Associate Professor Gerry Devlin

Clinical Cardiologist and Interventional Cardiologist

NZ Heart Foundation

Hamilton

Sunday, August 11, 2019

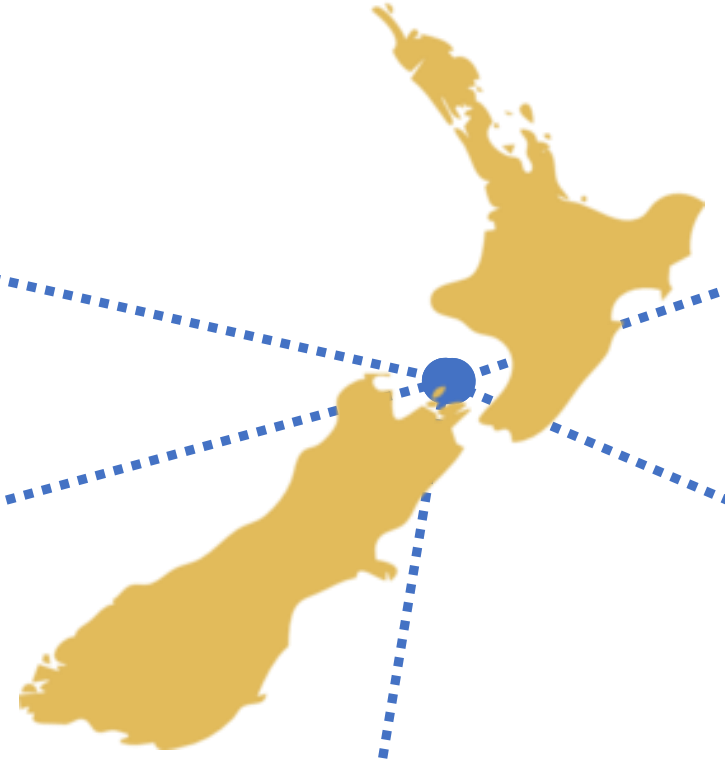
(Plenary)

7:15 - 8:25 Novartis Breakfast Session - An Update on Heart Failure

Heart failure affects a large number of New Zealanders each year, placing a significant burden on the healthcare system[1,2]

Est. 82,000 adults in New Zealand have heart failure 2016/17 [1]

Every 90 minutes a New Zealander dies from heart disease [2]



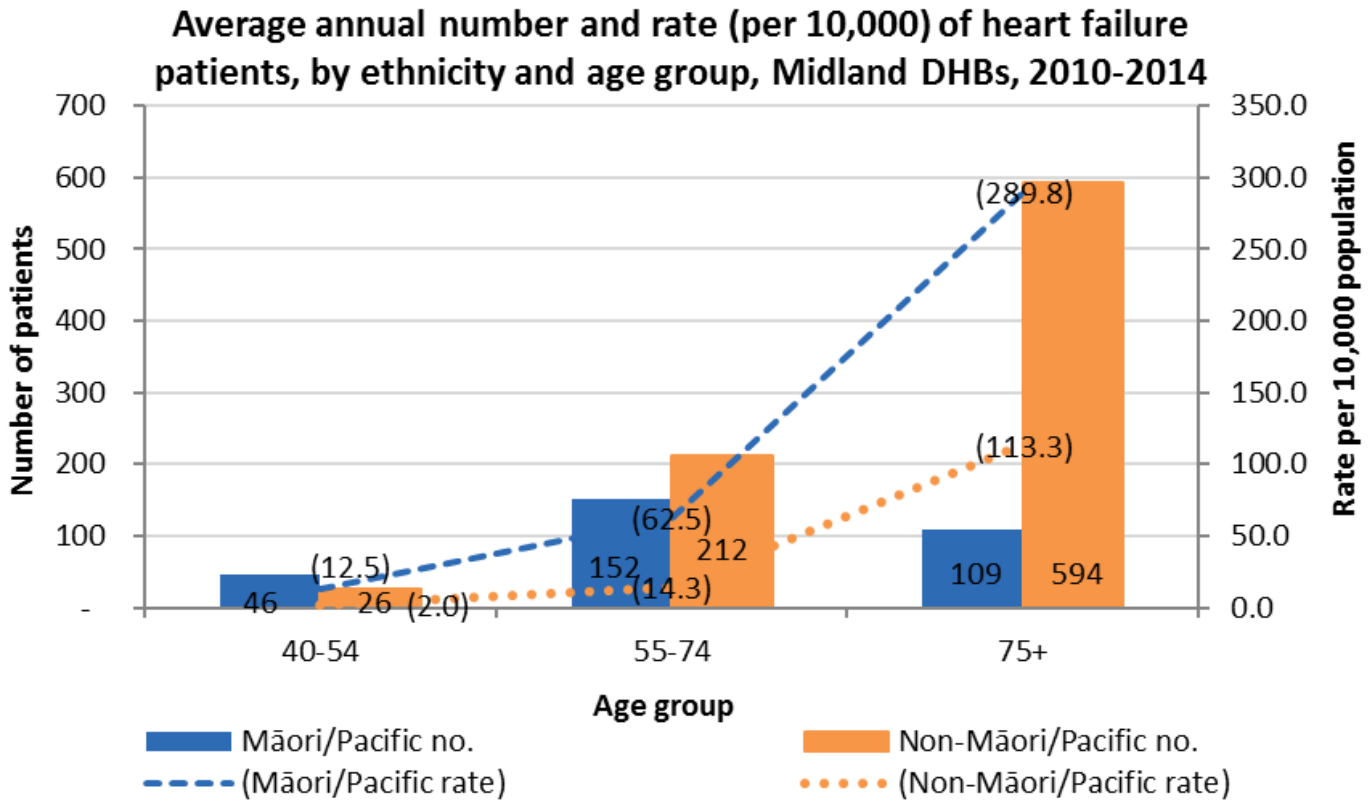
Higher prevalence in Maori & Pacific Islanders (2.5% and 2.6%) [1]

9,160 hospital discharges for HF in NZ in 2013/14 with an average stay of 15.4 days[3]

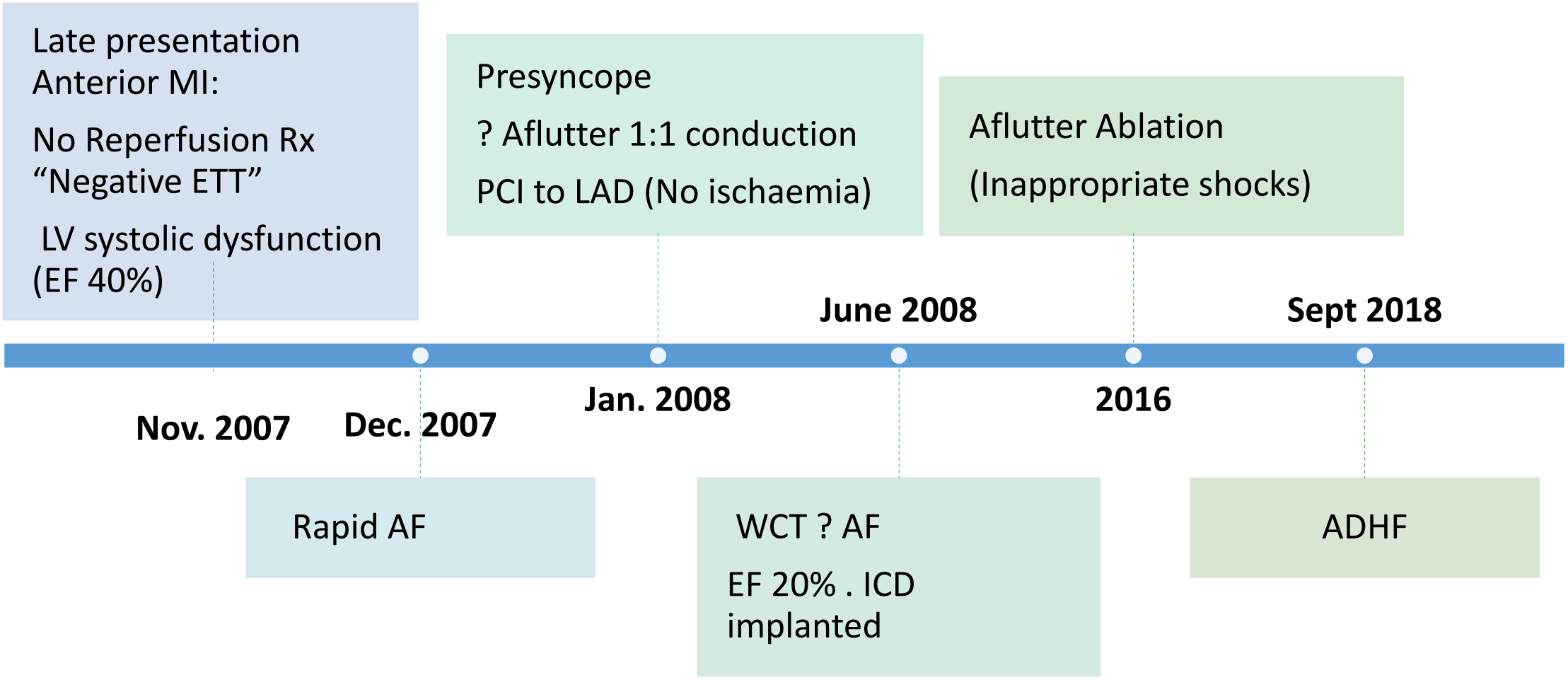
HF accounts for 1.5-2.0% of the total health budget [3]
(mainly driven by the costs of hospitalisations)

1. Ministry of Health - https://minhealthnz.shinyapps.io/nz-health-survey-2016-17-annual-data-explorer/_w_d4eef949/#!/explore-indicators
2. Heart Foundation – www.heartfoundation.org.nz/statistics
3. Ministry of Heath - https://www.health.govt.nz/publication/publicly-funded-hospital-discharges-1-july-2013-30-june-2014

Maori and Pacific 5 times more likely to be admitted with HF < 75



64 year old Maori man NYHA II symptoms



Co-Morbidities

- Type II DM
- Hypertension
- Overweight (BMI 48)
- OSAS

Nov 2018
NYHA II

- Perindopril 4 mg/day
- Spironolactone 50mg/day
- Bisoprolol 10 mg/day
- Digoxin PG III/day
- Metformin 1500mg BD
- PenMix Insulin
- Warfarin
- Frusemide 80 mg/day

Late 2018
NYHA II-III

BP 110/70

HR 76 (paced)

120 kg

Late 2018
NYHA II

NT pro-BNP 290 pmol/l

Creatinine 100umol/l

Severe LV Dilatation: EF 15%

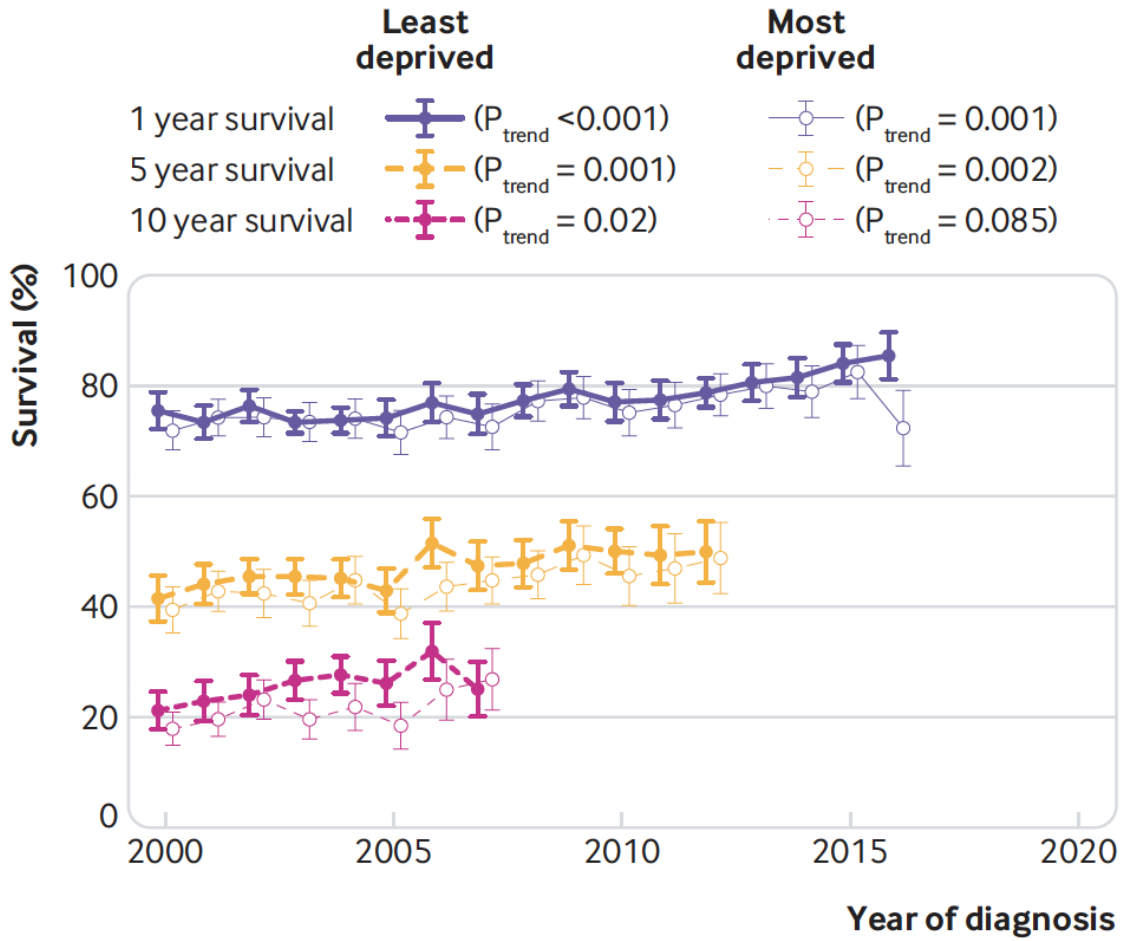
What Now?

Standard of care has been based on decades-old therapies

1. The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316(23):1429–35. 2. The SOLVD Investigators. *N Engl J Med* 1991;325(5):293–302. 3. The SOLVD Investigators. *N Engl J Med* 1992;327(10):685–91. 4. The CIBIS-II Investigators. *Lancet* 1999;353(9146):9–13. 5. MERIT-HF Working Group. *Lancet* 1999;353(9169):2001-–7. 6. Pitt B *et al. N Engl J Med.* 1999;341(10):709–17. 7. Cohn J *et al. N Engl J Med* 2001;345(23):1667–75. 8. Dargie HJ. *Lancet* 2001;357(9266):1385–90. 9. Packer M *et al. N Engl J Med* 2001;344(22):1651–8. 10. Granger CB *et al. Lancet.* 2003;362(9386):772–6. 11. Taylor AL *et al. N Engl J Med* 2004;351(20):2049–57. 12. Zannad F *et al. N Engl J Med* 2011;364(1):11–21.

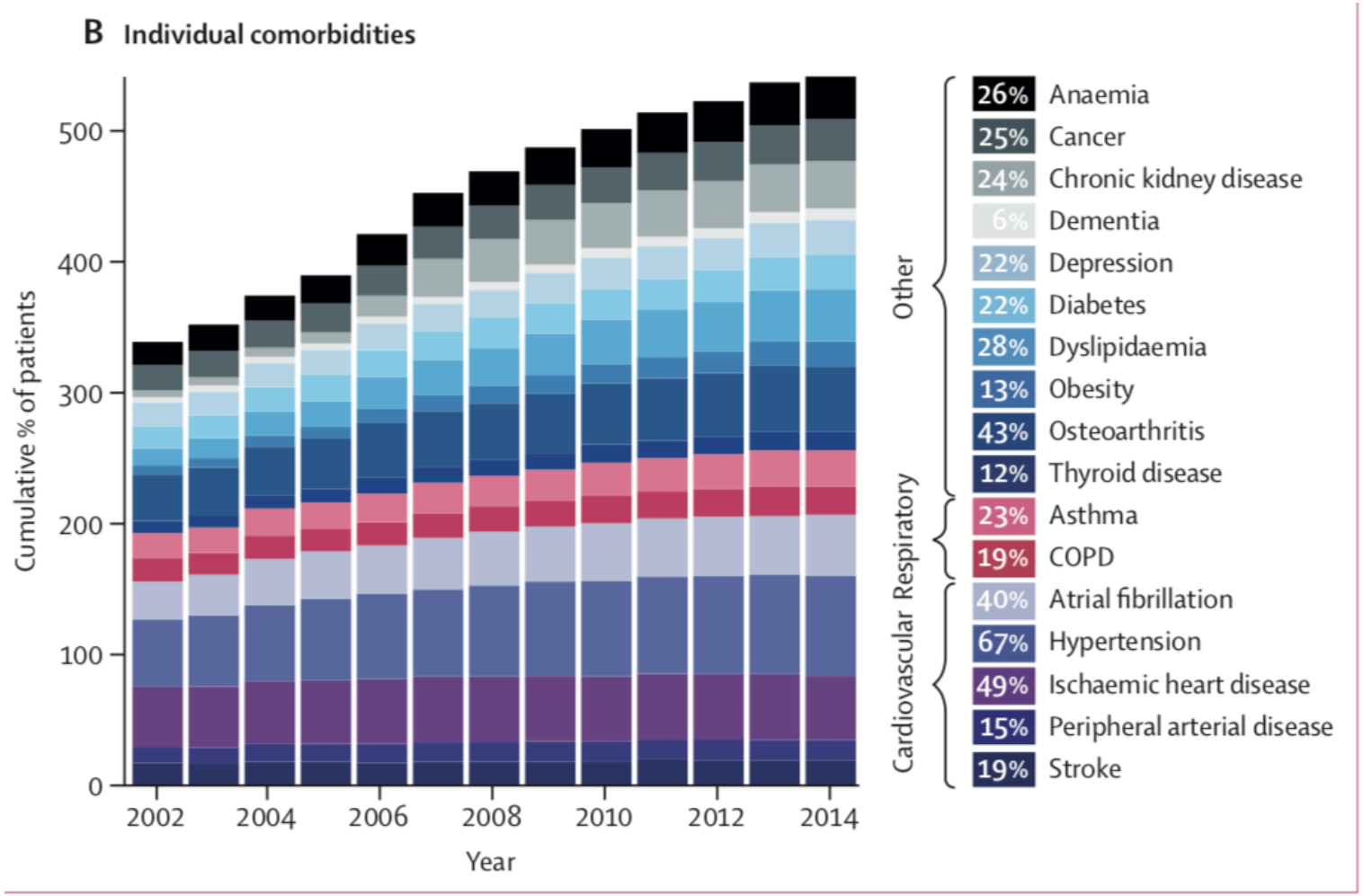
Improvement in survival since 2000 has been modest and socioeconomic inequalities persist

Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study



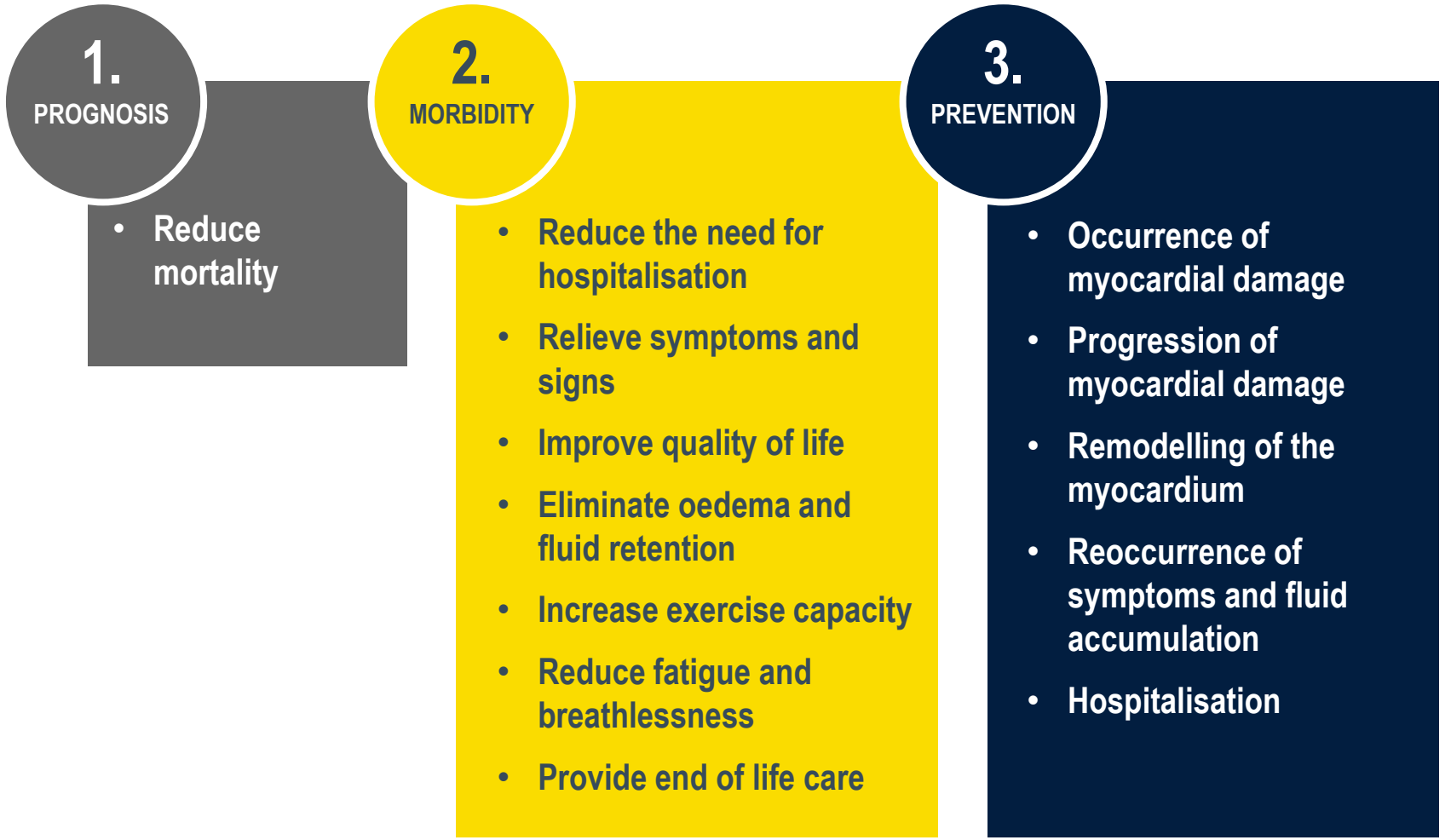
Taylor et al BMJ 2019;364:l223 | doi: 10.1136/bmj.l223

The Heart Failure patient is becoming more complex



Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals
The Lancet **http://dx.doi.org/10.1016/S0140-6736(17)32520-51**

The treatment objectives with chronic HF



HF: heart failure.

1.Dickstein K *et al*. *Eur Heart J* 2008;29:2388–442.

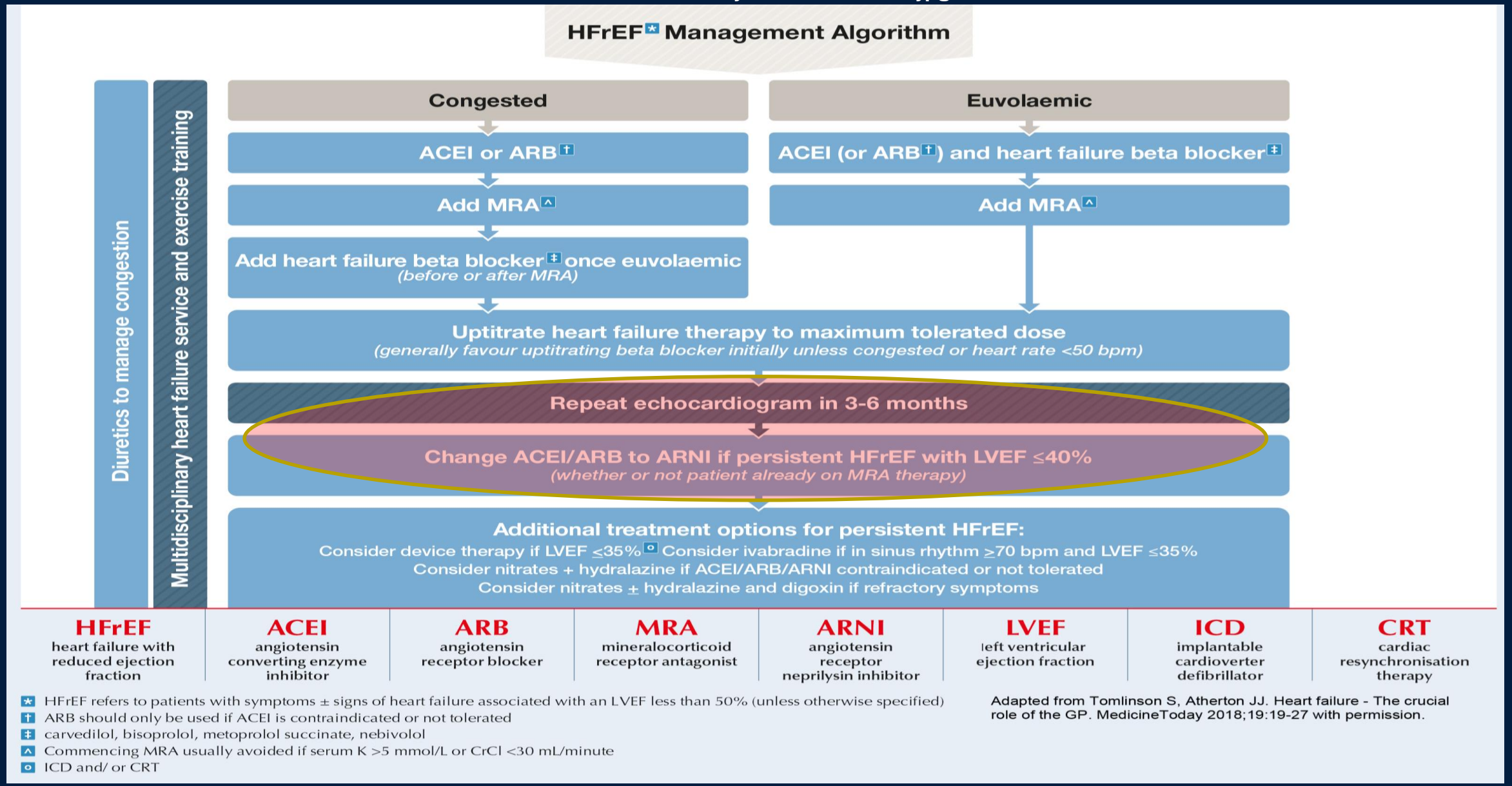
Adapted from Dickstein et al. (2008).[1]

Heart Failure Reduced EF (Class II-IV)

Recommendations	Class	Level
An ACE-I is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition an ACE-I, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

Updated CSANZ 2018 Guidelines

https://www.heartfoundation.org.au/images/uploads/publications/HF_Figure_3_Management_of_patients_with_heart_failure_and_reduced_ejection_fraction.jpg



PARADIGM-HF Trial

The NEW ENGLAND JOURNAL of MEDICINE

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

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

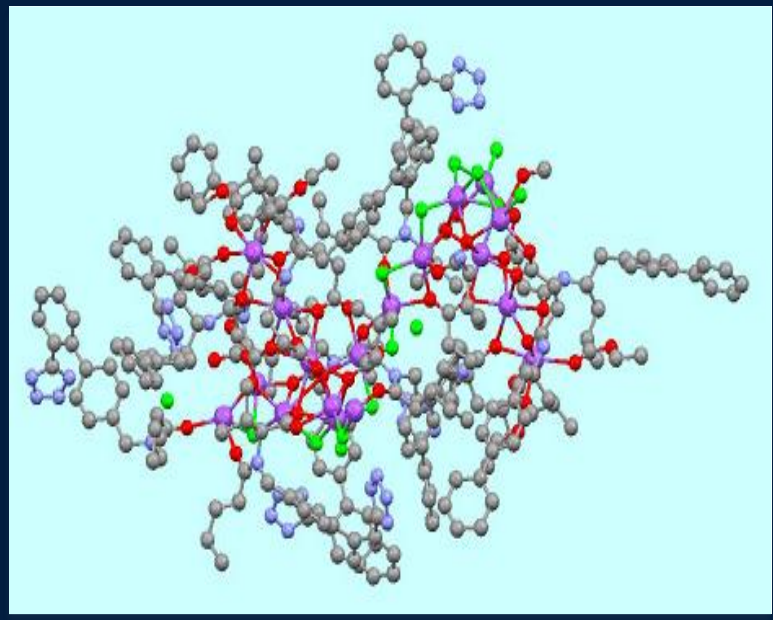
John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators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

(all comparisons are vs.
enalapril 10 mg bd, not versus placebo)

ENTRESTO® is a first-in-class angiotensin-receptor neprilysin inhibitor (ARNI)[1]

- ENTRESTO® is a novel drug which delivers simultaneous neprilysin inhibition and AT_1 receptor blockade[2–4]

- ENTRESTO® is a salt complex that comprises the two active components:[3,4]
  - sacubitril (AHU377) – a pro-drug; further metabolised to the neprilysin inhibitor, LBQ657, and
  - valsartan – an AT_1 receptor blocker
  - in a 1:1 molar ratio



ENTRESTO® 3D structure[3]

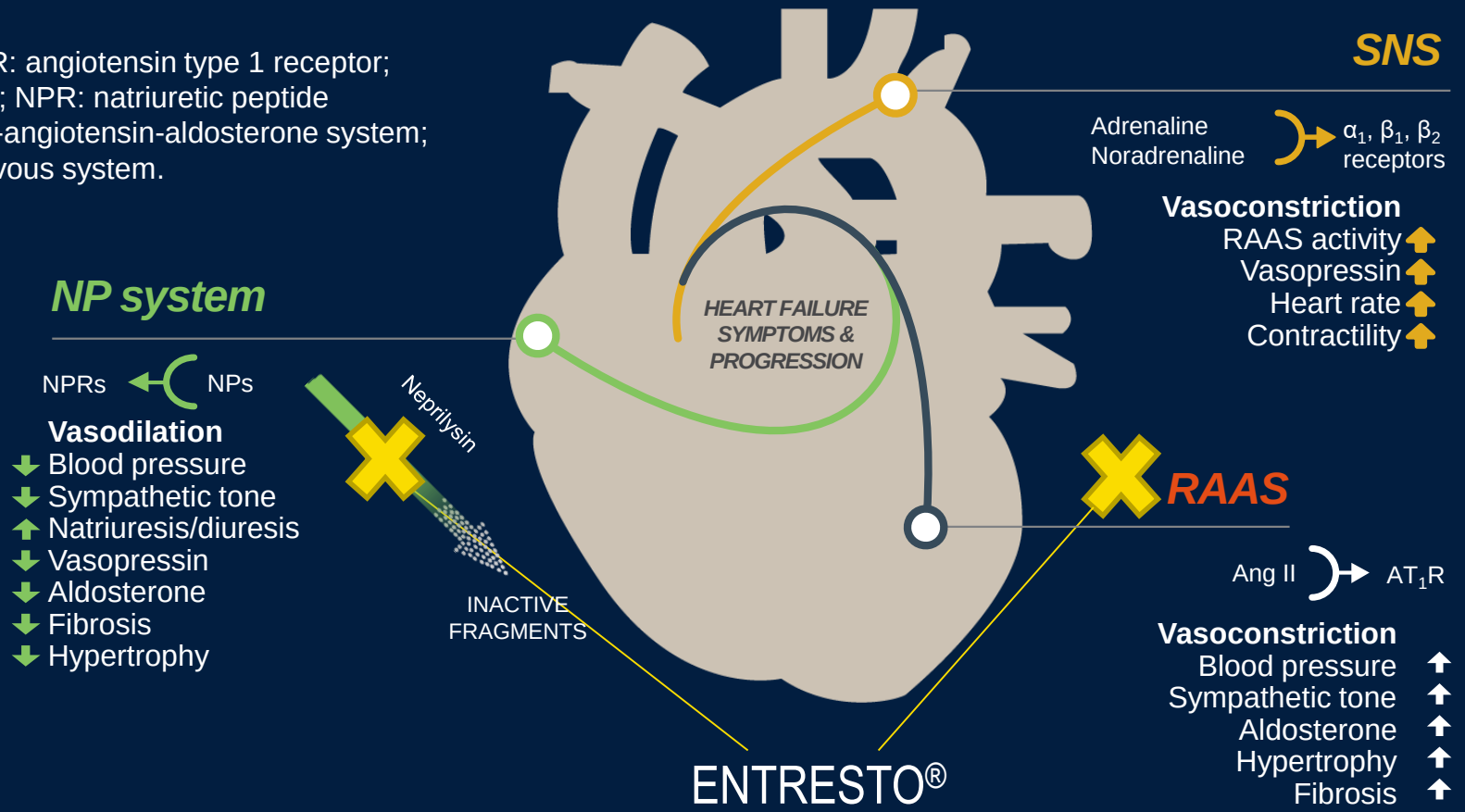
ARNI: angiotensin receptor neprilysin inhibitor; AT1: angiotensin II type 1.

1. Vardeny O *et al. JACC Heart Fail* 2014;2:663–70. 2. Bloch *et al. J Clin Hypertens* 2010;12:809–12. 3. Gu *et al. J Clin Pharmacol* 2010;50:401–14. 4. Langenickel *et al. Drug Discov Today: Ther Strateg* 2012;9:e131–9.

ENTRESTO® simultaneously inhibits neprilysin and blocks AT_1Rs, and has the potential to restore the natural balance of the RAAS and NP system[1]

Ang: angiotensin; AT_1R: angiotensin type 1 receptor; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system.

ENTRESTO® potentiates the positive effects of natriuretic peptides via sacubitril



ENTRESTO® blocks the detrimental effects of the over-active RAAS via valsartan

1. Vardeny O *et al*. *JACC Heart Fail* 2014;2:663–70.

PARADIGM-HF

Trial design: Participants with NYHA class II-IV and LVEF ≤40% were randomized to **ENTRESTO** 200 mg twice daily (n = 4,187) vs. **enalapril** 10 mg twice daily (n = 4,212).

Largest trial ever HFrEF

Mean EF 30 %

60 % Ischaemic Cause

70% NYHA II

- Compared against enalapril, the most trialled ACEI in HFrEF[2]
- ***Stopped early due to the finding of both significantly reduced risk of CV death vs. enalapril (HR: 0.80, p<0.001) and the primary endpoint being met[1]***

ACE: angiotensin-converting enzyme; CV: cardiovascular; HF: heart failure; HF-rEF: heart failure with reduced ejection fraction; HR: hazard ratio; PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

1. McMurray JJ *et al. N Engl J Med* 2014;371(11):993–1004. 2. McMurray JJ *et al. Eur J Heart Fail* 2014;16(7):817–25.

Extensive use of guideline-recommended therapies at baseline[1]

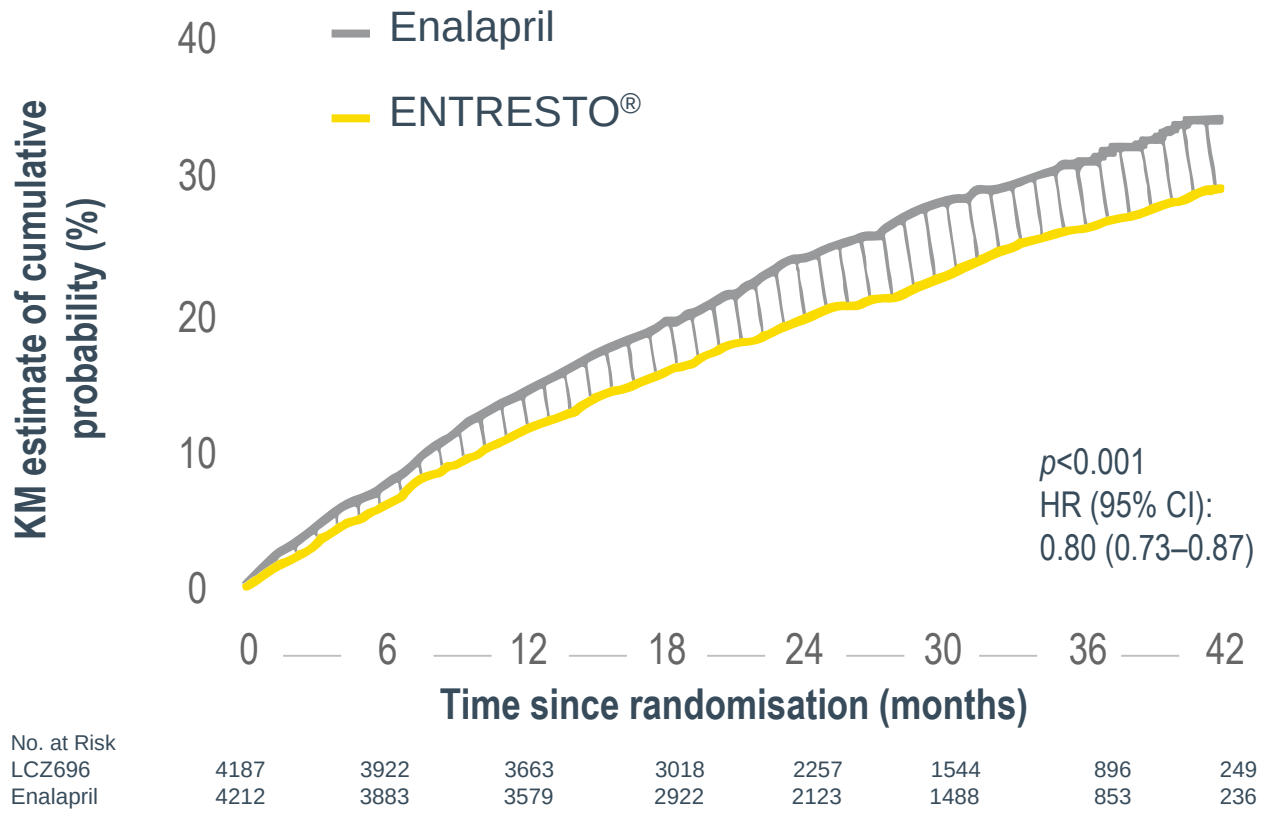
Therapies and treatments at randomisation, % (n)	ENTRESTO® (n=4187)	Enalapril (n=4212)
Pretrial use of ACEI*	78.0 (3266)	77.5 (3266)
Pretrial use of ARB*	22.2 (929)	22.9 (963)
Beta-blocker	93.1 (3899)	92.9 (3912)
Diuretic	80.3 (3363)	80.1 (3375)
Mineralocorticoid antagonist	54.2 (2271)	57.0 (2400)
Digitalis	29.2 (1223)	31.2 (1316)
ICD	14.9 (623)	14.7 (620)
Cardiac resynchronisation therapy	7.0 (292)	6.7 (282)

Adapted from McMurray JJ *et al.* (2014).[1]
*At the screening visit, 20 patients were not receiving the protocol-required treatment with an ACEI or an ARB, and 45 patients were taking both drugs.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ICD: implantable cardioverter defibrillator.

1. McMurray JJ *et al. N Engl J Med* 2014;371(11):993–1004.

ENTRESTO® reduced the risk of CV death or first HF hospitalisation (primary endpoint) by 20% vs enalapril[1]*

**HR: 0.80, p<0.001.[1]*



At a median duration of 27 months, death from CV causes or first HF hospitalisation occurred in **21.8%** of patients in the ENTRESTO® group and **26.5%** of patients in the enalapril group.[1]

20% RRR, *p*<0.001

4.7% ARR

NNT=21 over a median duration of 27 months[1]

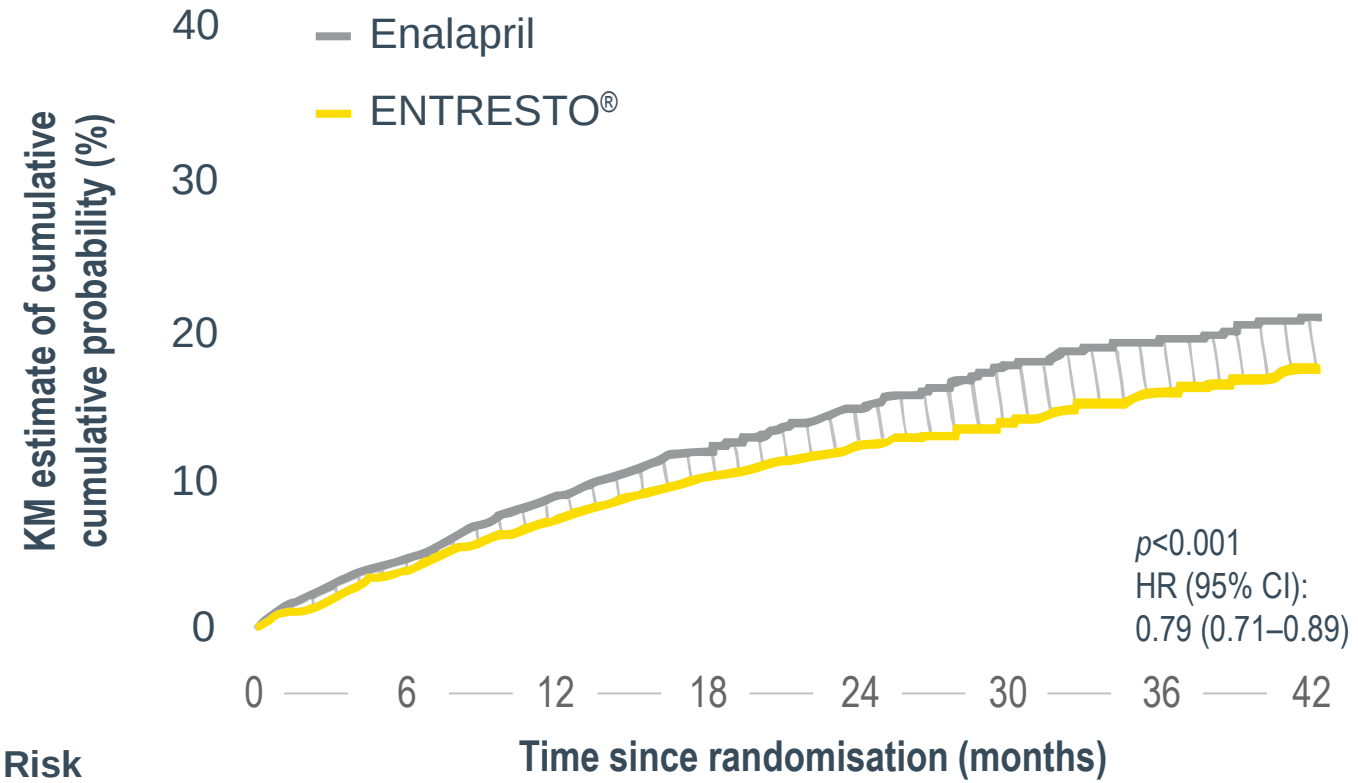
Trial stopped early after median follow-up of 27 months.[1]

ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier; NNT: number needed to treat; RRR: relative risk reduction.

1. McMurray JJ et al. N Engl J Med 2014;371(11):993–1004.

ENTRESTO® reduced the risk of first HF hospitalisation* by 21% vs enalapril[1†]

†HR: 0.79, p<0.001.[1]



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

At a median duration of 27 months, first HF hospitalisation occurred in **12.8%** of patients in the ENTRESTO® group and **15.6%** of patients in the enalapril group.[1]

21% RRR

2.8% ARR

NNT=36 over a median duration of 27 months[1]

Adapted from McMurray JJ et al. (2014).[1]

*Analyses of the components of the primary composite end point were not prospectively planned to be adjusted for multiplicity.

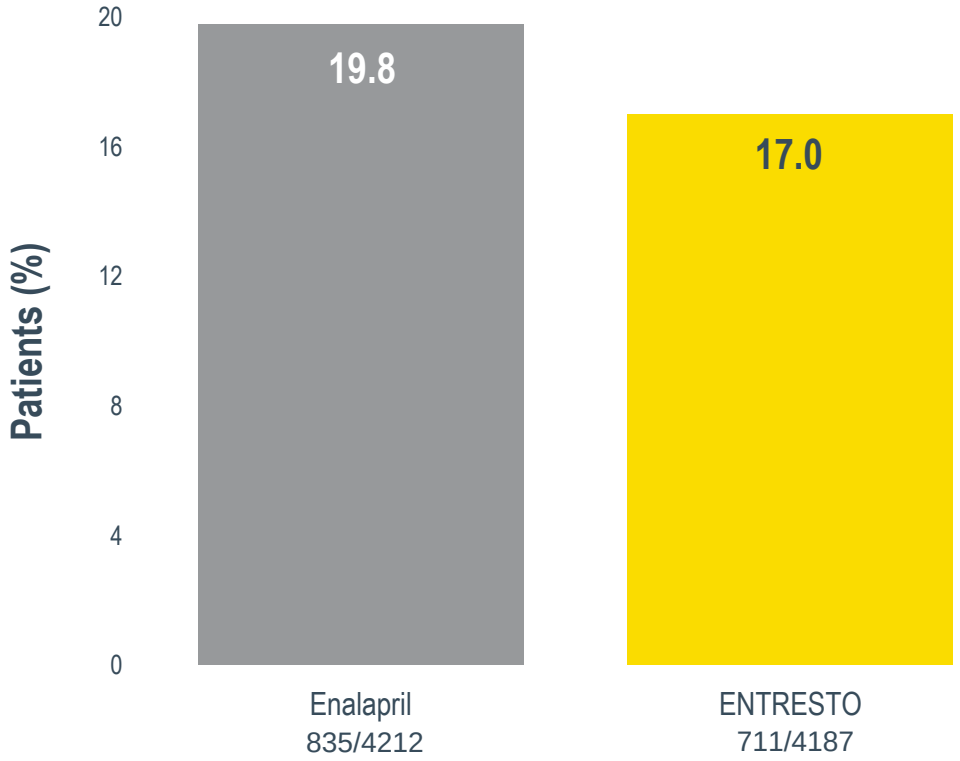
ARR: absolute risk reduction; CI: confidence interval; HF: heart failure; HR: hazard ratio; KM: Kaplan-Meier; NNT: number needed to treat; RRR: relative risk reduction.

1. McMurray JJ et al. N Engl J Med 2014;371(11):993–1004.

ENTRESTO® reduced the risk of all-cause death by 16% vs enalapril[1]*†

†HR:0.84, *p*<0.001.[1]

At a median duration of 27 months, ENTRESTO® improved overall survival; this finding was driven entirely by a lower incidence of CV mortality on ENTRESTO®.[1]



16% RRR

2.8% ARR

NNT=36 over a median duration of 27 months[1]

HR (95% CI): 0.84 (0.76–0.93) *p*<0.001

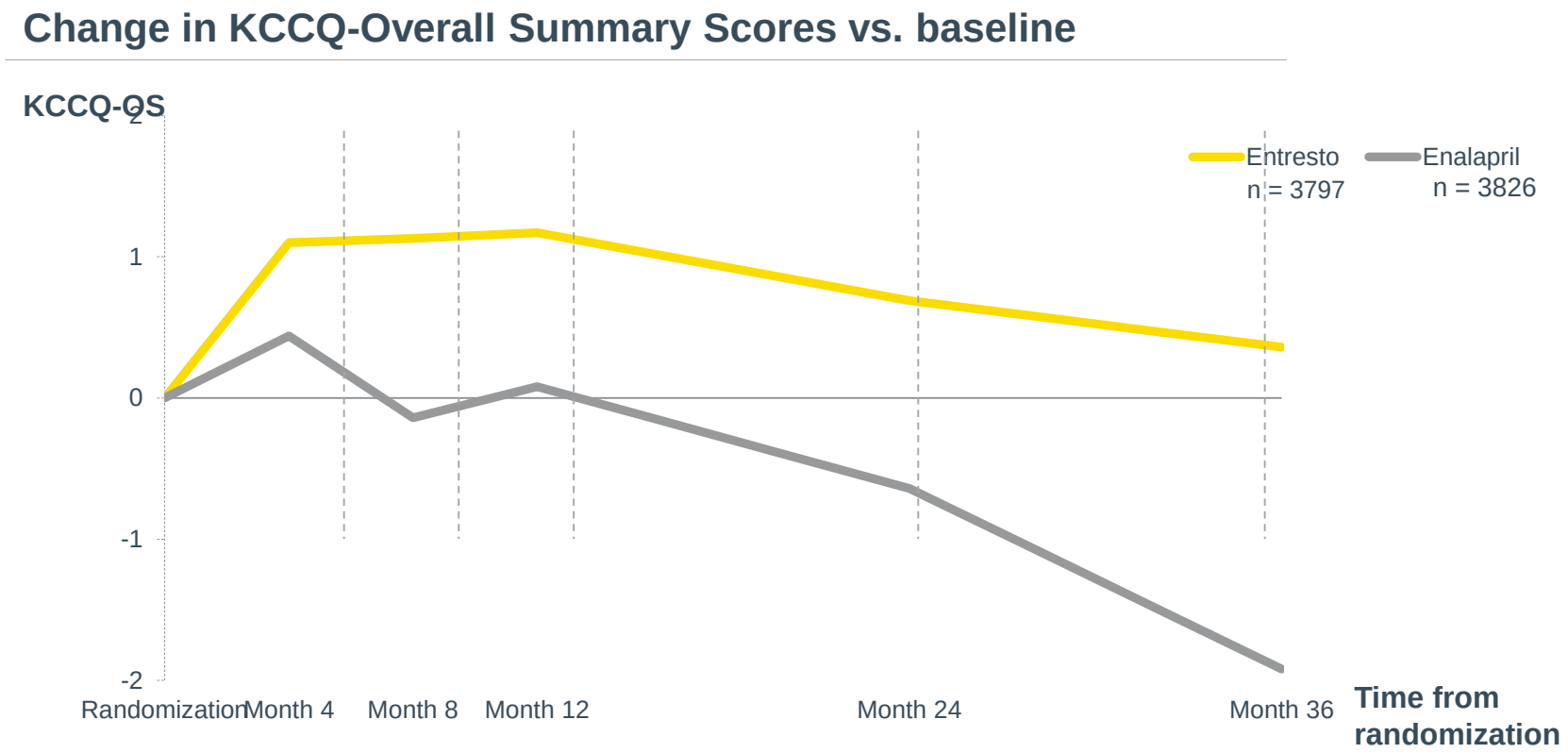
*This was driven entirely by a lower incidence of CV mortality on ENTRESTO®.

ARR: absolute risk reduction; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; NNT: number needed to treat; RRR: relative risk reduction.

1. McMurray JJ *et al. N Engl J Med* 2014;371(11):993–1004.

Patients QOL is better with ENTRESTO® vs enalapril*

PARADIGM-HF study



- Treatment with Entresto improves patients' Quality of Life*, including HF symptoms and physical limitations (as measured based on the KCCQ)
- The effect of Entresto on Quality of Life is sustained for up to 36 months; over the same treatment period, patients treated with enalapril experience a Quality of Life decline
- Entresto had similar improvements as were seen with cardiac resynchronization therapy

* In surviving patients

Results from post hoc analyses should be interpreted with caution

Source: Lewis E. F. et al, Health-Related Quality of Life Outcomes in PARADIGM-HF, Circ Heart Fail. 2017;10:e003430. DOI: 10.1161/CIRCHEARTFAILURE.116.003430

Prospectively defined safety events[1]

Event, n (%)	ENTRESTO® (n=4,187)	Enalapril (n=4,212)	*p* value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10*
Elevated serum potassium			
>5.5 mmol/L	674 (16.1)	727 (17.3)	0.15*
>6.0 mmol/L	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema (adjudicated by a blinded expert committee)			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19*
Catecholamines or glucocorticoids without hospitalisation	6 (0.1)	4 (0.1)	0.52*
Hospitalised without airway compromise	3 (0.1)	1 (<0.1)	0.31*
Airway compromise	0	0	---

SBP: systolic blood pressure. AE=adverse **event**; SBP=systolic blood pressure * = Not significant

1. McMurray JJ *et al. N Engl J Med* 2014;371:993–1004.

Results of the primary endpoint were consistent across subgroups[1,2]

Subgroups			
Age	Gender	Weight	Race
Region	NYHA Class	eGFR (mL/min/1.73m^2)	Diabetes
SBP (mmHg)	EF (%)	Atrial fibrillation	NT-proBNP
Hypertension	Prior use of ACEI	Prior use of ARB	Prior use of aldosterone antagonist
Prior hospitalisation for HF	Time since diagnosis of HF	Cause of HF	Any ICD (including CRT-D)

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CRT-D: cardiac resynchronisation therapy-defibrillator; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure; ICD: implantable cardioverter defibrillator; NYHA: New York Heart Association; SBP: systolic blood pressure.

1. McMurray JJ *et al. N Engl J Med* 2014;371(11):993–1004. 2. ENTRESTO® New Zealand Data Sheet

Benefit of ENTRESTO® across NYHA classes II–IV and across those with and without a history of HF hospitalisation[1]

		% of patients having a primary end point event	
Subgroup	**Percentage of total population**	**ENTRESTO® % (n/N)**	**Enalapril % (n/N)**
NYHA Class			
NYHA Class II	70.5	19.3 (578/2998)	25.4 (742/2921)
NYHA Class III	24.0	30.1 (292/969)	31.4 (329/1049)
NYHA Class IV	0.7	30.3 (10/33)	40.7 (11/27)
Prior hospitalisation for HF			
No	37.2	16.6 (262/1580)	22.5 (348/1545)
Yes	62.8	25.0 (652/2607)	28.8 (769/2667)

Adapted from ENTRESTO® New Zealand Data Sheet.[1]

HF: heart failure; NYHA: New York Heart Association.

1. ENTRESTO® New Zealand Data Sheet

ENTRESTO® Indication and Special Authority criteria

ENTRESTO® is indicated in adult patients for the treatment of chronic HF (NYHA Class II–IV) with reduced ejection fraction.[1]

Special Authority Criteria.[2]

Initial application from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following

1. Patient has heart failure; and
2. Any of the following:
   - Patient is in NYHA/WHO functional class II; or
   - Patient is in NYHA/WHO functional class III; or
   - Patient is in NYHA/WHO functional class IV; and
3. Patient has a documented left ventricular ejection fraction (LVEF) of less than or equal to 35%; and
4. Patient is receiving concomitant optimal standard chronic heart failure treatments.

Renewals from any relevant practitioner. Approvals valid for 12 months for applications where treatment remains appropriate and the patient is benefiting from treatment.

Note: Due to the angiotensin II receptor blocking activity of sacubitril with valsartan it should not be co-administered with an ACE inhibitor or ARB.

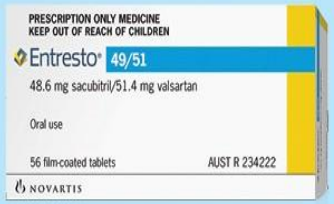
ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; HF: heart failure; NYHA: New York Heart Association;.

1. ENTRESTO® New Zealand Data Sheet .
2. Special Authority Form SA 1751 – https://www.pharmac.govt.nz/2018/10/01/SA1751.pdf

How to start a patient on ENTRESTO®

ENTRESTO® Recommended dosing for patients with HF-rEF

For patients currently on an ACEI;
36 – hour washout period is required



one tablet twice daily
Recommended starting dose
49 mg/51 mg

one tablet twice daily
Target dose
97 mg/103 mg

- *Step up after 2-4 weeks*
- *Check blood pressure and consider dose adjustment of diuretics and concomitant therapies*

ENTRESTO® New Zealand Data Sheet

ENTRESTO® Recommended dosing for patients with HF-rEF

For the following types of patients;

SBP 100-110, ≥75 years, severe renal impairment, moderate hepatic impairment, prior treatment with a low dose ACEI or ARB, or ACEI or ARB naive

a lower starting dose is recommended

ENTRESTO® New Zealand Data Sheet

Concomitant use with ACEI is contraindicated[1]

36-hour washout period required

- The concomitant use of ENTRESTO® with ACEI is contraindicated.
- The concomitant inhibition of neprilysin and ACEI therapy may increase the risk of angioedema.
- ENTRESTO® must not be started until 36 hours after taking the last dose of ACEI therapy.
- ACEI therapy must not be started until 36 hours after the last dose of ENTRESTO®.

ACEI: angiotensin-converting enzyme inhibitor.

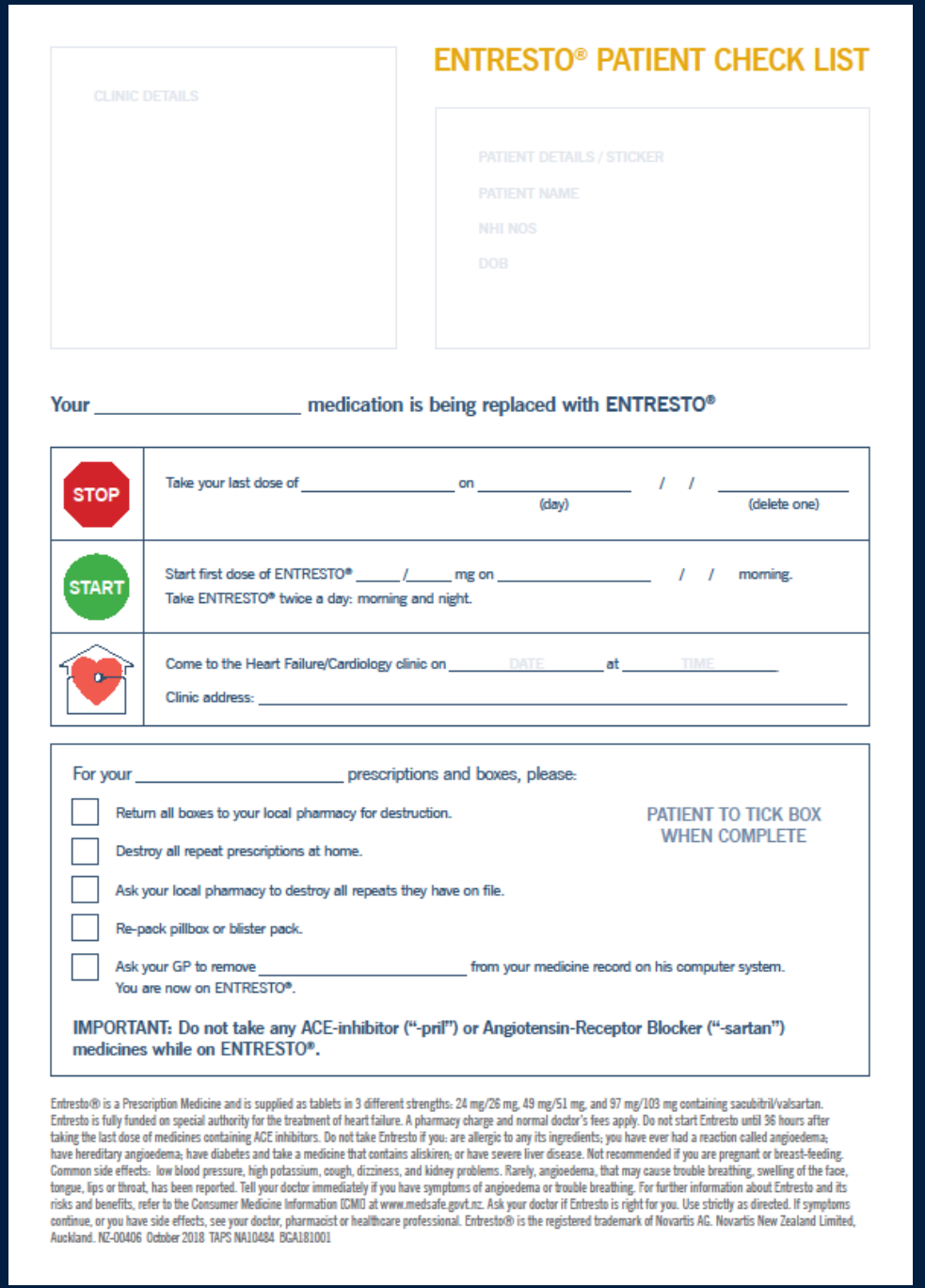
1. ENTRESTO® New Zealand Data Sheet

ENTRESTO® Patient Check List

An interactive PDF Form is available for patients being started on ENTRESTO to help with the switch from an ACE inhibitor to ENTRESTO

This PDF form has been sent to all Heart Failure Clinics and is available from Novartis

ACE: angiotensin-converting enzyme inhibitor.



ENTRESTO® PATIENT CHECK LIST

CLINIC DETAILS

PATIENT DETAILS / STICKER

PATIENT NAME

NHI NOS

DOB

Your _____ medication is being replaced with ENTRESTO®

STOP

Take your last dose of _____ on _____ / / _____
(day) (delete one)

START

Start first dose of ENTRESTO® _____/_____ mg on _____ / / morning.
Take ENTRESTO® twice a day: morning and night.

Come to the Heart Failure/Cardiology clinic on _____DATE_____ at _____TIME_____

Clinic address: _____

For your _____ prescriptions and boxes, please:

PATIENT TO TICK BOX WHEN COMPLETE

- ☐ Return all boxes to your local pharmacy for destruction.
- ☐ Destroy all repeat prescriptions at home.
- ☐ Ask your local pharmacy to destroy all repeats they have on file.
- ☐ Re-pack pillbox or blister pack.
- ☐ Ask your GP to remove _____ from your medicine record on his computer system.
  You are now on ENTRESTO®.

IMPORTANT: Do not take any ACE-inhibitor ("-pril") or Angiotensin-Receptor Blocker ("-sartan") medicines while on ENTRESTO®.

Entresto® is a Prescription Medicine and is supplied as tablets in 3 different strengths: 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg containing sacubitril/valsartan. Entresto is fully funded on special authority for the treatment of heart failure. A pharmacy charge and normal doctor's fees apply. Do not start Entresto until 36 hours after taking the last dose of medicines containing ACE inhibitors. Do not take Entresto if you: are allergic to any its ingredients; you have ever had a reaction called angioedema; have hereditary angioedema; have diabetes and take a medicine that contains aliskiren; or have severe liver disease. Not recommended if you are pregnant or breast-feeding. Common side effects: low blood pressure, high potassium, cough, dizziness, and kidney problems. Rarely, angioedema, that may cause trouble breathing, swelling of the face, tongue, lips or throat, has been reported. Tell your doctor immediately if you have symptoms of angioedema or trouble breathing. For further information about Entresto and its risks and benefits, refer to the Consumer Medicine Information (CMI) at www.medsafe.govt.nz. Ask your doctor if Entresto is right for you. Use strictly as directed. If symptoms continue, or you have side effects, see your doctor, pharmacist or healthcare professional. Entresto® is the registered trademark of Novartis AG. Novartis New Zealand Limited, Auckland. NZ-00406 October 2018 TAPS NA10484 BGA181001

Our Patient

Perindopril

stopped for 2 days

Commenced Entresto (24mg/26mg) I BD (BP110/70)

July 2019

NYHA I Symptoms

Entresto 97mg/103mg I BD

Spironolactone reduced 25 mg/day

Frusemide 40 mg /day

BNP 160 pmol/l

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

Entresto was *more effective* than enalapril in . . .

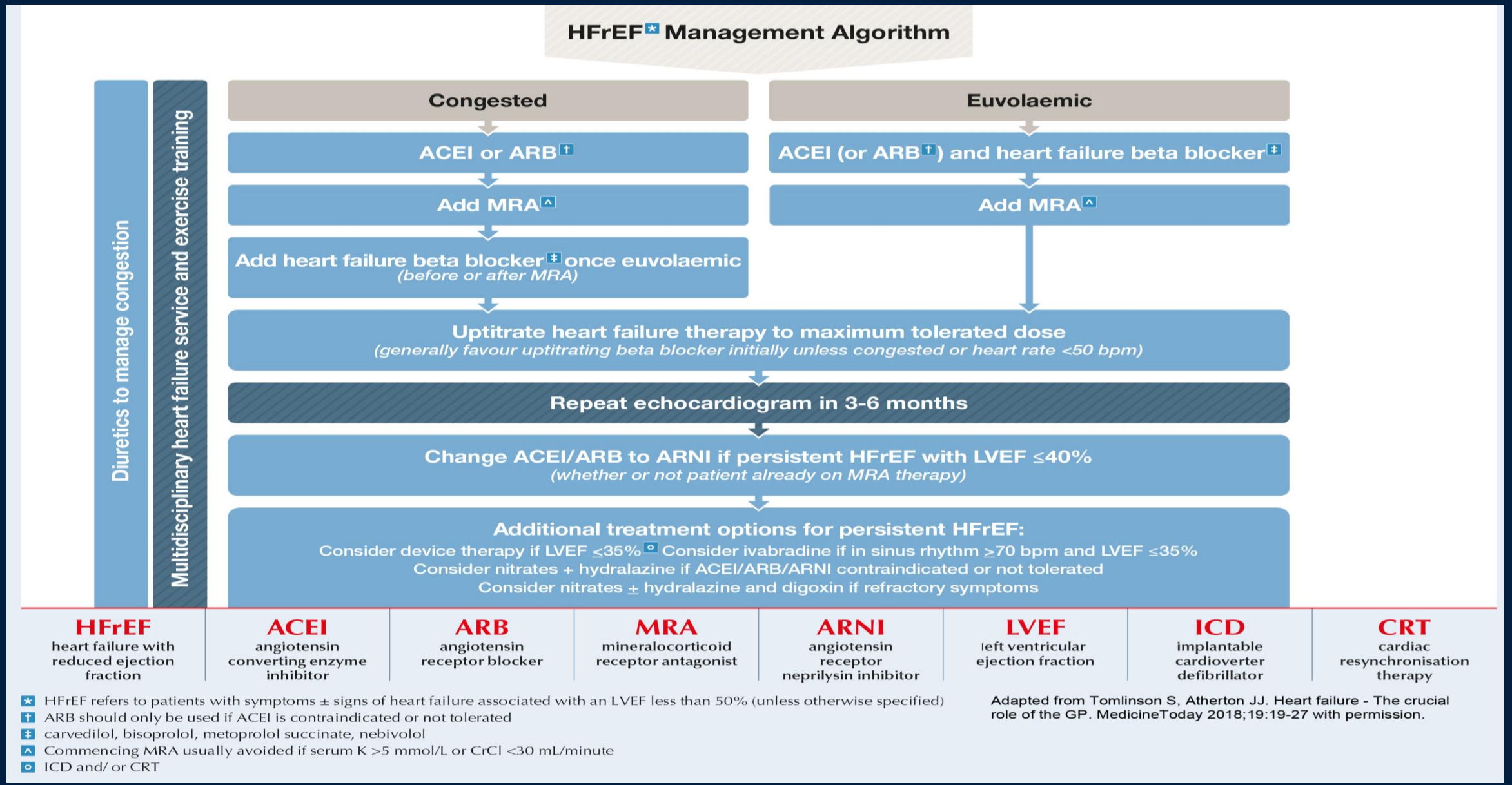
- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

Entresto was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

Updated CSANZ 2018 Guidelines

https://www.heartfoundation.org.au/images/uploads/publications/HF_Figure_3_Management_of_patients_with_heart_failure_and_reduced_ejection_fraction.jpg



* HFrEF refers to patients with symptoms ± signs of heart failure associated with an LVEF less than 50% (unless otherwise specified)
† ARB should only be used if ACEI is contraindicated or not tolerated
‡ carvedilol, bisoprolol, metoprolol succinate, nebivolol
^ Commencing MRA usually avoided if serum K >5 mmol/L or CrCl <30 mL/minute
o ICD and/ or CRT

Adapted from Tomlinson S, Atherton JJ. Heart failure - The crucial role of the GP. MedicineToday 2018;19:19-27 with permission.