

Use of Sacubitril/Valsartan in Heart Failure



Entresto™
(sacubitril/valsartan) tablets

24/26mg • 49/51mg • 97/103mg

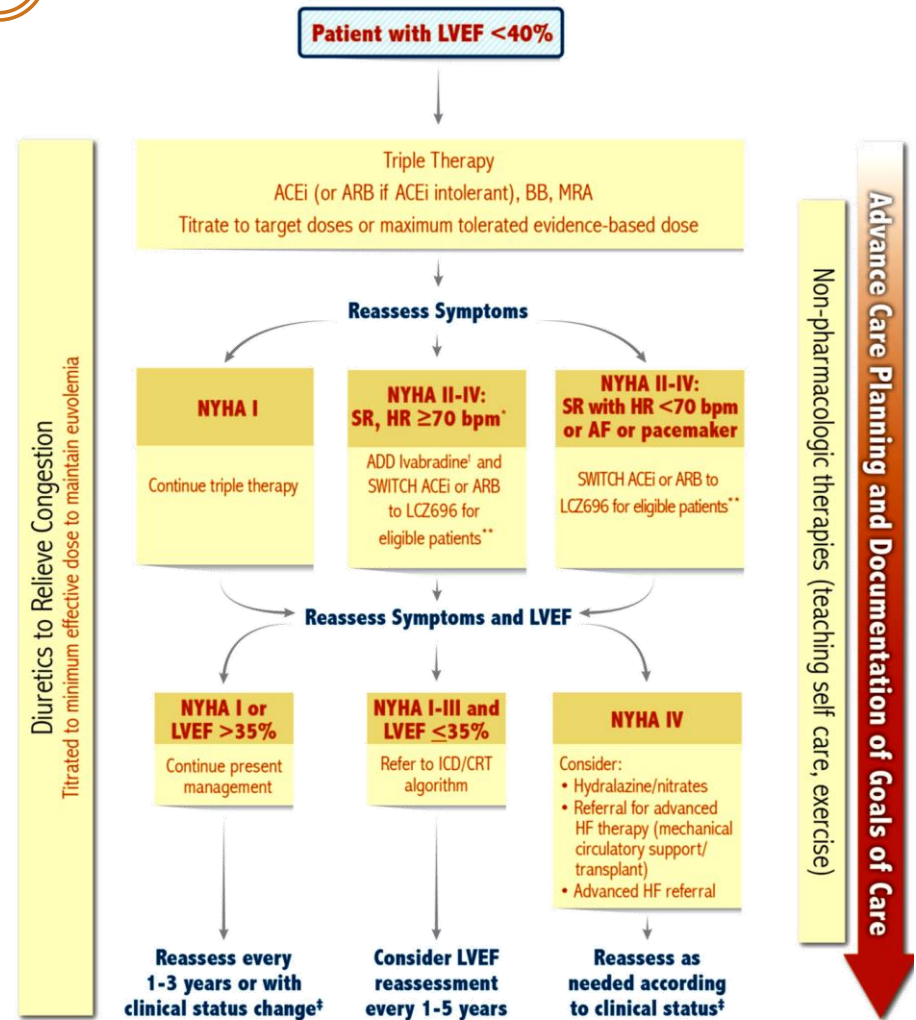
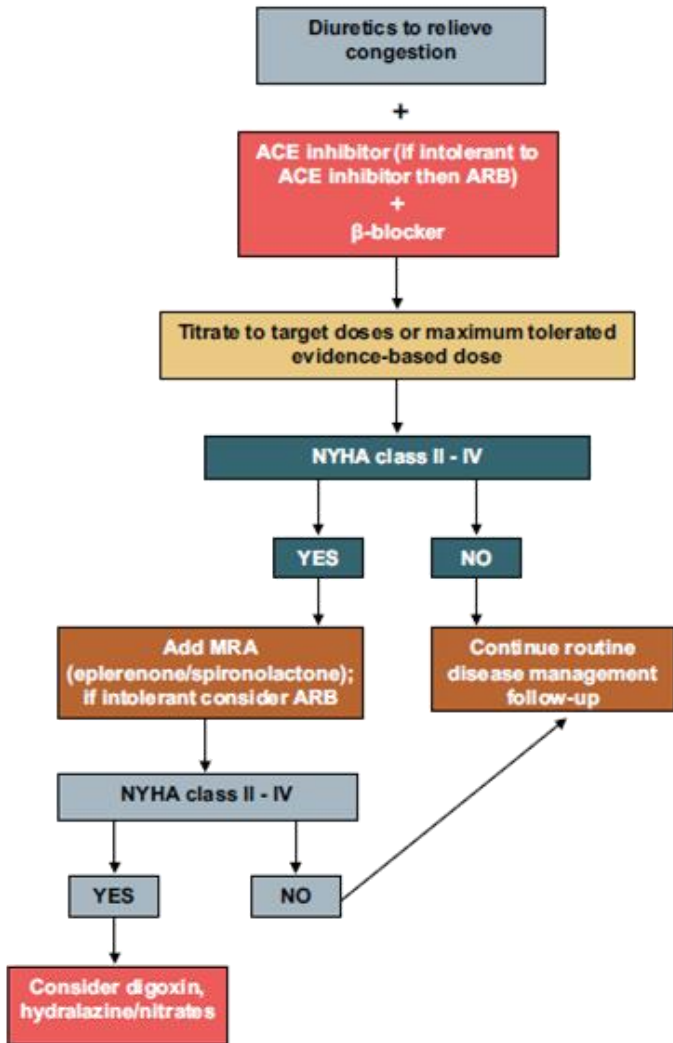
& the PARADIGM-HF trial

Presentation Outline



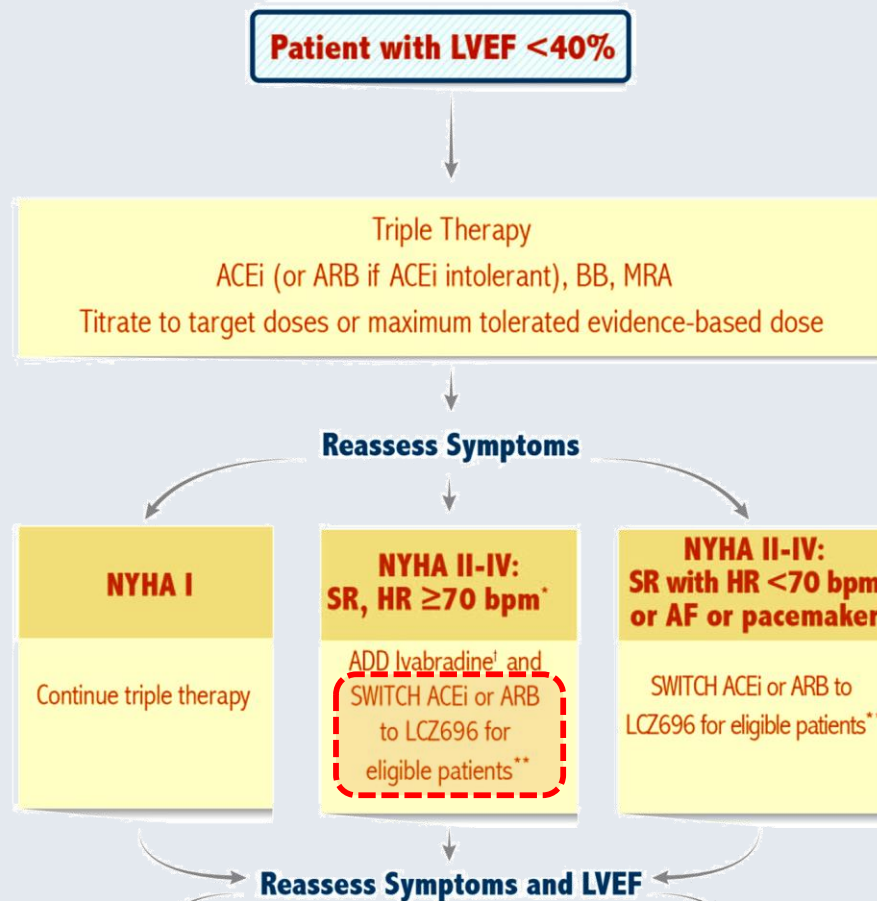
- Overview of:
 - Entresto
 - PARADIGM-HF trial
- Critical Appraisal

Canadian Cardiovascular Society Guidelines



Canadian Cardiovascular Society Guidelines

Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction

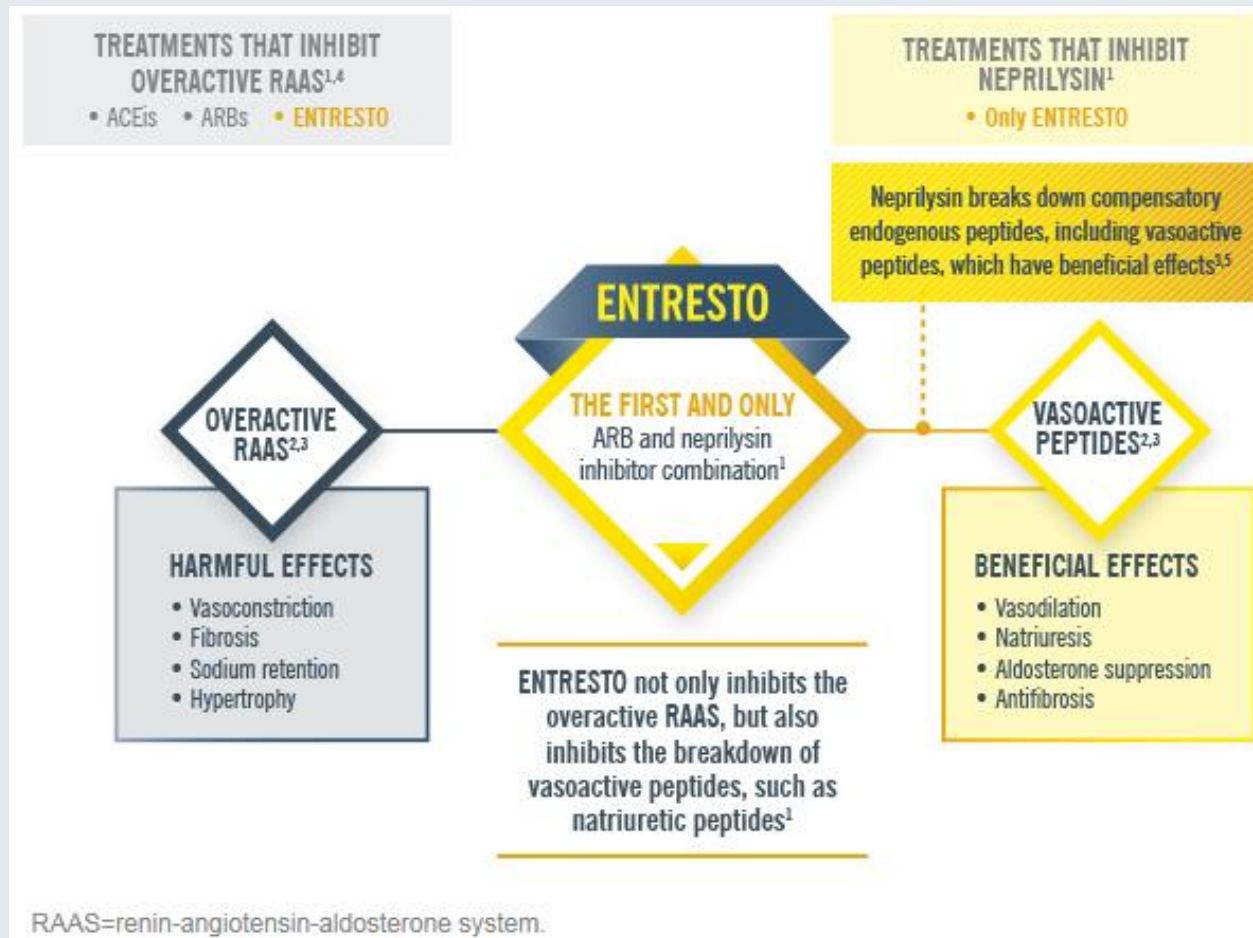


ENTRESTO



Sacubitril/Valsartan

Mechanism of Action



Pharmacokinetics of Interest



- Absorption
 - Bioavailability of Valsartan in Entresto is greater than that of Valsartan in other formulations
 - ✦ 26 mg of Valsartan in Entresto is equivalent to 40 mg in other formulations
 - ✦ 51 mg of Valsartan in Entresto is equivalent to 80 mg in other formulations
 - ✦ 103 mg of Valsartan in Entresto is equivalent to 160 mg in other formulations

Approved Indication



- Indicated for the treatment of heart failure with reduced ejection fraction (LVEF < 40%):
 - In patients with NYHA Class II or III (to reduce the incidence of cardiovascular death and hospitalization due to heart failure);
 - In place of an ACE inhibitor or ARB;
 - In combination with other heart failure therapies (e.g., beta-blockers, diuretics); and,
 - Initiated and titrated by a physician experienced in the treatment of heart failure.

PARADIGM-HF



Angiotensin-Nepriylsin Inhibition versus Enalapril in Heart Failure

**The New England Journal of Medicine, 2014
371(11); 993-1004**

PARADIGM-HF



- Overview:
 - Superiority trial
 - Multicentre (1043 centres in 47 countries)
 - ✦ N = 8,442
 - Randomization and concealed assignment
 - Intention-to-treat analysis

PARADIGM-HF

• Inclusion Criteria

- 18 yrs or older
- NYHA II, III, or IV symptoms (very few in class IV ~ 0.7%)
- LVEF \leq 40%
- BNP \geq 150 pg/mL or NT-proBNP \geq 600 pg/mL or if hospitalized for heart failure in the last 12 months BNP \geq 100 pg/mL or NT-proBNP \geq 400 pg/mL
- Taking a stable dose of an ACE inhibitor or an ARB equivalent to at least 10 mg of Enalapril daily
 - ✦ Ramapril 5 mg daily
 - ✦ Captopril 100 mg daily
 - ✦ Perindopril 4 mg daily
 - ✦ Trandolapril 2 mg daily
 - ✦ Fosinopril 20 mg daily
 - ✦ Candesartan 16 mg daily
 - ✦ Irbesartan 150 mg daily
 - ✦ Losartan 50 mg daily
 - ✦ Telmisartan 40 mg daily
 - ✦ Valsartan 160 mg daily

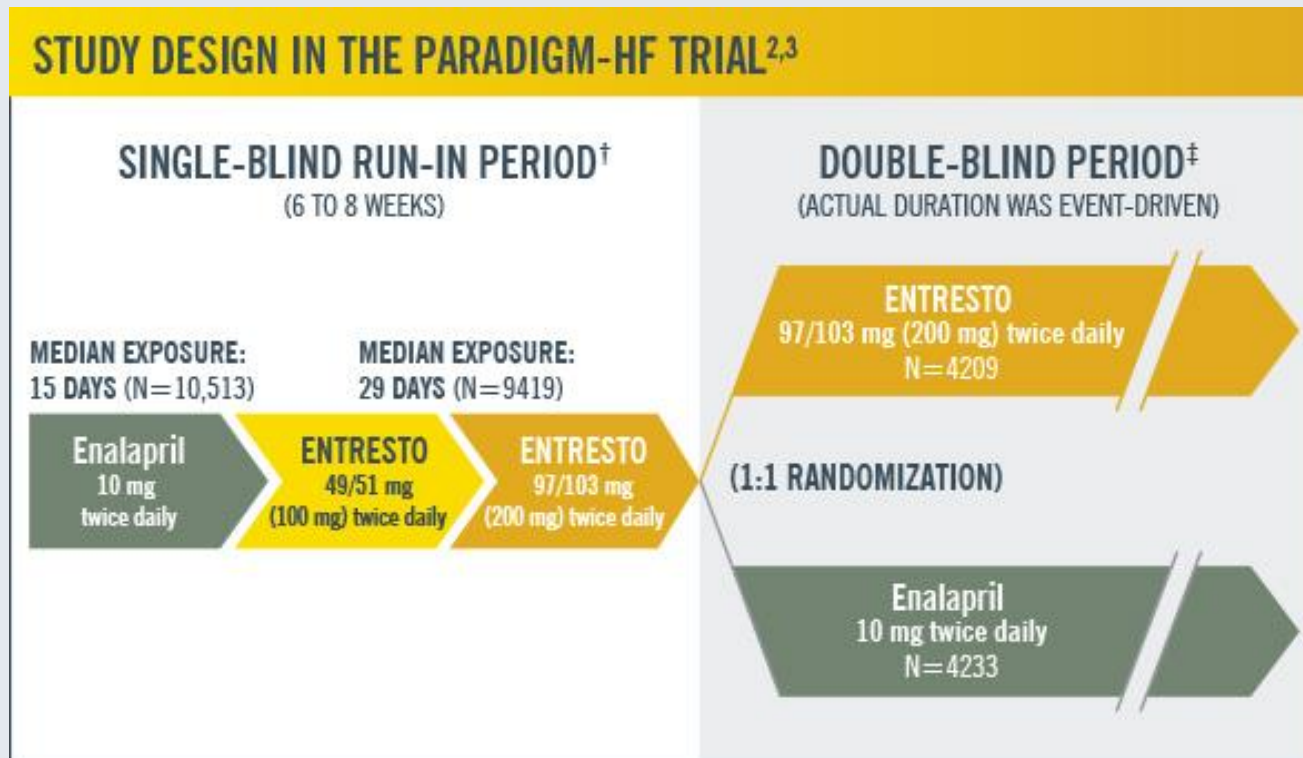
• Exclusion Criteria

- History of hypersensitivity, allergy to any of the study drugs, or drugs of similar classes ACE inhibitors, ARBs, or known or suspected contraindications
- Previous history of intolerance to recommended target doses of ACE inhibitors or ARBs
- History of angioedema
- Current acute decompensated heart failure
- Symptomatic hypotension and/or SBP $<$ 100 mmHg at screening or $<$ 95 mmHg at randomization
- eGFR $<$ 30 ml/min/1.73m² or $>$ 25% decline prior to randomization
- K⁺ $>$ 5.2 or $>$ 5.4 at randomization
- ACS, stroke, TIA, major CV surgery, PCI, angioplasty, or ICD implantation within last 3 months
- Coronary or carotid artery disease likely to require intervention within the next 6 months
- Severe pulmonary disease
- Life expectancy $<$ 5 years

PARADIGM-HF trial



- Study Design:



Median duration: 27 months

PARADIGM-HF



Angiotensin-Nepriylsin Inhibition versus Enalapril in Heart Failure

**The New England Journal of Medicine, 2014
371(11); 993-1004**

CRITICAL APPRAISAL

Critical Appraisal Components



- **Are the results of the study valid?**
 - Was the assignment of patients truly randomized?
 - Were all patients who entered the study accounted for appropriately at the end?
 - Were participants, health care providers, and those doing the assessments blind to the treatment?
 - Was similarity between groups documented?
 - Aside from the intervention, were the groups treated in the same way?
 - Free of selective outcome reporting?
 - Other sources of bias?
- **What are the results?**
 - How large was the treatment effect?
 - How precise was the estimate of the treatment effect?
- **Will the results help me care for my patient?**
 - Can the results be applied to my patient's care?
 - Were all clinically important outcomes considered?
 - Are the likely treatment benefits worth the potential harms and costs?

Finding the Information



- Full-text Article
- Supplementary Material or Publication of Methods

The screenshot displays the homepage of The New England Journal of Medicine. The header includes the journal's logo and name. Below the header is a navigation bar with links for HOME, ARTICLES & MULTIMEDIA, ISSUES, SPECIALTIES & TOPICS, FOR AUTHORS, and CME. A search bar is located on the right side of the navigation bar. The main content area features an article titled "Angiotensin–Nepriylsin Inhibition versus Enalapril in Heart Failure" by John J.V. McMurray, M.D., et al. The article is categorized as an ORIGINAL ARTICLE. On the right side of the article, there is a TOOLS section with various options: PDF, Print, Download Citation, Slide Set, Supplementary Material (highlighted with a red box), E-Mail, Save, Article Alert, Reprints, Permissions, and Share/Bookmark. Below the article, there are social media sharing options and a comments section. At the bottom of the page, there is a navigation bar with links for Abstract, Article, References, Citing Articles (471), Comments (14), Letters, and Metrics. A RELATED ARTICLES section is also visible at the bottom right.

Finding the Information



- Full-text Article
- Supplementary Material or Publication of Methods

The screenshot shows the article page for "Angiotensin–Nephrilysin Failure" in The New England Journal of Medicine. The page includes the journal logo, navigation tabs (HOME, ARTICLES & MULTIMEDIA), and a sidebar with options like "Abstract", "Article", and "References". The main content area is divided into sections: "ORIGINAL ARTICLE", the title, authors, and a "STUDY DESIGN" section. The "STUDY DESIGN" section is highlighted with a red border and contains the following text:

STUDY DESIGN

The study design has been reported previously.^{23,24} The trial protocol and the statistical analysis plan (included in the Supplementary Appendix) are available with the full text of this article at NEJM.org. The trial was approved by the ethics committee at each study center. All the patients provided written informed consent.

The study consisted of three phases: the screening period; a single-blind run-in period during which all patients received enalapril, which was followed by a single-blind run-in period during which all patients received LCZ696, to ensure an acceptable side-effect profile of the study drugs at target doses; and double-blind treatment in the two study groups.

On the right side of the page, there is a "SUBSCRIBE OR RENEW TODAY" button, an "Advanced Search" field, and a list of options: E-Mail, Save, Article Alert, Reprints, Permissions, and Share/Bookmark. A red box highlights the "Supplementary" link in the sidebar.

Are the Results of the Study Valid?



- Was the assignment of patients truly randomized?

Patients who had no unacceptable side effects of the target doses of the two study medications were randomly assigned in a 1:1 ratio to double-blind treatment with either enalapril (at a dose of 10 mg twice daily) or LCZ696 (at a dose of 200 mg twice daily) with the use of a computerized randomization system involving concealed study-group assignments. Patients were evaluated every 2 to 8 weeks during the first 4 months of double-blind therapy and every 4 months thereafter. The dose of the study drug could be reduced in patients who had unacceptable side effects at target doses.

But what does that mean?

Are the Results of the Study Valid?



- Was the assignment of patients truly randomized?
 - Random Sequence Generation & Allocation Concealment
- Randomization = allocating treatment by chance rather than by choice
 - Coin toss, random number table, computer
- Allocation Concealment = person recruiting patients does not know what group the next subject will be assigned to



Are the Results of the Study Valid?

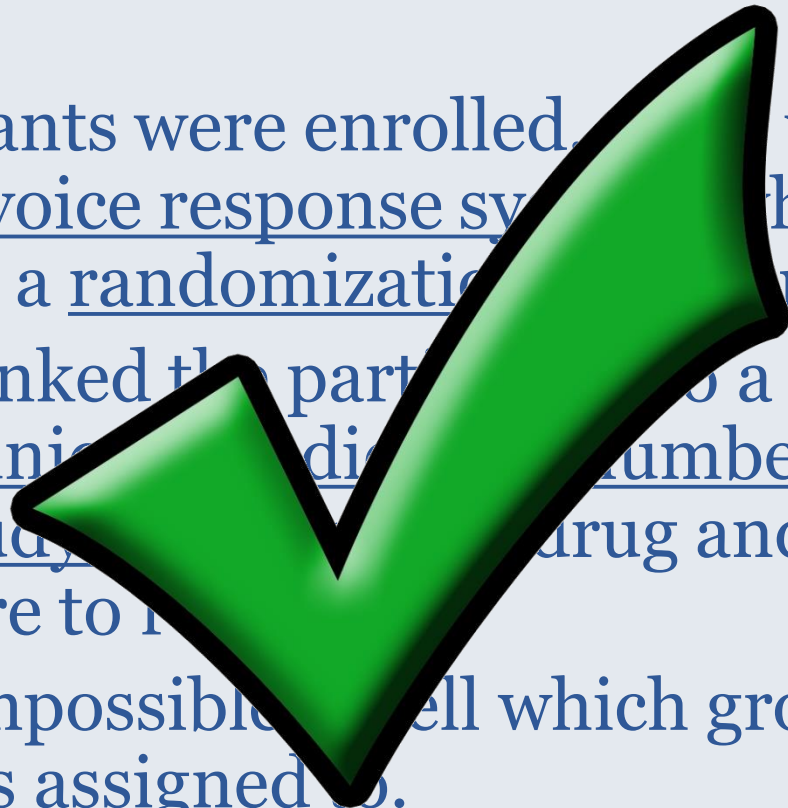


- Was the assignment of patients truly randomized?

When participants were enrolled, they were placed to an interactive voice response system which assigned the participant a randomization number.

This number linked the participant to a treatment arm and specified unique identification numbers for the packages of study drug and placebo which they were to receive.

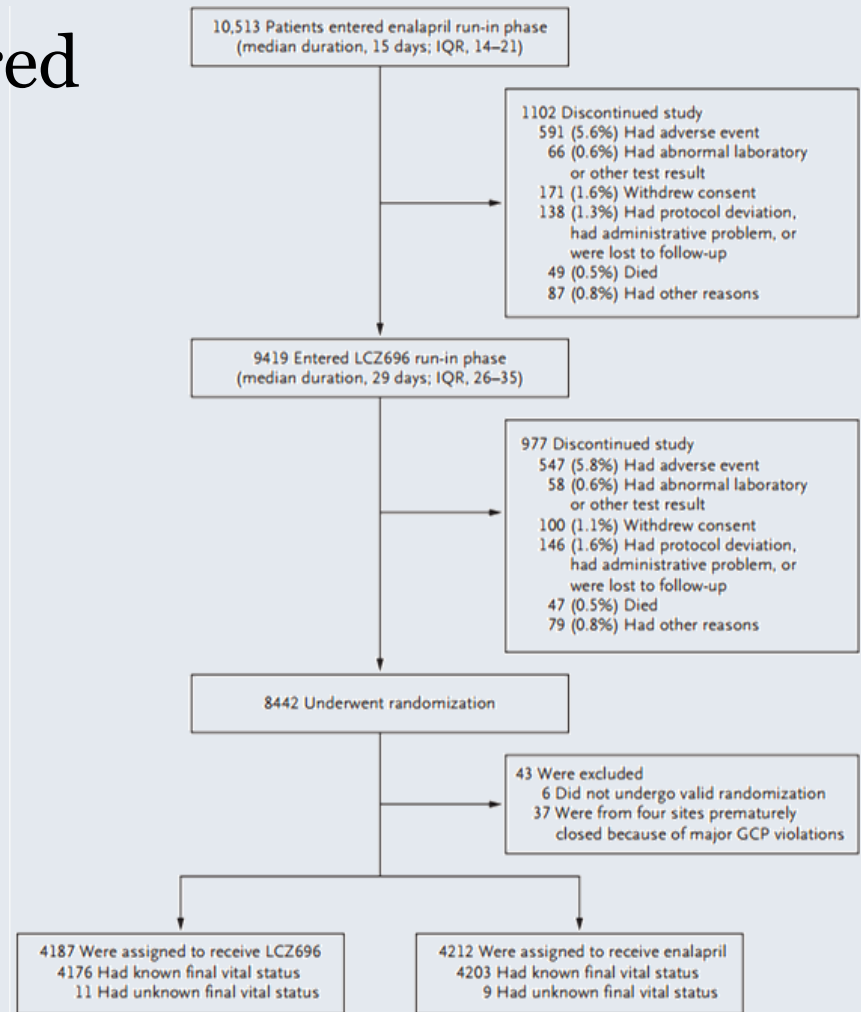
This made it impossible to tell which group the participant was assigned to.



Are the Results of the Study Valid?



- Were all patients who entered the study accounted for appropriately at the end?



Are the Results of the Study Valid?



- Were all patients who entered the study accounted for appropriately at the end?
 - Is incomplete outcome data adequately addressed?
 - Were patients analyzed in the groups to which they were randomized?

We included data from all patients who had undergone a valid randomization in the analyses of the primary and secondary outcomes, according to the intention-to-treat principle. A sequentially rejective procedure was used for analysis of the secondary efficacy end points, with the first two secondary end points at the highest level of the testing sequence. (For details, see the statistical analysis plan in the Supplementary Appendix.) Time-to-event data were evaluated with the use

Are the Results of the Study Valid?



- Were all patients who entered the study accounted for appropriately at the end?
 - Is incomplete outcome data adequately addressed?
 - Were patients analyzed in the groups to which they were randomized?

Novartis staff reviewed the data entered into the database by investigators for completeness and accuracy and instructed the site personnel to make corrections or additions.

What was deemed an 'obvious error' was corrected directly by Novartis staff.

UNCLEAR

→ *Since 'obvious error' was not defined, nor does the reader know what may be deemed inaccurate, it is unknown whether data were altered inappropriately.*

Are the Results of the Study Valid?



- Were participants, health care providers, and those doing the assessments blind to the treatment?

Patients who had no unacceptable side effects of the target doses of the two study medications were randomly assigned in a 1:1 ratio to **double-blind treatment** with either enalapril (at a dose of 10 mg twice daily) or LCZ696 (at a dose of 200 mg twice daily) with the use of a computerized randomization system involving concealed study-group assignments. Patients were evaluated every 2 to 8 weeks during the first 4 months of double-blind therapy and every 4 months thereafter. The dose of the study drug could be reduced in patients who had unacceptable side effects at target doses.

But this doesn't specify who is blind or how

Are the Results of the Study Valid?



- Were participants, health care providers, and those doing the assessments blind to the treatment?

Study drugs were created as double-dummy (to ensure blinding throughout the course of the study, participants were required to take their assigned active treatment and placebo (identical to the opposite treatment)).

For subsequent supplies of study drug, an investigator called the interactive voice response system, which asked the caller whether there is a change in the medication number. The system provided unique medication numbers for each study drug that should be dispensed.

Participants, investigators, and data analysts were kept blind to the treatment allocation from the time of randomization until conclusion of the study, with the exception of the data monitoring committee (independent of Novartis, but reported to them), the independent statistician, or in the case of an emergency.



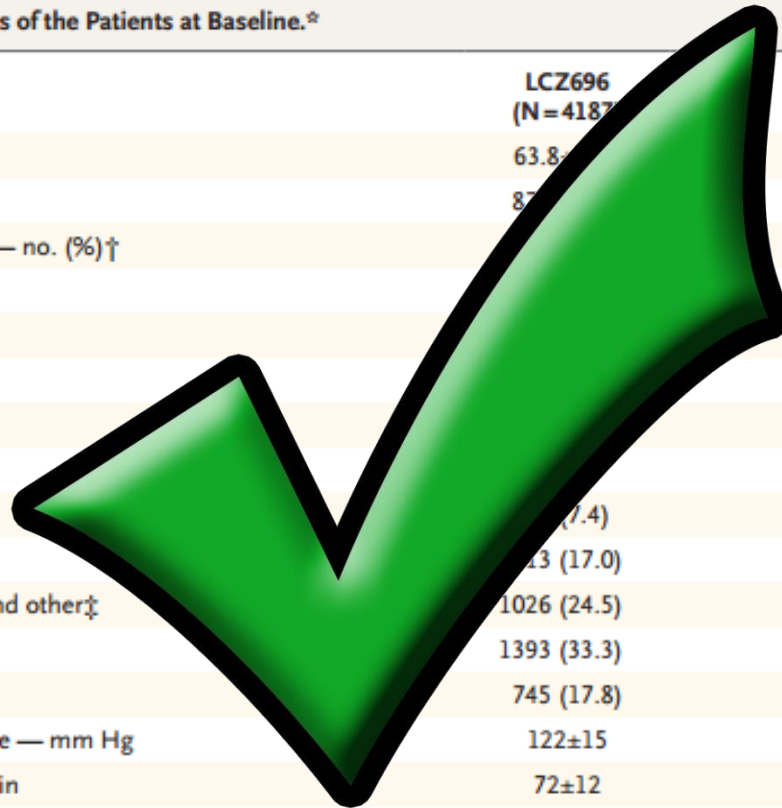
Are the Results of the Study Valid?



- Was similarity between groups documented?

Table 1. Characteristics of the Patients at Baseline.*

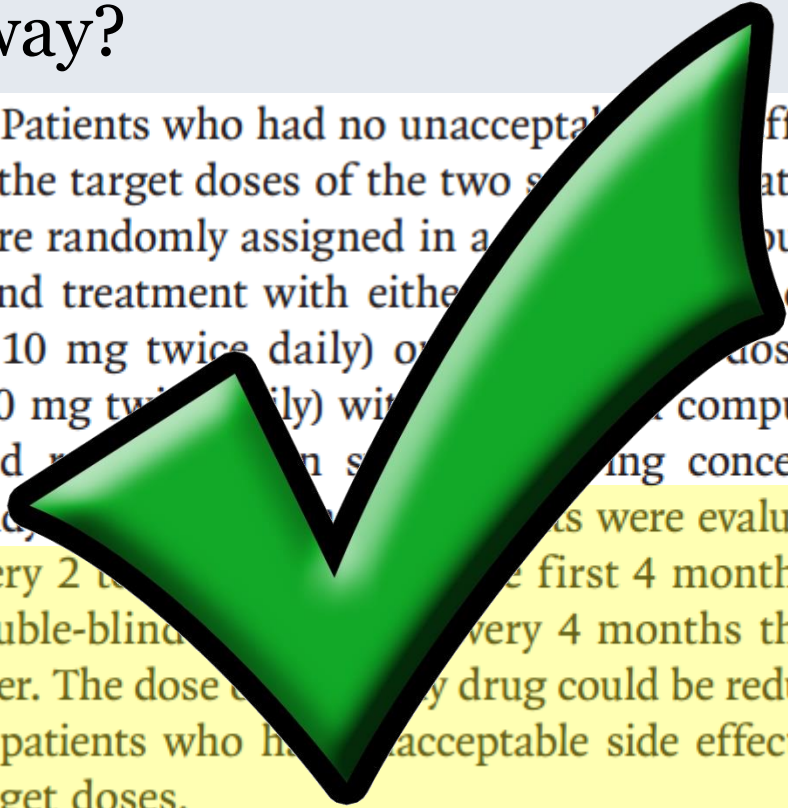
Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8	63.8±11.3
Female sex — no. (%)	877 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2781 (66.4)	2781 (66.0)
Black	215 (5.1)	215 (5.1)
Asian	750 (17.8)	750 (17.8)
Other	466 (11.1)	466 (11.1)
Region — no. (%)		
North America	292 (7.0)	292 (6.9)
Latin America	720 (17.2)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1433 (34.0)
Asia-Pacific	745 (17.8)	742 (17.6)
Systolic blood pressure — mm Hg	122±15	121±15
Heart rate — beats/min	72±12	73±12
Body-mass index‡	28.1±5.5	28.2±5.5
Serum creatinine — mg/dl	1.13±0.3	1.12±0.3



Are the Results of the Study Valid?



- Aside from the intervention, were the groups treated in the same way?



Patients who had no unacceptable side effects of the target doses of the two study medications were randomly assigned in a double-blind treatment with either a dose of 10 mg twice daily) or a dose of 200 mg twice daily) with a computerized randomization system using concealed study. Patients were evaluated every 2 to 4 weeks during the first 4 months of double-blind treatment and every 4 months thereafter. The dose of any drug could be reduced in patients who had unacceptable side effects at target doses.

Are the Results of the Study Valid?



- Free of selective outcome reporting?
 - Methods Section
 - ✦ Study Outcomes
 - ✦ Statistical Analyses
 - Compare to Results Section
 - Check clinicaltrials.gov



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Results database of publicly and privately supported clinical trials conducted around the world. Learn more about the database, including relevant [history](#), [policies](#), and [laws](#).

Now Available: Policy on Clinical Trial Reporting

Find Studies ▾ About Clinical Studies ▾ Resources ▾ About This Site ▾

ClinicalTrials.gov currently lists 230,823 studies with 193 countries.

Text Size ▾

Search for Studies
Example: "Heart attack" AND "Los Angeles"

Advanced Search | See Studies by Topic | See Studies on Map

Locations of Recruiting Studies

• How to find results of studies
• How to read a study record

Legend:
Non-U.S. only (56%)
U.S. only (39%)
Both U.S. and non-U.S. (5%)

Total N = 40,367 studies
(Data as of November 24, 2016)

Are the Results of the Study Valid?



- Other sources of bias?

All but one of the authors received support from Novartis, be it grants, personal fees, or non-financial support.

Data were collected, managed, and analyzed by Novartis.

The independent statistician was only to replicate the analyses.

Are the Results of the Study Valid?



- Other sources of bias?

A large percentage of participants discontinued the study prior to randomization. This was true for over 2,000 participants.

- Of those who did not randomize, 54.7% withdrew during the run-in phase. The most common reason for withdrawal was an adverse event (cough, hyperkalemia, renal dysfunction, or hypertension).

There is no data readout on how these individuals differed from those who were randomized into the active phase of the trial (e.g., age, gender, etc.).



What are the Results?



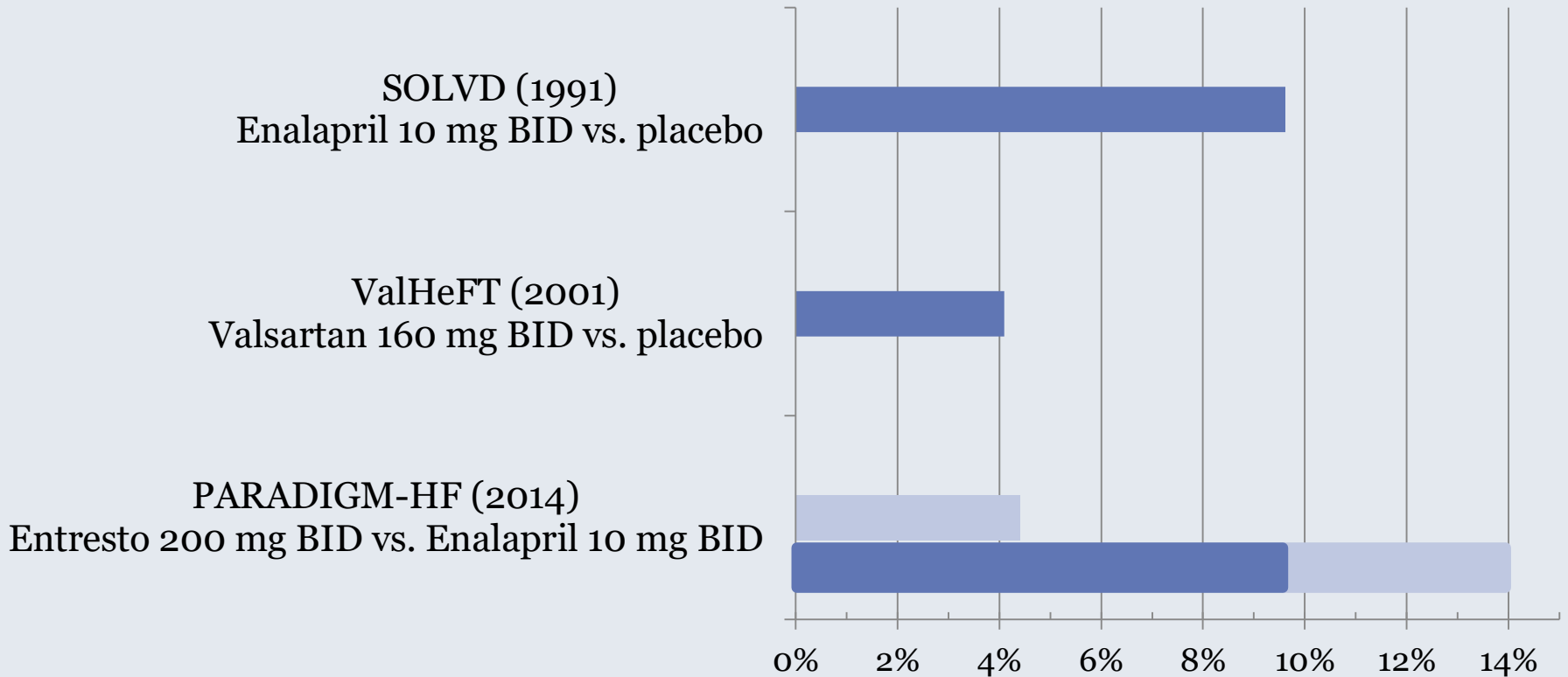
- How large was the treatment effect?

	RR	ARR	RRR	NNT/2 ¼ years
Primary end-point				
CV death or 1 st hospitalization for heart failure 21.8% vs. 26.5%	0.823	4.7%	0.177	21
Secondary end-points				
CV death 13.3% vs. 16.5%	0.810	3.1%	0.190	32
1 st hospitalization for heart failure 12.8% vs. 15.6%	0.821	2.8%	0.179	36
All-cause mortality 17.0% vs. 19.8%	0.857	2.8%	0.143	35
Safety end-points				
Symptomatic hypotension 14.0% vs. 9.2%	1.447	-4.1%	-0.447	24 (NNH)

PARADIGM-HF



- Comparison to other studies
 - ARR in All-Cause Mortality & Hospitalization for Heart Failure



What are the Results?



- How precise was the estimate of the treatment effect?

	HR
Primary end-point	
CV death or 1 st hospitalization for heart failure 21.8% vs. 26.5%	0.80 (<u>0.73-0.87</u>) p < 0.001
Secondary end-points	
CV death 13.3% vs. 16.5%	0.80 (<u>0.71-0.89</u>) p < 0.001
1 st hospitalization for heart failure 12.8% vs. 15.6%	0.79 (<u>0.71-0.89</u>) p < 0.001
All-cause mortality 17.0% vs. 19.8%	0.84 (<u>0.76-0.93</u>) p < 0.001

Will the Results Help Me Care for My Patient?



- Can the results be applied to my patient's care?
 - Are study patients similar to my patient?
- Were all clinically important outcomes considered?
 - Were the most important outcomes used? Or surrogate outcomes? (e.g., fracture or BMD?)
- Are the likely treatment benefits worth the potential harms and costs?

Overall Conclusion of Critical Appraisal



- **Good Internal Validity**

- Randomization & blinding were well done
- Follow-up of participants who were randomized was nearly 100%
- High level of similarity between groups

- **Poor External Validity**

- Individuals were ineligible unless previously tolerated on a high enough, stable dose of ACE inhibitor or ARB
- Patients with heart failure seen at HSN are generally older (study avg. age 64 yrs) & are admitted with decompensated heart failure or another cardiac issue, which would preclude them from the study and as a result switching to Entresto would not be indicated.

Thank You



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