



UNIVERSITY OF UTAH  
COLLEGE OF PHARMACY  
L. S. SKAGGS PHARMACY INSTITUTE

**UTAH MEDICAID DUR REPORT  
FEBRUARY 2016**

**HEART FAILURE:  
ANGIOTENSIN II RECEPTOR BLOCKER & NEPRILYSIN  
INHIBITOR COMBINATION**

Entresto™ (sacubitril/valsartan)

**Drug Regimen Review Center**

Joanita Lake B.Pharm, MSc EBHC (Oxon), Clinical Pharmacist

Natalia Ruiz, PharmD Student

Gary M. Oderda Pharm D, M.P.H, Professor

## Contents

Introduction .....	3
Methodology.....	4
Treatment options & Entresto formulation.....	5
Off-label use.....	5
Hospitalizations.....	5
Clinical Guidelines and related evidence .....	5
Implementation of Guidelines in Clinical Practice .....	7
Clinical Efficacy of Entresto .....	8
Systematic Reviews & Meta-analyses.....	8
Randomized Controlled Trials (RCTs).....	8
The US Institute for Clinical and Economic Review (ICER).....	9
Safety .....	10
Entresto’s place in therapy and potential criteria to be reviewed .....	11
Utah Medicaid Utilization Data.....	13
Conclusions .....	16
Potential clinical criteria.....	17
Appendix 1 – Drug information.....	19
Appendix 2 – Systematic review(s) & RCT(s) .....	29
Appendix 3 – Heart Failure Diagnoses .....	34
References .....	36

## Introduction

Heart failure (HF) is a chronic, progressive and debilitating condition in which the heart (or heart muscle) becomes dysfunctional due to structural or functional impairment of ventricular filling or ejection of blood and it cannot pump blood effectively.<sup>1-3</sup> Guidelines define cardinal manifestations of HF as dyspnea and fatigue (may limit exercise tolerance), and fluid retention (may lead to pulmonary and/or splanchnic congestion and/or peripheral edema).<sup>3</sup> Not all patients experience volume overload and therefore guidelines state that the term “heart failure” is preferred over “congestive heart failure”.<sup>3</sup> “The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function.”<sup>3</sup>

Based on the occurrence of heart failure hospitalizations and case fatalities between 2005 and 2011, it is estimated that there are 870,000 new cases of heart failure annually.<sup>4</sup> According to a 2009-2012 National Health and Nutrition Examination Survey, Heart failure affects approximately 5.7 million patients aged  $\geq 20$  years in the United States (US) and it is projected to affect more than 8 million patients aged  $\geq 18$  years in the US by 2030.<sup>5,6</sup> The lifetime risk of developing heart failure is estimated to be around 20% for Americans  $\geq 40$  years old.<sup>3,7</sup> In general, however, men have been associated with a greater incidence of heart failure.<sup>8,9</sup> HF incidence increases with age; 20 per 1000 individuals 65-69 years old to  $>80$  per 1000 individuals  $\geq 80$  years old.<sup>3</sup> It is important to consider this as one in five Americans will be  $>65$  years of age by 2050.<sup>3,10</sup> An epidemiologic study that followed patients 45 years of age and older with at least one hospitalization for heart failure concluded that the incidence of heart failure was higher in African Americans than in Caucasians across all age groups.<sup>9</sup> This same study estimated the 5-year case fatality after incident heart failure hospitalization to be approximately 42%.<sup>9</sup> “Around 30-40% of patients diagnosed with HF die within a year but thereafter mortality rate falls to less than 10% per year.”<sup>11</sup> Risk factors for heart failure include coronary artery disease, hypertension, diabetes, smoking, poor nutrition, inactivity, and obesity.<sup>4</sup>

HF is diagnosed based on a careful history and physical examination.<sup>3</sup> It may be staged using the New York Heart Association (NYHA) Functional Classification. It “focuses on exercise capacity and the symptomatic status of disease.”<sup>3</sup> This set of criteria rates the severity of the patients’ symptoms on a I-IV scale. Greater Roman numerals indicate more severe symptoms and more advanced heart failure.<sup>12</sup> Class I is associated with no limitation of physical activity where ordinary physical activity does not cause undue fatigue, palpitations, and dyspnea. Class II-IV is associated with limitation of physical activity.<sup>13</sup> There is another set of criteria developed by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) that can also be used to stage heart failure. It “emphasizes the development and progression of disease and can be used to describe individuals and populations.”<sup>3</sup> It uses the patients’ symptoms and structural abnormalities to stage them on an A-D scale. Similar to the NYHA classification, advanced stages are indicative of more advanced heart failure.<sup>12</sup> Depending on their stage, patients with heart failure may require treatment with more than one medication. The strongest levels of evidence are available for the use of angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists. In clinical trials it has been shown that these treatments in combination with conventional treatments such as diuretics, digoxin, and spironolactone decrease mortality and hospitalization rates.<sup>2,14</sup> Treatments with moderate levels of evidence for heart failure include diuretics, ivabradine, digoxin (and digitalis-related glycosides), and hydralazine/nitrates.<sup>2,3,12,14</sup> The efficacy of beta-blockers in the treatment of chronic heart failure has been controversial, and because of their negative inotropic effects they have not been used traditionally.<sup>15</sup> However, randomized controlled trials (RCTs) have shown that some beta blockers reduces mortality and hospitalization rate, and improve symptoms, hemodynamics and cardiac performance in patients with heart failure.<sup>15</sup>

Ejection fraction (EF) is a measurement that indicates whether the heart is pumping blood effectively.<sup>5,16</sup> “EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies and because most clinical trials selected patients based on EF.”<sup>3,17</sup> If the heart muscle does not contract effectively, the ejection fraction would be reduced as is the case in systolic heart failure. Normally the heart pumps slightly more than half its volume with each beat, and a normal left ventricular ejection fraction (LVEF) ranges around 55–70% (that percentage of the blood in the left ventricle is pumped out with each beat).<sup>11</sup> A reduced LVEF of  $\leq 35\%$  is associated with an increased risk of life-threatening irregular heartbeats that can cause cardiac arrest and sudden cardiac death.<sup>11</sup> Some guidelines define HfrEF as LVEF  $\leq 35\%$ , whereas others define it as  $\leq 40\%$ .<sup>3,14,18,19</sup> Randomized controlled trials in patients with HF have mainly enrolled patients with HfrEF with an EF  $\leq 35\%$  or  $\leq 40\%$ , and it is only in these patients that efficacious therapies have been demonstrated to date.<sup>3</sup> In diastolic heart failure the ejection fraction is preserved; the heart muscle contracts effectively, but the ventricles are not functioning properly (do not relax as they should).<sup>5,16</sup> Ejection fraction can be measured with imaging techniques, including echocardiogram, cardiac catheterization, magnetic resonance imaging (MRI), computerized tomography (CT), or nuclear medicine scan.<sup>20</sup>

Entresto™ (sacubitril/valsartan) is a combination drug manufactured by Novartis®, which was approved in July 2015 (still commonly referred to as LCZ696<sup>21</sup>; it was granted fast-track status by the US FDA and the application was accepted for priority review in February 2015).<sup>22,23</sup> It is indicated for use as adjunct therapy in patients with NYHA Class II–IV heart failure with reduced ejection fraction to decrease the risk of cardiovascular death and hospitalization. It is meant to be used instead of an ACEI or an ARB. Concomitant use with these agents is contraindicated due to increased risk of angioedema. The first component of Entresto™, sacubitril, is a neprilysin inhibitor, while the second, valsartan, is an ARB (inhibiting angiotensin II and the release of aldosterone).<sup>24</sup> Whilst valsartan has been on the market since 1996 as Diovan®,<sup>25</sup> sacubitril is the first drug in its class to be approved by the FDA.<sup>26</sup>

Nepilysin is an enzyme found mostly in the kidneys that is involved in the degradation of various endogenous peptides, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), bradykinin, and adrenomedullin.<sup>24</sup> Natriuretic peptides are hormones that help regulate the sodium and fluid balance of the body. Greater than normal levels of these peptides are secreted when the heart begins to enlarge, as can be the case in heart failure. However, in heart failure, these naturally elevated levels are ineffective at bringing the body’s fluid status back to baseline. Researchers believed that further elevation of ANP and BNP through the inhibition of neprilysin would allow for better endogenous fluid regulation (decreasing vasoconstriction, sodium retention, and maladaptive remodeling).<sup>24,26</sup> As can be seen in the *Clinical Efficacy* section below, the clinical evidence suggests that this strategy is effective in the therapeutic management of heart failure.

In 2012, the annual estimated cost of heart failure in the US was \$31 billion; \$21 billion in direct medical costs of which 80% was for hospitalizations (so over half of the total annual HF cost) and \$10 billion indirect which included lost productivity from morbidity and premature mortality.<sup>5,27</sup> The cost of heart failure in the US is projected to rise to \$77.7 billion by 2030.<sup>2,28</sup>

## Methodology

The Agency for Healthcare Research and Quality (AHRQ; [www.guideline.gov](http://www.guideline.gov)), Cochrane Library, the FDA website (including product labeling information), PubMed, UpToDate, Micromedex, Lexicomp, the Institute for Clinical and Economic Review (ICER) website, and the National Institute for Health and Clinical Excellence (NICE) website, were searched for systematic reviews, clinical trials, guidelines, other reports, reviews,

efficacy and safety information. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first, followed by phase 3 randomized controlled trials.

## Treatment options & Entresto formulation

Appendix 1 contains a drug summary table containing information on Entresto (sacubitril/valsartan), ACEIs, ARBs, and beta-blockers used in the treatment of heart failure. “Sacubitril/valsartan is indicated in adults with NYHA Class II to IV chronic heart failure (HF) and reduced ejection fraction to reduce the risks for hospitalization for HF and cardiovascular (CV) death. Sacubitril/valsartan is normally used along with other therapies for HF, in place of an ACE inhibitor or other angiotensin receptor blocker.”<sup>29</sup>

It is important to note that Entresto formulations contains sacubitril (24 mg, 49 mg, or 97 mg) and valsartan (26 mg, 51 mg, or 103 mg), and it is advised to use caution when prescribing since dosing in clinical trials was based on the total amount of both components (ie, 24/26 mg, 49/51 mg and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively). It is recommended to include the doses of both ingredients (eg, Entresto 24/26 mg) when prescribing Entresto to reduce the risk of errors. “The valsartan in Entresto is more bioavailable than the valsartan in other marketed tablet formulations; valsartan 26 mg, 51 mg, and 103 mg in Entresto is equivalent to valsartan 40 mg, 80 mg, and 160 mg in other marketed tablet formulations, respectively.”<sup>30</sup>

## Off-label use

No off-label uses are documented in Micromedex (in Non-FDA section) for Entresto. Several studies found in PubMed and ClinicalTrials.gov funded by Novartis® suggest possible use in the treatment of essential hypertension and patients with heart failure and a preserved ejection fraction.<sup>31-34</sup>

## Hospitalizations

“HF is the primary diagnosis in >1 million hospitalizations annually” and it is important to consider that “patients hospitalized for HF are at high risk for all-cause rehospitalization, with 1-month readmission rate of 25%.”<sup>3,35,36</sup> It was found that hospitalizations were common after HF diagnosis (83% at least once and 43% at least 4 times), and the mean cost of HF-related hospitalizations has been reported as \$23,077 per patient.<sup>3,37</sup> Entresto is indicated in specific patients with heart failure to reduce the risk of cardiovascular death and hospitalization.

## Clinical Guidelines and related evidence

In the United States, there are two different heart failure management guidelines: (1) The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) Task Force on Practice Guidelines (2013 ACCF/AHA Guideline for the Management of Heart Failure),<sup>12</sup> and (2) The Heart Failure Society of America (HFSA) Guidelines.<sup>18</sup> These guidelines stratify their recommendations differently: the ACCF/AHA guidelines make their recommendations based on their own heart failure staging (as described in the *Background* section) and the HFSA guidelines make their recommendations based on the various types of heart failure (asymptomatic with reduced ejection fraction, symptomatic with reduced ejection fraction, preserved left ventricular ejection fraction, and acute decompensated heart failure). Despite this, both guidelines recommend the use of ACEI and beta-blockers in the treatment of heart failure with reduced

ejection fraction (one of three beta-blockers that has been shown to improve symptoms, clinical status, decrease death and hospitalizations in randomized controlled trials). "The ACCF/AHA 2013 heart failure guidelines recommend the use of 1 of the 3 beta blockers (ie, bisoprolol, carvedilol, or extended-release metoprolol succinate) for all patients with recent or remote history of MI or ACS and reduced ejection fraction (rEF) to reduce mortality, for all patients with rEF to prevent symptomatic HF (even if no history of MI), and for all patients with current or prior symptoms of HF with reduced ejection fraction (HFrEF), unless contraindicated, to reduce morbidity and mortality."<sup>3,38</sup>

If a patient is intolerant to ACEI, an ARB may be used second line. The ACCF/AHA guidelines state that an ARB can be used first line in patients with heart failure with reduced ejection fraction if they are already taking an ARB for another indication.<sup>12</sup> Similarly, the HFSA guidelines state that an ARB can be used first line instead of an ACEI in the setting of heart failure post-myocardial infarction and chronic heart failure with reduced left ventricular ejection fraction.<sup>18</sup>

Doses in the studies were not based upon a clinical response but rather increased until a predetermined target was reached. Guidelines suggest matching doses used in clinical trials to achieve similar outcomes.<sup>39</sup> Target maintenance doses have been included in the drug table in appendix 1. It is recommended to aim for target doses or, failing that, the highest tolerated doses.<sup>40</sup> Jessup reports that numerous registries acknowledge that lower doses are commonly used in clinical practice.<sup>39</sup>

Other medications can be added in select patients with heart failure depending on symptoms and condition including diuretics (i.e. for volume overload/fluid retention), aldosterone antagonists, hydralazine- isosorbide dinitrate (i.e. in African-American patients with NYHA class III–IV HFrEF, and is considered potentially useful in patients who are ACE inhibitor- or ARB-intolerant<sup>41</sup>), and digoxin (potentially beneficial in patients with HFrEF to decrease hospitalizations for HF<sup>41</sup>).<sup>42</sup> "Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is considered potentially harmful and is not recommended."<sup>41</sup>

The latest ACCF/AHA guidelines are from 2013, and thus do not mention Entresto™. Similarly, the HFSA guidelines have not been updated since 2010 and therefore contain no recommendations on the use of Entresto™. It is unclear what this new medication's place in therapy will be within the United States.

Expert opinion in UpToDate suggest use of an ACE inhibitor (or single agent ARB) rather than Entresto as initial medical therapy in patients with a new diagnosis of HF NYH II-IV HFrEF (LVEF ≤40%). Entresto™ is suggested by some experts as initial therapy, but UpToDate experts suggest its place in therapy in place of an ACEI or ARB as follows:

"For patients with stable mild to moderate HFrEF (LVEF ≤40 percent), an elevated natriuretic peptide level or hospitalization for HF in the past 12 months, a systolic blood pressure ≥ 100 mm Hg, and eGFR ≥ 30 mL/min/1.73 m<sup>2</sup> and who have tolerated high-doses of ACE inhibitor or ARB therapy (equivalent to at least enalapril 10 mg twice daily) for ≥4 weeks, we suggest use of sacubitril-valsartan in place of the ACE inhibitor (or single agent ARB) component of therapy (Grade 2B). Factors that impact the decision to switch to sacubitril-valsartan in place of ACE inhibitor (or single agent ARB) include patient acceptance/tolerance of drug changes (including need for a 36-hour ACE inhibitor washout period prior to starting sacubitril-valsartan), limited experience with the use of sacubitril-valsartan outside of controlled trials, and cost."<sup>42</sup>

The Canadian Cardiovascular Society (CCS) released a 2014 update to their guidelines that included their conditional recommendation regarding what was then known as LCZ696 (now Entresto™). The CCS "recommend[s] that in patients with mild to moderate HF, an LVEF < 40%, an elevated NP level or hospitalization for HF in the past 12 months, a serum potassium < 5.2 mmol/L, and an eGFR ≥ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and

creatinine.”<sup>43</sup> Use of Entresto™ in patients with elevated serum potassium levels or with decreased renal function could increase their risk of developing hyperkalemia or renal failure. In the update, the CCS states that its recommendation is conditional because the medication has yet to be approved in Canada and its price therefore remains unknown.

According to draft NICE guidance, sacubitril/valsartan is recommended for use in patients with heart failure with reduced ejection fraction with NYH II-III symptoms who are on a stable dose of ACE inhibitors (or ARBs if intolerant) and who have a LVEF of  $\leq 35\%$ .<sup>11,23</sup> It is also recommended that sacubitril/valsartan treatment be started by a heart failure specialist with access to a multidisciplinary HF team, and that dose titration and monitoring be done by the heart failure specialist, or in primary care by a GP with a special interest in HF or a HF specialist nurse.<sup>11</sup> Clinical experts explained to the NICE Committee that they would likely offer sacubitril/valsartan to newly diagnosed chronic HF patients, but “that they would be reluctant to give sacubitril/valsartan to people who had not previously received ACE inhibitors or ARBs because of the lack of evidence for clinical effectiveness and safety of sacubitril/valsartan in this population.”<sup>11</sup> The majority of patients in the PARADIGM-HF trial were taking ACEIs or ARBs at entry (99%) so the Committee agreed that there is insufficient evidence in ACEI or ARB naïve patients.<sup>11</sup>

## Implementation of Guidelines in Clinical Practice

Despite the evidence and available guidance, many physicians are reluctant to their use in actual clinical practice.<sup>2</sup> Patients are not receiving evidence-based treatments or are receiving sub-therapeutic doses.<sup>2,44,45</sup>

### Physician reluctance to up-titrate beta-adrenergic blockers, ACEIs, and ARBs

According to the authors of a recent systematic review (Driscoll et al. 2015; abstract in appendix 2) primary care physicians are often reluctant to up-titrate beta-adrenergic blockers, ACEIs, and ARBs despite evidence supporting dose response (the higher the dose of these medications, the greater the improvement in patient outcomes).<sup>46</sup> The authors state that new ways of up-titration of these medications is needed. The objective of their review was to assess the effects of nurse-led titration (NLT) of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) in patients with heart failure in terms of safety and patient outcomes. The authors concluded that “participants in the NLT group experienced fewer hospital admissions for any cause and an increase in survival and number of participants reaching target dose within a shorter time period. However, the quality of evidence regarding the proportion of participants reaching target dose was low and should be interpreted with caution. We found high-quality evidence supporting NLT as one strategy that may improve the optimization of beta-adrenergic blocking agents resulting in a reduction in hospital admissions. Despite evidence of a dose-dependent relationship of beta-adrenergic blocking agents, ACEIs, and ARBs with improving outcomes in patients with HFrEF, the translation of this evidence into clinical practice is poor. NLT is one strategy that facilitates the implementation of this evidence into practice.”<sup>46</sup>

### Interventions that have been used

Bazzano et al. in a protocol for a Cochrane systematic review (“Interventions to improve evidence-based prescribing in heart failure”) report that interventions that have been used to improve evidence-based prescribing aimed at clinician prescribers include educational outreach visits to health professionals and interactive educational activities for clinicians; electronic and manual reminders in the medical charts of individuals with HF, establishing standardized protocols within inpatient and outpatient settings; providing summaries of clinician’s prescribing behavior and feedback; and educational materials designed for clinicians such as lectures and pamphlets.<sup>2</sup>

The IMPROVE-HF trial for example aimed at improving adherence to evidence-based prescribing guidelines. It included a guideline-based clinical decision support tool kit (evidence-based best practice algorithm charts, clinical pathway flow charts, standardized encounter forms, checklists, pocket cards, chart stickers, and educational materials aimed at individuals with HF), educational materials, practice-specific data reports, benchmarked quality-of-care reports and structured educational outreach visits.<sup>2,47,48</sup>

### **What can be done?**

Bazano et al states that interventions to improve the prescribing of guideline-based medications in HF work by addressing factors at the organizational or individual level that contribute to the prescribing behavior including the “organizational culture and its resources, information management strategies (e.g. the presence of reminders or prompts in patient records or the electronic medical system), local healthcare setting and resources, provider’s knowledge, communication strategies, and availability of feedback.”<sup>2,49-52</sup>

### **What we have done so far (University of Utah Drug-Regimen Review Centre):**

In January 2016, a variable rule was created for the DRRC for patient selection of patients on sub-therapeutic doses of antihypertensive medications (patients who are taking an anti-hypertensive medication at a daily dosage less than what is specified as a target dosage). Current JNC 8 guidelines recommend dosing of antihypertensive medications to the doses associated with favorable outcomes in clinical trials in order to achieve similar outcome benefits. Reviews are done for each individual patient and letters are being sent where appropriate to prescribers to encourage up-titration to match the target doses in clinical trials that have shown improved outcomes (as recommended by the guidelines).

### **What else can be done for the Utah Medicaid Population?**

Bazano et al states that educational outreach visits, interactive educational activities and reminders (electronic or manual) are interventions that have been shown in systematic reviews to be consistently effective.<sup>2,49,51,53,54</sup> Patients with HF diagnosis can be reviewed on an individual basis by the DRRC and letters can be sent to prescribers where appropriate to encourage implementation of guideline recommendations.

## **Clinical Efficacy of Entresto**

### **Systematic Reviews & Meta-analyses**

No Cochrane reviews or other reviews meeting the criteria for the Database of Abstracts of Reviews of Effects (DARE) regarding sacubitril were identified in the Cochrane Library.

### **Randomized Controlled Trials (RCTs)**

The effectiveness of Entresto was shown in the PARADIGM HF phase 3, double-blind, RCT.

#### **PARADIGM-HF (2014)<sup>55</sup>**

In this trial, Entresto™ was compared to enalapril (an ACEi) in patients with NYHA Class II-IV heart failure with reduced ejection fraction (number of patients randomized = 8,442). The primary outcome was a composite of cardiovascular death and hospitalization for heart failure. The secondary outcomes included all-cause mortality and change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).<sup>11</sup> At the time of the trial’s interim analysis, a total of 914 patients in the Entresto™ group and 1,117 patients in the enalapril group met the primary outcome. With a hazard ratio of 0.80 (95% CI 0.73-0.87,  $P < 0.001$ ) for the composite primary outcome, the trial was ended early (“after a median follow-up of 27 months, when sacubitril plus valsartan crossed the prespecified margin for a

significant reduction in the risks for CV death and hospitalizations in patients with heart failure compared with enalapril”).<sup>5,55,56</sup> In short, Entresto™ reduced the risk of cardiovascular death by 20% (p=0.00004), reduced heart failure hospitalization by 21% (p=0.00004), and reduced the risk of all-cause mortality by 16% (p=0.0005).<sup>23</sup> “Overall there was a 20% risk reduction on the primary endpoint, a composite measure of CV death or heart failure hospitalization (p=0.0000002).”<sup>23</sup> The reduction in KCCQ patient scores was less with sacubitril vs enalapril (2.99 vs. 4.63 points).<sup>11</sup> A subsequent analysis of this trial carried out by Packer M et al further evaluated the clinical effects of Entresto™ in the trial’s surviving patients. The authors concluded that Entresto™ prevents the clinical progression of patients with heart failure and reduced ejection fraction more effectively than enalapril.<sup>57</sup>

In this trial sacubitril/valsartan 200 mg twice daily (n=4,187) was compared with enalapril 10 mg twice daily (n=4,212).<sup>58</sup> The Entresto dose used in the study was optimal (200 mg is the 97/103 mg formulation) and the valsartan in Entresto is more bioavailable than the valsartan in other marketed tablet formulations; 103 mg in Entresto is equivalent to valsartan 160 mg in other marketed tablet formulations; so participants in the trial received the equivalent of valsartan 320 mg daily.<sup>30</sup> In a recent evidence-based drug review it is stated that “about 20% of patients in each arm discontinued the study prematurely, which is concerning after accounting for the additional 20% of eligible patients who were not randomized due to intolerability of either drug in the initial run-in phases.” The author report that “It is unclear how many patients in real world settings will be able to tolerate the dose studied in the trial; lower doses may be better tolerated but may not be any more effective than far less costly ACE-inhibitor or ARB.”<sup>58</sup> Also, it has been questioned whether enalapril 40 mg daily would have been a more reasonable comparator, and “it is unclear if the efficacy seen with sacubitril/valsartan can be attributed to the addition of sacubitril to bioequivalent 320 mg daily dose of valsartan used in the trial or if it can be attributed to the high valsartan dose alone.”<sup>58</sup> It has been speculated that a comparison of sacubitril/valsartan to valsartan 320 mg daily would be helpful to explain its place in therapy in HFREF.<sup>58</sup>

For safety reasons, the run-in phase involved a single-blind run-in period to determine which eligible patients could tolerate enalapril 10 mg twice daily; followed by a second single-blind run-in period to determine which of those patients could tolerate sacubitril/valsartan 200 mg twice daily. It has been commented that the specific order of the single-blind run-in phases likely introduced bias early in the trial.<sup>58</sup>

Please refer to appendix 2 table 5 for abstracts of additional studies.

## **The US Institute for Clinical and Economic Review (ICER)**

The ICER report provides analyses of long-term cost-effectiveness and the potential budget impact of an intervention and provides a value-based price benchmark for each intervention which reflects how much better it is at improving patient outcomes.<sup>59</sup> In the September 2015 draft report, ICER concluded that “At the list price of \$4,560 per year, Entresto does not save money over the long term but its added costs are well-aligned with the degree of benefit it brings to patients, meaning that Entresto can be judged “cost-effective” in the long-term according to commonly accepted cost-effectiveness thresholds.” The California Technology Assessment Forum (CTAF) is a core program of ICER that “reviews objective evidence and holds public meetings to develop recommendations for how stakeholders can apply evidence to improve quality and value of care.”<sup>60</sup> The final ICER report includes a “summary of CTAF’s votes on effectiveness and value, value-based price benchmarks, and key policy recommendations for coverage policy and clinical practice”; it includes the results of the October 29, 2015 public meeting of CTAF regarding Entresto.<sup>61</sup> ICER also released an action guide for clinicians, payers, and policymakers (and one for patients) to supplement the final report and to help stakeholders understand and implement the evidence- and value- based policy.<sup>61</sup>

At the October 2015 public meeting of CTAF, the CTAF panel voted in favor of Entresto that it provides greater net health benefits to patients than standard care with ACE inhibitors, and that it provides intermediate care value (representing long-term benefit to patients, based on clinical- and cost-effectiveness).<sup>61</sup> Compared to ACE inhibitors, the costs are higher and a large number of patients would be eligible for treatment.<sup>61</sup> The majority of the CTAF panel therefore voted that Entresto provides low provisional health system value because of its large potential budget impact.<sup>61</sup> “Among the key recommendations for coverage policy and clinical practice arising from the discussion, votes, and subsequent policy debate were the following:

1. Provider groups and payers should consider limiting prescribing of Entresto to cardiologists or require other clinicians to consult with cardiologists due to potential side effects, the importance of selecting appropriate patients for therapy, and the large cost of Entresto compared to ACE inhibitors or ARBs.
2. Based on the combination of clinical benefit to patients, pricing aligned with patient benefit, and short-term affordability, payers and purchasers should consider placing Entresto in the “preferred brand” category of their formulary, especially if they are able to reach ICER’s value-based price benchmark through negotiations.”<sup>61</sup> (“ICER’s analysis found that to prevent an excessive cost burden on the health care system, the price of Entresto would have to be discounted from its wholesale acquisition cost of \$4,560 to \$4,168, a discount of 9%.”<sup>61</sup>).

## Safety

The most common adverse reactions in clinical trials (occurring  $\geq 5\%$ ) are hypotension, hyperkalemia, cough, dizziness, and renal failure.<sup>56</sup> The median exposure time in the PARADIGM-HF study was 24 months (some patients up to 4.3 years). Discontinuation of treatment due to adverse effects was seen in 10.7% sacubitril plus valsartan patients vs. 12.2% enalapril patients.<sup>5,56</sup>

Please refer to table 1 for information on contraindications and precautions. Angioedema occurred in 0.5% of patients treated with sacubitril/valsartan vs. 0.2% of those treated with enalapril.<sup>24</sup>

### **Inhibiting neprilysin - What are the effects on the brain?**

Sacubitril inhibits neprilysin in the kidney which leads to increased levels of neuropeptides and vasodilators that has the desired effect on the cardiovascular system, but there is theoretical concern about the long-term effects on cognition because neprilysin is also one of many enzymes clearing amyloid-beta ( $A\beta$ ) peptides from the brain.<sup>23,62</sup> These  $A\beta$  peptides form amyloid plaques in the brain and it is therefore questioned whether sacubitril could increase the risk of Alzheimer’s disease (AD).<sup>63</sup> Cannon et al. examined dementia-related adverse effects in PARADIGM-HF and found no evidence that LCZ696 (sacubitril/valsartan), compared with enalapril, increased dementia-related adverse events.<sup>62</sup> The process involved in Alzheimer’s disease is complex and it has been reported that heart failure is likely an important contributor to cognitive decline.<sup>63</sup> Improving heart function may lessen the vascular contribution to AD, but more evidence is needed to evaluate whether sacubitril crosses the blood brain barrier and to determine whether it leads to changes in the  $A\beta$  peptides and ultimately its effect on the brain and cognitive function. Some researchers question whether the PARADIGM-HF trial was too brief to see a cognitive effect, but Packer (co-principal investigator) noted that “the life expectancy for people with CHF is short even with medication, so few would likely live long enough to manifest any potential long-term effects of  $A\beta$ .”<sup>63</sup> Rebecca Gottesman (Johns Hopkins School of Medicine) commented: “The PARADIGM study was not long enough to detect any differences in cognitive outcomes, nor was it designed to evaluate cognitive outcomes, but I think it will be important to evaluate surrogate outcomes, which might evaluate  $A\beta$  levels, as well as longer-term cognitive outcomes, before knowing the true potential utility of this new drug. Any studies taking these outcomes into account may be

difficult to interpret since controlling heart failure has the potential to improve cognition, so they will need to be carefully designed.”<sup>64</sup>

Sacubitril is also being evaluated in clinical trials for patients with preserved ejection fraction and for treating hypertension so this is an important question if patients are potentially going to be taking it long-term.<sup>63</sup>

## Entresto's place in therapy and potential criteria to be reviewed

Factors and limitations to consider:

- **Mainstay of pharmacological therapy for HF with HfrEF according to 2013 ACCF/AHA Guideline (optimal medical therapy recommended with a class I indication):** ACEIs or ARBs when ACEI intolerant;  $\beta$ -blockers; and, in select patients, aldosterone antagonists, hydralazine-nitrates, and diuretics.<sup>3,41</sup>
- **Appropriate use according to Entresto product label:** Adults with NYHA Class II to IV chronic heart failure (HF) and reduced ejection fraction which is not specified.<sup>29</sup> The PARADIGM trial LVEF entry criterion was initially  $\leq 40\%$  but was subsequently reduced to  $\leq 35\%$  to ensure an adequate event rate in the study population and the NICE Committee concluded that sacubitril valsartan should only be initiated in people with an ejection fraction of  $\leq 35\%$ , normally shown on an echocardiogram.<sup>11</sup> Note that  $<1\%$  of patients in the PARADIGM trial had NYHA Class IV HF (ne=60, 0.7%) and because the NYHA class was not specified in the UK marketing authorization of sacubitril valsartan, the NICE Committee agreed that it should only be initiated in people with class II or III chronic HF (insufficient evidence in class IV).<sup>11</sup> The US product label states that it is usually administered in conjunction with other heart failure therapies, in place of an ACE or other ARB.<sup>56</sup> The PARADIGM trial criteria also required hospitalization for HF within the last 12 months.<sup>11</sup>
- **Place in therapy:** Normally used along with other therapies for HF, in place of an ACE inhibitor or other angiotensin receptor blocker.<sup>29</sup> “Despite the enthusiasm regarding this novel compound, real world data on its efficacy and safety are eagerly expected.”<sup>21</sup> Guidelines for treatment of Heart Failure suggest as initial therapy for classes I-IV HF the use of an ACEI or ARB AND one of three beta-blockers that has been shown to improve symptoms, clinical status, decrease death and hospitalizations in randomized controlled trials.<sup>3</sup> The three beta-blockers that are recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality, are bisoprolol, carvedilol, and sustained-release metoprolol succinate.<sup>3</sup> Inclusion criteria for the PARADIGM-HF trial specified that patients must have been taking a stable dose of an ACEI or an ARB for at least 4 weeks before entering the study, and the NICE Committee concluded that sacubitril valsartan should be started by a heart failure specialist (see NICE guidance section; also regarding titration and monitoring), in people who are receiving a stable, optimized dose of an ACEI or ARB.<sup>11</sup>
- **Evidence:** “Superiority was shown in comparison with enalapril for the risk of the composite endpoint of death from CV causes or hospitalization for HF.”<sup>29,56</sup>
- **Physician reluctance to up-titrate beta-adrenergic blocking agents, ACEIs, and ARBs** despite evidence that there is a dose response (the higher the dose of these medications, the greater the improvement in patient outcomes).<sup>46</sup> According to the authors of a recent systematic review new strategies aimed at facilitating this up-titration are warranted e.g. nurse-led titration (NLT).<sup>46</sup>
- **Adherence:** This is an important factor that needs to be monitored
- **Special Populations:**
  - **Pregnancy & lactation:** Entresto has a boxed warning that it should be discontinued as soon as possible when pregnancy is detected because it can cause fetal harm, and breast feeding is not recommended during treatment with Entresto.
  - **Pediatrics:** Safety and effectiveness of sacubitril plus valsartan in this population has not been established.

- **Geriatrics:** “No relevant pharmacokinetic differences were observed in the elderly (>65 years) or in very elderly (≥75 years) compared to the overall population.”<sup>5,56</sup>
- **Adverse effects/Safety:** Refer to safety section and appendix 1. Note hypotension and angioedema that could be problematic.<sup>24</sup> Hypotension is related to the greater vasodilator effect (there was no increase in discontinuation rate in the PARADIGM-HF trial) and the NICE Committee concluded that Sacubitril valsartan had a manageable adverse event profile.<sup>11</sup>
- **Dependence:** No risk of abuse.
- **Duplication of therapy/Concomitant use (Drug Interactions):**
  - Concurrent use of Entresto with an ACE inhibitor is contraindicated due to risk of serious angioedema (occurs more often in black patients)<sup>24</sup>
  - Concurrent use with potassium-sparing diuretics or potassium supplements could lead to hyperkalemia (especially in renal impairment, diabetes, or hypoaldosteronism)<sup>24</sup>
  - Concurrent use with NSAIDs could lead to worsening of renal function and acute renal failure<sup>24</sup>
  - Lithium toxicity (has occurred in patients taking lithium and an ARB; ARB may increase serum concentration of lithium)<sup>24,30</sup>
- **Risk factors for HF – Hypertension, Diabetes Mellitus, Metabolic Syndrome, and Atherosclerotic Disease:** The appropriate identification and treatment of these conditions can significantly reduce the development or forestall the onset of HF.<sup>3</sup>

## Utah Medicaid Utilization Data

Only one patient has been identified that has filled a prescription for Entresto 24/26 mg in the Utah Medicaid population, prescribed by a Nurse Practitioner (specialty in Family Medicine). The claim was an ACO claim and not a fee-for-service claim.

In order to determine the potential pool of patients that could receive Entresto in the future, an attempt was made to identify the number of patients with diagnosis codes for heart failure. Please refer to appendix 3.

The limitations of diagnosis code information should be considered. Coding in heart failure is a challenge for coders<sup>65</sup> and diagnosis codes are not always submitted so the data should be interpreted with caution.

“Patients with a diagnosis of heart failure can be broadly divided into two groups: (1) those who have a reduced left ventricular ejection fraction, and (2) those who have a preserved ejection fraction i.e. the left ventricular (LV) ejection fraction is within normal limits.”<sup>66</sup> However, diagnosis codes (i.e. ICD-10) do not adequately capture information about LV ejection fraction.

Some organizations such as The Scottish Patient Safety Programme and Health Improvement Scotland have been working with NHS Boards to implement a Heart Failure Care Bundle (a set of recommended clinical practices aimed at improving acute care outcomes for heart failure patients). To enable them to measure outcomes they are therefore requiring the addition of a fifth digit to certain relevant ICD10 codes (e.g. 0= reduced ejection fraction, 1=preserved ejection fraction, 9= no information on ejection fraction).<sup>66</sup>

It is reported that doctors recording certain diagnoses will often (not always) include information describing LV ejection fraction. If it is not included, doctors may use other terms to describe ‘**reduced ejection fraction**’ such as<sup>66</sup>:

Left ventricular	Impaired or reduced
- dysfunction	- LV function
- systolic dysfunction (LVSD)	- LV systolic function
- systolic impairment	- systolic function

Terms to describe ‘preserved ejection fraction’ (e.g. diastolic heart failure) may include<sup>66</sup>:

Preserved	Normal
- LV function	- ejection fraction
- systolic function	- LV function
- systolic function	

This is relevant because Entresto is indicated in patients with reduced ejection fraction.

It is important to understand that “HF is not synonymous with either cardiomyopathy or LV dysfunction; these terms describe possible structural or functional reasons for the development of HF.”<sup>3</sup>

**Number of unique patients with a HF diagnosis (as defined in appendix 1) that are currently eligible and who are receiving treatment with (within last 3 months):**

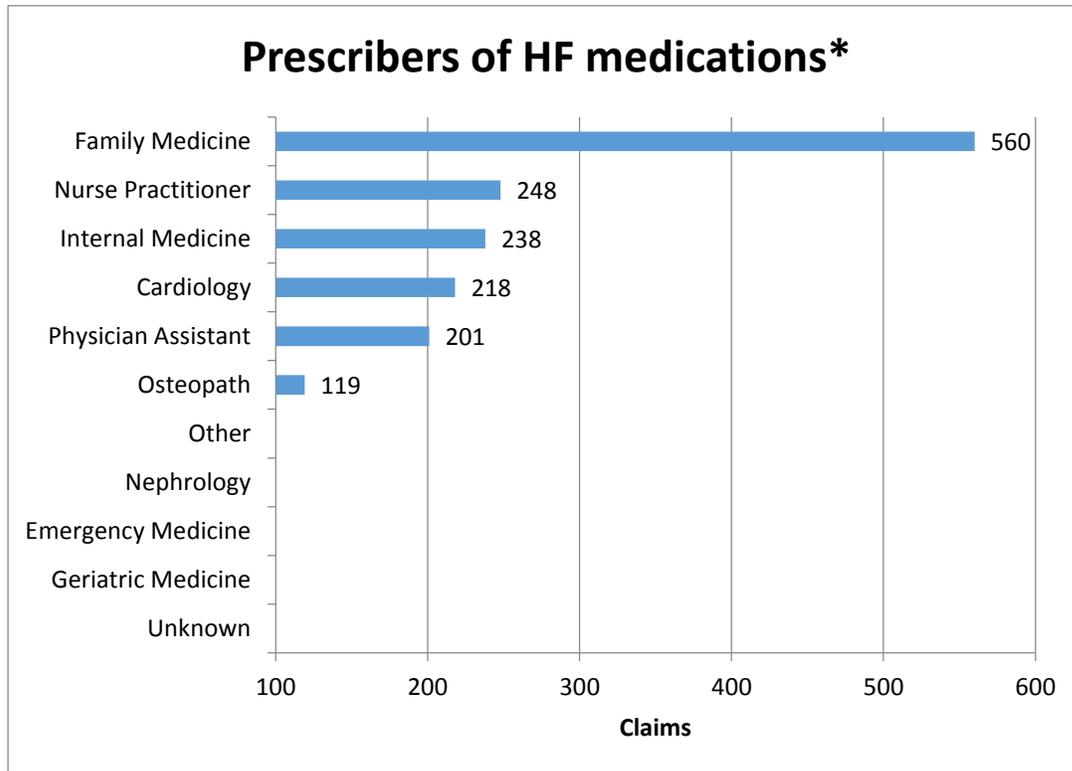
- a) An ACE inhibitor defined as captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, or trandolapril
- b) An ARB defined as azilsartan, candesartan, losartan, or valsartan
- c) A beta-blocker defined as bisoprolol, carvedilol, or metoprolol succinate (only succinate and not the other metoprolol salts)
- d) An (ACE OR ARB as defined above) AND a beta-blocker

**Table 1**

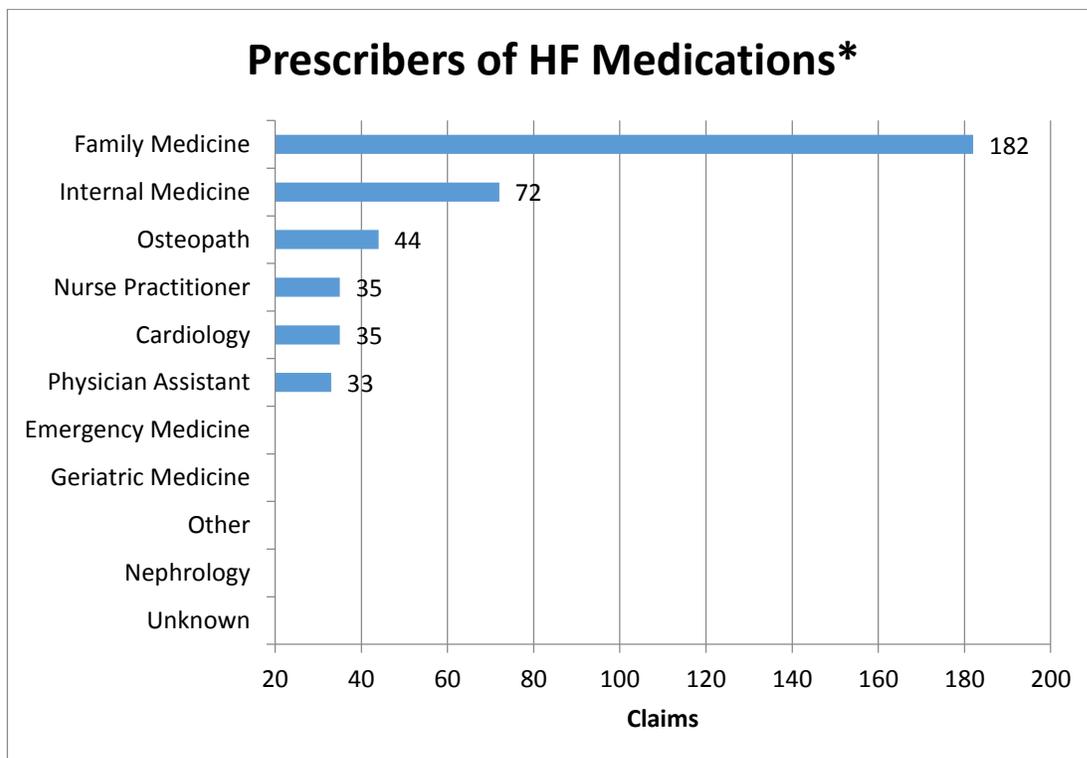
	Patients - Medication ALL 3 Past Months	Patients - Medication any time in Past 3 Months	Patients - Medication any time in the Past Two Years
Patients Receiving an <b>ACE Inhibitor</b> from October 2015 to December 2015 (captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril or trandolapril)	177	439	782
Patients Receiving an <b>ARB</b> from October 2015 to December 2015 (azilsartan, candesartan, losartan or valsartan)	45	114	193
Patients Receiving a <b>Beta Blocker</b> from October 2015 to December 2015 (bisoprolol, carvedilol or metoprolol succinate)	83	199	364
Patients Receiving an <b>ACE Inhibitor</b> OR an <b>ARB</b> AND a <b>Beta Blocker</b> from October 2015 to December 2015	51	118	268
Patients with HF DX in 2014-2015 and Eligibility in January 2016 and Receiving <b>ANY MEDICATION</b> (not just HF medications above) between October 2015 and December 2015	<b>1,532</b>		
<b>Total Patients with Heart Failure DX in 2014-2015 and Eligibility in January 2016</b>	<b>3,417</b>		

Note: Patients could appear in more than one row

**All Prescribers (Fee for service & ACO)**



**FFS Prescribers**



\*Medications in Table 1

## Conclusions

Guidelines for treatment of Heart Failure suggest as initial therapy for classes I-IV HF the use of an ACEI or ARB AND one of three beta-blockers that has been shown to improve symptoms, clinical status, decrease death and hospitalizations in randomized controlled trials.<sup>3</sup> Entresto should normally be used along with other therapies for HF, in place of an ACE inhibitor or ARB, but some experts believe that it should be used as initial therapy.<sup>29,42</sup> Based on the available evidence and guidance, it appears appropriate to use it as a second line treatment after an ACEI or ARB has been tried at optimal doses; at least until further real world data on its efficacy and safety is available.<sup>21</sup>

The evidence and guidelines exist for medications shown to improve morbidity and mortality in individuals with HF, but guidelines may not be implemented in clinical practice. It is important to perform drug utilization reviews to identify inappropriate prescribing and to identify effective interventions to maximize the prescribing of evidence-based medication regimens. The limitations of diagnosis codes make it difficult to monitor prescribing effectively especially for monitoring utilization and outcomes in heart failure. Prior authorization criteria for Entresto and electronic reminders to prescribers of patients with HF would enable Utah Medicaid to better manage prescribing trends leading to improved patient outcomes and reduced healthcare costs.

## Potential clinical criteria

You may wish to consider Entresto™ (sacubitril/valsartan) as a second-line agent in the management of patients with heart failure and reduced ejection fraction. Given that there is only one claim so far, you may wish to monitor utilization or a PA could be created. For PA criteria (now or in the future) you could consider the following:

1. Prescription by a cardiologist or specialist in cardiac care, or in consultation with
2. Minimum age requirement 18 years old
3. Documentation of heart failure diagnosis and staging (must be NYHA class II-IV) and reduced left ventricular ejection fraction (LVEF)  $\leq 35\%$
4. Evidence of failure or documentation of intolerance to an ACEI or an ARB; stable on therapy for at least 4 weeks on maximally tolerated dose for heart failure treatment; aiming for ACCF/AHA target dose that has proven mortality benefit in a heart failure clinical trial
  - a. Documentation of discontinuation of the ACEI or ARB in question (ACE inhibitors must be discontinued at least 36 hours prior to Entresto).
5. Evidence of trial or currently receiving beta-blocker; bisoprolol, carvedilol, or sustained-release metoprolol succinate; stable on therapy for at least 4 weeks on maximally tolerated dose for heart failure treatment; aiming for ACCF/AHA target dose that has proven mortality benefit in a heart failure clinical trial; or evidence of contraindication/intolerance;
6. Must have had at least one hospitalization related to chronic heart failure
7. Confirmation of:
  - a. NO history of angioedema related to previous ACE inhibitor or ARB therapy;
  - b. NOT taking aliskiren (e.g. Tekturna or Tekturna HCT) in a patient with diabetes;
  - c. NOT pregnant (if applicable)

Quantity Limit: 60 tablets in 30 days

Authorization: 6 months

Re-authorization: Updated letter of medical necessity and evidence that patient is responding to treatment

### Notes:

#### **Place in therapy**

- If the patient is currently taking an ACE inhibitor or ARB, Entresto will replace that current therapy.
- Entresto is usually administered in conjunction with other heart failure therapies (beta blockers, loop diuretics, hydralazine-nitrates, aldosterone antagonists, and digoxin) and in place of ACE inhibitor or other ARB
- Black box warning: Not to be used in pregnancy

#### **Concomitant use**

- Concomitant use of Entresto with an ACE inhibitor is contraindicated because of the increased risk of angioedema
- Concomitant use of Entresto and ARB should be avoided since Entresto contains an ARB (valsartan)

**ALSO:**

**Letters to prescribers of patients with HF diagnoses**

Identify all patients that are not receiving first-line medications for heart failure as recommended by guidelines or who are not receiving the target dose (matching study doses) as recommended.

- To make prescribers aware of the HF guideline recommendations (if they are not already) and recommend to consider guideline recommendations and implement if appropriate.

**Electronic reminder to prescribers of heart failure medications regarding:**

- Guideline recommendations (ACE/ARB AND one of 3 beta-blockers)
- To up-titrate to recommended dose

## Appendix 1 – Drug information

**Table 2: Entresto™, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs) used in Heart Failure**

Sources: Product Labeling<sup>25,56,67-74</sup>, Lexicomp<sup>30,75-83</sup>, and MICROMEDEX<sup>2.0</sup><sup>84-92</sup>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
<b>Entresto™ (sacubitril/valsartan)</b>  <b>Oral tablet (brand only)</b> <ul style="list-style-type: none"> <li>• 24/26 mg</li> <li>• 49/51 mg</li> <li>• 97/103 mg</li> </ul>	<p><i>Starting dose:</i> 49/51 mg twice daily; titrate as tolerated after 2-4 weeks</p> <p><i>Target maintenance dose:</i> 97/103 mg twice daily</p>	<p>To reduce the risk of cardiovascular death and hospitalization in patients with NYHA Class II-IV heart failure and reduced ejection fraction</p> <p>*Meant to be used in place of an ACE inhibitor or an ARB*</p>	<p>Several studies found in PubMed and ClinicalTrials.gov funded by Novartis® suggesting possible use in the treatment of essential hypertension and patients with heart failure and a preserved ejection fraction.<sup>31-34</sup></p>	<p>Hypotension Hyperkalemia Cough Dizziness Renal failure</p> <p><i>Serious, rare –</i> Angioedema</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use with an ACE inhibitor or an ARB.</li> <li>• Space dosing at least 36 hours apart when switching between Entresto™ and an ACE inhibitor.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal and hepatic starting dose adjustments may be necessary; use not recommended in severe hepatic impairment.</li> </ul>
<p><b>ACE Inhibitors with FDA-Approved Indications for Heart Failure<sup>b</sup></b> (perindopril not approved by the FDA for HF<sup>24</sup>)</p>					
<b>Prinivil® or Zestril® (lisinopril)</b>  <b>Oral tablet (generic available)</b> <ul style="list-style-type: none"> <li>• 2.5 mg</li> <li>• 5 mg</li> <li>• 10 mg</li> <li>• 20 mg</li> <li>• 30 mg</li> </ul>	<p><b>HF:</b> <i>Starting dose:</i> 2.5-5 mg once daily; titrate by 10 mg increments no less than 2 weeks at a time to a daily dose of 40 mg daily. Usual maintenance: 5 to 40 mg daily as a single dose.</p>	<p>Treatment of hypertension</p> <p>Treatment of systolic heart failure (in combination with other drugs)</p> <p>Treatment of acute myocardial infarction within 24 hours of onset</p>	<p>Treatment of autosomal dominant polycystic kidney disease</p> <p>To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy</p>	<p>Hypotension Hyperkalemia Chest pain Cough Dizziness Syncope Headache Elevated BUN<sup>a</sup> Elevated SCr<sup>a</sup></p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal dose adjustments may be necessary.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
<ul style="list-style-type: none"> <li>• 40 mg</li> </ul>	<p><i>Target dose:</i> 20 to 40 mg once daily (ACCF/AHA [Yancy, 2013])</p>		<p>Prevention and treatment of diabetic retinopathy</p> <p>To reduce the need for phlebotomy in patients with erythrocytosis</p> <p>Treatment of hypertension in patients with cardiac transplantation</p> <p>To reduce blood pressure and proteinuria in patients with nondiabetic kidney disease</p> <p>Migraine prophylaxis</p> <p>Prevention of recurrent atrial fibrillation</p>	<p><i>Serious, rare –</i> Angioedema Cholestatic jaundice Stevens-Johnson syndrome</p>	
<p><b>Capoten® (captopril)</b></p> <p><b>Oral tablet (generic available)</b></p> <ul style="list-style-type: none"> <li>• 12.5 mg</li> <li>• 25 mg</li> <li>• 50 mg</li> <li>• 100 mg</li> </ul>	<p><b>HF with HF<sub>rEF</sub>:</b> <i>Starting dose:</i> 6.25 mg three times daily; titrate as tolerated</p> <p><i>Target maintenance dose:</i> 50 mg three times daily (ACCF/AHA [Yancy, 2013])</p>	<p>Treatment of hypertension</p> <p>Treatment of congestive heart failure (in combination with other drugs)</p> <p>To improve survival of patients with left ventricular dysfunction after a myocardial infarction</p> <p>Treatment of diabetic nephropathy in patients with type 1 diabetes</p>	<p>Treatment of malignant hypertension</p> <p>Treatment of malignant hypertension in patients with acute scleroderma renal crisis</p> <p>Treatment of acute ST segment elevation myocardial infarction</p> <p>Prevention of diabetic retinopathy in patients with type 2 diabetes</p> <p>To reduce the need for phlebotomy in patients with erythrocytosis</p>	<p>Hypotension Hyperkalemia Chest pain Cough Dizziness Syncope Headache Skin rash Loss of taste</p> <p><i>Serious, rare –</i> Agranulocytosis Angioedema Cholestatic jaundice Neutropenia Proteinuria Stevens-Johnson syndrome</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning:</b> <i>Fetal Toxicity.</i> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal dose adjustments may be necessary.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
			<p>To reduce blood pressure and proteinuria in patients with nondiabetic kidney disease</p> <p>To evaluate plasma renin activity in patients with suspected renovascular hypertension</p> <p>Treatment of renovascular hypertension</p> <p>To diagnose primary aldosteronism</p> <p>Treatment of pseudopriary hyperaldosteronism</p> <p>Treatment of acute pulmonary edema (in combination with other drugs)</p> <p>Treatment of cystinuria</p> <p>Treatment of pre-eclampsia</p>		
<p><b>Altace® (ramipril)</b></p> <p><b>Oral capsule</b> <i>(generic available)</i></p> <ul style="list-style-type: none"> <li>• 1.25 mg</li> <li>• 2.5 mg</li> <li>• 5 mg</li> <li>• 10 mg</li> </ul>	<p><b>Heart failure post-myocardial infarction:</b> <i>Starting dose:</i> 2.5 mg twice daily for one week; may reduce dose to 1.25 mg twice daily for hypotension. Reduce the dose of any concomitant diuretics, if possible; titrate every 3 weeks</p>	<p>To reduce the risk of cardiovascular events in patients ≥ 55yo with high cardiovascular risk</p> <p>Treatment of heart failure after a myocardial infarction (in combination with other drugs)</p> <p>Treatment of hypertension</p>	<p>Treatment of Cardiac Syndrome X</p> <p>To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy</p> <p>To reduce the need for phlebotomy in patients with erythrocytosis in patients with a kidney transplant</p>	<p>Hypotension Cough Dizziness Headache Fatigue</p> <p><i>Serious, rare –</i> Angioedema Cholestatic jaundice Stevens-Johnson syndrome</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal dose adjustments may be necessary.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
	<p><i>Target maintenance dose:</i> 5 mg twice daily</p> <p><b>Heart failure (off-label use):</b> Starting dose: 1.25 to 2.5 mg once daily;</p> <p><i>Target dose:</i> 10 mg once daily (ACCF/AHA [Yancy, 2013])</p>		<p>Treatment of essential hypertension in patients with left ventricular hypertrophy</p> <p>Treatment of heart failure</p> <p>To reduce blood pressure and proteinuria in patients with nondiabetic kidney disease</p> <p>Treatment of peripheral arterial occlusive disease</p> <p>Treatment of myocardial infarction</p> <p>Prevention of recurrent atrial fibrillation</p> <p>Treatment of renovascular hypertension</p>		
<p><b>Epaned® or Vasotec® (enalapril)</b></p> <p><b>Oral tablet (generic available)</b></p> <ul style="list-style-type: none"> <li>• 2.5 mg</li> <li>• 5 mg</li> <li>• 10 mg</li> <li>• 20 mg</li> </ul>	<p><b>HF with HFrEF:</b></p> <p><i>Starting dose:</i> 2.5 mg twice daily; titrate as tolerated every 1-2 weeks</p> <p><i>Target dose:</i> 10-20 mg twice daily (ACCF/AHA [Yancy, 2013])</p>	<p>Treatment of hypertension</p> <p>Treatment of congestive heart failure (in combination with other drugs)</p> <p>To improve survival of patients with asymptomatic left ventricular dysfunction</p>	<p>Treatment of Alport Syndrome-like hereditary nephritis</p> <p>Treatment of cardiomyopathy caused by an antineoplastic agents</p> <p>Prevention of new-onset diabetes mellitus in patients with heart failure</p> <p>To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy</p>	<p>Hypotension</p> <p>Hyperkalemia</p> <p>Cough</p> <p>Dizziness</p> <p>Fatigue</p> <p>Serum creatinine elevation</p> <p>Serum BUN elevation</p> <p><i>Serious, rare –</i></p> <p>Angioedema</p> <p>Cholestatic jaundice</p> <p>Stevens-Johnson syndrome</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning:</b> <i>Fetal Toxicity.</i> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal dose adjustments may be necessary.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
			<p>To reduce the need for phlebotomy in patients with erythrocytosis</p> <p>To reduce blood pressure and proteinuria in patients with nondiabetic kidney disease</p> <p>Migraine prophylaxis</p> <p>Treatment of myocardial infarction (in combination with other drugs)</p> <p>Treatment of neutrally-mediated syncope (NMS)</p> <p>Prevention and treatment of recurrent atrial fibrillation post-cardioversion</p> <p>Treatment of renovascular hypertension</p>		
<p><b>Accupril® (quinapril)</b></p> <p><b>Oral tablet (generic available)</b></p> <ul style="list-style-type: none"> <li>• 5 mg</li> <li>• 10 mg</li> <li>• 20 mg</li> <li>• 40 mg</li> </ul>	<p><b>Heart failure:</b></p> <p><i>Starting dose:</i> 5 mg twice daily, titrated at weekly intervals to 20 to 40 mg daily in 2 divided doses;</p> <p><i>Target dose:</i> 20 mg twice daily (ACCF/AHA [Yancy, 2013])</p>	<p>Treatment of hypertension</p> <p>Adjunct therapy in the management of heart failure</p>	<p>To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy</p> <p>Prevention of postoperative hypertension</p> <p>Treatment of valvular regurgitation</p> <p>Treatment of myocardial infarction (in combination with other drugs)</p>	<p>Hypotension</p> <p>Chest pain</p> <p>Cough</p> <p>Dizziness</p> <p>Headache</p> <p>Fatigue</p> <p>Nausea</p> <p>Vomiting</p> <p>Myalgias</p> <p><i>Serious, rare –</i></p> <p>Angioedema</p> <p>Cholestatic jaundice</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal dose adjustments may be necessary.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
<b>Monopril® (fosinopril)</b>  <b>Oral tablet (generic available)</b> <ul style="list-style-type: none"> <li>• 10 mg</li> <li>• 20 mg</li> <li>• 40 mg</li> </ul>	<p><b>Heart failure:</b>  <i>Starting dose (manufacturer):</i>  10 mg once daily (5 mg once daily if moderate to severe renal dysfunction or if aggressively diuresed); titrated as tolerated over several weeks.  Usual dosage range: 20 to 40 mg once daily (maximum: 40 mg once daily).</p> <p><i>ACCF/AHA 2013 heart failure guidelines:</i>  <i>Initial:</i> 5 to 10 mg once daily.  <i>Target dose:</i> 40 mg once daily (Yancy 2013).</p>	<p>Treatment of hypertension</p> <p>Adjunct therapy in the management of heart failure</p>	<p>To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy</p> <p>Treatment of microalbuminuria</p> <p>To reduce the need for phlebotomy in patients with erythrocytosis</p> <p>To reduce blood pressure and proteinuria in patients with nondiabetic kidney disease</p> <p>Treatment of myocardial infarction (in combination with other drugs)</p>	<p>Hypotension  Hypokalemia  Cough  Dizziness  Headache  Nausea  Vomiting  Myalgia</p> <p><i>Serious, rare –</i>  Angioedema  Cholestatic jaundice  Stevens-Johnson syndrome</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal dose adjustments may be necessary.</li> </ul>
<b>Mavik® (trandolapril)</b>  <b>Oral tablet (generic available)</b> <ul style="list-style-type: none"> <li>• 1 mg</li> <li>• 2 mg</li> <li>• 4 mg</li> </ul>	<p><b>Post-MI heart failure or LV dysfunction; HF with HFrEF (off-label use):</b>  <i>Starting dose:</i> 1 mg once daily; titrate as tolerated</p> <p><i>Target dose:</i> 4 mg once daily (ACCF/AHA [Yancy 2013]).</p>	<p>To reduce the risk of cardiovascular death and hospitalization in patients with left ventricular dysfunction or heart failure after a myocardial infarction</p> <p>Treatment of hypertension</p>	<p>Treatment of acute ST segment elevation myocardial infarction</p> <p>To reduce risk of cardiovascular events</p> <p>To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy</p> <p>To reduce blood pressure and proteinuria in patients with nondiabetic kidney disease</p>	<p>Hypotension  Hyperkalemia  Cough  Dizziness  Syncope  Elevated BUN<sup>a</sup>  Elevated Scr<sup>a</sup>  Indigestion  Bradycardia  Hypocalcemia  Shock  Stroke</p> <p><i>Serious, rare –</i>  Angioedema</p>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with prior history of angioedema.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Renal and hepatic dose adjustments may be necessary.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
				Cholestatic jaundice Stevens-Johnson syndrome	
<b>ARBs with FDA-Approved Indications for Heart Failure<sup>c</sup></b> (azilsartan and losartan not approved by the FDA for HF <sup>24</sup> )					
<b>Diovan® (valsartan)</b>  <b>Oral tablet</b> <b>(generic available)</b>  • 40 mg • 80 mg • 160 mg • 320 mg	<b>Heart failure:</b> <i>Starting dose:</i> 40 mg twice daily; titrate dose to 80 to 160 mg twice daily, as tolerated; maximum daily dose: 320 mg.  ACCF/AHA 2013 HF guidelines: <i>Starting dose:</i> 20 to 40 mg twice daily  <i>Target dose:</i> 160 mg twice daily (Yancy, 2013).  <b>Left ventricular dysfunction after MI:</b> <i>Starting dose:</i> 20 mg twice daily; titrate dose <i>Target dose:</i> 160 mg twice daily as tolerated	Adjunct therapy in the management of heart failure  Treatment of hypertension  To improve survival of patients with left-ventricular diastolic dysfunction after a myocardial infarction	To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy  Treatment of erectile dysfunction  Treatment of hypertension in the renally impaired  Treatment of impaired cognition  Treatment of left ventricular hypertrophy  Reduction of coronary artery stenosis after stenting in patients with restenotic lesion of the coronary artery  Treatment of isolated systolic hypertension  Prevention of new-onset type 2 diabetes in patients with glucose tolerance  Prevention of new-onset atrial fibrillation	Hypotension Cough Dizziness Headache Elevated BUN Elevated SCr Diarrhea Fatigue  <i>Severe, rare –</i> Angioedema	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> </ul>

Drug & Dosage Form	Recommended Dosing in Heart Failure	Labeled Indications	Off-Label Uses	Adverse Drug Reactions	Contraindications/Precautions
<b>Atacand® (candesartan)</b>  <b>Oral tablet (generic available)</b> <ul style="list-style-type: none"> <li>• 4 mg</li> <li>• 8 mg</li> <li>• 16 mg</li> <li>• 32 mg</li> </ul>	<b>Heart failure:</b> <i>Starting dose: 4 mg once daily (U.S. labeling) or 4 to 8 mg once daily (ACCF/AHA [Yancy, 2013]; double the dose at 2-week intervals, as tolerated;</i>  <i>Target dose: 32 mg once daily (ACCF/AHA [Yancy, 2013]).</i>	Adjunct therapy in the management of patients with NYHA Class II-IV heart failure and reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization  Treatment of hypertension	Prevention of cerebrovascular accidents  To reduce blood pressure and urinary albumin excretion rate in patients with diabetic nephropathy  Treatment of essential hypertension in patients with left ventricular hypertrophy  To reduce proteinuria in patients with kidney disease  Migraine prophylaxis  Prevention of recurrent atrial fibrillation  Treatment of hypertension in transplant patients	Hypotension Hyperkalemia Chest pain Dizziness Backache Upper respiratory tract infections Rhinitis  <i>Severe, rare – Angioedema</i>	<ul style="list-style-type: none"> <li>• <b>Black Box Warning: Fetal Toxicity.</b> Do not use in pregnant women.</li> <li>• Do not use in patients with diabetes taking aliskiren.</li> <li>• Hepatic dose adjustments may be necessary.</li> </ul>

<sup>a</sup> BUN = Blood Urea Nitrogen; SCr = Serum Creatinine

<sup>b</sup> The following drugs are ACE Inhibitors that do not currently have an FDA-approved indication in the treatment of heart failure: benazepril, enalaprilat, moexipril, perindopril.

<sup>c</sup> The following drugs are ARBs that do not currently have an FDA-approved indication in the treatment of heart failure: azilsartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan.

**Table 3: Beta-blockers recommended in Heart Failure<sup>3,15,93,94</sup>**

Drug & Dosage Form	Recommended Dosing in Heart Failure*	Labeled Indications	Off-Label Uses	Contraindications
<b>Zebeta (bisoprolol)</b>  <b>Oral tablet (generic available)</b> <ul style="list-style-type: none"> <li>• 5 mg</li> <li>• 10 mg</li> </ul>	<i>Starting dose:</i> 1.25 mg once daily <i>Maximum dose:</i> 10 mg once daily.	Treatment of hypertension	Heart failure  Atrial fibrillation (rate control)	<ul style="list-style-type: none"> <li>• Cardiogenic shock</li> <li>• Overt cardiac failure</li> <li>• Atrioventricular block, second or third degree</li> <li>• Sinus bradycardia, severe</li> </ul>
<b>Coreg CR or Coreg (carvedilol)</b>  <b>Capsule Extended Release 24 Hour</b> <ul style="list-style-type: none"> <li>• 10 mg</li> <li>• 20 mg</li> <li>• 40 mg</li> <li>• 80 mg</li> </ul> <b>Tablet (generic available)</b> <ul style="list-style-type: none"> <li>• 3.125 mg</li> <li>• 6.25 mg</li> <li>• 12.5 mg</li> <li>• 25 mg</li> </ul>	<p><b>Heart Failure:</b>  <i>Immediate release:</i> 3.125 mg twice daily for 2 weeks; if tolerated, may increase to 6.25 mg twice daily.            Double the dose every 2 weeks to the highest dose tolerated by patient.  <i>Maximum recommended dose:</i>            Mild-to-moderate heart failure:            &lt;85 kg: 25 mg twice daily            &gt;85 kg: 50 mg twice daily            Severe heart failure: 25 mg twice daily (Packer, 2001)</p> <p><i>Extended release:</i> Initial: 10 mg once daily for 2 weeks; if tolerated, increase dose to 20 mg, 40 mg, and 80 mg over successive intervals of at least 2 weeks. Maintain on lower dose if higher dose is not tolerated.</p> <p><i>2013 ACCF/AHA HF guidelines recommend a maximum dose of 80 mg once daily</i></p> <p><b>Left ventricular dysfunction following MI:</b>            Immediate release: Initial 3.125 to 6.25 mg twice daily; increase dosage incrementally (ie, from 6.25 to 12.5 mg twice daily) at intervals of 3 to 10 days, based on tolerance, to a target dose of 25 mg twice daily.</p>	Management of hypertension  Heart failure: Mild to severe chronic heart failure of ischemic or cardiomyopathic origin (usually in addition to standard therapy [eg, diuretics, ACE inhibitors]).  Left ventricular dysfunction following myocardial infarction (MI) (clinically stable with LVEF ≤40%)	Atrial fibrillation (rate control)  Chronic stable angina  Gastroesophageal varices	Serious hypersensitivity to carvedilol or any component of the formulation; decompensated cardiac failure requiring intravenous inotropic therapy; bronchial asthma or related bronchospastic conditions; second- or third-degree AV block, sick sinus syndrome, and severe bradycardia (except in patients with a functioning artificial pacemaker); cardiogenic shock; severe hepatic impairment  Documentation of allergenic cross-reactivity for drugs alpha/beta adrenergic blocking agents is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-

	<p><i>Extended release:</i> Initial: Extended release: Initial: 10 to 20 mg once daily; increase dosage incrementally at intervals of 3 to 10 days, based on tolerance, to a target dose of 80 mg once daily.</p> <p><i>2013 ACCF/AHA HF guidelines recommend a maximum dose of 50 mg twice daily</i></p>			sensitivity cannot be ruled out with certainty
<p><b>Toprol XL (Sustained-release metoprolol succinate)</b></p> <p><b>Tablet Extended Release 24 Hour (generic available)</b></p> <ul style="list-style-type: none"> <li>• 25 mg</li> <li>• 50 mg</li> <li>• 100 mg</li> <li>• 200 mg</li> </ul>	<p><i>Starting dose:</i> 25 mg once daily (reduce to 12.5 mg once daily in NYHA class higher than class II); may double dosage every 2 weeks as tolerated (target dose: 200 mg daily).</p> <p><i>2013 ACCF/AHA Heart Failure Guidelines:</i> <i>Initial: 12.5 to 25 mg once daily;</i> <i>maximum daily dose: 200 mg</i></p>	<p>Treatment of angina pectoris or hypertension</p> <p>To reduce mortality/hospitalization in patients with heart failure (HF) (stable NYHA Class II or III) already receiving ACE inhibitors, diuretics, and/or digoxin</p>	<p>Atrial fibrillation (rate control) Cardiac risk reduction during surgery Episodic migraine prevention (adults)</p> <p>Additional Off-Label Uses :</p> <p>Atrial ectopy; Atrial fibrillation/flutter (prevention); Atrial flutter (rate control); Essential tremor; Hypertrophic obstructive cardiomyopathy (symptomatic treatment); Multifocal atrial tachycardia; Prevention of reinfarction and sudden death after myocardial infarction; Ventricular arrhythmias; Thyrotoxicosis</p>	<p>Severe bradycardia, second- and third degree heart block; cardiogenic shock; decompensated heart failure; sick sinus syndrome (except in patients with a functioning artificial pacemaker)</p>

\*Note: *Should be initiated only after patient is hemodynamically stable and fluid retention has been minimized.*

Initiate only in stable patients or hospitalized patients after volume status has been optimized and IV diuretics, vasodilators, and inotropic agents have all been successfully discontinued. Caution should be used when initiating in patients who required inotropes during their hospital course. Increase dose gradually and monitor for congestive signs and symptoms of HF making every effort to achieve target dose shown to be effective (ACCF/AHA [Yancy, 2013]; CIBIS-II Investigators and Committees, 1999; HFSA [Lindenfeld, 2010]).

## Appendix 2 – Systematic review(s) & RCT(s)

Table 4: Cochrane Reviews

Author(s)	Title	Objectives	Main Results	Author's Conclusions
Driscoll A, et al (2015) <sup>46</sup>	Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction	“To assess the effects of NLT of beta-adrenergic blocking agents, ACEIs, and ARBs in patients with heart failure with reduced ejection fraction (HFrEF) in terms of safety and patient outcomes.”	“We included seven studies (1684 participants) in the review. One study enrolled participants from a residential care facility, and the other six studies from primary care and outpatient clinics. All-cause hospital admission data was available in four studies (556 participants). Participants in the NLT group experienced a lower rate of all-cause hospital admissions (RR 0.80, 95% CI 0.72 to 0.88, high-quality evidence) and fewer hospital admissions related to heart failure (RR 0.51, 95% CI 0.36 to 0.72, moderate-quality evidence) compared to the usual-care group. Six studies (902 participants) examined all-cause mortality. All-cause mortality was also lower in the NLT group (RR 0.66, 95% CI 0.48 to 0.92, moderate-quality evidence) compared to usual care. Approximately 27 deaths could be avoided for every 1000 people receiving NLT of beta-adrenergic blocking agents, ACEIs, and ARBs. Only three studies (370 participants) reported outcomes on all-cause and heart failure-related event-free survival. Participants in the NLT group were more likely to remain event free compared to participants in the usual-care group (RR 0.60, 95% CI 0.46 to 0.77, moderate-quality evidence). Five studies (966 participants) reported on the number of participants reaching target dose of beta-adrenergic blocking agents. This was also higher in the NLT group compared to usual care (RR 1.99, 95% CI 1.61 to 2.47, low-quality evidence). However, there was a substantial degree of heterogeneity in this pooled analysis.	“Participants in the NLT group experienced fewer hospital admissions for any cause and an increase in survival and number of participants reaching target dose within a shorter time period. However, the quality of evidence regarding the proportion of participants reaching target dose was low and should be interpreted with caution. We found high-quality evidence supporting NLT as one strategy that may improve the optimisation of beta-adrenergic blocking agents resulting in a reduction in hospital admissions. Despite evidence of a dose-dependent relationship of beta-adrenergic blocking agents, ACEIs, and ARBs with improving outcomes in patients with HFrEF, the translation of this evidence into clinical practice is poor. NLT is one strategy that facilitates the implementation of this evidence into practice.”

		<p>We rated the risk of bias in these studies as high mainly due to a lack of clarity regarding incomplete outcome data, lack of reporting on adverse events associated with the intervention, and the inability to blind participants and personnel. Participants in the NLT group reached maximal dose of beta-adrenergic blocking agents in half the time compared with participants in usual care. Two studies reported on adverse events; one of these studies stated there were no adverse events, and the other study found one adverse event but did not specify the type or severity of the adverse event.”</p>	
--	--	--	--

[Additional Information from Abstract](#)

[“Background](#)

Heart failure is associated with high mortality and hospital readmissions. Beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) can improve survival and reduce hospital readmissions and are recommended as first-line therapy in the treatment of heart failure. Evidence has also shown that there is a dose-dependent relationship of these medications with patient outcomes. Despite this evidence, primary care physicians are reluctant to up-titrate these medications. New strategies aimed at facilitating this up-titration are warranted. Nurse-led titration (NLT) is one such strategy.

[Search methods](#)

We searched the Cochrane Central Register of Controlled Trials in the Cochrane Library (CENTRAL Issue 11 of 12, 19/12/2014), MEDLINE OVID (1946 to November week 3 2014), and EMBASE Classic and EMBASE OVID (1947 to 2014 week 50). We also searched reference lists of relevant primary studies, systematic reviews, clinical trial registries, and unpublished theses sources. We used no language restrictions.

[Selection criteria](#)

Randomised controlled trials (RCTs) comparing NLT of beta-adrenergic blocking agents, ACEIs, and/or ARBs comparing the optimisation of these medications by a nurse to optimisation by another health professional in patients with HFrEF.

[Data collection and analysis](#)

Two review authors (AD & JC) independently assessed studies for eligibility and risk of bias. We contacted primary authors if we required additional information. We examined quality of evidence using the GRADE rating tool for RCTs. We analysed extracted data by risk ratio (RR) with 95% confidence interval (CI) for dichotomous data to measure effect sizes of intervention group compared with usual-care group. Meta-analyses used the fixed-effect Mantel-Haenszel method. We assessed heterogeneity between studies by Chi<sup>2</sup> and I<sup>2</sup>.”

[Plain language summary: Quality of the evidence](#)

We rated the quality of evidence regarding the proportion of participants that reached optimal dose of these medications as low. This indicates uncertainty as to whether the number of participants reaching optimal dose of beta-adrenergic blocking agents was different due to NLT or usual care. We found high-quality evidence that NLT reduced hospitalisations for any cause compared to usual care. This indicates that we are confident that the reduction in all-cause hospitalisations was due to NLT, and further research is unlikely to change this finding.”

**Table 5: Abstracts of Selected Randomized Controlled Trials (RCTs)**

**Entresto™ in Heart Failure with Reduced Ejection Fraction**

McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. (2014)<sup>55</sup>

**“BACKGROUND** - We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

**METHODS** - In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

**RESULTS** - The trial was stopped early, according to prespecified rules, after a median followup of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P = 0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

**CONCLUSIONS** - LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)”

Packer M, McMurray JJV, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. (2015)<sup>57</sup>

**“Background**—Clinical trials in heart failure have focused on the improvement in symptoms or decreases in the risk of death and other cardiovascular events. Little is known about the effect of drugs on the risk of clinical deterioration in surviving patients.

**Methods and Results**—We compared the angiotensin-neprilysin inhibitor LCZ696 (400 mg daily) with the angiotensin-converting enzyme inhibitor enalapril (20 mg daily) in 8399 patients with heart failure and reduced ejection fraction in a double-blind trial. The analyses focused on prespecified measures of nonfatal clinical deterioration. In comparison with the enalapril group, fewer LCZ696-treated patients required intensification of medical treatment for heart failure (520 versus 604; hazard ratio, 0.84; 95% confidence interval, 0.74–0.94; P=0.003) or an emergency department visit for worsening heart failure (hazard ratio, 0.66; 95% confidence interval, 0.52–0.85; P=0.001). The patients in the LCZ696 group had 23% fewer hospitalizations for worsening heart failure (851 versus 1079; P<0.001) and were less likely to require intensive care (768 versus 879; 18% rate reduction, P=0.005), to receive intravenous positive inotropic agents (31% risk reduction, P<0.001), and to have implantation of a heart failure device or cardiac transplantation (22% risk reduction, P=0.07). The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization. Worsening of symptom scores in surviving patients was consistently more common in the enalapril group. LCZ696 led to an early and sustained reduction in biomarkers of myocardial wall stress and injury (N-terminal pro-B-type natriuretic peptide and troponin) versus enalapril.

**Conclusions**—Angiotensin-neprilysin inhibition prevents the clinical progression of surviving patients with heart failure more effectively than angiotensin-converting enzyme inhibition.”

**Entresto™ in Heart Failure with Preserved Ejection Fraction**

Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. (2012)<sup>31</sup>

**“BACKGROUND:**

Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), in patients with this disorder.

**METHODS:**

PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II-III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.

**FINDINGS:**

149 patients were randomly assigned to LCZ696 and 152 to valsartan; 134 in the LCZ696 group and 132 in the valsartan group were included in analysis of the primary endpoint. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group (LCZ696: baseline, 783 pg/mL [95% CI 670-914], 12 weeks, 605 pg/mL [512-714]; valsartan: baseline, 862 pg/mL [733-1012], 12 weeks, 835 [710-981]; ratio LCZ696/valsartan, 0.77, 95% CI 0.64-0.92,  $p=0.005$ ). LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan had one or more serious adverse event.

**INTERPRETATION:**

In patients with heart failure with preserved ejection fraction, LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated. Whether these effects would translate into improved outcomes needs to be tested prospectively.

**FUNDING:**

Novartis.”

**Entresto™ in Hypertension**

Ito S, Satoh M, Tamaki Y, et al. Safety and efficacy of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with hypertension and renal dysfunction. (2015)<sup>32</sup>

“This 8-week, multi-center, open-label study assessed the safety and efficacy of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with hypertension and renal dysfunction. Patients ( $n=32$ ) with mean sitting systolic blood pressure (msSBP)  $\geq 140$  mm Hg (after a 2-5-week washout of previous antihypertensive medications) and estimated glomerular filtration rate (eGFR)  $\geq 15$  and  $< 60$  ml min<sup>-1</sup> 1.73 m<sup>-2</sup> received LCZ696 100 mg with an optional titration to 200 and 400 mg in a sequential manner starting from Week 2 in patients with inadequate BP control (msSBP  $\geq 130$  mm Hg and mean sitting diastolic blood pressure (msDBP)  $\geq 80$  mm Hg) and without safety concerns. Safety was assessed by monitoring and recording all adverse events (AEs) and change in potassium and creatinine. Efficacy was assessed as change from baseline in msSBP/msDBP. The mean baseline BP was 151.6/86.9 mm Hg, urinary albumin/creatinine ratio (UACR) geometric mean was 7.3 mg mmol<sup>-1</sup> and eGFR was  $\geq 30$  and  $< 60$  in 25 (78.1%) patients and was  $\geq 15$  and  $< 30$  in 7 (21.9%) patients. Fourteen (43.8%) patients reported at least one AE, which were mild in severity. No severe AEs or deaths were reported. There were no clinically meaningful changes in creatinine, potassium, blood urea nitrogen and eGFR. The geometric mean reduction in UACR was 15.1%, and the mean reduction in msSBP and msDBP was 20.5 $\pm$ 11.3 and 8.3 $\pm$ 6.3 mm Hg, respectively, from baseline to Week 8 end point. LCZ696 was generally safe and well tolerated and showed effective BP reduction in Japanese patients with hypertension and renal dysfunction without a decline in renal function.”

Ruilope LM, Dukat A, Bohm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. (2010)<sup>34</sup>

**“BACKGROUND:**

LCZ696 is a first-in-class inhibitor of the angiotensin II receptor and neprilysin. We aimed to establish whether the dual actions of LCZ696 lead to further lowering of blood pressure, compared with the angiotensin-receptor blocker valsartan.

**METHODS:**

1328 patients aged 18-75 years with mild-to-moderate hypertension were randomly assigned (double-blind) to 8 weeks' treatment in one of eight groups: 100 mg ( $n=156$  patients), 200 mg ( $n=169$ ), or 400 mg ( $n=172$ ) LCZ696; 80 mg ( $n=163$ ), 160 mg ( $n=166$ ), or 320 mg ( $n=164$ ) valsartan; 200 mg AHU377 ( $n=165$ ); or placebo ( $n=173$ ). The primary endpoint was the mean difference across the three single-dose pairwise comparisons of LCZ696 versus valsartan (100 mg vs 80 mg, 200 mg vs 160 mg, and 400 mg vs 320 mg) in mean

---

sitting diastolic blood pressure during the 8-week treatment period. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00549770.

**FINDINGS:**

1215 patients completed the 8-week treatment period. The average reduction in mean sitting diastolic blood pressure across the doses of LCZ696 versus the appropriate comparator dose of valsartan showed significantly greater reductions with LCZ696 (mean reduction: -2.17 mm Hg, 95% CI -3.28 to -1.06;  $p < 0.0001$ ). The reduction in mean sitting diastolic blood pressure was significantly different for 200 mg LCZ696 versus 160 mg valsartan (-2.97 mm Hg, 95% CI -4.88 to -1.07,  $p = 0.0023$ ) and for 400 mg LCZ696 versus 320 mg valsartan (-2.70 mm Hg, -4.61 to -0.80,  $p = 0.0055$ ). LCZ696 was well tolerated and no cases of angio-oedema were reported; only three serious adverse events occurred during the 8-week treatment period, of which none was judged to be related to the study drug, and no patients died.

**INTERPRETATION:**

Compared with valsartan, dual-acting LCZ696 provides complementary and fully additive reduction of blood pressure, which suggests that the drug holds promise for treatment of hypertension and cardiovascular disease.

**FUNDING:**

Novartis.”

---

### Appendix 3 – Heart Failure Diagnoses

DIAGNOSIS <sup>20</sup>	ICD-9	ICD-10	TOTAL PATIENTS 2014-2015	CURRENTLY ELIGIBLE JAN 2016	ACO	FFS
<b>Heart Failure</b>	<b>428</b>	<b>I500</b>	<b>4,717</b>	<b>3,002</b>	<b>2,005</b>	<b>997</b>
<b>Unspecified Congestive Heart Failure</b>	<b>4280 4289</b>	<b>I509</b>	<b>4,155</b>	<b>2,636</b>	<b>1,766</b>	<b>870</b>
<b>Left Ventricular Heart Failure</b>	<b>4281</b>	<b>I501</b>	<b>176</b>	<b>120</b>	<b>77</b>	<b>43</b>
<b>Systolic Heart Failure</b>	<b>4282</b>		<b>880</b>	<b>570</b>	<b>436</b>	<b>134</b>
Unspecified Systolic Heart Failure	42820	I5020	250	160	117	43
Acute Systolic Heart Failure	42821	I5021	184	107	84	23
Chronic Systolic Heart Failure	42822	I5022	555	374	294	80
Acute on Chronic Systolic Heart Failure	42823	I5023	228	145	109	36
<b>Diastolic Heart Failure</b>	<b>4283</b>		<b>886</b>	<b>571</b>	<b>432</b>	<b>139</b>
Unspecified Diastolic Heart Failure	42830	I5030	390	256	190	66
Acute Diastolic Heart Failure	42831	I5031	105	67	57	10
Chronic Diastolic Heart Failure	42832	I5032	394	264	205	59
Acute on Chronic Diastolic Heart Failure	42833	I5033	209	120	90	30
<b>Combined Systolic and Diastolic Heart Failure</b>	<b>4284</b>		<b>231</b>	<b>157</b>	<b>120</b>	<b>37</b>
Unspecified Combined Systolic and Diastolic Heart Failure	42840	I5040	35	20	11	9
Acute Combined Systolic and Diastolic Heart Failure	42841	I5041	38	29	24	5
Chronic Combined Systolic and Diastolic Heart Failure	42842	I5042	104	76	57	19
Acute on Chronic Combined Systolic and Diastolic Heart Failure	42843	I5043	88	53	42	11

DIAGNOSIS <sup>20,66</sup>	ICD-9	ICD-10	TOTAL PATIENTS 2014-2015	CURRENTLY ELIGIBLE	ACO	FFS
Hypertensive Heart Disease with Congestive Heart Failure	40201 40211 40291	I110	199	128	95	33
Hypertensive Heart and Renal Disease with Congestive Heart Failure	40401 40411 40491	I130	47	27	21	6
Hypertensive Heart and Renal Disease with Congestive Heart Failure and Renal Failure	40403 40413 40493	I132	20	13	11	2
Ischaemic Cardiomyopathy	4148	I255	429	291	242	49
Dilated Cardiomyopathy	4254	I420	1,246	812	646	166
Unspecified Cardiomyopathy	4254 4259	I429	1,325	874	689	185
Heart Failure	428	I500	4,717	3,002	2,005	997
Unspecified Congestive Heart Failure	4280 4289	I509	4,155	2,636	1,766	870
Left Ventricular Heart Failure	4281	I501	176	120	77	43
Abnormal Findings on Diagnostic Imaging of Heart and Coronary Circulation		R931	24	23	16	7
<b>TOTAL UNIQUE PATIENTS</b>			<b>5,355</b>	<b>3,417</b>	<b>2,319</b>	<b>1,098</b>

## References

1. Association AH. About Heart Failure.  
[http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/About-Heart-Failure\\_UCM\\_002044\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/About-Heart-Failure_UCM_002044_Article.jsp). Accessed August 12, 2015.
2. Bazzano LAL, Marshall MK, Harrold R, Pak KJ, van Driel ML. Interventions to improve evidence-based prescribing in heart failure (Protocol). *Cochrane Database of Systematic Reviews* 2014, Issue 8. Art. No.: CD011253. DOI: 10.1002/14651858.CD011253. .  
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011253/abstract>.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. Oct 15 2013;62(16):e147-239.
4. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. Jan 27 2015;131(4):e29-322.
5. Fala L. Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure. *Am Health Drug Benefits*. Sep 2015;8(6):330-334.
6. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. Jan 27 2015;131(4):e29-322.
7. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. Dec 10 2002;106(24):3068-3072.
8. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *Jama*. Jul 21 2004;292(3):344-350.
9. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *The American journal of cardiology*. Apr 1 2008;101(7):1016-1022.
10. The Booming Dynamics of Aging: From Awareness to Action. The White House Conference on Aging. Washington, DC: US Department of Health and Human Services; 2011.
11. Heart failure - sacubitril valsartan [ID822] NICE in development [GID-TAG516] Anticipated publication date: May 2016 <http://www.nice.org.uk/guidance/indevelopment/gid-tag516/documents>. Accessed January 2016.
12. Writing Committee M, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. Oct 15 2013;128(16):e240-327.
13. Classes of Heart Failure.  
[http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure\\_UCM\\_306328\\_Article.jsp#.VqakbMv2ZXI](http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.VqakbMv2ZXI). Accessed 25 January 2016.
14. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European journal of heart failure*. Aug 2012;14(8):803-869.
15. Bisoprolol Fumarate. Micromedex.  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/51F293/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/753E7E/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=bisoprolol&UserSearchTerm=bisoprolol&SearchFilter=filterNone&navitem=searchALL#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/51F293/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/753E7E/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=bisoprolol&UserSearchTerm=bisoprolol&SearchFilter=filterNone&navitem=searchALL#).

16. American Heart Association. Ejection fraction heart failure measurement. Updated June 1, 2015. [www.heart.org/HEARTORG/Conditions/HeartFailure/SymptomsDiagnosisofHeartFailure/Ejection-Fraction-Heart-Failure-Measurement UCM\\_306339\\_Article.jsp#](http://www.heart.org/HEARTORG/Conditions/HeartFailure/SymptomsDiagnosisofHeartFailure/Ejection-Fraction-Heart-Failure-Measurement_UCM_306339_Article.jsp#). Accessed July 27, 2015.
17. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *Journal of the American College of Cardiology*. Aug 21 2007;50(8):768-777.
18. Heart Failure Society of A, Lindenfeld J, Albert NM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *Journal of cardiac failure*. Jun 2010;16(6):e1-194.
19. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *Journal of the American College of Cardiology*. Apr 14 2009;53(15):e1-e90.  
<http://www.icd9data.com/2012/Volume1/390-459/420-429/428/default.htm>.
21. Gori M, Senni M. Sacubitril/valsartan (LCZ696) for the treatment of heart failure. *Expert review of cardiovascular therapy*. Jan 8 2016:1-9.
22. Administration USFaD. FDA approves new drug to treat heart failure. 2015; <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm>. Accessed July 8, 2015.
23. UKMi New Drugs Online Report for sacubitril valsartan. [http://www.ukmi.nhs.uk/applications/ndo/record\\_view\\_open.asp?newDrugID=4937](http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4937). Accessed 21 January 2016.
24. Sacubitril/Valsartan (Entresto) for Heart Failure. *JAMA*. Aug 18 2015;314(7):722-723.
25. Diovan® (valsartan) Tablets. Product Label [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021283s037lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021283s037lbl.pdf). Accessed July 10, 2015.
26. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC. Heart failure*. Dec 2014;2(6):663-670.
27. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. May 2013;6(3):606-619.
28. National Heart, Lung, and Blood Institute. Morbidity & mortality: 2012 chart book on cardiovascular, lung, and blood diseases. [www.nhlbi.nih.gov/resources/docs/cht-book.htm](http://www.nhlbi.nih.gov/resources/docs/cht-book.htm).
29. Sacubitril/Valsartan. Micromedex. [http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/E60BC3/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/9DC52E/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=931463&contentSetId=100&title=Sacubitril%2FValsartan&servicesTitle=Sacubitril%2FValsartan&br andName=Entresto#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/E60BC3/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/9DC52E/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=931463&contentSetId=100&title=Sacubitril%2FValsartan&servicesTitle=Sacubitril%2FValsartan&br andName=Entresto#). Accessed 25 January 2016.
30. Sacubitril and Valsartan. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/5725052](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5725052). .
31. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. Oct 20 2012;380(9851):1387-1395.
32. Ito S, Satoh M, Tamaki Y, et al. Safety and efficacy of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with hypertension and renal dysfunction. *Hypertension research : official journal of the Japanese Society of Hypertension*. Apr 2015;38(4):269-275.
33. ClinicalTrials.gov. Search Results: LCZ696. <https://clinicaltrials.gov/ct2/results?term=lcz696&Search=Search>. Accessed July 10, 2015.

34. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet*. Apr 10 2010;375(9722):1255-1266.
35. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. Jan 1 2013;127(1):e6-e245.
36. Krumholz HM, Merrill AR, Schone EM, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. *Circulation. Cardiovascular quality and outcomes*. Sep 2009;2(5):407-413.
37. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. Mar 1 2011;123(8):933-944.
38. Carvedilol (Lexi-Drugs). [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6545](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6545).
39. Jessup M. Neprilysin inhibition--a novel therapy for heart failure. *The New England Journal of Medicine*. Sep 11 2014;371(11):1062-1064.
40. SIGN Guideline 95: Management of chronic heart failure  
<http://www.sign.ac.uk/guidelines/fulltext/95/annexes.html>.
41. What's New in the 2013 ACCF/ AHA Guidelines for the Management of Heart Failure? From an Author's Perspective. Biykem Bozkurt, MD., Ph.D. June 5, 2013.  
[http://my.americanheart.org/professional/ScienceNews/What-is-New-in-the-2013-ACCF-AHA-Guidelines-for-the-Management-of-Heart-Failure\\_UCM\\_452903\\_Article.jsp#.VrJK8cv2ZXI](http://my.americanheart.org/professional/ScienceNews/What-is-New-in-the-2013-ACCF-AHA-Guidelines-for-the-Management-of-Heart-Failure_UCM_452903_Article.jsp#.VrJK8cv2ZXI).
42. Use of angiotensin II receptor blocker and neprilysin inhibitor in heart failure with reduced ejection fraction. [http://www.uptodate.com.ezproxy.lib.utah.edu/contents/use-of-angiotensin-ii-receptor-blocker-and-neprilysin-inhibitor-in-heart-failure-with-reduced-ejection-fraction?source=search\\_result&search=http%3A%2F%2Fwww.uptodate.com%2Fcontents%2Fuse-of-angiotensin-ii-receptor-blocker-and-neprilysin-inhibitor-in-heart-failure-with-reduced-ejection-fraction%23H24&selectedTitle=1%7E150](http://www.uptodate.com.ezproxy.lib.utah.edu/contents/use-of-angiotensin-ii-receptor-blocker-and-neprilysin-inhibitor-in-heart-failure-with-reduced-ejection-fraction?source=search_result&search=http%3A%2F%2Fwww.uptodate.com%2Fcontents%2Fuse-of-angiotensin-ii-receptor-blocker-and-neprilysin-inhibitor-in-heart-failure-with-reduced-ejection-fraction%23H24&selectedTitle=1%7E150).
43. Moe GW, Ezekowitz JA, O'Meara E, et al. The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications. *The Canadian journal of cardiology*. Jan 2015;31(1):3-16.
44. Swennen MHJ, Rutten FH, Kalkman CJ, van der Graaf Y, Sachs APE, van der Heijden GJMG. Do general practitioners follow treatment recommendations from guidelines in their decisions on heart failure management? A cross-sectional study. *BMJ Open*. 2013;3(9):e002982.
45. Williamson M, Cardona-Morrell M, Elliott JD, et al. Prescribing Data in General Practice Demonstration (PDGPD) project--a cluster randomised controlled trial of a quality improvement intervention to achieve better prescribing for chronic heart failure and hypertension. *BMC Health Serv Res*. 2012;12:273.
46. Driscoll A, Currey J, Tonkin A, Krum H. Nurse-led titration of angiotensin converting enzyme inhibitors, beta-adrenergic blocking agents, and angiotensin receptor blockers for people with heart failure with reduced ejection fraction. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD009889. DOI: 10.1002/14651858.CD009889.pub2. .  
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009889.pub2/abstract>.
47. Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation*. Aug 10 2010;122(6):585-596.
48. Walsh MN, Albert NM, Curtis AB, et al. Lack of association between electronic health record systems and improvement in use of evidence-based heart failure therapies in outpatient cardiology practices. *Clin Cardiol*. Mar 2012;35(3):187-196.

49. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *Bmj*. 1998;317(7156):465-468.
50. Feder G, Eccles M, Grol R, Griffiths C, Grimshaw J. Clinical guidelines: using clinical guidelines. *Bmj*. 1999;318(7185):728-730.
51. Grimshaw JM, Eccles MP, Walker AE, Thomas RE. Changing physicians' behavior: what works and thoughts on getting more things to work. *J Contin Educ Health Prof*. 2002;22(4):237-243.
52. McEntee ML, Cuomo LR, Dennison CR. Patient-, provider-, and system-level barriers to heart failure care. *The Journal of cardiovascular nursing*. 2009;24(4):290-298.
53. Grimshaw J, McAuley LM, Bero LA, et al. Systematic reviews of the effectiveness of quality improvement strategies and programmes. *Qual Saf Health Care*. 2003;12(4):298-303.
54. Grimshaw JM, Thomson MA. What have new efforts to change professional practice achieved? Cochrane Effective Practice and Organization of Care Group. *J R Soc Med*. 1998;91 Suppl 35:20-25.
55. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England journal of medicine*. Sep 11 2014;371(11):993-1004.
56. ENTRESTO™ (sacubitril and valsartan) tablets. Product Label <http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf>. Accessed July 10, 2015
57. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation*. Jan 6 2015;131(1):54-61.
58. The Oregon State Drug Review. Does Sacubitril/Valsartan Pose a Treatment Conundrum for Management of Heart Failure? December 2015. Volume 5, Issue 8. Andrew Gibler, Pharm.D., Oregon State University College of Pharmacy. [http://www.orpdl.org/durm/newsletter/osdr\\_articles/volume5/osdr\\_v5\\_i8.pdf](http://www.orpdl.org/durm/newsletter/osdr_articles/volume5/osdr_v5_i8.pdf).
59. ICER Draft Report on CardioMEMS and Entresto for Management of Congestive Heart Failure Posted for Public Comment <http://www.icer-review.org/chf-draft-report-posted/>. Accessed 21 January 2016.
60. California Technology Assessment Forum (CTAF). <http://ctaf.org/about-ctaf>.
61. ICER Releases Final Report on CardioMEMS HF System™ and Entresto™ for Management of Congestive Heart Failure. Boston, Mass., December 1, 2015 <http://www.icer-review.org/chf-final-report-released/>.
62. Cannon J, et al. Dementia-related adverse effects in the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF (2015), Abstracts. *European Journal of Heart Failure*, 17: 5–441. doi: 10.1002/ejhf.277. <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/759/CN-01088759/frame.html>.
63. Inhibiting Neprilysin Is Good for the Heart: What About the Brain? 12 Sep 2014. <http://www.alzforum.org/news/research-news/inhibiting-neprilysin-good-heart-what-about-brain>.
64. Comments on News and Primary Papers. Paper: Angiotensin-neprilysin inhibition versus enalapril in heart failure. Rebecca Gottesman, Johns Hopkins University School of Medicine. Posted: 16 Sep 2014 <http://www.alzforum.org/news/research-news/inhibiting-neprilysin-good-heart-what-about-brain>.
65. Challenges for Coding Heart Failure. Prepared by Ingenix Inc. Staff. Posted on: May 22, 2007 <http://health-information.advanceweb.com/Article/Challenges-for-Coding-Heart-Failure.aspx>.
66. Scottish Clinical Coding Standards - ICD10. Number 3 - September 2013. <http://www.isdscotland.org/Products-and-Services/Terminology-Services/Clinical-Coding-Guidelines/Docs/coding-standards-Sep13.pdf>.
67. ZESTRIL® (lisinopril) tablets. Product Label [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/019777s064lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019777s064lbl.pdf). Accessed July 10, 2015.
68. Leppert W. Role of oxycodone and oxycodone/naloxone in cancer pain management. *Pharmacol Rep*. Jul-Aug 2010;62(4):578-591.

69. ALTACE® (ramipril capsule). Product Label  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/019901s060lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019901s060lbl.pdf). Accessed July 10, 2015.
70. VASOTEC® (enalapril). Product Label  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/018998s076lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018998s076lbl.pdf). Accessed July 10, 2015.
71. ACCUPRIL® (quinapril hydrochloride tablets). Product Label  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/019885s040lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019885s040lbl.pdf). Accessed July 10, 2015.
72. MONOPRIL® (fosinopril sodium tablets). Product Label  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2003/19915se5-037\\_monopril\\_lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/19915se5-037_monopril_lbl.pdf). Accessed July 10, 2015.
73. MAVIK® (trandolapril tablets) Product Label  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/020528s018lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020528s018lbl.pdf). Accessed July 10, 2015.
74. ATACAND® (candesartan cilexetil) Tablets. Product Label  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020838s031lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020838s031lbl.pdf). Accessed July 10, 2015.
75. Lisinopril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/7185](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7185). Accessed July 10, 2015.
76. Captopril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6522](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6522). Accessed July 10, 2015.
77. Ramipril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/7611](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7611). Accessed July 10, 2015.
78. Enalapril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6815](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6815). Accessed July 10, 2015.
79. Quinapril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/7599](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7599). Accessed July 10, 2015.
80. Fosinopril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6953](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6953). Accessed July 10, 2015.
81. Trandolapril. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/7797](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7797). Accessed July 10, 2015.
82. Valsartan. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/7854](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7854). Accessed July 10, 2015.
83. Candesartan. Lexi-Drugs [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6515](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6515). Accessed July 10, 2015.
84. Lisinopril: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/EDABD9/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/F2C864/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=lisinopril&UserSearchTerm=lisinopril&SearchFilter=filterNone&navitem=searchALL#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/EDABD9/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/F2C864/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=lisinopril&UserSearchTerm=lisinopril&SearchFilter=filterNone&navitem=searchALL#). Accessed July 10, 2015.
85. Captopril: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/C5FBC1/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/F9FA29/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=106355&contentSetId=100&title=Captopril&servicesTitle=Captopril&brandName=Capoten#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/C5FBC1/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/F9FA29/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=106355&contentSetId=100&title=Captopril&servicesTitle=Captopril&brandName=Capoten#). Accessed July 10, 2015.
86. Ramipril: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/EDABD9/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/F2C864/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=ramipril&UserSearchTerm=ramipril&SearchFilter=filterNone&navitem=searchALL#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/EDABD9/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/F2C864/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=ramipril&UserSearchTerm=ramipril&SearchFilter=filterNone&navitem=searchALL#). Accessed July 10, 2015.

[expert/CS/61C6DB/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/7077A0/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=502480&contentSetId=100&title=Ramipril&servicesTitle=Ramipril&brandName=Altace#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/61C6DB/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/7077A0/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=502480&contentSetId=100&title=Ramipril&servicesTitle=Ramipril&brandName=Altace#). Accessed July 10, 2015.

87. Enalapril Maleate: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/7EC52E/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/87C75A/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=enalapril&UserSearchTerm=enalapril&SearchFilter=filterNone&navitem=searchALL#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/7EC52E/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/87C75A/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=enalapril&UserSearchTerm=enalapril&SearchFilter=filterNone&navitem=searchALL#). Accessed July 10, 2015.
88. Quinapril Hydrochloride: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/7D0580/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/059E26/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=499555&contentSetId=100&title=Quinapril+Hydrochloride&servicesTitle=Quinapril+Hydrochloride&brandName=Accupril#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/7D0580/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/059E26/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=499555&contentSetId=100&title=Quinapril+Hydrochloride&servicesTitle=Quinapril+Hydrochloride&brandName=Accupril#). Accessed July 10, 2015.
89. Fosinopril Sodium: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/CF6A83/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/573C24/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=239400&contentSetId=100&title=Fosinopril+Sodium&servicesTitle=Fosinopril+Sodium&brandName=Monopril#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/CF6A83/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/573C24/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=239400&contentSetId=100&title=Fosinopril+Sodium&servicesTitle=Fosinopril+Sodium&brandName=Monopril#). Accessed July 10, 2015.
90. Trandolapril: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/7D8C27/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/7C4373/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=923605&contentSetId=100&title=Trandolapril&servicesTitle=Trandolapril&brandName=Mavik#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/7D8C27/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/7C4373/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=923605&contentSetId=100&title=Trandolapril&servicesTitle=Trandolapril&brandName=Mavik#). Accessed July 10, 2015.
91. Valsartan: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/BF6DF5/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/BD3770/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=valsartan#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/BF6DF5/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/BD3770/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=valsartan#). Accessed July 10, 2015.
92. Candesartan Cilexetil: Dosing/Administration Non-FDA Uses. MICROMEDEX® 2.0  
[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/DAD99C/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/0FCC8D/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=924785&contentSetId=100&title=Candesartan+Cilexetil&servicesTitle=Candesartan+Cilexetil&brandName=Atacand#](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/DAD99C/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/0FCC8D/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=924785&contentSetId=100&title=Candesartan+Cilexetil&servicesTitle=Candesartan+Cilexetil&brandName=Atacand#). Accessed July 10, 2015.
93. Bisoprolol (Lexi-Drugs).  
[http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/6461#f\\_preparations](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6461#f_preparations).
94. Lexicomp Online. <http://online.lexi.com/>.