for patients not taking or on low dose ACEI or ARB, severe renal impairment (eGFR <30ml/min/1.73 m2) and moderate hepatic impairment (Child-Pugh B classification). If already on dose appropriate ACEI or ARB, starting dose is 49/51mg twice daily. Entresto dose should be doubled every 2-4 weeks until a target dose of 97/103 mg bid is attained or as tolerated by patient. No starting dose adjustment is needed for mild hepatic impairment (Child-Pugh A classification) and mild-moderate renal impairment. Entresto is not recommended in patients with Child-Pugh C hepatic disease. Of note, valsartan in Entresto is more bioavailable than valsartan in other formulations with 26mg, 51mg and 103mg equivalent to 40mg, 80mg and 160mg, respectively. If a patient is switched from an ACEI to Entresto, allow a washout period of 36 hours between administrations of the two drugs to avoid risk of hyperkalemia, angioedema and kidney injury.

Adverse effects of Entresto include angioedema, hypotension, hyperkalemia, impaired renal function, cough and dizziness. Avoid use of ACEI, Aliskiren, potassium sparing diuretics and non-steroidal anti-inflammatory drugs due to increased risk of renal injury as well as hyperkalemia. Also avoid concomitant use of lithium due to increased risk of lithium toxicity. Use in pregnancy is contraindicated.

Compared to Enalapril, Entresto is more costly at a rate of $12.50 per day which amounts to $1140 over a three month period. However, it is more effective and has a 6.49 QALY gained over lifetime (compared to 5.74 QALY with Enalapril) at a cost of $50,959 per QALY which is noted to be cost effective in the long run depending on patients willingness-to-pay.

Conclusion

Over the past few years the introduction of new therapies for heart failure, such as Entresto and Ivabradine, have allowed for improvement in survival and reduction in hospitalizations for patients with HFrEF. In the recent 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapies for Heart Failure, these new therapies are included in the recommendations, in addition to the traditional well-known GDMT. The use of ACEI, ARB or ANRI is recommended in addition to β-Blockers, aldosterone antagonist in patients with HFrEF to reduce morbidity and mortality as a Class I indication. The ACC/AHA/ HFSA guideline update gives a Class I recommendation (Level of Evidence: B-R) to replace an ACE inhibitor or ARB by an ARNI in selected patients with chronic symptomatic HFrEF (New York

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Heart Association [NYHA class II/III] with an adequate blood pressure who are already tolerating a reasonable dose of ACE inhibitor or ARB. In addition, The ACC/AHA/HFSA guideline update gives a Class IIa recommendation (Level of Evidence: B-R) for use of Ivabradine to reduce HF hospitalization in patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35 percent) receiving guideline-directed evaluation and management, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70. The cost-effectiveness models suggest that these medications are associated with cost savings and improved clinical outcome.

References


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Implantable PA Pressure Monitoring for Heart Failure Management: A Single Center Experience

By Sumant Lamba, MD, FACC

Abstract: With greater than five million Americans affected, the societal burden of heart failure (HF) continues to increase. Early identification of acute decompensated heart failure with the use of an implantable pulmonary artery (PA) pressure monitor has been associated with decreased all-cause hospitalizations and mortality.

Introduction

Acute decompensated heart failure (ADHF) is the leading cause of hospitalization in patients over the age of 65. In conjunction, there are greater than one million hospitalizations occurring annually for ADHF. Heart failure hospitalizations are strong predictors of subsequent mortality and carry a high risk for future readmission of approximately 25 percent at 30 days and 50 percent at six months. Roughly 1.4 million U.S. patients have New York Heart Association (NYHA) Class III heart failure, and historically these patients account for nearly half of all HF hospitalizations.

Various processes intersect when a patient transitions from chronic heart failure (CHF) to ADHF, including neurohormonal activation, up-regulation of inflammatory mediators, and cardio-renal interactions. These pathways lead to an elevation in ventricular filling pressures and signs of congestion. Worsening symptoms of congestion account for the majority of admissions for heart failure; however, many clinical signs have poor sensitivity for detecting acute decompensation. Clinical signs typically demonstrate late manifestations of significantly elevated intra-cardiac filling pressures. Weight changes are a poor predictor of decompensation. By the time patients gain weight, they are symptomatic. Oftentimes, an increase in weight may not reflect an increase in intravascular filling pressures. Given the limited sensitivity of signs and symptoms of congestion, studies evaluating the efficacy of tele-monitoring have failed to show a benefit in reducing heart failure readmissions.

The CardioMEMS Champion Heart Failure Monitoring System (St. Jude Medical) is a permanently implantable pressure measurement system designed to provide daily pulmonary artery (PA) pressure measurements in an ambulatory setting. The system helps guide HF management in an outpatient setting to reduce HF hospital stays. The system consists of an implantable sensor/monitor, which is a battery-free capacitive pressure sensor permanently implanted in the PA (Figure 1), a transvenous delivery system designed to deploy the implantable sensor in the distal PA, and the Champion Electronics System (CardioMEMS), which acquires and processes signals from the implantable sensor/monitor and transfers PA pressure measurements to a secure database accessible by the treating physician (Figure 2).

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The implantable sensor is small, does not require batteries or leads, and is designed to last the lifetime of the patient (Figure 3). Placement is completed in the catheterization lab. The femoral vein is accessed using an 11 French sheath. A limited PA gram is completed in order to determine adequate targets for sensor implant. The CardioMEMS sensor is then delivered to the target pulmonary artery using a delivery catheter that is advanced over the wire with confirmation by fluoroscopy. The implanted sensor is then calibrated using pulmonary artery pressures obtained from the PA catheter. Once implanted, the sensor can wirelessly send PA pressure readings to an external patient electronic system (Figure 4).

At home, HF patients use a portable electronic unit and a special pillow containing an antenna to take daily sensor readings. This is a simple process that takes only a few minutes. There is no pain or sensation for the patient during the readings. The external unit transmits the readings to a secure website where the data can be seen by the patient’s clinician.

On December 8, 2011, the Food and Drug Administration (FDA) Circulatory System Devices Panel reviewed the CardioMEMS Champion HF Monitoring System premarket approval (PMA) application. The CardioMEMS™ HF System is the first and only FDA-approved heart failure (HF) monitor proven to significantly reduce HF hospital admissions and improve quality of life in NYHA class III patients. When used by clinicians to manage HF, the CardioMEMS HF System is safe and reliable, clinically proven, proactive and personalized.

Methods

One-year experience with the CardioMEMS, pulmonary artery pressure monitoring system at First Coast Cardiovascular Institute is described. Patients who underwent CARDIOMEMs implantation at the Orange Park Medical Center from June 2015-2016 were included in this observational cohort. Implantation of the device was per protocol as previously described. Daily assessment of patient PA pressure readings were completed via an external patient electronic system by a nurse practitioner and overseen by a heart failure specialist. Adjustments to diuretic therapy were similar to the protocol described in the CHAMPION trial. Data of this observational cohort were obtained through chart review and through the CVI CardioMEMS database.

Results

Forty-one devices were implanted from June 2015-2016. There were no device related complications. All but one patient was discharged home within three hours of device implant. The remaining patient was kept overnight for diuresis.

Forty-one patients had a cumulative 72 admissions in the two years prior to device implant due to exacerbation of CHF. Of the patients implanted, 31 (75 percent) had a primary diagnosis of HFrEF and 10 had HFpEF. Two patients expired after implant: One patient expired of progressive pump failure within three months of implant and one patient expired due to non-associated complications of pancreatitis. Of the 39 living patients, only five were admitted over a period of one year with a total of 10 cumulative readmissions:

1. Patient 1: Admitted for 72 hours for exacerbation of CHF and again in three weeks for prerenal azotemia. At 95 years of age, this is the oldest patient in the country to receive the device. PA diastolic pressures average between 40-45 mmHg.
2. Patient 2: Admitted for hypotension and renal insufficiency when started on valsartan/sacubitril.

4. Patient 4: Admitted for stroke related to atrial fibrillation and another hospitalization for pericardial effusion which was suspected because of damped pressure waveforms from the CardioMEMS.

5. Patient 5: Admitted with prosthetic mitral valve stenosis, renal insufficiency and sepsis.

Four additional patients were admitted for 23-hour observation for aggressive diuresis in the heart failure observational unit due to elevated filling pressures. They were discharged within 23 hours and did not count as hospital admissions.

Discussion

This single center result from a “real world setting” replicates the data seen in the CHAMPION trial supporting utilization of implantable PA pressure monitors for patients with advanced heart failure. The CHAMPION trial was a randomized, controlled, single-blind study of 550 patients with New York Heart Association functional class III HF with a HF hospitalization in the prior year. All patients undergoing implantation of the ambulatory PA pressure monitoring system were randomized to the active monitoring group (PA pressure-guided HF management plus standard of care) or to the blind therapy group (HF management by standard clinical assessment), and followed for a minimum of six months. Medical therapy data were compared between groups to understand what interventions produced significant reduction in HF hospitalizations in the active monitoring group. On top of optimal medical therapy, including Cardiac Resynchronization Therapy (CRT) or Implantable Cardioverter Defibrillator (ICD) devices, PA pressure (PAP) management still resulted in additional benefit to decrease all-cause hospitalizations and mortality. The number needed to treat to prevent one hospitalization with PAP management is two patients needed to treat to prevent one hospitalization.

At six months, there was a 28 percent reduction in heart failure hospitalizations, with 84 hospitalizations in the treatment group, compared to 120 in the control group (hazard ratio [HR] 0.72, 95 percent confidence interval [CI] 0.60-0.85; p = 0.0002).11 There was a 37 percent reduction in heart failure-related hospitalizations in the treatment group during the entire follow-up period, which averaged 15 months (HR 0.63, 95 percent CI 0.52-0.77, p < 0.0001).11 Further, there was a significant improvement in quality of life in the treatment group, as demonstrated by improvement in Minnesota Living with Heart Failure Questionnaire.11 Not surprisingly, the length of stay for heart failure-related hospitalizations was significantly shorter in the treatment group, as compared to the control group (2.2 days vs. 3.8 days, p = 0.02) and the treatment group had more changes to heart failure medications compared to the control group (9.1 per patient versus 3.8, p <0.0001). The rate of device related or system related complications was low (n = 8) with 98.6 percent freedom from complications.11 Complications included bleeding, atrial dysrhythmias, fever/infection, cardiogenic shock and arterial embolization in the setting of interruption of anticoagulation for procedure completion. Although pulmonary embolism is a potential and concerning risk, there were no pulmonary embolisms noted during the CHAMPION trial.

There have not been many effective treatment options that have been shown to improve outcomes in patients with heart failure with preserved ejection fraction. Approximately 20 percent of the patients enrolled in the CHAMPION trial had heart failure with preserved ejection fraction defined as heart failure with a left ventricular ejection fraction of ≥ 40 percent.11 In this pre-specified subgroup of patients, heart failure hospitalizations were 46 percent lower in the treatment group compared to the control group by primarily adjusting diuretic therapy based on pulmonary artery pressure tracings (incidence rate ratio 0.54; 95 percent CI 0.38-0.70; p < 0.0001).11

In a retrospective analysis of the CHAMPION clinical data for heart failure with reduced ejection fraction (HFrEF) patients already on guideline-directed medical therapy, pulmonary artery pressure guided management reduced HF hospitalization by 43 percent and mortality by 57 percent.12

The results of the CHAMPION trial suggest that hemodynamic-guided medical management of heart failure patients via an invasive wireless implantable heart monitor can improve symptoms and reduce heart failure hospitalizations by approximately one-third.9 It must be emphasized that these pressure-monitoring tools were used to implement a protocol-defined medical strategy that involved a team-based approach to care coordination and delivery. In addition to frequent clinic visits, there was online access to review pulmonary pressures daily, and an automatic email notification system was in place to notify study personnel if the daily pulmonary pressures were outside of the user-defined range. The protocol considered patients with elevated pulmonary pressures to be volume overloaded with the initial recommendation to increase diuretic therapy. If pulmonary pressures re-
mained persistently elevated despite optimal diuretic medication changes, vasodilator therapy was recommended. The majority of medication adjustments were around diuretic therapy. The below-average rate of heart failure hospitalizations observed in the control group highlighted the importance of CHF management.11 The CHAMPION trial mandated monitoring of pressures twice a week and management decisions on adjustment of diuretics and vasodilators based on symptoms. Costanzo and colleagues monitored pressures daily and made adjustments based on PA catheter targeted algorithm and showed an additional 50 percent decrease in hospitalizations.13

While the single center data also demonstrated a reduction in hospitalization rates after CardioMEMS implantation, there were several patient-practice related insights that were learned while managing this cohort: Patients with normal transpulmonary gradients improve functionally when the PA diastolic pressure was targeted to 15-20 mmHg and PA mean targeted between 25-25 mmHg. It was important that achievement of these pressure goals was completed slowly over a period of weeks to preserve renal function. A combination of daily torsemide with intermittent metolazone was usually sufficient to achieve an optivolemic state; however, intermittent intravenous diuresis in a heart failure observational unit was needed to avoid admissions for those with cardiorenal syndrome. Most importantly, the cornerstone of this personalized therapy required a dedicated, concerted, programmatic and multidisciplinary approach headed by a nurse practitioner, overseen by a heart failure specialist with input from administrative, dietary and social services with home health care, if required.

Conclusion

Incorporation of a PA pressure-guided treatment algorithm to decrease filling pressures to targeted changes, particularly diuretics and vasodilators, is more effective in reducing HF hospitalizations than management of patient clinical signs or symptoms alone. The ongoing CardioMEMS registry will hopefully continue to demonstrate the beneficial effects of this device in decreasing hospitalizations, improving quality of life and also prolonging survival.  

References:

INDICATIONS

Adult Ulcerative Colitis (UC)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission.

Adult Crohn’s Disease (CD)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission.

IMPORTANT SAFETY INFORMATION

- ENTYVIO (vedolizumab) for injection is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

- Infusion-related reactions and hypersensitivity reactions including anaphylaxis have occurred. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.

- Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.
Engineered for UC and CD

- Provides remission for patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD)
  - Studied in patients who have failed conventional therapies or a biologic
  - Individual results may vary

- Clinical trials evaluated safety in more than 3300 adults on Entyvio
  - Including more than 800 patients who received Entyvio for more than 2 years

- A distinct mechanism of action that specifically blocks lymphocyte migration that is a key contributor to inflammation in the gut

- Entyvio specifically binds to α4β7 integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells

- 300-mg dose for adult patients

IMPORTANT SAFETY INFORMATION (continued)

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.

- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.

- Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see brief summary of Prescribing Information on adjacent pages.

Brief Summary of Full Prescribing Information

ENTYVIO (vedolizumab) for injection, for intravenous use

Indications and Usage

Adult Ulcerative Colitis (UC)

ENTYVIO (vedolizumab) is indicated for:
- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Adult Crohn’s Disease (CD)

ENTYVIO (vedolizumab) is indicated for:
- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Contraindications

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate).

Warnings and Precautions

Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) (see Adverse Reactions). Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYVIO may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and institute appropriate treatment (e.g., epinephrine and antihistamines).

Infections

Patients treated with ENTYVIO are at increased risk for developing infections (see Adverse Reactions). The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasopharynx (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML) (see Warnings and Precautions).

Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury (see Adverse Reactions).

Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO (see Adverse Reactions).

Adverse Reactions

The following topics are also discussed in detail in the Warnings and Precautions section:
- Infusion-Related Reactions and Hypersensitivity Reactions (see Warnings and Precautions)
- Infections (see Warnings and Precautions)
- Progressive Multifocal Leukoencephalopathy (see Warnings and Precautions)
- Liver Injury (see Warnings and Precautions)

Clinical Trials Experience

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

The data described below reflect exposure to ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 935 exposed for greater than two years.

The safety data described in Table 1 are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

In these trials, 1,434 patients received ENTYVIO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn’s disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVIO and 45% of patients treated with placebo (UC Trials I and II; 45% with ENTYVIO and 37% with placebo; CD Trials I and III; 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II; 8% with ENTYVIO and 7% with placebo; CD Trials I and III; 12% with ENTYVIO and 9%, with placebo).

The most common adverse reactions reported in ≥5% of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, ophthalmic pain and pain in extremities (Table 1).
Table 1. Adverse Reactions in ≥3% of ENTYVIOTreated Patients and ≥1% Higher than in Placebo (UC Trials I and II and CD Trials I and III).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENTYVIO† (N=1334)</th>
<th>Placebo† (N=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Or pharyngeal pain</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Pain in extremities</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Data from patients receiving open-label ENTYVIOTreatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

†Patients who received ENTYVIOTreatment for up to 52 weeks.

‡Patients who received placebo for up to 52 weeks.

Safely data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn’s disease trial, are similar to those listed in Table 1.

In controlled and open-label long-term extension trials in adults treated with ENTYVIO, serious infections have been reported, including sepsis, sepsis (some fatal), tuberculosis, salmonella sepsis, listeria meningitis, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn’s disease patients treated with ENTYVIO due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn’s disease receiving ENTYVIO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

**Liver injury**

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO [see Warnings and Precautions]. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of AL and AST elevations >2 x ULN was 2% in patients treated with ENTYVIO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

**Malignancies**

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphomas, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary nonendothecial carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

**Live and Oral Vaccines**

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg rectal dose (twice the repeat dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titer relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

**Immunogenicity**

As with all therapeutic proteins, there is potential for immunogenicity. In UC Trials I and II and CD Trials I and II, in patients who received ENTYVIO, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVIO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 8 or 52 in the controlled trials.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced...
by several factors, including sample handling, timing of sample collection, concomitant medications, presence of vecolizumab, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENTIVIO with the incidence of antibodies to other products may be misleading.

**DRUG INTERACTIONS**

**Natalizumab**
Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTIVIO with natalizumab.

**TNF Blockers**
Because of the potential for increased risk of infections, avoid the concomitant use of ENTIVIO with TNF blockers.

**Live Vaccines**
Live vaccines may be administered concurrently with ENTIVIO only if the benefits outweigh the risks [see Warnings and Precautions].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

*Pregnancy Exposure Registry*
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTIVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDAT (1-877-825-3327).

*Pregnancy Category B*

*Risk Summary*
There are no studies with ENTIVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

*Clinical Considerations*
Any adverse pregnancy effect from ENTIVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

*Animal Data*
A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

*Nursing Mothers*
It is unknown whether vecolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

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

**Geriatric Use**
Clinical trials of ENTIVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn’s and ulcerative colitis patients aged 65 and over were treated with ENTIVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

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Three, Two, One: A Look at Crohn’s Disease Diagnosis

By Mark R. Fleisher, MD

Introduction

Numbers are fascinating. People find solace in numbers. People look and find meaning in numbers. People give answers in numbers. They find strength in numbers. And yet, numbers can be made to dance. A number, to one person, can mean something else to a number of others. However, no one can argue that “3, 2, 1” has a certain cache. It is a NASA countdown. It is the drop of the ball on New Year’s Eve. To those who love Immune Mediated Inflammatory Disorders (IMID), it is the essence of IMID. There are 300 million citizens in our nation. Three percent have Psoriasis. Two percent have Rheumatoid Arthritis. One percent has Inflammatory Bowel Disease. Six percent of our nation has an IMID.¹ That makes 1.8 million people. That is a seemingly abstract number. However, if you go to a sold out game at Yankee Stadium, take a look at the upper deck. One entire section has an IMID. Every seat in that section has one of these three illnesses.² Nonetheless, to try to distinguish these illnesses as separate entities is foolhardy. These three illnesses are actually all the same. They are all a result of an over-exuberant explosion of cytokines and leukotrienes with a myriad of phenotypic expressions. Some people get joint pains. Some get skin issues. Some have digestive problems. Yet if you look at the commercials, the same drug can be applied to all of these seemingly unrelated illnesses.³ That is how I feel when I see biologic therapy being sold on TV or in our journals. By selling these biologics for seemingly unrelated illnesses, a great opportunity is lost. The customer and physicians could be behaviorally modified to start unifying these illnesses instead of compartmentalizing them.

Case 1

Here is an example that demonstrates why, when we see one, we need to think all three.

A 45-year-old African American male comes to the office for colon screening. He thinks he may be too early but he is not. He is right on time. The recommended screening in this population is 45 years old and not 50 due to an increased risk of colon cancer in African Americans.⁴ After assuaging his fears that his primary care physician is too aggressive, we obtained his history. The patient has psoriasis of the elbows and knees. He uses a topical cream for his outbreaks. Moreover, he has some joint pains that he attributes to just getting older. He has some irregular bowel habits and has been told he has irritable bowel syndrome. Immediately, my Spider Sense is tingling. Three, two, one!

Discussion:

Colonoscopy is normal to the terminal ileum. Labs are all normal including rheumatoid factor and anti-nuclear antibody. However, realizing that our job is not done, the patient undergoes a video capsule endoscopy.⁵ The jejunum is studded with erosions and ulcers. Labs reveal serologic changes such as an elevated ASCA (anti saccharomyces cerevisiae antibody).⁶ The patient most assuredly has psoriasis. However, in the setting of one IMID, the patient has been found to have Crohn’s disease. The joint pains may be either a Crohn’s arthropathy or a psoriatic arthritis. The patient was receiving a topical agent for what is a systemic illness.

Upon starting a biologic agent in the form of ustekinumab, all components of the illness have been addressed. The patient’s psoriasis has quelled. The arthritis has vanished and the irregular bowel habits attributed to irritable bowel syndrome have now normalized. The interruption of the activity of IL-12 dampens the immune cascade and further deleterious overproduction of subsequent cytokines have been blocked.⁷
Let’s Review

Three, two, one should be our mantra. When we see one IMID, it behooves us to wonder if the other two are lurking. Moreover, the patient who presents for screening is actually presenting for a thorough evaluation. If all that is considered is the colon, we are missing our opportunity to find what may have been overlooked. Our government has been brilliantly created with a system of checks and balances. So it is with medicine. The gastroenterologist whose approach to the patient begins in the mouth and ends in the rectum is missing the joy of medicine. What else can I find? What else is lurking? My wife is an enigma, but each patient is a mystery. That is why home and work are different but both fun.

Just as I love numbers, I thoroughly enjoy words. A word to the wise is sufficient. May I have a word with you? These are great phases and yet some people claim that they can’t find the right words or that words can’t express how they feel. Of course they can. They may not know the right words but they are there. Just keep looking and string them together. Don’t let words escape you. Capture the moment, not with a photo but with a phrase. One of my favorite phrases is forme fruste. Taught to me by my brilliant colleague, Dr. Robert Kanner, forme fruste is an atypical and usually incomplete manifestation of a disease. Of course, we are always thinking “three, two, one.” However, we are also always thinking forme fruste.

Case 2

Here is an example of how being on high alert for an IMID can be quite revealing:

I was the GI fellow at Lenox Hill Hospital in Manhattan. As I walked through the ER looking for colons that haven’t been introduced to me or my colonoscope, I passed by a stretcher upon which held a tearful and trembling little girl. Her mother, a police officer, and a social worker were convened. The mother was sobbing. The social worker looked stern and concerned. The police officer was listening intently but compassionately.

As I passed by, I could hear snippets of conversation. The child had what seemed to be a giant deep cigarette burn of the lower extremity. The mother was denying child abuse and so was her daughter. They claimed that they have no idea how the cigarette burn got there. They claimed that she just awakened with it. She had multiple healing scars on both legs. They sure did look like old burns. Being a native New Yorker, everything is my business. I stopped by and asked the little girl, “Does your abdomen hurt?” My boys, around 10 years old, love it when I use words like abdomen. She was crying and very scared. I pressed on her right lower quadrant. She recoiled. I asked her if she tends to get diarrhea. Her mother told me that her daughter had a nervous stomach. I told all four persons that this was not a cigarette burn. It is acute leukocytoclastic vasculitis and the patient has Crohn’s Disease. The girl was admitted to the hospital. Endoscopy revealed numerous ulcers of the terminal ileum. No joint pains. No bloody diarrhea. No growth stunting. No lab abnormalities. Just a weird rash and maybe some bouts of irregular bowel habits. It was forme fruste Crohn’s Disease with a presentation purely of an extraintestinal manifestation.

Conclusion

As the senior GI fellow, I had the pleasure to round on the medical service as the wingman of the Chief of Gastroenterology and President of the American College of Gastroenterology, Dr. Burton Korelitz. At the end of every single case, he would mention, “We sometimes see this in Crohn’s Disease.” Whether it was heart failure or renal failure or lung nodules, he reminded everyone that “it could be Crohn’s disease.”

It is with this in mind that we remain mindful of three important lessons: “three, two, one” signifies that IMIDs are plentiful. When you see one, think all three. Forme fruste means that you don’t need every characteristic to have the illness. Lastly, be on high alert because everything could be Crohn’s disease.
References:


People always talk about the Hippocratic Oath. You know, the whole “do no harm” thing. I never took it. I’m a doctor, but I never took that Oath. I went to the Sackler School of Medicine in Tel Aviv, Israel. We took the Oath of Maimonides. It’s a little different. In it, we are gently reminded to be gentle. Every life is so precious that if you save one it is as if you have saved the universe. It’s a little more positive. A little more uplifting. A little less medicolegal. A little more spiritual. I’m sure that Hippocrates was a good physician. I’m certain that he aced his boards. I’m confident his waiting room was packed. I’m positive herb reps couldn’t wait to detail him on the latest uses of eye of newt. However, I’ll bet Maimonides was probably just as good and probably better dinner company. I remember the day I took my Oath: Graduation Day. The marathon was over, or so I thought. Actually, the end of medical school merely signals the beginning of a career that is itself a joyous marathon. But that is another story. On the day I graduated, we all stood for The Oath. The Dean told us that he had only one goal for us: to save one life every year, in honor of Maimonides.

My friend Bob leaned past Eric and asked me, “Fleish, what did he say?”

I couldn’t believe it. “Bob! For G-d’s sake, you never pay attention! This is the last time I’m going to tell you what the professor said.”

Bob flashed his biggest smile and said, “I hate to tell you this, Mark, but it’s graduation. I can guarantee you this is the last time you’ll have to tell me what the professor said.”

Ever since that day, Bob calls me annually in October. He finds me in the hospital and pages me overhead, usually on a weekend, often at night. I don’t know how he knows where I am, but he does. Without even a salutation, he says “So, did you save a life this year?”

After we took The Oath, we were called up one by one to receive a cardboard tube. The Dean, in classic Israeli honesty, told us, “Don’t open the tube. There’s nothing in there. It’s just a prop. Your diplomas will be mailed to you.” When they called my name, I went on stage, received my empty baton and shook hands with all the dignitaries. At the end of the stage was a podium. On it was a book and a pen. Each student signed the book. The book of graduates. It was the first time I ever affixed M.D. after my name. I signed. My hand shook. I closed my eyes, and I spoke directly to G-d. I thanked him for allowing me to reach this day. I promised that I would never forget what this meant to me. I promised to show my gratitude in such a way that He knew I was in His debt.

Apparently, I was speaking to Him so long, that I was holding up the line. Jeffrey poked me and said, “Let’s go, Fleish! What are you doing?” I turned and replied, “If you don’t mind, I’m talking to G-d. Gimme a minute for G-d’s sake!” At which point, I closed my eyes again and asked G-d to forgive Jeffrey. You know how he is. I then added that I would keep my word. I put down the pen and patted the book with the corner of my gown. To me it was a holy scripture.

That was some day. I promised to keep my word. Since that day, I can tell you that I have often not kept my word to others. Even worse, I have not kept my word to myself. How disappointing. How human. However, from the day I graduated, I have tried to keep my word about graduation. I made my family live in an apartment before buying a home. I donated $100,000 to my medical school and only then started to look for a house. I told my family that you have to take care of first things first. I taught them not to wait to be successful in order to be charitable. Be charitable and success will most assuredly follow you everywhere. In fact, if you are not charitable, you will never be successful.

Recently, I was contacted by the Dean of my medical school. He invited me to give The Oath of Maimonides at the upcoming graduation in Israel. It is the highlight of my career. Before I render it, I will close my eyes and talk to G-d. I’m sure He remembers me. I have to thank Him. For everything.

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