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Are Mandatory Bundled Payments Coming to Cardiology?

In several previous columns, we presented a framework for success in the post-reform environment by describing the five key attributes of a value-based enterprise. To date, the transition to value-based care has been driven mainly—albeit slowly—by commercial payors or voluntary CMS programs. However, the introduction of CMS' Comprehensive Care for Joint Replacement (CCJR) initiative has hastened the pace of change. CCJR is a **mandatory** bundled payment program for hip and knee joint replacement procedures that will apply to hospitals and other health care providers in 75 metropolitan statistical areas (MSAs) across the country. Tentatively set to be implemented on January 1, 2016, this 5-year program sends a clear message that CMS is serious about moving away from traditional fee-for-service reimbursement. Organizations are wondering what service line(s) will be next for bundled payments, and many expect cardiology to be on deck.

CCJR Background

The CCJR program was announced in July 2015. If finalized as outlined in the proposed rule (after a 2-month comment period), all hospitals in the respective MSAs will be required to accept bundled payments for joint replacement procedures.¹ The program uses a retrospective bundled payment structure, meaning that providers will continue to receive fee-for-service reimbursement for Medicare patients. Then, on an annual basis, the total cost of care (both acute and post-acute) provided during the 90-day joint replacement episode is compared to a regional target price. As “episode initiators,” hospitals accept all of the financial risk for the total cost of care for the joint replacement episode and are also required to meet minimum quality standards. Hospitals pay a penalty to CMS if total costs exceed the regional target price but are eligible for a shared savings payment if the total cost is below the target price. Program collaborators (i.e., physicians, therapists, rehabilitation staff, and home health providers) are eligible to share in the financial risks and rewards if shared savings are achieved.

Relevance for Cardiologists

For cardiologists and cardiac service line administrators, proactively preparing for value-based reimbursement programs can yield substantial benefits. If the

CCJR program is successful in driving down costs for joint replacements, cardiac procedures are potential targets for bundled payments. Of particular focus within the voluntary Bundled Payments for Care Improvement (BPCI) initiative have been congestive heart failure and coronary artery bypass procedures. Congestive heart failure ranked as the second most common clinical episode chosen by participating providers in BPCI Model 2 (behind joint replacements), with over 34% participating as of Q1 2014.² The complexity and high costs associated with these procedures have drawn increased attention from CMS. And regardless of whether a mandatory bundled payment program is implemented within cardiology, there are clinical benefits associated with redesigning care processes to be more coordinated and cost-effective. Organizations taking a proactive approach to bundled payments are seeing increased profitability and improved quality of care through the care review process.

Ways to Prepare

There are several key steps that cardiology programs can take to prepare for value-based reimbursement.

- **Analyze the Total Cost of Care** - Traditional fee-for-service reimbursement does not incentivize hospitals and physicians to manage care costs in the post-acute setting. Incentives do exist, however, under a bundled payment structure. Hospitals must be proactive in partnering with physicians and post-acute care providers to better understand and control the total cost of care for an episode. By comparing their average acute and post-acute care costs to the costs of other providers in the region, hospitals can make informed decisions about how to manage costs for their patients, should bundled or other value-based payments take hold more broadly. This is particularly relevant for cardiac patients, whose costs for post-acute care can vary widely due to the complexity of the procedures or preexisting medical conditions.
- **Assess Care Management Processes** - As organizations pursue more effective care management processes, understanding ways to control costs for cardiac patients, especially chronically ill patients, is vital. Patient navigators can be helpful in efficiently

managing patients transitioning across post-acute care settings. Additionally, increasing the role of advanced practice clinicians (APCs) in patient care allows cardiologists to be more efficient with their time. By directing patients with more manageable post-acute care needs to lower-cost alternatives, such as home health, hospitals can be better prepared to reap financial rewards for savings achieved under a bundled payment structure.

- **Partner with Physicians** - Given that physicians are able to share in the financial risks and rewards associated with bundled payments, administrative leaders must look to develop greater alignment with physicians and include them in the process to identify cost-saving opportunities. Savings opportunities can include supply chain, implant, provider staffing, and post-acute costs. Given that cardiology groups have already been active over the years in developing tighter hospital alignment structures, collaboration under a bundled payment structure could prove less challenging relative to other specialties.

Ride the Value Wave

Provider organizations are entering a new world that requires much stronger partnerships across the care continuum. Proactively developing relationships among cardiologists, hospitals, and post-acute care providers will prepare your cardiac service line for anticipated reimbursement changes. Regardless of whether mandatory bundled payments expand to cardiology, reviewing care management processes to increase efficiency and drive cost savings is vital as payors continue shifting toward value-based reimbursement models. ■

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REFERENCES

1. Excludes hospitals with extremely low historical joint replacement volumes, Critical Access Hospitals, and hospitals already in the Bundled Payments for Care Improvement (BPCI) Model 1 or risk-bearing Model 2 or 4 for joint replacement.
2. Based on statistics from the *CMS Bundled Payments for Care Improvement (BPCI) Initiative Models 2-4: Year 1 Evaluation & Monitoring Annual Report* prepared for CMS by The Lewin Group.

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

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

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

WARNING: FETAL TOXICITY

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

1 INDICATIONS AND USAGE

1.1 Heart Failure

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

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

4 CONTRAINDICATIONS

ENTRESTO is contraindicated:

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

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

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

5.2 Angioedema

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

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

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

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

5.3 Hypotension

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

5.4 Impaired Renal Function

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

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

5.5 Hyperkalemia

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

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Angioedema [see Warnings and Precautions (5.2)]
- Hypotension [see Warnings and Precautions (5.3)]
- Impaired Renal Function [see Warnings and Precautions (5.4)]
- Hyperkalemia [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

Laboratory Abnormalities

Hemoglobin and Hematocrit

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

Serum Creatinine

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

Serum Potassium

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

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

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

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

The concomitant use of ENTRESTO with aliskiren is contraindicated in patients with diabetes [see Contraindications (4)]. Avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 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 concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

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

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

Data

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

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

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

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

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