

Cardiovascular Outcomes of Dapagliflozin (Sodium-Glucose Co-transporter-2): A Systematic Review and Meta-Analysis Usman Bhatti MD, Khawaja H Akhtar MD, Heyyan Khalil MD, Ali H Jafry MD, Abdul Iqbal MD, Christina Murray MD **University of Oklahoma Health Sciences Center**

Background

Dapagliflozin (SGLT-2 inhibitor) has show reduce mortality and hospitalization for failure patients with and without diabete mellitus, through mechanisms independ glucose transport. We seek to assess the recent published evidence on use of SGI inhibitor and cardiovascular outcomes by conducting a meta-analysis.

Methods

Extensive search was performed by two independent researchers on PubMed and Ovid using key words Dapagliflozin, heart failure and cardiovascular outcomes yielding 739 studies. Review articles, abstracts and unrelated studies were excluded. 20 full length articles were assessed leading to final selection of 4 randomized controlled studies comparing outcomes of Dapagliflozin with placebo. We compared clinical outcomes including hospitalization for heart failure, all-cause mortality and cardiovascular mortality between Dapagliflozin and placebo. Study-level analysis was done with Review manager. The results are reported as OR, 95% confidence interval and P < 0.005.

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A	Dapagli	iflozin	P	acebo		
Study or Subgroup	Events	Total	Events	Total	Weight	IV
Kosiborod et al, 2017	1	171	7	149	0.7%	1
McMurray et al, 2019	231	2373	318	2371	49.7%	
Nassif et al, 2019	0	131	0	132		
Wiviott et al, 2018	212	8582	286	8578	49.6%	
Total (95% CI)		11257		11230	100.0%	
Total events	444		611			
Heterogeneity: Tau ² = 0	.01; Chi ² =	2.93, df	= 2 (P =	0.23); l ^e :	= 32%	
Test for overall effect: Z	= 3.88 (P =	= 0.0001)			
B	Dapagli	iflozin	Place	bo		
Study or Subgroup	Events	Total	Events	Total	Weight	IV
Kosiborod et al, 2017	0	171	1	149	0.1%	
McMurray et al, 2019	276	2373	329	2371	33.7%	
Nassif et al, 2019	1	131	1	132	0.1%	
Wiviott et al, 2018	529	8582	570	8578	66.1%	
Total (95% CI)		11257		11230	100.0%	
Total events	806		901			
Heterogeneity: Tau ² = 0	.00; Chi ² =	1.77, df	= 3 (P =	0.62); I ² :	= 0%	
_Test for overall effect: Z	= 2.41 (P =	= 0.02)				
C	Dapag	liflozin	Placebo			
Study or Subgroup	Events	Total	Events	Total	Weight	IV
Kosiborod et al, 2017	0	171	0	149	14211422	
McMurray et al, 2019	227	2373	273	2371	48.1%	
Nassifiet al, 2019	1	131	1	132	0.2%	
Wiviott et al, 2018	245	8582	249	8578	51.7%	
Total (95% CI)		11257		11230	100.0%	
Total events	473		523			
Heterogeneity: Tau ^z = 0	.00; Chi ^z =	2.09, df	= 2 (P =	0.35); l²÷	= 4%	
Test for overall effect: 7	= 1.58 (P -	= 0.11)				

Panel A: Hospitalization from heart failure. Panel B: All cause mortality. Panel C: Cardiovascular mortality

Baseline Demographics

Study	Groups	Sample (n)	Male %	Age Mean	DM %	CHF %	LVEF, Mean	BMI, Mean	HF Hospitalization %	AF %	CAD %	ICD/CRT %
Kosiborod et al.	Dapagliflozin	171	64.3	63.6	100	100	_	34.1	_	9.9	86	_
	Placebo	149	61.1	64.9	100	100	-	34.3	_	12	81.2	-
McMurray et al.	Dapagliflozin	2373	76.2	66.2	41.8	100	31.2	28.2	47.4	38.6	55.5	26.2/8.0
	Placebo	2371	77	66.5	41.8	100	30.9	28.1	47.5	38.0	57.3	26.1/6.9
Nassif et al.	Dapagliflozin	131	72.5	62.2	61.8	100	27.2	30.7	77.1	43.5	53.4	67.2/32.8
	Placebo	132	74.2	60.4	64.4	100	25.7	30.6	81.8	37.1	52.3	56.8/18.9
Wiviott et al.	Dapagliflozin	8582	63.1	63.9	100	9.9	-	32.1	_	-	32.9	-
	Placebo	8578	62.1	64.0	100	10.2	-	32.0	-	-	33.0	-
Total	Dapagliflozin	11257			87.2	31.3			9.99			
	Placebo	11230			87.3	31.4			10.99			

Forest plot



Engl J Med 2019

2019 DAPA-HF Trial. Mikhail N. Kosiborod. Circulation. 2020





Results

22,487 patients included in 4 trials

- Dapagliflozin : 11,257 patients
- Placebo: 11,230 patients
- Hospitalizations for heart failure:
- OR: 0.71; 95% CI: 0.59-0.84; p= 0.0001
- All-cause mortality: OR: 0.88; CI: 0.80-0.98; p=0.02
- Cardiovascular mortality: OR: 0.90; CI: 0.78-1.03; p= 0.11
- Heterogeneity assessment reported I² < 30% in cardiovascular mortality and all-cause mortality.

Conclusion

- Dapagliflozin is associated with significant decrease in hospitalization due to heart failure and all-cause mortality with positive trend towards improvement in cardiovascular mortality.
- Benefits of Dapagliflozin on clinical improvement in heart failure appear to extend to patients without type 2 diabetes mellitus.
- Dapagliflozin should be identified as a potential add-on therapy to improve clinical outcomes in suitable patients.

References

The DEFINE-HF Trial. Michael E. Nassif. Circulation. 2019 Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. John J.V. McMurray. N • Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. Stephen D. Wiviott. N Engl J Med