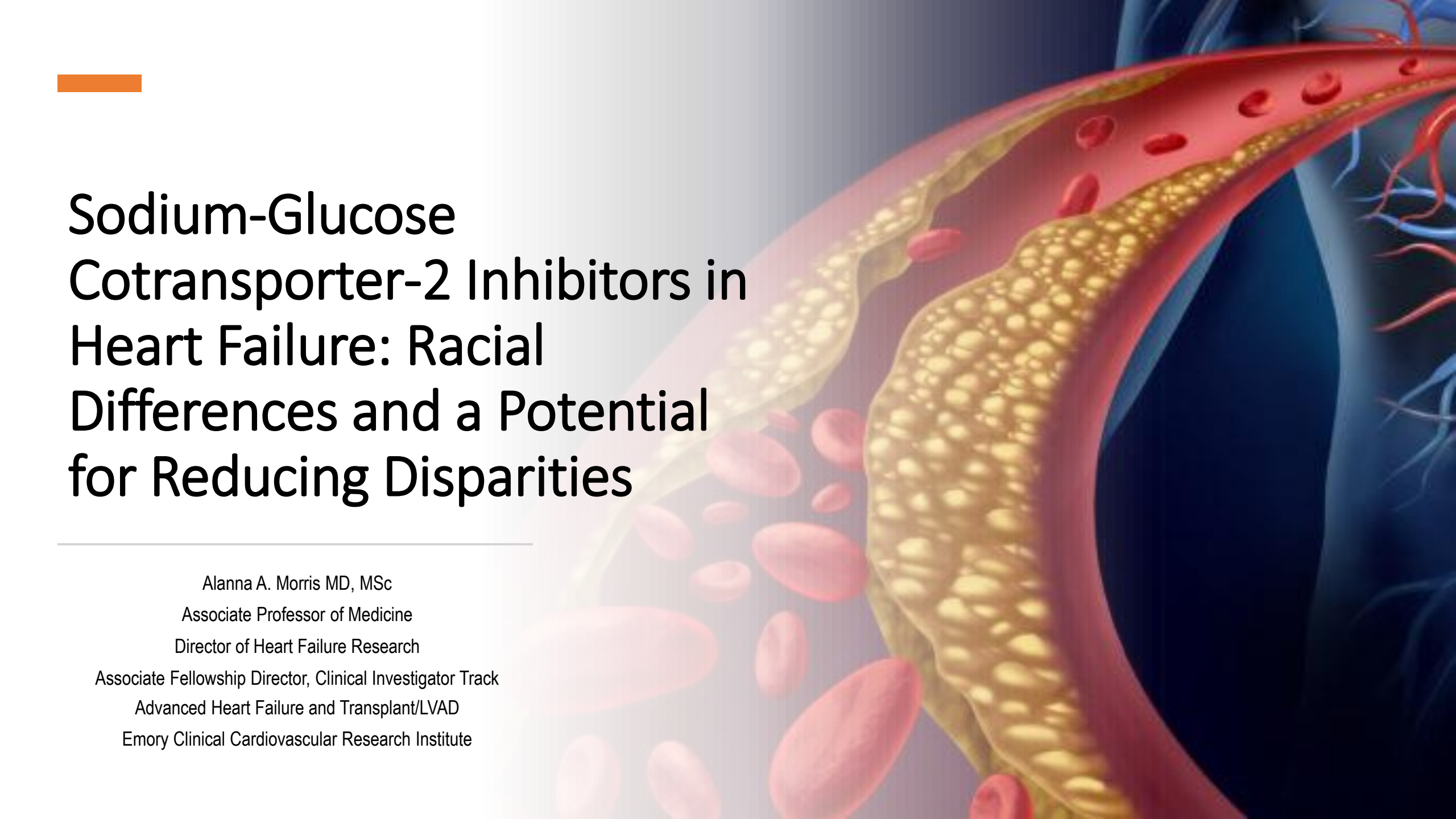
Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure: Racial Differences and a Potential for Reducing Disparities



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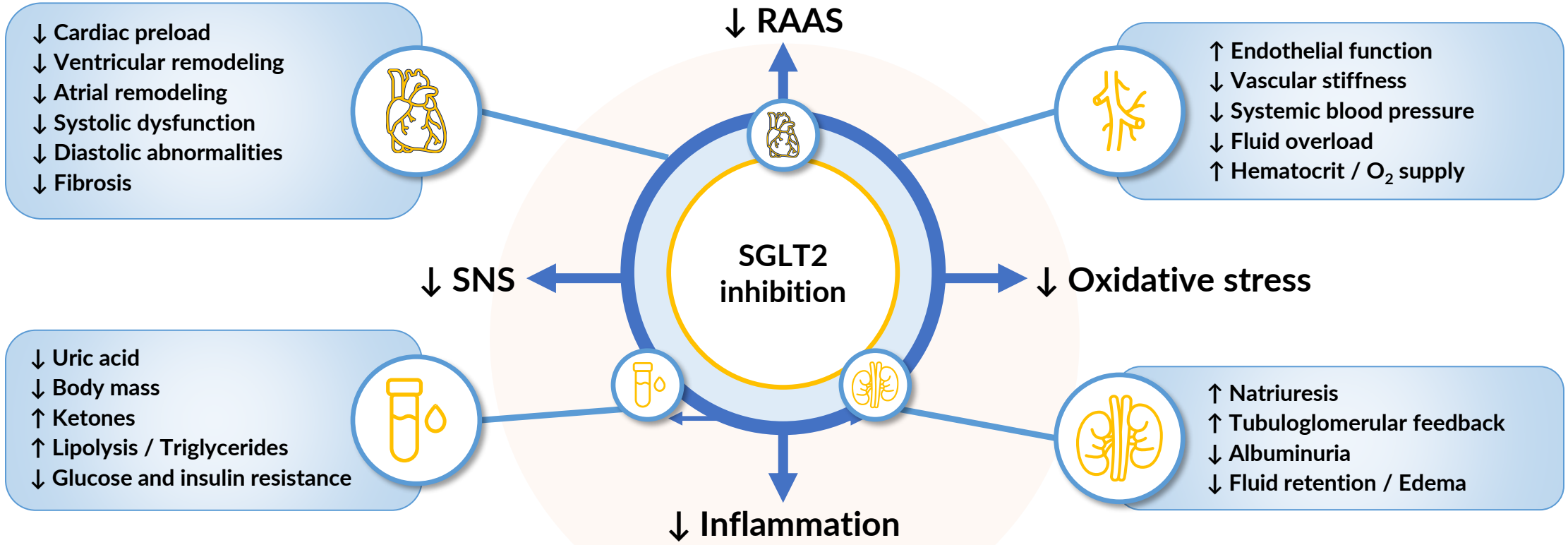
Disclosures

- Research grants – NHLBI, AHRQ, AHA, Woodruff Foundation, Association of Black Cardiologists
- Consultant – Acorai, Bayer, BI Lilly, Cytokinetics, Edwards Lifesciences, Ionis, Merck
- Ownership Interest – Gilead Sciences

Direct and Indirect Actions of SGLT2 Inhibitors



ATP, adenosine triphosphate; CRM, cardiovascular, renal and metabolic; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Givens RC, Schulze PC. In: Eisen H, ed. Heart Failure: A Comprehensive Guide to Pathophysiology and Clinical Care. London: Springer Verlag; 2017:1–26; Ronco C et al., *J Am Coll Cardiol*. 2008;52:1527; Santos-Ferreira D, et al. *Cardiology*. 2020; 145:311–20; Cowie M, Fisher M. *Nat Rev Cardiol*. 2020;17:761–72; Scheen AJ. *Nat Rev Endocrinol*. 2020;16:556–77.

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Guideline Directed Medical Therapy for HFrEF includes 4 medication classes

COR	LOE	Recommendations
1	A	In patients with HFrEF and NYHA class II to III symptoms, the use of **ARNi** is recommended to reduce morbidity and mortality
1	A	In patients with previous or current symptoms of chronic HFrEF, the use of **ACEi** is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible
1	B - R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, **replacement by an ARNi** is recommended to further reduce morbidity and mortality
1	A	In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 **beta blockers** proven to reduce mortality is recommended to reduce mortality and hospitalizations
1	A	In patients with HFrEF and NYHA class II to IV symptoms, an **MRA** is recommended to reduce morbidity and mortality, if eGFR >30 mL/min/ 1.73 m2 and serum potassium is <5.0 mEq/L
1	A	In patients with symptomatic chronic HFrEF, **SGLT2i** are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

SGLT2i are now Guideline Directed Medical Therapy for HFmrEF and HFpEF

COR	LOE	Recommendations
2a	**B - R**	In patients with ***HFmrEF***, **SGLT2i** can be beneficial in decreasing HF hospitalizations and cardiovascular mortality

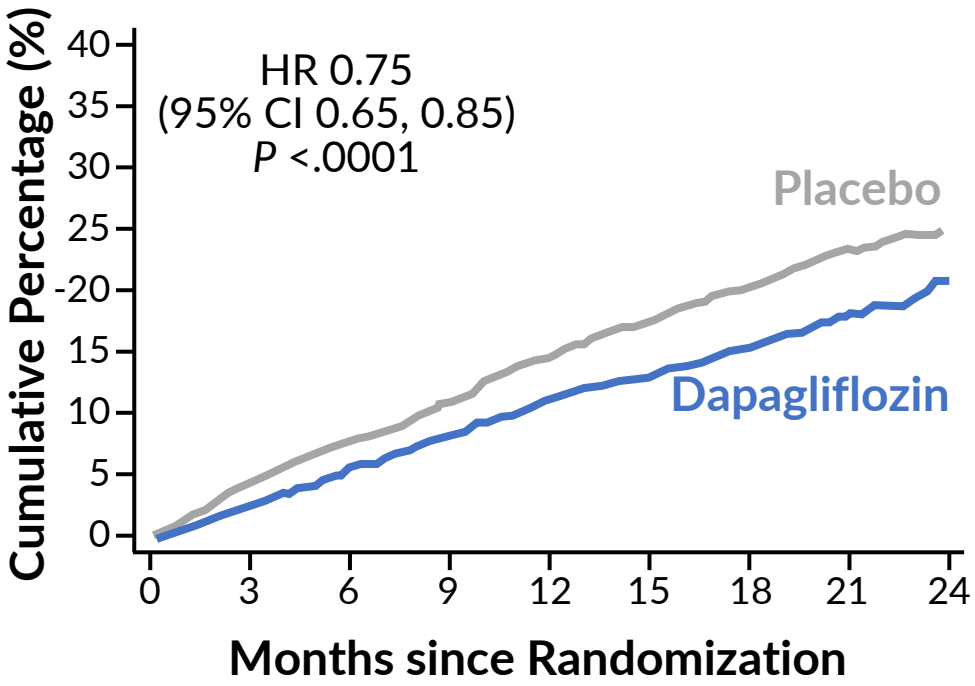
COR	LOE	Recommendations
2a	**B - R**	In patients with ***HFpEF***, **SGLT2i** can be beneficial in decreasing HF hospitalizations and cardiovascular mortality

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

SGLT2 Inhibitors in Patients with Chronic HFrEF

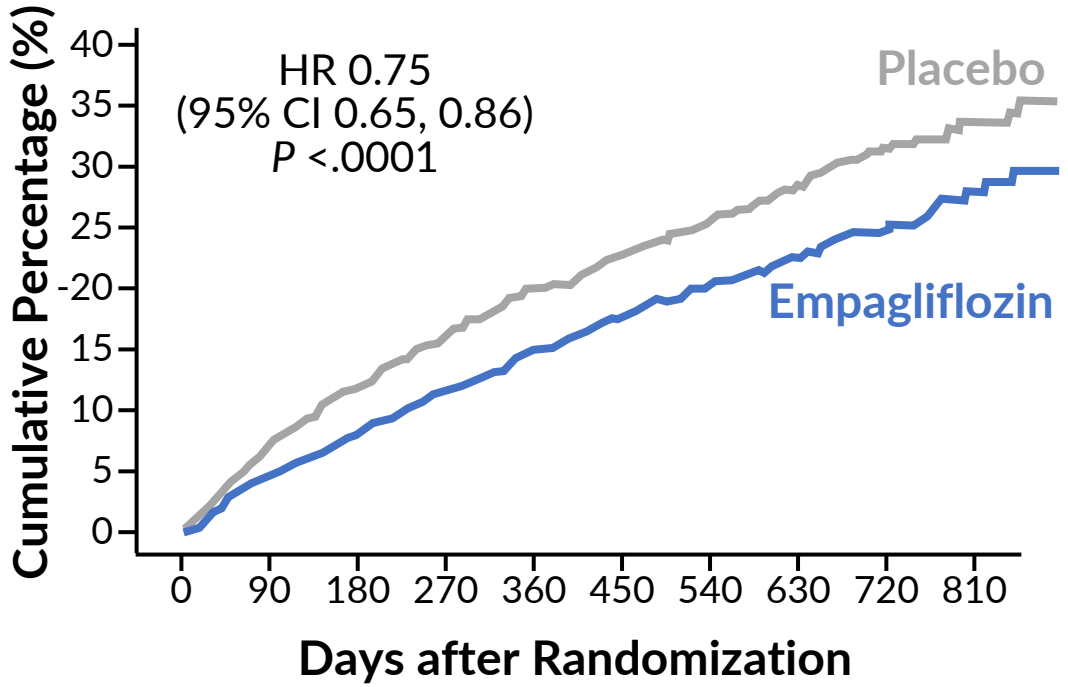
DAPA-HF

CV Death/ HF hospitalization



EMPEROR-Reduced

CV Death/ HF hospitalization



Outcomes similar with or without comorbid diabetes

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McMurray et al. *N Engl J Med*. 2019;381:1995-2008.

Packer M et al *N Engl J Med*. 2020;383(15):1413-1424.

SGLT2 Inhibitors in Patients with Chronic HFrEF

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Age — yr	66.2±11.0	66.5±10.8
Female sex — no. (%)	564 (23.8)	545 (23.0)
Body-mass index†	28.2±6.0	28.1±5.9
Race — no. (%)‡		
White	1662 (70.0)	1671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region — no. (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1094 (46.1)	1060 (44.7)
Asia–Pacific	543 (22.9)	553 (23.3)

McMurray et al. *N Engl J Med*. 2019;381:1995-2008.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Age — yr	67.2±10.8	66.5±11.2
Female sex — no. (%)	437 (23.5)	456 (24.4)
Race — no. (%)†		
White	1325 (71.1)	1304 (69.8)
Black	123 (6.6)	134 (7.2)
Asian	337 (18.1)	335 (17.9)
Other or missing	78 (4.2)	94 (5.0)
Region — no. (%)		
North America	212 (11.4)	213 (11.4)
Latin America	641 (34.4)	645 (34.5)
Europe	676 (36.3)	677 (36.3)
Asia	248 (13.3)	245 (13.1)
Other	86 (4.6)	87 (4.7)

Packer M et al *N Engl J Med*. 2020;383(15):1413-1424.

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Efficacy of Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in the Management of Left Ventricular Systolic Dysfunction According to Race, Gender, and Diabetic Status

A Meta-Analysis of Major Clinical Trials

Table 5. Effect of ACE Inhibitors on Mortality From Heart Failure in Black and White Patients

Study Name	Total N	White N	Non-White N	Black N	Non-Black N	RR White (95% CI)	RR Black (95% CI)	RRR (95% CI)
SAVE	2,231	1,993	238			0.84 (0.71–0.99)	0.78 (0.50–1.21)	1.08 (0.67–1.73)
SOLVD-Prevention	4,228	3,657	571	404	3,824	0.95 (0.81–1.12)	0.87 (0.60–1.25)	0.91 (0.61–1.36)
SOLVD-Treatment	2,569	2,061	508	396	2,173	0.89 (0.79–1.00)	0.93 (0.74–1.17)	1.04 (0.81–1.35)
Random effects pooled estimate		7,711	1,317	800	5,997	0.89 (0.82–0.97)	0.89 (0.74–1.06)	1.01 (0.83–1.24)

Table 8. Effect of Beta-Blockers on Mortality From Heart Failure in Black and White Patients

						RR Analysis		
Study Name	Total N	White N	Non-White N	Black N	Non-Black N	RR White (95% CI)	RR Black (95% CI)	RRR (95% CI)
COPERNICUS	2,287	2,069	218	121	2,166	0.66 (0.53–0.82)	0.62 (0.19–2.01)	0.94 (0.28–3.11)
MERIT-HF	3,991	3,755	236	207	3,784	0.67 (0.54–0.82)	0.79 (0.36–1.76)	1.19 (0.52–2.70)
U.S. Carvedilol HF	1,094			217	877	0.38 (0.20–0.70)	0.53 (0.19–1.48)	1.41 (0.43–4.68)
BEST	2,708			627	2,081	0.85 (0.74–0.96)	1.17 (0.94–1.47)	1.39 (1.07–1.79)
Random effects pooled estimate (with BEST)		5,824	454	1,172	8,908	0.69 (0.55–0.85)	0.97 (0.68–1.37)	1.35 (1.07–1.71)
Random effects pooled estimate (without BEST)		5,824	454	545	6,827	0.63 (0.52–0.77)	0.67 (0.38–1.16)	1.17 (0.65–2.11)

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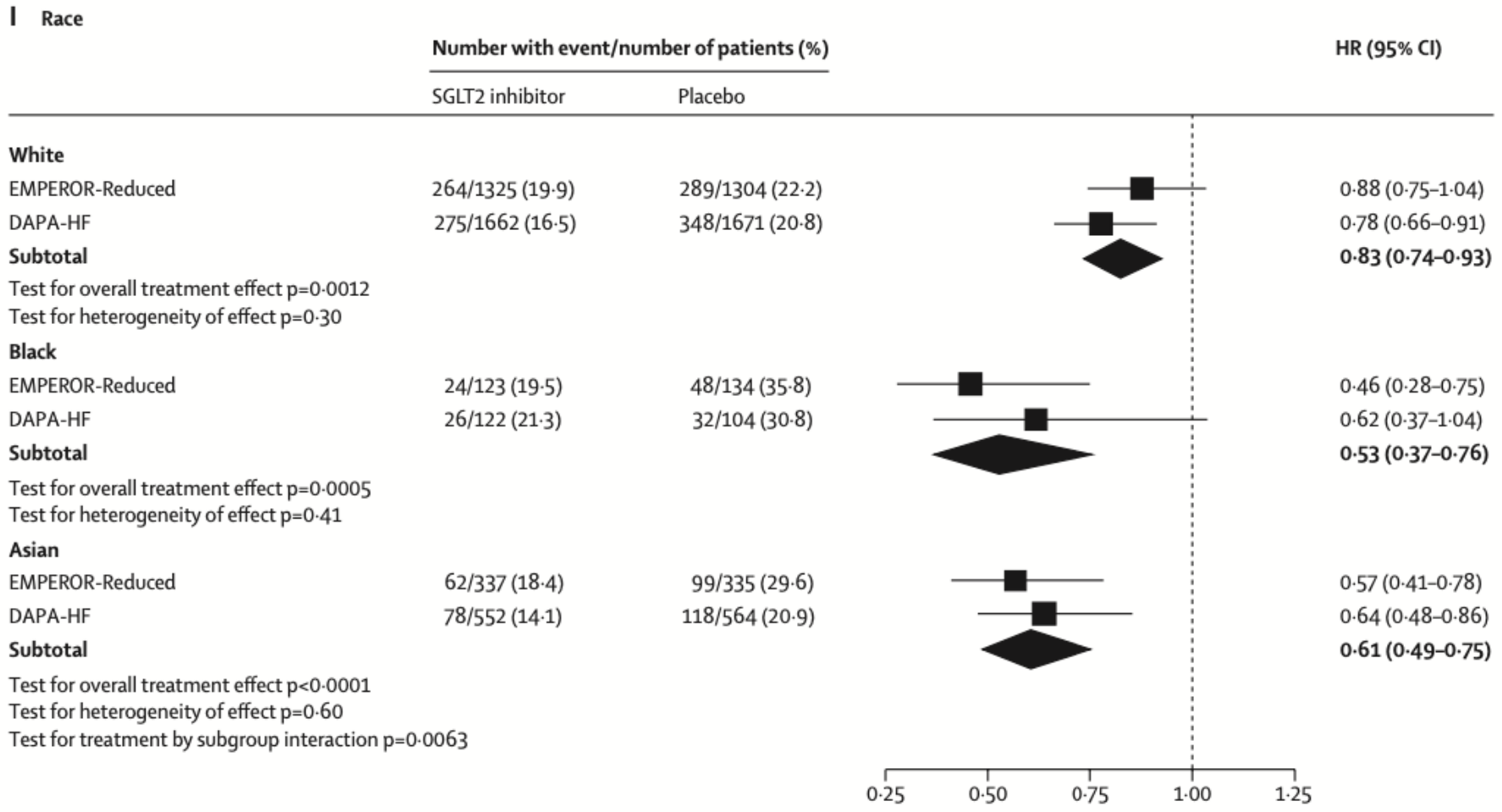
Shekelle PG et al. JACC 2003

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials



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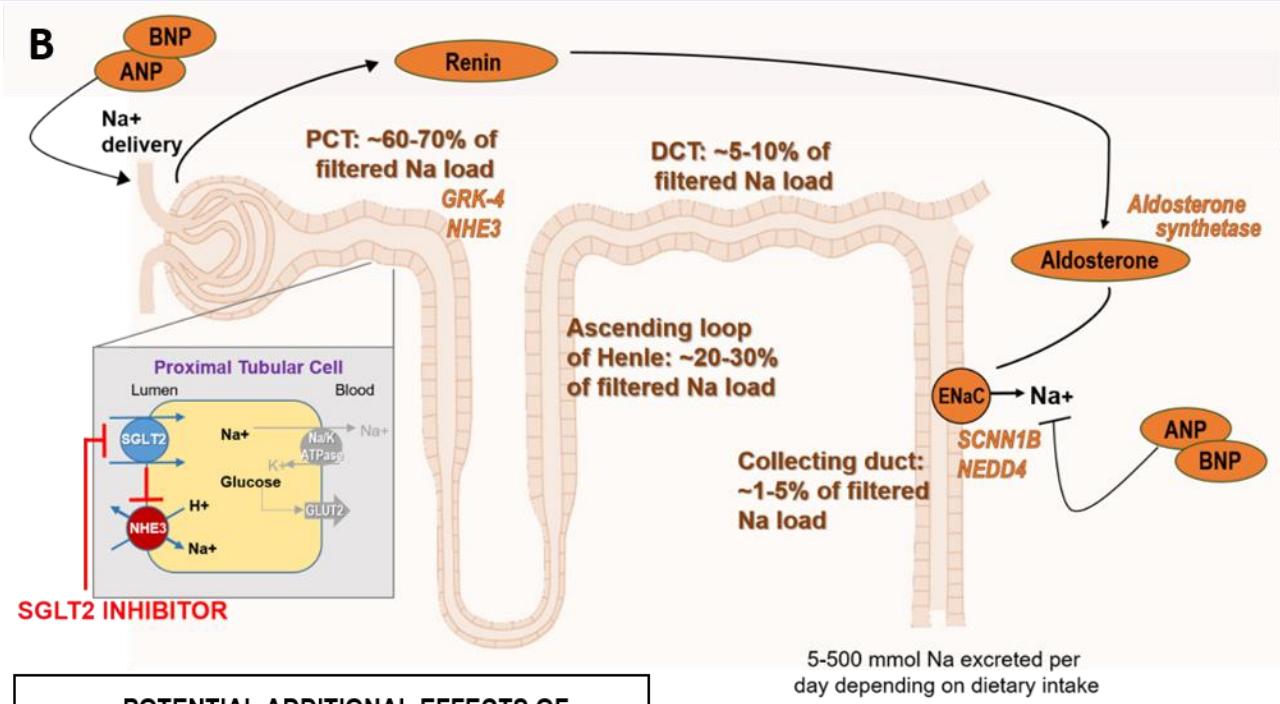
Zannad F et al. Lancet 2020;396:919-29

PERSPECTIVE

Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure

Racial Differences and a Potential for Reducing Disparities

Alanna A. Morris, MD, MSc; Jeffrey M. Testani, MD, MTR; Javed Butler, MD, MPH, MBA



POTENTIAL ADDITIONAL EFFECTS OF SGLT2 INHIBITION

- NHE3 activity → reduced Na reabsorption
- ? Direct/indirect effect on endothelial function
- Nitric oxide / Oxidative stress
- Markers of inflammation
- Increased sodium and chloride delivery to the macula densa can affect tubuloglomerular feedback and RAAS/SNS activity

POTENTIAL DISPARITIES THAT COULD LIMIT BENEFITS OF SGLT2 INHIBITION

- Differential Prescribing of GDMT
- Medical Inertia
- Financial Toxicity

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Morris AA, Testani J, Butler J. Circulation 2021;143(24):2329-2331

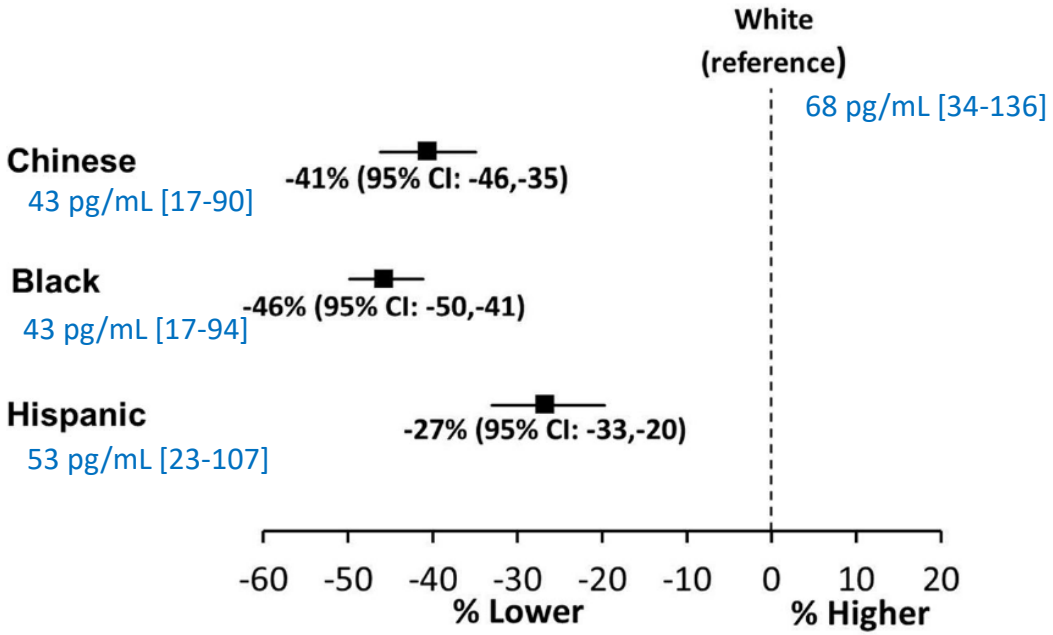
Relative Deficiency of Natriuretic Peptides in Black Individuals at Risk for HF

N=3,148 subjects from Dallas Heart Study (51% Black, 31% White, 18% Hispanic)

TABLE 2 Association Between Race/Ethnicity and Plasma NT-proBNP Levels in Multivariable Linear

Model	White	Black	p Value
Age, sex	Reference	-0.283 (-0.373 to -0.192)	<0.0001
Age, sex, HR, anti-HTN medication, SBP, DM, BMI, eGFR, microalbumin	Reference	-0.390 (-0.483 to -0.296)	<0.0001
Age, sex, HR, anti-HTN medication, SBP, DM, BMI, eGFR, microalbumin, education, income	Reference	-0.464 (-0.570 to -0.359)	<0.0001
Age, sex, HR, anti-HTN medication, SBP, DM, BMI, eGFR, microalbumin, education, income, LV mass index, LVEF	Reference	-0.492 (-0.608 to -0.376)	<0.0001
Age, sex, HR, anti-HTN medication, SBP, HOMA-IR, BMI, eGFR, microalbumin, education, income, LV mass index, LVEF	Reference	-0.502 (-0.624 to -0.380)	<0.0001

N=5,597 subjects from MESA (24% black, 40% white, 23% Hispanic, 13% Chinese)



P=0.0001 for race/ethnic difference in NT-proBNP

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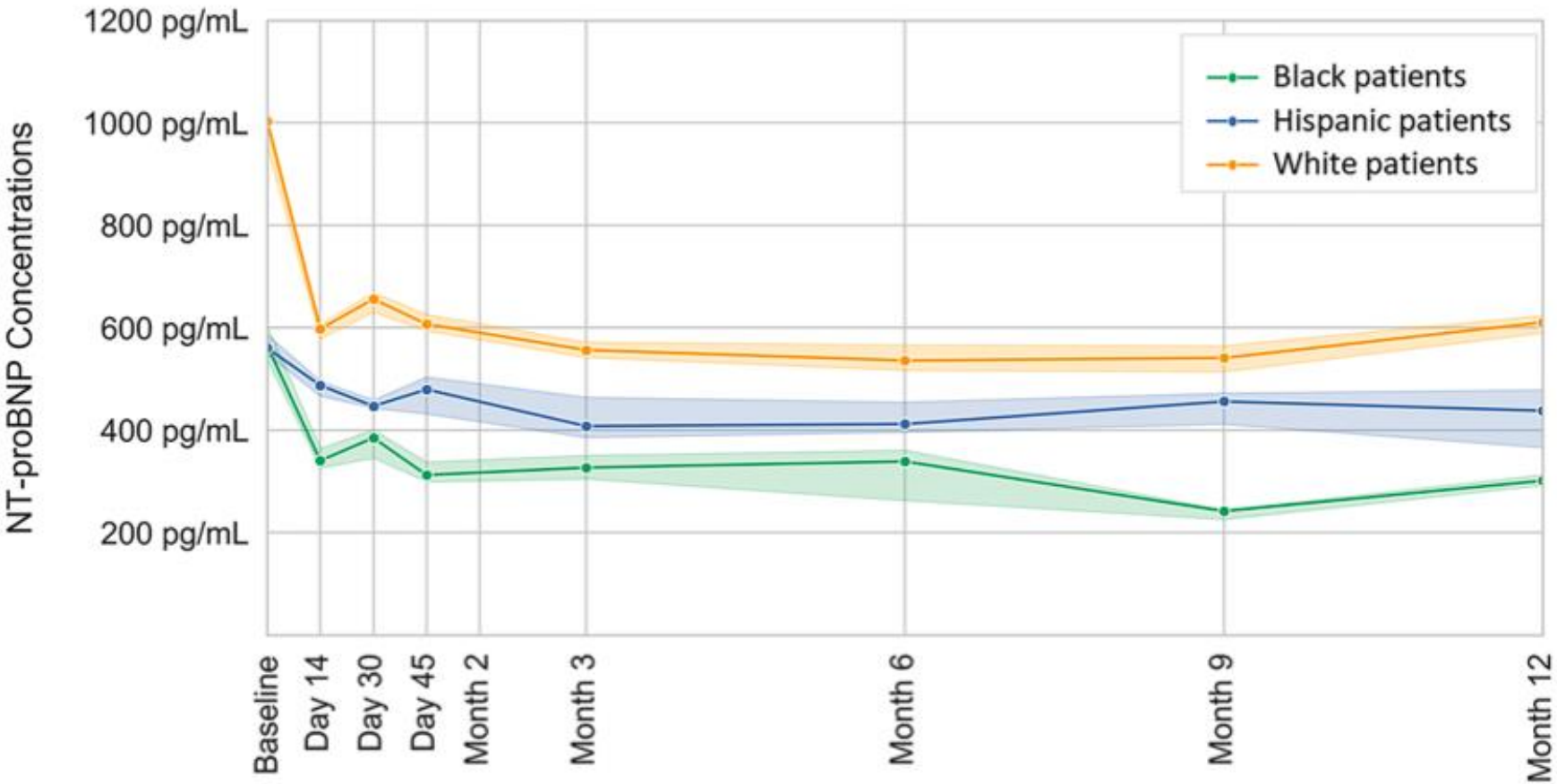
Relative deficiency of natriuretic peptides in Black patients with HF

N=782 subjects in PROVE-HF (mean age 68±13 years, 22% Black)



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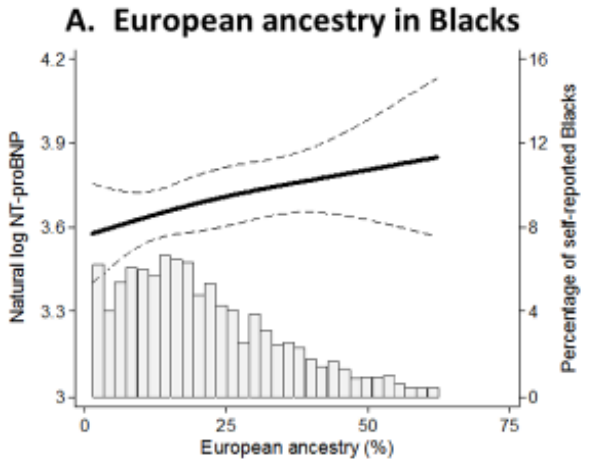
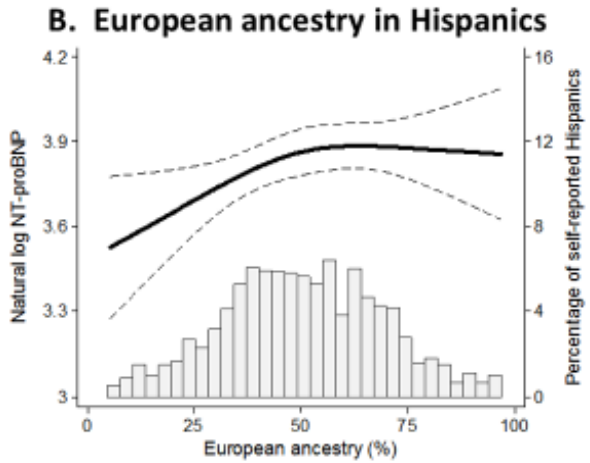
Ibrahim N et al. Circulation HF 2020

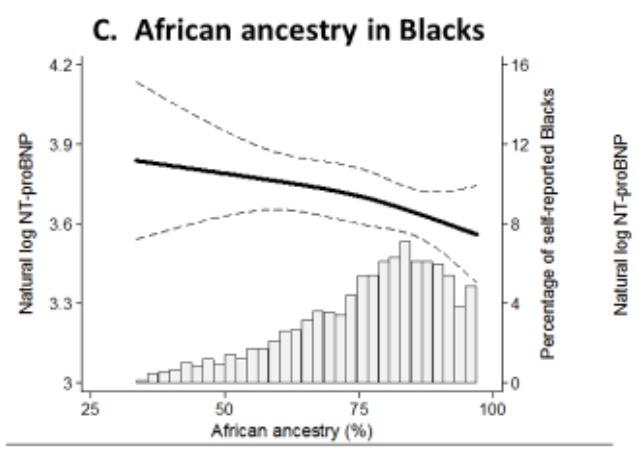
Relative Deficiency of Natriuretic Peptides in Black Individuals at Risk for HF



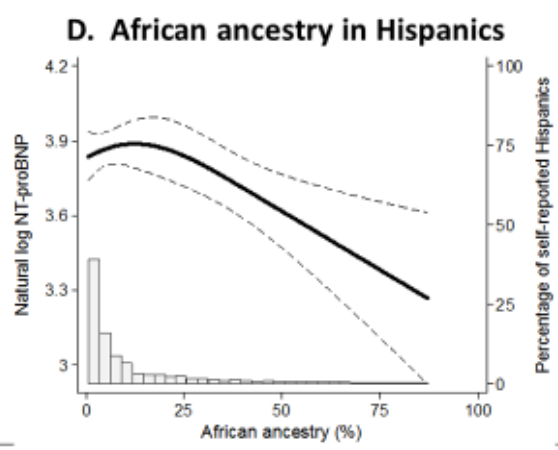
A 20% ⬆ in European ancestry
→ 12% ⬆ in NT-pro BNP



A 20% ⬆ in European ancestry
→ 7% ⬆ in NT-pro BNP



A 20% ⬆ in African ancestry
→ 10% ⬇ in NT-pro BNP



A 20% ⬆ in African ancestry
→ 10% ⬇ in NT-pro BNP

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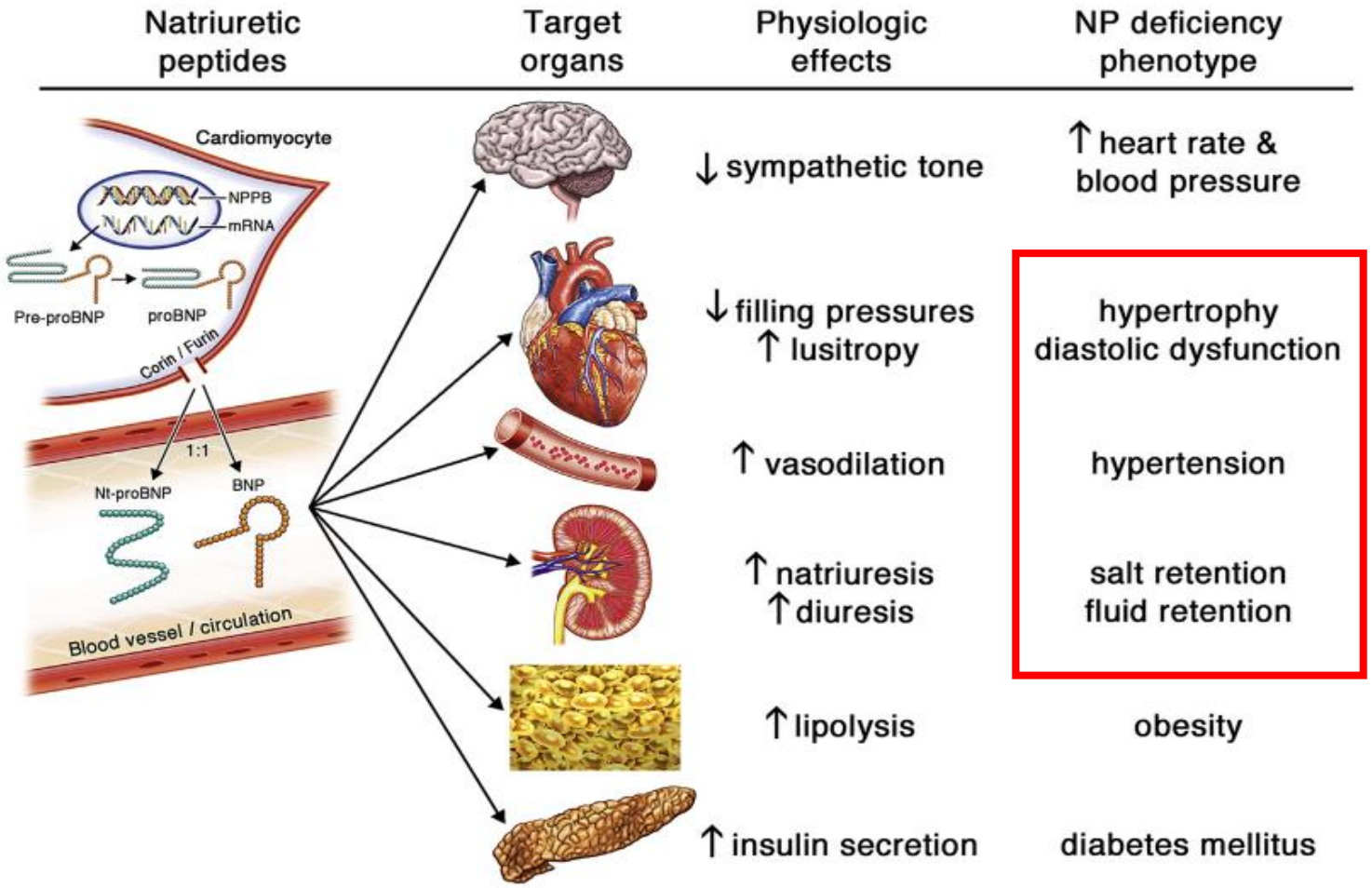
Gupta et al. Am J Cardiol 2017

Physiologic Consequences of Relative Natriuretic Peptide Deficiency



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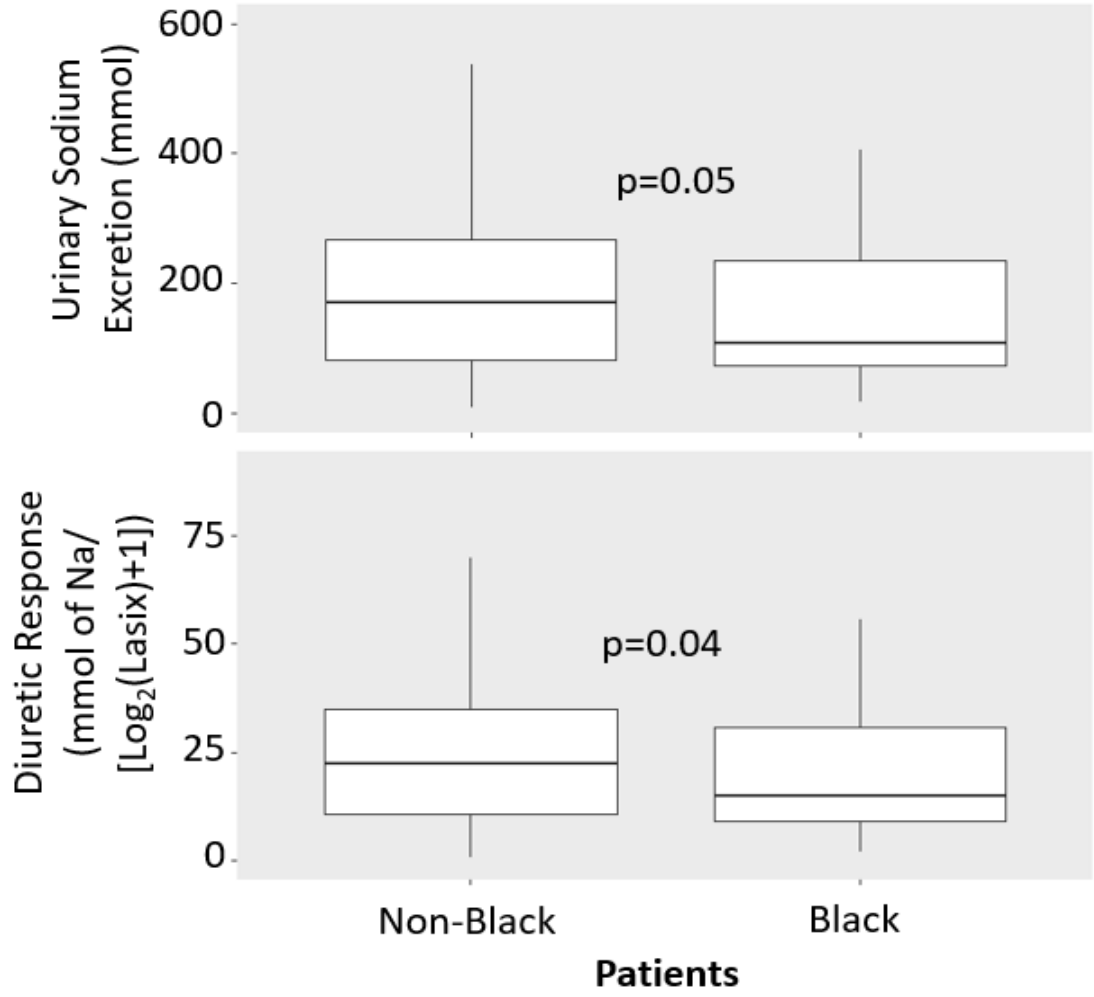
Gupta et al. JACC HF 2015

Physiologic Consequences of Relative Natriuretic Peptide Deficiency

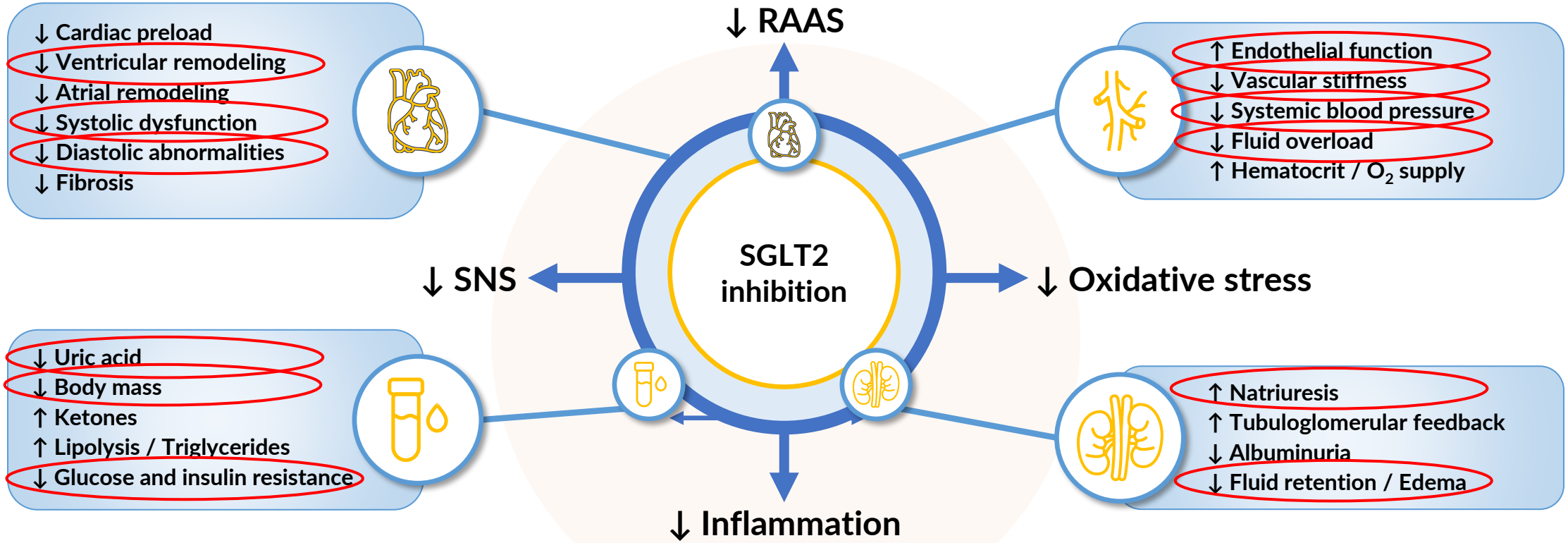
Post-Hoc Analysis of ROSE-AHF with EF ≤50%

	Black (n=50)	Non-Black (n=178)	P-value
Age (years)	**63.1 ± 12.3**	**70.6 ± 11.2**	**< 0.001**
Male	**32 (64%)**	**149 (83.7%)**	**0.004**
BMI (kg/m^2)	33.3 ± 8.9	31.7 ± 7.6	0.2
Diabetes	27 (54%)	100 (56.2%)	0.9
Heart Rate (BPM)	**82 ± 14.7**	**74 ± 12.4**	**< 0.001**
Systolic BP (mmHg)	119 ± 18	115 ± 17.7	0.1
LVEF (%)	**24.7 ±11.1**	**29.6 ± 11.4**	**0.01**
Ischemic Cardiomyopathy	**16 (32%)**	**125 (70.2%)**	**<0.001**
ACE-I/ARB	32 (64%)	89 (50%)	0.1
Beta Blocker	42 (84%)	155 (87.1%)	0.7
Aldosterone Antagonist	16 (32%)	54 (30.3%)	0.9
eGFR (mL/min/1.73 m^2)*	40.8 ± 11.1	41.4 ± 14.5	0.7
NT-proBNP	5960 [3670 – 9720]	6550 [3200 – 11400]	0.7

Data are mean ± SD, median [interquartile range], or N (%).



Direct and Indirect Actions of SGLT2 Inhibitors



ATP, adenosine triphosphate; CRM, cardiovascular, renal and metabolic; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

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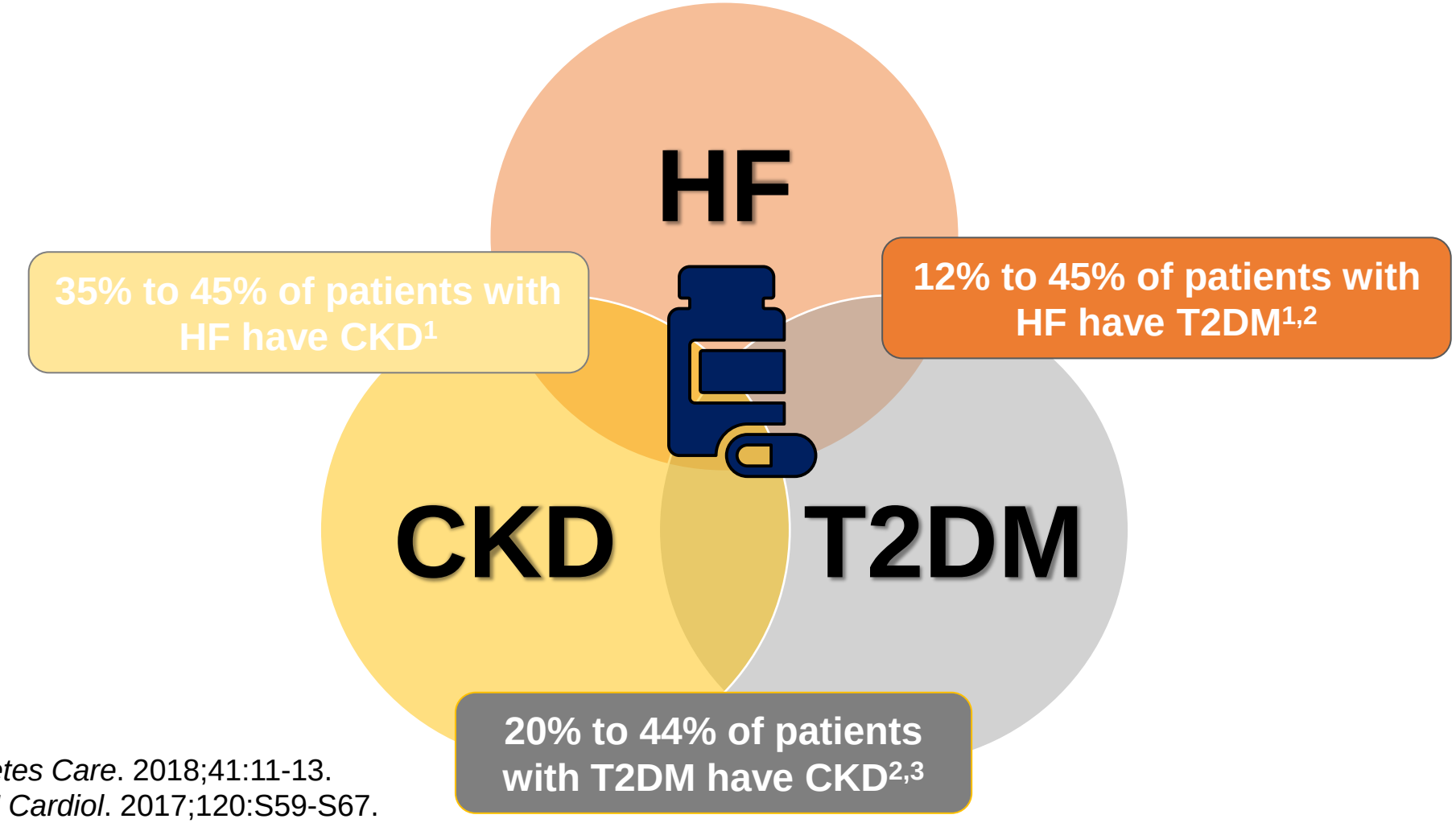
SGLT2i = Foundational Cardio-Renal-Metabolic Therapy



1. Packer M. *Diabetes Care*. 2018;41:11-13.
2. Wanner C. *Am J Cardiol*. 2017;120:S59-S67.
3. https://www.cdc.gov/nchs/data/databriefs/db319.pdf. Accessed November 7, 2019.
4. Wang T et al. *Diabetes Metab Syndr*. 2019;13:612-615.

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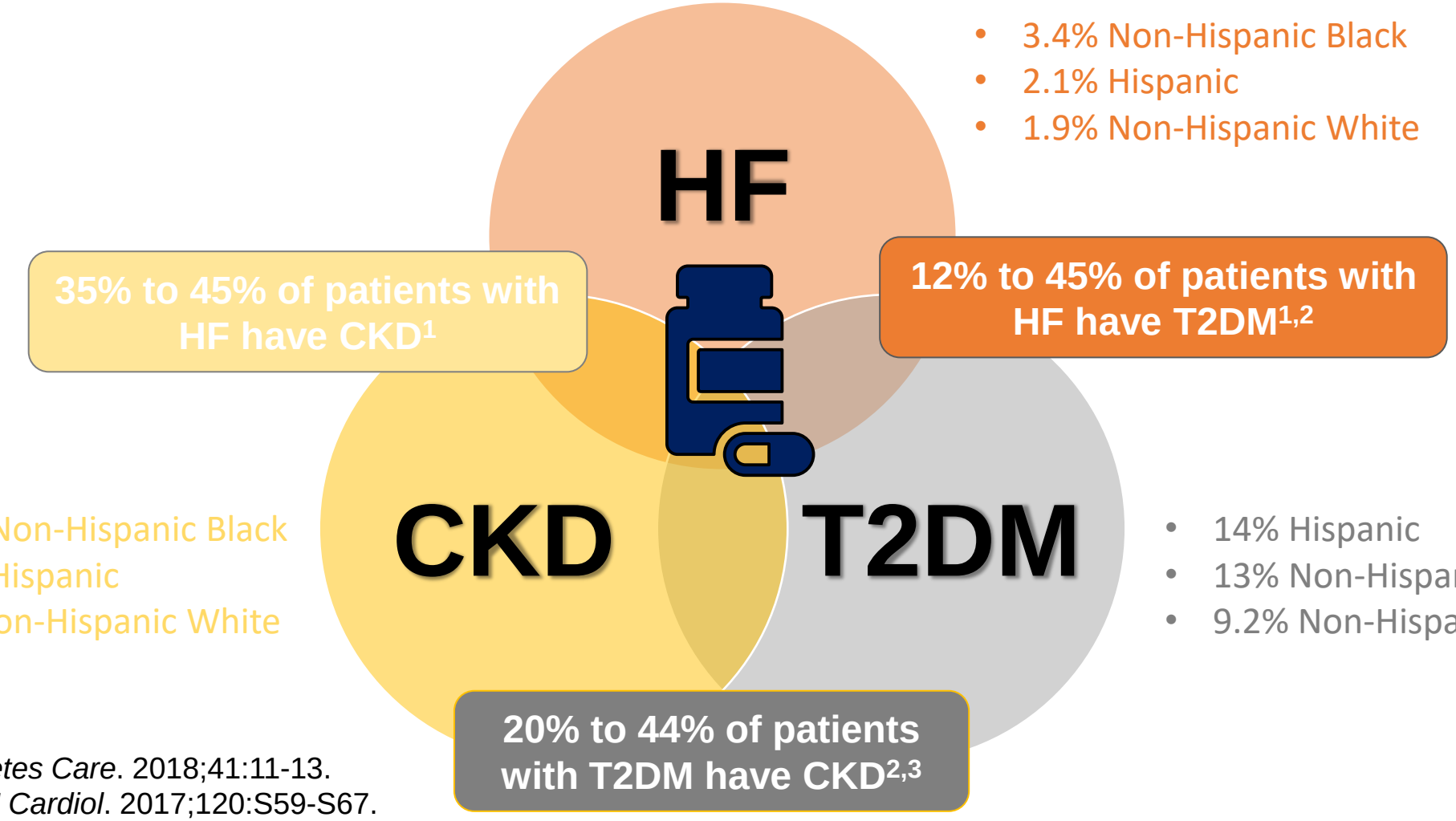
Slide courtesy of Muthu Vaduganathan MD

SGLT2i = Foundational Cardio-Renal-Metabolic Therapy



- 3.4% Non-Hispanic Black
- 2.1% Hispanic
- 1.9% Non-Hispanic White

- 12.4% Non-Hispanic Black
- 10.2% Hispanic
- 9.4% Non-Hispanic White

- 14% Hispanic
- 13% Non-Hispanic Black
- 9.2% Non-Hispanic White

1. Packer M. *Diabetes Care*. 2018;41:11-13.
2. Wanner C. *Am J Cardiol*. 2017;120:S59-S67.
3. https://www.cdc.gov/nchs/data/databriefs/db319.pdf. Accessed November 7, 2019.
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Slide courtesy of Muthu Vaduganathan MD

Pharmacoequity: A Policy Prescription for Reducing Health Disparities

Black & Hispanic Individuals Report: ↑ Highest Rates of Medication Cost-Related Delays ↓ Lower Access to High Quality Medication

$370 Billion
on retail prescriptions

$1,100
out-of-pocket costs

29 Million
uninsured Americans

Enhancing Access to Medications

- Adopt Universal, Low-Cost Prescription Drug Coverage
- Increase Access to Pharmacies
- Address Differential Prescribing Practices
- Increase Underrepresented Groups in Clinical Trials

Reducing Cost of Medications

- Reduce High Drug Prices
- Improve Medicare Part D Drug Benefits
- Reduce Out-of-Pocket Spending for Commercially Insured
- Equity Impact Analysis on Novel Therapies

Improving Quality of Medications

- Quality Improvement Programs Prioritize Pharmacoequity
- Systematically Identify Prescribing Inequities
- Track & Report Improvements in Prescribing Equity
- Share Best Practices

Ensuring that all individuals, regardless of race, ethnicity, socioeconomic status, or availability of resources, have access to the highest quality medications required to manage their health is "pharmacoequity".

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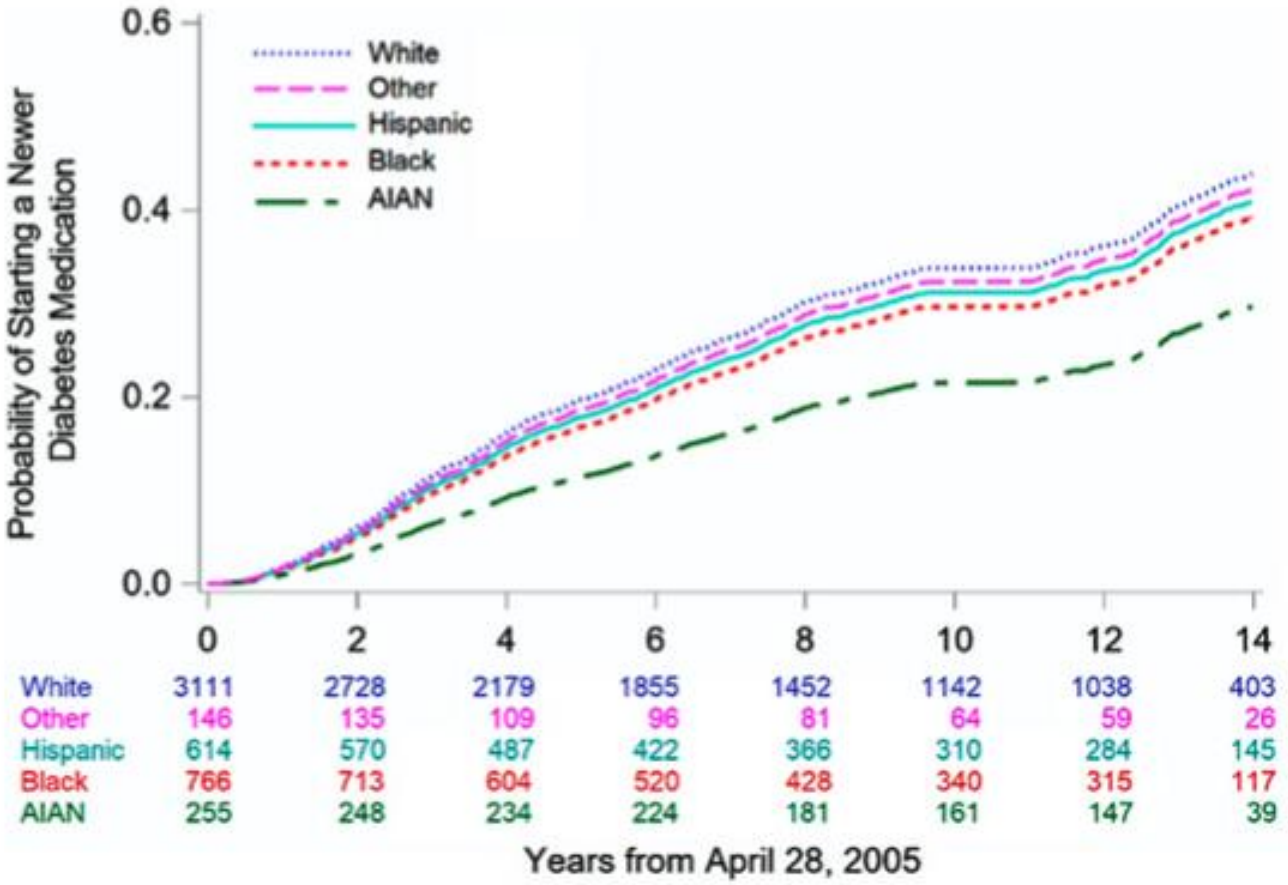
Department of Medicine

Essien U, Dusetzina S, Gellad WF. JAMA 2021

Disparities in Prescriptions of SGLT2i by Race and Ethnicity



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Elhussein et al. Lancet Reg Health Am. 2022

Disparities in Prescriptions of SGLT2i by Race and Ethnicity

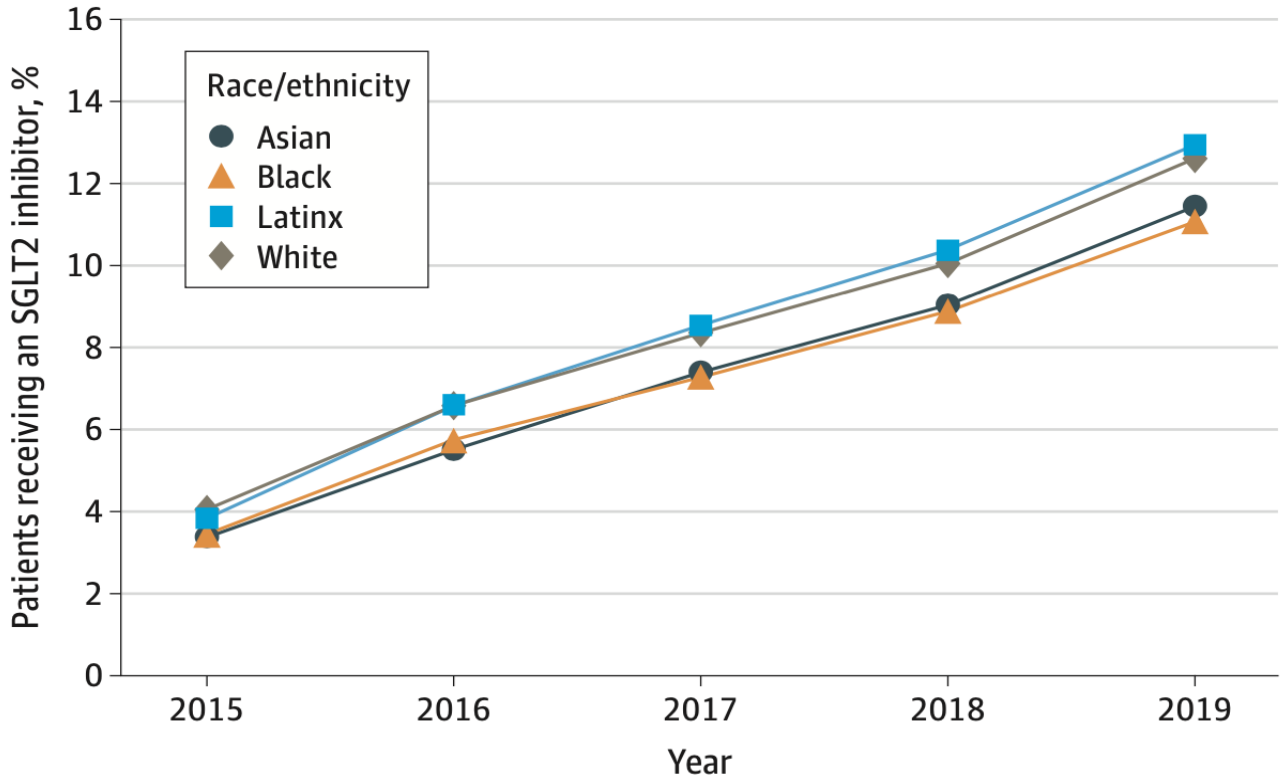
Use of newer diabetes medication classes during the study period, overall and by race/ethnicity.

Medication class	Overall (*N* = 4892)	White (*N* = 3111)	Black (*N* = 766)	Hispanic (*N* = 614)	AI/AN* (*N* = 255)
First newer diabetes medication class used					
GLP-1 receptor agonist (%)	976 (20.0)	724 (23.3)	120 (15.7)	97 (15.8)	13 (5.1)
DPP-4 inhibitor (%)	1154 (23.6)	712 (22.9)	206 (26.9)	157 (25.6)	42 (16.5)
SGLT-2 inhibitor (%)	81 (1.7)	56 (1.8)	12 (1.6)	12 (2.0)	0 (0.0)
Any use of diabetes medication class during the study period					
GLP-1 receptor agonist (%)	1215 (24.8)	886 (28.5)	152 (19.8)	131 (21.3)	15 (5.9)
DPP-4 inhibitor (%)	1384 (28.3)	878 (28.2)	239 (31.2)	181 (29.5)	44 (17.3)
SGLT-2 inhibitor (%)	309 (6.3)	219 (7.0)	36 (4.7)	40 (6.5)	3 (1.2)

Elhussein et al. Lancet Reg Health Am. 2022

Disparities in Prescriptions of SGLT2i by Race and Ethnicity

Figure 3. Rates of Treatment With Sodium-Glucose Cotransporter 2 Inhibitor by Race/Ethnicity in the Cohort Over Time



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Disparities in Prescriptions of SGLT2i by Race and Ethnicity

Table 2. Factors Associated With SGLT2 Inhibitor Use Among All Patients in the Multivariable Analysis

Characteristic	Adjusted OR (95% CI)	*P* value
Age	0.98 (0.97-0.98)	<.001
Female	0.84 (0.82-0.85)	<.001
Race/ethnicity		
White	1 [Reference]	NA
Asian	0.94 (0.90-0.98)	.002
Black	0.83 (0.81-0.85)	<.001
Latinx	1.03 (1.01-1.06)	.009
Region of residence		
West	1 [Reference]	NA
Midwest	1.06 (1.03-1.09)	<.001
Northeast	0.93 (0.90-0.97)	<.001
South	1.33 (1.29-1.36)	<.001
Zip code–linked household median income, $		
<500 000	1 [Reference]	NA
≥100 000	1.08 (1.05-1.10)	<.001
50 000-99 999	1.05 (1.03-1.07)	<.001
Commercial insurance	2.17 (2.12-2.22)	<.001
Medicare Advantage	1 [Reference]	NA
Comorbidities		
Dyslipidemia	1.61 (1.56-1.65)	<.001
Myocardial infarction	1.00 (0.97-1.04)	.84
Cerebrovascular disease	0.98 (0.95-1.00)	.09
Chronic kidney disease	1.03 (0.99-1.07)	.14
Obesity	1.33 (1.30-1.36)	<.001
Hypertension	1.49 (1.45-1.53)	<.001
Peripheral vascular disease	1.04 (1.01-1.07)	.03
HFrEF	0.85 (0.79-0.91)	<.001
HFpEF	0.83 (0.77-0.89)	<.001
No. of Elixhauser comorbidities	0.90 (0.89-0.90)	<.001
Visits to an endocrinology specialist, No. per 12 mo		
0	1 [Reference]	NA
1	2.06 (1.99-2.12)	<.001
>1	2.84 (2.76-2.92)	<.001
Visits to a cardiology visits, No. per 12 mo		
0	1 [Reference]	NA
1	1.19 (1.16-1.22)	<.001
>1	1.15 (1.12-1.18)	<.001
Metformin use	1.55 (1.52-1.58)	<.001
Insulin use	1.57 (1.53-1.60)	<.001

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Conclusions

- Black patients have a high prevalence of HF, diabetes, and chronic kidney disease, and a high risk of adverse outcomes. Thus, the potential therapeutic benefit of SGLT2i in this population is very high
- Despite this, recent data confirm that Black patients are less likely than other race-ethnic groups to be prescribed SGLT2i
- Much work remains to achieve health equity in HF – achieving pharmacequity is one mechanism to reduce healthcare disparities