Principles of focused ultrasound

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Title

Sacubitril and Valsartan fixed combination to reduce heart failure events in post-acute myocardial infarction patients

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Background

Heart failure is a term used to define a constellation of symptoms and signs that are commonly attributed to the inability of the heart to produce a cardiac output that meets the demands of the body. Exertional dyspnoea, peripheral oedema as well as orthopnoea are the usual findings following history taking and physical examination. It remains a deadly disease and increasingly effective treatments in modern day medicine mean that patients are living longer and are more likely to have multiple co-morbidities when they present to hospital. It affects between 1-2% of the population and is more common in the elderly; around 6-10% of patients over 65 years of age suffer from the condition.{ ADDIN PAPERS2_CITATIONS <citation><uuid>ADB7A6D0-FC09-4EA6-9CA7-4CC1EE58C391</uuid><priority>0</priority><publications><publication><uuid>C56A60A3-A3BF-4BC4-9B6A-62834ED24C3D</uuid><volume>365</volume><doi>10.1016/S0140-6736(05)66621-4</doi><startpage>1877</startpage><publication_date>99200506001200000000220000</publication_date><url>http://linkinghub.elsevier.com/retrieve/pii/S0140673605666214</url><type>400</type><title>Heart failure.</title><institution>Department of Cardiology, Western Infirmary, Glasgow, UK. j.mcmurray@bio.gla.ac.uk <j.mcmurray@bio.gla.ac.uk></institution><number>9474</number><subtype>400</subtype><endpage>1889</endpage><bundle><publication><title>Lancet (London, England)</title><type>-100</type><subtype>-100</subtype><uuid>0930CC52-3772-4166-8F8F-CED21EE013A0</uuid></publication></bundle><authors><author><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author><author><firstName>Marc<

/firstName><middleNames>A</middleNames><lastName>Pfeffer</lastName></author></authors></publication></publications><cites></cites></citation>**}**

The term “heart failure with reduced ejection fraction” and “heart failure with preserved ejection fraction” describe 2 completely different diseases and underlying pathophysiology. Around 50% of patients with heart failure have preserved ejection fraction. However, in day to day clinical practice, unless explicitly stated otherwise, the use of the term heart failure is commonly understood to refer to heart failure with reduced ejection fraction. The reduction in systolic function of the left ventricle commonly results from a variety of causes. This is also dependent on geographical location and prevalence of other environmental risks such as communicable diseases, malnutrition, and low socioeconomic status. In North America and Western Europe, coronary artery disease remains the biggest underlying cause of heart failure with reduced ejection fraction (HFrEF). Whilst in Africa and Asia, rheumatic heart disease is still a major cause, similar to the role played by hypertension in the African-American cohort.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>A31A0292-4490-4D99-94FC-5ACD260766F4</uuid><priority>0</priority><publications><publication><volume>80</volume><publication_date>99200109001200000000220000</publication_date><number>2-3</number><institution>Cardiac Medicine, National Heart & Lung Institute, Imperial College School of Medicine, Dovehouse Street, London SW3 6LY, UK. g.mendez@abdn.ac.uk</institution><startpage>213</startpage><title>The epidemiological features of heart failure in developing countries: a review of the literature.</title><uuid>5539FF82-EBCE-4C75-BEFF-3B36534CA226</uuid><subtype>400</subtype><endpage>219</endpage><type>400</type><url>http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=115

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rstName>M</firstName><middleNames>R</middleNames><lastName>Cowie</lastName><
/author></authors></publication></publications><cites></cites></citation>}

Physiological consequences of heart failure

A reduction in ejection fraction activates a sequence of adaptive mechanisms to maintain adequate cardiac output. The renin-angiotensin-aldosterone system (RAAS) as well as the adrenergic system are activated which leads to increased left ventricular contractility and vasoconstriction. The resulting increase in sodium and water retention, heart rate and blood pressure synergistically aim to maintain adequate cardiac output. Although this neuroendocrine activation initially aims to meet cardiac output demand, continuous activation results in maladaptive cardiac remodelling and has deleterious effects on left ventricular function.{ ADDIN PAPERS2_CITATIONS <citation><uuid>6F94B444-04F7-4193-
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tpage><publication_date>992016100012000000000220000</publication_date><url>http://linkinghub.elsevier.com/retrieve/pii/S0163725816301243</url><type>400</type><title>Pharmacology of heart failure: From basic science to novel therapies.</title><submission_date>992016031812000000000222000</submission_date><institution>Institute of Experimental and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Freiburg, Freiburg, Germany; Heart Center, Department of Cardiology and Angiology I, Faculty of Medicine, University of Freiburg, Freiburg, Germany. Electronic address: achim.lother@universitaets-herzzentrum.de.</institution><subtype>400</subtype><endpage>149</endpage><bundle><publication><title>Pharmacology & therapeutics</title><type>-100</type><subtype>-100</subtype><uuid>E9EB397B-C635-4623-A825-EA17B778845B</uuid></publication></bundle><authors><author><firstName>Achim</firstName><lastName>Lother</lastName></author><author><firstName>Lutz</firstName><lastName>Hein</lastName></author></authors></publication></publications><cites></cites></citation>} The circulating levels of angiotensin-2 (AT-2) have been shown to increase in heart failure, impacting on cell function and altering intrinsic myocardial contractility, ventricular stiffness, and diastolic function. { ADDIN PAPERS2_CITATIONS <citation><uuid>D21EA77E-D941-4762-81A0-3DE47E6EF8D4</uuid><priority>0</priority><publications><publication><uuid>CAEAABF7-3224-4BB7-8889-EE2C9069FF83</uuid><volume>131</volume><accepted_date>992017073112000000002220000</accepted_date><doi>10.1042/CS20171167</doi><startpage>2319</startpage><revision_date>992017072612000000000222000</revision_date><publication_date>992017091512000000000222000</publication_date><url>http://clinsci.org/lookup/doi/10.1042/CS2017

1167</url><type>400</type><title>Mechanisms contributing to cardiac remodelling.</title><publisher>Portland Press Limited</publisher><submission_date>992017062312000000000222000</submission_date><number>18</number><institution>Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan 430060, China.</institution><subtype>400</subtype><endpage>2345</endpage><bundle><publication><title>Clinical science (London, England : 1979)</title><type>-100</type><subtype>-100</subtype><uuid>767A7C8E-CDDD-4897-8793-7CE83B27123B</uuid></publication></bundle><authors><author><firstName>Qing-Qing</firstName><lastName>Wu</lastName></author><author><firstName>Yang</firstName><lastName>Xiao</lastName></author><author><firstName>Yuan</firstName><lastName>Yuan</lastName></author><author><firstName>Zhen-Guo</firstName><lastName>Ma</lastName></author><author><firstName>Hai-Han</firstName><lastName>Liao</lastName></author><author><firstName>Chen</firstName><lastName>Liu</lastName></author><author><firstName>Jin-Xiu</firstName><lastName>Zhu</lastName></author><author><firstName>Zheng</firstName><lastName>Yang</lastName></author><author><firstName>Wei</firstName><lastName>Deng</lastName></author><author><firstName>Qi-Zhu</firstName><lastName>Tang</lastName></author></authors></publication></publications><cites></cites></citation>} Meanwhile continuous sympathetic drive has been shown to result in eccentric left ventricular hypertrophy, maladaptive remodelling, and worsening heart failure.{ ADDIN PAPERS2_CITATIONS <citation><uuid>5FEABC15-5807-451F-A05D-89BFFDB3CE74</uuid><priority>0</priority><publications><publication><uuid>CAEAABF7-3224-4BB7-8889-

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impact on cardiac function. This occurs through mechanisms such as magnesium/potassium loss, sympathetic activation, parasympathetic inhibition, and also myocardial fibrosis.{ ADDIN PAPERS2_CITATIONS <citation><uuid>CA04E514-3A1E-4B87-97AF-382332E7BE97</uuid><priority>0</priority><publications><publication><volume>16 Suppl N</volume><publication_date>99199512001200000000220000</publication_date><institution>Department of Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee, U.K.</institution><startpage>103</startpage><title>Aldosterone escape during ACE inhibitor therapy in chronic heart failure.</title><uuid>119F3189-66BB-4621-A83C-24AC2E176A80</uuid><subtype>400</subtype><endpage>106</endpage><type>400</type><url>http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=8682054&retmode=ref&cmd=prlinks</url><bundle><publication><title>European heart journal</title><type>-100</type><subtype>-100</subtype><uuid>A88C210F-86E4-4EA0-A1BC-A00668944A28</uuid></publication></bundle><authors><author><firstName>A</firstName><middleNames>D</middleNames><lastName>Struthers</lastName></author></authors></publication><publication><uuid>6CE538BA-C1D2-4650-9AEC-770ECCEFB12A</uuid><volume>47</volume><doi>10.1046/j.1365-2125.1999.00954.x</doi><subtitle>Chronic heart failure</subtitle><startpage>479</startpage><publication_date>99199905001200000000220000</publication_date><url>http://doi.wiley.com/10.1046/j.1365-2125.1999.00954.x</url><type>400</type><title>Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure?</title><publisher>Wiley-Blackwell</publisher><institution>Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee, DD1 9SY,

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Contemporary heart failure therapy

Based on the above hypotheses, multiple randomised controlled trials (RCTs) have been conducted over the last 3 decades to investigate and establish treatment for heart failure. Blockade of the adrenergic as well as the RAAS formed the basis of therapy. Beta-blockers have been shown in trials such as CIBIS-II, COPERNICUS and MERIT-HF to reduce mortality by up to a third.{ ADDIN PAPERS2_CITATIONS <citation><uuid>ABA34291-7FA0-4FBA-A2F0-03D04E33EC3F</uuid><priority>0</priority><publications><publication><volume>353</volume><publication_date>99199901021200000000222000</publication_date><number>9146</number><startpage>9</startpage><title>The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial.</title><uuid>D11ACA8B-91F4-4C3B-9B69-321831A42420</uuid><subtype>400</subtype><endpage>13</endpage><type>400</type><url>http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=10023943&retmode=ref&cmd=prlinks</url><bundle><publication><title>Lancet (London, England)</title><type>-100</type><subtype>-100</subtype><uuid>0930CC52-3772-4166-8F8F-CED21EE013A0</uuid></publication></bundle></publication><publication><volume>353

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Almost a decade earlier, CONSENSUS and SOLVD investigators also confirmed the mortality benefit of angiotensin-converting enzyme (ACE) inhibitors when added to standard heart failure therapy.{ ADDIN PAPERS2_CITATIONS <citation><uuid>2C7F5D74-C627-4FF4-9092-88F9544CFC31</uuid><priority>0</priority><publications><publication><uuid>BE49D6D7-BEDD-4AC5-B5CE-1AD6525FDFF1</uuid><volume>316</volume><doi>10.1056/NEJM198706043162301</doi><startpage>1429</startpage><publication_date>99198706041200000000222000</publication_date><url>http://www.nejm.org/doi/abs/10.1056/NEJM198706043162301</url><typ

e>400</type><title>Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).</title><publisher> Massachusetts Medical Society</publisher><number>23</number><subtype>400</subtype><endpage>1435</endpage><bundle><publication><title>New England Journal of Medicine</title><type>-100</type><subtype>-100</subtype><uuid>FE4FA51B-4995-4E1D-84B6-622D071084A1</uuid></publication></bundle><authors><author><lastName>CONSENSUS Trial Study Group</lastName></author></authors></publication><publication><uuid>91C54CE2-DDB1-4D67-81C2-3E525B7670D2</uuid><volume>325</volume><doi>10.1056/NEJM199108013250501</doi><startpage>293</startpage><publication_date>99199108011200000000222000</publication_date><url>http://www.nejm.org/doi/abs/10.1056/NEJM199108013250501</url><type>400</type><title>Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure.</title><publisher> Massachusetts Medical Society</publisher><number>5</number><subtype>400</subtype><endpage>302</endpage><bundle><publication><title>New England Journal of Medicine</title><type>-100</type><subtype>-100</subtype><uuid>FE4FA51B-4995-4E1D-84B6-622D071084A1</uuid></publication></bundle><authors><author><lastName>SOLVD Investigators</lastName></author><author><firstName>Salim</firstName><lastName>Yusuf</lastName></author><author><firstName>Bertram</firstName><lastName>Pitt</lastName></author><author><firstName>Clarence</firstName><middleNames>E</middleNames><lastName>Davis</lastName></author><author><firstName>William</firstName><middleNames>B</middleNames><lastName>Hood</lastName></author><author><firstName>Jay

</firstName><middleNames>N</middleNames><lastName>Cohn</lastName></author></authors></publication></publications><cites></cites></citation>**}**

Despite treatment with ACE inhibitors and the progress that was made, mortality from heart failure remained high. The concept of “aldosterone escape” led researchers to test the hypothesis of aldosterone antagonists to improve heart failure mortality.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>C4EEE7D5-A2E4-4F61-B6BA-4B9CD8C10E2D</uuid><priority>0</priority><publications><publication><volume>9</volume><publication_date>99199502001200000000220000</publication_date><number>1</number><institution>Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, USA.</institution><startpage>145</startpage><title>"Escape" of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin converting enzyme inhibitor: implications for therapy.</title><uuid>F01823EE-1E18-4908-AA0E-CE7944D1E34E</uuid><subtype>400</subtype><endpage>149</endpage><type>400</type><url>http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=7786835&retmode=ref&cmd=prlinks</url><bundle><publication><title>Cardiovascular drugs and therapy</title><type>-100</type><subtype>-100</subtype><uuid>52D12DFE-2912-4A36-B63A-618DEA0A81A1</uuid></publication></bundle><authors><author><firstName>B</firstName><lastName>Pitt</lastName></author></authors></publication></publications><cites></cites></citation>**}** This led to the design of the RALES trial which sought to answer this question with the drug Spironolactone. The trial was stopped early due to marked mortality benefit in the Spironolactone arm.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>3498F813-E76D-

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The role of natriuretic peptide and neprilysin inhibition

The natriuretic peptide system counteracts the effects of RAAS activation, inhibits secretion of arginine vasopressin and modulates the autonomic nervous system.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>D24A936A-CF54-4103-A5E8-8E1550D280E0</uuid><priority>0</priority><publications><publication><uuid>8842F963-9379-4205-927D-FB9BBC5ACC55</uuid><volume>102</volume><accepted_date>992016041412000000002 22000</accepted_date><doi>10.1136/heartjnl-2014-306775</doi><startpage>1342</startpage><publication_date>992016090112000000000222 000</publication_date><url>http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2014-306775</url><type>400</type><title>The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan.</title><submission_date>992015100512000000000222000</submission _date><number>17</number><institution>BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.</institution><subtype>400</subtype><endpage>1347</endpage><bundle><publicatio n><title>Heart (British Cardiac Society)</title><type>-100</type><subtype>-100</subtype><uuid>A45DD53C-F831-4B55-A6D7-81DBA9A853AF</uuid></publication></bundle><authors><author><firstName>Pardeep</fi rstName><middleNames>S</middleNames><lastName>Jhund</lastName></author><auth or><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author></authors></publication></ publications><cites></cites></citation>**}** The release of brain natriuretic peptide (BNP) and

N-terminal proBNP (NT-proBNP) promotes natriuresis and vasodilatation and occurs as a response to the resulting increase in ventricular preload and afterload seen in heart failure.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>B51ED6DC-F5B7-4972-A978-2A672580C536</uuid><priority>0</priority><publications><publication><uuid>8842F963-9379-4205-927D-FB9BBC5ACC55</uuid><volume>102</volume><accepted_date>9920160414120000000022000</accepted_date><doi>10.1136/heartjnl-2014-306775</doi><startpage>1342</startpage><publication_date>9920160901120000000022200</publication_date><url>http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2014-306775</url><type>400</type><title>The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan.</title><submission_date>992015100512000000000222000</submission_date><number>17</number><institution>BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.</institution><subtype>400</subtype><endpage>1347</endpage><bundle><publication><title>Heart (British Cardiac Society)</title><type>-100</type><subtype>-100</subtype><uuid>A45DD53C-F831-4B55-A6D7-81DBA9A853AF</uuid></publication></bundle><authors><author><firstName>Pardeep</firstName><middleNames>S</middleNames><lastName>Jhund</lastName></author><author><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author></authors></publication></publications><cites></cites></citation>**}** In the atrium, atrial natriuretic peptide (ANP) is also released as a response to atrial stretch and plays a similar role to BNP and NT-proBNP.

Naturally, efforts have been made to try and manipulate this pathway to improve heart failure outcomes. Initial strategies have focused on two aspects; the administration of exogenous natriuretic peptide as well as the inhibition of its breakdown. BNP and NT-proBNP are broken down by neprilysin, a membrane bound endopeptidase. Disappointingly, the administration of the recombinant BNP nesiritide in the ASCEND-HF study which was a large randomised, double-blind, placebo-controlled trial did not show any mortality benefit nor did it reduce the rate of heart failure hospitalisations.

Early attempts at neprilysin inhibition with the hope of raising the levels of natriuretic peptide and its activity unmasked another factor that had to be considered. Compounds such as racecadotril and candoxatrilat, which although were successful in raising levels of ANP, did not produce a sustained haemodynamic effect that was desired.{ ADDIN PAPERS2_CITATIONS <citation><uuid>476EC450-1331-4A4C-A77F-96B2C455B24F</uuid><priority>0</priority><publications><publication><uuid>8842F963-9379-4205-927D-FB9BBC5ACC55</uuid><volume>102</volume><accepted_date>992016041412000000002 22000</accepted_date><doi>10.1136/heartjnl-2014-306775</doi><startpage>1342</startpage><publication_date>992016090112000000000222 000</publication_date><url>http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2014-306775</url><type>400</type><title>The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan.</title><submission_date>992015100512000000000222000</submission _date><number>17</number><institution>BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow,

UK.</institution><subtype>400</subtype><endpage>1347</endpage><bundle><publication><title>Heart (British Cardiac Society)</title><type>-100</type><subtype>-100</subtype><uuid>A45DD53C-F831-4B55-A6D7-81DBA9A853AF</uuid></publication></bundle><authors><author><firstName>Pardeep</firstName><middleNames>S</middleNames><lastName>Jhund</lastName></author><author><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author></authors></publication></publications><cites></cites></citation>**}** It soon became apparent that due to the role that neprilysin also plays in AT-2 breakdown, lone neprilysin inhibition without concurrent inhibition of the RAAS was not likely to succeed due to persistent circulating levels of AT-2.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>ECBB1095-FAC8-4F9A-A682-4176104BA353</uuid><priority>0</priority><publications><publication><uuid>8842F963-9379-4205-927D-FB9BBC5ACC55</uuid><volume>102</volume><accepted_date>99201604141200000000222000</accepted_date><doi>10.1136/heartjnl-2014-306775</doi><startpage>1342</startpage><publication_date>99201609011200000000222000</publication_date><url>http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2014-306775</url><type>400</type><title>The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan.</title><submission_date>99201510051200000000222000</submission_date><number>17</number><institution>BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK.</institution><subtype>400</subtype><endpage>1347</endpage><bundle><publication><title>Heart (British Cardiac Society)</title><type>-100</type><subtype>-

100</subtype><uuid>A45DD53C-F831-4B55-A6D7-81DBA9A853AF</uuid></publication></bundle><authors><author><firstName>Pardeep</firstName><middleNames>S</middleNames><lastName>Jhund</lastName></author><author><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author></authors></publication></publications><cites></cites></citation>**}** The vasodilatory effects obtained were offset by the vasoconstriction caused by AT-2.

Chemical structure, pharmacokinetics and metabolism

Sacubitril/Valsartan (LCZ696) is a combined neprilysin inhibitor and AT-2 receptor blocker. Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O with a molecular mass of 957.99. The chemical structure is shown in Figure 1.

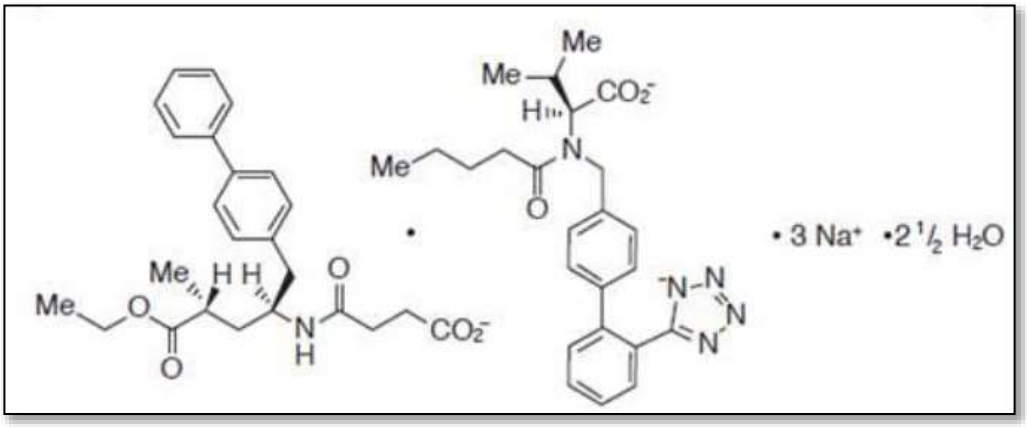

*Figure **{** SEQ Figure * ARABIC **}** - Chemical structure of Sacubitril/Valsartan (LCZ696) – owned and provided by Novartis©*

Sacubitril is a prodrug and the therapeutic effect of Sacubitril/Valsartan is partly achieved via the action of the active metabolite of Sacubitril, LBQ657 which inhibits neprilysin. At the same time, blockade of the AT-2 type 1-receptor is provided by the action of Valsartan and it is this

concurrent inhibition of both pathways that leads to Sacubitril/Valsartan's overall therapeutic effect (Figure 2).

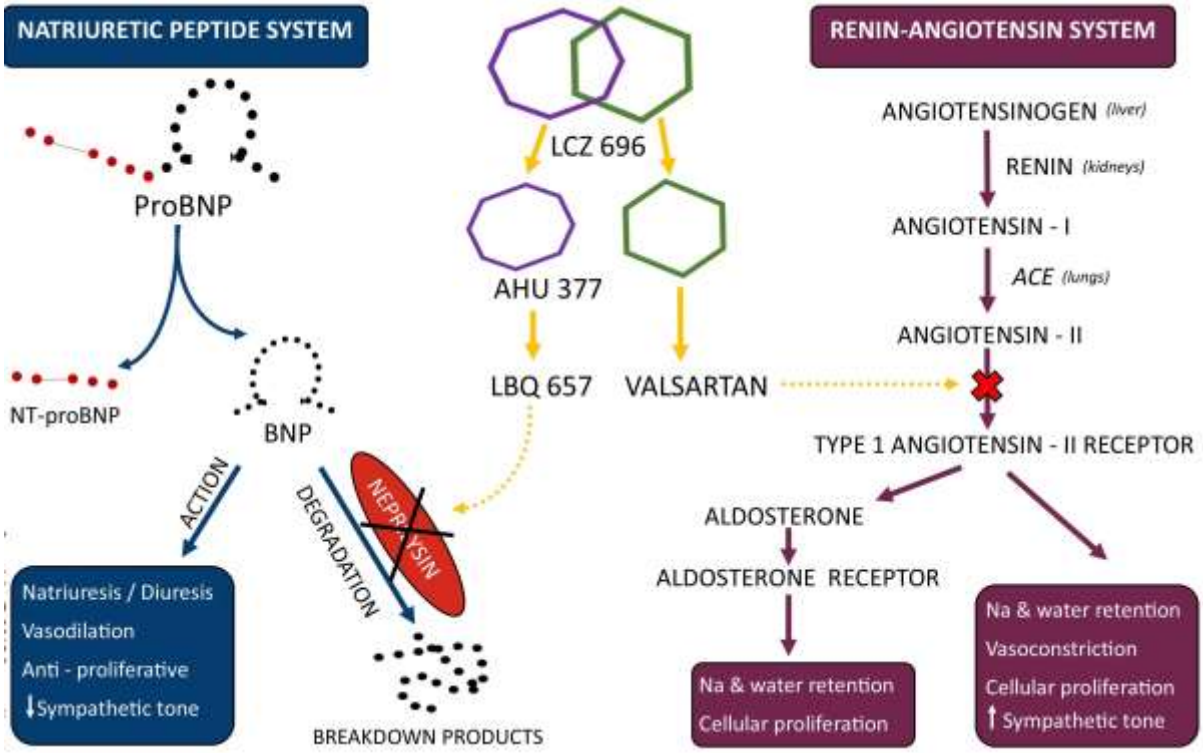

*Figure { SEQ Figure * ARABIC } - Mechanism of action for Sacubitril/Valsartan (LCZ696)*

In a study involving 30 selected patients who were given the drug in dosages of 100 mg twice daily and 200 mg twice daily, plasma concentrations of Sacubitril, LBQ657, and Valsartan increased rapidly and reached plasma concentration within 0.5, 2.5 and 2 hours respectively.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>038BFCFB-3A51-4B19-A771-7A33AB334044</uuid><priority>0</priority><publications><publication><uuid>61DD8B59-42BB-4F66-8219-6BDDFF714ED0</uuid><volume>34</volume><doi>10.1111/1755-5922.12183</doi><startpage>191</startpage><publication_date>99201608001200000000220000</publication_date><url>http://doi.wiley.com/10.1111/1755-

5922.12183</url><type>400</type><title>Pharmacodynamic and Pharmacokinetic Profiles of Sacubitril/Valsartan (LCZ696) in Patients with Heart Failure and Reduced Ejection Fraction.</title><institution>Center of Applied Clinical Pharmacology, Peoples Friendship University of Russia, Moscow, Russia.</institution><number>4</number><subtype>400</subtype><endpage>198</endpage><bundle><publication><title>Cardiovascular therapeutics</title><type>-100</type><subtype>-100</subtype><uuid>77142040-7869-4A3F-8B94-8BBE2CA91746</uuid></publication></bundle><authors><author><firstName>Zhanna</firstName><lastName>Kobalava</lastName></author><author><firstName>Yulia</firstName><lastName>Kotovskaya</lastName></author><author><firstName>Oleg</firstName><lastName>Averkov</lastName></author><author><firstName>Elena</firstName><lastName>Pavlikova</lastName></author><author><firstName>Valentine</firstName><lastName>Moiseev</lastName></author><author><firstName>Diego</firstName><lastName>Albrecht</lastName></author><author><firstName>Priya</firstName><lastName>Chandra</lastName></author><author><firstName>Surya</firstName><lastName>Ayalasomayajula</lastName></author><author><firstName>Margaret</firstName><middleNames>F</middleNames><lastName>Prescott</lastName></author><author><firstName>Parasar</firstName><lastName>Pal</lastName></author><author><firstName>Thomas</firstName><middleNames>H</middleNames><lastName>Langenickel</lastName></author><author><firstName>Pierre</firstName><lastName>Jordaan</lastName></author><author><firstName>Iris</firstName><lastName>Rajman</lastName></author></authors></publication></publications><cites></cites></citation>} C_{max} and $AUC_{0\text{-}12\ h}$ for Sacubitril and LBQ657 were dose-proportional while for Valsartan it was less so.{ ADDIN PAPERS2_CITATIONS <citation><uuid>C754230D-4422-4D33-94F8-

9D8AE45EC628</uuid><priority>0</priority><publications><publication><uuid>61DD8B59-42BB-4F66-8219-6BDDFF714ED0</uuid><volume>34</volume><doi>10.1111/1755-5922.12183</doi><startpage>191</startpage><publication_date>99201608001200000000220000</publication_date><url>http://doi.wiley.com/10.1111/1755-5922.12183</url><type>400</type><title>Pharmacodynamic and Pharmacokinetic Profiles of Sacubitril/Valsartan (LCZ696) in Patients with Heart Failure and Reduced Ejection Fraction.</title><institution>Center of Applied Clinical Pharmacology, Peoples Friendship University of Russia, Moscow, Russia.</institution><number>4</number><subtype>400</subtype><endpage>198</endpage><bundle><publication><title>Cardiovascular therapeutics</title><type>-100</type><subtype>-100</subtype><uuid>77142040-7869-4A3F-8B94-8BBE2CA91746</uuid></publication></bundle><authors><author><firstName>Zhanna</firstName><lastName>Kobalava</lastName></author><author><firstName>Yulia</firstName><lastName>Kotovskaya</lastName></author><author><firstName>Oleg</firstName><lastName>Averkov</lastName></author><author><firstName>Elena</firstName><lastName>Pavlikova</lastName></author><author><firstName>Valentine</firstName><lastName>Moiseev</lastName></author><author><firstName>Diego</firstName><lastName>Albrecht</lastName></author><author><firstName>Priya</firstName><lastName>Chandra</lastName></author><author><firstName>Surya</firstName><lastName>Ayalasomayajula</lastName></author><author><firstName>Margaret</firstName><middleNames>F</middleNames><lastName>Prescott</lastName></author><author><firstName>Parasar</firstName><lastName>Pal</lastName></author><author><firstName>Thomas</firstName><middleNames>H</middleNames><lastName>Langenickel</lastName></author><author><firstName>Pierre</firstName><lastName>Jordaan</lastName></author><author><firstName>Iris</firstName><

lastName>Rajman</lastName></author></authors></publication></publications><cites></cites></citation>**}**

Levels of cyclic guanosine monophosphate (cGMP) in the urine and plasma as well as levels of ANP in the urine were increased in volunteer subjects. Plasma renin markers (plasma renin activity, plasma renin concentration) were significantly raised during the same period. All of these biomarker trends reflect neprilysin inhibition and AT-2 type 1 receptor blockade.**{**

ADDIN PAPERS2_CITATIONS <citation><uuid>722C3C8E-7912-4CB8-8F13-1EADE0EE87BE</uuid><priority>0</priority><publications><publication><uuid>61DD8B59-42BB-4F66-8219-6BDDFF714ED0</uuid><volume>34</volume><doi>10.1111/1755-5922.12183</doi><startpage>191</startpage><publication_date>99201608001200000000220000</publication_date><url>http://doi.wiley.com/10.1111/1755-5922.12183</url><type>400</type><title>Pharmacodynamic and Pharmacokinetic Profiles of Sacubitril/Valsartan (LCZ696) in Patients with Heart Failure and Reduced Ejection Fraction.</title><institution>Center of Applied Clinical Pharmacology, Peoples Friendship University of Russia, Moscow, Russia.</institution><number>4</number><subtype>400</subtype><endpage>198</endpage><bundle><publication><title>Cardiovascular therapeutics</title><type>-100</type><subtype>-100</subtype><uuid>77142040-7869-4A3F-8B94-8BBE2CA91746</uuid></publication></bundle><authors><author><firstName>Zhanna</firstName><lastName>Kobalava</lastName></author><author><firstName>Yulia</firstName><lastName>Kotovskaya</lastName></author><author><firstName>Oleg</firstName><lastName>Averkov</lastName></author><author><firstName>Elena</firstName><lastName>Pavlikova</lastName></author><author><firstName>Valentine</firstName><lastName>Moiseev</lastName></author><author><firstName>Diego</firstName><lastName>Albrecht</la

stName></author><author><firstName>Priya</firstName><lastName>Chandra</lastName></author><author><firstName>Surya</firstName><lastName>Ayalasomayajula</lastName></author><author><firstName>Margaret</firstName><middleNames>F</middleNames><lastName>Prescott</lastName></author><author><firstName>Parasar</firstName><lastName>Pal</lastName></author><author><firstName>Thomas</firstName><middleNames>H</middleNames><lastName>Langenickel</lastName></author><author><firstName>Pierre</firstName><lastName>Jordaan</lastName></author><author><firstName>Iris</firstName><lastName>Rajman</lastName></author></authors></publication></publications><cites></cites></citation>**}** Oral bioavailability is estimated to be around at least 60%. The terminal half-lives of Sacubitril, LBQ657, and Valsartan have been 1.3, 12, and 21 hours respectively.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>5541C1D5-2F46-489A-AAA8-1218AF6E6DB7</uuid><priority>0</priority><publications><publication><uuid>4A8EC034-AA75-4262-88ED-DA2AE1254223</uuid><volume>46</volume><doi>10.3109/00498254.2015.1014944</doi><startpage>986</startpage><publication_date>99201611001200000000220000</publication_date><url>http://www.tandfonline.com/doi/full/10.3109/00498254.2015.1014944</url><type>400</type><title>Disposition and metabolism of [(14)C] Sacubitril/Valsartan (formerly LCZ696) an angiotensin receptor neprilysin inhibitor, in healthy subjects.</title><institution>a Department of Drug Metabolism and Pharmacokinetics .</institution><number>11</number><subtype>400</subtype><endpage>1000</endpage><bundle><publication><title>Xenobiotica; the fate of foreign compounds in biological systems</title><type>-100</type><subtype>-100</subtype><uuid>06163418-A17C-4FC1-9234-34864EDF48F4</uuid></publication></bundle><authors><author><firstName>Jimmy</first

Name><lastName>Flarakos</lastName></author><author><firstName>Yancy</firstName><lastName>Du</lastName></author><author><firstName>Timothy</firstName><lastName>Bedman</lastName></author><author><firstName>Qusai</firstName><lastName>Al-Share</lastName></author><author><firstName>Pierre</firstName><lastName>Jordaan</lastName></author><author><firstName>Priya</firstName><lastName>Chandra</lastName></author><author><firstName>Diego</firstName><lastName>Albrecht</lastName></author><author><firstName>Lai</firstName><lastName>Wang</lastName></author><author><firstName>Helen</firstName><lastName>Gu</lastName></author><author><firstName>Heidi</firstName><middleNames>J</middleNames><lastName>Einolf</lastName></author><author><firstName>Su-Er</firstName><lastName>Huskey</lastName></author><author><firstName>James</firstName><middleNames>B</middleNames><lastName>Mangold</lastName></author></authors></publication></publications><cites></cites></citation>} Steady state levels of Sacubitril/Valsartan with a twice daily dosing regimen are achieved in 3 days.

Drug elimination is primarily through renal excretion in the form of the active metabolite LBQ657. An estimated 51-68% is excreted through the urine whilst the remainder is excreted through the faeces. In-vivo studies have demonstrated a low risk of inhibiting or inducing the cytochrome P450 (CYP) enzymes.{ ADDIN PAPERS2_CITATIONS <citation><uuid>6F42D01B-AE7F-460E-B9E2-4761E3043577</uuid><priority>0</priority><publications><publication><uuid>4A8EC034-AA75-4262-88ED-DA2AE1254223</uuid><volume>46</volume><doi>10.3109/00498254.2015.1014944</doi><startpage>986</startpage><publication_date>99201611001200000000220000</publicati

on_date><url>http://www.tandfonline.com/doi/full/10.3109/00498254.2015.1014944</url><type>400</type><title>Disposition and metabolism of [(14)C] Sacubitril/Valsartan (formerly LCZ696) an angiotensin receptor neprilysin inhibitor, in healthy subjects.</title><institution>a Department of Drug Metabolism and Pharmacokinetics .</institution><number>11</number><subtype>400</subtype><endpage>1000</endpage><bundle><publication><title>Xenobiotica; the fate of foreign compounds in biological systems</title><type>-100</type><subtype>-100</subtype><uuid>06163418-A17C-4FC1-9234-34864EDF48F4</uuid></publication></bundle><authors><author><firstName>Jimmy</firstName><lastName>Flarakos</lastName></author><author><firstName>Yancy</firstName><lastName>Du</lastName></author><author><firstName>Timothy</firstName><lastName>Bedman</lastName></author><author><firstName>Qusai</firstName><lastName>Al-Share</lastName></author><author><firstName>Pierre</firstName><lastName>Jordaan</lastName></author><author><firstName>Priya</firstName><lastName>Chandra</lastName></author><author><firstName>Diego</firstName><lastName>Albrecht</lastName></author><author><firstName>Lai</firstName><lastName>Wang</lastName></author><author><firstName>Helen</firstName><lastName>Gu</lastName></author><author><firstName>Heidi</firstName><middleNames>J</middleNames><lastName>Einolf</lastName></author><author><firstName>Su-Er</firstName><lastName>Huskey</lastName></author><author><firstName>James</firstName><middleNames>B</middleNames><lastName>Mangold</lastName></author></authors></publication></publications><cites></cites></citation>}

Clinical studies

PARAMOUNT and PARADIGM-HF

The PARAMOUNT study was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II-III symptoms and heart failure with preserved ejection fraction (HFpEF). This was defined as having an ejection fraction of more than 45% and NT-proBNP > 400 pg/mL.{ ADDIN PAPERS2_CITATIONS <citation><uuid>BE1F3173-BC90-4566-8515-51BE8BF7DCAF</uuid><priority>0</priority><publications><publication><uuid>6645ABA4-A35A-4DAF-8552-76F992D3FA65</uuid><volume>380</volume><doi>10.1016/S0140-6736(12)61227-6</doi><startpage>1387</startpage><publication_date>99201210201200000000222000</publication_date><url>http://linkinghub.elsevier.com/retrieve/pii/S0140673612612276</url><type>400</type><title>The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial.</title><institution>Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA. ssolomon@rics.bwh.harvard.edu</institution><number>9851</number><subtype>400</subtype><endpage>1395</endpage><bundle><publication><title>Lancet (London, England)</title><type>-100</type><subtype>-100</subtype><uuid>0930CC52-3772-4166-8F8F-CED21EE013A0</uuid></publication></bundle><authors><author><firstName>Scott</firstName><middleNames>D</middleNames><lastName>Solomon</lastName></author><auth

or><firstName>Michael</firstName><lastName>Zile</lastName></author><author><firstName>Burkert</firstName><lastName>Pieske</lastName></author><author><firstName>Adriaan</firstName><lastName>Voors</lastName></author><author><firstName>Amil</firstName><lastName>Shah</lastName></author><author><firstName>Elisabeth</firstName><lastName>Kraigher-Krainer</lastName></author><author><firstName>Victor</firstName><lastName>Shi</lastName></author><author><firstName>Toni</firstName><lastName>Bransford</lastName></author><author><firstName>Madoka</firstName><lastName>Takeuchi</lastName></author><author><firstName>Jianjian</firstName><lastName>Gong</lastName></author><author><firstName>Martin</firstName><lastName>Lefkowitz</lastName></author><author><firstName>Milton</firstName><lastName>Packer</lastName></author><author><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author><author><lastName>Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators</lastName></author></authors></publication></publications><cites></cites></citation>**}** Patients were assigned to receive either LCZ696, titrated to 200 mg twice daily or Valsartan, titrated to 160 mg twice daily. The trial was designed to investigate the safety and efficacy of LCZ696 in patients with HFpEF. The primary endpoint was change from baseline in the levels of NT-proBNP at 12 weeks.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>E57A39C6-78D0-4684-8F52-DB53414A213A</uuid><priority>0</priority><publications><publication><uuid>6645ABA4-A35A-4DAF-8552-76F992D3FA65</uuid><volume>380</volume><doi>10.1016/S0140-6736(12)61227-

6</doi><startpage>1387</startpage><publication_date>99201210201200000000222000</publication_date><url>http://linkinghub.elsevier.com/retrieve/pii/S0140673612612276</url><type>400</type><title>The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial.</title><institution>Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA. ssolomon@rics.bwh.harvard.edu</institution><number>9851</number><subtype>400</subtype><endpage>1395</endpage><bundle><publication><title>Lancet (London, England)</title><type>-100</type><subtype>-100</subtype><uuid>0930CC52-3772-4166-8F8F-CED21EE013A0</uuid></publication></bundle><authors><author><firstName>Scott</firstName><middleNames>D</middleNames><lastName>Solomon</lastName></author><author><firstName>Michael</firstName><lastName>Zile</lastName></author><author><firstName>Burkert</firstName><lastName>Pieske</lastName></author><author><firstName>Adriaan</firstName><lastName>Voors</lastName></author><author><firstName>Amil</firstName><lastName>Shah</lastName></author><author><firstName>Elisabeth</firstName><lastName>Kraigher-Krainer</lastName></author><author><firstName>Victor</firstName><lastName>Shi</lastName></author><author><firstName>Toni</firstName><lastName>Bransford</lastName></author><author><firstName>Madoka</firstName><lastName>Takeuchi</lastName></author><author><firstName>Jianjian</firstName><lastName>Gong</lastName></author><author><firstName>Martin</firstName><lastName>Lefkowitz</lastName></author><author><firstName>Milton</firstName><lastName>Packer</lastName></author><author><firstName>John</firstName><middleNames>J

V</middleNames><lastName>McMurray</lastName></author><author><lastName>Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators</lastName></author></authors></publication></publications><cites></cites></citation>} Secondary endpoints measured were echocardiographic parameters, blood pressure, NYHA class, and quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).{ ADDIN PAPERS2_CITATIONS <citation><uuid>7874D0F4-3B85-4589-809B-5B04967980D6</uuid><priority>0</priority><publications><publication><uuid>6645ABA4-A35A-4DAF-8552-76F992D3FA65</uuid><volume>380</volume><doi>10.1016/S0140-6736(12)61227-6</doi><startpage>1387</startpage><publication_date>99201210201200000000222000</publication_date><url>http://linkinghub.elsevier.com/retrieve/pii/S0140673612612276</url><type>400</type><title>The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial.</title><institution>Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA. ssolomon@rics.bwh.harvard.edu</institution><number>9851</number><subtype>400</subtype><endpage>1395</endpage><bundle><publication><title>Lancet (London, England)</title><type>-100</type><subtype>-100</subtype><uuid>0930CC52-3772-4166-8F8F-CED21EE013A0</uuid></publication></bundle><authors><author><firstName>Scott</firstName><middleNames>D</middleNames><lastName>Solomon</lastName></author><author><firstName>Michael</firstName><lastName>Zile</lastName></author><author><firstN

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USA.</institution><subtype>400</subtype><endpage>127</endpage><bundle><publication><title>Journal of clinical pharmacy and therapeutics</title><type>-100</type><subtype>-100</subtype><uuid>7D805DA7-CDB9-4A03-AFF7-DCE49D75C76F</uuid></publication></bundle><authors><author><firstName>A</firstName><middleNames>J</middleNames><lastName>Ansara</lastName></author><author><firstName>D</firstName><middleNames>M</middleNames><lastName>Kolanczyk</lastName></author><author><firstName>J</firstName><middleNames>M</middleNames><lastName>Koehler</lastName></author></authors></publication></publications><cites></cites></citation>**}** Although the initial change in NT-proBNP was significant at 12 weeks in the LCZ696 group, this was no longer significant at 36 weeks. Despite an improvement in NYHA class, there was no significant difference in echocardiographic parameters or quality of life.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>7D59EEC2-4F97-4A8B-8963-093A2B6D0EC3</uuid><priority>0</priority><publications><publication><uuid>61101215-530E-4A06-BBB0-BECFA015C112</uuid><volume>41</volume><accepted_date>992016012112000000000222000</accepted_date><doi>10.1111/jcpt.12363</doi><startpage>119</startpage><publication_date>99201604001200000000220000</publication_date><url>http://doi.wiley.com/10.1111/jcpt.12363</url><type>400</type><title>Neprilysin inhibition with sacubitril/valsartan in the treatment of heart failure: mortality bang for your buck.</title><submission_date>992015081412000000000222000</submission_date><number>2</number><institution>Department of Pharmacy, Indiana University Health Methodist Hospital, Indianapolis, IN, USA.</institution><subtype>400</subtype><endpage>127</endpage><bundle><publication><title>Journal of clinical pharmacy and therapeutics</title><type>-100</type><subtype>-

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The PARADIGM-HF trial was another trial designed to compare the effects of sacubitril/valsartan (LCZ696), an angiotensin receptor-neprilysin inhibitor against enalapril in patients with heart failure and reduced ejection fraction. It was a double-blind trial and 8442 patients with NYHA class II – IV symptoms and an ejection fraction of at least 40% were randomised to either LCZ696 (at a dose of 200 mg daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>EACDF52E-C134-42B6-AF34-1F6498A705D1</uuid><priority>0</priority><publications><publication><uuid>F9208EF6-

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The primary outcome was a composite of death from a cardiovascular cause or hospitalisation for heart failure.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>9483C81A-1A3E-44C3-99F4-7F2431C77C5C</uuid><priority>0</priority><publications><publication><uuid>F9208EF6-1421-43D8-89E8-097272B42915</uuid><volume>371</volume><doi>10.1056/NEJMoa1409077</doi><startpage>993</startpage><publication_date>99201409111200000000222000</publication_date><url>http://www.nejm.org/doi/10.1056/NEJMoa1409077</url><type>400</type><title>Angiotensin-neprilysin inhibition versus enalapril in heart failure.</title><publisher>Massachusetts Medical Society</publisher><institution>From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham

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 Committees</lastName></author></authors></publication></publications><cites></cites></citation>} There was an overwhelming mortality benefit in the LCZ696 arm and the trial had to be stopped early. The primary outcome had occurred in 914 (21.8%) of the patients who received LCZ696, compared to 1117 (26.5%) of the patients who received enalapril (hazard ratio 0.80 in the LCZ696 group; 95% confidence interval 0.73 to 0.87; p<0.001). { ADDIN PAPERS2_CITATIONS <citation><uuid>73B3EB73-46F1-488C-A9A6-594757910859</uuid><priority>0</priority><publications><publication><uuid>F9208EF6-1421-43D8-89E8-097272B42915</uuid><volume>371</volume><doi>10.1056/NEJMoa1409077</doi><startpage>993</startpage><publication_date>99201409111200000000222000</publication_date><url>http://www.nejm.org/doi/10.1056/NEJMoa1409077</url><type>400</type><title>Angiotensin-neprilysin inhibition versus enalapril in heart failure.</title><publisher>Massachusetts Medical Society</publisher><institution>From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.).</institution><number>11</number><subtype>400</subtype><endpage>1004</endpage><bundle><publication><title>The New England journal of medicine</title><type>-

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The most frequent adverse effect seen in the study was hypotension, which was more common in patients given LCZ696. However, this did not cause a significant number of patients to discontinue the drug as there were only 36 patients (0.9%) in the LCZ696 and 29 (0.7%) in the enalapril group who had to discontinue the drug because of hypotension.

Hypotension is a risk factor for renal failure and although this has been a concern, the study findings suggest lower incidents of clinically relevant rise in serum creatinine and drug discontinuation in the LCZ696 arm.{ ADDIN PAPERS2_CITATIONS <citation><uuid>EF2C1695-C87E-4095-955A-4D3CE7B7AE04</uuid><priority>0</priority><publications><publication><uuid>F9208EF6-1421-43D8-89E8-097272B42915</uuid><volume>371</volume><doi>10.1056/NEJMoa1409077</doi><startpage>993</startpage><publication_date>99201409111200000000222000</publication_date><url>http://www.nejm.org/doi/10.1056/NEJMoa1409077</url><type>400</type><title>Angiotensin-neprilysin inhibition versus enalapril in heart failure.</title><publisher>Massachusetts Medical Society</publisher><institution>From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.).</institution><number>11</number><subtype>400</subtype><endpage>1004</endpage><bundle><publication><title>The New England journal of medicine</title><type>-100</type><subtype>-100</subtype><uuid>00A4EDD2-0215-4449-A5F2-82299A749642</uuid></publication></bundle><authors><author><firstName>John</firstN

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n><title>Journal of clinical pharmacy and therapeutics</title><type>-100</type><subtype>-100</subtype><uuid>7D805DA7-CDB9-4A03-AFF7-DCE49D75C76F</uuid></publication></bundle><authors><author><firstName>A</firstName><middleNames>J</middleNames><lastName>Ansara</lastName></author><author><firstName>D</firstName><middleNames>M</middleNames><lastName>Kolanczyk</lastName></author><author><firstName>J</firstName><middleNames>M</middleNames><lastName>Koehler</lastName></author></authors></publication><publication><uuid>F9208EF6-1421-43D8-89E8-097272B42915</uuid><volume>371</volume><doi>10.1056/NEJMoa1409077</doi><startpage>993</startpage><publication_date>99201409111200000000222000</publication_date><url>http://www.nejm.org/doi/10.1056/NEJMoa1409077</url><type>400</type><title>Angiotensin-neprilysin inhibition versus enalapril in heart failure.</title><publisher>Massachusetts Medical Society</publisher><institution>From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.).</institution><number>11</number><subtype>400</subtype><endpage>1004</endpage><bundle><publication><title>The New England journal of medicine</title><type>-

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author><author><firstName>Adel</firstName><middleNames>R</middleNames><lastNam e>Rizkala</lastName></author><author><firstName>Jean</firstName><middleNames>L</ middleNames><lastName>Rouleau</lastName></author><author><firstName>Victor</first Name><middleNames>C</middleNames><lastName>Shi</lastName></author><author><fi rstName>Scott</firstName><middleNames>D</middleNames><lastName>Solomon</lastN ame></author><author><firstName>Karl</firstName><lastName>Swedberg</lastName></ author><author><firstName>Michael</firstName><middleNames>R</middleNames><lastN ame>Zile</lastName></author><author><lastName>PARADIGM-HF Investigators and Committees</lastName></author></authors></publication></publications><cites></cites> </citation>**}**

What is also worth noting in the PARADIGM-HF study is the higher proportion of patients on contemporary heart failure therapy. This is in contrast to earlier heart failure trials and reflects modern day practice. More than 90% of patients were on a beta blocker, at least 80% were on a diuretic, and more than half were on a mineralocorticoid antagonist.**{** ADDIN PAPERS2_CITATIONS <citation><uuid>5993B7B5-2767-483B-B6D2-015F7EB9FFAA</uuid><priority>0</priority><publications><publication><uuid>F9208EF6-1421-43D8-89E8-097272B42915</uuid><volume>371</volume><doi>10.1056/NEJMoa1409077</doi><start page>993</startpage><publication_date>99201409111200000000222000</publication_dat e><url>http://www.nejm.org/doi/10.1056/NEJMoa1409077</url><type>400</type><title> Angiotensin-neprilysin inhibition versus enalapril in heart failure.</title><publisher>Massachusetts Medical Society</publisher><institution>From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow,

Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.).</institution><number>11</number><subtype>400</subtype><endpage>1004</endpage><bundle><publication><title>The New England journal of medicine</title><type>-100</type><subtype>-100</subtype><uuid>00A4EDD2-0215-4449-A5F2-82299A749642</uuid></publication></bundle><authors><author><firstName>John</firstName><middleNames>J V</middleNames><lastName>McMurray</lastName></author><author><firstName>Milton</firstName><lastName>Packer</lastName></author><author><firstName>Akshay</firstName><middleNames>S</middleNames><lastName>Desai</lastName></author><author><firstName>Jianjian</firstName><lastName>Gong</lastName></author><author><firstName>Martin</firstName><middleNames>P</middleNames><lastName>Lefkowitz</lastName></author><author><firstName>Adel</firstName><middleNames>R</middleNames><lastName>Rizkala</lastName></author><author><firstName>Jean</firstName><middleNames>L</middleNames><lastName>Rouleau</lastName></author><author><firstName>Victor</firstName><middleNames>C</middleNames><lastName>Shi</lastName></author><author><firstName>Scott</firstName><middleNames>D</middleNames><lastName>Solomon</lastName></author><author><firstName>Karl</firstName><lastName>Swedberg</lastName></

author><author><firstName>Michael</firstName><middleNames>R</middleNames><lastName>Zile</lastName></author><author><lastName>PARADIGM-HF Investigators and Committees</lastName></author></authors></publication></publications><cites></cites></citation>**}** Despite what is perceived to be optimum medical therapy, LCZ696 still offered significant mortality benefit above and beyond standard treatment. These findings are compelling and have indeed begun to change the landscape of chronic heart failure treatment.

The future: PARADISE-MI

Currently, Sacubitril/Valsartan is indicated for patients who remain symptomatic despite being on optimum heart failure therapy, including an optimum dose of ACE inhibitor. This can be defined as having a hospital admission for heart failure exacerbation or worsening symptoms in an outpatient setting.

The next logical step however, is to investigate whether Sacubitril/Valsartan could be used at an earlier stage, prior to the use of an ACE inhibitor in patients who have suffered a myocardial infarction and therefore are at risk of heart failure. The early haemodynamic changes post infarction resulting from stimulation of the sympathetic nervous system, RAAS, and release of ANP and BNP often leads to deleterious left ventricular remodelling. Sacubitril/Valsartan has already proven itself to be more influential than conventional ACE inhibitors in altering the course of chronic heart failure patients. It is hoped that earlier intervention in the myocardial remodelling process post infarction will translate into better outcomes for patients.

The Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) aims to answer this clinical question and is currently recruiting and the study is expected to be completed in 2020. It is a multi-centre, randomised, double-blind, controlled trial and will evaluate the effect of Sacubitril/Valsartan titrated to a target dose of 200 mg twice daily against Ramipril titrated to a target dose of 5 mg twice daily in patients following a myocardial infarction, on top of standard post myocardial infarction treatment.

Primary outcome will be a composite endpoint of cardiovascular death, heart failure hospitalisation, and outpatient heart failure (time-to-first event analysis) with evidence of left ventricular systolic impairment or pulmonary congestion with no previous history of chronic heart failure (ClinicalTrials.gov ID NCT02924727). With such promising results from PARADIGM-HF, it is hoped that PARADISE-MI will further offer clinicians treatment options to reduce the incidence of heart failure in post myocardial infarction patients and reduce cardiovascular mortality.

Conclusion

Sacubitril/Valsartan is opening up a wealth of opportunities for patients with HFrEF. In an area where there has been limited pharmacological advances in the last 10 years, this is a game changer and a much welcomed addition to contemporary heart failure therapy. The clinical data is robust, and it has been proven to offer marked mortality benefit over ACE inhibitors in chronic heart failure patients with a good drug safety profile. Its use in patients with HFpEF

is unclear as phase 2 trial data to date have not shown significant difference with standard therapy.

Whether Sacubitril/Valsartan will change outcomes in the post myocardial infarction cohort who are at risk of developing heart failure remains to be seen, and results from PARADISE-MI will be awaited by the global cardiology community with great interest.

References

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