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CSANZ Annual Scientific Meeting Wellington NZ 2019

The "Stable Heart Failure" Patient and Beyond

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Disclosures

- **Speakers Fees – Novartis**
- **Advisory Board – Novartis, Vifor Pharma, Boehringer Ingelheim, Cytokinetics**
- **Research Funding – Boehringer Ingelheim**
- **Other – Director GCTP Ltd**

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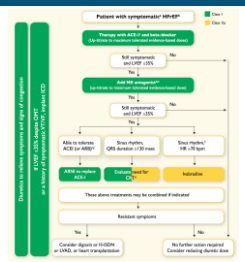
The ESC guidelines



CRT=cardiac resynchronization therapy; H-ISDN=hydralazine and isosorbide dinitrate; HR=heart rate; ICD=implantable cardioverter defibrillator; LVAD=left ventricular assist device; MR=mineralocorticoid receptor; OMT=optimal medical therapy; VTVF=ventricular tachycardia/ventricular fibrillation

Ponikowski et al. *Eur Heart J* 2016;37:2129–2200

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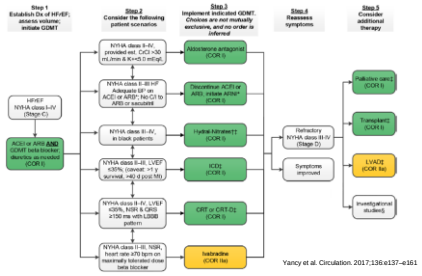
ACC/AHA/HFSA 2017 heart failure guidelines update



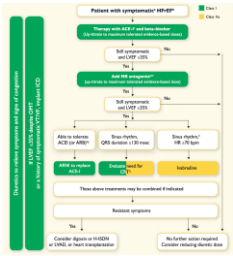
Yancy et al. Circulation. 2017;136:e137–e161

5

Why don't we do this?

6

The ESC guidelines



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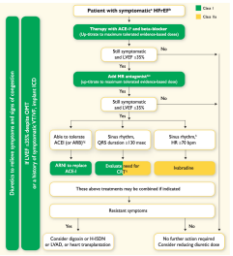
The ESC guidelines



ACEI + BB ✔

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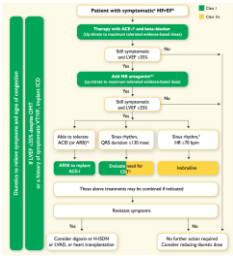

ACEI + BB ✔

MRA ✔

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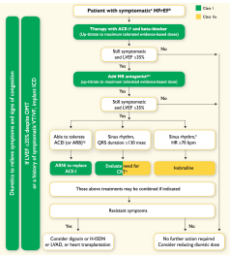
The ESC guidelines



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MRA ✔

(Partially!)

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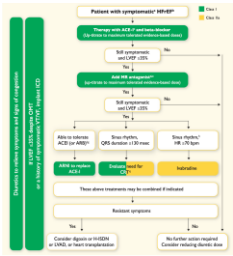

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ARNI ✘

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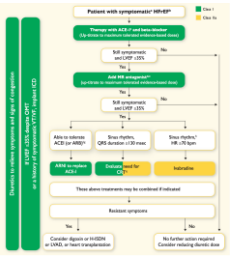

ACEI + BB ✔

MRA ✔

ARNI ✘

CRT/ICD ✘

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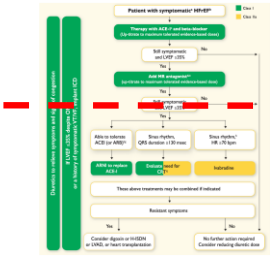

ACEI + BB ✓

MRA ✓

ARNI ✗

CRT/ICD ✗

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Ponikowski et al. *Eur Heart J* 2016;37:2129–2200

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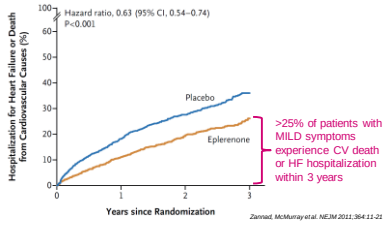
EMPHASIS-HF

Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure

2737 patients, ≥55 years, NYHA class II, with CV hospitalization within 6 months (or elevated BNP/NT pro BNP) and LVEF ≤0.30 (or ≤0.35 if QRS duration >130msec. Followed for a median of 21 months



>25% of patients with MILD symptoms experience CV death or HF hospitalization within 3 years

Zannad, McMurray et al. *NEJM* 2011;364:11-21

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PARADIGM-HF: Baseline Characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
CRT	7.0%	6.7%
ICD	15%	15%

McMurray et al. *N Engl J Med* 2014;371:993-1004

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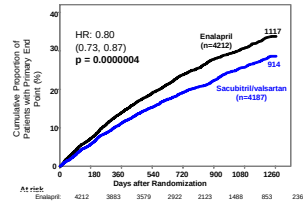
PARADIGM-HF: Primary outcome

Cardiovascular death or heart failure hospitalization

Even in well treated patients outcomes were improved
So why don't we act on this?



McMurray, Packer et al. *N Engl J Med* 2014; 371(11):993-1004

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"My patient is stable"

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What does "stable" mean?

adjective: **stable**

(of a patient or their medical condition) not deteriorating in health after an injury or operation.

"he is now in a stable condition in hospital"

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What does “stable” mean?

Are patients with HFREF ever “stable”?

Does ”stable” mean remaining in the same clinical state (not deteriorating)?

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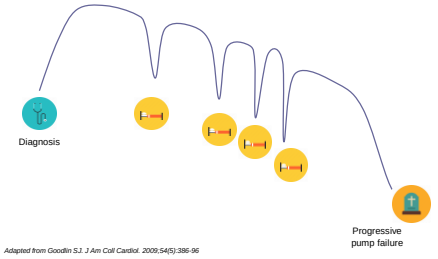
The natural history of HF



Adapted from Goodlin SJ. J Am Coll Cardiol. 2009;54(5):386-96

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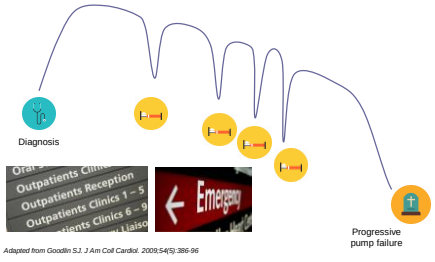
The natural history of HF



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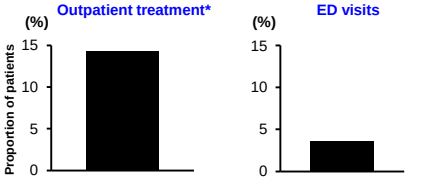
Other manifestations of worsening/instability

Enalapril group in PARADIGM-HF
ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%



*Addition of a new drug for treatment of WHF, need for IV therapy or increase in diuretic dose >1 month

McMurray et al. N Eng J Med 2014;371:993-1004
Packer et al. Circulation 2015;131:54-61

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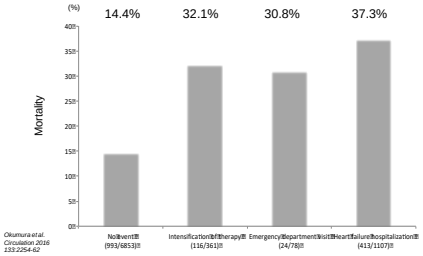
All-cause mortality (%) after a first event (or in patients with no event)



Okumura et al. Circulation 2016 133:2254-62

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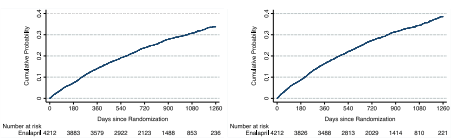
Cumulative rate of adverse outcomes over time

Enalapril group in PARADIGM-HF
ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

Primary composite endpoint
CV death or HF hospitalization

Expanded composite
CV death, hospitalization, ED visit or intensification of therapy



McMurray et al. N Eng J Med 2014;371:993-1004; Okumura et al Circulation 2016 133:2254-62.

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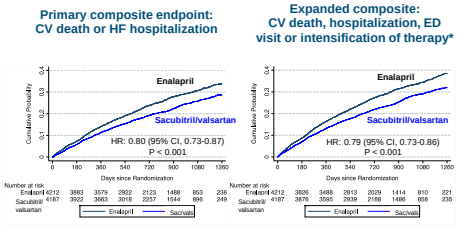
Benefit of sacubitril/valsartan on multiple manifestations of progression/worsening



* *Post hoc analysis*

McMurray et al. N Eng J Med 2014;371:993-1004; Okumura et al Circulation 2016 133:2254-62

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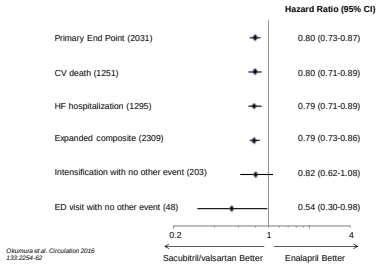
Effect of sacubitril/valsartan versus enalapril for each outcome



Okumura et al. Circulation 2016 133:2254-62

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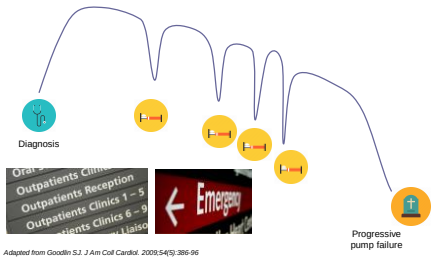
The natural history of HF



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Recurrent HF hospitalizations

Mogensen et al. Eur J Heart Fail. 2018:17;49–50.

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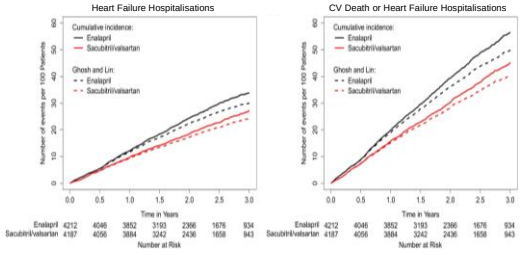
Recurrent HF hospitalisations



Mogensen et al. Eur J Heart Fail. 2018:17;49–50.

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Summary: The myth of clinical "stability" in heart failure

- **Patients with mild symptoms are not stable and progress rapidly, even on optimal treatment. Over 11% patients per year in the control (enalapril) group in PARADIGM-HF exhibited some manifestation of worsening**

McMurray et al. N Eng J Med 2014;371:993-1004; Okumura et al Circulation 2016 133:2254-62.

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Does “stable” mean low risk?

31

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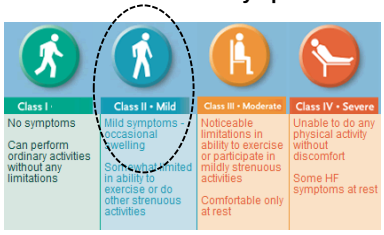
Mild symptoms

NYHA class II: Mild symptoms



Raphael et al. Heart 2007;93:476-482

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MAGGIC risk score

1. Age
2. Sex
3. Diabetes
4. COPD
5. BMI
6. Smoker
7. NYHA class
8. Diagnosis ≤18 months
9. Creatinine
10. SBP
11. LVEF
12. ACEi/ARB
13. Beta-blocker

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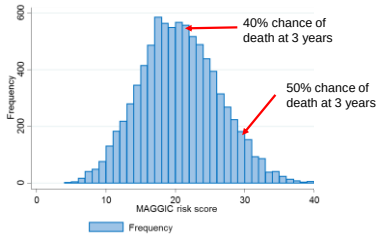
MAGGIC Risk Score in PARADIGM-HF



Simpson et al. J Am Coll Cardiol 2015;66:2059-2071

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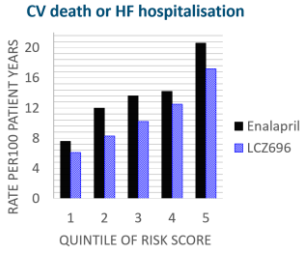
Benefit of LCZ696 across MAGGIC risk score quintiles



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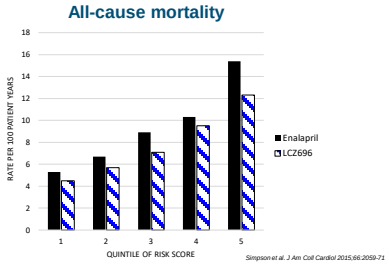

Simpson et al. J Am Coll Cardiol 2015;66:2059-71

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Does "stable" mean the patient feels well?

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Kansas City Cardiomyopathy Questionnaire (KCCQ)

23 items covering 5 domains

- Symptoms
- Physical limitation
- Self-efficacy
- Quality of life
- Social interference

Flynn K et al. Am Heart J. 2012;163:88-94

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KCCQ: Significance of a 5-point change

- **A 5-point change in KCCQ overall score corresponds to:**
  - 112 metre change in 6-minute walking distance and
  - 2.50 ml/kg/min change in peak VO_2 in HF-REF patients
- **A 5-point *decrease* in KCCQ overall score corresponds to a *deterioration* in the patient's condition**

Flynn K et al. Am Heart J. 2012;163:88-94

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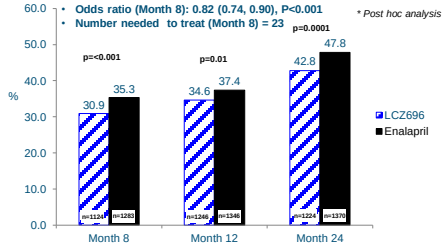
PARADIGM-HF: Percent of patients with at least 5 Points deterioration in KCCQ clinical summary score*



Clinical summary score based on the physical limitation and total symptom score domains.
The analysis included all patients with at least one KCCQ data. For patients who died the KCCQ scores are imputed by zero at all subsequent scheduled visits.

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Summary: The myth of clinical "stability" in heart failure

- **Patients with mild <u>symptoms</u> are not stable and progress rapidly, even on optimal treatment. Over 11% patients per year in the control (enalapril) group in PARADIGM-HF exhibited some manifestation of worsening**
- **An even higher proportion experience a deterioration in symptoms/QoL**

Packer et al. Circulation 2015;131:54-61
McMurray et al. N Eng J Med 2014;371:993-1004; Okumura et al Circulation 2016;133:2254-62.

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“Stable” means patients are not likely to die?

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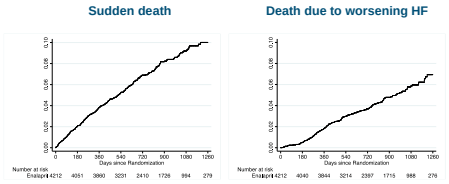
The two major modes of death in HF



Desai et al. Eur Heart J 2015;36:1990-7

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”Stable” means nothing happens to my patient

763 of 2309 (33%) of first primary endpoints (intensification of medical therapy, ED visit, HF hospitalization or CV deaths) were CV deaths

467 of these 763 deaths (61%) were sudden

McMurray et al. N Eng J Med 2014;371:993-1004; Desai As et al Eur Heart J. 2015;36:1990-7.

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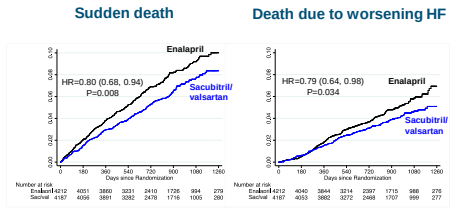
Effect of sacubitril/valsartan on the two major modes of death in HF



Desai et al. Eur Heart J 2015;36:1990-7

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- **Patients with mild symptoms are not stable and progress rapidly, even on optimal treatment. Over 11% patients per year in the control (enalapril) group in PARADIGM-HF exhibited some manifestation of worsening**
- **An even higher proportion experience a deterioration in symptoms/QoL**
- **In a third (33%) of patients, the first manifestation of progression/worsening is cardiovascular death (mainly sudden death) – which is preventable**

Packer et al. Circulation 2015;131:54-61; Desai et al. Eur Heart J 2015;36:1990-7.
McMurray et al. N Eng J Med 2014;371:993-1004; Okumura et al Circulation 2016;133:2254-62

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”Stable” suggests you have time

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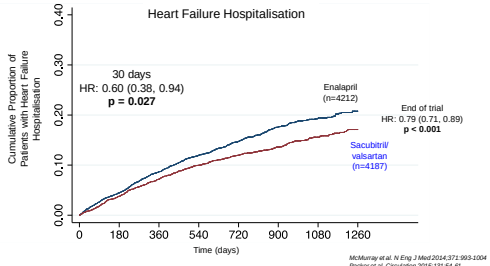
PARADIGM-HF: Make a difference quickly



McMurray et al. N Eng J Med 2014;371:993-1004
Packer et al. Circulation 2015;131:54-61

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"Only for outpatients – what about the *"unstable"* patient?"

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PIONEER-HF: Sacubitril/valsartan in the hospitalized HF patient

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

- **Hypothesis:** **Initiation of sacubitril–valsartan therapy is safe and effective among patients who are hospitalized for acute decompensated HF**
- **Population:** **881 patients; hospitalised HF; EF ≤40%; BNP ≥400 pg/ml or NT-proBNP ≥ 1600 pg/ml – 52% ACEI/ARB naïve**
- **Intervention:** **Sacubitril/valsartan vs enalapril**
- **Primary endpoint:** **Change in NTproBNP**

Velazquez et al NEJM N Engl J Med 2019; 380:539-548

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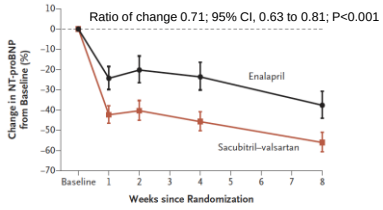
PIONEER-HF: Sacubitril/valsartan in the hospitalized HF patient



Velazquez et al NEJM N Engl J Med 2019; 380:539-548

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PIONEER-HF: Sacubitril/valsartan in the hospitalized HF patient

Outcome	Sacubitril/valsartan	Enalapril	Relative risk
Worsening renal function	60(14%)	65(15%)	0.93(0.67-1.28)
Hyperkalemia	51(12%)	41(9%)	1.25(0.84-1.84)
Hypotension	66(15%)	56(13%)	1.18(0.85-1.64)
Composite	249(57%)	264(60%)	0.93(0.78-1.10)
Death	10(2%)	15(3%)	0.66(0.30-1.48)
HF hospitalization	35(8%)	61(14%)	0.56(0.37-0.84)
LVAD implant	1(0.2%)	1(0.2%)	0.99(0.06-15.97)
Listed for heart transplant	0	0	-
Unplanned outpatient visit leading to the use of IV diuretics	2(0.5%)	2(0.5%)	1.00(0.14-7.07)

Velazquez et al NEJM N Engl J Med 2019; 380:539-548

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TRANSITION

Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study

- **Hypothesis:** **Initiation of sacubitril–valsartan pre-discharge is safe in patients who are hospitalized for acute decompensated HF**
- **Population:** **1002 patients; hospitalised HF; EF ≤40%;– 24% ACEI/ARB naïve**
- **Intervention:** **Sacubitril/valsartan pre or post discharge**
- **Primary endpoint:** **Proportion achieving target dose**

Wachter et al. Eur J Heart Fail. 2019 May 27. doi: 10.1002/ejhf.1498

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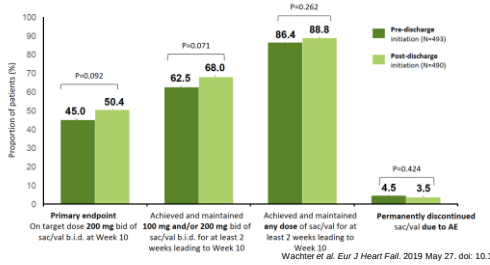
TRANSITION



Wachter *et al. Eur J Heart Fail*. 2019 May 27. doi: 10.1002/ejhf.1498

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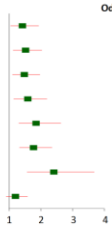
TRANSITION

Predictor	Odds ratio	95% CI	P value
Age (<65 years vs. ≥65 years)	1.42	(1.05, 1.93)	0.023
eGFR at baseline (≥60 mL/min.1.73m² vs. <60 mL/min.1.73m²)	1.52	(1.13, 2.03)	0.005
SBP at baseline ≥120 mmHg vs. >120 mmHg	1.48	(1.11, 1.97)	0.008
No prior history of HF	1.59	(1.15, 2.19)	0.005
Medical history of hypertension (Yes vs. No)	1.85	(1.31, 2.63)	<0.001
Sinus rhythm at baseline	1.77	(1.33, 2.35)	<0.001
Starting dose of sac/val (100 mg vs. 50 mg)	2.41	(1.57, 3.68)	<0.001
Treatment (post-discharge vs. pre-discharge)	1.20	(0.91, 1.58)	0.196



Wachter *et al. Eur J Heart Fail*. 2019 May 27. doi: 10.1002/ejhf.1498

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TRANSITION: Safety

Outcome	Pre-discharge	Post-discharge	P value
Hyperkalaemia	**55 (11.1)**	**56 (11.3)**	**0.9201**
Hypotension	**61 (12.3)**	**45 (9.1)**	**0.1229**
Worsening heart failure	**34 (6.8)**	**42 (8.5)**	**0.3426**
Dizziness	**28 (5.6)**	**21 (4.2)**	**0.3795**
Peripheral oedema	**17 (3.4)**	**24 (4.8)**	**0.2696**
Renal impairment	**25 (5.0)**	**15 (3.0)**	**0.1455**
Diarrhoea	**12 (2.4)**	**23 (4.6)**	**0.0604**
Urinary tract infection	**20 (4.0)**	**15 (3.0)**	**0.4918**
Hyperkalaemia	**55 (11.1)**	**56 (11.3)**	**0.9201**

Wachter *et al. Eur J Heart Fail*. 2019 May 27. doi: 10.1002/ejhf.1498

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"My patients are not suitable candidates"

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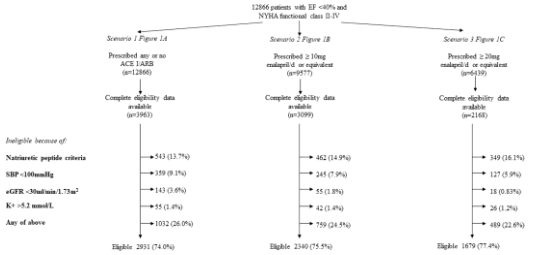
How many people meet the inclusion criteria in a real world registry?



Simpson et al Cardiovasc Drugs Ther. 2019 Mar 23. doi: 10.1007/s10557-019-06873-1

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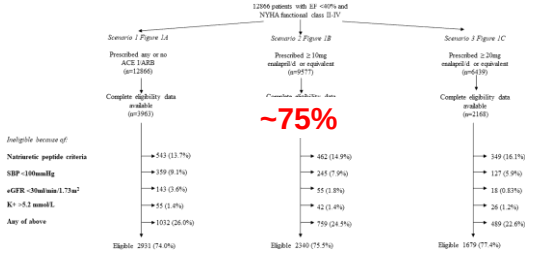
How many people meet the inclusion criteria?



Simpson et al Cardiovasc Drugs Ther. 2019 Mar 23. doi: 10.1007/s10557-019-06873-1

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Summary: The myth of clinical "stability" in heart failure

- **Patients with HFREF are not "stable"**
- ***They change clinical state and risk state frequently***
- ***They are not low risk***
- ***They will experience a deterioration in their symptoms***
- ***They are at a substantial risk of dying suddenly***
- ***We have evidence for the safe use of the drug in hospital and treatment naïve patients***
- ***Most patients are eligible for evidence based therapies it is up to us to provide them!***

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Thank You

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