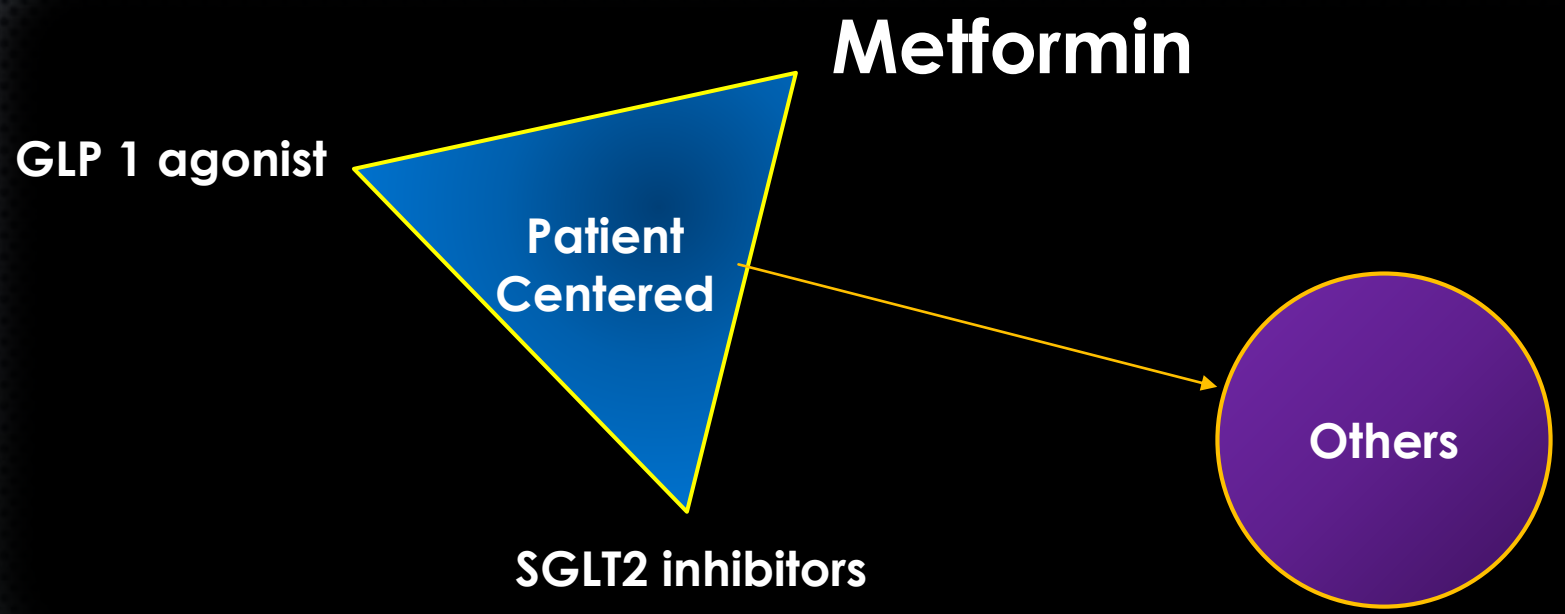
New Diabetes Therapeutics and CV Risk Reduction



Professor Robert Chilton
University of Texas Health Science Center
San Antonio, Texas
Director of Cath Lab
Director clinical proteomics center
Associate program director for interventional cardiology

Overview

Summary of GLP1-RA cardiovascular outcomes trials

	CAD (%)	HF (%)	eGFR<60 (%)
Liraglutide	72.5	17.8	23.1
2.1 yrs/ 9340 **Semaglutide**	83	23.6	28.5
2.1 yrs/ 3297 **Exenatide**	73.1	16.2	21.6
3.2 yrs/ 14752 **Lixisenatide**	100	20.3	23.2
2.1 yrs/ 6068			

HARMONY-albiglutide GFR N/A

Summary of SGLT-2 inhibitors cardiovascular outcomes trials

	CAD (%)	HF (%)	eGFR<60 (%)
Empagliflozin	100	10.1	25.9
3.1 yrs/ 7020 **CANVAS**	66	14.4	20.1
2.4 yrs/ 10142 **DECLARE-TIMI**	41	10	7.4
4.2 yrs/ 17160			

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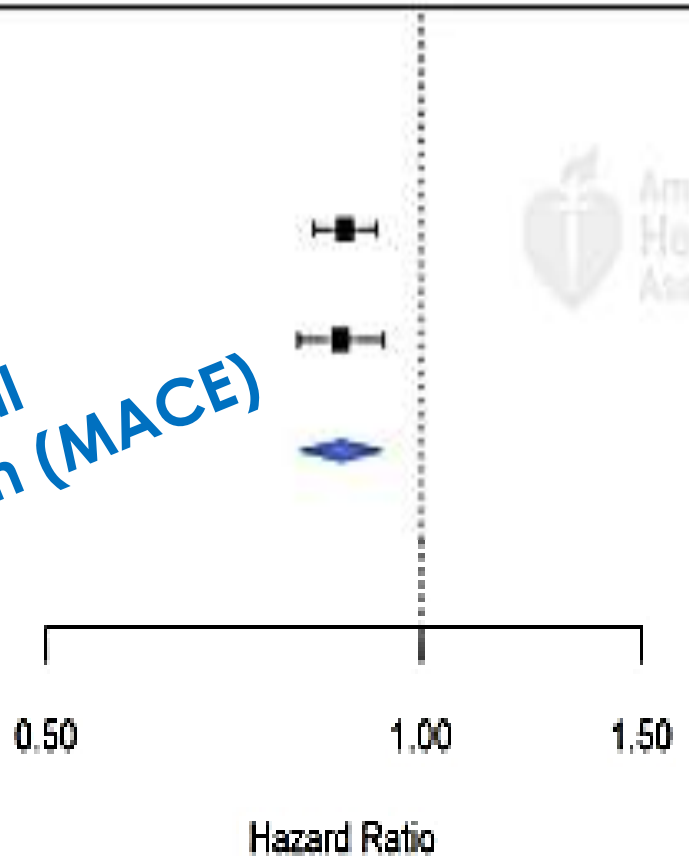
Trials	Patients	Events	Weights	HR [95% CI]
Established Atherosclerotic Cardiovascular Disease				
GLP1-RA	35823	4365	62.1	0.87 [0.82, 0.92]
SGLT2i	20650	2588	37.9	0.86 [0.80, 0.93]
Random Effects for ASCVD (P-value=0.002)				0.86 [0.80, 0.93]



Composite of myocardial infarction, stroke, and CV death (MACE)

10.1161/CIRCULATIONAHA.118.038868

Trials	Patients	Events	Treatment Events per 100 ptyrs	Placebo Events per 100 ptyrs	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6068	249	1.8	1.9	19.7	0.96 [0.75, 1.23]
LEADER	9340	466	1.2	1.4	36.4	0.87 [0.73, 1.05]
SUSTAIN-6	3297	113	1.8	1.6	8.8	1.11 [0.77, 1.61]
EXSCEL	14752	450	0.9	1.0	35.0	0.94 [0.78, 1.13]
Fixed Effects for HHF (P-value=0.20)						0.93 [0.83, 1.04]
SGLT2i						
EMPA-REG OUTCOME	7020	221	0.9	1.4	24.0	0.65 [0.50, 0.85]
CANVAS Program	10142	243	0.6	0.9	25.6	0.67 [0.52, 0.87]
DECLARE-TIMI 58	17160	498	0.6	0.8	50.4	0.73 [0.61, 0.88]
Fixed Effects for HHF (P-value<0.001)						0.69 [0.61, 0.79]

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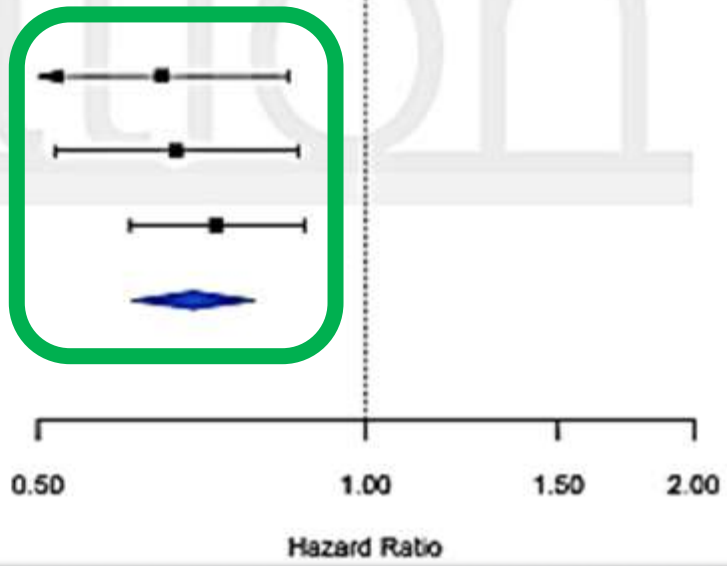
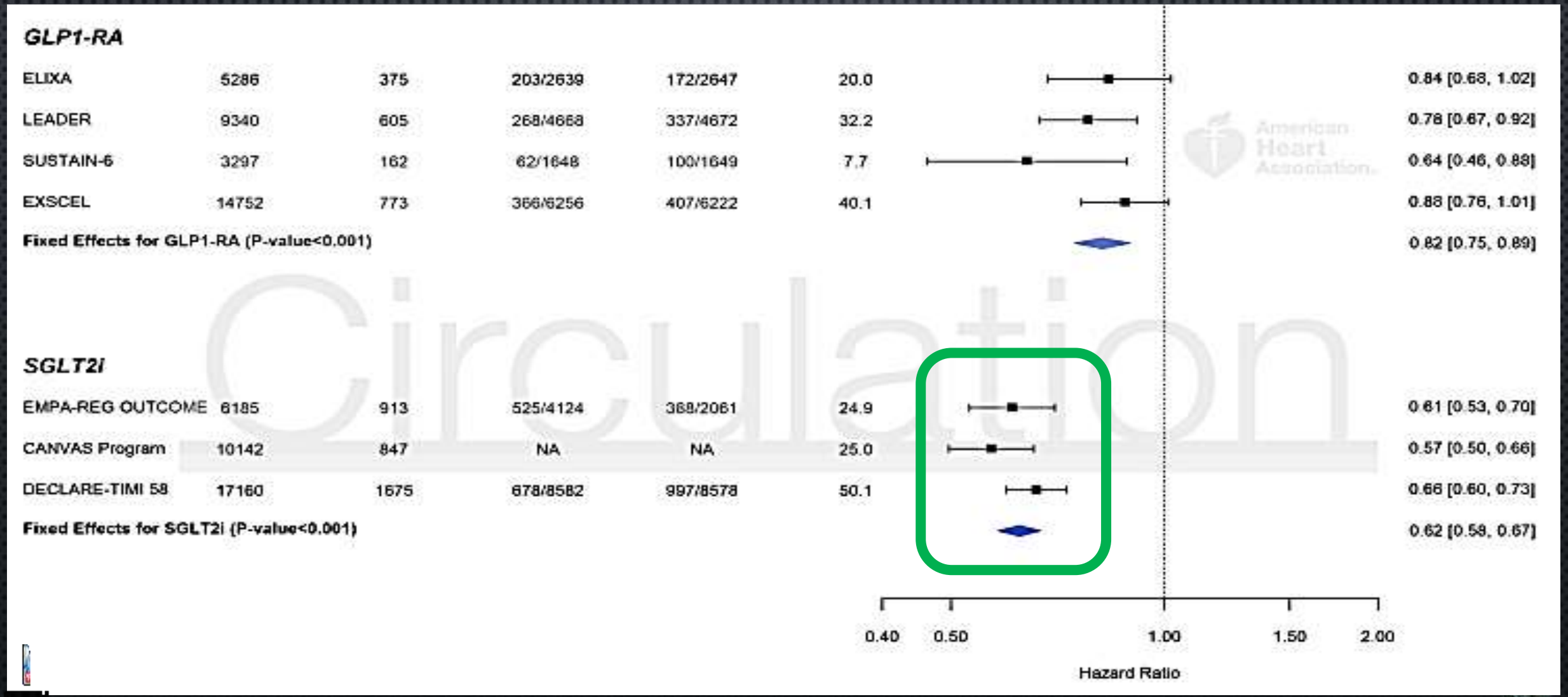


Hospitalizations for Heart Failure

Hospitalization (broad renal endpoint)
-new- onset macroalbuminuria sustained doubling of serum creatinine or a 40% decline in eGFR, ESRD, or death of renal cause



Trials	Patients	Events	Treatment n/N	Placebo n/N	Weights	HR [95% CI]
GLP1-RA						
ELIXA	6063	76	35/3032	41/3031	9.5	1.16 [0.74, 1.83]
LEADER	9340	184	87/4668	97/4672	23.4	0.89 [0.67, 1.19]
SUSTAIN-6	3297	32	18/1648	14/1649	4.0	1.28 [0.64, 2.59]
EXSCEL	12914	519	246/6456	273/6458	63.1	0.88 [0.74, 1.05]
Fixed Effects for GLP1-RA (P-value=0.24)						0.92 [0.80, 1.06]
SGLT2i						
EMPA-REG OUTCOME	6968	152	81/4645	71/2323	20.9	0.54 [0.40, 0.75]
CANVAS Program	10142	249	NA	NA	34.0	0.60 [0.47, 0.77]
DECLARE-TIMI 58	17160	365	127/8582	238/8578	45.1	0.53 [0.43, 0.66]
Fixed Effects for SGLT2i (P-value<0.001)						0.55 [0.48, 0.64]

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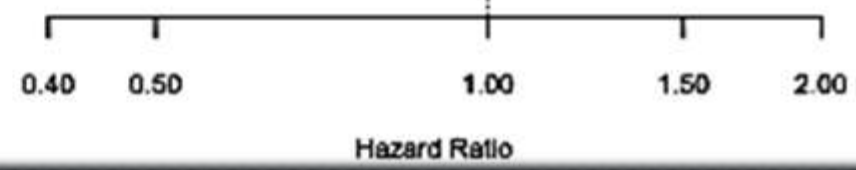

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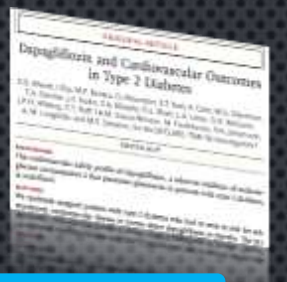
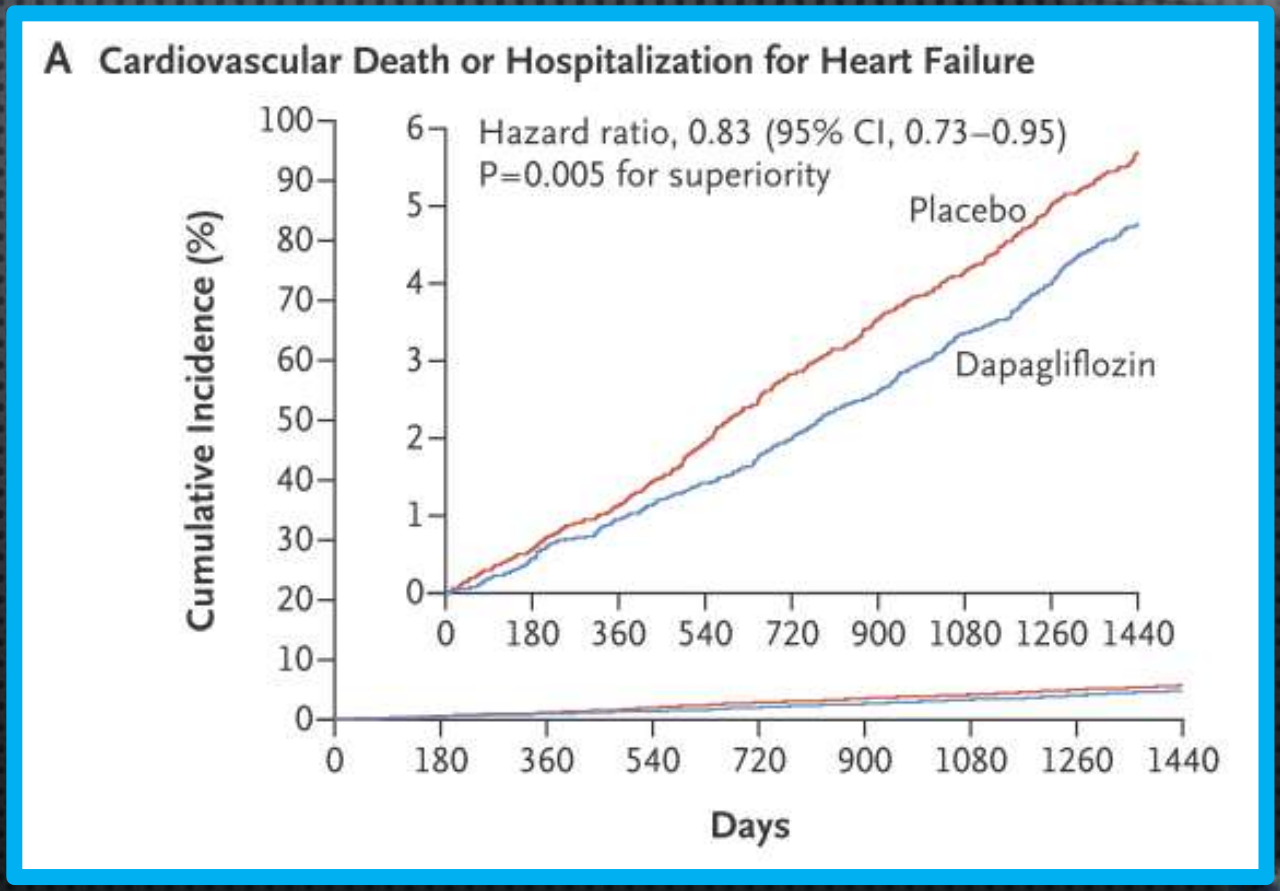
ACC 2019 New Orleans: SGLT2 inhibitors

DECLARE-TIMI 58



- N=17160 patients T2DM
  - 10186 without known atherosclerotic CV disease
- Follow up 4.2 years
- Meets: non inferiority to placebo
- Two primary efficacy analyses
  - Dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P = 0.17)
  - Cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P = 0.005)



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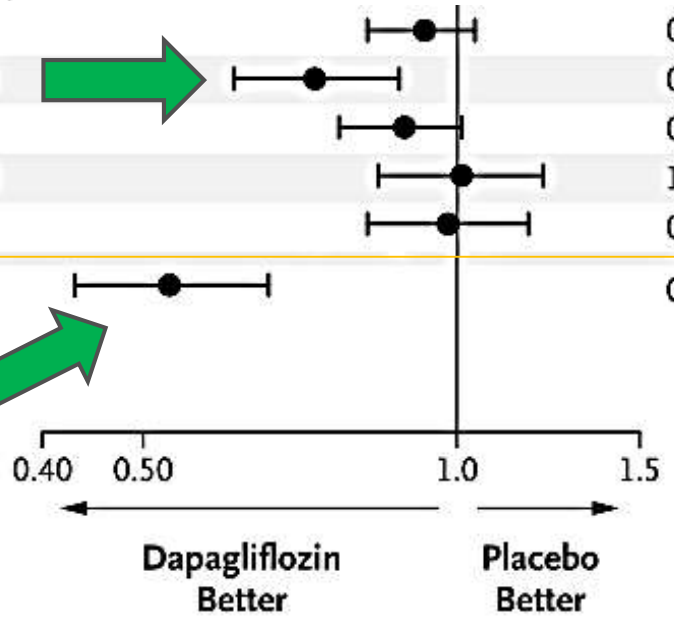
N Engl J Med 2019;380:347-57.

Key Efficacy Outcomes and Their Components

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



N Engl J Med 2019;380:347-57.

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Effect of Dapagliflozin on Heart Failure and Mortality

DECLARE-TIMI 58 is the only SGLT2i with detailed baseline information on patients' left ventricular ejection fraction

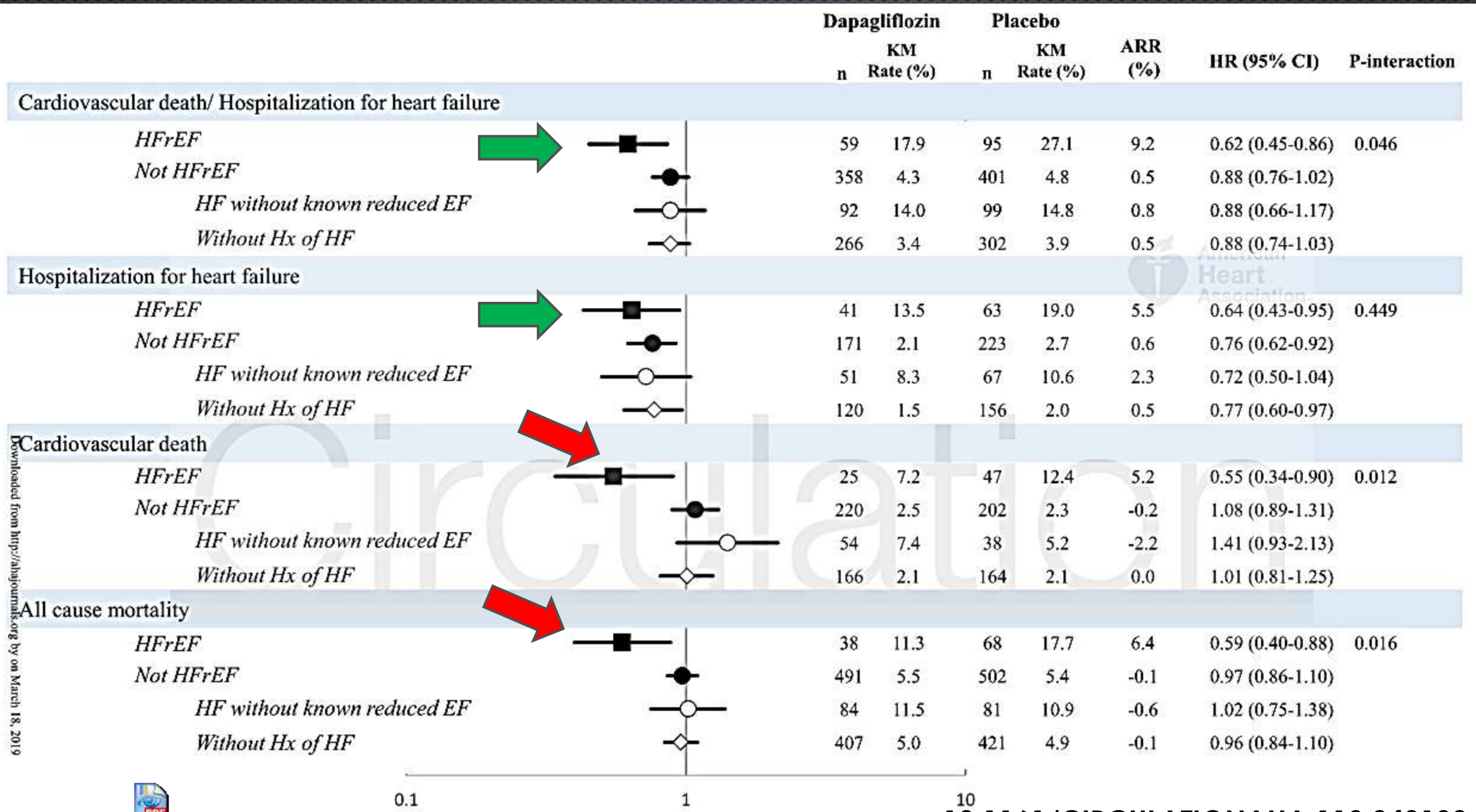
N=671/17160 (3.9% of total trial cohort) EF <45%
N= 1316/17160 (7.7% of the total trial cohort)
Heart failure history- normal EF

N=15173 no history of heart failure
3723 EF>45%
11450 no documented EF

	Dapagliflozin		Placebo				
	n	KM Rate (%)	n	KM Rate (%)	ARR (%)	HR (95% CI)	P-interaction
Cardiovascular death/ Hospitalization for heart failure							
HFrEF	59	17.9	95	27.1	9.2	0.62 (0.45-0.86)	0.046
Not HFrEF	358	4.3	401	4.8	0.5	0.88 (0.76-1.02)	
HF without known reduced EF	92	14.0	99	14.8	0.8	0.88 (0.66-1.17)	
Without Hx of HF	266	3.4	302	3.9	0.5	0.88 (0.74-1.03)	

10.1161/CIRCULATIONAHA.119.040130

Eri Toda Kato / Wiviott



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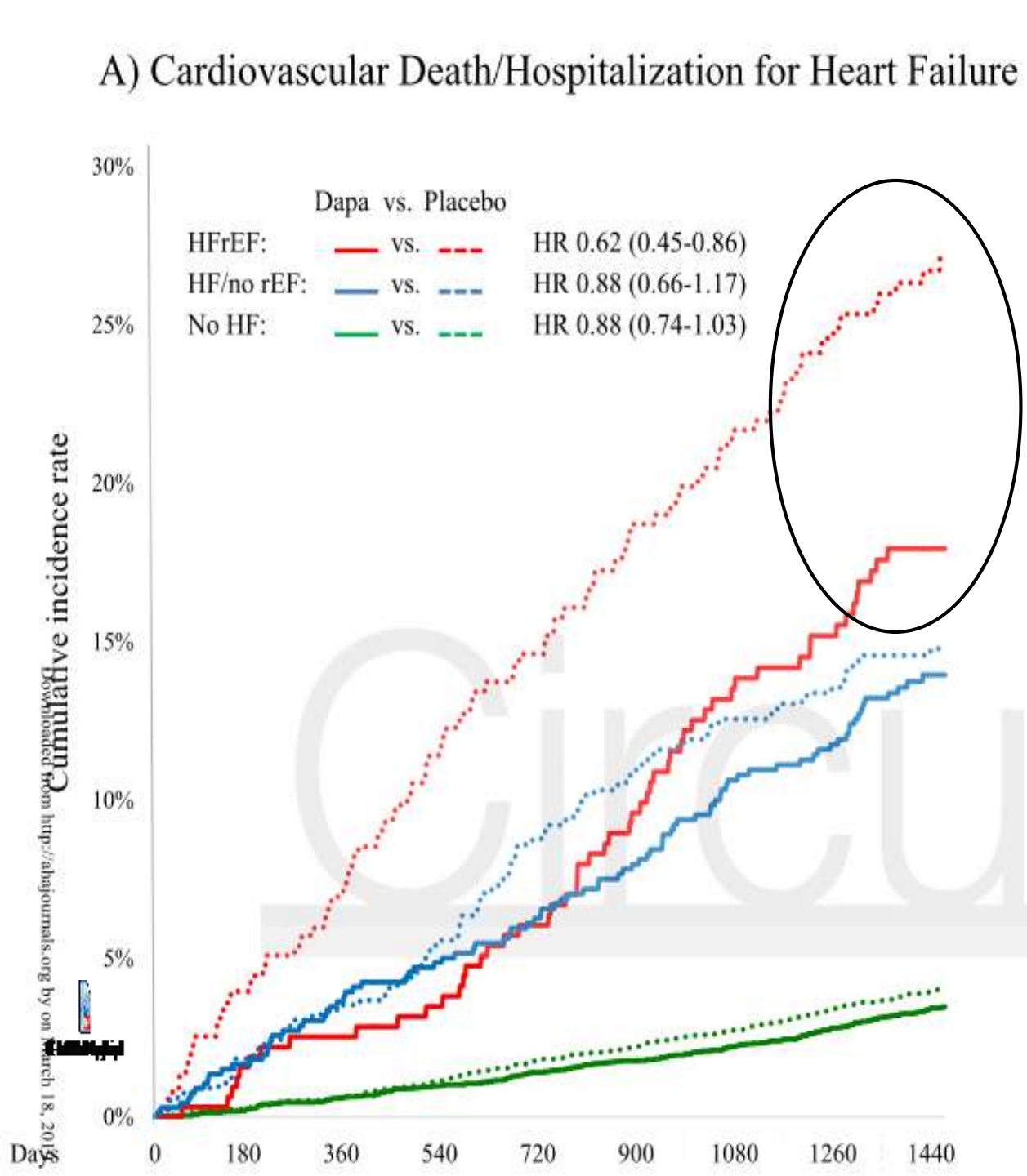

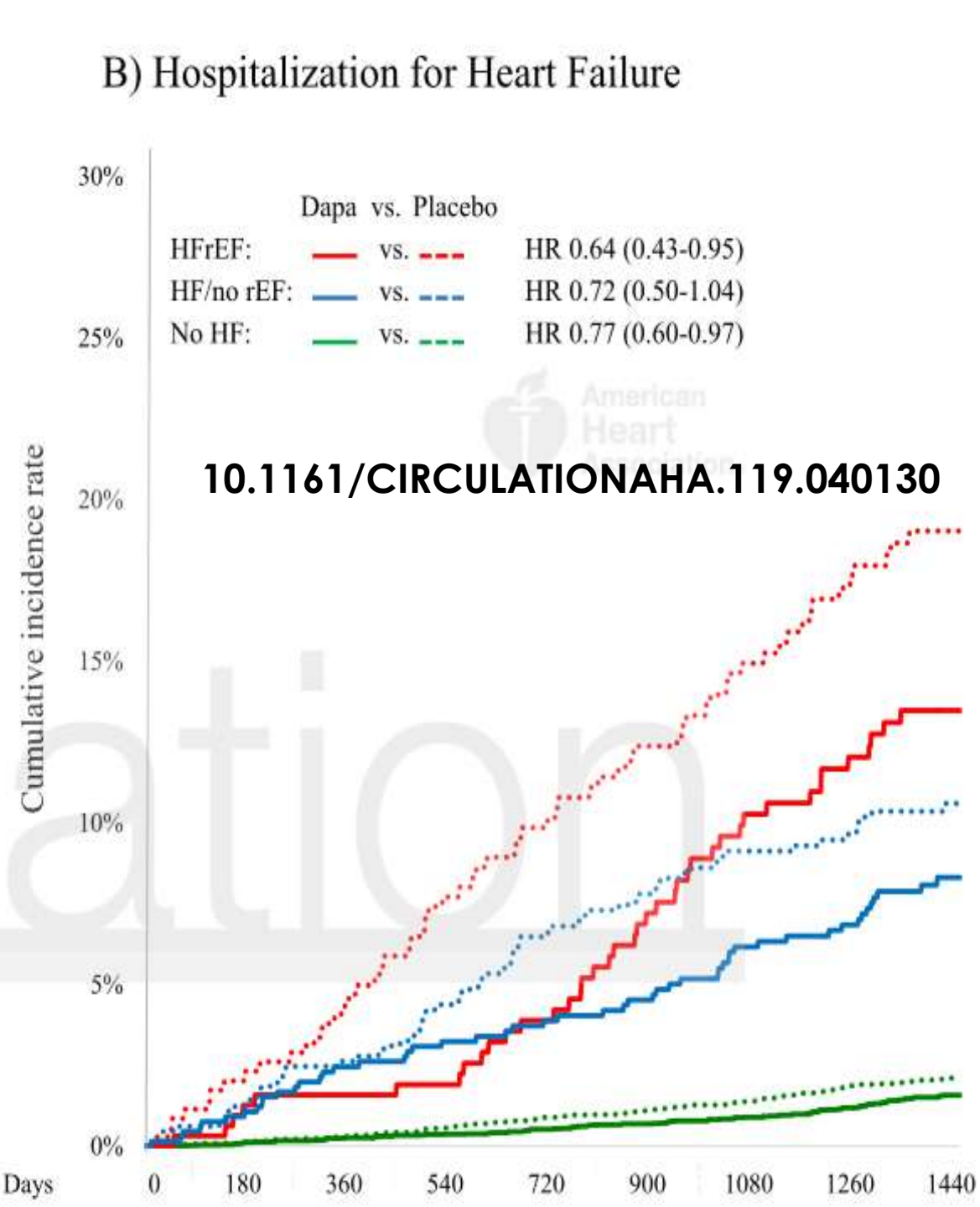

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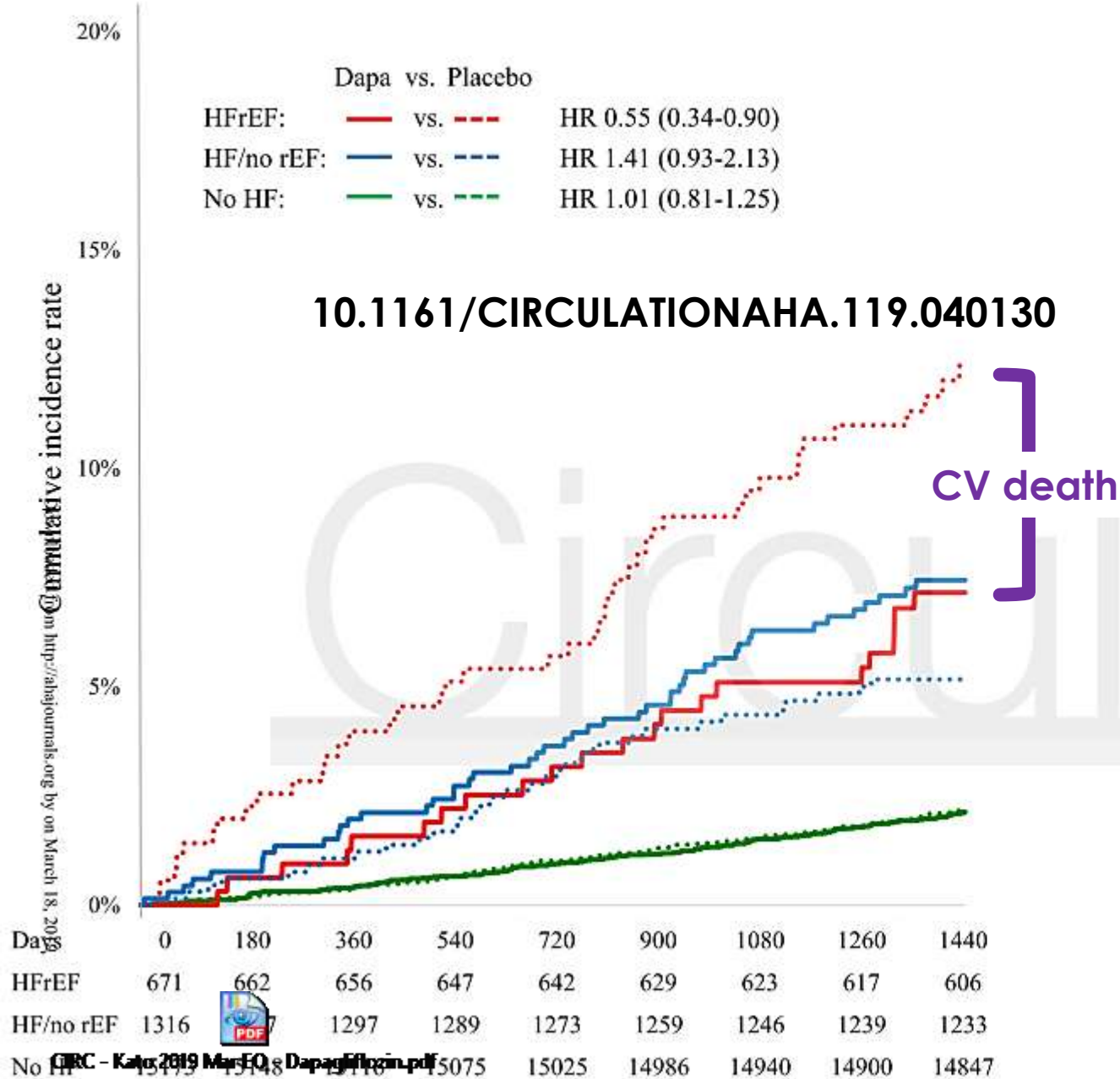
C) Cardiovascular Death

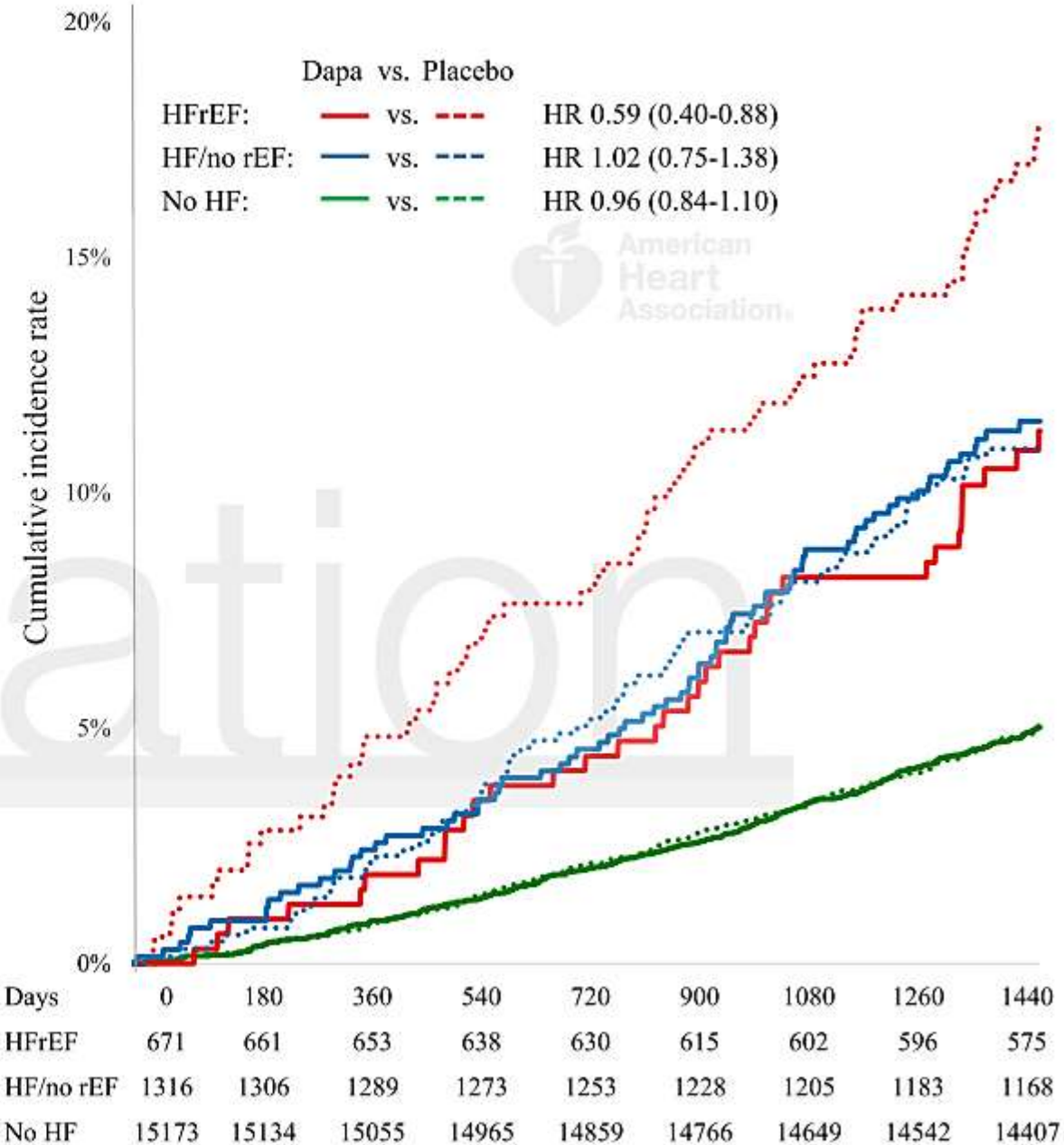


Days	0	180	360	540	720	900	1080	1260	1440
HFrEF	671	662	656	647	642	629	623	617	606
HF/no rEF	1316	[illegible]	1297	1289	1273	1259	1246	1239	1233
No HF	[illegible]	[illegible]	[illegible]	[illegible]	15075	15025	14986	14940	14900	14847

10.1161/CIRCULATIONAHA.119.040130

CV death

D) All Cause Mortality



Days	0	180	360	540	720	900	1080	1260	1440
HFrEF	671	661	653	638	630	615	602	596	575
HF/no rEF	1316	1306	1289	1273	1253	1228	1205	1183	1168
No HF	15173	15134	15055	14965	14859	14766	14649	14542	14407

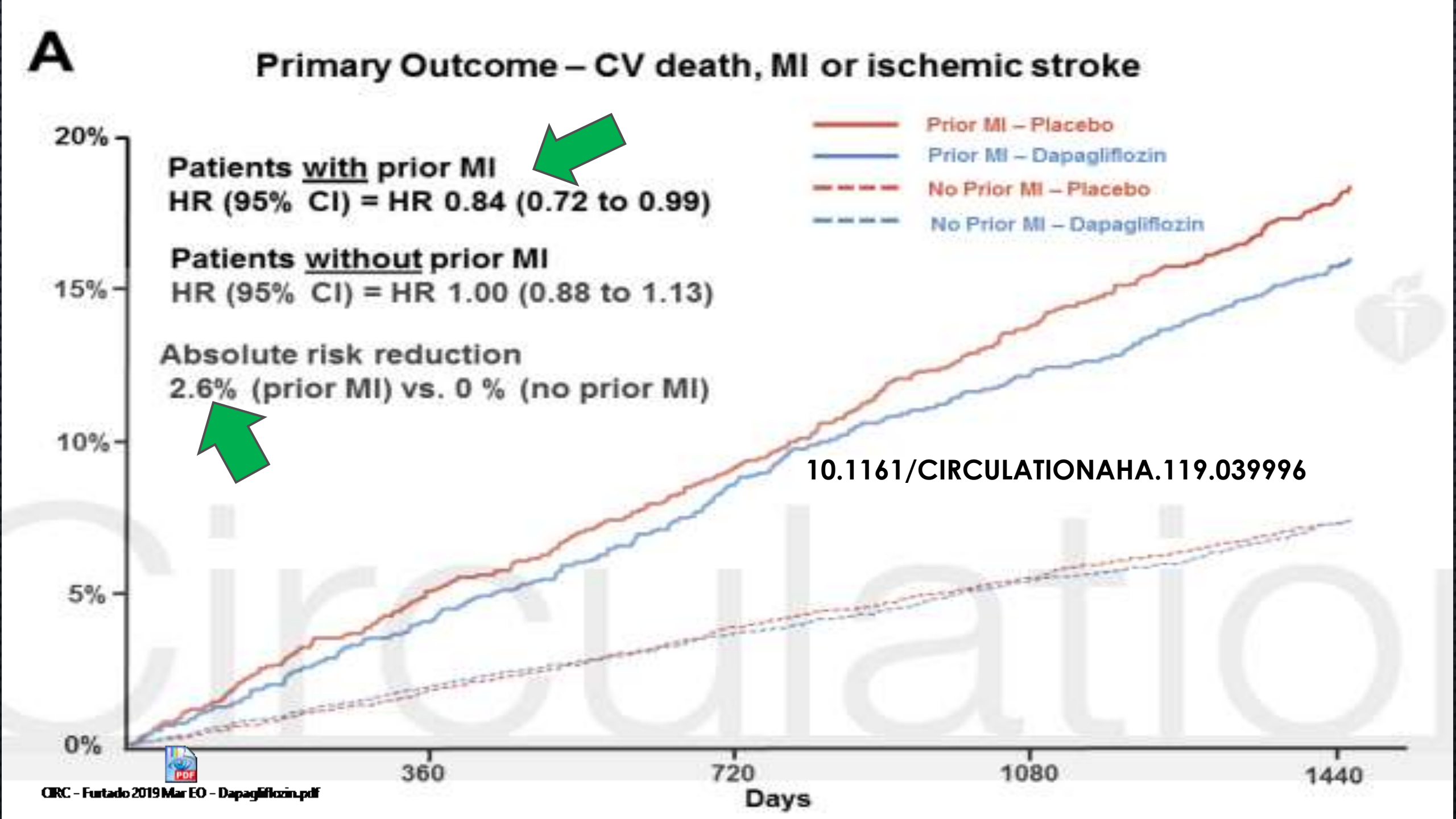
Sub-analysis From DECLARE TIMI-58 Trial

Prior Myocardial Infarction

	Prior MI N = 1,807	No prior MI N = 6,771	Adjusted HR	P-value
MACE (CV death, MI or ischemic stroke)	321 (17.8%)	482 (7.1 %)	2.28 (1.96 – 2.65)	<0.001
CV death/HHF	190 (10.5%)	306 (4.5%)	1.77 (1.46 – 2.14)	<0.001
Renal composite*	152 (8.4 %)	328 (4.8%)	1.53 (1.25 – 1.89)	<0.001
All-cause death	187 (10.3%)	383 (5.7%)	1.65 (1.37 – 1.99)	<0.001
MI	211 (11.7%)	230 (3.4%)	3.05 (2.50 – 3.71)	<0.001
Type 1 MI	150 (8.3%)	157 (2.3%)	3.33 (2.63 – 4.22)	<0.001
Type 2 MI	57 (3.2%)	58 (0.9%)	2.82 (1.92 – 4.15)	<0.001
Ischemic Stroke	71 (3.9%)	160 (2.4%)	1.58 (1.17 – 2.12)	0.002
CV death	96 (5.3%)	153 (2.3%)	1.90 (1.45 – 2.51)	<0.001
CHD death	71 (3.9%)	113 (1.7%)	1.87 (1.36 – 2.58)	<0.001

10.1161/CIRCULATIONAHA.119.039996

CIRC – Furtado 2019 Mar EO – Dapagliflozin.pdf


A
Primary Outcome – CV death, MI or ischemic stroke
Patients with prior MI
HR (95% CI) = HR 0.84 (0.72 to 0.99)
Patients without prior MI
HR (95% CI) = HR 1.00 (0.88 to 1.13)
Absolute risk reduction
2.6% (prior MI) vs. 0 % (no prior MI)
Prior MI – Placebo
Prior MI – Dapagliflozin
No Prior MI – Placebo
No Prior MI – Dapagliflozin
20%
15%
10%
5%
0%
360
720
1080
1440
Days
10.1161/CIRCULATIONAHA.119.039996
CIRC - Furtado 2019 Mar EO - Dapagliflozin.pdf

1 TYPE 1 MYOCARDIAL INFARCTION

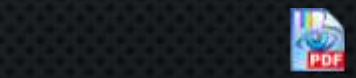
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection

2 TYPE 2 MYOCARDIAL INFARCTION

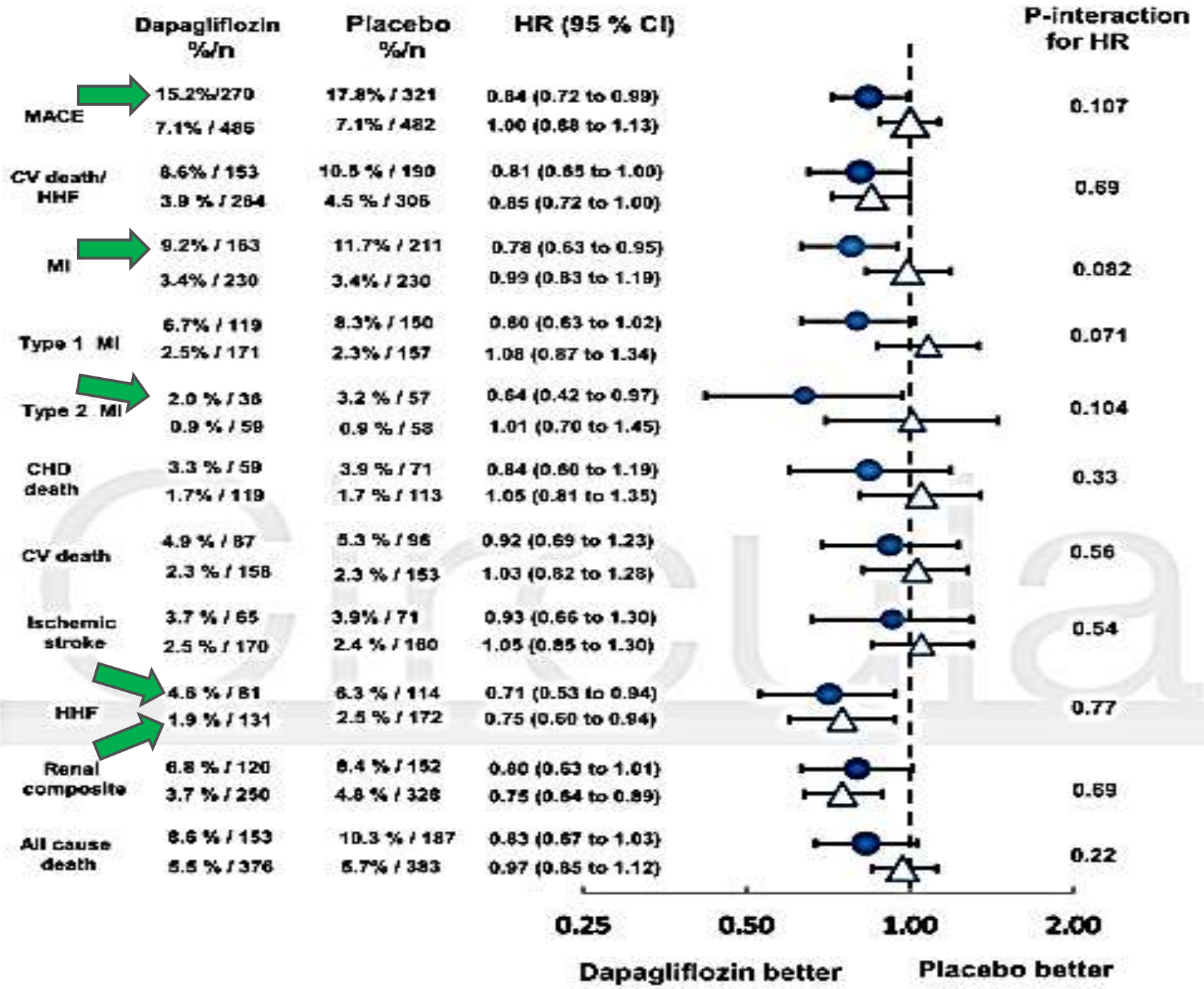
Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply

Prior MI (N = 3,584)

No Prior MI (N = 13,576)

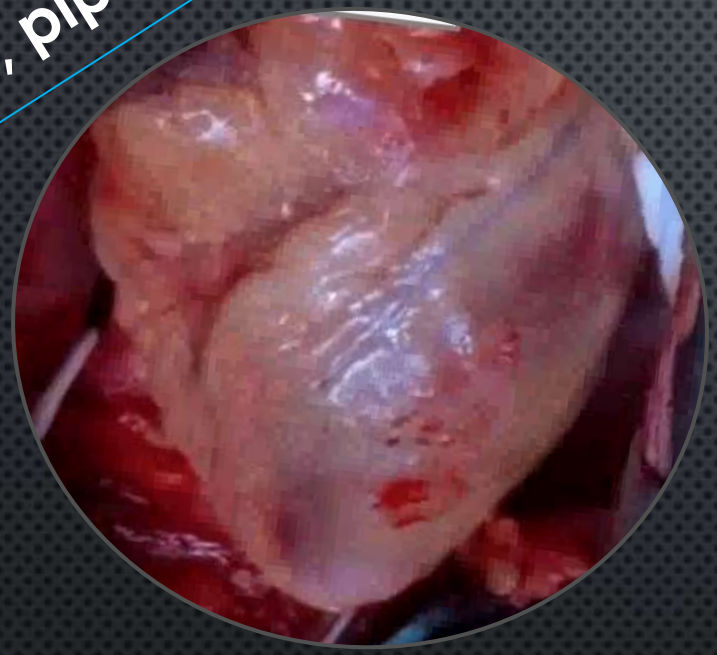


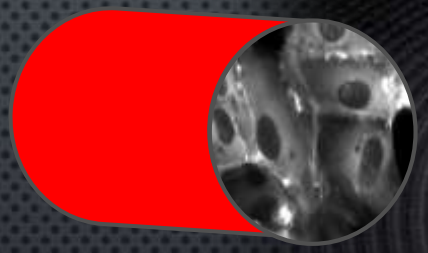
CIRC - Furtado 2019 MarEO - Dapagliflozin.pdf

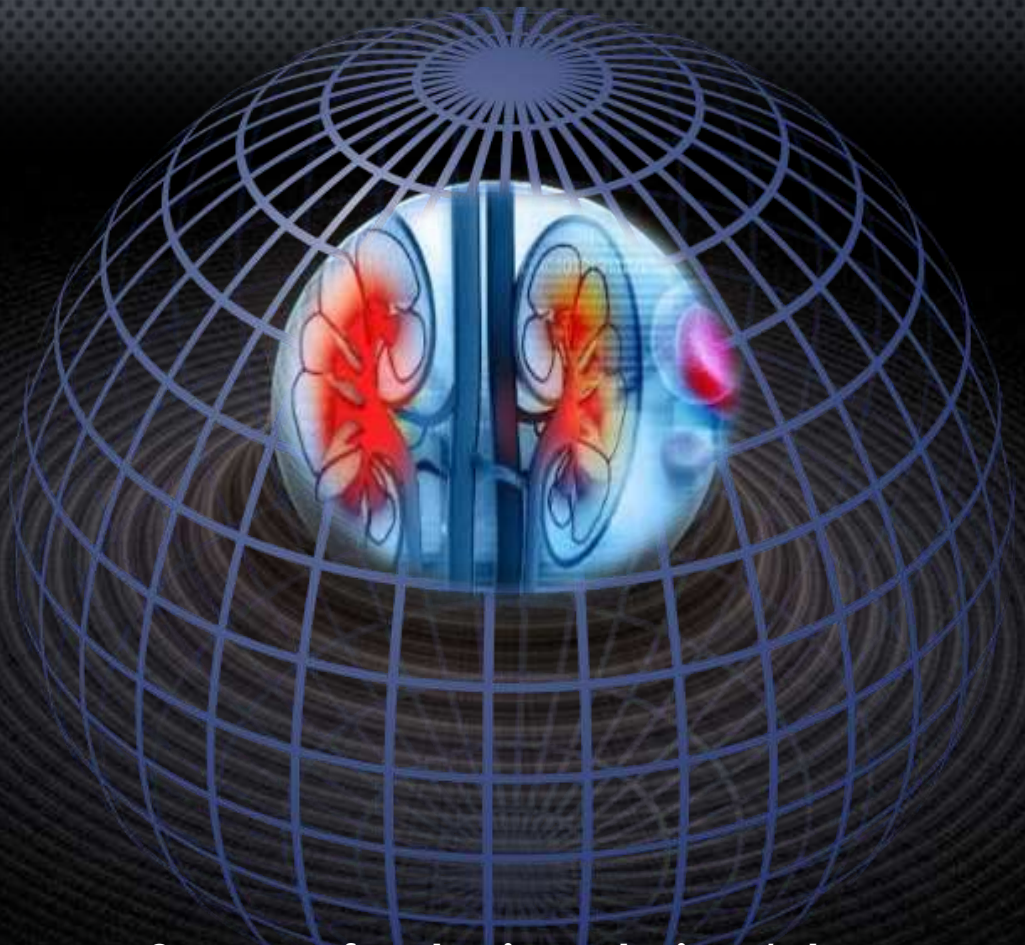


Translational biology

Pumps, pipes and filters

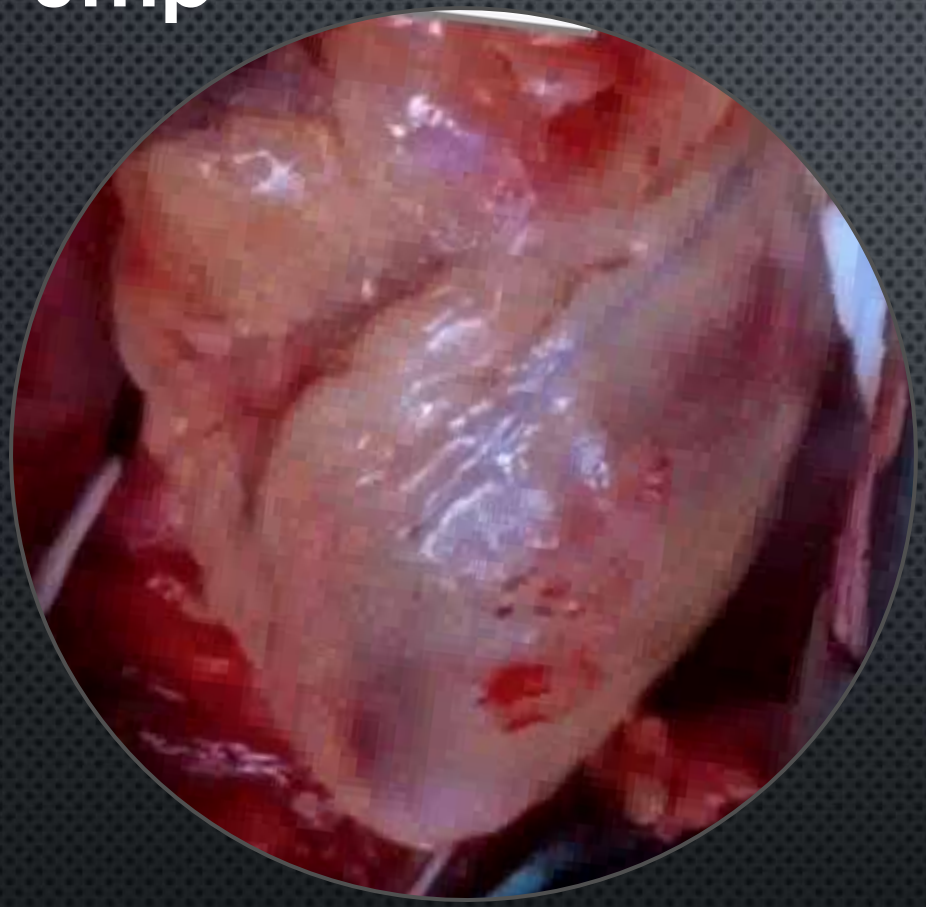






2 cans of coke in calories / day
800 cc urine
BP drop 4-5 mm Hg
Weight loss

Pump

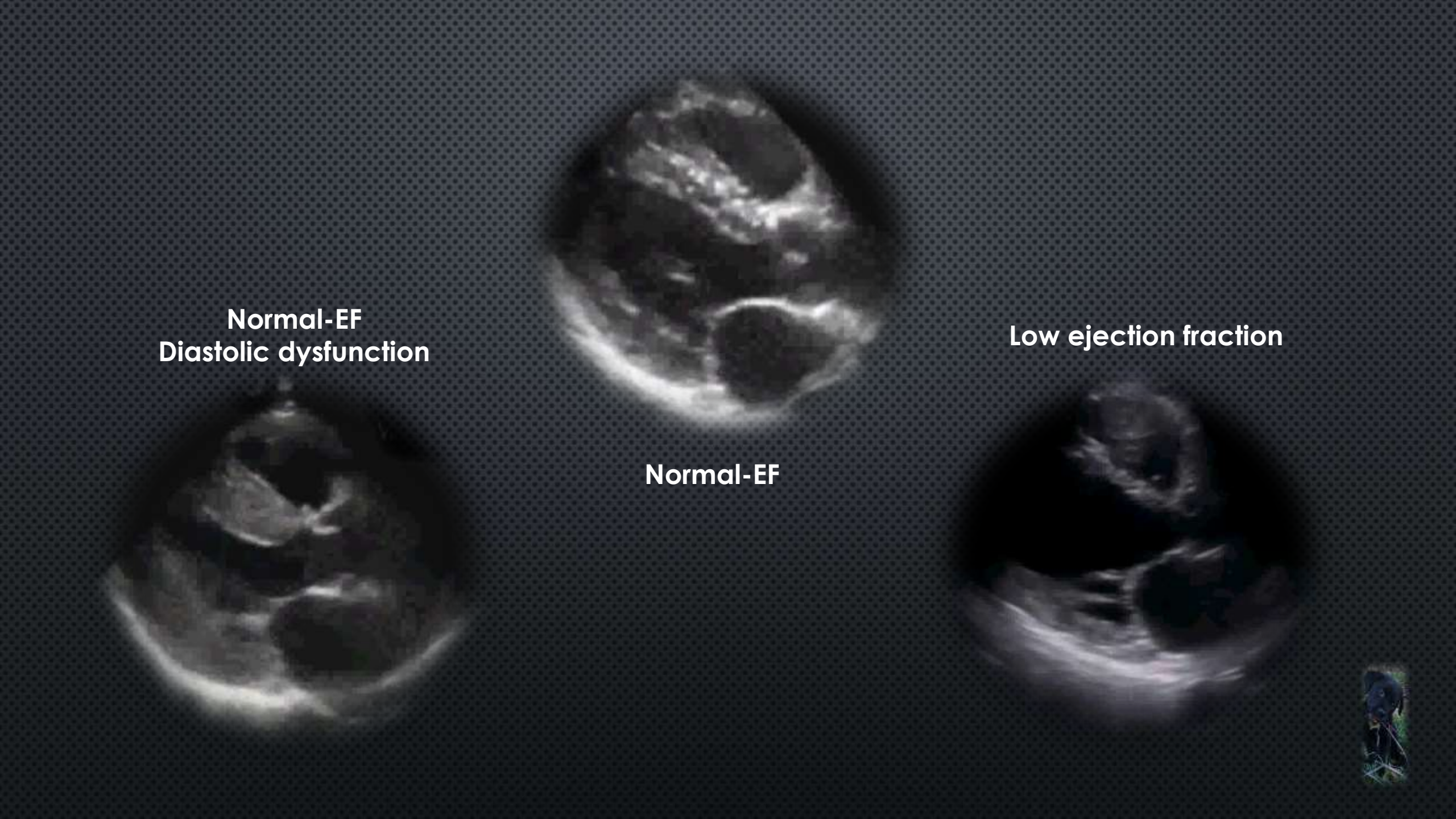


Human output: 4500 cc of blood/min

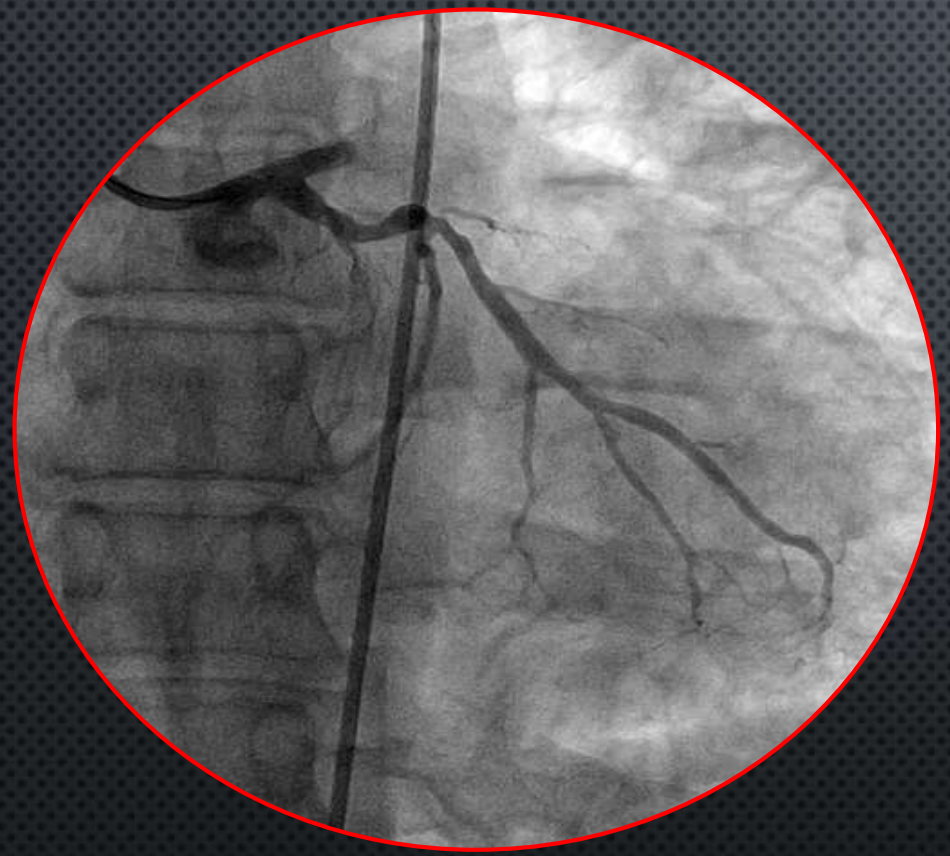
Elite cyclist can produce close to 400 watts of mechanical power over an hour

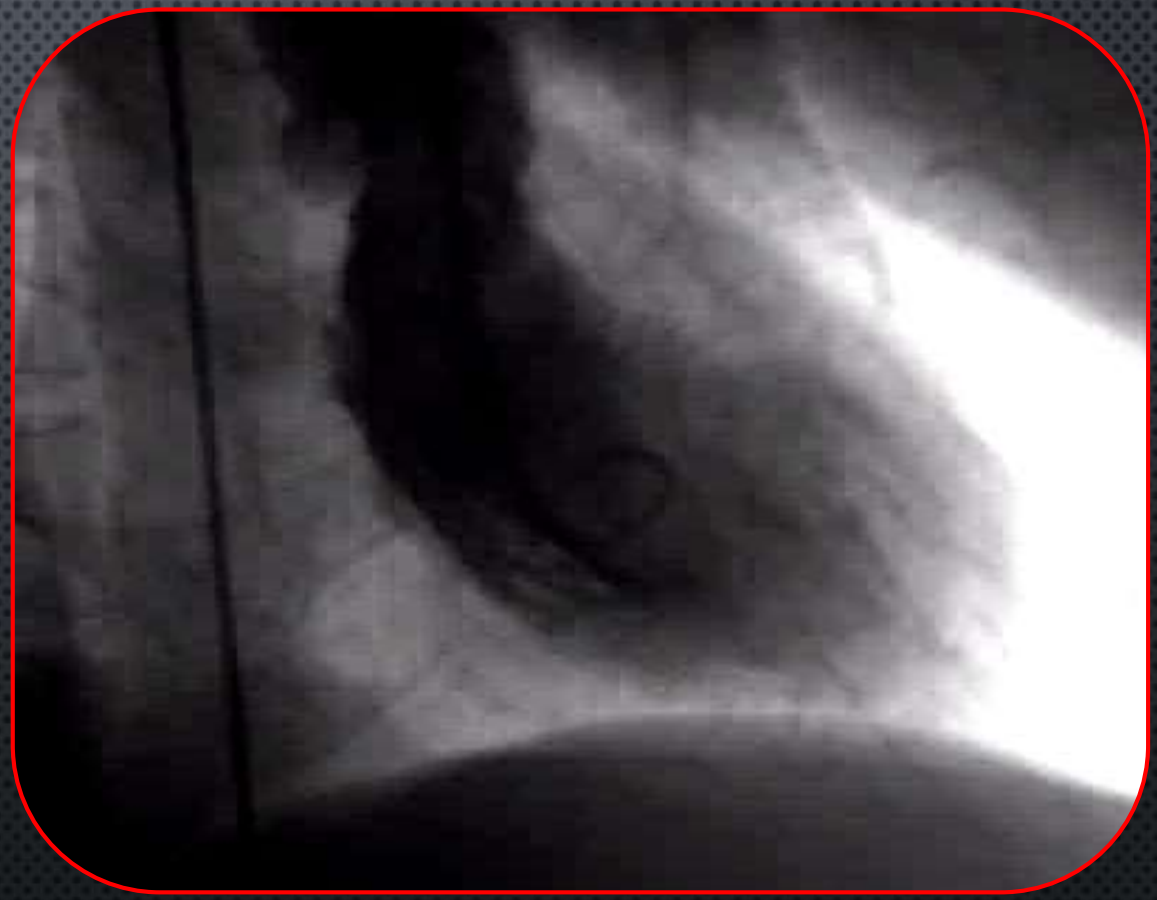
0.536409

Horsepower

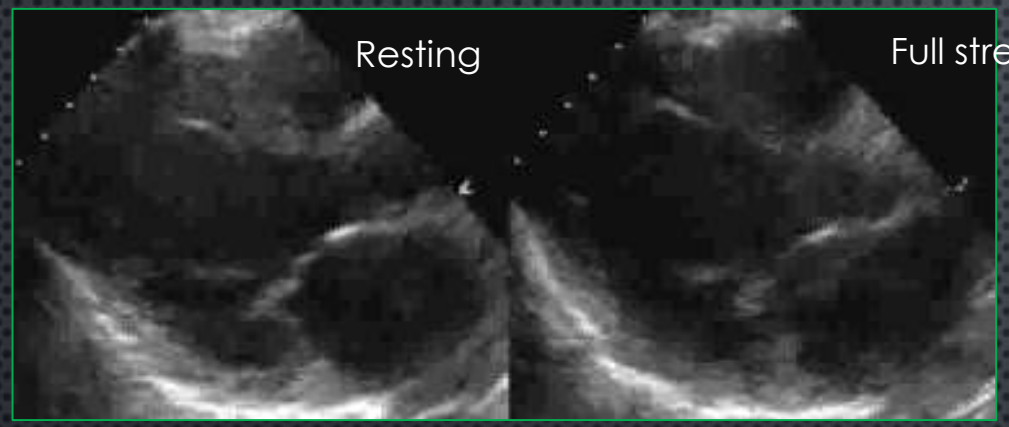

Normal-EF
Diastolic dysfunction
Normal-EF
Low ejection fraction

Heart failure-reduced ejection fraction from coronary artery disease



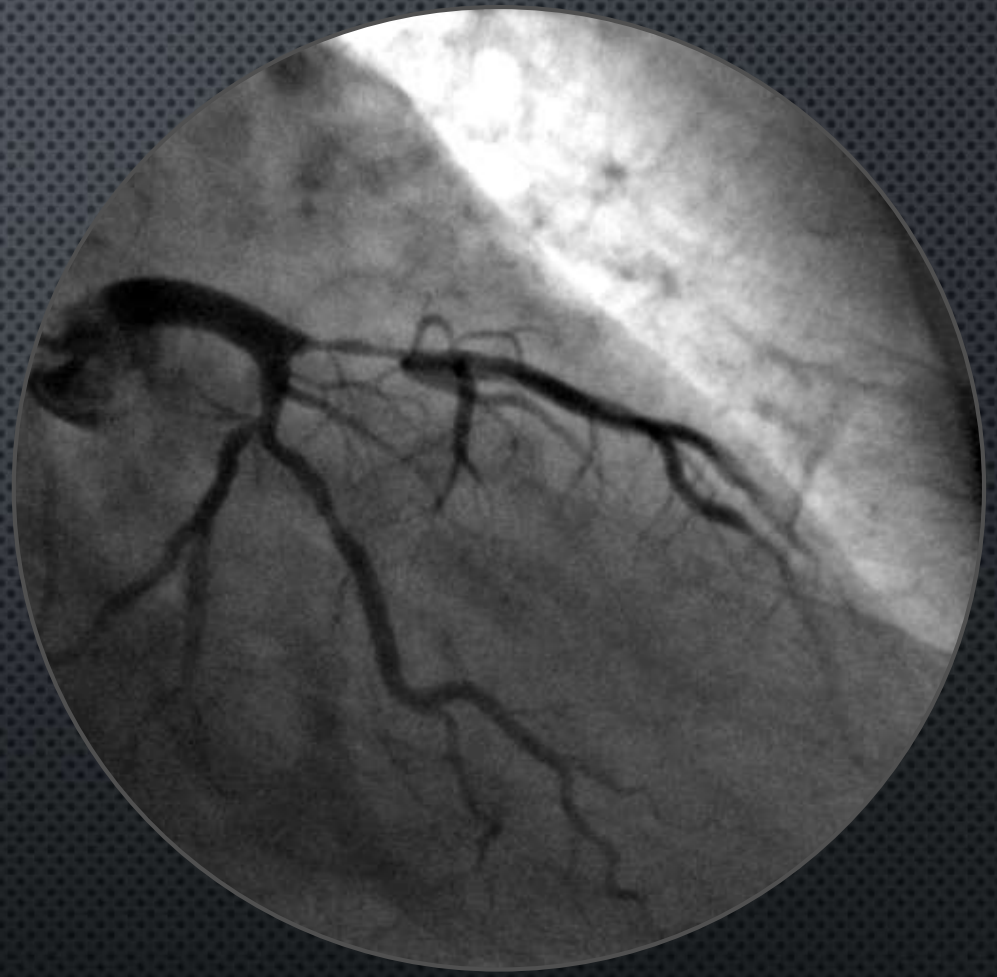


Classic cardiology case from primary care physician



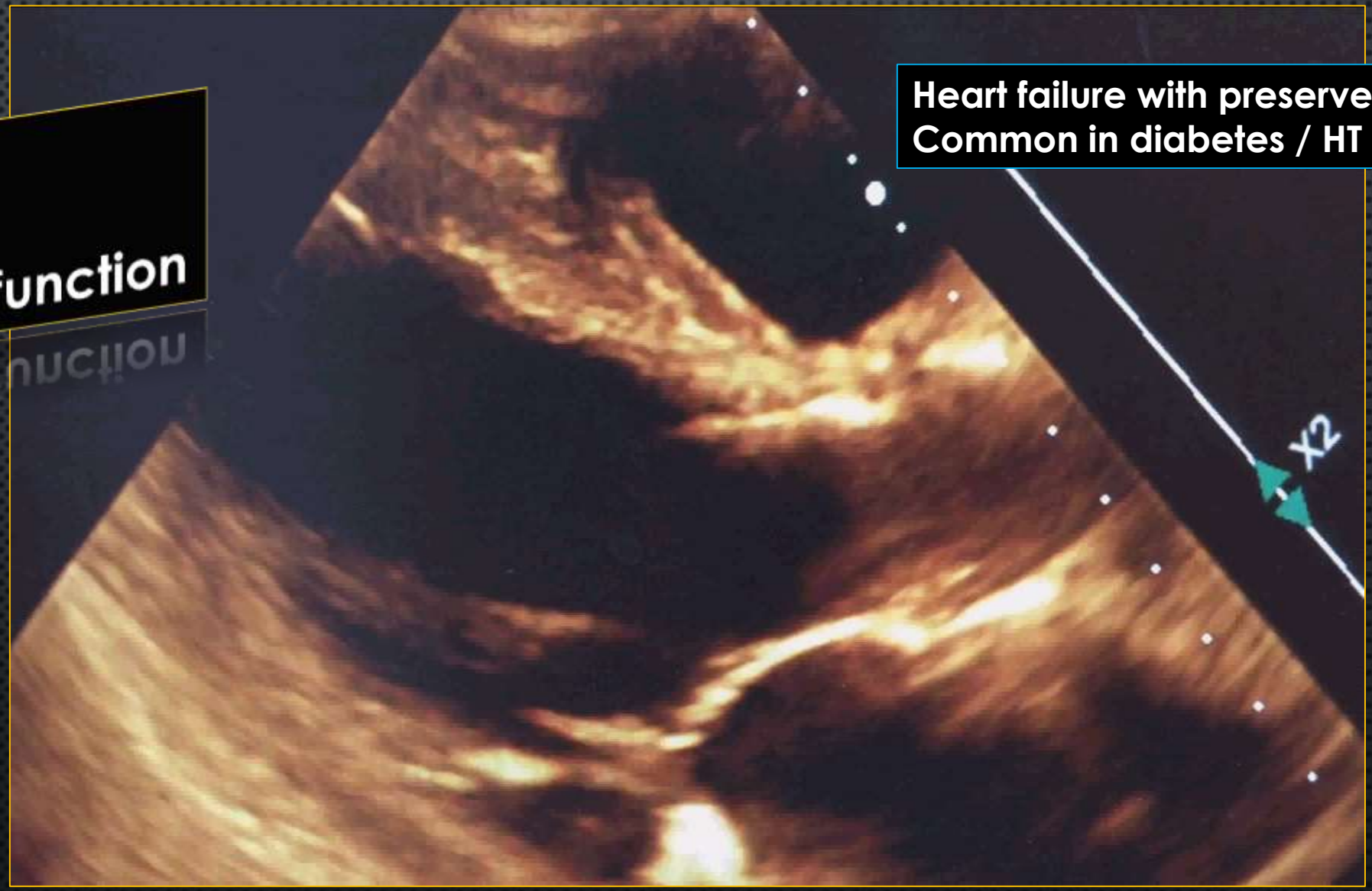
47 y/o Obese Hispanic
Women-no chest pain SOB
-multiple times

3 children
HbA1c 7.6 (normal <5.5)
Normal EKG

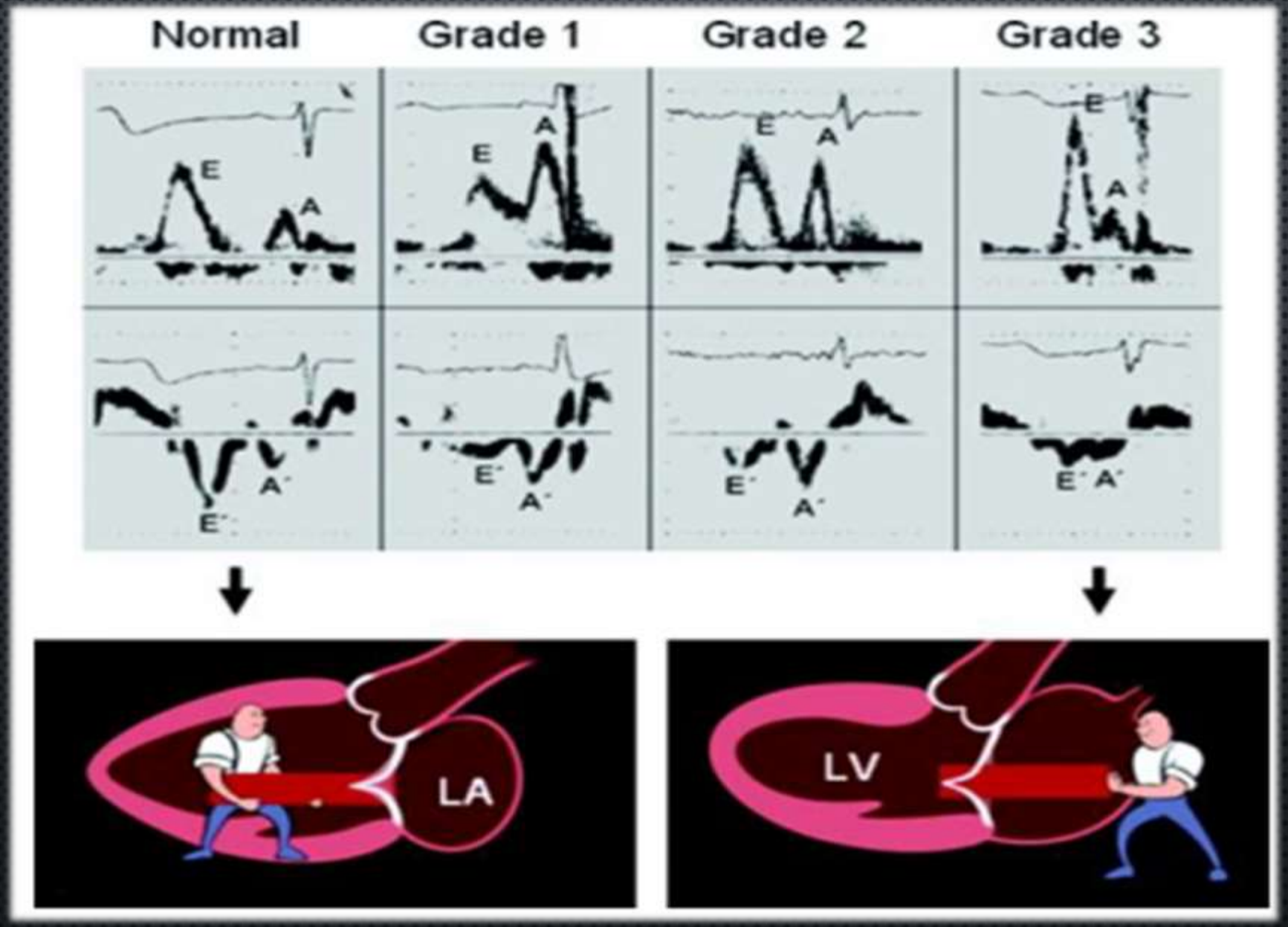


Right radial due to obesity
BMI 48

EF-55%
LVH
Diastolic dysfunction



Heart failure with preserved EF
Common in diabetes / HT



Gandhi et al 2014 Am J Card

HEART FAILURE: BULLET POINTS

- HFrEF <40%
- HFpEF >50%

50% each

- Lifetime risk of developing HF 20% for >40 age
- Ambulatory patient with new onset dyspnea – ACC guidelines **CLASS 1 (NT proBNP)**
- **Class II for use of fibrosis biomarkers**

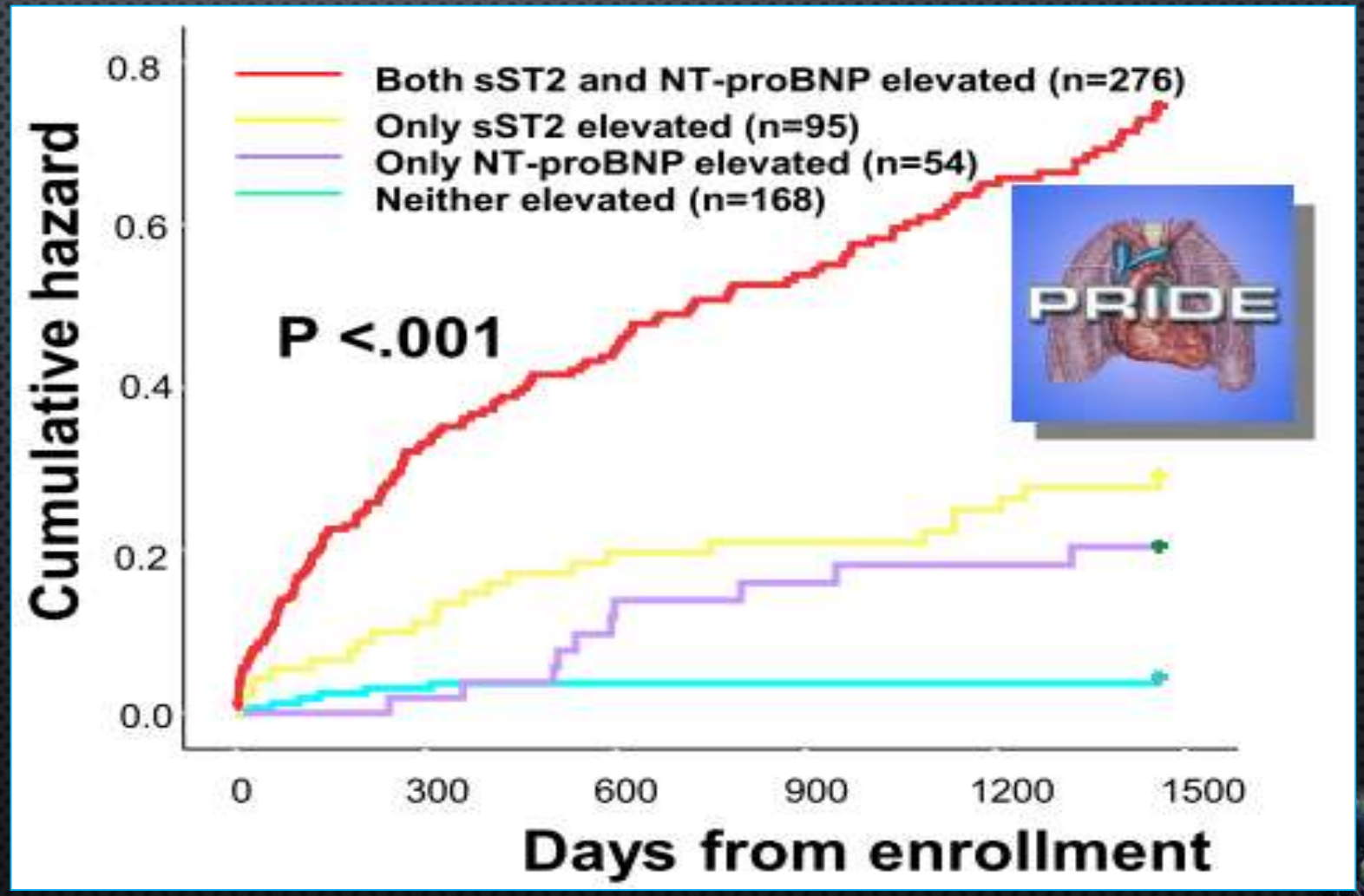
Cardiomyocyte Hypertrophy and Fibrosis

Sanada J Clin Invest 2007

ST2 circulating soluble ST2 concentrations reflect cardiovascular stress and fibrosis

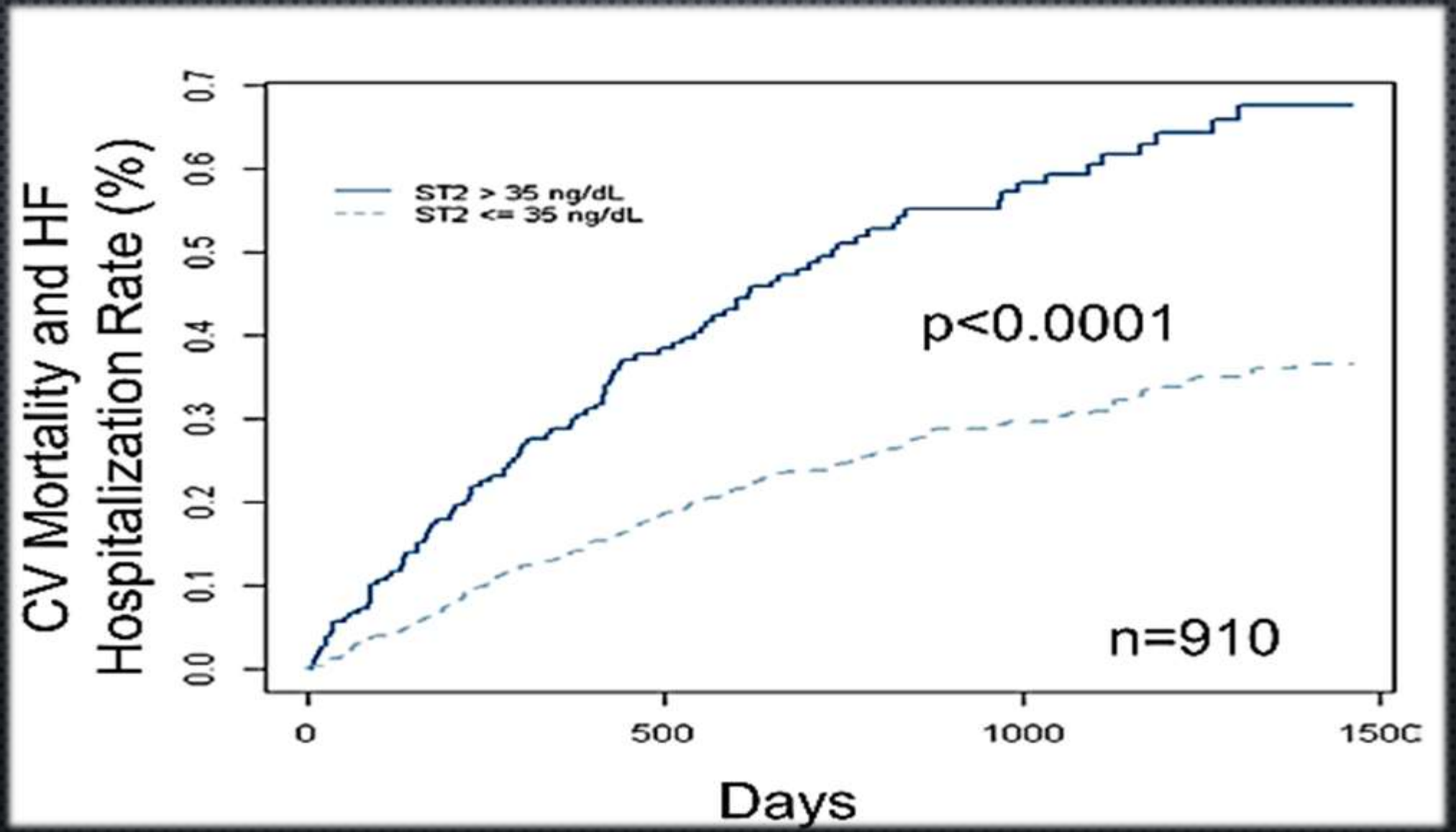
Predicts death out to 4 years

Combined with NTproBNP better



Januzzi et al. Clin Chem 2010

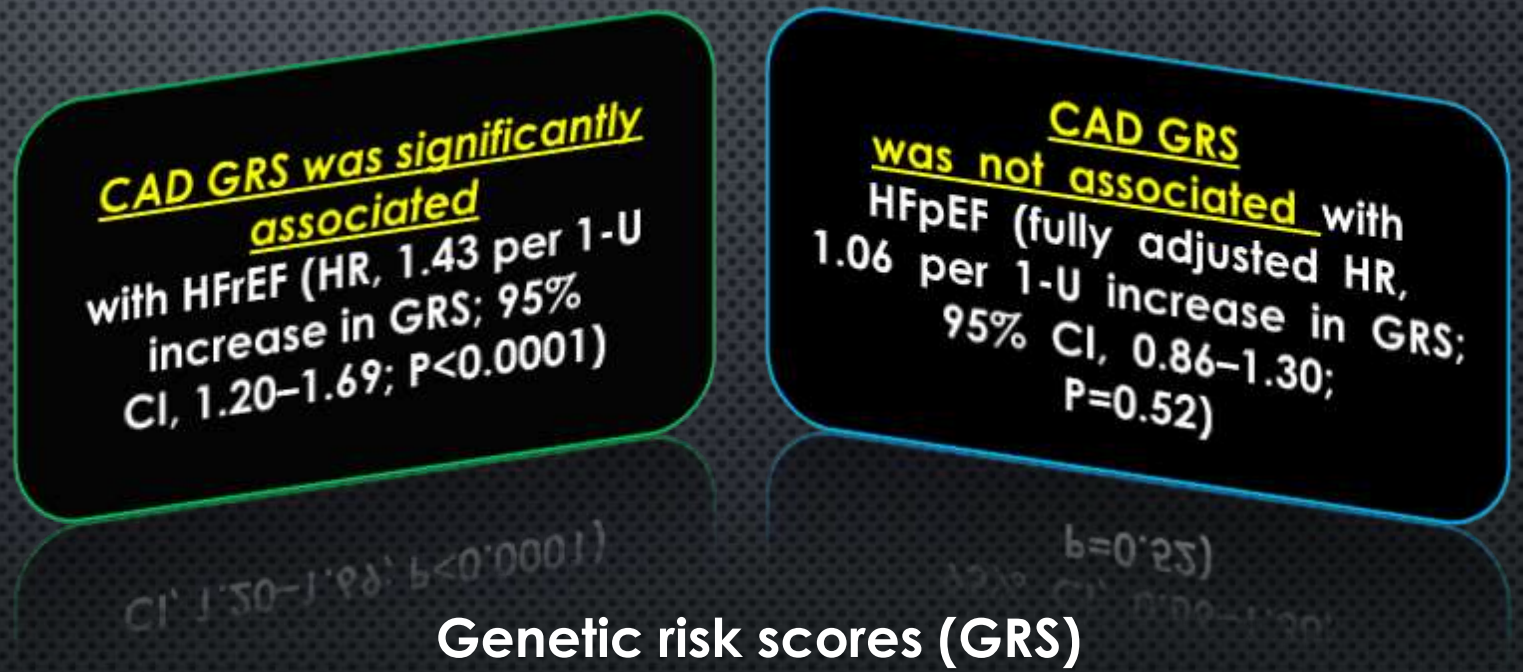
sST2 and Cardiovascular Mortality and HF Hospitalization



Felker, et al. Circ Heart Fail. 2013

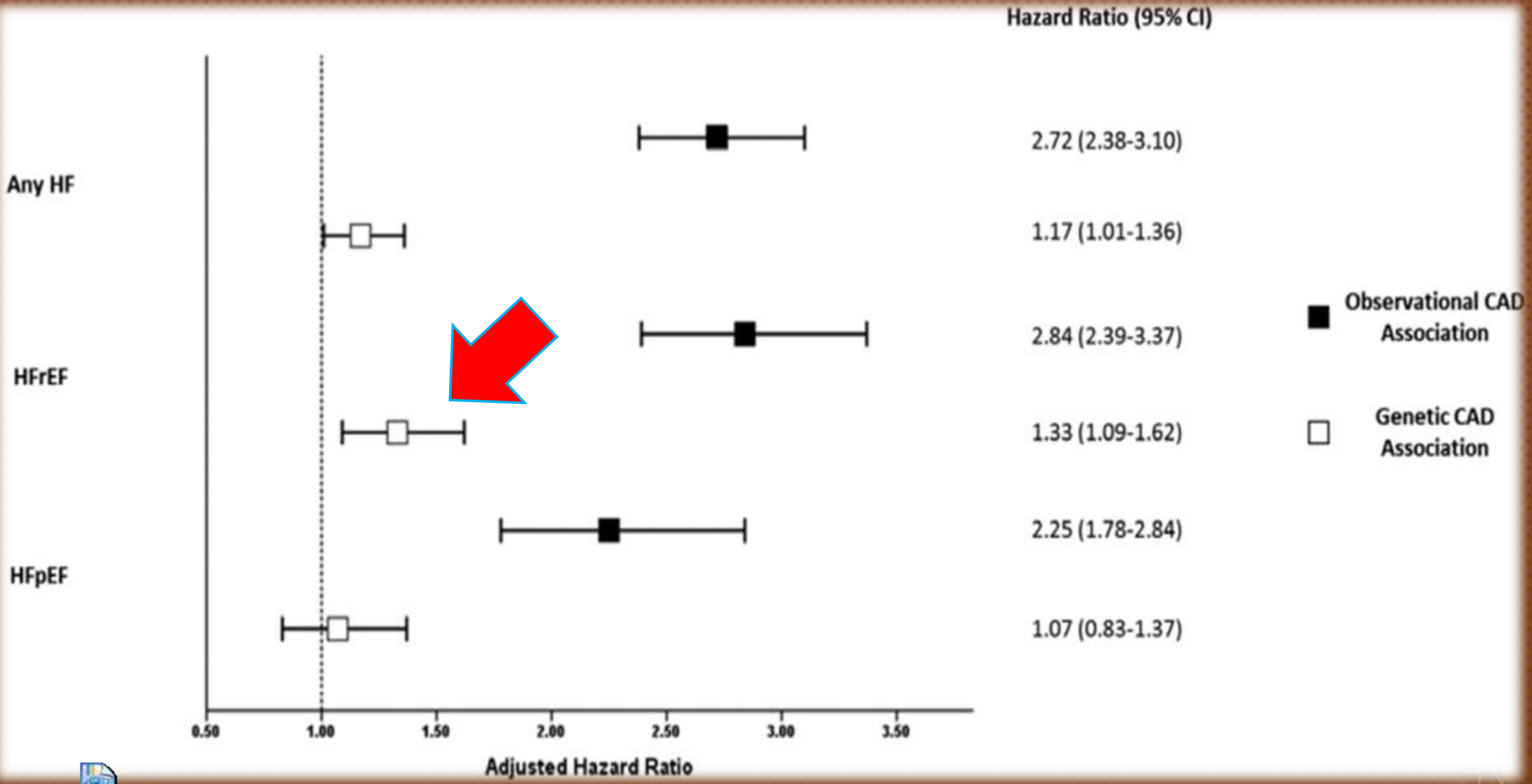
WHAT'S NEW WITH HEART FAILURE

- Framingham cohort suggested that a CAD GRS of 58 genetic variants was associated with HFrEF not HFpEF
- Genetics of Diabetes Audit and Research Tayside Scotland
- HF mortality and hospitalization were obtained from electronic health records
- 12919 individuals with available genetic data
- 64.5% have diabetes
- 1293 HF events



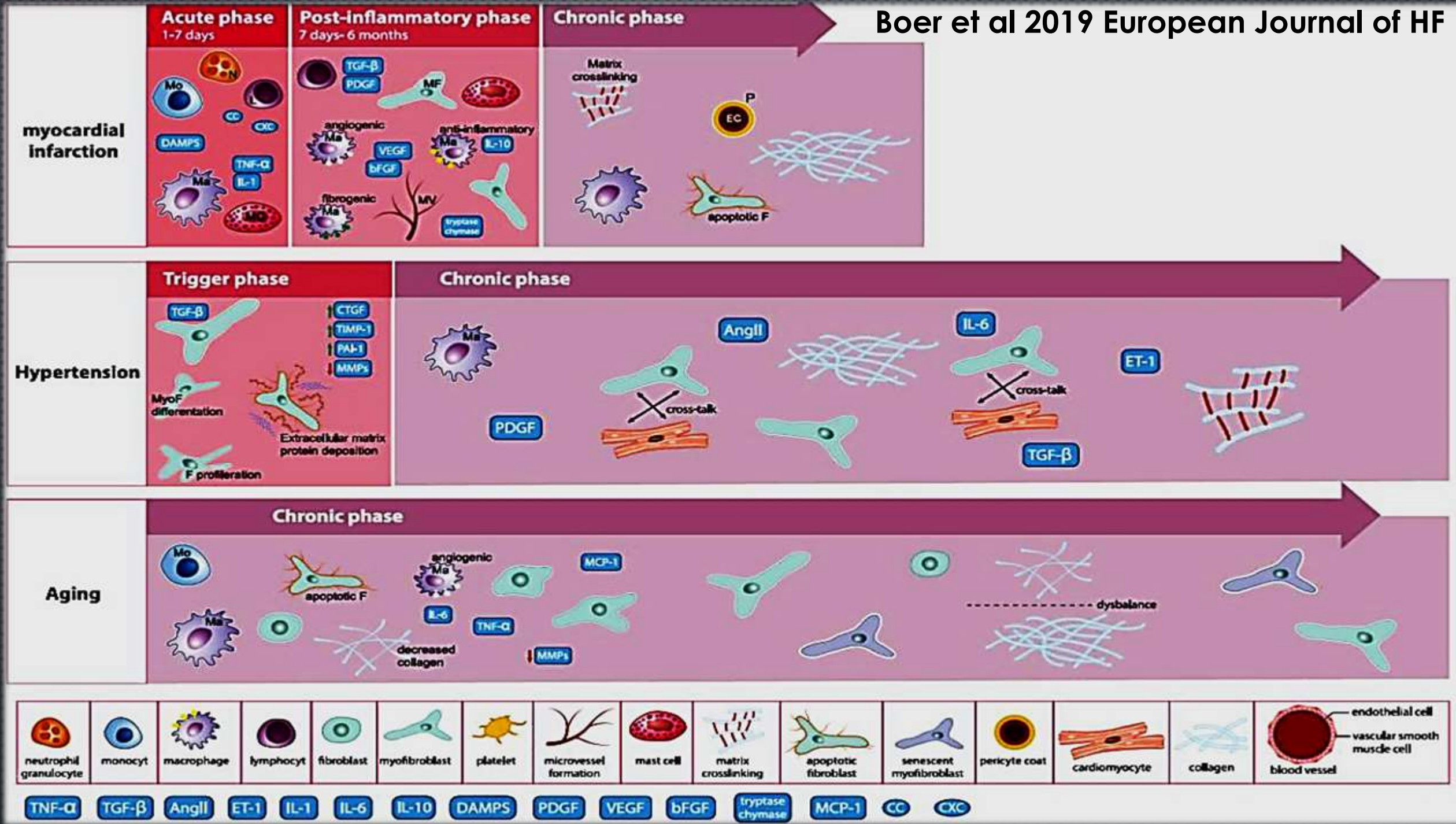
Circulation. 2019;139:986–988

00003017-201902120-00016.pdf



Circulation. 2019;139:986–988

Boer et al 2019 European Journal of HF



TAKE HOME

Patients with established ASCVD

Patients without established ASCVD

Negative

- Both reduce risk for major cardiovascular events to similar degree
- Heart failure and progression of kidney disease favors -- SGLT2 inhibitors

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