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Determinants of the effects of SGLT2i on progression of CKD: Further results from the EMPA-KIDNEY trial

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Disclosures

- The EMPA-KIDNEY trial was initiated by the University of Oxford who led its design, analysis, and reporting with a Steering Committee of expert collaborators
- The trial was funded and sponsored by Boehringer Ingelheim
- Other financial support from:
 - Eli Lilly & the UK Medical Research Council (MRC)
 - Novo-Nordisk for the ASCEND-PLUS trial
 - Follow a long-standing departmental policy to decline honoraria

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Introduction

In EMPA-KIDNEY, the effects of empagliflozin on annual rate of change in eGFR appear to be modified by the key subgroups of baseline diabetes status, eGFR & uACR.

However, it is not known whether some of this effect modification may be due to correlation with other key subgroups.









Methods

- Shared parameter models are used to estimate absolute and relative effects of empagliflozin on chronic slopes in subgroups of interest using all available eGFR values from centrally measured creatinine
- Analyses in key subgroups were conducted before and after inclusion of interactions with other key subgroups
- This allows distribution of other key subgroups to be standardised across the levels of the subgroup of interest









Absolute effects on chronic slopes – diabetes subgroup

■ Before including interactions with other key subgroups

—☐— After including interactions with other key subgroups

Mean/modelled slope (mL per minute per 1.73m² per year)

	Empagliflozin	Placebo	Absolute difference (95% CI) Het	test
Diabetes				
Present	-1.05 (0.12)	-2.73 (0.12)	$1.68 (1.36, 2.00) \qquad \chi_1^2 = 6$	6.93;
Absent	-1.66 (0.11)	-2.75 (0.11)	1.09 (0.79, 1.39) p=0.0	0085
Present	-1.13 (0.11)	-2.93 (0.11)	$\frac{1}{1.81} - 1.81 (1.51, 2.11) + \chi_1^2 = 13$	3.38;
Absent	-1.69 (0.10)	-2.72 (0.10)	1.03 (0.75, 1.32) p=0.0	0003
All participants	-1.37 (0.08)	-2.75 (0.08)	1.37 (1.16, 1.59)	
			-1 -0.5 0 0.5 1 1.5 2 Placebo better Empagliflozin better	









Absolute effects on chronic slopes – eGFR subgroup

── Before including interactions with other key subgroups

Mean/modelled slope – (mL per minute per 1.73m² per year)

—☐— After including interactions with other key subgroups

	Empagliflozin	Placebo		Ab	osolute difference (95% CI)	Trend test
Estimated glomerul	ar filtration rate (mL ր	per minute per	1.73m²)			
<30	-1.84 (0.14)	-2.85 (0.14)			1.01 (0.63, 1.39)	$\chi_1^2 = 9.87;$
≥30 <45	-1.18 (0.12)	-2.50 (0.12)			1.32 (0.99, 1.65)	p=0.0017
≥45	-1.58 (0.17)	-3.60 (0.17)		\longrightarrow	2.01 (1.53, 2.49)	
<30	-1.67 (0.13)	-2.65 (0.13)			0.98 (0.62, 1.34)	$\chi_1^2 = 9.6;$
≥30 <45	-1.39 (0.11)	-2.78 (0.11)		— <u></u>	1.39 (1.07, 1.70)	p=0.0019
≥45	-1.39 (0.16)	-3.28 (0.17)		—□	1.90 (1.44, 2.36)	
All <mark>partici</mark> pants	-1.37 (0.08)	-2.75 (0.08)			1.37 (1.16, 1.59)	
						
			-1 -0.5 0 Placebo better	0.5 1 1.5 2 Empagliflozin better		









Absolute effects on chronic slopes – uACR subgroup

Mean/modelled slope

(mL per minute per 1.73m² per year)

■ Before including interactions with other key subgroups

—☐— After including interactions with other key subgroups

	Empagliflozin	Placebo	Absolute difference (95% CI)	Trend test
Urinary albumin-to-	creatinine ratio (mg/s	g)		
<30	-0.11 (0.17)	-0.89 (0.16)	0.78 (0.32, 1.23)	$\chi_{1}^{2} = 13.8;$
≥30 <300	-0.49 (0.14)	-1.69 (0.14)	1.20 (0.81, 1.59)	p=0.0002
≥300	-2.35 (0.11)	-4.11 (0.11)		
<30	-0.21 (0.17)	-0.95 (0.17)	0.74 (0.27, 1.22)	$\chi_{\perp}^{2} = 15.87;$
≥30 <3 <mark>00</mark>	-0.58 (0.14)	-1.76 (0.14)	1.17 (0.78, 1.57)	p<0.0001
≥300	-2.40 (0.11)	-4.21 (0.11)	—□→ 1.82 (1.52, 2.11)	
All participants	-1.37 (0.08)	-2.75 (0.08)	1.37 (1.16, 1.59)	
			-1 -0.5 0 0.5 1 1.5 2	
			Placebo better Empagliflozin better	









Relative effects on chronic slopes – diabetes subgroup

Before including interactions with other key subgroups

After including interactions with other key subgroups

Mean/modelled slope (mL per minute per 1.73m² per year)

	Empagliflozin	Placebo		Relative difference, % (95% CI)	Het test
Diabetes					
Present	-1.05 (0.12)	-2.73 (0.12)	-■-	-62 (-50, -73)	$\chi_1^2 = 7.17;$
Absent	-1.66 (0.11)	-2.75 (0.11)	-■-	-40 (-29, -51)	p=0.0074
Present	-1.13 (0.11)	-2.93 (0.11)	-0-	-62 (-51, -72)	$\chi_1^2 = 9.97;$
Absent	-1.69 (0.10)	-2.72 (0.10)	-0-	-38 (-28, -48)	p=0.0016
All participants	-1.37 (0.08)	-2.75 (0.08)	\langle	-50 (-42, -58)	
		_	, , , 		
		-15	0 -100 -50 0 Empagliflozin better	50 Placebo better	









Relative effects on chronic slopes – eGFR subgroup

Before including interactions with other key subgroups

Mean/modelled slope (mL per minute per 1.73m² per year)

—☐— After including interactions with other key subgroups

	Empagliflozin	Placebo		Relative difference, % (95% CI)	Trend test
Estimated glomerul	ar filtration rate (mL	per minute per 1.7	/3m²)		
<30	-1.84 (0.14)	-2.85 (0.14)	-■-	-35 (-22, -49)	$\chi_1^2 = 4.66;$
≥30 <45	-1.18 (0.12)	-2.50 (0.12)	-	-53 (-40, -66)	p=0.03
≥45	-1.58 (0.17)	-3.60 (0.17)	-	-56 (-43, -69)	
<30	-1.67 (0.13)	-2.65 (0.13)		-37 (-24, -51)	$\chi_1^2 = 4.42;$
≥30 <45	-1.39 (0.11)	-2.78 (0.11)	- - -	-50 (-39, -61)	p=0.04
≥45	-1.39 (0.16)	-3.28 (0.17)		-58 (-44, -72)	
All <mark>partici</mark> pants	-1.37 (0.08)	-2.75 (0.08)		-50 (-42, -58)	
		-15(50	
				Placebo better	









Relative effects on chronic slopes – uACR subgroup

Mean/modelled slope

(mL per minute per 1.73m² per year)

■ Before including interactions with other key subgroups

—□— After including interactions with other key subgroups

	Empagliflozin	Placebo		Relative difference, % (95% CI)	
Urinary albumin-to-	creatinine ratio (mg/g	g)			
<30	-0.11 (0.17)	-0.89 (0.16)		-87 (-36, -138)	$\chi_1^2 = 7.61;$
≥30 <300	-0.49 (0.14)	-1.69 (0.14)	-	-71 (-48, -94)	p=0.0058
≥300	-2.35 (0.11)	-4.11 (0.11)	■	-43 (-36, -50)	
<30	-0.21 (0.17)	-0.95 (0.17)		-78 (-28, -128)	$\chi_1^2 = 5.41;$
≥30 < <mark>300</mark>	-0.58 (0.14)	-1.76 (0.14)		-67 (-44, -89)	p=0.02
≥300	-2.40 (0.11)	-4.21 (0.11)	-	-43 (-36, -50)	
All participants	-1.37 (0.08)	-2.75 (0.08)	⇔	-50 (-42, -58)	
		-150			
		100		icebo better	









Absolute effects on chronic slopes – expanded diabetes subgroup

Mean slope (mL per minute per 1.73m² per year)

	Empagliflozin	Placebo		d	Absolute lifference (95% CI)	Het test
Diabetes status						
Type 1 diabetes	-0.23 (0.72)	-2.78 (0.73)			2.55 (0.54, 4.55)	$\chi_1^2 = 7.68;$
Type 2 diabetes	-1.07 (0.12)	-2.73 (0.12)			1.66 (1.34, 1.98)	p=0.02
No diabetes	-1.66 (0.11)	-2.75 (0.11)		-	1.09 (0.79, 1.39)	
All participants	-1.37 (0.08)	-2.75 (0.08)			1.37 (1.16, 1.59)	
		_		1 1 1		
		-1	-0.5 0	0.5 1 1.5 2	2	
		Pla	acebo better	Empagliflozin bette	r	









Absolute effects on chronic slopes – expanded eGFR subgroup

Mean slope

(mL per minute per 1.73m² per year)

	Empagliflozin	Placebo	di	fference (95% CI)	Het test
Estimated glomerula	ar filtration rate (mL _l	oer minute per	3m²)		
<20	-3.08 (0.44)	-3.77 (0.43)		0.69 (-0.51, 1.88)	$\chi_1^2 = 10.28;$
≥20 <30	-1.70 (0.14)	-2.73 (0.14)	<u>■</u>	1.03 (0.63, 1.42)	p=0.0013
≥30 <45	-1.18 (0.12)	-2.50 (0.12)		1.32 (0.99, 1.65)	
≥45	-1.58 (0.17)	-3.59 (0.17)	\longrightarrow	2.01 (1.53, 2.49)	
All participants	-1.37 (0.08)	-2.75 (0.08)		1.37 (1.16, 1.59)	
		ſ			
		-1 PI	-0.5 0 0.5 1 1.5 2 ebo better Empagliflozin better		





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Absolute effects on chronic slopes – expanded uACR subgroup

Mean slope

(mL per minute per 1.73m² per year)

	Empagliflozin	Placebo	•			d	ifference (95% CI)	Het test
Urinary albumin-to-c	creatinine ratio (mg/g	j)				74(7)		
<30	-0.24 (0.16)	-0.99 (0.16)			_		0.76 (0.32, 1.19)	χ_1^2 =16.33;
≥30 <300	-0.62 (0.13)	-1.78 (0.14)					1.16 (0.79, 1.53)	p<0.0001
≥300 <1000	-1.50 (0.14)	-2.84 (0.15)				-	1.34 (0.94, 1.74)	
≥1000 <2000	-2.56 (0.18)	-4.70 (0.19)				\rightarrow	2.13 (1.61, 2.65)	
≥2000	-4.69 (0.23)	-6.53 (0.22)					1.84 (1.23, 2.45)	
All participants	-1.37 (0.08)	-2.75 (0.08)			<	\Diamond	1.37 (1.16, 1.59)	
			-1 -0.5	0 0.5	. 1	1.5 2		
			Placebo bette	_		l.5 Z lozin better		





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Other subgroup analyses

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No evidence of effect modification for chronic slopes for:

- Age
- Sex
- Race
- History of cardiovascular disease
- Systolic blood pressure
- Diastolic blood pressure
- Body mass index
- NT-proBNP
- Use of RAS inhibitors
- Diuretic use
- Use of lipid lowering medication
- 5 year risk of kidney failure









Sensitivity analyses

Results are not materially changed when:

- Restricted to eGFR measurements taken while patients where still on study treatment
- Using eGFR measurements based on local creatinine measurements









Conclusions

Oifferences in the absolute effect of empagliflozin on chronic eGFR slope by baseline diabetes status, eGFR & uACR are not explained by baseline differences in other key baseline characteristics.

Future work will further explore proportional effects of empagliflozin on eGFR slopes as well as seeking to further understand the relevance of the effect of uACR to the treatment effects observed.



