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Sex Differences in Baseline Cardiometabolic Phenotype and HbA1c Treatment Response to Dapagliflozin With or Without Semaglutide: Real-World Evidence From Saudi Arabia

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Abstract

Sex differences in cardiometabolic risk profiles are well recognized, yet treatment response data for dapagliflozin with or without semaglutide remain limited in real-world settings, particularly in Middle Eastern populations. Using a descriptive, sex-disaggregated analysis of a real-world cohort of 391 patients (213 female, 178 male) from a tertiary care hospital in Saudi Arabia, we examined sex-related differences in baseline cardiometabolic phenotype and treatment response across BMI, HbA1c, eGFR, blood pressure, and lipid parameters. Women presented with significantly higher BMI and a more obesity-dominant phenotype, higher HDL-C, and lower diastolic blood pressure at baseline. Unadjusted sex-disaggregated comparisons of change scores showed no statistically significant sex difference for any outcome. A revised primary analysis (an ANCOVA model of follow-up HbA1c: baseline HbA1c, sex, treatment group, sex-by-treatment interaction, age, follow-up duration, an indicator for baseline HbA1c in the diabetes diagnostic range, and baseline eGFR) found no statistically detectable sex-by-treatment interaction (β = 0.060; 95% CI − 0.58 to 0.70; p = 0.86, heteroscedasticity-robust). In sex-specific contrasts from this model, DAPA+SEMA was associated with a smaller HbA1c reduction than DAPA alone in both men (β = 0.470; 95% CI 0.017 to 0.923; p = 0.042) and women (β = 0.530; 95% CI 0.091 to 0.968; p = 0.018). Sex-specific treatment effects for BMI, eGFR, and systolic BP were not formally tested. Because treatment was not randomized and DAPA+SEMA patients had substantially higher baseline HbA1c, these adjusted associations are presented as hypothesis-generating rather than causal. These findings do not support a sex-specific difference in short-term HbA1c response to dapagliflozin with or without semaglutide in this cohort. The observational design and modest sample limit generalizability.

1. Introduction

Sex is a fundamental biological variable with well-established effects on cardiometabolic physiology. Women and men differ in adipose tissue distribution, hormonal milieu, lipid metabolism, and the clinical expression of diabetes, hypertension, and heart failure.[1, 2] These differences have mechanistic implications for drug pharmacodynamics, cardiovascular risk trajectories, and treatment response. Despite this, clinical trials have historically underrepresented women, and real-world outcome data are rarely stratified by sex — a gap that major journals, funding bodies, and cardiology societies now require researchers to address.[3]

In Saudi Arabia, the burden of cardiometabolic disease is substantial in both sexes, but phenotypic patterns differ markedly. Surveillance data consistently show that obesity prevalence is higher among women than among men, driven by lower physical activity rates, postpartum weight retention, and sociocultural factors specific to the Gulf Cooperation Council (GCC) region.[4, 5] Women aged 40 years and older bear a disproportionate share of the obesity burden, and older Saudi women exhibit higher rates of diabetes and metabolic syndrome than their male counterparts.[6] Whether pharmacological treatment responses mirror or diverge between the sexes in this population has direct relevance to cardiovascular risk management and prescribing decisions.

Dapagliflozin, an SGLT2 inhibitor, and semaglutide, a GLP-1 receptor agonist, are cornerstone agents in contemporary guideline-directed cardiometabolic therapy, with evidence supporting weight reduction, glycemic control, renal protection, and heart failure outcomes.[7, 8] Pooled analyses of DAPA-HF and DELIVER have confirmed that dapagliflozin reduces cardiovascular death and worsening heart failure events comparably in men and women (p-interaction = 0.77).[9] For GLP-1 receptor agonists, emerging data suggest that women may achieve greater absolute weight reduction with semaglutide, though glycemic responses appear broadly comparable.[10, 11] Real-world sex-disaggregated data on the combined cardiometabolic response to dapagliflozin, with or without semaglutide, remain scarce, particularly in Middle Eastern populations.[12, 13] This study addresses that gap by presenting a multivariable-adjusted, sex-disaggregated analysis of a real-world cohort at a tertiary care hospital in Saudi Arabia.

2. Methods

2.1 Study Design and Setting

This descriptive, sex-disaggregated, real-world observational cohort study was conducted at King Abdulaziz Hospital, Ministry of National Guard Health Affairs (MNGHA), in Al-Ahsa, Saudi Arabia. Data were extracted from a curated patient-level dataset of adult patients prescribed dapagliflozin alone (DAPA only) or in combination with semaglutide (DAPA + SEMA) as part of routine clinical care.

2.2 Ethical Approval

The study was approved by the Institutional Review Board of the King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard Health Affairs (MNGHA), Saudi Arabia (Protocol No. NRA26/004/2). Individual informed consent was waived because the data were retrospective and anonymized.

2.3 Study Population

Adults aged ≥18 years who received dapagliflozin ± semaglutide and had a valid follow-up window of 90–360 days were eligible. Patients with follow-up outside this window or with implausible data entries were excluded. The analytical cohort comprised 391 patients: 213 female (54.5%) and 178 male (45.5%), after excluding one age-indeterminate patient (see Section 2.5).

2.4 Outcomes and Variables

The primary outcome was the change in HbA1c (ΔHbA1c) from baseline to follow-up, selected as the primary glycaemic efficacy endpoint given the high diabetes burden in this cohort. Secondary exploratory outcomes included changes from baseline in BMI (ΔBMI, kg/m²), eGFR (ΔeGFR, mL/min/1.73 m²), systolic blood pressure (ΔSBP, mmHg), and HDL-C. Heart failure hospitalization was not analyzed as an outcome: the underlying field was missing for 62% of the cohort and its definition could not be reconciled with the structured heart-failure diagnosis flag, so any hospitalization comparison would be

unreliable. Baseline variables included BMI, HbA1c, eGFR, systolic and diastolic BP, LDL-C, HDL-C, triglycerides, and diabetes status. Structured diagnosis flags for hypertension and heart failure were found to substantially undercount measured/clinical burden (e.g., hypertension diagnosis codes captured 5% of the cohort versus 46% meeting a simple measured-BP threshold of SBP≥140 or DBP≥90 mmHg) and are therefore not used for cohort characterization; measured baseline BP is reported instead, and hypertension and heart-failure diagnosis codes are omitted from Table 1.

2.5 Statistical Analysis

All continuous variables were non-normally distributed (assessed by visual inspection of the distributions); therefore, medians and interquartile ranges (IQRs) are reported throughout. Sex-disaggregated comparisons of continuous outcomes used the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test when expected cell counts were <5. A two-tailed p-value <0.05 was considered statistically significant. No multiple-comparison correction was applied, given the exploratory nature of the secondary analyses; findings should be interpreted accordingly.

Missing data were handled using available-case analysis; no imputation was performed. Missing data were moderate: ΔHbA1c was available for 324/391 (82.9%), ΔBMI for 343/391 (87.7%), ΔeGFR for 333/391 (85.2%), and ΔSBP for 337/391 (86.2%). Missingness in the primary outcome was found to depend on baseline glycemic status rather than being random (detailed below).

The primary analysis was revised after peer review to an ANCOVA-type model of follow-up HbA1c, with baseline HbA1c, sex, treatment group, a sex-by-treatment interaction term, age, follow-up duration (days), an indicator for baseline HbA1c in the diabetes diagnostic range (baseline HbA1c≥6.5%, used in place of the unreliable structured diabetes diagnosis code — see Section 2.4), and baseline eGFR as covariates. This was not part of a dated statistical analysis plan predating the original submission and is reported as a revised primary analysis, not a pre-specified one. The sex-by-treatment interaction coefficient, with its 95% confidence interval (CI), is the statistic that determines whether treatment response differs by sex; a non-significant interaction does not by itself establish equivalent response, only the absence of a statistically detectable difference. Sex was not tested as a stand-alone predictor of treatment response, since a main-effect coefficient for sex, adjusted only for treatment group, cannot distinguish "no sex effect" from "no sex-by-treatment interaction" — this distinction was raised in peer review of an earlier version of this manuscript and is addressed here directly. Because the model includes an interaction term, the treatment and sex main-effect coefficients are conditional, not average, effects (see Results 3.4 for sex-specific contrasts). Residual diagnostics identified heteroscedasticity (Breusch-Pagan p<0.001), motivating the HC3 robust standard errors reported throughout, and non-normality of residuals (Shapiro-Wilk p<0.001, driven by excess kurtosis rather than skew), consistent with the non-normal distribution of the underlying laboratory values; coefficient point estimates are retained under ordinary least squares, but the non-normality is a further reason to treat p-values and CIs as approximate rather than exact. This interaction analysis was conducted for HbA1c only, the primary outcome; the three secondary outcomes

(BMI, eGFR, systolic BP) were not re-analyzed with an interaction term, and no claim about sex-specific treatment response is made for them in this manuscript (see title, Abstract, and Discussion, which are scoped accordingly). All analyses were performed in Python (NumPy v2.4, SciPy v1.17; statsmodels for the interaction model). Age was recorded in the source data as 10-year bands (e.g., "11–20," "21–30") rather than exact age, with the band midpoint used as a continuous proxy throughout. One enrolled patient fell in the "11–20" band (midpoint 15.5); because this band spans both minors and adults and no exact age or birth date was available to confirm eligibility, this patient was excluded from all analyses rather than retained pending verification (final analytic cohort n=391 of the original n=392). Excluding this patient did not materially change any reported estimate. Treatment group was defined as ever having a recorded dapagliflozin prescription during the study period ("DAPA only") or a recorded prescription for both dapagliflozin and semaglutide ("DAPA+SEMA"), regardless of the order or timing of initiation; no single index date anchors the two-drug comparison, so this is an ever-treated rather than a time-anchored exposure definition. Given a related analysis in this cohort was previously found to have substantial immortal-time bias, exposure timing was checked directly: among DAPA+SEMA patients with dated prescription records for both drugs (87/133, 65%), the median gap between first dapagliflozin and first semaglutide fill was 0 days, 76% (66/87) started semaglutide within 30 days of dapagliflozin in either direction, but 22% (19/87) started semaglutide more than 30 days after dapagliflozin (median lag 87 days) and 23% (20/87) more than 30 days before. This is a materially smaller degree of exposure misalignment than was found in the related analysis, but it is not negligible, and the current ever-treated exposure definition does not fully eliminate immortal-time risk; a time-varying exposure definition anchored to a common index date is recommended before this analysis is extended or used to support a stronger causal claim, and is noted as a limitation. Exact calendar study dates, prescribing doses, treatment duration prior to outcome measurement, and the rule used to resolve a single baseline-follow-up HbA1c pair when a patient had multiple recorded encounters are not available in the extract used for this analysis; the latter, in particular, is disclosed here as a limitation rather than resolved, since the resolution logic was applied upstream of the file used for this analysis and could not be reconstructed from the data dictionary provided. A cohort flow from the source population (662 patients with any dapagliflozin or semaglutide record) to the final analytic sample (391 patients meeting the 90–360 day follow-up window, after excluding the one age-indeterminate minor) is summarized in the Results. Missingness in the primary outcome (17.9% of the 391-patient cohort) was compared between patients with and without observed follow-up HbA1c across sex, treatment group, age, follow-up duration, baseline HbA1c, the baseline HbA1c diagnostic-range indicator, and baseline eGFR. Missingness was not significantly associated with sex ($p=0.28$) or treatment group ($p=0.075$, though numerically lower missingness in the DAPA+SEMA group), age ($p=0.18$), follow-up duration ($p=0.09$), or baseline eGFR ($p=0.83$). It was strongly associated with baseline glycemic status: patients without diabetic-range baseline HbA1c (<6.5%) had substantially higher missingness (64%, 34/53) than those with diabetic-range HbA1c (10%, 33/338; $p<0.001$), consistent with less frequent HbA1c monitoring in patients without diabetes. Missingness is therefore not plausibly missing-completely-at-random with respect to baseline glycemic status, and the 13–17% per-variable missingness across outcomes is characterized as moderate, not minimal; available-case analysis was retained given the exploratory nature of the study,

but this dependency should be considered when interpreting the HbA1c results, particularly in the non-diabetic subgroup.

3. Results

3.1 Sample Characteristics

Of 662 patients in the source population with any recorded dapagliflozin or semaglutide prescription, applying the 90–360 day follow-up criterion and requiring non-missing baseline sex, age, and treatment-group data yielded 392 patients, one of whom (age-band midpoint 15.5 years) was excluded because eligibility as an adult could not be confirmed (see Methods), leaving a final analytic cohort of 391 patients (213 female, 178 male). Age and follow-up duration were similar between sexes (p=0.121 and p=0.626, respectively). The distribution of treatment groups did not differ significantly by sex (DAPA+SEMA: 35.7% female vs 32.0% male; p=0.514). BMI class differed markedly between sexes (p<0.001). Women were more commonly in obesity classes II and III (28.2% and 27.7%, respectively), whereas men were more evenly distributed across overweight and obesity class I. Measured cardiometabolic markers and recorded diagnoses were broadly similar by sex; using a measured-BP threshold (SBP≥140 or DBP≥90 mmHg), elevated BP was somewhat more common in women than men (50.3%, 94/187 women vs 44.4%, 72/162 men; p=0.328), though structured hypertension diagnosis coding under-captured this in both sexes (see Methods). Baseline characteristics are presented in Table 1.

Table 1. Baseline Characteristics Stratified by Sex

Variable	Female (n = 213)	Male (n = 178)	p-value
Age, years — median (IQR)	55.5 (55.5–65.5)	65.5 (55.5–65.5)	0.121
Follow-up, days — median (IQR)	190 (167–230)	189 (170–242)	0.626
Treatment group			
DAPA + SEMA	76/213 (35.7%)	57/178 (32.0%)	
DAPA only	137/213 (64.3%)	121/178 (68.0%)	0.514
BMI class			
Normal weight	4/192 (2.1%)	23/169 (13.6%)	
Overweight	18/192 (9.4%)	40/169 (23.7%)	
Obesity class I	51/192 (26.6%)	51/169 (30.2%)	
Obesity class II	60/192 (31.3%)	33/169 (19.5%)	
Obesity class III	59/192 (30.7%)	22/169 (13.0%)	<0.001
Measured cardiometabolic markers			
Baseline HbA1c in diabetes diagnostic range (≥6.5%)	180/193 (93.3%)	158/168 (94.0%)	0.930
Elevated measured blood pressure (SBP≥140 or DBP≥90 mmHg)	94/187 (50.3%)	72/162 (44.4%)	0.328
Baseline eGFR <60 mL/min/1.73 m²	40/194 (20.6%)	46/168 (27.4%)	0.166
Recorded diagnoses			
Coronary artery disease	2/213 (0.9%)	6/178 (3.4%)	0.185
Atrial fibrillation	1/213 (0.5%)	2/178 (1.1%)	0.880
Prior cardiovascular events			
Myocardial infarction	11/213 (5.2%)	14/178 (7.8%)	0.387
Stroke	8/213 (3.8%)	6/178 (3.4%)	1.000

Categorical variables are n/N (%), where N is the number with non-missing data; continuous variables are median (IQR). p-values were calculated using the Mann–Whitney U test for continuous variables and the chi-square or Fisher exact test, as appropriate, for categorical variables. The HbA1c and eGFR rows describe single baseline measurements and do not independently establish diabetes or chronic kidney disease. Coronary artery disease, atrial fibrillation, myocardial infarction, and stroke are structured-code counts and should be interpreted as minimum documented prevalence. DAPA = dapagliflozin; SEMA = semaglutide; IQR = interquartile range.

3.2 Baseline Cardiometabolic Profile by Sex

Two baseline parameters differed significantly between sexes. Women had substantially higher BMI (median 36.6 vs 32.1 kg/m²; p<0.001) and higher HDL-C (1.1 vs 0.9 mmol/L; p<0.001). Diastolic BP was lower in women than in men (68 vs 71 mmHg; p=0.013). Baseline HbA1c, eGFR, systolic BP, LDL-C, and triglycerides did not differ significantly by sex.

3.3 Treatment Response by Sex

Table 2 summarizes cardiometabolic parameters at baseline and follow-up, including change scores, stratified by sex. Both sexes showed modest reductions in BMI, HbA1c, and systolic BP. No statistically significant sex differences were observed in any delta parameter: ΔBMI (−0.6 vs −0.4 kg/m²; p=0.533), ΔHbA1c (−0.3% vs −0.5%; p=0.956), ΔeGFR (0.0 vs 0.0 mL/min/1.73 m²; p=0.845), ΔSBP (0 vs −2 mmHg; p=0.502), and ΔHDL-C (0.0 vs 0.0 mmol/L; p=0.288). These unadjusted comparisons describe sex differences in change scores; they do not test sex-by-treatment interaction or establish equivalence of effect. Heart failure hospitalization was not analyzed as an outcome (see Methods).

Table 2. Cardiometabolic Parameters at Baseline and Follow-up, by Sex

Variable	Female (n = 213)			Male (n = 178)			p*
	Baseline	*Follow-up*	*Δ*	*Baseline*	*Follow-up*	*Δ*	
BMI (kg/m²)	36.6 (32.5–40.8)	36.1 (31.2–39.9)	−0.6 (−1.7–0.1)	32.1 (27.5–36.2)	31.4 (26.6–35.4)	−0.4 (−1.4–0.0)	0.533
HbA1c (%)	8.7 (7.6–9.8)	8.0 (7.1–9.2)	−0.3 (−1.4–0.2)	8.1 (7.4–9.7)	7.6 (7.0–8.7)	−0.5 (−1.2–0.2)	0.956
eGFR (mL/min/1.73 m²)	81.0 (64.2–93.0)	81.0 (65.0–91.8)	0.0 (−7.0–8.0)	81.0 (57.0–96.0)	81.0 (58.0–98.0)	0.0 (−6.2–7.2)	0.845
Systolic BP (mmHg)	139 (127–151)	135 (127–145)	0 (−13–8)	136 (123–149)	135 (121–145)	−2 (−15–6)	0.502
Diastolic BP (mmHg)	68 (63–76)	67 (63–74)	−1 (−9–5)	71 (65–80)	72 (65–80)	0 (−7–6)	0.258
LDL-C (mmol/L)	2.4 (1.9–3.0)	2.3 (2.0–3.0)	0.0 (−0.3–0.3)	2.3 (1.7–2.8)	2.2 (1.6–2.8)	−0.1 (−0.5–0.2)	0.353
HDL-C (mmol/L)	1.1 (0.9–1.4)	1.2 (1.0–1.4)	0.0 (−0.1–0.1)	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.0 (−0.1–0.1)	0.288
Triglycerides (mmol/L)	1.3 (1.0–1.8)	1.3 (1.0–1.8)	0.0 (−0.4–0.2)	1.4 (1.1–1.9)	1.3 (0.9–1.8)	0.0 (−0.4–0.2)	0.680

*Values are median (IQR). * p-value for sex comparison of the change score (Δ) using the Mann–Whitney U test. BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.*

3.4 Sex-by-Treatment Interaction and Multivariable-Adjusted Treatment Response

In the revised primary ANCOVA model of follow-up HbA1c (n=313; baseline HbA1c, sex, treatment group, sex-by-treatment interaction, age, follow-up duration, an indicator for baseline HbA1c in the diabetes diagnostic range, and baseline eGFR; heteroscedasticity-robust [HC3] standard errors; Table 3; Figure 1), the sex-by-treatment interaction was not statistically significant (β=0.060; 95% CI −0.582 to 0.702; p=0.855). DAPA+SEMA was associated with a smaller adjusted HbA1c reduction than DAPA alone in men (β=0.470; 95% CI 0.017 to 0.923; p=0.042) and women (β=0.530; 95% CI 0.091 to 0.968; p=0.018). Sex was not associated with follow-up HbA1c within the DAPA-only group (β=0.111; 95% CI −0.208 to 0.430; p=0.495) or within the DAPA+SEMA group (β=0.171; 95% CI −0.405 to 0.746; p=0.559). Age, follow-up duration, the baseline HbA1c diagnostic-range indicator, and baseline eGFR were not

statistically significant. This interaction analysis addresses HbA1c only; treatment-effect modification by sex was not tested for BMI, eGFR, or systolic BP.

Table 3. Primary Analysis: Sex-by-Treatment Interaction Model for Follow-up HbA1c

ANCOVA model: follow-up HbA1c ~ baseline HbA1c + sex + treatment group + sex×treatment + age + follow-up duration + baseline HbA1c diagnostic-range indicator + baseline eGFR. This is the revised primary analysis, added after peer review (not part of a dated pre-submission analysis plan); the sex×treatment interaction coefficient, not the sex main effect, is the statistic that tests whether treatment response differs by sex.

Variable	β	95% CI	p-value	Sig.
Baseline HbA1c (%)	0.569	0.443 to 0.695	**<0.001**	*
Sex (Female vs Male)	0.111	−0.208 to 0.430	0.495	**ns**
Treatment (DAPA+SEMA vs DAPA)	0.470	0.017 to 0.923	**0.042**	*
Sex × Treatment (interaction)	0.060	−0.582 to 0.702	0.855	**ns**
Age (years)	0.017	−0.001 to 0.035	0.061	**ns**
Follow-up duration (days)	0.0002	−0.002 to 0.003	0.887	**ns**
Baseline HbA1c in diabetes diagnostic range (≥6.5%)	−0.044	−0.780 to 0.692	0.906	**ns**
Baseline eGFR (mL/min/1.73m²)	0.0010	−0.004 to 0.006	0.693	**ns**

*n=313 complete cases | R^2=0.434 | Model p=3.9×10⁻¹⁹ (heteroscedasticity-robust [HC3] standard errors). Bold p-values indicate statistical significance (p<0.05). Sig. column: * p<0.05, ns = not significant.*

Figure 1. Sex-by-Treatment Interaction Estimates for HbA1c Response (Forest Plot)

4. Discussion

This sex-disaggregated real-world analysis produced two principal observations. Women entered treatment with a distinct baseline cardiometabolic phenotype, including higher BMI, more severe obesity distribution, and higher HDL-C. For the primary outcome, no statistically detectable sex-by-treatment interaction was identified for HbA1c response. This finding is exploratory and does not establish equivalent response between women and men.

The higher BMI burden in women aligns with national Saudi and GCC surveillance data, which show that female obesity prevalence consistently exceeds that of men.[4,5] In the Saudi Heart Health Promotion Study, obesity was more prevalent among females aged 40–49 years and older.[6] Cardiometabolic clinicians in the Gulf region should anticipate that women may present with more advanced adiposity-related phenotypes, warranting sex-aware baseline risk stratification.

The absence of a statistically detectable sex-by-treatment interaction in HbA1c response is broadly consistent with pooled DAPA-HF and DELIVER analyses, in which dapagliflozin reduced cardiovascular death and worsening heart-failure events similarly in men and women (p-interaction=0.77).[9] DAPA-CKD likewise reported preserved renoprotective effects across sexes.[14] Direct comparison remains limited because those trials evaluated randomized dapagliflozin effects on cardiovascular or renal outcomes, whereas the present observational study compared treatment regimens using short-term HbA1c. A 2024 meta-analysis also suggested a modestly lower relative reduction in primary cardiac outcomes among women receiving SGLT2 inhibitors,[15] underscoring that sex-related treatment effects may vary by drug class, endpoint, and study design.

In sex-specific contrasts from the revised primary model, DAPA+SEMA was associated with a smaller adjusted HbA1c reduction than DAPA alone in both men and women. This should not be interpreted as evidence that semaglutide produced less clinical benefit. Combination treatment was not randomized, patients receiving DAPA+SEMA had higher baseline HbA1c, treatment timing was heterogeneous, and information on indication, adherence, dose, exposure duration, and concomitant glucose-lowering therapy was incomplete. The estimates therefore represent noncausal adjusted associations that remain susceptible to confounding by indication and residual confounding.

The interaction estimate was imprecise, with a confidence interval compatible with potentially relevant effects in either direction. Accordingly, the absence of statistical significance should be interpreted as no detectable interaction in this sample, not evidence of equivalence or comparable clinical benefit.

Limitations

This study has several limitations. First, the observational, single-center design precludes causal inference and limits generalizability beyond similar GCC tertiary care settings. Second, the 90–360-day follow-up window captures only early treatment response and may not reflect long-term cardiometabolic or cardiovascular trajectories. Third, structured diagnosis codes for hypertension, heart failure, diabetes, and chronic kidney disease were all found to substantially undercount measured or laboratory-defined burden in this cohort (e.g., diabetes: 50% coded vs 94% with baseline HbA1c in the diabetes diagnostic range; chronic kidney disease: 6% coded vs 24% with baseline eGFR <60 mL/min/1.73 m²), and coronary artery disease, atrial fibrillation, myocardial infarction, and stroke — for which no comparable objective check was available — should be assumed to be undercounted similarly; all comorbidity prevalence in this manuscript should be read as a floor, not a validated estimate. The gap between diabetes diagnosis coding and HbA1c-based diabetic-range status is expected in part because dapagliflozin is indicated for chronic kidney disease and heart failure independent of diabetes status, so a substantial minority of patients without a diabetes diagnosis are nonetheless monitored with HbA1c as part of routine metabolic safety monitoring; treatment indication and concomitant glucose-lowering therapy were not available in the data extract used and are not adjusted for. Fourth, the semaglutide assignment was not randomized; confounding by indication for the semaglutide-HbA1c association cannot be ruled out. Fifth, residual confounding from unmeasured variables — including medication adherence, concomitant

medications, lifestyle factors, and socioeconomic determinants — cannot be ruled out. Sixth, missing outcome data (13–17% per variable) were handled by available-case analysis. Missingness was not significantly associated with sex or treatment group but was strongly associated with baseline glycemic status, which may limit interpretation, particularly among patients without diabetic-range baseline HbA1c. Seventh, sex was recorded as a binary variable; gender identity and hormonal status were not available. Eighth, no multiple-comparison correction was applied to secondary analyses, given their exploratory nature. Ninth, this study was not powered a priori to detect a sex-by-treatment interaction; the wide confidence interval around the interaction coefficient (95% CI −0.58 to 0.70) is compatible with both a true null effect and with clinically relevant interactions that this sample could not reliably detect — absence of significance should not be read as evidence of equivalence. Tenth, one patient in the 11–20-year age band was excluded because exact age was unavailable and adult eligibility could not be confirmed; exclusion did not materially change the reported estimates.

5. Conclusion

Women in this Saudi real-world cohort had higher adiposity and a more obesity-dominant baseline phenotype than men. In the revised primary analysis, no statistically detectable sex-by-treatment interaction was found for short-term HbA1c response to dapagliflozin with or without semaglutide. The estimate was imprecise and does not establish equivalence. These findings are hypothesis-generating and require confirmation in prospectively defined, adequately powered studies with time-anchored treatment exposure and longer follow-up.

Declarations

Ethics approval: Approved by the Institutional Review Board of KAIMRC, MNGHA, Saudi Arabia (Protocol No. NRA26/004/2). Individual informed consent was waived due to retrospective anonymized data.

Consent to Participate declaration: Not applicable.

Conflict of interest: None declared.

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Data availability: Data are available from the corresponding author upon reasonable request, subject to approval by the institution's data governance.

Author contributions: M.O.A. (AlTaweel): conceptualization, study design, data curation, statistical analysis, interpretation, manuscript drafting and revision, and final approval. R.A. (Alharajin): manuscript review, critical revision, and final approval.

Artificial intelligence: AI tools were used to support manuscript preparation and language editing. The author reviewed, interpreted, and verified all content.

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Figures

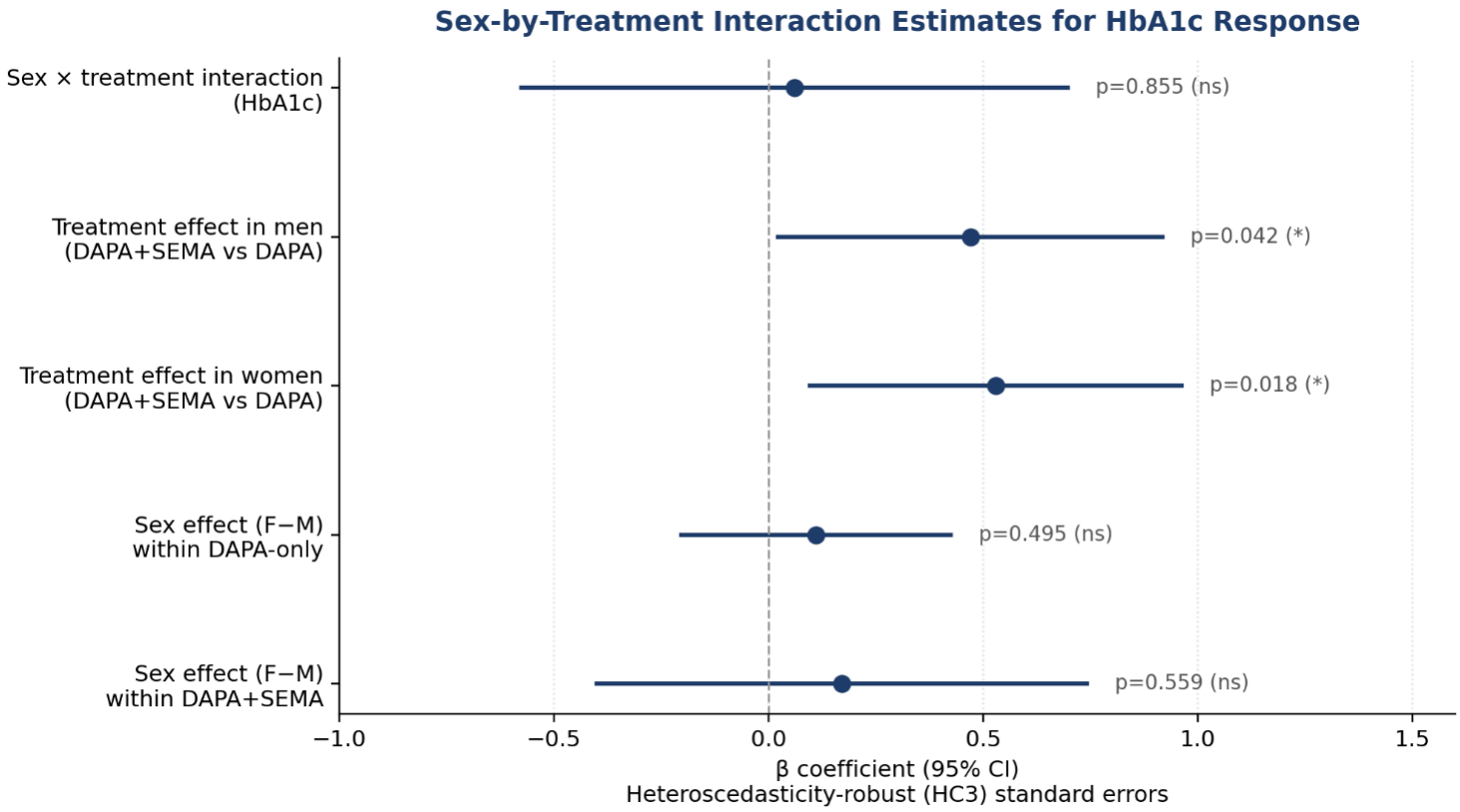


Figure 1

Sex-by-Treatment Interaction Estimates for HbA1c Response (Forest Plot)

Forest plot of estimates from the revised primary ANCOVA model of follow-up HbA1c (Table 3): the sex-by-treatment interaction coefficient, the DAPA+SEMA-versus-DAPA treatment contrast estimated separately in men and women, and the female-versus-male contrast estimated within the DAPA-only and DAPA+SEMA groups. Error bars indicate 95% confidence intervals calculated using heteroscedasticity-robust (HC3) standard errors. The dashed vertical line denotes β=0. DAPA = dapagliflozin; SEMA = semaglutide.