#AHA24

COMMENT ON: ROUTINE SPIRONOLACTONE IN ACUTE MYOCARDIAL INFARCTION, RESULTS FROM THE CLEAR SYNERGY OASIS 9

Marc P. Bonaca MD MPH
Professor of Medicine
William R. Hiatt Endowed Chair In Cardiovascular Research
University of Colorado School of Medicine

American Heart Association.

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DISCLOSURES

Dr. Bonaca is the Executive Director of CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives or has received research grant/consulting funding from: Abbott Laboratories, Alnylam Pharmaceuticals, Inc., Amgen Inc., Angionetics, Inc., Anthos Therapeutics, Array BioPharma, Inc., AstraZeneca and Affiliates, Atentiv LLC, Bayer and Affiliates, Bristol-Meyers Squibb Company, CellResearch Corp., Cleerly Inc., CSL Behring LLC, Eidos Therapeutics, Inc., Esperion Therapeutics, Inc., Faraday Pharmaceuticals, Inc., HDL Therapeutics Inc., HeartFlow Inc., Hummingbird Bioscience, Insmed Inc., Ionis Pharmaceuticals, Johnson and Johnson Affiliates, Lexicon Pharmaceuticals, Inc., Merck & Affiliates, Nectero Medical Inc., Novartis Pharmaceuticals Corp., Novo Nordisk, Inc., Osiris Therapeutics Inc., Pfizer Inc., PhaseBio Pharmaceuticals, Inc., Prothena Biosciences Limited, Regeneron Pharmaceuticals, Inc., Regio Biosciences, Inc., Sanofi-Aventis Groupe, Silence Therapeutics PLC, Silence, Stealth BioTherapeutics Inc., Structure Therapeutics

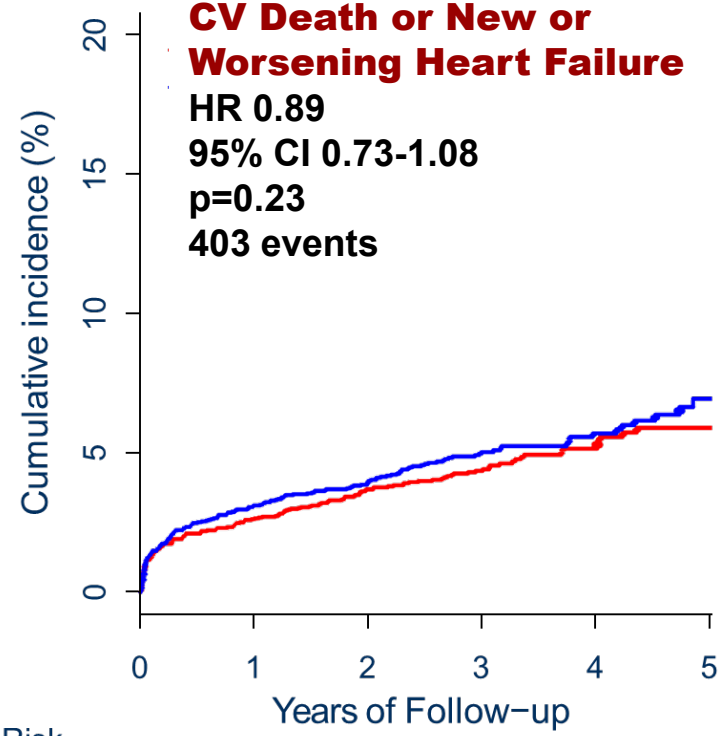
CLEAR SYNERGY

Spironolactone

Spironolactone placebo

CV Death or New or Worsening Heart Failure

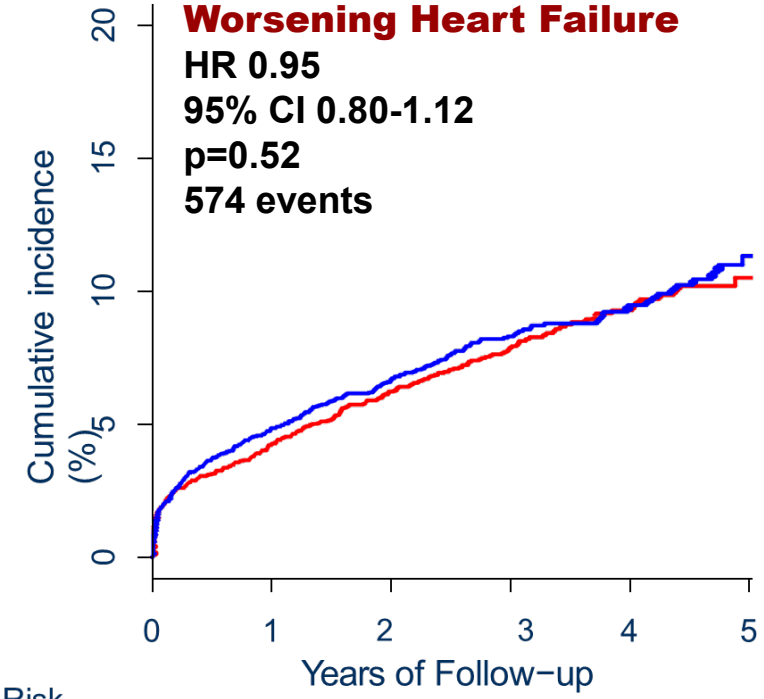
HR 0.89
95% CI 0.73-1.08
p=0.23
403 events



No. at Risk						
Spironolactone	3537	3422	2788	1778	704	183
Placebo	3525	3392	2785	1754	735	194

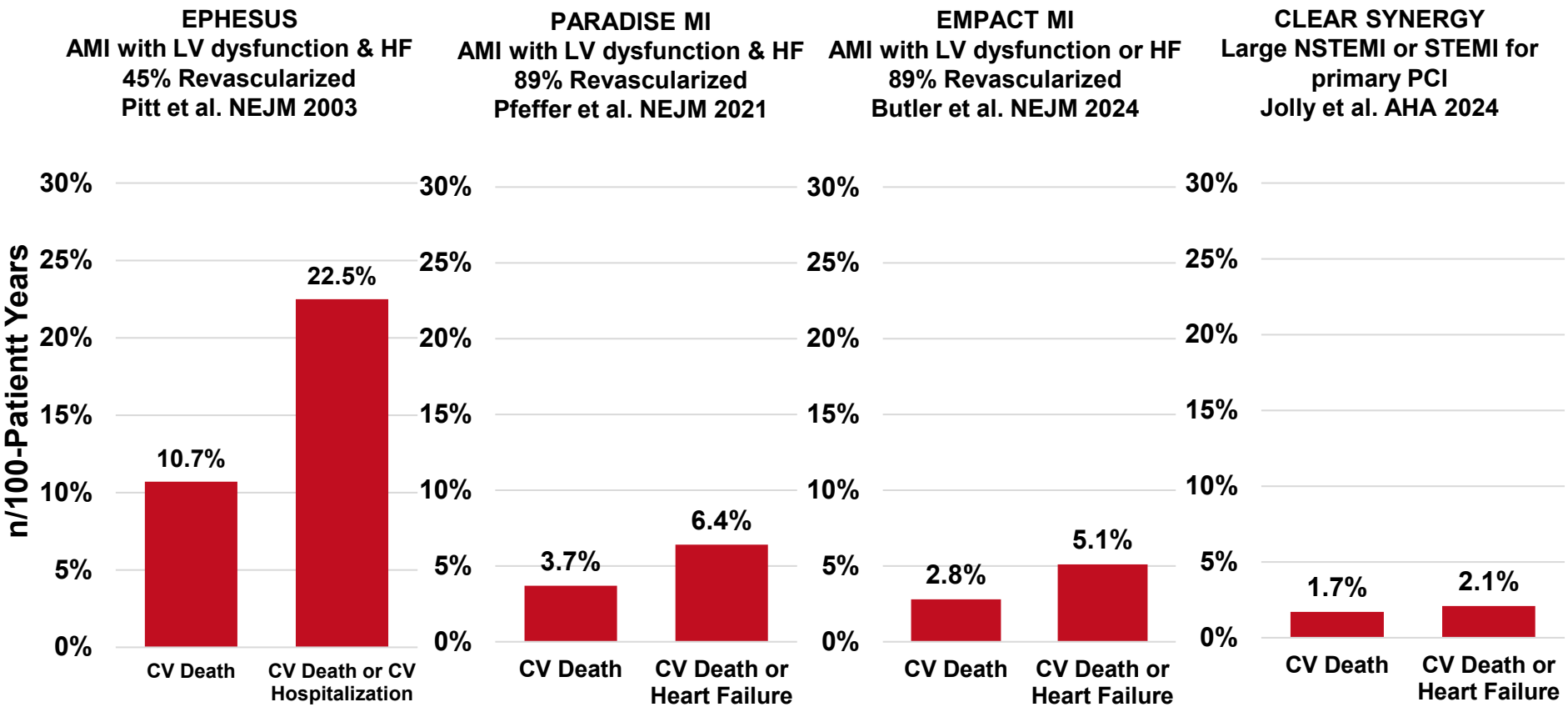
CV Death, MI, Stroke or New or Worsening Heart Failure

HR 0.95
95% CI 0.80-1.12
p=0.52
574 events



No. at Risk						
Spironolactone	3537	3365	2712	1721	681	173
Placebo	3525	3331	2707	1695	707	184

ESTIMATED ANNUALIZED EVENT RATE IN AMI TRIALS – PLACEBO ARMS



PATIENT SELECTION AND BACKGROUND THERAPY

All patients treated with primary PCI

Baseline Characteristics

	Spironolactone N=3537	Placebo N=3525
Mean Age (years)	60.9	60.4
Female	21.5%	19.2%
STEMI	95.3%	94.9%
Killip ≥ 2 at presentation	0.7%	0.7%
Anterior STEMI	39.0%	39.3%
Previous heart failure	0.7%	1.0%

Medications at Discharge

	Spironolactone N=3537	Placebo N=3525
Aspirin	96.6%	96.9%
Clopidogrel	42.4%	41.9%
Ticagrelor	45.1%	45.0%
Prasugrel	11.1%	11.4%
ACE or ARB	77.6%	78.7%
Statin	96.4%	96.9%
SLGT2 inhibitor	3.2%	2.8%

WHAT EVENTS ARE MODIFIABLE WITH MRA?

EPHESUS

Death from cardiovascular causes or hospitalization for cardiovascular events (no. of patients)	885	993	0.87 (0.79–0.95)	0.002
Death from cardiovascular causes (no. of patients)	407	483	0.83 (0.72–0.94)	0.005
Hospitalization for cardiovascular events (no. of patients)	606	649	0.91 (0.81–1.01)	0.09
Acute myocardial infarction	224	229	0.97 (0.80–1.16)	0.71
Heart failure	345	391	0.85 (0.74–0.99)	0.03
Stroke	70	51	1.34 (0.94–1.93)	0.11
Ventricular arrhythmia	52	54	0.95 (0.65–1.39)	0.79

Pitt B et al. NEJM 2003

CLEAR SYNERGY

CV death or new or worsening HF	0.89 (0.73 – 1.08)
CV death	0.98 (0.80 – 1.12)
Recurrent MI	0.99 (0.75 – 1.29)
New or worsening HF	0.69 (0.49 – 0.96)
Stroke	1.21 (0.81 – 1.83)

Jolly et al. AHA 2024

	Spironolactone (N=3537) (%)	Placebo (N=3525) (%)	HR	95% CI	p
Co – primary 1: CV death or new or worsening heart failure	1.7%	2.1%	0.89	0.73-1.08	0.23
Co – primary 2: CV death, MI, stroke or new or worsening heart failure	7.9%	8.3%	0.95	0.80-1.12	0.52

PLANNED VS. OBSERVED TREATMENT EFFECT

Initial sample size of 4000 - powered for a 25% RRR – estimating an event rate of 15% (512 events) at 3 years

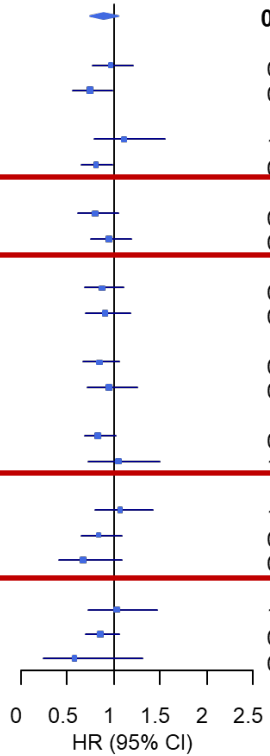
Sample size of 7000 estimated to provide 84% power for 31.5% RRR assuming placebo event rate of 6% (357 events) at 3 years

Outcome	Protocol Plan	EPHESUS	CLEAR SYNERGY
CV death or new/worsening HF	0.685	0.87*	0.89 (0.80 in Ant, MI)
CV Death		0.83 (0.80 for HF death)	0.98
HF		0.85	0.69

**CV death or CV hospitalization*

SUBGROUPS

	Spironolactone Count(Rate)	Placebo Count(Rate)	Hazard Ratio (95% CI)	P value for Interaction
Co-Primary 1				
CVD/New or Worsening HF	**183 (1.72)**	**220 (2.07)**	**0.88 (0.74-1.05)**	
Age				**0.212**
Age>= 65	114 (1.07)	127 (1.19)	0.96 (0.77-1.21)	
Age<65	69 (0.65)	93 (0.88)	0.74 (0.56-0.99)	
Sex				**0.276**
Female	49 (0.46)	56 (0.53)	1.11 (0.79-1.56)	
Male	134 (1.26)	164 (1.54)	0.81 (0.66-0.99)	
MI type				**0.408**
Anterior STEMI	83 (0.78)	114 (1.07)	0.80 (0.62-1.04)	
Other	111 (1.04)	123 (1.16)	0.95 (0.75-1.19)	
Baseline serum Potassium level				**0.797**
Potassium>=4 mmol/L	101 (0.95)	110 (1.04)	0.87 (0.68-1.11)	
Potassium<4 mmol/L	82 (0.77)	110 (1.04)	0.91 (0.70-1.18)	
History of Hypertension				**0.502**
Yes	106 (1.00)	142 (1.34)	0.85 (0.67-1.07)	
No	77 (0.72)	78 (0.73)	0.95 (0.72-1.24)	
GFR level				**0.158**
GFR>=60	132 (1.24)	170 (1.60)	0.83 (0.68-1.02)	
GFR<60	51 (0.48)	50 (0.47)	1.04 (0.73-1.50)	
Covid Phase				**0.052**
pre-covid	73 (0.69)	72 (0.68)	1.07 (0.80-1.43)	
During covid	87 (0.82)	108 (1.02)	0.84 (0.65-1.08)	
post- covid	23 (0.22)	40 (0.38)	0.67 (0.41-1.09)	
Region				**0.099**
North America	49 (0.46)	49 (0.46)	1.04 (0.73-1.47)	
Europe	126 (1.19)	154 (1.45)	0.86 (0.70-1.07)	
Other region	8 (0.08)	17 (0.16)	0.58 (0.26-1.30)	



No interaction…but possible effect in anterior MI?

Potential impact of COVID on adherence / event ascertainment?

ADHERENCE AND ADVERSE EVENTS

premature treatment cessation

Median 3 years treatment

Spironolactone 28.0%
Placebo 24.4%

Results - On Treatment

	Spironolactone (N=3497) (%)	Placebo (N=3483) (%)	HR	95% CI	p
Co – primary 1: CV death or new or worsening heart failure	1.5%	2.0%	0.79	0.63-1.00	0.047
Co – primary 2: CV death, MI, stroke or new or worsening heart failure	5.8%	7.2%	0.83	0.69-1.00	0.046

Adverse Events

	Spironolactone (N=3537) (%)	Placebo (N=3525) (%)	p
Serious Adverse Events	7.2%	6.8%	0.54
HyperK+ leading to study drug discontinuation	1.1%	0.05%	0.01
Gynecomastia	2.3%	0.5%	<0.001

CONCLUSIONS

Congratulations to the Investigators and thanks to the Participants

Patients presenting with AMI treated with primary PCI…selected for and consenting for an RCT…appear to have very low event rates in the modern era

MRAs reduce HF and CV death with benefit driven by the risk of the population

CLEAR SYNERGY does not support the routine use of spironolactone in patients with AMI treated with primary PCI…however…observations (e.g. lower incidence of HF, anterior MI) support known benefit in LV dysfunction

Whether novel MRAs that are better tolerated and have shown benefit in HFpEF (e.g. Finerenone) are beneficial in AMI requires investigation

THANK YOU

Scientific Sessions

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