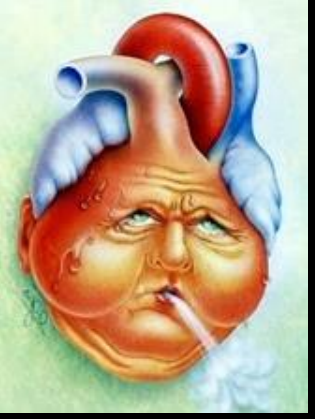

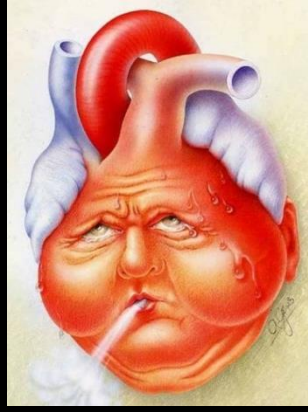

The Roles of Angiotensin II Receptor Blocker Neprilysin Inhibitor (ARNI)in HFrEF Tx from PARADIGM-HF to Real World Evidence

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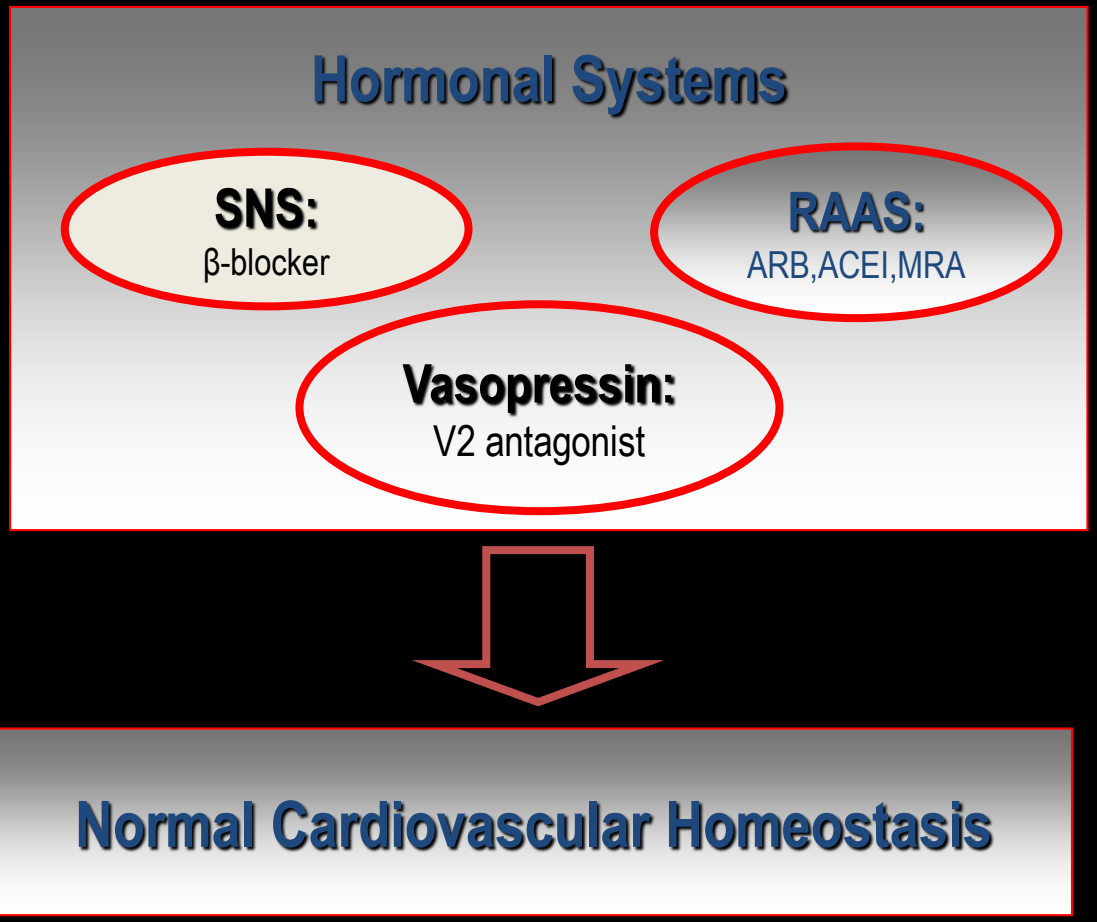
教授
陽明大學醫學院

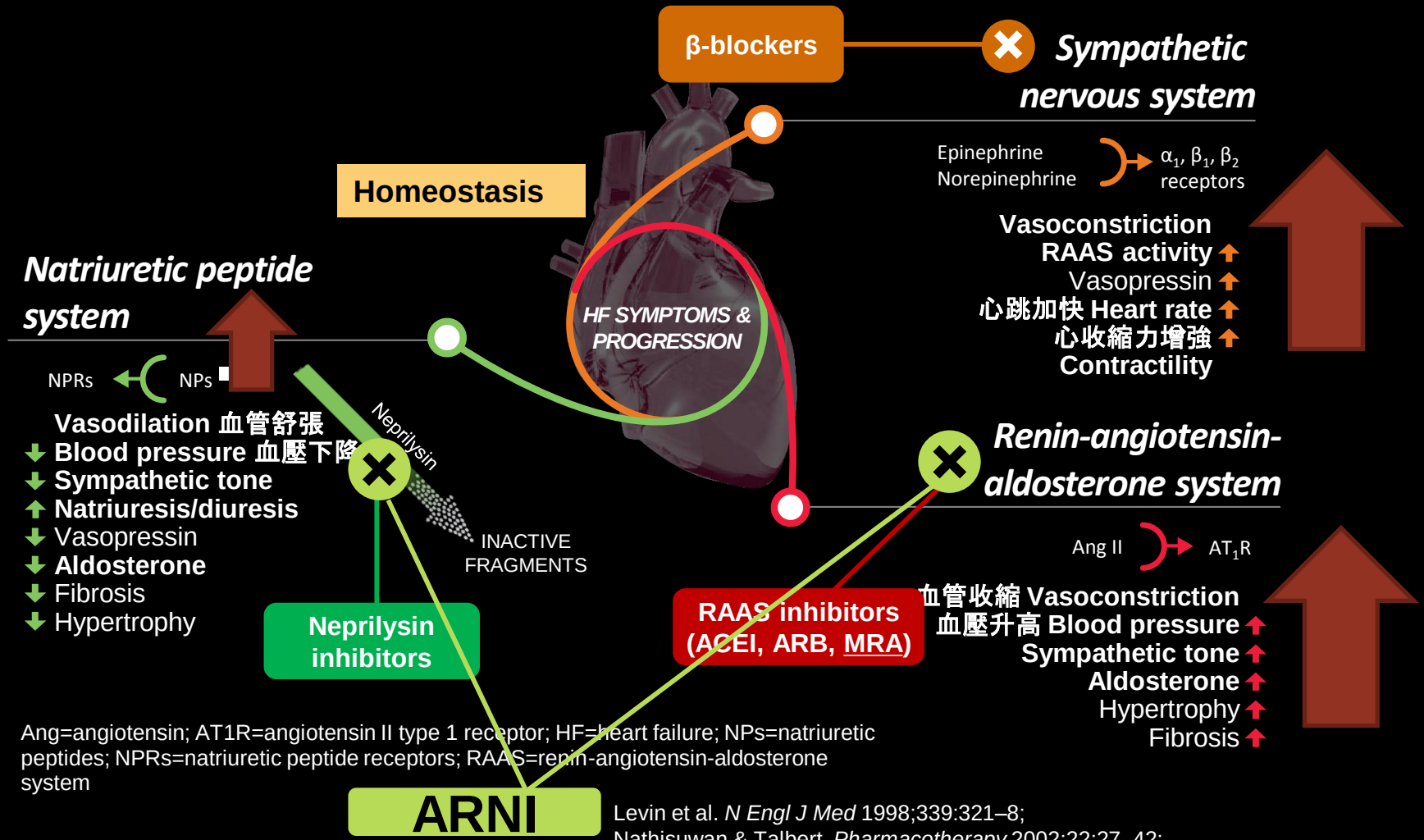
Current Pharmacological Treatment

Neuro Hormonal Activation Mechanism in CHF



Mechanism of Action (MoA)

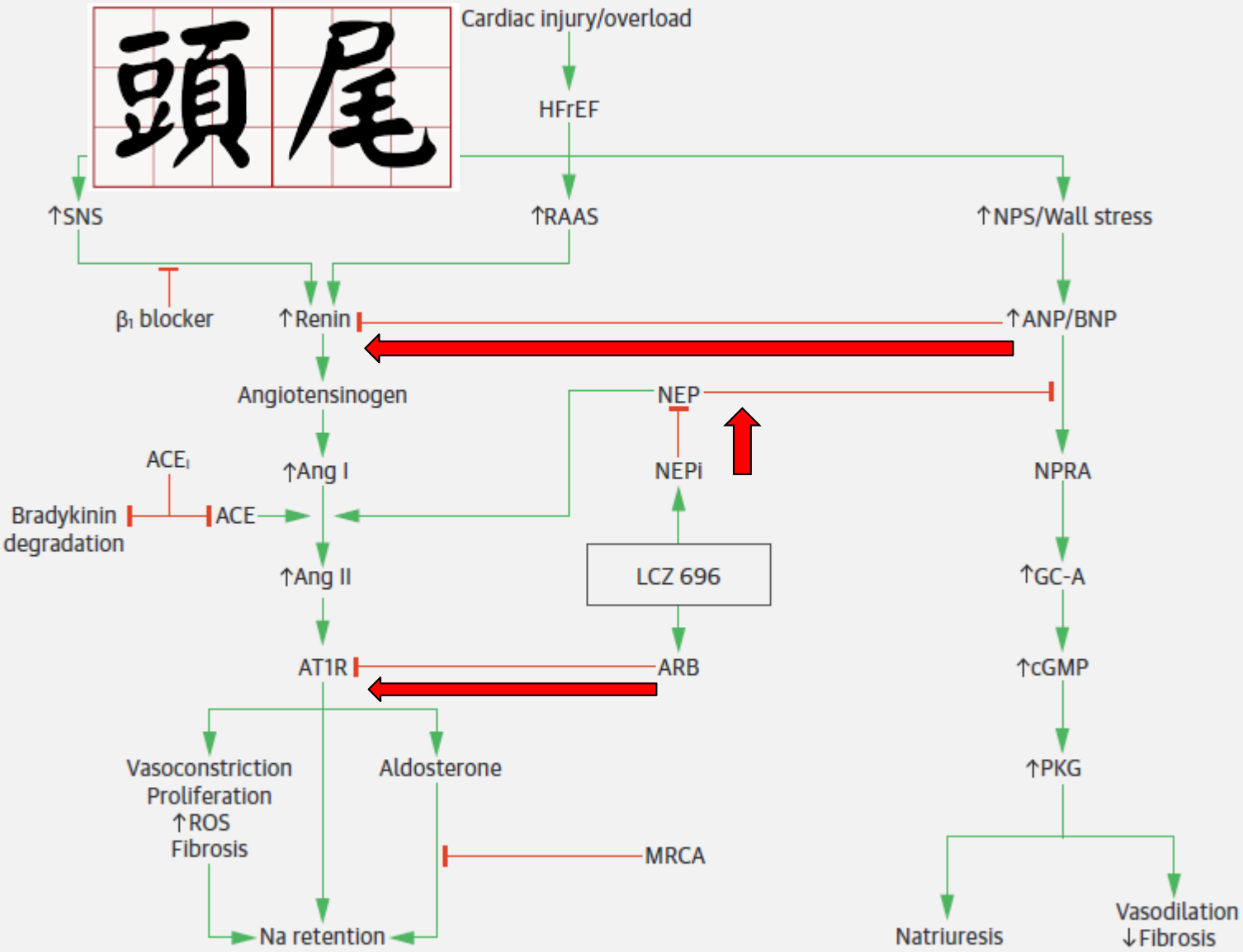
ARNI – angiotensin receptor neprilysin inhibitor



Ang=angiotensin; AT1R=angiotensin II type 1 receptor; HF=heart failure; NPs=natriuretic peptides; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system

Levin et al. *N Engl J Med* 1998;339:321–8;
Nathisuwan & Talbert. *Pharmacotherapy* 2002;22:27–42;
Kemp & Conte. *Cardiovascular Pathology* 2012;365–71;
Schrier & Abraham. *N Engl J Med* 2009;341:577–85

CENTRAL ILLUSTRATION **Angiotensin-Neprilysin Inhibition in Heart Failure: Central Role of LCZ696 in Cardiovascular Regulation**



Braunwald, E. J Am Coll Cardiol. 2015; 65(10):1029-41.

I	ARNI: B-R

- BNP ≥
  pg/mL
  prece
  tolerat
  mg bi
- Not c
  angio

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A

- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

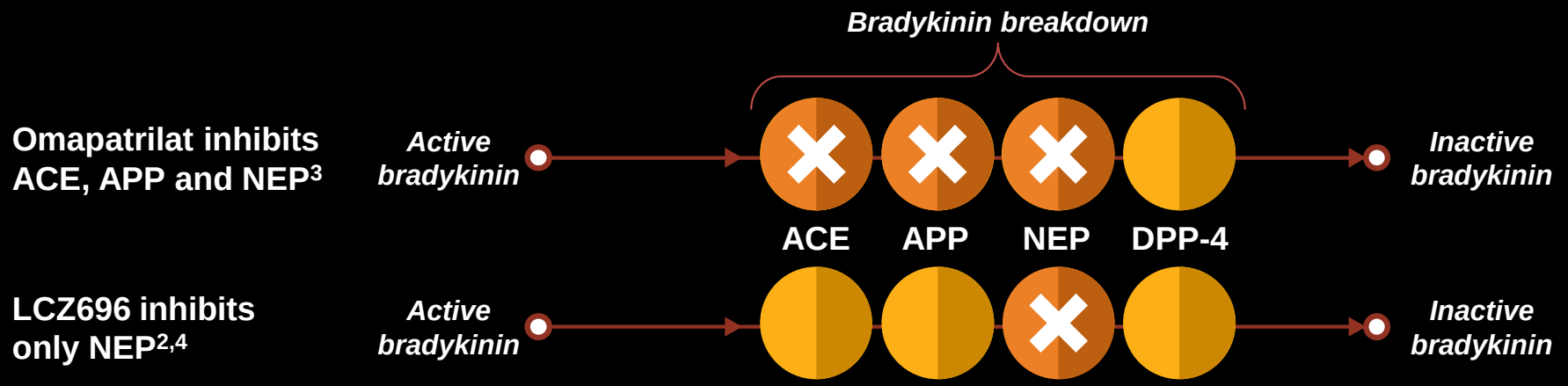
LEVEL B-NR (Nonrandomized)

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

ARNI shows promise in patients with HF

The LCZ696 clinical development program for HF took into consideration the learnings from the omapatrilat program. For example:

- *LCZ696 BID (not QD as per omapatrilat) ensured optimal 24 h inhibition of the AT_1R and NEP*[1,2]
- *LCZ696 delivers NEP inhibition together with RAAS inhibition via AT_1R blockade rather than ACE inhibition (i.e. omapatrilat), in an effort to reduce the risk of serious angioedema*[2]



1. Fryer et al. Br J Pharmacol 2008;153: 947–55;
2. McMurray et al. Eur J Heart Fail 2014;16:817–25; 3. Gu et al. J Clin Pharmacol 2010;50: 401–14
4. McMurray et al. Eur J Heart Fail 2013;15: 1062–73

Acute Decompendated HF

- **Chronic** ACE inhibitors, ARBs, or ARNI should be administered with caution or avoided during the first few hours of hospitalization.
- **Initiation of therapy** — For patients who are not already taking an ACE inhibitor, single-agent ARB, or ARNI, we suggest **not** initiating such therapy at the time of presentation with an episode of ADHF.

UpToDate 2017

PARADIGM-HF Study

- The most geographically diverse trial in patients with HFrEF

- 8,442 patients were randomized at 985 sites in 47 countrie

McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray et al. Eur J Heart Fail 2013;15:1062–73.

Key Entry Criteria

- Inclusion and exclusion criteria

Inclusion criteria

- Chronic HF NYHA **class II–IV** with LVEF ≤40%*
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- **≥4 weeks on stable treatment with an ACEI or an ARB#, and a β-blocker**
- Aldosterone antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

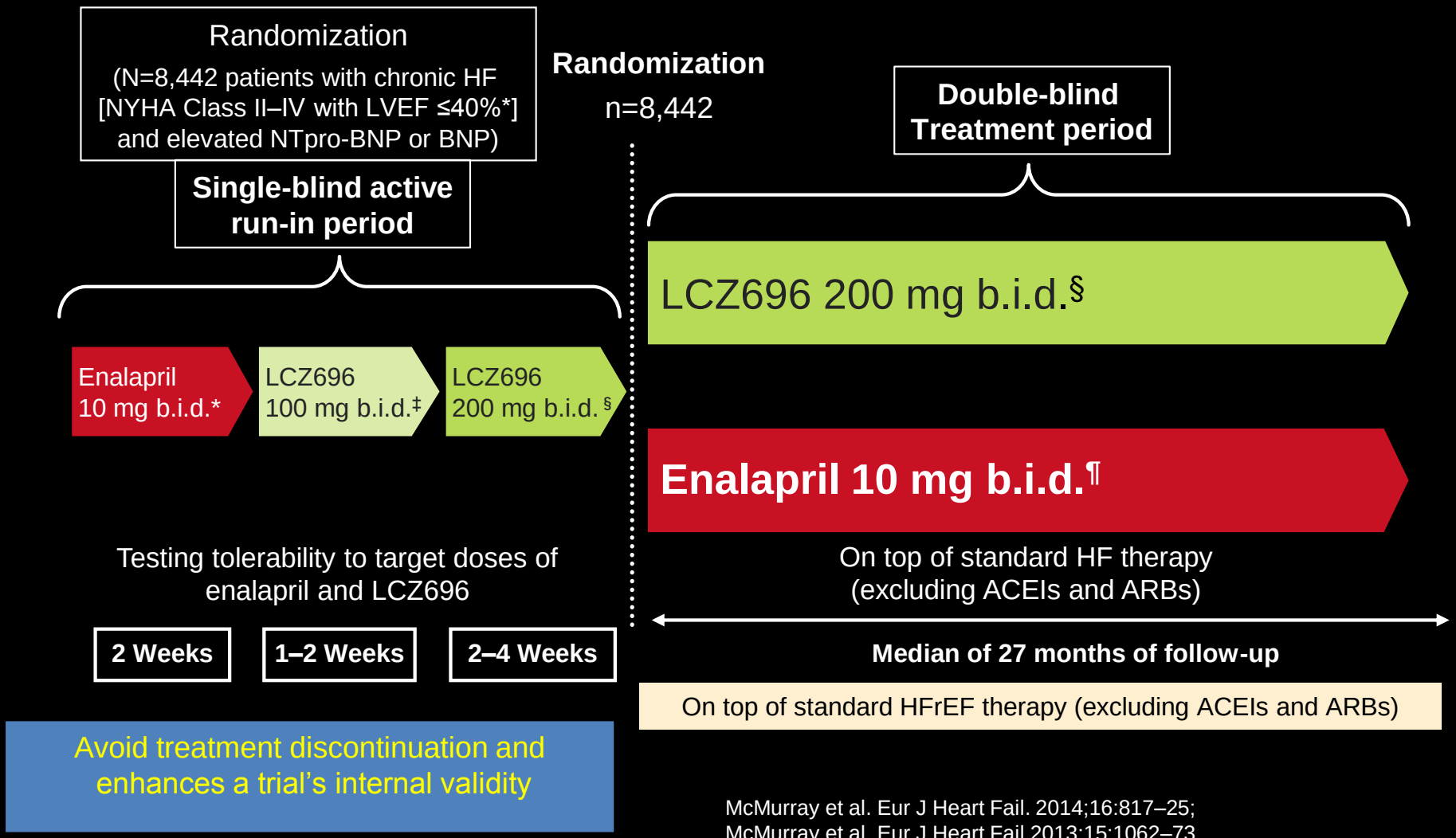
Exclusion criteria

- History of angioedema
- **eGFR <30** mL/min/1.73 m^2 at screening
- Serum potassium >5.2 mmol/L at screening
- Symptomatic hypotension, SBP **<100** mmHg at screening
- Current acute decompensated HF
- History of severe pulmonary disease

McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray et al. Eur J Heart Fail 2013;15:1062–73.

Study Design

- A randomized, double-blind, parallel-group, active-controlled study



McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray et al. Eur J Heart Fail 2013;15:1062–73.

ACEI- Enalapril HF Trial

Trial	Patient population	Comparator arm	dose	Enalapril administered
CONSENSUS (1987)	NYHA class IV	Placebo	40 mg/day (20 mg b.i.d.)	18 mg/day
SOLVD-trial (1991)	NYHA class II-IV	Placebo	20 mg/day (10 mg b.i.d.)	17 mg/day
V-HeFT II (1991)	NYHA class II (51%) or III	Hydralazine And ISDN	20 mg/day	15 mg/day
PARADIGM-HF(2014)	HFrEF (all NYHA classes	Enalapril	20 mg/day (10 mg b.i.d.)	18.9 mg/day

Baseline Characteristics

- No significant differences between two groups

Characteristic*	LCZ696 (n=4,187)	Enalapril (n=4,212)
Age, years	63.8±11.5	63.8±11.3
Women, n (%)	879 (21.0)	953 (22.6)
Ischemic cardiomyopathy, n (%)	2,506 (59.9)	2,530 (60.1)
LV ejection fraction, %	29.6±6.1	29.4±6.3
NYHA functional class, n (%) II III	 2,998 (71.6) 969 (23.1)	 2,921 (69.3) 1,049 (24.9)
SBP, mmHg	122±15	121±15
Heart rate, beats/min	72±12	73±12
NT pro-BNP, pg/mL (IQR)	1,631 (885–3,154)	1,594 (886–3,305)
BNP, pg/mL (IQR)	255 (155–474)	251 (153–465)
History of **diabetes**, n (%)	1,451 (34.7)	1,456 (34.6)
Treatments at randomization, n (%)		
Diuretics	3,363 (80.3)	3,375 (80.1)
Digitalis	1,223 (29.2)	1,316 (31.2)
β-blockers	3,899 (93.1)	3,912 (92.9)
MRAs	2,271 (54.2)	2,400 (57.0)
ICD	623 (14.9)	620 (14.7)
CRT	292 (7.0)	282 (6.7)

McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray et al. Eur J Heart Fail 2013;15:1062–73.

PARADIGM-HF: Effect of ARNI-LCZ696 vs Enalapril on Primary Endpoint and Its Components

	LCZ696 (n=4187)	Enalapril (n=4212)		P Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71- 0.89)	0.00004

Prof John J McMurray

The University of Glasgow

- The P-value for the primary endpoint (2x 10^{-7}) in PARADIGM-HF is equivalent to having 4-5 trials each with $p < 0.05$
- All-cause mortality, the equivalent number is 2-3 trials.

FDA JULY 2015

Entresto LCZ696 (Valsartan/sacubitril)

CAS# 936623-90-4

Entresto LCZ696
(Valsartan/sacubitril)
FDA approved July 7, 2015

LGM PHARMA

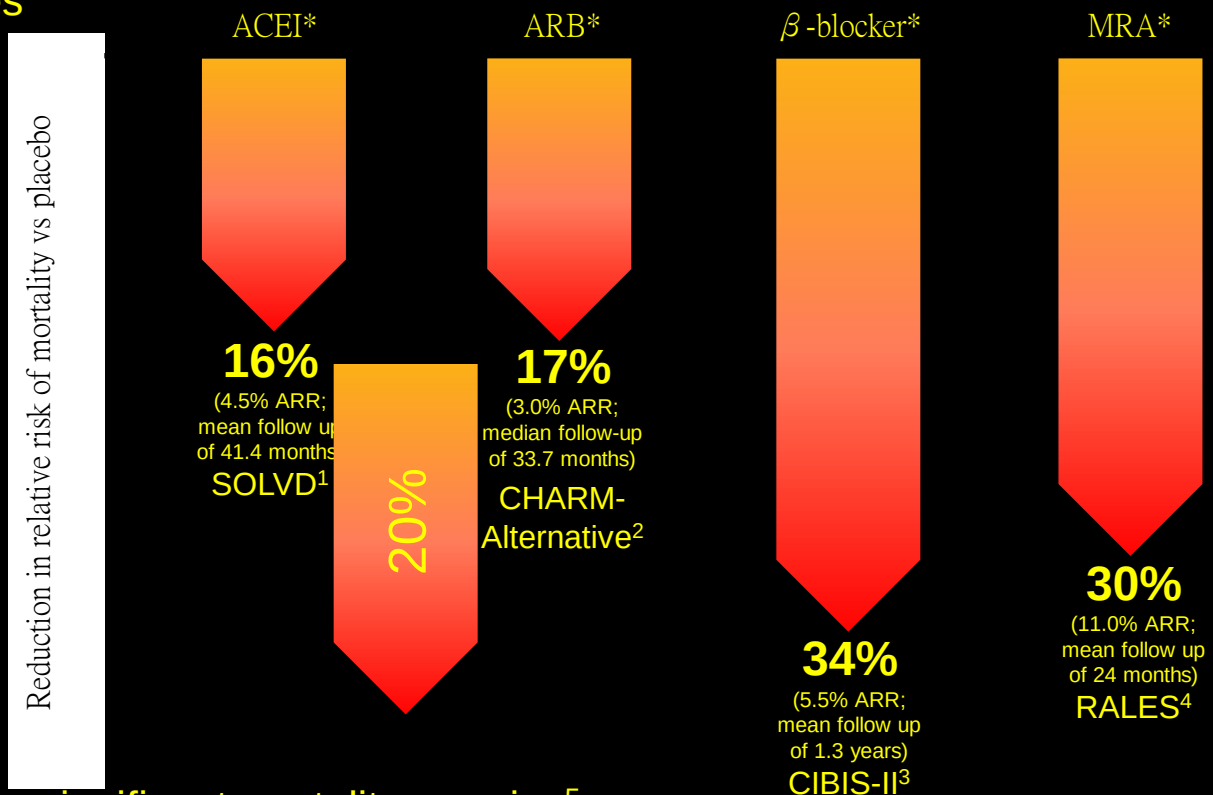
ESS
14

EUROPEAN SOCIETY OF CARDIOLOGY®

HF

HFrEF mortality remains high despite the introduction of new therapies that improve survival

- Chronic HFrEF survival rates have improved over time with the introduction of new therapies



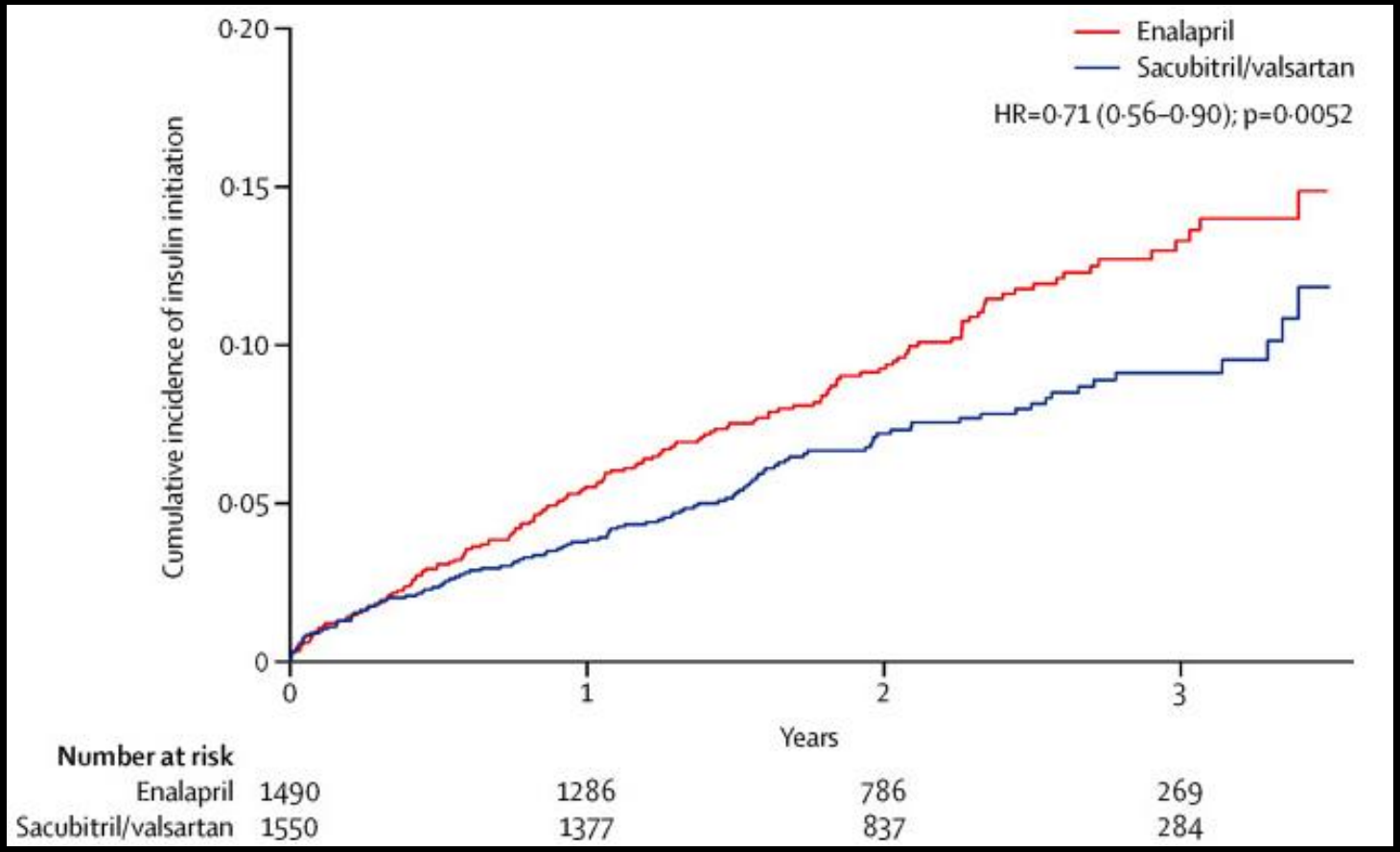
- However, significant mortality remains[5]

*On top of standard therapy at the time of study (except in CHARM-Alternative where background ACEI therapy was excluded). Patient populations varied between trials and as such relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with LVEF≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF≤40%.

ARR=absolute risk reduction; MRA=mineralocorticoid receptor antagonist; RRR=relative risk reduction

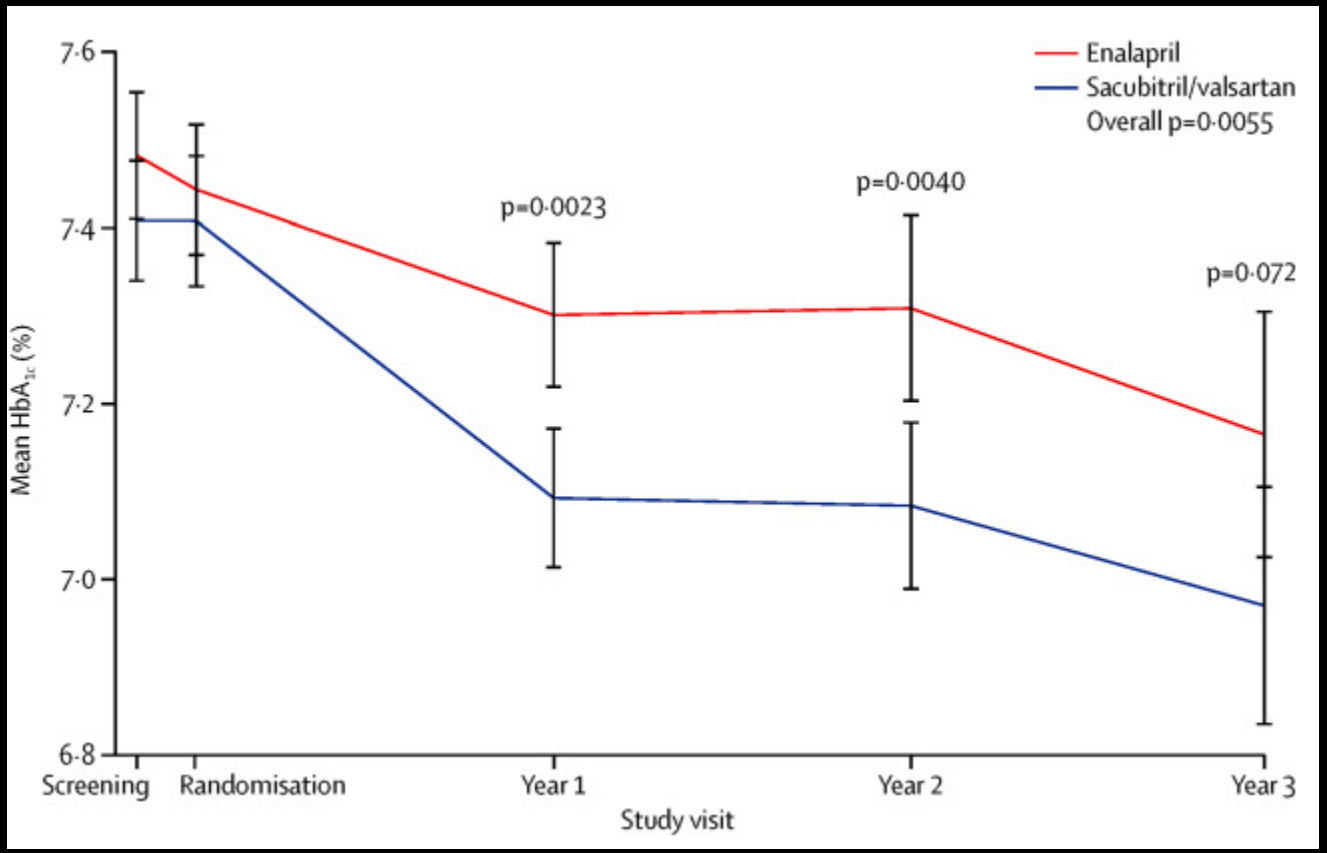
1. SOLVD Investigators. N Engl J Med 1991;325:293–302; 2. Granger et al. Lancet 2003;362:772–6
3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17; 5. Roger et al. JAMA 2004;292:344–50

PARADIGM-HF: Time to initiation of insulin in patients with baseline diabetes

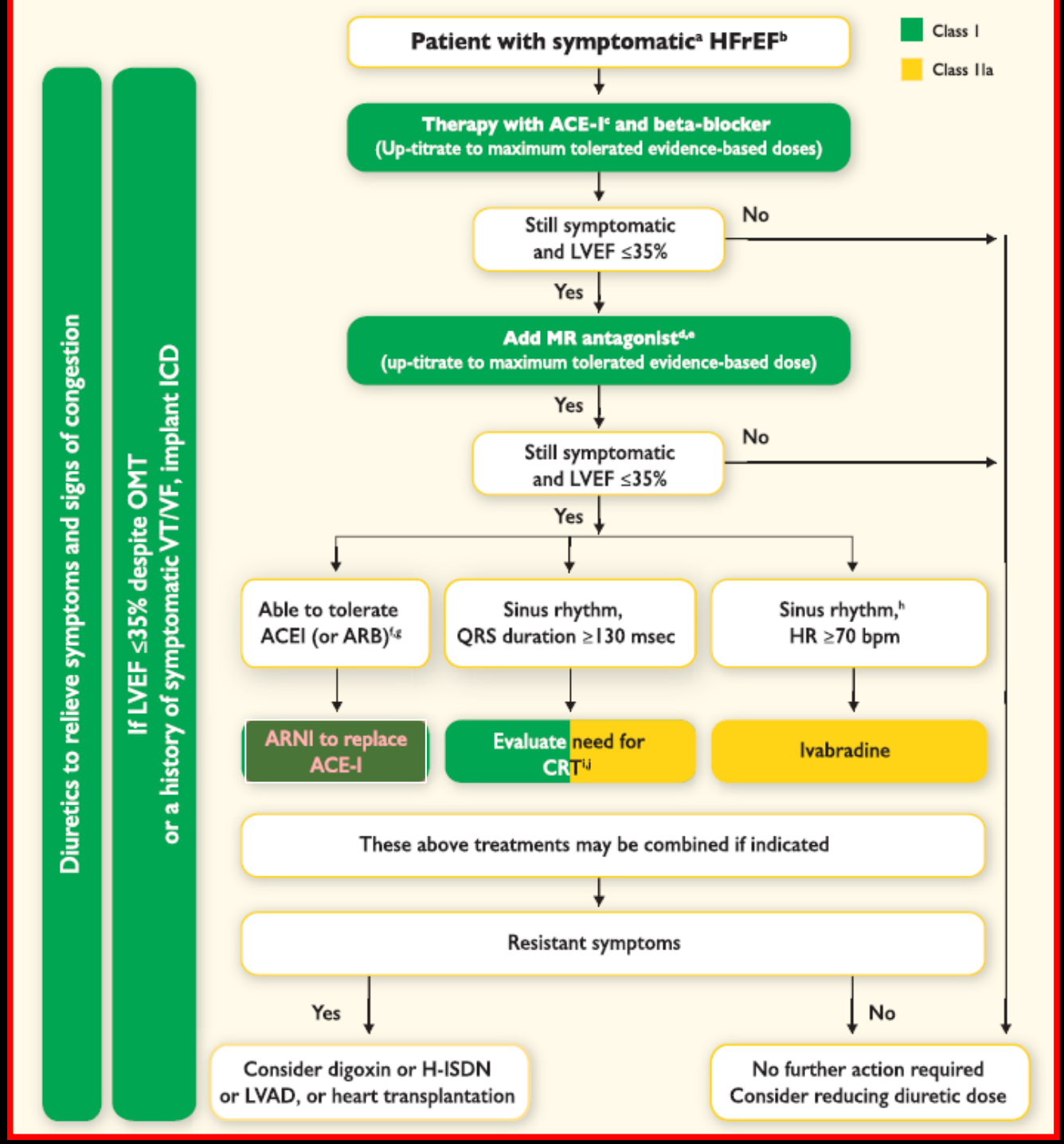


Lancet Diabetes Endocrinol. 2017; 5:333-340.

PARADIGM-HF: Change in HbA1c in patients with a baseline diabetes



Lancet Diabetes Endocrinol. 2017; 5:333-340.

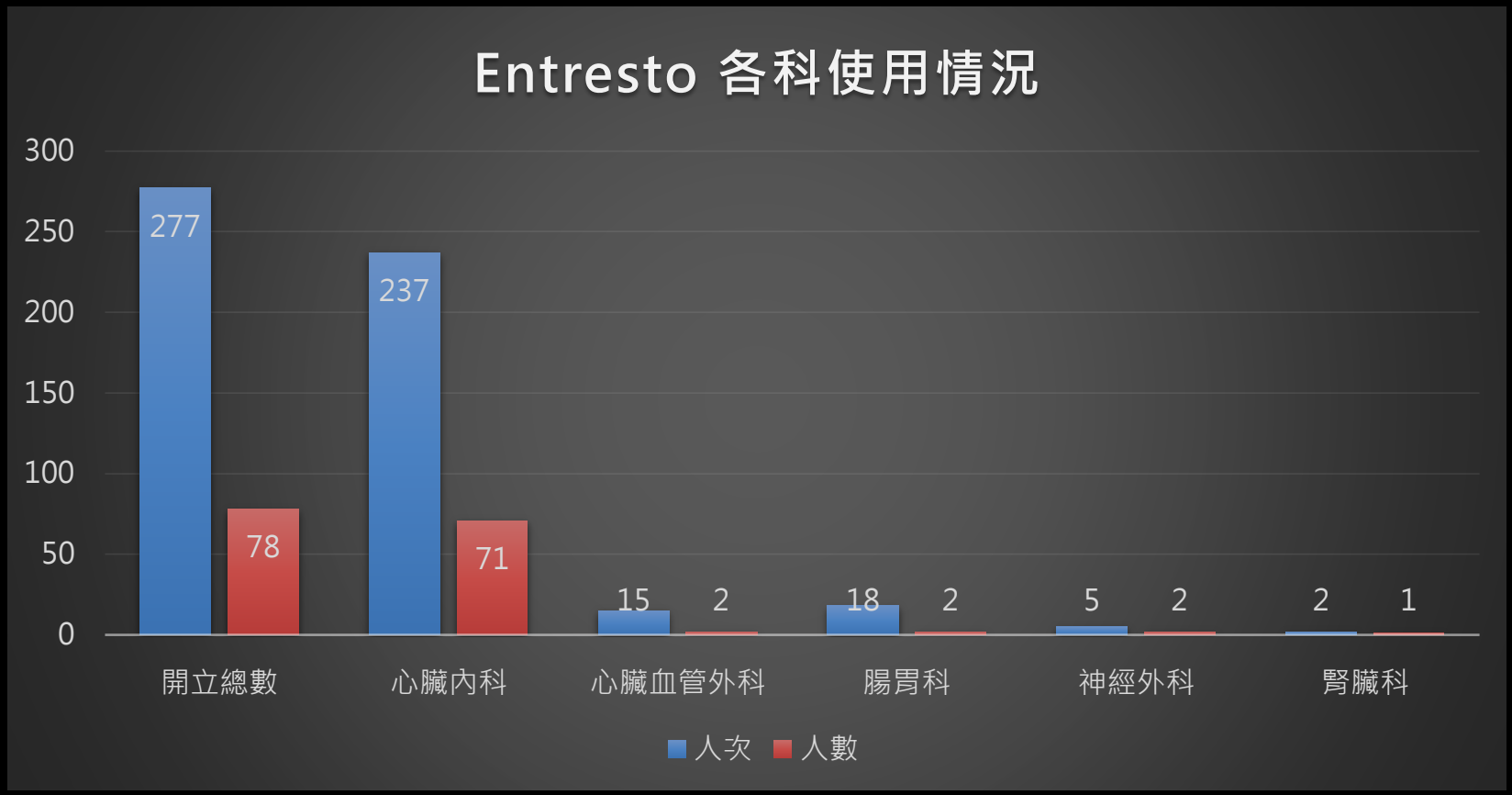

Class I
Class IIa
Patient with symptomatic[a] HFrEF[b]
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Yes
Still symptomatic and LVEF ≤35%
No
Yes
Able to tolerate ACEI (or ARB)[f,g]
Sinus rhythm, QRS duration ≥130 msec
Sinus rhythm,[h] HR ≥70 bpm
ARNI to replace ACE-I
Evaluate need for CRT[i,j]
Ivabradine
These above treatments may be combined if indicated
Resistant symptoms
Yes
No
Consider digoxin or H-ISDN or LVAD, or heart transplantation
No further action required
Consider reducing diuretic dose
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

2016 ESC

2.14. Sacubitril+Valsartan (Entresto):(106/3/1)

限符合下列各項條件之慢性心衰竭患者使用:

- (1) 依紐約心臟協會(NYHA)衰竭功能分級為第二級或第三級。左心室收縮功能不全，左心室射出分率(LVEF)≦35%。
- (2) 經ACEI或ARB，及合併β-阻斷劑穩定劑量治療達**4週**以上，仍有症狀者。
- 每日限最多使用2粒。
- 不應與ACEI合併使用，開始使用本藥，至少要和ACEI間隔36小時。曾有血管性水腫(angioedema)病史者，禁止使用。



	人次	人數
總開立數量	277	78
心臟內科	237	71
心臟血管外科	15	2
腸胃科	18	2
神經外科	5	2
腎臟科	2	1

Clinical Changes

N=36	pre	post	P-value
Age	61.5±14.6	-	-
LVEF(%)	30.6±11.1	-	-
CHF Fc (III/II/I)	30/6/0	10/20/6	
SBP(mmHg)	120.8±16.8	**110±14.7**	0.012
DBP(mmHg)	70.2±14.6	64.6±14.8	0.103
HR(bpm)	79.7±13	79.2±11	0.887
BUN(mg/dl)	30.6±21.6	44.1±30.7	0.142
Creat(mg/dl)	1.65±2.14	1.8±1.26	0.392

Clinical Critical Issues

- Safety
- Efficacy

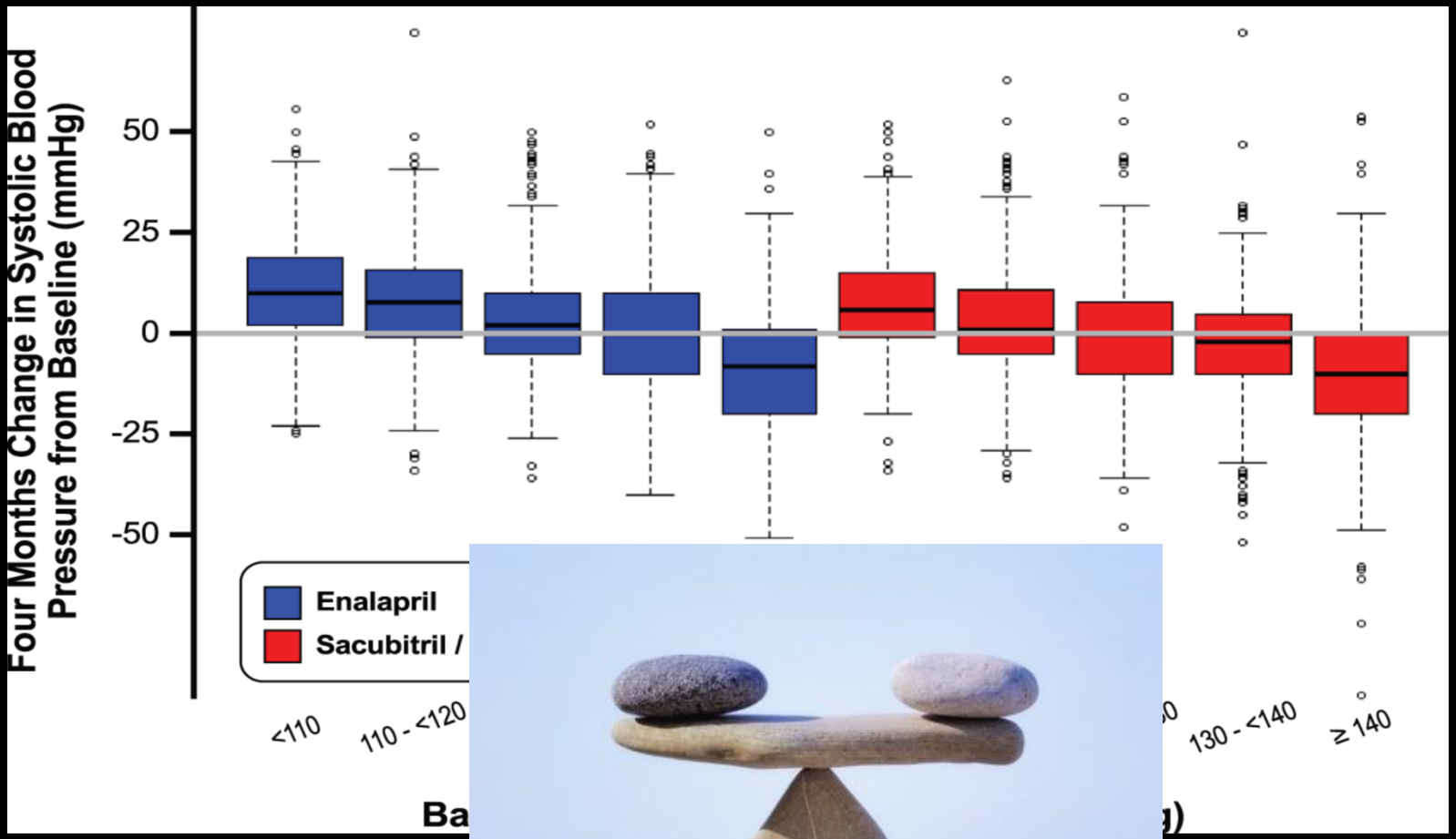
Adverse effect

表 1：雙盲期接受 ENTRESTO® 治療的患者中，發生率 ≥ 5% 的不良反應

	enalapril (4,229 人) %	ENTRESTO® (4,203 人) %
低血壓	12	18
高血鉀	14	12
咳嗽	13	9
暈眩	5	6
腎衰竭 / 急性腎衰竭	5	5

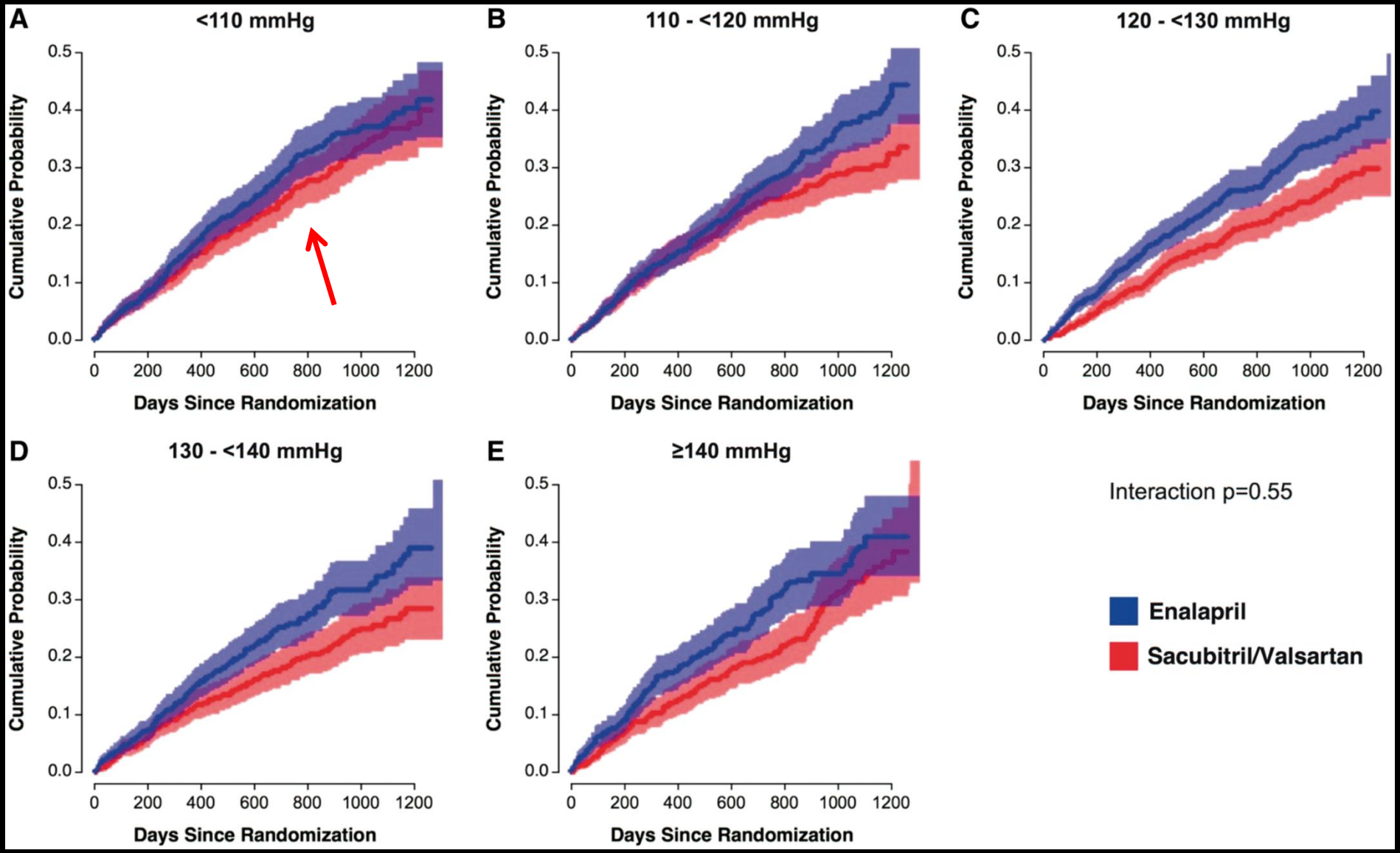
PARADIGM-HF 試驗中，隨機分配至 ENTRESTO® 的患者，最長接受4.3 年的治療，用藥持續時間中位數為 24 個月；3,271 位患者接受超過一年的治療。在該試驗雙盲期內，450 位 (10.7%) 接受 ENTRESTO® 治療的患者，和 516 位 (12.2%) 接受 enalapril 治療的患者，因為不良事件而停止治療。

Change in systolic blood pressure at 4 months according to systolic blood pressure at baseline



From: Systolic blood pressure, carc of sacubitril/valsartan (LCZ696) in patients with chronic h ts from PARADIGM-HF

Eur Heart J. 2017;38(15):1132-1143. doi:
Eur Heart J | Published on behalf of the E



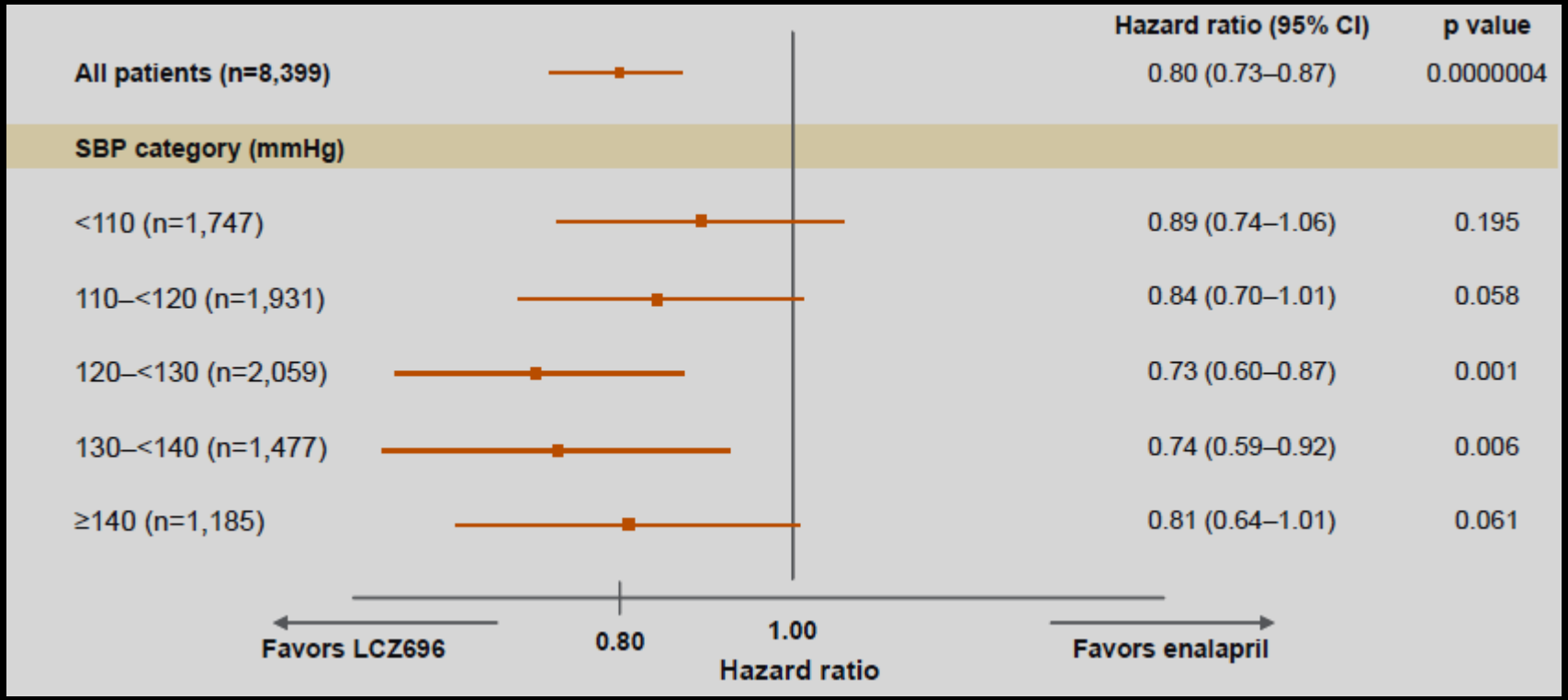
From: Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF

Eur Heart J. 2017;38(15):1132-1143. doi:10.1093/eurheartj/ehw570

.

Baseline SBP did not influence the treatment effect of ARNI compared with enalapril

The reduction in the primary outcome for LCZ696 compared with enalapril was consistent across SBP categories (p=0.67 for treatment by SBP category interaction)



Bohm et al. Eur J Heart Fail 2015;17(Suppl 1):393

Hypotension No Reason to Avoid Sacubitril/Valsartan

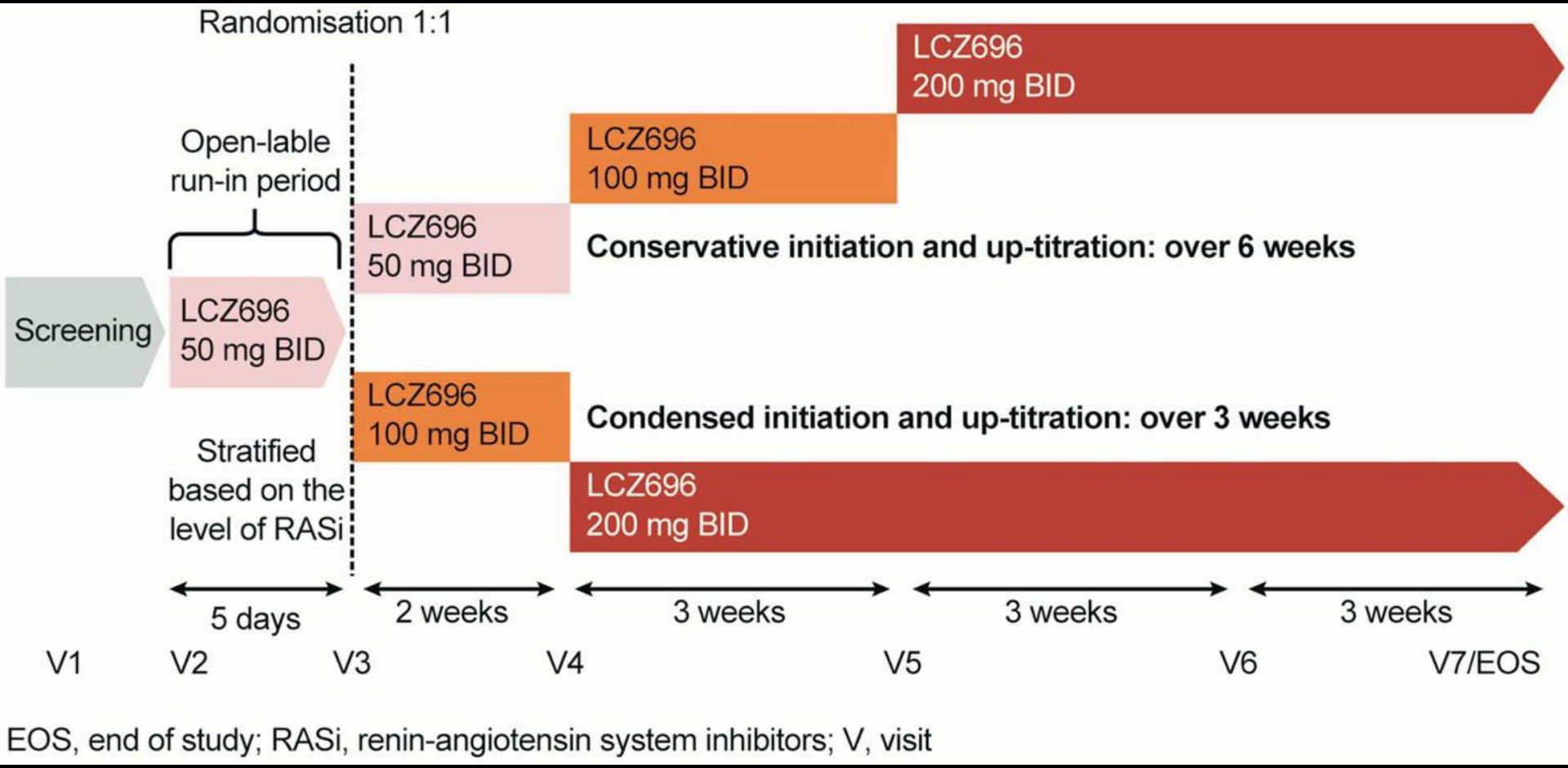
Responses to Hypotension* Events in PARADIGM-HF Randomization Phase by Treatment Group

Response to hypotension event	Enalapril, n=4212 (% of 1109 events)	Sacubitril/Valsartan, n=4187 (% of 1525 events)	*P*
Hospitalization	12.3	7.5	<0.001
Dose adjustment or temporary interruption	34.3	39	0.014
Permanent discontinuation	2.6	2.6	0.93
Change in other meds	12.7	12.9	0.92
Nondrug therapy	2.1	2.6	0.42
No action	43.6	42.4	0.51

*Hypotension defined as "hypotension or orthostatic hypotension, or postural dizziness, or dizziness, or presyncope, or syncope, or depressed consciousness, or loss of consciousness." Results were similar for the alternative definition of "hypotension or postural hypotension, or postural dizziness."

Heart Failure Society of America 2016 Scientific Meeting

TITRATION trial

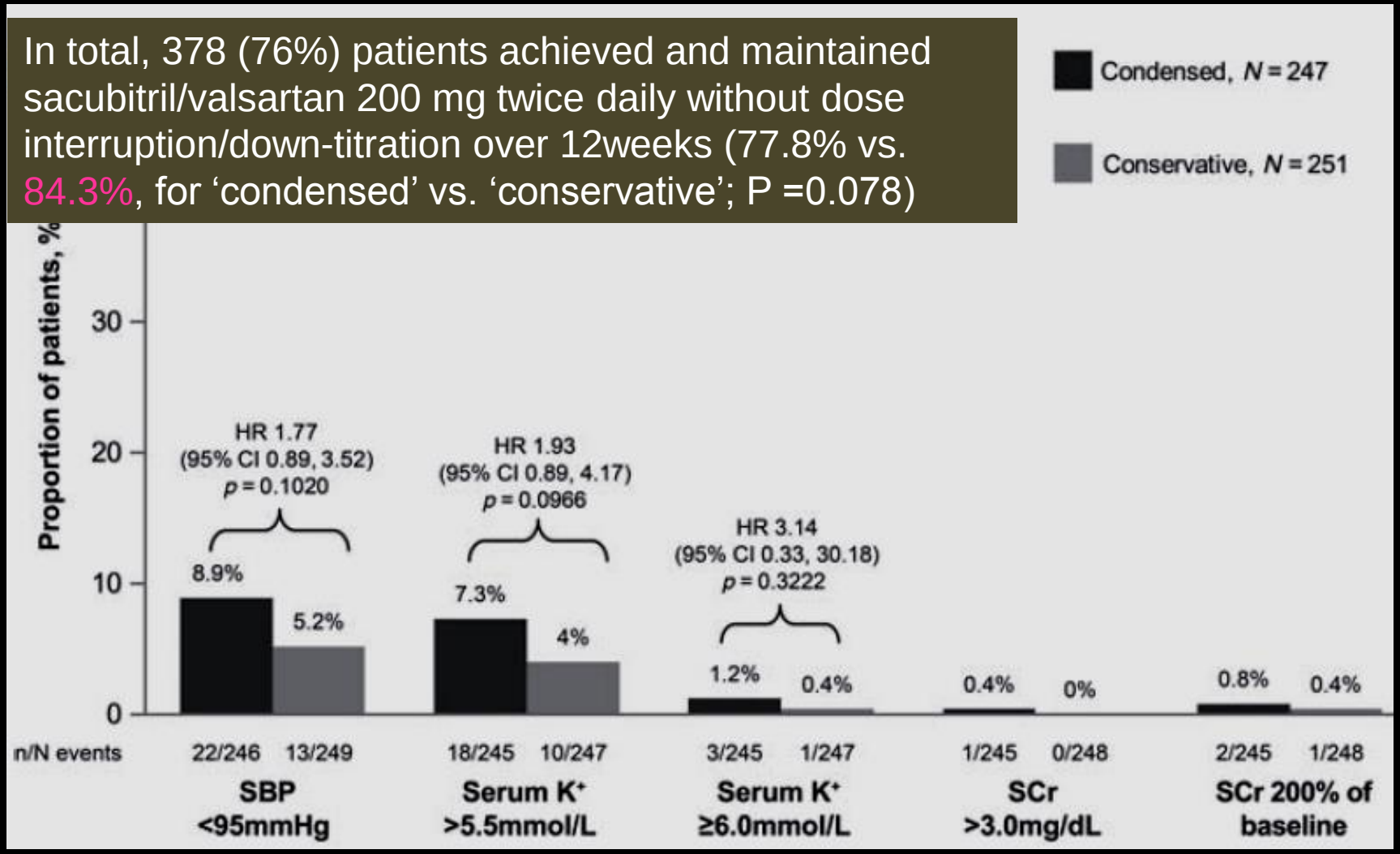


EOS, end of study; RASi, renin-angiotensin system inhibitors; V, visit

European Journal of Heart Failure (2016) 18, 1193–1202

Condense vs Converative

In total, 378 (76%) patients achieved and maintained sacubitril/valsartan 200 mg twice daily without dose interruption/down-titration over 12weeks (77.8% vs. 84.3%, for ‘condensed’ vs. ‘conservative’; P =0.078)



1 適應症及用法

1.1 心臟衰竭

ENTRESTO® 核准用於治療慢性心臟衰竭 (紐約心臟學會 [NYHA] 第二級至第四級) 且心室射出分率降低的患者，減少心血管死亡和心臟衰竭住院風險。

說明 : ENTRESTO® 可以和其他心臟衰竭療法併用，用於取代血管收縮素轉化酶抑制劑 (ACEI) 或血管收縮素受體阻斷劑 (ARB)。

2 用法用量

2.1 劑量

ENTRESTO® 禁止與 ACEI 併用。如欲從原本使用的 ACEI 轉換為 ENTRESTO®，兩種藥物之間須間隔 36 小時的藥物排除期 (washout period) *[參閱禁忌症 (4) 及藥物交互作用 (7.1)]*。

ENTRESTO® 的建議起始劑量為每日兩次 100 毫克。

依據患者耐受情況於 2 至 4 週後加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

2.2 未服用 ACEI 或 ARB，或之前使用低劑量前述藥物患者之劑量調整

目前未服用 ACEI 或 ARB 的患者，或是之前使用低劑量前述藥物的患者，建議之起始劑量為每日兩次 50 毫克。依據患者耐受情況，每 2 至 4 週加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

2.3 重度腎功能不全患者之劑量調整

重度腎功能不全 (eGFR < 30 mL/min/1.73 m^2) 患者之建議起始劑量，為每日兩次 50 毫克。依據患者耐受情況，每 2 至 4 週加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

輕度或中度腎功能不全患者，不需要調整起始劑量。

2.4 肝功能不全患者之劑量調整

中度肝功能不全 (Child-Pugh B 級) 患者之建議起始劑量，為每日兩次 50 毫克。依據患者耐受情況，每 2 至 4 週加倍 ENTRESTO® 劑量，達到每日兩次 200 毫克的目標維持劑量。

輕度肝功能不全患者，不需要調整起始劑量。

不建議重度肝功能不全患者使用此藥物。

Managing Hypotension

- Correct volume or salt depletion prior to administration of ENTRESTO, or start at a lower dose.
- If hypotension occurs, consider dose adjustment of **diuretics**, antihypertensive drugs, and treatment of other causes of hypotension (eg, hypovolemia).
- Permanent discontinuation of therapy is usually not required.

Clinical Critical Issues

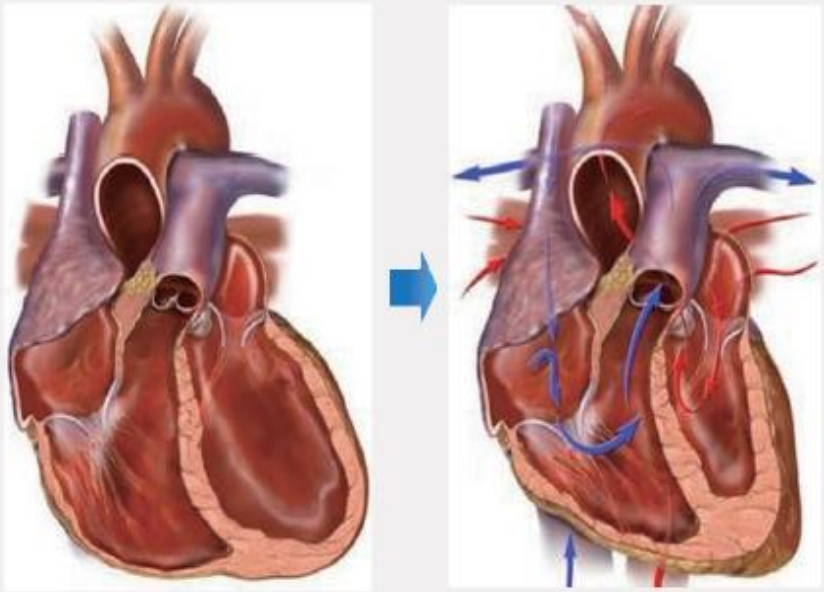
- Safety
- Efficacy

Entresto進一步改善心臟功能與結構

相較於baseline，來自法國的Real World Evidence

- 86% HFrEF病患達到目標劑量 (97/103 mg), 8%使用減半劑量 (49/51mg), 2% 使用最低劑量 (24/26mg)，furosemide 劑量顯著降低 (83 vs 153 mg, P<0.0001).
- 80 位接受Entresto的HFrEF病患，心臟超音波檢查在使用前及使用後三個月比較顯示:

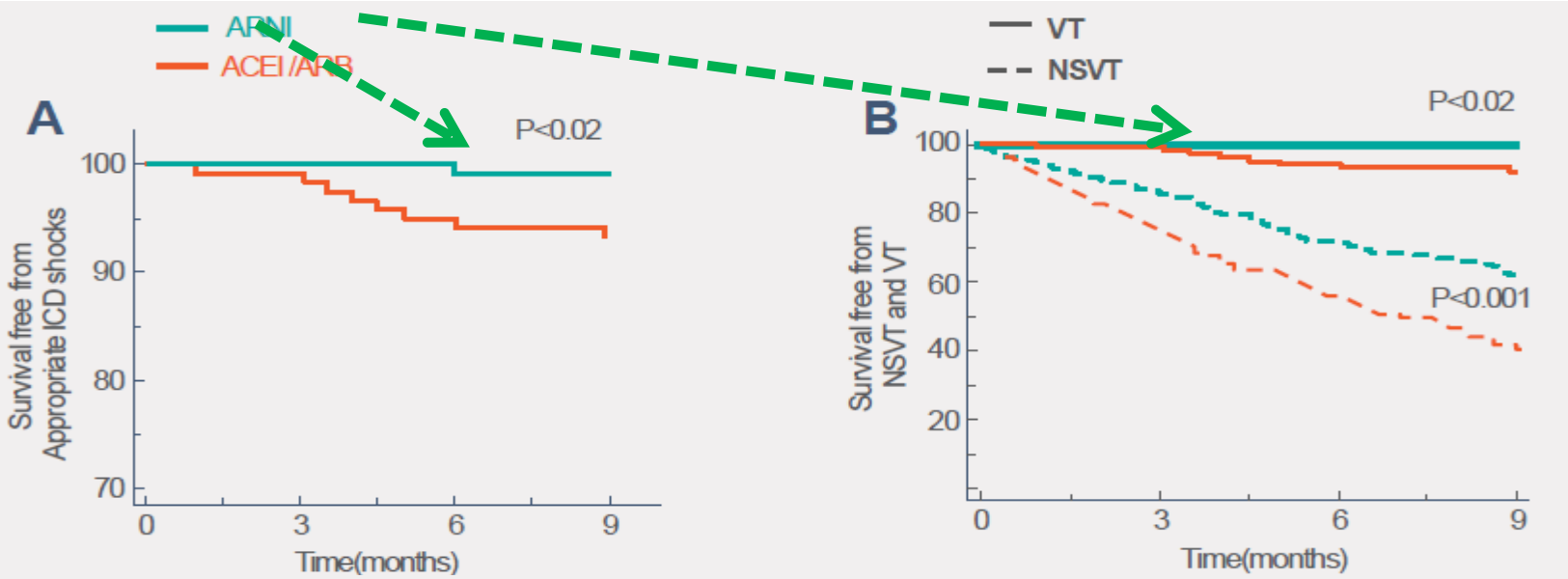
	Baseline	3 Month After	p value
LVED diameter	67.2±8.6 mm	64.8±10.9 mm	p=0.003
LVED volume	218.8±79.1 mL	204.1±79.3 mL	p<0.001
LVES volume	158.9±68.0 mL	142.7±70.1 mL	p<0.001
Left atrial Volume index	43.7±15.2 mL/m²	39.5±13.9 mL/m2	p=0.005
LVEF	28.4±7.7%	31.9±8.2%	p<0.0011



LVED: left ventricular end-diastolic, LVEF: left ventricular ejection fraction, LVES: left ventricular end-systolic

1. Poster presented at: 2017 European Society of Cardiology Heart Failure Congress; April 29-May 2, 2017; Paris, France.
2. Image from: http://berkscardiologists.com/congestive-heart-failure-chf/

Entresto 進一步降低ICD Shock以及ventricular arrhythmia發生率

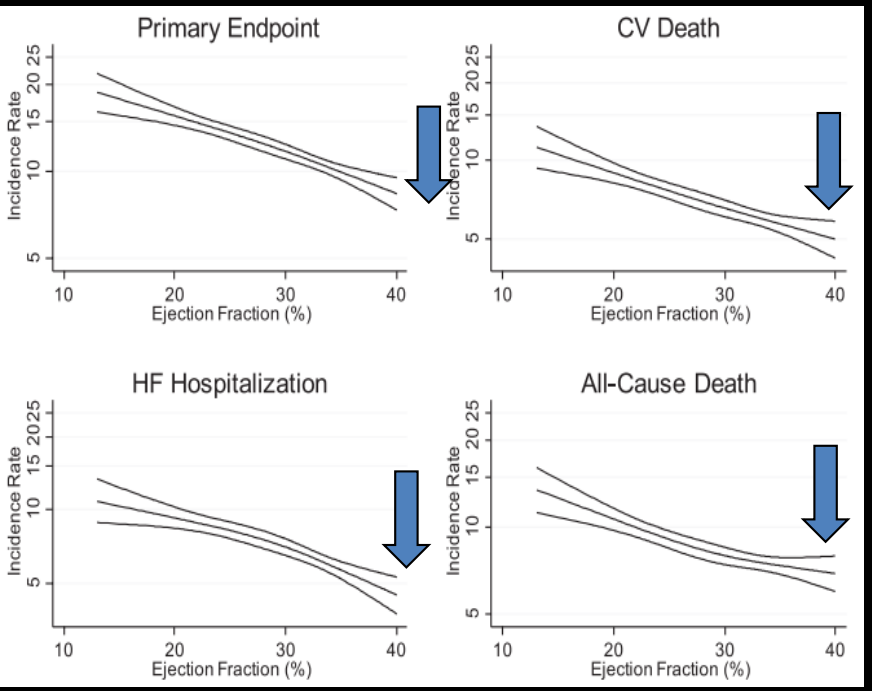


以Kaplan–Meier curve 比較Entresto (n=120)與ACEI/ARB (n=120) ，心室顫動(ventricular arrhythmia)和 appropriate ICD shocks. A: Entresto 較ACEI/ARB 顯著降低appropriate ICD shocks (P <.02). B: Entresto 較ACEI/ARB 顯著降低VT (P <.02) 與NSVT (P <.001)

方法	本研究納入**120位ICD及HFrEF病患，納入條件為** **(1) NYHA functional class≧II** **(2) LVEF≦40** **(2) 遠程監控** **病患接受ACEI / ARB, BB和MRA治療9個月後，將ACEI / ARB轉換為Entresto，持續觀察9個月。分析appropriate ICD shocks，非持續性室性心搏過速 (NSVT)，心室性早期收縮負擔 (PVC burden)和雙心室起搏百分比 (biventricular pacing percentage)。**
結論	**Entresto與ACEI / ARB相比，可降低心室顫動 (ventricular arrhythmia)和appropriate ICD shocks的機率。**

Carlos de Diego et al. Heart Rhythm 2018;15:395-402

Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in HFrEF - (PARADIGM-HF) Trial



Outcome	Crude (HR, 95% CI)	Adjust (HR, 95% CI)
CV death or HF Hospitalization	1.15 (1.12, 1.19)	1.09 (1.05, 1.13)
CV death	1.17 (1.12, 1.22)	1.09 (1.04, 1.14)
HF Hospitalization	1.17 (1.12, 1.22)	1.09 (1.04, 1.14)
All-cause death	1.14 (1.09, 1.18)	1.07 (1.03, 1.12)

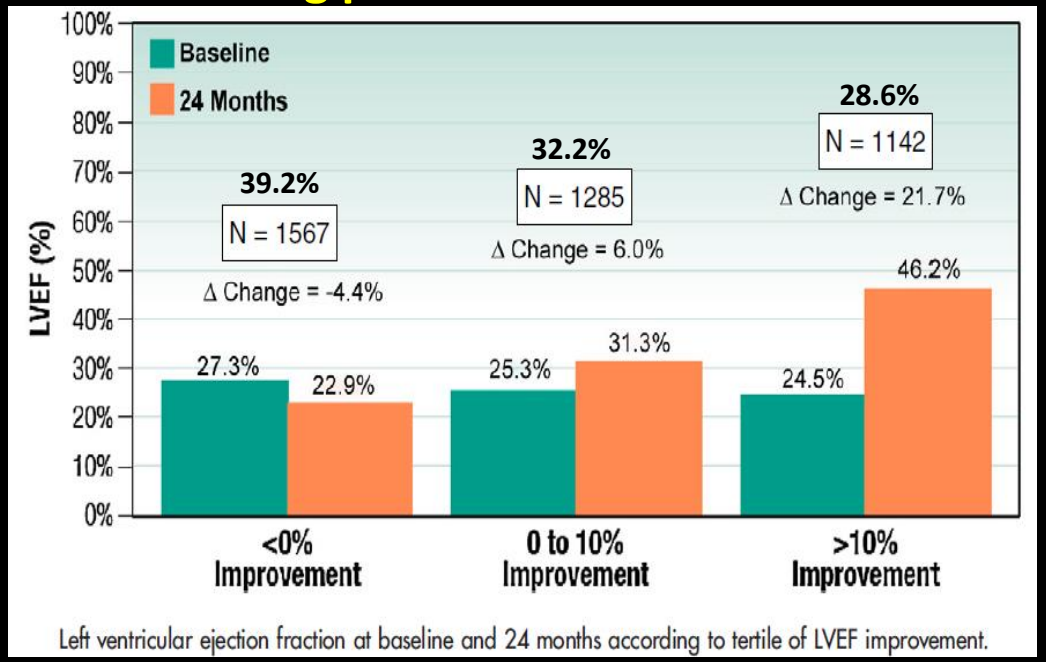
Improving LVEF => ⇊ Total Mortality

⇊ CV Death

⇊ HF Hospitalization

Solomon Scott D et al. Circulation Heart Failure 2016;9:e002744

Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: Findings from IMPROVE HF



Left ventricular ejection fraction at baseline and 24 months according to tertile of LVEF improvement.

ACEI/ARB: **83%**

B-Blocker: **88%**

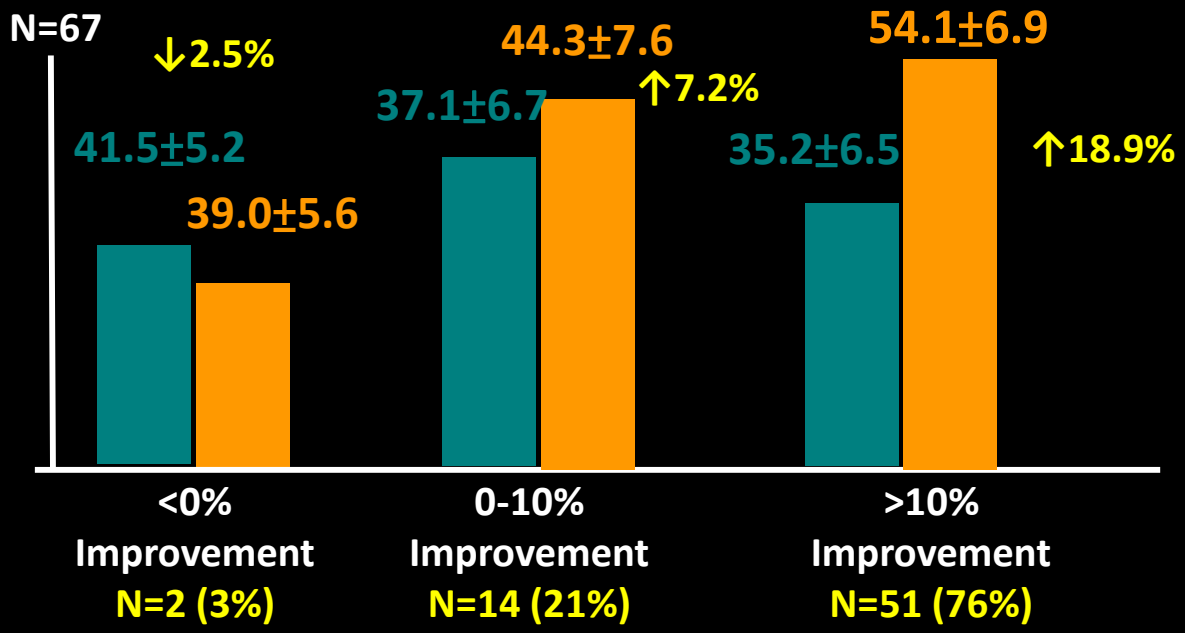
MRA: **28%**

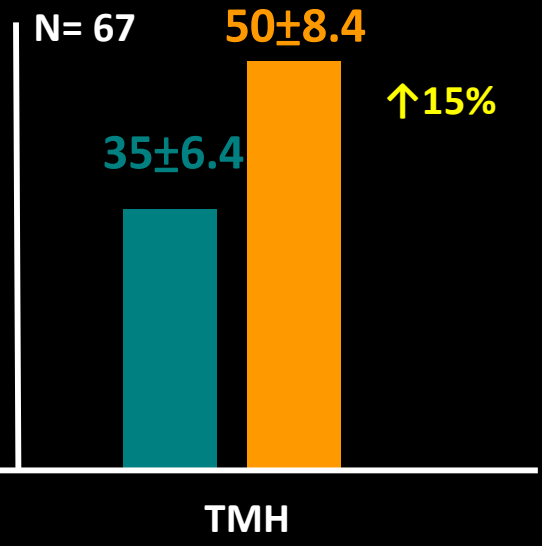
CRT-P/ CRT-D: **18%**

Baseline LVEF: **25.8%**

24 Months LVEF: **32.3%**

=> **+6.4%**

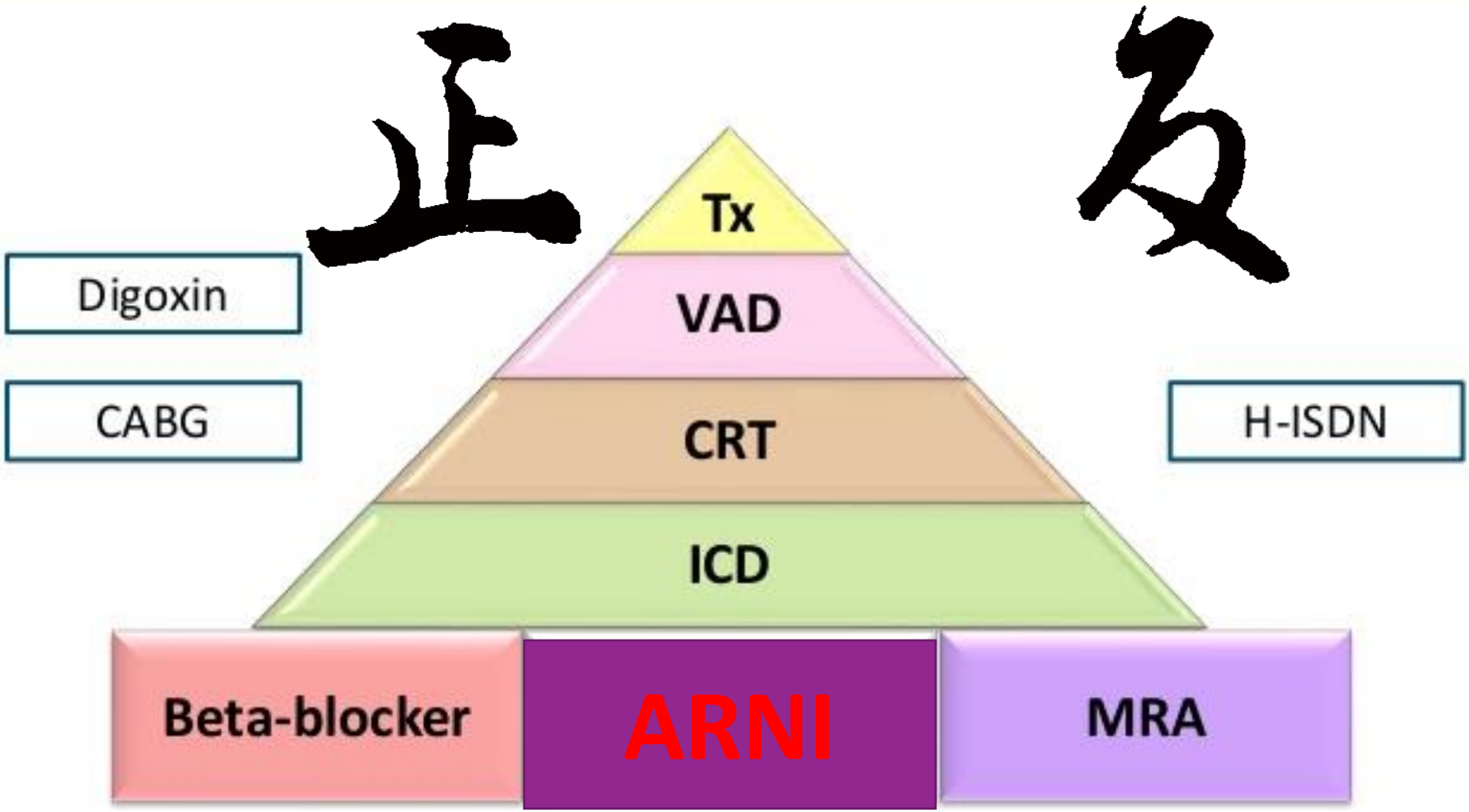




From Dr Fang et al. TMH

The Management of Heart Failure – A PARADIGM Shift?

HF-REF: The building blocks of therapy



What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan?

Of patients with HFrEF referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomization criteria, on which the ESC Guidelines are based; this proportion rises to 60% if background medication is ignored.

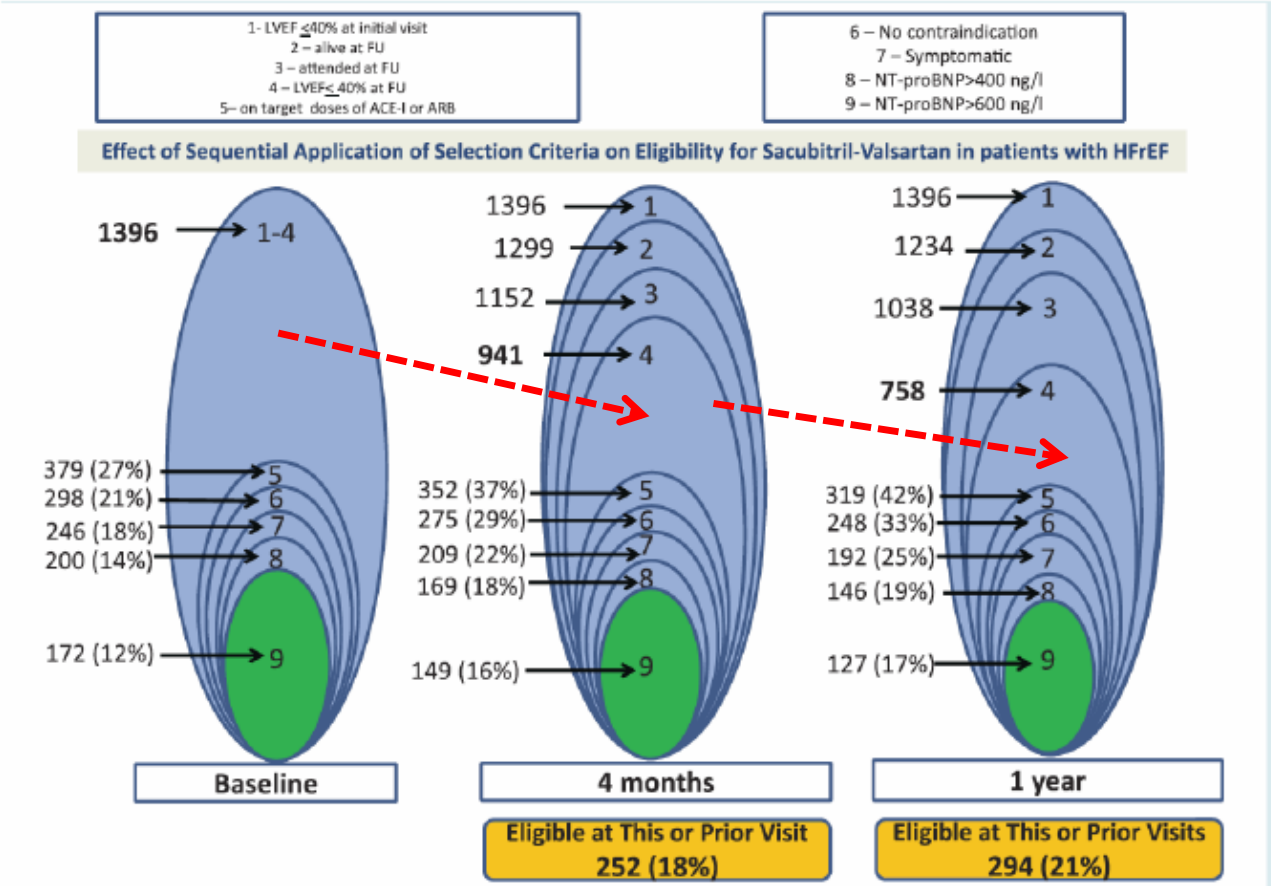


Figure 1 Venn diagram showing the number of patients eligible for sacubitril–valsartan following the strict criteria used in the PARADIGM-HF trial. The orange box shows cumulative, unique patients. ACE-I, ACE inhibitor; FU, follow-up.

2001-2014
Community HF clinic
(n=6,131)

Eur J Heart Fail. 2017 Jun;19(6):768-778. doi: 10.1002/ejhf.788. Epub 2017 Feb 27.

TCVGH Experience

Entresto in TCVGH <2016/9-2018/3>

Baseline (n=51)	
Age	63.8±14.8
Gender	
F/M	15(29.4%)/36(70.6%)
Etiology	
DCM	31(60.8%)
ICM	18(35.3%)
other	2(3.9%)
Fc	
I	1(2%)
II	4(7.8%)
III	26(51%)
IV	16(31.4%)
Unkown	4(7.8%)
HTN	16(31.4%)
DM	13(25.5%)
CKD	20(39.2%)
Device	33(64.7%)
CRT	18(35.3%)
CRTD	10(19.6%)
ICD	5(9.8%)

Medication (n=51)	
Pre	
ACEI	13(25.5%)
ARB	21(41.2%)
B_blocker	47(92.2%)
MRA	35(68.6%)
Digitalis	19(37.3%)
Diuretic	35(68.6%)
Entresto	
50 mg bid	16 (31.4%)
100 mg bid	31(60.8%)
200 mg bid	4(7.8%)
Combined beta-blocker	48(94.1%)
Combined MRA	39(76.5%)

Device: 64.7%

Clinical Characteristics

	Pre-Entresto (n=51)	Post-Entresto (n=51)	p-value
SBP (mmHG)	119.4±18.1	113.9±16.8	0.014
DBP (mmHG)	69.3±12	63±12.1	0.004
HR (/min)	80.5±11.2	77.9±13.3	0.307
VT (/day)	0.9±4.8	0.9±3.5	0.929
AF (%)	10.7±28.9	9.4±28.1	0.227
Lab data			
UA	8.3±3.3	7.2±2.2	0.21
Na	138.7±2.8	139.1±2.8	0.792
K	4.4±0.6	4.4±0.5	0.813
BUN	27.8±17	28.5±19.5	0.537
Cr	1.81±2.27	1.72±2.06	0.757
Glucose	118.8±42	129.4±52.9	0.923
HBA1C	6.6±0.9	6.9±1.3	0.208
Chol	173.4±33.2	158±47.1	0.692
HDL	42.4±8.6	46±4.8	NE
TG	143±115.1	150.7±126.4	0.468
LDL	104.9±30.4	93.5±28	0.201
LA	18.9±10.7	17.3±7.4	0.807

Echocardiography

	Pre-Entresto (n=48)	Post-Entresto (n=48)	p-value
LVIDd (mm)	62.9±11.8	59.1±11	<0.001
LVIDs (mm)	49.7±12.2	46.2±12.4	0.006
LVEF (%)	30.1±8.9	32.9±10.4	0.011
AR			0.97
0.5	14(27.5%)	13(27.7%)	
1	20(39.2%)	18(38.3%)	
1.5	6(11.8%)	6(12.8%)	
2	10(19.6%)	8(17%)	
3	1(2%)	2(4.3%)	
MR			0.428
0.5	3(5.9%)	4(8.5%)	
1	22(43.1%)	19(40.4%)	
1.5	9(17.6%)	9(19.1%)	
2	11(21.6%)	13(27.7%)	
2.5	0(0%)	1(2.1%)	
3	6(11.8%)	1(2.1%)	
PSPG (mmHG)	32.6±15.8	30.3±9.8	0.241

- 28(58%) pts have LVEF improvement,
- 16(33%) patients improved LVEF $\geqq$ 5%.

Conclusions

- Sudden death and pumping failure: two major mortality
- Who will use Entresto? for people with heart failure and a reduced ejection fraction (forward squeeze of the heart) of < 35%, or for people who have been hospitalized for heart failure in the past 12 months.
- A washout period of 36 hours is required prior to starting Entresto. This means you will need to stop taking all ACE inhibitors or ARBs for 36 hours prior to starting Entresto.
- Low dose initially, 50 mg bid when BP>100 mmhg.

THANK YOU FOR YOUR ATTENTION !