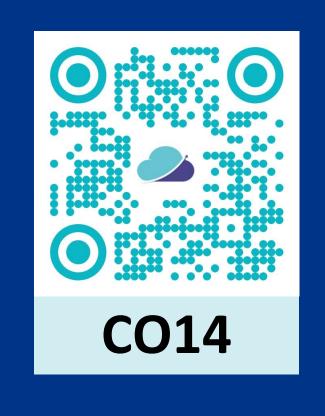
Glycaemic Control, Obesity Management, and Cardiovascular Outcomes of Semaglutide for Type 2 Diabetes Mellitus Patients: An Umbrella Review and Meta-meta-analysis Barman P¹, Kamboj G¹, Kumar N¹, <u>Rathi H¹</u> ¹Skyward Analytics Pvt. Ltd., Gurugram, Haryana, India



OBJECTIVE

To evaluate glycaemic control, obesity management, and cardiovascular outcomes associated with semaglutide in patients with type 2 diabetes mellitus (T2DM)

INTRODUCTION

- As of 2024, an estimated 540 million adults (aged between 20-79 years) are living with diabetes, with 90% diagnosed with T2DM. This is projected to increase to 643 million by 2030 and 783 million by 2045¹
- Diabetes led to approximately 966 billion USD in global health expenditure, a 316% rise over the past 15 years¹
- Semaglutide, developed to treat T2DM and obesity, is the only GLP-1 receptor agonist currently available as both peroral (PO) and subcutaneous (SC) formulations

1. Glycaemic control

The findings demonstrate that semaglutide is more effective than placebo in reducing HbA1c levels across dosages and administration routes (mean various difference [MD]: -1.22; 95% CI: -1.28, -1.15) (Figure 2a)

Figure 2a. Change in HbA1c (%) from baseline

Study	Mean Difference	MD	95%-CI	Wei
subgroup = Semaglutide (SC)_0.5 mg				
Zhong 2021		-1.14	[-1.74; -0.54]	1
Karagiannis 2024	<u> </u>		[-1.24; -0.94]	
Hu 2023			[-1.32; -0.62]	
Andreadis 2018			[-1.46; -0.56]	
Alhindi 2022			[-1.57; -1.21]	
Ding 2024	-		[-1.26; -0.96]	
Witkowski 2018			[-1.48; -0.98]	
Nuhoho 2019		-1.18	[-1.38; -0.98]	3
Kanters 2019		-1.12	[-1.35; -0.89]	3
Random effects model	٠	-1.16	[-1.25; -1.07]	
Heterogeneity: $I^2 = 12\%$, $\tau^2 = 0.0044$, $\chi_8^2 = 9.14$ ($p = 0.0044$)	0.33)			
subgroup = Semaglutide (SC)_1.0 mg				
Zhong 2021		_1 37	[-1.63; -1.11]	3
•				
Karagiannis 2024			[-1.52; -1.26]	
Hu 2023			[-1.59; -1.13]	
Andreadis 2018			[-1.70; -1.06]	
Alhindi 2022		-1.55	[-1.74; -1.36]	4
Ding 2024		-1.40	[-1.53; -1.27]	4
Witkowski 2018			[-1.71; -1.23]	
Nuhoho 2019			[-1.62; -1.24]	
Kanters 2019			[-1.59; -1.17]	
Random effects model			[-1.48; -1.35]	
	•	-1.41	[-1.40, -1.35]	33
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_8^2 = 2.73$ (<i>p</i> = 0.95)				
subgroup = Semaglutide (Oral)_7 mg				
Zhong 2021		-0.96	[-1.39; -0.53]	1
Alhindi 2022		-1.13	[-1.41; -0.85]	2
Ding 2024		-0.93	[-1.11; -0.75]	4
Li 2021			[-1.43; -0.79]	
Li 2023			[-1.30; -0.82]	
Random effects model			[-1.13; -0.90]	
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_A^2 = 2$ ($p = 0.74$)	•	-1.02	[-1.15, -0.90]	14
subgroup = Semaglutide (Oral)_14 mg		1 00		2
Zhong 2021			[-1.27; -0.77]	
Alhindi 2022	<u> </u>		[-1.46; -1.12]	
Ding 2024		-1.05	[-1.19; -0.91]	4
Li 2021		-1.08	[-1.31; -0.85]	3
Li 2023			[-1.22; -0.80]	
Nuhoho 2019			[-1.43; -1.01]	
Random effects model	—		[-1.22; -1.02]	
Heterogeneity: $I^2 = 32\%$, $\tau^2 = 0.0054$, $\chi_5^2 = 7.34$ ($p = 0$	0.20)	-1.12	L-1.22, -1.V2]	23
Random effects model		1 22	[_1 29+ 1 4E1	100
		-1.22	[-1.28; -1.15]	100
	-1.5 -1 -0.5 0 0.5 1	1 1.5		
	0	s Placebo		
Heterogeneity: $I^2 = 64\%$, $\tau^2 = 0.0196$, $\chi^2_{28} = 77.53$ (<i>p</i> < Test for subgroup differences: $\chi^2_3 = 51.77$, df = 3 (<i>p</i> <				

- The most substantial reduction was observed at the 1.0 mg SC dose (MD: -1.41; 95% CI: -1.48, -1.36)
- When compared with other anti-diabetic drugs (OADs), semaglutide shows a consistent HbA1c reduction across all subgroups (MD: -0.55; 95% CI: -0.69, -0.42), with the largest reduction evident at the 1.0 mg SC dose (MD: -0.79; 95% CI: -1.00, -0.59) (**Figure 3**)

2. Obesity management

• Semaglutide shows greater reduction in body weight placebo across all dosages to compared and administration routes (MD: -3.01; 95% CI: -3.38, -2.65) (Figure 2b); largest reduction observed at the 1.0 mg SC

METHODS

- A comprehensive literature search was conducted using multiple databases from inception till June 2024.
- Studies were screened at two levels (title-abstract and full-text) based on pre-specified inclusion and exclusion to identify meta-analyses of randomized criteria controlled trials (RCTs) comparing semaglutide with placebo or other anti-diabetic drugs (OADs)
- Meta-meta-analyses were conducted to combine the meta-analysis results from reviews with comparable outcome using the 'meta' package in R software

Databases

- Pub Med[®]
- **Europe PMC T** Epistemonikos
- T2DM patients. Outcomes: change in HbA1c %, body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP)

• Meta-analyses of RCTs comparing Semaglutide

(oral or subcutaneous) with placebo or OADs in

• Exclude

Include

Mixed or paediatric populations, and studies assessing single trials for semaglutide

Figure 2b. Change in body weight from baseline

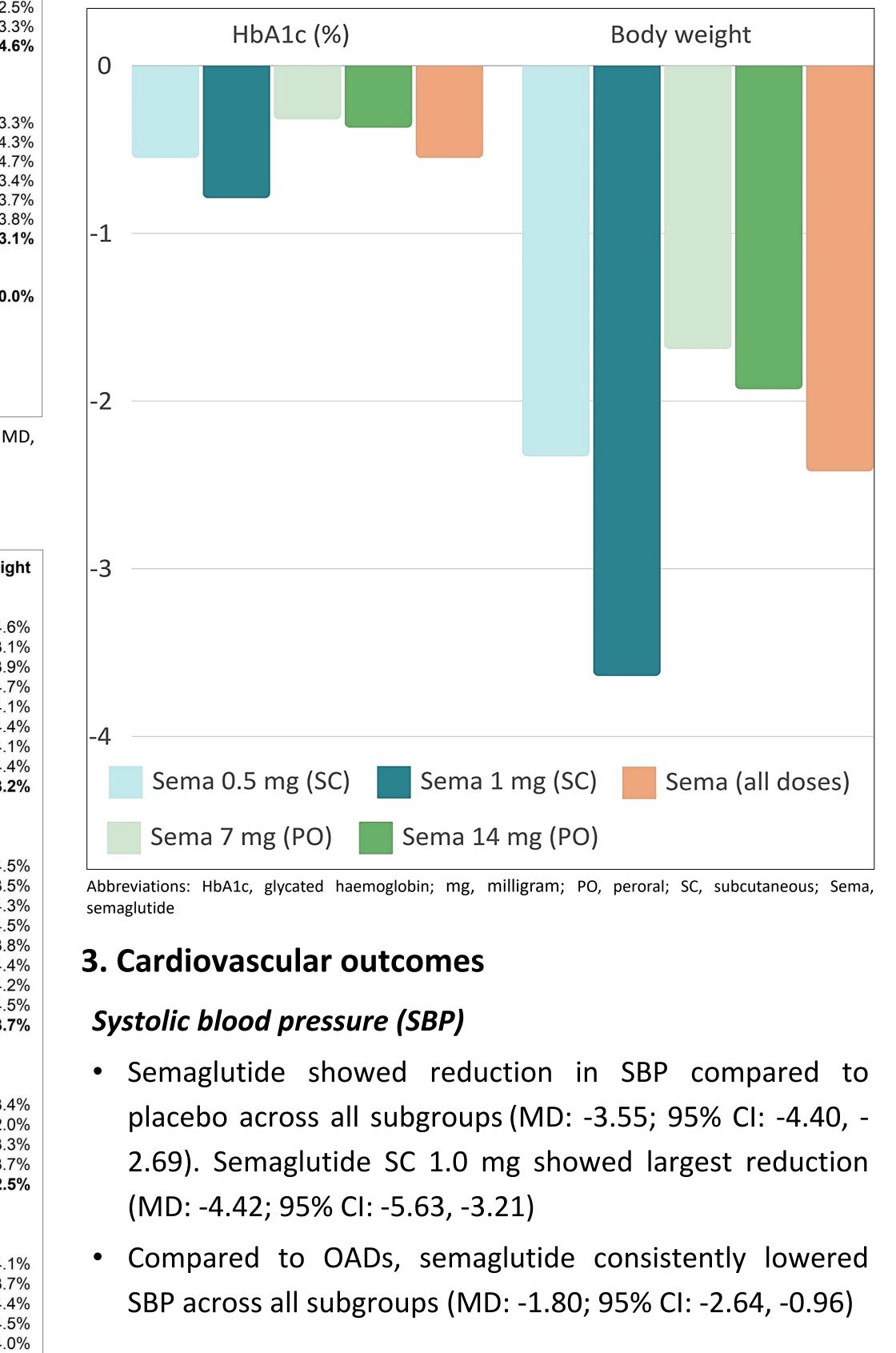
RESULTS

Google Scholar

dose (MD: -4.08; 95% CI: -4.30, -3.85)

• When compared with OADs, semaglutide reduces body weight across all subgroups (MD: -2.42; 95% CI: -2.84, -2.00), with the 1.0 mg SC dose showing the most substantial reduction (MD: -3.64; 95% CI: -3.99, -3.30) (Figure 3)

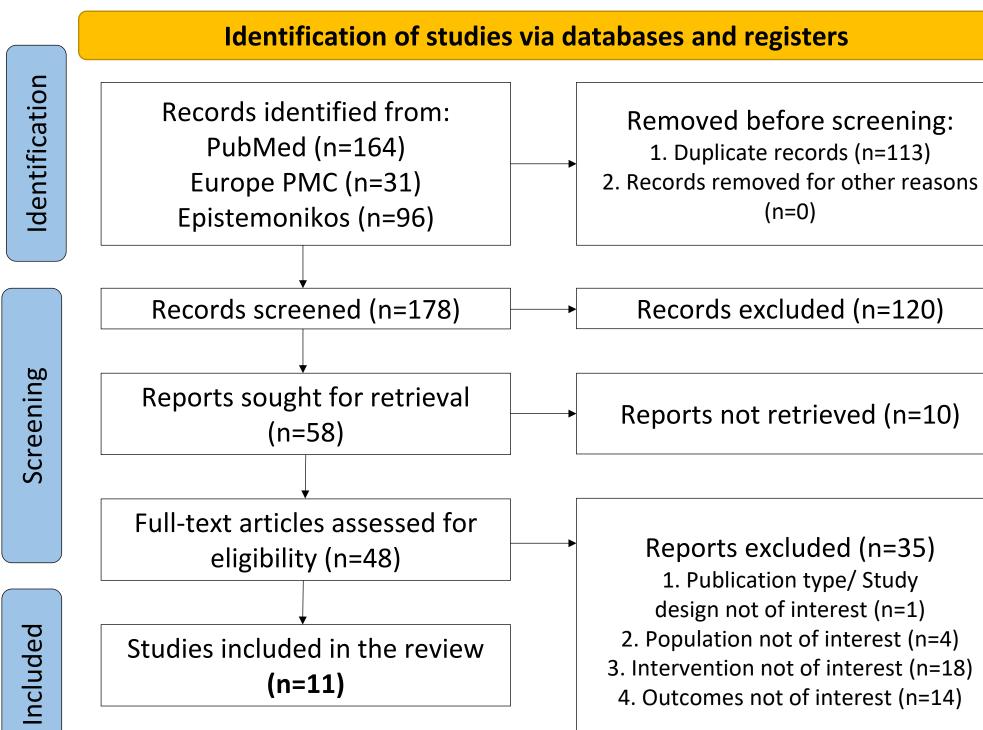
Figure 3. Change from baseline in HbA1c (%) and body weight between semaglutide and other anti-diabetic drugs (OADs)



Study

- Eleven studies were included in this review (Figure 1)²⁻¹²
- The characteristics of the meta-analyses included in the review are presented in **Table 1**
- All the studies reported data on glycaemic control, ten reported obesity, and six reported cardiovascular outcomes. Risk of bias assessment of the included studies using AMSTAR 2.0 checklist was conducted

Figure 1. PRISMA flow diagram depicting study selection process



subgroup = Semaglutide (SC)_0.5 mg	
Zhong 2021	-2.73 [-3.20; -2.26] 4.6%
Karagiannis 2024	-2.52 [-3.78; -1.26] 3.1% -2.06 [-2.94; -1.18] 3.9%
Andreadis 2018	-2.06 [-2.94; -1.18] 3.9% -2.83 [-3.25; -2.41] 4.7%
Alhindi 2022	-2.50 [-3.26; -1.74] 4.1%
Witkowski 2018	-2.45 [-3.03; -1.87] 4.4%
Nuhoho 2019	-2.71 [-3.45; -1.97] 4.1%
Kanters 2019	-2.62 [-3.21; -2.03] 4.4%
Random effects model	-2.64 [-2.85; -2.42] 33.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_7^2 = 3.19$ (<i>p</i> = 0.87)	
subgroup = Semaglutide (SC)_1.0 mg	
Zhong 2021	-4.09 [-4.63; -3.55] 4.5%
Karagiannis 2024	-4.17 [-5.25; -3.09] 3.5%
Hu 2023	-3.89 [-4.54; -3.24] 4.3%
Andreadis 2018	-4.39 [-4.89; -3.89] 4.5%
Alhindi 2022 Witkowski 2018 Nuhoho 2019 Kanters 2019 Bandom effects model	-4.15 [-5.04; -3.26] 3.8%
Witkowski 2018	-3.83 [-4.39; -3.27] 4.4%
Nuhoho 2019 Kanters 2019	-4.11 [-4.82; -3.40] 4.2%
Random effects model	-3.98 [-4.53; -3.43] 4.5% -4.08 [-4.30; -3.85] 33.7%
	-4.06 [-4.30, -3.65] 33.7 %
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_7^2 = 2.7$ (<i>p</i> = 0.91)	
subgroup = Semaglutide (Oral)_7 mg	
Zhong 2021	-1.14 [-2.27; -0.01] 3.4%
Alhindi 2022	-1.59 [-3.56; 0.38] 2.0%
Li 2021	-1.12 [-2.27; 0.03] 3.3%
Li 2023	-1.18 [-2.13; -0.23] 3.7%
Random effects model \leftarrow	-1.19 [-1.78; -0.60] 12.5%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_3^2 = 0.18$ (<i>p</i> = 0.98)	
subgroup = Semaglutide (Oral)_14 mg	
Zhong 2021	-2.97 [-3.74; -2.20] 4.1%
Alhindi 2022	-3.18 [-4.16; -2.20] 3.7%
Li 2021	-2.89 [-3.47; -2.31] 4.4%
Li 2023	-2.96 [-3.49; -2.43] 4.5%
Nuhoho 2019	-3.47 [-4.26; -2.68] 4.0%
Random effects model	-3.04 [-3.35; -2.73] 20.6%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\chi_4^2 = 1.59$ ($p = 0.81$)	
Random effects model	-3.01 [-3.38; -2.65] 100.0%
-4 -2 (0 2 4
Favours Semaglutide	Favours Placebo
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.7068$, $\chi^2_{24} = 138.97$ ($p < 0.01$) Test for subgroup differences: $\mu^2 = 121.21$ df = 2 ($p < 0.01$)	
Test for subgroup differences: $\chi_3^2 = 131.31$, df = 3 ($p < 0.01$)	

• Compared to placebo, semaglutide showed a slight reduction in DBP (MD: -0.03; 95% CI: -0.06, -0.00)

• Only two studies compared changes in DBP between

Abbreviations: PRISMA, preferred reporting items for systematic reviews and meta-analyses

Abbreviations: CI, confidence interval; df, degree of freedom; MD, mean differences; mg, milligram; SC, subcutaneous

Table 1. Characteristics of the included meta-analyses

Studies	Trials included	Semaglutide	Comparators	Study type
Ding 2024 ²	38 trials (n = 34166)	PO: 7 mg and 14 mg, SC: 0.5 mg and 1 mg	Placebo, OADs	NMA (Bayesian)
Karagiannis 2024 ³	28 trials (n = 23622)	SC: 0.5 mg and 1 mg	Placebo, OADs	NMA (Frequentist)
Hu 2023 ⁴	17 trials (n = 14940)	SC: 0.5 mg and 1 mg	Placebo, OADs	MA
Li 2023 ⁵	11 trials (n = 9821)	PO: 7 mg and 14 mg	Placebo, OADs	MA
Alhindi 2022 ⁶	12 trials (n = 6840)	PO: 7 mg and 14 mg, SC: 0.5 mg and 1 mg	Placebo, OADs	NMA (Frequentist)
Li 2021 ⁷	10 trials (n = 8536)	PO: 7 mg and 14 mg	Placebo, OADs	MA
Zhong 2021 ⁸	24 trials (n = 22185)	PO: 7 mg and 14 mg, SC: 0.5 mg and 1 mg	Placebo, OADs	MA
Kanters 2019 ⁹	21 trials (n = NR)	SC: 0.5 mg and 1 mg	Placebo	NMA (Bayesian)
Nuhoho 2019 ¹⁰	27 trials (n = NR)	PO: 14 mg, SC: 0.5 mg and 1 mg	Placebo	NMA (Bayesian)
Andreadis 2018 ¹¹	12 trials (n = NR)	SC: 0.5 mg and 1 mg	Placebo, OADs	MA
Witkowski 2018 ¹²	41 trials (n = NR)	SC: 0.5 mg and 1 mg	Placebo	NMA (Bayesian)

Abbreviations: MA, meta-analysis; NMA, network meta-analysis; NR, not reported; OADs, other anti-diabetic drugs; PO, peroral; SC, subcutaneous; T2DM, type 2 diabetes mellitus. Note: All studies had T2DM as the patient population, except Kanters (2019), which focused on 'inadequately controlled T2DM' patients.

semaglutide SC (doses of 0.5 mg and 1.0 mg) and OADs (MD: -0.42; 95% CI: -0.74, -0.10), indicating a reduction in DBP

CONCLUSIONS

Diastolic blood pressure (DBP)

Semaglutide consistently demonstrates robust efficacy in reducing HbA1c level, body weight, DBP, and SBP across various doses and administration routes. Subgroup analysis reveals that the 1.0 mg SC dosage has the largest mean reduction when compared to oral forms. These findings are consistent with previous studies⁸

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REFERENCES

1. International Diabetes Federation. https://idf.org/about-diabetes/diabetes-facts-figures; 2. Ding, Y. et al. Pharmacological Research, 2023, p.107031; 3. Karagiannis, T. et al. Diabetologia, 2024, pp.1-17; 4. Hu, S., et al. Diabetology & Metabolic Syndrome, 2023 15(1), p.218; 5. Li, A. et al. Diabetes Research and Clinical Practice, 2023 198, p.110605; 6. Alhindi, Y. et al. Contemporary clinical trials communications, 2022 28, p.100944; 7. Li, J. et al. Frontiers in pharmacology, 2021 12, p.695182; 9. Kanters, S. et al. BMJ open, 2019 9(7), p.e023458; 10. Nuhoho, S. et al. Diabetes Therapy, 2019 10, pp.2183-2199; 11. Andreadis, P. et al. Diabetes, Obesity and Metabolism, 2018 20(9), pp.2255-2263; 12. Witkowski, M. et al. Diabetes Therapy, 2018 9, pp.1149-1167.

