

Heart-Failure and Diabetes Mellitus

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DISCLOSURE

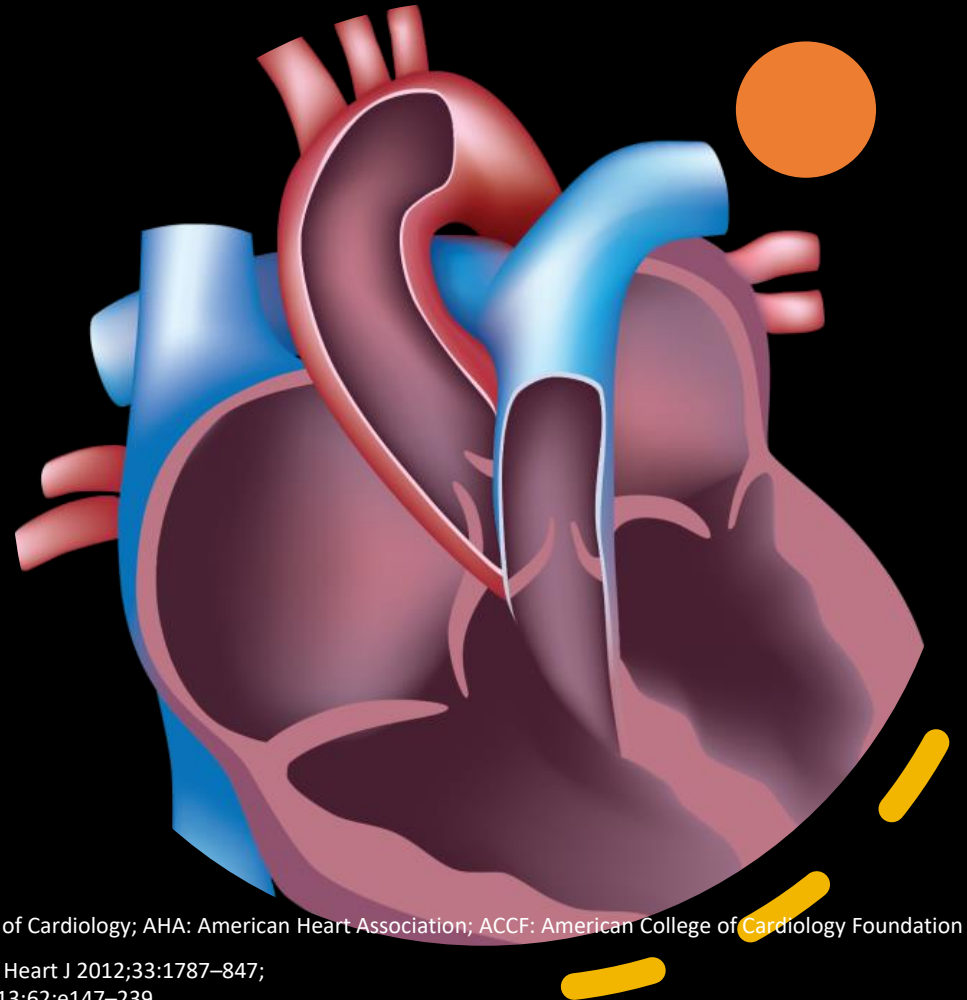
- VA EMPLOYEE

OBJECTIVES

- Heart Failure definition
- HF staging and classification
- Medical Therapy in HF
- NEW guidelines for treatment
- SGLT2i mechanism of action

HEART FAILURE DEFINITION

- **ESC 2012:** Heart failure (HF) is an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues¹
- **ACCF/AHA 2013:** HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood²



ESC: European Society of Cardiology; AHA: American Heart Association; ACCF: American College of Cardiology Foundation

1. McMurray et al. Eur Heart J 2012;33:1787–847;

2. Yancy et al. JACC 2013;62:e147–239

STAGES OF HF

ACCF/AHA Stages of HF (38)

- A At high risk for HF but without structural heart disease or symptoms of HF
 - B Structural heart disease but without signs or symptoms of HF
 - C Structural heart disease with prior or current symptoms of HF
 - D Refractory HF requiring specialized interventions
-

FUNCTIONAL CLASSIFICATION

NYHA Functional Classification (46)

None

- I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
- III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
- IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

Types of Heart Failure

Systolic Dysfunction

- Coronary Artery Disease
- Dilated cardiomyopathy (DCM)
 - 50% idiopathic (at least 25% familial)
 - 9 % myocarditis (viral)
 - Ischemic heart disease, peripartum, hypertension, HIV, connective tissue disease, substance abuse, doxorubicin
- Hypertension
- Valvular Heart Disease

Diastolic Dysfunction

- Hypertension
- Coronary artery disease
- Hypertrophic obstructive cardiomyopathy (HCM)
- Restrictive cardiomyopathy

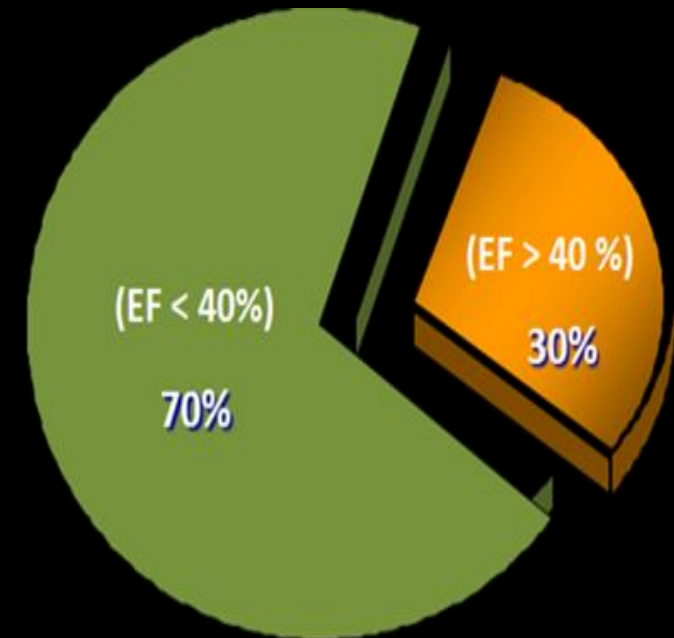


Table 3. Definitions of HFrEF and HFpEF

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HFrEF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HFpEF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HFpEF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF.
b. HFpEF, improved	>40	It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

EF indicates ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

Relationship of Hemoglobin A1C and Mortality in Heart Failure Patients With Diabetes

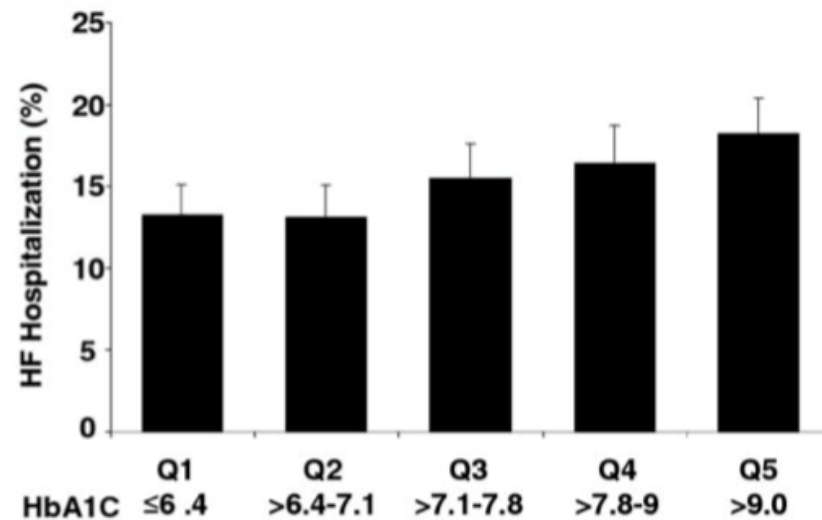


Figure 2

Proportion of Patients With HF Hospitalization at 2-Year Follow-Up by Quintiles

The graph represents the proportion of patients with heart failure (HF) hospitalization at 2-year follow-up by quintiles. Global chi-square $p = 0.002$. **Error bars** indicate the 95% confidence intervals. Abbreviations as in [Figure 1](#).

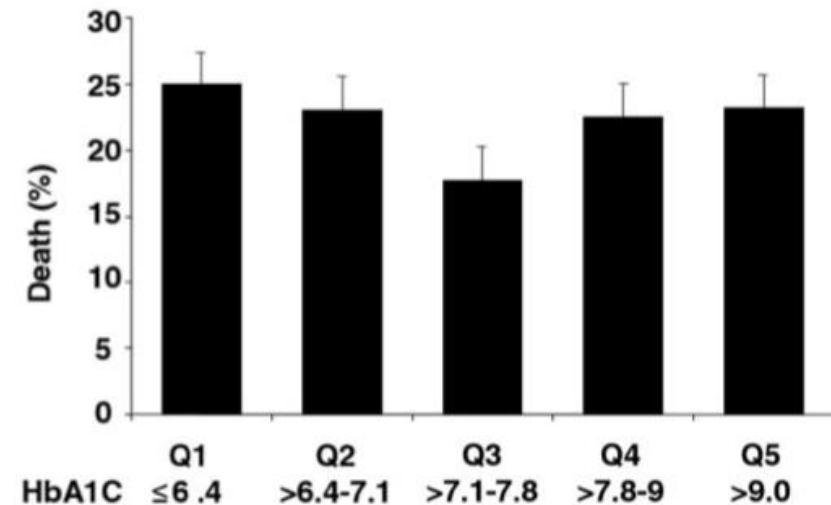


Figure 1

Proportion of Patients Who Died at 2-Year Follow-Up by Quintiles of HbA1C

The graph represents the proportion of patients who died at 2-year follow-up by quintiles (Q) of glycosylated hemoglobin (HbA1C). Global chi-square $p = 0.001$. **Error bars** indicate the 95% confidence intervals.

TABLE 1 Pathophysiological Mechanisms That Contribute to the Development of Heart Failure in Patients With Type 2 Diabetes Mellitus

Altered myocardial substrate metabolism

Mitochondrial bioenergetics

Oxidative stress

Lipotoxicity

Inflammation

Endoplasmic reticulum stress

Insulin signaling

Beta-2 adrenergic receptor signaling

G protein-coupled receptor kinase 2 signaling

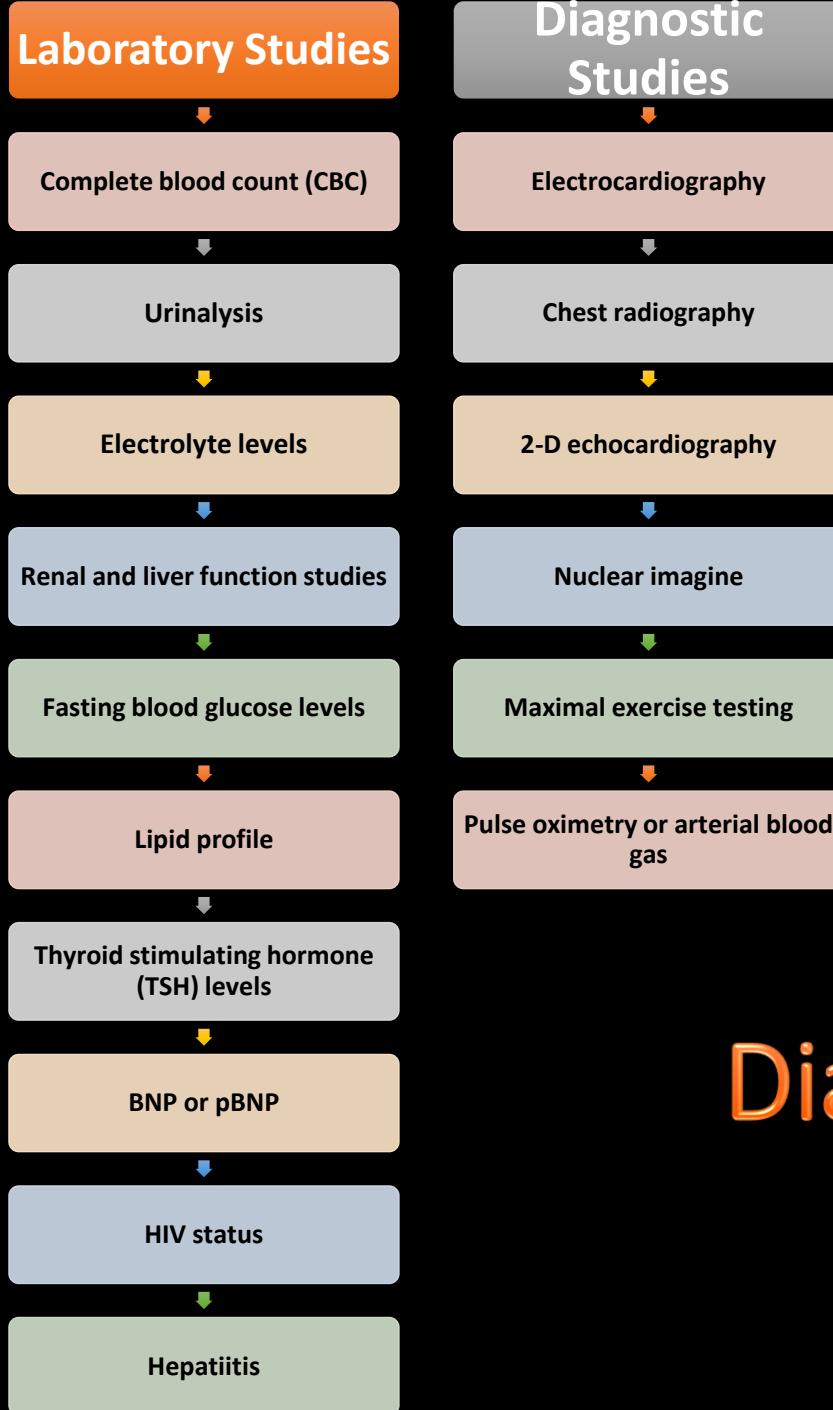
Renin angiotensin aldosterone signaling

Autophagy

Advanced glycation end products

Modified with permission from Kenny and Abel (26).

Diabetic Cardiomyopathy

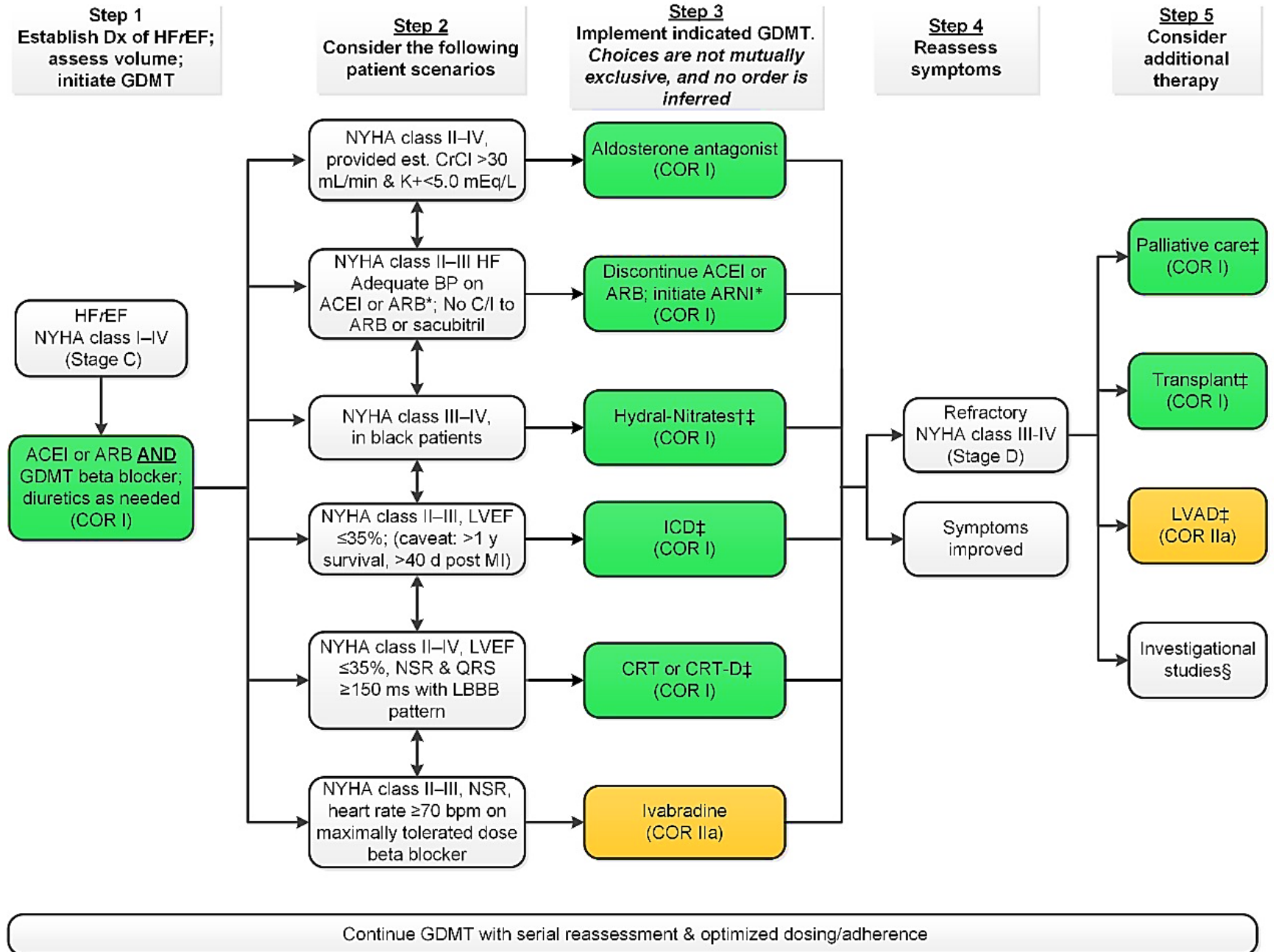


Diagnostic Studies

J Am Coll Cardiol. Apr 14 2009;53(15):e1-e90.

J Card Fail. Jun 2010;16(6):e1-194.

TREATMENT





Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,^{1,2} David A. D'Alessio,³
Judith Fradkin,⁴ Walter N. Kernan,⁵
Chantal Mathieu,⁶ Geltrude Mingrone,^{7,8}
Peter Rossing,^{9,10} Apostolos Tsapas,¹¹
Deborah J. Wexler,^{12,13} and John B. Buse¹⁴

Diabetes Care 2018;41:2669–2701 | <https://doi.org/10.2337/dci18-0033>

- Medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended.
- CKD or clinical HF and atherosclerotic cardiovascular disease, an **SGLT2 inhibitor** with proven benefit is recommended. **GLP-1 receptor** agonists are generally recommended as the first injectable medication.

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

TO AVOID
CLINICAL INERTIA
REASSESS AND
MODIFY TREATMENT
REGULARLY
(3–6 MONTHS)

ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

**EITHER/
OR**

GLP-1 RA
with proven
CVD benefit¹

SGLT2i with
proven CVD
benefit¹,
if eGFR
adequate²

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

If HbA_{1c} above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶

NO

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i²

TZD

If HbA_{1c} above target

If HbA_{1c} above target

If HbA_{1c} above target

If HbA_{1c} above target

SGLT2i²
OR
TZD

SGLT2i²
OR
TZD

GLP-1 RA
OR
DPP-4i
OR
TZD

SGLT2i²
OR
DPP-4i
OR
GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU⁶ **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

**EITHER/
OR**

GLP-1 RA with
good efficacy
for weight loss⁸

SGLT2i²

If HbA_{1c} above target

SGLT2i²

GLP-1 RA with
good efficacy
for weight loss⁸

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA)
based on weight neutrality

COST IS A MAJOR ISSUE⁹⁻¹⁰

SU⁶

TZD¹⁰

If HbA_{1c} above target

TZD¹⁰

SU⁶

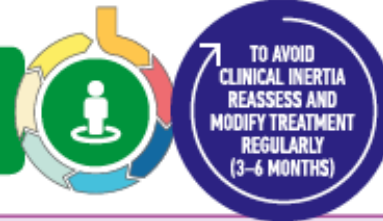
If HbA_{1c} above target

- Insulin therapy basal insulin with lowest acquisition cost
- OR**
- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost¹⁰

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use principles in Figure 1



Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit¹ (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit¹ (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates



GLP-1 RA with proven CVD benefit¹

**EITHER/
OR**

SGLT2i with proven CVD benefit¹, if eGFR adequate²

HF or CKD predominates



PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit^{1,4}

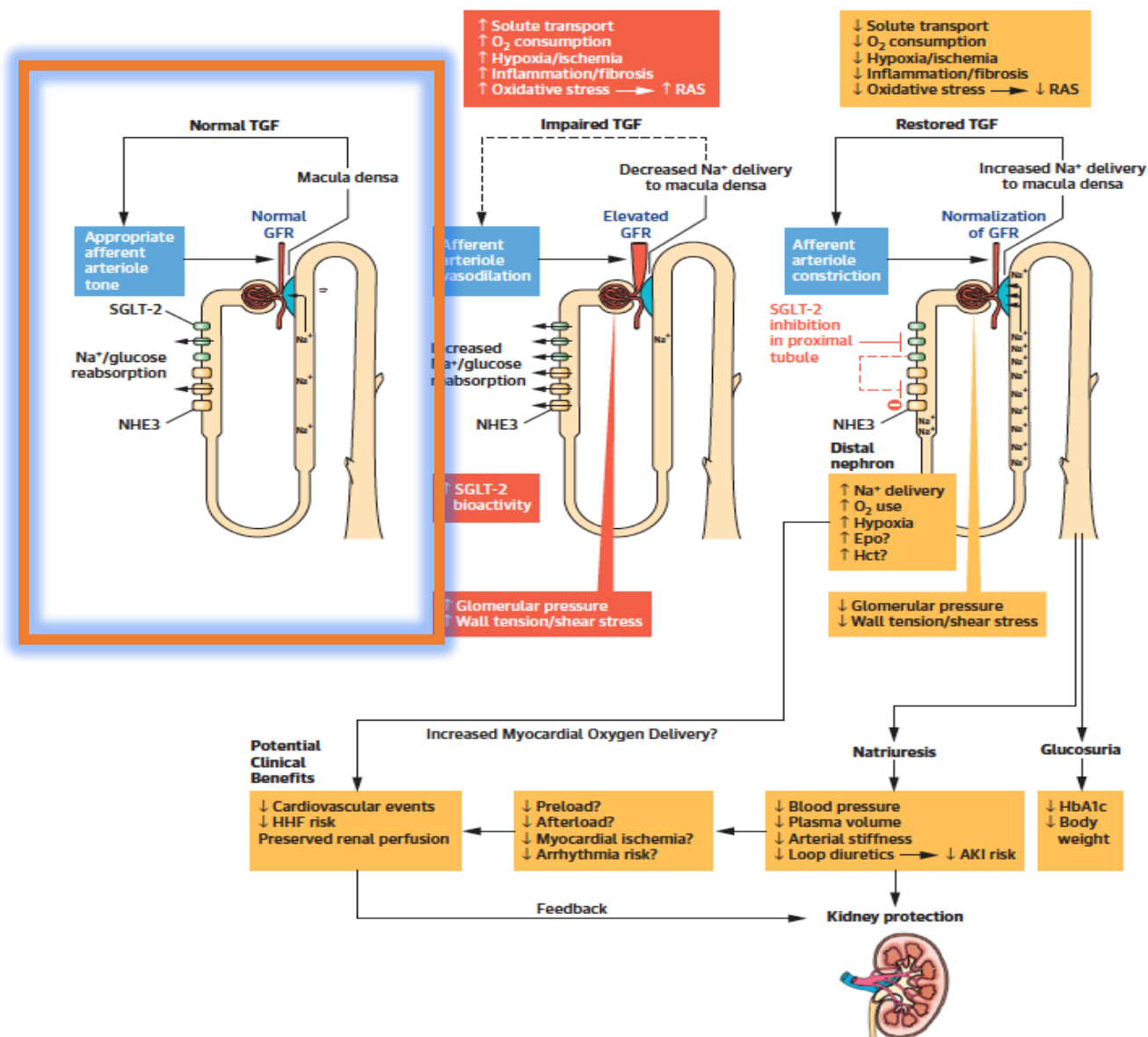


SGLT2 INHIBITORS

JACC VOL. 74,
NO. 20, 2019
Cherney et al.

NOVEMBER 19,
2019: 2511-24

FIGURE 1 Selected Physiological Mechanisms Associated With Cardiovascular and Renal Protection With SGLT2 Inhibitors

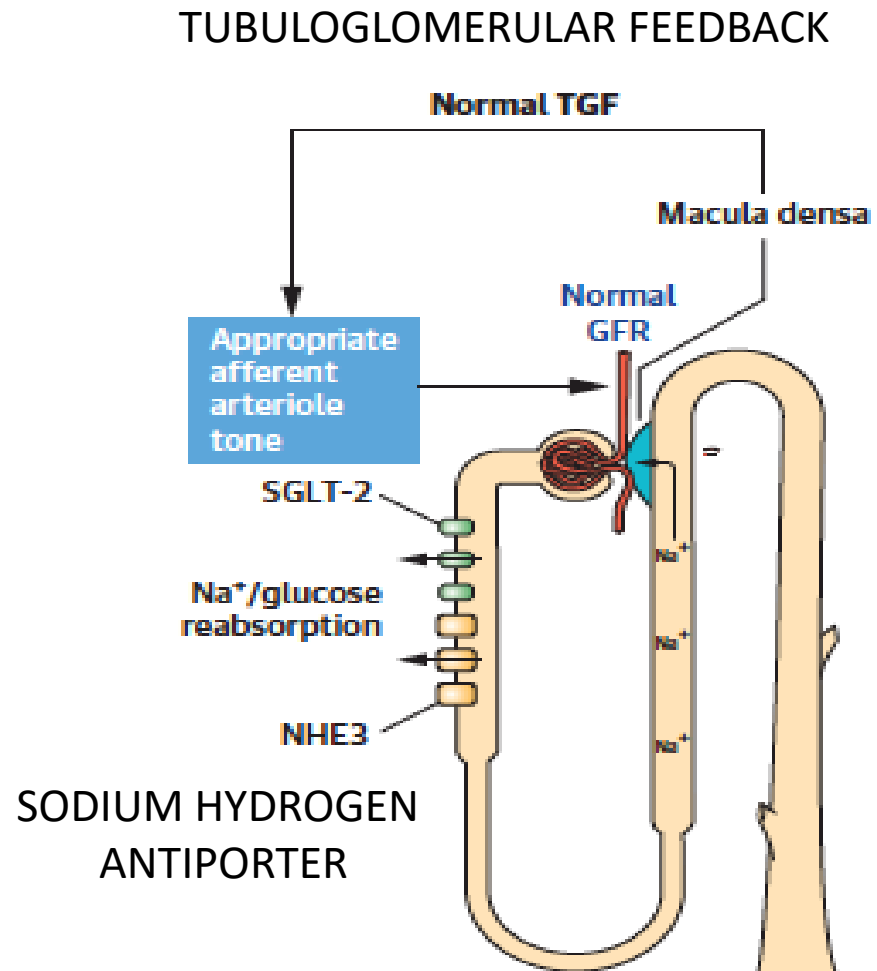


Physiological changes that occur in the setting of SGLT2 inhibitors, as well as their potential contribution to cardiovascular and renal protection, are depicted. **Red boxes** represent aberrant changes, whereas **yellow boxes** represent protective changes. **Small red circle with a white line** represent inhibition of function. AKI = acute kidney injury; Epo = erythropoietin; GFR = glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; Hct = hematocrit; HHF = hospitalization for heart failure; GFR = glomerular filtration rate; Na⁺ = sodium; NHE3 = sodium-hydrogen antiporter 3; O₂ = oxygen; SGLT2 = sodium-glucose cotransporter-2; TGF = tubuloglomerular feedback; RAS = renin-angiotensin system.

JACC VOL. 74,
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FIGURE 1 Selected Physiological Mechanisms Associ

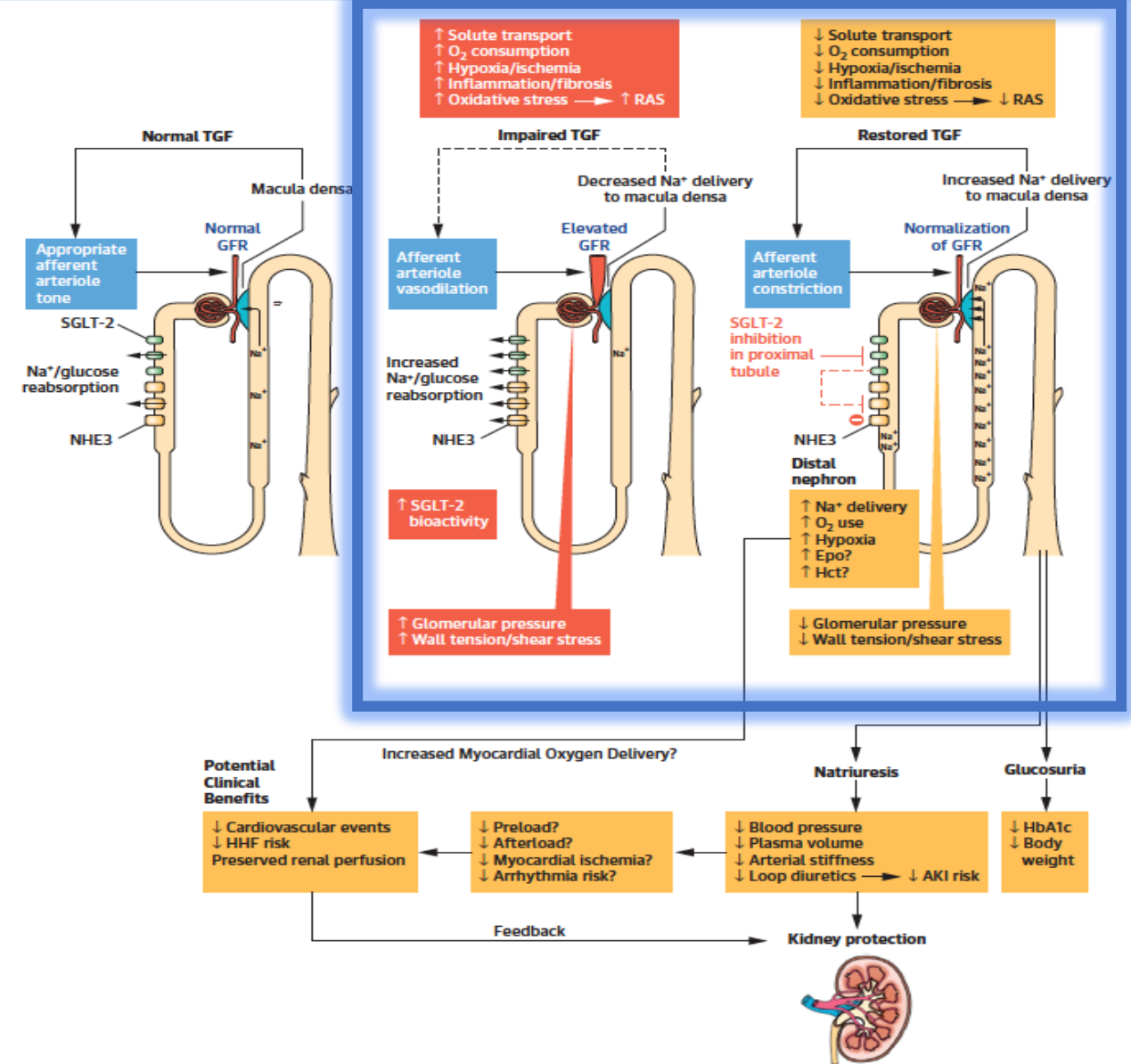


- 1) 180g glucose filter and reabsorbed per day
- 2) Threshold 200mg/dl
- 3) SGLT2 --90%

JACC VOL. 74,
NO. 20, 2019
Cherney et al.

NOVEMBER 19,
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FIGURE 1 Selected Physiological Mechanisms Associated With Cardiovascular and Renal Protection With SGLT2 Inhibitors



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ated With Cardiovascular and Renal Protection With SGLT2 Inhibitors

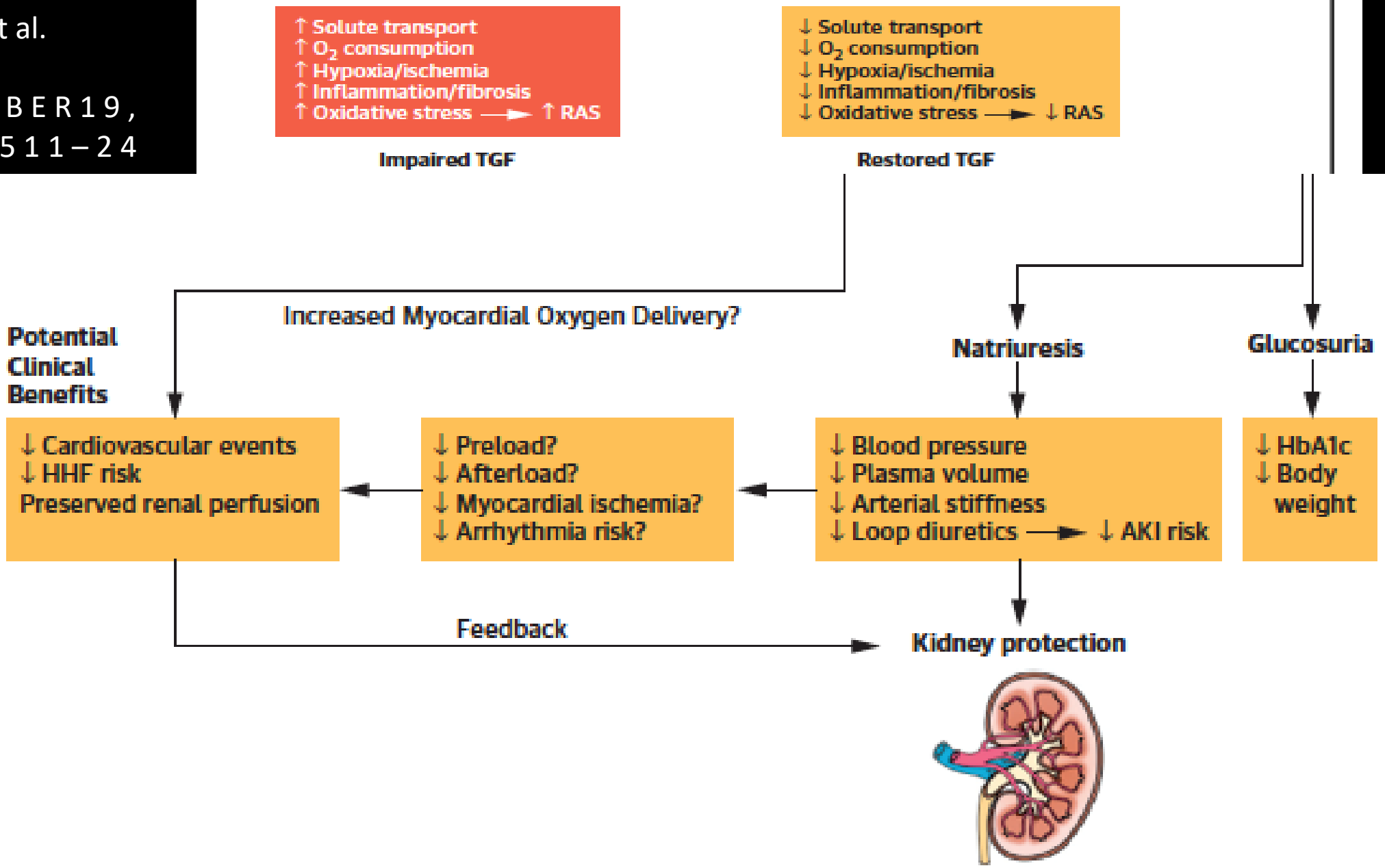
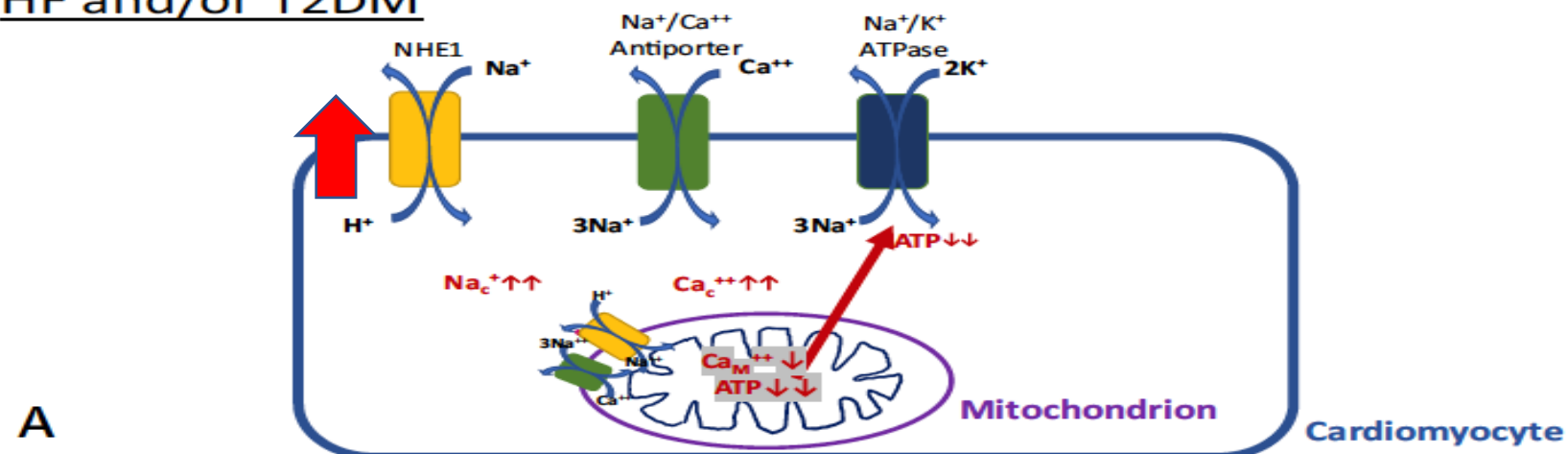
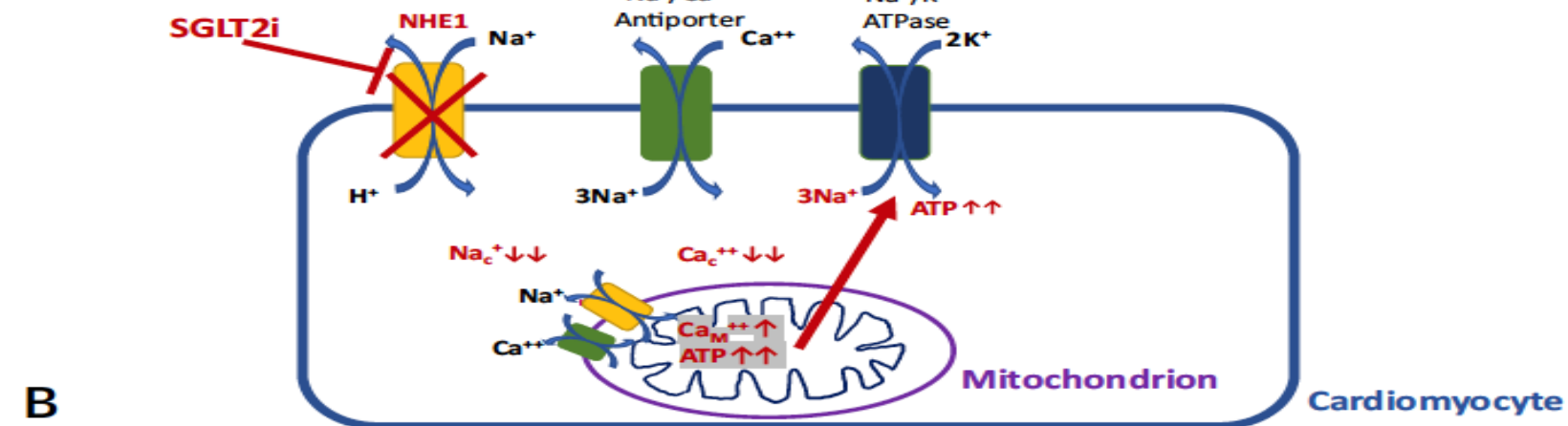


FIGURE 2 Direct Effects of SGLT2i on the Cardiomyocyte

HF and/or T2DM



SGLT2i

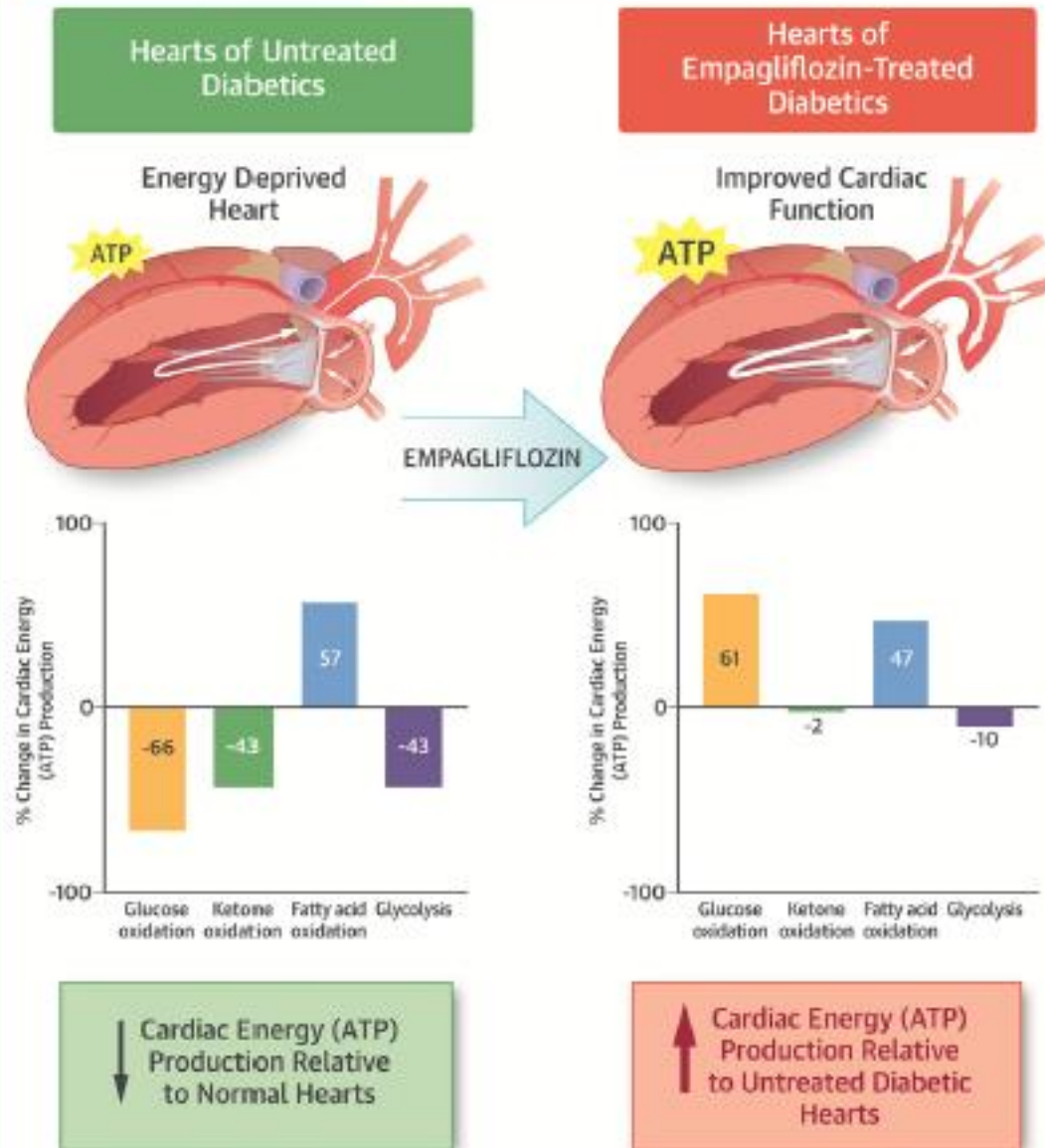


(A) Conditions, such as heart failure and/or type 2 diabetes mellitus (T2DM), increase the expression of Na^+ /Hydrogen exchanger 1 (NHE-1) and result in increased cytosolic Na^+ and Ca^{++} concentrations, but reduced mitochondrial Ca^{++} and mitochondrial ATP generation.

(B) Inhibition of cardiac NHE-1 reduces cytoplasmic Na^+ and Ca^{++} levels and increases mitochondrial Ca^{++} levels, resulting in improved mitochondrial respiration (and increase in ATP production) and viability of cardiomyocytes. Modified from Uthman et al. (55).

SGLT2i = sodium-glucose cotransporter 2 inhibitors.

VISUAL ABSTRACT

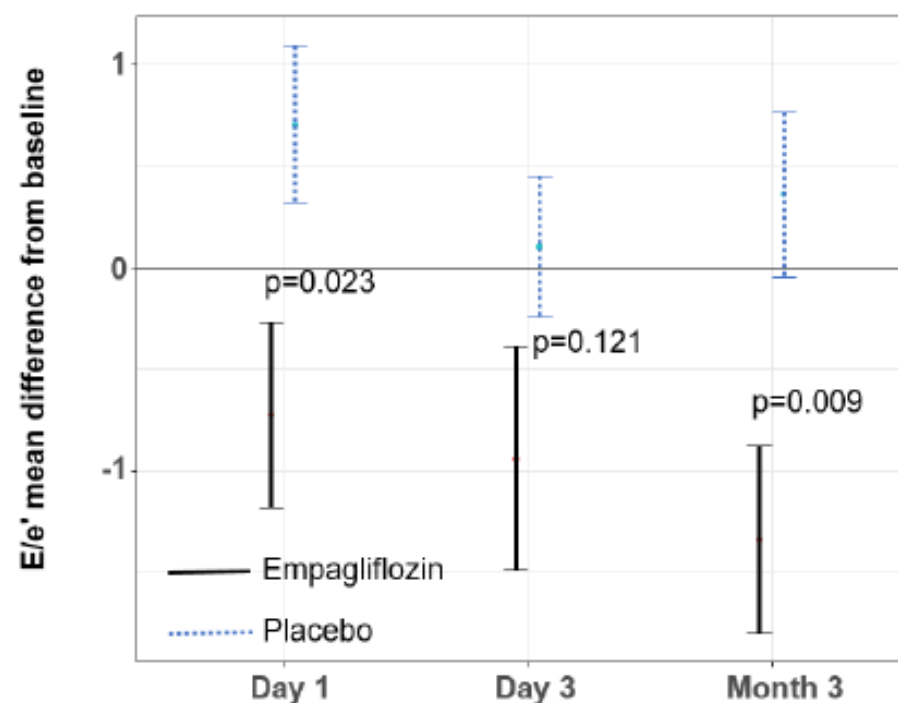
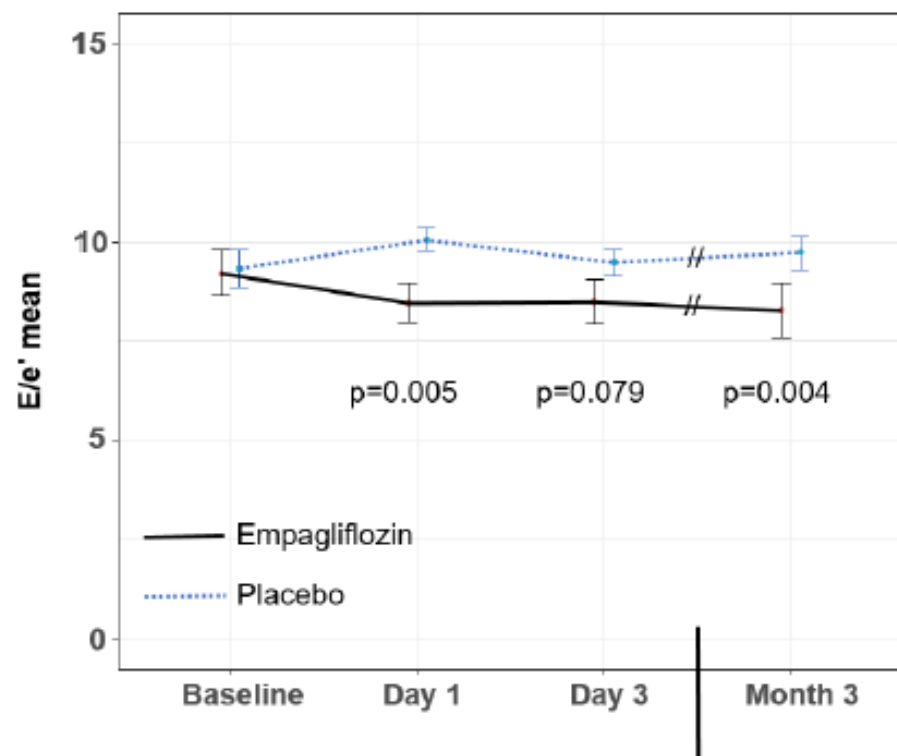
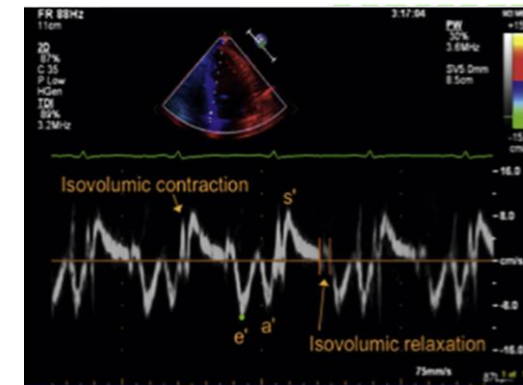
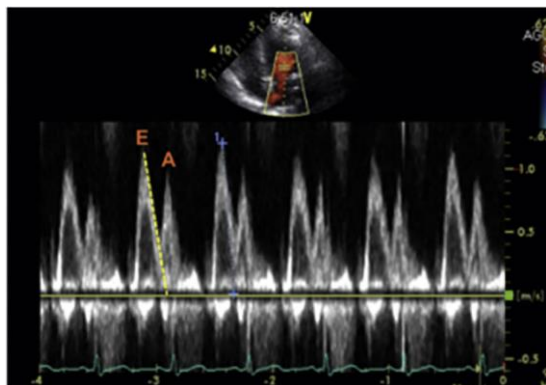


More consumption of ketone bodies to
Improve the ATP supply of the failing heart

Beta-hydroxybutyrate has been suggested to
act as the “superfuel”

EMPA Hemodynamics

Echocardiography E/e'



➔ Empagliflozin leads to an acute improvement in measures of LV filling pressure

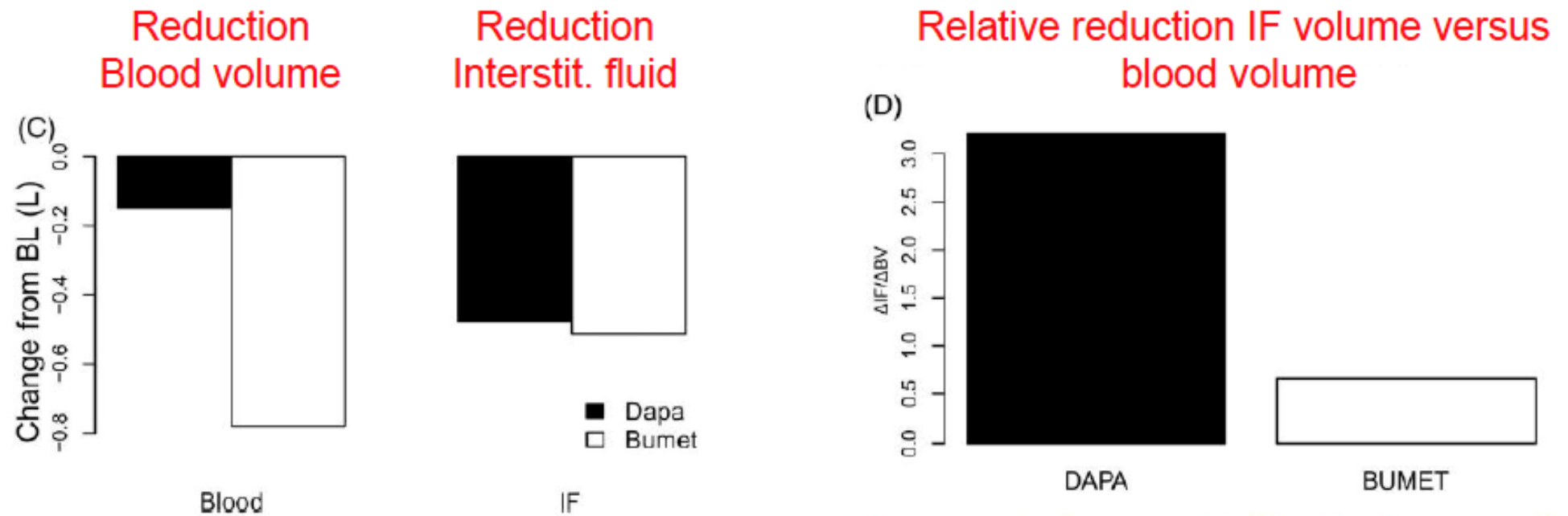
TABLE 1 Anticipated Effects of SGLT2 Inhibitors on Clinical Parameters in Patients With T2DM

CKD Stage	SBP (53,54)	DBP (53,55)	HbA _{1c} (53,54,56)	Weight (53,54,56)	Albuminuria (57)	eGFR (54,56)	Uric Acid (58)	Hematocrit (59)
1-2	↓3-5 mm Hg	↓1-2 mm Hg	↓0.6-0.9%	↓2-3 kg	↓30%-50%	↓3-5 ml/min/1.73 m ²	↓10%-15%	↑3%-5%
3a	↓3-5 mm Hg	↓1-2 mm Hg	↓0.3-0.5%	↓1-2 kg	↓30%-50%	↓3-5 ml/min/1.73 m ²	↓10%-15%	↑3%-5%
3b	↓3-5 mm Hg	↓1-2 mm Hg	↔	↓1-2 kg	↓30%-50%	↓3-5 ml/min/1.73 m ²	↔	↑3%-5%
4	↓3-5 mm Hg	↓1-2 mm Hg	↔	↓1-2 kg	↓30%-50%	↓3-5 ml/min/1.73 m ²	NA	NA
5	NA	NA	NA	NA	NA	NA	NA	NA

Double arrow indicates no change.

↑ = increase; ↓ = decrease; ↔ = no change; CKD = chronic kidney disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; NA = not available; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

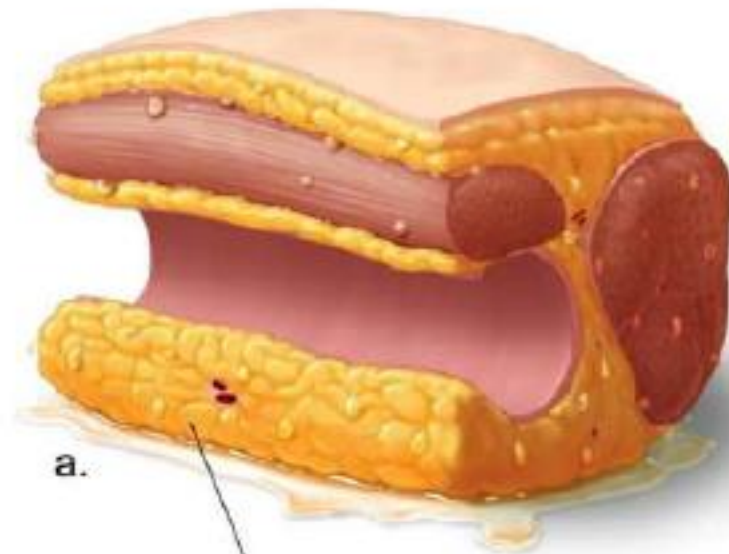
SGLT2 inhibitors versus diuretics: Differential regulation of interstitial versus intravascular compartment



➔ SGLT2 inhibition leads to a reduction of interstitial volume with limited effects on blood volume

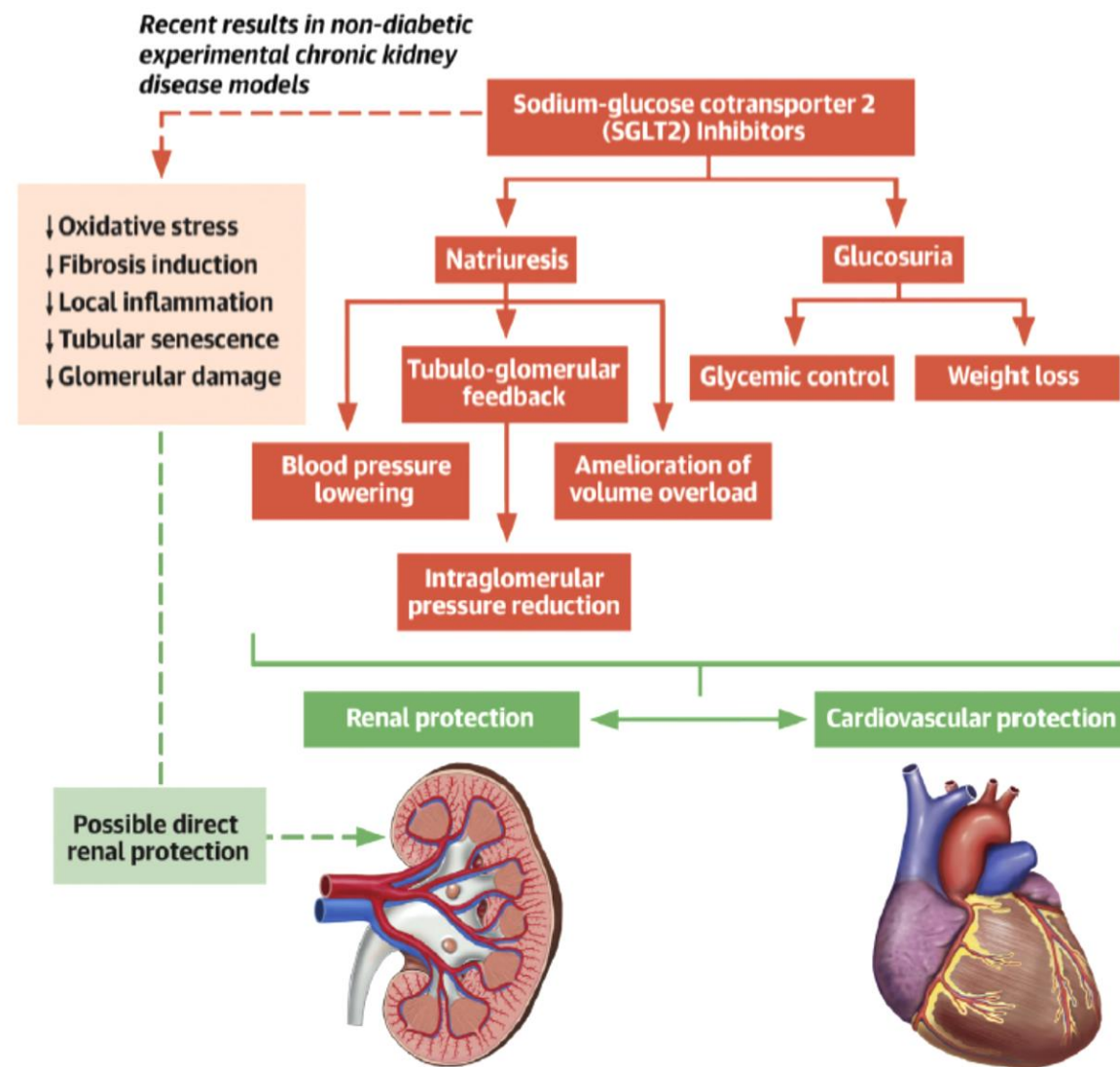
SGLT2 inhibitors

Loop diuretics



Interstitial edema in
congestive heart failure

CENTRAL ILLUSTRATION Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview



EXPERT CONSENSUS DECISION PATHWAY

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the American Diabetes Association

Writing Committee

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TABLE 2

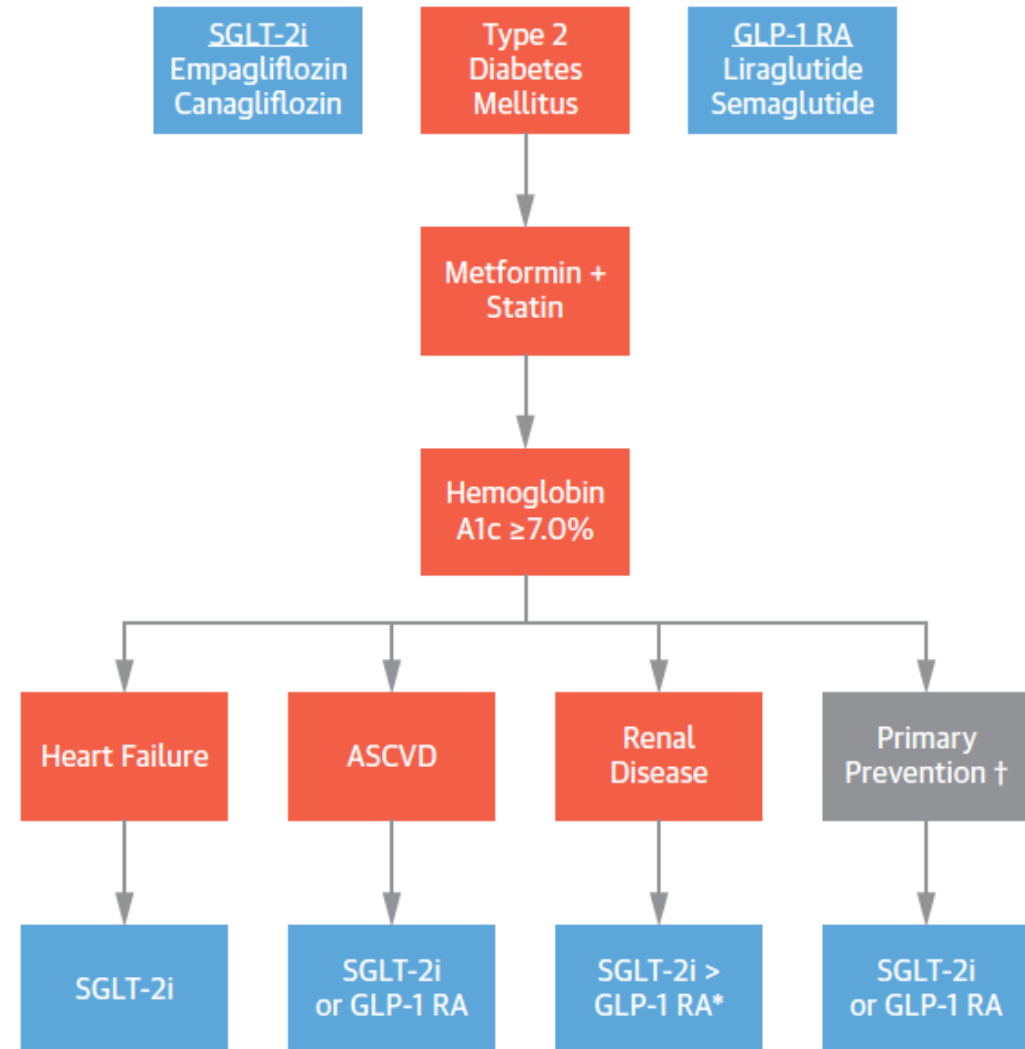
Doses, Indications, Dose Modifications, Contraindications, Cautions, and Adverse Effects of SGLT2 Inhibitors With Demonstrated CV Benefit

	Canagliflozin	Dapagliflozin	Empagliflozin
Recommended doses for CV benefit*	■ 100 mg PO daily	■ 10 mg PO daily	■ 10 mg PO daily
Indications	<ul style="list-style-type: none"> ■ Improve glycemic control in adults with T2D as an adjunct to diet and exercise ■ Reduce risk of MI, stroke, or CV death in adults with T2D and CV disease ■ Reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in patients with T2D and diabetic nephropathy with albuminuria 	<ul style="list-style-type: none"> ■ Improve glycemic control in adults with T2D as an adjunct to diet and exercise ■ Reduce the risk of hospitalization for HF in adults with T2D and established CV disease or multiple CV risk factors ■ Reduce the risk of CV death and hospitalization for HF in adults with HFrEF 	<ul style="list-style-type: none"> ■ Improve glycemic control in adults with T2D as an adjunct to diet and exercise ■ Reduce risk of CV death in adults with T2D and established CV disease
Dose modifications	<ul style="list-style-type: none"> ■ eGFR 30 to 59 mL/min/1.73 m²: max dose 100 mg daily ■ eGFR <30 mL/min/1.73 m²: use is not recommended for glycemic control 	<ul style="list-style-type: none"> ■ eGFR <45 mL/min/1.73 m²: use is not recommended for glycemic control ■ eGFR <30 mL/min/1.73 m²: use is contraindicated. 	<ul style="list-style-type: none"> ■ eGFR <45 mL/min/1.73 m²: use is not recommended.
Contraindications	<ul style="list-style-type: none"> ■ History of serious hypersensitivity reaction to drug ■ Pregnancy or breastfeeding ■ On dialysis ■ eGFR <30 mL/min/1.73 m² (dapagliflozin) ■ ESRD (dapagliflozin and empagliflozin) ■ Severe renal impairment (empagliflozin) 		
Cautions	<ul style="list-style-type: none"> ■ Discontinue at least 3 days before a planned surgery to prevent postoperative ketoacidosis. ■ If HbA1c well-controlled at baseline, or known history of frequent hypoglycemic events, wean or stop sulfonylurea or glinide and consider reducing total daily insulin dose by ~20% when starting therapy. ■ May contribute to intravascular volume contraction; consider stopping or reducing diuretic dose if applicable. ■ Use with caution in patients with prior amputation, severe peripheral neuropathy, severe peripheral vascular disease, or active diabetic foot ulcers or soft tissue infections. ■ Possible increased risk of bone fractures (canagliflozin) 		
Adverse effects to monitor	<ul style="list-style-type: none"> ■ Genital fungal infections ■ Urinary tract infections ■ Euglycemic diabetic ketoacidosis ■ Lower limb ulcerations and soft tissue infections 		

TAKE HOME MESSAGE

J Am Coll Cardiol 2018;72:1856–69

FIGURE 5 A New Algorithm for CVD Risk Reduction in Type 2 Diabetes



Dr. Harry Jimenez-Rodriguez

SGLT2i STUDIES

Reduction in CV Disease

- EMPA-REG OUTCOME trial
- CANVAS
- DECLARE TIMI 58
- VERTIS-CV

Reduction in HF events

- EMPEROR PRESERVED
- EMPEROR REDUCED
- EMPERIAL
- EMPA-VISION
- DAPA-HF
- DELIVER
- SOLOIST WHF

THANKS



2019 new recommendations (9)

DM treatment to reduce HF risk

SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are recommended to lower risk of HF hospitalization if eGFR >30 mL/min/1.73 m²

Metformin should be considered in patients with DM and HF if eGFR >30 mL/min/1.73 m²

GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of HF and may be considered

Insulin treatment in HF may be considered

DPP4 inhibitor saxagliptin in HF is not recommended

Thiazolidinediones (pioglitazone, rosiglitazone) in HF is not recommended

TABLE 3 Overview of Mechanisms of Favorable Cardio-Metabolic-Renal Effects

	Heart Failure	Atherosclerotic Effect	Diabetic Kidney Disease
Glucose lowering			✓
Reduction in body weight	✓	✓	✓
Lowering of blood pressure	✓	✓	✓
Natriuresis	✓		✓
Anti-inflammation	✓	✓	✓
Antifibrotic	✓		✓
Reduction in extracellular matrix turnover	✓		✓
Amelioration of intrarenal hypoxia			✓
Restoration of the tubuloglomerular feedback			✓
Reduction in natriuretic peptides	✓		✓
Reduction in energy demand	✓		✓
Reduction in liver fat		✓	