



Identifying Best Responders to Rx: Biomarkers & Protein Networks

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CURRENTLY DISCONNECTED

LV RAIDERS LETS GO!!!



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HF Case Question

- **72 F with prev MI, on vacation quarantine, has progressive SOB, SOA, orthopnea, cough**
 - No fever, no COVID testing
 - ER: pulm congestion on CXR
 - BP 115/85, HF 89, chest crackles
 - RNA: LVEF 23%, LV volume increased
- **Started on Furosemide, ACEi and bB**
- **Cr 120, K 4.5, NTproBNP 4,500**



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HF Case Question

- **With so many evidence based HFrEF medications, what is your preferred approach for this patient?**

Question:

1. **Use of ACEi/ β B/Spiro good enough**
2. **Must add Entresto $\pm$ Ivabradine**
3. **Consider also DAPA + Vericiguat**
4. **Time to personalize HFrEF Rx for Pt**



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HF Therapy Inequality

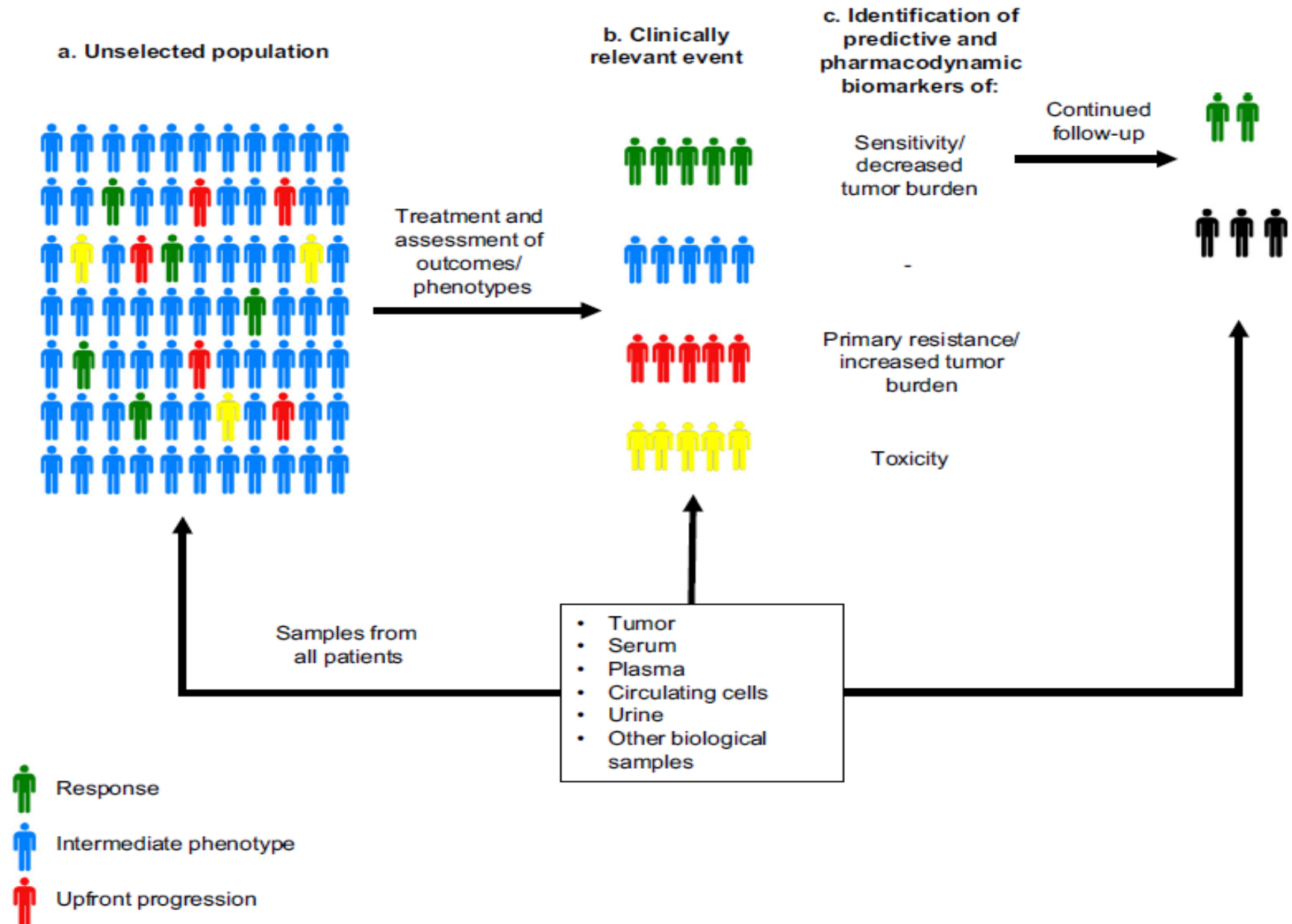
HFrEF

- ACEi/ARB
- B-Blockers
- Mineralcorticoid antagonists
- Ivabradine
- Sacubitril/valsartan
- SGLT2i (Dapa)
- Vericiguat

HFpEF

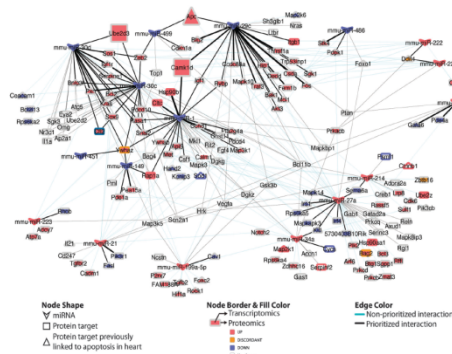
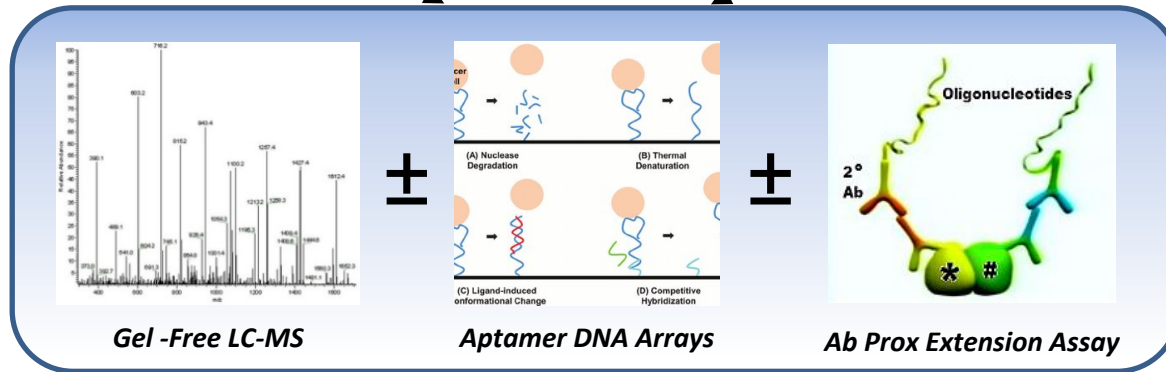
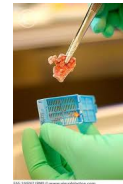
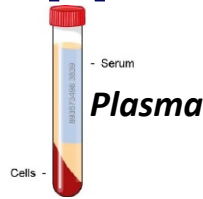
- Mineralcorticoid antagonists
- Sacubitril/valsartan

Prospective Search of Rx Markers



Proteomic Applications in Heart Failure

Patient Samples
from **(Nested) Case
Control Cohorts**



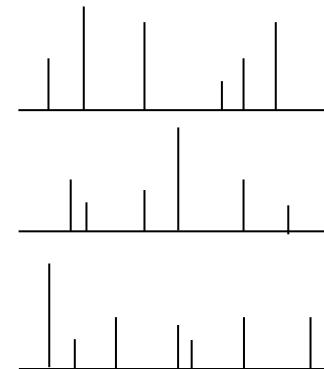
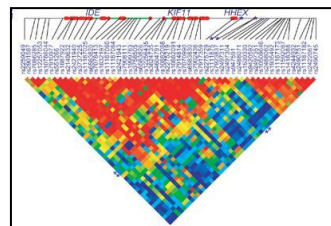
Bioinformatics

± Machine Learning/AI

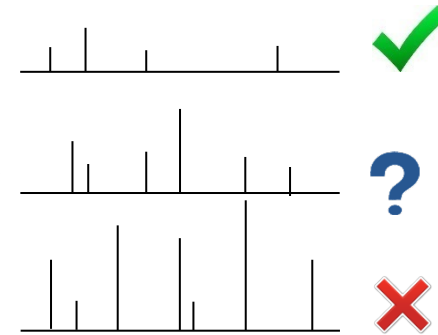
Network A
(e.g. Immunity, Senescence)

Network B
(e.g. Metabolism)

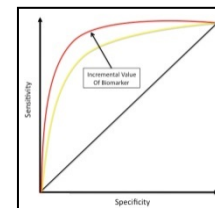
Network C
(e.g. Matrix Remodeling)



**Rx
Trial**



**Response
to Rx**



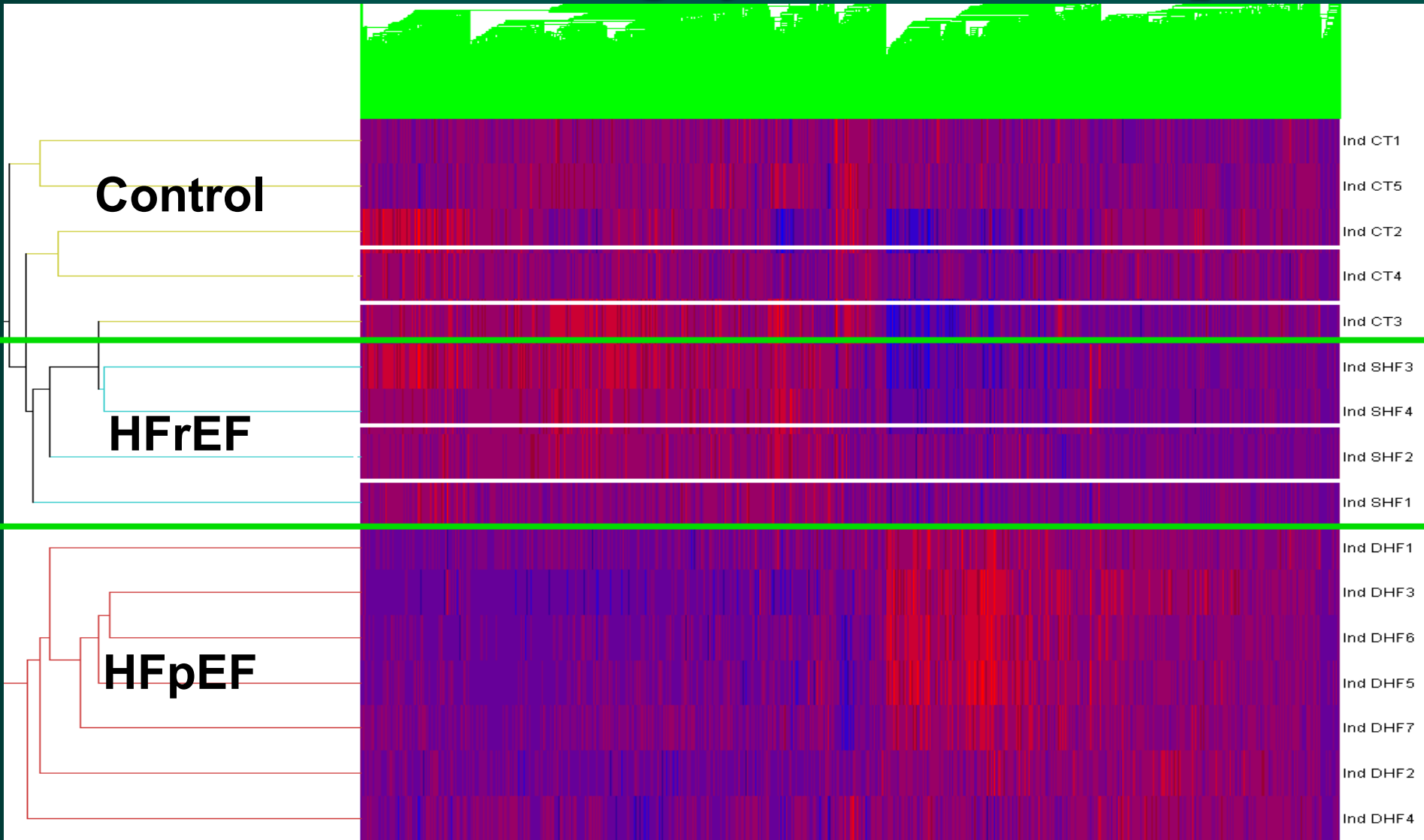
Bayes-Genis A, Liu P,
Januzzi, et al, Eur Hrt J 2020

System Biol Integration

Biomarker Validation

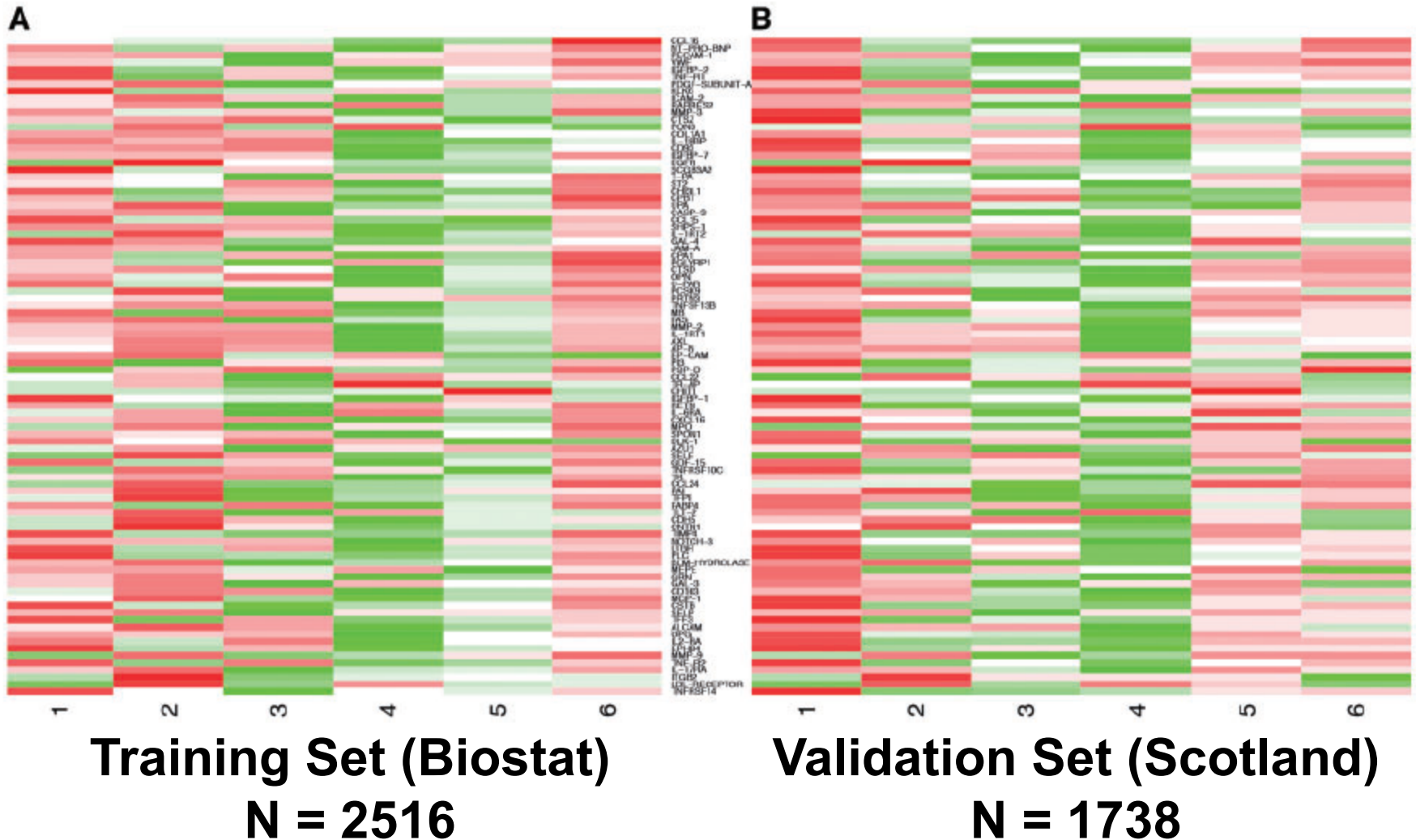
Precision Medicine

Protein Clustering of HFrEF & HFpEF



Statistically significant by 1-way ANOVA

HF Biomarker Phenotypes





HF Biomarker Phenotypes

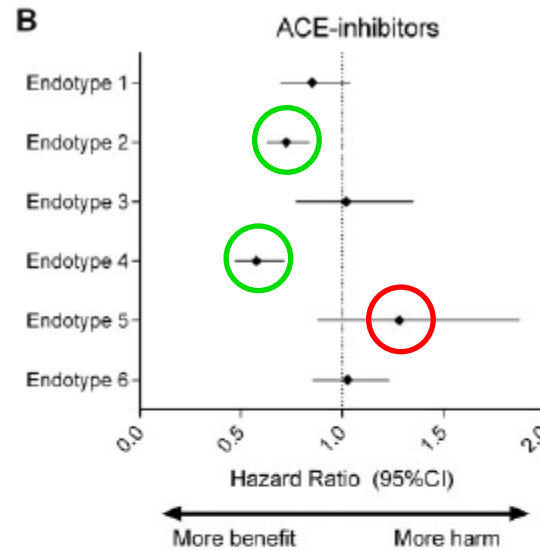
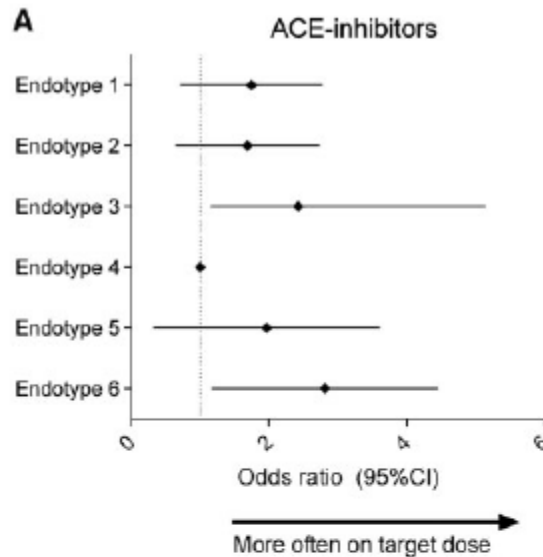
Table I Biomarkers subgroup identification

Endotype 1		Endotype 2		Endotype 3	
Marker	C-index	Marker	C-index	Marker	C-index
IGFBP1	0.83	PAI	0.77	SELP	0.93
IGFBP2	0.70	PDGFsA	0.74	PECAM1	0.93
NT-proBNP	0.65	SELP	0.7	JAMA	0.97
Combined	0.83	Combined	0.78	Combined	0.97
Endotype 4		Endotype 5		Endotype 6	
Marker	C-index	Marker	C-index	Marker	C-index
ST2	0.81	CHIT1	0.99	TPA	0.70
NT-proBNP	0.80			NT-proBNP	0.70
IGFBP1	0.80			VWF	0.70
Combined	0.86	Combined	NA	Combined	0.78



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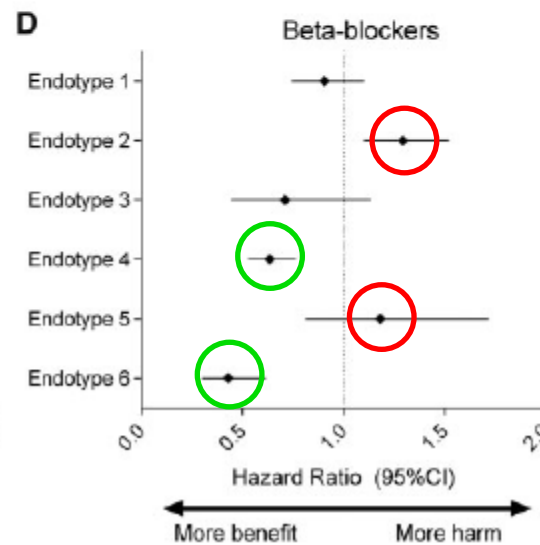
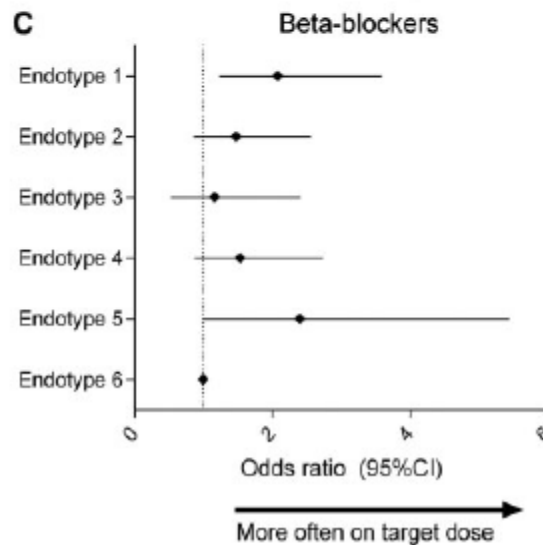
HF Biomarker Phenotypes



Growth/Hypertrophy

Inflammatory

Ageing



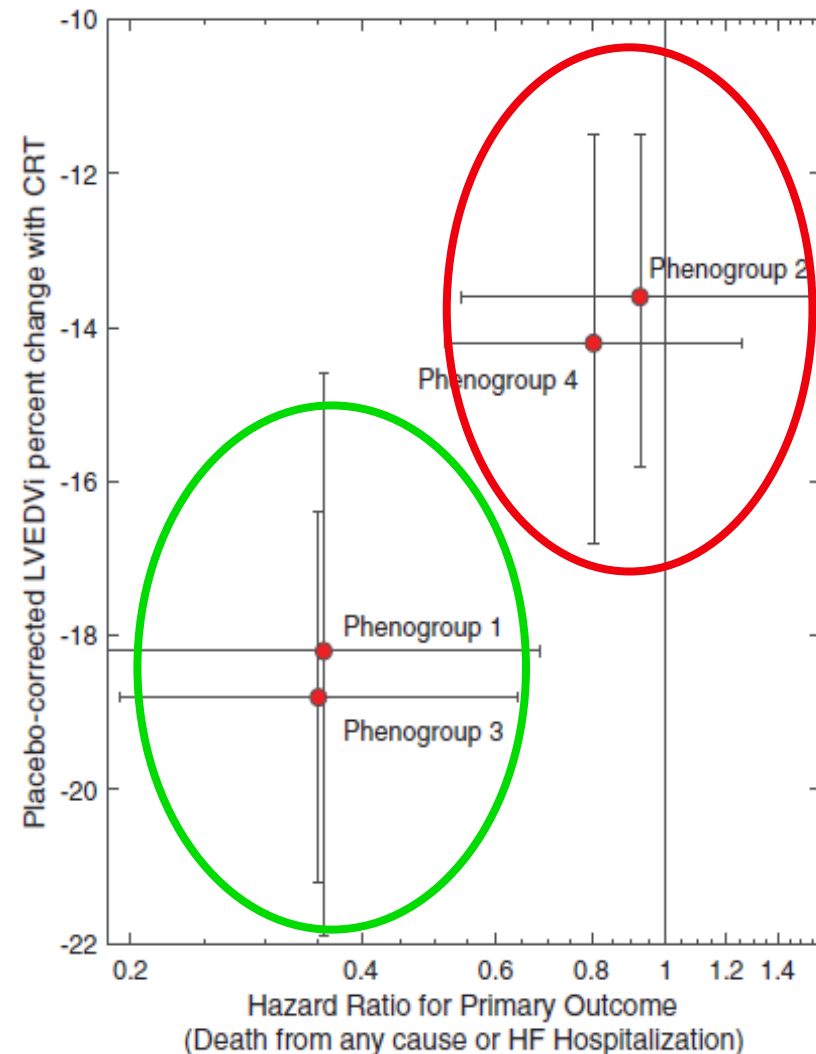
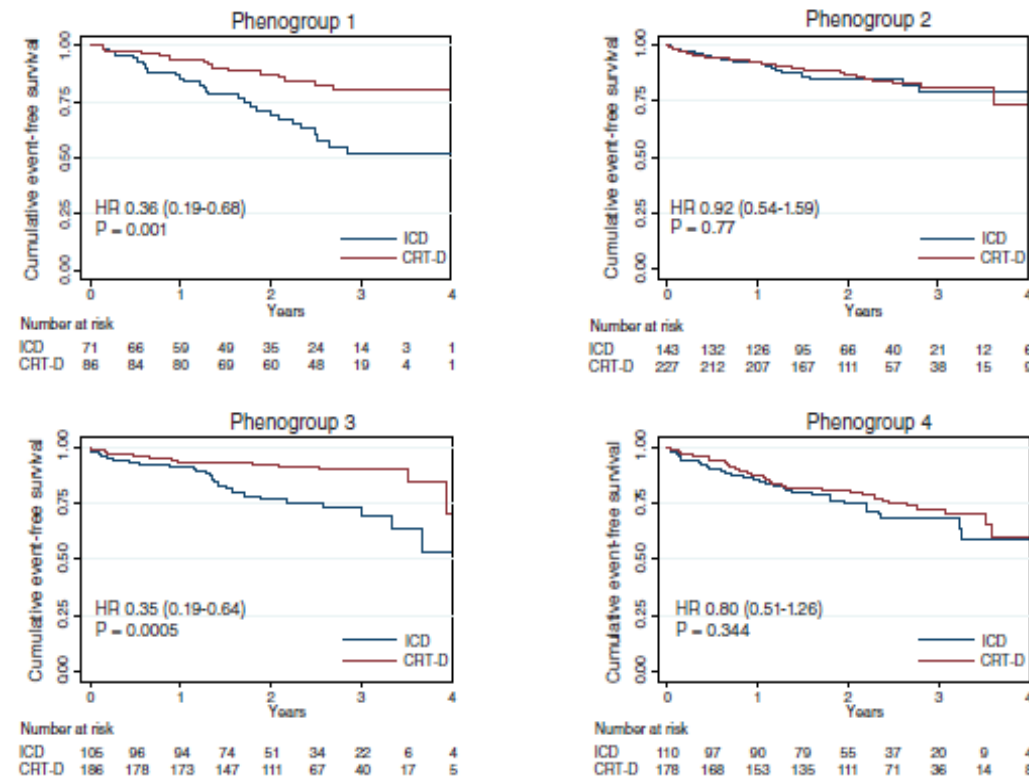
Growth/Hypertrophy

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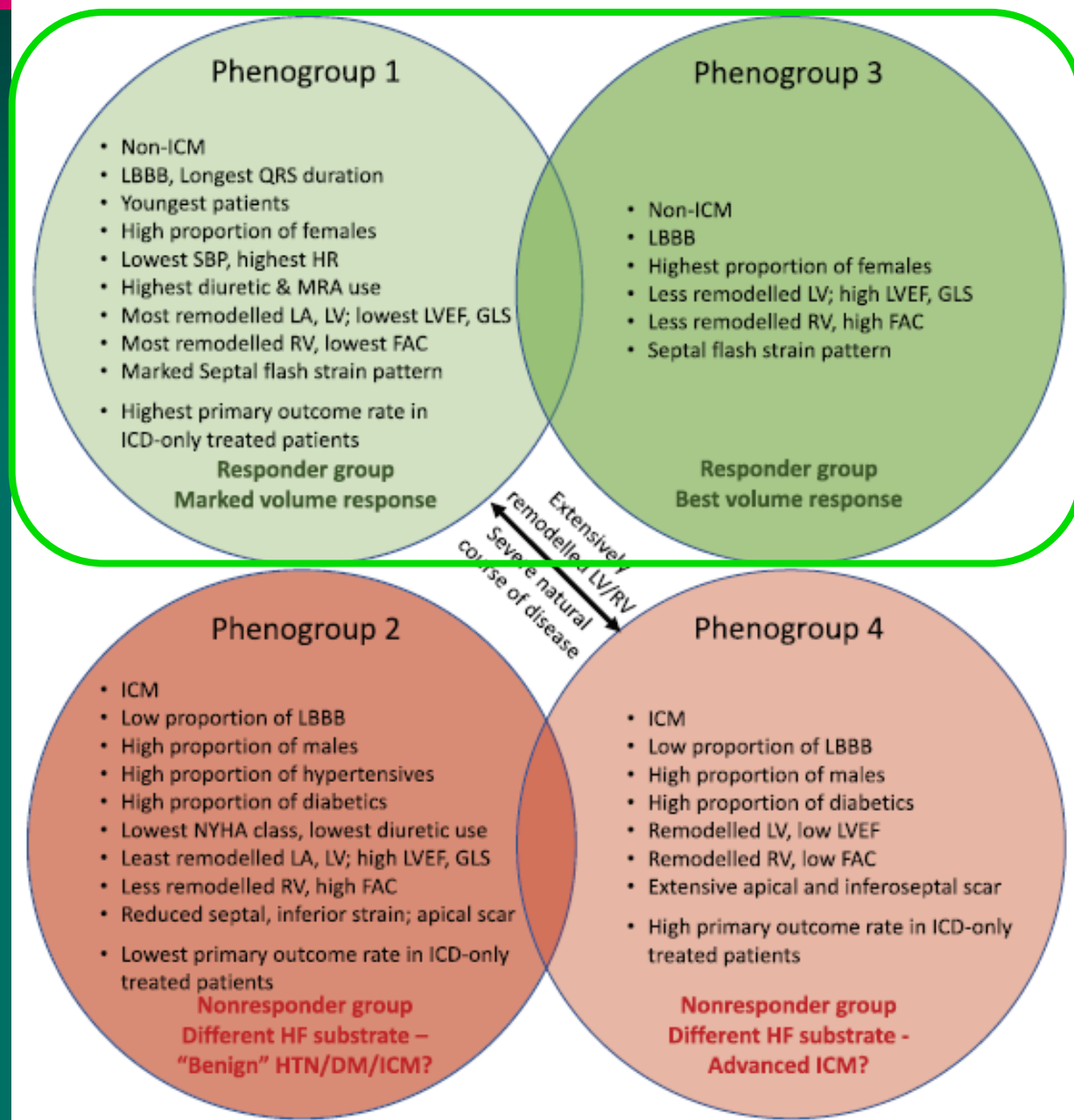
Metabolic

Who R Responders to CRT?



	Phenogroup 1 (N=157)	Phenogroup 2 (N=370)	Phenogroup 3 (N=291)	Phenogroup 4 (N=288)
Primary Outcome				
Participants with event, n (%)	41 (26.11%)	55 (14.86%)	45 (15.46%)	79 (27.43%)
Event rate per 100 person -years	11.9 (8.8 - 16.2)	7.4 (5.7 - 9.6)	7.2 (5.4 - 9.6)	12.8 (10.3 - 16.0)

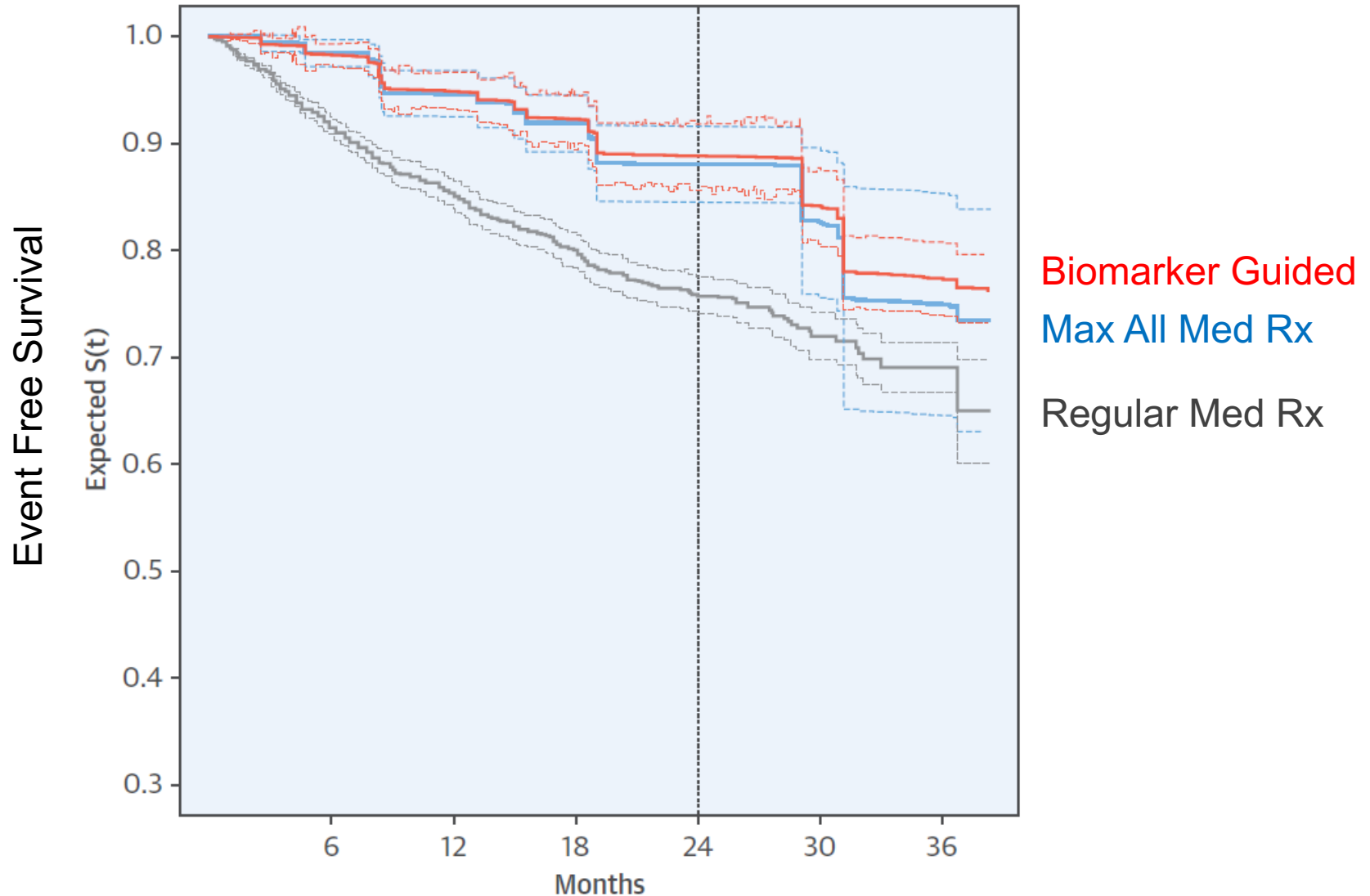
Who R Responders to CRT?





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Models for Rx Outcomes





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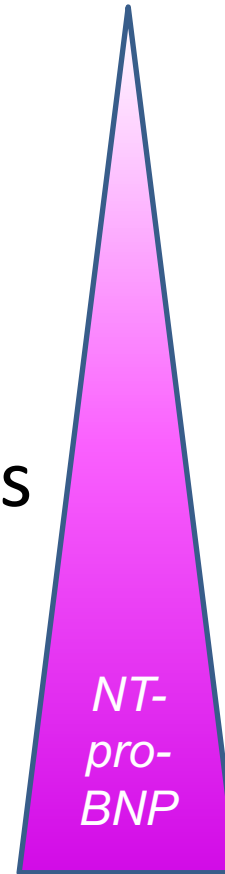
HFrEF Precision Rx

Heart Rate

- B-Blockers
- Ivabradine

RAASi

- ACEi/ARB
- Mineralo-corticoid antagonists
- Sacubitril/valsartan



NO/Metab

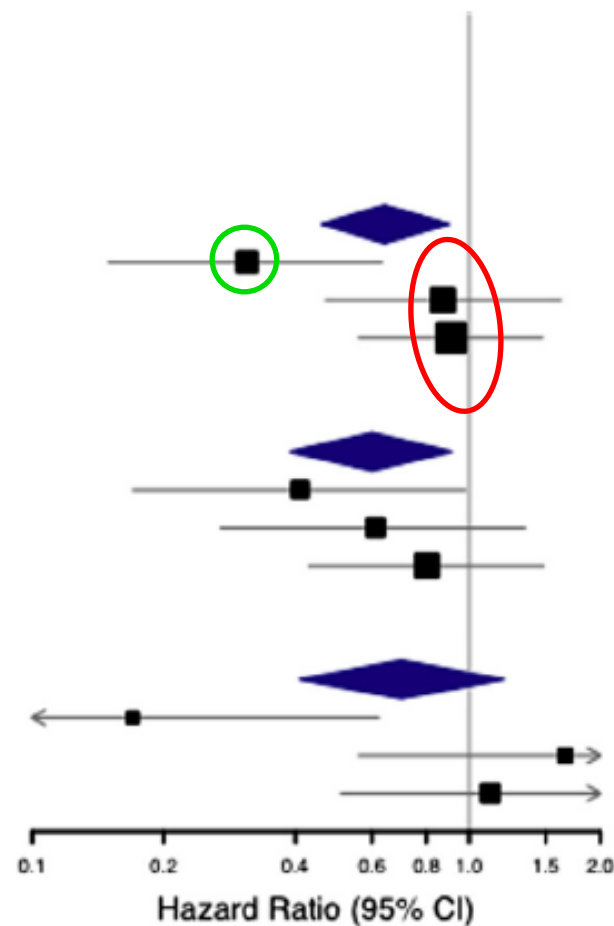
- Vericiguat
(~~Cr~~, ~~eGFR~~)
- SGLT2i
(Dapa)
IGFBP7 (?)



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TOPCAT Spiro Effect Best in Low NTproBNP Pts

Subgroup	Placebo No. of Events/Patients	Spironolactone No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
BNP/NTBNP (n=687)				
Overall	91/355 (25.6%)	57/332 (17.2%)	0.64 (0.46, 0.90)	0.017
Tertile 1	30/117 (25.6%)	10/113 (8.8%)	0.31 (0.15, 0.63)	
Tertile 2	21/110 (19.1%)	19/120 (15.8%)	0.87 (0.47, 1.62)	
Tertile 3	40/128 (31.2%)	28/99 (28.3%)	0.91 (0.56, 1.47)	
BNP (n=430)				
Overall	60/224 (26.8%)	34/206 (16.5%)	0.60 (0.39, 0.91)	0.216
Tertile 1	19/79 (24.1%)	7/65 (10.8%)	0.41 (0.17, 0.98)	
Tertile 2	16/70 (22.9%)	10/74 (13.5%)	0.61 (0.27, 1.34)	
Tertile 3	25/75 (33.3%)	17/67 (25.4%)	0.80 (0.43, 1.48)	
NTBNP (n=257)				
Overall	31/131 (23.7%)	23/126 (18.3%)	0.70 (0.41, 1.20)	0.027
Tertile 1	11/38 (28.9%)	3/48 (6.2%)	0.17 (0.05, 0.62)	
Tertile 2	5/40 (12.5%)	9/46 (19.6%)	1.66 (0.56, 4.97)	
Tertile 3	15/53 (28.3%)	11/32 (34.4%)	1.12 (0.51, 2.46)	





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HF Response Biomarkers

- **Enable Precision Medicine Practice**
 - Maximize benefit for responders
 - Minimize SE or waste for non-responders
 - Maximize cost-effectiveness of Rx
- **Provide insight into biology**
- **Facilitate future therapeutic development**



The End
Thank You