Diabetes Connect 2019: A Cardiologist's View of DM management

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Disclosure Statement of Financial Interest

I, (Mina Madan) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

As an Interventional Cardiologist, performing both coronary and peripheral interventions, I struggle with the end organ damage caused by diabetes on a daily basis.

Objectives

- Scope of the Problem
- Screening for Cardiovascular Risk
- Primary/Secondary Prevention (Low/Mdm/High)
- Stable and Unstable CAD/Revascularization strategies
- Diabetes and CHF
- Summary

Diabetes

One disease,
Multiple Consequences
Trans-disciplinary approach

2013-2014: 3M Canadians with diabetes (8.1%)

200,000 new cases that year,

Incidence increases with advancing age, men>women

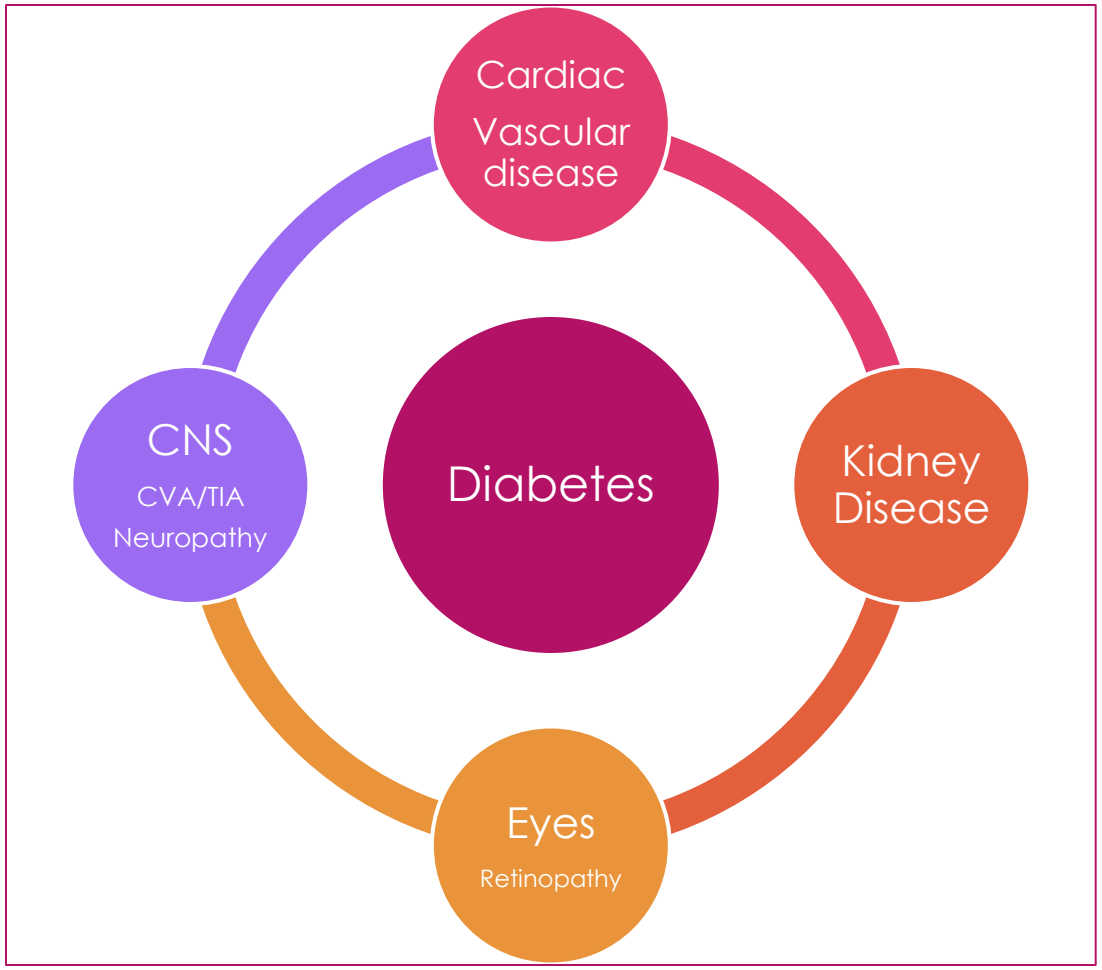
30% of strokes

40% of myocardial infarction

50% of kidney failure requiring dialysis

70% of non-traumatic leg and foot amputations

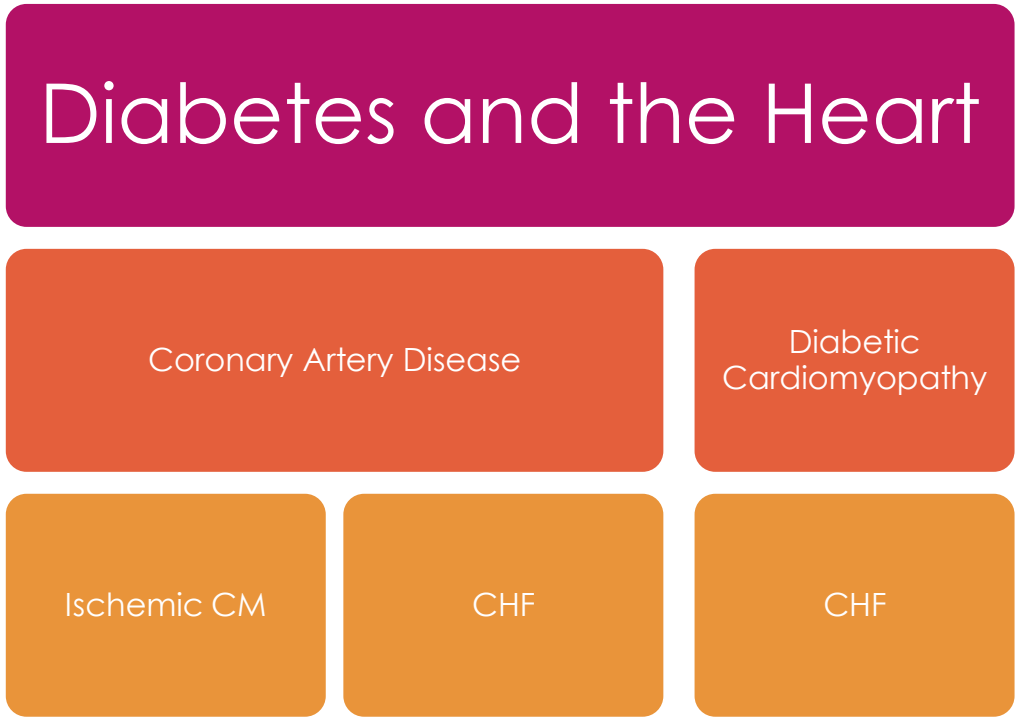
Leading cause of blindness



https://www.canada.ca/en/public-health/services/publications/diseases-conditions/diabetes-canada-highlights-chronic-disease-surveillance-system.html

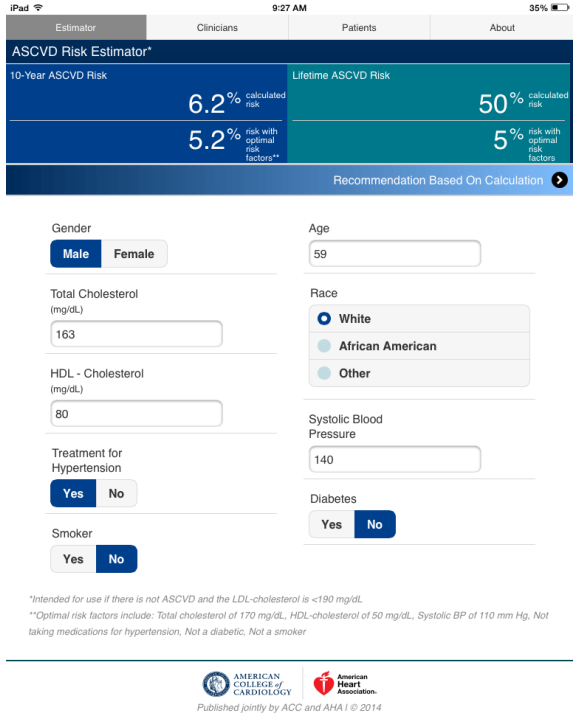
Scope of the Problem

- Compared to people without diabetes, individuals with diabetes are at higher risk of developing heart disease, and at an earlier age.
- A large proportion of individuals will have little to no symptoms before an MI. Therefore screening is desirable to identify people at high risk of CVD, or established silent CVD.



Screening for Cardiovascular Risk

ASCVD Risk Calculator



Low: <10%
Medium: 10-20%
High: >20%

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Société canadienne de cardiologie
Communauté. Connaissances. Leadership.

Other tools

- Framingham Risk Score (my CCS app)
- My Heart Age Calculator
  - myhealthcheckup.com
  - http://cardiometabolicage.com
- Estimates the 10 year risk of ASCVD for pts aged 40-75
  - Derived with data mainly from Caucasians and African Americans
  - The higher the baseline risk, the greater the benefit from preventative therapies like statins, or BP lowering drugs
  - Opens a conversation with the patient-patient armed with data is more likely to take action.

tools.acc.org/ASCVD-Risk-Estimator-Plus

Diabetes Canada-ABCDEs of Management

- **A – A1C**—Aim for an A1C of 7% or less by managing blood sugars well.
- **B – Blood pressure**—BP<130/80 mmHg.
- **C – Cholesterol**—LDL cholesterol target <2.0 mmol/L *(ideally <1.8 mmol/L)*.
- **D – Drugs** to protect your *vital organs*(ACE inhibitors or ARBs), cholesterol-lowering pills (statins), Aspirin, Clopidogrel and **others (SGLT2I, or GLP-1 agonists)**.
- **E – Exercise & Eating**—Regular physical activity, maintaining a healthy diet can help to achieve/ maintain a healthy body weight.
- **S – Screening for complications**—heart, *legs*, feet, kidneys, and eyes.
- **S – Smoking cessation**
- **S – Self management, stress, and other barriers**—Set goals for yourself to reach your targets and live well with diabetes, such as managing stress effectively.
- Source: www.diabetes.ca

Who should be Screened for CVD?

(controversial area)

Age >40 years

Duration of diabetes >15 years + Age >30 years

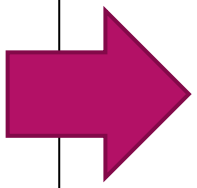
End organ damage

Microvascular

Cardiovascular

>1 CVD risk factor(s)

Age >40 years and planning to undertake very vigorous or prolonged exercise



- Baseline resting ECG
  - simple
  - Inexpensive
  - If Q waves: silent MI
- Repeat every 2 years
- *discriminatory ability marginal*
- *?Useless*

Source: www.diabetes.ca

Who should be Screened for CVD by Stress Test?

- Typical or atypical cardiac symptoms
- Associated diseases:
  - PAD
  - Carotid bruits
  - TIA
  - Stroke
- Resting ECG abnormalities (e.g. Q waves)

- Exercise ECG stress testing
  - Exercise (or Pharmacologic) stress echo
  - Exercise (or Pharmacologic) myocardial perfusion imaging
- Other imaging techniques depending of local expertise (coronary CTA, calcium score, ABI)-presence of CVD, no functional information

If Stress Test abnormal → Referral to a Cardiologist is next step for consideration of coronary angiography

Source: www.diabetes.ca

Stable CAD

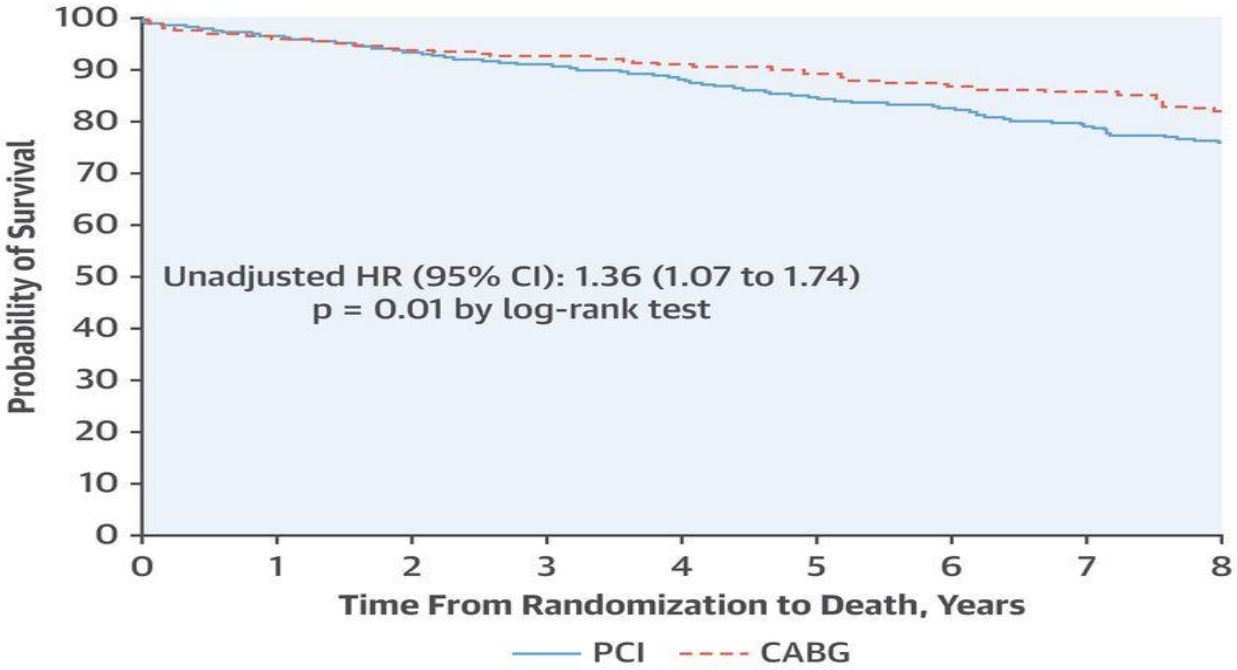
- For all-address all concomitant risk factors: OPTIMAL MEDICAL THERAPY (OMT)
- Patients with diabetes can have focal CAD, but most often we observe diffuse CAD
- For mild to moderate CAD (less than 70%); OMT advised
- Single vessel disease: PCI
- Double vessel disease: PCI (CABG)
- Triple vessel disease: CABG preferred strategy (BARI, FREEDOM studies)

FREEDOM study

- N=1900 DM 1 or 2
- Angiographically confirmed multivessel coronary artery disease and amenable to either PCI or CABG
  - Critical (>70%) lesions in at least two major epicardial vessels and in at least two separate coronary artery territories (left anterior descending, left circumflex, right coronary artery)
  - Indication for revascularization based on symptoms of angina and/or objective evidence of myocardial ischemia
- Duration of follow-up: 5 years
  Mean patient age: 63.2 years
  Percentage female: 29%
  Ejection fraction: 66%, * 1st generation DES, 83% had 3 VD
- The primary outcome (D/MI/ CVA)occurred more frequently in the PCI group (P=0.005), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group. The benefit of CABG was driven by differences in rates of both myocardial infarction (P<0.001) and death from any cause (P=0.049). Stroke was more frequent in the CABG group, with 5-year rates of 2.4% for PCI group and 5.2% for CABG group (P=0.03).
- **Conclusion: Among diabetic patients with multivessel coronary artery disease, revascularization with CABG reduces the rates of death and MI compared to PCI, but causes an increase in the rate of stroke.**

Farkouh M, et al. N Engl J Med 2012; 367:2375-2384

CENTRAL ILLUSTRATION: Survival Curves According to the Revascularization Strategy in the FREEDOM Follow-On Study



Number of patients at risk

PCI	953	897	845	745	611	460	333	260	206
CABG	947	854	807	721	589	445	313	252	191

Farkouh, M.E. et al. J Am Coll Cardiol. 2019;73(6):629–38.

Michael E. Farkouh et al. JACC 2019;73:629-638

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Unstable CAD

- **Less clear answers-no dedicated ACS revascularization strategy trials in this population**
- STEMI: primary PCI
- NSTEMI, UA
  - Single vessel CAD: PCI
  - Double vessel CAD: PCI
  - Focal 3VD amenable to PCI: PCI > CABG/ patient preference
  - Diffuse 3VD /Complex disease: CABG > PCI

Diabetes and Revascularization in ACS

- Patients with DM have more severe CAD and higher mortality with ACS than patients without DM.
- The optimal mode of revascularization remains controversial in this setting.
  - DM + STEMI: Primary PCI is generally preferable.
  - DM + NSTE-ACS: the decision on mode of revascularization is more challenging.
- In mostly stable CAD pts with DM: Trials of CABG vs. PTCA, using BMS, and first-generation DES with multi-vessel disease have demonstrated **decreased mortality in those receiving CABG**.
- Trials and registries to date comparing CABG vs. PCI with second-generation DES in DM patients have shown mixed results. **Heart team**: Patient anatomy, ability to achieve complete revascularization, preference, compliance, age, frailty, co-morbidities, LVEF

Back to the patient…What Medications?

- EC ASA-lifelong
- Ticagrelor for 1 year
- ACE Inhibitor-lifelong
- Beta Blocker-at least 2 years
- Statin therapy-high intensity, maybe adding ezetimibe if LDL> 1.8 mmol/L-life long
- Metformin-life long

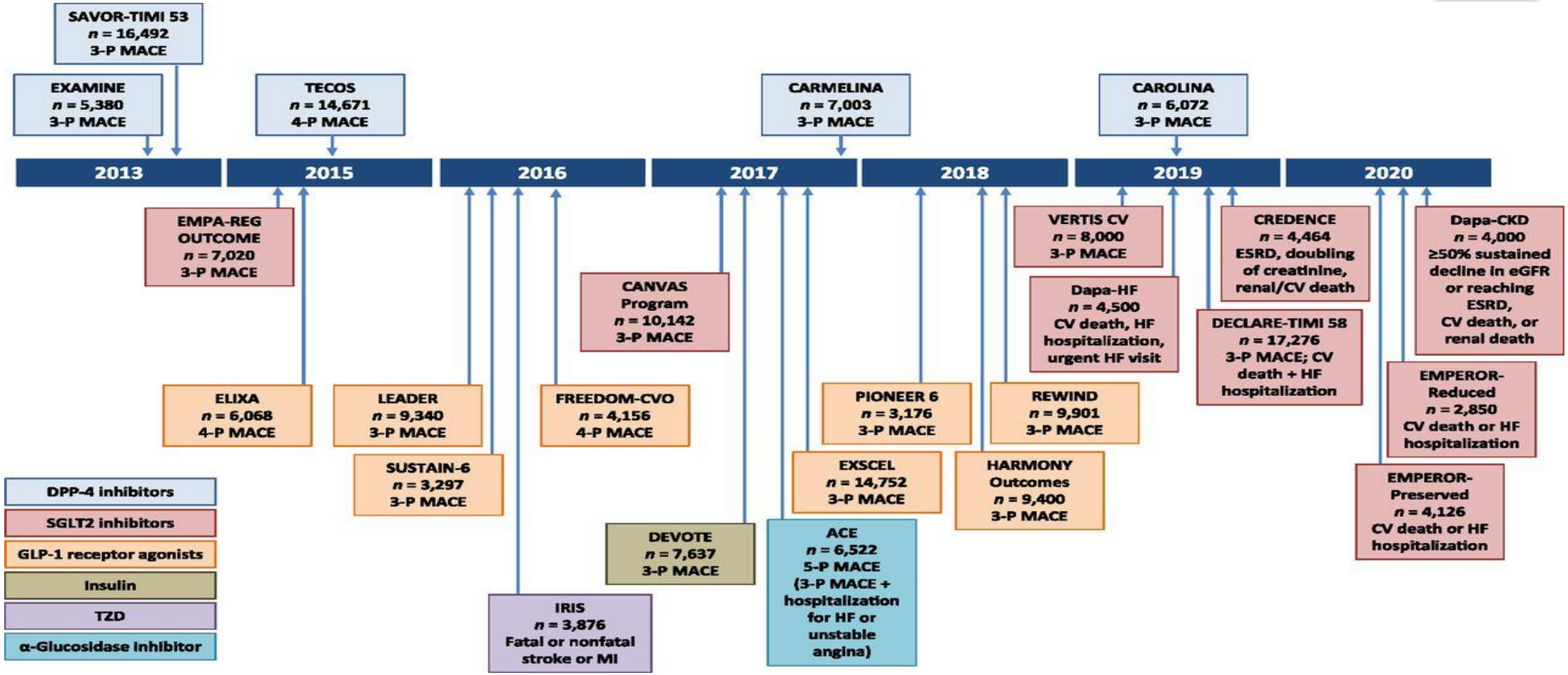
The patient is uninsured, so-called "working poor"

- *What about SGLT2 Inhibitor, or GLP-1 agonist?*
- *What about PCSK9 inhibitor injections, if LDL is > 1.8 mmol/L?*
- *What about long term low dose ticagrelor? (Pegasus study), what about low dose rivaroxaban/ASA (COMPASS trial)?*

Diabetes and CV Outcomes-non diabetes RX

- **Antiplatelet drugs**
  - ASA no longer clearly indicated for primary prevention
  - Secondary prevention
    - Stable CAD: no net benefit of dual antiplatelet therapy for patients with diabetes
      - bleeding>modest ischemic benefit **THEMIS**
    - Short term after ACS/PCI (<1 year) (ASA, and ticagrelor, ASA and prasugrel) **TRITON, PLATO**
    - Long term after ACS/hi risk (beyond 1 year) (long term ticagrelor, clopidogrel) **PEGASUS, DAPT**
- **Anticoagulant drugs**
  - Long term prevention (low dose rivaroxaban and ASA) **COMPASS**
- **Cholesterol lowering drugs**
  - PCSK9 inhibitors (evolocumab, alirocumab) **FOURIER, ODYSSEY OUTCOMES**

Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.



William T. Cefalu et al. Dia Care 2018;41:14-31

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American Diabetes Association

New drugs…Cardiologist's Perspective

GLP-1 AGONISTS (INJECTABLE and ORAL)

- reduce blood sugar (A1c 1.5%), incretin mimetic, delays gastric emptying, early satiety, weight loss (2.5-5 kg in first year), slight↓BP
- Low risk of hypogylcemia
- Side effects: Nausea, GI upset, and injection site reactions

- LIRAGLUTIDE (Victoza), DULAGLUTIDE (Trulicity), SEMAGLUTIDE (Ozempic)

GLP-1 Agonists

LEADER

N= 9340, **LIRAGLUTIDE** vs. placebo

DM2 at high CV risk

CV Death/MI/CVA **RRR 13%,** P=0.01

Death and CV death were sig lower RRR 15% and 22%, P<0.05

More GI side effects with liraglutide

SUSTAIN-6 (SC)

PIONEER-6 (PO)

SEMAGLUTIDE vs. placebo

DM2 at high CV risk

SUSTAIN-6 N=3297, 40% female

CV Death/MI/CVA **RRR 26%,** P 0.02

40% RRR for stroke

More GI side effects with semaglutide

PIONEER-6 N=3183

Oral Semaglutide vs placebo

DM2 at high CV risk

CV Death/MI/CVA **21% RRR** P,0.001 for non-inferiority

Sig reductions in death and CV death

REWIND

N= 9901, **DULAGLUTIDE** vs. placebo

DM2 at high CV risk

46% female

CV Death/MI/CVA **RRR 12%,** P=0.026

GI side effects 47% among those receiving dulaglutide

New drugs…Cardiologist's Perspective

SGLT2 INHIBITORS (oral):

- reduce blood sugar/glycosuria (A1c 0.5-0.6%), ↓BP, weight loss, osmotic diuresis
- Reduces MACE (CV death, MI, CVA) (11%) among those with established ASCVD
- Reduces CHF, and CHF hospitalization (31%) in all patients regardless of baseline ASCVD or CHF.
- Reduces progression of renal disease (45%) in all patients…
- EMPAGLIFLOZIN (Jardiance), CANAGLIFLOZIN (Invokana), DAPAGLIFLOZIN (Farxiga)

SGLT2-Inhibitors

CANVAS

N=10,142 pts Cana vs. Placebo

DM2 and High CV risk

65% established CVD, 35% primary prevention

Primary EP: MACE RRR 14%, p=0.02

Secondary EP:

***CV Death or HHF 22%**

CV Death RRR13%

***HHF RRR 33%**

***Worsening Nephropathy RRR 40%**

↑ fractures

2X ↑ amputations, esp among those with PAD

EMPA-REG OUTCOME

N=7,020 pts, Empa vs Placebo

DM2 and established CVD (99%)

Primary EP: MACE RRR 14%, p=0.04

Secondary EP:

***CV Death or HHF RRR 34%**

***CV Death RRR 38%**

***HHF RRR 35%**

***Worsening Nephropathy RRR 39%**

DECLARE TIMI 58

N=17,160 pts: Dapa vs. Placebo

DM2 and High CV risk

40% established CVD 60% Primary prevention

Primary EP: MACE RRR 7%, p=NS

Secondary EP:

***CV Death or HHF RRR 17%**

CV Death RRR 2%

***HHF RRR 27%**

***Worsening Nephropathy RRR 24%**

*P<0.05

2018 Meta-analysis

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039	1447	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**

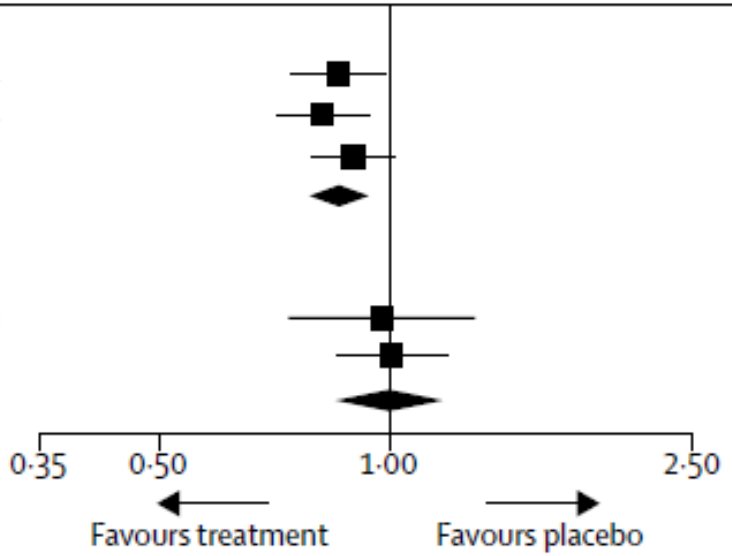


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Lancet 2019; 393: 31–39

2018 Meta-analysis

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687	2333	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756	2900	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474	3500	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039	1447	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108	5078	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**

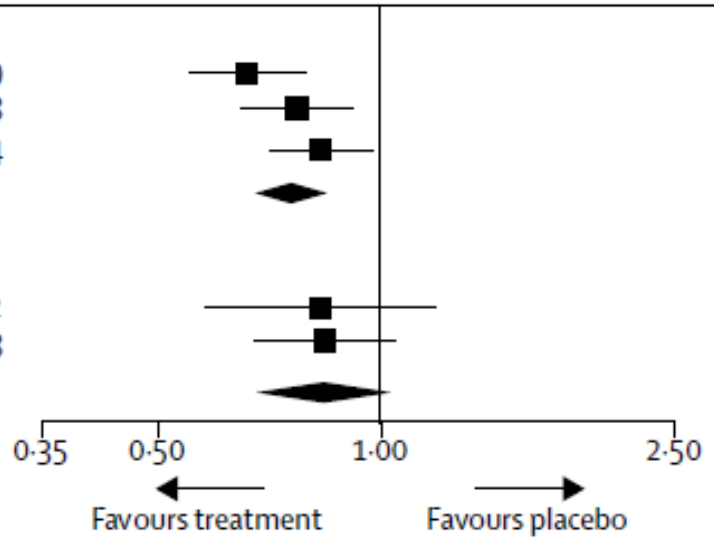


Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I^2=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I^2=0%. The p value for subgroup differences was 0·41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Lancet 2019; 393: 31–39

DAPA-HF: a dedicated CHF trial

- NEJM Sept 19, 2019
- 4744 pts, class II-IV CHF, LVEF<40%
- Receiving CHF therapies: ACEI/ARB/MRA/ BB
- DAPA vs placebo
- Primary EP= CV death or HHF or urgent HF visit

Key Baseline Characteristics

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/mL)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (mL/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)[a]	45	45

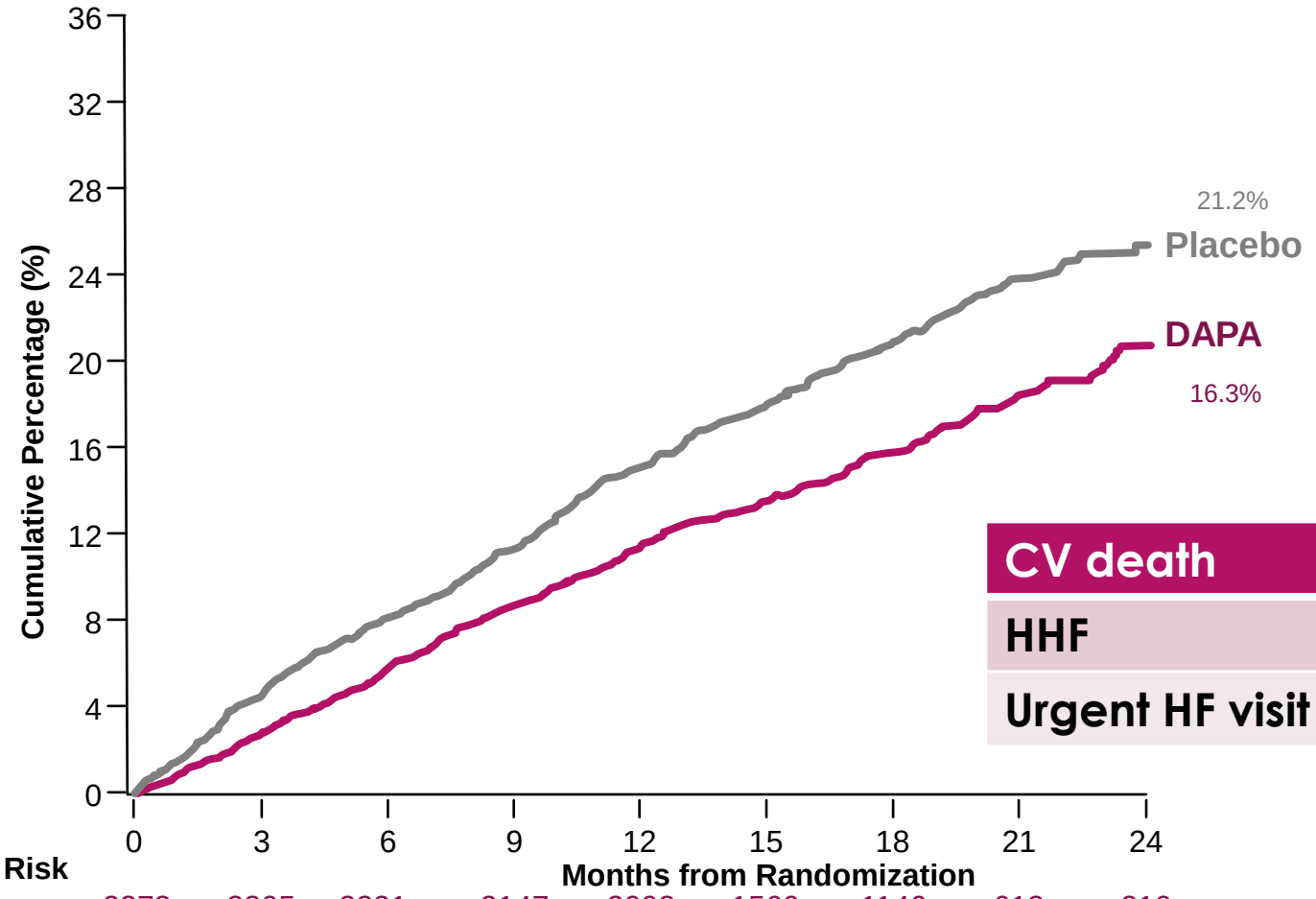
- [a] Includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol).
- McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

Baseline Treatment

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

- *ICD or CRT-D, **CRT-P or CRT-D
- ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.
- McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

Primary Endpoint: CV Death or HHF or an Urgent HF Visit[1,2]



26% RRR

HR 0.74 (0.65, 0.85)
p=0.00001

NNT = 21

CV death	18% RRR	P=0.029
HHF	30% RRR	P=<0.001
Urgent HF visit	30% RRR	P=0.00003

No. at Risk									
DAPA	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

- DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.
- 1. McMurray JJV et al. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303. Accessed September 19, 2019. 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

New agents-Final thoughts

- So SGLT2 inhibitors may be CHF drugs, in their own right!, regardless of diabetes. This may be practice altering.
- Among patients with DM2 and established CAD, the use of GLP-1 agonists or SGLT2 inhibitors must be considered in addition to glycemic control with metformin.
- Will guidelines be changed to reflect this? More **outcome-focused??**
- Changing minds takes time, will these new agents be prescribed at all?
  - Physician inertia can be huge
  - Ticagrelor example: 2009→2014-2015

Barriers to Cardiologists prescribing…

- **GLP-1 agonists**
  - Injectable medications
  - GI side effects in most patients (N/V Diarrhea)
  - Costly
- **SGLT2 Inhibitors:**
  - Genitorurinary infections (UTI, Yeast infections)
  - Increased diuretic effect of thiazides, and loop diuretics (dose adjustment is necessary)
  - ↑ DKA, and Euglycemic DKA during other illnesses
  - Sick day counselling
  - Costly
  - Fournier Gangrene (perineum-rare)
  - Increased risk of boney fractures and possible increased risk of amputations with canagliflozin

- **Prior examples: Prasugrel (prior CVA/TIA. Body weight, age), PCSK9 Inhibitors (costly, injectable, paperwork!), Entresto-low uptake, cost**

Summary

- DM/Cardiology field is exploding!
- The CHF benefits of SGLT2 inhibitors are intriguing, and currently not well understood (more than just diuresis, or BNP lowering)
- Now there are now a plethora of approaches to consider- while exciting, this can be rather confusing and daunting
- Partnerships between Cardiology-Endocrinology and Primary Care are crucial to make sure our patients are being offered best therapies.
- Societal perspective: How will our patients afford all this?