Canadian VIGOUR Centre
Bridging Hearts and Minds

Late-breaking Heart Failure Trials 2.0

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ZoomDay 2020

Disclosures / COI / RWI / RWA

- Available online: thecvc.ca
- VICTORIA: Executive Committee

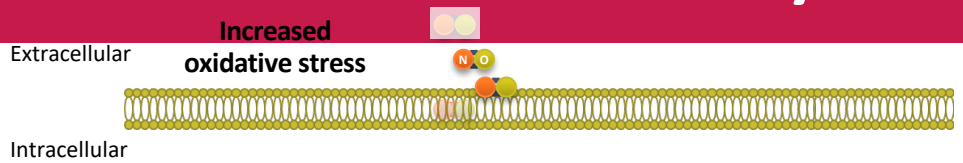
ACC 2020

- VICTORIA Primary
- DAPA-HF NT-proBNP
- GALACTIC Baseline


Shelley
Stephanie
Jonathan
Nadia
Michael
Chris
Mona
Serge
Sean

VICTORIA (sGC)

Soluble Guanylate Cyclase (sGC)



cGMP=cyclic guanosine monophosphate; HF=heart failure; NO=nitric oxide; PDE5=phosphodiesterase 5; RAAS=renin-angiotensin-aldosterone system; sGC=soluble guanylate cyclase; SNS=sympathetic nervous system.

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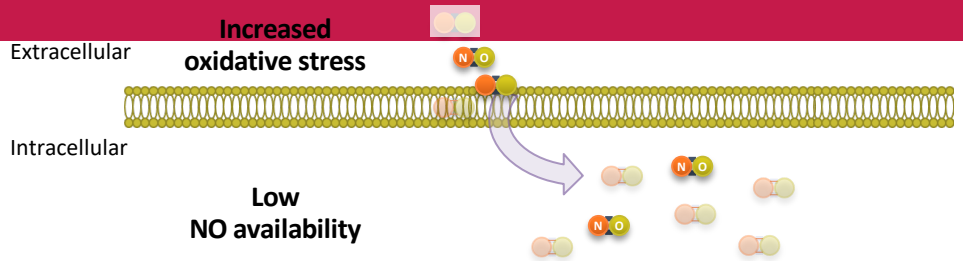

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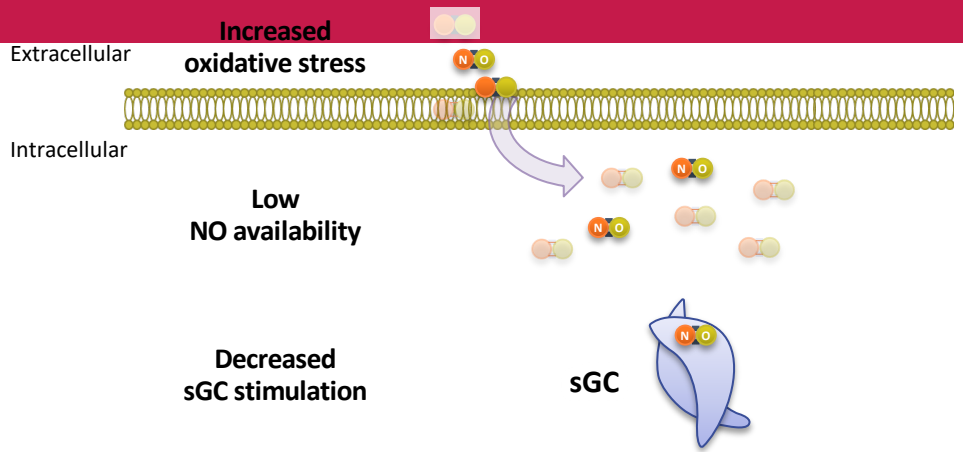

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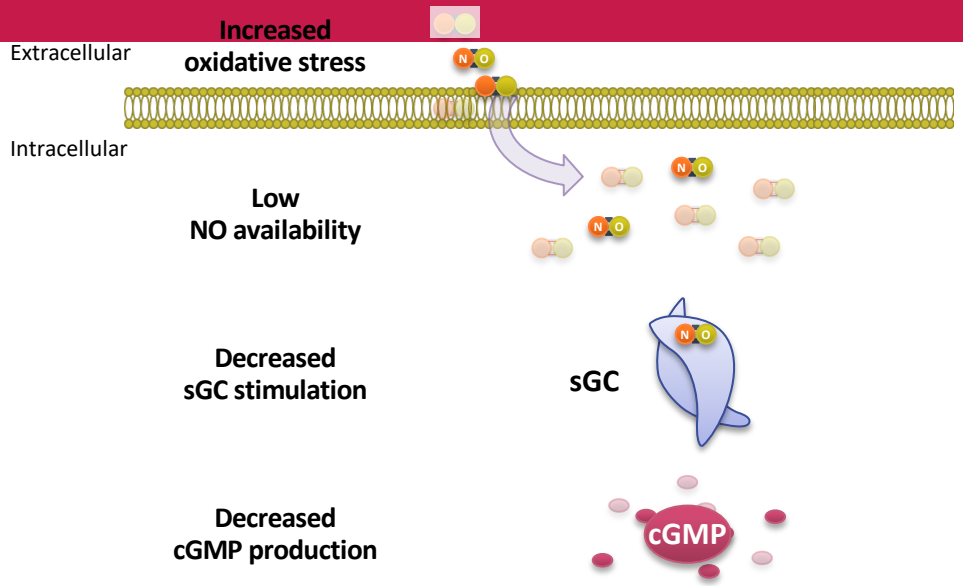

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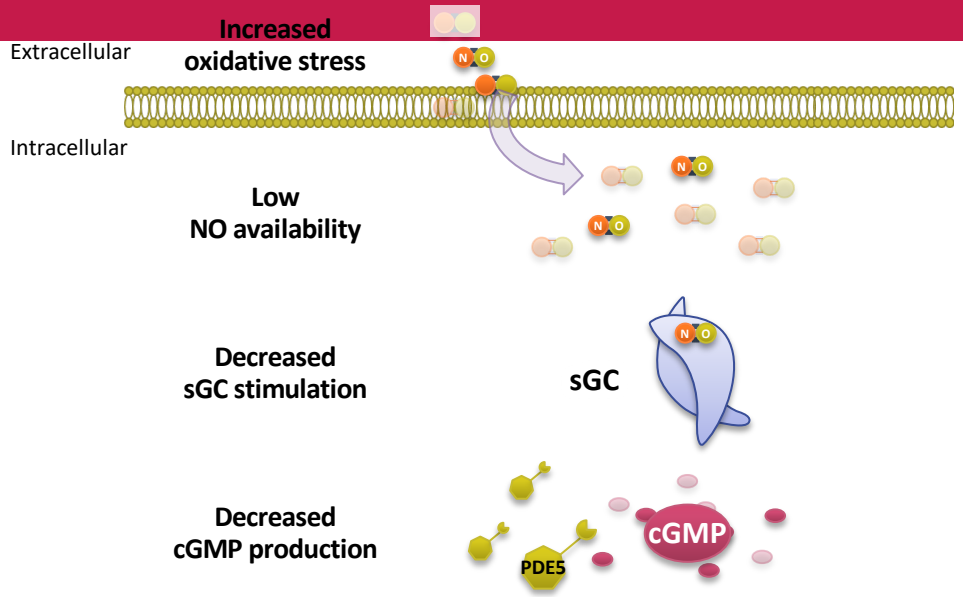

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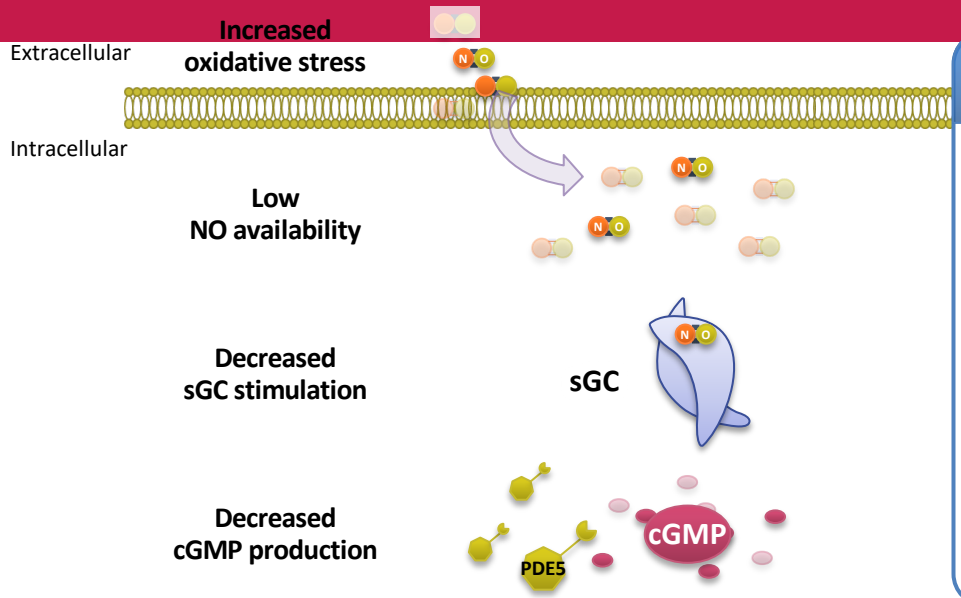

Clinical Effects of an Impaired sGC-cGMP Pathway

- Progressive myocardial dysfunction
- Adverse left-ventricular remodeling
- Vascular dysfunction
- Increased fibrosis
- Increased inflammation

Oxidative stress and the resulting deficiency in NO can lead to insufficient stimulation of the sGC, decreased production of cGMP, and subsequent cardiovascular dysfunction and HF[1,3]

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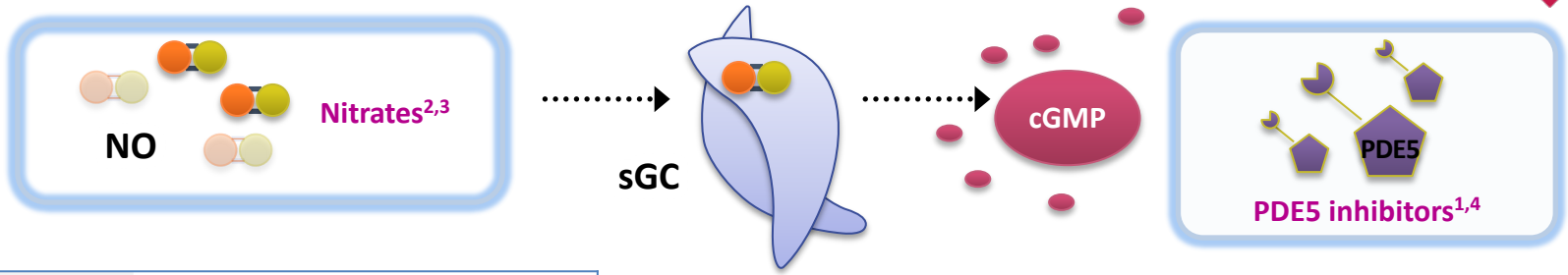
sGC not targeted by current Rx



MOA	Upstream of sGC-cGMP[2]
Benefit	Improved LV function and exercise capacity in combination with hydralazine[2]
Challenge	• Development of tolerance[3] • Confirmatory data lacking

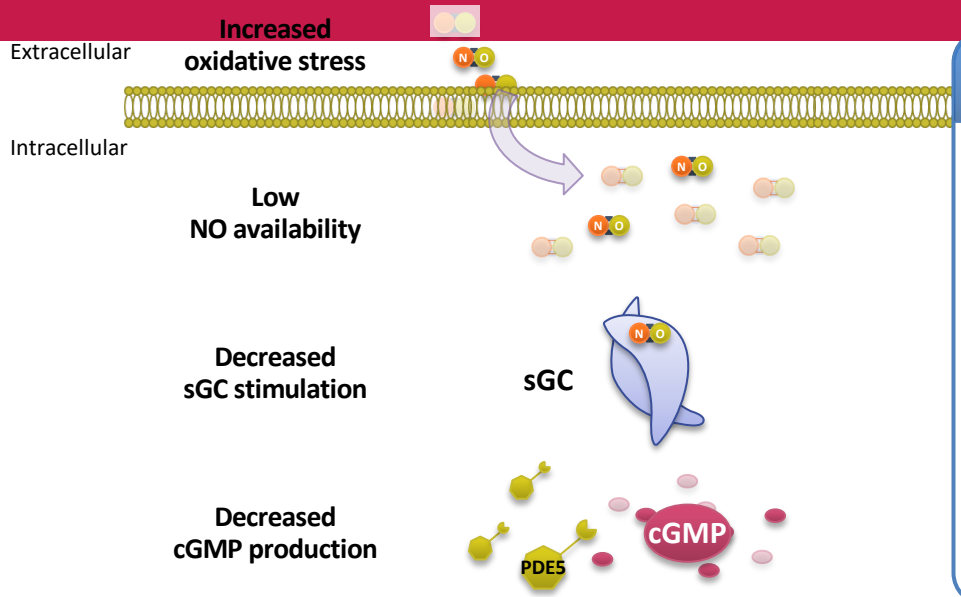
MOA	Downstream of sGC-cGMP[4]
Benefit	Mitigates myocardial remodeling[4]
Challenge	PDE5 is dependent on NO-sGC activity and cGMP production—often impaired in HF[1]

The impact of nitrates and PDE5 inhibitors is limited, and they do not directly stimulate sGC

cGMP=cyclic guanosine monophosphate; HF=heart failure; LV=left ventricular; MOA=mechanism of action; NO=nitric oxide; PDE5=phosphodiesterase type 5; sGC=soluble guanylate cyclase.

1. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225-247. 2. Münzel T et al. *Circulation*. 2011;123(19):2132-2144. 3. Watanabe H et al. *J Am Coll Cardiol*. 1998;32(5):1194-1200. 4. Michalak M et al. *Circ Heart Fail*. 2018;11(3):e004813.

sGC and HF: vericiguat



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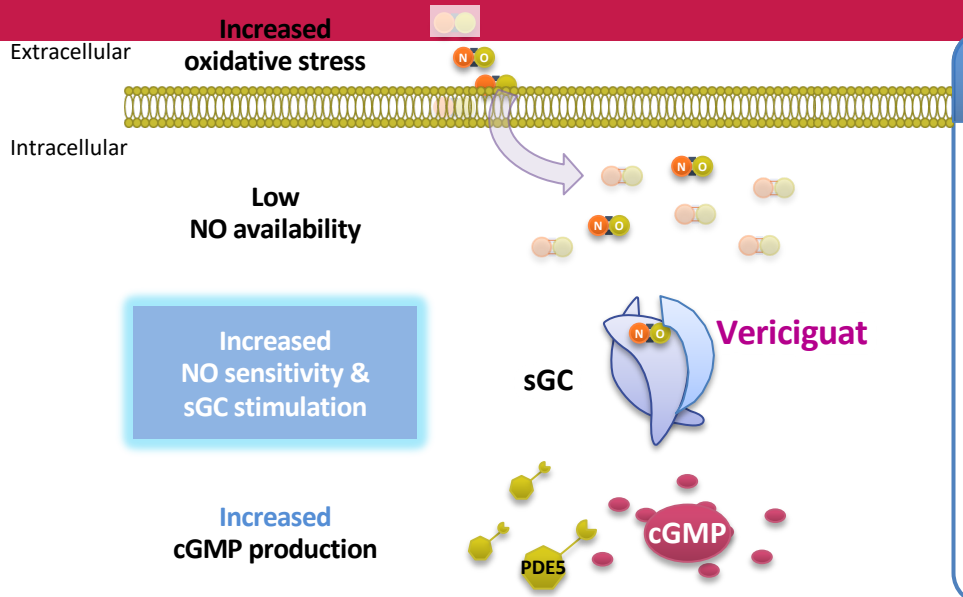

Clinical Effects of Vericiguat on an Impaired sGC-cGMP Pathway

- **Improved** myocardial function
- **Reduced** left-ventricular remodeling
- **Improved** vascular function
- **Decreased** fibrosis
- **Decreased** inflammation

Vericiguat directly and selectively stimulates sGC to increase cGMP production even under low-NO conditions in HF[4]

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4. Armstrong PW et al. *JACC Heart Fail*. 2018;6(2):96-104.

VICTORIA

ACC March 2020

N=4872

Worsening chronic HFrEF population:

- EF <45%
- NYHA II-IV
- Prior HF hospitalization or outpatient IV diuretic for HF
- Elevated natriuretic peptides
- SBP ≥100 mmHg
- eGFR ≥15 mL/min/1.73 m^2

1:1

Randomized, double blind

2.5 mg QD → 5 mg QD → 10 mg QD

Vericiguat

Up-titration at 2-week intervals

Placebo

Event-driven study duration

Estimated median follow-up 18 months

Primary endpoint: Composite of CV death or hospitalization for HF

Secondary endpoints:

- Time to CV death
- Time to first and subsequent HF hospitalizations
- Time to composite all-cause mortality or HF hospitalization
- Time to all-cause mortality
- Safety and tolerability

Exploratory endpoints:

- Time to first occurrence of composite HF hospitalization or urgent HF visits; first CV hospitalization
- Number of HF hospitalizations
- Change in QoL (KCCQ and EQ-5D)

CV=cardiovascular; EF=ejection fraction; eGFR=estimated glomerular filtration rate; EQ-5D=EuroQol 5-dimension; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; IV=intravenous; KCCQ=Kansas City Cardiomyopathy Questionnaire; NYHA=New York Heart Association; QD=once daily; QoL=quality of life; SBP=systolic blood pressure.

1. Armstrong PW et al. *JACC Heart Fail.* 2018;6(2):96-104. 2. Clinicaltrials.gov. NCT02861534. Accessed April 9, 2019.

VICTORIA: Inclusion Criteria

"Chronic HF"

- NYHA class II–IV
- LVEF < 45%
- Guideline based HF therapies
- eGFR > 15

after

"Worsening event"

- Recent HFH or IV diuretic use
- With very elevated natriuretic peptides (BNP or NT-proBNP)

BNP ≥ 300 & pro-BNP ≥ 1000 pg/ml NSR
BNP ≥ 500 & pro-BNP ≥ 1600pg/ml AF

Patients may have been randomized as an inpatient or outpatient but must have met criteria for clinical stability (e.g., SBP ≥ 100 mmHg, off IV treatments ≥ 24 hours)

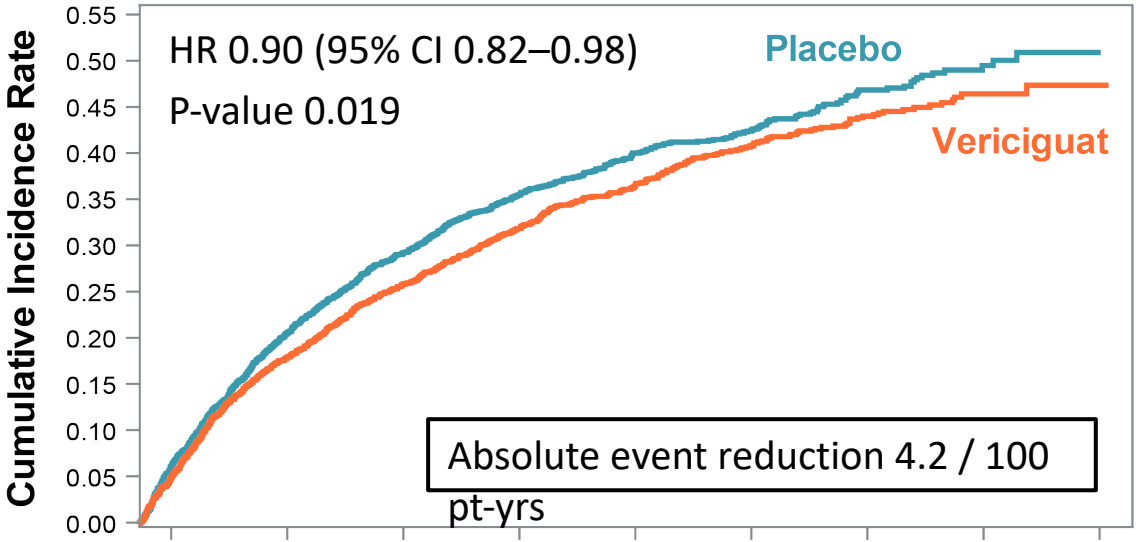
No run-in

VICTORIA: Baseline Characteristics

	Vericiguat (N=2526)	Placebo (N=2524)
Age mean (SD)	67.5 (12.2)	67.2 (12.2)
Female sex	605 (24.0%)	603 (23.9%)
Index event at Randomization		
HF hospitalization < 3 mos	1673 (66.2%)	1705 (67.6%)
HF hospitalization 3 to 6 mos	454 (18.0%)	417 (16.5%)
IV diuretic for HF < 3 mos (no hospitalization)	399 (15.8%)	402 (15.9%)
EF % (SD)	29.0 (8.3)	28.8 (8.3)
NYHA class III–IV baseline,	1045 (41.4%)	1024 (40.6%)
NT-proBNP Median (25^{th} – 75^{th}) pg/mL	2804 (1572- 5380)	2821(1548 – 5206)
Triple guide-based therapy *	1480 (58.7%)	1529 (60.7%)
ICD, BV pacemaker (or both) *	813 (32.2%)	802 (31.8%)

* For vericiguat / placebo %'s are of n's 2521 & 2519

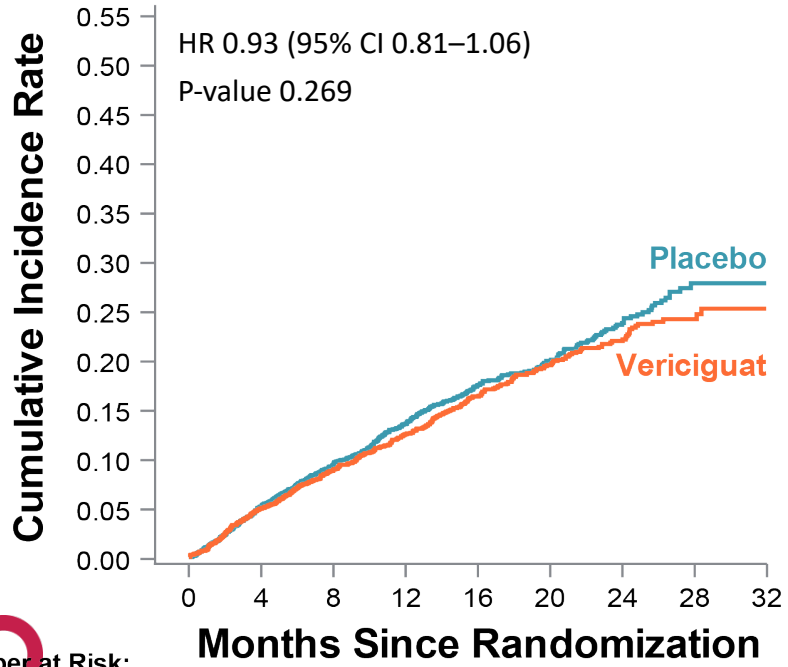
Primary Endpoint: CVD/HFH



Number at Risk:									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

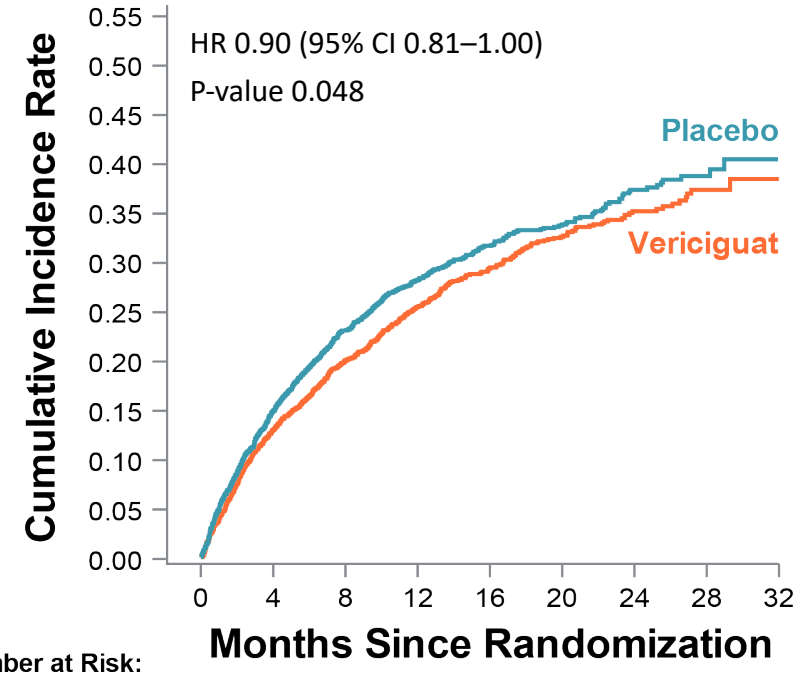
Secondary Endpoints

CVD



Number at Risk:									
Vericiguat	2526	2376	1968	1468	1070	779	487	185	1
Placebo	2524	2370	1951	1439	1045	768	471	157	0

First HF Hospitalization



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Safety & Tolerability

- Symptomatic hypotension + syncope more common w/ vericiguat
- More anemia developed with vericiguat (7.6%) than placebo (5.7%)
- SAE were similar: vericiguat (32.8%), placebo (34.8%)
- **No effects of vericiguat on either electrolytes or renal function**
- At 12 months, 10 mg target dose achieved: vericiguat (89.2%), placebo (91.4%)

VICTORIA Summary

- Vericiguat was significantly more effective than placebo in reducing:
  - The composite endpoint of CV death or HF hospitalization (primary endpoint)
  - HF hospitalization (first and recurrent)
- There was directionally aligned reduction in CV death
- No significant change in all-cause mortality
- Vericiguat generally safe and well tolerated
- There was excellent guideline-based HF therapy and patient follow-up

VICTORIA in Context

	PARADIGM-HF		DAPA HF		VICTORIA	
	Comparator	Sacubitril/ Valsartan	Comparator	Dapagliflozin	Comparator	Vericiguat
Primary Endpoint*	13.2	10.5	15.6	11.6	37.8	33.6
Absolute Rate Reduction	**2.7**		**4.0**		**4.2**	
CV Death*	7.5	6.0	7.9	6.5	13.9	12.9
Absolute Rate Reduction	**1.5**		**1.4**		**1.0**	
First HF Hospitalization*	NA	NA	9.8	6.9	29.1	25.9
Absolute Rate Reduction	**1.6**		**2.9**		**3.2**	

*Rates expressed / 100 patient years

Butler et al. *Circulation*

Omecamtiv mecarbil

GALACTIC-HF

Omecamtiv mecarbil

- Mitotropes vs. Calcitropes vs. Myotropes
- OME:
  - Direct cardiac myosin activator
  - duration of systole by overall # of active cross-bridges
  - stroke volume
  - No increase in MVO2 observed

1. Teerlink J. *Heart Fail Rev*. doi:10.1007/s10741-009-9135-0.
2. Malik FI, et al. *Science*. 2011;331:1439-43.

Cardiac Calcitropes, Myotropes, and Mitotropes

JACC Review Topic of the Week

Mitchell A. Psotka, MD, PhD,[a] Stephen S. Gottlieb, MD,[b] Gary S. Francis, MD,[c] Larry A. Allen, MD, MHS,[d] John R. Teerlink, MD,[e] Kirkwood F. Adams, Jr, MD,[f] Giuseppe M.C. Rosano, MD, PhD,[g] Patrizio Lancellotti, MD, PhD[h]

Myo / Mitotropes are where its at

TABLE 1 Currently Available and Developmental Direct Inotropic Agents

Pharmacological Agent	Mechanism	dP/dt	Hemodynamic Effects	Patient Outcomes
Cardiac calcitropes				
Dobutamine	Catecholamine: β-adrenergic receptor→ cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Dopamine	Catecholamine: β-adrenergic receptor→ cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Epinephrine	Catecholamine: β-adrenergic receptor→ cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Milrinone	Phosphodiesterase-3 inhibitor: cAMP→ ↑ Ca^{2+}	↑	↑ Cardiac output	↑ Mortality
Levosimendan	Phosphodiesterase-3 inhibitor (and calcium sensitizer): ↓ Troponin and tropomyosin inhibition; cAMP → ↑ Ca^{2+}	↑	↑ Cardiac output	?↑ Mortality
Cardiac glycosides	Na^{+}-K^{+} ATPase inhibitor: ↓NCX Ca^{2+} extrusion → ↑ Ca^{2+}	↑	↔ Cardiac output	? ↔Mortality ↓ Hospitalizations
Istaroxime	Na^{+}-K^{+} ATPase Inhibitor & SERCA2a Activator: ↓Ca^{2+} extrusion → ↑ Ca^{2+}, ↑ SERCA2a → ↑ Ca^{2+} in SR	↑	↑ Cardiac output	?
Cardiac myotropes				
Omecamtiv mecarbil	Direct myosin activator ↑ Myosin participation in systole	↔	↑ Cardiac output	?
Cardiac mitotropes				
Perhexiline	Carnitine palmitoyl transferase inhibitor: ↓ Mitochondrial fatty acids → ↑ Glucose metabolism	↔	↑ Cardiac output	?
Trimetazidine	Thiolase I inhibitor: ↓ Fatty acid oxidation → ↑ Glucose metabolism	↑	↑ Cardiac Output	?
Elamipretide	Cardiolipin stabilizer ↑ Adenosine triphosphate synthesis	?	?	?

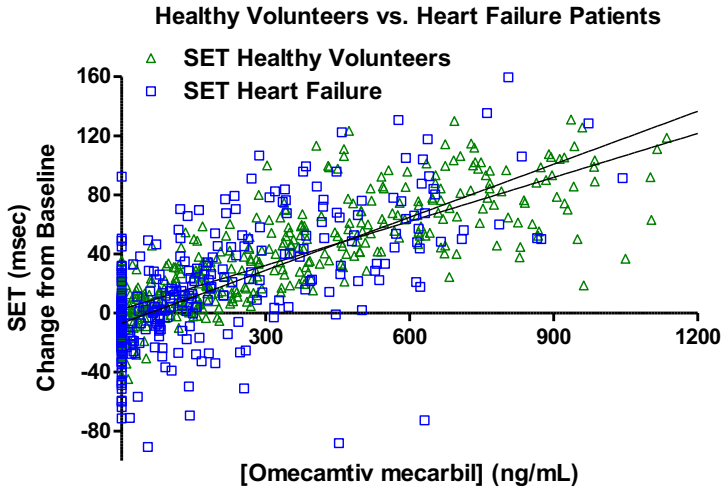
↑ = increase; ↓ = decrease; ↔ = no change; ? = unknown or possible; ATPase = adenosine triphosphatase; Ca^{2+} = calcium ion; cAMP = cyclic adenosine monophosphate; K = potassium; Na = sodium; NCX = sodium ion/calcium ion exchanger; SERCA2a = sarcoplasmic/endoplasmic reticulum calcium ATPase; SR = sarcoplasmic reticulum.

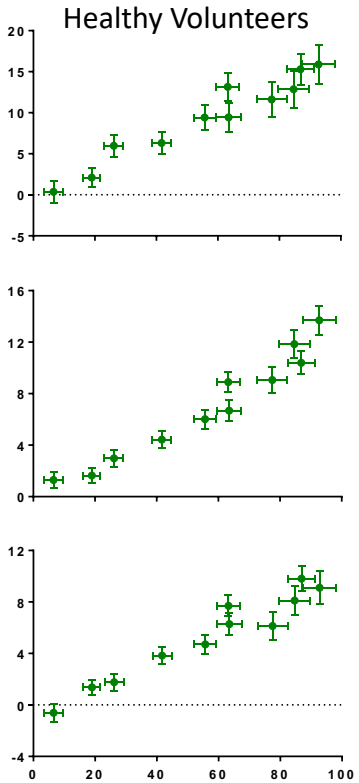
Calcitropes = bad

Myotropes = maybe

Mitotropes = maybe

Omecamtiv mecarbil





Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

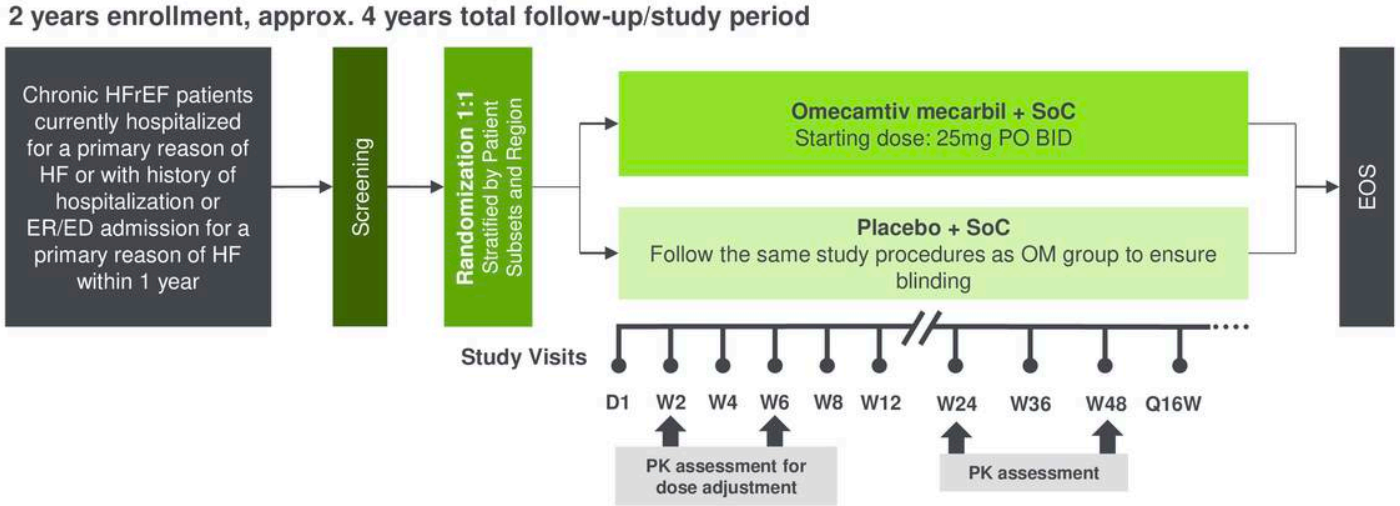
Δ Ejection Fraction (% points)

Teerlink JR, et al. *Lancet* 2011; 378: 667–75.
Cleland JGF, et al. *Lancet* 2011; 378: 676–83.

Δ = placebo corrected change from baseline Mean ± SEM

GALACTIC-HF

- ~8000 patients randomized 1:1 to *omecamtiv mecarbil* versus placebo, stratified by inpatient versus outpatient at randomization
- *Omecamtiv mecarbil* started at 25 mg BID: PK-guided dose optimization to one of 3 target doses (25, 37.5, 50mg BID)
- Event-driven; patients will be followed indefinitely until CV death events have accumulated (90% powered for CV Mortality)



AHA 2020

GALACTIC Baseline

- 65 year old, 79% male
- EF 27%
- NT-proBNP 1998 pg/ml
- eGFR 59

	Overall (N=8,256)	Inpatient (N=2,083)	Outpatient (N=6,173)
Time from most recent HF hospitalization/ ED visit (months), median (Q1-Q3)	2 (1-5)	-	3 (2-6)
Region NA/LA/(WE,SA,OCE)/EE/Asia, %	17/ 19/ 23/ 33/ 8	9/ 16/ 23/ 44/ 9	20/ 20/ 23/ 29/ 8
Age (years), mean (SD)	65 (11)	65 (11)	64 (11)
Male, %	79	80	78
White, %	78	82	76
LVEF (%), mean (SD)	27 (6)	27 (6)	27 (6)
MAGGIC Score, mean (SD)	23 (6)	25 (6)	23 (6)
NYHA Class II/III/IV, %	53/ 44/ 3	37/ 57/ 6	59/ 39/ 2
NT-proBNP (pg/mL), median (Q1-Q3)	1998 (990-4078)	2509 (1240-5133)	1884 (923-3772)
hsTnI (ng/mL), median (Q3)	0.027 (0.051)	0.037 (0.068)	0.024 (0.046)
Ischemic Heart Disease Etiology, %	55	56	54
KCCQ Total Symptom Score, mean (SD)	66 (25)	53 (25)	71 (23)
Coronary Artery Disease, %	62	63	61
Peripheral Artery Disease, %	10	10	10
Stroke, %	9	9	9
Atrial Fibrillation or Flutter History, %	42	48	40
Hypertension, %	70	72	70
Type 2 Diabetes Mellitus, %	40	42	40
Chronic Kidney Disease, %	36	39	35
eGFR (mL/min/1.73m^2), median (Q1-Q3)	59 (44-74)	54 (41-70)	60 (45-75)
SBP (mmHg), mean (SD)	117 (15)	114 (14)	117 (16)
Heart rate (beats/min), mean (SD)	72 (12)	73 (12)	72 (12)
ACEi, ARB or ARNi, %	87	83	88
ARNi, %	19	16	21
BB, %	94	93	95
MRA, %	77	81	76
Diuretics other than MRAs, %	90	92	89
Digitalis Glycosides, %	17	17	17
CRT and/or ICD, %	34	31	35
SGLT2 Inhibitors, %	3	3	3
Ivabradine, %	6	7	6


SGLTi

Differences in study designs

	DAPA-HF[1]	EMPEROR-Reduced[2]	SOLOIST-WHF
Patient population	• Patients with NYHA class II-IV heart failure with Reduced EF (<40%) and elevated NT-proBNP • eGFR ≥30 mL/min/1.73 m^2 • Diabetes and no Diabetes	• Patients with NYHA class II-IV heart failure with Reduced EF (<40%) and elevated NT-proBNP • eGFR ≥20 mL/min/1.73 m^2 • Diabetes and no diabetes	• Patients with NYHA class II-IV heart failure with ANY EF and elevated NT-proBNP • eGFR ≥30 mL/min/1.73 m^2 • Diabetes only
Sample size	N=4500	N=2850	N=4000
Study duration	33 months	38 months	32 months
Primary outcome	Time to first occurrence of any component of the composite: • CV death • or hHF • or an urgent HF visit	Time to the first occurrence of any of the components of the composite: • CV death • or hHF	Time to the first occurrence of any of the components of the composite: • CV death • or hHF
Secondary outcomes	• Time to first occurrence of hHF • Time to first occurrence of CVD • Total number of hHF and CVD • Change in KCCQ at 8 months • Time to the composite of ≥5% decline in eGFR, reaching ESRD or renal death • All-cause mortality	• Total number of hHF • eGFR slope change from baseline • Time to occurrence of sustained reduction of eGFR • Time to first hHF • Time to CVD • Time to all-cause mortality • Time to diabetes onset • Change in KCCQ at 12 months • Total all-cause hospitalisation	• Total number of hHF incl recurrent events • eGFR slope change from baseline • Time to occurrence of sustained reduction of eGFR • Time to first hHF • Time to CVD • Time to all-cause mortality • Change in KCCQ at 12 months • Total all-cause hospitalization • Above and EF<50%

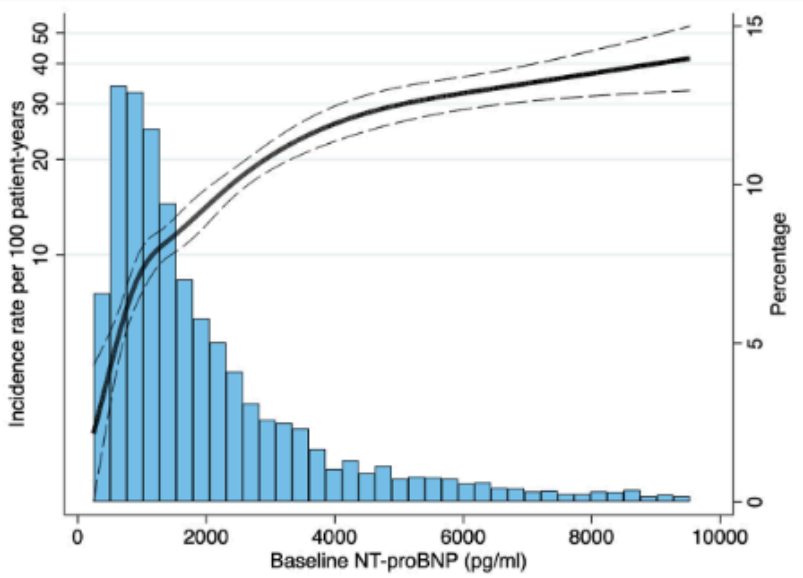
ESC 2020

Cancelled

1. I

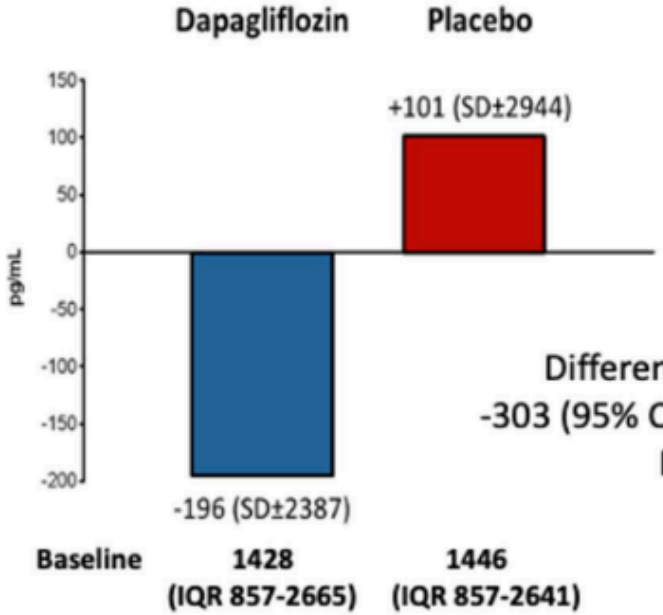
DAPA-HF and NT-proBNP

FIGURE 1 – INCIDENCE OF PRIMARY ENDPOINT BY NT-PROBNI



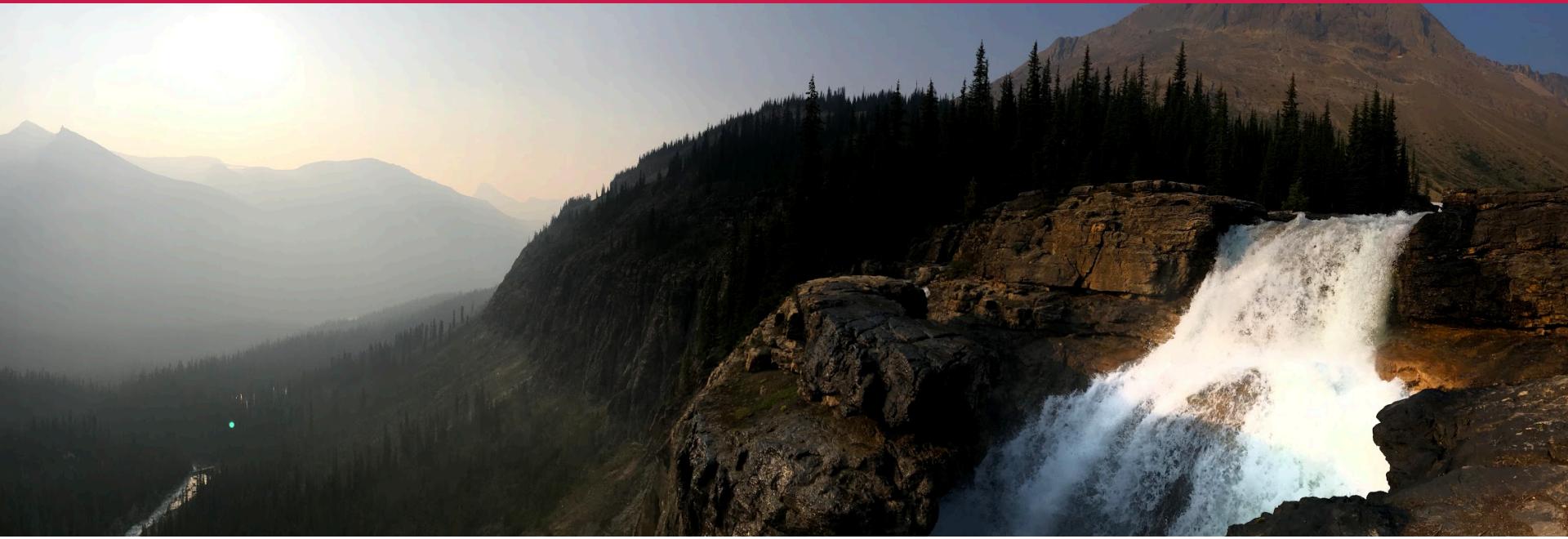
Blue bars indicate distribution of baseline NT-proBNP (right hand side Y axis).

FIGURE 2 – EFFECT OF DAPAGLIFLOZIN ON NT-PROBNP AT 8 M



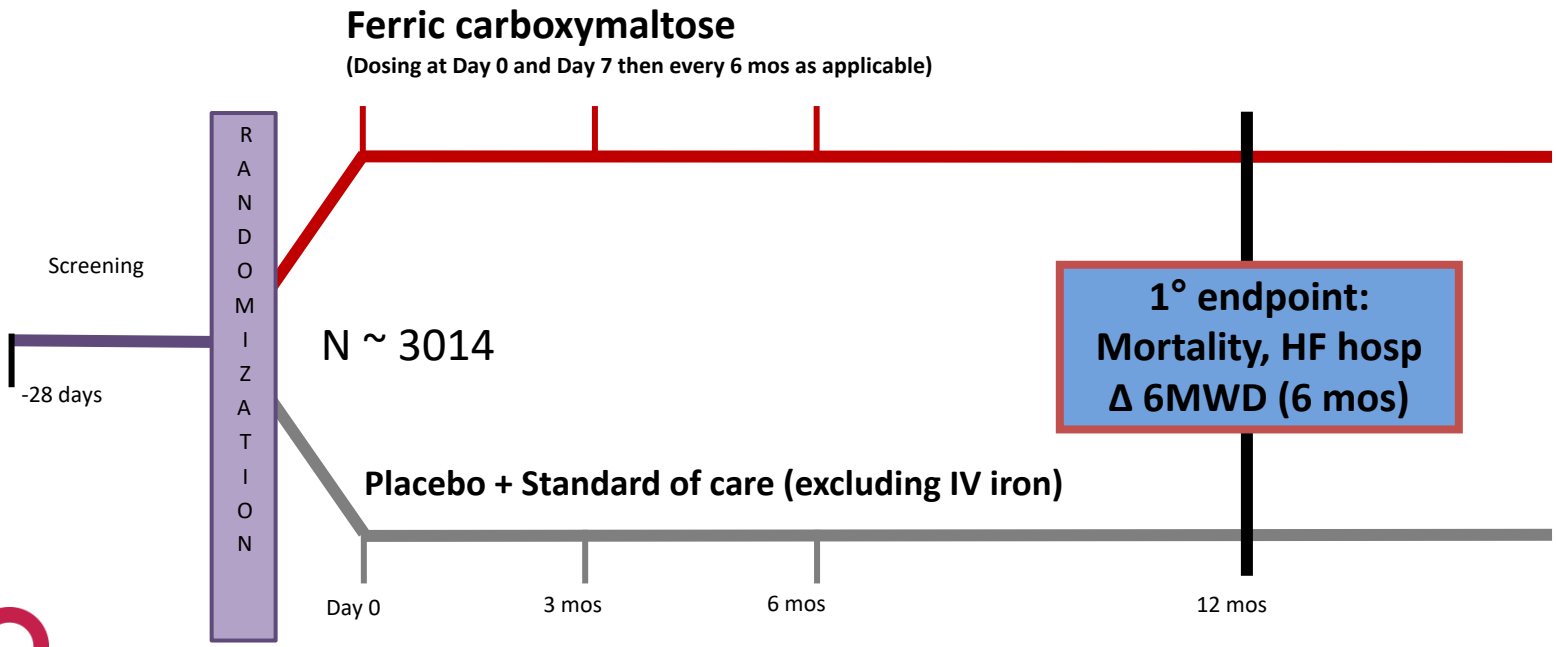
ACC 2020

IV Iron



HEART-FID

Patients with HFrEF, EF < 40%, iron deficiency (tsat <20%, ferritin < 100)

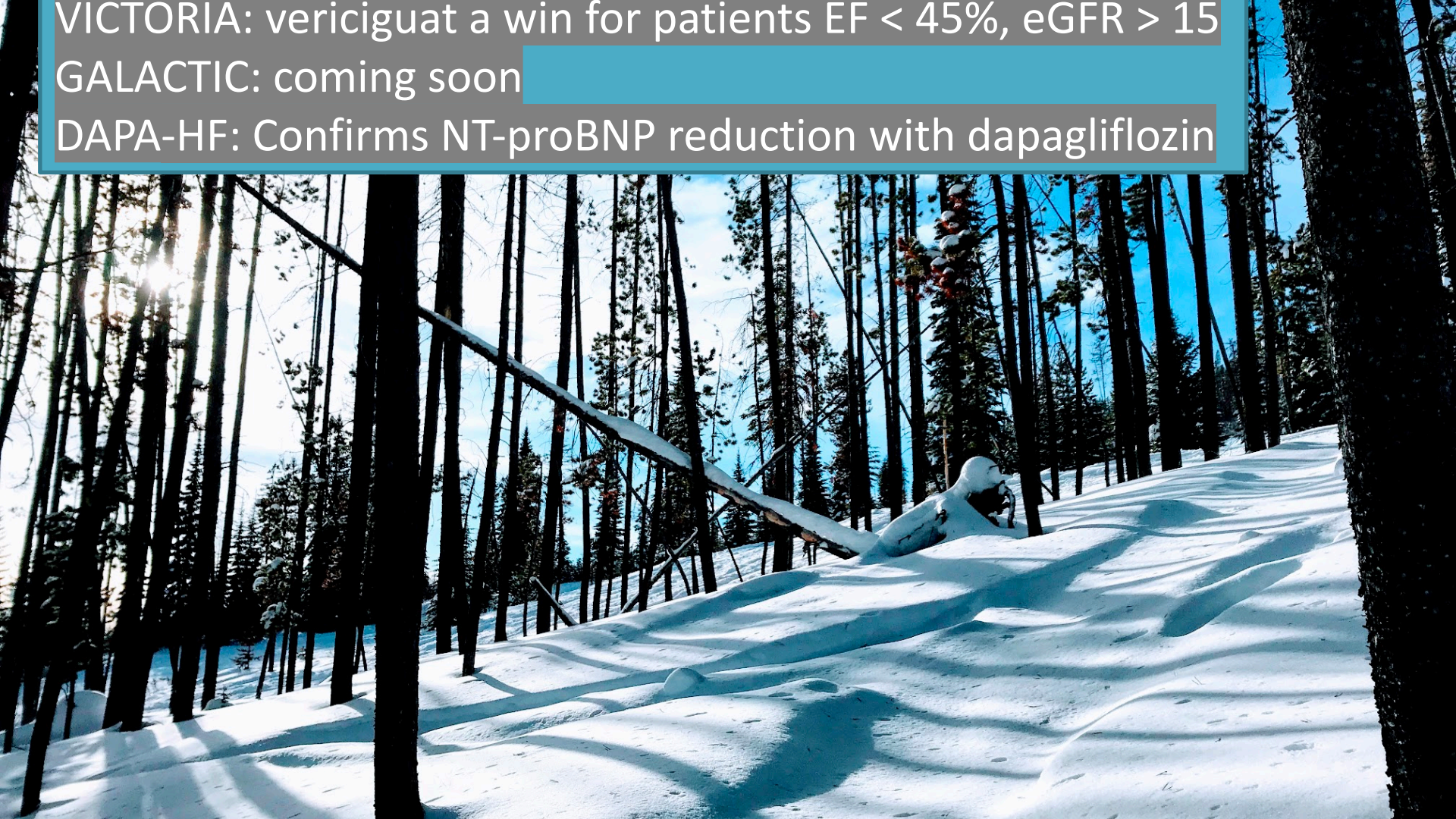


*Canada sites

VICTORIA: vericiguat a win for patients EF < 45%, eGFR > 15

GALACTIC: coming soon

DAPA-HF: Confirms NT-proBNP reduction with dapagliflozin

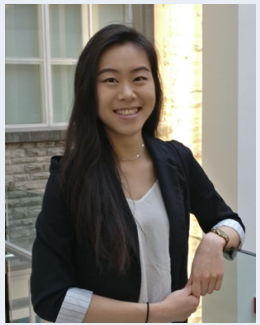


The future is often inverted

Vericiguat (now)
Omecamtiv (maybe)
Dapagliflozin (now)

Heart Failure Update Trainee Research Competition

	Winner David Bobrowski University of Toronto ***Statins Are Associated with Lower Risk of Heart Failure After Anthracycline and Trastuzumab Chemotherapy for Early Stage Breast Cancer***
	Finalist Justin Chow McMaster University ***Pulmonary Artery Catheterization in Cardiogenic Shock: A Systematic Review and Meta-Analysis***

Image not available.	Finalist Patrick Prud'homme Université de Sherbrooke ***High Sensitivity Troponin T and Nt-pro-BNP Prognostic Value in Predicting Cardiovascular Outcomes in Patients Undergoing Chronic Hemodialysis***
	Finalist Felicia Tai University of Toronto ***Prognosis of heart failure following cardiotoxic breast cancer chemotherapy: a retrospective population-based matched cohort study***