

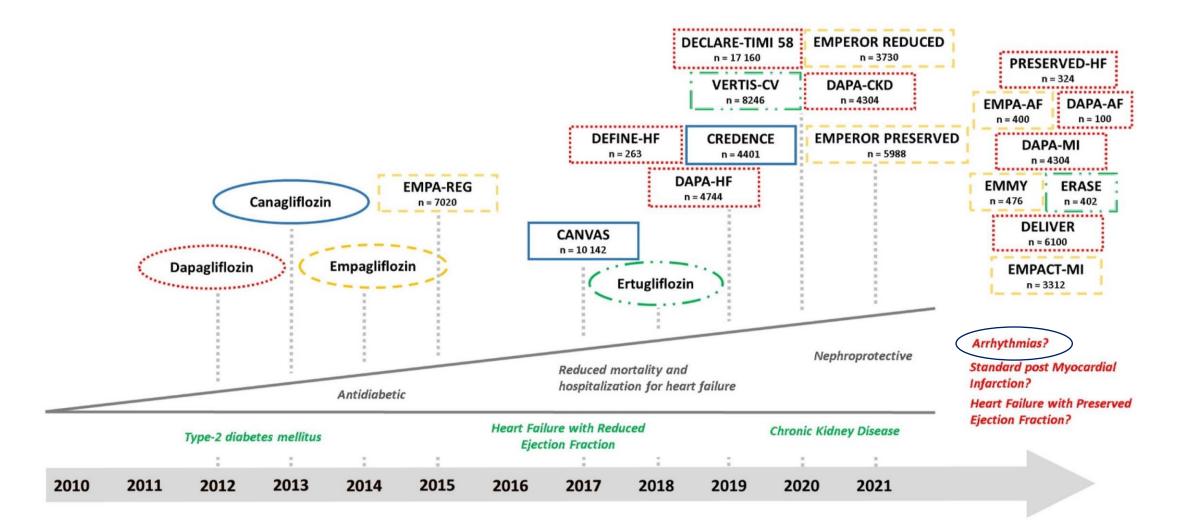


# Effects of SGLT-2 Inhibitors on Cardiac Arrhythmias

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## History, Completed, and Ongoing Clinical Trials of SGLT2 Inhibitors



Kolesnik E, et al. Int J Mol Sci 2022;23:1678-1690.

## Treatment Effect of SGLT2i on Cardiorenal Outcomes

Updated meta-analysis of 38,723 patients including EMPA-REG OUTCOME, CANVAS program, DECLARE-TIMI 58 trial, and the CREDENCE trial

Outcome	# Events	HR (95% CI)		
MACE	3,828	0.88 (0.82-0.94)	<	
CV death/HHF	2,460	0.76 (0.70-0.82)		
CV death	1,506	0.83 (0.75-0.92)		
HHF	1,192	0.68 (0.60-0.76)		
Composite Renal Endpoint	1,351	0.61 (0.55-0.68)		
All-cause Mortality	2,493	0.85 (0.79-0.92)		
		0.	.50 0.75	1.0 1.25
Zolnikor & Branwuald E I Am C	oll Cardial 20	120.75.425 44	Favors SGLT2i $\leftarrow \rightarrow$	Favors Placebo

Zelniker & Branwuald E. J Am Coll Cardiol 2020;75:435-44.

## Meta-Analysis of EMPEROR-Reduced and DAPA-HF Trials

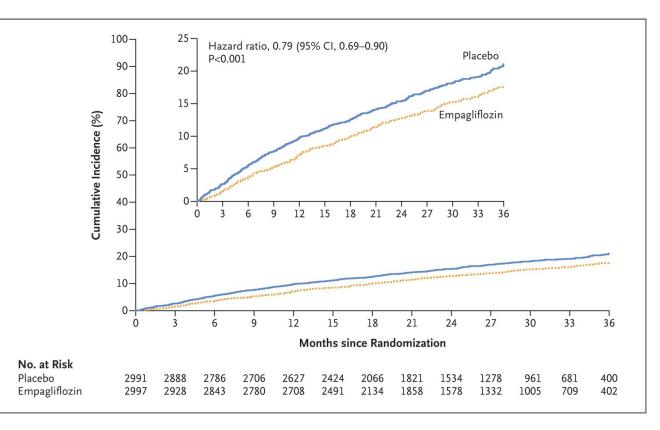
A All-cause mortality								
	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 inhibitor	Placebo						
EMPEROR-Reduced	249/1863 (13·4%)	266/1867 (14-2%)				<b>.</b>		0.92 (0.77-1.10)
DAPA-HF	276/2373 (11.6%)	329/2371 (13.9%)				_		0.83 (0.71–0.97)
Total								0.87 (0.77–0.98)
Test for overall treatment effect p=0·018 Test for <u>heterogeneity</u> of effect p=0·39			0-25	0.50	0.75	1.00	1.25	
B Cardiovascular death	Number of the second for	where frontion to (a)						
	Number with event/n							HR (95% CI)
	SGLT2 inhibitor	Placebo						
EMPEROR-Reduced	187/1863 (10.0%)	202/1867 (10.8%)						0.92 (0.75-1.12)
DAPA-HF	227/2373 (9.6%)	273/2371 <b>(11</b> ·5%)			_	_		0.82 (0.69–0.98)
Total								0.86 (0.76–0.98)
Test for overall treatment effect p=0·027 Test for heterogeneity of effect p=0·40			0.25	0.50	0.75	1.00	1.25	
C First hospitalisation for heart failure of								
	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 inhibitor	Placebo						
EMPEROR-Reduced	361/1863 (19-4%)	462/1867 (24.7%)						0.75 (0.65-0.86)
DAPA-HF	386/2373 (16-3%)	502/2371 (21-2%)			<b>_</b>			0.74 (0.65–0.85)
Total								0·74 (0·68–0·82)
Test for overall treatment effect p<0.0001 Test for heterogeneity of effect p=0.89			0.25	0.50	0.75	1.00	1.25	
D First hospitalisation for heart failure								
	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 inhibitor	Placebo						
EMPEROR-Reduced	246/1863 (13-2%)	342/1867 (18-3%)						0.69 (0.59-0.81)
DAPA-HF	231/2373 (9.7%)	318/2371 (13·4%)		_				0.70 (0.59-0.83)
Total		5=0,=5,=(=5,1,0,			Ā			0.69 (0.62-0.78)
Test for overall treatment effect p<0.0001					<u> </u>			
Test for heterogeneity of effect p=0.90			0.25	0.50	0.75	1.00	1.25	
E First kidney outcome composite								
	Number with event/n	umber of patients (%)						HR (95% CI)
	SGLT2 inhibitor	Placebo						
EMPEROR-Reduced	18/1863 (1.0%)	33/1867 (1.8%)				_		0.52 (0.29-0.92)
DAPA-HF	28/2373 (1-2%)	39/2371 (1.6%)			_		_	0.71 (0.44–1.16)
Total		55,-5,-(,				-		0.62 (0.43-0.90)
Test for overall treatment effect p=0.013								
Test for heterogeneity of effect p=0.42			0.25	0.50	0.75	1.00	1.25	
F All (first and recurrent) hospitalisation	n for heart failure or card Number with event/n							RR (95% CI)
	SGLT2 inhibitor	Placebo						
EMPEROR-Reduced	575/1863 (30-9%)	753/1867 (40-3%)				-		0.76 (0.65–0.89)
DAPA-HF	567/2373 (23.9%)	742/2371 (31-3%)						0.75 (0.65-0.88)
Total								0.75 (0.68–0.84)
Test for overall treatment effect p<0.0001 Test for heterogeneity of effect p=0.91			0.25	0.50	0.75	1.00	1.25	
rescrot neterogeneity of effect p=0.91			0.25	0.20	0.75	T-00	1.22	

Zannad et al. Lancet. 2020;396:819-829.

## Primary Outcome: A Composite of CV Death or Hospitalization for HF

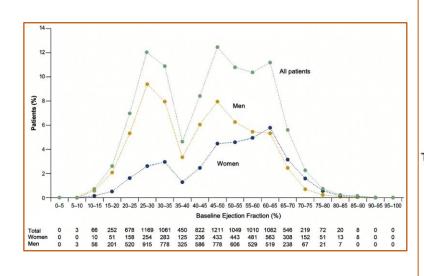
- 5988 patients with class II–IV HF and an EF of >40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy
- The primary outcome was a composite of CV death or HF hospitalization

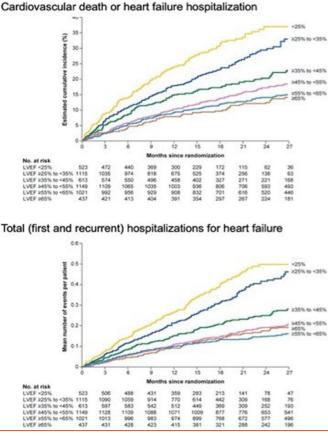
 The effects of empagliflozin appeared consistent in patients with or without diabetes

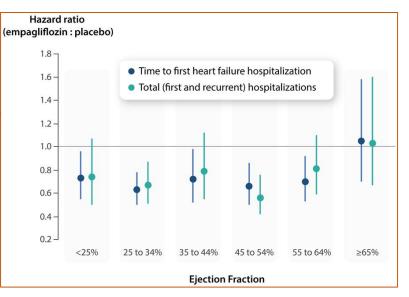


## Effect of Empagliflozin in Patients With Heart Failure Across the Spectrum of LVEF

 A pooled analysis of both the EMPEROR-Reduced and EMPEROR-Preserved trials (9,718 pts)



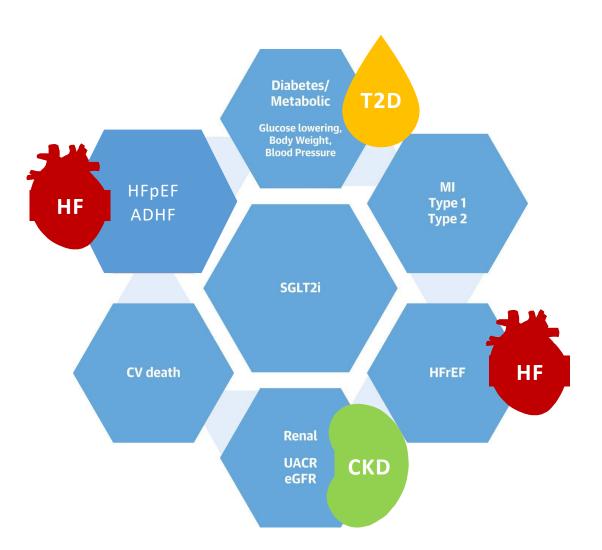




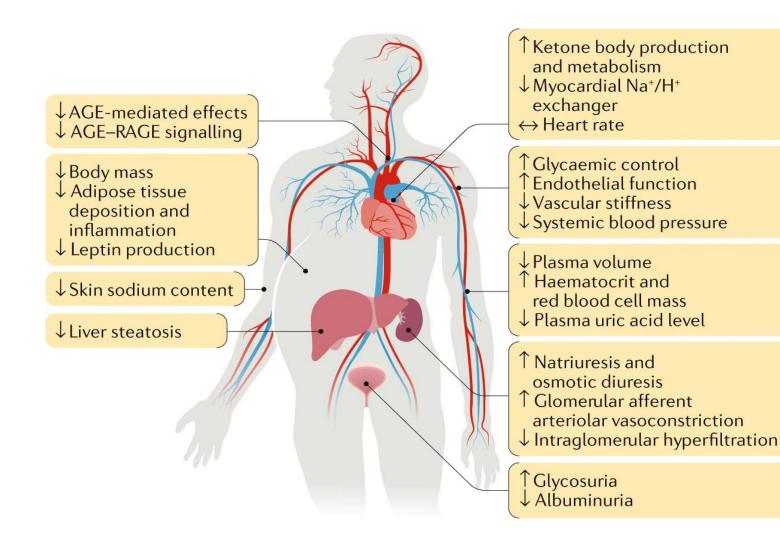
	Empagliflozin	Placebo	Hazard ratio (95% CI)
Cardiovascular death or	heart failure hospita	lization	
LVEF <25%	117/476	154/523	0.77 (0.60–0.98)
LVEF ≥25 to <35%	191/1115	255/1115	<b>HH</b> 0.72 (0.59–0.87)
LVEF ≥35 to <45%	115/659	128//613	0.82 (0.63–1.05)
LVEF ≥45 to <55%	159/1111	215/1149	
LVEF ≥55 to <65%	134/1071	161/1021	0.78 (0.62–0.97)
LVEF ≥65%	60/428	60/437	0.98 (0.68–1.40)
First heart failure hospit	alization		
LVEF <25%	84/476	113/523	0.73 (0.55–0.96)
LVEF ≥25 to <35%	124/1115	192/1115	0.63 (0.50-0.78)
LVEF ≥35 to <45%	69/659	87/613	0.72 (0.52–0.98)
LVEF ≥45 to <55%	90/1111	139/1149	0.66 (0.50–0.86)
LVEF ≥55 to <65%	90/1071	118/1021	0.70 (0.53–0.92)
LVEF ≥65%	48/428	45/437	1.05 (0.70–1.58)
Total (first and recurren	t) heart failure hospi	talizations	
LVEF <25%	126	179	<b>→→→→</b> 0.74 (0.50–1.07)
LVEF ≥25 to <35%	199	313	• ■ 0.67 (0.51–0.87)
LVEF ≥35 to <45%	118	143	0.79 (0.55–1.12)
LVEF ≥45 to <55%	125	218	0.56 (0.42–0.76)
LVEF ≥55 to <65%	140	161	0.81 (0.59–1.10)
LVEF ≥65%	87	80	1.03 (0.67–1.60)
Cardiovascular death			
LVEF <25%	57/476	69/523	0.93 (0.65–1.32)
LVEF ≥25 to <35%	105/1115	108/1115	0.95 (0.72–1.24)
LVEF ≥35 to <45%	70/659	63/613	1.07 (0.76–1.51)
LVEF ≥45 to <55%	86/1111	115/1149	0.77 (0.58–1.02)
LVEF ≥55 to <65%	65/1071	65/1021	0.99 (0.70–1.40)
LVEF ≥65%	23/428	26/437	0.83 (0.47–1.45)
			0.125 0.25 0.5 1.0 2.0 4.0
			Empagliflozin better Placebo better

Butler J et al. Eur Heart J. 2021 Dec 8: 8:ehab798. doi:10.1093/eurheartj/ehab798.

## Effects of SGLT2 inhibitor on cardio-metabolic-renal events

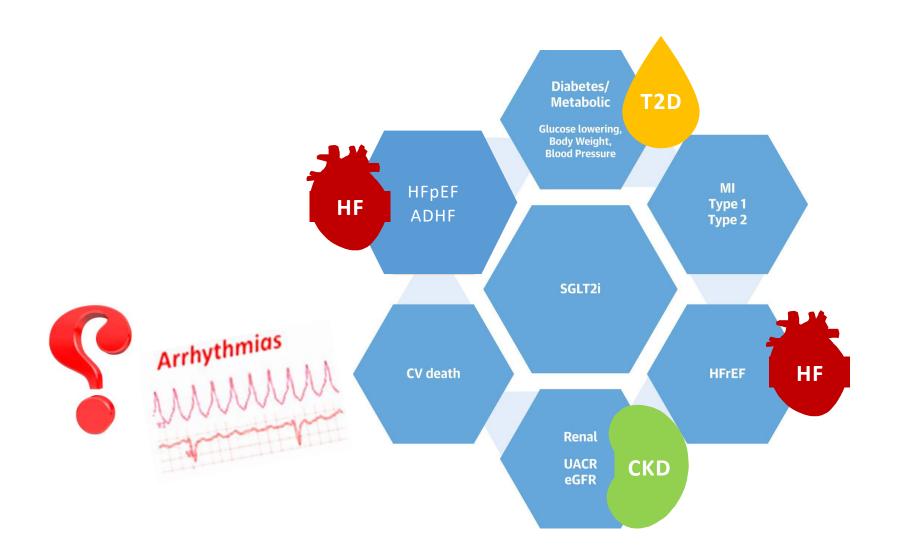


### Suggested Mechanisms of the Cardiovascular and Renal Benefits of SGLT2 Inhibitors



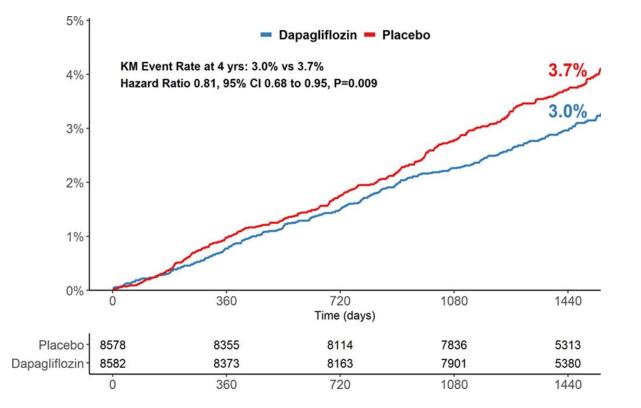
#### Cowie & Fisher. Nat Rev Cardiol. 2020;17:761-772.

## Effects of SGLT2 inhibitor on cardio-metabolic-renal events



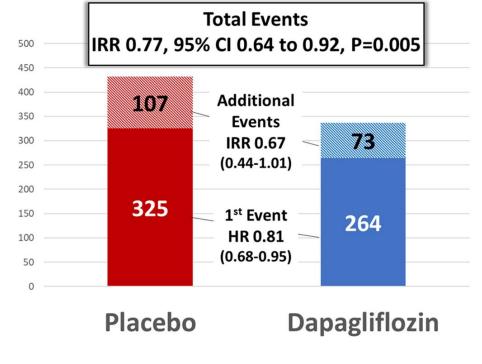
Insights from the DECLRARE-TIMI 58 Trial

- DECLARE-TIMI 58 Trial: 17,160 patients with T2DM and either multiple risk factors for ACVD (n=10,186) or known ACVD disease (n=6974)
- Dapagliflozin decreased the incidence of reported episodes of AF/AFL adverse events in high-risk patients with T2DM



Insights from the DECLRARE-TIMI 58 Trial

- First event, additional events, and total events of atrial fibrillation and atrial flutter with dapagliflozin versus placebo
- This effect was consistent regardless of the patient's previous history of AF, ACVD, or HF

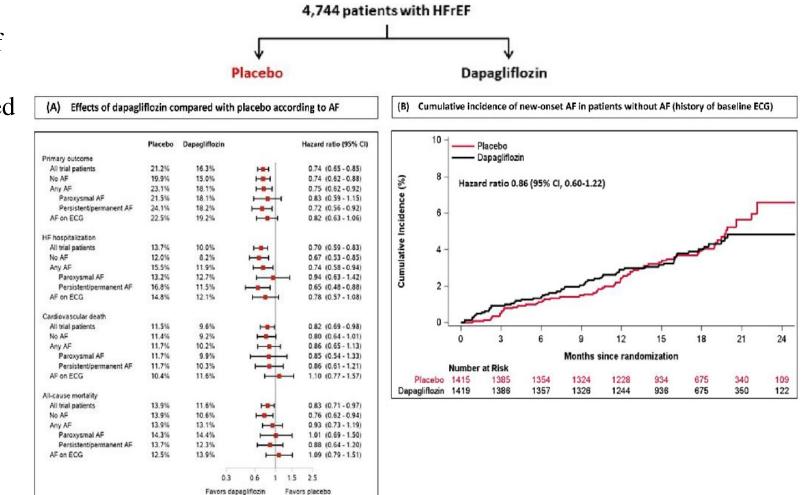


Subgroups	Dapa n (%)	Placebo n (%)		HR (95%CI)	P interaction
AF/AFL	264 (3.1)	325 (3.8)		0.81 (0.68, 0.95)	
Age					0.66
Age < 70	192 (2.8)	228 (3.3)	·	0.83 (0.68, 1.00)	
Age ≥70	72 (4.3)	97 (5.6)		0.76 (0.56, 1.03)	
Sex					1.00
Male	186 (3.4)	226 (4.2)	⊢ <b></b>	0.80 (0.66, 0.98)	
Female	78 (2.5)	99 (3.0)	⊢ <b>−</b>	0.80 (0.60, 1.08)	
ASCVD vs. MRF					0.72
ASCVD	141 (4.1)	170 (4.9)	·	0.83 (0.66, 1.04)	
MRF	123 (2.4)	155 (3.1)	<b>⊢−−−−</b> 1	0.78 (0.62, 0.99)	
HF					0.88
HF	55 (6.5)	70 (8.0)	·	0.78 (0.55, 1.11)	
No HF	209 (2.7)	255 (3.3)	▶ <b>──</b> ₩	0.81 (0.68, 0.97)	
schemic stroke					0.88
Prior ischemic stroke	21 (3.8)	27 (4.8)	← ■	0.84 (0.47, 1.48)	
No prior ischemic stroke	243 (3.0)	298 (3.7)	▶ <b></b>	0.81 (0.68, 0.96)	
AF/AFL					0.89
Hx of AF/AFL	68 (12.4)	86 (15.2)	F	0.79 (0.58, 1.09)	
No Hx of AF/AFL	196 (2.4)	239 (3.0)	▶ <b>──</b>	0.81 (0.67, 0.98)	
SBP					0.20
SBP <135	123 (2.9)	135 (3.2)	⊢ <b></b>	0.91 (0.71, 1.16)	
SBP ≥135	141 (3.2)	190 (4.4)	<b>⊢■</b>	0.73 (0.59, 0.91)	
HbA1c					0.54
HbA1c <8%	135 (3.3)	174 (4.3)	<b>⊢−−−−</b> 1	0.77 (0.61, 0.96)	
HbA1c ≥8%	129 (2.9)	151 (3.4)		0.85 (0.67, 1.07)	
вмі					0.75
BMI ≥30 kg/m²	199 (3.9)	246 (4.88)		0.78 (0.65, 0.94)	
BMI <30 kg/m <sup>2</sup>	64 (1.9)	79 (2.24)		0.83 (0.60, 1.15)	
eGFR					0.88
eGFR ≥90 ml/min/1.73m²	95 (2.3)	107 (2.7)		0.85 (0.65, 1.12)	
eGFR 60-90 ml/min/1.73m <sup>2</sup>	136 (3.5)	176 (4.5)	<b>⊢−−−−</b>	0.78 (0.62, 0.98)	
eGFR <60 ml/min/1.73m <sup>2</sup>	32 (5.3)	42 (6.4)		0.82 (0.52, 1.30)	
			0.50 0.75 1.0 1.5 Favors Dapagliflozin $\leftarrow \rightarrow$ Favors Placebo		

Zelniker TA, et al. Circulation 2020; 15:1227-1234

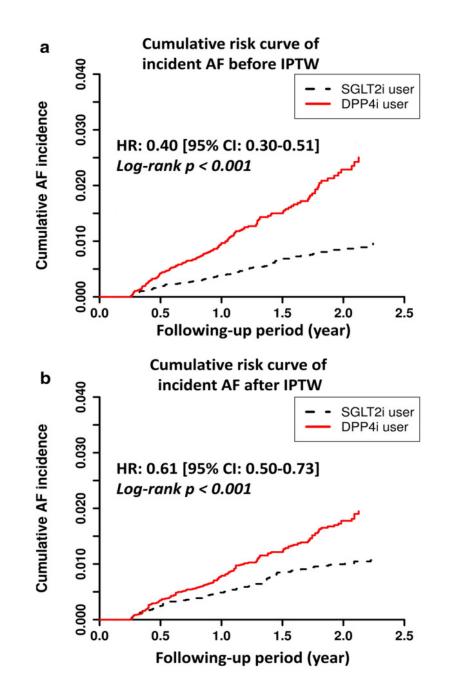
Insights from the DAPA-HF Trial

- Dapagliflozin reduced the risk of worsening HF events, CV death, and all-cause death, and improved outcomes in patients with and without AF (irrespective of definition or type)
- Dapagliflozin did not reduce the risk of new-onset AF



Insights from Real-World Practice

- Medical data from 15,606 and 12,383 patients with T2DM treated with SGLT2i and DPP4i, respectively
- The use of SGLT2i was associated with a lower risk of newonset AF compared with DPP4i after propensity-score weighting
- The advantage of SGLT2i over DPP4i persisted with different SGLT2i (dapagliflozin or empagliflozin)



Ling A, et al. Cardiovasc Diabetol. 2020;19:188-199.

Meta-Analysis of Randomized Controlled Trails

- Overall, 31 eligible trials reported on AF events (75,279 patients, mean age 62, 35.0% women).
- Moderate quality evidence supported a lower risk of <u>serious AF/AFL events</u> with SGLTi (1.1% versus 1.5%; risk ratio 0.75 [95% CI, 0.66–0.86]; I<sup>2</sup>=0%).
- A similar reduction in <u>total AF events</u> was also noted with SGLT inhibitors.

	SGL	Г-і	Placebo/C	ontrol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bailey et al. 2013	1	409	0	137	0.2%	1.01 [0.04, 24.64]	
Bode et al. 2015	4	477	2	237	0.6%	0.99 [0.18, 5.39]	
CANTATA-MSU	1	313	0	156	0.2%	1.50 [0.06, 36.61]	
CANVAS	53	2886	32	1441	8.9%	0.83 [0.54, 1.28]	
CANVAS-R	19	2904	25	2903	4.7%	0.76 [0.42, 1.38]	
Cefalu et al. 2015	0	460	1	462	0.2%	0.33 [0.01, 8.20]	· · · · · · · · · · · · · · · · · · ·
CREDENCE	18	2200	21	2197	4.3%	0.86 [0.46, 1.60]	
DAPA-CKD	9	2149	20	2149	2.7%	0.45 [0.21, 0.99]	
DAPA-HF	36	2368	46	2368	9.0%	0.78 [0.51, 1.21]	
DECLARE-TIMI 58	163	8582	221	8578	41.8%	0.74 [0.60, 0.90]	=
DELIGHT	0	145	0	148		Not estimable	
DURATION-8	0	231	2	230	0.2%	0.20 [0.01, 4.13]	· · · · · · · · · · · · · · · · · · ·
EMPA-REG BASAL	2	324	0	170	0.2%	2.63 [0.13, 54.49]	
EMPA-REG EXTEND MONO	0	1655	3	822	0.2%	0.07 [0.00, 1.37]	· · · · · · · · · · · · · · · · · · ·
EMPA-REG EXTEND PIO	2	333	0	165	0.2%	2.49 [0.12, 51.47]	
EMPA-REG OUTCOME	48	4687	19	2333	6.0%	1.26 [0.74, 2.13]	
EMPA-REG RENAL	1	419	2	319	0.3%	0.38 [0.03, 4.18]	
EMPEROR-Reduced	27	1863	55	1863	8.1%	0.49 [0.31, 0.77]	
Ferrannini et al. 2010	0	410	1	75	0.2%	0.06 [0.00, 1.50]	· · · · · · · · · · · · · · · · · · ·
inTandem1	1	525	1	268	0.2%	0.51 [0.03, 8.13]	
inTandem3	1	699	0	703	0.2%	3.02 [0.12, 73.94]	
Leiter et al. 2014	2	482	3	483	0.5%	0.67 [0.11, 3.98]	
Mathieu et al. 2015	1	160	0	160	0.2%	3.00 [0.12, 73.09]	
Roden et al. 2013	0	534	0	229		Not estimable	
Søfteland et al. 2017	1	222	0	110	0.2%	1.49 [0.06, 36.36]	
VERTIS CV	61	5493	37	2745	10.2%	0.82 [0.55, 1.24]	
VERTIS FACTORIAL	0	487	1	247	0.2%	0.17 [0.01, 4.14]	· · · · ·
VERTIS-MET	4	412	0	209	0.2%	4.58 [0.25, 84.60]	
VERTIS RENAL	1	313	0	154	0.2%	1.48 [0.06, 36.14]	
Wilding et al. 2012	0	610	1	197	0.2%	0.11 [0.00, 2.64]	· · · · · · · · · · · · · · · · · · ·
Yale et al. 2014	2	179	0	90	0.2%	2.53 [0.12, 52.10]	
Total (95% CI)		42931		32348	100.0%	0.75 [0.66, 0.86]	•
Total events	458		493				
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i <sup>2</sup> = 23.14,	df = 28	(P = 0.73); l <sup>2</sup>	<sup>e</sup> = 0%			
Test for overall effect: Z = 4.31	,		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				0.01 0.1 1 10 10 Favours SGLT-i Favours Placebo/Control

Meta-Analysis of Randomized Controlled Trails

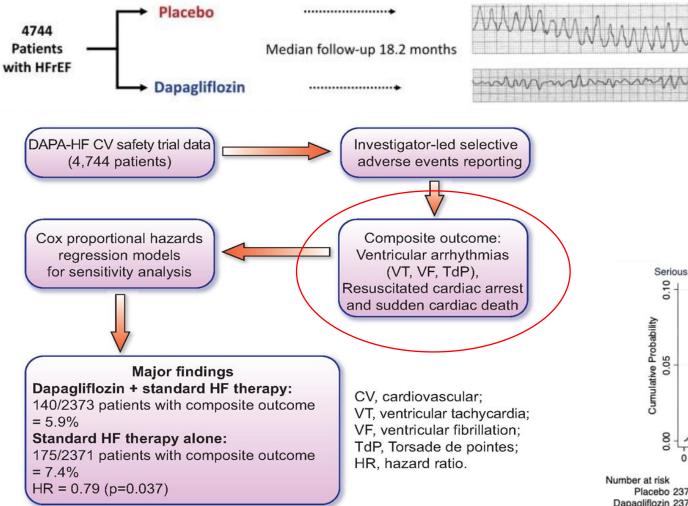
- Three trials reported on HF hospitalization/CV death stratified by a baseline h/o of AF (18,832 patients)
- SGLT inhibitors resulted in a lower risk in HF hospitalization or CV death (HR 0.70 [95% CI, 0.57–0.85]; I<sup>2</sup>=0%) similar to the effect estimate for patients without AF

				Hazard Ratio		Hazar	d Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Rando	om, 95% Cl	
2.2.1 AF/AFlutter								
EMPA-REG OUTCOME AF: n=389	-0.5447	0.2433	17.8%	0.58 [0.36, 0.93]				
SCORED AF/AFI: n=1504	-0.2744	0.1468	48.9%	0.76 [0.57, 1.01]			ł	
SOLOIST AF/AFI: n=576 Subtotal (95% CI)	-0.3857	0.1777	33.3% <b>100.0%</b>	0.68 [0.48, 0.96] <b>0.70 [0.57, 0.85]</b>		•		
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 0.94$ , c Test for overall effect: Z = 3.50 (P = 0.000	· //	6						
2.2.2 No AF/AFlutter								
EMPA-REG OUTCOME No AF: n=6631	-0.4005	0.1007	42.7%	0.67 [0.55, 0.82]				
SCORED No AF/AFI: n=9086	-0.3711	0.1746	14.2%	0.69 [0.49, 0.97]				
SOLOIST no AF/AFI: n=646 Subtotal (95% CI)	-0.3147	0.1001	43.2% 100.0%	0.73 [0.60, 0.89] <b>0.70 [0.61, 0.79]</b>		•		
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.37, c	lf = 2 (P = 0.83); l <sup>2</sup> = 0%	6						
Test for overall effect: Z = 5.46 (P < 0.000	01)							
					⊢ 0.1	0.2 0.5		10
Test for subgroup differences: Chi <sup>2</sup> = 0.00	, df = 1 (P = 1.00), l <sup>2</sup> =	0%				Favours SGLT2-i	Favours Placebo	

Pandey AK, et al. JAHA. 2021;10: 0(17):e022222.

## Effects of SGLTi on Ventricular Arrhythmias and SCD Insights from the DAPA-HF Trial

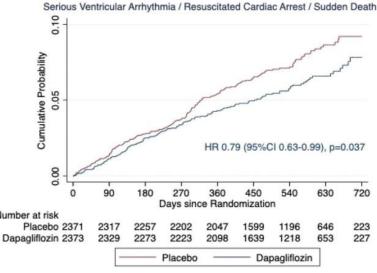
Investigator Reports (Serious Adverse Events)



#### Curtain JP, et al. Eur Heart J 2021;42:3727–3738.

 Table 2
 Backward stepwise logistic regression multivariable model to predict any serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death

Predictor variable <sup>a</sup>	Odds ratio (95% CI)	<i>P</i> -value <sup>b</sup>	χ <sup>2</sup>	
Log-transformed NT-proBNP (per 1 unit increase)	1.54 (1.34–1.77)	<0.001	36.	
Previous ventricular arrhythmia	1.93 (1.41–2.64)	<0.001	16.	
LVEF (per 5% increase)	0.86 (0.78-0.94)	0.001	11.	
Systolic BP (per 10mmHg increase)	0.88 (0.81-0.96)	0.004	8	
Previous MI	1.42 (1.11–1.82)	0.005	7.	
Male sex	1.53 (1.10-2.12)	0.012	6	
BMI (per 1 kg/m² increase)	1.03 (1.00-1.05)	0.020	5.	
Sodium (per 1 mmol/L increase)	0.96 (0.92-0.99)	0.039	4	
Non-white race	0.85 (0.72-0.99)	0.038	4	
Dapagliflozin	0.80 (0.63-1.02)	0.067	3.	
Cardiac resynchronization therapy	0.64 (0.39–1.04)	0.070	3	
Previous HF hospitalization	0.99 (0.78-1.27)	0.985	0	



# Effects of SGLTi on Ventricular Arrhythmias and SCD Insights from the DAPA-HF Trial

#### Table 3 Cox proportional hazards models of clinical outcomes according to the individual components and the composite of serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death and randomized treatment

	Dapagliflozin		Placebo		
Outcome	n/N (%)	Event rate per 100 person-years	n/N (%)	Event rate per 100 person-years	Hazard ratio <sup>a</sup> (95% CI)
Serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death	140/2373 (5.9)	4.1 (3.4-4.8)	175/2371 (7.4)	5.1 (4.4–6.0)	0.79 (0.63–0.99) <i>P</i> = 0.037
Serious ventricular arrhythmia	50/2373 (2.1)	1.4 (1.1–1.9)	65/2371 (2.7)	1.9 (1.5–2.4)	0.76 (0.53-1.10)
Resuscitated cardiac arrest	5/2373 (0.2)	0.14 (0.06-0.34)	3/2371 (0.1)	0.09 (0.03-0.27)	_
Sudden death	93/2373 (3.9)	2.7 (2.2–3.3)	113/2371 (4.8)	3.3 (2.7–3.9)	0.81 (0.62-1.07)
VT/VF/torsade de pointes/resuscitated car- diac arrest/sudden death	134/2373 (5.6)	3.9 (3.3–4.6)	171/2371 (7.2)	5.0 (4.3–5.8)	0.77 (0.62–0.97) P=0.025
VT/VF/torsade de pointes	60/2373 (2.5)	1.8 (1.4–2.3)	44/2371 (1.9)	1.3 (0.9–1.7)	0.72 (0.49-1.07)
Serious ventricular arrhythmia ( <i>minus</i> NSVT)/resuscitated cardiac arrest/sudden death	138/2373 (5.8)	4.0 (3.4-4.7)	169/2373 (7.1)	5.0 (4.3–5.8)	0.81 (0.64–1.01) P = 0.060
VT (minus NSVT)/VF/torsade de pointes/ resuscitated cardiac arrest/sudden death	132/2373 (5.6)	3.8 (3.2–4.5)	165/2371 (7.0)	4.8 (4.2–5.6)	0.79 (0.63–0.99) P=0.043

Cl, confidence interval; NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

<sup>a</sup>Models included factors for randomized treatment, history of heart failure hospitalization and were stratified by diabetes status. A hazard ratio was not calculated where there were fewer than 10 events overall.

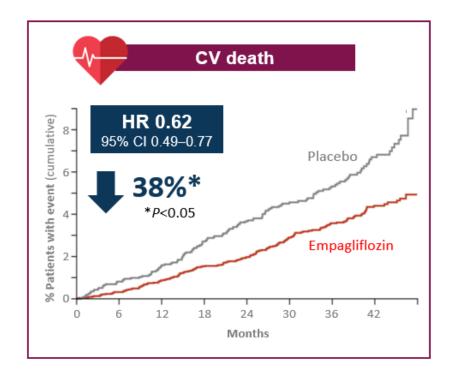
#### Curtain JP, et al. Eur Heart J 2021;42:3727–3738.

 Table 4
 Cox proportional hazards models for a serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death according to randomized treatment assignment in key patient subgroups

	Dapagliflozin		Placebo			Interaction P-value	
Outcome	n/N (%)	Event rate per 100 person-years	n/N (%)	Event rate per 100 person-years	Hazard ratio <sup>a</sup> (95% Cl)	P-value	
Ischaemic aetiolog	y						
Yes	84/1316 (6.4)	4.4 (3.5-5.4)	113/1358 (8.3)	5.8 (4.8-7.0)	0.76 (0.57-1.00)	0.597	
No	56/1057 (5.3)	3.7 (2.8-4.8)	62/1013 (6.1)	4.3 (3.3-5.5)	0.86 (0.60-1.23)	0.377	
MRA at baseline							
Yes	110/1696 (6.5)	4.5 (3.7-5.4)	132/1674 (7.9)	5.5 (4.7-6.6)	0.81 (0.63-1.05)	0.621	
No	30/677 (4.4)	3.0 (2.1-4.3)	43/697 (6.2)	4.2 (3.1-5.7)	0.71 (0.45-1.14)	0.021	
ICD/CRT-D at bas	eline						
Yes	51/622 (8.2)	5.8 (4.4-7.6)	51/620 (8.2)	5.9 (4.5-7.7)	0.99 (0.67-1.45)	0.474	
No	89/1751 (5.1)	3.5 (2.8-4.3)	124/1751 (7.1)	4.9 (4.1-5.8)	0.71 (0.54-0.93)	0.174	
Time from diagnos	is of HF						
<1 year	19/531 (3.6)	2.5 (1.6-3.8)	30/567 (5.3)	3.7 (2.6-5.3)	0.67 (0.38-1.20)		
≥1year	121/1842 (6.6)	4.5 (3.8-5.4)	145/1804 (8.0)	5.6 (4.8-6.6)	0.81 (0.64-1.03)	0.533	
Diabetes mellitus							
Yes	57/993 (5.7)	3.9 (3.0-5.1)	81/990 (8.2)	5.8 (4.7-7.2)	0.69 (0.49-0.96)	0.273	
No	83/1380 (6.0)	4.1 (3.3-5.1)	94/1381 (6.8)	4.7 (3.8-5.7)	0.88 (0.66-1.18)	0.275	
Previous ventricula	ar arrhythmia						
Yes	26/278 (9.4)	6.7 (4.5-9.8)	34/242 (14.0)	10.1 (7.2-14.1)	0.66 (0.40-1.10)	0.492	
No	114/2095 (5.4)	3.7 (3.1-4.5)	141/2129 (6.6)	4.6 (3.9-5.4)	0.81 (0.63-1.04)	0.472	
NYHA class							
Ш	82/1606 (5.1)	3.5 (2.8-4.3)	108/1597 (6.8)	4.7 (3.9-5.7)	0.74 (0.55-0.98)	0.454	
ШЛV	58/767 (7.6)	5.4 (4.1-6.9)	67/774 (8.7)	6.0 (4.7-7.7)	0.87 (0.61-1.24)	0.454	
NT-proBNP (pg/m	l) <sup>b</sup>						
≤Median	45/1193 (3.8)	2.5 (1.9-3.4)	76/1179 (6.4)	4.4 (3.5-5.5)	0.58 (0.40-0.84)	0.032	
>Median	95/1179 (8.1)	5.7 (4.6-6.9)	99/1191 (8.3)	5.9 (4.9-7.2)	0.96 (0.72-1.27)	0.032	
LVEF (%)							
≤Median	87/1230 (7.1)	5.0 (4.0-6.2)	113/1239 (9.1)	6.5 (5.4-7.8)	0.77 (0.58-1.02)	0.740	
>Median	53/1143 (4.6)	3.1 (2.4-4.1)	62/1132 (5.5)	3.7 (2.9-4.8)	0.83 (0.58-1.20)	0.740	
Systolic BP (mmHg	3)						
≤Median	87/1171 (7.4)	5.3 (4.3-6.5)	101/1223 (8.3)	5.9 (4.9-7.2)	0.89 (0.67-1.19)	0.226	
>Median	53/1202 (4.4)	2.9 (2.2-3.9)	74/1148 (6.4)	4.4 (3.5-5.5)	0.67 (0.47-0.96)	0.226	

BP, blood pressure; CI, confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-8-type natriuretic peptide; NYHA, New York Heart Association. <sup>a</sup>Models included factors for randomized treatment, history of HF hospitalization and were stratified by diabetes status. <sup>b</sup>Missing data for *n* = 2 patients.

# Effects of SGLTi on Ventricular Arrhythmias and SCD EMPA-REG OUTCOME and SCD



#### Section L. Categories of cardiovascular death

Table S5. Categories of cardiovascular death.

		Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)								
ł		no. (%)											
	Patients with cardiovascular death	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)								
	Sudden death	38 (1.6)	30 (1.3)	23 (1.0)	53 (1.1)								
r	Worsening of heart failure	19 (0.8)	7 (0.3)	4 (0.2)	11 (0.2)								
ľ	Acute myocardial infarction	11 (0.5)	6 (0.3)	9 (0.4)	15 (0.3)								
f	Stroke	11 (0.5)	9 (0.4)	7 (0.3)	16 (0.3)								
ľ	Cardiogenic shock	3 (0.1)	1 (<0.1)	2 (0.1)	3 (0.1)								
ł	Other cardiovascular death*	55 (2.4)	37 (1.6)	37 (1.6)	74 (1.6)								

\*Includes fatal cases that were not assessable due to a lack of information and were presumed to be cardiovascular deaths as per conventional definition.

- EMPA-REG OUTCOME trial: 5687 (empagliflozin) vs. 2333 (placebo)
- Empagliflozin reduced incidence of SCD: 53 (1.1%) vs. 38 (1.6%) events

## Effects of SGLTi on Ventricular Arrhythmias and SCD

Meta-Analysis of Randomized Controlled Trails

#### Incidence of SCD

ean Heart

nm Association

	SGLT	'2i	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
CANVAS 2017	9	2886	5	1441	10.9%	0.90 [0.30, 2.68]	
CANVAS-R 2017	0	2904	1	2903	2.5%	0.33 [0.01, 8.18]	
CREDENCE 2019	2	2200	2	2197	3.3%	1.00 [0.14, 7.08]	
DAPA-CKD 2020	1	2149	2	2149	3.3%	0.50 [0.05, 5.51]	
DAPA-HF 2019	18	2368	27	2368	44.2%	0.67 [0.37, 1.21]	
DECLARE - TIMI 58 2018	14	8574	16	8569	26.2%	0.87 [0.43, 1.79]	
DEFINE-HF 2019	0	131	1	132	2.4%	0.34 [0.01, 8.17]	
EMPA-REG OUTCOME 2015	4	4687	2	2333	4.4%	1.00 [0.18, 5.43]	
EMPA-REG RENAL 2014	0	419	1	319	2.8%	0.25 [0.01, 6.21]	
Total (95% CI)		26318		22411	100.0%	0.74 [0.50, 1.08]	•
Total events	48		57				
Heterogeneity: Chi <sup>2</sup> = 1.66, df =	8 (P = 0.9	9); l² = 0	0%				
Test for overall effect: Z = 1.55 (	P = 0.12)						0.01 0.1 1 10 100 Favours [SGLT2i] Favours [placebo]

• SGLT2i therapy was not associated with an overall lower risk of SCD or VAs in patients with T2DM and/or HF and/or CKD.

Sfairopoulos D, et al. Europace 2022;24:20-30.

• Further research is needed since the number of SCD and VA events were relatively small.

## Incidence of VAs

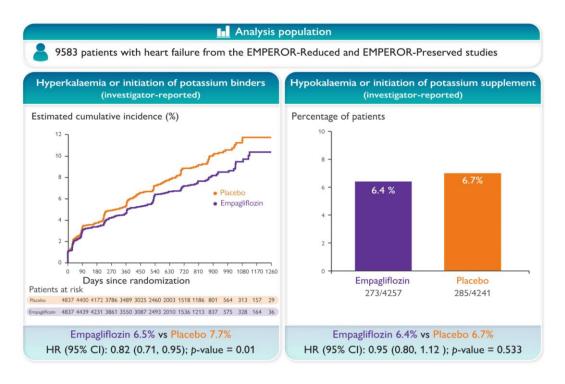
	SGLT	[2i	Cont	rol		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	<u> </u>	M-H, Fixe	ed, 95% CI	
CANDLE 2020	0	118	1	123	1.0%	0.35 [0.01, 8.44]	_			
CANTATA-SU 2015	0	968	1	482	1.4%	0.17 [0.01, 4.07]	+			
CANVAS 2017	10	2886	9	1441	8.1%	0.55 [0.23, 1.36]			-	
CANVAS-R 2017	4	2904	5	2903	3.4%	0.80 [0.21, 2.98]				
CREDENCE 2019	4	2200	6	2197	4.1%	0.67 [0.19, 2.36]				
DAPA-CKD 2020	1	2149	0	2149	0.3%	3.00 [0.12, 73.60]				
DAPA-HF 2019	58	2368	68	2368	46.0%	0.85 [0.60, 1.21]		-	-	
DECLARE - TIMI 58 2018	33	8574	28	8569	18.9%	1.18 [0.71, 1.95]		1		
DIA3004 2014	0	179	1	90	1.3%	0.17 [0.01, 4.10]	+	,		
EMBLEM 2019	1	52	0	53	0.3%	3.06 [0.13, 73.36]			•	
EMPA-REG H2H-SU 2018	1	765	0	780	0.3%	3.06 [0.12, 74.97]				-
EMPA-REG OUTCOME 2015	11	4687	13	2333	11.7%	0.42 [0.19, 0.94]				
EMPERIAL-Reduced 2020	0	155	1	156	1.0%	0.34 [0.01, 8.17]				
Leiter 2014	1	482	0	483	0.3%	3.01 [0.12, 73.61]				
Mathieu 2015	1	160	0	160	0.3%	3.00 [0.12, 73.09]				_
Nauck 2011	1	406	0	408	0.3%	3.01 [0.12, 73.79]		1.		_
PIONEER 2 2019	0	409	1	410	1.0%	0.33 [0.01, 8.18]	_	× .		
Total (95% CI)		29462		25105	100.0%	0.84 [0.66, 1.06]		•		
Total events	126		134							
Heterogeneity: Chi <sup>2</sup> = 12.14, df	= 16 (P = 0	0.73); l <sup>2</sup>	= 0%					0.1	1 10	40
Test for overall effect: Z = 1.46	(P = 0.14)						0.01	0.1 Favours [SGLT2i]	1 10 Favours [control]	10

#### Incidence of VAs

	SGLT2i Control				Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
2.8.1 Low dosage							
CANDLE 2020	0	118	1	123	4.3%	0.35 [0.01, 8.44]	
CANTATA-SU-100mg 2015	0	483	1	482	4.4%	0.33 [0.01, 8.15]	
CANVAS-100mg 2017	5	1445	9	1441	26.1%	0.55 [0.19, 1.65]	
CREDENCE 2019	4	2200	6	2197	17.4%	0.67 [0.19, 2.36]	
DIA3004-100mg 2014	0	90	1	90	4.3%	0.33 [0.01, 8.08]	
EMBLEM 2019	1	52	0	53	1.4%	3.06 [0.13, 73.36]	
EMPA-REG OUTCOME-10mg 2015	3	2345	13	2333	37.8%	0.23 [0.07, 0.80]	
EMPERIAL-Reduced 2020	0	155	1	156	4.3%	0.34 [0.01, 8.17]	
Subtotal (95% CI)		6888		6875	100.0%	0.45 [0.25, 0.82]	<b>~</b>
Total events	13		32				
Heterogeneity: Chi <sup>2</sup> = 3.14, df = 7 (P =	0.87); l <sup>2</sup> =	= 0%					
Test for overall effect: $Z = 2.62$ ( $P = 0$ .	009)						
2.8.2 High dosage							
Lioiz ingil doolage							
CANTATA-SU-300mg 2015	0	485	1	482	5.9%	0.33 [0.01, 8.11]	
	0 5	485 1441	1 9	482 1441	5.9% 35.3%	0.33 [0.01, 8.11] 0.56 [0.19, 1.65]	
CANTATA-SU-300mg 2015	•		100				
CANTATA-SU-300mg 2015 CANVAS-300mg 2017	•	1441	100	1441	35.3%	0.56 [0.19, 1.65]	
CANTATA-SU-300mg 2015 CANVAS-300mg 2017 DIA3004-300mg 2014	•	1441 89	9 1	1441 90	35.3% 5.8%	0.56 [0.19, 1.65] 0.34 [0.01, 8.16]	
CANTATA-SU-300mg 2015 CANVAS-300mg 2017 DIA3004-300mg 2014 EMPA-REG H2H-SU 2018	5 0 1	1441 89 765	9 1 0	1441 90 780	35.3% 5.8% 1.9%	0.56 [0.19, 1.65] 0.34 [0.01, 8.16] 3.06 [0.12, 74.97]	
CANTATA-SU-300mg 2015 CANVAS-300mg 2017 DIA3004-300mg 2014 EMPA-REG H2H-SU 2018 EMPA-REG OUTCOME-25mg 2015	5 0 1	1441 89 765 2342	9 1 0	1441 90 780 2333	35.3% 5.8% 1.9% 51.0%	0.56 [0.19, 1.65] 0.34 [0.01, 8.16] 3.06 [0.12, 74.97] 0.61 [0.25, 1.48]	
CANTATA-SU-300mg 2015 CANVAS-300mg 2017 DIA3004-300mg 2014 EMPA-REG H2H-SU 2018 EMPA-REG OUTCOME-25mg 2015 Subtotal (95% CI)	5 0 1 8 14	1441 89 765 2342 5122	9 1 0 13	1441 90 780 2333	35.3% 5.8% 1.9% 51.0%	0.56 [0.19, 1.65] 0.34 [0.01, 8.16] 3.06 [0.12, 74.97] 0.61 [0.25, 1.48]	
CANTATA-SU-300mg 2015 CANVAS-300mg 2017 DIA3004-300mg 2014 EMPA-REG H2H-SU 2018 EMPA-REG OUTCOME-25mg 2015 Subtotal (95% CI) Total events	5 0 1 8 14 0.87); l <sup>2</sup> =	1441 89 765 2342 5122	9 1 0 13	1441 90 780 2333	35.3% 5.8% 1.9% 51.0%	0.56 [0.19, 1.65] 0.34 [0.01, 8.16] 3.06 [0.12, 74.97] 0.61 [0.25, 1.48]	
CANTATA-SU-300mg 2015 CANVAS-300mg 2017 DIA3004-300mg 2014 EMPA-REG H2H-SU 2018 EMPA-REG OUTCOME-25mg 2015 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.28, df = 4 ( <i>P</i> =	5 0 1 8 14 0.87); l <sup>2</sup> =	1441 89 765 2342 5122	9 1 0 13	1441 90 780 2333	35.3% 5.8% 1.9% 51.0%	0.56 [0.19, 1.65] 0.34 [0.01, 8.16] 3.06 [0.12, 74.97] 0.61 [0.25, 1.48]	

## Effects of SGLTi on Hyperkalemia EMPEROR-Pooled Cohort

- EMPEROR-Pooled (EMPEROR-Reduced and EMPEROR-Preserved combined) included 9,583 patients with HF and available potassium levels at baseline.
- Empagliflozin reduced the composite of investigator-reported hyperkalemia or initiation of potassium binders
   [6.5% vs. 7.7%, HR 0.82, 95% (CI) 0.71–0.95, P = 0.01].



Subgroup Category	N with event Empa 10mg	/ N analysed vs Placebo	Hazard ratio (95% CI)	Interaction p-value	Empa better	Placebo bette
Overall	313/4837	371/4837	0.82 (0.71, 0.95)		H	
Study				0.8241	_	
EMPEROR-Preserved	195/2986	235/2980	0.81 (0.67, 0.98)	0.0241		
EMPEROR-Reduced	118/1851	136/1857	0.84 (0.65, 1.07)			
A == (+====)				0.2498		
Age (years) <65	81/1264	400/4244	0.00 (0.00 4.44)	0.2430		
<05 65 to <75	121/1799	100/1344 114/1715	0.83 (0.62, 1.11)			
≥75	111/1774	157/1778	1.00 (0.77, 1.29) 0.69 (0.54, 0.88)			
Race						
White	000/0004	040/0550	0.07 (0.70.4.04)	0.4862		
	222/3604	246/3552	0.87 (0.73, 1.04)		H <b>B</b> +	
Black/African-American	18/ 256	30/ 259	0.55 (0.30, 0.98)			
Asian	56/ 735	69/ 733	0.76 (0.54, 1.08)			
Other including mixed race	14/ 214	21/ 261	0.84 (0.43, 1.65)		· · · · ·	
Baseline BMI (kg/m <sup>2</sup> )				0.4631		
<25	82/1259	110/1248	0.68 (0.51, 0.91)		<b>-</b>	
≥25 to <30	104/1640	116/1640	0.98 (0.75, 1.27)		· <b>₽</b> 1	
≥30	127/1938	145/1909	0.81 (0.63, 1.02)		F-■-1	
Baseline eGFR (CKD-EPI) (mL	/min/1.73 m <sup>2</sup> )			0.0120		
≥60	111/2457	102/2463	1.10 (0.84, 1.43)		⊢ <b></b> (	
45 to <60	81/1221	110/1238	0.74 (0.56, 0.99)		⊢ <b></b>	
30 to <45	92/ 899	116/ 888	0.78 (0.59, 1.02)		·	
<30	29/ 259	43/ 245	0.54 (0.34, 0.87)		· · · · · ·	
Baseline UACR (mg/g)				0.9975		
Normal (<30)	141/2758	180/2777	0.78 (0.63, 0.97)		⊢ <b>_</b>	
Microalbuminuria (30 to ≤300)	114/1535	125/1544	0.92 (0.71, 1.18)		F <b>■</b> 1	
Macroalbuminuria (>300)	57/ 521	65/ 495	0.72 (0.51, 1.03)		F	
Baseline NYHA				0.3953		
1/11	228/3817	268/3838	0.85 (0.71, 1.01)		H	
III/IV	85/1020	103/ 999	0.73 (0.55, 0.98)		⊢_ <b>=</b> (	
History of hypertension				0.9411		
No	36/ 789	44/ 804	0.83 (0.54, 1.29)		► <b></b>	
Yes	277/4048	327/4033	0.82 (0.70, 0.96)		H	
History of HHF (in the last 12 r	nonths)			0.0317		
No	234/3568	256/3600	0.91 (0.76, 1.08)		- <b></b>	
Yes	79/1269	115/1237	0.63 (0.47, 0.84)			
Baseline diabetes status				0.3785		
Diabetic	186/2377	230/2390	0.78 (0.64, 0.94)	0.0100		
Non-diabetic	127/2460	141/2447	0.89 (0.70, 1.13)		<b>-</b>	
Baseline use of MRA				0.2610		
No	138/2423	142/2363	0.91 (0.72, 1.16)	0.2010		
Yes	175/2414	229/2474	0.77 (0.63, 0.93)			
						-
					0.25 0.5 1	2
					Hazard ratio	

Ferreira JP, et al. Eur Heart J 2022 Jun 10;ehac306.doi:10.1093/eurhearti/ehac306.

## Effects of SGLTi on Hyperkalemia CREDENCE Trial

Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: European The CREDENCE trial **Heart** Journal RESULTS **METHODS** 15-Incidence of hyperkalaemia (>6.0 mmol/L) 4401 patients with type 2 diabetes and CKD randomized to: HR 0.77 (95% CI 0.61-0.98) (%) Placebo 10 ulat Canagliflozin Placebo 5 Canaoliflozin đ 99.9% maximum labelled Ø or tolerated RAS blockade T 0eGFR 56 12 18 24 30 36 42 Months since randomization mL/min/1.73m<sup>2</sup> **CONCLUSION** Among patients treated with RAS blockade, canagliflozin reduces the risk of hyperkalaemia in people with T2DM and CKD without Serum potassium increasing the risk of hypokalaemia. The lower risk of hyperkalaemia with SGLT2 4.5 mmol/L inhibition may enable greater use of RAS blockade and mineralocorticoid receptor antagonists in CKD and/or heart failure. ESC European Society of Cardiology

Neuen BL, et al. Eur Heart J 2021;42:4891-4901.

## Effects of SGLTi on Hyperkalemia

Meta-Analysis of Randomized Controlled Trails

• Nearly 50,000 participants from clinical outcome trials of SGLT2i in people with T2DM at high CV risk or with CKD, SGLT2i reduced the risk of serious hyperkalemia ( $\geq 6.0 \text{ mmol/L}$ ) with no increased risk of hypokalemia.

	SGL	SGLT2 inhibitors		Placebo		
	n/N	Events per 1000 patient-years	n/N	Events per 100 patient-years	0	Hazard Ratio (95% Cl)
CANVAS Program	137/5795	8.2	85/4347	9.2		0.89 (0.67, 1.17)
CREDENCE	121/2202	21.6	154/2199	27.9		0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3		0.88 (0.71, 1.09)
DECLARE-TIMI 58	53/8582	1.6	78/8578	2.3		0.67 (0.47, 0.95)
EMPA-REG OUTCOME	216/4687	17.2	124/2333	20.5		0.83 (0.67, 1.04)
VERTIS CV	291/5493	18.7	157/2745	21.2		0.90 (0.74, 1.09)
<b>Overall</b> (I <sup>2</sup> =0.0%; P <sub>heterogeneity</sub> =0.71)				.5	•	<b>0.84 (0.76, 0.93)</b> P<0.001
				0.4 <del>•</del>		<b>→</b>

Favors SGLT2 inhibitors Favors placebo

Neuen BL, et al. Circulation 2022 8 April;145:1460-1470.

## Effects of SGLTi on Hyperkalemia

Meta-Analysis of Randomized Controlled Trails

• The lower risk of hyperkalemia with SGLT2i was consistent across a range of participant characteristics, including different levels of kidney function, albuminuria, history of HF, and use of diuretics.

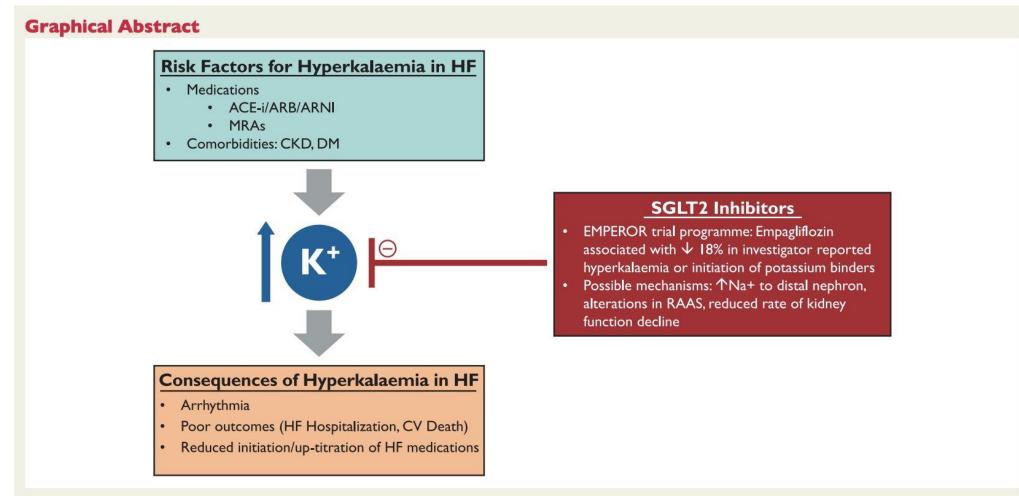
	n/i	N		Hazard ratio	Study: P for	Subgroup: P for
	SGLT2i	Placebo		(95%CI)	interaction	interaction
Overall	977/28,214	777/21,653	•	0.84 (0.76, 0.93)	0.71	
HbA1c ≤8%	495/14,298	382/11,073	⊢ <b>●</b> +	0.90 (0.78, 1.03)	0.86	0.19
HbA1c >8%	481/13,888	394/10,553	<b>⊢</b> ●-1	0.79 (0.69, 0.90)	0.47	
eGFR ≥60 mL/min/1.73m <sup>2</sup>	521/21,511	335/16,273	⊢ <b>●</b> -I	0.90 (0.79, 1.04)	0.89	0.20
eGFR <60 mL/min/1.73m <sup>2</sup>	456/6,699	442/5,379	<b>⊢●</b> -1	0.79 (0.70, 0.91)	0.54	
UACR <30 mg/g	377/15,823	224/11,814	F	0.90 (0.77, 1.07)	0.93	0.23
UACR ≥30 mg/g	585/11,957	549/9,515	⊢●⊣	0.80 (0.70, 0.90)	0.39	
No heart failure	735/24,305	604/18,701	⊢●⊣	0.82 (0.73, 0.92)	0.40	0.31
Heart failure	242/3,909	173/2,952	<b>⊢</b> ● <mark> </mark> -1	0.92 (0.74, 1.13)	0.37	
No RAAS inhibitor use	118/4,730	107/3,512	<b>⊢</b> •−−1	0.56 (0.43, 0.74)	0.65	0.002
RAAS inhibitor use	859/23,534	670/18,141	⊢●-	0.89 (0.79, 0.99)	0.32	
No diuretic use	519/16,054	398/12,260	<b>⊢</b> ●-1	0.84 (0.73, 0.96)	0.88	0.97
Diuretic use	458/12,160	379/9,393	<b>⊢</b> ●-1	0.84 (0.73, 0.97)	0.38	
No MRA use	895/26,861	729/20,732	⊢●⊣	0.83 (0.75, 0.92)	0.93	0.25
MRA use	82/1,353	48/921	<b>⊢_</b> •i	1.04 (0.72, 1.52)	0.47	- 20 - 20 aug
			0.3 0.5 1 2			
			Favors SGLT2 inhibitors Favors place	<b>b</b> 0		

## Effects of SGLT2i on hyperkalemia across the spectrum of kidney function in CREDENCE and DAPA-CKD

	SGL	2 inhibitiors		Placebo		
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	1	Hazard Ratio (95% CI)
Overall						
CREDENCE	121/2202	21.6	154/2199	27.9		0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3		0.88 (0.71, 1.09)
Subtotal (I2=0.0%; Pheterogenei	<sub>ity</sub> =0.41)				-	0.83 (0.71, 0.97)
-						P=0.02
eGFR 60 to <90 mL/min/1.	73m²					
CREDENCE	35/905	15.1	33/904	14.2		1.06 (0.66, 1.70)
DAPA-CKD	13/179	31.8	11/169	30.0		→ 1.07 (0.48, 2.39)
Subtotal (I2=0.0%; Pheterogenei	<sub>ity</sub> =0.98)					1.06 (0.71, 1.60)
						P=0.77
eGFR 45 to <60 mL/min/1.	73m²					
CREDENCE	33/640	19.9	47/639	29.1		0.68 (0.44, 1.06)
DAPA-CKD	28/450	31.9	42/468	45.8		0.71 (0.44, 1.14)
Subtotal (I2=0.0%; Pheterogenei	<sub>ity</sub> =0.90)					0.69 (0.50, 0.96
						P=0.03
eGFR <45 mL/min/1.73m <sup>2</sup>						
CREDENCE	53/657	32.4	74/656	46.4		0.70 (0.49, 0.99)
DAPA-CKD	118/826	78.4	126/814	86.5		0.92 (0.71, 1.19)
Subtotal (I2=34.4%; Pheterogen	neity=0.22)					0.83 (0.64, 1.07)
						P=0.15
P <sub>heterogeneity</sub> for subgroups=	=0.27	)		0.4	0.6 0.8 1.0 1.2 1.6	2.0
		•				→
				Favo	ors SGLT2 inhibitors Favors place	00

Neuen BL, et al. Circulation 2022 8 April;145:1460-1470.

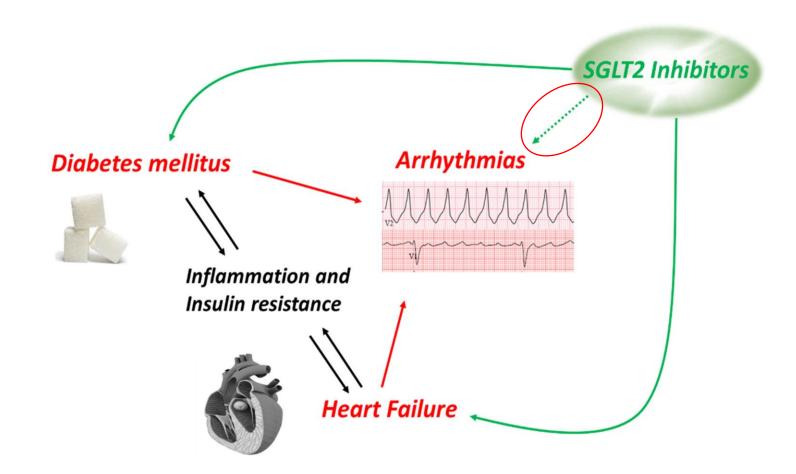
## Emerging Role for SGLT2 Inhibitors in Mitigating the Risk of Hyperkalemia



Emerging role for SGLT2 inhibitors in mitigating the risk of hyperkalaemia in heart failure.

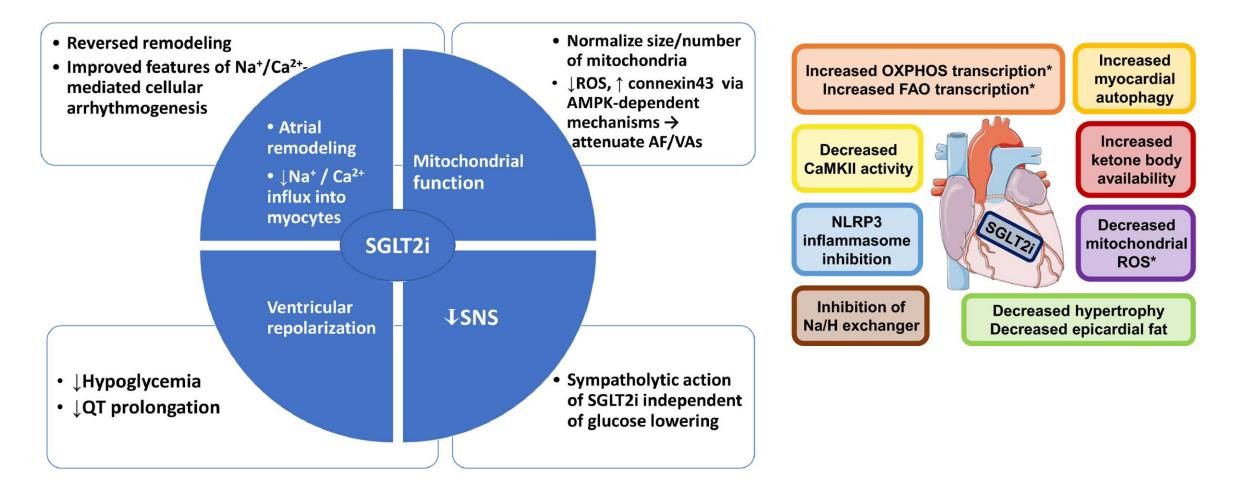
Verma S. Eur Heart J 2022 2022 Jun 10;ehac304. doi: 10.1093/eurheartj/ehac304.

### Connection and Interaction Between Diabetes Mellitus, Heart failure, and Arrhythmias

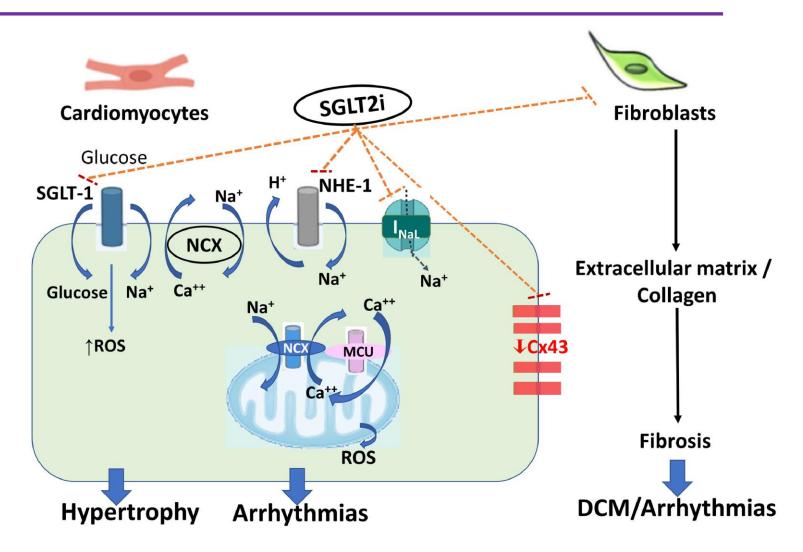


Kolesnik E, et al. Int J Mol Sci 2022;23:1678-1690.

# Suggested Mechanisms Underlying the Antiarrhythmic Effects of SGLT2 Inhibitors at the Myocardial Level



### Mechanisms and Pathways Responsible for Antiarrhythmic Properties of SGLT2 Inhibitors



Manolis AA, et al. Trends Cardiovasc Med 2022 April; 18:S1050-1738(22)00062-7.

## Conclusions

- SGLT2 inhibitors are associated with reduced risk of hyperkalemia and atrial arrhythmias (AF/AFL), and they may confer protection against ventricular arrhythmia and reduce sudden cardiac death.
- This may, at least partially, explain the decreased risk of CV death in patients with T2DM and HF.
- Most data are derived from subgroup analysis of large RCTs and based on investigator reports rather than monitoring devices.
- Multiple mechanisms are suggested for the underlying antiarrhythmic effects of SGLT2 inhibitors.
- Further prospective studies are warranted to specifically examine the impact of SGLT2 inhibitors on arrhythmic burden in patients with T2DM, CKD and HF, and using recording systems.



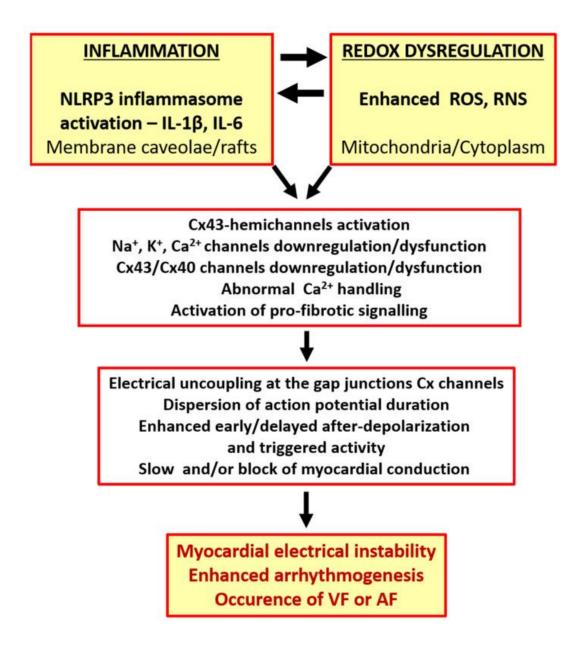


# Thank You

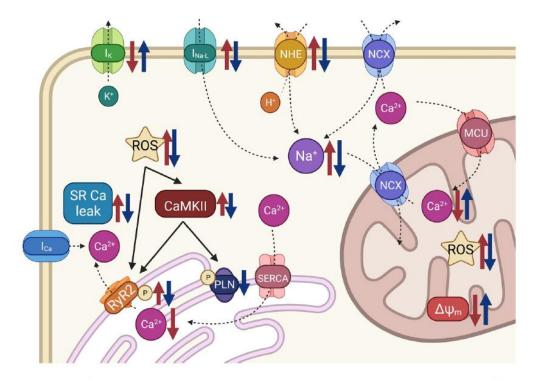
## **Questions?**



Rabea Asleh rasleh@hadassah.org.il Mechanisms and Pathways Responsible for Antiarrhythmic Properties of SGLT2 Inhibitors

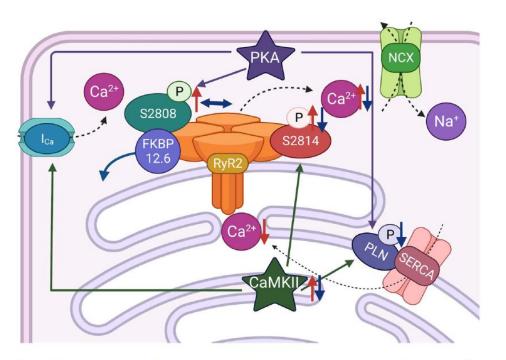


### Mechanisms and Pathways Responsible for Antiarrhythmic Properties of SGLT2 Inhibitors



**FIGURE 1** Potential effects of SGLT-2 inhibitors on cardiac ion current, calcium handling homeostasis and oxidative stress in a HF model. Red arrows indicate the change in a HF model compared to the control. Blue arrows indicate the change after being exposed to SGLT-2 inhibitors in comparison to disturbance in the HF model. Figure created with BioRender.com.  $I_{Ca}$ , L-type calcium channel current;  $I_{K}$ , delayed-rectified potassium outward current;  $I_{Na}$ , sodium channel current;  $I_{Na-late}$ , late sodium channel current; MCU, mitochondrial calcium uniporter; NCX, Na<sup>+</sup>/Ca<sup>2+</sup>exchanger; NHE, Na<sup>+</sup>/H<sup>+</sup>exchanger; P, phosphorylation; PLN, phospholamban; ROS, reactive oxygen species; RYR2, ryanodine receptor 2; SERCA, sarco/endoplasmic reticulum calcium ATPase 2a; SGLT-2, sodium-glucose co-transporter 2;  $\Delta\Psi_m$ , mitochondrial membrane potential

### Mechanisms and Pathways Responsible for Antiarrhythmic Properties of SGLT2 Inhibitors



**FIGURE 2** Potential roles of PKA and CaMKII in RyR2 phosphorylation and calcium handling proteins in the HF model. Purple arrows indicate the proposed mechanism of PKA dependent RyR2 phosphorylation on SR Ca<sup>2+</sup> leakage in a HF model. Green arrows indicate the effect of CaMKII on SR Ca<sup>2+</sup> leakage in the HF model. Red arrows indicate the change in the HF model, in comparison to the control. Blue arrows indicate the change after being exposed to SGLT-2 inhibitors in comparison to disturbance in the HF model. Figure created with BioRender.com. CaMKII, Ca<sup>2+</sup>/calmodulin dependent protein kinase II; FKBP12.6, FK 506-binding protein-12.6; *I*<sub>Ca</sub>, L-type calcium channel current; NCX, Na<sup>+</sup>/ Ca<sup>2+</sup>exchanger; P, phosphorylation; PKA, protein kinase A; PLN, phospholamban; RYR2, ryanodine receptor 2; S2808, serine-2808; S2814, serine-2814; SERCA, sarco/endoplasmic reticulum calcium ATPase 2a; SGLT-2, sodium-glucose co-transporter 2