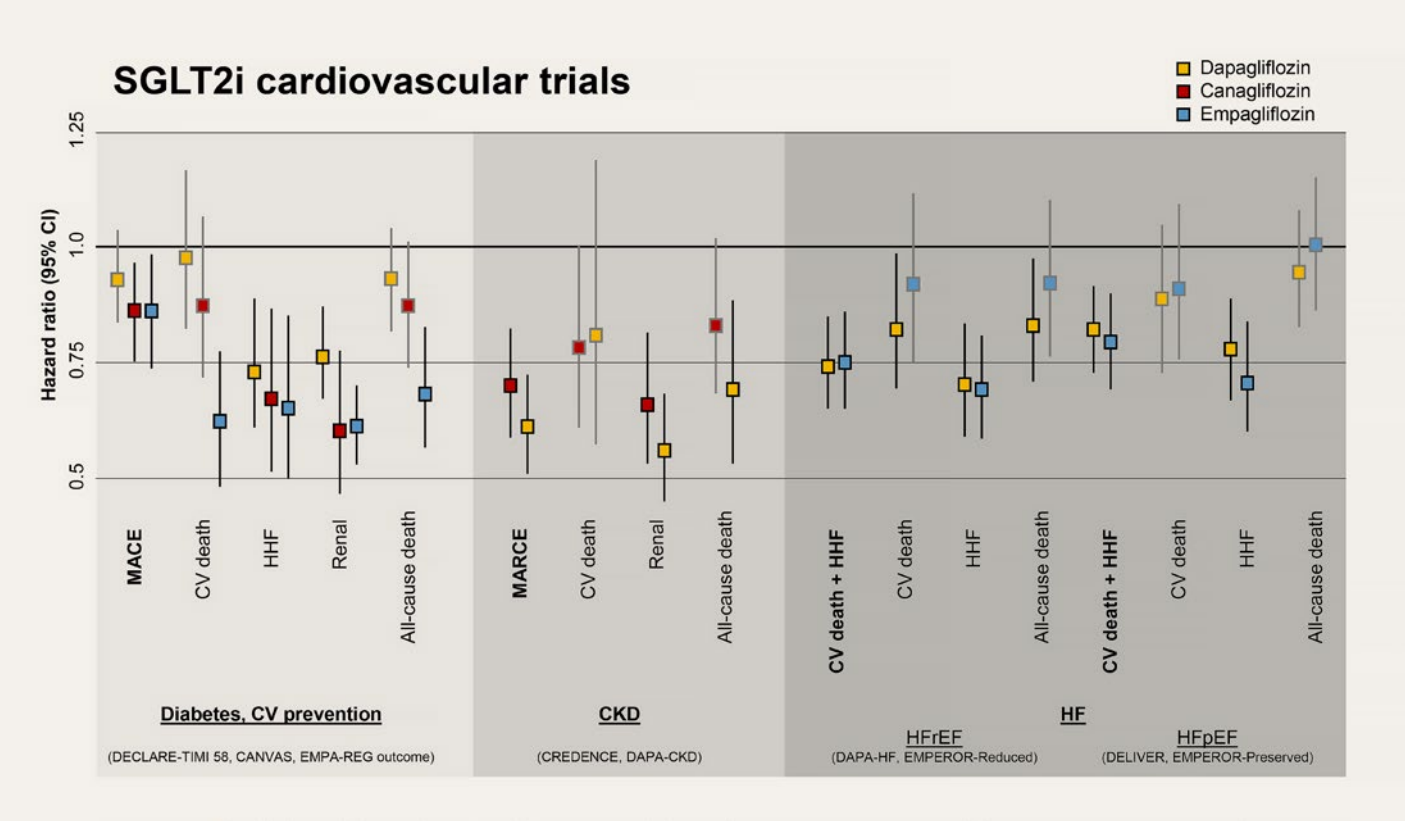

Figure 1: Primary, cardiovascular and renal endpoints of the largest randomised clinical trials investigating SGLT2 inhibitors.

Letter to the editor

Cardiovascular trials with SGLT2 inhibitors – a primer to survive in the jungle

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We read with interest the review article by Maeder, Rickli, and Buser on the role of sodium-glucose co-transporter 2 (SGLT2) inhibitors in heart failure [1]. During the last decade, nine large randomised trials testing the efficacy of three different compounds with respect to cardiovascular and renal endpoints have been published and others are expected soon (e.g. EMPA-Kidney trial investigating empagliflozin in patients with chronic kidney disease). Although the interest in SGLT2 inhibitors has paralleled the increasing evidence of beneficial effects, clinicians might also be confused by the rapidly growing body of evidence with (many) consistencies and (some) contradictory results. This "jungle" of results might discourage clinicians from selectively using SGLT2 inhibitors. Indeed, although we acknowledge that, at least to some degree, a "class effect" of SGLT2 inhibitors likely exists, relevant differences in study design, tested end-points and results preclude the generalisability of the observed findings to all compounds. Of note, the clinical setting (e.g., primary vs secondary cardiovascular prevention), the proportion of diabetic patients (ranging from 42% to 100%), the range of prevalence of arteriosclerotic cardiovascular disease (from 35% to 100%) and heart failure (from 10% to 100%) substantially differ across the trials.

Hence, cautious use of the tested compound in the appropriate setting seems the most reasonable approach. Accordingly, the 2021 European Society for Cardiology (ESC) guidelines for the treatment of heart failure recommend the use of dapagliflozin or empag-

Table 1: Main characteristics of the large published randomized clinical trials investigating SGLT2 inhibitors for cardiovascular and renal endpoints

Setting	Diabetes	Diabetes	Diabetes	Diabetes and CKD	CKD	HF	HF	HF	HF
Drug	Dapagliflozin	Canagliflozin	Empagliflozin	Canagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin	Dapagliflozin	Empagliflozin
Trial	DECLARE-TIMI-58	CANVAS	EMPA-REG outcome	CREDENCE	DAPA-CKD	DAPA-HF	EMPEROR-REDUCED	DELIVER	EMPEROR-PRESERVED
Year	2019	2017	2015	2019	2020	2019	2020	2022	2021
Cohort	Diabetes, ASCVD or multiple risk factors, eGFR ≥60 ml/min	Diabetes, ASCVD or multiple risk factors, eGFR ≥30 ml/min	Diabetes, ASCVD, eGFR ≥30 ml/min	Diabetes, CKD (eGFR 30–90 ml/min and albuminuria)	CKD (eGFR 25–75 ml/min and albuminuria)	HF, LVEF ≤40%	HF, LVEF ≤40%	HF, LVEF >40%	HF, LVEF >40%
N =	17160	10142	7020	4401	4304	4744	3730	6263	5988
Age (y)	64	63	63	63	62	66	67	72	72
Diabetes	100%	100%	100%	100%	67%	42%	50%	45%	49%
ASCVD	41%	72%	100%	50%	37%	56%	51%	57%	35%
eGFR (ml/min /1.73 m^2)	85	76	74	56	43	66	62	61	61
HF	10%	14%	10%	15%	11%	100%	100%	100%	100%
LVEF (%)	NA	NA	NA	NA	NA	31	27	54	54
Follow-up (y)	4.2	2.4	3.1	2.6	2.4	1.5	1.4	2.3	2.2
Primary Outcome	MACE: CV death, MI, stroke	MACE: CV death, MI, stroke	MACE: CV death, MI, stroke	MARCE: CV death, renal death, ESRD, creatinine doubling	MARCE: CV death, renal death, ESRD, GFR –50%	CV death + HHF + HF urgent visit	CV death + HHF	CV death + HHF + HF urgent visit	CV death + HHF
HR (CI)	0.93 (0.84–1.03)	0.86 (0.75-0.97)	0.86 (0.74–0.99)	0.70 (0.59–0.82)	0.61 (0.51–0.72)	0.74 (0.65–0.85)	0.75 (0.65–0.86)	0.82 (0.73–0.92)	0.79 (0.69–0.90)
All-cause mortality	0.93 (0.82–1.04)	0.87 (0.74–1.01)	0.68 (0.57–0.82)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	0.94 (0.83–1.07)	1.00 (0.87–1.15)
CV mortality + HHF	0.83 (0.73–0.95)	0.78 (0.67–0.91)	0.66 (0.55–0.79)	0.69 (0.57–0.83)	0.71 (0.55–0.92)	0.75 (0.65–0.85)	0.75 (0.65–0.86)	0.77 (0.67–0.89)	0.79 (0.69–0.90)
CV mortality	0.98 (0.82–1.17)	0.87 (0.72–1.06)	0.62 (0.49–0.77)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.88 (0.74–1.05)	0.91 (0.76–1.09)
HHF	0.73 (0.61–0.88)	0.67 (0.52–0.87)	0.65 (0.50–0.85)	0.61 (0.47–0.80)	x	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.77 (0.67–0.89)	0.71 (0.60–0.83)
MACE	0.93 (0.84–1.03)	0.86 (0.75–0.97)	0.86 (0.74–0.99)	0.80 (0.67–0.95)	x	x	x	x	x
Renal outcomes	0.76 (0.67–0.87)	0.60 (0.47–0.77)	0.61 (0.53–0.70)	0.66 (0.53–0.81)	0.56 (0.45–0.68)	0.71 (0.44–1.16)	0.50 (0.32–0.77)	x	0.95 (0.73–1.24)
Reference	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)

Legend: ASCVD atherosclerotic cardiovascular disease; CKD chronic kidney disease; CV cardiovascular; eGFR estimated glomerular filtration rate; ESRD end-stage renal disease; HF heart failure; HHF hospitalization for heart failure; LVEF left ventricular ejection fraction; MACE major adverse cardiovascular event; MARCE major adverse cardiovascular and renal event; MI myocardial infarction

liflozin for patients with reduced ejection fraction, since only for these two compounds dedicated trials in heart failure exist [2]. Similarly, in patients with preserved or mildly reduced ejection fraction, both compounds showed beneficial prognostic effects and they will likely be included in future guidelines updates.

With this primer, we hope to facilitate the optimal use of SGLT2 inhibitors in daily clinical care of cardiovascular patients.

As survival kit for busy clinicians within the "SGLT2 inhibitors' data jungle", we provide here the cornerstones of the largest published randomised clinical trials (table 1) and a figure visualising the results for the main cardiovascular and renal endpoints tested (fig. 1). With this primer, we hope to facilitate the optimal use of SGLT2 inhibitors in daily clinical care of cardiovascular patients.

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Credits
The results for each endpoint are depicted as a box indicating the hazard ratio (HR) and bars indicating the 95% confidence interval (CI). The colours of the box indicate the different tested substances, the bars are black if statistical significance is met, grey if not. Trials are grouped according to the clinical setting (i.e., cardiovascular prevention in diabetic patients, chronic kidney disease (CKD), heart failure (HF) with reduced (HFrEF) and preserved (HFpEF) ejection fraction. CV: cardiovascular; HHF: hospitalisation for heart failure.

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References
1 MT Maeder SGLT-2 inhibitors and heart failure. Cardiovasc Med. 2022;25:w10138.1664-2031
2 ESC Scientific Document Group, TA McDonagh, M Metra, M Adamo, RS Gardner, A Baumbach, M Böhm. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep;42(36):3599–726. http://dx.doi.org/10.1093/eurheartj/ehab368 PubMed 1522-9645
3 DECLARE–TIMI 58 Investigators, SD Wiviott, I Raz, MP Bonaca, O Mosenzon, ET Kato, A Cahn. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan;380(4):347–57. http://dx.doi.org/10.1056/NEJMoa1812389 PubMed 1533-4406
4 CANVAS Program Collaborative Group, B Neal, V Perkovic, KW Mahaffey, D de Zeeuw, G Fulcher, N Erondu. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug;377(7):644–57. http://dx.doi.org/10.1056/NEJMoa1611925 PubMed 1533-4406
5 EMPA-REG OUTCOME Investigators, B Zinman, C Wanner, JM Lachin, D Fitchett, E Bluhmki, S Hantel. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov;373(22):2117–28. http://dx.doi.org/10.1056/NEJMoa1504720 PubMed 1533-4406
6 CREDENCE Trial Investigators, V Perkovic, MJ Jardine, B Neal, S Bompoint, HJ Heerspink, DM Charytan. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun;380(24):2295–306. http://dx.doi.org/10.1056/NEJMoa1811744 PubMed 1533-4406
7 DAPA-CKD Trial Committees and Investigators, HJ Heerspink, BV Stefánsson, R Correa-Rotter, GM Chertow, T Greene, FF Hou. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct;383(15):1436–46. http://dx.doi.org/10.1056/NEJMoa2024816 PubMed 1533-4406
8 DAPA-HF Trial Committees and Investigators, JJ McMurray, SD Solomon, SE Inzucchi, L Køber, MN Kosiborod, FA Martinez. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov;381(21):1995–2008. http://dx.doi.org/10.1056/NEJMoa1911303 PubMed 1533-4406
9 EMPEROR-Reduced Trial Investigators, M Packer, SD Anker, J Butler, G Filippatos, SJ Pocock, P Carson. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct;383(15):1413–24. http://dx.doi.org/10.1056/NEJMoa2022190 PubMed 1533-4406
10 DELIVER Trial Committees and Investigators, SD Solomon, JJ McMurray, B Claggett, RA de Boer, D DeMets, AF Hernandez. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction [published online ahead of print, 2022 Aug 27]. N Engl J Med. 2022 Aug;NEJMoa2206286. http://dx.doi.org/10.1056/NEJMoa2206286 http://dx.doi.org/10.1056/NEJMoa2206286 PubMed 1533-4406
11 EMPEROR-Preserved Trial Investigators, SD Anker, J Butler, G Filippatos, JP Ferreira, E Bocchi, M Böhm. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct;385(16):1451–61. http://dx.doi.org/10.1056/NEJMoa2107038 PubMed 1533-4406

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