Effects of SGLT-2 Inhibitors on Cardiac Arrhythmias

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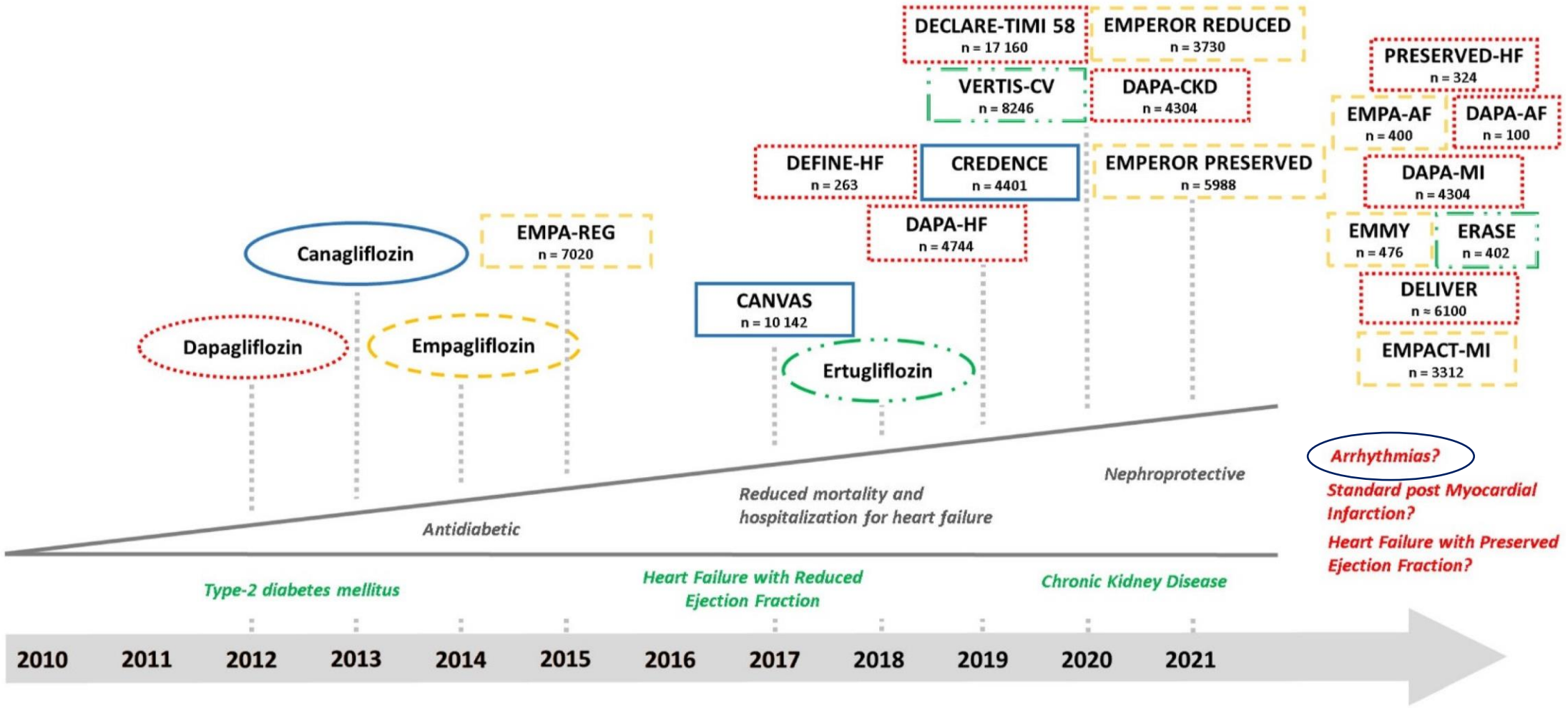
History, Completed, and Ongoing Clinical Trials of SGLT2 Inhibitors

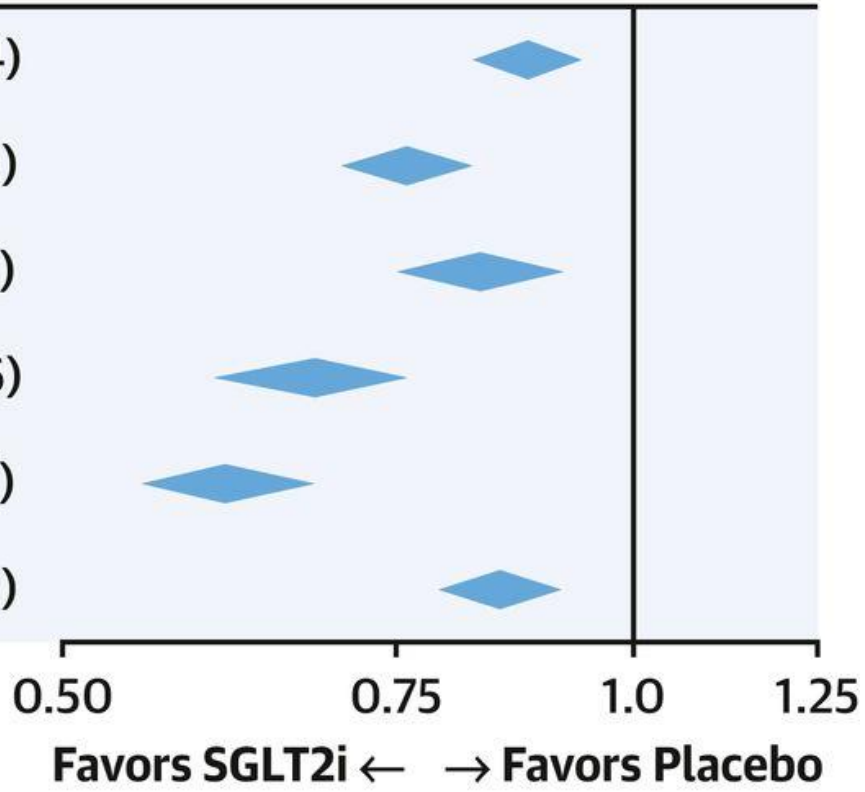


Kolesnik E, et al. Int J Mol Sci 2022;23:1678-1690.

Treatment Effect of SGLT2i on Cardiorenal Outcomes

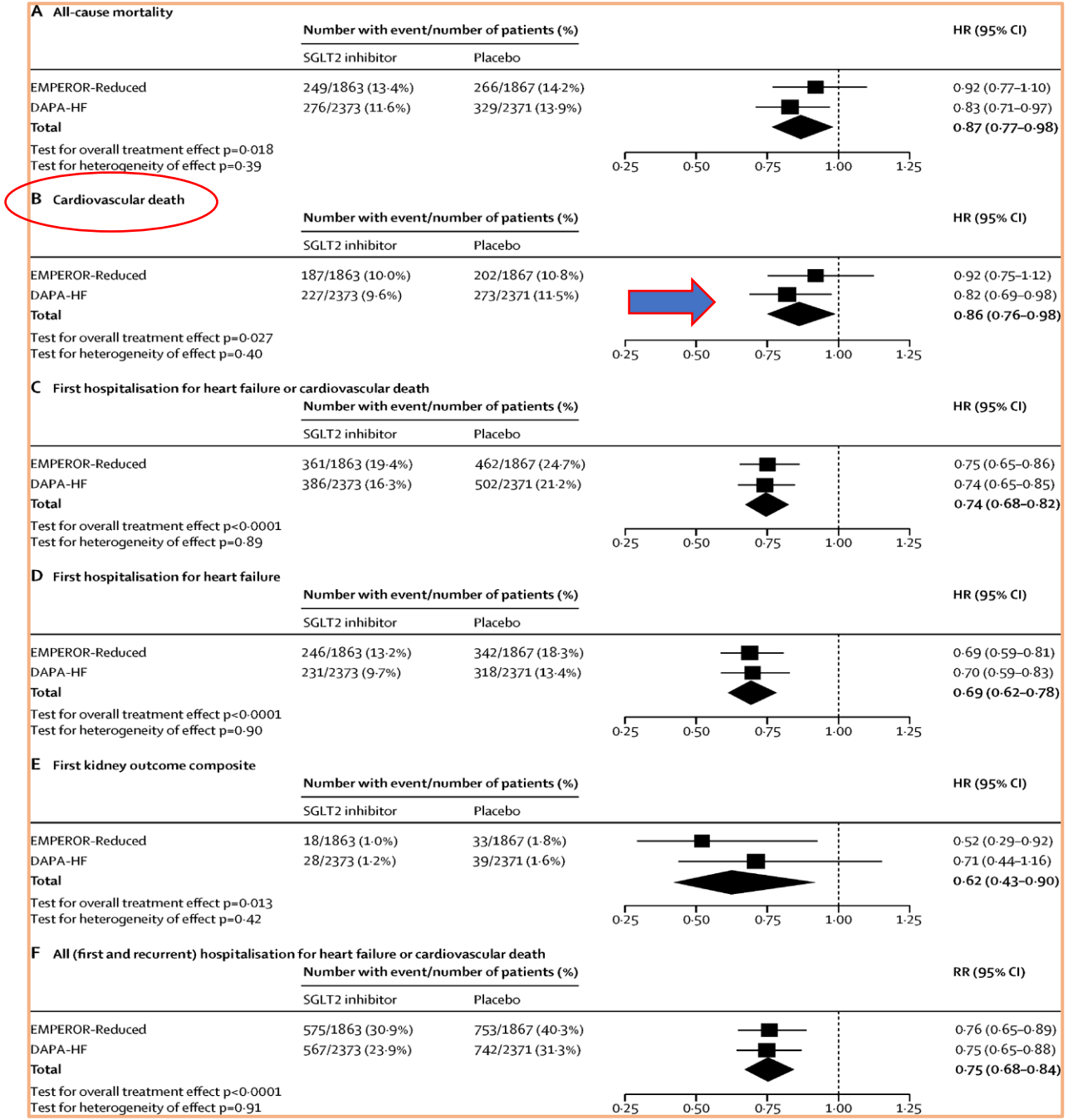
Updated meta-analysis of 38,723 patients including EMPA-REG OUTCOME, CANVAS program, DECLARE-TIMI 58 trial, and the CREDENCE trial

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)



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

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

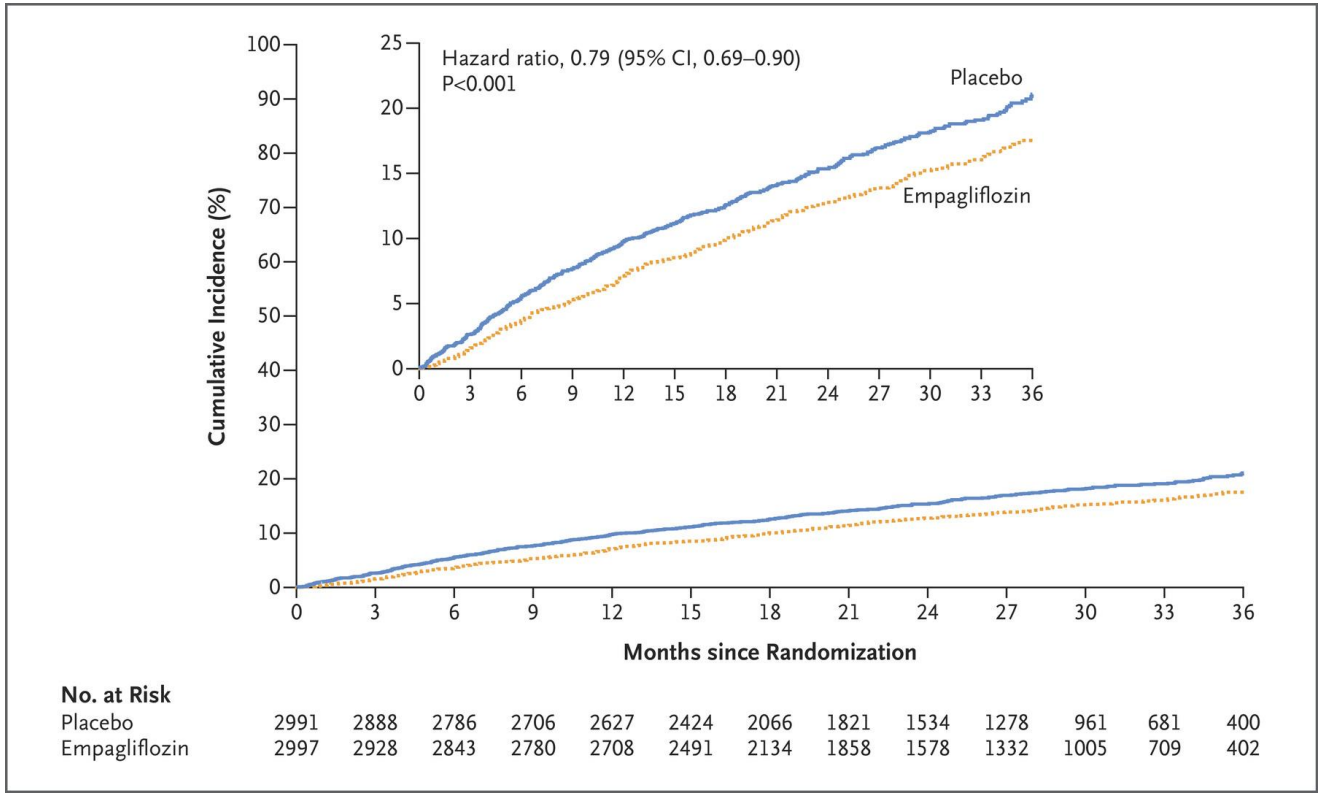


Zannad et al. Lancet. 2020;396:819-829.

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

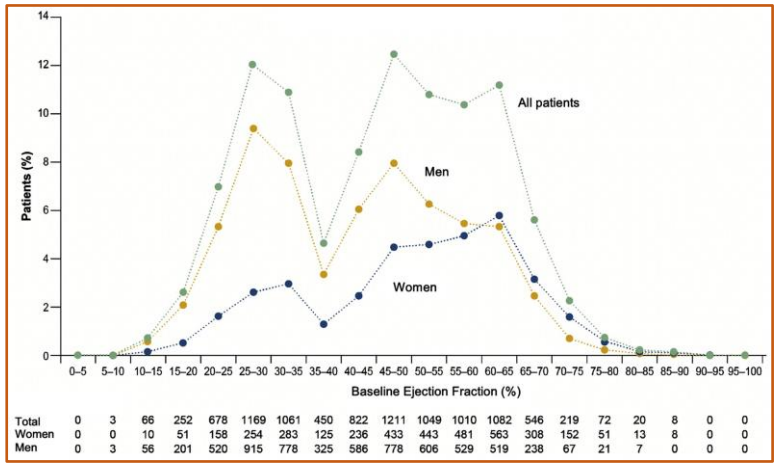
- **5988** patients with class II–IV HF and an EF of >40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy
- The primary outcome was a composite of CV death or HF hospitalization

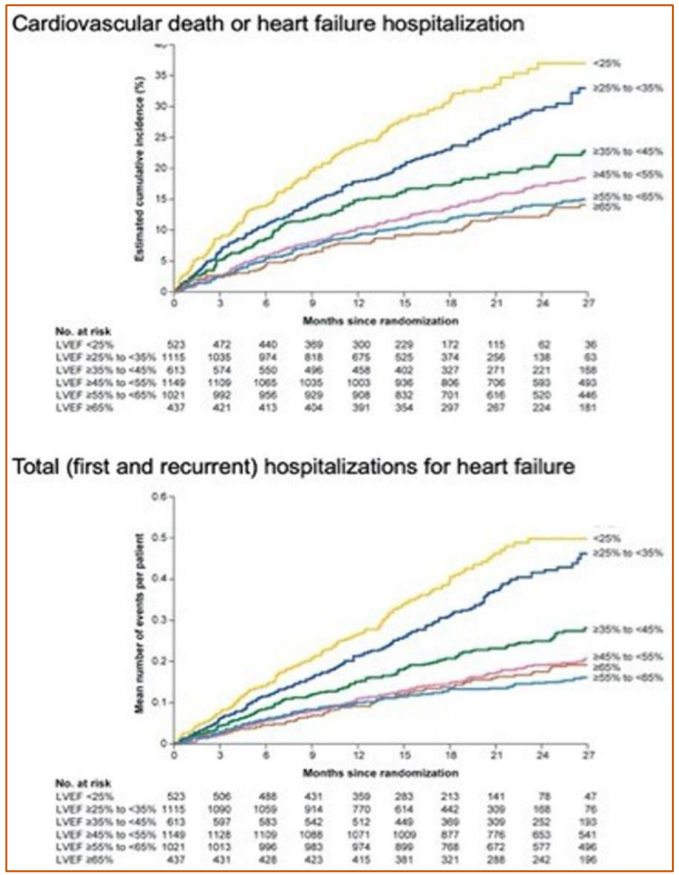
❖ The effects of empagliflozin appeared consistent in patients with or without diabetes

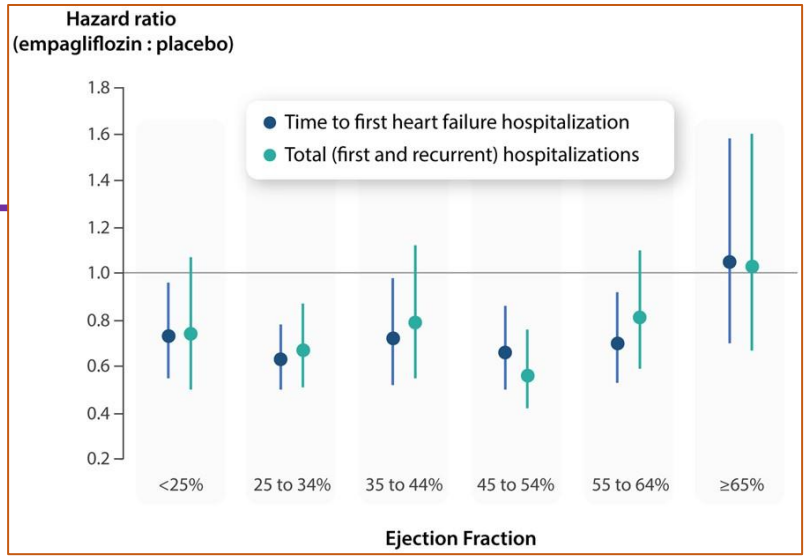


Effect of Empagliflozin in Patients With Heart Failure Across the Spectrum of LVEF

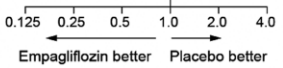
- A pooled analysis of both the EMPEROR-Reduced and EMPEROR-Preserved trials (9,718 pts)





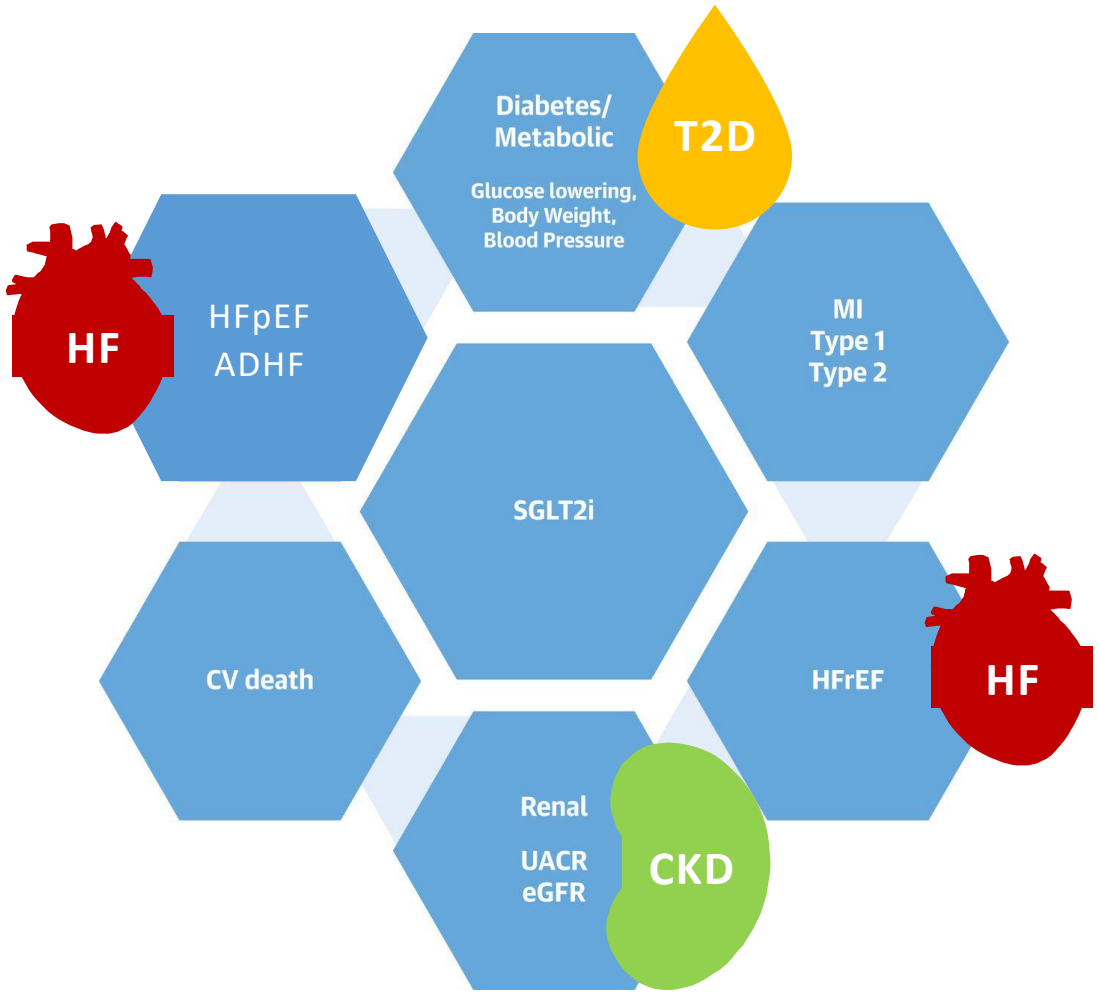


	Empagliflozin	Placebo	Hazard ratio (95% CI)
Cardiovascular death or heart failure hospitalization			
LVEF <25%	117/476	154/523	0.77 (0.60–0.98)
LVEF ≥25 to <35%	191/1115	255/1115	0.72 (0.59–0.87)
LVEF ≥35 to <45%	115/659	128//613	0.82 (0.63–1.05)
LVEF ≥45 to <55%	159/1111	215/1149	0.74 (0.61–0.91)
LVEF ≥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 hospitalization			
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 recurrent) heart failure hospitalizations			
LVEF <25%	126	179	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)

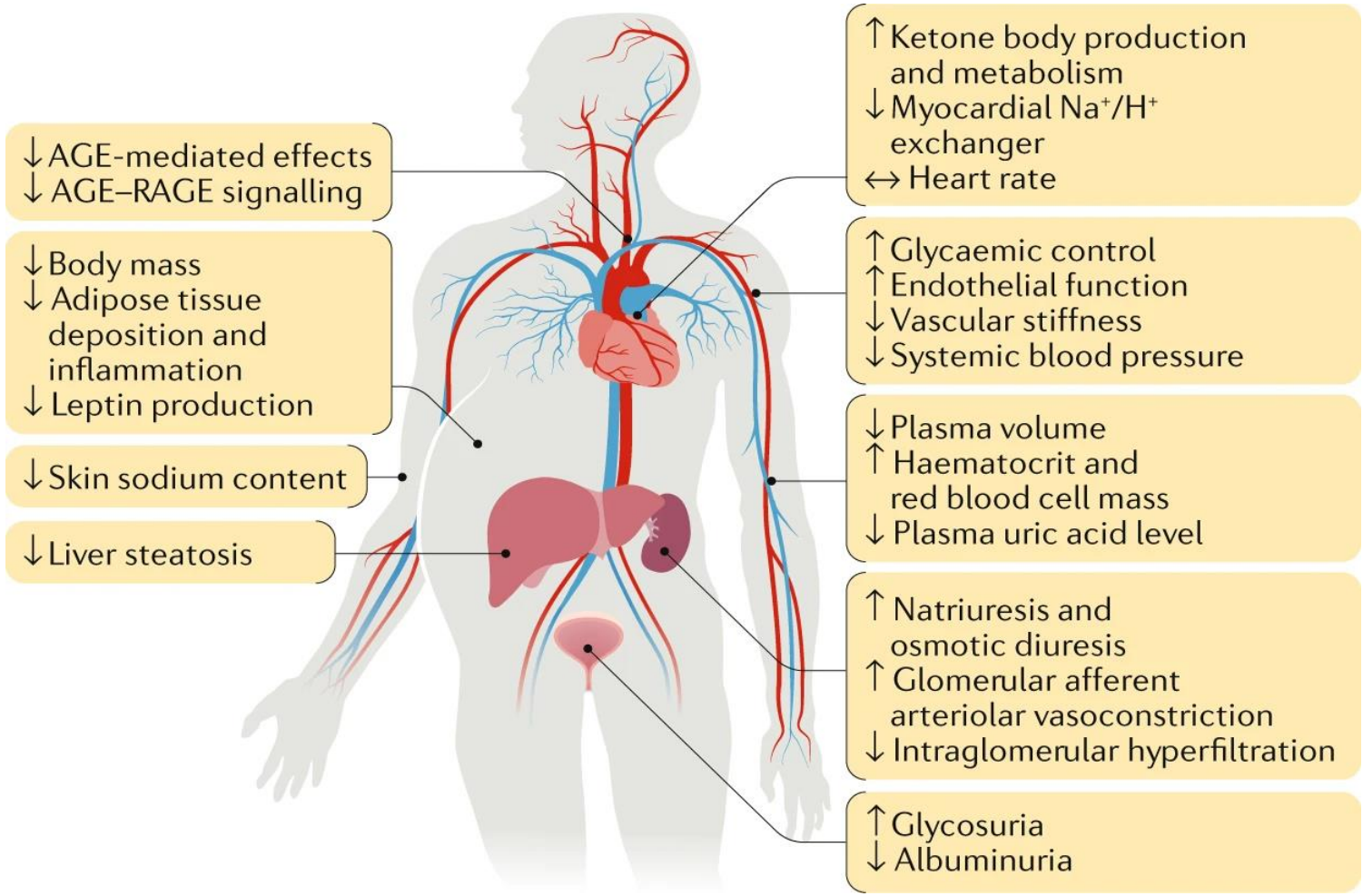


Butler J et al. Eur Heart J. 2021 Dec 8: 8:ehab798. doi:10.1093/eurheartj/ehab798.

Effects of SGLT2 inhibitor on cardio-metabolic-renal events

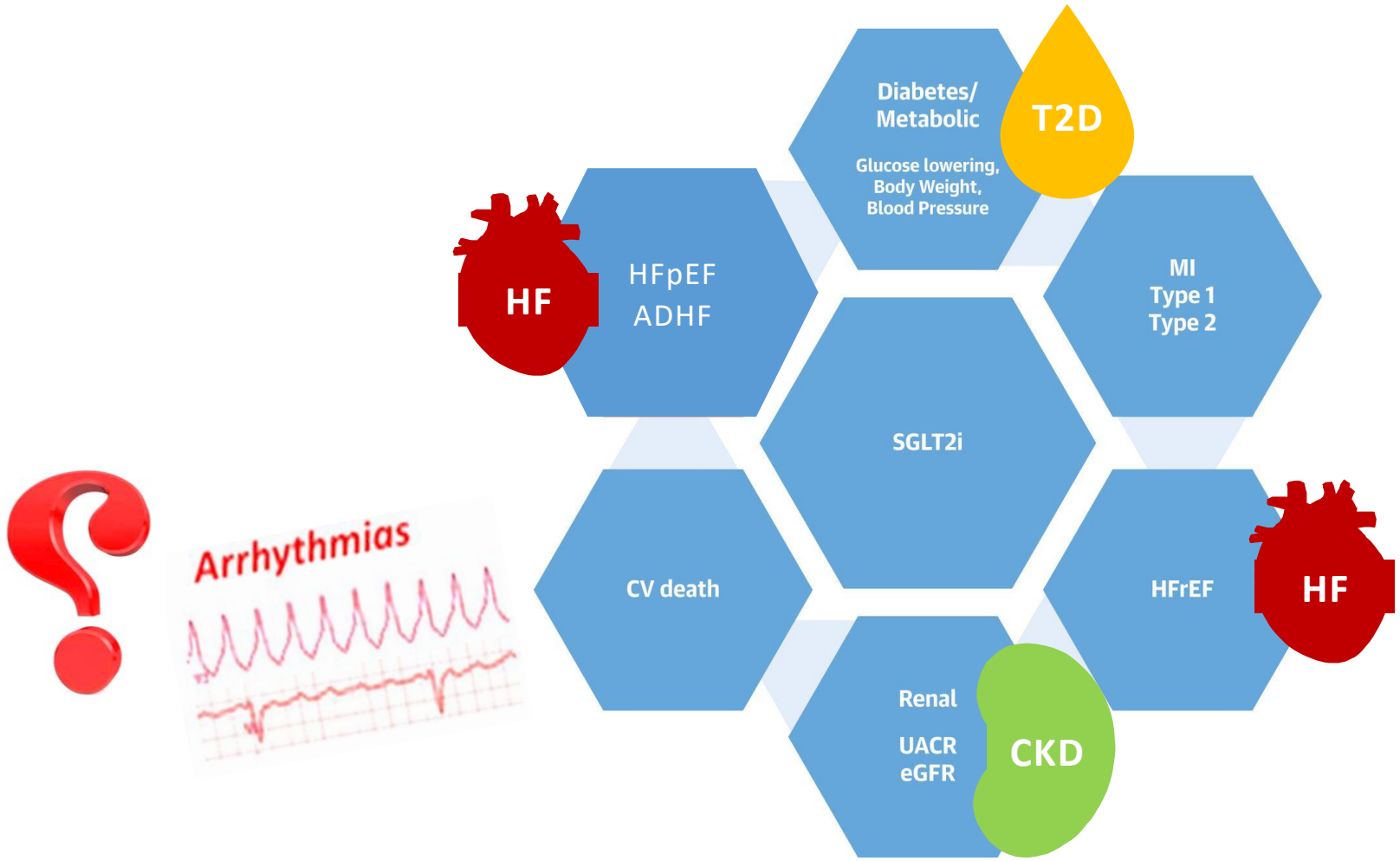


Suggested Mechanisms of the Cardiovascular and Renal Benefits of SGLT2 Inhibitors



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

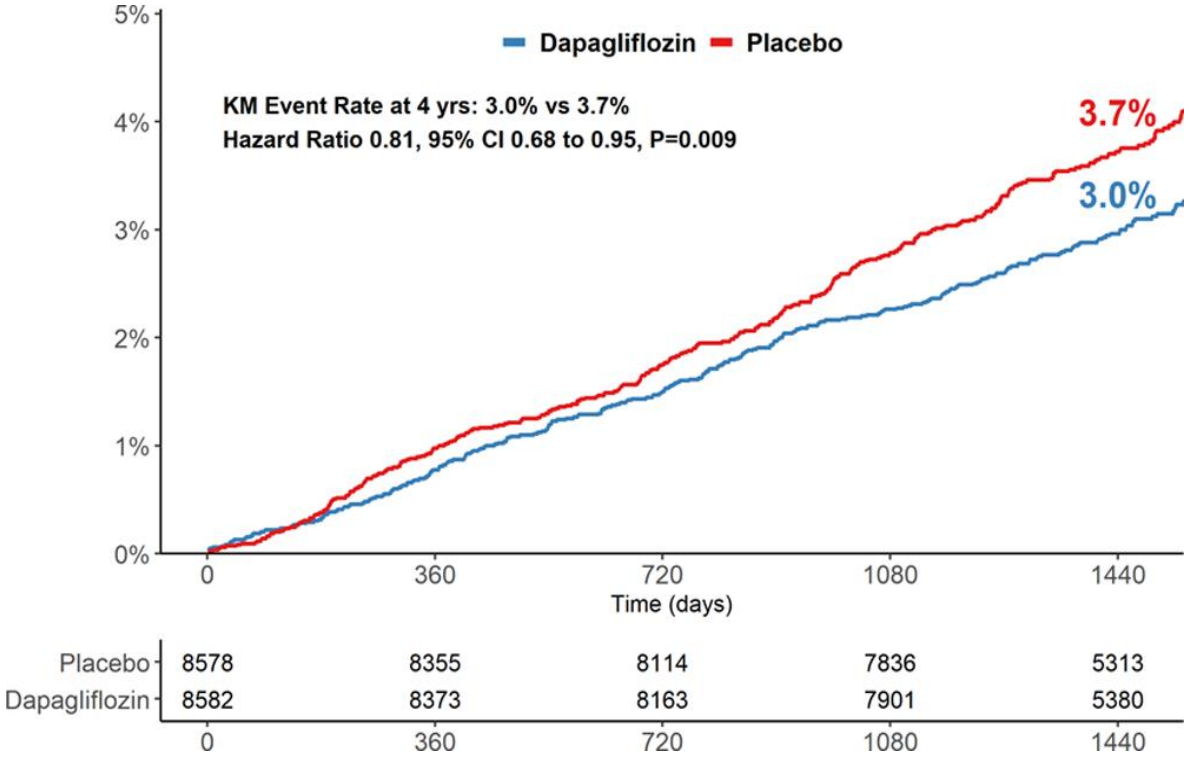
Effects of SGLT2 inhibitor on cardio-metabolic-renal events



Effects of SGLTi on Atrial Arrhythmias

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



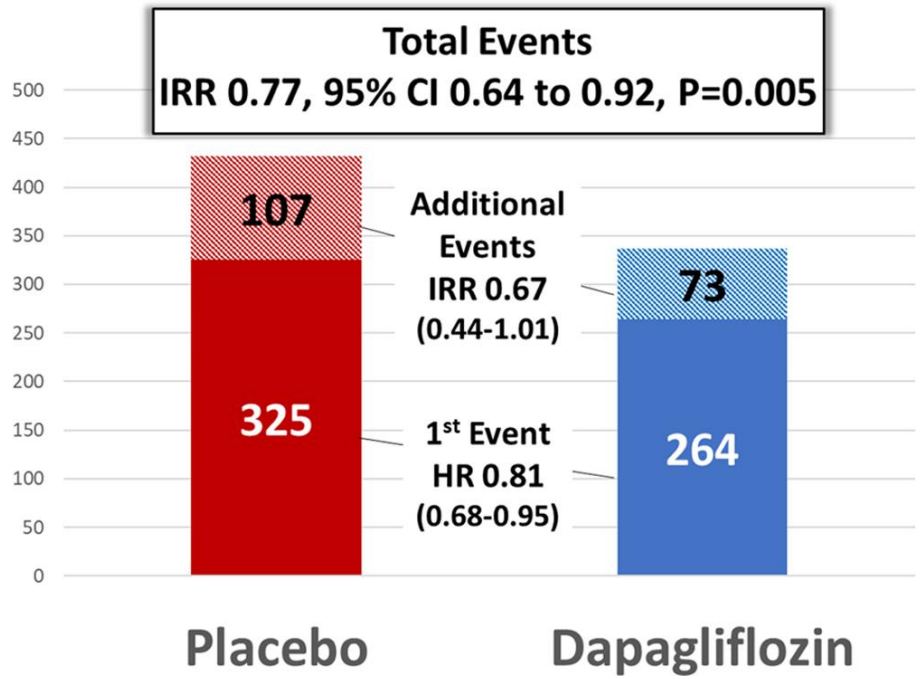
Zelniker TA, et al. Circulation 2020; 15:1227-1234

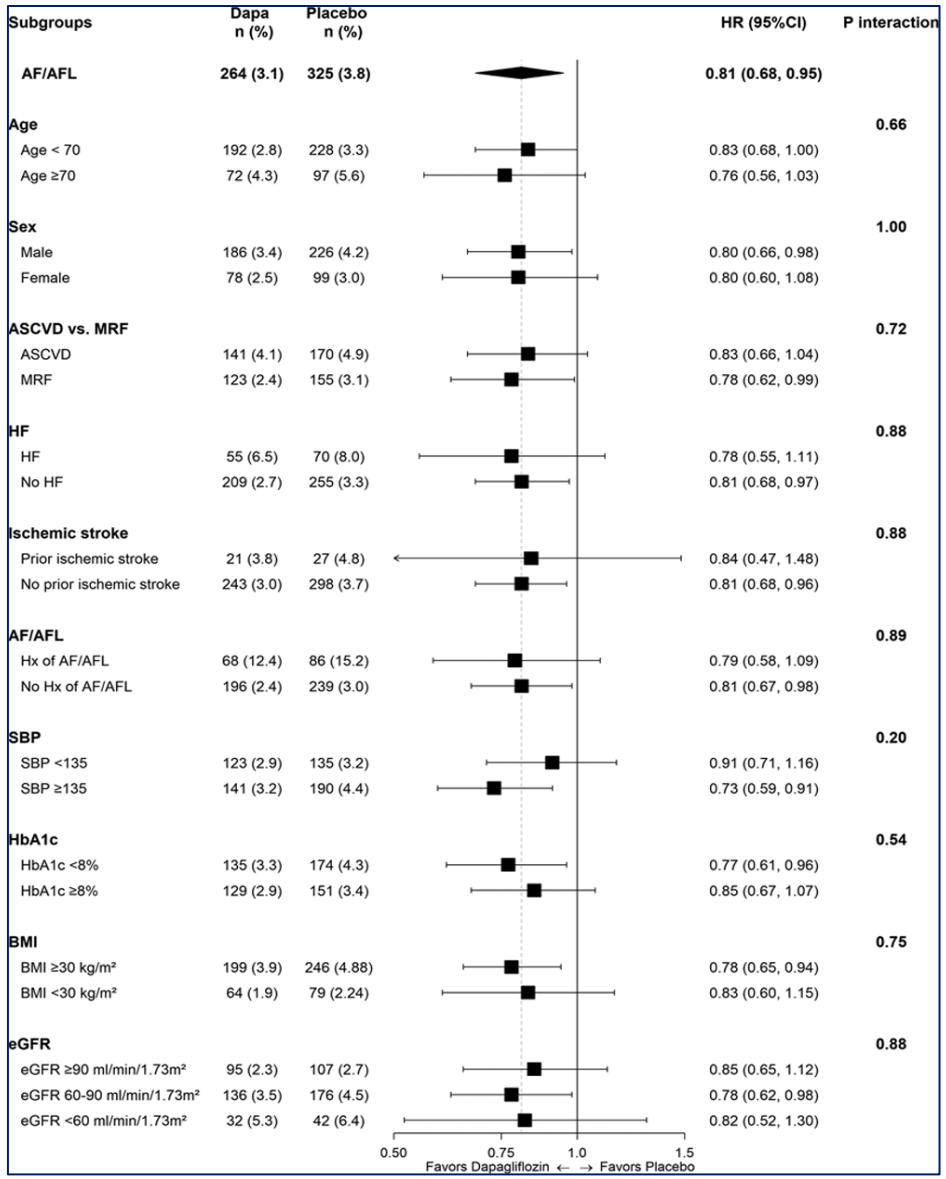
Effects of SGLTi on Atrial Arrhythmias

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



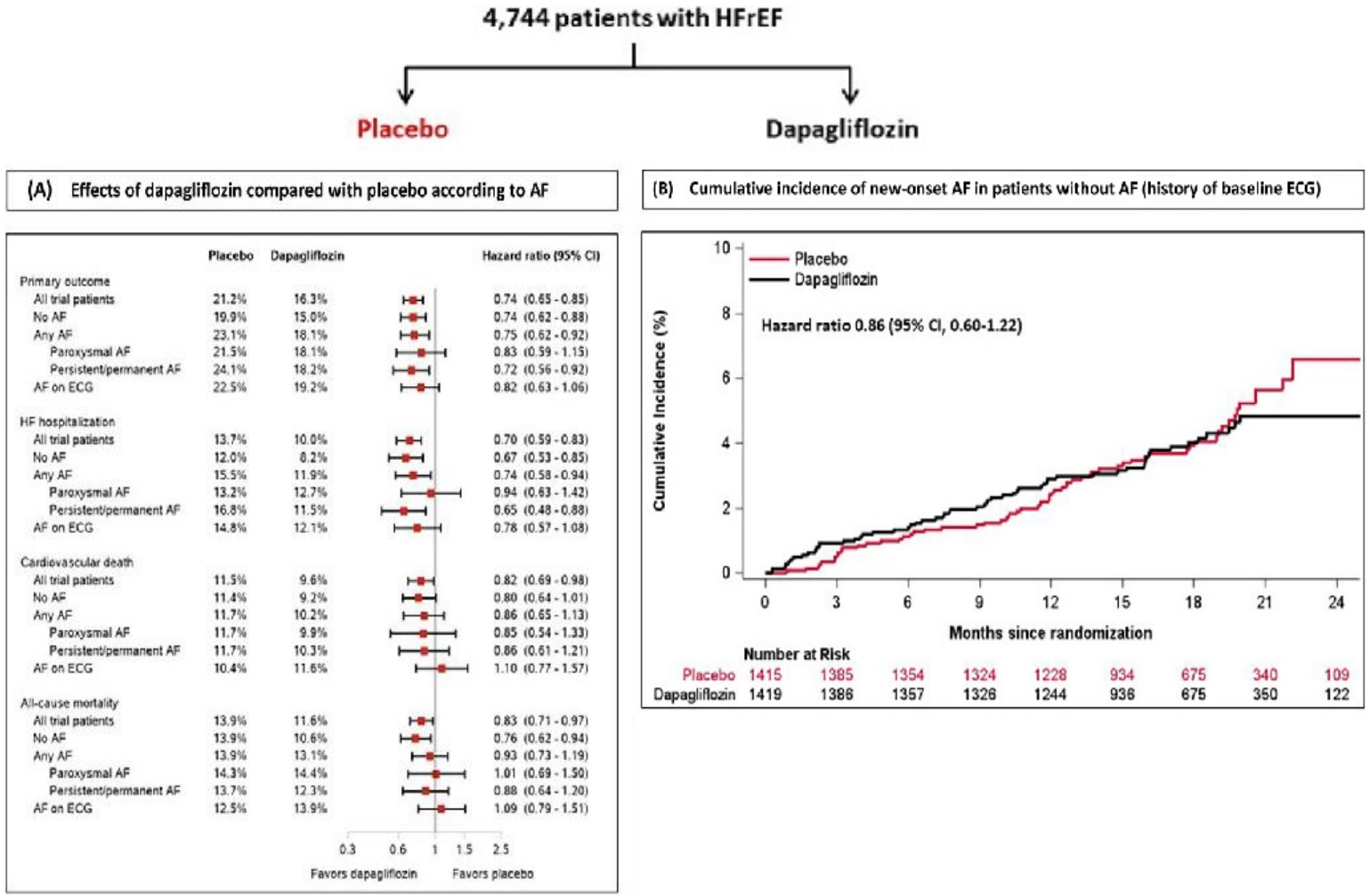


Zelniker TA, et al. Circulation 2020; 15:1227-1234

Effects of SGLTi on Atrial Arrhythmias

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

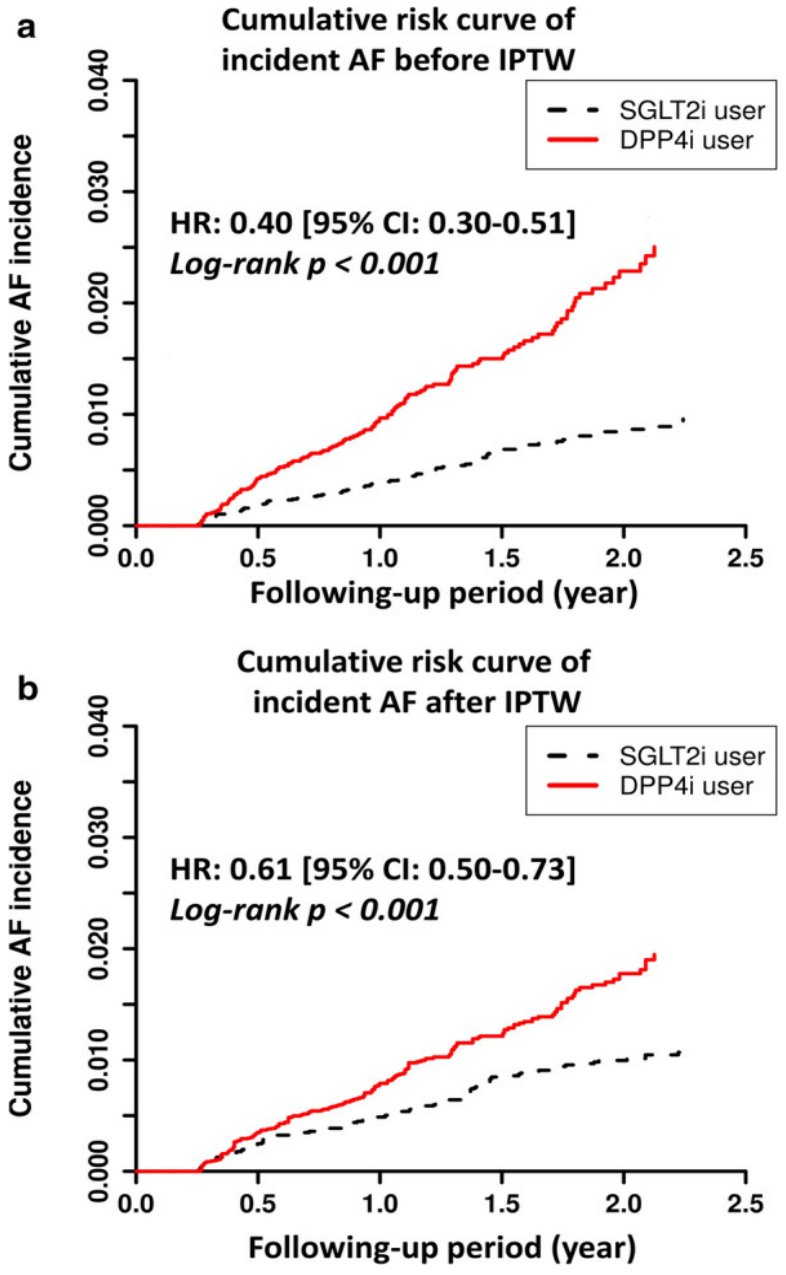


Butt JH, et al. Eur J Heart Fail. 2022;24:513-525.

Effects of SGLTi on Atrial Arrhythmias

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 new-onset AF compared with DPP4i after propensity-score weighting
- The advantage of SGLT2i over DPP4i persisted with different SGLT2i (dapagliflozin or empagliflozin)

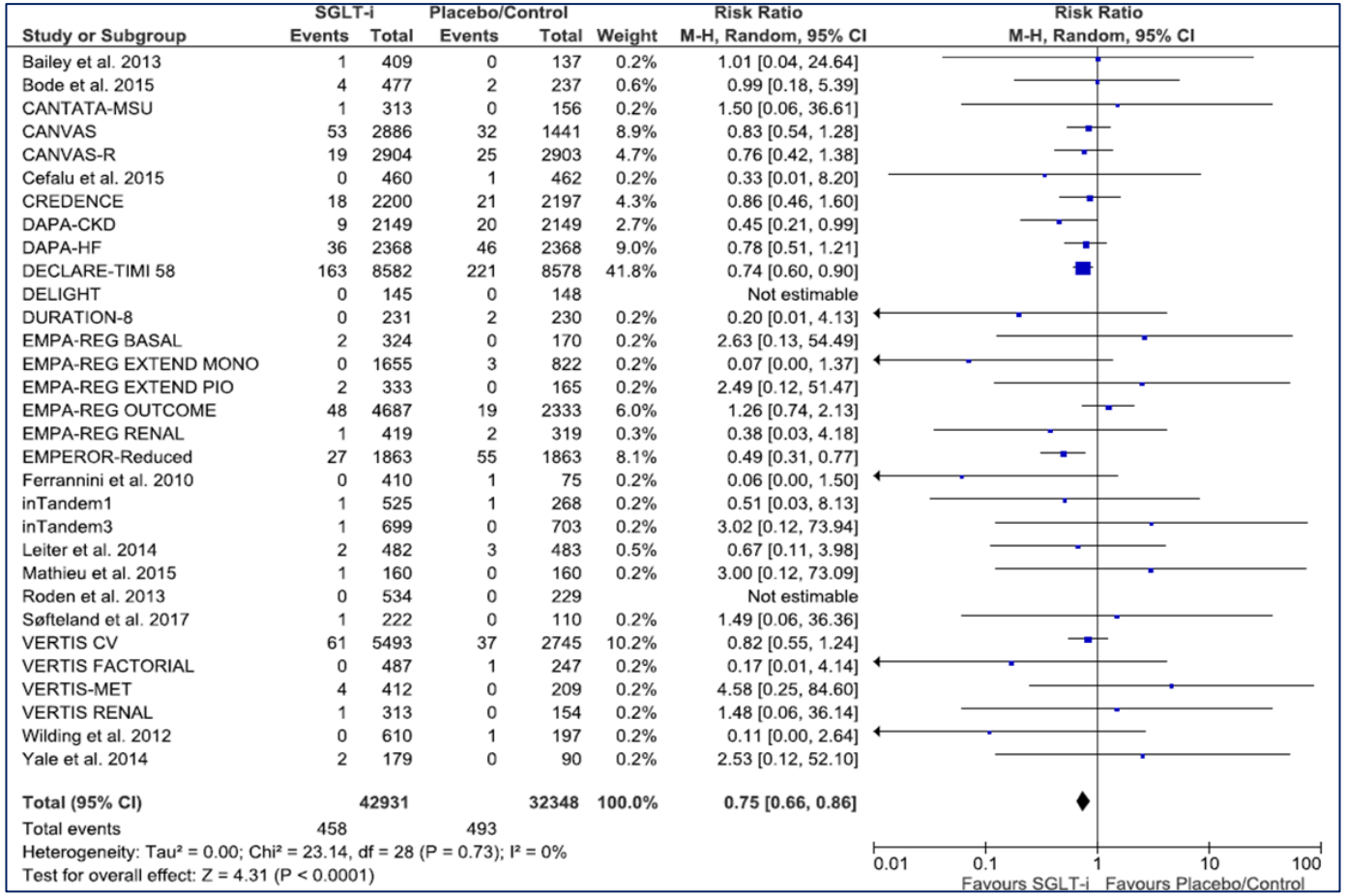


Ling A, et al. Cardiovasc Diabetol. 2020;19:188-199.

Effects of SGLTi on Atrial Arrhythmias

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 serious AF/AFL events with SGLTi (1.1% versus 1.5%; risk ratio 0.75 [95% CI, 0.66–0.86]; I^2=0%).
- A similar reduction in total AF events was also noted with SGLT inhibitors.



Study or Subgroup	SGLT-i Events	SGLT-i Total	Placebo/Control Events	Placebo/Control Total	Weight	Risk Ratio M-H, Random, 95% CI
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: Tau² = 0.00; Chi² = 23.14, df = 28 (P = 0.73); I² = 0%

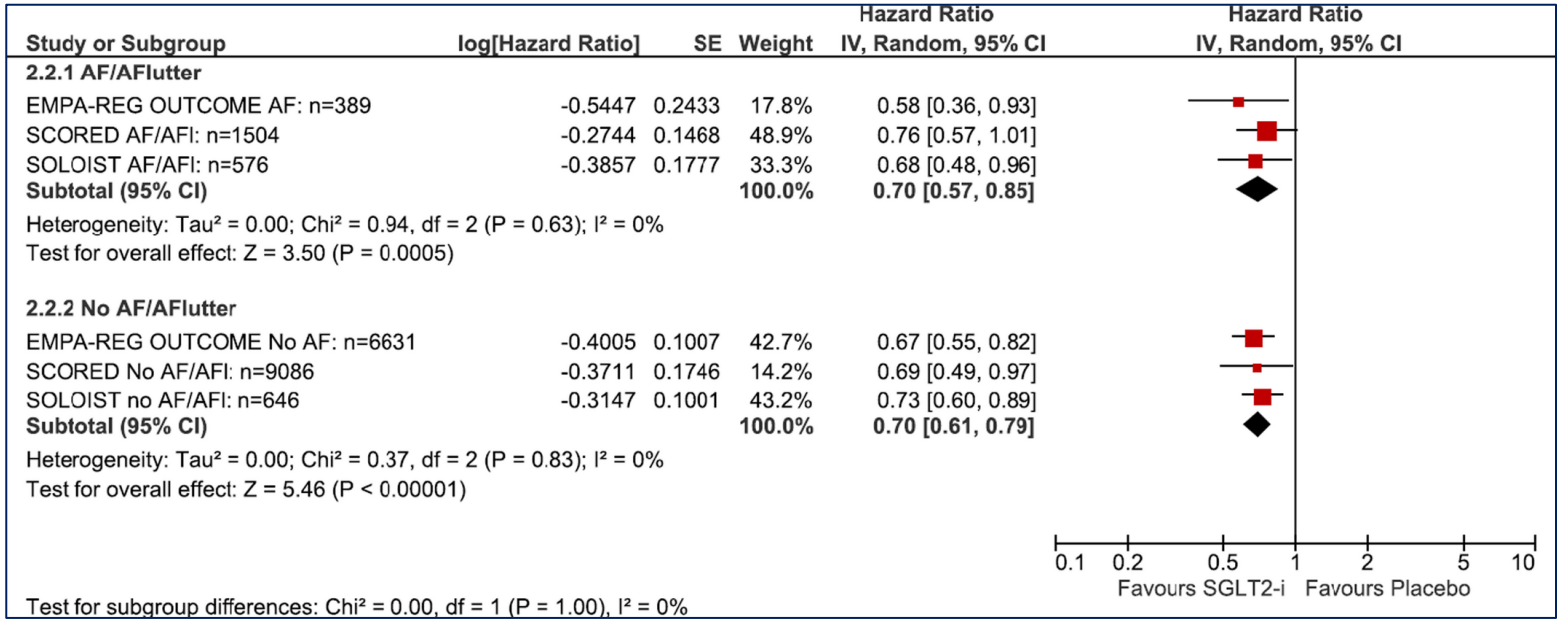
Test for overall effect: Z = 4.31 (P < 0.0001)

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

Effects of SGLTi on Atrial Arrhythmias

Meta-Analysis of Randomized Controlled Trails

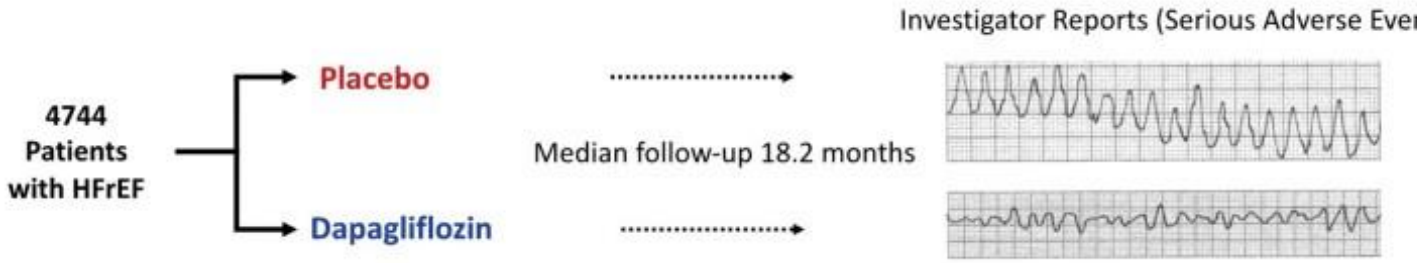
- Three trials reported on HF hospitalization/CV death stratified by a baseline h/o of AF (18,832 patients)
- SGLT inhibitors resulted in a lower risk in HF hospitalization or CV death (HR 0.70 [95% CI, 0.57–0.85]; I^2=0%) similar to the effect estimate for patients without AF

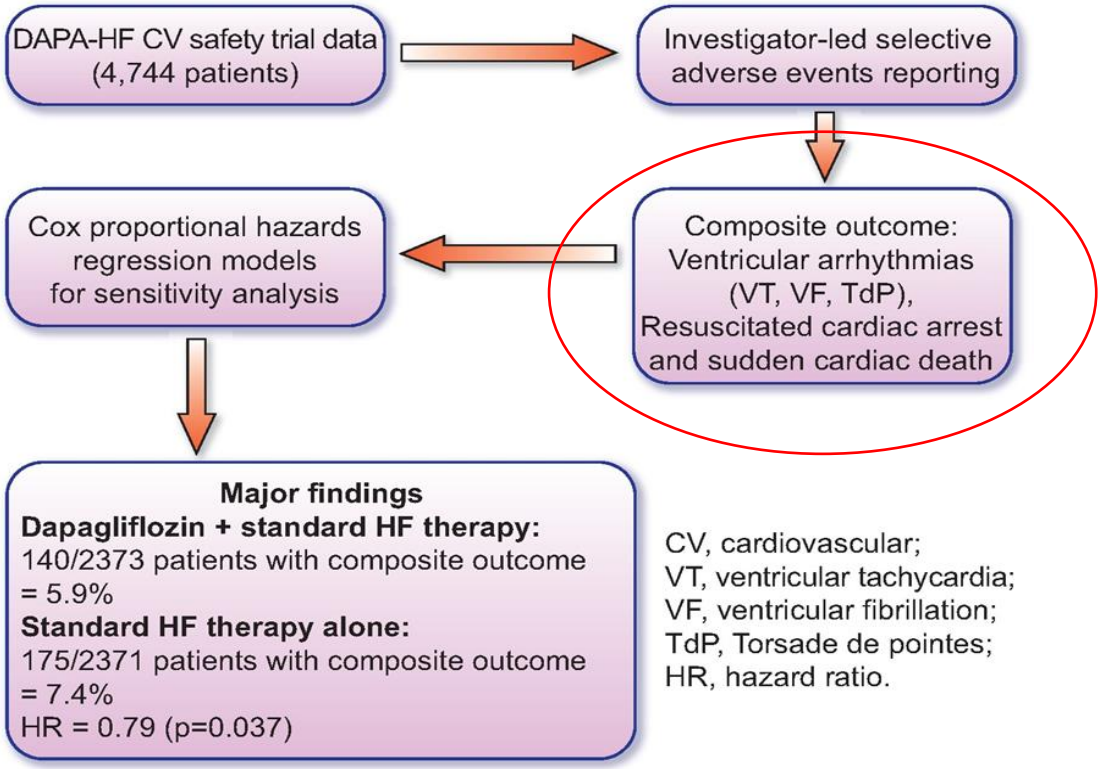


Pandey AK, et al. JAHA. 2021;10: 0(17):e022222.

Effects of SGLTi on Ventricular Arrhythmias and SCD

Insights from the DAPA-HF Trial

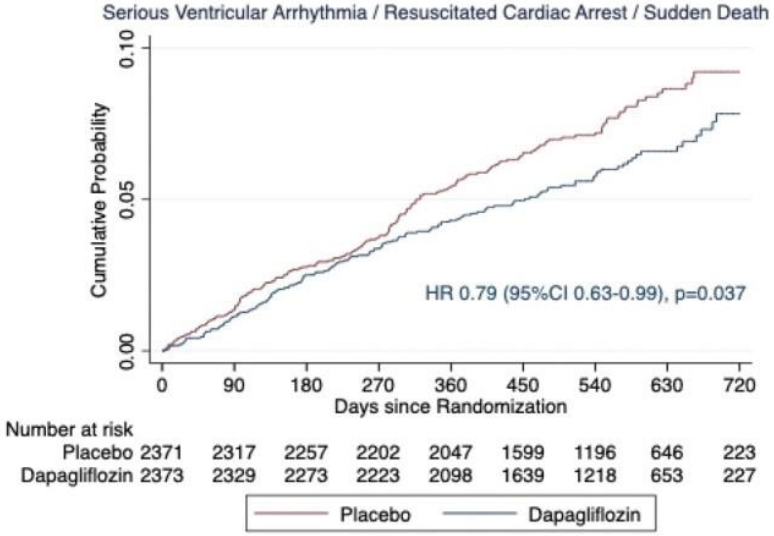




CV, cardiovascular;
VT, ventricular tachycardia;
VF, ventricular fibrillation;
TdP, Torsade de pointes;
HR, hazard ratio.

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

Predictor variable[a]	Odds ratio (95% CI)	P-value[b]	χ^2
Log-transformed NT-proBNP (per 1 unit increase)	1.54 (1.34–1.77)	<0.001	36.0
Previous ventricular arrhythmia	1.93 (1.41–2.64)	<0.001	16.8
LVEF (per 5% increase)	0.86 (0.78–0.94)	0.001	11.9
Systolic BP (per 10 mmHg increase)	0.88 (0.81–0.96)	0.004	8.1
Previous MI	1.42 (1.11–1.82)	0.005	7.8
Male sex	1.53 (1.10–2.12)	0.012	6.3
BMI (per 1 kg/m^2 increase)	1.03 (1.00–1.05)	0.020	5.4
Sodium (per 1 mmol/L increase)	0.96 (0.92–0.99)	0.039	4.3
Non-white race	0.85 (0.72–0.99)	0.038	4.3
Dapagliflozin	0.80 (0.63–1.02)	0.067	3.4
Cardiac resynchronization therapy	0.64 (0.39–1.04)	0.070	3.3
Previous HF hospitalization	0.99 (0.78–1.27)	0.985	0.0



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

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

Outcome	Dapagliflozin *n/N* (%)	Dapagliflozin Event rate per 100 person-years	Placebo *n/N* (%)	Placebo Event rate per 100 person-years	Hazard ratio[a] (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) *P* = 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 cardiac 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 (*minus 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

CI, confidence interval; NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]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.

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

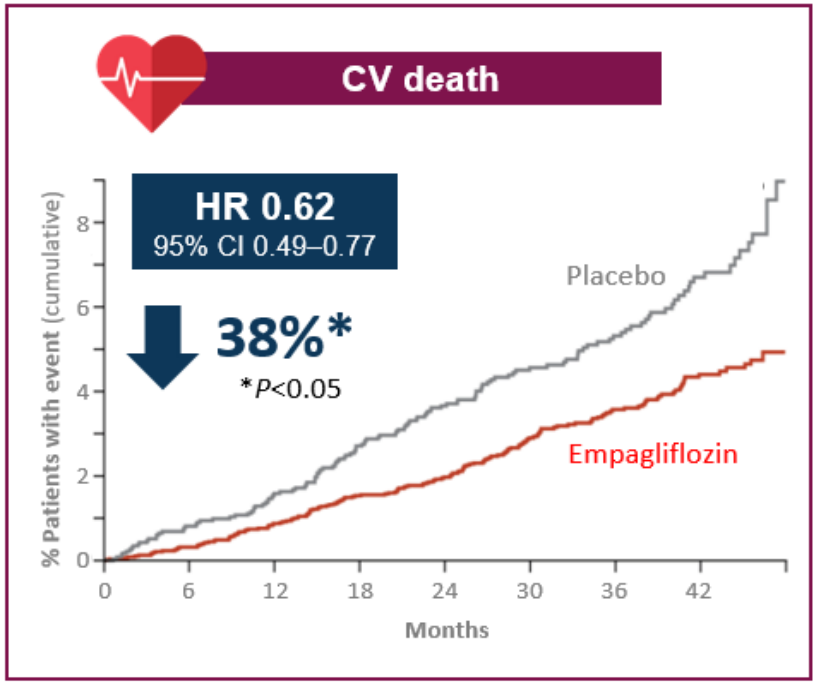
Outcome	Dapagliflozin *n/N* (%)	Dapagliflozin Event rate per 100 person-years	Placebo *n/N* (%)	Placebo Event rate per 100 person-years	Hazard ratio[a] (95% CI)	Interaction *P*-value
Ischaemic aetiology						
Yes	84/1316 (6.4)	4.4 (3.5–5.4)	113/1358 (8.3)	5.8 (4.8–7.0)	0.76 (0.57–1.00)	0.597
No	56/1057 (5.3)	3.7 (2.8–4.8)	62/1013 (6.1)	4.3 (3.3–5.5)	0.86 (0.60–1.23)	
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)	
ICD/CRT-D at baseline						
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)	0.174
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)	
Time from diagnosis 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)	0.533
≥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)	
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)	
Previous ventricular 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)	
NYHA class						
II	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
III/IV	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)	
NT-proBNP (pg/ml)[b]						
≤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)	
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)	
Systolic BP (mmHg)						
≤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)	

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-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]Models included factors for randomized treatment, history of HF hospitalization and were stratified by diabetes status.
[b]Missing data for *n* = 2 patients.

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

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)
	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)
Worsening of heart failure	19 (0.8)	7 (0.3)	4 (0.2)	11 (0.2)
Acute myocardial infarction	11 (0.5)	6 (0.3)	9 (0.4)	15 (0.3)
Stroke	11 (0.5)	9 (0.4)	7 (0.3)	16 (0.3)
Cardiogenic shock	3 (0.1)	1 (<0.1)	2 (0.1)	3 (0.1)
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.

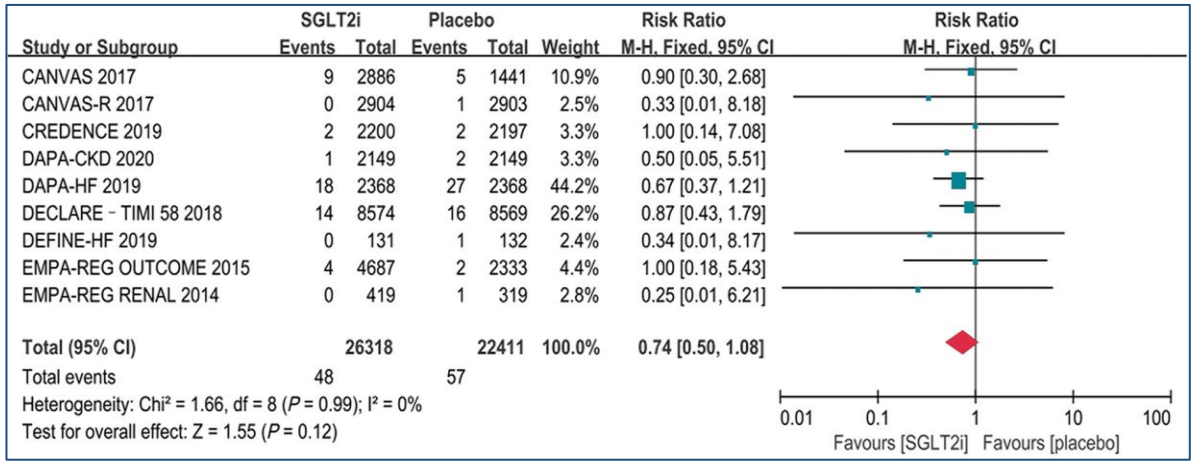
- EMPA-REG OUTCOME trial: 5687 (empagliflozin) vs. 2333 (placebo)
- Empagliflozin reduced incidence of SCD: 53 (1.1%) vs. 38 (1.6%) events

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128.

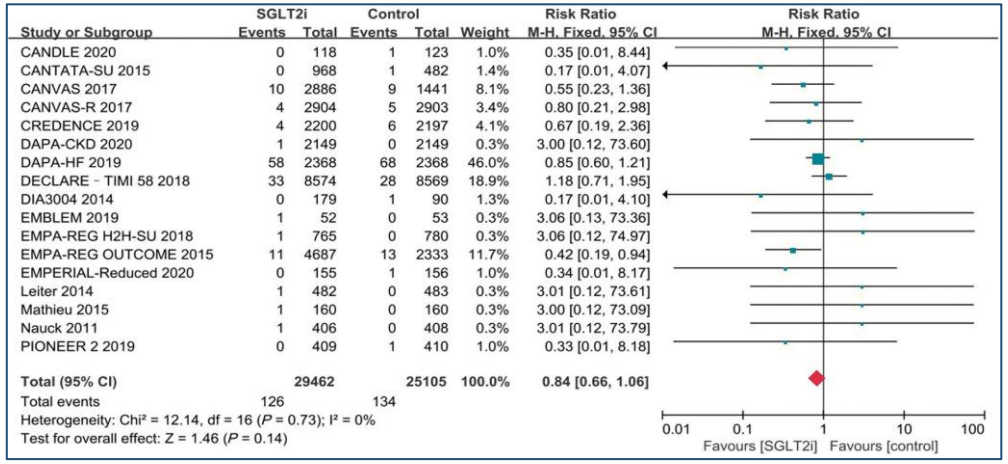
Effects of SGLTi on Ventricular Arrhythmias and SCD

Meta-Analysis of Randomized Controlled Trails

Incidence of SCD

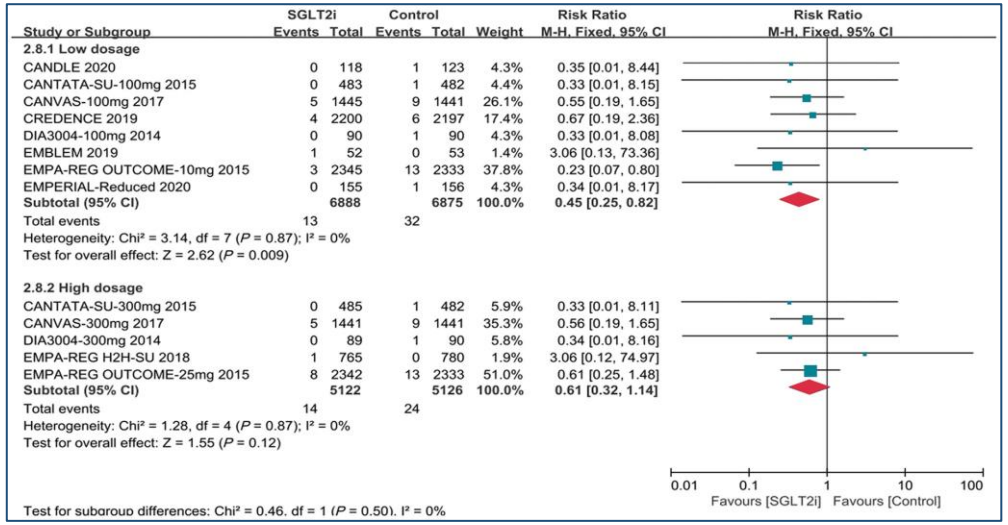


Incidence of VAs



- SGLT2i therapy was not associated with an overall lower risk of SCD or VAs in patients with T2DM and/or HF and/or CKD.
- Further research is needed since the number of SCD and VA events were relatively small.

Incidence of VAs



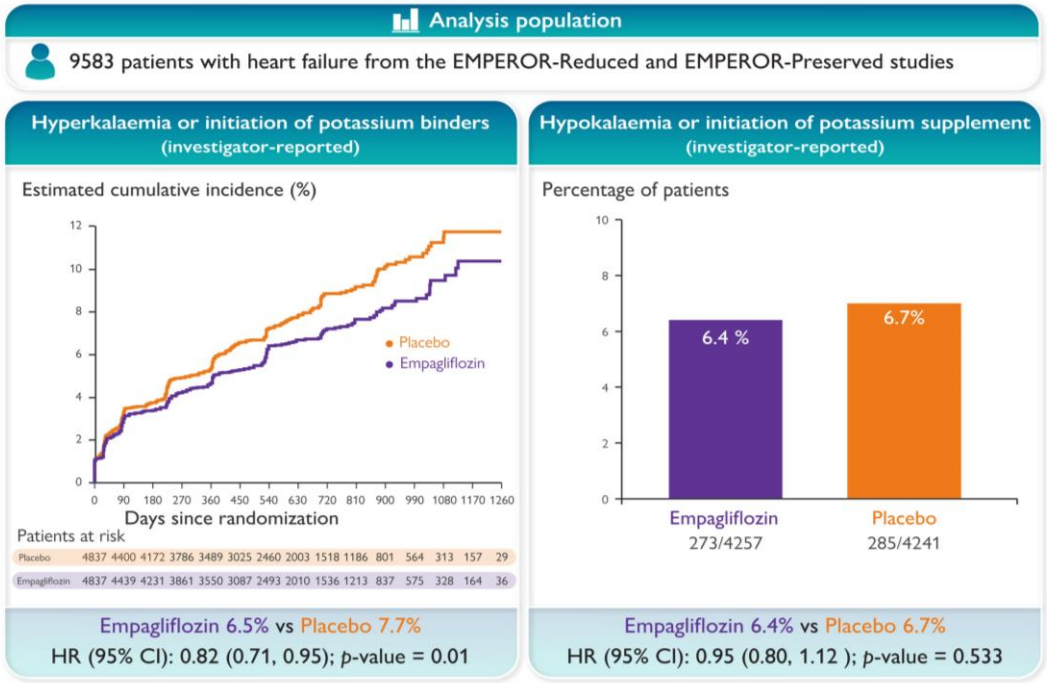
EHRA European Heart Rhythm Association
European Society of Cardiology

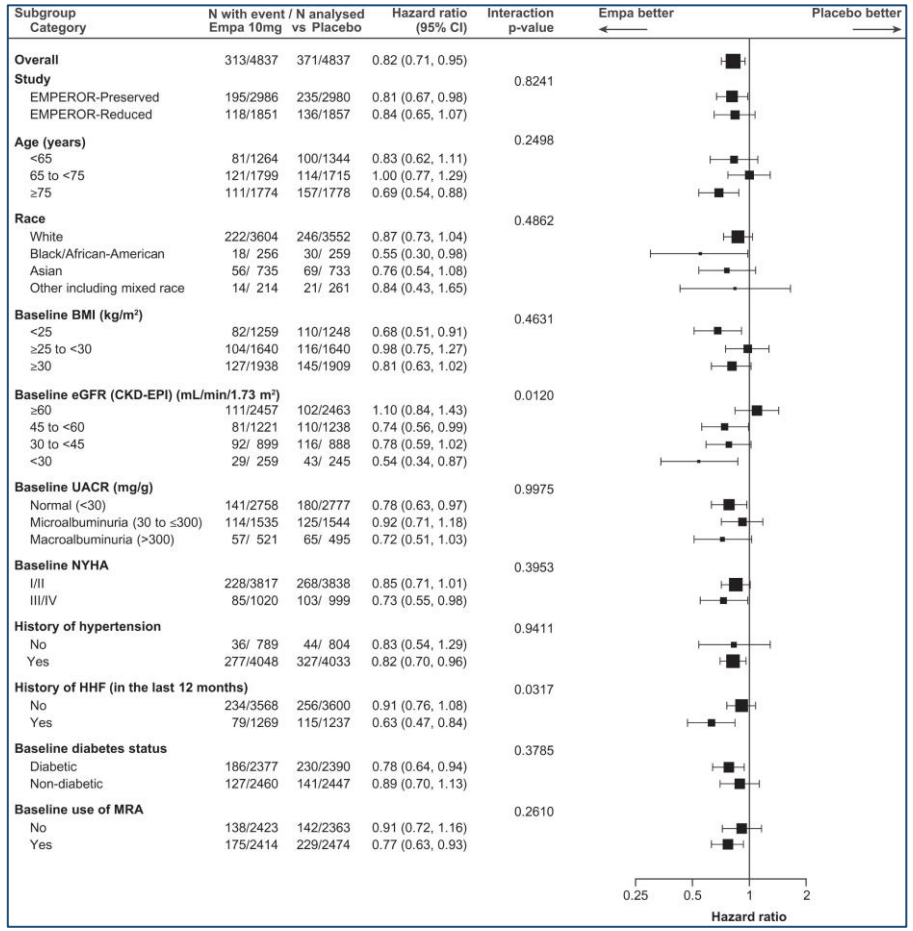
Sfairopoulos D, et al. Europace 2022;24:20-30.

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, $P = 0.01$].

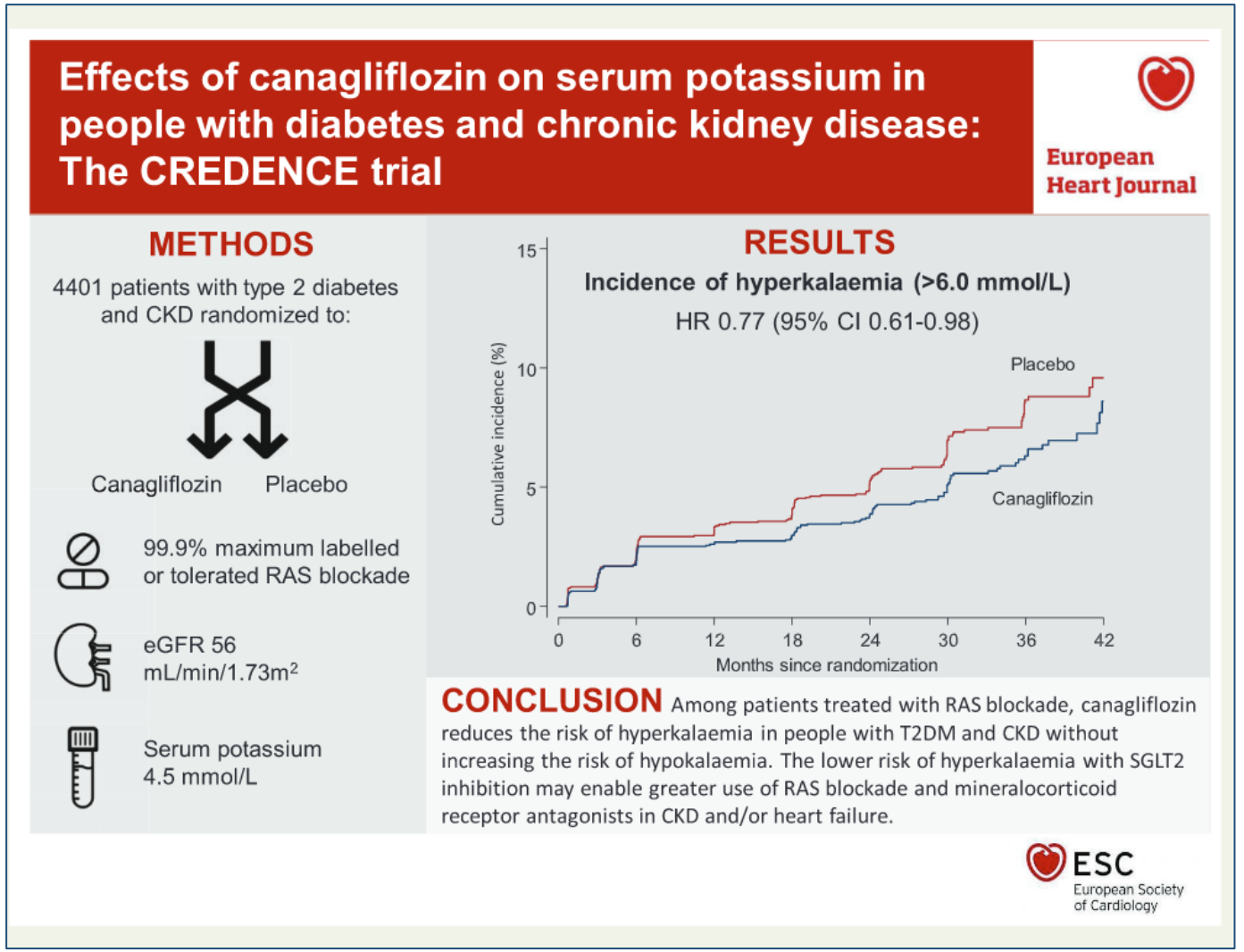




Ferreira JP, et al. Eur Heart J 2022 Jun 10;ehac306.doi:10.1093/eurhearti/ehac306.

Effects of SGLTi on Hyperkalemia

CREDENCE Trial



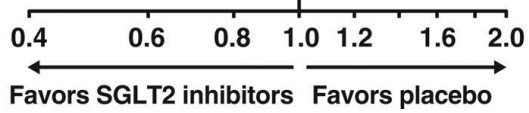
Neuen BL, et al. Eur Heart J 2021;42:4891-4901.

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 (≥6.0 mmol/L) with no increased risk of hypokalemia.

	SGLT2 inhibitors		Placebo		
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	Hazard Ratio (95% CI)
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)
Overall (I^2=0.0%; $P_{heterogeneity}$=0.71)					**0.84 (0.76, 0.93)** P<0.001

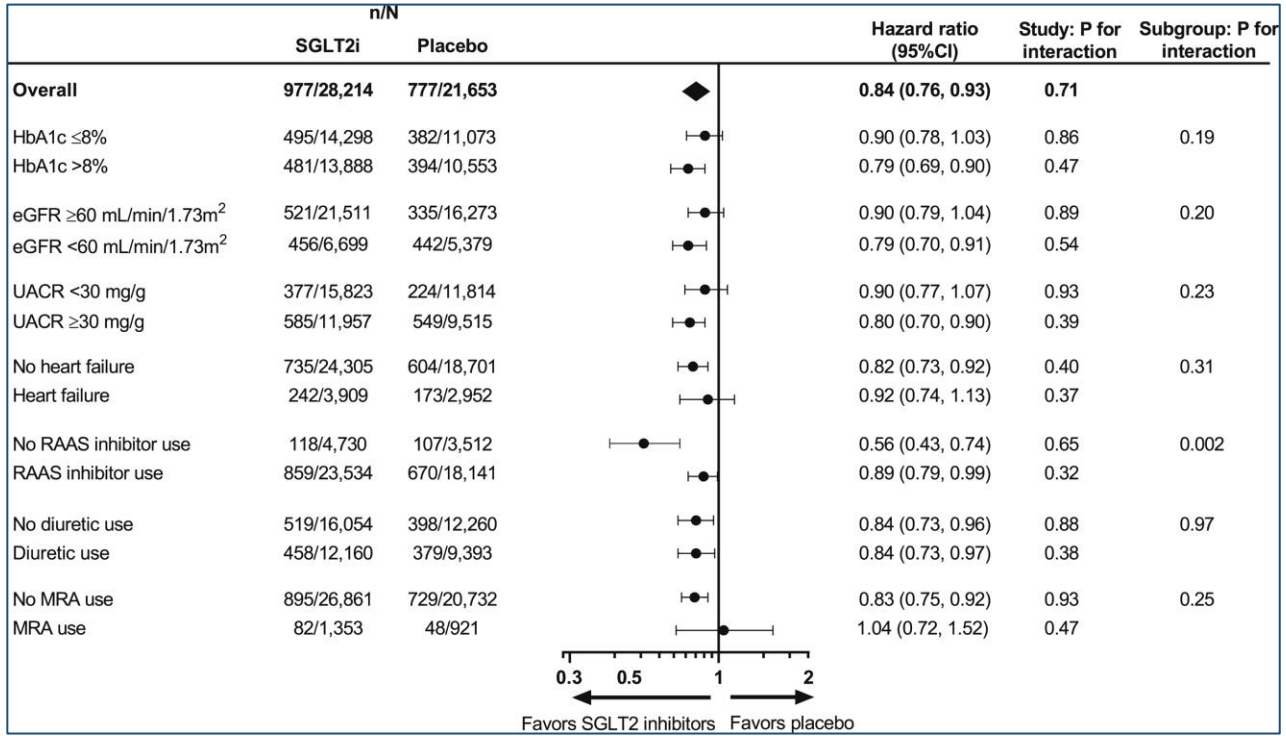


Neuen BL, et al. Circulation 2022 8 April;145:1460-1470.

Effects of SGLTi on Hyperkalemia

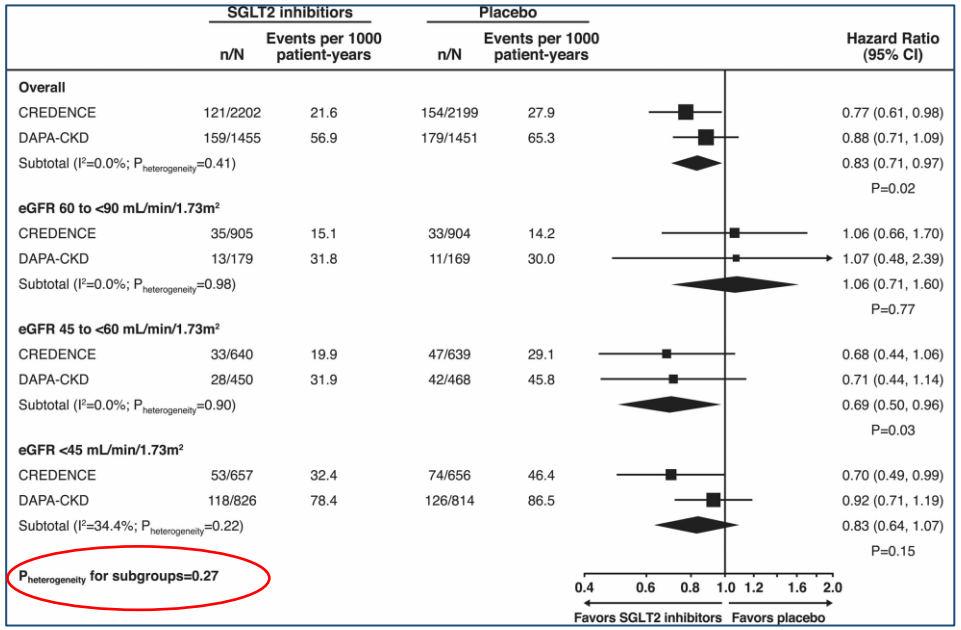
Meta-Analysis of Randomized Controlled Trails

- 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/N SGLT2i	n/N Placebo	Hazard ratio (95%CI)	Study: P for interaction	Subgroup: P for interaction
Overall	**977/28,214**	**777/21,653**	**0.84 (0.76, 0.93)**	**0.71**	
HbA1c ≤8%	495/14,298	382/11,073	0.90 (0.78, 1.03)	0.86	0.19
HbA1c >8%	481/13,888	394/10,553	0.79 (0.69, 0.90)	0.47	
eGFR ≥60 mL/min/1.73m^2	521/21,511	335/16,273	0.90 (0.79, 1.04)	0.89	0.20
eGFR <60 mL/min/1.73m^2	456/6,699	442/5,379	0.79 (0.70, 0.91)	0.54	
UACR <30 mg/g	377/15,823	224/11,814	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	0.92 (0.74, 1.13)	0.37	
No RAAS inhibitor use	118/4,730	107/3,512	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	0.84 (0.73, 0.96)	0.88	0.97
Diuretic use	458/12,160	379/9,393	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	1.04 (0.72, 1.52)	0.47	

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

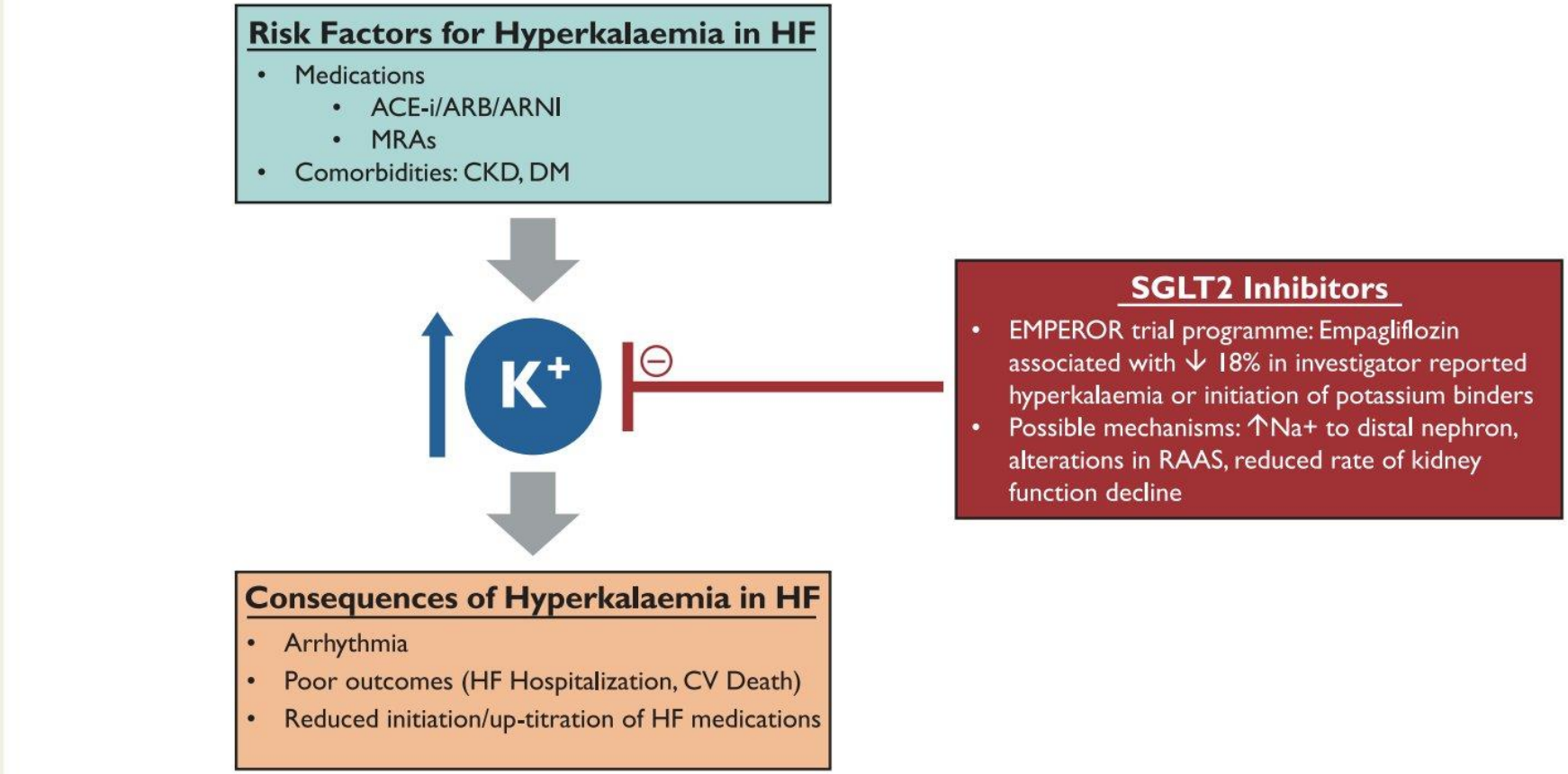


	SGLT2 inhibitors n/N	SGLT2 inhibitors Events per 1000 patient-years	Placebo n/N	Placebo Events per 1000 patient-years	Hazard Ratio (95% CI)
Overall					
CREDENCE	121/2202	21.6	154/2199	27.9	0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3	0.88 (0.71, 1.09)
Subtotal (I^2=0.0%; $P_{heterogeneity}$=0.41)					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 (I^2=0.0%; $P_{heterogeneity}$=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 (I^2=0.0%; $P_{heterogeneity}$=0.90)					0.69 (0.50, 0.96)
					P=0.03
eGFR <45 mL/min/1.73m²					
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 (I^2=34.4%; $P_{heterogeneity}$=0.22)					0.83 (0.64, 1.07)
					P=0.15
$P_{heterogeneity}$ for subgroups=0.27					

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

Emerging Role for SGLT2 Inhibitors in Mitigating the Risk of Hyperkalemia

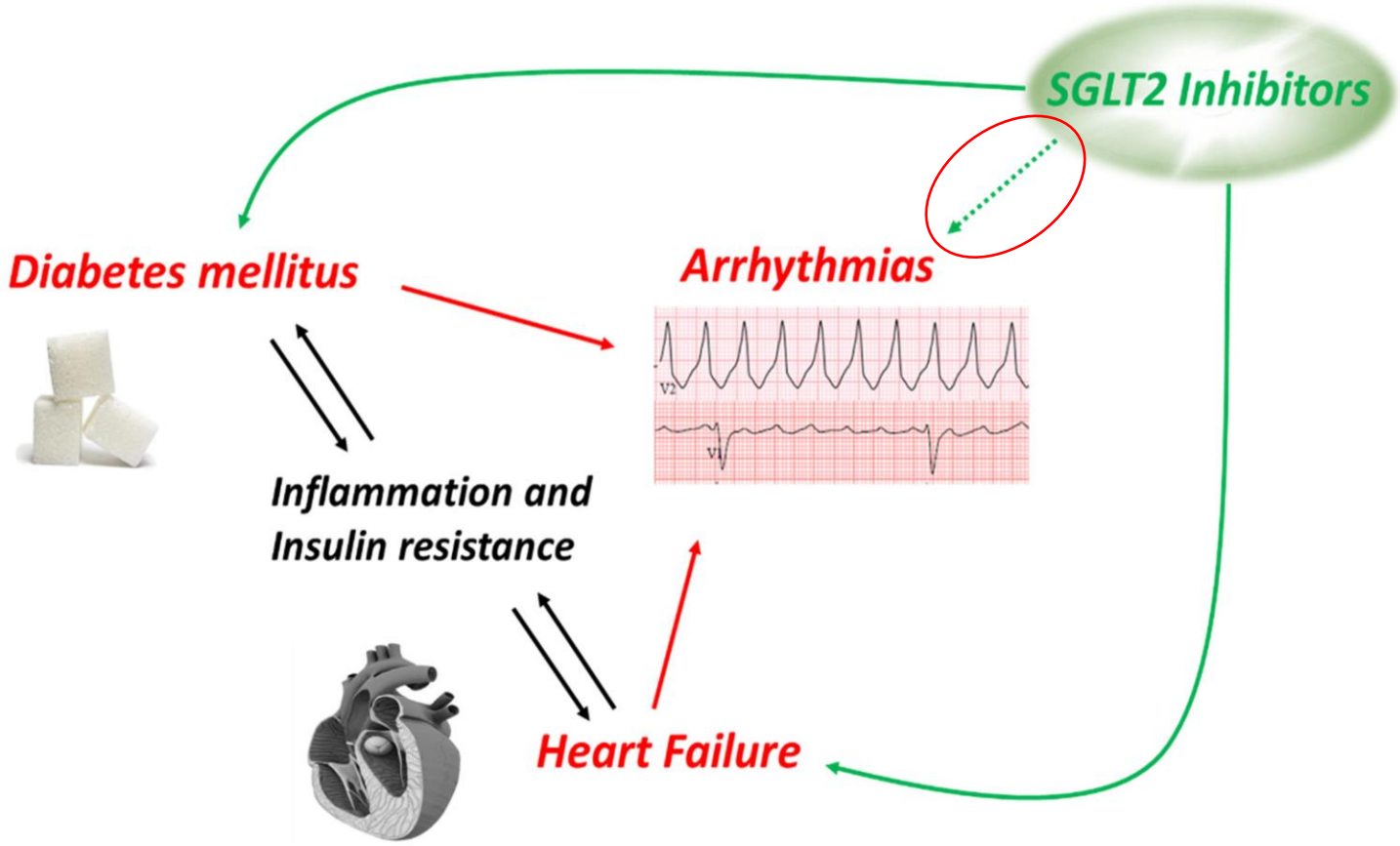
Graphical Abstract



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

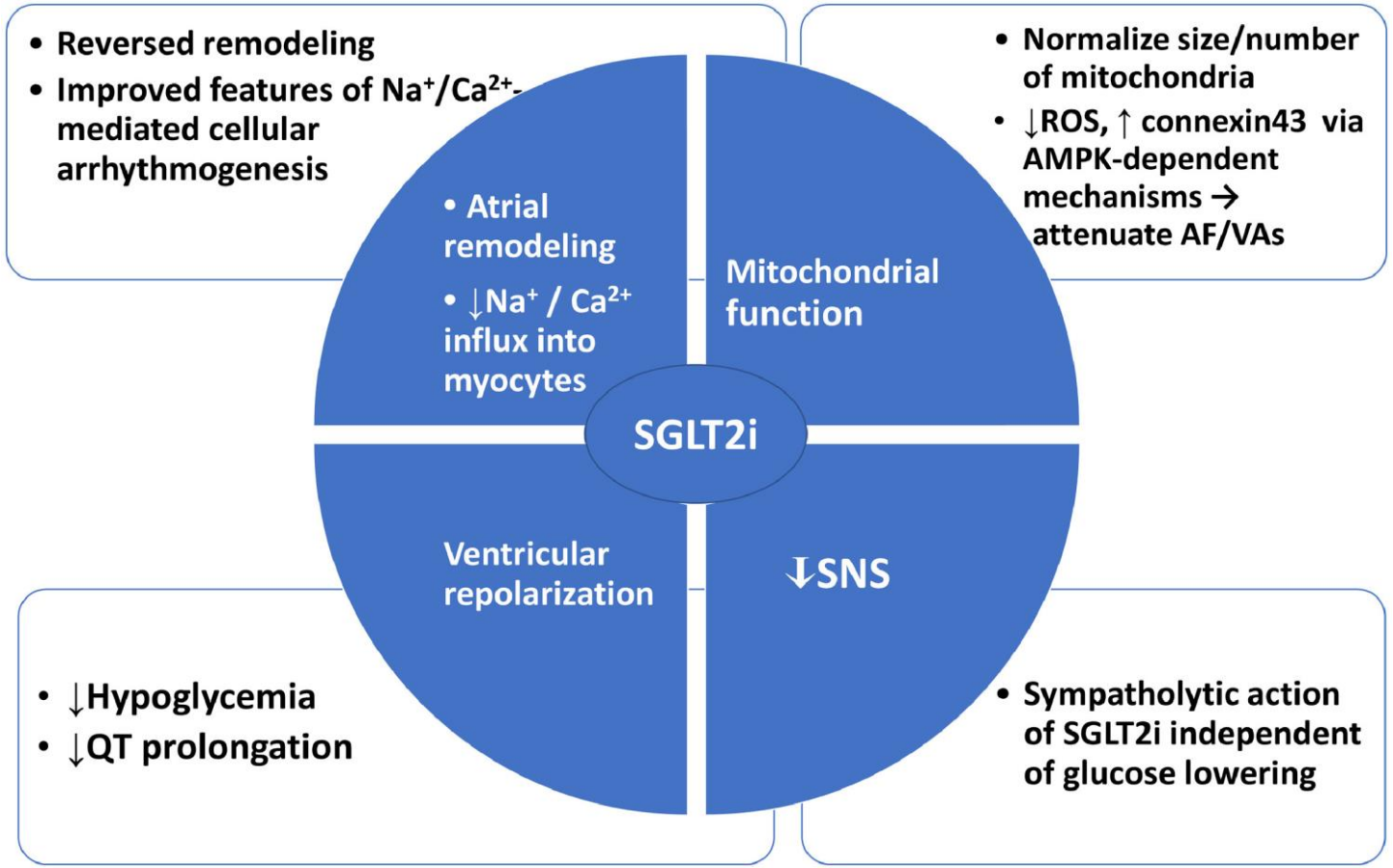
Verma S. Eur Heart J 2022 2022 Jun 10;ehac304. doi: 10.1093/eurheartj/ehac304.

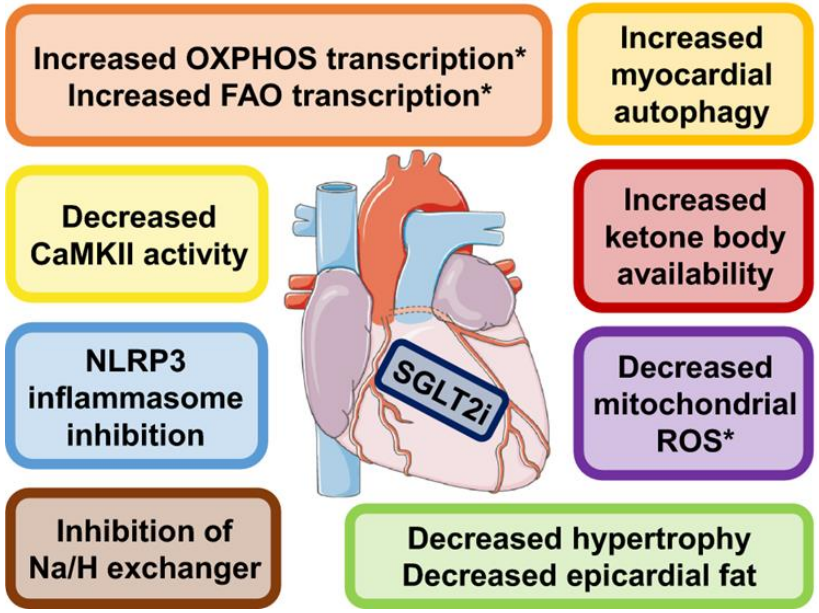
Connection and Interaction Between Diabetes Mellitus, Heart failure, and Arrhythmias



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

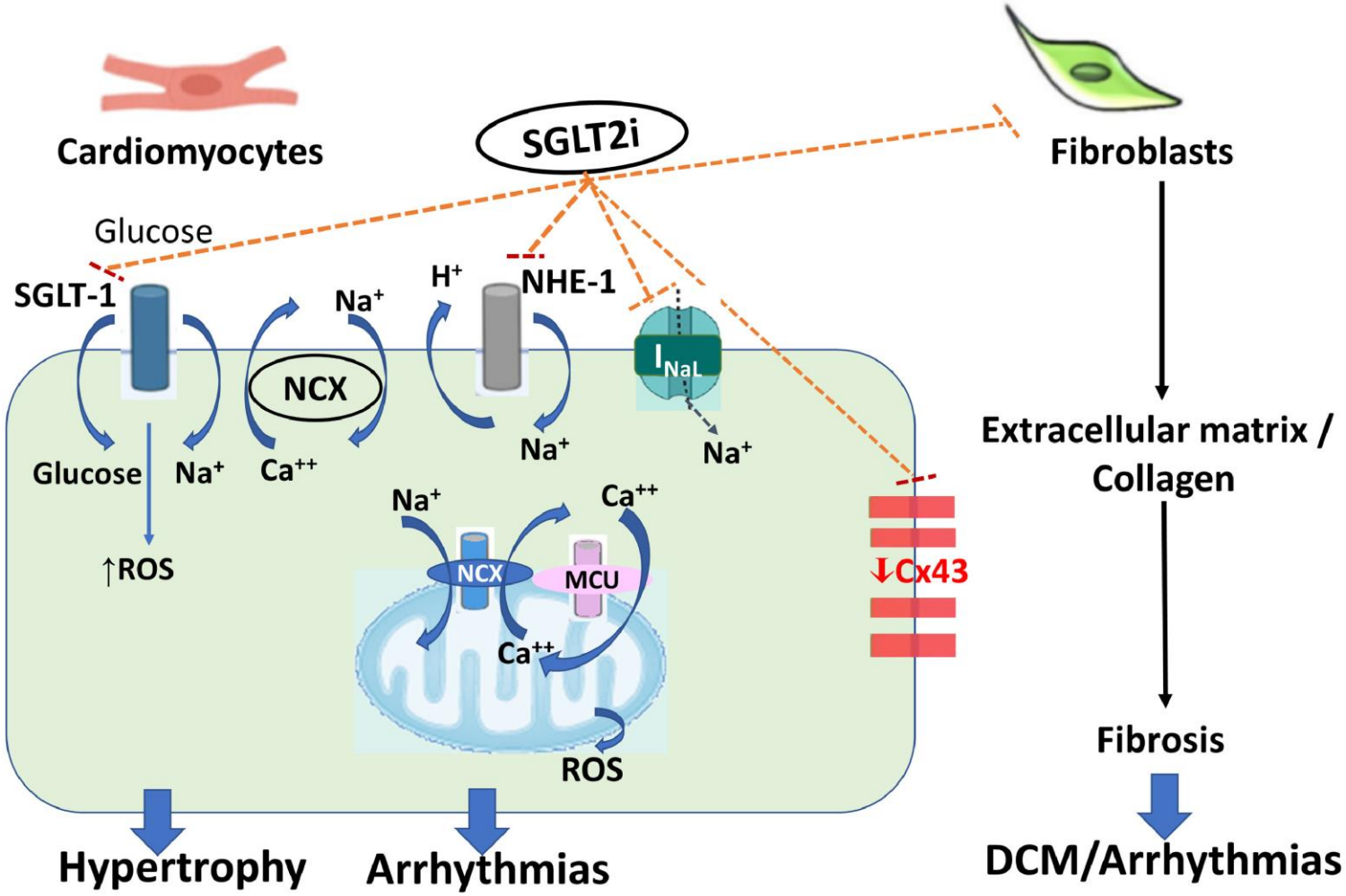
Suggested Mechanisms Underlying the Antiarrhythmic Effects of SGLT2 Inhibitors at the Myocardial Level





Manolis AA, et al. Trends Cardiovasc Med 2022 April; 18:S1050-1738(22)00062-7.
Sawacki KT, et al. JAHA 2021;10:e021949. doi: 10.1161/JAHA.121.021949.

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

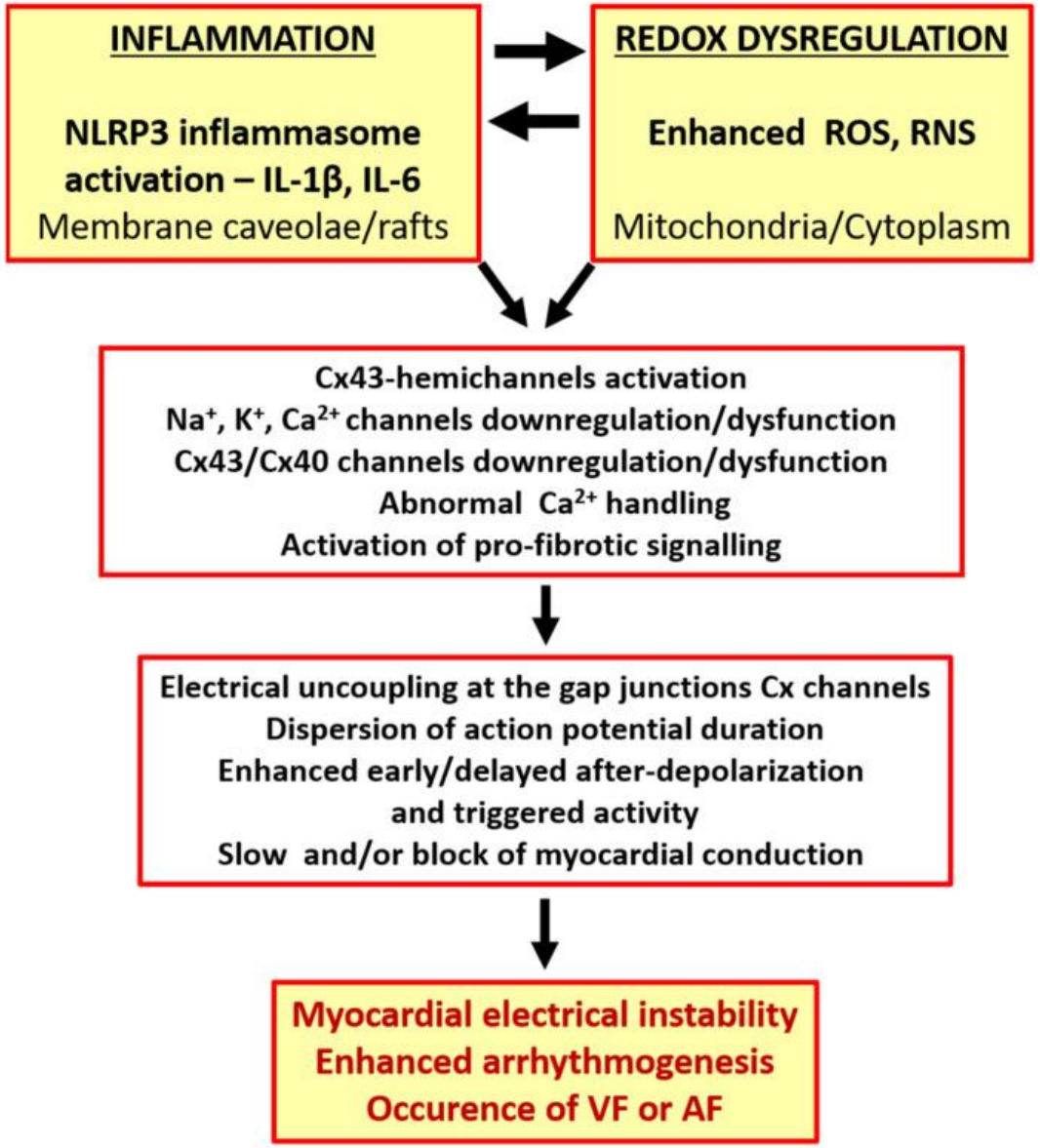
- SGLT2 inhibitors are associated with reduced risk of hyperkalemia and atrial arrhythmias (AF/AFL), and they may confer protection against ventricular arrhythmia and reduce sudden cardiac death.
- This may, at least partially, explain the decreased risk of CV death in patients with T2DM and HF.
- Most 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



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Mechanisms and Pathways Responsible for Antiarrhythmic Properties of SGLT2 Inhibitors

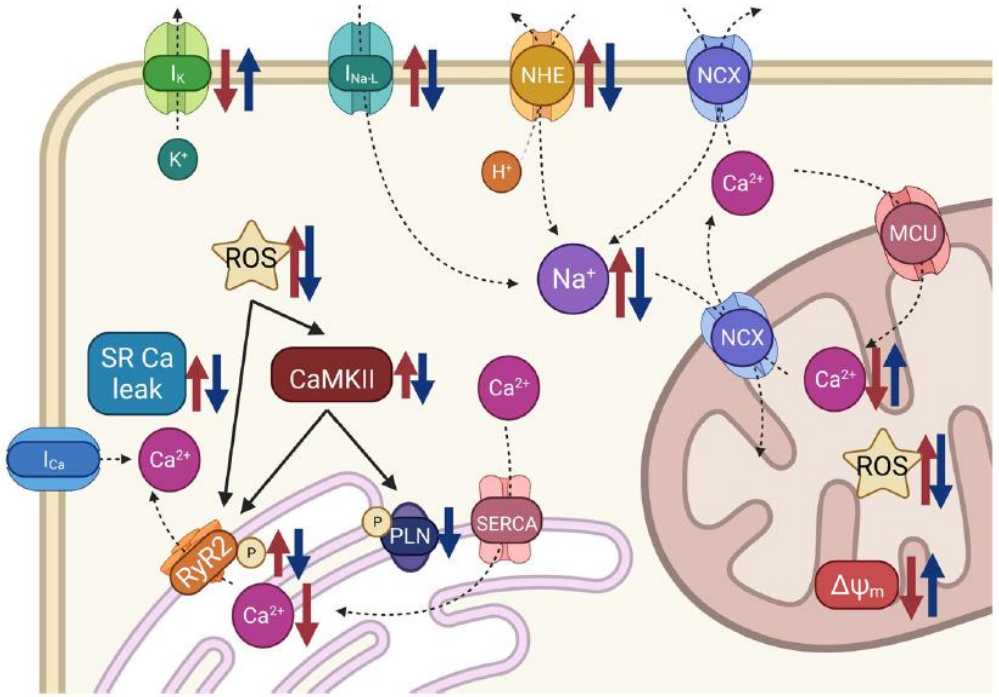

FIGURE 1 Potential effects of SGLT-2 inhibitors on cardiac ion current, calcium handling homeostasis and oxidative stress in a HF model. Red arrows indicate the change in a HF model compared to the control. Blue arrows indicate the change after being exposed to SGLT-2 inhibitors in comparison to disturbance 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; $I_{Na\text{-}late}$, late sodium channel current; MCU, mitochondrial calcium uniporter; NCX, Na^+/Ca^{2+}exchanger; NHE, Na^+/H^+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

Manolis AA, et al. Trends Cardiovasc Med 2022 April; 18:S1050-1738(22)00062-7.
Sawacki KT, et al. JAHA 2021;10:e021949. doi: 10.1161/JAHA.121.021949.

Mechanisms and Pathways Responsible for Antiarrhythmic Properties of SGLT2 Inhibitors

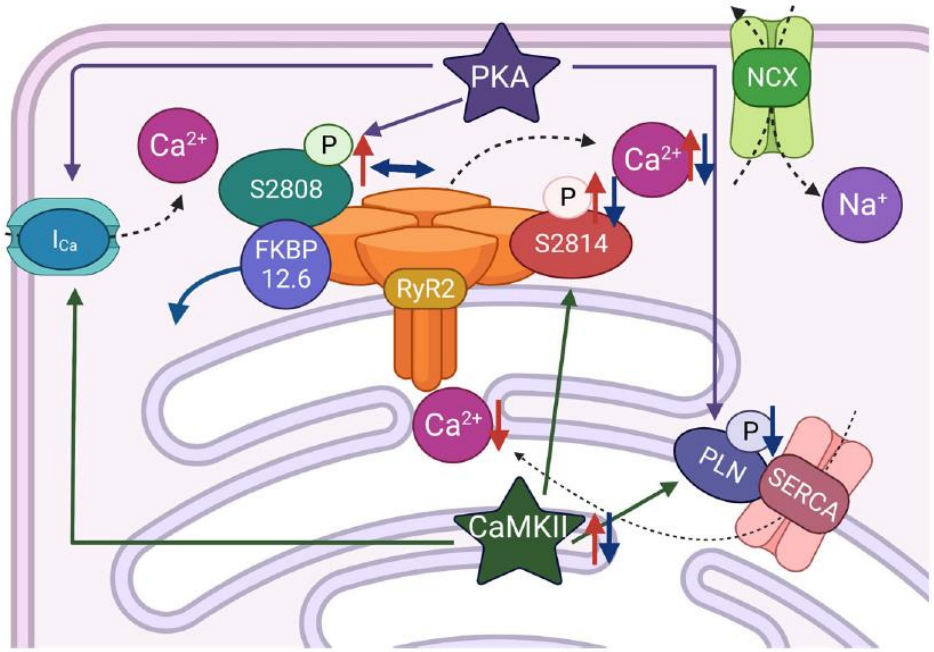

FIGURE 2 Potential roles of PKA and CaMKII in RyR2 phosphorylation and calcium handling proteins in the HF model. Purple arrows indicate the proposed mechanism of PKA dependent RyR2 phosphorylation on SR Ca^{2+} leakage in a HF model. Green arrows indicate the effect of CaMKII on SR Ca^{2+} leakage in 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^{2+}/calmodulin dependent protein kinase II; FKBP12.6, FK 506-binding protein-12.6; I_{Ca}, L-type calcium channel current; NCX, Na^{+}/Ca^{2+}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

Manolis AA, et al. Trends Cardiovasc Med 2022 April; 18:S1050-1738(22)00062-7.
Sawacki KT, et al. JAHA 2021;10:e021949. doi: 10.1161/JAHA.121.021949.