10th BSH Heart Failure Day for Revalidation and Training 2018

Presentation title: ACEis, ARBs and ARNIs; when should we be using sacubitril /valsartan?

Speaker: Dr Lisa Anderson

Conflicts of interest: 2015 Novartis Research nurse funding for RELAX-EU trial

ACE- and ARBs

- Renin-Angiotensin-Aldosterone system inhibition is cornerstone of HF therapy since CONSENSUS 1987
- Mortality benefit of ACE- in HFrEF well established
- Mortality benefit of ARBs less consistent
  - Candesartan reduced CV mortality by 16% in CHARM 2004 (55% on ACE-)
  - Valsartan no effect on mortality (but reduced HF hosp) Val-HEFT 2001 – (92% on ACE-)

PARADIGM-HF

Stopped early at 27 months as benefit boundary crossed

20% reduction in PEP of CV death/HF hosp (p=0.0000004)

16% reduction in death any cause

20% reduction in CV death

21% reduction in HF hosp

Sacubitril Valsartan Development

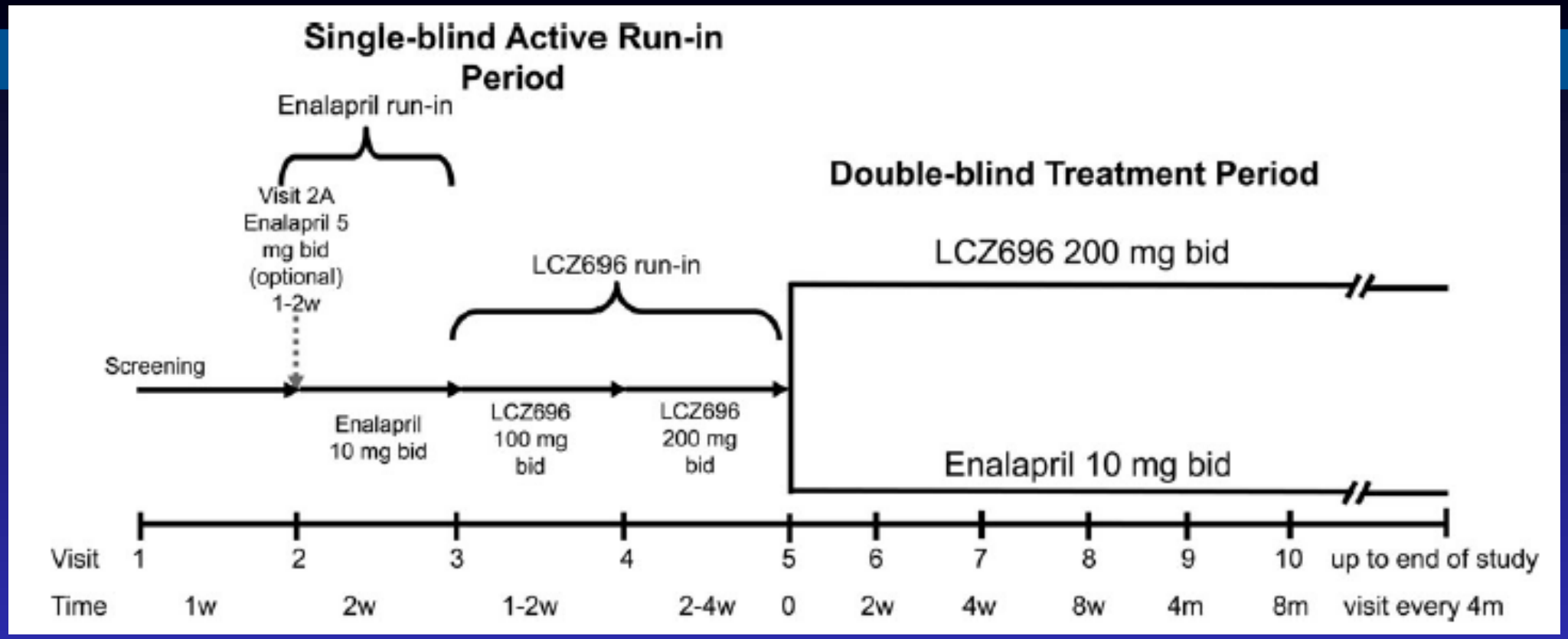
- Sacubitril = Neprilysin inhibitor
- Neprilysin = endopeptidase that degrades
  - NPs
  - Bradykinin
  - Adrenomedullin (vasodilator, natriuretic)
- But earlier NIs had short lasting effect on BP as neprilysin also ↑angiotensin II levels in addition to ↑natriuretic peptides
- →→combined ACE- and NI
- But Omapatrilat (NI and ACE-) development discontinued due to high rates of serious angio-oedema as both inhibit bradykinin breakdown

Sacubitril Valsartan

- Sacubitril metabolised to sacubitrilat (active metabolite)
- Sacubitril increases BNP level – not useful for monitoring
- NTproBNP (inactive terminal) not affected

Paradigm-HF

- 10521 patients entered single-blind run-in periods
- 8442 patients (80%) tolerated both → randomized
- 28 March 2014 DMC notified PIs that the boundary for overwhelming benefit had been crossed.
- At the time the study was terminated, enrolment completed and median FU = 27m



Criticisms:

Design does not allow for full safety assessment

No information on ACE/ARB naïve patients

Relatively low dose of enalapril cf valsartan 160mg bd

BP lower by 3.2mmHg in SV group

FDA Conditions for Approval

- Novartis required to conduct an observational registry to further clarify the risk of angioedema in black patients

- Neprilysin plays a role in removing amyloid-beta peptides from the brain.
- Novartis required to conduct an RCT to evaluate the effects of sacubitril/valsartan vs. valsartan on cognitive function. (New Drug Application 207620 Approval accessdata.fda.gov).

What do the guidelines say?

NICE Guidelines TA 388 April 2016

- 1 Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people:
  - with New York Heart Association (NYHA) class II to IV symptoms and
  - with a left ventricular ejection fraction of 35% or less and
  - who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs)

- 2 Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team.

Scottish Medicines Consortium

Providing advice about the status of all newly licensed medicines

www.scottishmedicines.org.uk

Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

NHS SCOTLAND

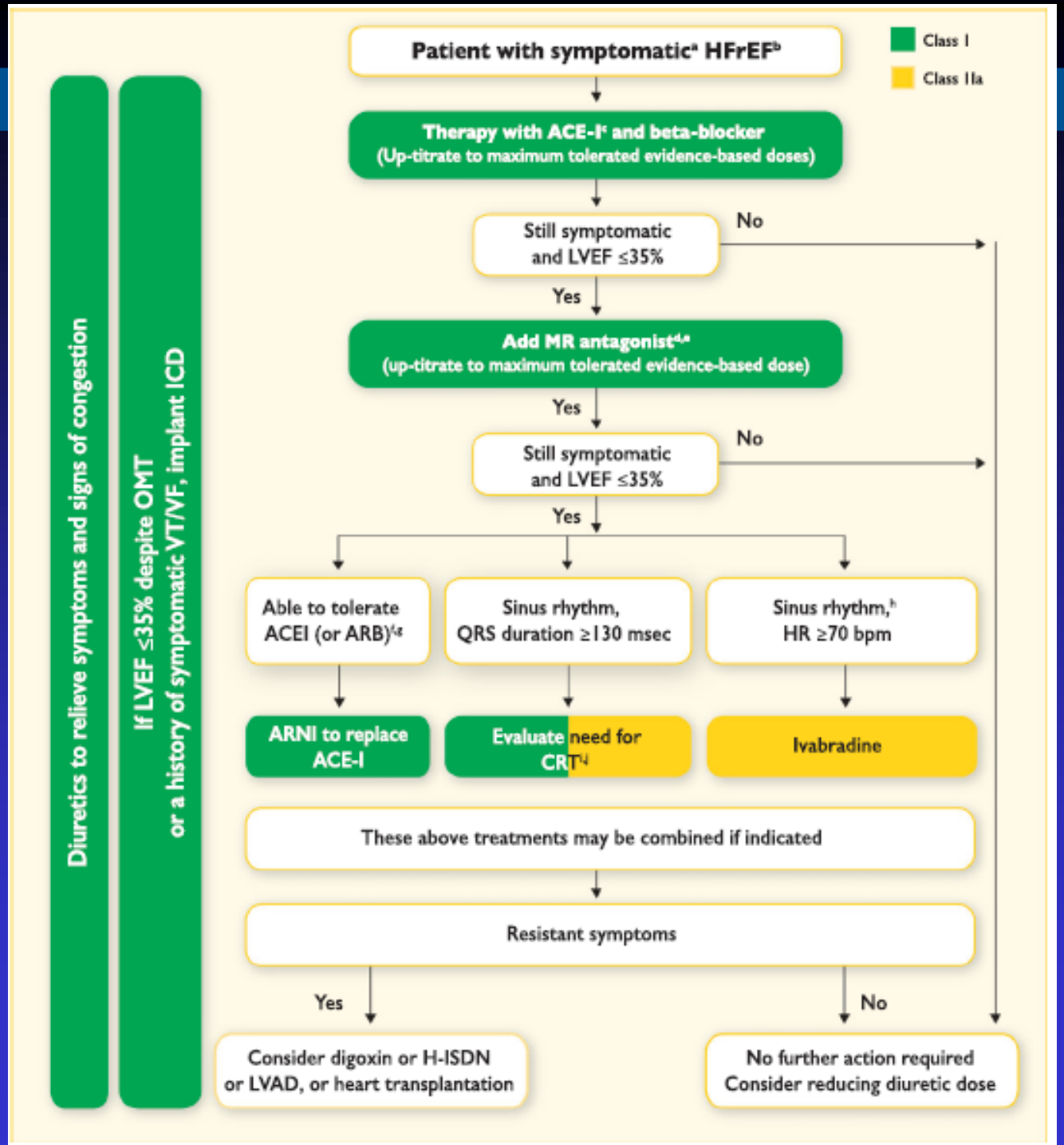
sacubitril/valsartan 24mg/26mg, 49mg/51mg and 97mg/103mg film-coated tablets (Entresto®) SMC No. (1132/16)

Novartis Pharmaceuticals UK Ltd

05 February 2016

- **Indication**
- In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

ESC 2016 Guidelines



What were the study patients like?

- Inclusion criteria
  - Adults stable HF NYHA II-IV
  - LVEF ≤40% (Dec 09-10) → ≤35% (Dec 10-Nov 12)
  - BNP>150, NTproBNP>600ng/L (400 if hosp <12m)
  - ACE/ARB equivalent of enalapril 10mg bd stable 4/52
- Exclusion criteria
  - BP <100mmHg
  - GFR <30ml/min
  - K >5.2 mmol/l
  - Angio-oedema/ ACE- side effects

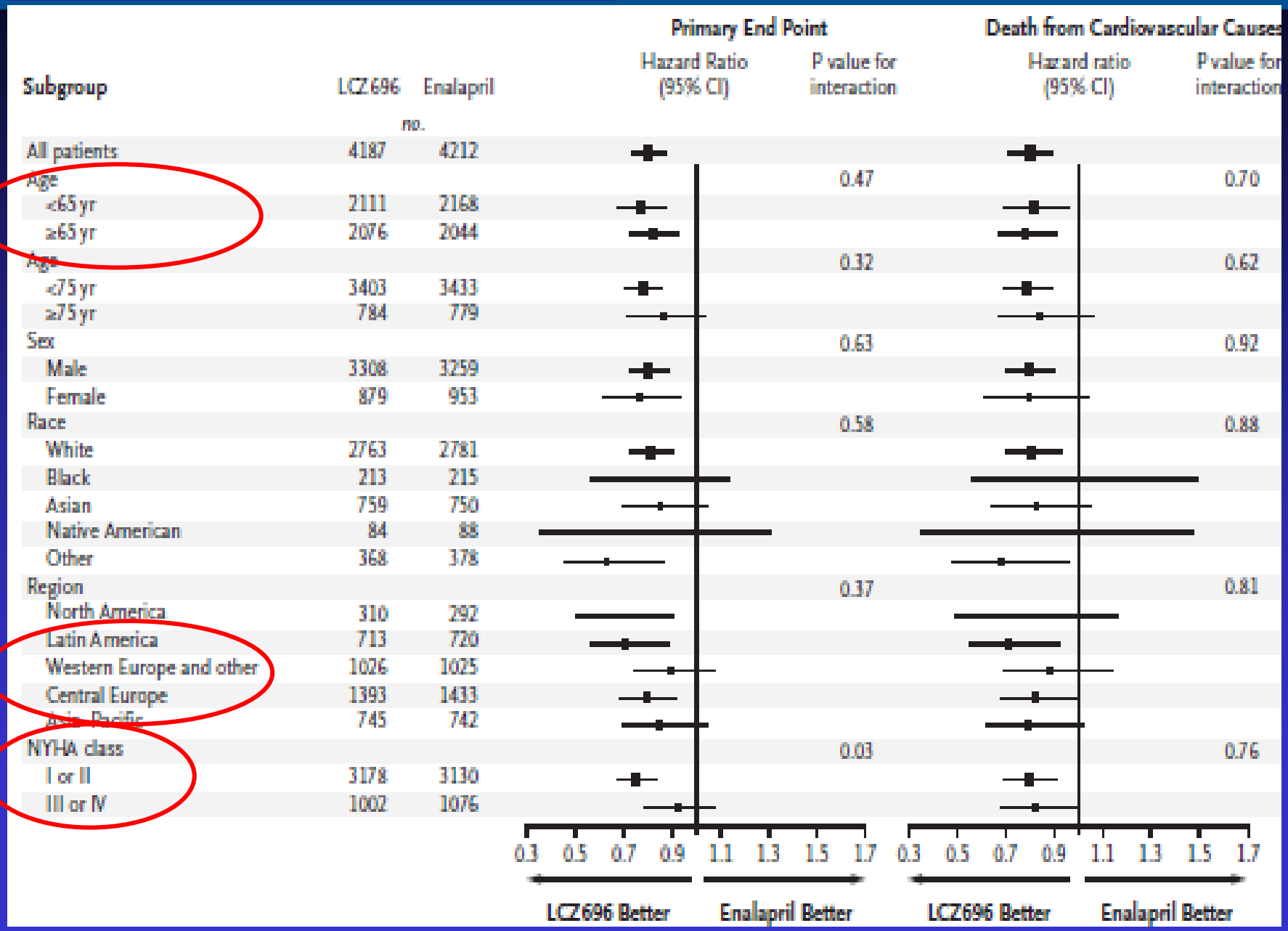
Adverse Effects

- Symptomatic hypotension in 14% SV group cf 9.2% ($p<0.001$)
- Angio-oedema 0.4% SV group cf 0.2% NS
- Elevated creatinine or K less frequent in SV group

Characteristics of Patients in Trial

- Age 63.8 ± 11 years
- 79% male, 66% caucasian (only 5% black)
- Systolic BP 122mmHg (on enalapril 10mg bd)
- PMH: Hypertension in 71%
- NYHA
  - II 71%
  - III 23%

Who benefitted most?



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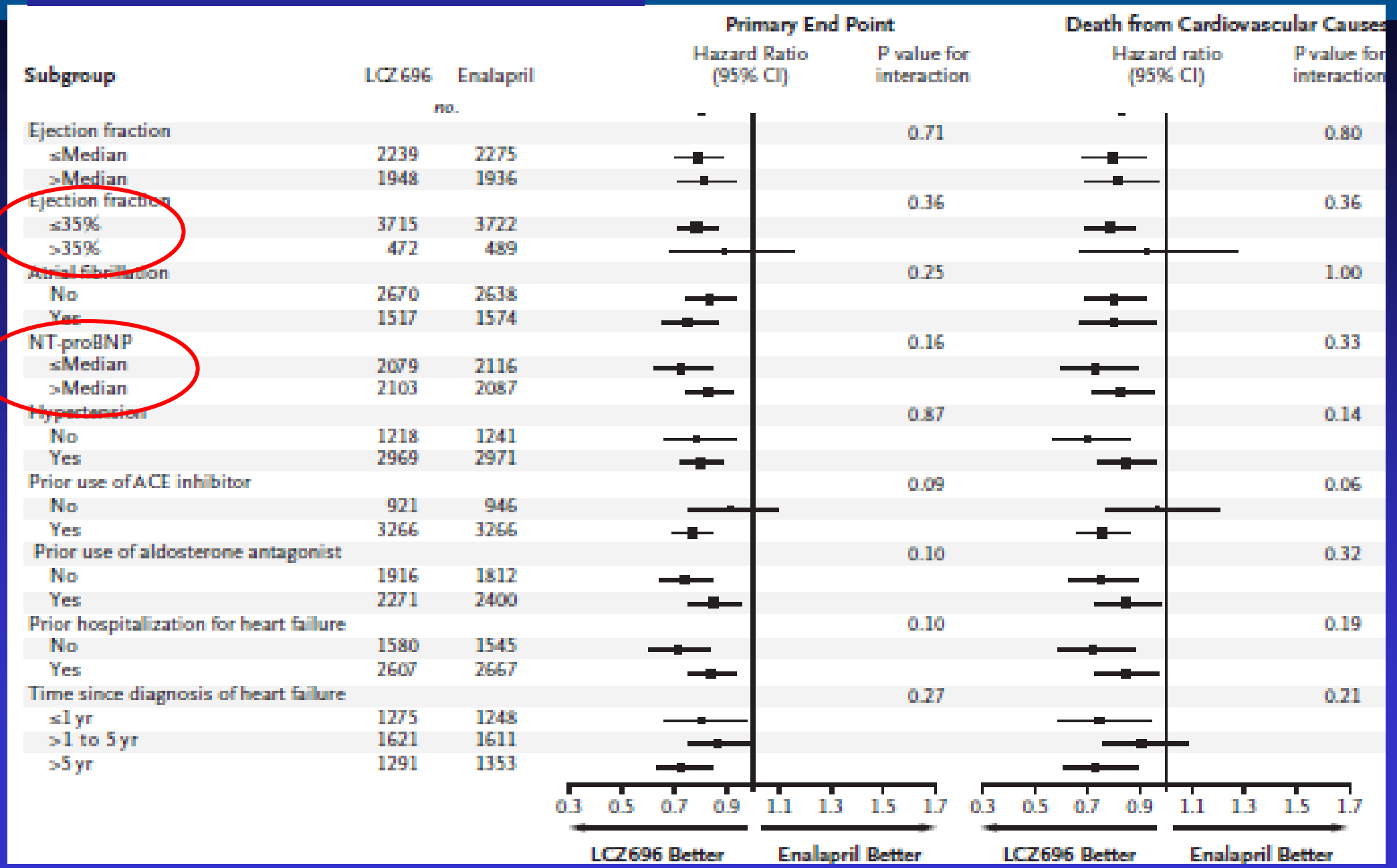


Most Likely to Benefit?

- Stable HF
- NYHA II
- Severe LVSD
- Good BP on high dose ACE-/ARB
- Less comorbidities

….these patients may not be encountered in hospital HF clinics, so active identification and dedicated SV clinics are most likely to be effective

Sacubitril Valsartan and Diabetes

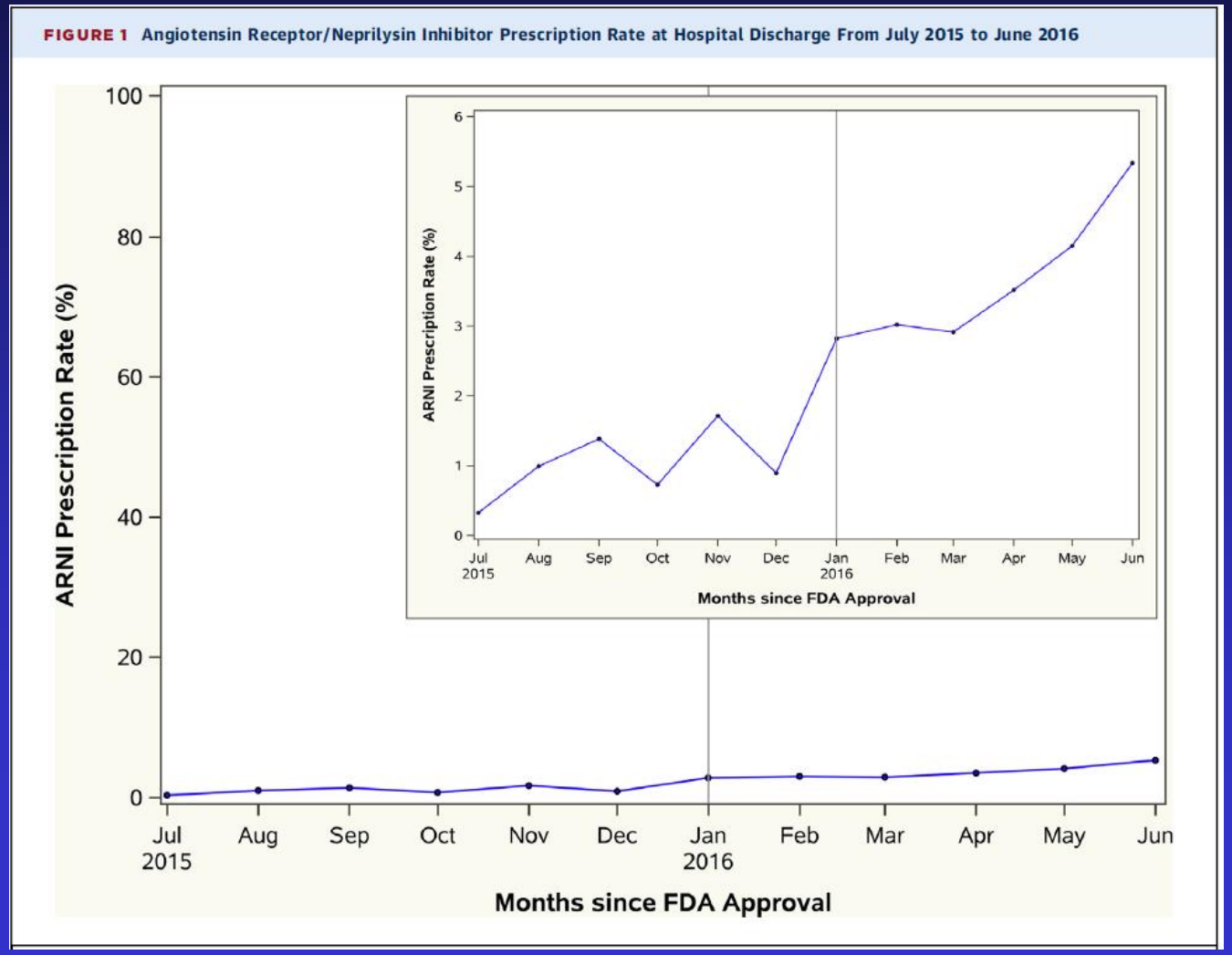
- Fewer patients treated with sacubitril/valsartan than enalapril were initiated on insulin during FU
- Greater reduction in HbA1c was also seen compared to enalapril
- May be related to specific effects of neprilysin inhibition on enhancing insulin sensitivity

Where there isn't evidence

- Hospitalised patients…..(PIONEER-HF study)
- Acute MI….(PARADISE-MI)
- Newly diagnosed HF-REF
- HFPEF ..(PARAGON-HF)

Uptake of Sacubitril Valsartan

- UK date >60% community HF clinic eligible for ARNI therapy. (Pellicori EHJ 2015)
- In contrast, only 2.3% of patients hospitalised for HF in 12 months following FDA approval commenced on SV in US.



Example checklist for consideration when implementing NICE technology appraisal guidance on sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction

Grey boxes indicate criteria recommended in the NICE technology appraisal. The electronic medicines compendium (EMC) and clinical advice from experts planning the implementation of this NICE technology appraisal have been used to add further detail to this checklist.

Service delivery model

Governance

Is the drug being started by a heart failure specialist with access to a multidisciplinary heart failure team?	
Has the most appropriate member of the multidisciplinary heart failure team responsible for monitoring and dose titration been identified?	

Drug initiation

Has the patient been taking a stable dose of ACE inhibitors or ARBs up to this time?	
If the patient has been taking an ACE inhibitor, has there been **at least** a 36-hour washout period?	
If the patient has been taking an ARB has it been stopped?	
Has the patient been advised of the common and very common side effects (including hypotension, renal impairment and hyperkalaemia; see table 1, Section 4.8 EMC) and how to report side effects for the yellow card scheme.	

Maintenance

Have the plans for ongoing management in relation to sacubitril valsartan been communicated with the GP? If so by what means? • local shared care protocol • written letter detailing initiation of the drug and management plans.	

Patient selection

Exclusion criteria

If any of the following patient criteria are true, the patient should **not** be offered sacubitril valsartan.

Criteria	Tick if true
Symptomatic chronic heart failure with reduced ejection fraction of greater than 35%.	
Symptomatic chronic heart failure with reduced ejection fraction and NYHA class I symptoms.	
Not taking a stable, optimised dose of ACE inhibitors or ARBs for at least 4 weeks.	
A history of angioedema related to previous ACE inhibitor or ARB therapy.	
Systolic blood pressure less than 100 mmHg.	
Severe hepatic impairment, biliary cirrhosis and cholestasis (Child–Pugh C classification).	
End-stage renal failure.	
Hereditary or idiopathic angioedema.	
Taking aliskiren-containing products and either Diabetes mellitus or renal impairment (eGFR less than 60 ml/min/1.73 m2).	
Pregnant or breastfeeding. Not recommended during the first trimester of pregnancy or when breast-feeding, and contraindicated during the second and third trimesters of pregnancy.	
Taking direct renin inhibitors such as aliskiren.	
Taking ACE inhibitors or ARBs for another indication which means they cannot be stopped.	
Less than 18 years old.	

Precautions and patient considerations

If any of the following precautions are relevant to the patient, detail the action to be taken below.

Precautions	Y / N	Action
Serum potassium level greater than 5.4 mmol/l.		
Moderate renal impairment. Dose adjustment may be needed at initiation.		
Severe renal impairment. Use with caution. Lower dose for initiation.		
Moderate hepatic impairment (Child–Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Dose adjustment may be needed.		
Renal artery stenosis. Monitor renal function.		
Driving vehicles or operating machines; has a minor influence on the ability to drive and use machines.		

www.nice.org.uk/guidance/ta388/resources

Practicalities

- Issues with stock – some Trusts keeping 1-2 months stock readily available to give to patients
- Despite local agreements some GPs refusing to take on prescribing
- Unfamiliarity – SV stopped in CCU in local DGH
- Ensure patients are well educated

Summary

- Sacubitril Valsartan more effective than enalapril 10mg bd
- Hypotension is more common, otherwise well tolerated
- Those with severe LVSD, NYHA II and good BP on ACE-, less co-morbidities are most likely to benefit
- In short-term the uptake rate is likely limited by workforce