DukeHeart *On The Go*

Practice Changing Heart Failure Presentations from ACC 2022

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MedEd ON THE GO

Ejection Fraction, Biomarkers, and Outcomes in Heart Failure with Reduced Ejection Fraction and the Impact of Vericiguat on Outcomes in the VICTORIA Trial

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Background

- We assessed the relation between left ventricular ejection fraction (LVEF), heart failure (HF) biomarkers, and outcomes and investigated the relation between baseline LVEF and the efficacy and safety of vericiguat.

Methods

- VICTORIA randomized 5050 patients with worsening HF and LVEF <45% to vericiguat or placebo.
- In this analysis, patients were divided into subgroups based on LVEF tertiles (≤24, 25-33, and >33%); outcomes and treatment effects were examined across these groups and by considering LVEF as a continuous variable.
- NT-proBNP, cardiac troponin T, GDF-15, IL-6, hsCRP, and cystatin C were measured at baseline.

Results

- Mean LVEF was 29±8% (range 5-44%).
- Compared with other tertiles, those in the lowest tertile had higher NT-proBNP, hsCRP, and IL-6 and higher rates of cardiovascular death (CVD) or HF hospitalization (HFH) (42.0%, 35.2%, and 30.8% for tertiles ≤24, 25-33, >33%; ; P <0.001).
- The adjusted hazard ratio (95% CI) of vericiguat on CVD or HFH from lowest to highest LVEF tertiles was 0.79 (0.68-0.94), 0.95 (0.82-1.11), and 0.94 (0.79-1.11) (P=0.222).
- Similar results were seen for CVD and HHF (P interaction 0.964 [CVD]; 0.438 [HFH]).
- Discontinuation of treatment due to adverse events was consistent across tertiles (7.2%, 6.0%, 7.0%).

Table. Baseline biomarkers and clinical outcomes according LVEF at baseline

	Overall (N=5,036)	LVEF≤24 % (n=1,472)	LVEF 25 to 33 % (n=1,871)	LVEF 34 to 45 % (n=1,693)	P-value
Lab and biomarker, median (25th-75th)					
NT-proBNP, pg/mL	2816 (1556-5312)	3442 (1847-6356)	2876 (1544-5336)	2464 (1396-4525)	<0.001
(Valid n)	(n=4805)	(n=1401)	(n=1785)	(n=1608)	
hs-cTnT, ng/L	29.6 (18.8-48.6)	29.6 (18.9-49.1)	30.1 (19.1-49.9)	29.2 (18.2-47.0)	0.369
(Valid n)	(n=4614)	(n=1372)	(n=1697)	(n=1533)	
GDF-15, pg/mL	3047 (1917-5145)	3166 (1915-5466)	3007 (1871-5144)	3009 (1969-4859)	0.053
(Valid n)	(n=4395)	(n=1313)	(n=1609)	(n=1462)	
hsCRP, mg/L	3.9 (1.5-9.4)	4.4 (1.7-11.7)	3.8 (1.5-9.3)	3.6 (1.3-8.6)	<0.001
(Valid n)	(n=4519)	(n=1341)	(n=1662)	(n=1504)	
IL-6, pg/mL	6.8 (4.6-11.2)	7.4 (4.8-12.7)	6.7 (4.6-10.8)	6.5 (4.4-10.1)	<0.001
(Valid n)	(n=4577)	(n=1364)	(n=1688)	(n=1513)	
Cystatin C, mg/L	1.3 (1.1-1.8)	1.3 (1.0-1.7)	1.3 (1.1-1.8)	1.4 (1.1-1.8)	<0.001
(Valid n)	(n=4506)	(n=1337)	(n=1657)	(n=1500)	
Clinical outcomes, event per 100 patient-year					
CVD/HFH	35.6	42.0	35.2	30.8	<0.001
CVD	13.4	17.2	12.9	10.7	<0.001
HFH	27.4	31.8	27.8	23.5	<0.001

Conclusions:

- Patients with lower LVEF had a distinctive biomarker profile reflecting a higher risk for adverse clinical outcomes.
- There was no statistically significant interaction for the benefit of vericiguat across LVEF tertiles, but the effect was nominally less at higher LVEF.

FUNDING: The VICTORIA trial (NCT02861534) was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Bayer AG, Wuppertal, Germany.

DISCLOSURES: Butler: Consulting: Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Roche, and Vifor. Zheng, Bonderman, Westerhout: None. Lund: Consulting/Honoraria: Bayer, Merck, Vifor, AstraZeneca, Pharmacosmos, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier, Abbott, Radcliffe, Novartis; Grants: AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis; Patent: AnaCardio; Stock: AnaCardio. DeFilippi: Research grants: Abbott Diagnostics, Roche Diagnostics, Siemens Healthineers, Ortho Diagnostics; Consulting: FujiRebio, Roche Diagnostics, Siemens Healthineers, Ortho Diagnostics. Blaustein: Employee of Merck. Ezekowitz: Research grants: Bayer, Merck, Servier, Amgen Sanofi, Novartis, Cytokinetics, American Regent, Applied Therapeutics, Consulting: Bayer, Merck, Servier, Amgen, Sanofi, Novartis, Cytokinetics, American Regent, Applied Therapeutics. Freitas: Employee of Bayer. Hernandez: Research grants: Merck, AstraZeneca, Novartis, Verily; Honoraria: Merck, Bayer, Amgen, AstraZeneca, Novartis. O'Connor: Research grants: Merck; Consulting: Bayer, Dey LP, Bristol Myers Squibb Foundation. Voors: Research grants: Boehringer Ingelheim, Roche Diagnostics; Consulting: Merck, Bayer, Amgen, AstraZeneca, Boehringer Ingelheim, Cytokinetics, Myokardia, Novartis, Servier, Roche Diagnostics. Lam: Research grants: Bayer, National Medical Research Council of Singapore, Boston Scientific, Roche Diagnostic, Medtronic, Vifor Pharma, and AstraZeneca; Consulting: Merck, Bayer, Boston Scientific, Roche Diagnostic, Vifor Pharma, AstraZeneca, Novartis, Amgen, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, Novo Nordisk, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd, and Corpus. Patents pending: PCT/SG2016/050217, 16/216929; Co-founder & non-executive director: eKo.ai. Armstrong: Research grants: Merck, Bayer, Sanofi-Aventis Recherche & Développement, Boehringer Ingelheim, CSL Limited; Consulting: Merck, Bayer, AstraZeneca, Novartis.

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VICTORIA Trial: Methods

- VICTORIA randomized 5050 patients with worsening HF and LVEF <45% to vericiguat or placebo
- In this analysis, patients were divided into subgroups based on LVEF tertiles (≤24, 25-33, and >33%); outcomes and treatment effects were examined across these groups and by considering LVEF as a continuous variable
- NT-proBNP, cardiac troponin T, GDF-15, IL-6, hsCRP, and cystatin C were measured at baseline

Table. Baseline biomarkers and outcomes according to LVEF at screening

	Overall (N=5,036)	Tertile 1 (≤24%) (n=1,472)	Tertile 2 (25 to 33 %) (n=1,871)	Tertile 3 (34 to 45 %) (n=1,693)	P-value
CVD/HFH, n (%)	1860 (36.9%)	614(41.7%)	680 (36.3%)	566 (33.4%)	<0.001
CVD, n (%)	851 (16.9%)	313 (21.3%)	302 (16.1%)	236 (13.9%)	<0.001
HFH, n (%)	1431 (28.4%)	464 (31.5%)	535 (28.6%)	432 (25.5%)	<0.001
NT-proBNP, pg/mL	2816 (1556-5312)	3442 (1847-6356)	2876 (1544-5336)	2464 (1396-4525)	<.001
hs-cTnT, ng/L	29.6 (18.8-48.6)	29.6 (18.9-49.1)	30.1 (19.1-49.9)	29.2 (18.2-47.0)	0.369
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IL-6, pg/mL	6.8 (4.6-11.2)	7.4 (4.8-12.7)	6.7 (4.6-10.8)	6.5 (4.4-10.1)	<.001
Cystatin, mg/L	1.3 (1.1-1.8)	1.3 (1.0-1.7)	1.3 (1.1-1.8)	1.4 (1.1-1.8)	<.001

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VICTORIA Trial: Conclusions

- Patients with lower LVEF had a distinctive biomarker profile reflecting a higher risk for adverse clinical outcomes
- There was no statistically significant interaction for the benefit of vericiguat across LVEF tertiles, but the effect was nominally less at higher LVEF

Classification and Implications of Heart Failure Events from the VICTORIA Trial

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Abstract

Background: Heart failure hospitalization (HFH) is a major source of morbidity, consumes significant resources, and is a key endpoint in HF clinical trials. While HFH events vary in severity and implications, they are generally considered equally in analyzing clinical trial outcomes.

Methods: VICTORIA, a global, double-blind randomized trial, compared vericiguat vs placebo in patients with HFrEF (EF <45%) and a recent worsening HF event. All HFHs were prospectively adjudicated by a blinded, central clinical events committee (CEC). We evaluated the frequency and clinical impact of HF events by severity, categorized by highest intensity of HF treatment (urgent outpatient visit or hospitalization treated with oral diuretics, IV diuretics, IV vasodilators, IV inotropes, or mechanical support); and treatment effect by event categories.

Results: In VICTORIA, 2559 HF events occurred in 5050 enrolled patients. Overall total CEC HF events for placebo vs vericiguat were 42.8 vs 38.3 events/100 pt-yrs (p=0.025). Hospitalization for IV diuretics was the most common type of HFH event (54%). The treatment effect of vericiguat was similar across HF event types (p=0.65 for heterogeneity of treatment effect).

Conclusion: HF events in large global trial vary significantly in severity and clinical implications. The treatment benefit of vericiguat was generally consistent across different HF event types.

Background

- Heart failure hospitalization (HFH) is a major driver of HF morbidity and costs.
- HF events vary widely in severity but are generally considered equivalent in clinical trials.
- Effective therapies may not just reduce events but may make them less severe.

Methods

- VICTORIA was a randomized double-blind placebo-controlled phase 3 trial of vericiguat vs. placebo in chronic HFrEF with EF<45%.
- All HF events were centrally adjudicated by a blinded clinical events committee (CEC).
- We classified all positively adjudicated HF events by severity according to the most intensive treatment received:
  - Urgent outpatient visits requiring IV therapy;
  - HFH/PO diuretics;
  - HFH/IV diuretics;
  - HFH/IV vasodilators;
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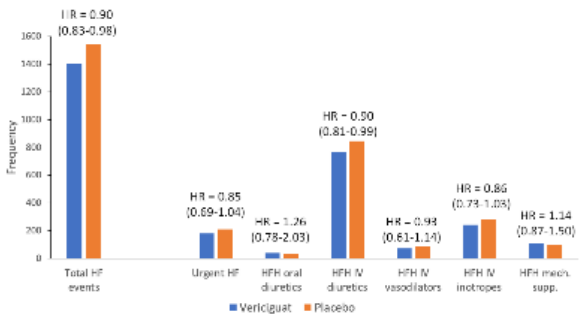
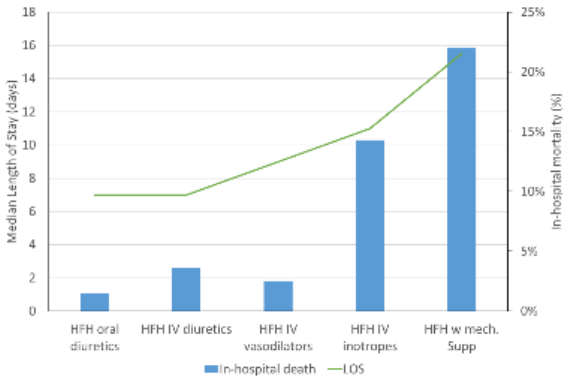
- For each event type, we analyzed the treatment effect of vericiguat as well as in hospital and post discharge outcomes.

Results

Frequency of HF Events by Event Type



Inpatient Outcomes by Event Type

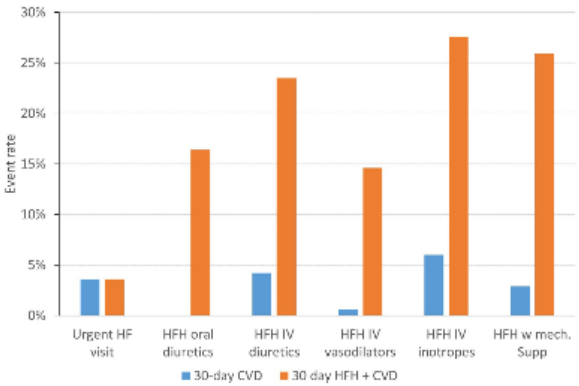


Treatment Effect of Vericiguat by Event Type

Outcome	Vericiguat (N=2,526) no. (%)	Vericiguat (N=2,526) events/ 100 pt-yr	Placebo (N=2,524) no. (%)	Placebo (N=2,524) events/ 100 pt-yr	HR (95% CI)	P Value
Total CEC HF events	1402 (28.9)	43.9	1546 (31.5)	49.1	0.90 (0.83, 0.98)	0.010
Urgent outpt HF visit requiring IV therapy	179 (4.5)	5.6	210 (5.0)	6.7	0.85 (0.69, 1.04)	0.107
HFH with PO diuretics	38 (1.3)	1.2	30 (1.1)	1.0	1.26 (0.78, 2.03)	0.348
HFH with IV diuretics	766 (19.4)	24.0	846 (21.1)	26.9	0.90 (0.81, 0.99)	0.037
HFH with IV vasodilators	72 (2.5)	2.3	85 (2.7)	2.7	0.83 (0.61, 1.14)	0.257
HFH with IV inotropes	242 (7.0)	7.6	280 (8.6)	8.9	0.86 (0.73, 1.03)	0.100
HFH with mechanical circulatory support or fluid removal	110 (3.8)	3.5	97 (2.9)	3.1	1.14 (0.87, 1.50)	0.353

Hazard ratio (95% CI) and p vales computed from stratified Anderson-Gill model.

Post Discharge Outcomes by Event Type



Conclusions

- HF events vary significantly in severity and clinical implications
- The treatment benefit of vericiguat was generally consistent across HF event types
- HFH treated w IV vasodilators tended to be lower risk
- These data may have implications for more nuanced interpretation of HF clinical trials

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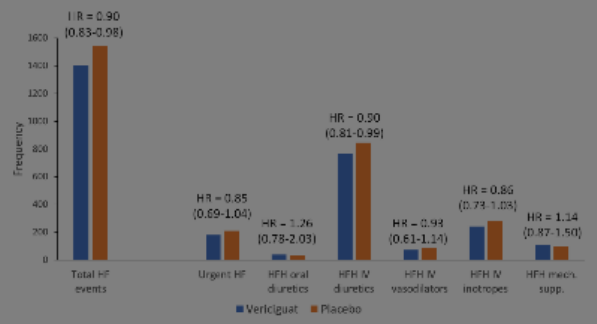

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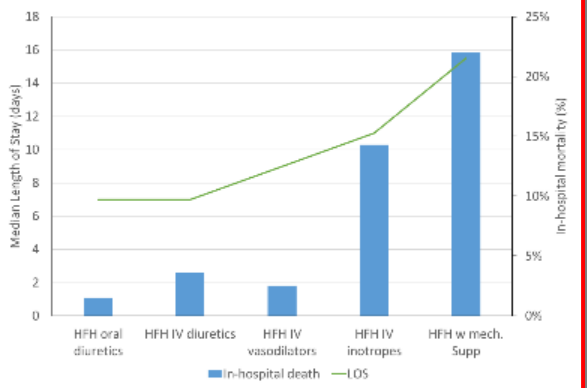

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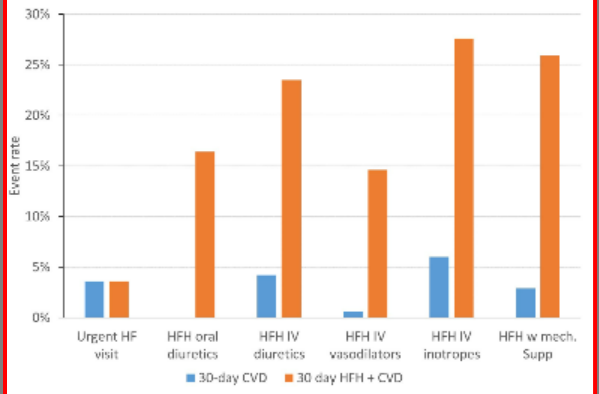

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- These data may have implications for more nuanced interpretation of HF clinical trials

FUNDING: The VICTORIA trial (NCT02861534) was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Bayer AG, Wuppertal, Germany.

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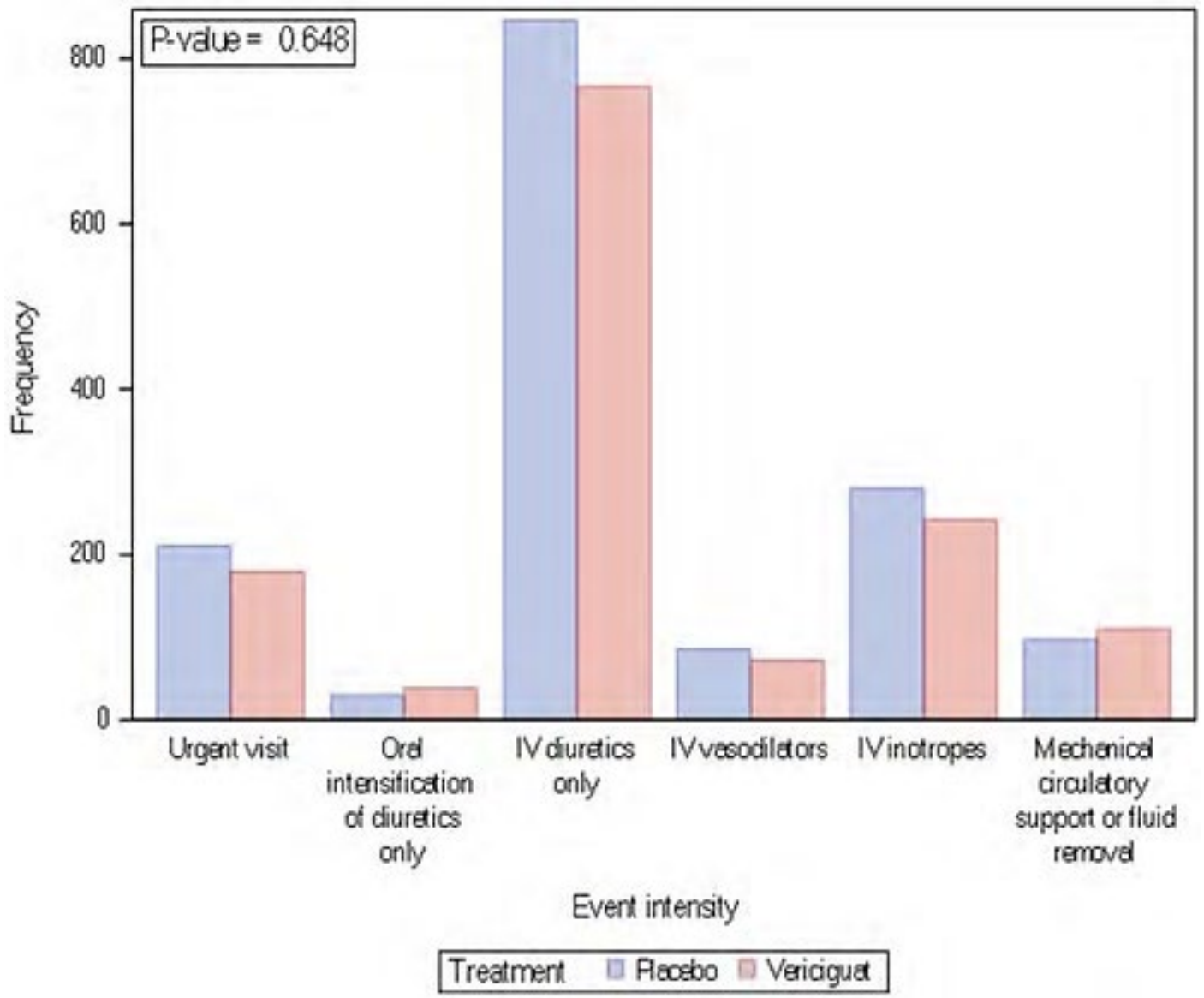

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Healthcare resource use, intensity, and costs among patients with heart failure with reduced ejection fraction treated with *omecamtiv mecarbil* in GALACTIC-HF

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BACKGROUND

- In GALACTIC-HF (NCT02929329), *omecamtiv mecarbil* (OM) added to standard of care for heart failure with reduced ejection fraction (HFrEF) reduced the risk of the primary composite endpoint of a first HF event or cardiovascular death.[1]
- Greater risk reduction was seen as baseline ejection fraction (EF) decreased.[2] Increased risk was seen in patients with both digoxin use plus atrial fibrillation/flutter (AF) together at baseline (digoxin+AF) but not for patients with either factor alone.[3] No benefit was observed for cardiovascular death.
- The purpose of this study was to examine HF-related resource utilization and costs in patients benefitting from OM.

METHODS

- We evaluated risk of first HF event (hospital and emergency room /urgent care visits, all adjudicated as due to HF), total HF events, and cumulative frequency of HF events, resource intensity, relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), and cost of HF events.
- Treatment effect was evaluated as function of baseline EF for the full study population and after excluding digoxin+AF. Selection of cut point for benefit reflected clinical practice of reporting EF in 5% intervals.
- Costs of HF events were based on unit cost estimates from published secondary studies inflated to 2021 US dollars, including $17,123 per HF hospitalization.[4]

RESULTS

- Of 8232 trial patients, 5369 (65%) met criteria for benefit from OM, after excluding those with digoxin+AF (692; 8.4%) or with EF >30 where little risk reduction was seen (**Fig 1**).
- In this subgroup with EF ≤30% without digoxin/AF:
  - OM was associated with significant reductions in risk of a first HF event (RRR 15%, ARR 3.8, NNT 26.2), total HF events (RRR 17%, ARR 6.8, NNT 14.7) **(Table 1)**, and cumulative HF events **(Fig 2)**.
  - OM also significantly reduced resource intensity, measured by total days in hospital among patients being hospitalized (rate ratio 0.90, 95% CI 0.82–0.99).
  - Estimated cost reductions related to HF events were $3,085 (19% reduction) per patient **(Fig 3)**. 99% of cost reductions were due to HF hospitalizations avoided with OM.

CONCLUSIONS

- Among HF patients with EF ≤30% and without digoxin+AF, OM led to significant clinical benefits, with reductions in resource utilization, intensity, and costs related to HF events.
- This large, clinically relevant and easily identifiable group of HFrEF patients may be where the clinical and economic benefits of OM are most evident.
- Modeling long-term cost-effectiveness (Cost/QALY) of OM is ongoing.

Omecamtiv mecarbil **significantly reduced clinical events, resource utilization, and costs related to HF events** in a clinically relevant and easily identifiable subgroup of HFrEF patients **where risk is most evident**

19%

Reduction in costs related to HF hospitalizations & emergency room/urgent care among patients with EF ≤30% and without digoxin+AF

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Cytokinetics

GALACTIC-HF

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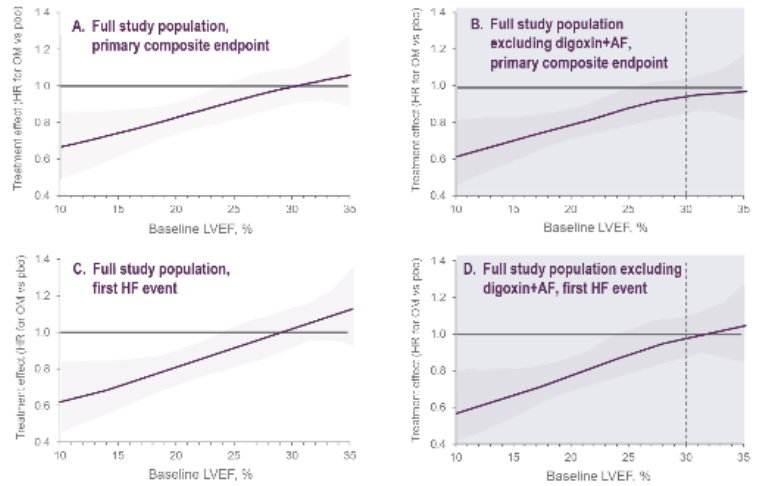
Fig 1: *Omecamtiv mecarbil* treatment effect as function of baseline EF



Solid line shows treatment effect (HR); shaded area shows 95% confidence interval.

Fig 2: Total HF events, cumulative incidence

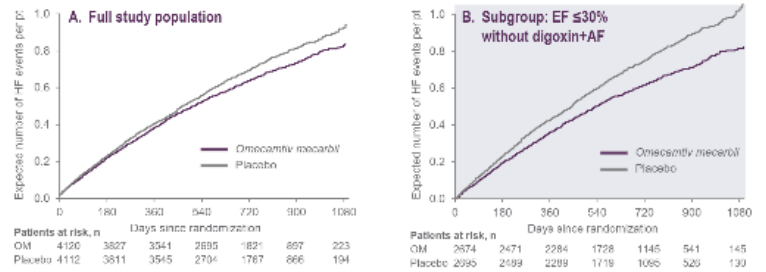
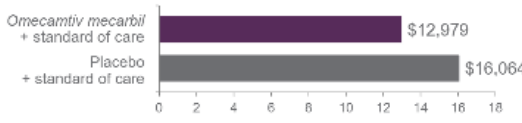


Table 1: First and total HF events (subgroup: EF ≤30% without digoxin+AF)

	OM (n=2674)	Placebo (n=2695)				
	Events per 100 pt-yr		HR (95% CI)	RRR	ARR	NNT
First HF event	18.8	22.7	0.85 (0.77–0.93)	15%	3.8	26.2
Total HF events	31.1	37.9	0.83 (0.74 0.93)	17%	6.8	14.7

NNT is the number of patients needed to be treated to prevent 1 HF event, over the 3 years studied.

Fig 3: Cost per patient of HF events (subgroup: EF ≤30% without digoxin+AF)



Cost offsets	
Per patient	$3085
% Reduction	19%

REFERENCES (1) Teerlink JR et al. *N Engl J Med* 2021:384:105-16. (2) Teerlink JR et al. *J Am Coll Cardiol* 2021:78:97-108. (3) Solomon SD et al. Heart Failure 2021; Florence, Italy (Abstract). (4) Gaziano TA et al. *JAMA Cardiol* 2020:5:1238-44.

Resource Use	OM (2674)	Pbo (2695)		
Time to first HFE/100 pt yrs	18.9	22.7	HR 0.85, CI 10.77-0.93	ARR 3.8 NNT 26.5
Frequency of HFE (all events) / 100 pt yrs	31.2	38.0	HR 0.85, CI 0.75-0.96	ARR 6.7 NNT 14.9
Cumulative rate of HFEs at 36 mos / 100 pts	81.8	102.4	Rate ratio 0.799	Increasing treatment effect over time
Resource Intensity	**/100 pt yrs**			
Total days in hospital	524.1	652.2	Rate ratio 0.80, CI 0.79-0.82	
IV diuretics/inotropes /vasodilators	35.7	42.3	Rate ratio 0.84, CI 0.79-0.90	
Mechanical circulatory support during HF hospitaliz'ns	2.2	2.4	*Low event rates precluded comparison with sufficient precision*	
Mechanical fluid removal during HF hospitaliz'ns	0.8	0.9		
Hospital Costs	**US $ over trial period**			
HFE med'l costs (excl Rx) / pt	$12,462	$15,487	Rate ratio 0.804	$3,025 / difference

ARR = absolute risk reduction. CI=95% confidence interval. HFE = heart failure event. NNT = number needed to treat. OM = omecamtiv mecarbil + standard care. Pbo = placebo + standard care. Cost per admission / event from literature may underestimate total cost as they do not incorporate lower resource intensity or length of stay or reductions in other observed hospitalizations not related to worsening HF such as stroke. Development of a lifetime projection model and full cost effectiveness analysis (Cost/QALY) is ongoing.

Study Conclusions

- Among HF patients with EF ≤30% and without digoxin+AF, OM led to significant clinical benefits, with reductions in resource utilization, intensity, and costs related to HF events
- This large, clinically relevant and easily identifiable group of HGrEF patients may be where the clinical and economic benefits of OM are most evident
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