NT-proBNP and Clinical Outcomes in VICTORIA

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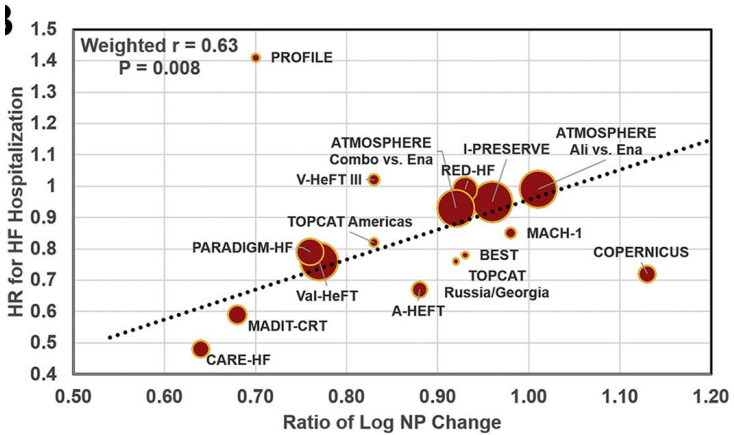
Disclosures / COI

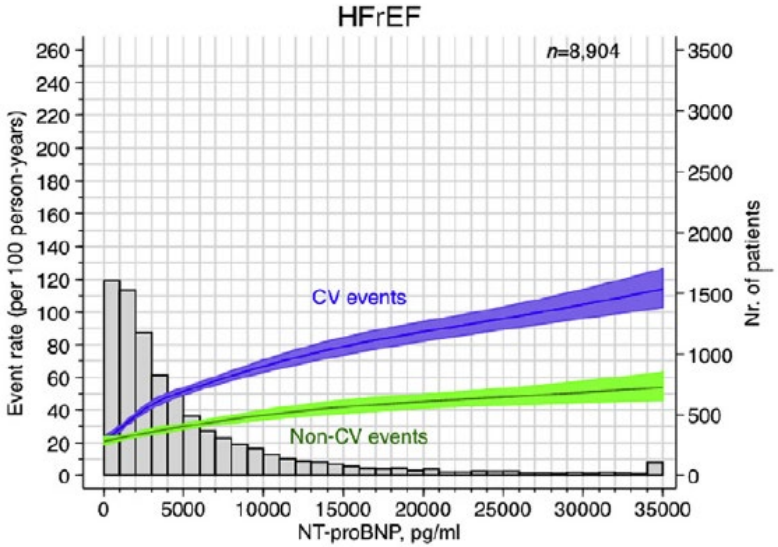
- Available online: thecvc.ca
- VICTORIA: Executive Committee

- The VICTORIA trial was funded by Bayer and Merck/MSD

Background

- NT-proBNP
  - marker of prognosis in patients w/ HFrEF
  - an inclusion criteria for clinical trials;
  - often linked to treatment efficacy.





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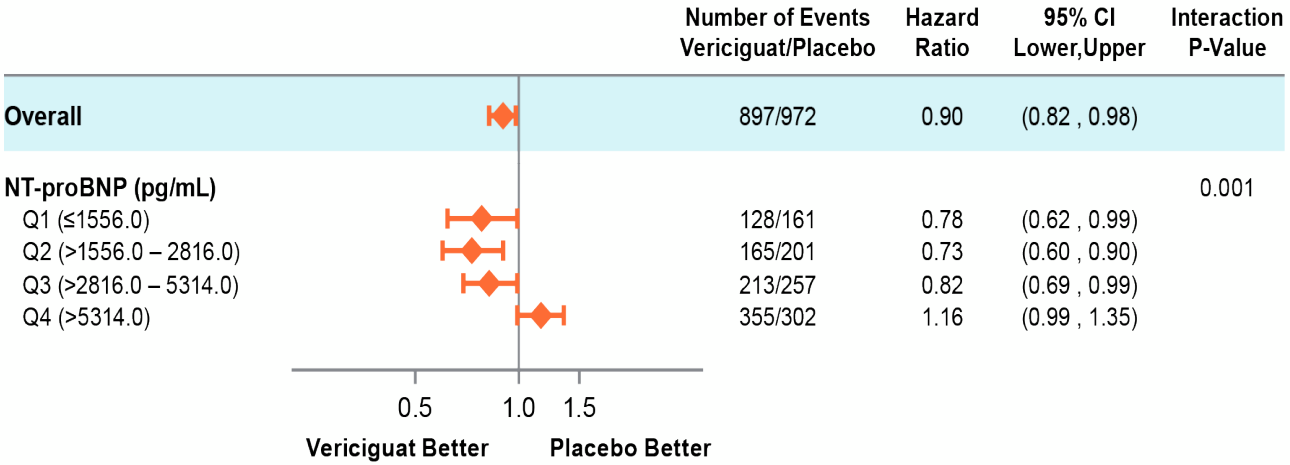
Savarese, *JACC-HF* 2018; Vaduganathan JACC-HF 2018

Background (2)

- Compared with placebo, vericiguat reduced the primary outcome of cardiovascular death (CVD) or heart failure hospitalization (HFH) in patients with HFrEF in VICTORIA.

A pre-specified subgroup analysis identified an interaction between treatment and the primary outcome according NT-proBNP



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Armstrong, NEJM 2020

Objectives

- We explored the relationship of NT-proBNP as a continuous variable at randomization with the treatment effect of vericiguat, as compared with placebo, in the VICTORIA trial
- We additionally describe and adjust for the baseline factors that could modify the relationship between NT-proBNP and outcomes

Methods: Patients, Trial and Outcomes

- VICTORIA: RCT of 5050 patients with HFrEF
- Key inclusion criteria:

  NYHA class II–IV

  left ventricular EF <45%

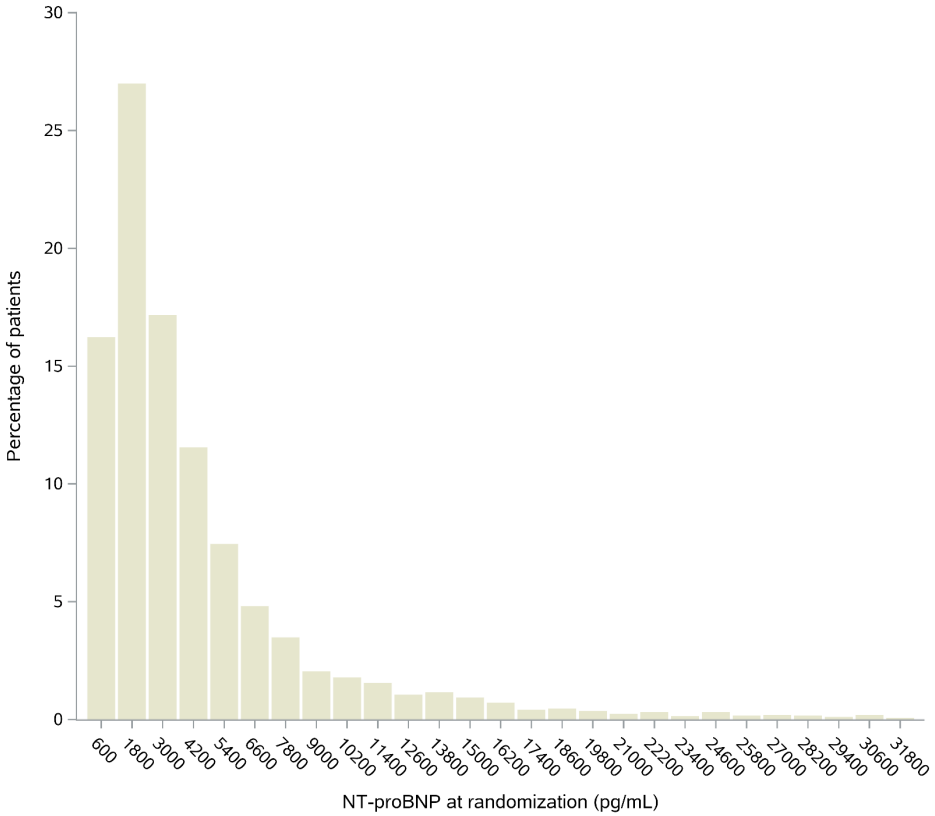
  Natriuretic peptides:

  Sinus rhythm: BNP ≥300 pg/ml or NT-proBNP ≥1000 pg/ml

  Atrial fibrillation: BNP ≥500 pg/ml or NT-proBNP ≥1600 pg/ml
- Primary outcome: Time to CVD or HFH
- NT-proBNP measured at randomization in a core lab
  - 245 patients excluded without NT-proBNP

Methods: Statistics

- NT-proBNP not normally distributed
- NT-proBNP log transformed (base 2)



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NT-proBNP Min:10 pg/ml Max: 175,000 pg/ml

Methods: Statistics

- NT-proBNP log transformed (base 2)
- Using restricted cubic spline with 4 knots, the linearity of the relationship of NT-proBNP (as a continuous variable) to the primary composite outcome was assessed
    - Data derived cutpoints of a HR change at 4000 and 8000 pg/ml
- Associations of study treatment (vericiguat vs placebo) with the primary composite endpoint (CVD/HFH) and its components across the spectrum of NT-proBNP are reported as:
    - hazard ratios (HRs) and 95% confidence intervals (CIs)
    - p(interaction) for study treatment and NT-proBNP
    - adjusted for the MAGGIC score, stratified by region/race
- Patient characteristics are summarized across the spectrum of NT-proBNP at randomization:
    - Quartiles
    - Data-derived values (≤4000; >4000–8000; >8000 pg/ml)

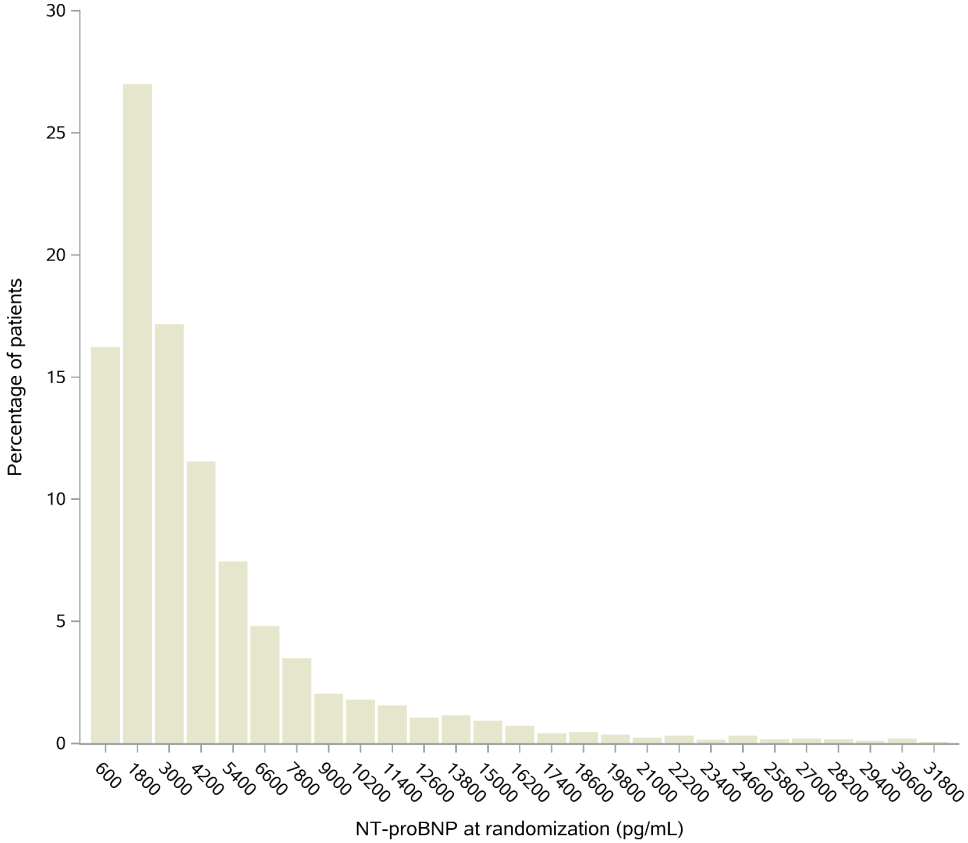
Results: Baseline characteristics

	NT-proBNP at Randomization (pg/ml)		
	≤4000 (n=3100 pts)	>4000 to 8000 (n=1033 pts)	>8000 (n=672 pts)
Age, years	67.0 (59, 75)	70.0 (62, 78)	70.0 (62, 79)
Male	2361 (76.2%)	803 (77.7%)	482 (71.7%)
Index Event			
HF Hospitalization < 3 Months	1972 (63.6%)	757 (73.3%)	486 (72.3%)
HF Hospitalization 3 to 6 Months	562 (18.1%)	156 (15.1%)	103 (15.3%)
IV diuretic for HF (without hospitalization) < 3 Months	566 (18.3%)	120 (11.6%)	83 (12.4%)

Results: Baseline characteristics (2)

	NT-proBNP at Randomization (pg/ml)		
	≤4000 (n=3100)	>4000 to 8000 (n=1033)	>8000 (n=672)
Ejection fraction, %	30 (24, 36)	27 (20, 35)	26 (20, 34)
NYHA Class II	1998 (64.5%)	546 (52.9%)	290 (43.2%)
NYHA Class III	1075 (34.7%)	469 (45.4%)	361 (53.7%)
Atrial fibrillation	1307 (42.2%)	519 (50.2%)	312 (46.4%)
Time from diagnosis of any HF to randomization, years	3.3 (1.0, 7.4)	3.3 (1.1, 7.5)	3.0 (1.0, 7.3)
eGFR, ml/min/1.73 m^2	63.6 (47.1, 82.7)	51.5 (36.8, 71.1)	42.4 (30.4, 61.2)
MAGGIC Risk Score	22 (18, 27)	26 (21, 30)	27 (23, 32)

Results: NT-proBNP distribution



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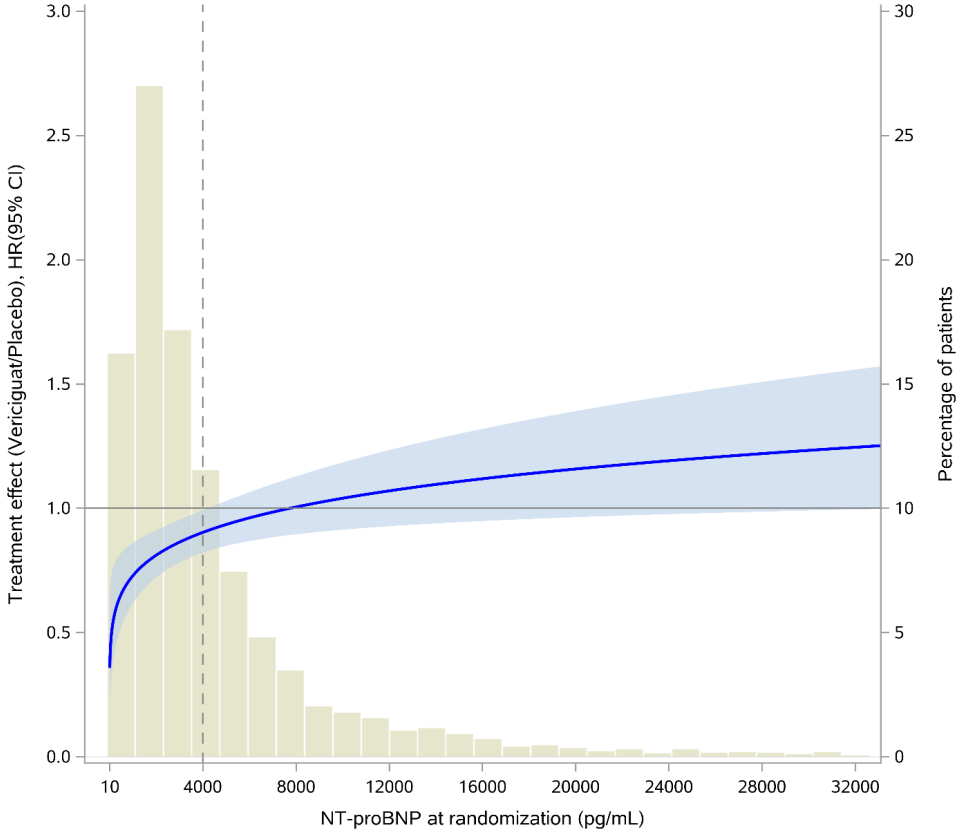
Results: NT-proBNP and Primary Endpoint



<4000 pg/ml:
HR 0.77 (0.68-0.88)

<8000 pg/ml:
HR 0.85 (0.76-0.95)

>8000 pg/ml:
HR 1.16 (0.94-1.41)

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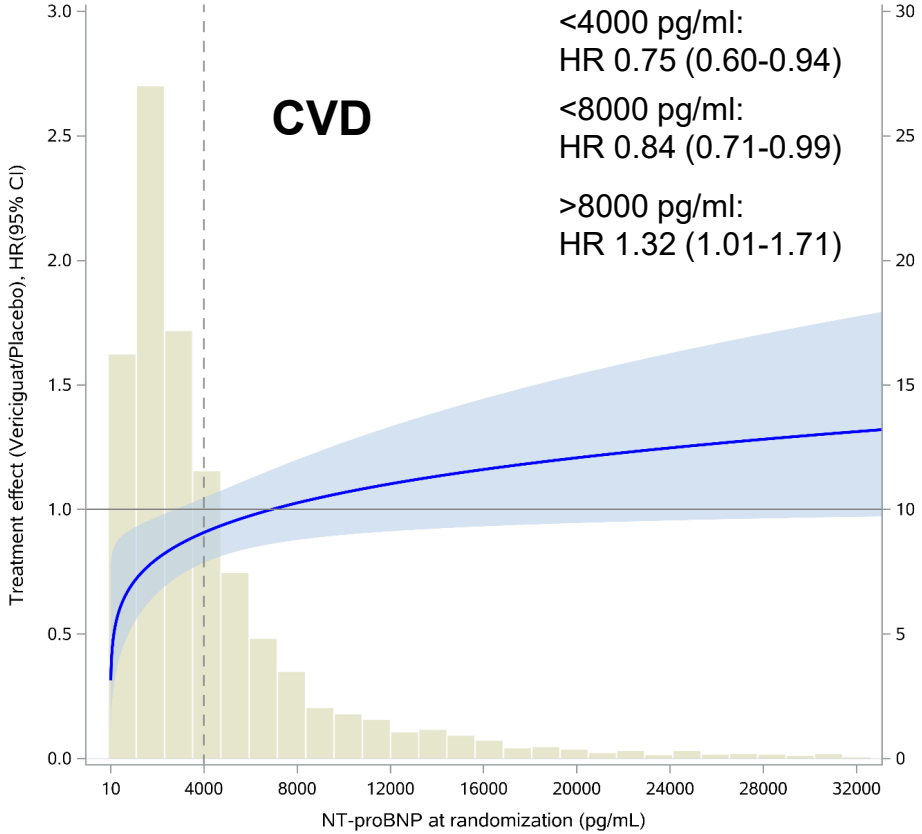
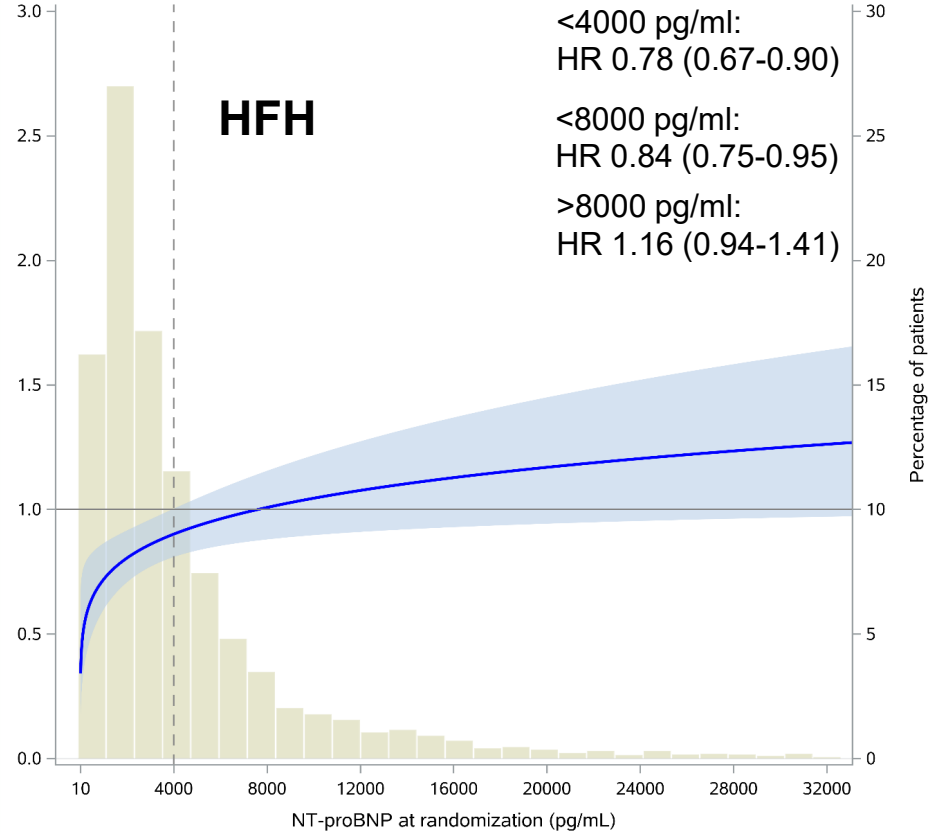
Results: NT-proBNP and Secondary endpoints





Limitations

- Post-hoc analysis using robust statistical methods
- Unmeasured confounders despite adjustment with MAGGIC

Summary/Conclusions

- Overall, vericiguat demonstrated a HR 0.90 for CVD/HFH
- The treatment effect of vericiguat, compared with placebo, on ***both components*** of the primary composite endpoint was:
    - Evident for 86% of the VICTORIA population with NT-proBNP <8000 pg/ml: 0.85 for CVC/HFH,0.84 for CVD and 0.78 for HFH
    - Further amplified in two thirds the VICTORIA population with NT-proBNP <4000 pg/ml: 0.77 for CVD/HFH, 0.75 for CVD and 0.78 for HFH
- These data provide further insight into the treatment effect of vericiguat extended to the individual endpoints of CVD and HFH