HeFSSA Practitioners Program 2016
"What is NEW in Heart Failure treatment?"

08:00	Registration
08:25	Welcome and Thank You to Sponsors
08:30	**The new kid on the block – " ARNI"**
09:15	How do I effectively diurese my patient? Anything new?
10:00	Tea Break
10:30	Drugs, devices and procedures to offer the atrial fibrillation patient- new and exciting
11:15	The NEW ESC Heart Failure Guidelines from Europe
11:45	Questionnaire
12:00	Departure

SA Heart

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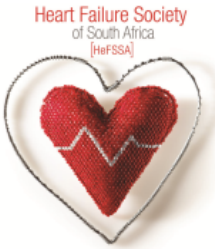
CASE STUDY:

The new kid on the block – “ARNI”



Case - History

- 53 year old male
- Long history of hypertension
- Currently on thiazide diuretic – intermittent adherence
- 20 pack year history of smoking – stopped 3 months ago
- No allergies
- No family history of vascular disease
- History of alcohol abuse
- Now presents with dyspnoea – class III NYHA, orthopnoea and leg swelling of a few weeks duration

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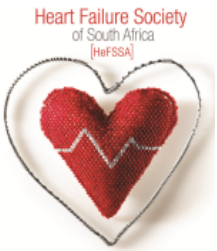
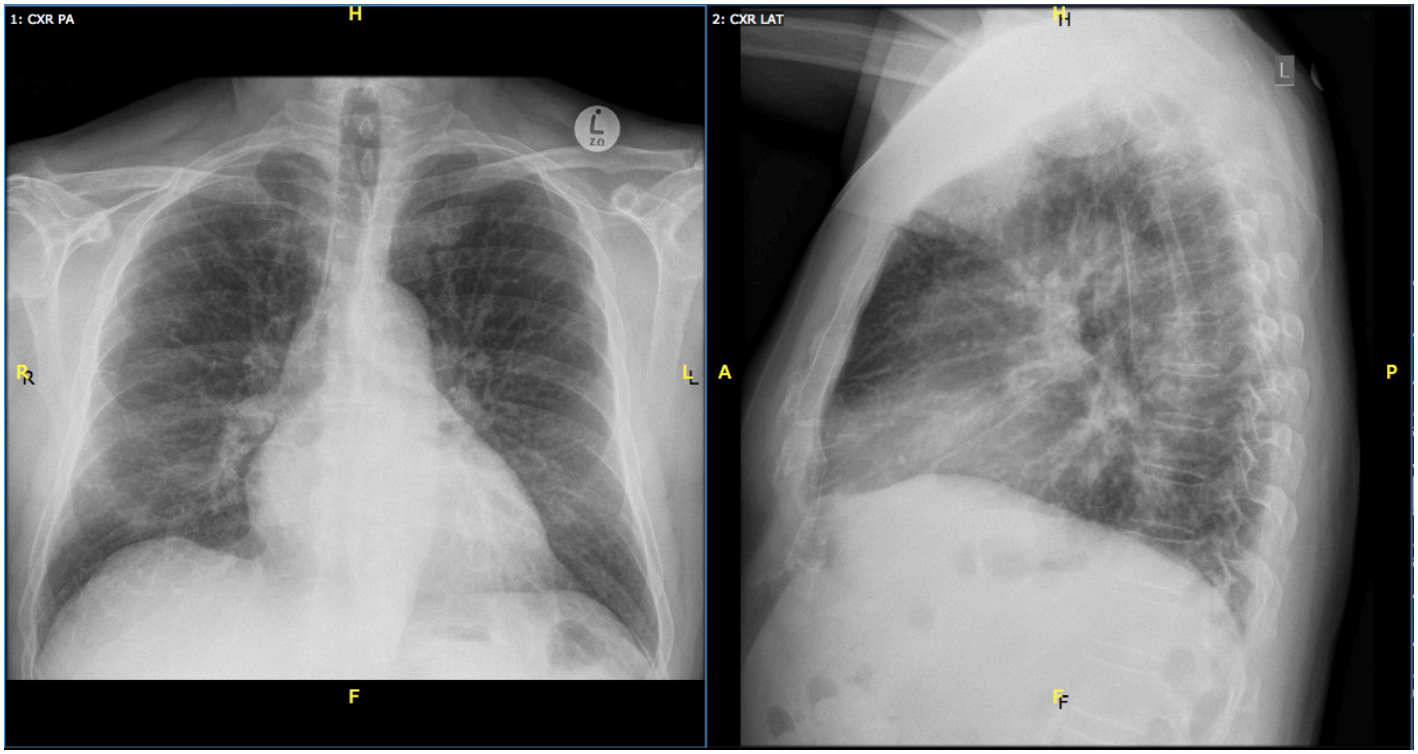
Case - Clinical

- Obese – BMI 35
- BP 163/92 mmHg
- No pallor, both legs oedematous
- Pulses all palpable – low volume, irregular and rapid
- JVP – angle of jaw
- Apex beat displaced lateral to the mid clavicular line
- Pansystolic murmur of mitral regurgitation
- Bilateral lung crepitations



Case – CXR

1. Cardiomegaly
2. Increased interstitial markings
3. Upper lobe blood diversion



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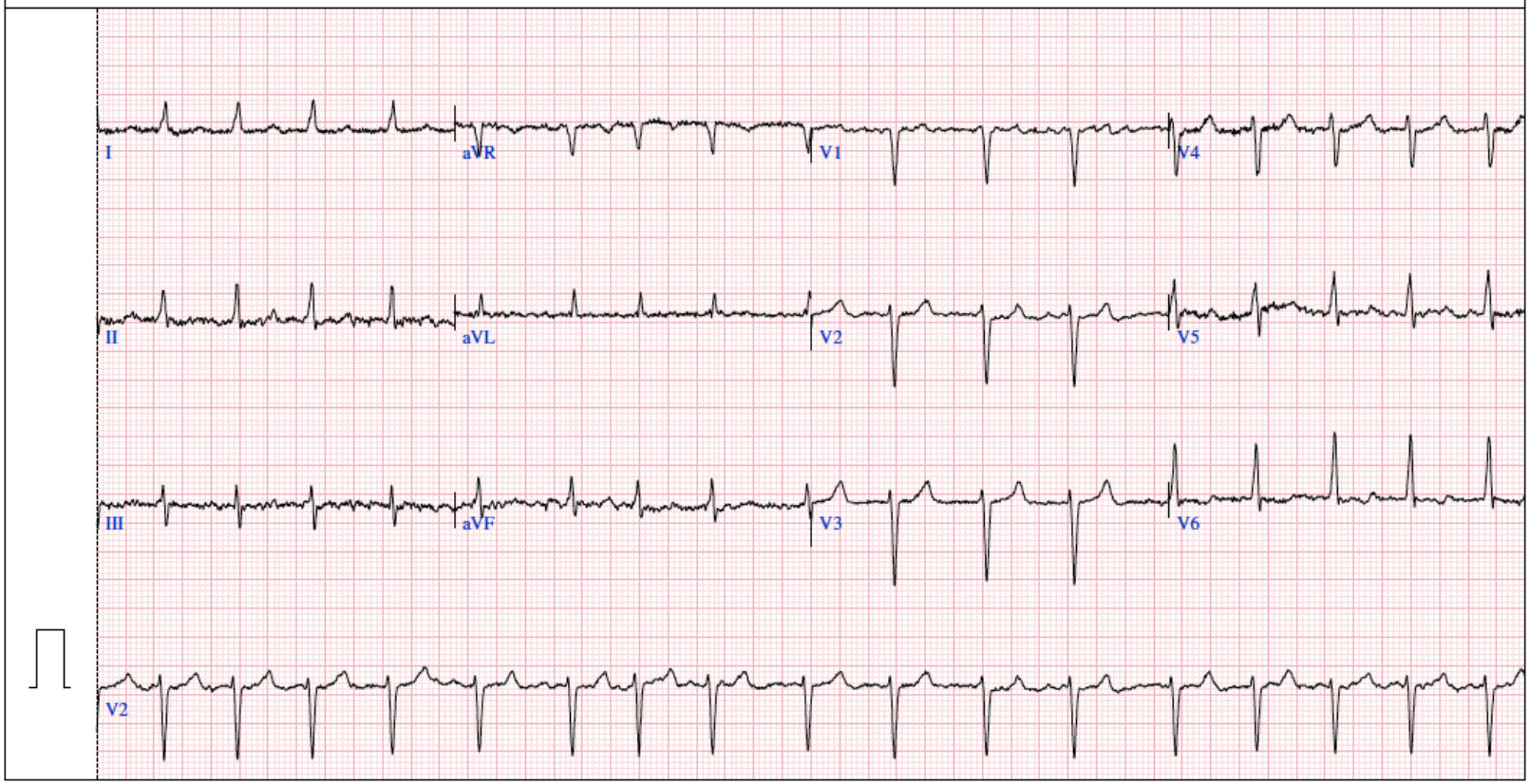
Case - ECG

Vent. Rate	103 bpm	**Technician:**	L Papenfus
PR interval	ms	**Interpretation:**	
QRS duration	78 ms	Atrial fibrillation with rapid ventricular response	
QT/QTC	358/468 ms	Abnormal ECG	
P-R-T axes	/23/29°		
P duration	ms		
RR/PP interval	580/555 ms		



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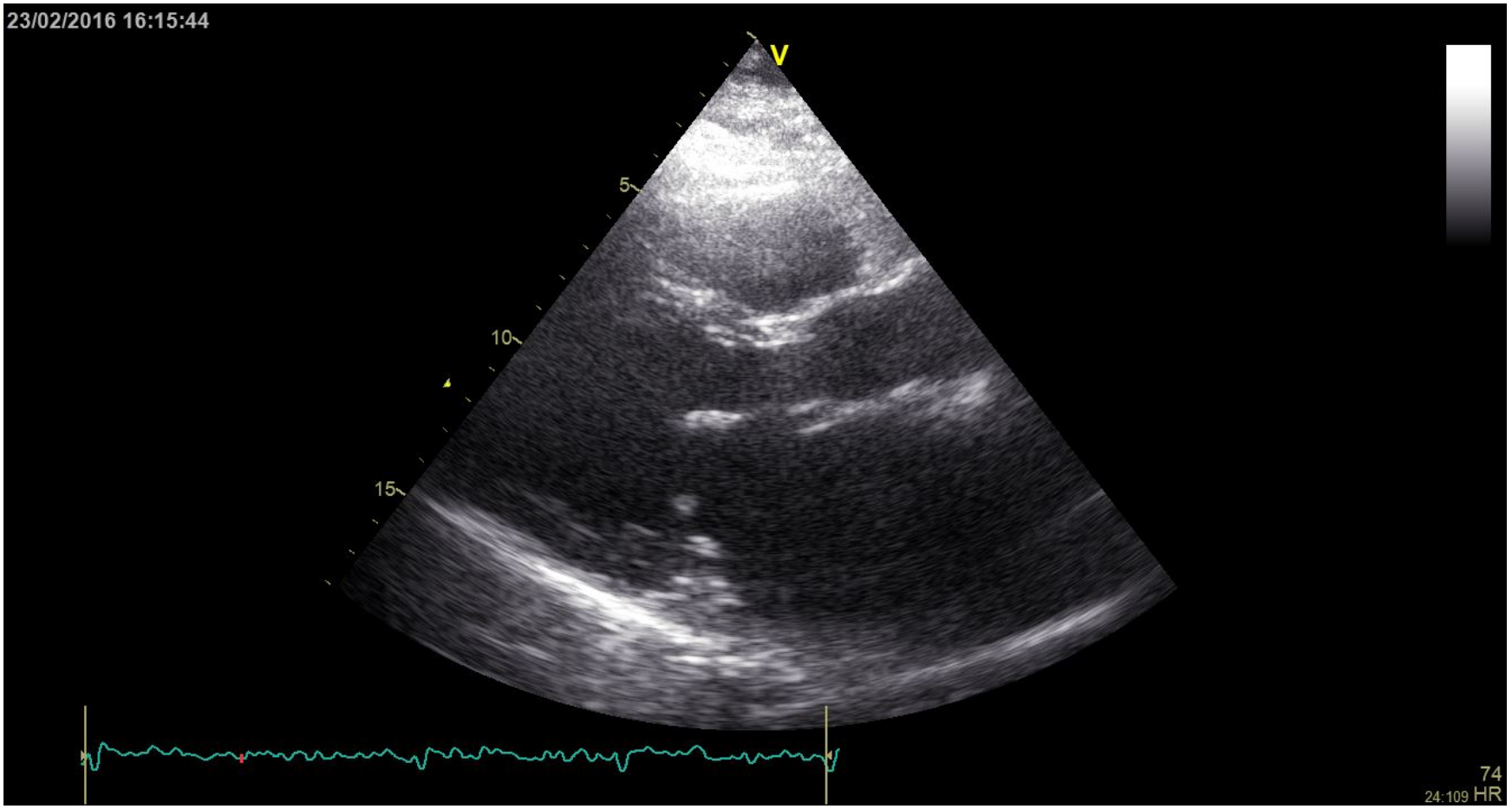
Case - Echocardiogram



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Case - Blood results

- U&E - normal
- TSH - normal
- FBC – Hb. 13.2 g/dL, normal WCC and platelets.
- proBNP – 990 pg/mL

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Case - Diagnosis

- Congestive cardiac failure
- LV systolic dysfunction – “HFreF”
- Cause:
  - Hypertension
  - Toxic – ethanol
  - ?genetic component
  - ?ischaemic

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CT coronary angiogram

- Calcium score – low
- No evidence of significant coronary stenosis

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Case - Management

- Carvedilol 25 mg BD
- Ramipril 5 mg BD
- Spironolactone 25 mg OD
- Furosemide 40 mg BD
- Amlodipine 5 mg OD
- Warfarin 5 mg OD

	Starting dose (mg)	Target dose (mg)
ACE-I		
Enalapril	2.5 BD	20 BD
Lisinopril	2.5 OD	20 OD
Ramipril	2.5 OD	10 OD
Beta-blockers		
Bisoprolol	1.25 OD	10 OD
Carvedilol	3.125 BD	25 BD
ARBs		
Candesartan	4 OD	32 OD
Valsartan	40 BD	160 BD
Losartan	50 OD	150 OD
MRAs		
Eplerenone	25 OD	50 OD
Spironolactone	25 OD	50 OD
ARNI		
Sacubitril/valsartan	49/51 BD	97/103 BD
If-channel blocker		
Ivabradine	5 BD	7.5 BD

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General Measures

* COUNSELLING - SYMPTOMS
  - PROGNOSIS
  - DRUGS
* REST / EXERCISE
* DIET
* ALCOHOL
* PREGNANCY
* DAILY WEIGHT RECORD

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6 month follow-up

- Patient improved
- Coping with medication
- Still complaining of shortness of breath on moderate exertion
- Next step?

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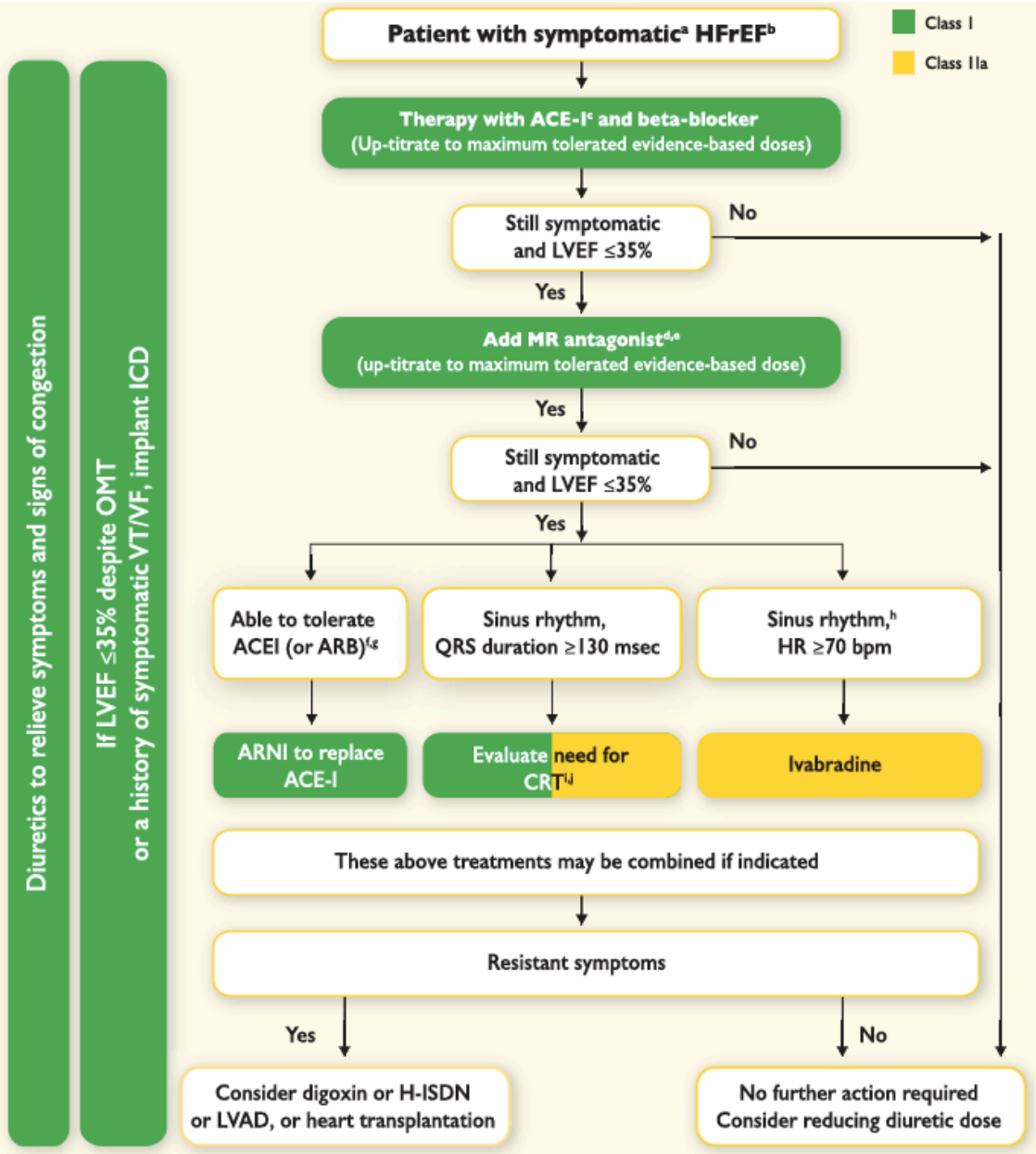
Case - Diagnosis



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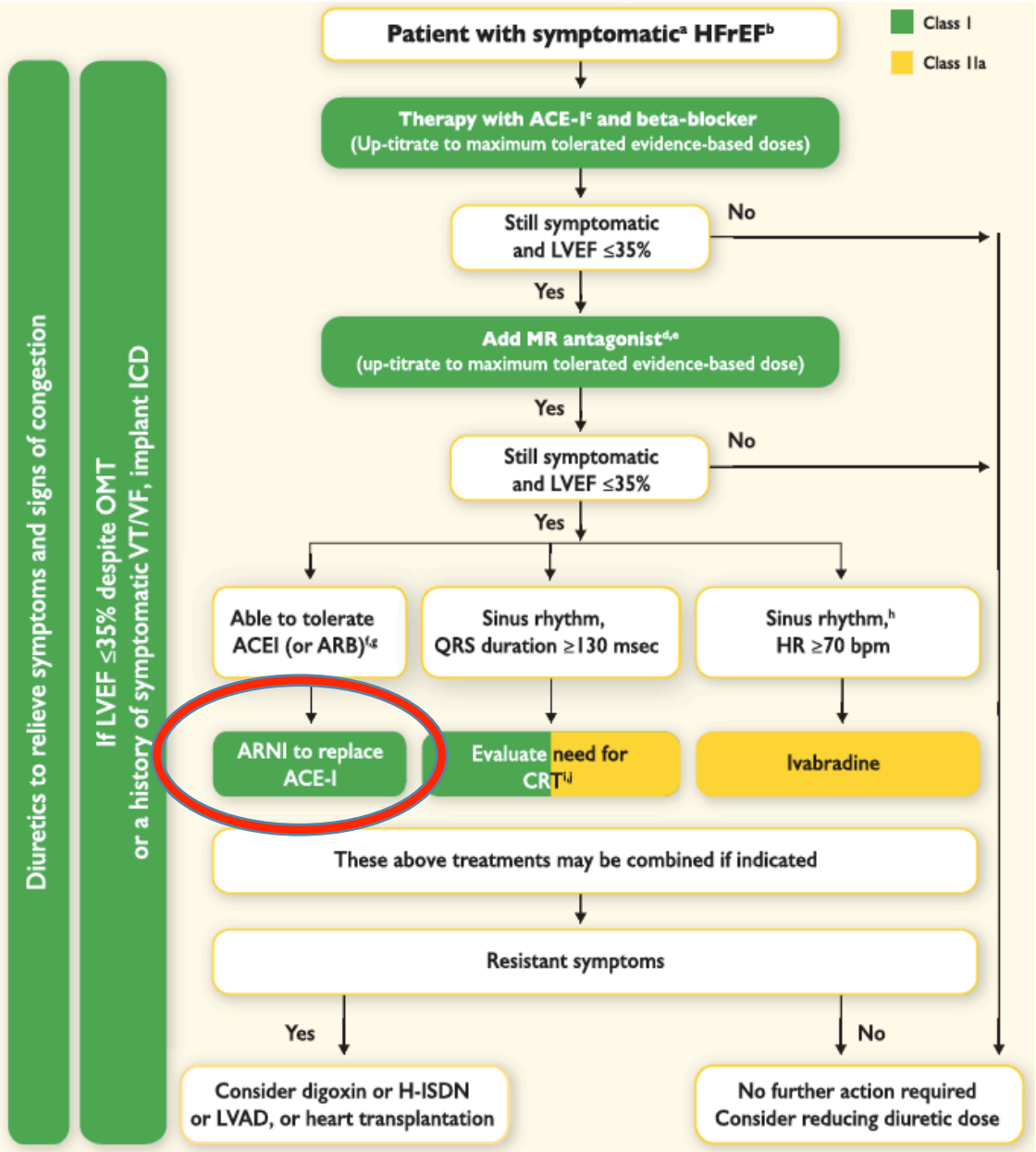
Case - Diagnosis



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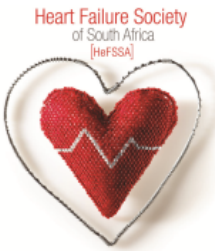
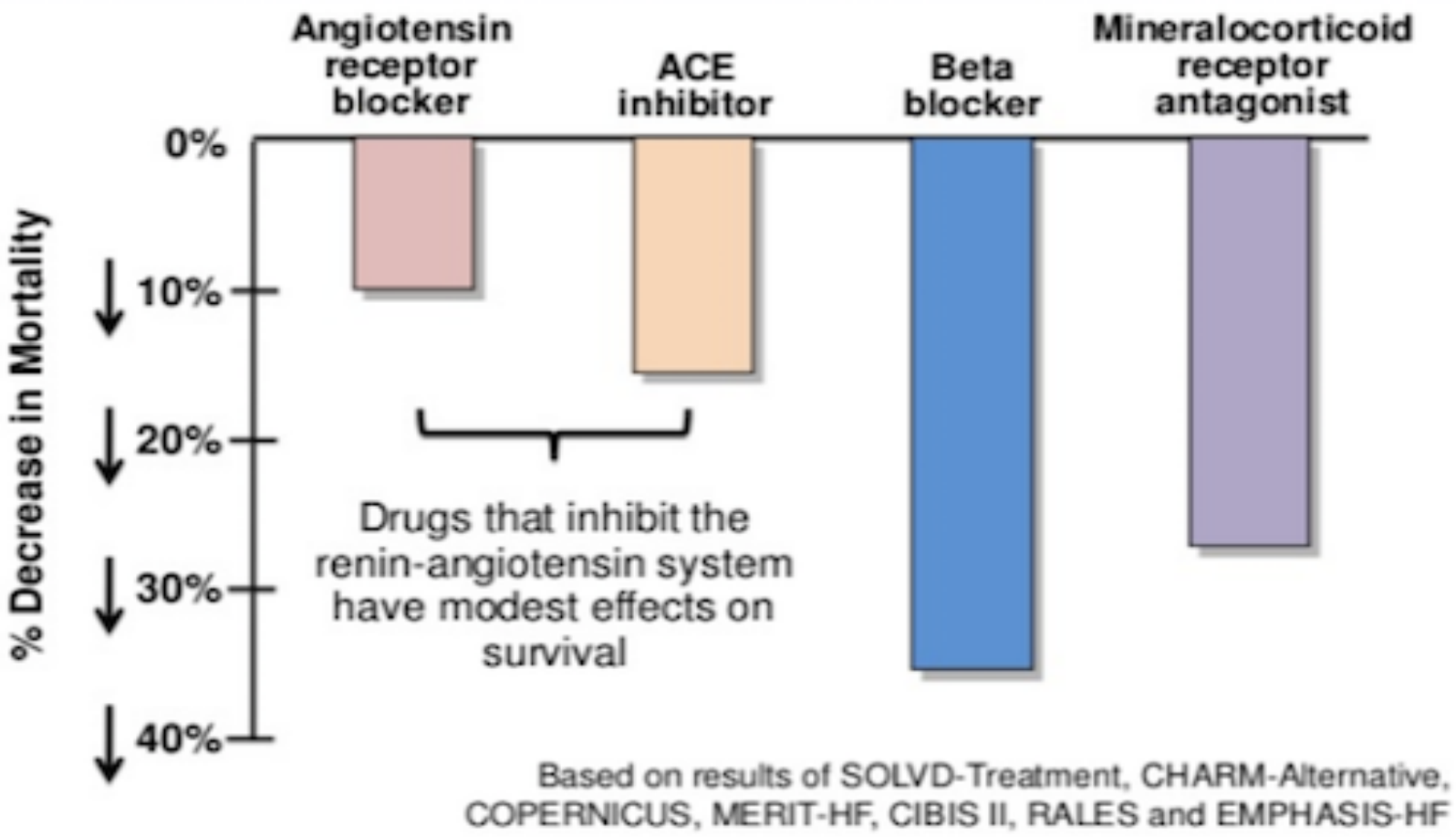
What is new in Heart Failure?



Drugs that reduce mortality in HFrEF



Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

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Case - Diagnosis

ARNI

- Angiotensin Receptor
- – Neprilysin Inhibitor

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Neprilysin Inhibition potentiates Actions of Vasoactive Peptides beneficial in Heart Failure

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

→

- ⬇ Neurohormonal activation
- ⬇ Vascular tone
- ⬇ Cardiac fibrosis, hypertrophy
- ⬇ Sodium retention

↓

Inactive metabolites

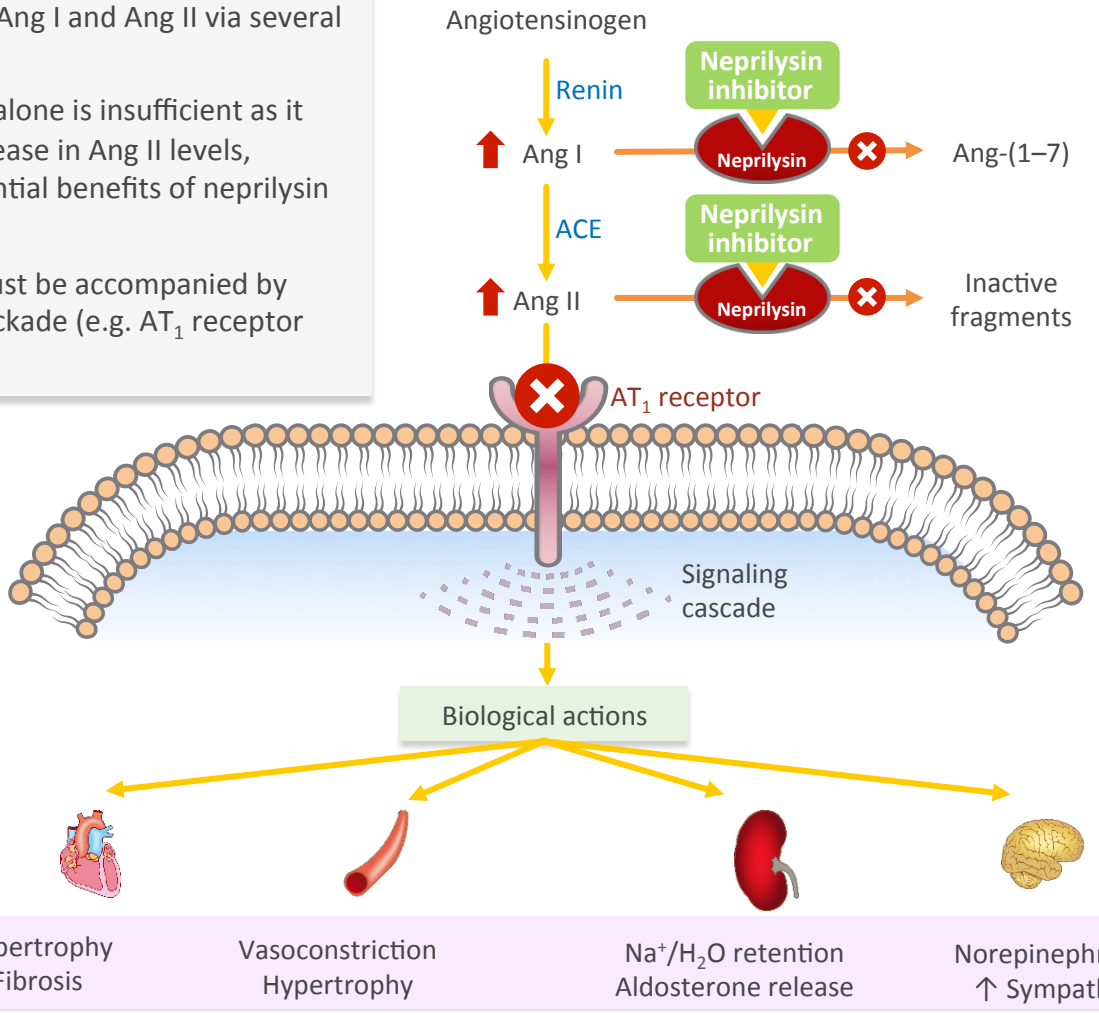
Neprilysin

←

Neprilysin inhibition

Neprilysin inhibition must be accompanied by simultaneous RAAS blockade

- Neprilysin metabolizes Ang I and Ang II via several pathways[1,2]
- Inhibition of neprilysin alone is insufficient as it associated with an increase in Ang II levels, counteracting the potential benefits of neprilysin inhibition[2]
- Neprilysin inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT_1 receptor blockade)[2]



ACE=angiotensin-converting enzyme; AT_1=angiotensin II type 1; Ang=angiotensin; H_2O=water; Na=sodium; RAAS=renin-angiotensin- aldosterone system

1. Von Lueder et al. Circ Heart Fail 2013;6:594–605
2. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

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Comparison of Omapatrilat and Enalapril in Patients With Chronic Heart Failure

The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)

Milton Packer, MD; Robert M. Califf, MD; Marvin A. Konstam, MD; Henry Krum, MBBS, PhD; John J. McMurray, MD; Jean-Lucien Rouleau, MD; Karl Swedberg, MD; for the OVERTURE Study Group*

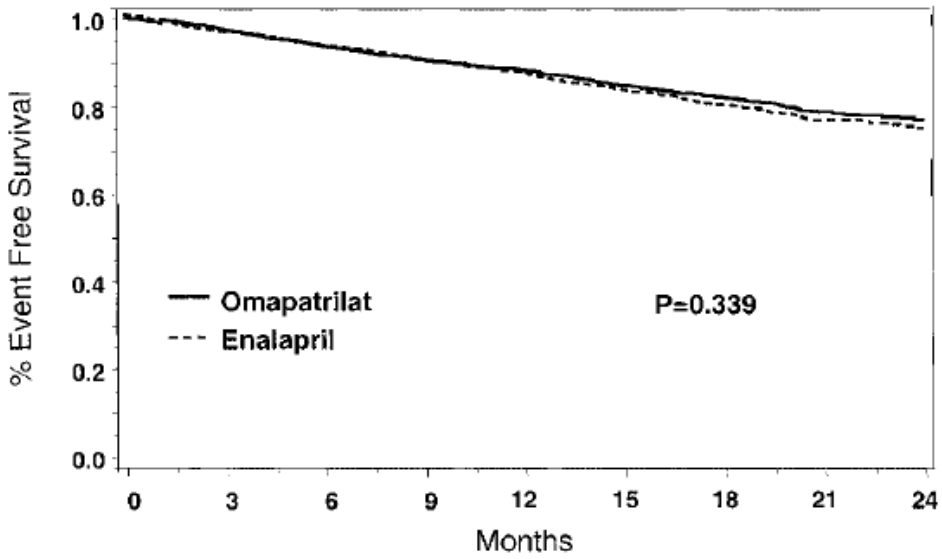

Figure 2. Kaplan-Meier analysis of time to death in the omapatrilat or enalapril groups.

Ultimately not approved due to increased risk of angioedema and no significant clinical benefit.

Circulation. 2002;106:920-926.

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The NEW ENGLAND JOURNAL of MEDICINE

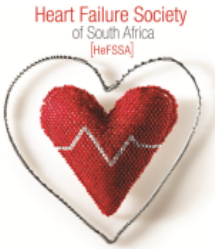
ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

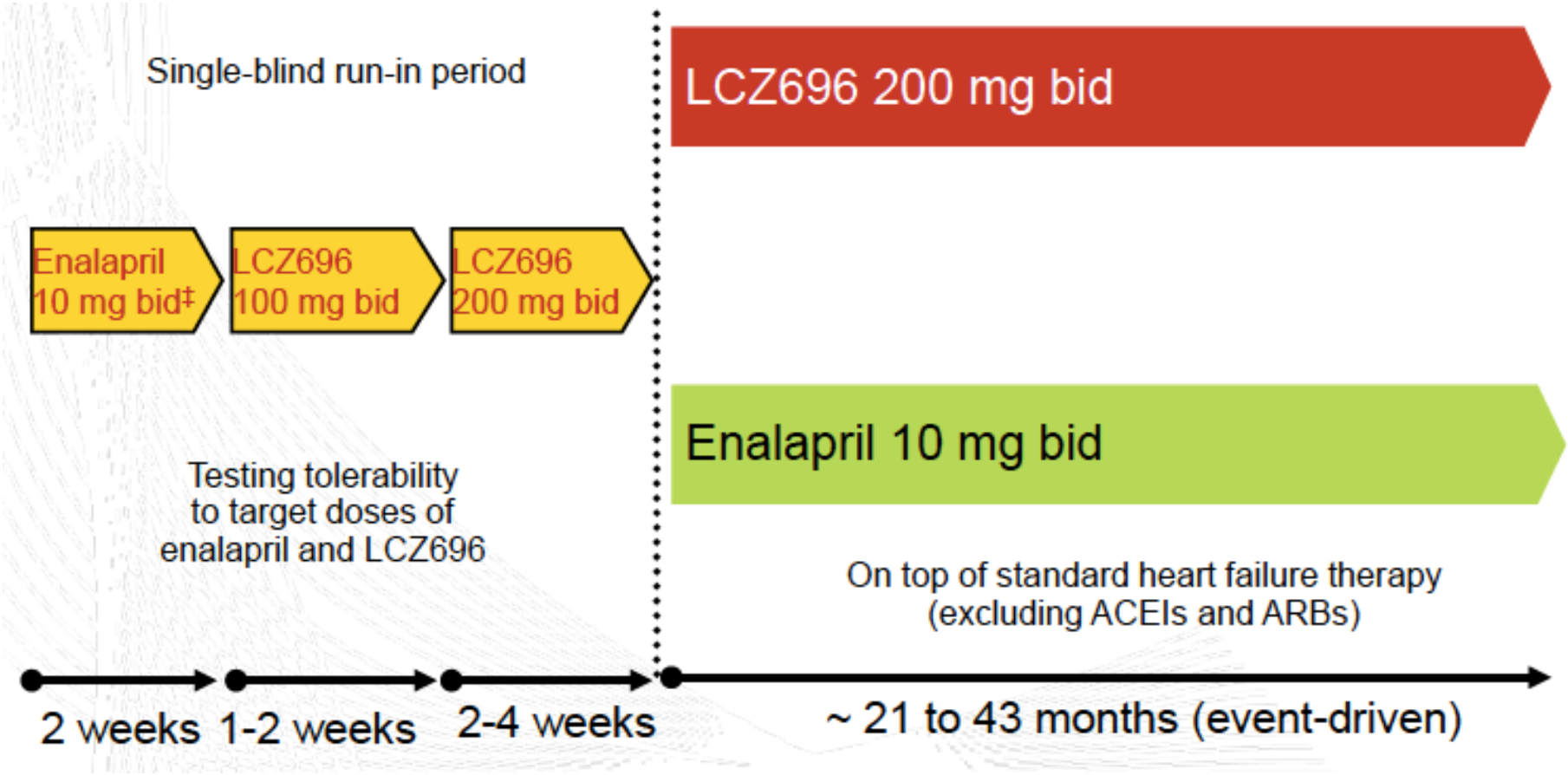
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

How was the trial done?

- 8442 patients
- Class II - IV heart failure
- EF <40%
- LCZ696 vs enalapril 10 mg bd
- Median follow-up 27 months – trial stopped early
- Run in period: all patients stopped the ACE-I or ARB they were on and were then given enalapril for 2 weeks – if they tolerated this they were then given LCZ696 for 4 weeks and if they tolerated this they were then entered into the trial and randomised to either LCZ696 or enalapril





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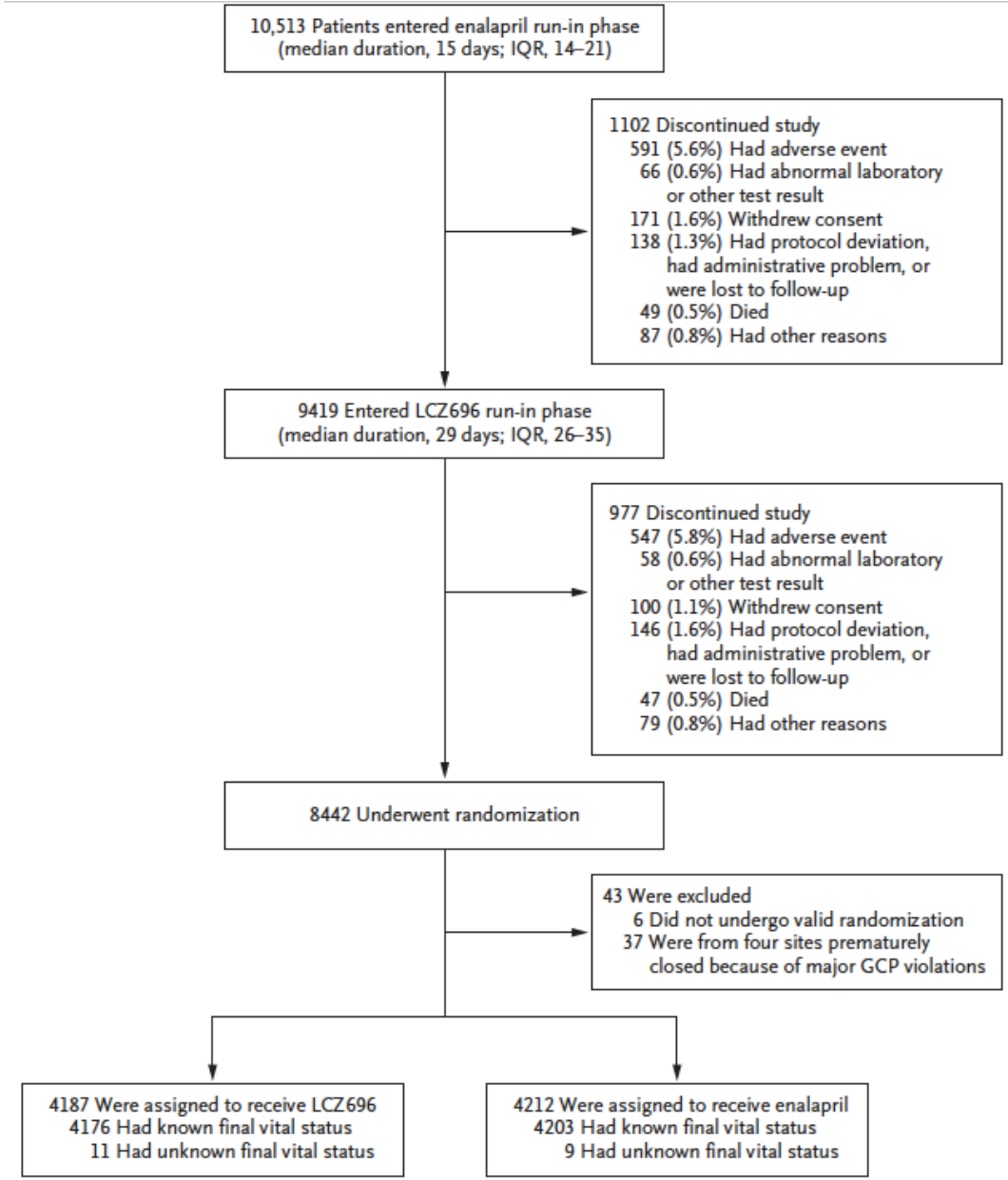
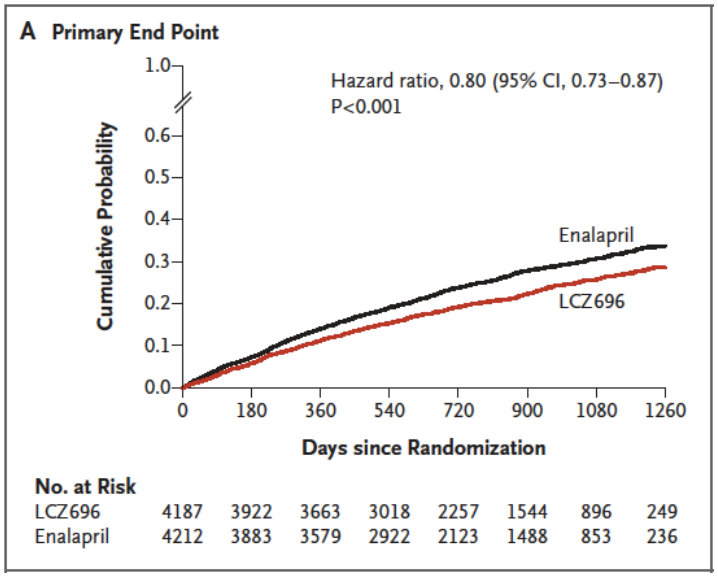
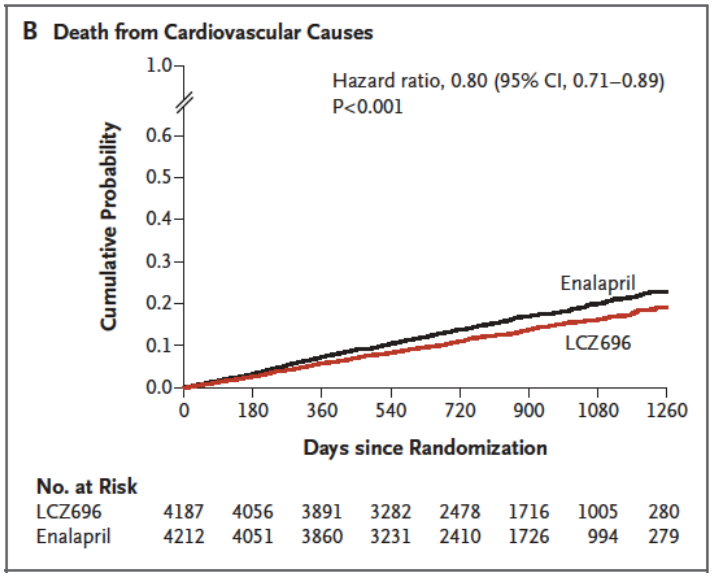
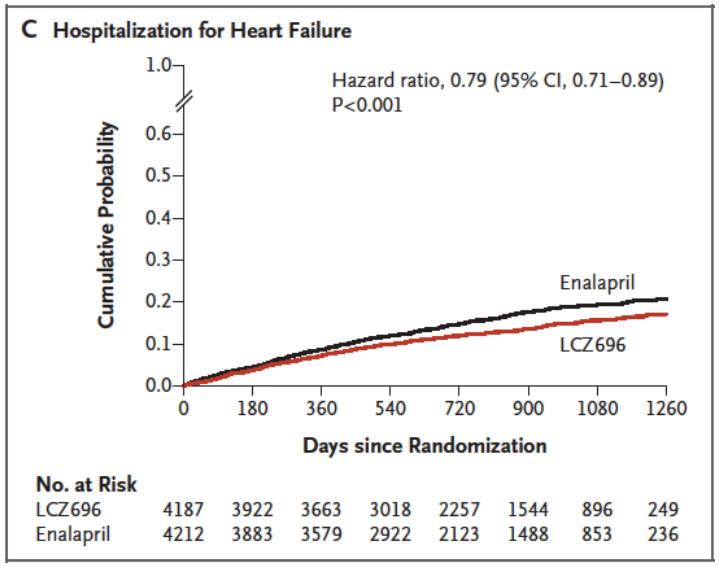
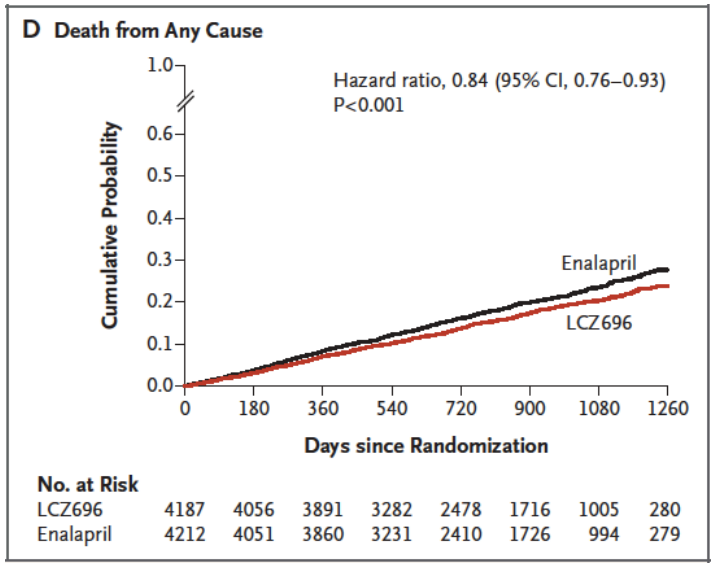


Case - Diagnosis









N Engl J Med 2014; 371: 993 - 1004

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Switching 1000 patients from an ACE inhibitor/ARB to LCZ696 avoided:

47 primary endpoints

31 cardiovascular deaths

28 patients hospitalized for HF

37 patients hospitalized for any reason

111 admissions for any reason

over a median treatment period of 27 months

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PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P-value
Prosepctively identified adverse events			
Symptomatic hypotension	588	388	<0.001
Serum potassium >6 mmol/L	181	236	0.007
Serum creatinine >220 mmol/L	139	188	0.007
Cough	474	601	<0.001
Discontinuation for adverse event	449	516	0.02
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalaemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema			
Medications, no hospitalisation	16	9	NS
Hospitalised, no airway compromise	3	1	NS
Airway compromise	0	0	N/A

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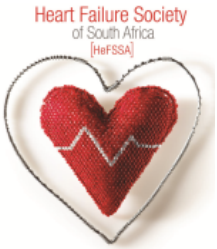
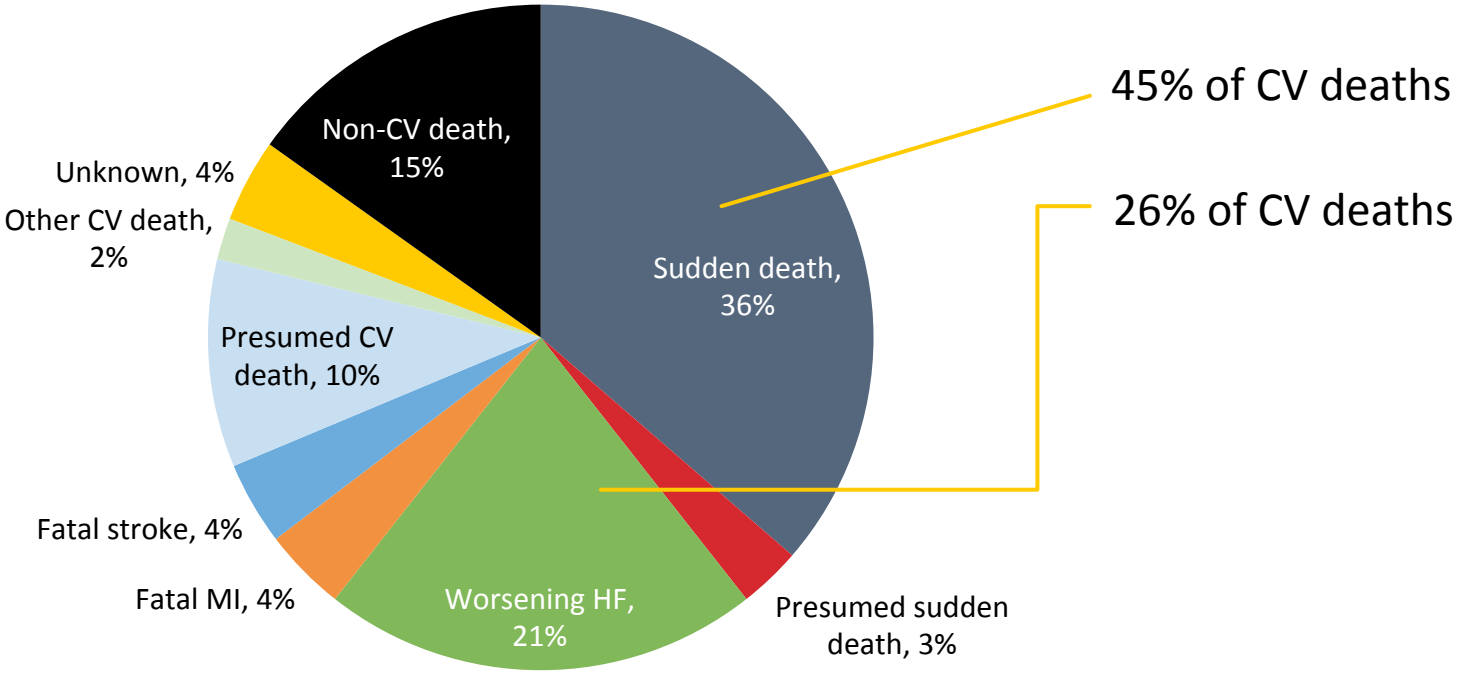
Should stable patients be switched?



In the PARADIGM-HF trial, CV causes accounted for 81% of all deaths



ACEI=angiotensin-converting-enzyme inhibitor; ARNI=angiotensin receptor neprilysin inhibitor; CV=cardiovascular; HF=heart failure; MI=myocardial infarction; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

Desai et al. Eur Heart J 2015; DOI: 10.1093/eurheartj/ehv186

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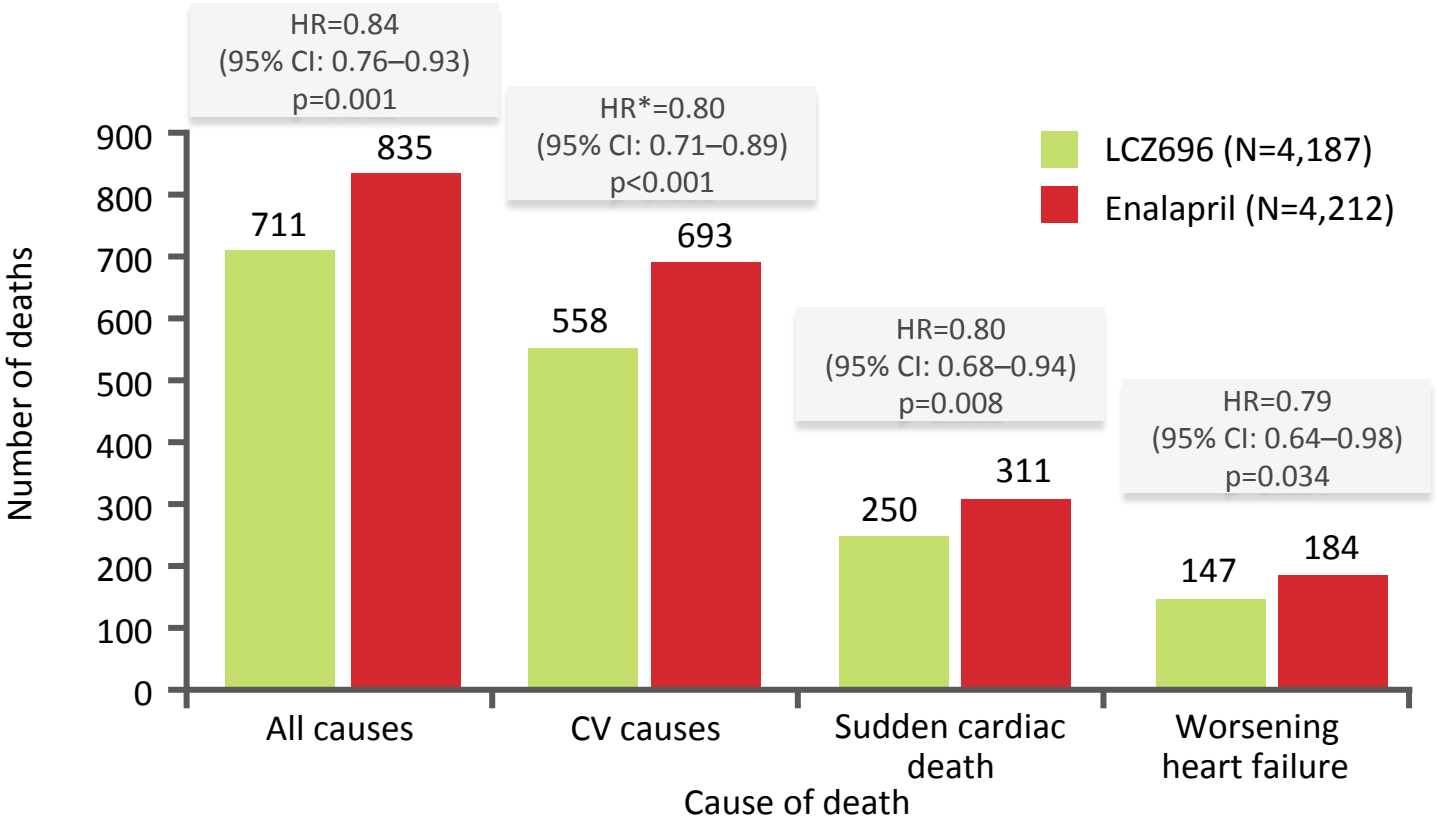
Summary



- The majority (>80%) of deaths in PARADIGM-HF had a CV cause[1]
- The mortality benefit of LCZ696 is related to the observed reduction in sudden cardiac death and death due to worsening heart failure[1]
- This distribution of cause of death in PARADIGM-HF is comparable to recent HFrEF trials[2]

*Results from death from CV causes as per those reported by McMurray et al. Note that the hazard ratio reported by Desai et al. was HR=0.80 (95%CI: 0.72–0.89); p<0.001

1.Desai et al. Eur Heart J 2015; DOI:10.1093/eurheartj/ehv186;
2.O'Connor et al. Am J Cardiol 1998;82:881–7

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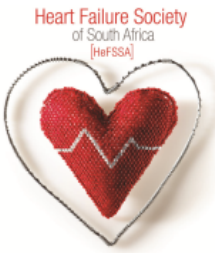
Some practical issues….

- The drug should be titrated upwards carefully as performed in the trial
- The drug was only evaluated in patients who had stable CCF (chronic)
- The drug was only evaluated in patients who did tolerate enalapril 10 mg 2x/day (in the run-in period) – Is it safe in other scenarios?
- ARNI - depending on lab assay may possibly result in elevated BNP measurements at follow-up due as they prevent the breakdown of BNP
- Watch out for hypotension
- Due to the risk of angioedema with neprilysin inhibition allow for a 3 day period between stopping patients ACE-I and starting ARNI



Specific HF patient subgroups representing a "challenge" for the implementation of LCZ696 in clinical practice

- Low blood pressure
- Hospitalized for AHF
- NYHA IV class / Advanced heart failure
- ACEi-naïve patients
- Intolerance to ACEi or ARB
- Low ACEi dose

- High ACEi dose
- Tolerant to low dose of ARNI
- Renal function worsening on ARNI

Modified from Filippatos G, et al. BMC Medicine 2015

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

1) Currently available in Europe and North America

Available in SA under Section 21

Approval of MCC hopefully 2017

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Thank you!