DiabeteScan

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Impact of age at T2D diagnosis on outcomes

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ARTICLE

Impact of age at type 2 diabetes mellitus diagnosis on mortality and vascular complications: systematic review and meta-analyses

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Nanayakkara N, et al. Diabetologia 2021;64:275–87.

Research in context

What is already known about this subject?

- T2D is increasingly diagnosed at a younger age
- Pathogenesis of long-term vascular complications associated with early- or late-onset T2D is not well characterised
- Studies examining the relationship between age at diagnosis and long-term complications vary widely in population characteristics or methodological rigour, and report inconsistent findings
  - For example, younger age at diagnosis is associated with increased/decreased risk of complications, no difference in risk, or variable effects in different end organs

What is the key question?

What is the risk of mortality, macro- and microvascular complications associated with age at diagnosis of T2D?

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Aims and methods

Aims/hypothesis:

- Few studies examine the association between age at diagnosis and subsequent T2D complications
- This paper aimed to summarise the risk of mortality, macro- and microvascular complications associated with age at diagnosis

Methods:

- Data sourced from MEDLINE and evidence-based medicine databases from inception to July 2018
- Observational studies investigating effect of age on macro- and microvascular complications in T2D selected according to pre-specified criteria
- Two investigators independently extracted data and evaluated all studies

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Criteria for inclusion

1

Study of adults with T2D investigating effect of age at diagnosis on macro- and microvascular complications

2

Assess one or more of the following outcome variables:

- All-cause mortality
- Macrovascular disease
- Microvascular disease
- Retinopathy
- Nephropathy
- Neuropathy
- Cardiovascular disease
- Cerebrovascular disease
- Peripheral vascular disease

3

Have available mortality/ complication rate, where mortality was either a pre-specified primary or secondary outcome, or methods indicated complete follow-up of participants

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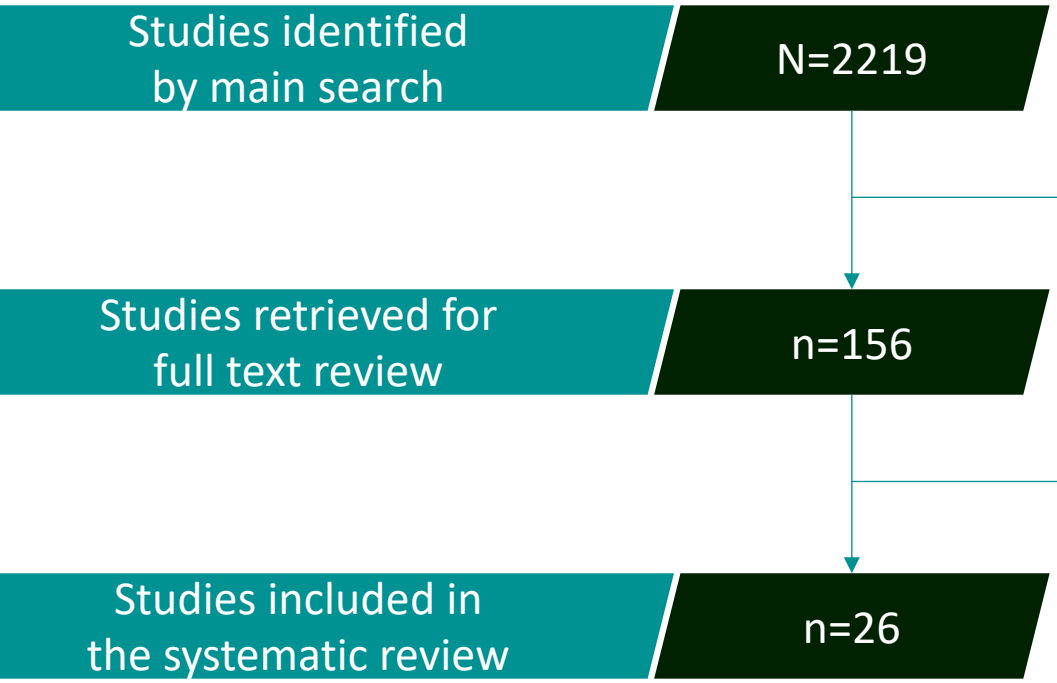
Study selection process



Studies excluded on review of title/abstract (n=2063)

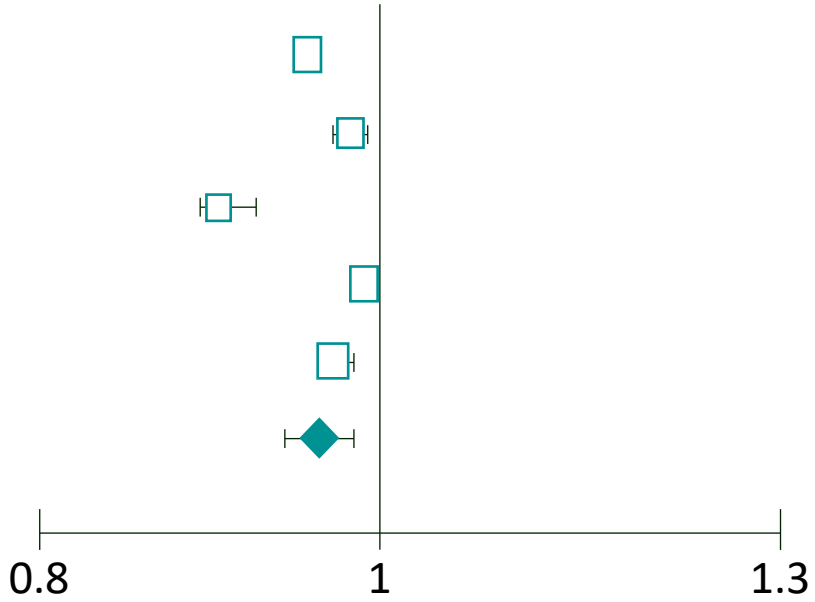
Studies excluded after review of full text (n=130)

- Data not available (7)
- Lack of complication data (13)
- Reviews, letters or editorials (17)
- Multiple articles on same dataset (6)
- Lack of age at T2D onset information (31)
- No analyses by age at T2D onset (31)
- No separate data for type 1/2 diabetes (10)
- No comparison between old and young patients (15)

Nanayakkara N, et al. Diabetologia 2021;64:275–87.

Primary outcome: All-cause mortality

All-cause mortality	OR (95% CI)	n
Huo L, et al	0.95 (0.95, 0.96)	744,188
Kenealy T, et al	0.98 (0.97, 0.99)	70,057
Pavkov ME, et al	0.90 (0.89, 0.92)	2,963
Penno G, et al	0.99 (0.99, 0.99)	15,733
Zoungas S, et al	0.97 (0.96, 0.98)	11,140
Overall (P<0.001, I^2=98%)	**0.96 (0.94, 0.99)**	**844,081**

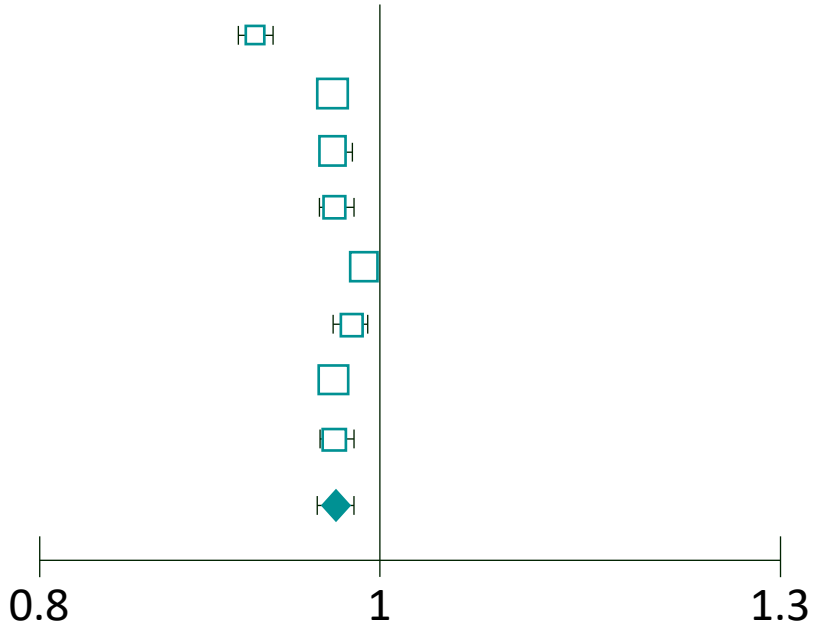


Data from 5 studies comprising 1,325,493 participants indicated that each 1-year increase in diagnosis was associated with a 4% decrease in all-cause mortality

The size of the symbols is proportional to the study weight and horizontal lines represent 95% CIs.
Nanayakkara N, et al. Diabetologia 2021;64:275–87.

Primary outcome: Macrovascular disease

Macrovascular disease	OR (95% CI)	n
Chan JC, et al	0.92 (0.91, 0.93)	9,506
Huo X, et al	0.97 (0.97, 0.97)	222,770
Kenealy T, et al	0.97 (0.97, 0.98)	48,444
Nanayakkara N, et al	0.97 (0.96, 0.98)	3,029
Pugliese G, et al	0.99 (0.98, 0.99)	15,933
Song SH, et al	0.98 (0.97, 0.99)	2,733
Yeung RO, et al	0.97 (0.97, 0.97)	42,453
Zoungas S, et al	0.97 (0.96, 0.98)	11,140
Overall (P<0.001, I^2=97%)	**0.97 (0.96, 0.98)**	**356,008**



Data from 8 studies comprising 566,011 participants indicated that each 1-year increase in diagnosis was associated with a 3% decrease in macrovascular disease

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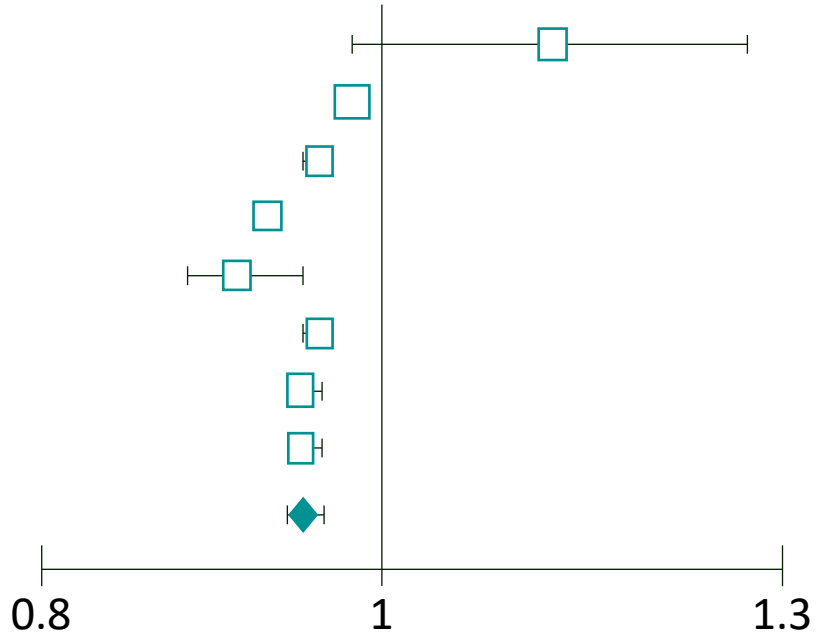
Nanayakkara N, et al. Diabetologia 2021;64:275–87.

Primary outcome: Microvascular disease

Microvascular disease	OR (95% CI)	n
Amutha A, et al	1.12 (0.98, 1.27)	90
Chan JC, et al	0.98 (0.97, 0.99)	9,506
Kenealy T, et al	0.96 (0.95, 0.96)	65,547
Nanakkara N, et al	0.93 (0.92, 0.93)	3,033
Pradeepa R, et al	0.91 (0.88, 0.95)	1,608
Pugliese G, et al	0.96 (0.95, 0.96)	15,733
Yeung RO, et al	0.95 (0.95, 0.96)	42,453
Zoungas S, et al	0.95 (0.94, 0.96)	11,140
Overall (P<0.001, I^2=93%)	**0.95 (0.94, 0.96)**	**149,110**



Data from 8 studies comprising 149,110 participants indicated that each 1-year increase in diagnosis was associated with a 5% decrease in microvascular disease

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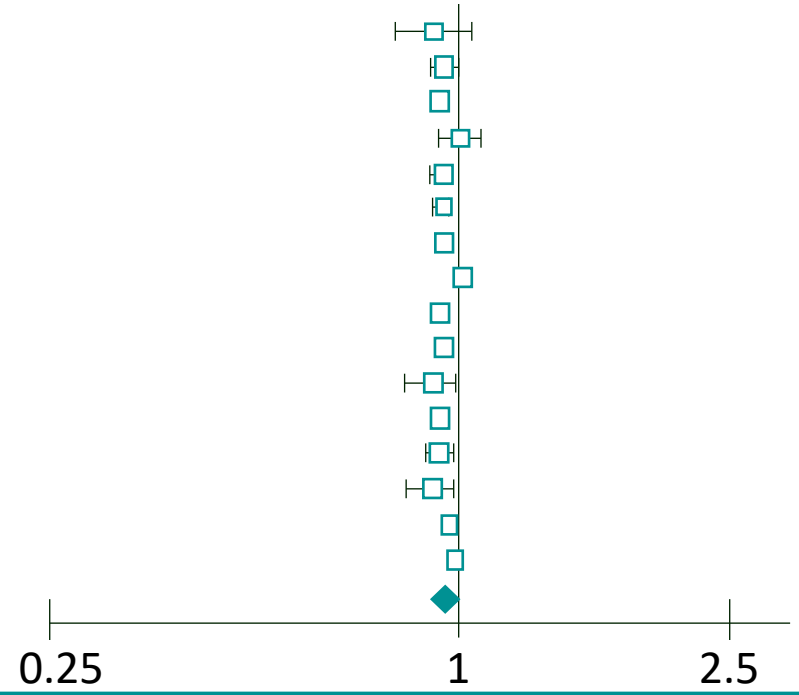
Nanayakkara N, et al. Diabetologia 2021;64:275–87.

Secondary outcomes: Retinopathy

Retinopathy	OR (95% CI)	n
Amutha A, et al	0.87 (0.71, 1.07)	90
Amutha A, et al	0.91 (0.85, 0.98)	743
Cai X, et al	0.90 (0.88, 0.91)	3,100
Chen MS, et al	0.99 (0.89, 1.10)	527
Huo X, et al	0.91 (0.86, 0.95)	222,770
Kenealy T, et al	0.91 (0.86, 0.96)	67,739
Nanayakkara N, et al	0.92 (0.91, 0.93)	3,261
Pugliese G, et al	1.01 (1.00, 1.03)	15,933
Rema M, et al	0.90 (0.88, 0.92)	1,715
Romera-Aroca P, et al	0.91 (0.89, 0.94)	15,030
Song SH, Gray TA	0.86 (0.75, 0.98)	2,516
Thomas RL, et al	0.90 (0.90, 0.90)	152,156
Unnikrishnan R, et al: Older onset	0.89 (0.83, 0.95)	240
Unnikrishnan R, et al: Younger onset	0.86 (0.75, 0.98)	177
Wong J, et al	0.94 (0.93, 0.95)	1,476
Zoungas S, et al	0.97 (0.96, 0.98)	11,140
Overall (P<0.001, I^2=97%)	**0.92 (0.90, 0.95)**	**498,613**

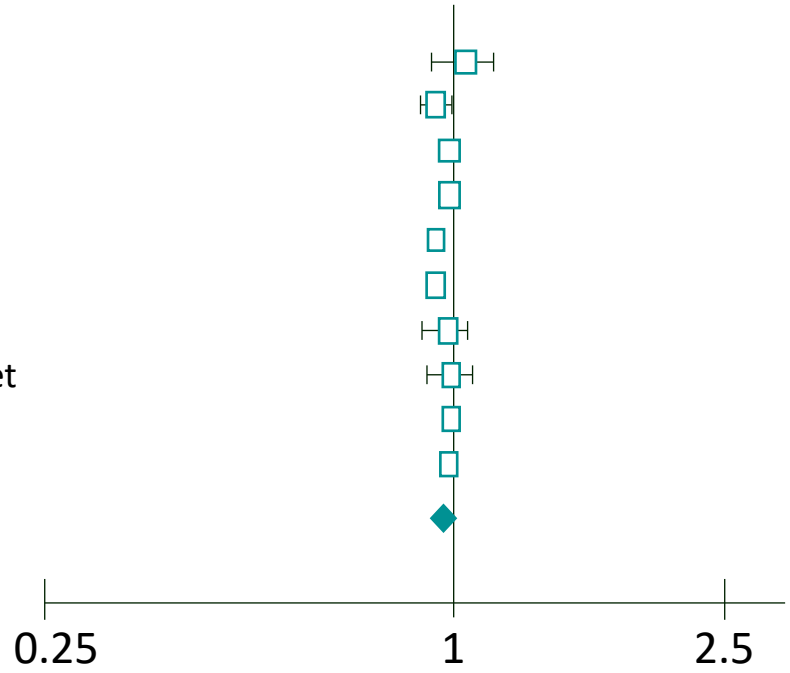


Each 1-year increase in diagnosis was associated with a 8% decrease in retinopathy

The size of the symbols is proportional to the study weight and horizontal lines represent 95% CIs.
For Unnikrishnan R, et al., older onset refers to those diagnosed aged >50 years and younger onset refers to those diagnosed aged ≤25 years.
Nanayakkara N, et al. Diabetologia 2021;64:275–87.

Secondary outcomes: Nephropathy

Nephropathy	OR (95% CI)	n
Amutha A, et al	1.04 (0.88, 1.22)	90
Amutha A, et al	0.89 (0.83, 0.96)	840
Kenealy T, et al	0.96 (0.95, 0.96)	66,128
Nanayakkara N, et al	0.95 (0.94, 0.97)	2,970
Pavkov ME, et al	0.90 (0.88, 0.91)	2,726
Romera-Aroca P, et al	0.90 (0.89, 0.92)	15,030
Unnikrishnan R, et al: Older onset	0.95 (0.85, 1.06)	267
Unnikrishnan R, et al: Younger onset	0.97 (0.87, 1.08)	173
Unnikrishnan R, Rema M, et al	0.97 (0.95, 0.99)	267
Zoungas S, et al	0.96 (0.95, 0.97)	11,140
Overall (P<0.001, I^2=92%)	**0.94 (0.92, 0.96)**	**99,631**



Each 1-year increase in diagnosis was associated with a 6% decrease in nephropathy

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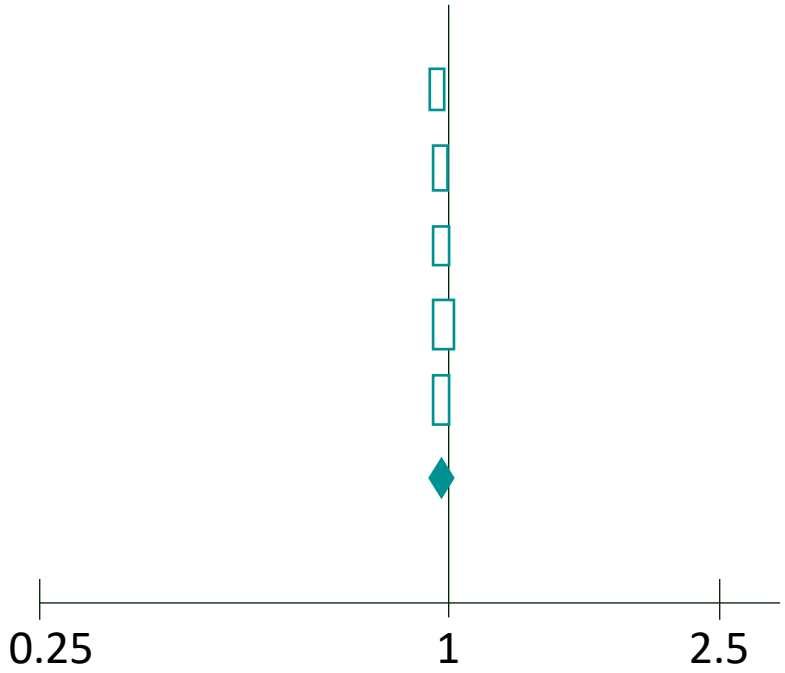
Secondary outcomes: Coronary heart disease

CHF	OR (95% CI)	n
Kenealy T, et al	0.97 (0.96, 0.98)	59,228
Nanayakkara N, et al	0.98 (0.97, 0.99)	3,037
Pugliese G, et al	0.98 (0.97, 0.98)	15,733
Song SH, et al	0.99 (0.97, 0.99)	2,733
Zoungas S, et al	0.98 (0.97, 0.99)	11,140
Overall (P<0.001, I^2=54%)	**0.98 (0.97, 0.98)**	**91,871**



Each 1-year increase in diagnosis was associated with a 2% decrease in coronary heart disease

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Results

26 observational studies | 1,325,493 individuals | from **30** countries

- Random-effects meta-analyses with inverse variance weighting used to obtain pooled ORs
- Age at T2D diagnosis was inversely associated with risk of all-cause mortality and macro- and microvascular disease (all P<0.001)
- Each 1-year increase in age at T2D diagnosis was associated with a 4%, 3% and 5% decreased risk of all-cause mortality, macro- and microvascular disease, respectively, adjusted for current age
  - Effects were consistent for individual components of composite outcomes (all P<0.001)
- Younger age at T2D diagnosis was associated with higher risk of mortality and vascular disease

Early and sustained interventions to delay T2D onset and improve blood glucose levels and cardiovascular risk profiles of those already diagnosed are essential to reduce morbidity and mortality

Nanayakkara N, et al. Diabetologia 2021;64:275–87.

How might this impact clinical practice?

Identification and quantification of the higher risk of mortality and vascular disease conferred by younger age at T2D diagnosis may enable risk stratification of people early in the condition

Providing greater opportunities for interventions to reduce the risk of adverse outcomes

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Baseline use of metformin in CVOTs

DPP-4i	% on MF
EXAMINE (Alogliptin)	**66.2**
SAVOR-TIMIS3 (Saxagliptin)	**69.6**
TECOS (Sitagliptin)	**81.6**
CARMELINA (Linagliptin)	***56.1**

CVOT, cardiovascular outcome trial.

Harrington JL, et al. Curr Diab Rep 2018:18(9):64.

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SGLT-2i	% on MF
EMPA-REG (Empagliflozin)	**74**
CANVAS Programme (Canagliflozin)	**77**
DECLARE (Dapagliflozin)	**82**
CREDENCE (Canagliflozin)	***58**
VERTIS CV (Ertugliflozin)	**76**

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CREDENCE (Canagliflozin)	***58**
VERTIS CV (Ertugliflozin)	**76**

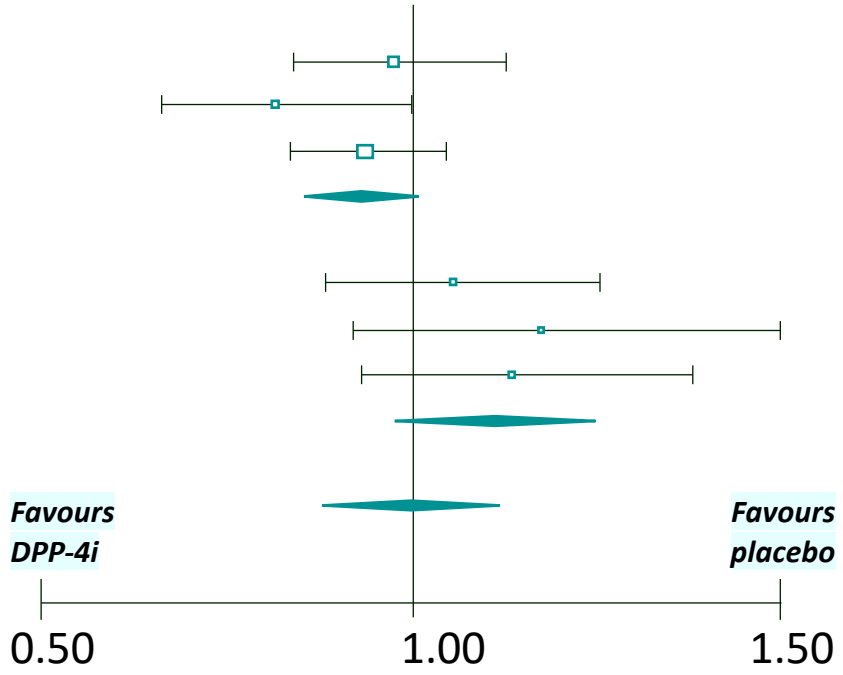
GLP-1RA	% on MF
ELIXA (Lixisenatide)	**65**
LEADER (Liraglutide)	**76**
SUSTAIN 6 (Semaglutide)	**74**
EXSCEL (Exenatide)	**85**
HARMONY (Albiglutide)	**74**
REWIND (Dulagludite)	**81**
PIONEER 6 (Oral Semaglutide)	**77**

CVOT, cardiovascular outcome trial.

Harrington JL, et al. Curr Diab Rep 2018:18(9):64.

Metformin may moderate the effect of DPP-4i on CV outcomes

Study	Metformin	N	Weight	HR (95% CI)
Scirica et al	Yes	11,473	19.89%	0.97 (0.84, 1.13)
White et al	Yes	3,568	13.35%	0.81 (0.66, 1.00)
Green et al	Yes	11,966	25.32%	0.93 (0.83, 1.04)
Summary (I^2=0.0%, Q=2.0, P=0.37)				**0.92 (0.84, 1.01)**
Scirica et al	No	5,019	16.53%	1.05 (0.88, 1.25)
White et al	No	1.812	10.62%	1.17 (0.92, 1.49)
Green et al	No	2,705	14.29%	1.13 (0.93, 1.38)
Summary (I^2=0.0%, Q=0.6, P=0.75)				**1.10 (0.97, 1.26)**
Overall summary **I^2=42.5%, Q=8.7, P=0.12**			**100.00%**	**0.99 (0.87, 1.13)**



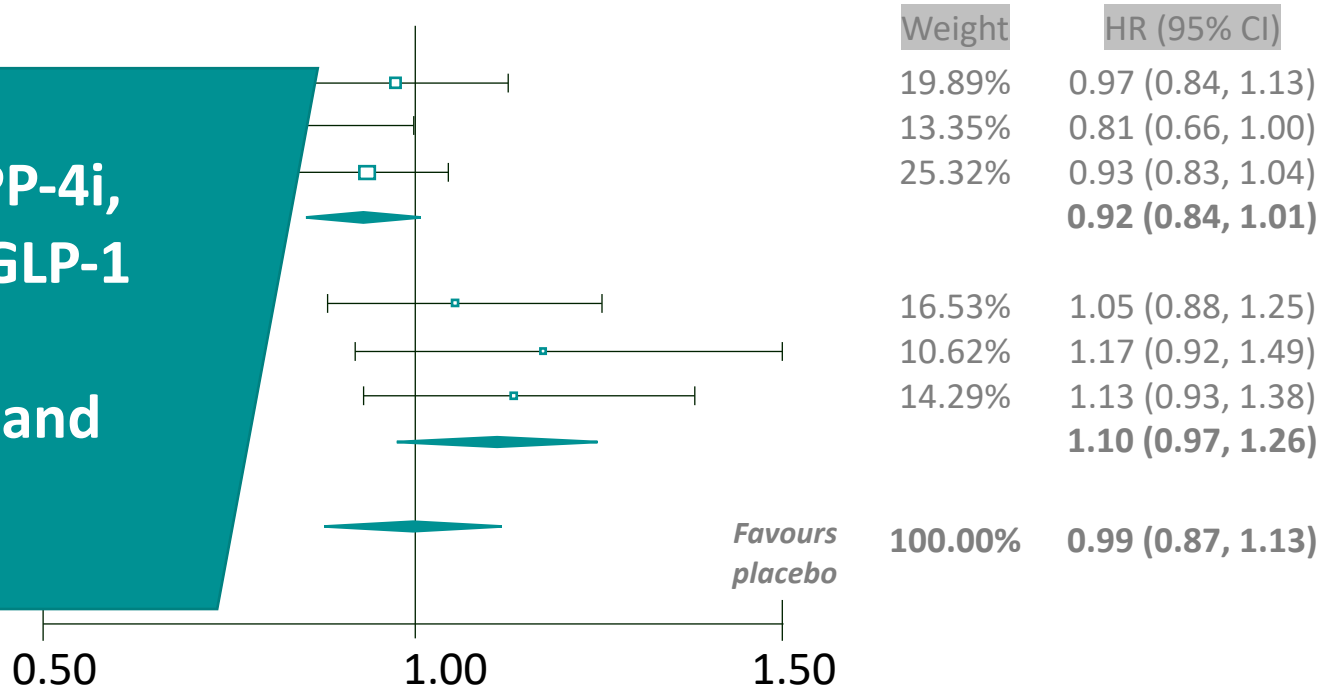
Using meta-regression, the difference in overall DPP-4i effect between prevalent metformin users and baseline nonusers was statistically significant (P=0.036), indicating a difference in the relative effects of DPP-4i based on metformin status

Crowley MJ, et al. Diabetes Care 2017:40;1787–9; Dore FJ, et al. Cardiovas Diabetol 2018;17:65.

Metformin may moderate the effect of DPP-4i on CV outcomes

Metformin raises GLP-1, DPP-4i, and blocks degradation of GLP-1

Synergistic effect of DPP-4i and metformin on CD34+ EPCs



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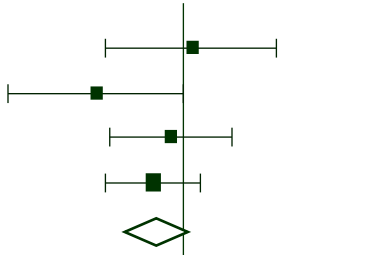
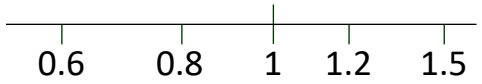
Individual and pooled RCT results for the primary outcome, stratified by metformin use at baseline

			HR (95% CI)
DPP-4i	Metformin	CARMELINA	1.02 (0.83, 1.25)
		EXAMINE	0.81 (0.66, 1.00)
		SAVOR-TIMI-53	0.97 (0.84, 1.13)
		TECOS	0.93 (0.83, 1.04)
			0.94 (0.87, 1.01)





Zaccardi F, et al. Diabetes Care 2020;dc202080.

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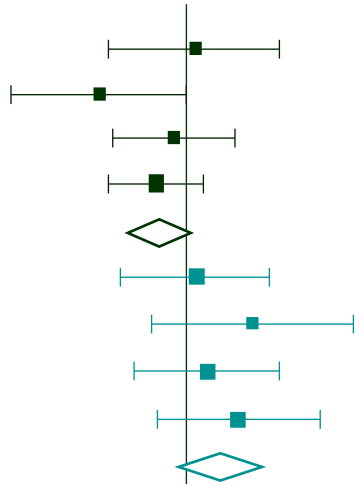
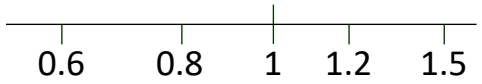
			0.94 (0.87, 1.01)
	No metformin	CARMELINA	1.02 (0.85, 1.22)
		EXAMINE	1.17 (0.92, 1.49)
		SAVOR-TIMI-53	1.05 (0.88, 1.25)
		TECOS	1.13 (0.93, 1.38)
			1.08 (0.98, 1.19)





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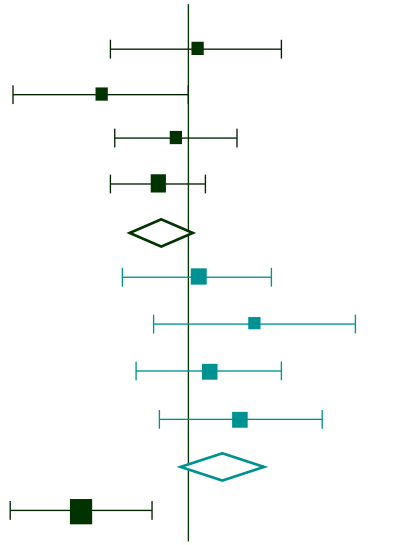
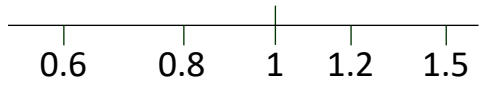
		TECOS	1.13 (0.93, 1.38)
			1.08 (0.98, 1.19)
GLP-1RA	Metformin	HARMONY-OUTCOMES	0.77 (0.65, 0.92)





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		TECOS	0.93 (0.83, 1.04)
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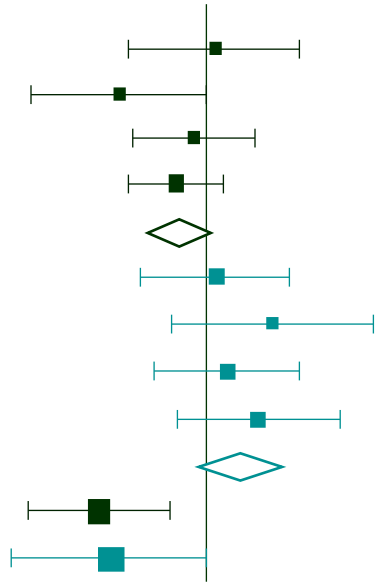
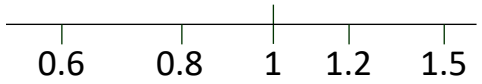
	No metformin	CARMELINA	1.02 (0.85, 1.22)
		EXAMINE	1.17 (0.92, 1.49)
		SAVOR-TIMI-53	1.05 (0.88, 1.25)
		TECOS	1.13 (0.93, 1.38)
			1.08 (0.98, 1.19)
GLP-1RA	Metformin	HARMONY-OUTCOMES	0.77 (0.65, 0.92)
	No metformin	HARMONY-OUTCOMES	0.79 (0.62, 1.00)





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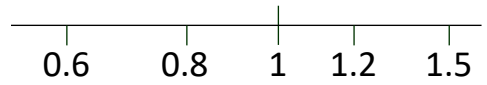
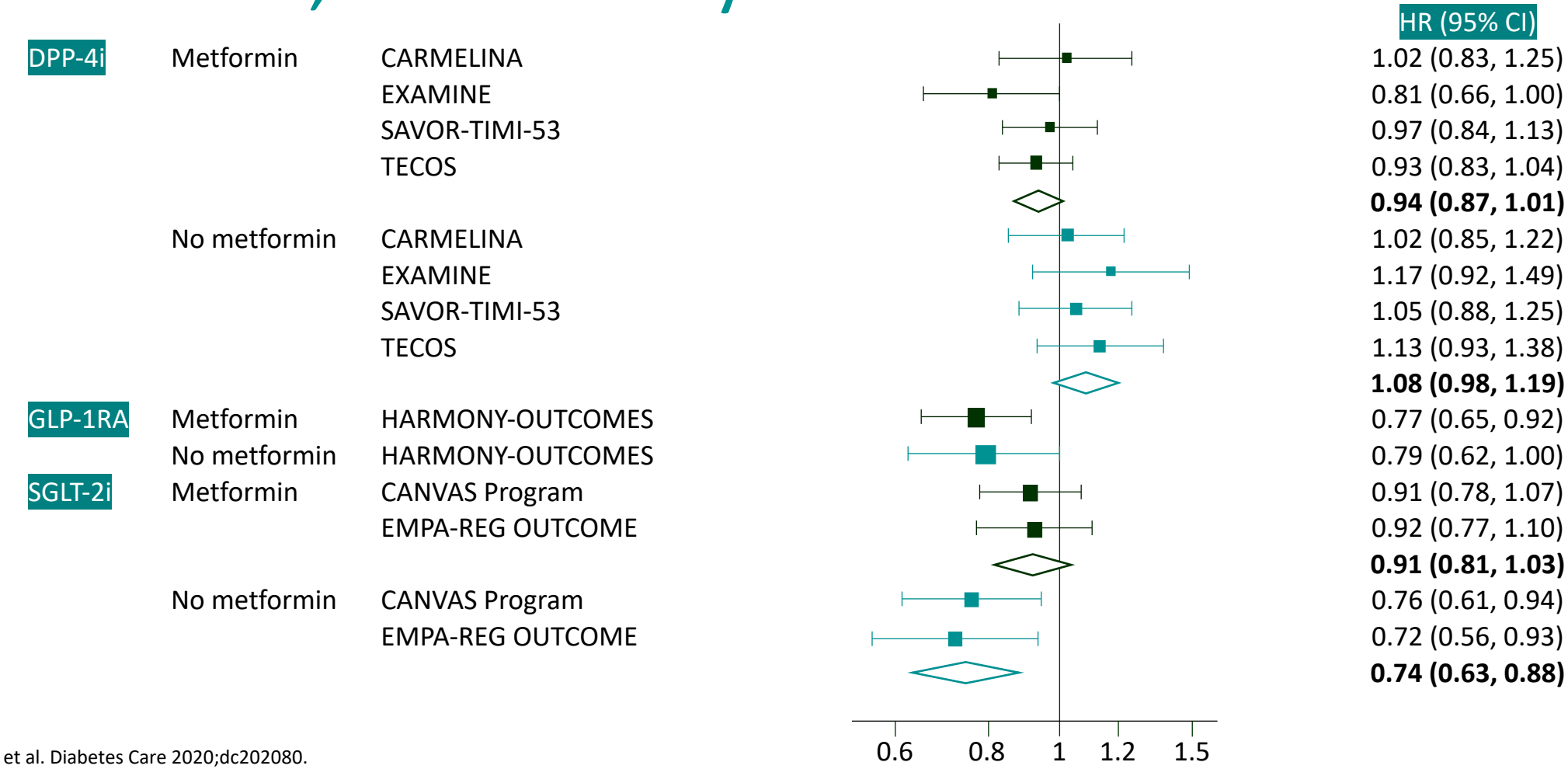
DPP-4i	Metformin	CARMELINA	1.02 (0.83, 1.25)
		EXAMINE	0.81 (0.66, 1.00)
		SAVOR-TIMI-53	0.97 (0.84, 1.13)
		TECOS	0.93 (0.83, 1.04)
			0.94 (0.87, 1.01)
	No metformin	CARMELINA	1.02 (0.85, 1.22)
		EXAMINE	1.17 (0.92, 1.49)
		SAVOR-TIMI-53	1.05 (0.88, 1.25)
		TECOS	1.13 (0.93, 1.38)
			1.08 (0.98, 1.19)
GLP-1RA	Metformin	HARMONY-OUTCOMES	0.77 (0.65, 0.92)
	No metformin	HARMONY-OUTCOMES	0.79 (0.62, 1.00)
SGLT-2i	Metformin	CANVAS Program	0.91 (0.78, 1.07)
		EMPA-REG OUTCOME	0.92 (0.77, 1.10)
			0.91 (0.81, 1.03)



Zaccardi F, et al. Diabetes Care 2020;dc202080.

Individual and pooled RCT results for the primary outcome, stratified by metformin use at baseline



Zaccardi F, et al. Diabetes Care 2020;dc202080.

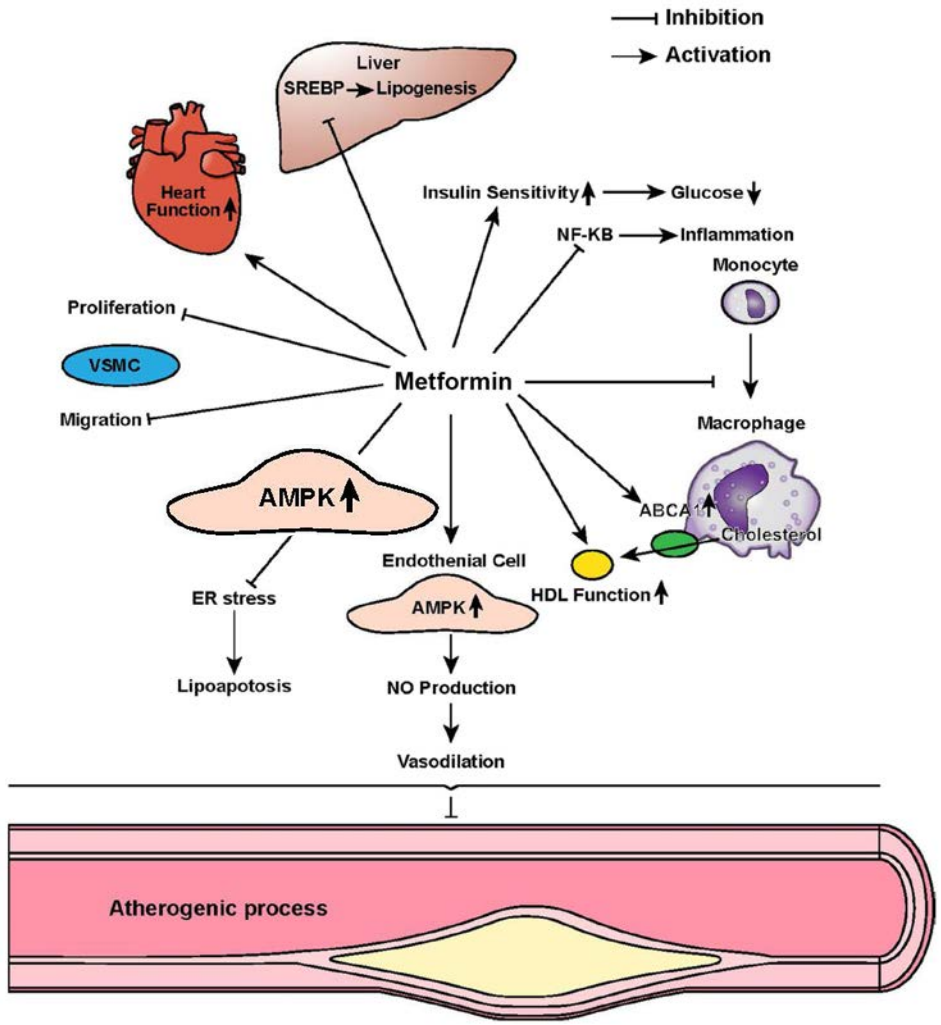
Potential interaction between metformin and SGLT-2i

Metformin stimulates AMPK (master regulator of genes)

- Protects heart from injury
- Activation of AMPK thought to be mechanism MF ameliorates cardiomyopathy in animal models but ? sufficient to expect cardio-protective effects

SGLT-2i via Sirtuin-1 (SIRT1)

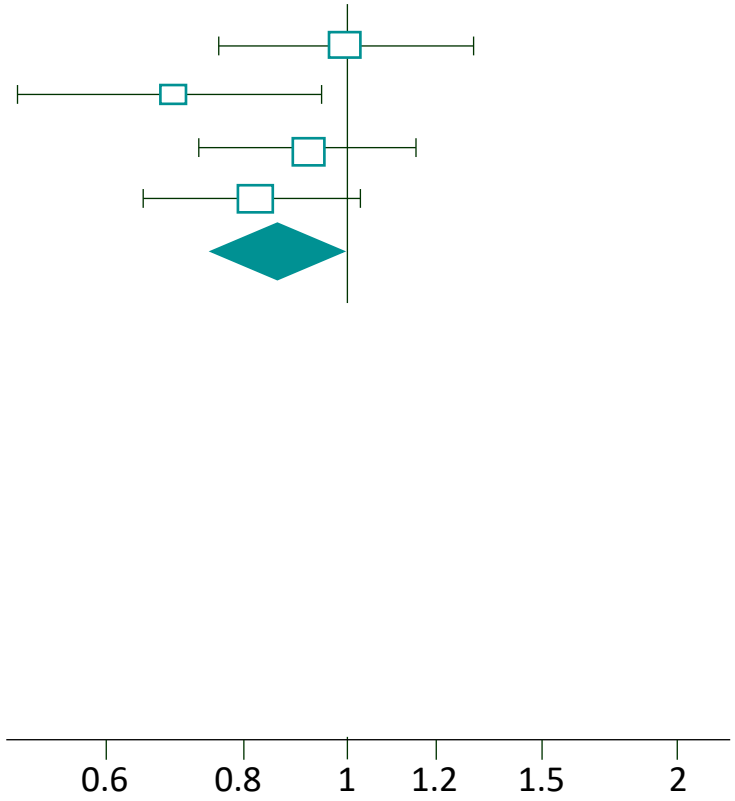
- Roles of AMPK/SIRT1 intertwined
- ? If AMPK already activated by metformin then cardio-protective effects dependent on SGLT-2i maybe attenuated



Luo F, et al. Cardiovasc Diabetol 2019;18(1):54; Packer M. AM Journal of Medicine 2020.

Interaction by baseline metformin for MACE

		HR_{met}/HR_{nomet}
DPP-4i	CARMELINA	1.00 (0.76, 1.31)
	EXAMINE	0.69 (0.50, 0.95)
	SAVOR-TIMI-53	0.92 (0.73, 1.16)
	TECOS	0.82 (0.66, 1.03)



HR_{met}/HR_{nomet} indicates the ratio between HR in participants with baseline metformin versus those without. If >1, indicates a smaller effect in those taking metformin.
For SGLT-2i, overall the effect was worse in those taking metformin while for DPP-4 was better. Shown are the within-group mean eGFR values.
Zaccardi F, et al. Diabetes Care 2020;dc202080.

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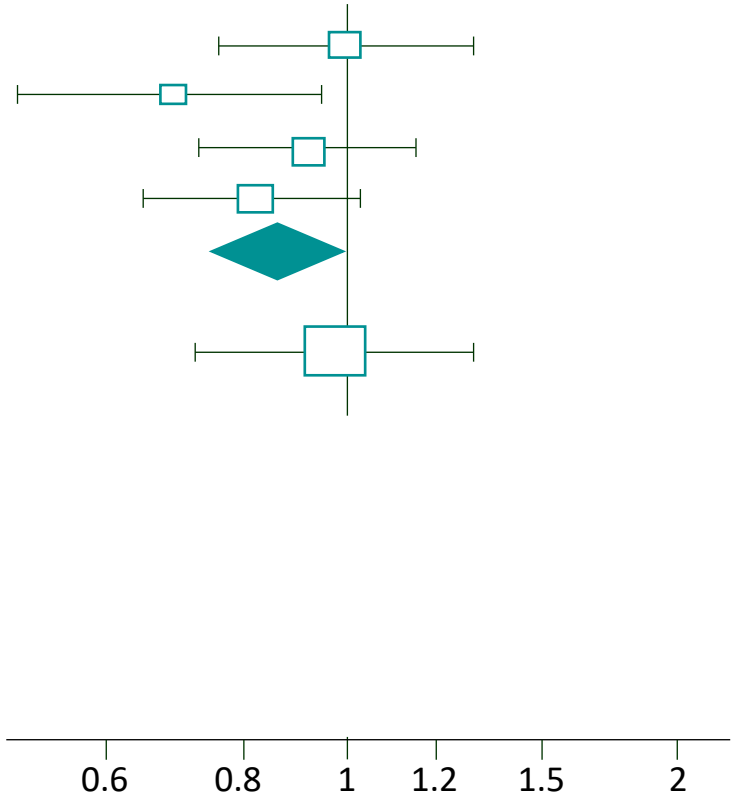

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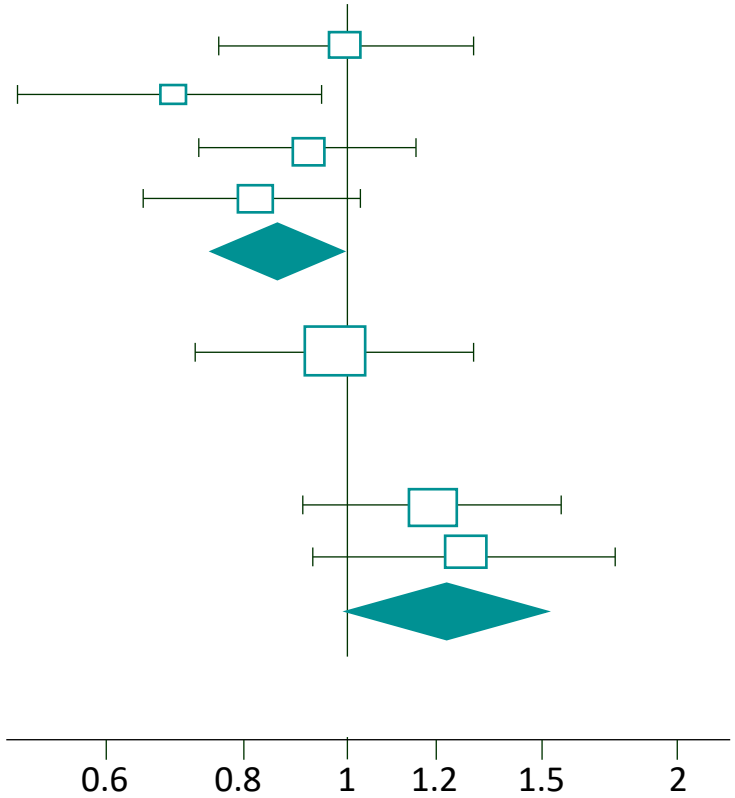
	SAVOR-TIMI-53		0.92 (0.73, 1.16)
	TECOS		0.82 (0.66, 1.03)
GLP-1RA	HARMONY-OUTCOMES		0.87 (0.76, 0.98)
SGLT-2i	CANVAS Program	79 (met), 67 (no met)	1.20 (0.92, 1.57)
	EMPA-REG OUTCOME	77 (met), 66 (no met)	1.28 (0.93, 1.75)
			1.23 (1.00, 1.51)



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Interaction by baseline metformin for MACE

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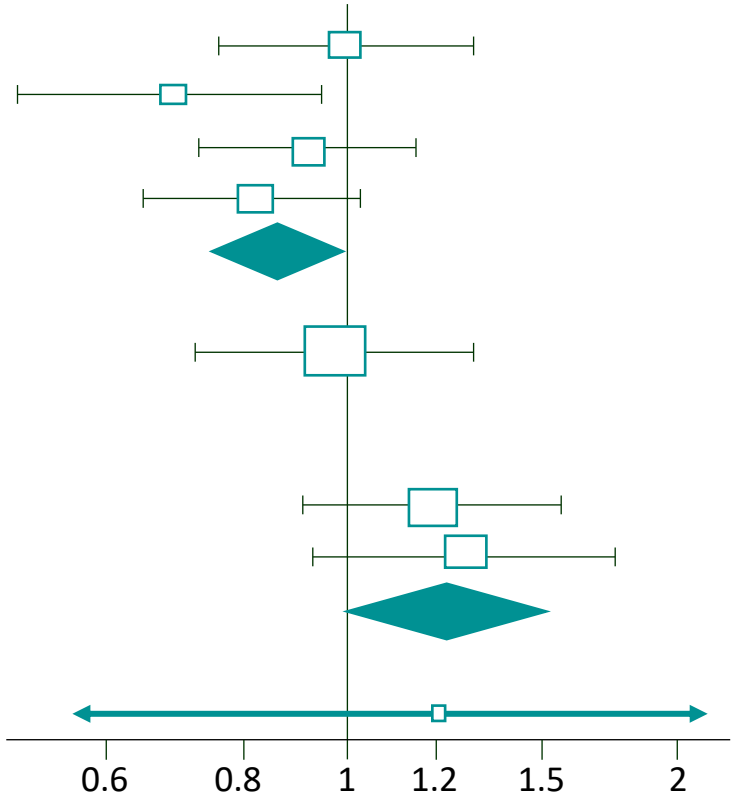
GLP-1RA	HARMONY-OUTCOMES		0.87 (0.76, 0.98)
SGLT-2i	CANVAS Program	79 (met), 67 (no met)	1.20 (0.92, 1.57)
	EMPA-REG OUTCOME	77 (met), 66 (no met)	1.28 (0.93, 1.75)
			1.23 (1.00, 1.51)
	Estimate adjusted for eGFR		**1.21 (0.11, 13.61)**



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Impact of baseline GLA on outcomes

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ORIGINAL ARTICLE

WILEY

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from DECLARE-TIMI 58

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Cahn A, et al. Diabetes Obes Metab 2021;23:29–38.

Aims and methods

Aims/hypothesis:

- To assess the associations between baseline glucose-lowering agents and cardiorenal outcomes with dapagliflozin versus placebo in the DECLARE-TIMI 58 study

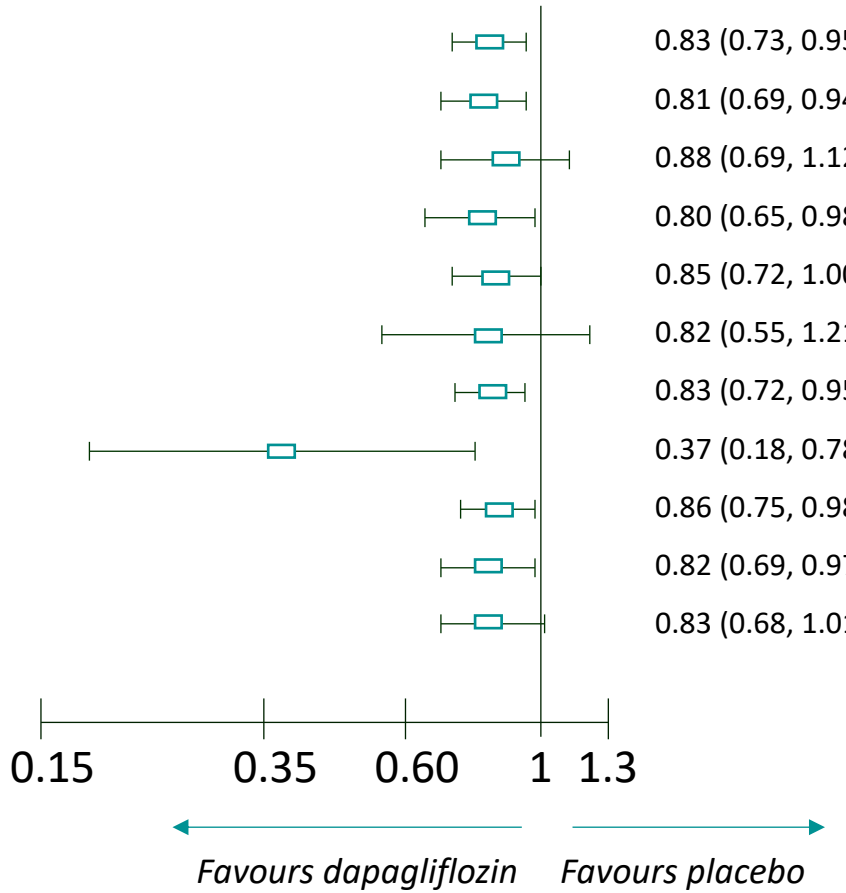
Methods:

- This post hoc analysis elaborates on the efficacy and safety outcomes by baseline glucose-lowering agent for treatment effect, and treatment interaction

Cahn A, et al. Diabetes Obes Metab 2021;23:29–38.

Impact of baseline GLA on CVD/HHF

Subgroups		Dapagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)	P-value	P-interaction
Overall		417/8582 (4.9)	496/8578 (5.8)	0.83 (0.73, 0.95)	0.0027	
Baseline metformin	Yes	293/7020 (4.2)	362/7048 (5.1)	0.81 (0.69, 0.94)	0.0063	0.5603
	No	124/1562 (7.9)	134/1530 (8.8)	0.88 (0.69, 1.12)	0.2914	
Baseline sulphonylurea	Yes	153/3615 (4.2)	196/3707 (5.3)	0.80 (0.65, 0.98)	0.0354	0.6386
	No	264/4967 (5.3)	300/4871 (6.2)	0.85 (0.72, 1.00)	0.0536	
Baseline DPP-4i	Yes	44/1418 (3.1)	58/1470 (3.9)	0.82 (0.55, 1.21)	0.3223	0.9709
	No	373/7164 (5.2)	438/7108 (6.2)	0.83 (0.72, 0.95)	0.0069	
Baseline GLP-1RA	Yes	10/397 (2.5)	24/353 (6.8)	0.37 (0.18, 0.78)	0.0085	0.0257
	No	407/8185 (5.0)	472/8225 (5.7)	0.86 (0.75, 0.98)	0.0229	
Baseline insulin	Yes	237/3567 (6.6)	274/3446 (8.0)	0.82 (0.69, 0.97)	0.0224	0.9142
	No	180/5015 (3.6)	222/5132 (4.3)	0.83 (0.68, 1.01)	0.0599	



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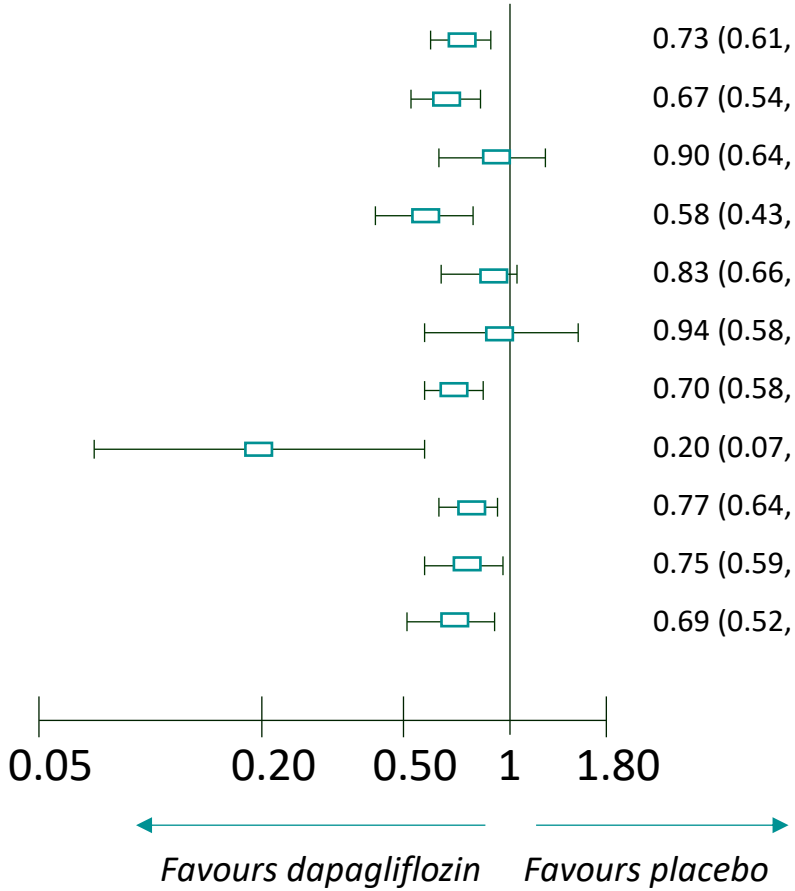
Impact of baseline GLA on HHF

Subgroups		Dapagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)	P-value	P-interaction
Overall		212/8582 (2.5)	286/8578 (3.3)	0.73 (0.61, 0.88)	0.0006	
Baseline metformin	Yes	146/7020 (2.1)	217/7048 (3.1)	0.67 (0.54, 0.83)	0.0002	0.1434
	No	66/1562 (4.2)	69/1530 (4.5)	0.90 (0.64, 1.26)	0.5471	
Baseline sulphonylurea	Yes	66/3615 (1.8)	116/3707 (3.1)	0.58 (0.43, 0.79)	0.0004	0.0631
	No	146/4967 (2.9)	170/4871 (3.5)	0.83 (0.66, 1.03)	0.0969	
Baseline DPP-4i	Yes	30/1418 (2.1)	35/1470 (2.4)	0.94 (0.58, 1.53)	0.7952	0.2839
	No	182/7164 (2.5)	251/7108 (3.5)	0.70 (0.58, 0.85)	0.0003	
Baseline GLP-1RA	Yes	4/397 (1.0)	18/353 (5.1)	0.20 (0.07, 0.60)	0.0038	0.0143
	No	208/8185 (2.5)	160/3446 (4.6)	0.77 (0.64, 0.92)	0.0050	
Baseline insulin	Yes	127/3567 (3.6)	160/3446 (4.6)	0.75 (0.59, 0.95)	0.0149	0.6594
	No	85/5015 (1.7)	126/5132 (2.5)	0.69 (0.52, 0.91)	0.0081	



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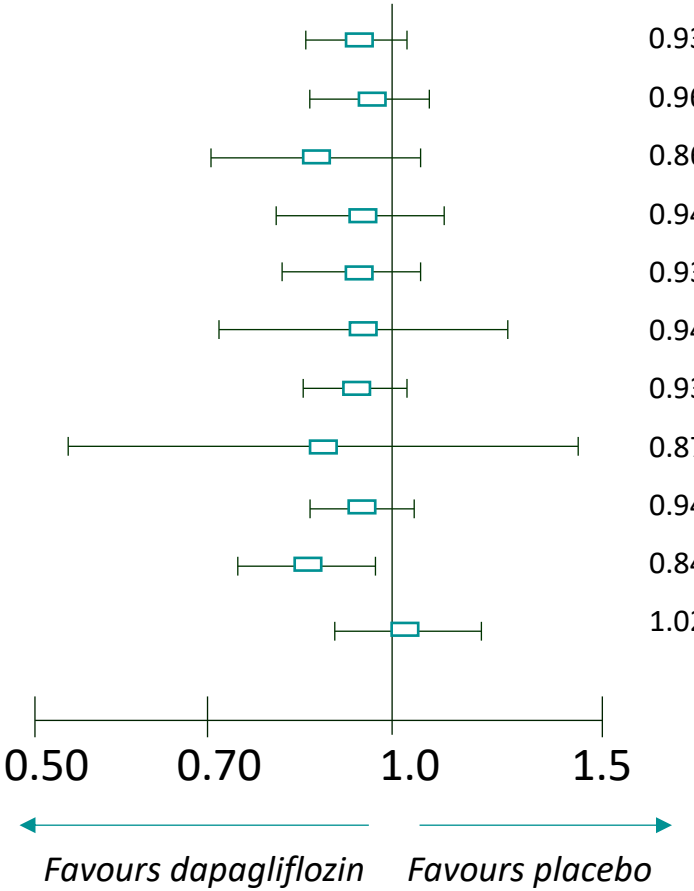
Impact of baseline GLA on MACE

Subgroups		Dapagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)	P-value	P-interaction
Overall		756/8582 (8.8)	803/8578 (9.4)	0.93 (0.84, 1.03)	0.1723	
Baseline metformin	Yes	584/7020 (8.3)	613/7048 (8.7)	0.96 (0.85, 1.07)	0.4284	0.3596
	No	172/1562 (11.0)	190/1530 (12.4)	0.86 (0.70, 1.05)	0.1376	
Baseline sulphonylurea	Yes	297/3615 (8.2)	324/3707 (8.7)	0.94 (0.80, 1.10)	0.4558	0.8663
	No	459/4967 (9.2)	479/4871 (9.8)	0.93 (0.81, 1.05)	0.2341	
Baseline DPP-4i	Yes	91/1418 (6.4)	105/1470 (7.1)	0.94 (0.71, 1.24)	0.6630	0.9848
	No	665/7164 (9.3)	698/7108 (9.8)	0.93 (0.84, 1.03)	0.1750	
Baseline GLP-1RA	Yes	31/397 (7.8)	31/353 (8.8)	0.87 (0.53, 1.43)	0.5838	0.8369
	No	725/8185 (8.9)	772/8225 (9.4)	0.94 (0.85, 1.04)	0.1981	
Baseline insulin	Yes	389/3567 (10.9)	433/3446 (12.6)	0.84 (0.74, 0.97)	0.0151	0.0586
	No	367/5015 (7.3)	370/5132 (7.2)	1.02 (0.89, 1.18)	0.7606	



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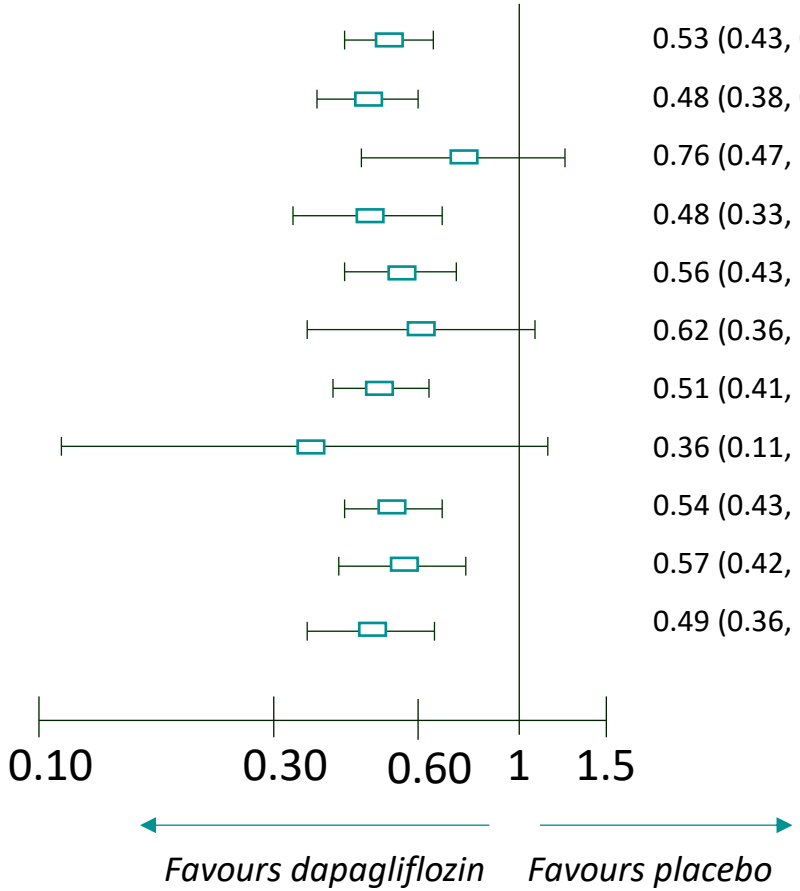
Impact of baseline GLA on renal outcomes

Subgroups		Dapagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)	P-value	P-interaction
Overall		127/8582 (1.5)	238/8578 (2.8)	0.53 (0.43, 0.66)	<0.0001	
Baseline metformin	Yes	97/7020 (1.4)	200/7048 (2.8)	0.48 (0.38, 0.61)	<0.0001	0.0946
	No	30/1562 (1.9)	38/1530 (2.5)	0.76 (0.47, 1.23)	0.2680	
Baseline sulphonylurea	Yes	44/3615 (1.2)	94/3707 (2.5)	0.48 (0.33, 0.68)	<0.0001	0.4980
	No	83/4967 (1.7)	144/4871 (3.0)	0.56 (0.43, 0.73)	<0.0001	
Baseline DPP-4i	Yes	21/1418 (1.5)	36/1470 (2.4)	0.62 (0.36, 1.06)	0.0826	0.5679
	No	106/7164 (1.5)	202/7108 (2.8)	0.51 (0.41, 0.65)	<0.0001	
Baseline GLP-1RA	Yes	4/397 (1.0)	10/353 (2.8)	0.36 (0.11, 1.15)	0.0836	0.4894
	No	123/8185 (1.5)	228/8225 (2.8)	0.54 (0.43, 0.67)	<0.0001	
Baseline insulin	Yes	67/3567 (1.9)	113/3446 (3.3)	0.57 (0.42, 0.77)	0.0003	0.4844
	No	60/5015 (1.2)	125/5132 (2.4)	0.49 (0.36, 0.66)	<0.0001	



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Conclusion

- The effects of dapagliflozin on cardiorenal outcomes were generally consistent regardless of baseline glucose-lowering agent
  - With consistent benefits regardless of baseline metformin use

- Given some evidence of cardiovascular risk, the potential clinical benefit of combining SGLT-2 inhibitors with GLP-1 RAs should be explored further

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