



Role of Neprilysin Inhibition in Heart Failure

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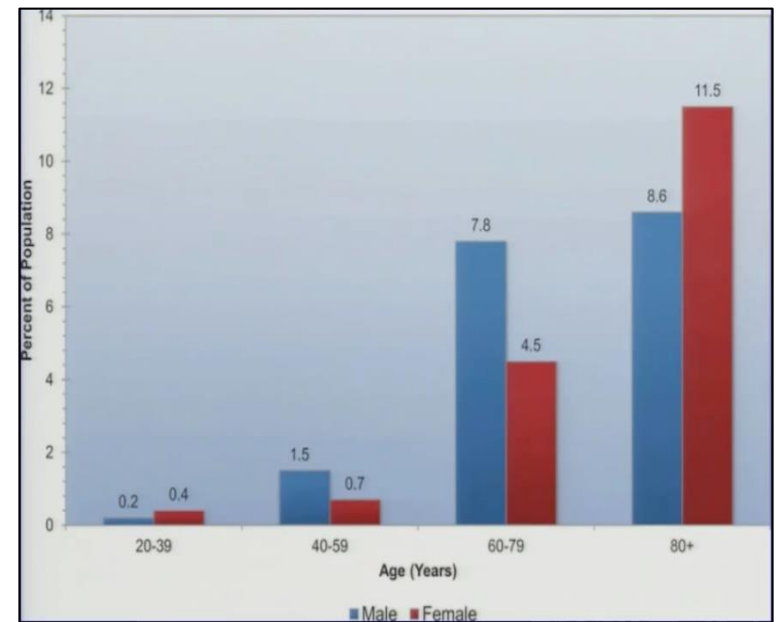
Oak Lawn, Illinois

Disclosures

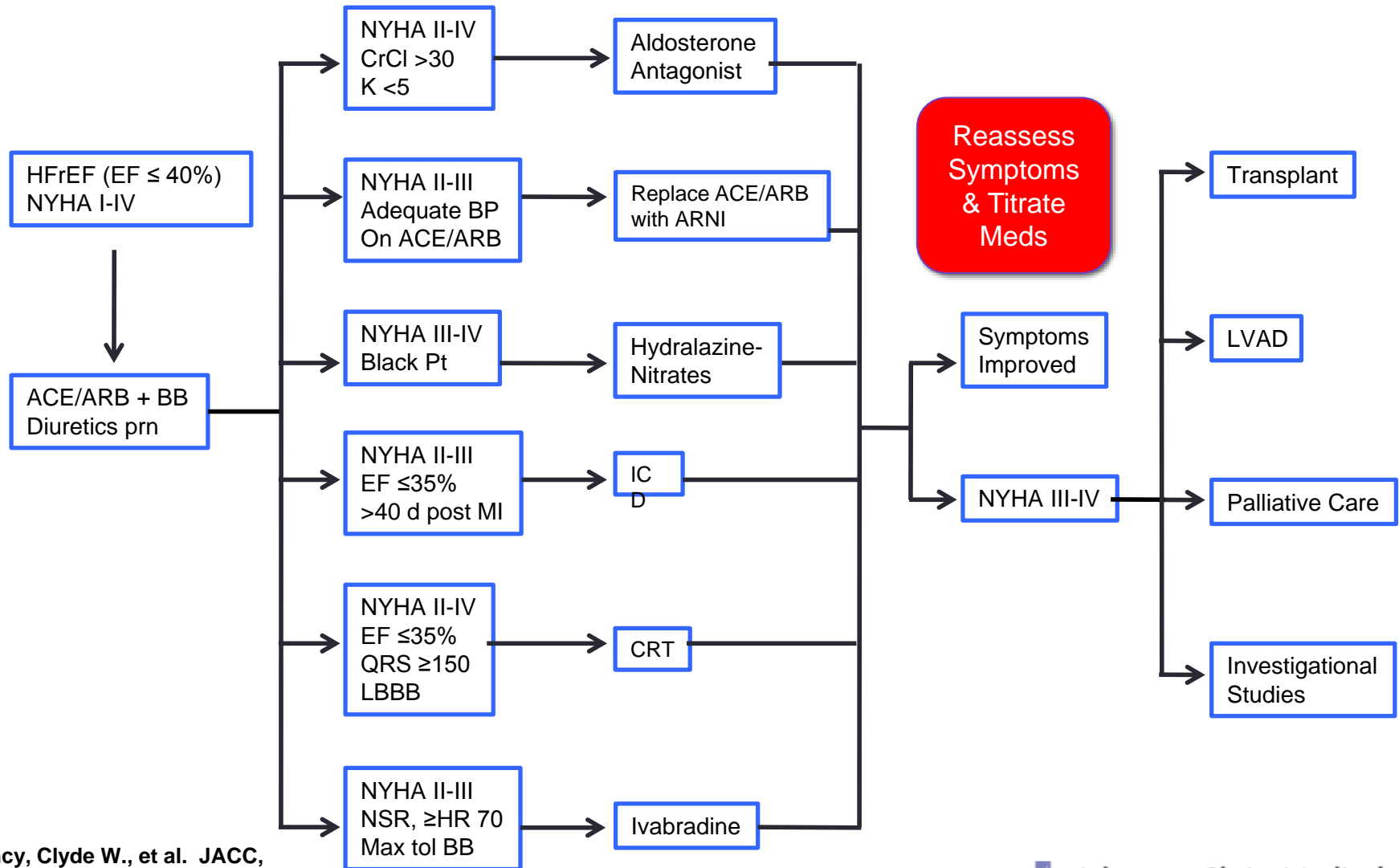
- No affiliations with pharmaceutical or device companies

Epidemiology of HF

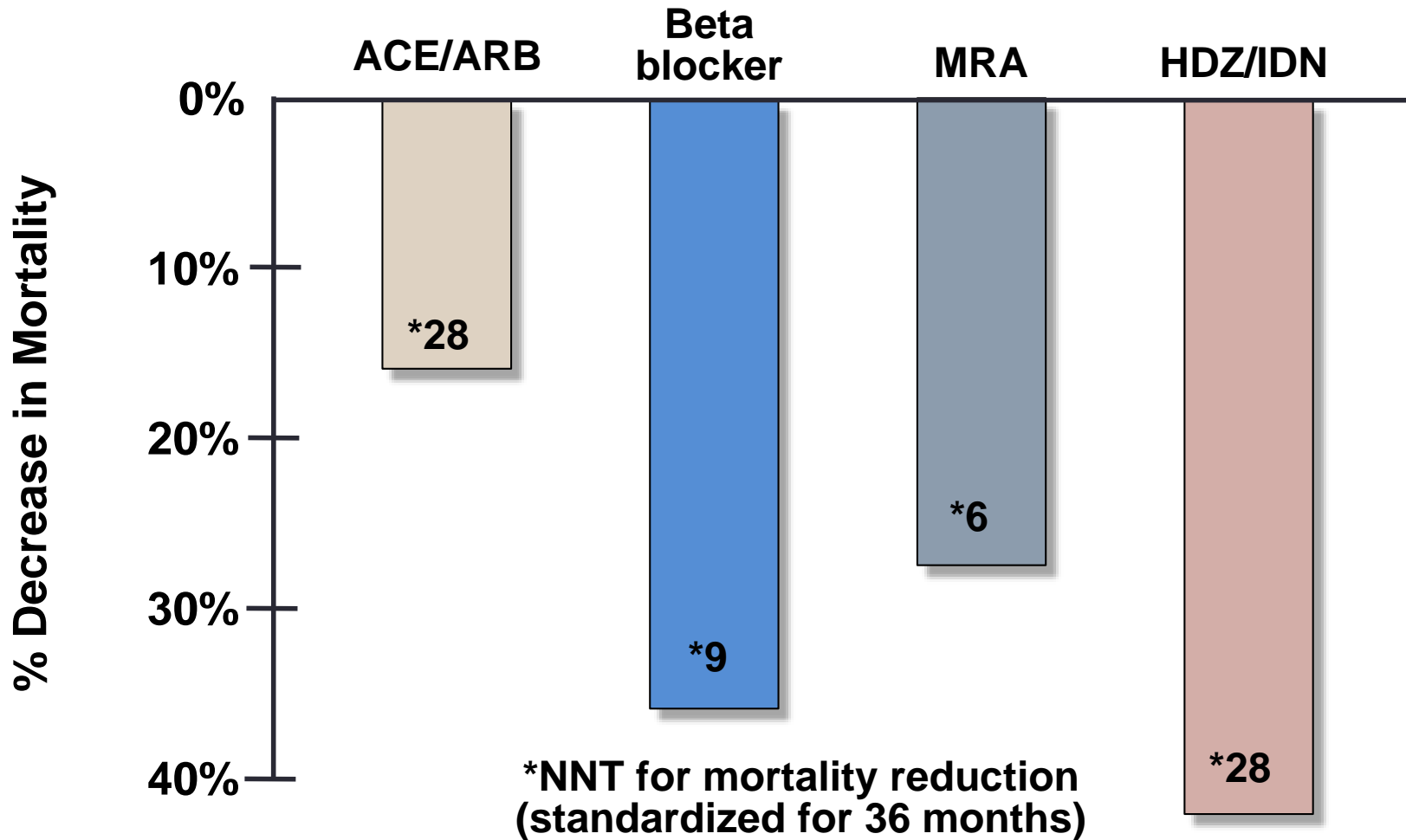
- 6 million with HF
- 1 million hospitalizations/yr
- >300,000 deaths/yr
- 50% mortality at 5 yrs
- 25% 30-day re-hospitalization
- >\$30 billion/yr



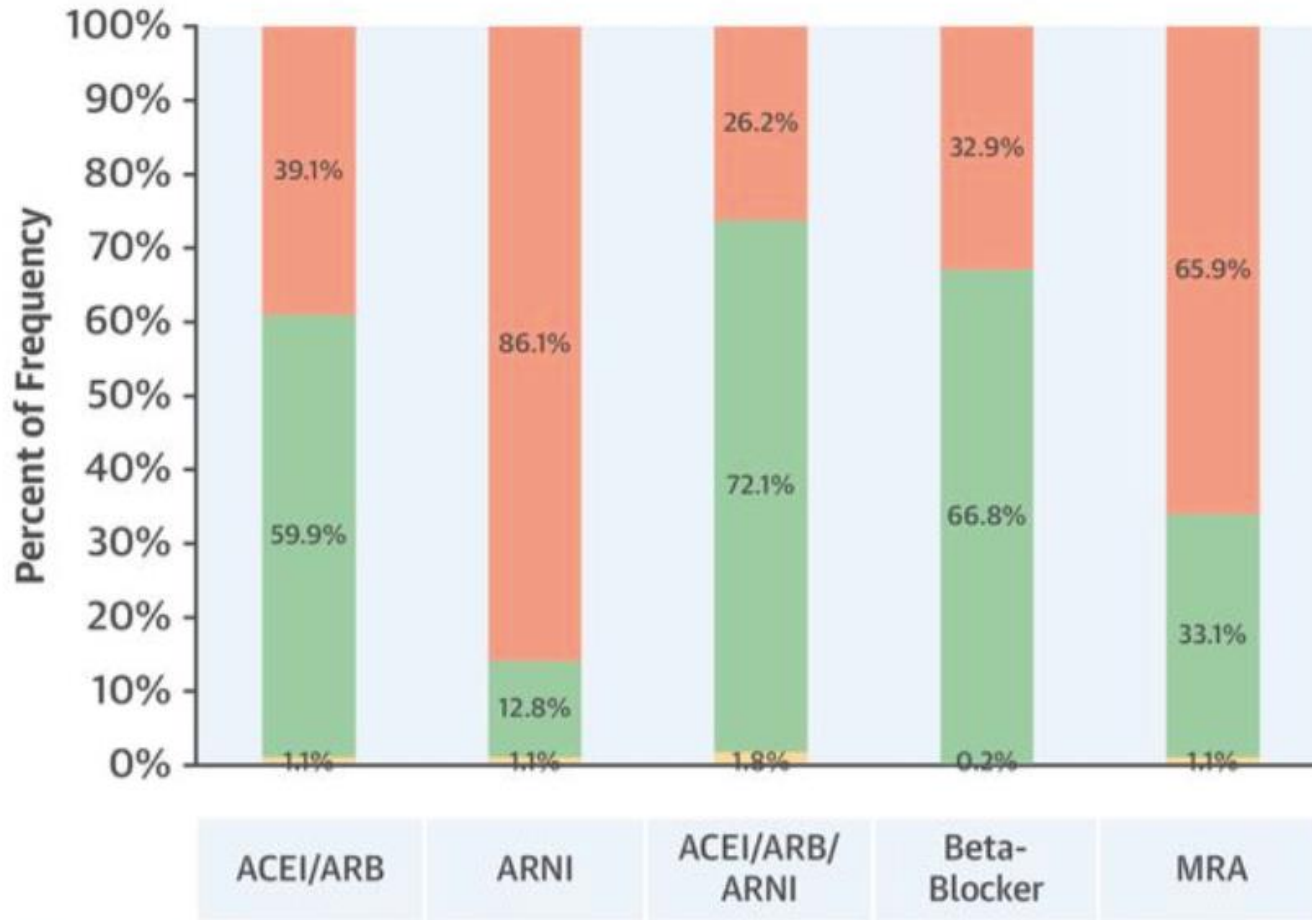
Guideline Directed Medical Therapy (GDMT)



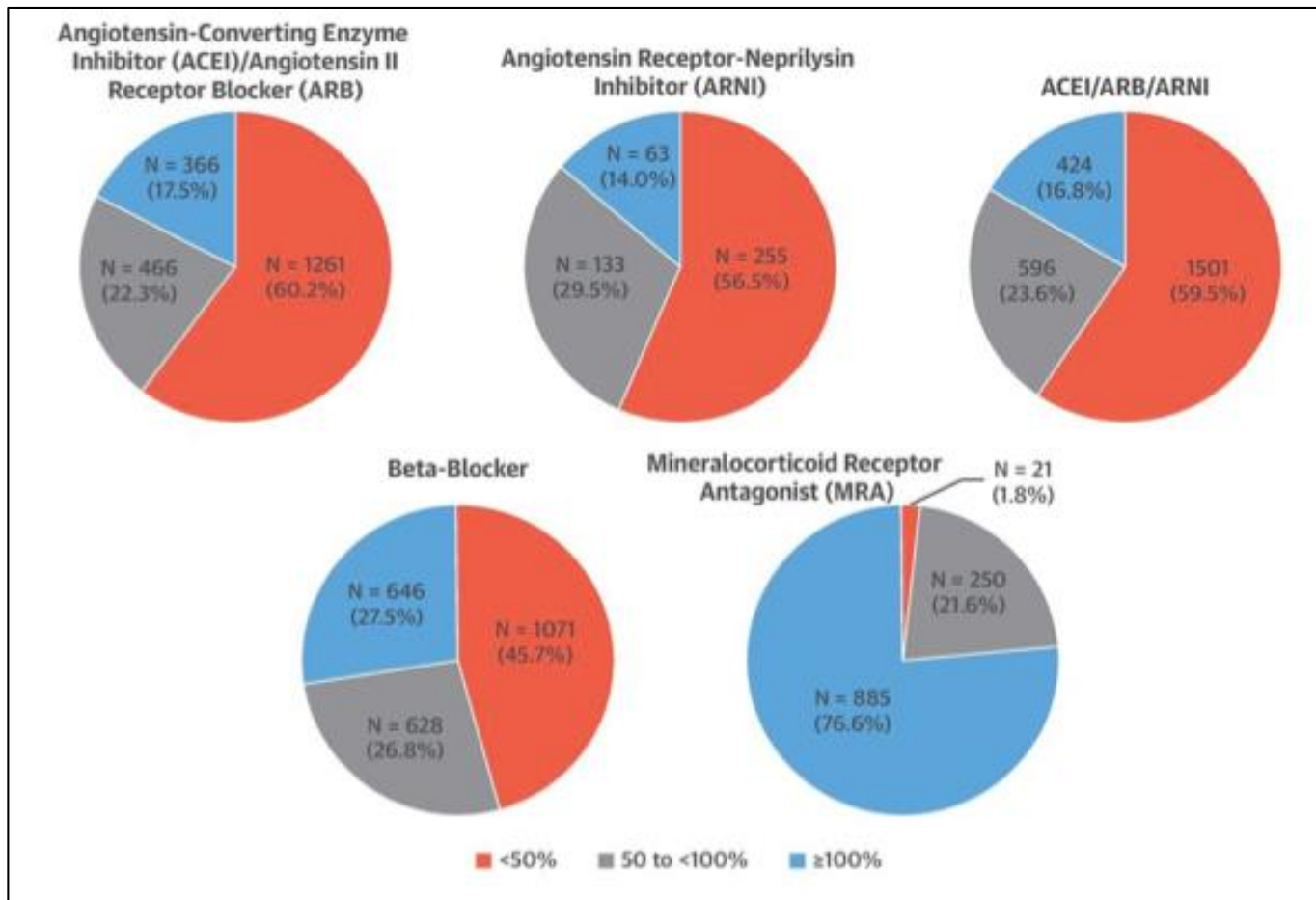
Impact of GDMT



So how are we doing?



So how are we doing?



Sacubitril/valsartan

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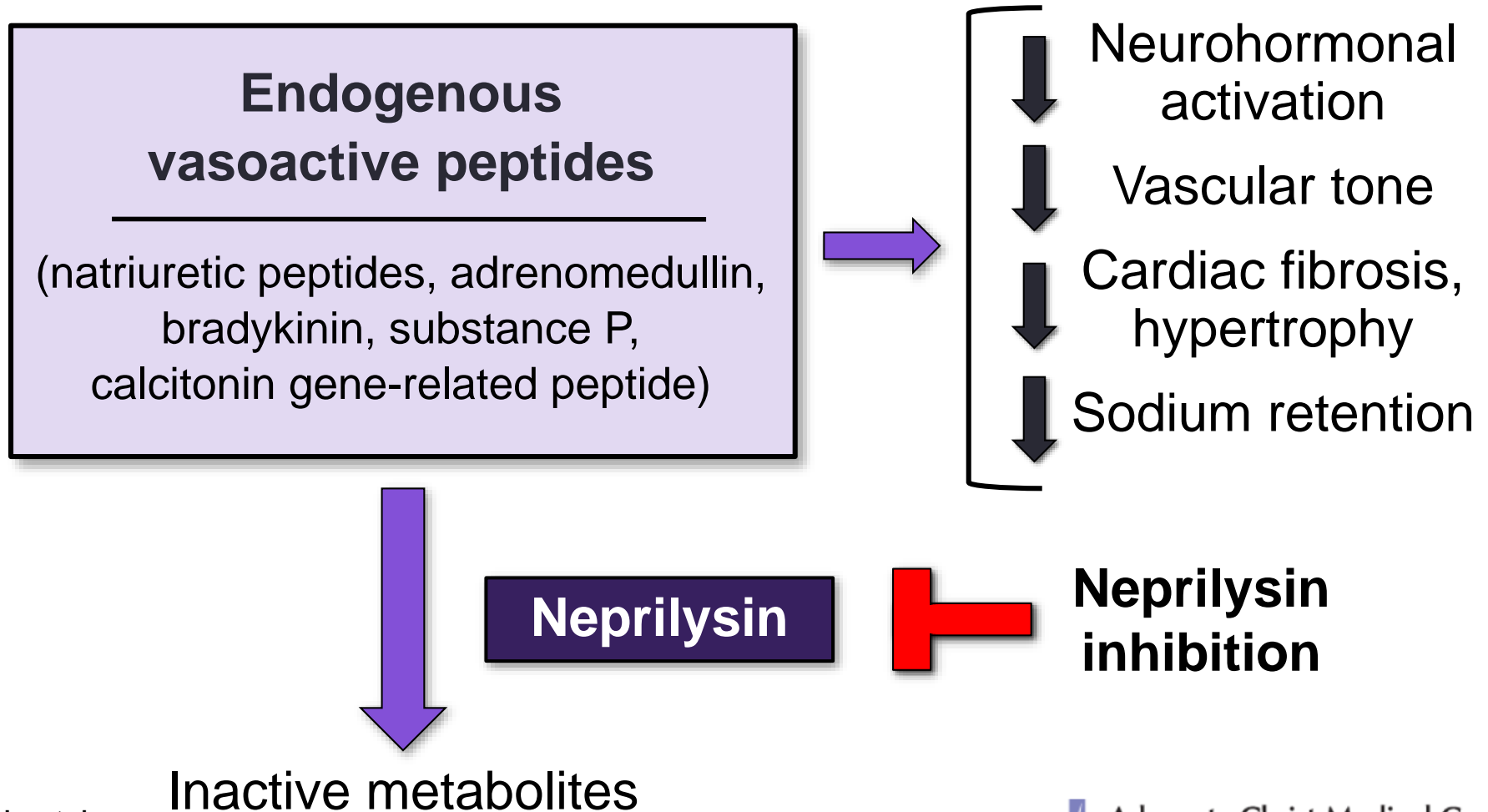
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Angiotensin–Neprilysin Inhibition versus Enalapril
in Heart Failure

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*

LCZ696 400 mg daily vs Enalapril 20 mg daily
(Sacubitril 97 mg/Valsartan 103 mg BID)

Sacubitril/valsartan



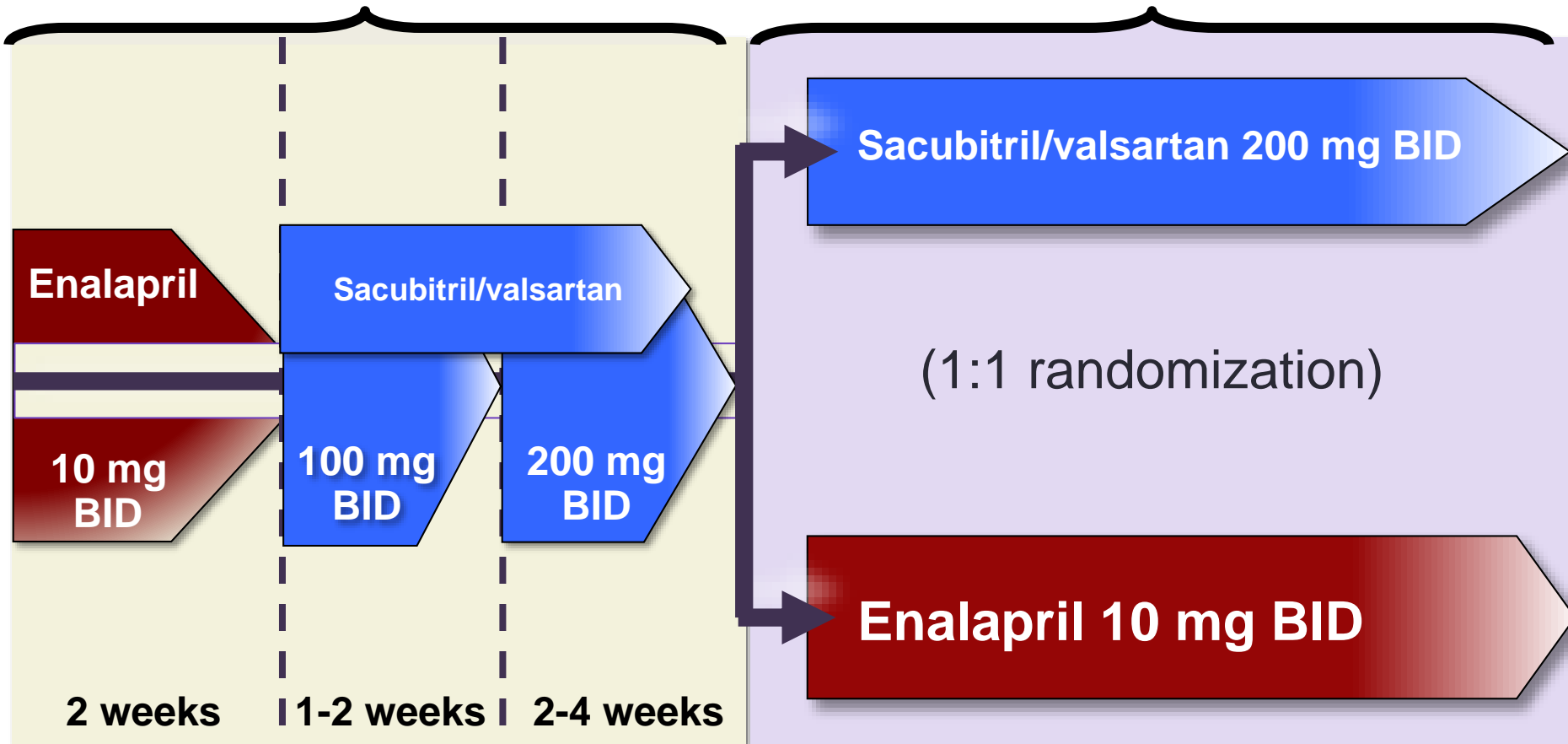
Sacubitril/valsartan

	Sacubitril/valsartan (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21	22.6
ICM (%)	59.9	61.1
LVEF (%)	29.6 ± 6.1	29.4 ± 6.4
NYHA II/III (%)	71.6 / 23.1	69.4 / 24.9
SBP (mmHg)	122 ± 15	121 ± 15
HR (bpm)	72 ± 12	73 ± 12
NT-pro-BNP (pg/ml)	1631	1594
BNP (pg/ml)	255	251
Diabetes (%)	35	35
Digoxin (%)	29.3	31.2
BB (%)	93.1	92.9
MRA (%)	54.2	57
ICD and/or CRT	16.5	16.3

Sacubitril/valsartan

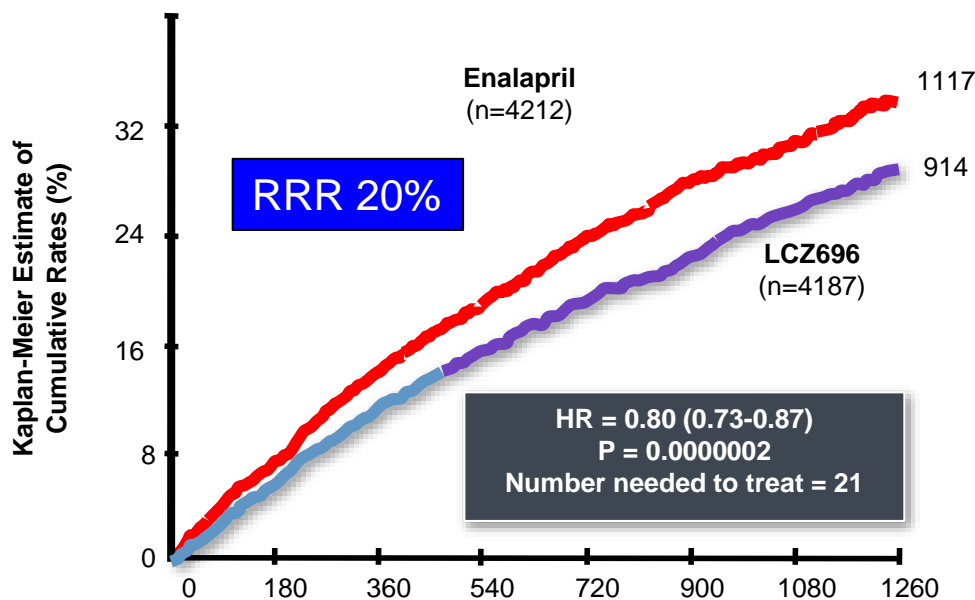
Single-blind run-in period

Double-blind period

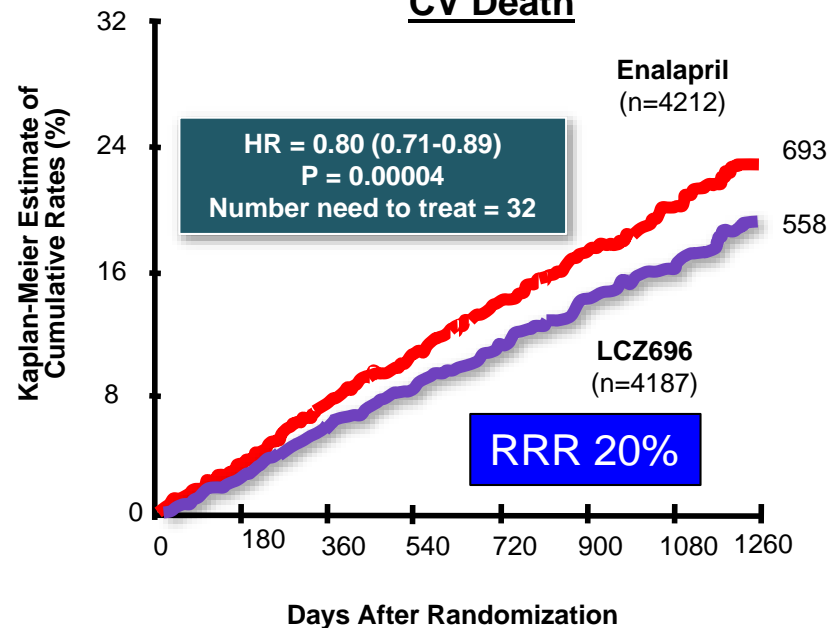


Sacubitril/valsartan

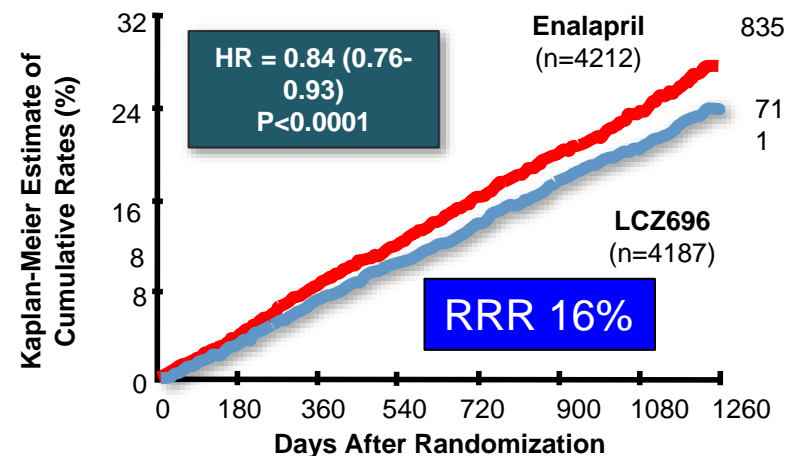
CV Death or HF Hospitalization



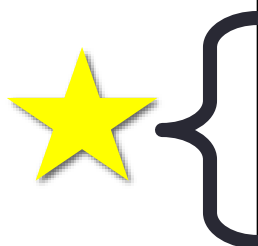
CV Death



All Cause Mortality



Sacubitril/valsartan



Adverse Event	Sacubatril/Val sartan	Enalapril	P Value
Symptomatic Hypotension	588	388	<0.001
K > 6	181	236	0.007
Cr ≥ 2.5	139	188	0.007
Cough	474	601	<0.001
D/C from adverse event	449	516	0.02
D/C for hypotension	36	29	NS
D/C for hyperkalemia	11	15	NS
D/C for renal impairment	29	59	0.001
Angioedema (adjuncted)			
Meds, No hospitalization	16	9	NS
Hospitalized, no airway compromise	3	1	NS
Hospitalized, airway compromise	0	0	--

Sacubitril/valsartan

Class	LOE	Recommendation for HFrEF
I	ACE-I/ARB: A	<i>Inhibition of RAAS</i> with ACE-I, ARB, or ARNI <i>plus</i> evidenced-based BB and aldosterone antagonists to reduce M&M
	ARNI: B-R	
I	ACE-I: A	ACE-I to reduce M&M
I	ARB: A	ARB to reduce morbidity and mortality <i>if intolerant</i> to ACE-I because of cough or angioedema
I	ARNI: B-R	<u>Replace ACE-I or ARB in NYHA II or III to further reduce M&M</u>
III: Harm	B-R	ARNI should not be used in combination or within 36 hours of ACE-I

Clinical use: Coverage

- No generic. Very expensive out-of-pocket!
 - \$12.50/day or \$400-500/month (GoodRx.com)
- Insurance coverage has improved
 - Most likely need prior authorization
 - 100% Medicare Part D and Medicare Advantage plans cover
 - Co-pay range \$18-508 (GoodRx.com)
- Cost effective

Clinical use: Prescribing

- Educate patients on doses

- 24/26 mg = 50 mg
- 49/51 mg = 100 mg
- 97/103 mg = 200 mg

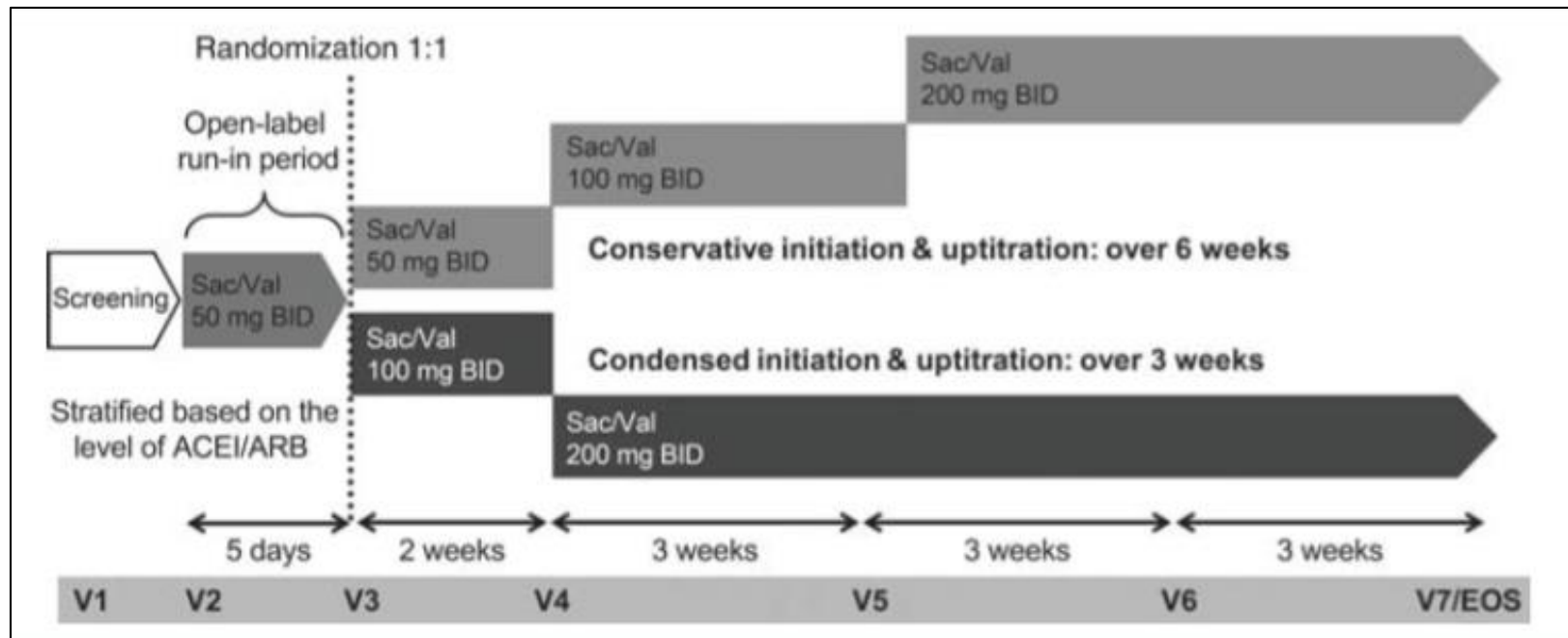


- Initiation approach

- “Aggressive”: Prescribe and see what happens
- “Cautious”: Start ACE/ARB until see sacubitril/valsartan cost/coverage

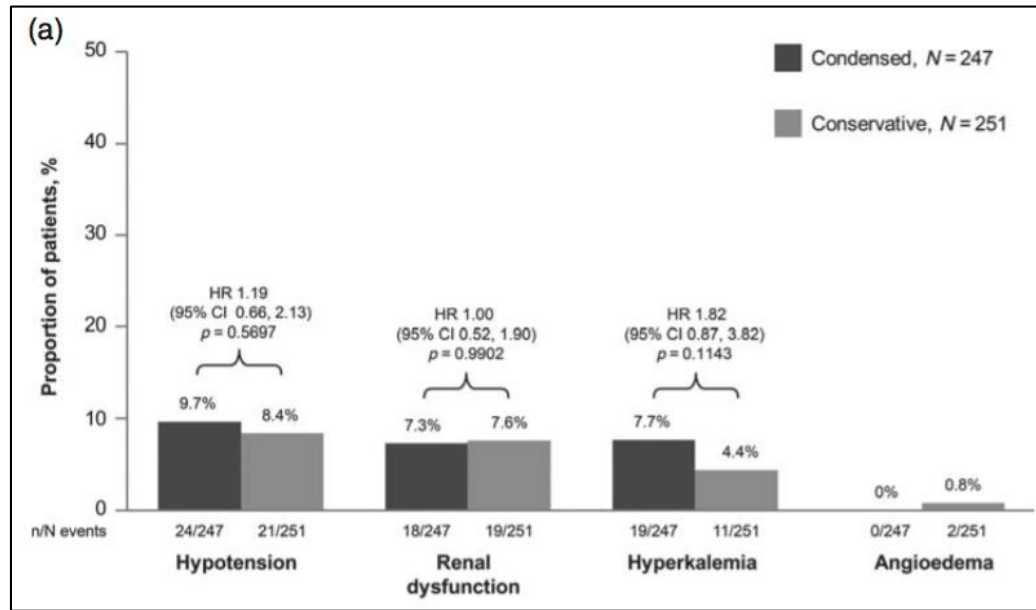
Clinical use: Prescribing

- Titrating



Clinical use: Prescribing

- Titrating



Pre-specified 'treatment success' and 'tolerability success'		Sacubitril/valsartan		Odds ratio (95% CI)	
		Condensed, n/N [†] (%)	Conservative, n/N [†] (%)		
Treatment success	High	90/109 (82.6)	98/117 (83.8)	0.91 (0.45, 1.83)	0.783
	Low	89/121 (73.6)	101/119 (84.9)	0.50 (0.26, 0.94)	0.030
	All	179/230 (77.8)	199/236 (84.3)	0.65 (0.41, 1.05)	0.078
Tolerability success	High	94/109 (86.2)	103/117 (88.0)	0.84 (0.38, 1.84)	0.657
	Low	97/121 (80.2)	103/119 (86.6)	0.63 (0.32, 1.26)	0.189
	All	191/230 (83.0)	206/236 (87.3)	0.72 (0.43, 1.20)	0.207

More to come...

- PARAGON-HF (3/2019)
 - HFpEF, NYHA II-IV
 - Sacubitril/valsartan vs. Valsartan
- PARADISE-MI (7/2019)
 - Post-MI + LV dysfunction/pulm congestion + No Hx HF
 - Sacubitril/valsartan vs. Ramipril
- PROVE-HF (10/2019)
 - HFrEF
 - Open label
 - Primary endpoint: Biomarkers, remodeling, patient-reported symptoms