Outpatient Worsening HF as an Endpoint in Clinical Trials: A Cross Trial Analysis of Patients with Mildly Reduced and Preserved Ejection Fraction

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Global CVCT **Forum**

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Evolution of Clinical Trial Endpoints in Heart Failure Trials

Mortality-Only Endpoints

All Cause Mortality

Composite Endpoint

CV Death+ HF Hospitalization

Expanded Morbidity Endpoints

CV Death + HF Hospitalization + Urgent Visit

US FDA standardized definition for CV and stroke endpoints includes urgent HF visits requiring IV diuretic outside the hospital

1980s-Early 1990s | Mid 1990 - Early2000s | 2010s | 2017

Worsening HF Occurs on a Spectrum

Worsening HF Event

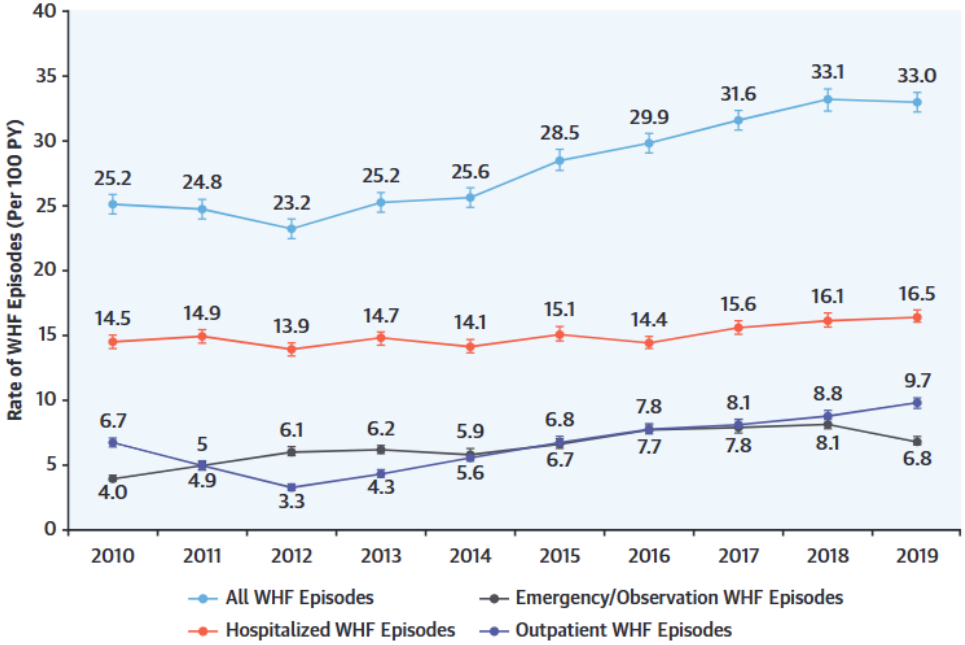
CV Death

HF Hospitalization

Urgent HF Visit

Oral Diuretic Intensification

Temporal Trends in Worsening HF Events



Worsening HF is increasingly driven by ED visits and outpatient encounters in recent years

Ambrosy AP, et al, JACC (2022)

Few trials have systemically captured outpatient worsening events

SUMMIT Trial

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*

CV death or worsening HF event (exacerbated symptoms of HF resulting in hospitalization, IV therapy in an urgent care setting or **intensification of oral diuretic therapy**

PARADISE-MI

Angiotensin Receptor–Neprilysin Inhibition in Acute Myocardial Infarction

M.A. Pfeffer, B. Claggett, E.F. Lewis, C.B. Granger, L. Køber, A.P. Maggioni, D.L. Mann, J.J.V. McMurray, J.-L. Rouleau, S.D. Solomon, P.G. Steg, O. Berwanger, M. Cikes, C.G. De Pasquale, C. East, A. Fernandez, K. Jering, U. Landmesser, R. Mehran, B. Merkely, F. Vaghaiwalla Mody, M.C. Petrie, I. Petrov, M. Schou, M. Senni, D. Sim, P. van der Meer, M. Lefkowitz, Y. Zhou, J. Gong, and E. Braunwald, for the PARADISE-MI Investigators and Committees*

CV death or incident HF (HFH and outpatient episodes of symptomatic HF treated with IV or **sustained oral diuretic therapy**

Standardized incorporation of oral diuretic intensification in clinical trial endpoints may have important implications for the **complete capture of worsening HF events** and **improved trial efficiencies**

Objectives

1) To assess the distribution of first worsening HF events, prognostic significance of outpatient ODI, treatment effects
2) Projected gains in trial efficiency using an expanded endpoint inclusive of outpatient worsening

Harmonized Definition of Outpatient ODI Across Trials

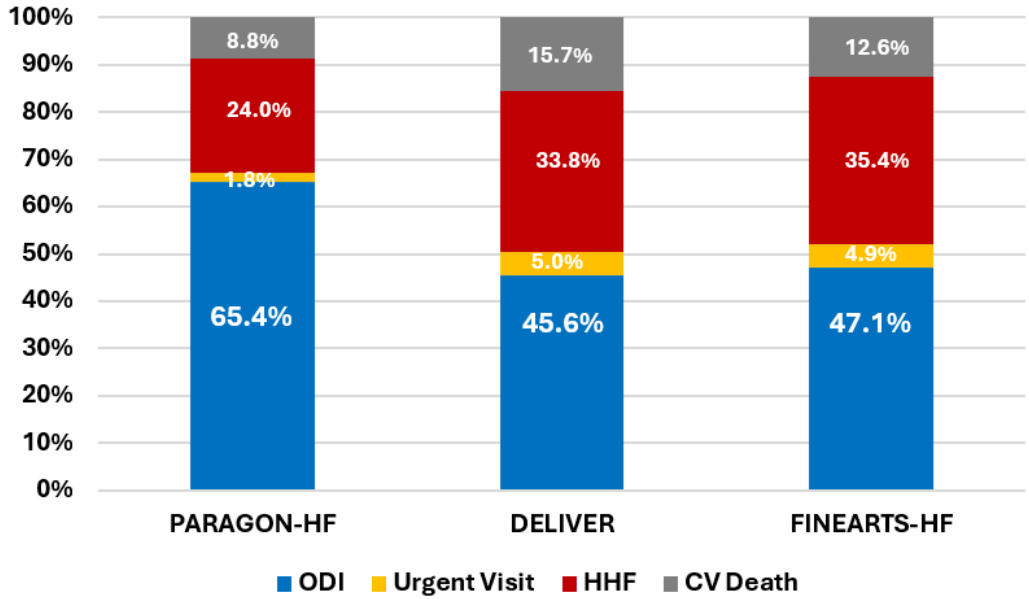
Outpatient oral diuretic intensification (ODI) was defined **according to medication data** (without requirement for signs or symptoms of HF) as any **new oral loop diuretic initiation** (among those not receiving loop diuretic at baseline) or **sustained dose increase of ≥30 days** (among those receiving loop diuretic at baseline).

Selected Baseline Characteristics Included Trials

	PARAGON-HF N=4,796	DELIVER N=6,263	FINEARTS-HF N=6,001
ACEi/ARB/ARNI	---------	77.2%	79.3%
sMRA	25.8%	42.6%	----------
SGLT2i	0.6%	----------	13.6%
Loop Diuretic	78.0%	76.8%	87.3%

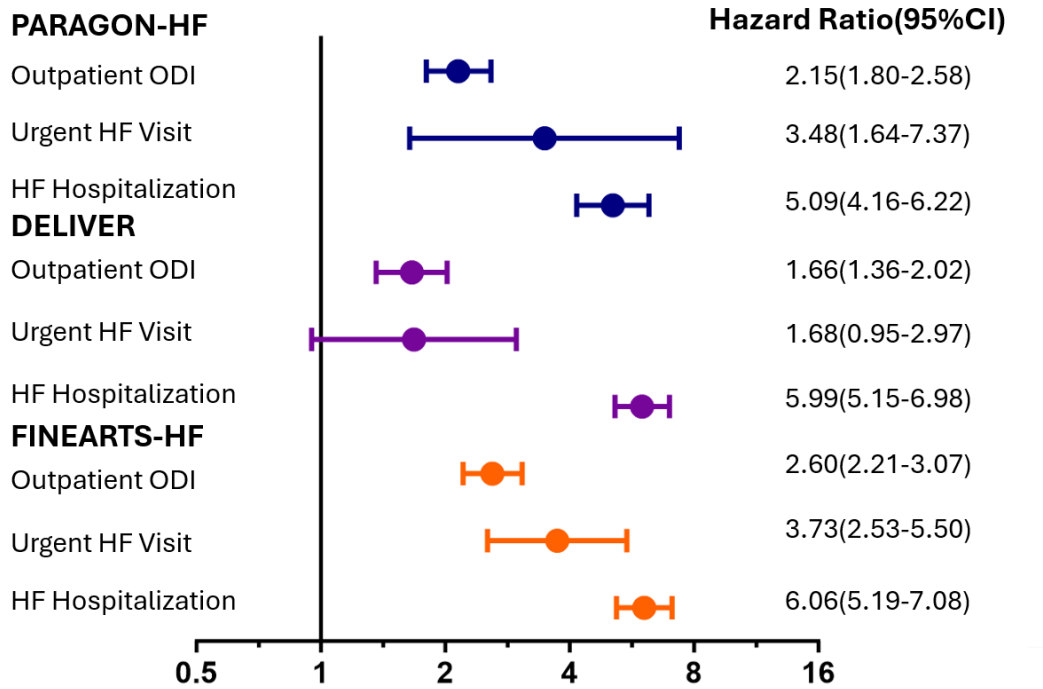
We included three phase 3 RCTs completed between 2019 and 2024 studying 3 different therapeutic classes

Distribution of First Worsening HF Events



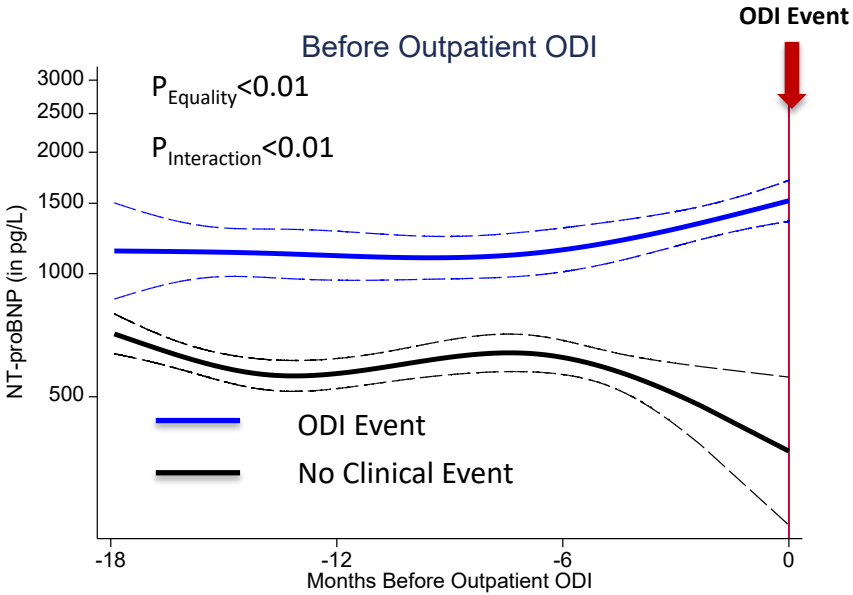
Prognosis After ODI As A First Non-Fatal Worsening HF Event

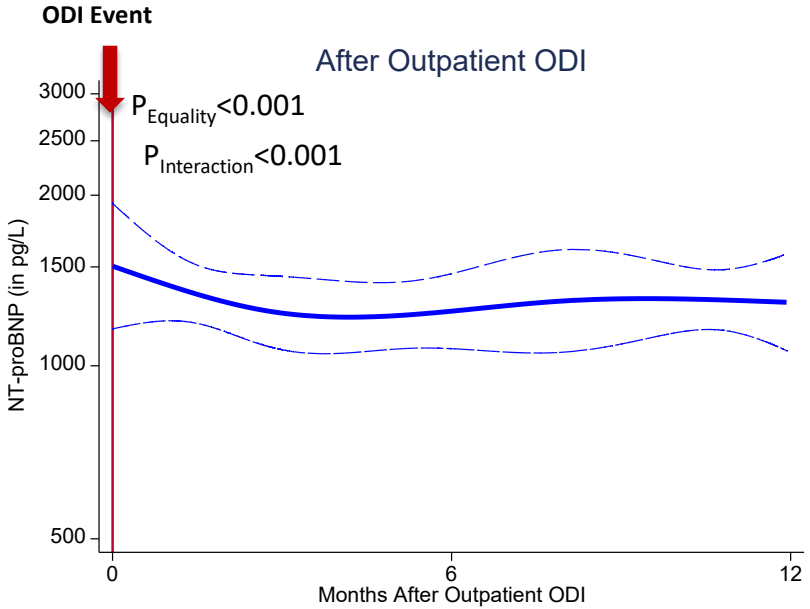
All Cause Mortality Following First Worsening HF Event



Outpatient ODI caries adverse prognostic significance

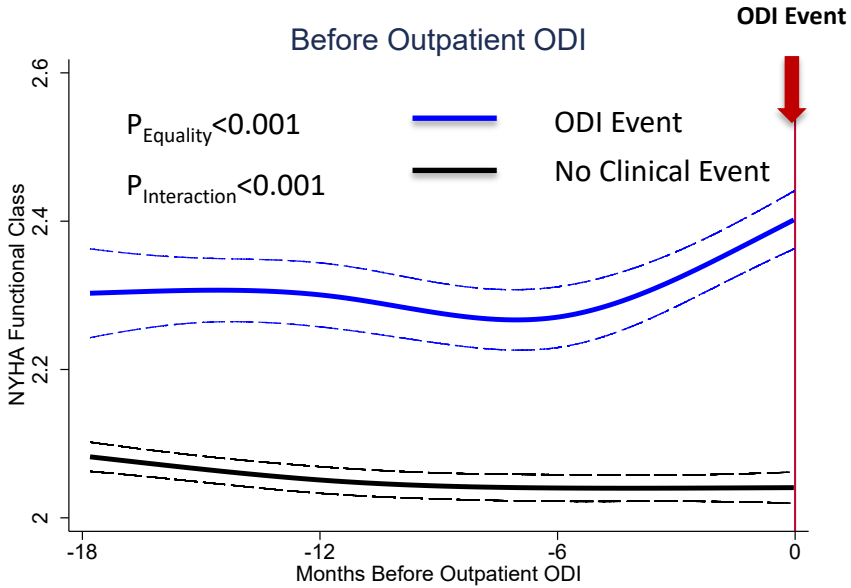
NT-proBNP Trajectory Before and After Outpatient ODI: FINEARTS-HF

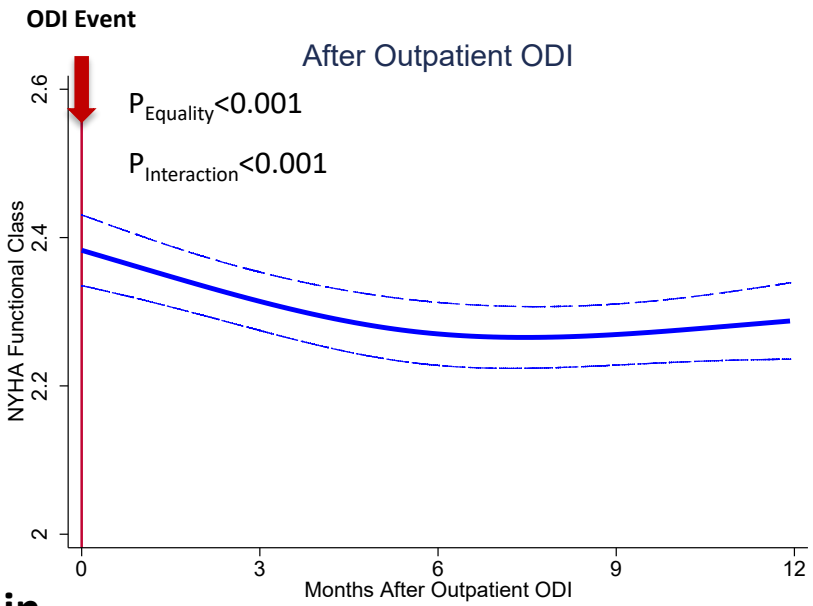




Δ NTproBNP ~20-25%

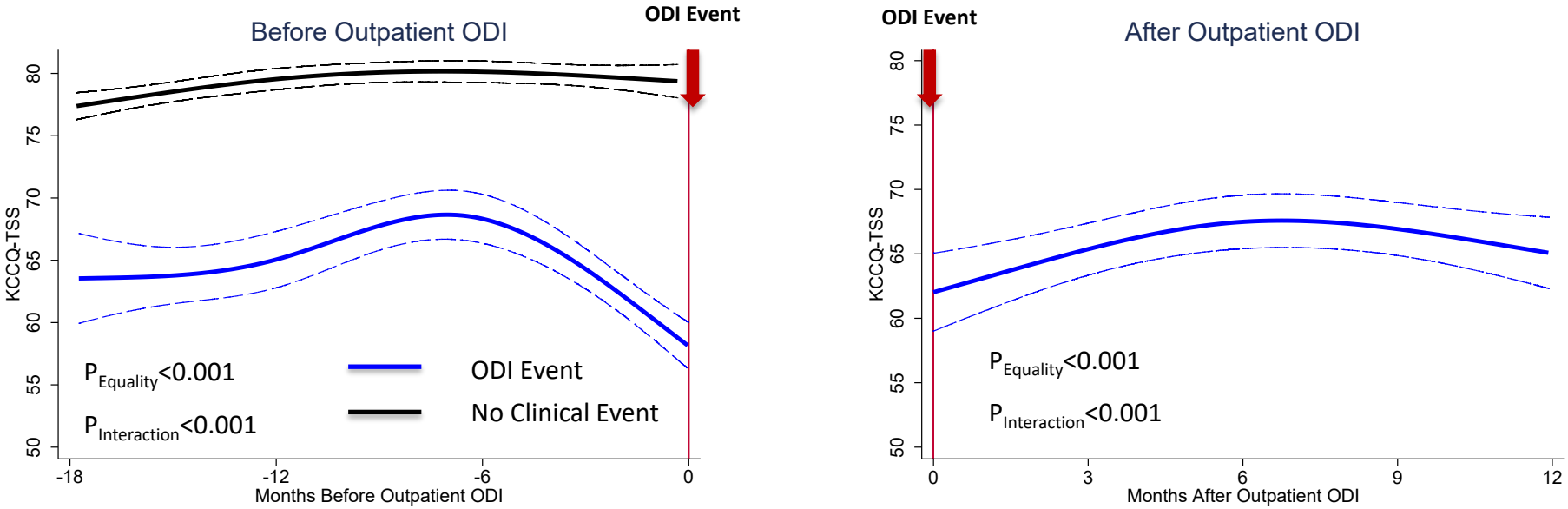
NYHA Functional Class Trajectory Before and After Outpatient ODI: FINEARTS-HF





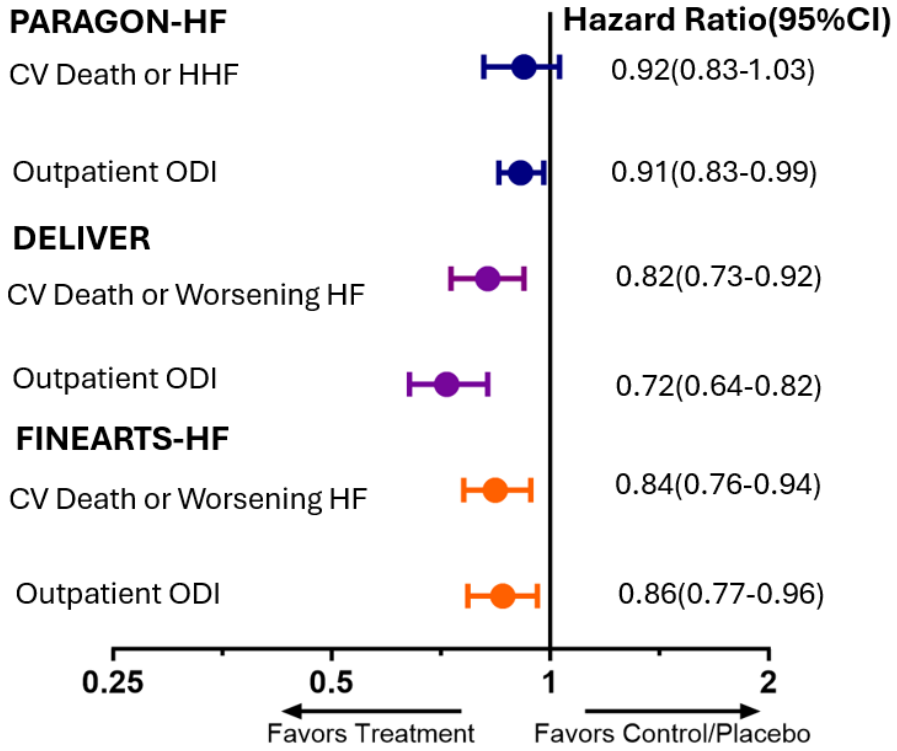
Decline in NYHA Class

KCCQ-TSS Trajectory Before and After Outpatient ODI: FINEARTS-HF



↓ Health Status (~5 points)

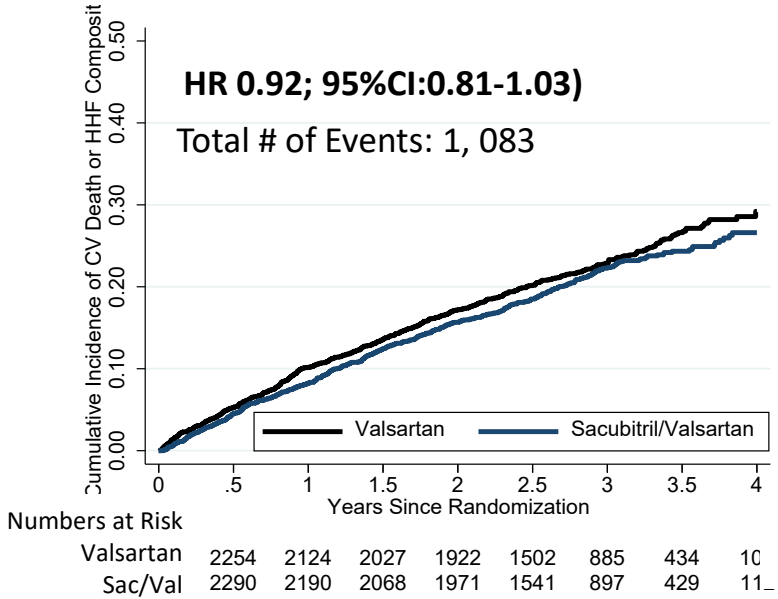
Treatment Effect on Oral Diuretic Intensification



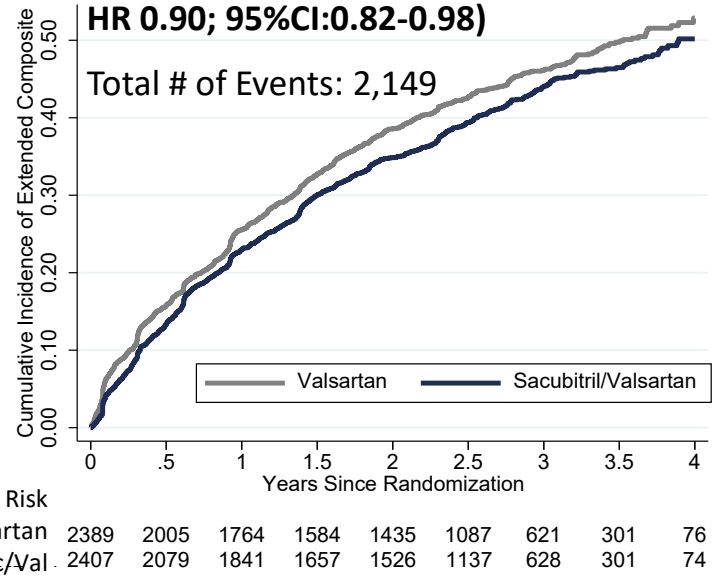
Active treatment significantly reduced the risk of ODI

Treatment Effect on Extended Composite Outcome Including ODI: PARAGON-HF

Composite of CV Death or HHF

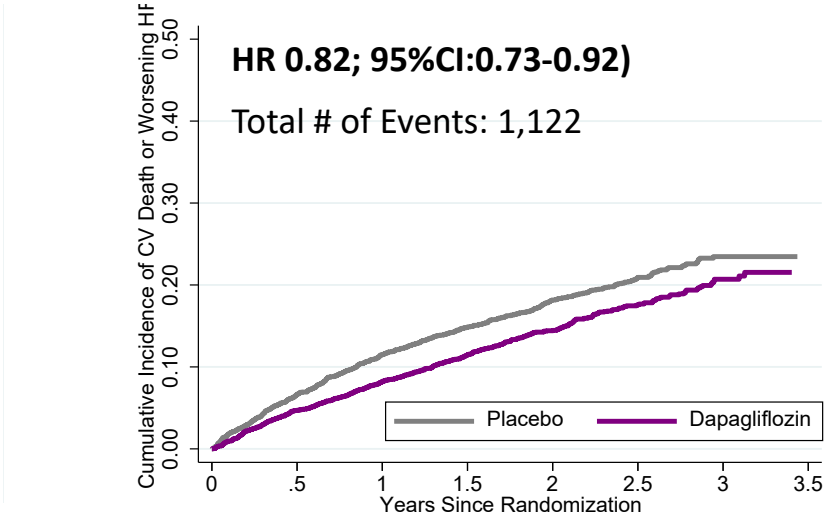


Extended Composite End Point Including Outpatient ODI



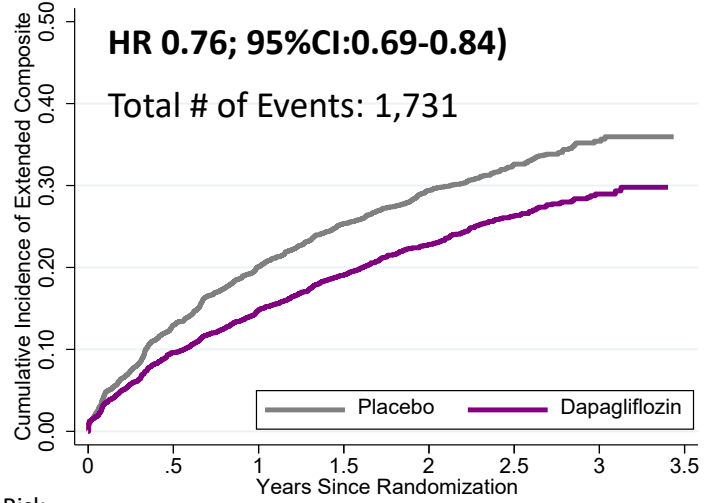
Treatment Effect on Extended Composite Outcome Including ODI: DELIVER

Composite of CV Death or Worsening HF



Numbers at Risk								
Placebo	3132	2892	2702	2302	1868	1074	311	0
Dapagliflozin	3131	2948	2799	2372	1934	1123	327	0

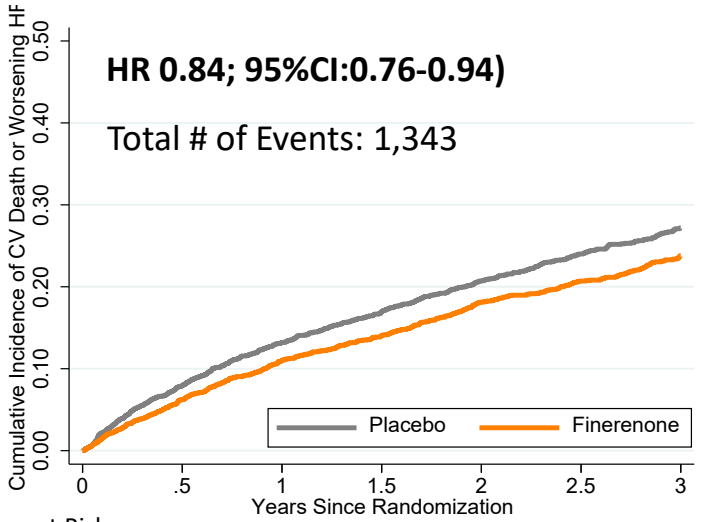
Extended Composite End Point Including Outpatient ODI



Numbers at Risk								
Placebo	3132	2696	2439	2014	1601	906	265	0
Dapagliflozin	3131	2794	2597	2168	1749	1008	300	0

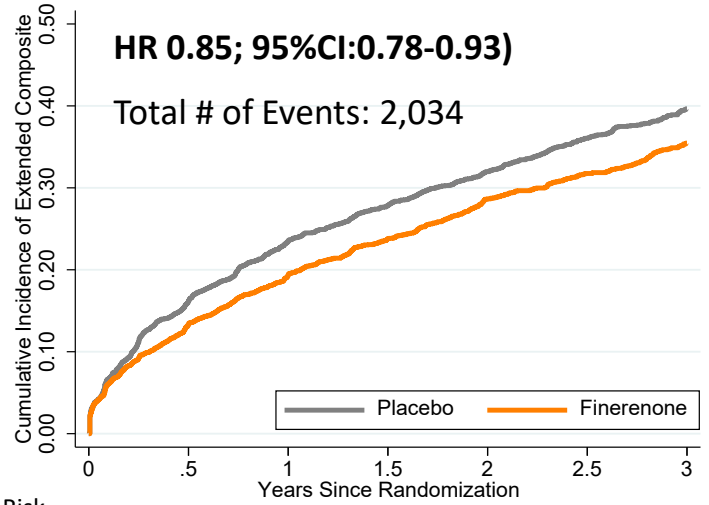
Treatment Effect on Extended Composite Outcome Including ODI: FINEARTS-HF

Composite of CV Death or Worsening HF



Numbers at Risk							
Placebo	2721	2527	2246	1895	1439	712	
Finerenone	2778	2595	2319	1932	1492	732	

Extended Composite End Point Including Outpatient ODI



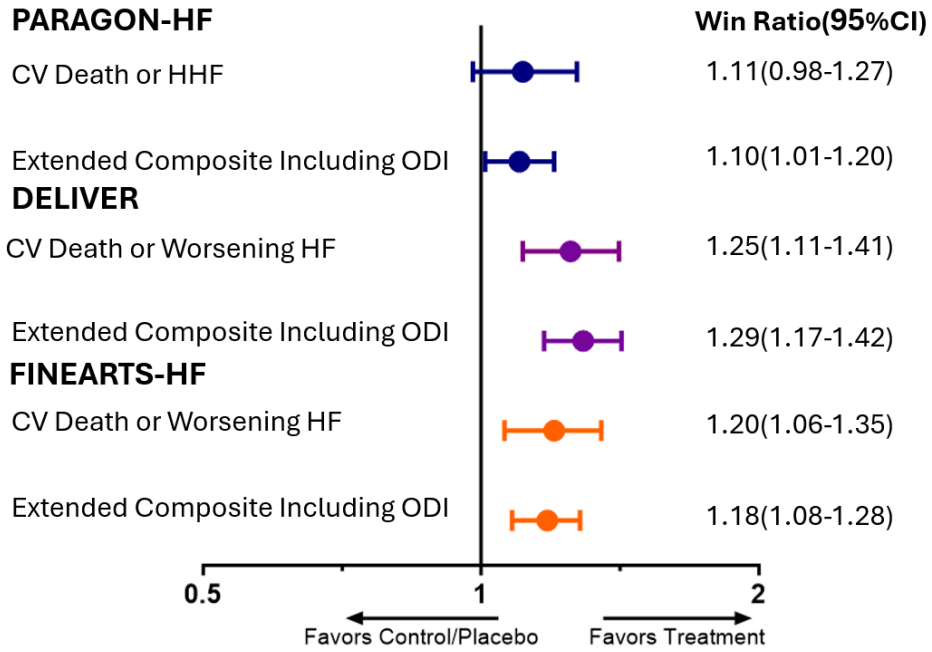
Numbers at Risk							
Placebo	2998	2480	2229	1954	1636	1228	609
Finerenone	3003	2573	2354	2063	1688	1289	634

Consistent Results in Win Ratio Analysis

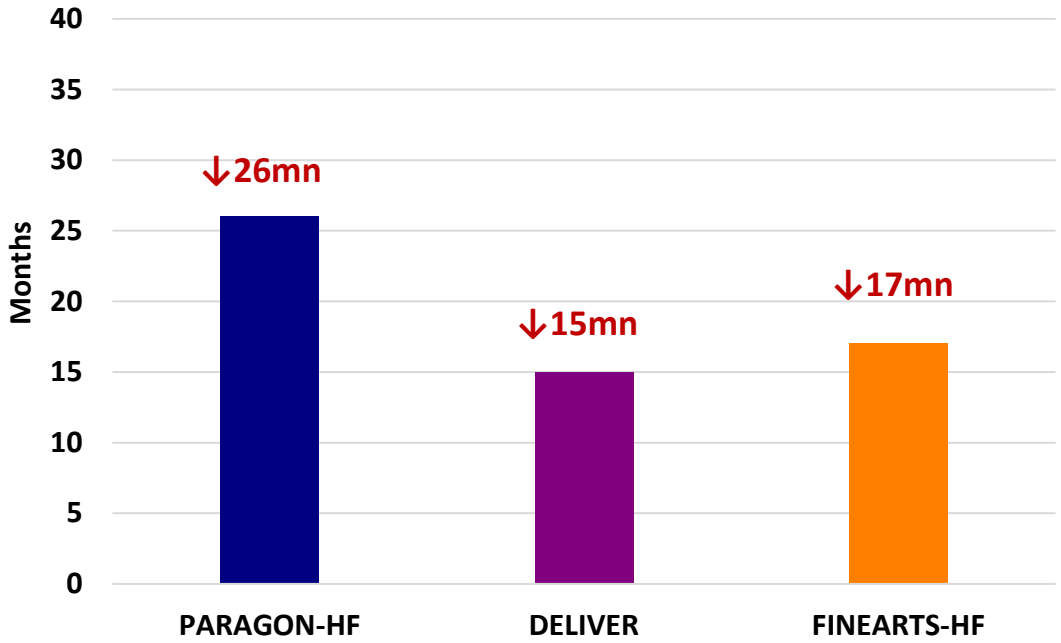
Effect of active treatment using win ratio method on exploratory 4-tier hierarchical outcome:

1)CV Death
2)HF Hospitalization
3)Urgent HF Visit
4)Outpatient ODI

Win Ratio= Total Number of Wins/Total Number of Losses



Estimated Reduction in Trial Duration



Estimated trial duration modeled by identifying the date on which the last primary end point occurred (trial level primary composite) relative to the date on which the last event would have occurred using an expanded primary composite inclusive of ODI

Treatment Effects on Expanded Composite Outcome and Its Components

Outcome	PARAGON-HF Original	PARGON-HF Truncated by 26 months	DELIVER Original	DELIVER Truncated by 15 months	FINEARTS-HF Original	FINEARTS-HF Truncated by 17months
CV death or HHF or Urgent visit or ODI	0.90(0.82-0.98)	0.87(0.77-0.98)	0.76(0.69-0.84)	0.74(0.65-0.83)	0.85(0.78-0.93)	0.84(0.76-0.94)
CV Death or HHF or Urgent Visit	0.90(0.80-1.01)	0.81(0.67-0.98)	0.82(0.73-0.92)	0.76(0.65-0.88)	0.84(0.76-0.94)	0.83(0.72-0.95)
CV death or HFH	0.92(0.81-1.03)	0.83(0.69-1.00)	0.80(0.71-0.91)	0.77(0.65-0.90)	0.89(0.79-0.99)	0.86(0.75-1.00)
CV death	0.95(0.79-1.16)	0.79(0.55-1.14)	0.88(0.74-1.05)	0.99(0.76-1.30)	0.93(0.78-1.11)	0.87(0.68-1.13)
HHF	0.90(0.79-1.04)	0.80(0.65-0.99)	0.77(0.67-0.89)	0.65(0.54-0.79)	0.86(0.76-0.97)	0.84(0.72-1.00)
Urgent Visit	0.60(0.38-0.95)	0.63(0.29-1.34)	0.76(0.55-1.08)	0.57(0.37-0.87)	0.63(0.47-0.85)	0.73(0.51-1.04)
ODI	0.90(0.81-0.99)	0.87(0.76-0.99)	0.72(0.64-0.82)	0.68(0.58-0.79)	0.86(0.77-0.96)	0.84(0.74-0.96)

*All time to first events; CV=Cardiovascular; HHF=HF Hospitalization; ODI=Oral Diuretic Intensification

Conclusions

- Outpatient **ODI episodes** occurred **frequently** across trials
- Such events carried **adverse prognostic significance** and were associated with **temporal changes** in **NT-proBNP**, physician assigned **functional status** and a **patient reported outcome**.
- ODI events **were significantly reduced by all therapeutic classes** evaluated reinforcing the primary findings of each trial
- Implications for trial efficiency

Inclusion of outpatient ODI as a standardized HF clinical trial endpoint?

Benefits

- Episodes of outpatient ODI occurred frequently across trials
- ODI caries adverse prognostic significance
- ODI events significantly reduced by all therapeutic classes evaluated
- Implications for overall trial efficiency

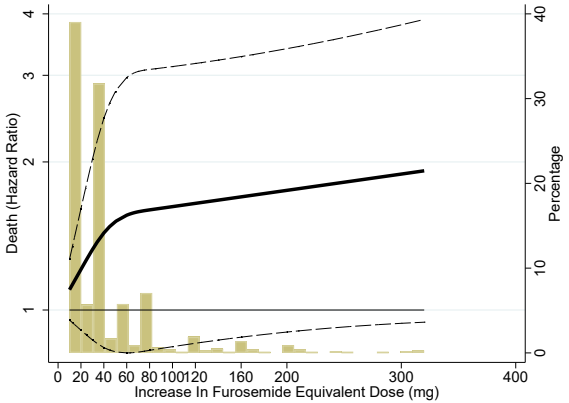
- Future prospective trials should necessitate, antecedent signs or symptoms of worsening HF and be centrally adjudicated

Challenges

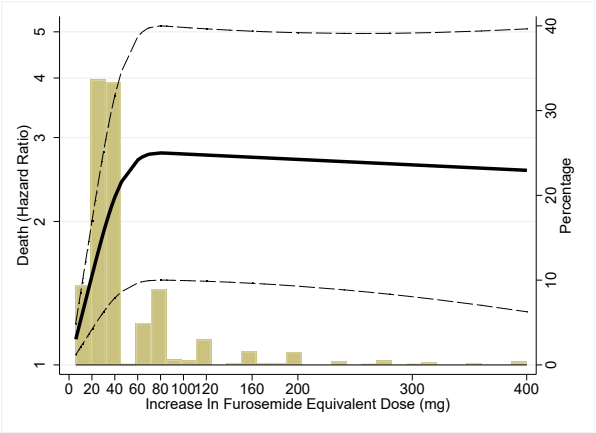
- Variable definitions: magnitude/duration of dose escalation, inclusion of adjunctive diuretics or non-diuretic oral therapies
- Events may be impacted by frequency of study follow up visits
- Differential impact on mortality, health status and cost relative to HF Hospitalization.

Take Home Point: ODI is a distinct and clinically meaningful entity which may more accurately reflecting the contemporary HF patient's disease burden while creating significant potential efficiencies in the conduct of clinical trials

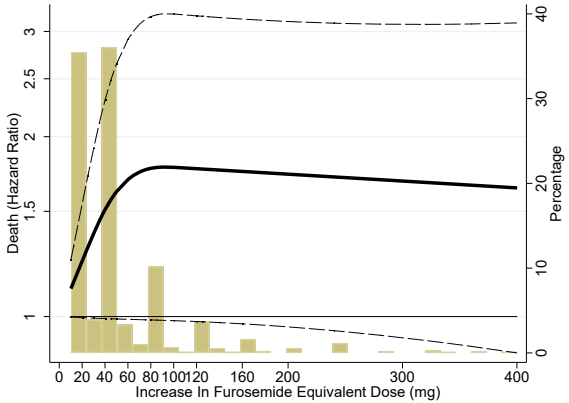
PARAGON-HF



DELIVER



FINEARTS-HF



Distribution of First WHF Events By Geographic Region: FINEARTS-HF