New HFrEF

When and how should we initiate an SGLT2 inhibitor?

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Disclosures

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Case

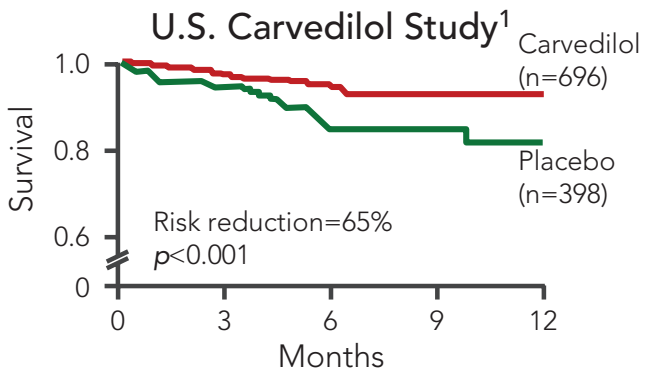
- 64-year-old female patient referred for evaluation of SOB for 6 weeks
- PMH: Hypertension
- Medications: ASA, amlodipine 10 mg
- S/H: Nonsmoker, no illicit use, teacher
- Examination: 120/78, 84 NSR, JVP 10cm, Chest - clear, CVS – soft MR murmur, no gallop, Abdomen – unremarkable, 1+ LE edema
- Echocardiogram: LVEF 30%, mild MR, normal RV
- Ischemia evaluation: Negative
- Lab: Na 142, K 4.6, Cr. 1.3, CBC normal
- Start on furosemide 40 mg PO daily
- Next?

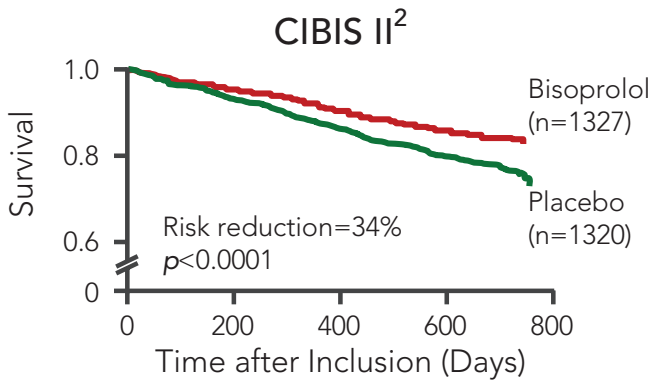
What is the Effect of Adding One GDMT to Another in HFrEF?

- Subtractive 1 + 1 = 0.5
- Redundant 1 + 1 = 1.0
- Partially Additive 1 + 1 = 1.5
- Fully Additive 1 + 1 = 2.0
- Synergistic 1 + 1 = 2.5

Beta Blockers in HFrEF

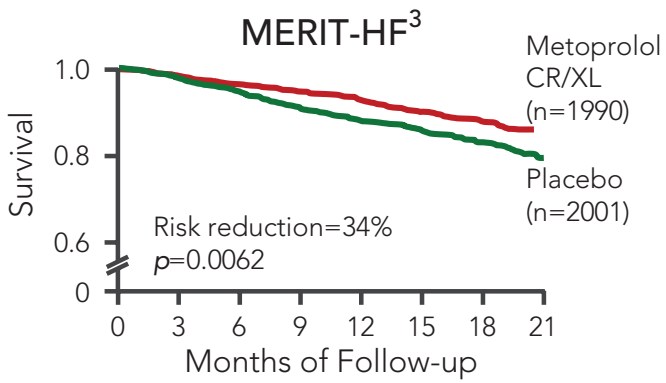
ACEI 95%

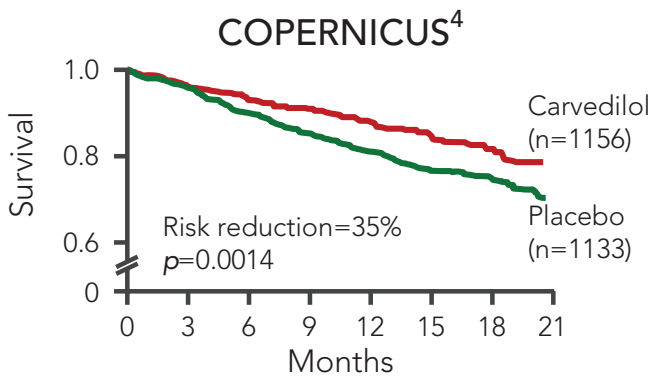




ACEI 96%

ACEI/ARB 95%





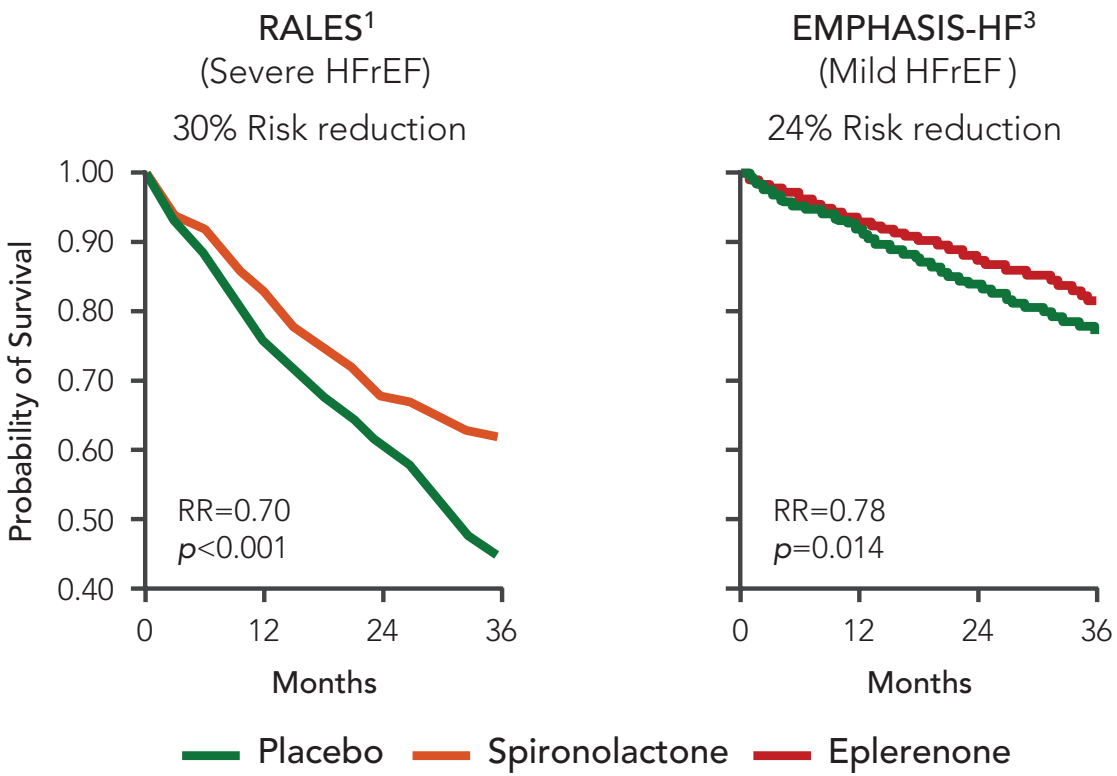
ACEI/ARB 97%

CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.

1. Packer M et al. *N Engl J Med.* 1996;334(21):1349-1355. 2. CIBIS II Investigators and Committees. *Lancet.* 1999;353(9146):9-13. 3. MERIT-HF Study Group. *Lancet.* 1999;353(9169):2001-2007. 3. COPERNICUS Study Group. *Am Heart J.* 2006. 151(1):55-61.

Aldosterone Antagonists in HFrEF

ACEI/ARB 94%
BB 10%



ACEI/ARB 94%
BB 87%

EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; RALES, Randomized Aldactone Evaluation Study; RR, risk ratio.

1. Pitt B et al. *N Engl J Med.* 1999:341(10):709-717. 2. Zannad F et al. *N Engl J Med.* 2011;364(1):11-21.

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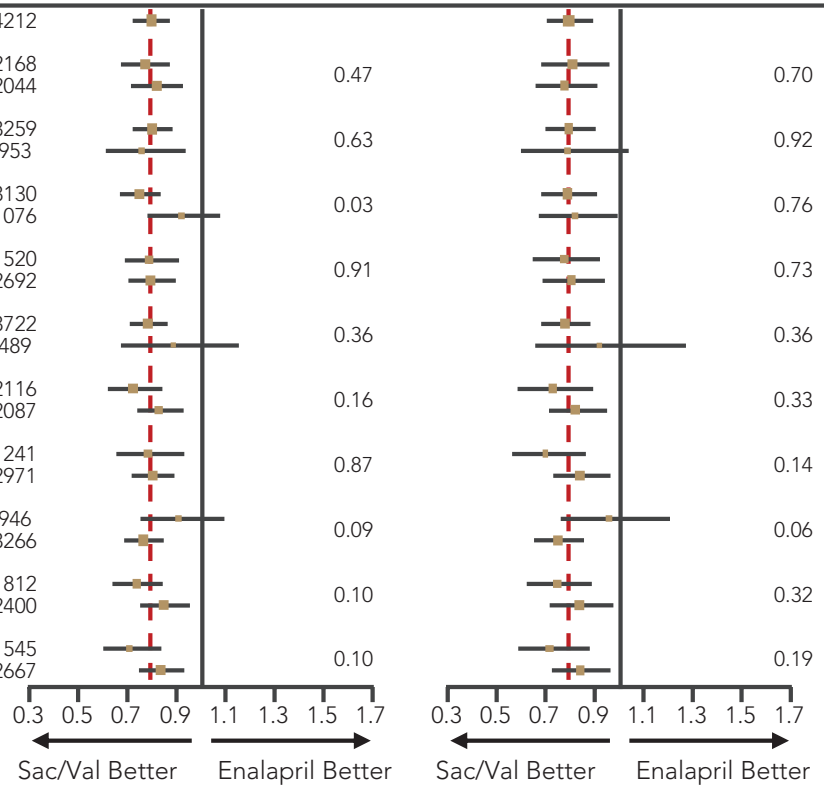
Sac/Val vs. Enalapril on Primary Endpoint and on CV Death by Subgroups

Subgroup	Sac/Val No.	Enalapril No.	Primary Endpoint Hazard Ratio (95% CI)	Primary Endpoint *p*-Value for Interaction	Death from Cardiovascular Causes Hazard Ratio (95% CI)	Death from Cardiovascular Causes *p*-Value for Interaction
All Patients	4187	4212				
Age						
<65 years	2111	2168		0.47		0.70
≥65 years	2076	2044				
Sex						
Male	3308	3259		0.63		0.92
Female	879	953				
NYHA Class						
I or II	3187	3130		0.03		0.76
III or IV	1002	1076				
Estimated GFR						
<60 mL/min/1.73 m^2	1541	1520		0.91		0.73
≥60 mL/min/1.73 m^2	2646	2692				
Ejection fraction						
≤35%	3715	3722		0.36		0.36
>35%	472	489				
NT-proBNP						
≤Median	2079	2116		0.16		0.33
>Median	2103	2087				
Hypertension						
No	1218	1241		0.87		0.14
Yes	2969	2971				
Prior use of ACE inhibitor						
No	921	946		0.09		0.06
Yes	3266	3266				
Prior use of aldosterone antagonist						
No	1916	1812		0.10		0.32
Yes	2271	2400				
Prior hospitalization for heart failure						
No	1580	1545		0.10		0.19
Yes	2607	2667				



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

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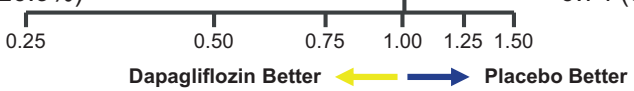
DAPA: HF Primary Endpoint by Concomitant Therapy

	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	Interaction *P* Value
Overall Effect (n=4744)	386/2373 (16.3%)	502/2371 (21.2%)	0.74 (0.65, 0.85)	
Diuretic				
Yes (n=4008)	358/2001 (17.9%)	457/2007 (22.8%)	0.76 (0.66, 0.87)	0.27
No (n=736)	28/372 (7.5%)	45/364 (12.4%)	0.57 (0.36, 0.92)	
MRA				
Yes (n=3370)	281/1696 (16.6%)	281/1674 (21.6%)	0.74 (0.63, 0.87)	0.97
No (n=1374)	105/677 (1.5%)	141/697 (20.2%)	0.74 (0.57, 0.95)	
Digoxin				
Yes (n=887)	98/445 (22.0%)	111/442 (25.1%)	0.86 (0.66, 1.13)	0.21
No (n=3857)	288/1928 (14.9%)	391/1929 (20.3%)	0.71 (0.61, 0.83)	
ARNI				
Yes (n=508)	41/250 (16.4%)	56/258 (21.7%)	0.75 (0.50, 1.13)	1.00
No (n=4236)	345/2123 (16.3%)	446/2113 (21.1%)	0.74 (0.65, 0.86)	
Ivabradine				
Yes (n=228)	24/119 (20.2%)	29/109 (26.6%)	0.73 (0.42, 1.25)	0.94
No (n=4516)	362/2254 (16.1%)	473/2262 (20.9%)	0.74 (0.65, 0.85)	



Docherty KF et al. *Eur Heart J.* 2020;ehaa183. doi:10.1093/eurheartj/ehaa183.

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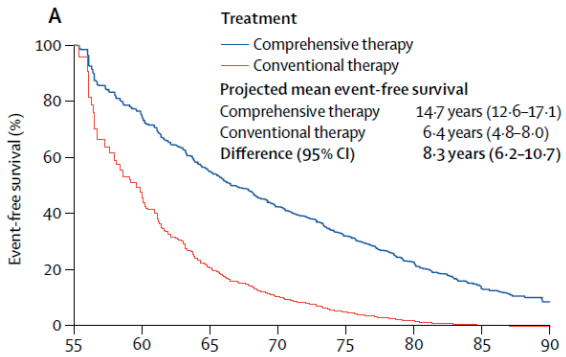
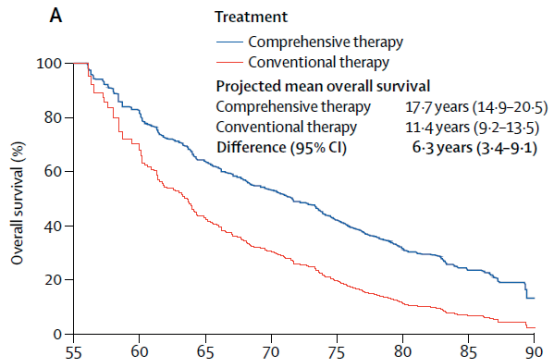
Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

Muthiah Vaduganathan, Brian L Claggett, Pardeep S Jhund, Jonathan W Cunningham, João Pedro Ferreira, Faiez Zannad, Milton Packer, Gregg C Fonarow, John J V McMurray, Scott D Solomon

Survival free from CV Death or HF Hospitalization



Survival free from All Cause Mortality



Compared to ACEI/ARB + BB:

1. Switch to ARNI
2. Start MRA
3. Start SGLT2i

→

Extend Your HFrEF Patient's Life by 6.3 Years

What is the Value to the Patient of Extending Median Survival by >6 Years?

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Sequencing of GDMT: Serial Strategy

28-56 weeks till GDMT fully implemented

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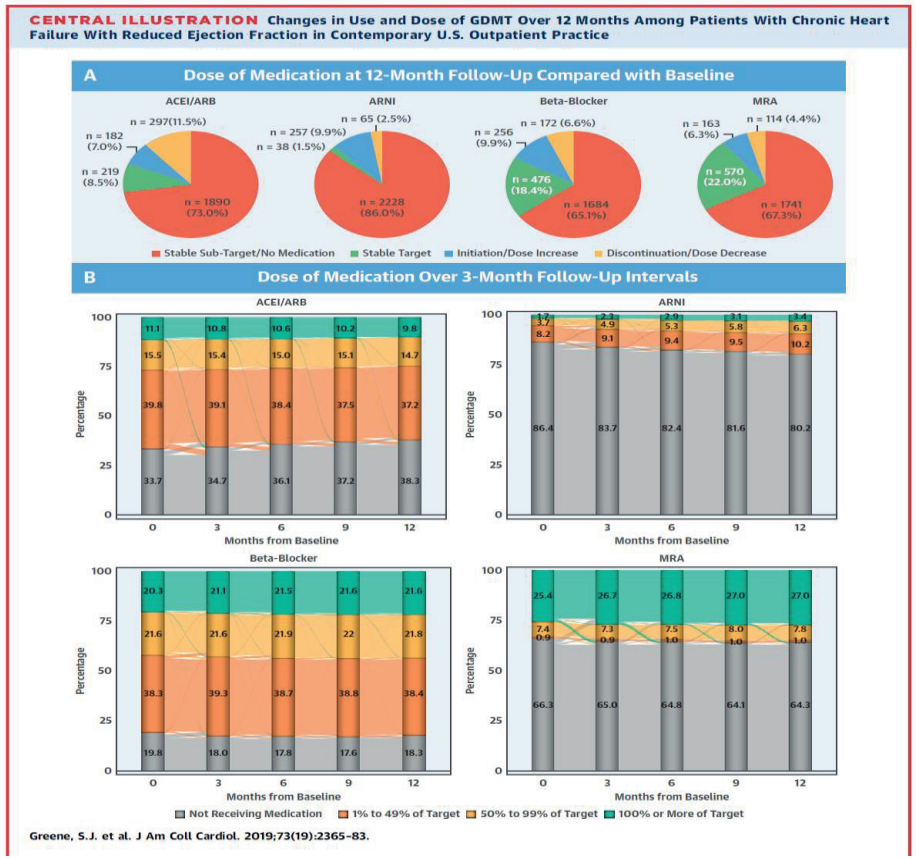
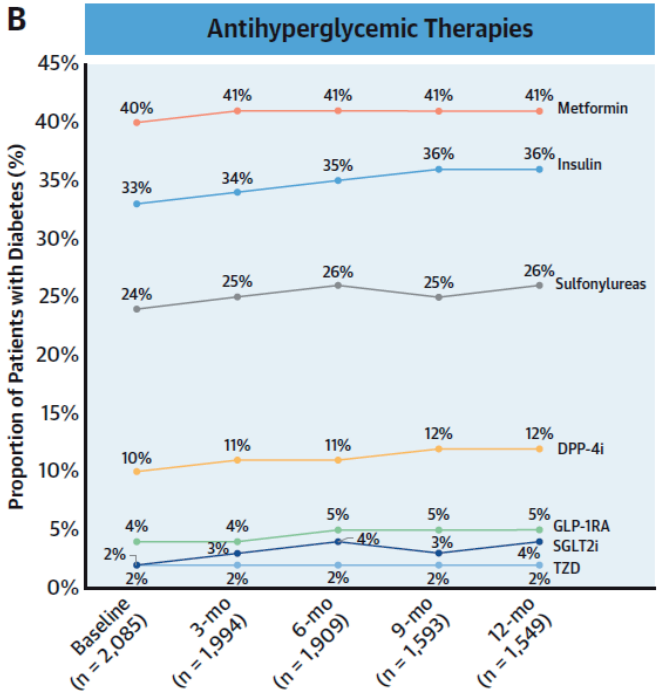
Longitudinal Use/Dosing of GDMT for HFrEF: CHAMP HF Registry Clinical Inertia





Vaduganathan, M. et al. *J Am Coll Cardiol HF*. 2020;8(6):469–80.

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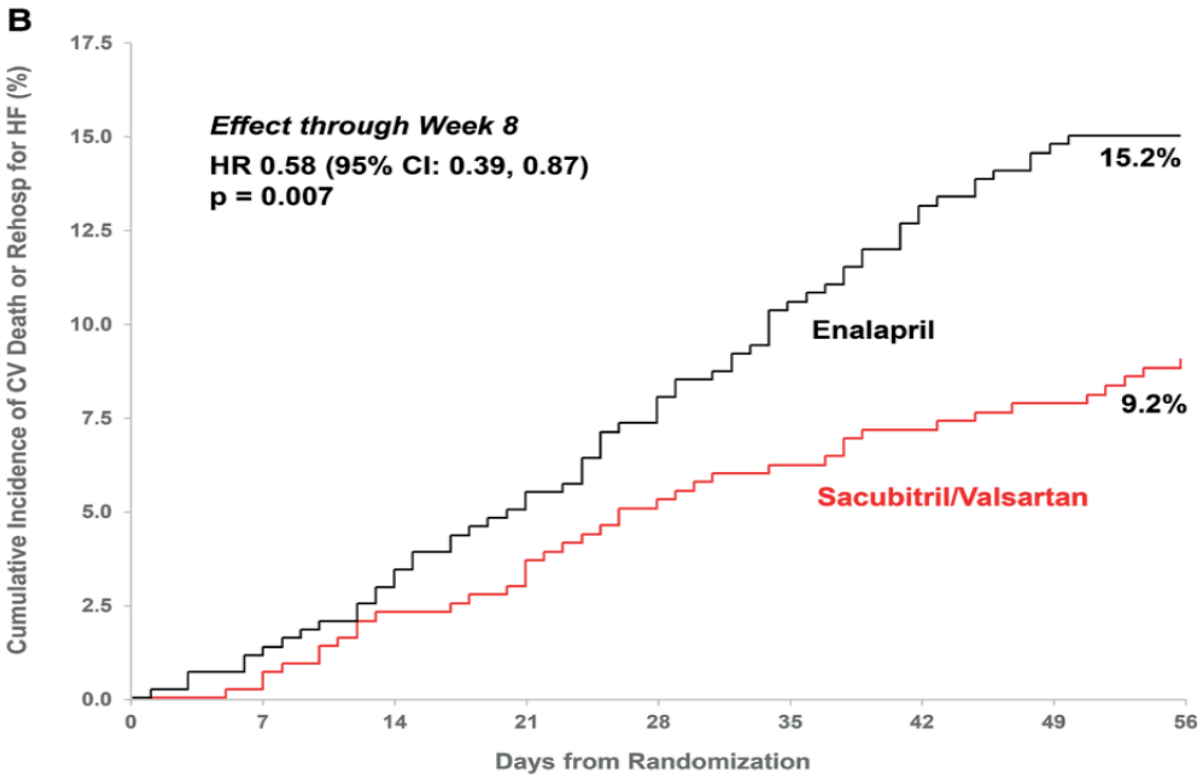
PIONEER-HF: CV Death or HF Rehospitalization



Significant Clinical Benefits within 30 Days

Morrow, et al. *Circulation* 2019;139:2285–2288

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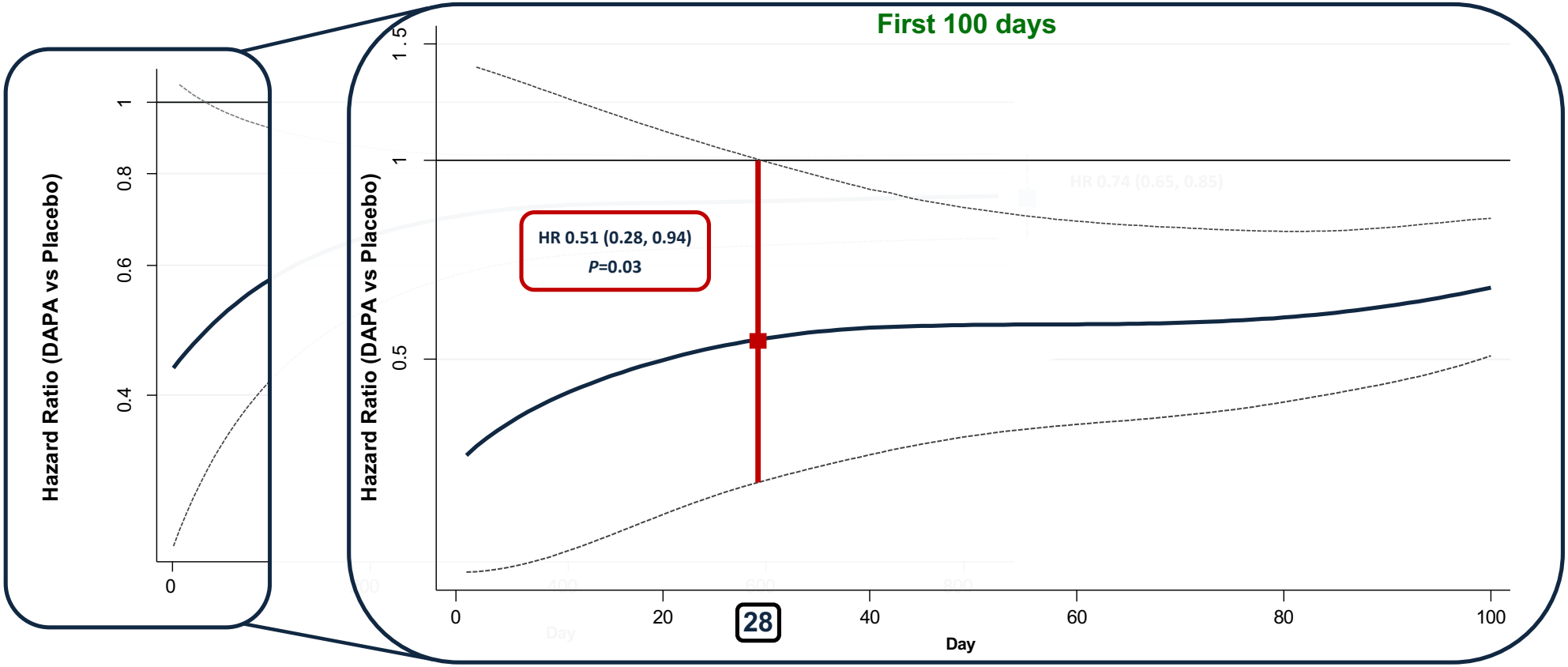
Early Benefit of Dapagliflozin on CV Death or WHF



Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

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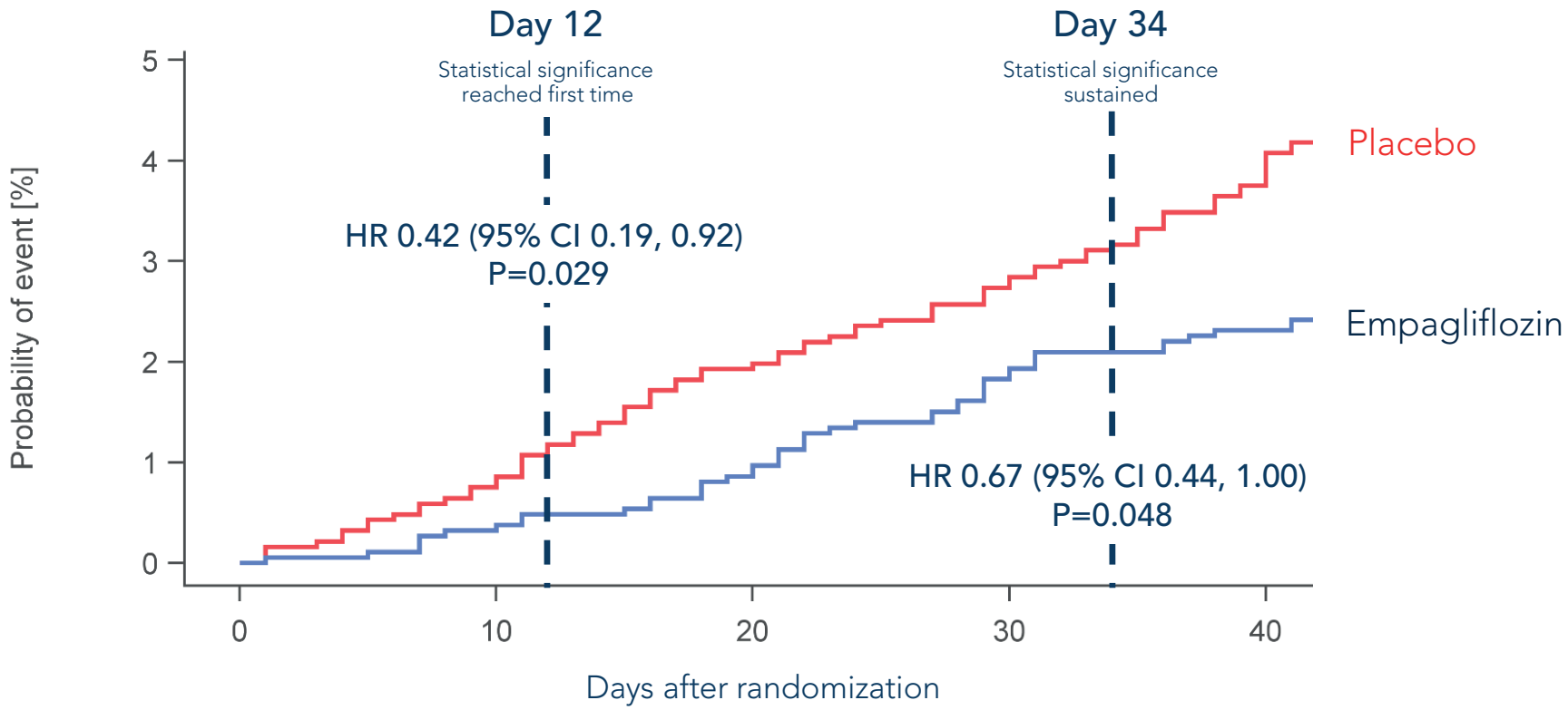

	Patients at risk				
Placebo	1867	1852	1830	1811	1792
Empagliflozin	1863	1855	1845	1826	1815

Early Relative Risk Reduction	Hospitalized or Outpatient				
	Day 1	**Day 7-14**	**Day 14-28**	**Day 21-42**	**Beyond**
↓42% of CV death or HF hospitalization	ARNI		Titrate, as Tolerated	Titrate, as Tolerated	Maintenance/Further Optimization of Foundational Therapies
↓25% of death	BB	Titrate, as Tolerated	Titrate, as Tolerated	Titrate, as Tolerated	Consideration of EP Device Therapies/Mitra-Clip
↓37% of CV death or HF hospitalization	MRA		Titrate, as Tolerated		Consideration of Add On Therapies or Advanced Therapies, if Refractory
↓58% of CV death or HF hospitalization	SGLT2i				Manage Comorbidities

Low Starting Doses
Prioritize Beta Blocker Titration

Benefits of each Rx demonstrated within 30 days of initiation
Cumulative benefits within 30 days (>75% relative risk reduction)

Simultaneous Initiation of GDMT

- Rationale for initiating all GDMT as first line Rx for HFrEF (as compared to sequential sequencing):
  - Rapid improvement in health status (within 1 to 8 weeks)
  - Rapid improvement in left ventricular remodeling parameters (within 12 weeks)
  - Rapid reduction in HF hospitalizations (within 2 to 4 weeks)
  - Rapid reduction in HF rehospitalizations (within 2 to 4 weeks)
  - Rapid reduction in mortality (within 2 to 4 weeks)

McMurray JJV, et al. *N Engl J Med.* 2014;371:993-1004.
Desai AS et al. *JAMA.* 2019;322(11):1077-1084.
Velazquez EJ, et al. *N Engl J Med* 2019;380:539–548
Morrow, et al. *Circulation* 2019;139:2285–2288
Seferovic PM et al., *EJHF* 2019;21:1169-1186
Khariton Y, et al. *JACC Heart Fail.* 2019;7(11):933-941.
Bhatt AS, et al. EJHF. 2020;22:313–314

Strategies to Facilitate GDMT Initiation

- Explain rationale and expected benefits from each medication
- Meticulous attention to volume status and adjustment of diuretics
- Spacing of hemodynamic active medications ARNI and beta blocker
- Close monitoring of laboratories
- Home blood pressure checks and/or remote monitoring
- Early follow-up visit or telehealth to assess tolerability, titration
- Emphasis on health benefits of adherence/persistence

The Approach to HFrEF Medications

- The benefits of HFrEF medications are additive/incremental
- No substantial overlap has been demonstrated for the 4 key evidence-based therapies for HFrEF: ARNI, beta blockers, MRA, and SGLT2 inhibitors
- The optimal approach is to utilize each medication demonstrated to reduce all-cause mortality in combination, so long as not contraindicated or not tolerated, and start all without delay
- A serial or selective approach will lead to delays and HF hospitalizations/deaths which could have been prevented with more comprehensive and earlier use of GDMT