Diabetes: Studies of Real Outcomes

Drug	Population (risk)	Time (yrs)	Surrogate	CVD	Death	Other
Dapigliflozin	17160 (high)	4.2	A1c 0.4%, BP 2.7/0.7	NS (~0.5%) HF 2.5% v 3.3%	NS (~0.5%)	DKA 0.3% v 0.1% Gen Inf 0.9 v 0.1%
Canagliflozin	4401 (Renal -High)	2.6	A1c 0.3% BP 3.3/1	9.9% vs 12.2%	NS (~1.5%)	DK 0.5% vs 0.04%
				Renal death, transplant, dialysis =3.5% v 4.8%		

4744 HF pts [2/3 Class II, 1/3 Class III], mostly max therapy, 42% diabetic. At 1.5 yrs,
- HF hospitalization or CVD death: 16% v 21%. (NNT ~21)
- Death from any Cause: 12% v 14% (NNT 44)

Dapigliflozin: likely a better CHF drug than a DM drug.
Canigliflozin: A drug that is helpful in diabetics with renal impairment.

NEJM 2019 DOI: 10.1056/NEJMoa1901118 NEJM 2019;380:347-57. NEJM 2019;380:2295-306. NEJM 2019 DOI: 10.1056/NEJMoa1911303

Diabetes: Studies of Real Outcomes

Drug	Population (risk)	Time (yrs)	Surrogate	CVD	Death	Other
Dulaglutide	9901 (Lower)	5.4	A1c 0.6%, BP 1.7/0.5	12% vs 13.4%	NS (~1% less)	Microalbumin, + 3% quit A/E
Semaglutide (oral)	3183 (Higher)	1.3	A1c 0.7%, Wgt 3.4 kg	NS (~1%)	1.4% vs 2.8%	+5% quit A/E

Dulaglutide: Small effect x5 years but mostly Primary Prevention

Oral Semaglutide: Larger effect in x1.5 years but mostly Secondary Prevention

Dulaglutide in DM for CVD

- RCT 9901 Diabetics, Dulaglutide 1.5mg s.c. 1/week, followed ~5.4 yrs.
  - Mean A1c 7.2%, Mean age 66, 54% male, 21% past CVD (others higher risk)
- Results: A1c down 0.6%, weight 1.5 kg, BP 1.7/0.5 mmHg
  - CVD HR=0·88 (0·79–0·99), 12% vs 13.4%, NNT 72
  - All-cause death HR=0·90 (0·80–1·01), 10.8% vs 12%
  - Microvascular HR=0·85 (0·77–0·93), 18.4% vs 21.6%, but lots of surrogate markers
    - New microalbuminuria (9% vs 11%); GFR decline ≥30% (9% vs 10%)
  - Discontinue due to AE: 9% vs 6%, NNH=36
  - Subgroups: US/Canada (no benefit but Europe did?)
- **Bottom-Line**: Dulaglutide probably is effective in reducing CVD & likely death buy a small amount. Similar to other GLP-1.

Lancet June 10, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31149-3
Just Renal: http://dx.doi.org/10.1016/S0140-6736(19)31150-X

Oral Semaglutide for Diabetes

- RCT 3183 diabetics, oral semaglutide 14 mg daily vs placebo, over 16 mons
  - Mean age 66, male 68%, A1c 8.2%, past CVD or CKD 85%
- Results: Decreased A1c 0.7% & Wgt 3.4 kg vs placebo
  - CVD HR=0.79 (95% CI, 0.57–1.11), 3.8% vs 4.8%
    - Mostly CVD death HR=0.49 (0.27–0.92) (MI slight up, stroke slight down, not stat sign)
  - Overall Mortality HR=0.51 (0.31–0.84), 1.4% vs 2.8%, NNT=72
  - Discontinue due to AE: 12% vs 7% (NNH=20) – mostly GI related.
- **Bottom-Line**: Oral Semaglutide seems similar to other GLP-1 subcutaneous, with small reductions in CVD and overall death but GI upset. Bigger trial would be better.

NEJM 2019 DOI: 10.1056/NEJMoa1901118

Dapigliflozin: Better Late than Never?

- RCT 17,160 diabetics, dapagliflozin 10mg OD vs placebo, followed 4.2 yrs
  - Mean age 64, 62% male, A1c 8.3%, Past CVD 41%,
- Results: A1c 0.4% better. BP was 2.7/0.7mmHg better
  - CVD: HR=0.93 (0.84−1.03), 8.8% vs 9.4%
  - Death: HR=0.93 (0.82−1.04), 6.2% vs 6.6%
  - Renal death, ESRD, ≥40% GFR decline: HR=0.53 (0.43−0.66), 1.5% vs 2.8%, NNT=77
  - HF hospitalization: HR=0.73 (0.61−0.88), 2.5% vs 3.3%, NNT=125
  - Diabetic ketoacidosis 0.3%vs 0.1% (NNH=500), genital infection 0.9% vs 0.1%, NNH=125
- **Bottom-Line:** This SGLT2 does not seem as effective as Empa or Cana.

N Engl J Med 2019;380:347-57.

Canagliflozin for renal (and CVD) outcomes

- RCT 4401 diabetics with GFR 30-89 and albumin/creat 300-5000 mg/g
  - In Canada, >30mg/mmol or 300mg/g is severe albuminuria
  - Canagliflozin 100mg OD vs Placebo, followed 2.6 years.
  - Mean age 63, 66% male, A1c 8.3%, mean GFR 56, mean ACR 927,
- Results: A1c 0.3% better, BP 3.3/1 mmHg better
  - Renal death, dialysis, transplant: HR=0.72 (0.54–0.97), 3.5% vs 4.8%, NNT=77
  - Pooled renal (doubling creatinine): HR=0.66 (0.53–0.81), 6.9% vs 10.2%, NNT=31
  - CVD: HR=0.80 (0.67–0.95), 9.9% vs 12.2%, NNT=44
  - Death: HR=0.83 (0.68–1.02), 7.6% vs 9.1%.
  - No diff in amputation or other except diabetic ketoacidosis (0.5% vs 0.04%, NNH ~225)
- **Bottom-Line**: Canagliflozin reduces CVD/renal events 1-3% over 2.5 years. It is a reasonable second-line option in diabetes.

N Engl J Med 2019;380:2295-306.