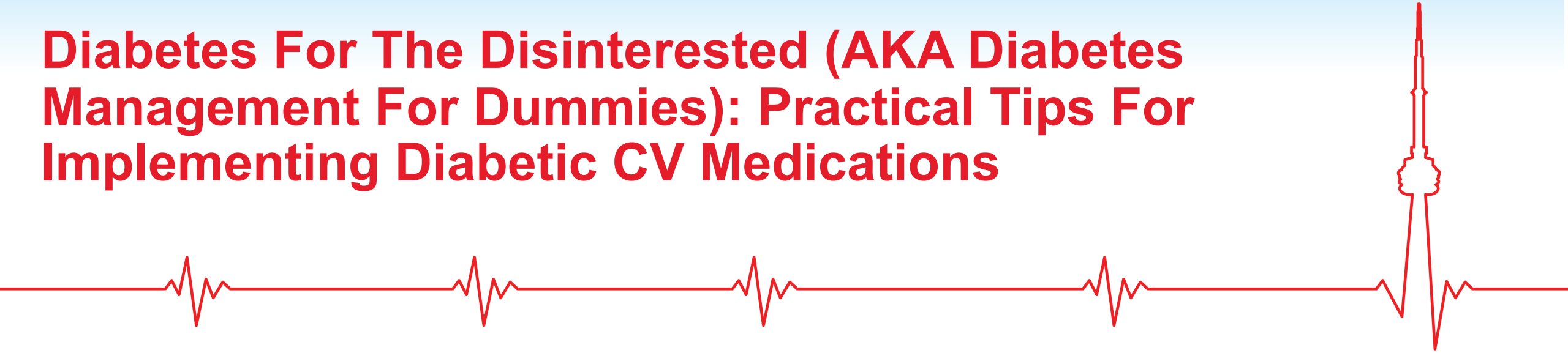
Diabetes For The Disinterested (AKA Diabetes Management For Dummies): Practical Tips For Implementing Diabetic CV Medications



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- **Speaker fees**: Novartis, Bayer AstraZeneca, Boehringer Ingelheim
- **Other**:

- I will discuss off-label uses for dapaglofolzin

Case 1-CY

- 53 yo ♀T2DM, dyslipidemia
- February 7 ER: for worsening SOB had been getting worse over 2-3 months given IV Lasix
- February 11 HFC: feeling slightly better, SOBOE ~ 200ft; Meds: ramipril 2.5 mg OD, Lasix 40 mg OD, insulin glargine, metformin 1gm BID, sitagliptin 100mg OD, simvastatin 20mg OD; Exam: BP 157/87, HR 98, O2%sat 98%, decreased BS bases, JVP 5cm ASA, 2/6 pansystolic murmur, 2+ pitting edema; Tests: POCUS: IVC 1.9cm ~50% collapse; Na+ 142, K+3.3, urea 7.2, Cr 80, HgbA1c 11.8%, TC 4.9, TG 2.1, HDL 1.1, LDL 2.8; ECHO: LVEF 30-35%, akinetic apex, 2+ MR, normal RV; PLAN: 1) stop ramipril, 2) start Entresto 49/51 mg BID, 3) start carvedilol 3.125 mg BID, 4) start spironolactone 12.5 mg OD, 5) continue Lasix 40 mg OD
- March 6 HFC: feeling better, less SOB able to walk ~ 150m before SOBOE, following fluid restriction; Meds: Entresto 49/51 mg BID, carvedilol 3.125 mg bID, Lasix 40 mg OD, spironolactone 12.5 mg OD, insulin glargine, metformin 1 gm BID, sitagliptin 100 mg OD, simvastatin 20 mg OD; Exam: BP 137/81, hr 81, JVP 2cm ASA, soft pansystolic murmur, no edema, chest clear; Tests: POCUS: IVC small and collapsing; Na+ 141, K+ 4.4, Cl- 104, urea 13.5, Cr 126, HgbA1c 10.8%

Case 2 - JV

- 52 yo ♂ ER August 12, 2019 severe symptoms SOBOE, developing over the prior month; admitted to hospital as complicated by atrial flutter, LVEF 20-25%
- August 22, 2019 HFC: feeling better, walks a block before SOBOE; Meds: Lasix 40 mg BID, spironolactone 12.5 mg OD, perindopril 8 mg OD, metoprolol 25 mg BID, apixaban 5 mg BID; Exam: BP 114/81, HR 106, chest clear, JVP 5cm ASA, no edema; Tests: Na+ 140, K+ 4.5, Cl- 102, urea 9.8, Cr 86, HgbA1c 5.6%; Plan: 1) FDR Lasix, 20 spironolactone 25 mg OD
- October 2, 2019 HFC: able 2 walk 2 blocks; Exam: BP 115/77, HR 82, JVP 1cm ASA, no edema, chest clear; Tests: Na+ 137, K+ 4.1, Cl- 98, urea 10.2, Cr 102, RBS 6.0, TC 6.93, TG 1.88, HDL 0.98, LDL 5.10; Plan: 1) stop perindopril, 2) start Entresto 49/51 mg BID 3) stop metoprolol 4) start bisoprolol 5mg OD, 5) start crestor 5mg OD
- October 30 2019 HFC: works out at gym; Exam: BP 100/68, HR 76, JVP 3cm ASA, chest clear, no edema; Tests: Na+ 139, k= 3.7, Cl- 98, urea 8.0, Cr 86, RBS 8.4; Plan: 1) Entresto 97/103 mg BID 2) bisoprolol 7.5 mg OD
- November 28, 2019 HFC: continues to workout at the gym; coronary angiogram November 18 demonstrates normal coronary arteries; Meds: Entresto 97/103 mg BID, bisoprolol 7.5 mg OD, Lasix FDR, spironolactone 25 mg OD, apixaban 5 mg BID, crestor 5 mg OD; Exam: BP 113/75, HR 80, JVP 1cm ASA, chest clear, no edema; Tests: Na+ 139, K+ 3.8, Cl- 97, urea 8.6, Cr 117, RBS 7.5

Question 1

How does diabetes cause heart failure?

1. Through the development of coronary artery disease
2. Independent of coronary artery disease
3. Both 1 and 2

Diabetic Cardiomyopathy??

- 1972 Rubler et al described new cardiomyopathy
- 4 diabetic patients with CHF; normal coronary arteries; no other etiologies for CHF
- Proposed diabetic cardiomyopathy

Rubler et al. Am J Cardiol 1972;30:595-602

Proposed Mechanisms of Cardiac Dysfunction in DM

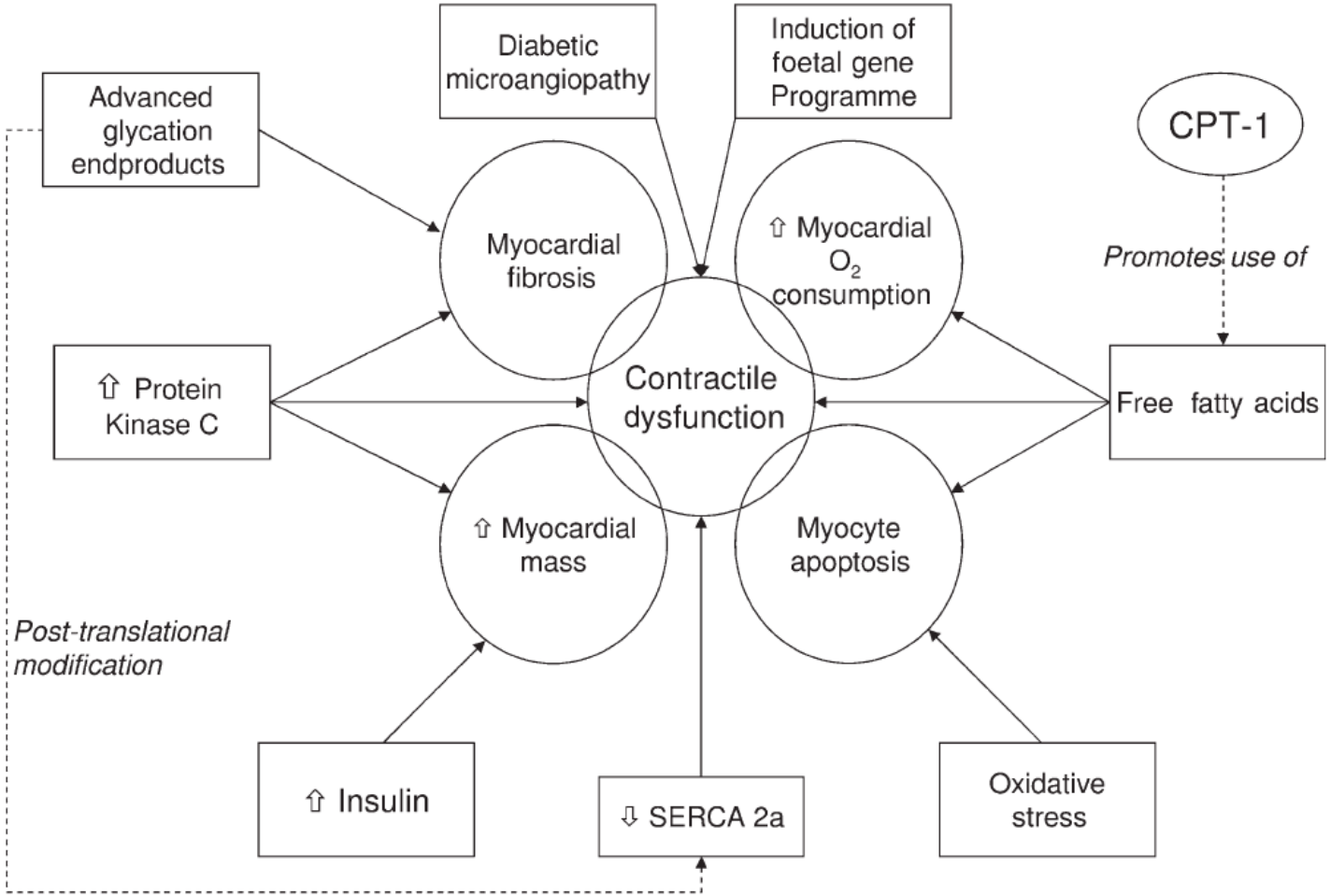


Figure 3 Proposed mechanisms of cardiac dysfunction in diabetics. CPT-1, carnitine palmitoyltransferase-1, SERCA 2a, sarcoplasmic endoplasmic-reticulum$Ca2^{+}$-ATPase2a

MacDonald et al EHJ 2008

Question 2

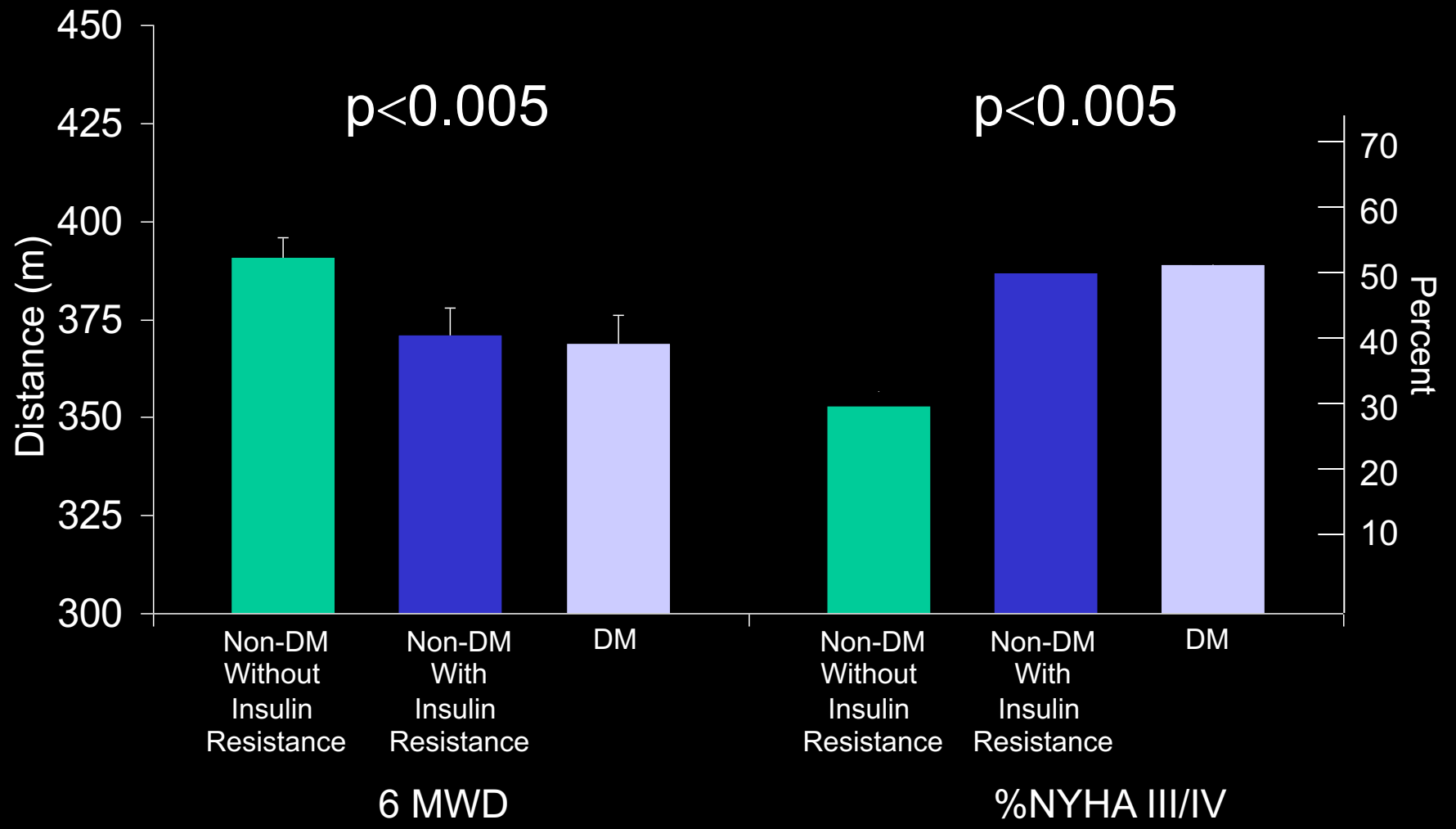
What is the prevalence of diabetes in heart failure patients?

1. 5-10%
2. 35-40%
3. 70-80%

Prevalence of Diabetes In Contemporary Heart Failure Studies

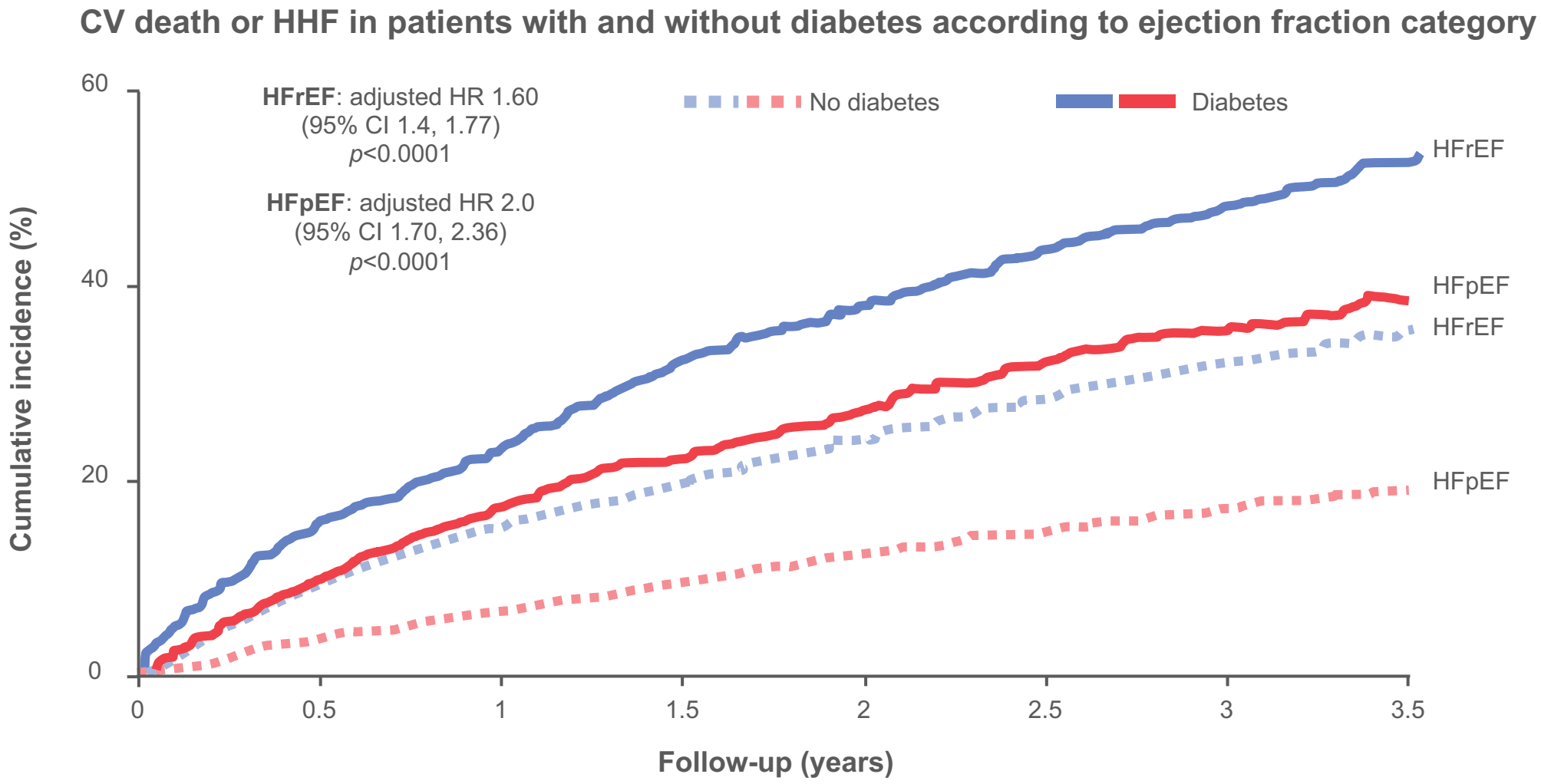
- EMPASIS 2010 34%
- PARADIGM 2014 35%
- DAPA-HF 2019 42%

6 Min Walk Distance of Diabetic Patients & Percent Diabetic Patients in NYHA-FC III/IV vs. Non-diabetic Patients With & Without Insulin Resistance



Suskin et a. Eur Heart J 2000;21:1368-1375

Diabetes is associated with worse outcomes



HHF, hospitalisation for heart failure
MacDonald MR *et al. Eur Heart J* 2008;29:1377

EMPEROR
HEART FAILURE STUDIES

Question 3

Which drug should not be used to treat diabetes in a heart failure patient?

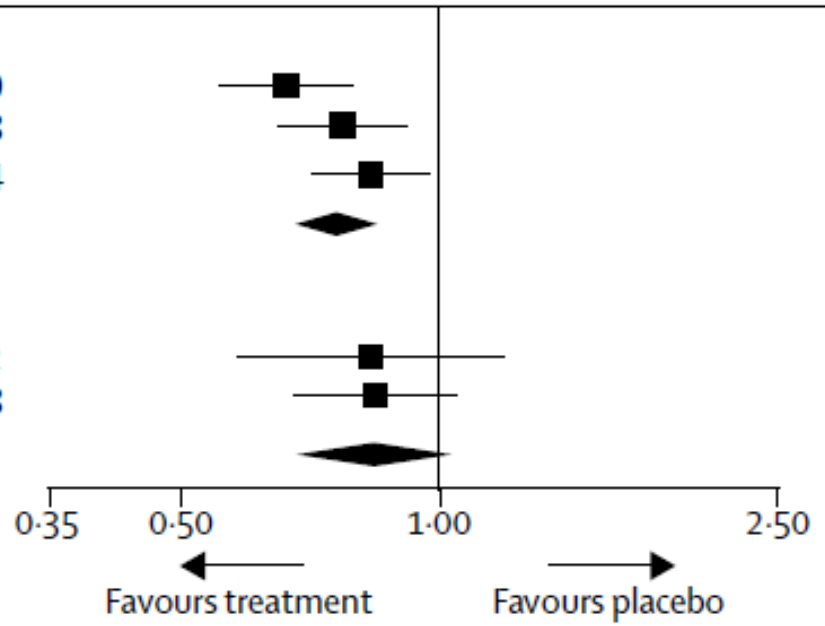
1. Metformin
2. Liraglutide (Victoza)
3. Sitagliptin (Januvia)
4. Saxagliptin (Onglyza)

Table 1 Phramacological classes and their effects

Pharmacological class	Effects on MACE (variably including CV death, overall death, MI, stroke)	Effects on heart failure events	Study
Biguanides			
Fenformin	Hazardous	Not addressed	UGDP [10, 11]
Metformin	Potentially beneficial on primary prevention	Not addressed	UKPDS [12]
Sulfonylureas			
Tolbutamide	Hazardous	Not addressed	UGDP [10, 11]
Glibenclamide, glipizide	No univocal results, decreased ischemic preconditioning	Potentially risky	No RCTs available
Glyclazide	No univocal results	Potentially risky	No RCTS available
Glimepiride	Ongoing results	Ongoing results	CAROLINA [13]
Thiazolidinediones			
Rosiglitazone	Likely safe	Hazardous	RECORD [14]
Pioglitazone	Potentially beneficial on II end point (death, MI, stroke)	Hazardous	PROACTIVE [15]
Alpha-glucosidase inhibitors			
Acarbose	Potentially beneficial	Not addressed	Meta-analysis [16]
Vogliobose, miglitol	Potentially beneficial on surrogate end points	Not addressed	Small, observational studies [17, 18]
DPP-4 inhibitors			
Saxagliptin	Likely safe	Probably hazardous	SAVOR-TIMI 53 [19]
Sitagliptin	Likely safe	Likely safe	TECOS [20]
Alogliptin	Likely safe	Likely safe	EXAMINE [21, 22]
Vildagliptin	Not addressed	Likely safe	VIVIDD [23]; Meta-analysis [24]
GLP-1 agonists			
Liraglutide	Potentially beneficial	Likely safe	LEADER [25]
Lixisenatide	Likely safe	Likely safe	ELIXA [26]

Hosp for HF endpoint by CV status

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**



www.thelancet.com Published online November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X

SGLT2 Inhibitors - Cardiac Protection Mechanisms

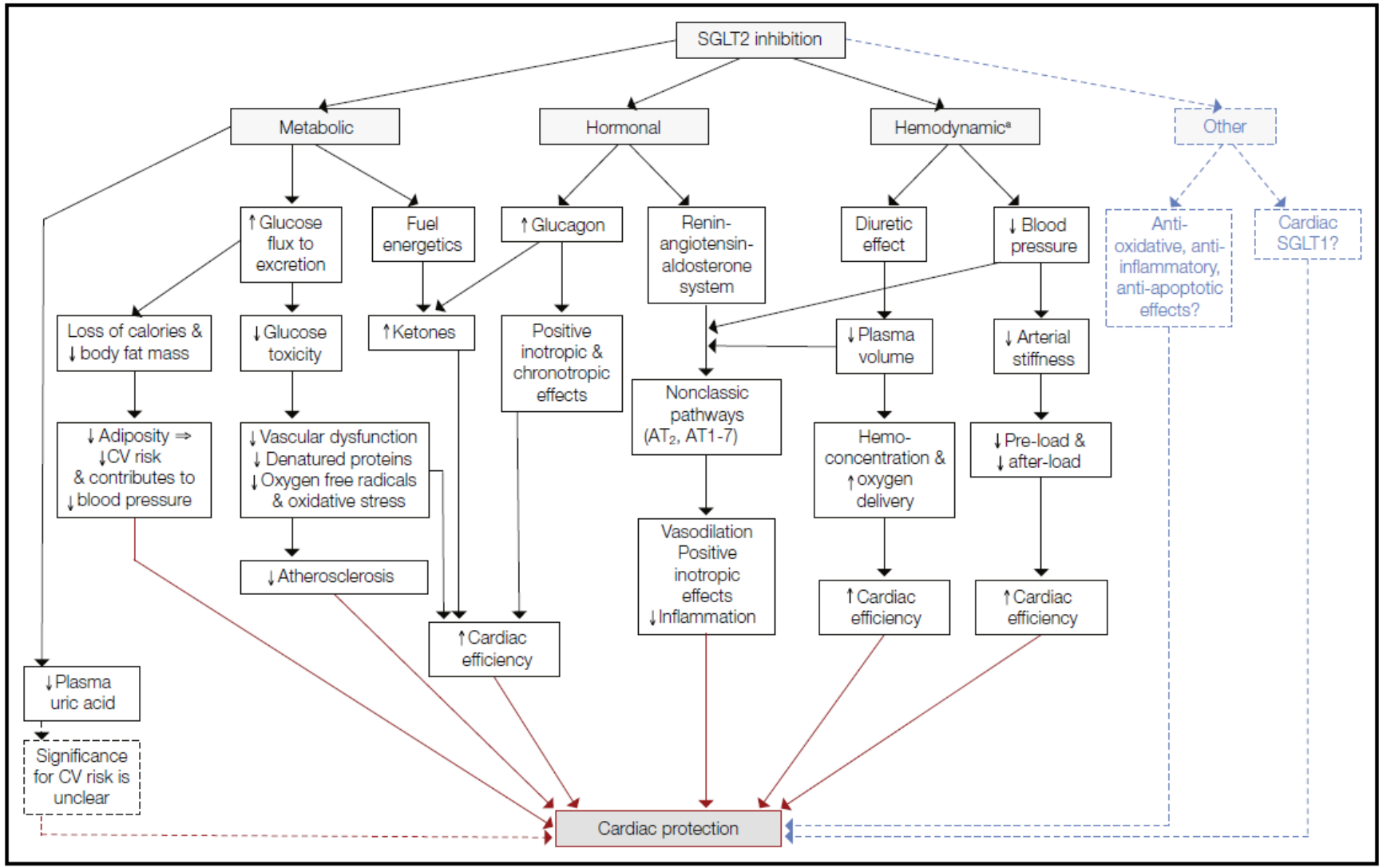


Figure 1. Summary of possible cardiac protection mechanisms in EMPA-REG OUTCOME. [a]Hemodynamic changes affecting the kidney are not shown, although they may impact on cardiac function; renal protection mechanisms are presented in Wanner's review.[7] AT_2 = type 2 angiotensin II receptor pathway; AT1-7 = angiotensin 1-7 activation; CV = cardiovascular; SGLT = sodium glucose cotransporter.

Staels Am J Cardiol 2017

Summary: Rationale for exploring SGLT2i for the treatment of heart failure in patients without diabetes

Patients with HF have similar pathophysiological features as patients with diabetes

Glucosuria, natriuresis and metabolic effects of SGLT2i are seen in patients with and without diabetes

The CV benefits observed in SGLT2i studies were largely independent of glucose levels

Hypothesis: Patients with HF without diabetes may benefit from SGLT2i

There is mechanistic rationale to investigate the CV outcomes of SGLT2i beyond T2D

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

DOI: 10.1056/NEJMoa1911303

Study Design

International, multicentre, event-driven, randomized, double-blind, parallel group, placebo-controlled study

Inclusion criteria

- Adults ≥18 yrs
- NYHA Class II-IV HF
- LVEF ≤40%
- Nt-proBNP ≥600 pg/ml*
- eGFR ≥30 ml/min/1.73 m^2
- Stable SoC HF treatment

1:1 Double-blind

Placebo once daily
Added to current background therapy

Dapagliflozin 10 mg once daily
Added to current background therapy

No. of randomized patients: 4,744

- **Duration is event-driven: 844 events**
- **Powered for superiority (power 90%)**
  - HR of 0.80 for dapagliflozin vs. placebo, and using a one-sided alpha of 2.5%

Estimated Study duration ~33 month

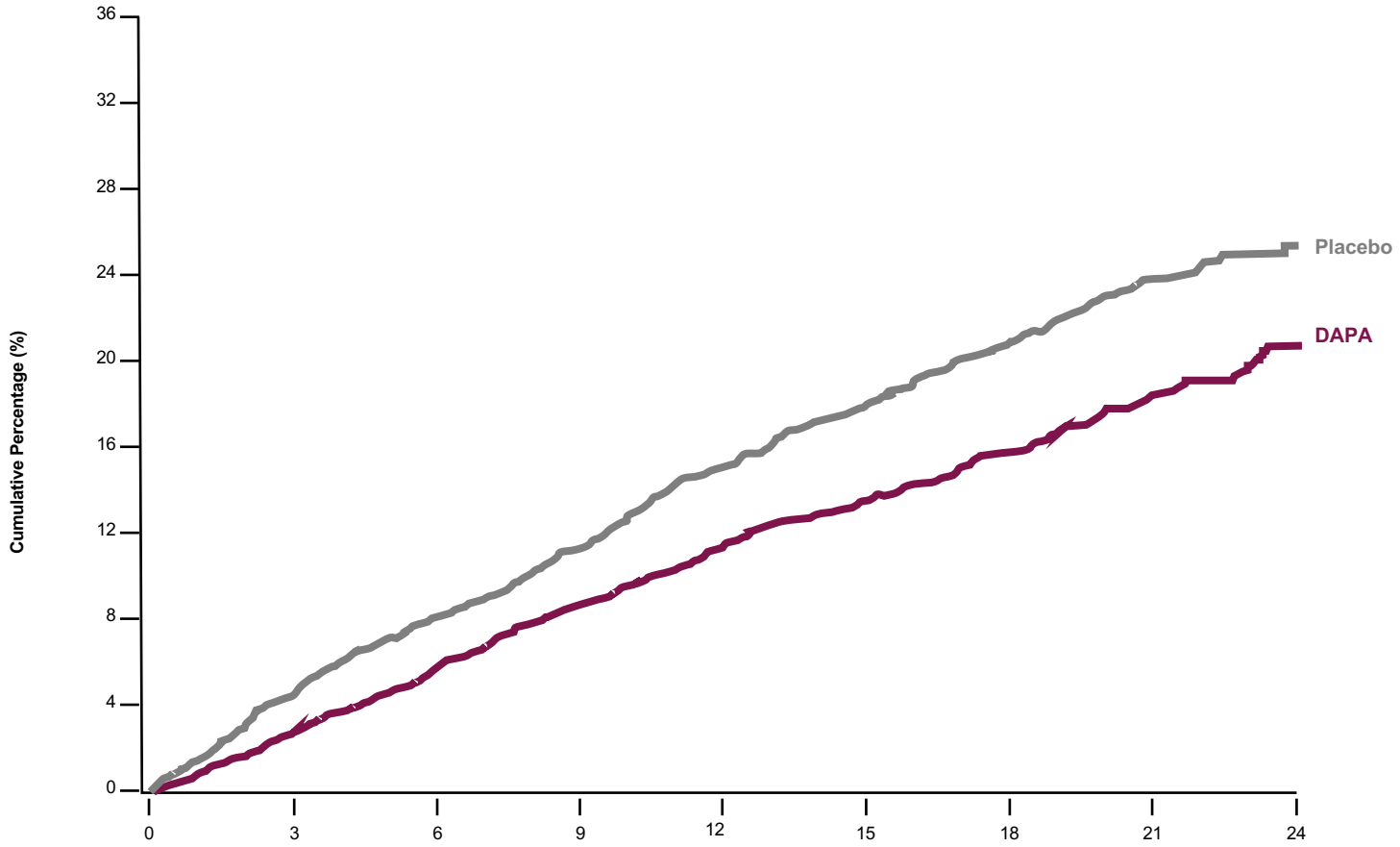
Estimated Average follow-up ~24 months

Primary endpoint: Composite of CV death or HF event

* ≥400 pg/mL if hospitalised for heart failure within the previous 12months; ≥900 pg/mL with atrial fibrillation or atrial flutter
HF event: hospitalisation for heart failure or urgent treatment visit for HF

McMurray et al European Journal of Heart Failure 2019 doi:10.1002/ejhf.1432

Primary Endpoint:
CV Death or hHF or an Urgent HF Visit[1]



26% RRR

HR 0.74 (0.65, 0.85)
p=0.00001

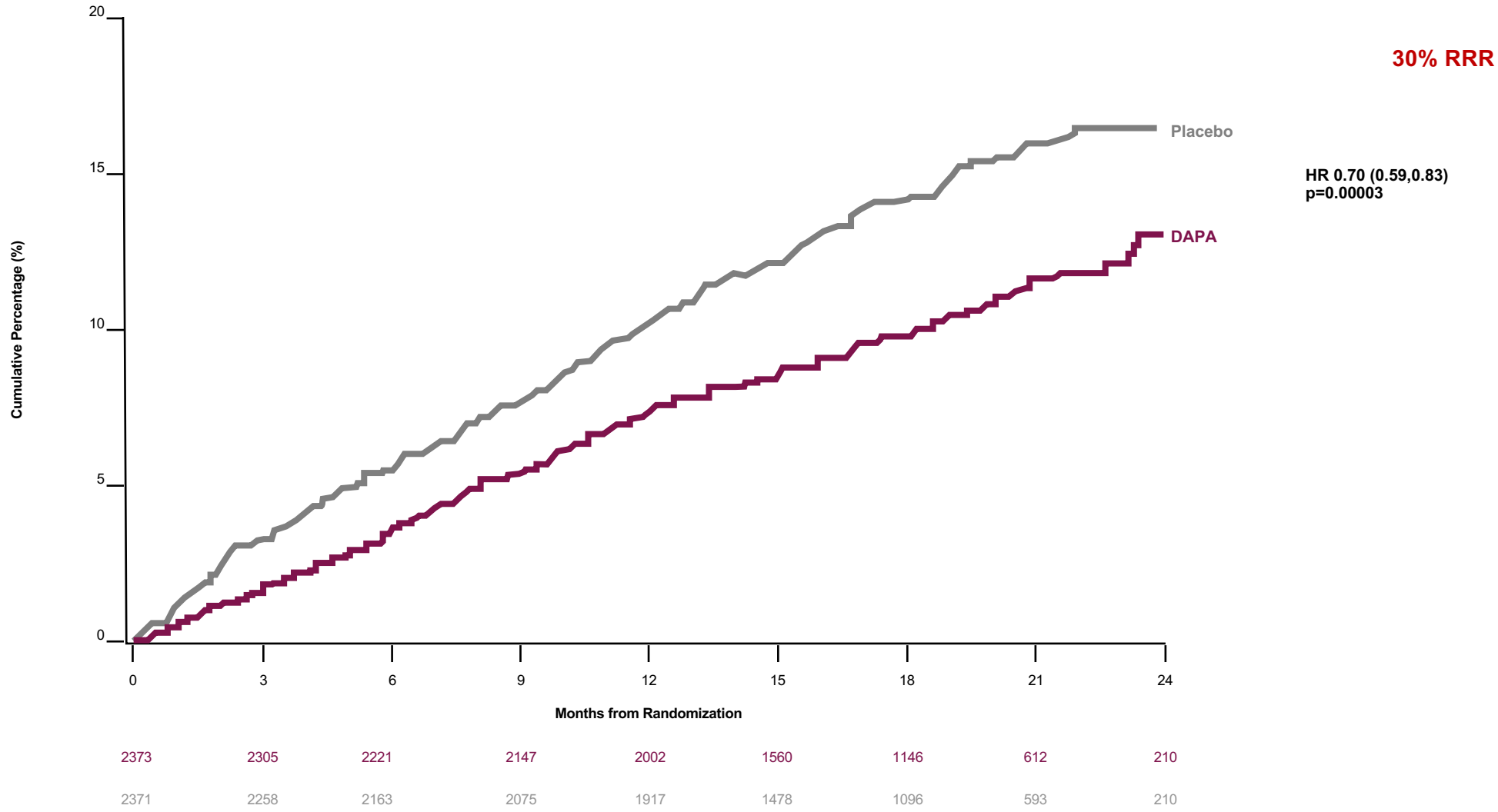
NNT = 21

No. at Risk									
DAPA	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

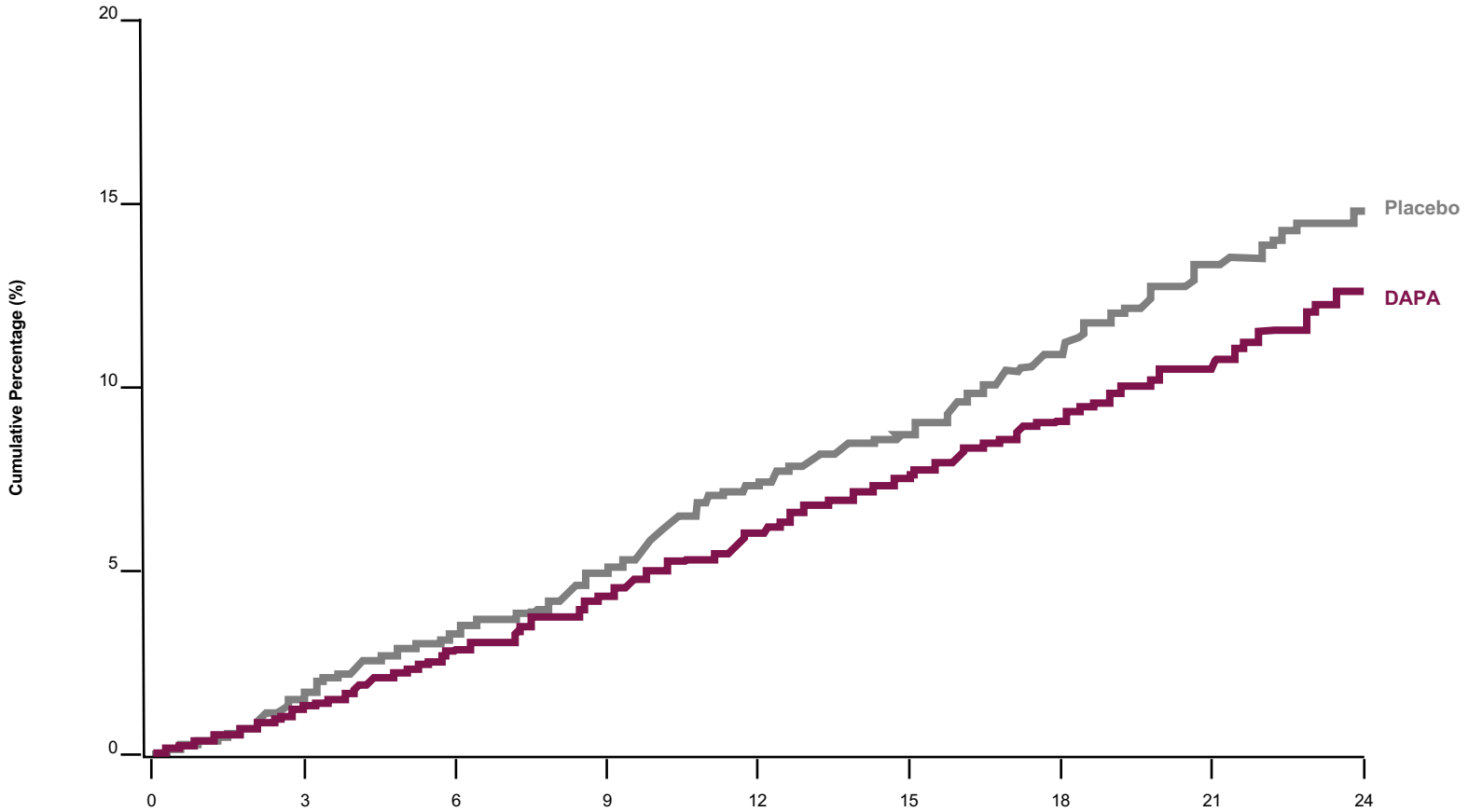
Component of Primary Endpoint: Worsening HF Event



DAPA = Dapagliflozin; HF = Heart failure; HR = Hazard ratio.

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

Component of Primary Endpoint: Cardiovascular Death



18% RRR

HR 0.82 (0.69,0.98)
p=0.029

No. at Risk									
DAPA	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

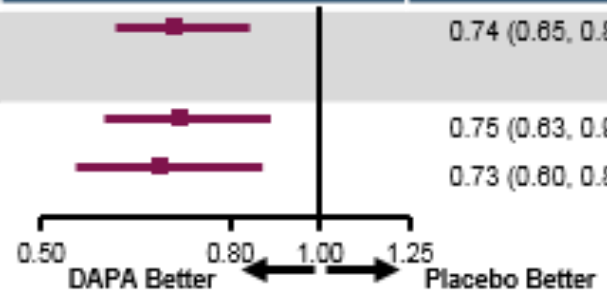
DAPA = Dapagliflozin; HR = Hazard ratio.

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

Primary Endpoint: Subgroup Analyses

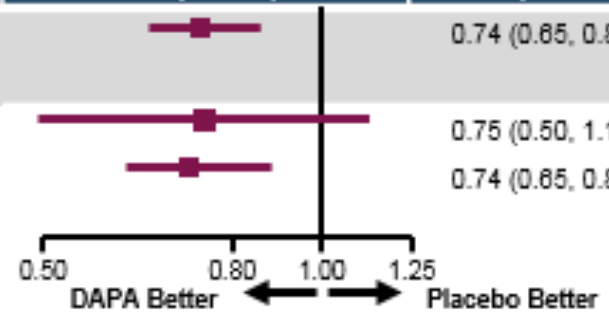
Prespecified Subgroup

Characteristics	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)	HR (95% CI)
All Patients	386/2373	502/2371		0.74 (0.65, 0.85)
Type 2 Diabetes at Baseline*				
Yes	215/1075	271/1064		0.75 (0.63, 0.90)
No	171/1298	231/1307		0.73 (0.60, 0.88)



Post-hoc Subgroup

Characteristics	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)	HR (95% CI)
All Patients	386/2373	502/2371		0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)				
Yes	41/250	58/258		0.75 (0.50, 1.13)
No	345/2123	446/2113		0.74 (0.65, 0.86)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

2017 CCS Recommendations
HF Prevention in DM

Recommendation 9: We recommend that diabetes should be treated according to the Canadian Diabetes Association's national guidelines to achieve optimal control of blood glucose levels (Strong Recommendation, Moderate Quality Evidence).

2019 CCS HF Recommendation

1. **UPDATED** We recommend SGLT2 inhibitors, such as empagliflozin, canagliflozin or dapagliflozin, be used for treatment of patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce the risk of HF hospitalization and death (**Strong Recommendation; High-Quality Evidence**).

2. **NEW** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with type 2 diabetes aged >50 years with additional risk factors for atherosclerotic cardiovascular disease to reduce the risk of hospitalization for HF (**Strong Recommendation; High-Quality Evidence**).

2019 HF Guidelines Update

4. **NEW** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate heart failure due to reduced left vent r ejection fraction (LVEF ≤ 40%) and *concomitant type 2 Diabetes,* to improve sy d quality of life and to reduce the risk of hospitalization and cardiovascular mortal **ommendation; High-Quality Evidence**).
5. **NEW** We recommend SGLT2 inhibit zin be used in patients with mild to moderate heart failure due to reduce fraction (LVEF ≤ 40%) and *without concomitant Diabetes,* to improv nd to reduce the risk of hospitalization and cardiovasc **endation; High-Quality Evidence**).

OFF LABEL FOR THOSE WITHOUT DIABETES!

Therapeutic Approach to Patients with HFrEF

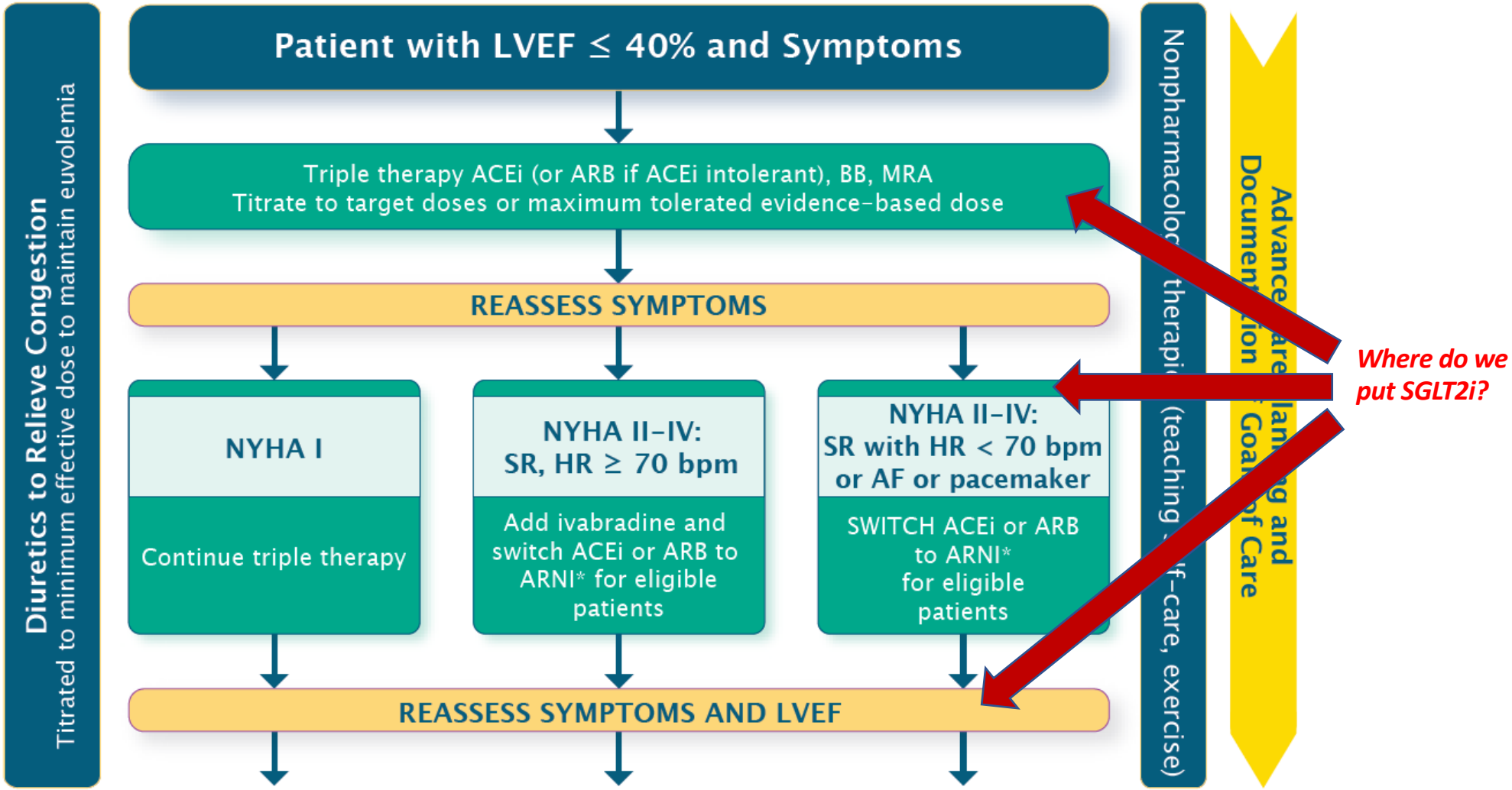


Table 3 from CCS 2019 guidelines O'Meare et al.

Table 3. Practical issues surrounding initiation of SGLT2 inhibitors

Issue	Concomitant diabetes	No concomitant diabetes
Glycemic control	• Collaboration with diabetes team if available • Concomitant insulin or sulfonurea therapy: no adjustment necessary with poorly controlled glucose, consider 25% reduction of each medication • Reinforce glucose monitoring • SGLT2 inhibitors contraindicated in type 1 diabetes	No concerns for hypoglycemia
Volume control	• Euvolemia: optional to reduce loop diuretic by 25-50% • Volume overloaded: no need to reduce concomitant loop diuretic • Hypovolemia: do not start until volume depletion corrected	Same as with diabetes
Renal function	Safe with eGFR 30 mL/min/1.73 m^2. Early 20% decrease in eGFR acceptable. With larger change in eGFR, evaluate clinically, consider reduction of loop diuretic	Same as with diabetes
Peripheral vascular disease	Caution with history of amputation or active peripheral arterial ulcer	Caution with history of amputation or active peripheral arterial ulcer
Perineal hygiene	Careful local hygiene—single dose of fluconazole typically effective in event of fungal infection	
Urinary tract infection	SGLT2 inhibitors might lead to increased urinary frequency but not directly associated with infection. However, urinary tract infection might occur independently of SGLT2 inhibitor use, and requires index of suspicion	Same as with diabetes
Diabetic ketoacidosis	As per CDA guidelines, this medication is on the "Sick Day" list. High index of suspicion for DKA required during clinical deterioration. Direct serum anion gap measurement suggested. In addition to volume-depleting conditions, hold for concomitant infection, trauma, surgery, or other major physiologic stressor	Hold during volume depleting intercurrent illness until oral intake adequate DKA not specifically recognized as a risk in nondiabetic patients

Case 1 – CY

Plan:

1. Hold Lasix
2. Carvedilol 6.25 mg BID
3. Start dapagliflozin 5 MG OD
4. Arrange for diabetes follow-up
5. Switch simvastatin to crestor 20 mg OD
6. Arrange for coronary angiogram

Case 2 – JV

Plan:

1. Increase bisoprolol to 10 mg OD
2. Start dapagliflozin 5 mg OD

QUESTIONS?

TO SUBMIT YOUR QUESTIONS, CLICK ON THE Q&A ICON ON YOUR SCREEN