



Update on hypoglycemic agents and cardiovascular protection

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วันที่ 23 สิงหาคม 2562

จุราพร พงศ์เวชรักษ์
สาขาวิชาการบริหารทางเภสัชกรรม

ที่มาที่ไป:

ทำไมยาเบาหวาน ต้องสนใจผลของยาต่อระบบหัวใจและหลอดเลือด

การศึกษาทางคลินิกโดย Nissen และคณะ ชื่อว่า “ROSIGLITAZONE”
ทำให้เกิด CV harm

NEJM 2007; 356: 2456-71.

2008 USFDA ออกแนวปฏิบัติสำหรับผู้ทำการศึกษาทางคลินิกของยาลดน้ำตาลในเลือด ต้องพิสูจน์ว่ายามี CV safety (CardioVascular Outcome Trial, CVOT)

⇒ CV mortality, non-fatal MI, non-fatal stroke

[MACE, major adverse cardiovascular events]

ยาใหม่ หลังจากปี 2008 :

Glucagon-like peptide 1 receptor agonists (GLP1-RA):....tide

Dipeptidyl peptidase 4 inhibitors (DPP4-i):gliptin

Sodium Glucose Cotransporter 2 inhibitors (SGLT2-i):flozin

ทำความรู้จักยาเบาหวาน 3 กลุ่มใหม่ หลังปี 2008

GLP1 RA (Glucagon-like peptide one receptor agonist) และ
DPP4-i (Dipeptidyl dipeptidase 4 inhibitor)

GLP1 คือฮอร์โมนสร้างจากลำไส้ส่วนปลาย หลังเมื่อมีน้ำตาลในเลือดสูงขึ้น
ไปกระตุ้นตับอ่อนให้หลั่ง (และสร้าง) อินซูลิน และยับยั้งการหลั่งกลูคากอน
GLP1 มีค่าครึ่งชีวิต ไม่เกิน 1.5 นาที ถูกทำลายด้วย dipeptidyl
dipeptidase 4

จึงเป็นที่มาของยา: GLP1-RA ยาฉีดใต้ผิวหนัง DPP4-i ยากิน



เครดิต https://www.bmj.com/sites/default/themes/bmj/the_bmj/img/incretin-gila.jpg

SGLT2-i (Sodium glucose cotransporter 2 inhibitor)

SGLT2 เป็นโปรตีนขนส่ง อยู่ที่ renal proximal tubule

ขนส่งเอากลูโคสที่กรองผ่านไต กลับเข้าสู่กระแสเลือด ร่วมกับโซเดียม



เครดิต :<https://www.maxpixel.net/>

OUTLINE

การศึกษาต่างๆ ตั้งแต่เริ่มมีกฎเกณฑ์ให้ทำการศึกษาเกี่ยวผลลัพธ์
ต่อระบบหัวใจและหลอดเลือด ของยารักษาโรคเบาหวาน
ผลการศึกษา: Systematic review and meta-analysis
DPP4-i, GLP1-RA, SGLT2-i
Place in clinical practice for CV protective antidiabetic agents

Note for general profile of antidiabetic CVOTs

- ❑ RCT
- ❑ T2DM on standard treatment
- ❑ Study drug added on vs Placebo added on
- ❑ A1C > 7%
- ❑ With established CVD, or without CVD but multiple risks, or mixture of both
- ❑ CVD: MI, angina, stroke, PAD, excl HF
- ❑ MACE as primary outcome

Completed or ongoing CVOTs

DPP4-i:

SAVOR-TIMI 53	(2013)	(saxagliptin)	harm (HF)
EXAMINE [*]	(2015)	(alogliptin)	neutral
TECOS	(2015)	(sitagliptin)	neutral
Vildagliptin	(2015)	(vildagliptin)	neutral
CARMELINA	(2019)	(linagliptin)	neutral

GLP1-RA:

ELIXA [@]	(2015)	(lixisenatide)	neutral
LEADER	(2016)	(liraglutide)	benefit
SUSTAIN-6	(2016)	(semaglutide)	benefit
EXSCEL	(2017)	(exenatide)	neutral
HARMANY [@]	(2018)	(albiglutide)	benefit
REWIND	(2019)	(dulaglutide)	benefit
PIONEER -6	(2019)	(<u>oral</u> semaglutide)	neutral

SGLT2-i:

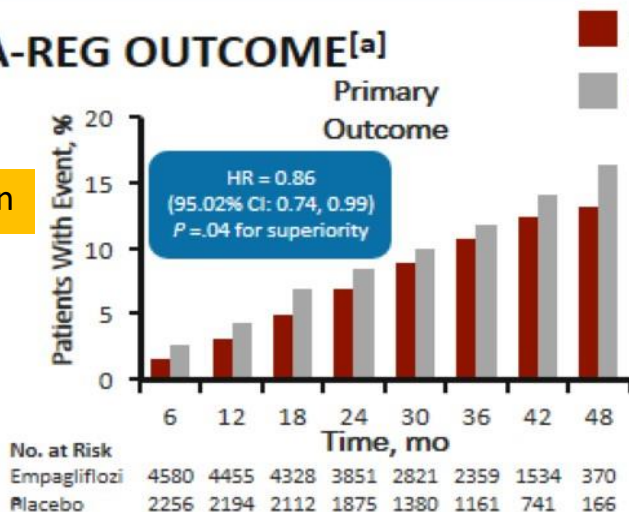
EMPAREG-OUTCOME [@]	(2016)	(empagliflozin)	benefit
CANVAS	(2017)	(canagliflozin)	benefit
DECLARE-TIMI 58 [#]	(2018)	(dapagliflozin)	benefit
VERTIS -CV	(by 2020)	(ertugliflozin)	

*

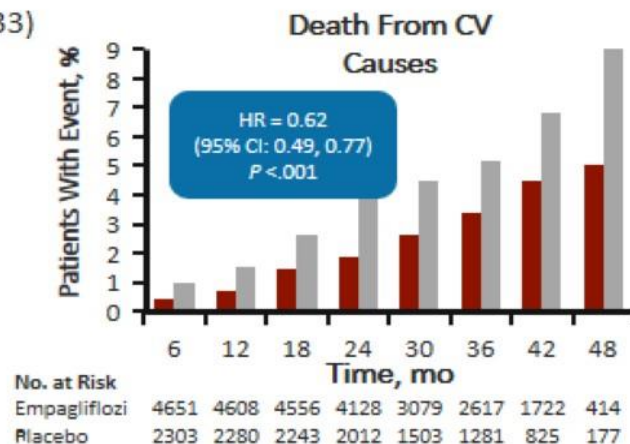
In recent acute coronary syndrome; [#]60% without CVD; [@] 100% with CVD

First Antihyperglycemic Agent to Show a CV Benefit -- Empagliflozin

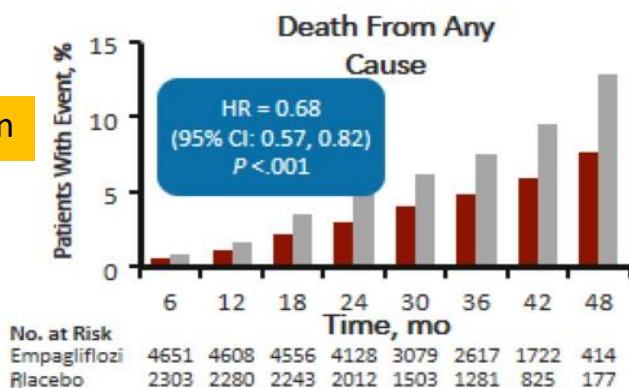
- EMPA-REG OUTCOME^[a]**



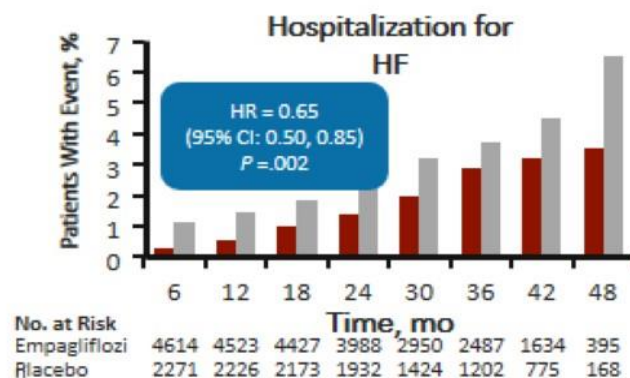
14% reduction



38% reduction



32% reduction



35% reduction

- EMPA-REG RENAL^[b]** -- incident or worsening nephropathy reduced by 39%

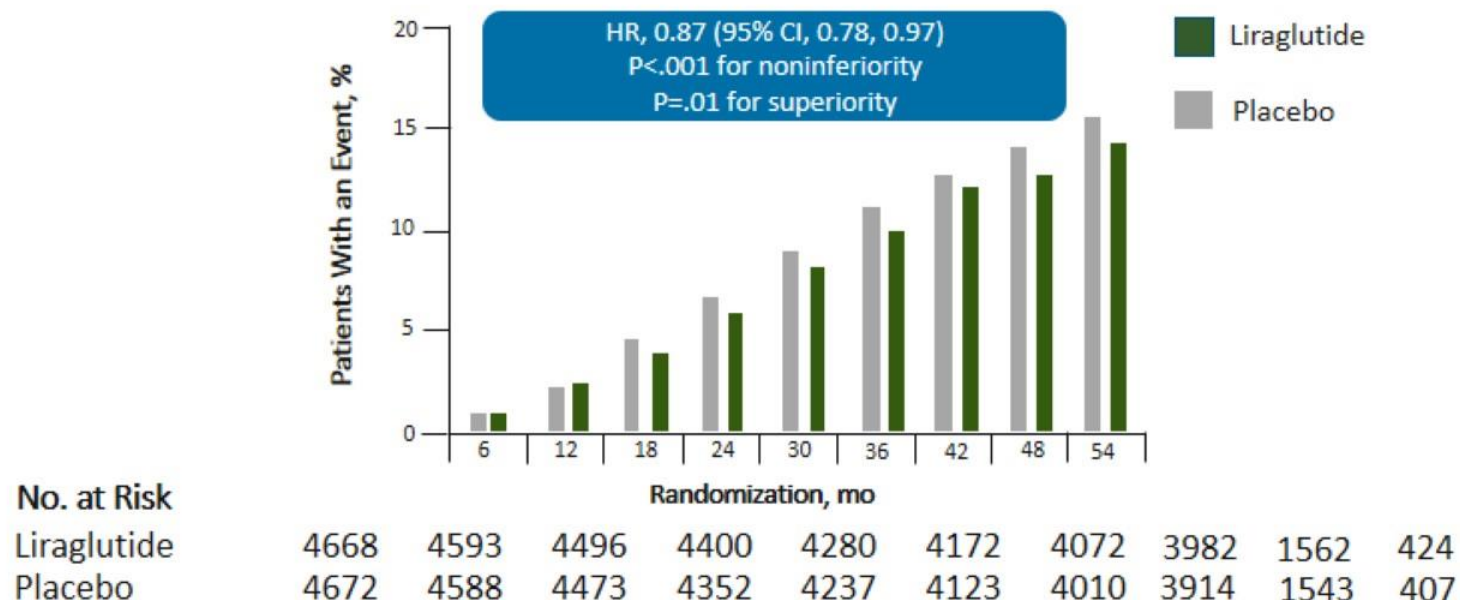
a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

b. Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

GLP-1 Receptor Agonists Have Also Shown CV Benefit

LEADER

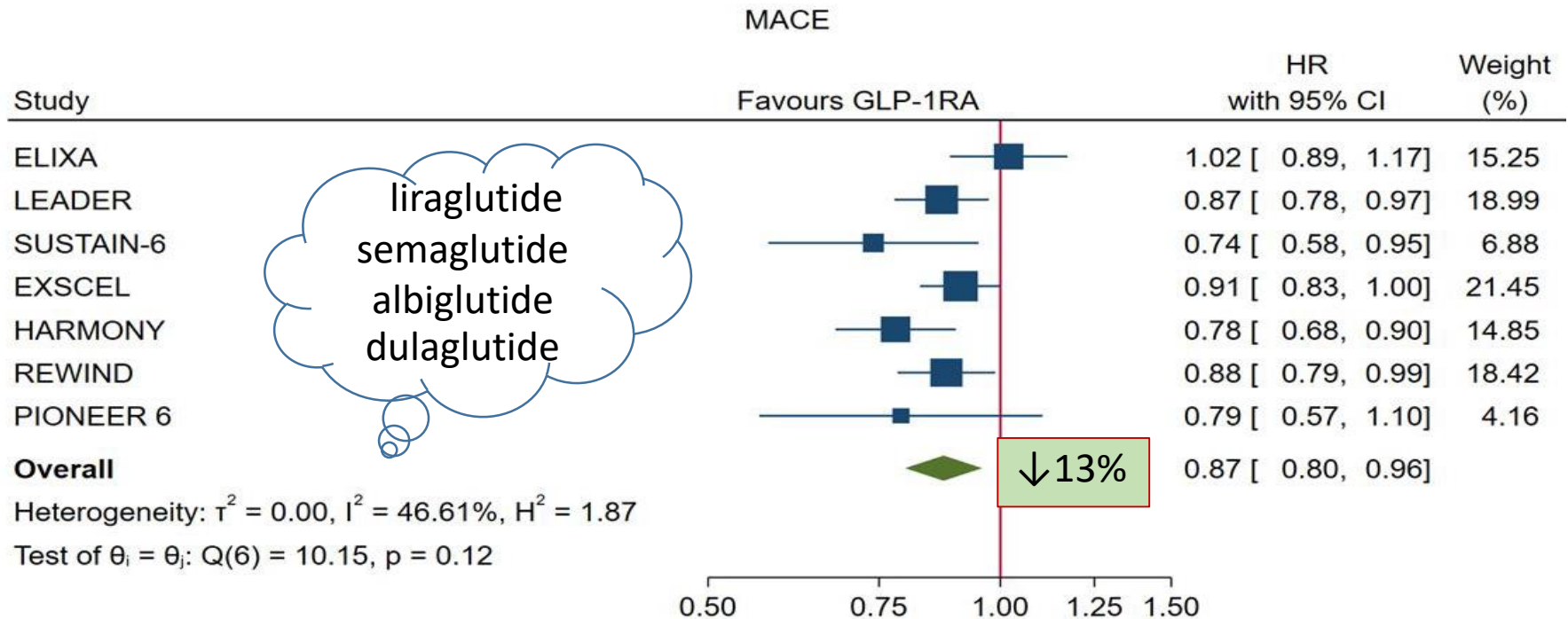
- 13% relative risk reduction in the major CV outcomes of CV death, nonfatal MI, and nonfatal stroke for those patients treated with liraglutide



80% of people had documented CVD or had important CV markers for CVD risk.

GLP1-RA
Meta-analysis of 5-7 CVOTs

Primary outcomes: MACE



GLP1-RA as a class have CV protection i.e., 13% reduction in (CV death + MI +Stroke) in T2D w/ or w/o established CVD, on standard treatment.

Primary outcomes: MACE stratified by with or without history of CVD at baseline

1: History of CVD

LEADER

SUSTAIN-6

EXSCEL

REWIND

PIONEER 6

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta_i = \theta_j$: $Q(4) = 2.90$, $p = 0.57$

2: No history of CVD

LEADER

SUSTAIN-6

EXSCEL

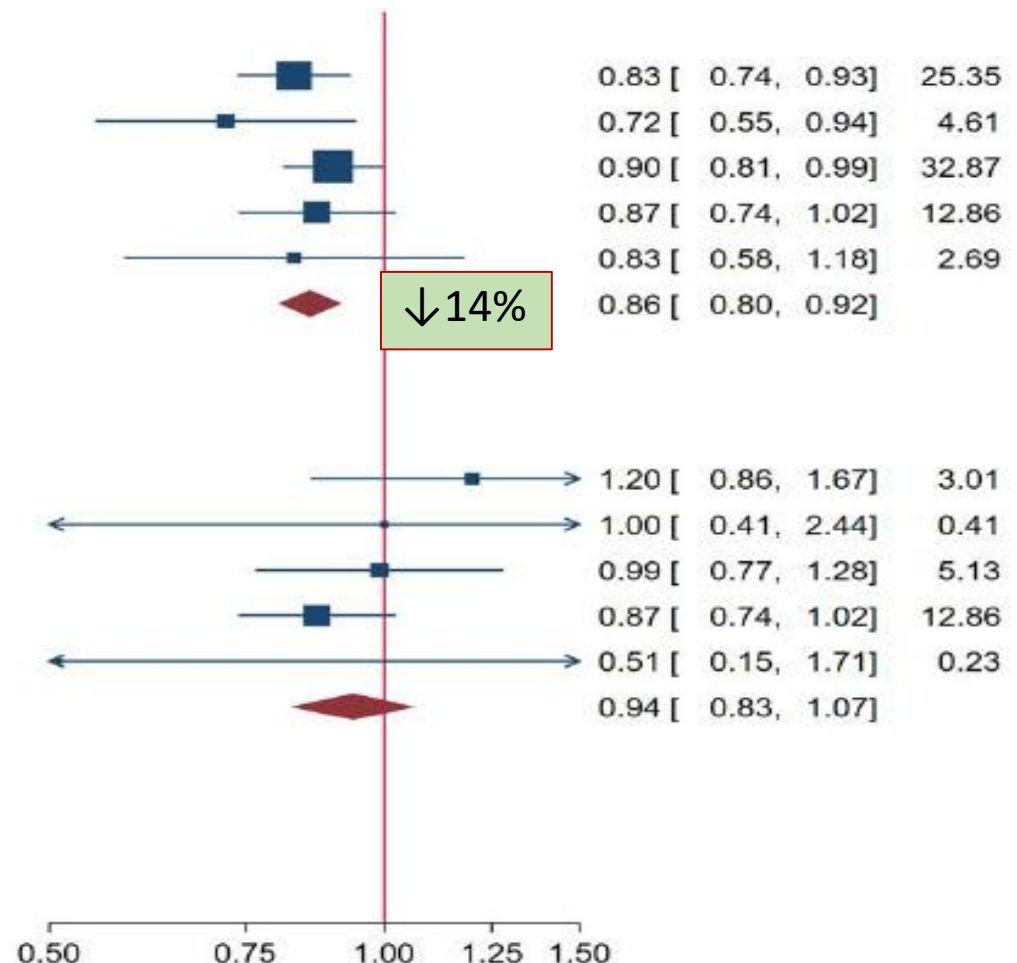
REWIND

PIONEER 6

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 2.32\%$, $H^2 = 1.02$

Test of $\theta_i = \theta_j$: $Q(4) = 4.13$, $p = 0.39$

Test of group differences: $Q_b(1) = 1.47$, $p = 0.22$



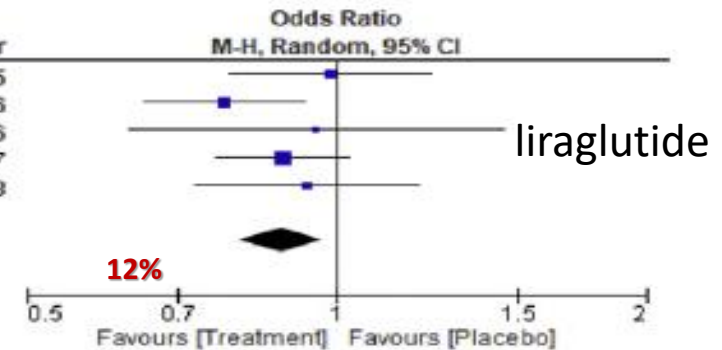
GLP1-RA as a class had CV protection i.e., 14% reduction in (CV death + MI +Stroke) in T2D w/ established, on standard treatment.

CV individual outcomes of 5 GLP1-RA CVOTs (1)

Alfayez et al. Can J Diabetes xxx (2019) 1-8. In Press

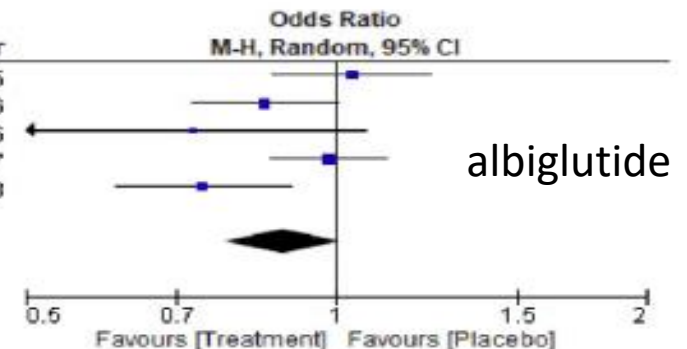
CV death

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
ELIXA 2015	156	3034	158	3034	16.7%	0.99 [0.79, 1.24]	2015
LEADER 2016	219	4668	278	4672	26.1%	0.78 [0.65, 0.93]	2016
SUSTAIN-6 2016	44	1648	46	1649	4.9%	0.96 [0.63, 1.45]	2016
EXSCEL 2017	340	7356	383	7396	38.5%	0.89 [0.76, 1.03]	2017
HARMONY 2018	122	4731	130	4732	13.8%	0.94 [0.73, 1.20]	2018
Total (95% CI)		21437		21483	100.0%	0.88 [0.80, 0.97]	
Total events	881		995				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.13$, $df = 4$ ($P = 0.54$); $I^2 = 0\%$							
Test for overall effect: $Z = 2.63$ ($P = 0.008$)							



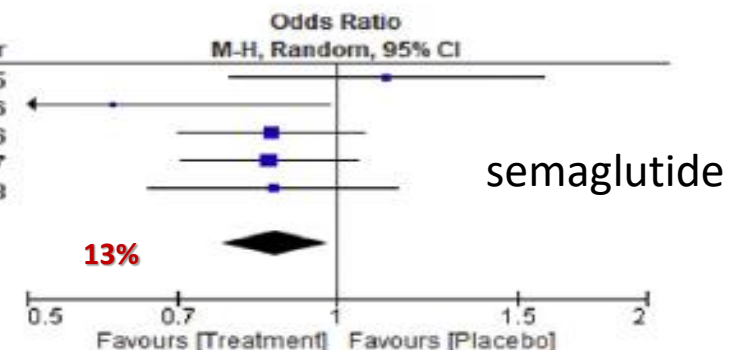
MI

Study or Subgroup	Treatment		Placebo		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
ELIXA 2015	270	3034	261	3034	21.6%	1.04 [0.87, 1.24]	2015
LEADER 2016	292	4668	339	4672	23.3%	0.85 [0.73, 1.00]	2016
SUSTAIN-6 2016	47	1648	64	1649	8.6%	0.73 [0.50, 1.07]	2016
EXSCEL 2017	483	7356	493	7396	26.8%	0.98 [0.86, 1.12]	2017
HARMONY 2018	181	4731	240	4732	19.7%	0.74 [0.61, 0.91]	2018
Total (95% CI)		21437		21483	100.0%	0.89 [0.78, 1.01]	
Total events	1273		1397				
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 9.39$, $df = 4$ ($P = 0.05$); $I^2 = 57\%$							
Test for overall effect: $Z = 1.81$ ($P = 0.07$)							



Stroke

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
ELIXA 2015	67	3034	60	3034	11.2%	1.12 [0.79, 1.59]	2015
SUSTAIN-6 2016	27	1648	44	1649	5.9%	0.81 [0.37, 0.99]	2016
LEADER 2016	173	4668	199	4672	31.2%	0.87 [0.70, 1.07]	2016
EXSCEL 2017	187	7356	218	7396	34.2%	0.86 [0.70, 1.05]	2017
HARMONY 2018	94	4731	108	4732	17.6%	0.87 [0.66, 1.15]	2018
Total (95% CI)		21437		21483	100.0%	0.87 [0.77, 0.98]	
Total events	548		629				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.10$, $df = 4$ ($P = 0.39$); $I^2 = 2\%$							
Test for overall effect: $Z = 2.30$ ($P = 0.02$)							

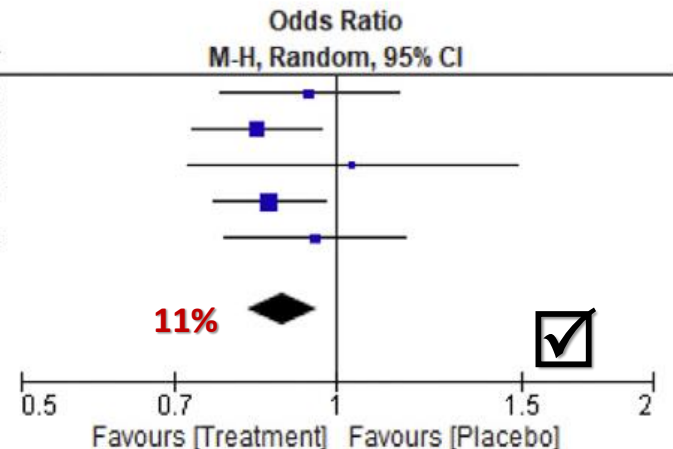


CV individual outcomes of 5 GLP1-RA CVOTs (2)

Alfayez et al. Can J Diabetes xxx (2019) 1-8. In Press

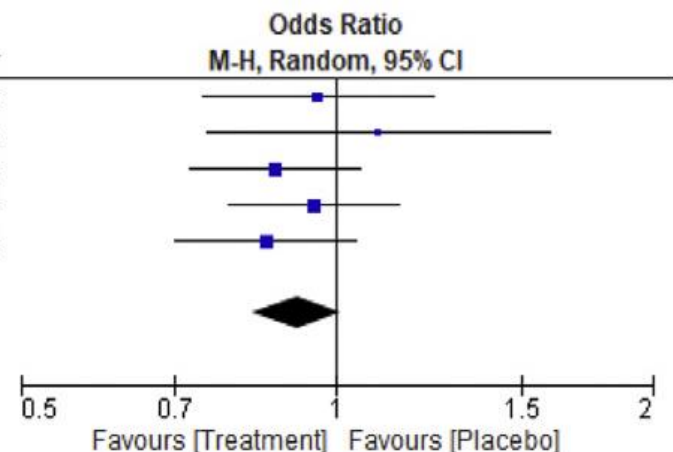
Death from any cause

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
Events	Total	Events	Total				
ELIXA 2015	211	3034	223	3034	15.1%	0.94 [0.77, 1.15]	2015
LEADER 2016	381	4668	447	4672	28.2%	0.84 [0.73, 0.97]	2016
SUSTAIN-6 2016	62	1648	60	1649	4.4%	1.04 [0.72, 1.49]	2016
EXSCEL 2017	507	7356	584	7396	37.8%	0.86 [0.76, 0.98]	2017
HARMONY 2018	196	4731	205	4732	14.4%	0.95 [0.78, 1.17]	2018
Total (95% CI)		21437		21483	100.0%	0.89 [0.82, 0.96]	
Total events	1357		1519				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.32$, $df = 4$ ($P = 0.68$); $I^2 = 0\%$							
Test for overall effect: $Z = 3.07$ ($P = 0.002$)							



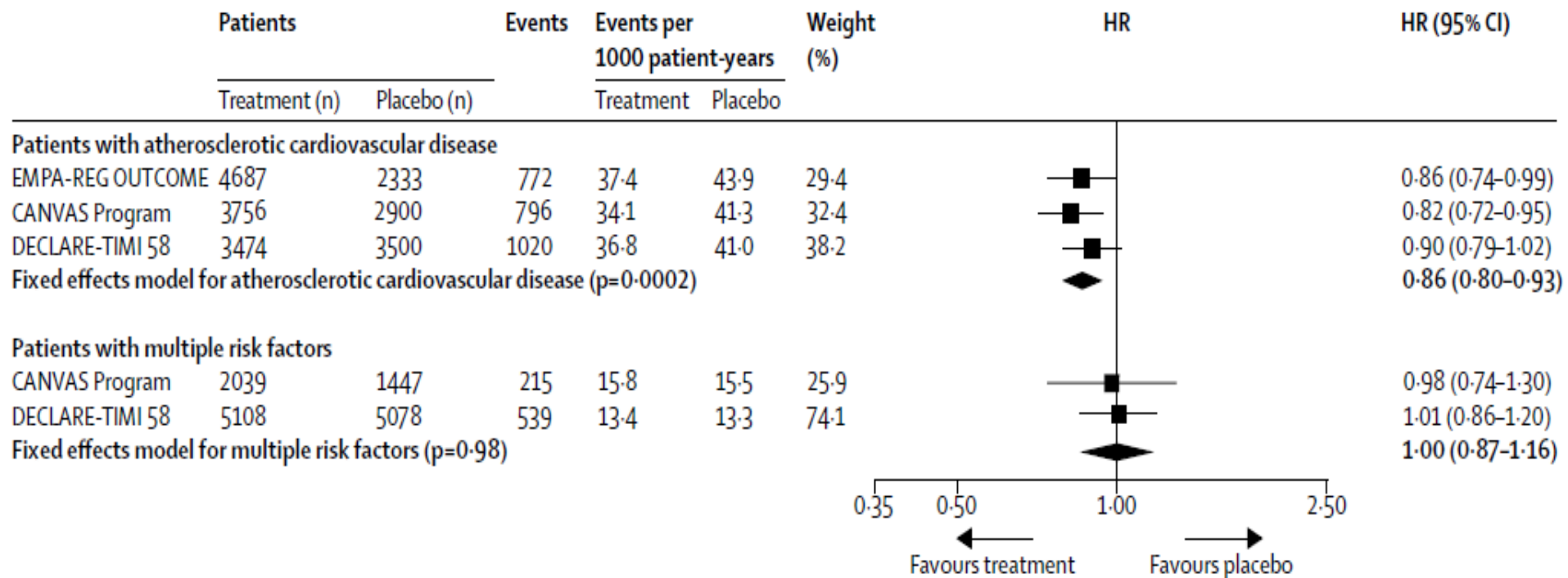
Hospitalization for HF

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
Events	Total	Events	Total				
ELIXA 2015	122	3034	127	3034	14.8%	0.96 [0.74, 1.24]	2015
SUSTAIN-6 2016	59	1648	54	1649	6.8%	1.10 [0.75, 1.60]	2016
LEADER 2016	218	4668	248	4672	27.4%	0.87 [0.73, 1.05]	2016
EXSCEL 2017	219	7356	231	7396	27.1%	0.95 [0.79, 1.15]	2017
HARMONY 2018	188	4731	218	4732	24.0%	0.86 [0.70, 1.05]	2018
Total (95% CI)		21437		21483	100.0%	0.92 [0.83, 1.01]	
Total events	806		878				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.84$, $df = 4$ ($P = 0.76$); $I^2 = 0\%$							
Test for overall effect: $Z = 1.75$ ($P = 0.08$)							



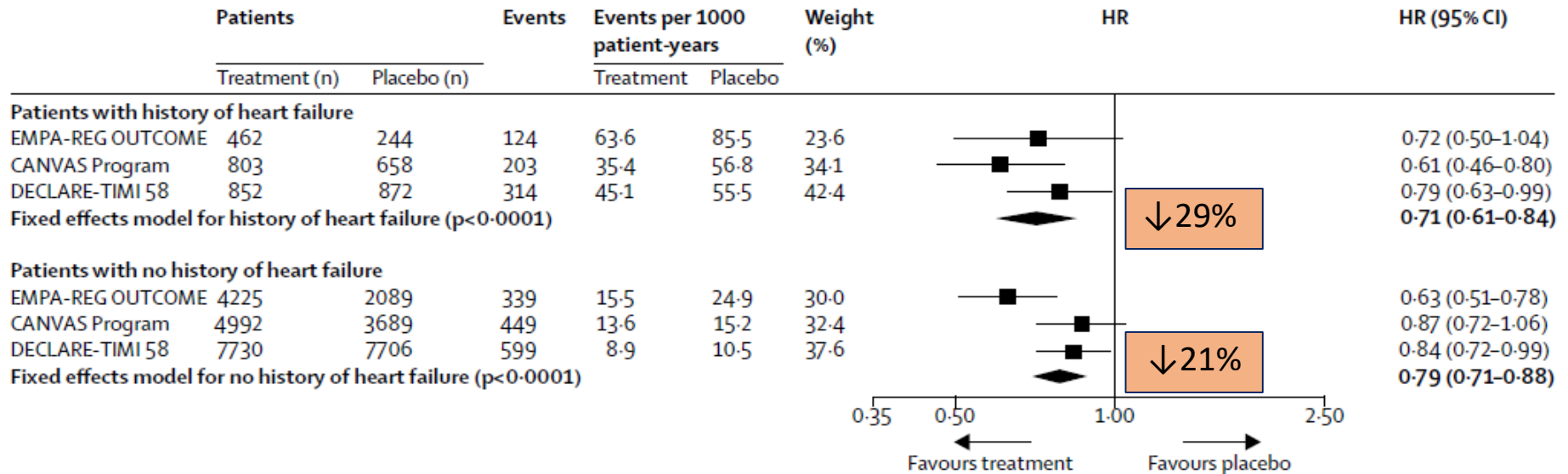
SGLT2- i Meta-analysis of 3 CVOTs

Primary outcome: MACE แยกตามการมีหรือไม่มี CVD อยู่ก่อน



SGLT2-I as a class prevented [CV death+ MI + stroke] 14% ในเบาหวานชนิดที่ 2 ที่มี CVD แล้ว แต่ไม่มีผลป้องกันสำหรับผู้ที่ยังไม่มี CVD

Secondary outcome: CV death + hospitalization for HF endpoint แยกตามการมีหรือไม่มีประวัติ HF



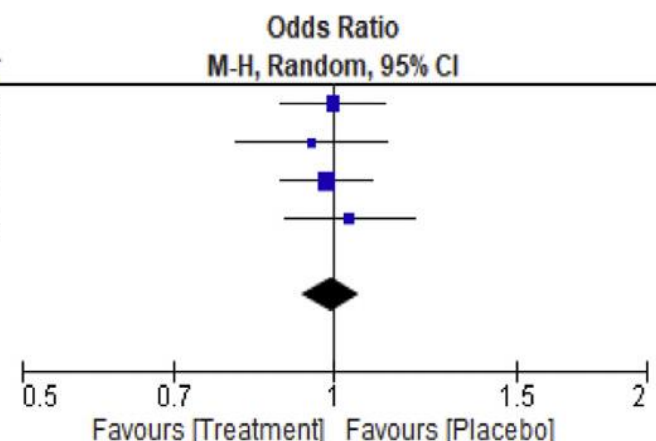
สรุป: SGLT2-i as a class prevented [CV death+ hHF] ใน
เบาหวานชนิดที่ 2 ไม่ว่าจะมึประวัติโรคหัวใจล้มเหลวมาก่อนหรือไม่
(29% and 21%)

DPP4- I

Meta-analysis of 4 CVOTs

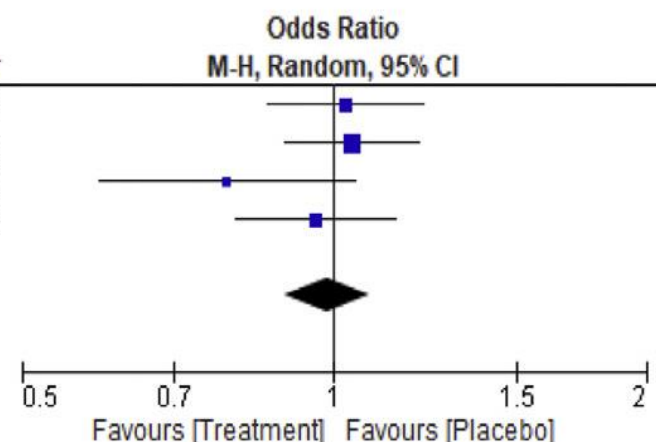
Major adverse cardiovascular events

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
SAVOR-TIMI 53 2013	613	8280	609	8212	28.8%	1.00 [0.89, 1.12]	2013
EXAMINE 2015	305	2701	316	2679	14.0%	0.95 [0.81, 1.13]	2015
TECOS 2015	839	7332	851	7339	38.1%	0.99 [0.89, 1.09]	2015
CARMELINA 2018	434	3494	420	3485	19.1%	1.04 [0.90, 1.19]	2018
Total (95% CI)		21807		21715	100.0%	0.99 [0.93, 1.06]	
Total events	2191		2196				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.60$, $df = 3$ ($P = 0.90$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.21$ ($P = 0.84$)							



Cardiovascular death

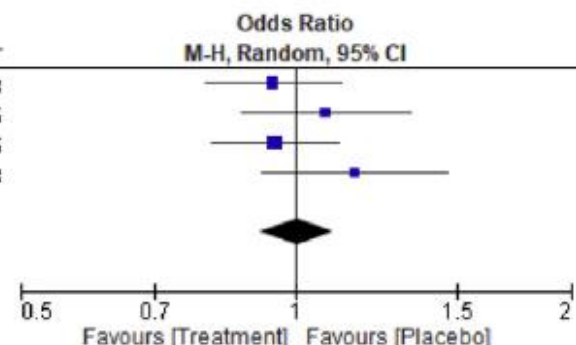
Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
SAVOR-TIMI 53 2013	269	8280	260	8212	27.2%	1.03 [0.86, 1.22]	2013
TECOS 2015	380	7332	366	7339	36.6%	1.04 [0.90, 1.21]	2015
EXAMINE 2015	89	2701	111	2679	10.6%	0.79 [0.59, 1.05]	2015
CARMELINA 2018	255	3494	264	3485	25.6%	0.96 [0.80, 1.15]	2018
Total (95% CI)		21807		21715	100.0%	0.99 [0.90, 1.08]	
Total events	993		1001				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.20$, $df = 3$ ($P = 0.36$); $I^2 = 6\%$							
Test for overall effect: $Z = 0.28$ ($P = 0.78$)							



DPP4-i as a class (and as an individual agent) did not have cardioprotective effects .

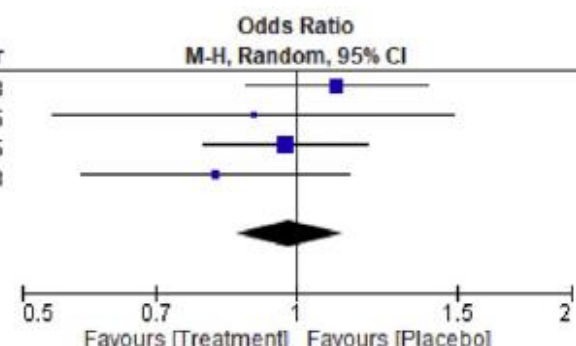
Myocardial infarction

Study or Subgroup	Treatment		Placebo		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
SAVOR-TIMI 53 2013	265	8280	278	8212	30.4%	0.94 [0.80, 1.12]	2013
EXAMINE 2015	187	2701	173	2679	19.4%	1.08 [0.87, 1.33]	2015
TECOS 2015	300	7332	316	7339	34.1%	0.95 [0.81, 1.11]	2015
CARMELINA 2018	156	3494	135	3485	16.1%	1.16 [0.92, 1.47]	2018
Total (95% CI)		21807		21715	100.0%	1.00 [0.91, 1.10]	
Total events	908		902				
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 2.85$, $df = 3$ ($P = 0.42$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.05$ ($P = 0.96$)							



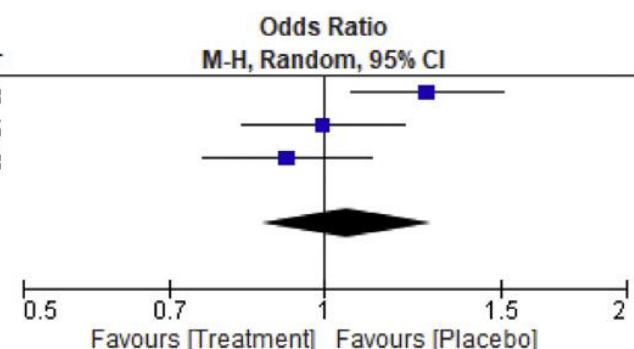
Stroke

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
SAVOR-TIMI 53 2013	157	8280	141	8212	34.8%	1.11 [0.88, 1.39]	2013
EXAMINE 2015	29	2701	32	2679	7.2%	0.90 [0.54, 1.49]	2015
TECOS 2015	178	7332	183	7339	42.0%	0.97 [0.79, 1.20]	2015
CARMELINA 2018	65	3794	73	3485	16.1%	0.81 [0.58, 1.14]	2018
Total (95% CI)		22107		21715	100.0%	0.98 [0.86, 1.13]	
Total events	429		429				
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 2.34$, $df = 3$ ($P = 0.50$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.25$ ($P = 0.80$)							



Hospitalization for heart failure

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
SAVOR-TIMI 53 2013	289	8280	228	8212	34.4%	1.27 [1.06, 1.51]	2013
TECOS 2015	228	7332	229	7339	33.3%	1.00 [0.83, 1.20]	2015
CARMELINA 2018	209	3494	226	3485	32.4%	0.92 [0.76, 1.11]	2018
Total (95% CI)		19106		19036	100.0%	1.05 [0.87, 1.28]	
Total events	726		683				
Heterogeneity: $\tau^2 = 0.02$; $\text{Chi}^2 = 6.46$, $df = 2$ ($P = 0.04$); $I^2 = 69\%$							
Test for overall effect: $Z = 0.53$ ($P = 0.60$)							



***DPP4-i as a class and as an individual agent did not reduce MI/stroke/hHF.**

***Saxagliptin increased risk of admission with HF. As a class, they tended to increase risk of hHF.**

เปรียบเทียบ 3 successful earlier CVOTs
Empagliflozin, Liraglutide, Semaglutide

Diabetes Care 2017;40:821–831

CV outcomes

Variable	EMPA-REG OUTCOME		LEADER		SUSTAIN-6	
	Empagliflozin	Placebo	Liraglutide	Placebo	Semaglutide	Placebo
<i>n</i>	4,687	2,333	4,668	4,672	1,648	1,649
Follow-up (median, years)	3.2	3.1	3.8	3.8	2.1	2.1
Primary outcome (3-point MACE)	490 (10.5%) 37.4/1,000 PY	282 (12.1%) 43.9/1,000 PY	608 (13.0%) 34/1,000 PY	694 (14.9%) 39/1,000 PY	108 (6.6%) 32.4/1,000 PY	146 (8.9%) 44.4/1,000 PY
	HR 0.86 (95% CI 0.74, 0.99)		HR 0.87 (95% CI 0.78, 0.97)		HR 0.74 (95% CI 0.58, 0.95)	
	<i>P</i> = 0.04		<i>P</i> = 0.01		<i>P</i> = 0.02	
CV death	172 (3.7%) 12.4/1,000 PY	137 (5.9%) 20.2/1,000 PY	219 (4.7%) 12/1,000 PY	278 (6.0%) 16/1,000 PY	44 (2.7%) 12.9/1,000 PY	46 (2.8%) 13.5/1,000 PY
	HR 0.62 (95% CI 0.49, 0.77)		HR 0.78 (95% CI 0.66, 0.93)		HR 0.98 (95% CI 0.65, 1.48)	
Nonfatal MI*	213 (4.5%) 16/1,000 PY	121 (5.2%) 18.5/1,000 PY	281 (6.0%) 16/1,000 PY	317 (6.8%) 18/1,000 PY	47 (2.9%) 14.0/1,000 PY	64 (3.9%) 19.2/1,000 PY
	HR 0.87 (95% CI 0.70, 1.09)		HR 0.86 (95% CI 0.73, 1.00)		HR 0.74 (95% CI 0.51, 1.08)	
Nonfatal stroke	150 (3.2%) 11.2/1,000 PY	60 (2.6%) 9.1/1,000 PY	159 (3.4%) 9/1,000 PY	177 (3.8%) 10/1,000 PY	27 (1.6%) 8/1,000 PY	44 (2.7%) 13.1/1,000 PY
	HR 1.18 (95% CI 0.89, 1.56)		HR 0.86 (95% CI 0.71, 1.06)		HR 0.61 (95% CI 0.38, 0.99)	
Key secondary outcome (4-point or expanded MACE)	599 (12.8%) 46.4/1,000 PY	333 (14.3%) 52.5/1,000 PY	948 (20.3%) 53/1,000 PY	1,062 (22.7%) 60/1,000 PY	199 (12.1%) 61.7/1,000 PY	264 (16%) 83.6/1,000 PY
	HR 0.89 (95% CI 0.78, 1.01)		HR 0.88 (95% CI 0.81, 0.96)		HR 0.74 (95% CI 0.62, 0.89)	
Hospitalization for heart failure	126 (2.7%) 9.4/1,000 PY	95 (4.1%) 14.5/1,000 PY	218 (4.7%) 12/1,000 PY	248 (5.3%) 14/1,000 PY	59 (3.6%) 17.6/1,000 PY	54 (3.3%) 16.1/1,000 PY
	HR 0.65 (95% CI 0.50, 0.85)		HR 0.87 (95% CI 0.73, 1.05)		HR 1.11 (95% CI 0.77, 1.61)	
All-cause death	269 (5.7%) 19.4/1,000 PY	194 (8.3%) 28.6/1,000 PY	381 (8.2%) 21/1,000 PY	447 (9.6%) 25/1,000 PY	62 (3.8%) 18.2/1,000 PY	60 (3.6%) 17.6/1,000 PY
	HR 0.68 (95% CI 0.57, 0.82)		HR 0.85 (95% CI 0.74, 0.97)		HR 1.05 (95% CI 0.74, 1.50)	
Hospitalization for unstable angina	133 (2.8%) 10/1,000 PY	66 (2.8%) 10/1,000 PY	122 (2.6%) 7/1,000 PY	124 (2.7%) 7/1,000 PY	22 (1.3%) 6.5/1,000 PY	27 (1.6%) 8/1,000 PY
	HR 0.99 (95% CI 0.74, 1.34)		HR 0.98 (95% CI 0.76, 1.26)		HR 0.82 (95% CI 0.47, 1.44)	

Data for incidence (%) and incidence rates per 1,000 patient-years (PY) are shown. 3-point MACE: CV death, nonfatal MI, or nonfatal stroke; 4-point MACE in EMPA-REG OUTCOME (3-point MACE or hospitalization for unstable angina); expanded MACE in LEADER (3-point MACE, coronary revascularization, or hospitalization for unstable angina or heart failure); expanded MACE in SUSTAIN-6 (3-point MACE, coronary or peripheral revascularization, or hospitalization for unstable angina or heart failure). *Silent MIs were screened and adjudicated in LEADER and SUSTAIN-6 but not in EMPA-REG OUTCOME.

Strength of evidence of CV outcomes of the 2 trials

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End point	Trial	Effect size		P value (z score)	Minimum Bayes factor	Decrease in probability of null hypothesis, %		Strength of evidence
		HR	NNT			From	To no less than	
3-point MACE	EMPA-REG OUTCOME	0.86	63	0.038 (2.02)	0.131	95	54	Moderate
						75	28	
						50	12	
	LEADER	0.87	66	0.01 (2.55)	0.038	95	42	Moderate to strong
						75	10	
						50	4	
All-cause deaths	EMPA-REG OUTCOME	0.68	39	0.0001 (3.94)	0.0006	95	0.49	Very strong
						75	0.16	
						50	0.06	
	LEADER	0.85	98	0.017 (2.39)	0.057	95	52	Moderate to strong
						75	15	
						50	5	
CV deaths	EMPA-REG OUTCOME	0.62	45	0.0001 (3.87)	0.0004	95	0.38	Very strong
						75	0.13	
						50	0.04	
	LEADER	0.78	104	0.007 (2.71)	0.024	95	31	Strong
						75	7	
						50	2	
Hospitalization for heart failure	EMPA-REG OUTCOME	0.65	71	0.0017 (2.93)	0.0137	95	11	Strong
						75	4	
						50	1	
	LEADER	0.87	NE	0.15 (1.42)	0.357	95	87	Weak
						75	52	
						50	26	

Bayes theorem: posterior odds = prior odds $\times$ evidence (Bayes factor). Bayes factor = probability (data/ H_0)/probability (data/ H_1) (likelihood ratio); H_0 = null hypothesis; H_1 = alternative hypothesis. Minimum Bayes factor = $\exp(-0.5z^2)$. Odds = probability/(1 - probability). Probability = odds/(1 + odds). NNT to prevent one event over 3 years, calculated as inverse of absolute risk difference based on Kaplan-Meier curve estimates, is only reported for

Empagliflozin is the first antidiabetic agent that was approved for the indication of reduction of CVD DEATH in T2D with existing CVD who have been treated with standard treatment (2016)

Liraglutide and **Canagliflozin** were approved for reduction of MACE (CV death+stroke+MI) in similar groups of T2D in 2017 and 2018, respectively

An ideal anti-diabetes drug

