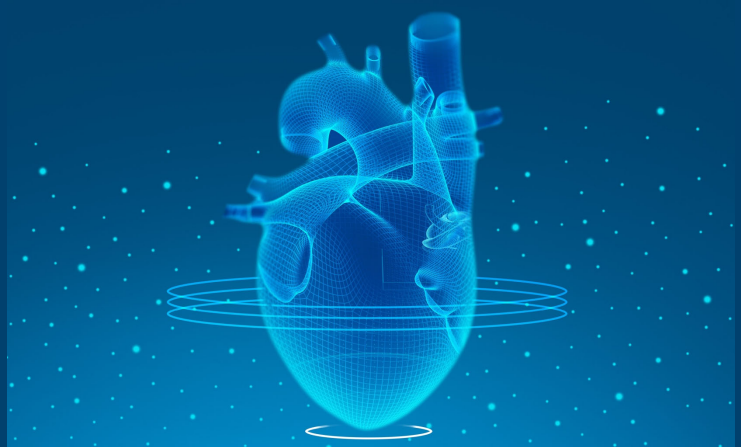
Minneapolis Heart Institute Foundation

GRAND ROUNDS



1

Effects of SGLT2-i and GLP1-RA on CV and Limb Events, Primarily in Patients with PAD

Nedaa Skeik, MD, FACC, FACP, FSVM, RPVI

Professor of Medicine

Section Head, Vascular Medicine

Medical Director, Thrombophilia/Anticoagulation Clinic

Medical Director, Vein Center

Medical Director, Vascular Laboratory

Minneapolis Heart Institute® Abbott Northwestern Hospital

HOPE DISCOVERED HERE

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Disclosures

- Consulting and speaking for Jenssen, A.Z., and Lexicon
- No financial conflict related to this talk
- Information: evidence-based

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Learning Objectives

- PAD: a major under-represented health problem with worse outcome than CAD and CVD!
- Effects of SGLT2-i and GLP1-RA in patients with CV risk or disease
- Effects of SGLT2-i and GLP1-RA in patients with PAD
- Current guidelines and evidence-based recommendations
- Summary

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PAD a Major Atherosclerotic Disease

- Globally, over 236 million people with PAD, up from 200 million in 2010.
- PAD: 3rd. most common ASO after CAD and CVD.

➢More significant cause of morbidity, mortality, and disability.

- Compared with CAD and CVD, evidence for optimal CV risk reduction therapy in patients with PAD is lacking.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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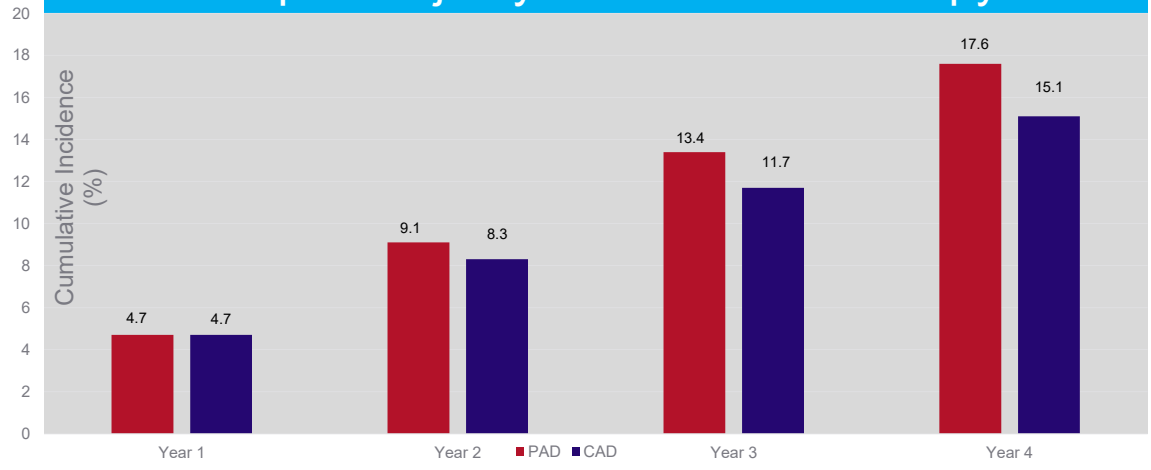
Major CV Event Rates Despite Majority on Standard Therapy



Abtan. J, et al. *Clin Card*. 2017;40:710-718

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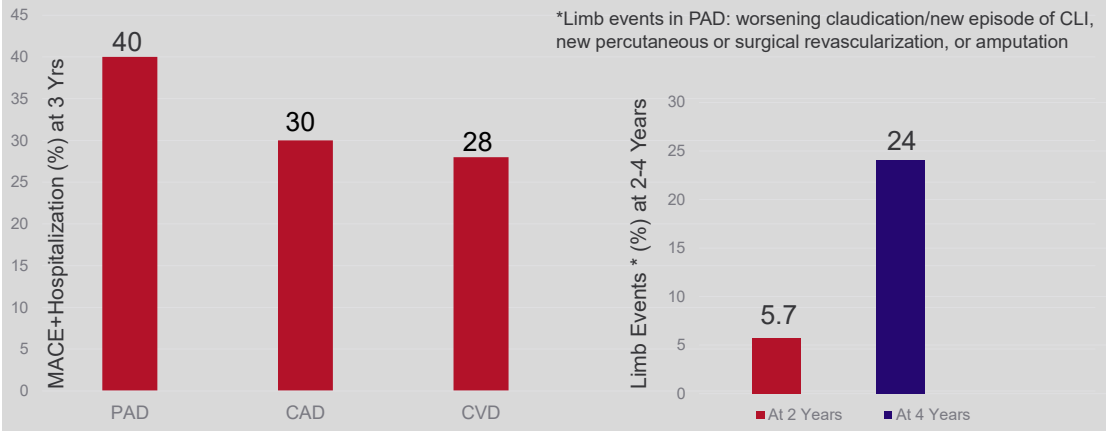
MACE and Hospitalization in PAD, CAD and CVD at 3 Years
Limb Events in PAD at 2 and 4 Years
Despite Standard Therapy



Bhatt DL, et al. *JAMA*. 2006.295:180-189.

7

DM and Cardiovascular Including PAD

- CVD: leading cause of morbidity and mortality in patients with T2D.
- 8.5 M Americans with PAD, 1/3rd have concurrent DM.
- PAD: underestimated in pts with DM due to neuropathy.
- Prediabetes: 20% with abnormal ABI.

- DM increases incidence of limb ischemia and amputation in pts with PAD:

➢ Mechanisms: increased inflammation, endothelial dysfunction, augmented vasoconstriction, and thrombosis.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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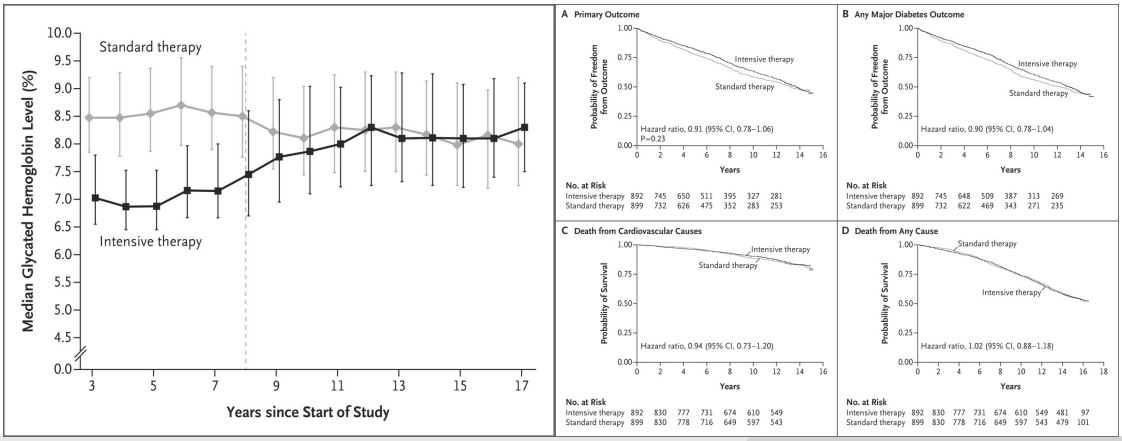
Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up (VADT Study)

Primary outcome: composite MI, stroke, new or worsening CHF, amputation for ischemic gangrene, or CV death



Reaven P et al. *N Engl J Med* 2019; 380:2215-2224.

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DM and Cardiovascular Disease

- Multiple SGLT2-i and GLP1-RA drugs: have shown significant reduction in MACE in patients with T2D and established or at risk for CVD.
- Some SGLT2-i have also shown substantial reduction in HHF and progression of CKD.
- PAD population was underrepresented in these CVOT.
- Will provide a general review of CVOT with SGLT2-i and GLP1-RA.
- Focus on PAD population when available.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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SGLT-i Mechanism of Action

- Blocks the Na-glc cotransporter at proximal tubule leading to glucosuria and natriuria.
- Lowers BP, weight, lipids and uric acid.
- Reduces arterial stiffness, pre and afterload, epicardial fat, and cardiac thrombosis
- Hyperketonemia..
- Exact mechanism for CV benefit is not well known!

- Available agents globally:

➢ *Canagliflozin, dapagliflozin, empagliflozin, sotagliflozin*, ertugliflozin, luseogliflozin, ipragliflozin, and tofogliflozin

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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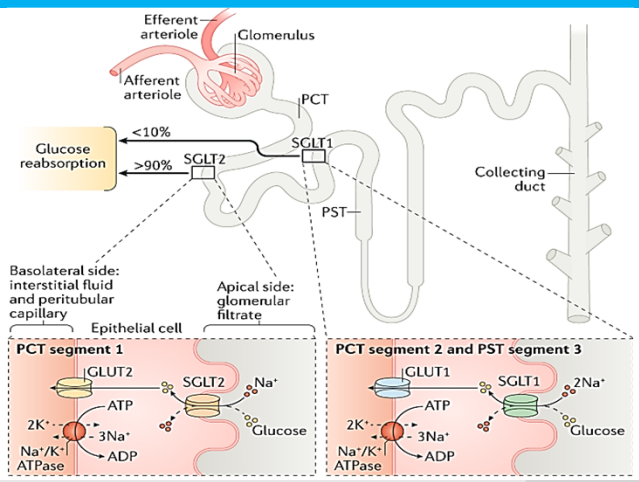
SGLT-i Mechanism of Action



Cowie MR et al. *Nature Reviews Cardiology* **volume 17**, pages 761–772 (2020)

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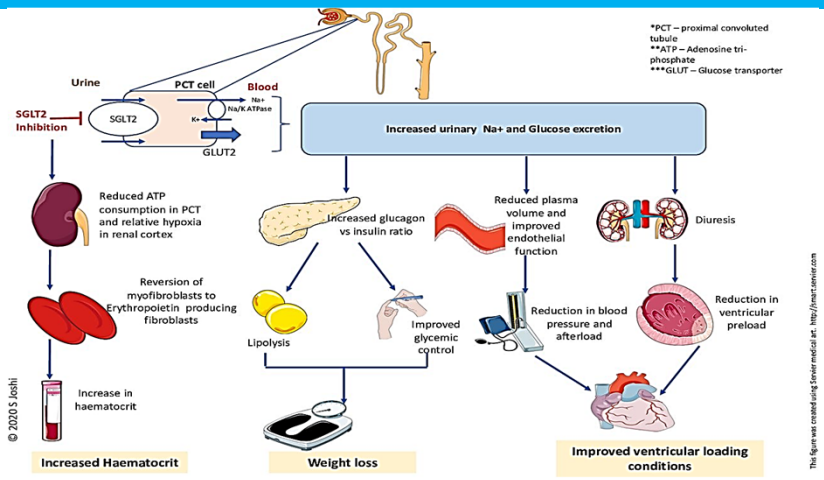
SGLT2-i Mechanism of Action
Exact Mechanism for CV Benefit is Unknown !



Joshi SS, et al. *Heart*. 2021. PMID: 33637556

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SGLT-i
Reduction in MACE
Empagliflozin *(EMPA-REG) Trial*

- 7020 patients with T2D and established CVD.
- 10 or 25 mg of empagliflozin or placebo as add on to the standard of care therapies.
- Study Duration: up to 3.1 years.
- Outcome: MACE.
- Results: significant reduction in *MACE* with empagliflozin, (mainly CV death reduction).
  - ➢ HR, 0.86; 95.02% CI, 0.74 to 0.99; P=0.04 for superiority.

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

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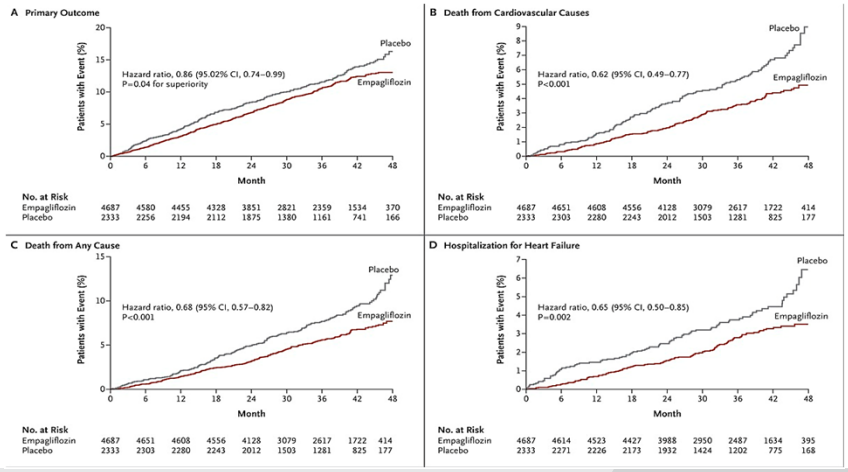
Reduction in MACE
Empagliflozin *(EMPA-REG) Trial*



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

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Reduction in MACE
Empagliflozin *(EMPA-REG) Trial-Sub-analysis - PAD*

- 1461 patients (20.8%) had PAD at baseline (982 treated with empagliflozin, 479 with placebo).
- Results were *consistent* between patients with and without PAD
- *MACE:* HR, 0.84; 95% CI, 0.62-1.14.
- *CV Death*: HR, 0.57; 95% CI, 0.37-0.88.
- *All-cause mortality:* HR, 0.62; 95% CI, 0.44-0.88.
- *HHF:* HR, 0.56; 95% CI, 0.35-0.92.
- *Incidence or worsening nephropathy:* HR, 0.54; 95% CI, 0.41-0.71.
- *Limb amputation*: not different, 5.5% vs 6.3% with placebo (HR, 0.84; 95% CI, 0.54-1.32).

Verma et al. *Circulation.* Volume: 137, Issue: 4, Pages: 405-407.

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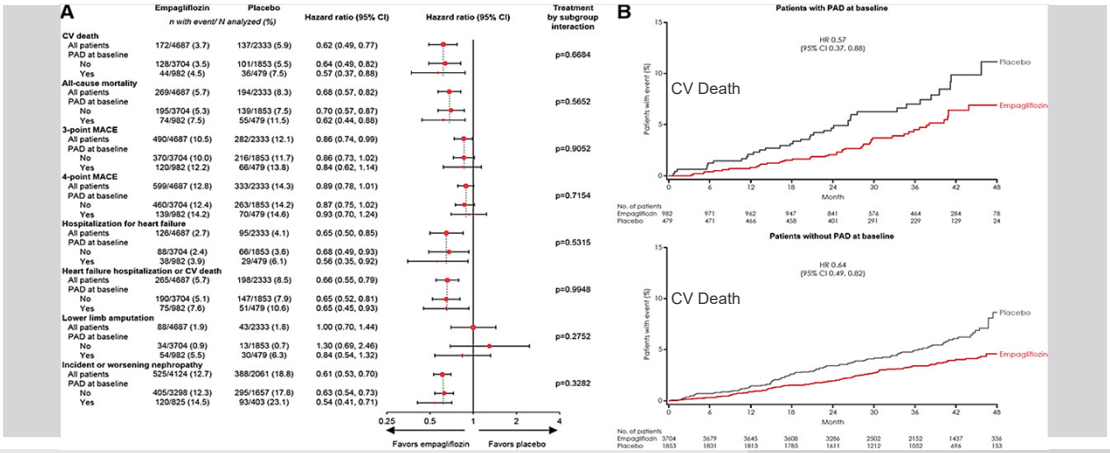
Reduction in MACE
Empagliflozin *(EMPA-REG) Trial-Sub-analysis - PAD*



Verma et al. *Circulation.* Volume: 137, Issue: 4, Pages: 405-407.

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Heart Failure and Renal Outcome
Empagliflozin *(EMPEROR Reduced)*

- 7020 patients with HF and EF ≤ 40%.
- Empagliflozin 10 mg/daily or placebo as add on to the standard of care therapies.
- Outcome: CV death and HHF.
- *Primary outcome,* significant reduction: 19.4 vs 24.7% (HR, 0.75; 95% CI, 0.65 to 0.86; P<0.001), (mainly HHF).
- *MACE,* significant reduction: HR, 0.86; 95.02% CI, 0.74 to 0.99; P=0.04 for superiority.
- *The annual rate of decline in the eGFR*: slower with empagliflozin.
  - ➢ –0.55 vs. –2.28 ml/min per year, P<0.001.

M Packer et al. *N Engl J Med* 2020;383:1413-1424.

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Heart Failure and Renal Outcome
Empagliflozin *(EMPEROR-Reduced)*

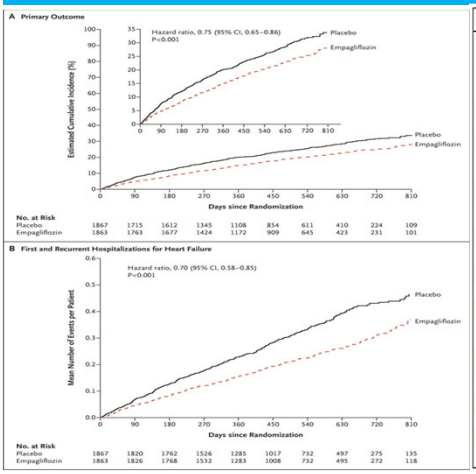

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=1863)	events/100 patient-yr	Placebo (N=1867)	events/100 patient-yr	Hazard Ratio or Absolute Difference (95% CI)†	P Value
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	388	—	553	—	0.70 (0.58 to 0.85)	<0.001
Mean slope of change in eGFR — ml/min/1.73 m² per year‡	−0.55±0.23	—	−2.28±0.23	—	1.73 (1.10 to 2.37)	<0.001
Other prespecified analyses						
Composite renal outcome — no. (%)§	30 (1.6)	1.6	58 (3.1)	3.1	0.50 (0.32 to 0.77)	
Change in quality-of-life score on KCCQ at 52 weeks¶	5.8±0.4	—	4.1±0.4	—	1.7 (0.5 to 3.0)	
No. of hospitalizations for any cause	1364	—	1570	—	0.85 (0.75 to 0.95)	
Death from any cause — no. (%)	249 (13.4)	10.1	266 (14.2)	10.7	0.92 (0.77 to 1.10)	
Onset of new diabetes in patients with prediabetes — no./total no. (%)	71/632 (11.2)	9.3	80/636 (12.6)	10.6	0.86 (0.62 to 1.19)	
Laboratory and other measurements (adjusted change from baseline to 52 wk)						
Glycated hemoglobin in patients with diabetes — %	−0.28±0.03	—	−0.12±0.03	—	−0.16 (−0.25 to −0.08)	
Hematocrit (%)	1.98±0.10	—	−0.38±0.10	—	2.36 (2.08 to 2.63)	
Median NT-proBNP (IQR) — pg/ml‖	−244 (−890 to 260)		−141 (−784 to 585)	—	0.87 (0.82 to 0.93)	
Body weight — kg	−0.73±0.13	—	0.08±0.13	—	−0.82 (−1.18 to −0.45)	
Systolic blood pressure — mm Hg	−2.4±0.4	—	−1.7±0.4	—	−0.7 (−1.8 to 0.4)	

M Packer et al. *N Engl J Med* 2020;383:1413-1424.

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Heart Failure and Renal Outcome
Empagliflozin *(EMPEROR- Preserved)*

- 5988 patients with HF and EF > 40%.
- Empagliflozin 10 mg/daily or placebo as add on to the standard of care therapies.
- Outcome: CV death and HHF.
- Results, *primary outcome*, significant reduction: 13.8% vs 17.1% (HR, 0.79; 95% CI, 0.69 to 0.90; P<0.001).
- *The annual rate of decline in the eGFR*: was slower with empagliflozin.
  - ➢ –0.55 vs. –2.28 ml/min per year, P<0.001.

SD Anker et al. *N Engl J Med* 2021;385:1451-1461.

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Heart Failure and Renal Outcome
Empagliflozin *(EMPEROR- Preserved)*

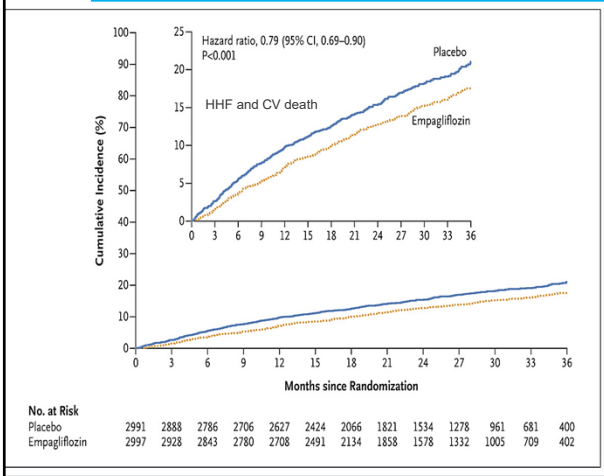

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
		events per 100 patient-yr		events per 100 patient-yr		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	407	—	541	—	0.73 (0.61–0.88)	<0.001
eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m^2	−1.25±0.11	—	−2.62±0.11	—	1.36 (1.06–1.66)	<0.001
Other prespecified analyses						
Change in KCCQ clinical summary score at 52 wk‡	4.51±0.31	—	3.18±0.31	—	1.32 (0.45–2.19)	
Total no. of hospitalizations for any cause	2566	—	2769	—	0.93 (0.85–1.01)	
Composite renal outcome — no. (%)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24)	
Onset of new diabetes in patients with prediabetes — no. (%)	120 (12.0)	6.1	137 (14.0)	7.4	0.84 (0.65–1.07)	
Death from any cause — no. (%)	422 (14.1)	6.6	427 (14.3)	6.7	1.00 (0.87–1.15)	

SD Anker et al. *N Engl J Med* 2021;385:1451-1461.

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PAD Subgroup Analysis
Empagliflozin *(EMPEROR- Pooled)*

- 821/9718 (8.4%) patients had PAD (261 in Reduced and 560 in Preserved).
- PAD pts were more likely to be men (70.5% vs 62.6%), white (83.9% vs 72.9%), and older (72.2±8.3 vs 69.7±10.5 years).
- **Patients with PAD were:**
  - More symptomatic: median KCCQ scores [PAD, 68.8 versus no PAD, 75.0].
  - NYHA class ≥III [PAD, 27.4% versus no PAD, 20.3%]).
  - More likely to have ischemic HF (60.5% versus 39.9%).
  - More likely to be previous/current smokers (65.0% versus 48.8%).
  - More likely to have DM (65.2% versus 47.9%).
  - More likely to have HTN (90.6% versus 82.9%).
  - More likely to have and HL (84.8% versus 62.9%).

Verma et al. *Arterioscler Thromb Vasc Biol*. 2023 Jul; 43(7): 1334–1337.

22

PAD Subgroup Analysis
Empagliflozin *(EMPEROR- Pooled)*

- PAD vs placebo group had an elevated risk of HF outcomes and mortality compared with no PAD.
- HHF, CV death, all-cause mortality, and composite of CV death/HHF were higher in pts with PAD.
  - HHF: *P*=0.007; CV death: *P*=0.02; all-cause mortality: *P*=0.002; HHF/CV death: *P*=0.08.
- The efficacy of empagliflozin on cardiorenal outcomes was consistent regardless of PAD history.
  - PAD: HR for total HHF, 0.64 [95% CI, 0.42–0.98] vs no PAD: HR for total HHF, 0.73 [95% CI, 0.63–0.84]; $P_{interaction}$, 0.56.
- Absolute risk reductions for total HHF events was higher (6.0% in PAD and 3.2% in no PAD groups).

Verma et al. *Arterioscler Thromb Vasc Biol*. 2023 Jul; 43(7): 1334–1337.

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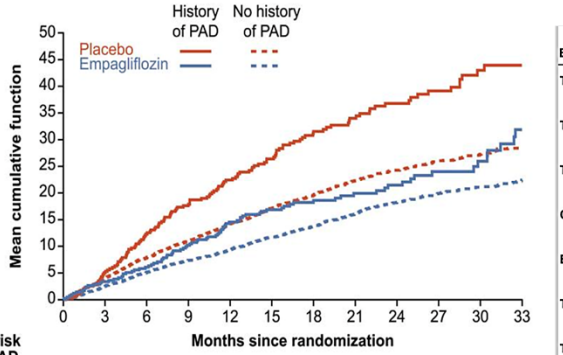
PAD Subgroup Analysis
Empagliflozin *(EMPEROR- Pooled)*



Patients at risk													
History of PAD													
Placebo	403	393	382	366	342	310	264	229	186	153	107	78
Empagliflozin	418	412	398	380	361	319	254	214	176	136	101	70
No history of PAD													
Placebo	4455	4372	4281	4015	3759	3325	2726	2266	1784	1396	983	673
Empagliflozin	4442	4376	4283	4021	3739	3293	2725	2258	1780	1411	1001	698

Endpoint	Empagliflozin 10 mg n/N	Empagliflozin 10 mg Events/100 py	Placebo n/N	Placebo Events/100 py	HR (95% CI)	HR (95% CI)	Interaction *p*-value
Total HHF							0.56
No history of PAD	703/4442	–	957/4455	–	0.73 (0.63, 0.84)		
History of PAD	92/418	–	137/403	–	0.64 (0.42, 0.98)		
Time to CV death							0.57
No history of PAD	353/4442	4.36	391/4455	4.82	0.90 (0.78, 1.04)		
History of PAD	53/418	6.90	55/403	7.07	1.01 (0.70, 1.48)		
Time to all-cause mortality							0.68
No history of PAD	581/4442	7.17	601/4455	7.41	0.96 (0.86, 1.08)		
History of PAD	90/418	11.72	92/403	11.83	1.03 (0.77, 1.37)		
Composite of CV death and time to first HHF							0.81
No history of PAD	689/4442	9.05	872/4455	11.78	0.76 (0.69, 0.85)		
History of PAD	87/418	12.01	101/403	14.62	0.79 (0.60, 1.06)		
Extended composite endpoint*							0.84
No history of PAD	1145/4442	16.34	1465/4455	22.10	0.74 (0.68, 0.80)		
History of PAD	141/418	21.47	169/403	28.24	0.72 (0.57, 0.90)		
Time to first HHF							0.71
No history of PAD	453/4442	5.95	623/4455	8.42	0.70 (0.62, 0.79)		
History of PAD	52/418	7.18	71/403	10.28	0.66 (0.46, 0.94)		
Time to composite renal endpoint							0.27
No history of PAD	55/4442	0.85	84/4455	1.32	0.64 (0.46, 0.91)		
History of PAD	13/418	2.10	11/403	1.86	1.06 (0.47, 2.37)		

*CV death or HHF equivalent events or reported intensification of diuretic since last visit

0.25 0.50 1.00 2.00 4.00
Favours empagliflozin · Favours placebo

Verma et al. *Arterioscler Thromb Vasc Biol*. 2023 Jul; 43(7): 1334–1337.

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Heart Failure and Renal Outcome
Empagliflozin *(EMPA-Kidney)*

- 6609 pts with CKD: (eGFR of at least 20) with a urinary albumin-to-creatinine ratio of at least 200.
- Empagliflozin 10 mg/daily or placebo.
- Outcome: composite of progression of kidney disease (ESRD, sustained decrease in eGFR to <10 ml/min, a sustained decrease in eGFR of ≥40% from baseline, or renal death) or CV death.
- Results, *primary outcome, significant reduction*: 13.1 vs 16.9% (HR: 0.72; 95% CI: 0.64 to 0.82; P<0.001).
- *Annual rate of decline in the eGFR*: was slower with empagliflozin.
  - ➢ –0.55 vs. –2.28 ml per minute per 1.73 m2 of body-surface area per year, P<0.001.

The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117-127.

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Heart Failure and Renal Outcome
Empagliflozin *(EMPA-Kidney)*

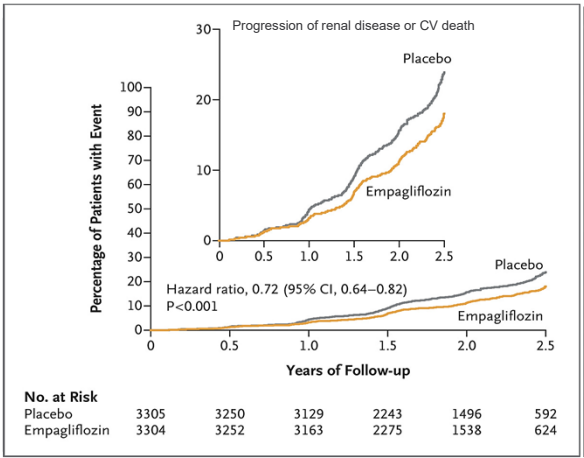

Table 2. Primary, Secondary, and Safety Outcomes.

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	no. of events/100 patient-yr	no. (%)	no. of events/100 patient-yr		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21
Other secondary outcomes						
Progression of kidney disease	384 (11.6)	6.09	504 (15.2)	8.09	0.71 (0.62–0.81)	
Death from cardiovascular causes	59 (1.8)	0.91	69 (2.1)	1.06	0.84 (0.60–1.19)	
End-stage kidney disease or death from cardiovascular causes§	163 (4.9)	2.54	217 (6.6)	3.40	0.73 (0.59–0.89)	
Safety outcomes						
Serious urinary tract infection	52 (1.6)	0.81	54 (1.6)	0.84	0.94 (0.64–1.37)	
Serious genital infection	1 (<0.1)	0.02	1 (<0.1)	0.02	—	
Serious hyperkalemia	92 (2.8)	1.44	109 (3.3)	1.72	0.83 (0.63–1.09)	
Serious acute kidney injury	107 (3.2)	1.67	135 (4.1)	2.11	0.78 (0.60–1.00)	
Serious dehydration	30 (0.9)	0.46	24 (0.7)	0.37	1.25 (0.73–2.14)	
Liver injury	13 (0.4)	0.20	12 (0.4)	0.19	1.09 (0.50–2.38)	
Ketoacidosis¶	6 (0.2)	0.09	1 (<0.1)	0.02	—	
Lower-limb amputation	28 (0.8)	0.43	19 (0.6)	0.29	1.43 (0.80–2.57)	
Bone fracture	133 (4.0)	2.09	123 (3.7)	1.93	1.08 (0.84–1.38)	
Severe hypoglycemia‖	77 (2.3)	1.20	77 (2.3)	1.21	1.00 (0.73–1.37)	
Symptomatic dehydration**	83 (2.5)	1.30	76 (2.3)	1.19	1.10 (0.81–1.51)	

The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117-127.

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Reduction in MACE
Canagliflozin *(CANVAS-CANVAS-Renal) Trials*

- 10,142 participants with T2D and high CV risk.
- Canagliflozin 300 mg, 100 mg, or a matching placebo.
- Study Duration: up to 3.6 years.
- Combined analysis primary outcome: MACE.
- Results, *MACE*: significant reduction
  - ➢ HR: 0.86, 95% CI, 0.75 to 0.97; P<0.001 for noninferiority and P=0.02 for superiority.
  - ➢ *CV Death:* no significant difference.

Neal B et al. *N Engl J Med* 2017; 377:644-657

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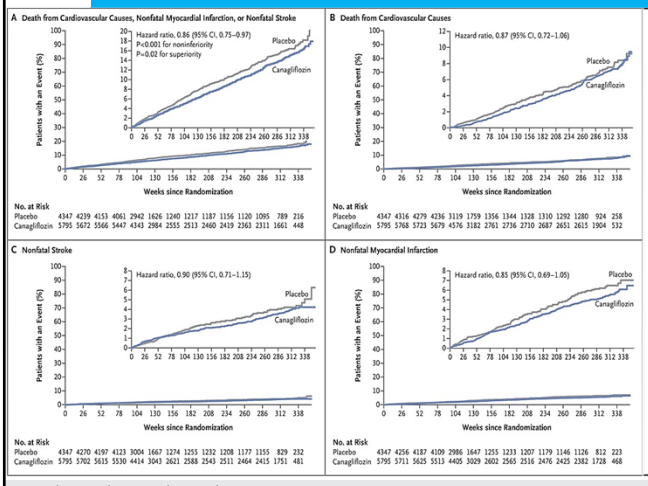
Reduction in MACE
Canagliflozin *(CANVAS-CANVAS-Renal) Trials*



Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

0.5 1.0 2.0
Canagliflozin Better Placebo Better

Neal B et al. *N Engl J Med* 2017; 377:644-657

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Amputation Risk
Canagliflozin *(CANVAS-CANVAS-Renal) Trials*

- The risk of LE amputation was *almost doubled* with canagliflozin.
  - 6.3 vs. 3.4 participants per 1000 pts-years: HR, CI, 1.41-2.75.
- 187 participants had amputation, with 290 amputation events.
  - 123 single amputation event.
  - 71% minor amputation at the level of the toe or metatarsal.
- The highest absolute risk of amputation occurred among patients with PAD.

Neal B et al. *N Engl J Med* 2017; 377:644-657

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Amputation Risk
Canagliflozin *(CANVAS-CANVAS-Renal) Sub-analysis*

- An *increased risk* of amputation (major and minor) with canagliflozin compared to placebo.
- Anticipated risk factors for amputation:
  - Prior history of amputation
  - PAD
  - Neuropathy
- No specific etiological mechanism or at-risk subgroup for canagliflozin was identified.

Mathews DR, Li Q et al. *Diabetologia 2019; 62: 926–938.*

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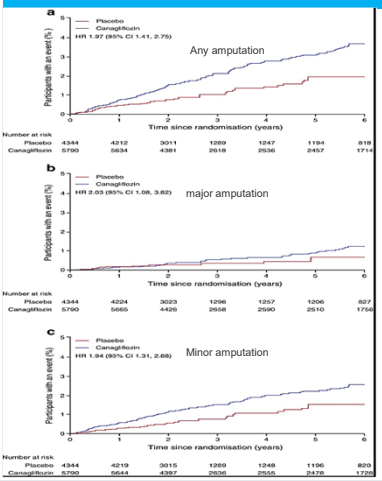
Amputation Risk
Canagliflozin *(CANVAS-CANVAS-Renal) Sub-analysis*



	Canagliflozin participants with an event per 1000 participant-years	Placebo participants with an event per 1000 participant-years	HR (95% CI)
All amputation	6.30	3.37	1.97 (1.41, 2.75)
Minor amputation	4.48	2.44	1.94 (1.31, 2.88)
Toe	3.44	2.16	1.65 (1.07, 2.53)
Transmetatarsal	1.04	0.29	4.17 (1.43, 12.16)
Major amputation	1.82	0.93	2.03 (1.08, 3.82)
Ankle	0.04	0.07	0.69 (0.04, 11.58)
Below knee	1.16	0.64	1.88 (0.87, 4.05)
Above knee	0.62	0.21	2.91 (0.83, 10.23)
Canagliflozin 100 mg vs placebo[a]	6.17	2.76	2.24 (1.36, 3.69)
Canagliflozin 300 mg vs placebo[a]	5.54	2.76	2.01 (1.20, 3.34)
Proximate aetiology			
Infection	2.43	1.15	2.18 (1.24, 3.83)
Chronic ischaemia	3.69	2.22	1.77 (1.17, 2.69)
Acute ischaemia	0.09	0.00	–
Undetermined	0.14	0.00	–

Mathews DR, Li Q et al. *Diabetologia 2019; 62: 926–938.*

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Renal Outcome
Canagliflozin *(CREDENCE) Trial*

- 4401 patients with T2D and albuminuric CKD.
- Canagliflozin 100 mg daily or placebo in addition to ACE-i
- Study Duration: up to 2.62 years.

- Combined analysis primary outcome: ESRD, a doubling of the serum CR level, or death from renal or CV causes.

- *Primary Results:* significant reduction with canagliflozin:
  - 43.2 and 61.2 per 1000 patient-years, (HR, 0.70; 95% [CI], 0.59 to 0.82; P=0.00001).
- *MACE*, lower: (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01).
- *HHF*, lower: (HR, 0.61; 95% CI, 0.47 to 0.80; P<0.001).
- *Amputation rate,* not significant: 12.3 and 11.2 per 1000 patient-years (HR, 1.11; 95% CI, 0.79 to 1.56).

V Perkovic et al. *N Engl J Med* 2019;380:2295-2306.

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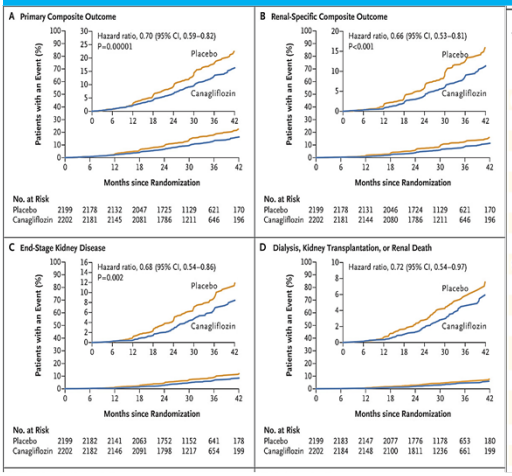
Renal Outcome
Canagliflozin *(CREDENCE) Trial*



Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		events/1000 patient-yr			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m²	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53–0.81)	<0.001
Death from any cause	168/2202	201/2199	29.0	35.0	0.83 (0.68–1.02)	NA
Cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure or unstable angina	273/2202	361/2199	49.4	66.9	0.74 (0.63–0.86)	NA
End-stage kidney disease, renal death, or cardiovascular death†	214/2202	287/2199	37.6	51.2	0.73 (0.61–0.87)	NA
Dialysis, kidney transplantation, or renal death†	78/2202	105/2199	13.6	18.6	0.72 (0.54–0.97)	NA

V Perkovic et al. *N Engl J Med* 2019;380:2295-2306.

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PAD Outcome
Canagliflozin *(CANVAS and CREDENCE) Pooled -Analysis*

- 3159 out of 14543 total pts (21.7%) had PAD at baseline.
- *Consistent* CV and renal benefits with or without PAD.
  - All P interaction > .268.
  - Absolute benefits of canagliflozin were greater in those with PAD.
- *MALE:* Not increased with canagliflozin regardless of PAD status.
  - P interaction > .864.
- The FDA removed the black box warning of lower limb amputations with the use of canagliflozin.

Barraclough JY et al. *Diabetes Obes Metab*. 2022 Jun;24(6):1072-1083

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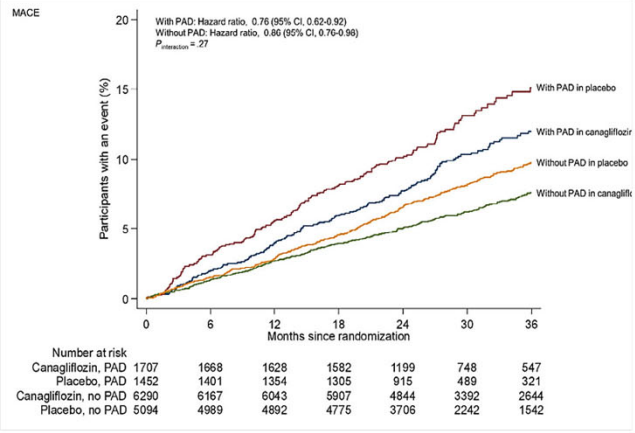
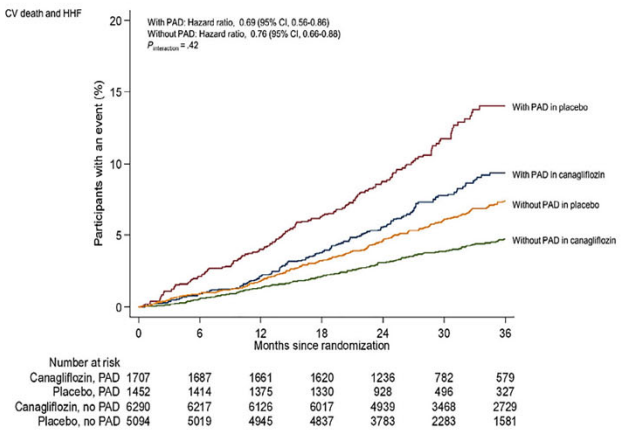
PAD Outcomes
Canagliflozin *(CANVAS and CREDENCE) Pooled -Analysis*





Barraclough JY et al. *Diabetes Obes Metab*. 2022 Jun;24(6):1072-1083

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Reduction in MACE
Dapagliflozin *(DECLARE-TIMI 58) Trial*

- 17,160 patients with T2D including 10,186 without ASCVD.
- Dapagliflozin (10 mg) or placebo.
- Combined analysis primary outcome: MACE

- Results: <u>No</u> significant reduction in MACE: HR, 0.93; 95% CI, 0.84 to 1.03; P=0.17.

- *CV death or HHF*, lower: 4.9% versus 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; P=0.005.

➢ Mostly driven by reduction in HHF: HR, 0.73; 95% CI, 0.61 to 0.88.

- 1025 out of 17,160 patients (6%) had PAD

➢ *Amputation*: <u>no evidence</u> of high risk.

SD Wiviott et al. *N Engl J Med* 2019;380:347-357.

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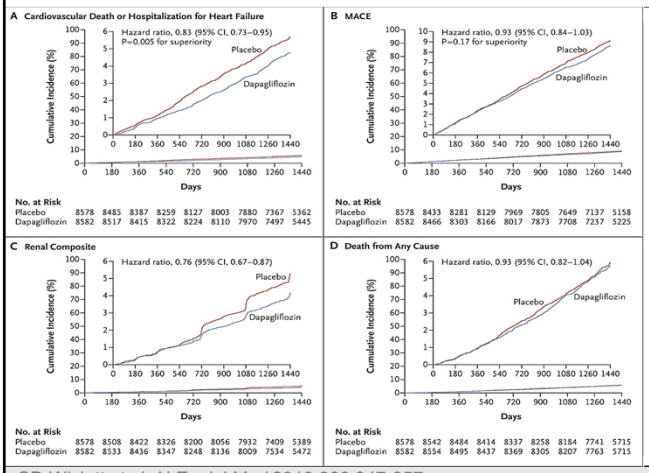
Reduction in MACE
Dapagliflozin *(DECLARE-TIMI 58) Trial*



Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

SD Wiviott et al. *N Engl J Med* 2019;380:347-357.

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PAD Outcomes
Dapagliflozin *(DECLARE-TIMI 58) Sub-analysis*

- Of the 17,160 patients,1025 (6%) had PAD.
- Patients with PAD had higher risk of MACE, CV death, HHF and renal events regardless of study drug.
- RRR with dapagliflozin in patients with PAD versus without was consistent:
  - CV death and HHF (P-interaction=0.79) and renal events (P-interaction=0.84).
- The ARR with dapagliflozin was greater among patients with PAD compared to those without:
  - 1.4% versus 0.9% for CV death or HHF, and 2.1% versus 1.3% for renal events.
- *Limb events:* No significant difference between dapagliflozin and placebo:
  - 3.37% versus 3.16% for limb ischemia (P=0.45) and 1.43% versus 1.32% for amputation (HR, P=0.53).

Bonaca MP et al. *Circulation.* 2020;142:734–747.

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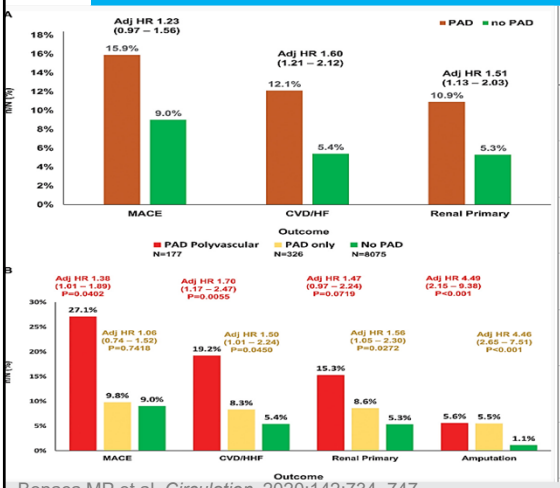
PAD Outcomes
Dapagliflozin *(DECLARE-TIMI 58) Sub-analysis*



Outcomes	PAD Placebo N=502 (n/N%)	PAD Dapagliflozin N=521 (n/N%)	PAD Hazard Ratio (95% CI)	No PAD Placebo N=8067 (n/N%)	No PAD Dapagliflozin N=8053 (n/N%)	No PAD Hazard Ratio (95% CI)	*P* Interaction
Limb ischemic adverse event	102 (20.3%)	101 (19.4%)	0.93 (0.71–1.23)	169 (2.1%)	188 (2.3%)	1.11 (0.90–1.37)	0.3046
Acute limb ischemia	17 (3.4%)	15 (2.9%)	0.84 (0.42–1.69)	11 (0.1%)	13 (0.2%)	1.19 (0.53–2.65)	0.4997
Critical limb ischemia	25 (5.0%)	30 (5.8%)	1.12 (0.66–1.91)	25 (0.3%)	40 (0.5%)	1.60 (0.97–2.64)	0.3412
Other limb ischemic adverse event	72 (14.3%)	57 (10.9%)	0.75 (0.53–1.06)	99 (1.2%)	114 (1.4%)	1.15 (0.88–1.51)	0.0447
Noncoronary revascularization	96 (19.1%)	88 (16.9%)	0.86 (0.65–1.15)	120 (1.5%)	150 (1.9%)	1.25 (0.99–1.59)	0.0443
Amputation	28 (5.6%)	44 (8.4%)	1.51 (0.94–2.42)	85 (1.1%)	79 (1.0%)	0.93 (0.68–1.26)	0.0926
Limb infection	41 (8.2%)	50 (9.6%)	1.15 (0.76–1.74)	265 (3.3%)	235 (2.9%)	0.88 (0.74–1.05)	0.2203

Bonaca MP et al. *Circulation.* 2020;142:734–747.

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Heart Failure
Dapagliflozin *(DAPA-HF) Trial*

- 4744 patients with NYHA class II, III, or IV HF and an EF of 40% or less.
- Dapagliflozin (10 mg once daily) or placebo.
- Primary outcome: composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death

- Results, *primary outcome*, reduced with dapa:16.3% vs 21.2%, (HR, 0.74; 95% [CI], 0.65 to 0.85; P<0.001).
  - ➢ HHF: HR, 0.70; 95% CI, 0.59 to 0.83.
  - ➢ CV death: HR, 0.82; 95% CI, 0.69 to 0.98.
  - ➢ Death from any cause: HR, 0.83; 95% CI, 0.71 to 0.97.

- *Amputation risk*: <u>No significant difference.</u>

JJ McMurray et al. *N Engl J Med* 2019;381:1995-2008.

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Heart Failure
Dapagliflozin *(DAPA-HF) Trial*

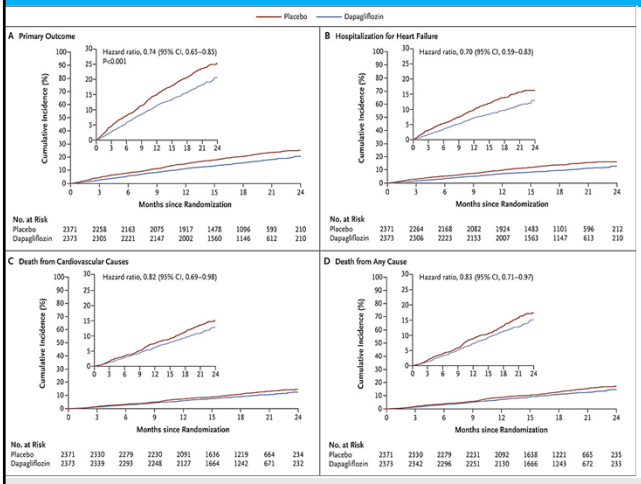

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths‡	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo§	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%)¶	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Death from any cause — no. (%)	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)	NA
Safety outcomes‖						

JJ McMurray et al. *N Engl J Med* 2019;381:1995-2008.

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Renal Outcomes
Dapagliflozin *(DAPA-CKD) Trial*

- 4304 pts with an eGFR of 25 - 75 and a urinary alb-to-Cr ratio of 200 to 5000.
- Dapagliflozin (10 mg once daily) or placebo.
- Primary outcome: composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or CV causes.
- Results, primary outcome: Significantly lower with dapagliflozin than placebo:
  - ➢ 9.2% vs14.5% (HR, 0.61; 95% [CI], 0.51 to 0.72; P<0.001).
- Death from renal causes was also significantly reduced.
  - ➢ HR, 0.56 ; 95% CI, 0.45 to 0.68; P<0.001.
- *Amputation risk:* no significant difference.

HJ Heerspink et al. *N Engl J Med* 2020;383:1436-1446.

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Renal Outcomes
Dapagliflozin *(DAPA-CKD) Trial*

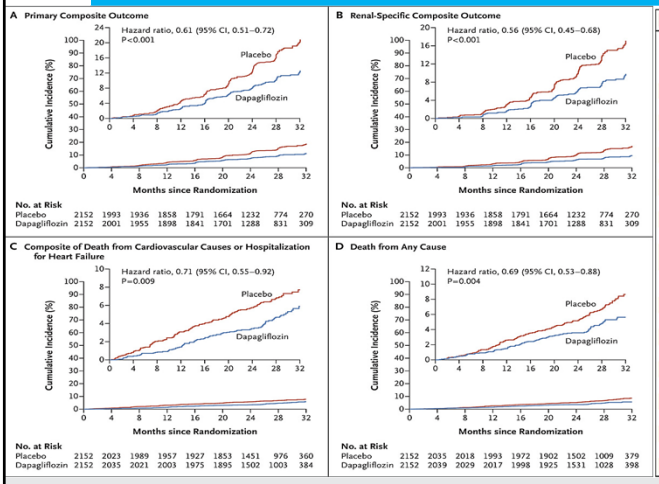

Table 2. Primary and Secondary Outcomes and Adverse Events of Special Interest.*

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	events/100 patient-yr	no./total no. (%)	events/100 patient-yr		
Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)	NA
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)	NA
Estimated GFR of <15 ml/min/1.73 m²	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—	NA
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—	NA
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004
Safety outcomes‡						
Discontinuation of regimen due to adverse event	118/2149 (5.5)	—	123/2149 (5.7)	—	—	0.79
Any serious adverse event	633/2149 (29.5)	—	729/2149 (33.9)	—	—	0.002
Adverse events of interest						
Amputation§	35/2149 (1.6)	—	39/2149 (1.8)	—	—	0.73
Any definite or probable diabetic ketoacidosis	0/2149	—	2/2149 (<0.1)	—	—	0.50
Fracture¶	85/2149 (4.0)	—	69/2149 (3.2)	—	—	0.22
Renal-related adverse event¶	155/2149 (7.2)	—	188/2149 (8.7)	—	—	0.07
Major hypoglycemia‖	14/2149 (0.7)	—	28/2149 (1.3)	—	—	0.04
Volume depletion¶	127/2149 (5.9)	—	90/2149 (4.2)	—	—	0.01

HJ Heerspink et al. *N Engl J Med* 2020;383:1436-1446.

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PAD Outcomes
Dapagliflozin *Pool-analysis of 2b-3a Trials*

- *LE amputation,* <u>not different</u>*:* 8 (0.1%) with dapagliflozin and 7 (0.2%) with placebo.

- Risk factors for amputation in both groups were:
  - ➢ Neuropathy
  - ➢ CVD
  - ➢ Dyslipidemia

Diabetes Obes Metab. 2018 Mar; 20(3): 620–628.

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CV Outcome
Sotagliflozin *(SGLT1 and 2-i)* *(SCORED) Trial*

- 10,584 patients with T2D, CKD (eGFR 25–60 mL/min/1.73 m2) and risks for CVD.
- Sotagliflozin or placebo.
- Primary outcome: CV death, HHF, and urgent visits for HF.
- Ended early due to loss of fund.

- Results, *primary outcome:* reduced with sotagliflozin.
  - 5.6 vs. 7.5%; HR 0.74; 95%; CI, 0.63 to 0.88; P<0.001.

- *MACE,* reduced: HR 0.84; 95% CI, 0.72 to 0.99.

Bhatt DL, et al. *N Engl J Med* 2021; 384:129-139

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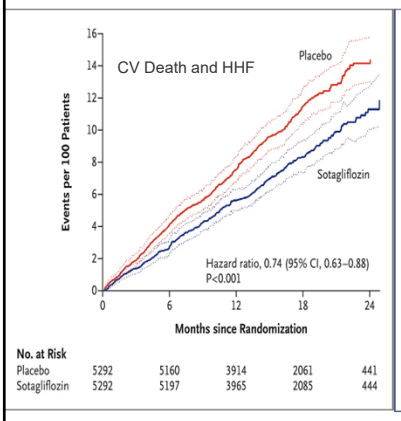
CV Outcome
Sotagliflozin *(SCORED) Trial*



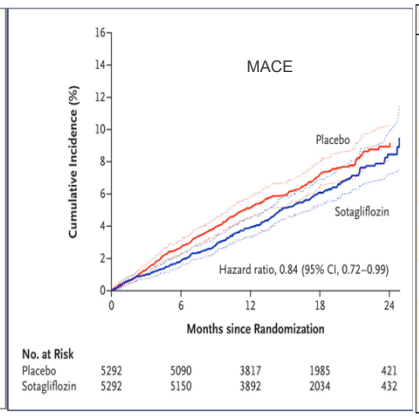


Table 2. Primary End Point and Secondary End Points.*

End Point	Sotagliflozin (N=5292)	Placebo (N=5292)	Hazard Ratio (95% CI)†	P Value
	no. of events/100 patient-yr (no. of events)			
Primary end point: total no. of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF	5.6 (400)	7.5 (530)	0.74 (0.63–0.88)	<0.001
Major secondary end points, in order of hierarchical testing				
Total no. or hospitalizations for HF and urgent visits for HF	3.5 (245)	5.1 (360)	0.67 (0.55–0.82)	<0.001
Deaths from cardiovascular causes	2.2 (155)	2.4 (170)	0.90 (0.73–1.12)	0.35‡
Total no. of deaths from cardiovascular causes, hospitalizations for HF, nonfatal myocardial infarctions, and nonfatal strokes	7.6 (541)	10.4 (738)	0.72 (0.63–0.83)	—
Total no. of deaths from cardiovascular causes, hospitalizations for HF, urgent visits for HF, and events of HF during hospitalization	6.4 (453)	8.3 (589)	0.76 (0.65–0.89)	—
First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m² for ≥30 days	0.5 (37)	0.7 (52)	0.71 (0.46–1.08)	—
Deaths from any cause	3.5 (246)	3.5 (246)	0.99 (0.83–1.18)	—
Total no. of deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes	4.8 (343)	6.3 (442)	0.77 (0.65–0.91)	—

Bhatt DL, et al. *N Engl J Med* 2021; 384:129-139

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Heart Failure Outcome
Sotagliflozin *(SOLOIST-WHF) Trial*

- 1222 patients with T2D and a *recent hospitalization for acute decompensated* HF *(either reduced or preserved EF%)*.
- Sotagliflozin or placebo.
- Primary outcome: CV death and hospitalizations and urgent visits for HF.
- Ended early due to loss of fund.

- Results, *primary outcome:* reduced with sotagliflozin.
  - ➢ 51.0 versus. 76.3%; HR, 0.67; 95% CI, 0.52 to 0.85; P<0.001.
- *Death from CV or any cause*: no significant difference.

Bhatt DL, et al. *N Engl J Med* 2021; 384:117-128

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Heart Failure Outcome
Sotagliflozin *(SOLOIST-WHF) Trial*

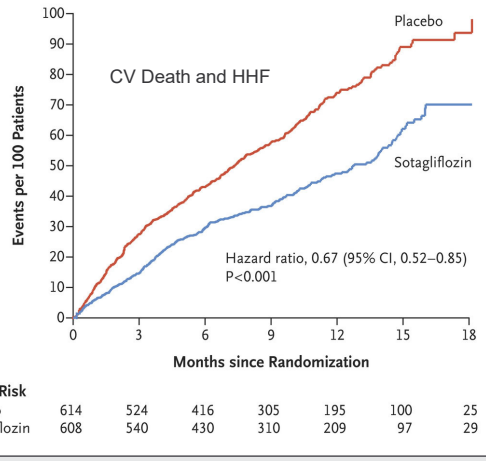

Table 2. Primary End Point and Secondary End Points.

End Point	Sotagliflozin (N=608)	Placebo (N=614)	Hazard Ratio or Difference (95% CI)*	P Value
Primary end point: deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure — total no. of events (rate)†	245 (51.0)	355 (76.3)	0.67 (0.52 to 0.85)	<0.001
Secondary end points in order of hierarchical testing				
Hospitalizations and urgent visits for heart failure — total no. of events (rate)†	194 (40.4)	297 (63.9)	0.64 (0.49 to 0.83)	<0.001
Deaths from cardiovascular causes — total no. of events (rate)†	51 (10.6)	58 (12.5)	0.84 (0.58 to 1.22)	0.36‡
Deaths from cardiovascular causes, hospitalizations for heart failure, nonfatal myocardial infarctions, and nonfatal strokes — total no. of events (rate)†	247 (51.4)	330 (71.0)	0.72 (0.56 to 0.92)	
Deaths from cardiovascular causes, hospitalizations and urgent visits for heart failure, and events of heart failure during hospitalization — total no. of events (rate)†	263 (54.7)	375 (80.6)	0.68 (0.54 to 0.86)	
Deaths from any cause — total no. of events (rate)†	65 (13.5)	76 (16.3)	0.82 (0.59 to 1.14)	
Least-squares mean change in KCCQ-12 score to month 4	17.7	13.6	4.1 (1.3 to 7.0)	
Least-squares mean change in estimated GFR — ml/min/1.73 m^2	−0.34	−0.18	−0.16 (−1.30 to 0.98)	

Bhatt DL, et al. *N Engl J Med* 2021; 384:117-128

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CV Outcome
Ertugliflozin *(VERTIS-CV) Trial*

- 8246 patients with T2D and ASCVD.
- Ertugliflozin 5 or 15 mg or placebo.
- Primary outcome: MACE.

- Results, *MACE:* not significant
  - HR, 0.97; 95.6% [CI], 0.85 to 1.11; P<0.001 for non-inferiority.
- *CV death or HHF:* were not significant
  - HR, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority.

- *Amputations:* in 54 pts (2.0%) with 5-mg of ertugliflozin and in 57 pts (2.1%) with15-mg, as compared with 45 pts (1.6%) with placebo.

Cannon CP, et al. *N Engl J Med* 2020; 383:1425-1435

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CV Outcome
Ertugliflozin *(VERTIS-CV) Trial*

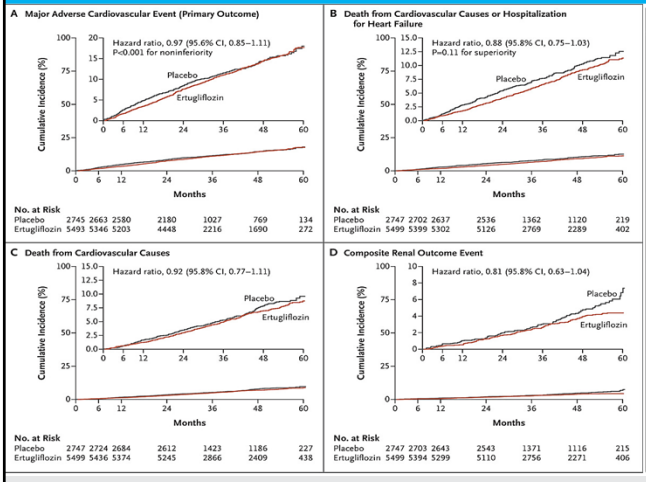

Table 2. Primary and Secondary Outcomes.*

Outcome	Ertugliflozin†		Placebo		Hazard Ratio (CI)‡	P Value§
	no. of patients/ total no. (%)	*no. of events/ 100 patient-yr*	*no. of patients/ total no. (%)*	*no. of events/ 100 patient-yr*		
Primary outcome						
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	653/5493 (11.9)	3.9	327/2745 (11.9)	4.0	0.97 (0.85–1.11)	<0.001
Key secondary outcomes						
Death from cardiovascular causes or hospitalization for heart failure	444/5499 (8.1)	2.3	250/2747 (9.1)	2.7	0.88 (0.75–1.03)	0.11
Death from cardiovascular causes	341/5499 (6.2)	1.8	184/2747 (6.7)	1.9	0.92 (0.77–1.11)	
Death from renal causes, renal replacement therapy, or doubling of the serum creatinine level	175/5499 (3.2)	0.9	108/2747 (3.9)	1.2	0.81 (0.63–1.04)	
Death from renal causes	0/5499	NA	0/2747	NA	NA	
Renal replacement therapy	7/5499 (0.1)	NA	3/2747 (0.1)	NA	NA	
Doubling of serum creatinine level	168/5499 (3.1)	NA	105/2747 (3.8)	NA	NA	
Other secondary outcomes						
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina	823/5499 (15.0)	4.5	439/2747 (16.0)	4.9	0.92 (0.82–1.04)	
Fatal or nonfatal myocardial infarction	330/5499 (6.0)	1.8	158/2747 (5.8)	1.7	1.04 (0.86–1.26)	
Fatal or nonfatal stroke	185/5499 (3.4)	1.0	87/2747 (3.2)	0.9	1.06 (0.82–1.37)	
Hospitalization for heart failure	139/5499 (2.5)	0.7	99/2747 (3.6)	1.1	0.70 (0.54–0.90)	
Nonfatal myocardial infarction	310/5499 (5.6)	1.7	148/2747 (5.4)	1.6	1.04 (0.86–1. 27)	
Nonfatal stroke	157/5499 (2.9)	0.8	78/2747 (2.8)	0.8	1.00 (0.76–1.32)	
Death from any cause	473/5499 (8.6)	2.4	254/2747 (9.2)	2.6	0.93 (0.80–1.08)	

Cannon CP, et al. *N Engl J Med* 2020; 383:1425-1435

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SGLT-i Drugs Dosing and Indications

Drug	Doses	Indications
Empagliflozin *Jardiance*®	10 mg daily	1- Improve glycemic control in T2D 2- Reduce the risk of CV death in adults with T2D and established CV disease 3- Reduce CV death and HHF in adults with HF 4- Reduce renal disease progression, CV death or hospitalization in patients with CKD
Canagliflozin *Invokana*®	100 mg daily	1- Improve glycemic control in T2D 2- Reduce MACE in adults with T2D and established CVD 3- Reduce risk of ESRD, doubling of Cr, CV death, and HHF in T2D with albuminuria (>300 mg/day)
Dapagliflozin *Farxiga*®	10 mg daily	1- Improve glycemic control in T2D 2- Reduce risk of HHF in adults with T2D and known CVD or multiple CV risks 3- Reduce risk of CV death and HHF in adults with HF 4- Reduce risk of worsening renal disease, ESRD, CV death and HHF in pts with CKD
Sotagliflozin *Inpefa*®	200-400 mg daily	1- Reduce risk of CV death/HHF in adults with HF 2- Reduce risk of CV death/HHF in adults with T2D, CKD, and other CV risks

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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SGLT-i: Summary

Empagliflozin: Reduction in MACE (EMPA-REG), HHF and CV death (EPERORs), and renal and CV outcomes (EMPA-Kidney). *No difference in amputation risk (EMPA-REG sub-analysis).*

Canagliflozin: Reduction in MACE (CANVAS). *Increased amputation risk.*
Reduction in CV and renal outcomes (CREDENCE). *No difference in amputation risk.*

Dapagliflozin: Reduction in HHF/CV death (DAPA-HF), renal/CV outcome (DAPA-CKD), no difference in MACE (DECLARE-TIMI 58). *No difference in amputation risk.*

Sotagliflozin: Reduction in HHF/CV death and MACE (SCORED/SOLOIST-WHF).

Ertugliflozin: No difference HHF/CV death (VERTIS-CV). *No difference in amputation risk.*

Skeik N et al. *Angiology*. 2022 Mar;73(3):197-206

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Glucagon Like Peptide Receptor Agonist (GLP1-RA) Mechanism of Action

- Food---GLP1 secretion from L-cells---inactivated after 2-3 mins by the DPP-4, (GLP-1 is reduced in T2D).
- GLP1-RA---increases GLP-1---increases insulin/reduces glucagon and delaying gastric emptying---reduces gluc.
- *CV benefits:* weight, BP and Tg reductions, natriuresis, anti-inflammatory properties.
  - Anti-atherosclerotic and thrombotic effects.

- **Six GLP1-RA SC agents:**
  - Short-acting: exenatide, lixisenatide
  - Intermediate-acting: liraglutide
  - Long-acting: exenatide, dulaglutide, albiglutide, and semaglutide (comes in oral too)

- **GIP** (glucose dependent insulinotropic polypeptide) **and GLP1-RA:** Tirzepatide *(Mounjaro)*

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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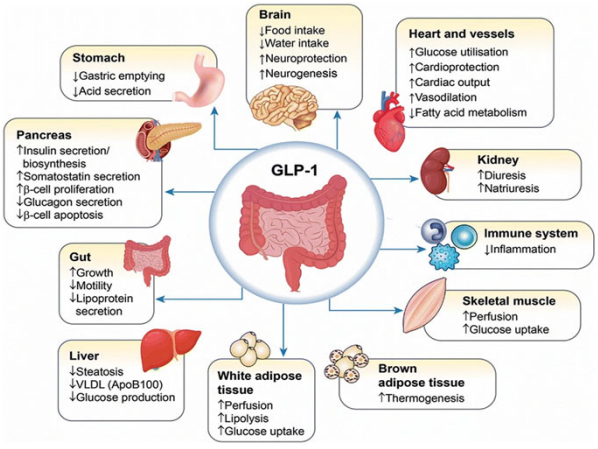
GLP1-RA Mechanism of Action
Exact Mechanism Behind CV Benefit Not Well Known!



Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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GLP1-RA
Reduction in MACE
Dulaglutide *(REWIND) Trial*

- 9,901 patients with T2D and previous CV events or risk.
- Weekly SC dulaglutide (1.5mg) or placebo.
- Outcome: MACE.
- Results, *MACE*: significant reduction with dulaglutide.
  - HR: 0.88; 95% CI: 0.79 to 0.99, P=0.026.
- Driven by reduction of *stroke*: HR: 0.76; 95% CI: 0.62 to 0.94.

Gerstein HC et al. *Lancet.* 2019 Jul 13;394(10193):121-130..

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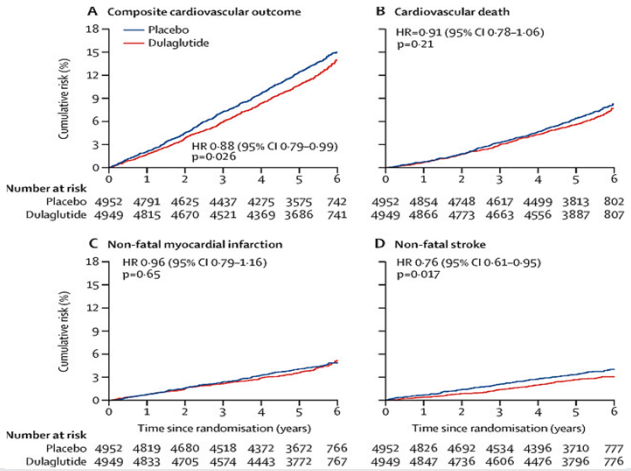
GLP1-RA
Reduction in MACE
Dulaglutide *(REWIND) Trial*



	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Primary composite outcome	594 (12·0%)	2·35	663 (13·4%)	2·66	0·88 (0·79–0·99)*	0·026
Myocardial infarction	223 (4·5%)	0·87	231 (4·7%)	0·91	0·96 (0·79–1·15)	0·63
Non-fatal myocardial infarction	205 (4·1%)	0·80	212 (4·3%)	0·84	0·96 (0·79–1·16)	0·65
Fatal myocardial infarction	26 (0·5%)	0·10	20 (0·4%)	0·08	1·29 (0·72–2·30)	0·40
Stroke	158 (3·2%)	0·61	205 (4·1%)	0·81	0·76 (0·62–0·94)	0·010
Non-fatal stroke	135 (2·7%)	0·52	175 (3·5%)	0·69	0·76 (0·61–0·95)	0·017
Fatal stroke	26 (0·5%)	0·10	33 (0·7%)	0·13	0·78 (0·47–1·30)	0·34
Cardiovascular death†	317 (6·4%)	1·22	346 (7·0%)	1·34	0·91 (0·78–1·06)	0·21
Non-cardiovascular death	219 (4·4%)	0·84	246 (5·0%)	0·95	0·88 (0·73–1·06)	0·18
All-cause death	536 (10·8%)	2·06	592 (12·0%)	2·29	0·90 (0·80–1·01)	0·067
Hospital admission for heart failure or urgent visit	213 (4·3%)	0·83	226 (4·6%)	0·89	0·93 (0·77–1·12)	0·46
Hospital admission for unstable angina	88 (1·8%)	0·34	77 (1·6%)	0·30	1·14 (0·84–1·54)	0·41
Composite microvascular outcome (eye or renal outcome)	910 (18·4%)	3·76	1019 (20·6%)	4·31	0·87 (0·79–0·95)	0·0020
Eye outcome‡	95 (1·9%)	0·37	76 (1·5%)	0·30	1·24 (0·92–1·68)	0·16
Renal outcome§	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004

Gerstein HC et al. *Lancet.* 2019 Jul 13;394(10193):121-130..

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PAD Outcome

Dulaglutide *(Effects of Dulaglutide on Endothelial Progenitor Cells and Arterial Elasticity in Patients with T2D) Study*

- Sixty patients with T2D.
- Metformin monotherapy group (n = 30), and metformin combined with dulaglutide group (MET-DUL group, n = 30).
- Outcome: number of CD34+CD133+ endothelial progenerator cells (EPCs) and the brachial–ankle pulse wave velocity (baPWV).
- Results: NO levels and EPCs increased with dulaglutide (P < 0.05).
- EPC proliferation, adhesion, migration, and tubule formation abilities were significantly enhanced (P < 0.05).

Xie Det al. *Cardiovasc Diabetol.* 2022; 21: 200.

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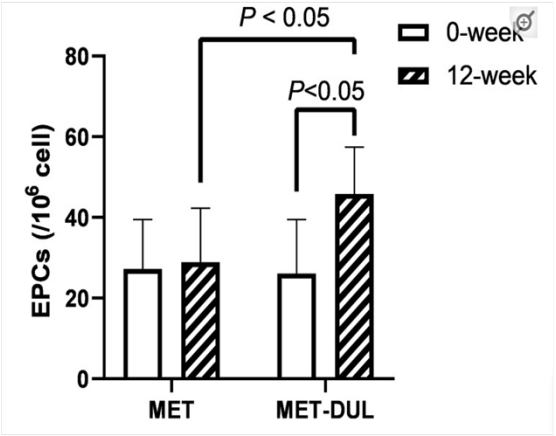
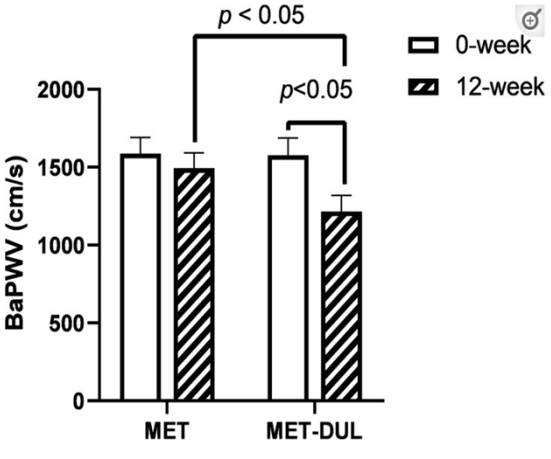
PAD Outcome

Dulaglutide *(Effects of Dulaglutide on Endothelial Progenitor Cells and Arterial Elasticity in Patients with T2D) Study*





Xie Det al. *Cardiovasc Diabetol.* 2022; 21: 200.

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Reduction in MACE
Liraglutide *(LEADER) Trial*

- 9,340 patients with T2D and high CV risk (81% had established CV disease).
- Weekly SC liraglutide or placebo.
- Outcome: MACE.
- Results, *MACE*, significant reduction: 13.0% vs14.9% (P<0.001 for non-inferiority; P=0.01 for superiority).
  - ➢ Driven by reduction of *CV death*: 4.7 vs 6.0% (HR, 0.78; 95% CI, 0.66 to 0.93; P=0.007).
- **Post-hoc analysis:**
  - ➢ In pts with DFU, significant reduction *in amputations* (HR 0.65, 95% CI 0.45, 0.95; P = 0.03).
  - ➢ No difference in foot infection or revascularization.

Marso SP et al. *N Engl J Med* 2016; 375:311-322.

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Reduction in MACE
Liraglutide *(LEADER) Trial*

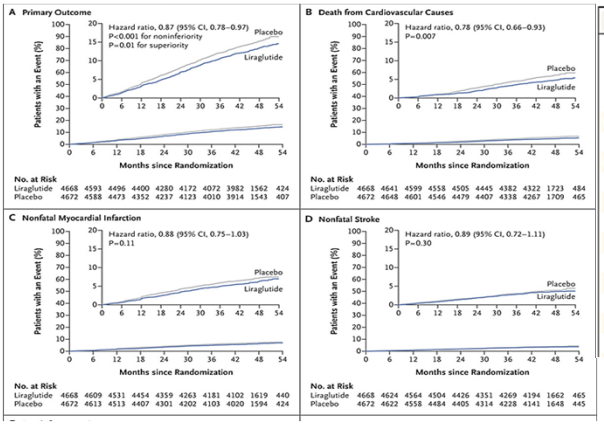

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668) no. of patients (%)	Incidence Rate no. of events/100 patient-yr	Placebo (N=4672) no. of patients (%)	Incidence Rate no. of events/100 patient-yr	Hazard Ratio (95% CI)	P Value
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30

Marso SP et al. *N Engl J Med* 2016; 375:311-322.

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Reduction in MACE
Semaglutide *(SUSTAIN-6 and PIONEER-6) Trials*

SUSTAIN-6 Trial

- 3,297 patients with T2D and high CV risk.
- Once weekly 0.5 -1 mg SC semaglutide or placebo, follow up 2.1 years.
- Outcome: MACE.
- Results, *MACE*, significant reduction: HR, 0.74; 95% [CI], 0.58 to 0.95; P<0.001 for non-inferiority.
- ➢ Driven by reduction of *non-fatal stroke*: HR, 0.61; 95% CI, 0.38 to 0.99; P=0.04.

PIONEER-6 Trial

- 3183 patients with established CV or CKD
- Oral semaglutide or placebo
- Outcome: MACE
- ➢ No significant difference 3.8% with semaglutide vs 4.8% in placebo: HR 0.79, 95% CI 0.57–1.11; P < 0.001 for non-inferiority.

Marso SP et al. *N Engl J Med* 2016; 375:1834-1844
Husain M, et al. *N Engl J Med* 2019; 381:841-851

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Reduction in MACE
Semaglutide *(SUSTAIN-6) Trial*

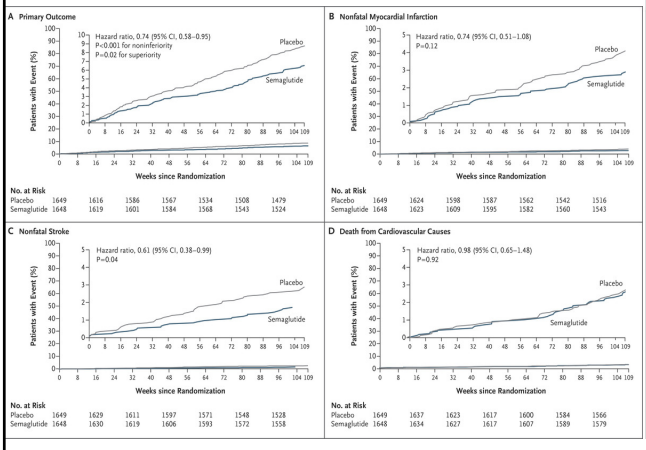

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

Marso SP et al. *N Engl J Med* 2016; 375:1834-1844.

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PAD Outcome
Liraglutide/Semaglutide *(LEADER and SUSTAIN-6) Post-hoc Analysis*

- In LEADER and SUSTAIN 6 trials, 1184/9340 (12.7%) and 460/3297 (14%) of pts had PAD.
- Patients with PAD had ~ 35% greater risk of MACE irrespective of treatment, compared to those without.
  - LEADER: hazard HR 1.36, 95% CI 1.17-1.58; SUSTAIN 6: HR 1.33, 95% CI 0.94-1.83.
- The benefit of MACE risk reduction was consistent in PAD.
  - (Liraglutide: HR 0.77, 95% CI 0.58-1.01; semaglutide: 0.61, 0.33-1.13) vs without (liraglutide: HR 0.89, 95% CI 0.79-1.00; semaglutide: HR 0.77, 95% CI 0.58-1.01; P interaction = .34 for liraglutide and .49 for semaglutide).
- Absolute risk reductions of MACE with both medications were greater in patients with PAD.
  - (Liraglutide: 4.13%-point, 95% CI −0.15-8.42; semaglutide: 4.63%-point, 95% CI −0.58-9.84) versus without (liraglutide: 1.42%-point, 95% CI −0.03-2.87; semaglutide: 1.90%-point, 95% CI 0.00-3.80).

Verma S, et al. *Diabetes Obes Metab.* 2022 Jul; 24(7): 1288–1299.

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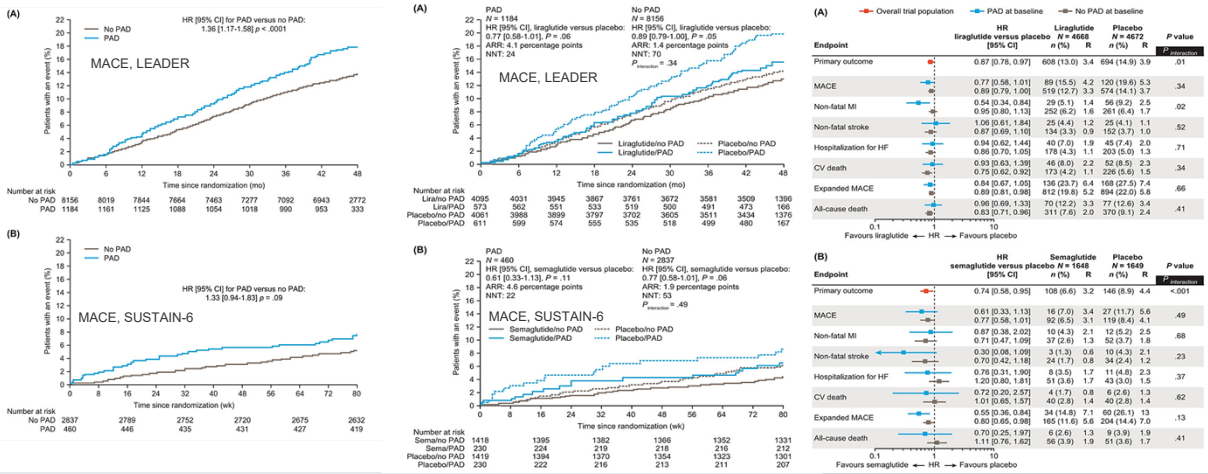
PAD Outcome
Liraglutide *(LEADER and SUSTAIN-6) Post-hoc Analysis*



Verma S, et al. *Diabetes Obes Metab.* 2022 Jul; 24(7): 1288–1299.

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Reduction in MACE
Albiglutide *(HARMONY) Trial*

- 9463 patients with T2D and CVD.
- Weekly SC albiglutide (30-50 mg based on glycemic control) or placebo.
- Outcome: MACE at 1.5 year.
- Results, *MACE*, significant reduction: HR: 0.78, 95% CI 0.68–0.90, p=0.0006.
  - ➢ Driven by risk reduction of MI.
- The drug was withdrawn from the market due to economic reasons.

Hernansez AF et al. *Lancet.* VOLUME 392, ISSUE 10157, P1519-1529.

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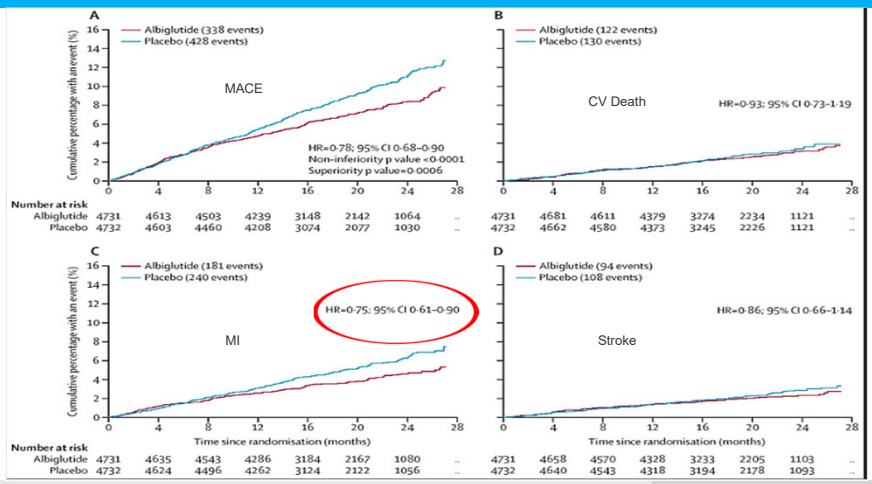
Reduction in MACE
Albiglutide *(HARMONY) Trial*



Hernansez AF et al. *Lancet.* VOLUME 392, ISSUE 10157, P1519-1529.

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Reduction in MACE
Exenatide *(EXCEL) Trial*

- 14,752 patients with T2D with or without CVD.
- Weekly SC exenatide (2 mg) or placebo.
- Outcome: MACE.
- Median follow up of 3.2 years.
- *MACE*, non-inferior: HR, 0.91; 95% [CI], 0.83 to 1.00, P<0.001 for non-inferiority and P=0.06 for superiority.

Holman RR et al. *N Engl J Med* 2017; 377:1228-1239.

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Reduction in MACE
Exenatide *(EXCEL) Trial*

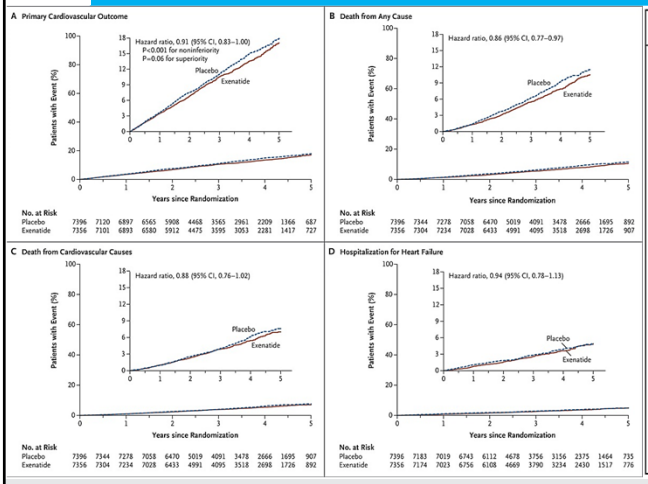

Table 1. Rates of the Primary Composite Outcome and Key Secondary Outcomes.*

Outcome	Exenatide (N=7356)		Placebo (N=7396)		Hazard Ratio (95% CI)†
	Patients with Event	Incidence Rate of First Event	Patients with Event	Incidence Rate of First Event	
	no. (%)	*no. of events/ 100 patient-yr*	*no. (%)*	*no. of events/ 100 patient-yr*	
Primary composite outcome	839 (11.4)	3.7	905 (12.2)	4.0	0.91 (0.83–1.00)
Secondary outcomes					
Death from any cause	507 (6.9)	2.0	584 (7.9)	2.3	0.86 (0.77–0.97)
Death from cardiovascular causes‡	340 (4.6)	1.4	383 (5.2)	1.5	0.88 (0.76–1.02)
Fatal or nonfatal myocardial infarction	483 (6.6)	2.1	493 (6.7)	2.1	0.97 (0.85–1.10)
Fatal myocardial infarction§	17 (0.2)	—	13 (0.2)	—	1.29 (0.63–2.66)
Fatal or nonfatal stroke	187 (2.5)	0.8	218 (2.9)	0.9	0.85 (0.70–1.03)
Fatal stroke§	18 (0.2)	—	25 (0.3)	—	0.71 (0.39–1.30)
Hospitalization for heart failure	219 (3.0)	0.9	231 (3.1)	1.0	0.94 (0.78–1.13)
Hospitalization for acute coronary syndrome	602 (8.2)	2.6	570 (7.7)	2.5	1.05 (0.94–1.18)

Holman RR et al. *N Engl J Med* 2017; 377:1228-1239.

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PAD Outcome
Exenatide *(EXCEL) Post-hoc Analysis*

- 2800 (19%) of the EXSCEL pts had PAD.
  - ➢ Higher *MACE*: 13.6% versus 11.4%: adjusted HR, 1.13 [95% CI, 1.00-1.27]; P=0.047.
  - ➢ Higher *all-cause mortality*: adjusted HR 1.38 [95% CI, 1.20-1.60]; P<0.001.
  - ➢ More frequent *lower extremity amputation*: adjusted HR 5.48 [95% CI, 4.16-7.22]; P<0.001.

- *MACE and amputation:* Similar with exenatide and placebo, regardless of PAD.
  - ➢ *All-cause mortality:* Lower with exenatide in patients with T2D and PAD (consistent with main trial).

Badjatiya A et al. *CIRCINTERVENTIONS.*119.008018.

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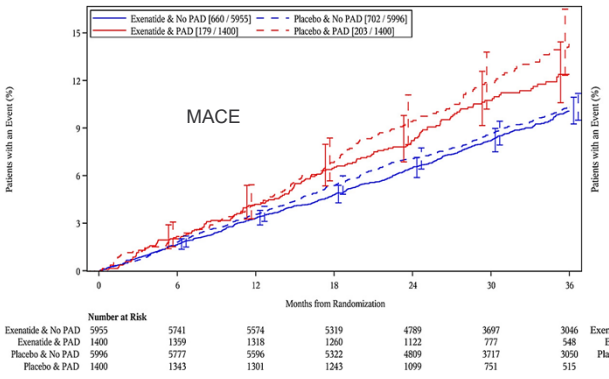
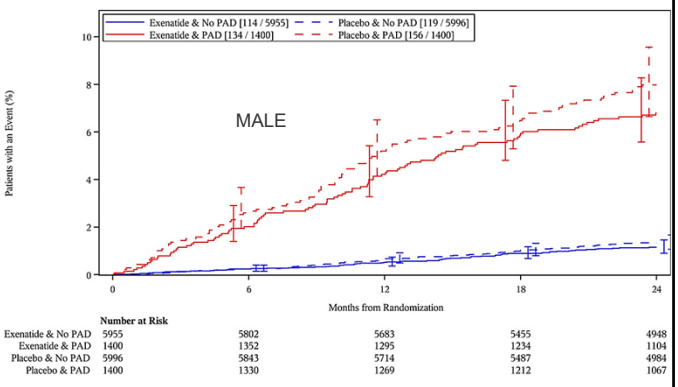
PAD Outcome
Exenatide *(EXCEL) Post-hoc Analysis*





Badjatiya A et al. *CIRCINTERVENTIONS.*119.008018.

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Reduction in MACE
Lixisenatide *(ELIXA) Trial*

- 6068 patients with T2D and a history of acute coronary syndrome.
- SC Lixisenatide or placebo.

- Outcome: 4-point MACE (CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina).
- Median follow up of 2.1 years.

- *4-Point MACE,* non-inferior: HR 1.02, 95% CI 0.89–1.17, p = 0.81.
- *HHF,* not different: HR 0.96; 95% CI, 0.75 to 1.23.
- *Rate of death,* not different: HR, 0.94; 95% CI, 0.78 to 1.13.

Pfeffer MA et al. *N Engl J Med* 2015; 373:2247-2257.

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Reduction in MACE
Lixisenatide *(ELIXA) Trial*

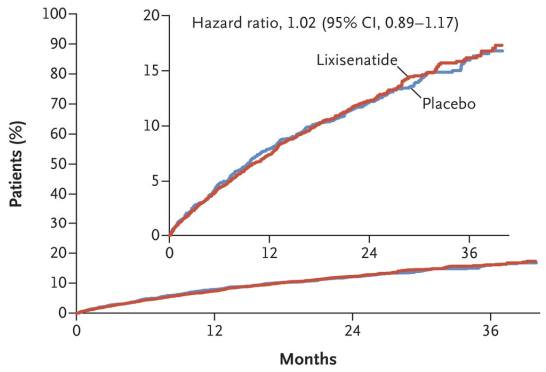

Table 2. Incidence Rates and Hazard Ratios, with Adjustment for Geographic Region, for the Primary Composite End Point, Its Components, and Other Efficacy Outcomes.

End Point	Placebo (N = 3034)		Lixisenatide (N = 3034)		Adjusted Hazard Ratio (95% CI)	P Value
	Patients with Event	No. of Events/ 100 Patient-Yr	Patients with Event	No. of Events/ 100 Patient-Yr		
Primary end point: death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or unstable angina — no. (%)	399 (13.2)	6.3	406 (13.4)	6.4	1.02 (0.89–1.17)	0.81
Components of primary end point — no./total no. (%)						
Death from cardiovascular causes	93/399 (23.3)	—	88/406 (21.7)	—	—	—
Nonfatal myocardial infarction	247/399 (61.9)	—	255/406 (62.8)	—	—	—
Nonfatal stroke	49/399 (12.3)	—	54/406 (13.3)	—	—	—
Unstable angina	10/399 (2.5)	—	9/406 (2.2)	—	—	—
Patients with each primary end-point event — no. (%)*						
Death from cardiovascular causes	158 (5.2)	2.4	156 (5.1)	2.3	0.98 (0.78–1.22)	0.85
Myocardial infarction	261 (8.6)	4.1	270 (8.9)	4.2	1.03 (0.87–1.22)	0.71
Stroke	60 (2.0)	0.9	67 (2.2)	1.0	1.12 (0.79–1.58)	0.54
Unstable angina	10 (0.3)	0.1	11 (0.4)	0.2	1.11 (0.47–2.62)	0.81
Secondary end points — no. (%)						
Primary end-point event or hospitalization for heart failure	469 (15.5)	7.6	456 (15.0)	7.3	0.97 (0.85–1.10)	0.63
Primary end-point event, hospitalization for heart failure, or revascularization	659 (21.7)	11.2	661 (21.8)	11.1	1.00 (0.90–1.11)	0.96
Additional end points — no. (%)						
Hospitalization for heart failure	127 (4.2)	1.9	122 (4.0)	1.8	0.96 (0.75–1.23)	0.75
Death from any cause	223 (7.4)	3.3	211 (7.0)	3.1	0.94 (0.78–1.13)	0.50

* Some patients had more than one component of the primary end point. In the analyses for the separate components, they were included once for each end point they had, regardless of whether it was their first event.

Pfeffer MA et al. *N Engl J Med* 2015; 373:2247-2257.

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Current and Future Research

- **STARDUST Trial:**
  - ➢ Open-label, randomized controlled trial, to evaluate the effects of liraglutide on peripheral perfusion, as compared to aggressive treatment of cardio-metabolic risk factors in people with T2D and PAD.
  - ➢ Pending results.
- **STRIDE Trial:**
  - ➢ Evaluates the effects of semaglutide vs placebo on walking ability in patients with T2D and PAD.
  - ➢ Closed with pending results.

Pfeffer MA et al. *N Engl J Med* 2015; 373:2247-2257.

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GLP1-RA Drugs Dosing and Indications

Drug	Doses	Indications
Dulaglutide *Trulicity*®	Initiate 0.75 mg SC/wk titrate to max	1- Improve glycemic control in adults with T2D. 2- Reduce MACE in adults with T2D with *established or at risk* for CVD.
Liraglutide *Victosa*® *Saxenda*®	Initiate 0.6 mg SC/day titrate to max	1- Improve glycemic control in adults with T2D. 2- Reduce MACE in adults with T2D and *established* CVD. 3- Weight reduction as adjunct to diet/exercise in obese or overweight+comorbidity.
Semaglutide *Ozempic*® *Wegovy*®	Initiate 0.25 mg SC/wk titrate to max	1- Improve glycemic control in adults with T2D. 2- Reduce MACE in adults with T2D and *established* CVD. 3- Weight reduction as adjunct to diet/exercise in obese or overweight+comorbidity.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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GLP1-RA: Summary

- **Dulaglutide:** Reduction in MACE (REWIND) driven by reduction in stroke.
- **Liraglutide:** Reduction in MACE (LEADER) driven by reduction in CV death.
  Significant reduction in amputation risk (Post-hoc).
- **Albiglutide**: Reduction MACE (HARMONY), driven by reduction of MI risk.
- **Exenatide:** non-inferior MACE (EXCEL).
  No significant difference in amputation risk
- **Lixisenatide**: non-inferior 4-point MACE (VELIXA).

Skeik N et al. *Angiology*. 2022 Mar;73(3):197-206

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SGLT2-i
Risk of Amputation

- Amputation risk: *increased* in CANVAS but *not* in a pooled analysis of CANVAS and CREDENCE trials.
- Not reported with other SGLT2-i agents.
- CANVAS and CREDENCE trials' populations are different but no confirmed explanation for difference in amputation.

- *Proposed mechanisms:* glycosuria-induced hypovolemia and hypo-perfusion.
  - *SURDIAGENE study*: worsened amputation with diuresis.

- A meta-analysis of CRTs of SGLT2-i drugs in pts with T2D:
  - *A positive association* between SGLT2i-induced BP/weight reduction and limb events including amputation and PAD.

- A cohort study using data from the Clinical Practice Research Datalink GOLD (2013-2019):
  - SGLT2-i drugs in 51,847 pts, with or without signs of hypovolemia, was *not associated* with an increased amputation!

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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SGLT2-i
Risk of Amputation, Cont.

- Six observational studies using the Truven Market Scan health claims database from the USA. The results vary:
  - ➢ *No difference* in amputation risk with canagliflozin compared with non-SGLT2-i agents in 3 studies.
  - ➢ *Lower amputation risk* with SGLT2-i drugs (canagliflozin comprised 70% of SGLT2-i use) compared with sulfonylurea, but not compared to DPP-4 inhibitors in 2 studies.
  - ➢ Only one study showed *a higher amputation* risk with SGLT2-i drugs compared with DPP-4 inhibitors, but not compared with sulfonylurea or non-metformin, non-SGLT2-i agents.
- Observational study using the U.S. Department of Defense Health System:
  - ➢ SGLT2-i associated with *twofold risk* of amputation vs non-SGLT2-i agents (HR 1.99; 95% CI 1.12–3.51 mostly with canagliflozin).
- Observational study using the Swedish/Danish National Register:
  - ➢ *Increased amputation* incidence with SGLT2-i drugs compared with GLP1-RA (HR 2.48; 95% CI 1.14–5.40).

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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SGLT2-i
Risk of Amputation, Cont.

- Large multicenter observational study from seven Canadian provinces and the U.K.:
  - ➢ *No association* with SGLT2-i drugs, including canagliflozin, compared with DPP-4 inhibitors.
- A retrospective analysis from Taiwan National Health Insurance Database:
  - ➢ *No difference* in amputation between SGLT2-i drugs compared to DDP-4, GLP1-RA, and other medications.
- **Heterogeneity of results**: differences in studies population, methods, comparator drugs, the extent of amputation recorded, follow-up duration, and inclusion or exclusion of patients with a history of amputations.
- **Until stronger data is available, SGLT2-i (mainly canagliflozin) may need to be avoided in patients with high risk for amputation (previous amputation, ischemic ulcers, or neuropathy).**

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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GLP1-RAs
Risk of Amputation

- Trials have *not exclusively* addressed PAD or lower limb complication as a primary or secondary endpoint.
- Although a post-hoc analysis of the *LEADER trial* demonstrated a *reduction in amputations* with liraglutide versus placebo, there is *no strong evidence* regarding the effect of *GLP1-RAs on MALE*.
- A real-world study has evaluated the role of GLP1-RA in 9772 patients in clinical practice:
  - ➢ GLP1-RAs were associated with *lower rates* of death, cerebrovascular disease and ischemic stroke, PVD, and lower limb complications compared with other therapies.
- Scandinavian population-based study:
  - ➢ *Lower risk* of limb outcome with liraglutide compared to DDP-4.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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GLP1-RAs
Risk of Amputation Cont.

- A retrospective analysis conducted using the Taiwan National Health Insurance database:
  - ➢ GLP1-RAs were associated with significantly *lower risks* of MALE when compared with DPP4i drugs.
  - ➢ This was mainly driven by the *reduction* of the amputation rate.
  - ➢ GLP1-RAs were associated with *lower risks* of MACE and death from any cause.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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SGLT-i Related Clinical Trial Data

Trials with SGLT-i	Study Design	Patients (n)	Primary End Point	Treatment Arms	Incidence	RR or HR [95% CI]	P-Value
EMPAGLIFLOZIN							
EMPA-REG 2015	RCT	7,020	MACE	Empagliflozin – 10 or 25 mg Placebo	10.5% 12.1%	HR 0.86 [0.74 – 0.99]	Non-inferiority: <0.001 Superiority: 0.04
EMPEROR REDUCED 2020	RCT	4744	CV death or HHF	Empagliflozin – 10 mg Placebo	19.4% 24.7%	HR 0.75 [0.65 – 0.86]	Superiority <0.001
EMPEROR PRESERVED 2021	RCT	5988	CV death or HHF	Empagliflozin – 10 mg Placebo	13.8% 17.1%	HR 0.79 [0.69 – 0.90]	Superiority <0.001
CANAGLIFLOZIN							
CANVAS & CANVAS-Renal 2017	RCT	10,142	MACE	Canagliflozin – 100 or 300 mg Placebo	26.9 patients/1000 patient-year 31.5 patients/1000 patient-year	HR 0.86 [0.75 - 0.97]	Non-inferiority: <0.001 Superiority: 0.02
CREDENCE 2019	RCT	4,401	ESRD, a doubling of the serum cr level, or death from renal or CV causes	Canagliflozin – 100 mg Placebo	43.2 events per 1000 61.2 events per 1000 patient-years	HR 0.70 [0.59 – 0.82]	0.00001

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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SGLT-i Related Clinical Trial Data, Cont.

DAPAGLIFLOZIN							
DECLARE-TIMI 2019	RCT	17,160	CV death or HHF	Dapagliflozin – 10 mg Placebo	4.9% 5.8%	HR 0.83 [0.73 – 0.95]	0.005
			MACE	Dapagliflozin – 10 mg Placebo	8.8% 9.4%	HR 0.93 [0.84 – 1.03]	0.17
DAPA-HF 2019	RCT	4,744	Composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death	Dapagliflozin – 10 mg Placebo	16.3% 21.2%	HR 0.74 [0.65 – 0.85]	<0.001
DAPA-CKD 2020	RCT	4,304	Composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or CV causes	Dapagliflozin – 10 mg Placebo	9.2% 14.5%	HR 0.61 [0.51 – 0.72]	<0.001
SOTAGLIFLOZIN							
SCORED 2021	RCT	10.584	CV death or HHF or urgent visit for HF	Sotagliflozin Placebo	5.6% 7.5%	HR 0.74 [0.63 – 0.88]	Superiority: <0.001
SOLOIST WHF 2021	RCT	1222	CV death and HHF and urgent visit for HF	Sotagliflozin Placebo	51.0% 76.3%	HR 0.67 [0.52 – 0.85]	Superiority: <0.001
ERTUGLIFLOZIN							
VERTIS-CV 2020	RCT	8,246	MACE	Ertugliflozin – 5 or 15 mg Placebo	11.9% 11.9%	HR 0.97 [0.85 – 1.11]	Non-inferiority: <0.001

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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GLP1-RA Related Clinical Trial Data

Trial with GLP1-RA	Study Design	Patients (n)	Primary End Point	Treatment Arms	Incidence	RR or HR [95%CI]	P-value
DULAGLUTIDE							
REWIND 2019	RCT	9,901	MACE	Dulaglutide – 1.5 mg Placebo	12% 13.4%	HR 0.88 [0.79 - 0.99]	0.026
LIRAGLUTIDE							
LEADER 2018	RCT	9,340	MACE	Liraglutide – 1.8 mg Placebo	13% 14.9%	HR 0.87 [0.78 – 0.97]	Non-inferiority: <0.001 Superiority: 0.01
SEMAGLUTIDE							
SUSTAIN-6 2016	RCT	3,297	MACE	Semaglutide – 0.5 or 1.0 mg Placebo	6.6% 8.9%	HR 0.74 [0.58 – 0.95]	Non-inferiority: <0.001 Superiority: 0.02
PIONEER 6 2019	RCT	3,183	MACE	Semaglutide – 14 mg Placebo	3.8% 4.8%	HR 0.79 [0.57 – 1.11]	Non-inferiority: <0.001 Superiority: 0.17
ALBIGLUTIDE							
Harmony Outcomes 2018	RCT	9,463	MACE	Albiglutide – 30 or 50 mg Placebo	7% 9%	HR 0.78 [0.68 – 0.90]	Non-inferiority: <0.001 Superiority: 0.0006
EXENATIDE							
EXSCEL 2017	RCT	14,752	MACE	Exenatide – 2mg Placebo	11.4% 12.2%	HR 0.91 [0.83 – 1.00]	Non-inferiority: <0.001 Superiority: 0.06
LIXISENATIDE							
ELIXA 2015	RCT	6,068	4 factor MACE	Lixisenatide – 10 or 20 µg Placebo	13.4% 13.2%	HR 1.02 [0.89 – 1.17]	Non-inferiority: <0.001 Superiority: 0.81

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SGLT-i and GLP1-RA with PAD Outcome

Trial	Study Design	Patients (n)	Primary End Point	Treatment Arms	Incidence	RR or HR [95% CI]	P-value
SGLT2i Drugs							
EMPAGLIFLOZIN							
EMPA-REG 2015	RCT	1,461 (PAD Subgroup)	MACE	Empagliflozin 10 or 25 mg Placebo	12.2% 13.8%	HR 0.84 [0.62 – 1.14], *P-interaction*:0.9052	NR
CANAGLIFLOZIN							
CANVAS & CANVAS-Renal 2017	RCT	2,113 (history of PAD)	MACE	Canagliflozin – 100 or 300 mg Placebo	33.9 43.2 patients/1000 pt-year	HR 0.75 [0.58 - 0.97] *P interaction* > .268.	NR
DAPAGLIFLOZIN							
DECLARE-TIMI 2019	RCT	6,974 (pts with any ASCVD)	CV death or HHF	Dapagliflozin – 10 mg Placebo	272/3474 = 7.8% 325/3500 = 9.3%	HR 0.83 [0.71 – 0.98] *P-interaction*=0.79	NR
			MACE	Dapagliflozin – 10 mg Placebo	483/3474 = 13.9% 537/3500 = 15.3%	HR 0.90 [0.79 – 1.02] P-interaction>0.05	
GLP1-RA Drugs							
LIRAGLUTIDE							
LEADER 2018	Post Hoc	9,340	Diabetic foot ulcers	Liraglutide – 1.8 mg Placebo	3.8% 4.1%	HR 0.92 [0.75 – 1.13]	0.41
			Amputation	Liraglutide – 1.8 mg Placebo	NR NR	HR 0.65 [0.45 – 0.95]	0.03
EXENATIDE							
EXSCEL 2017	Post Hoc	11,951 (without -PAD) 2,800 (with- PAD)	MACE	Exenatide – 2 mg Placebo	11.4% 13.6%	HR 1.13 [1 – 1.27] P-interaction>0.05	0.047

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Summary of Societal Guideline Recommendations

Societal Guidelines	Recommendations
2023-ADA	• T2D and high risk for or eASCVD, DKD, or HF: Recommend SGLT2-i or GLP1-RA with demonstrated CV benefit. • T2D and high risk for or eASCVD and DKD: Recommend SGLT2-i. • T2D and high risk for or eASCVD: Recommend GLP1-RA *or a combination with SGLT2-i (in CKD).* • HFrEF/HFpEF: Recommend SGLT2i with proven benefit (eGFR>20ml/min). • CKD and albuminuria: Recommend a SGLT2-i with evidence of reducing CKD progression.
2019-ACC/AHA: Primary Prevention of CVD	• Glycemic Control: Recommend metformin as first line pharmacological agent. • T2D and additional ASCVD risk factors: reasonable to initiate a SGLT2-i or a GLP1-RA as add on to metformin.
2020-ACC Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patients with T2D	• T2D and ASCVD: Recommend starting SGLT2-i or GLP1-RA with CV benefit. • DKD and/or HF: Consider a SGLT2-i. • eGFR <30 ml/min/1.73 m2: Consider a GLP1-RA as an alternative. • At discharge after ASCVD admission: Consider a SGLT2-i or GLP1-RA. • Consider SGLT2-i in case of HFrEF.
2022-AHA/ACC/HFSA Heart Failure	• HFrEF: Recommend SGLT2i regardless of T2D. • SGLT2-i can also be beneficial in HFmrEF and HFpEF.
2019-ESC on DM and CVD-2019	• T2D and CVD or high CV risk: Recommend empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, or dulaglutide to reduce CV events. • Recommend empagliflozin or liraglutide to reduce risk of CV death.

Skeik N et al. *Vasc Med*. 2023 Feb;28(1):62-76.

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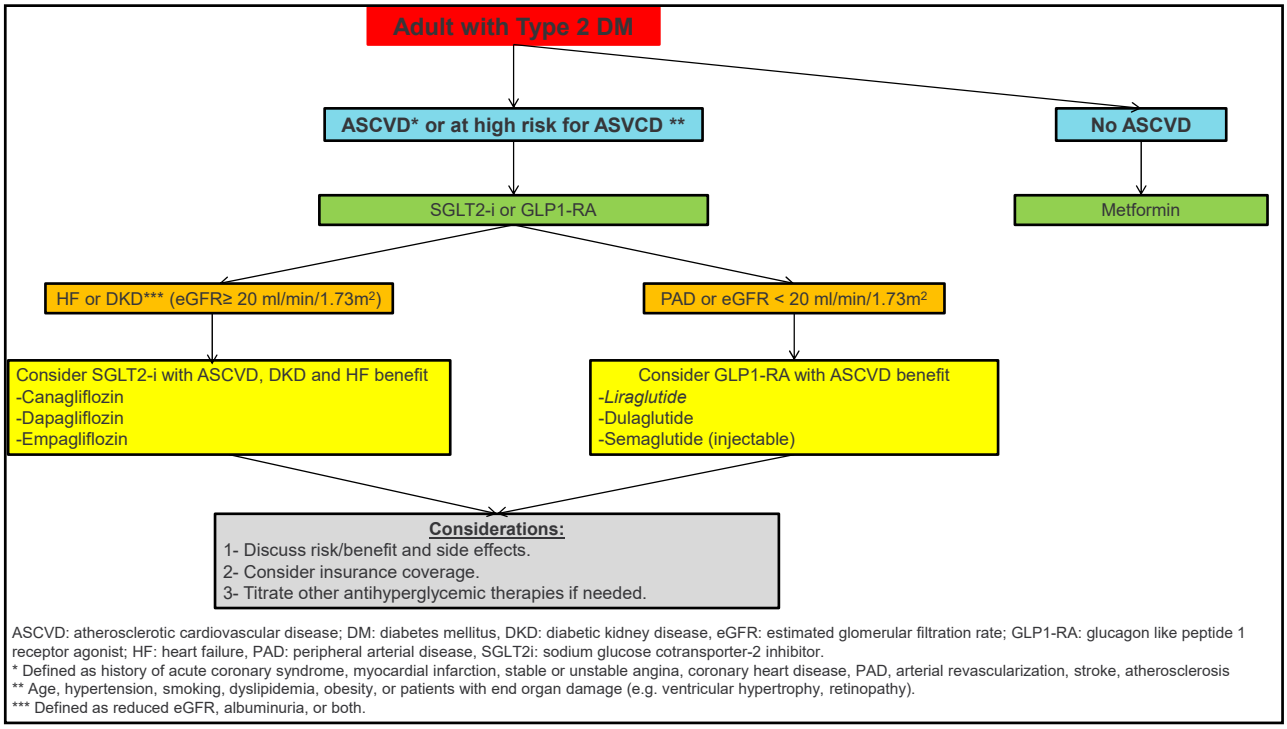

ASCVD: atherosclerotic cardiovascular disease; DM: diabetes mellitus, DKD: diabetic kidney disease, eGFR: estimated glomerular filtration rate; GLP1-RA: glucagon like peptide 1 receptor agonist; HF: heart failure, PAD: peripheral arterial disease, SGLT2i: sodium glucose cotransporter-2 inhibitor.
* Defined as history of acute coronary syndrome, myocardial infarction, stable or unstable angina, coronary heart disease, PAD, arterial revascularization, stroke, atherosclerosis
** Age, hypertension, smoking, dyslipidemia, obesity, or patients with end organ damage (e.g. ventricular hypertrophy, retinopathy).
*** Defined as reduced eGFR, albuminuria, or both.

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Summary

PAD and T2D are two prevalent and often concurrent major health problems with increased morbidity and mortality.

SGLT-i and GLP1-RA have shown a significant reduction of MACE in patients with T2D and CVD.

Some SGLT-i have shown a significant reduction in CV mortality, HHF, and renal outcome.
Few GLP1-RA drugs have weight and stroke risk reductions.

PAD had worse CV outcomes in most trials.
RRR of CV outcome was generally consistent and ARR was more in patients with and without PAD.

Amputation risk: Inconsistent data with SGLT-i (mainly with canagliflozin).
: Signal of reduced MALE with GLP1-RAs (mainly with liraglutide).

Skeik N et al. *Angiology*. 2022 Mar;73(3):197-206

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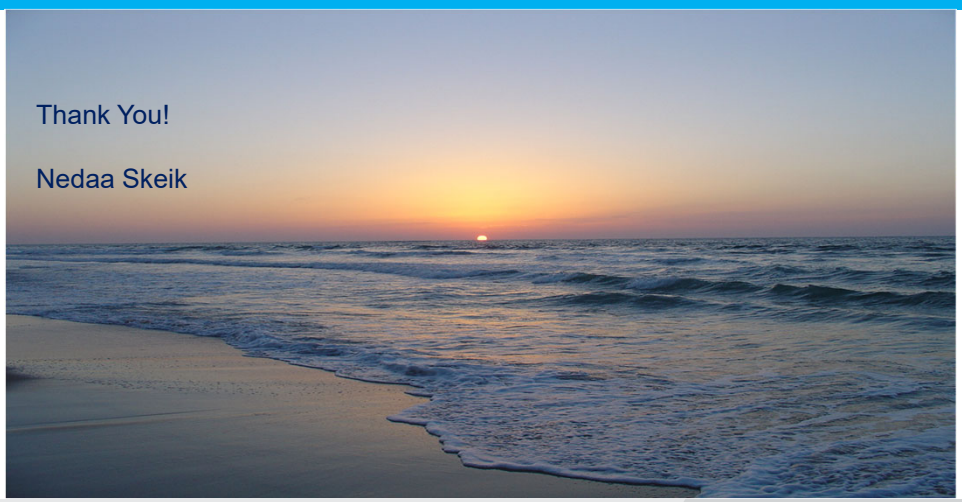
Sunset, Gaza City (Prayers for Peace!)



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