Use of Sacubitril/Valsartan in Heart Failure

Entresto™
(sacubitril/valsartan) tablets
24/26mg · 49/51mg · 97/103mg

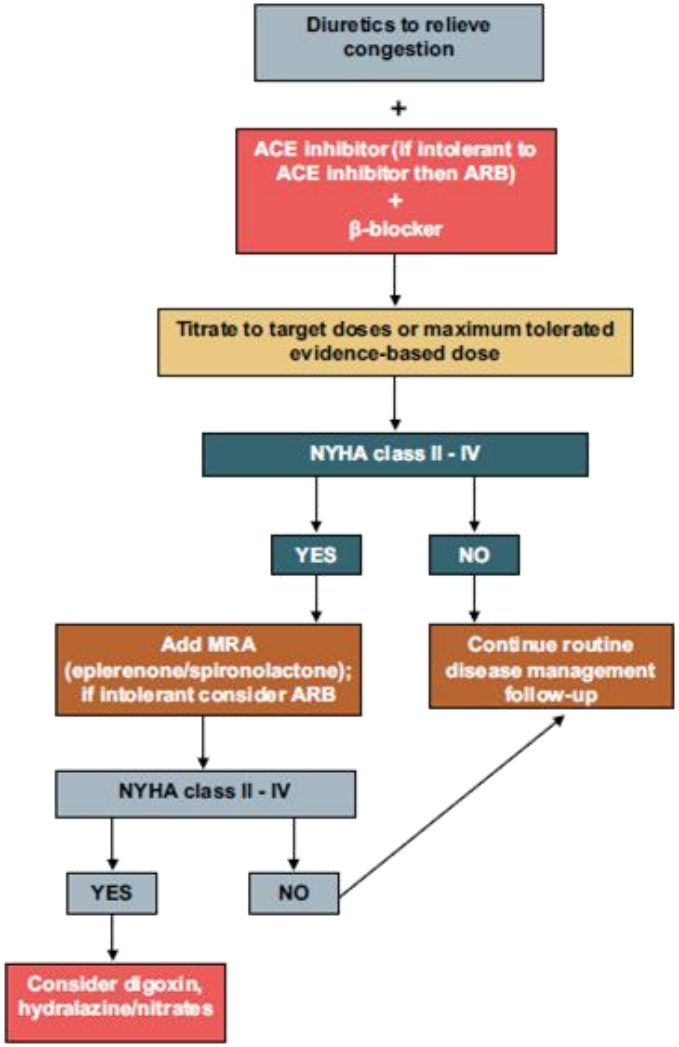
& the PARADIGM–HF trial

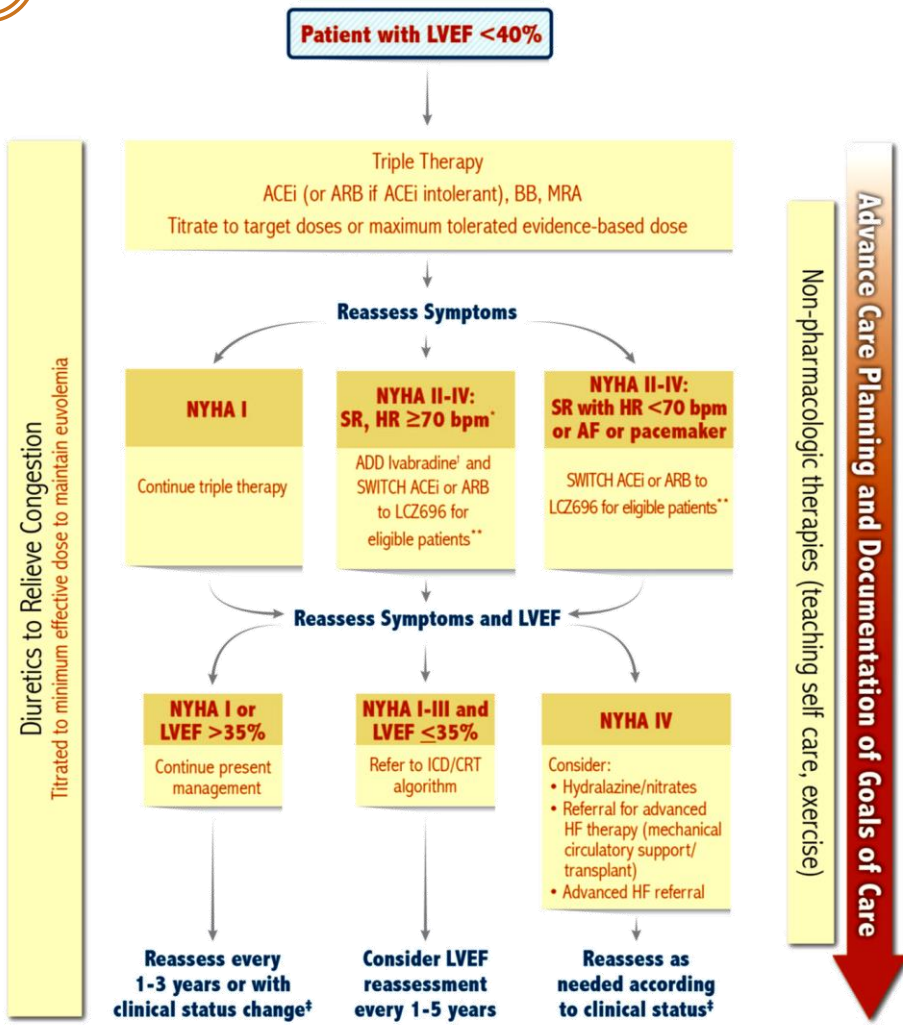
Sarah Mackenzie, PharmD student, University of Toronto

Presentation Outline

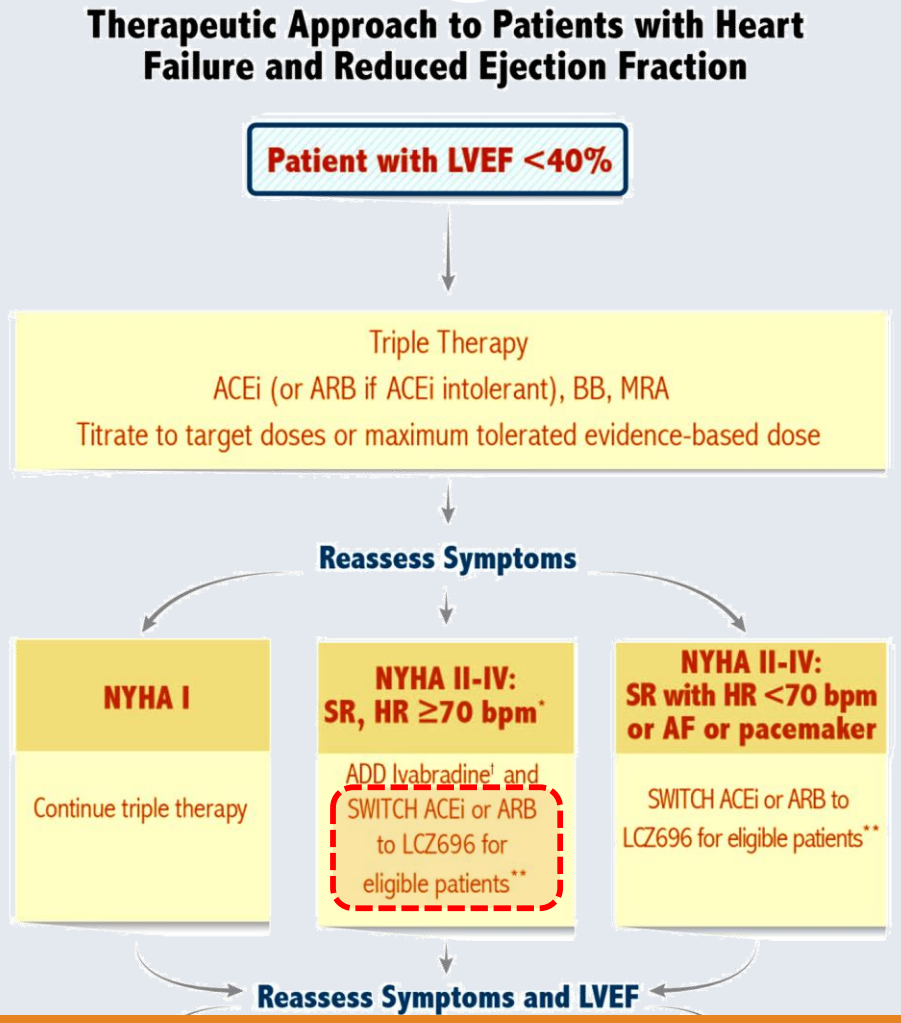
- Overview of:
  - Entresto
  - PARADIGM-HF trial
- Critical Appraisal

Canadian Cardiovascular Society Guidelines





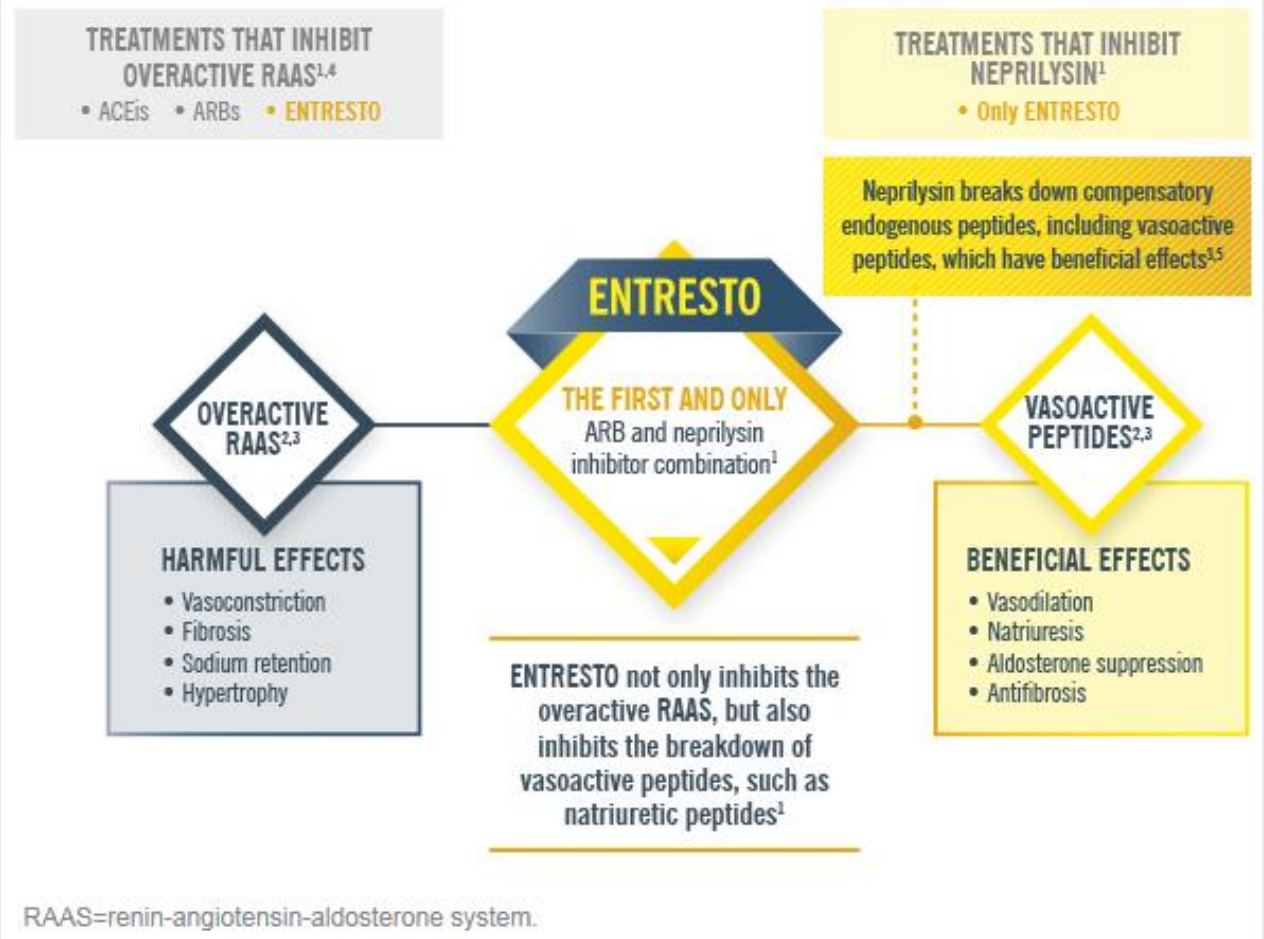
Canadian Cardiovascular Society Guidelines



ENTRESTO

Sacubitril/Valsartan

Mechanism of Action



https://www.entrestohcp.com/mechanism-of-action#

Pharmacokinetics of Interest

- Absorption
  - Bioavailbility 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-Neprilysin 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

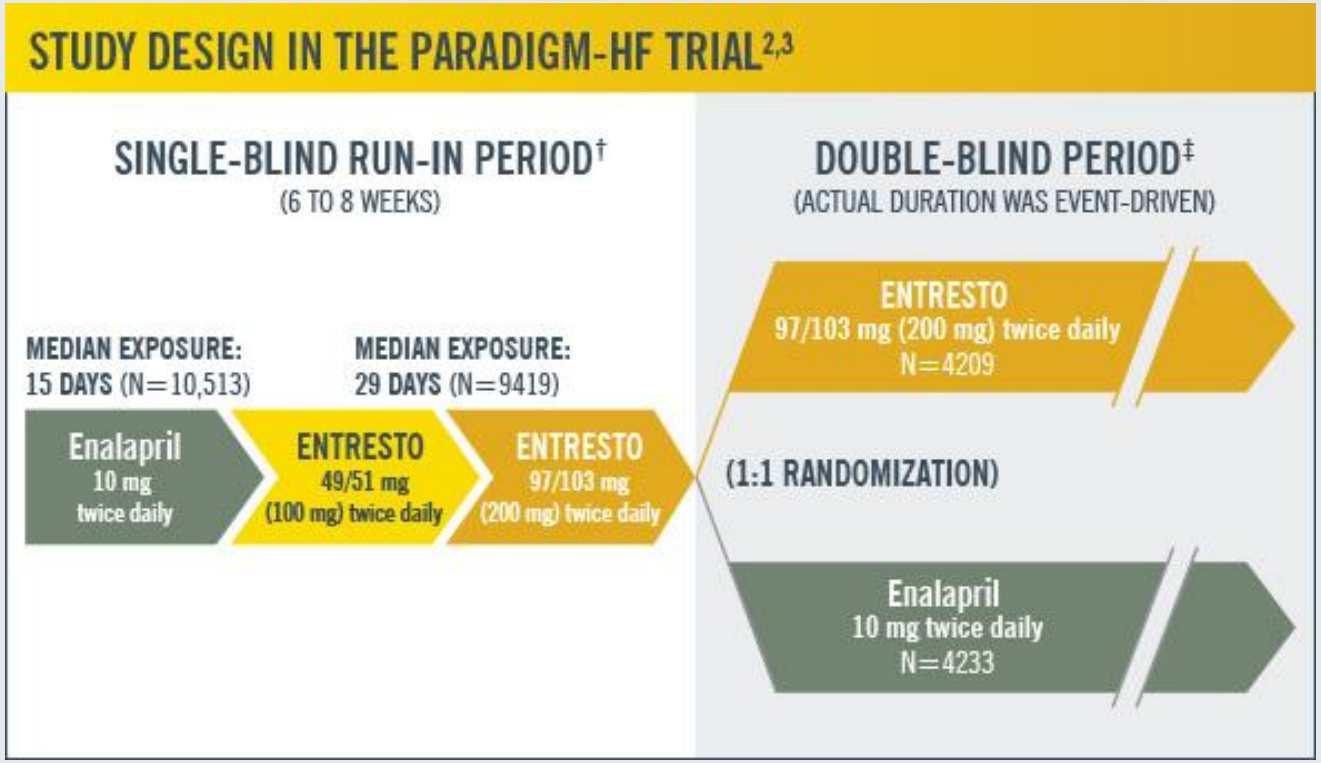
PARADIGM-HF

- Inclusion Criteria
  - 18 yrs or older
  - NYHA II, II, or IV symptoms (very few in class IV ~ 0.7%)
  - LVEF <= 40%
  - BNP >= 150 pg/mL or NT-proBNP >= 600 pg/mL or if hospitalized for heart failure in the last 12 months BNP >= 100 pg/mL or NT-proBNP >= 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-Neprilysin Inhibition versus Enalapril in Heart Failure

The New England Journal of Medicine, 2014
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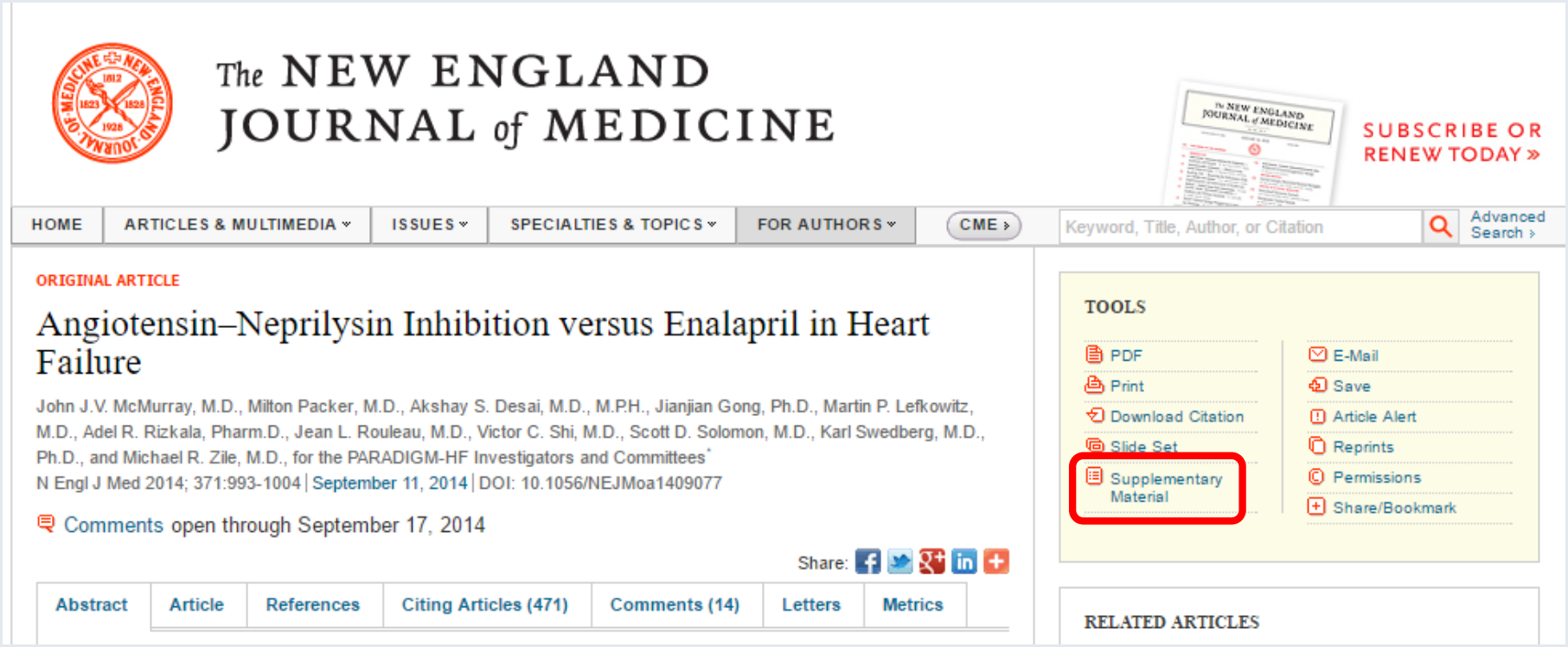
CRITICAL APPRAISAL

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



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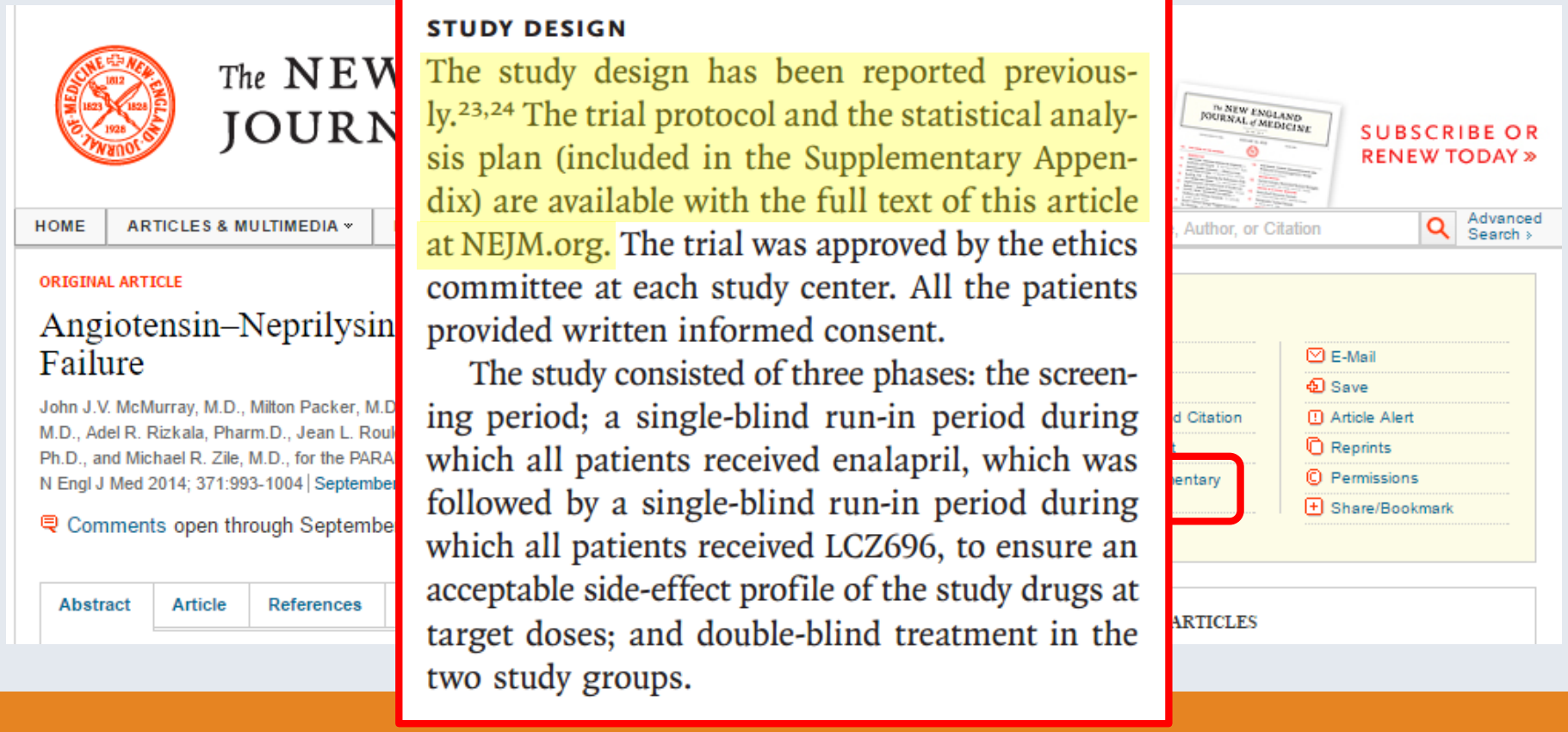


Are the Results of the Study Valid?

- 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?

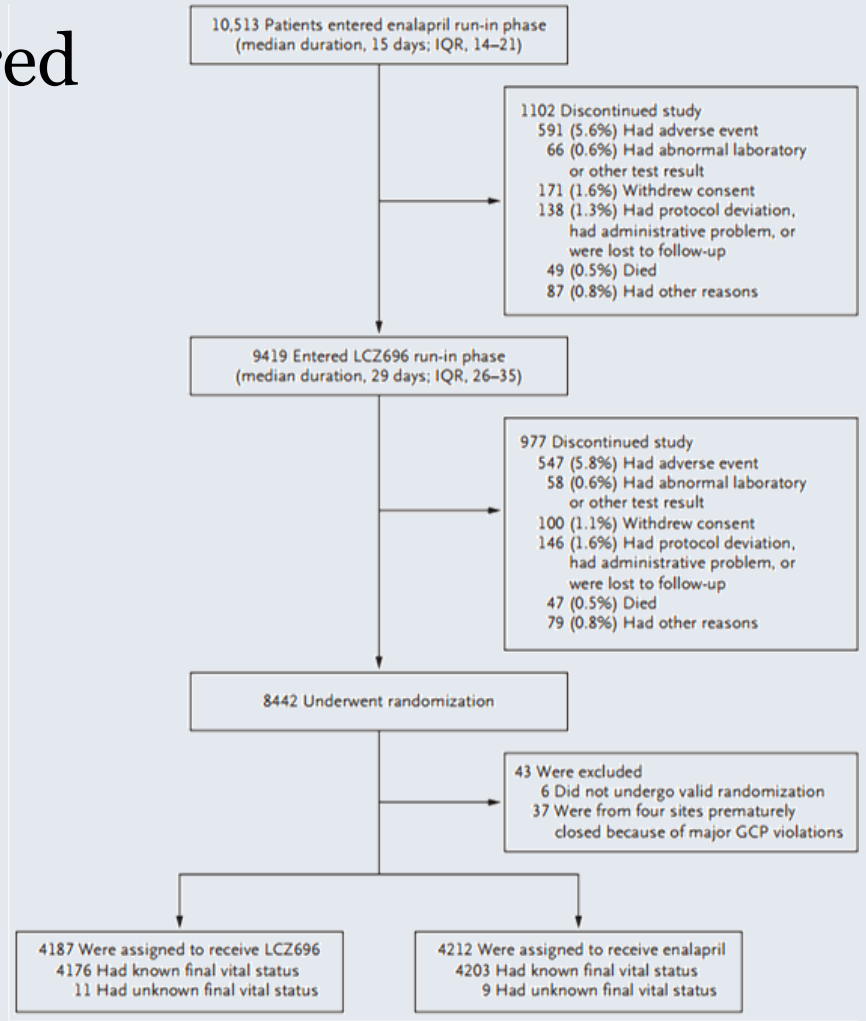
When participants were enrolled, [illegible] was placed to an interactive voice response sy[illegible]hich assigned the participant a randomizati[illegible]r.

This number linked t[illegible] part[illegible] a treatment arm and specified uni[illegible]di[illegible]umbers for the packages of study [illegible]rug and placebo) which they were to [illegible]

This made it impossible [illegible]ell 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?

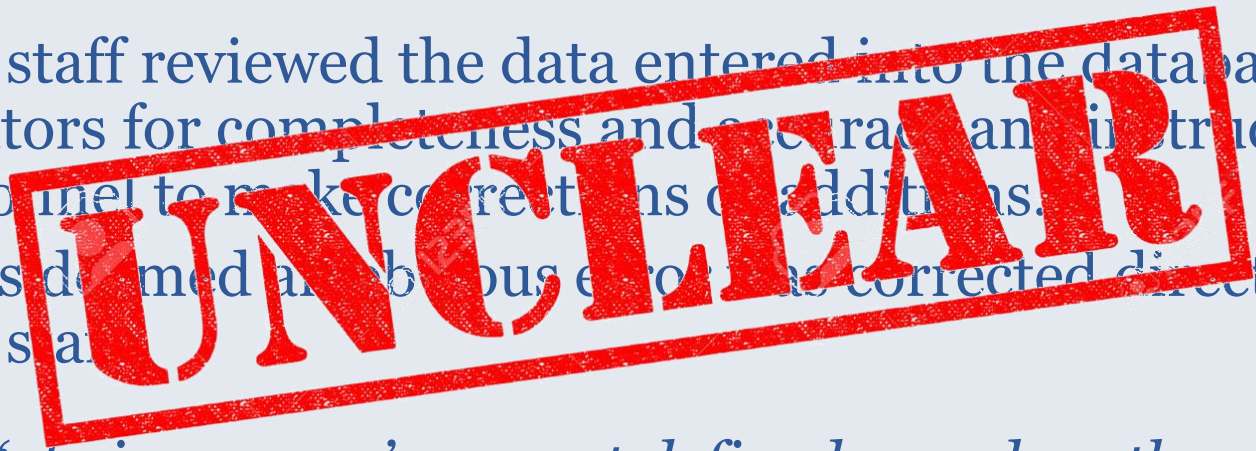
We included data from all patients who had undergone a valid randomization in the analyses of the primary and secondary outcomes, according to the intention-to-treat principle. A sequentially rejective procedure was used for analysis of the secondary efficacy end points, with the first two secondary 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.



→ *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 [illegible]sure blinding throughout the course of the study, partici[illegible]ere required to take their assigned active treatment and plac[illegible]ical to the opposite treatment).

For subsequent supplies of study dru[illegible]tigator called the interactive voice response [illegible]tem, w[illegible] the caller whether there is a change in th[illegible]d t[illegible]stem provided unique medication number[illegible]k[illegible]udy drugs that should be dispensed.

Participants, investigators, [illegible]and data analysts were kept blind to the treatment alloca[illegible]n the time of randomization until conclusion of the study, with t[illegible]ception of the data monitoring committee (independent of Nova[illegible]tis, but reported to them), the independent statistician, or in the case of an emergency.

Are the Results of the Study Valid?

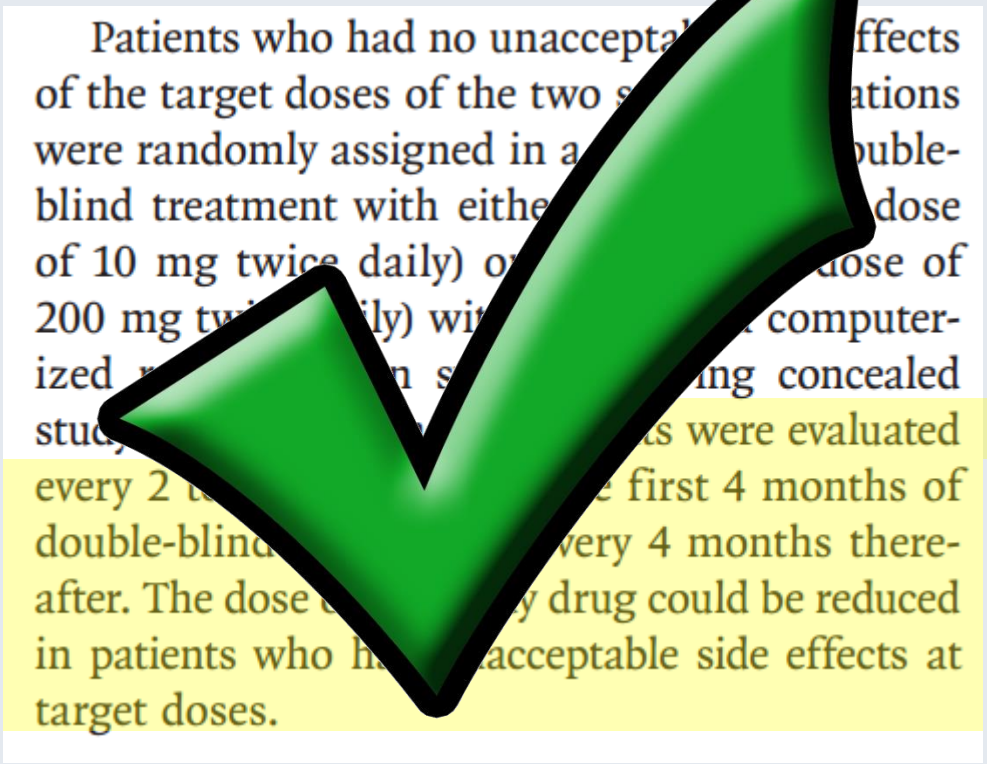
- Was similarity between groups documented?

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. (%)	8	953 (22.6)
Race or ethnic group — no. (%)†		
White		2781 (66.0)
Black		215 (5.1)
Asian		750 (17.8)
Other		466 (11.1)
Region — no. (%)		
North America	(7.4)	292 (6.9)
Latin America	13 (17.0)	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

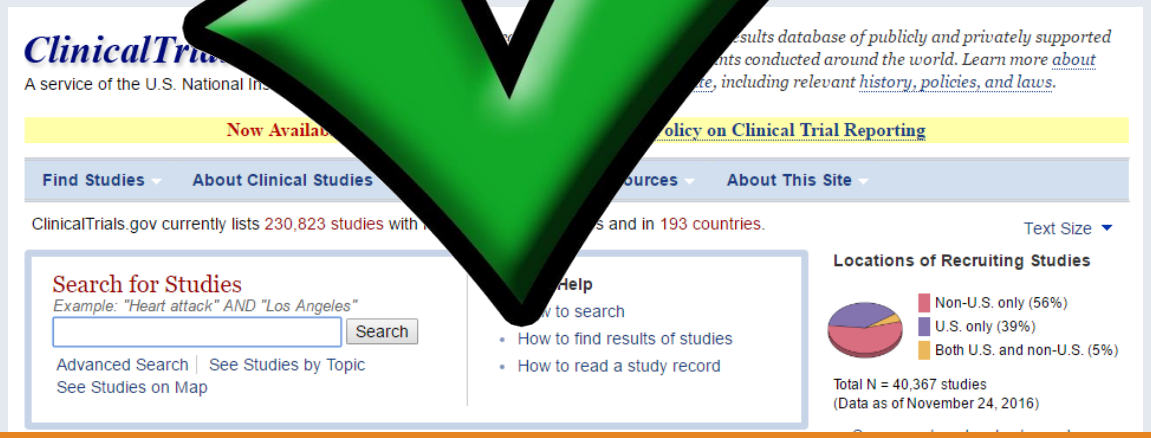
Are the Results of the Study Valid?

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



Are the Results of the Study Valid?

- Free of selective outcome reporting?
  - Methods Section
    - Study Outcomes
    - Statistical Analyses
  - Compare to Results Section
  - Check clinicaltrial



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 percentag of parti scontinued the study prior to rand this ver 2,000 participants.

- Of those who did not i ation, 54.7% withdrew during the run in phase se event (cough, hyperkalemia, renal dysf tension).

There is no data read how these individuals differed e w d into the active phase of the trial er, et

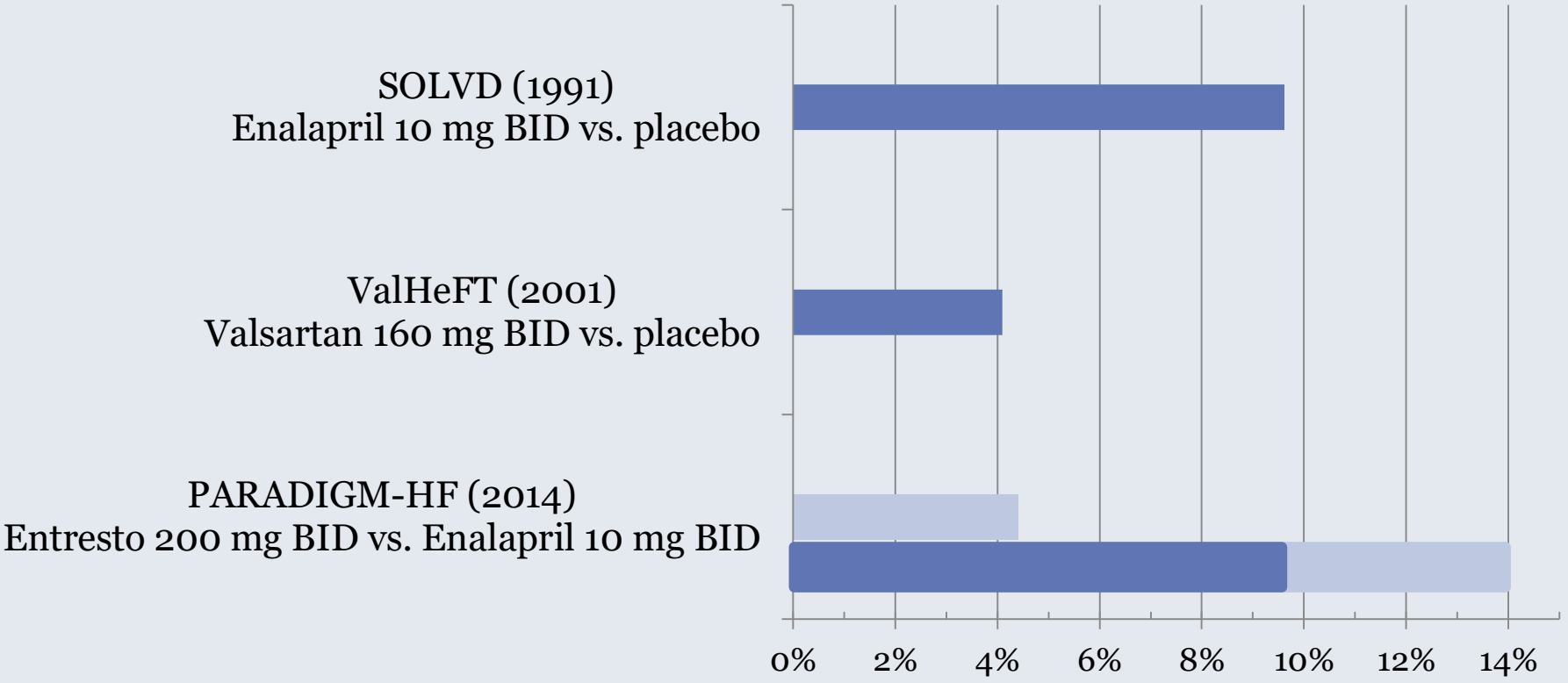
What are the Results?

- How large was the treatment effect?

	RR	ARR	RRR	NNT/2 ¼ years
Primary end-point				
CV death or 1st 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
1st 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 1st hospitalization for heart failure 21.8% vs. 26.5%	0.80 (0.73-0.87) p < 0.001
Secondary end-points	
CV death 13.3% vs. 16.5%	0.80 (0.71-0.89) p < 0.001
1st hospitalization for heart failure 12.8% vs. 15.6%	0.79 (0.71-0.89) p < 0.001
All-cause mortality 17.0% vs. 19.8%	0.84 (0.76-0.93) 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

SARAH MACKENZIE
DOCTOR OF PHARMACY STUDENT, CLASS OF 2017
UNIVERSITY OF TORONTO

S.BARNETT@MAIL.UTORONTO.CA