

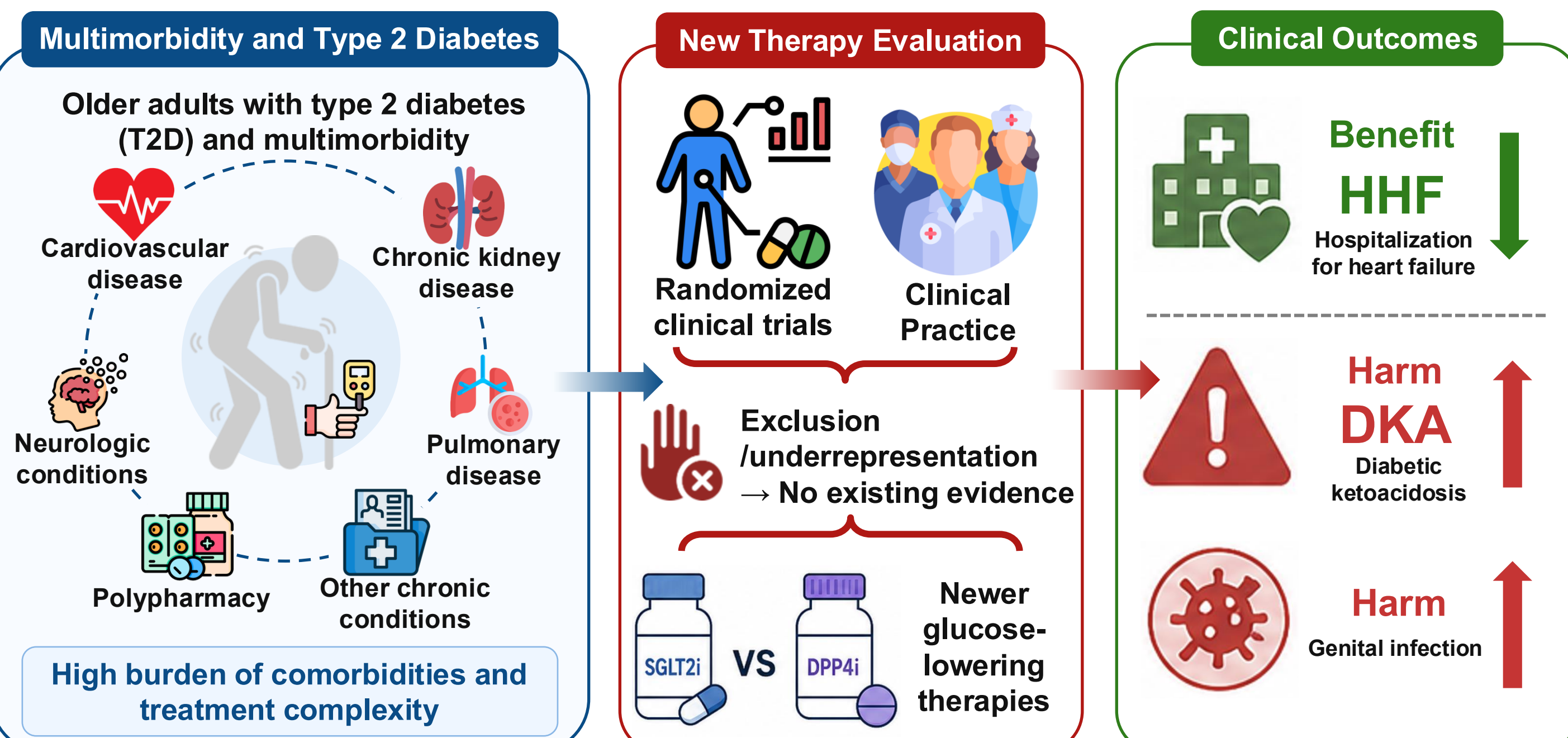


Association of Multimorbidity Burden with the Safety and Effectiveness of SGLT2 Inhibitors Versus DPP-4 Inhibitors Among Older Adults with Type 2 Diabetes: A Target Trial Emulation Study

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Background



Does multimorbidity burden modify this benefit-risk profile?

Objective

To assess whether multimorbidity burden modifies the effectiveness and safety of Sodium-glucose cotransporter-2 inhibitors (SGLT2i) compared with dipeptidyl peptidase-4 inhibitors (DPP4i) among older Medicare beneficiaries with T2D.

Methods

Study Design & Data Source

- Target trial emulation among older adults with T2D initiating SGLT2i or DPP4i.
- Medicare fee-for-service claims (2013-2021).

- ### Patient Population
- Medicare beneficiaries aged ≥ 66 years with T2D & ≥ 1 year of continuous enrollment before treatment initiation.
 - Patients with major contraindications (type 1 diabetes, end-stage kidney disease or dialysis, HIV, cancer except non-melanoma skin cancer) OR alternative indications were excluded.

Exposure & Outcomes

- New initiators
- SGLT2i vs DPP4i
- Primary benefit outcome: **HHF**.
- Primary harm outcome: **DKA**.
- Secondary safety outcome: **genital infection**.

Multimorbidity Burden

- Categorized by Combined Comorbidity Index (CCI) terciles
- Mild, moderate, and severe.

Statistical analyses

- IPTW within CCI strata
- Adjusted HRs and RDs per 1,000 person-years
- Cochran's Q for heterogeneity
- Sensitivity analyses: MWI, CFI; GLP-1RA comparator

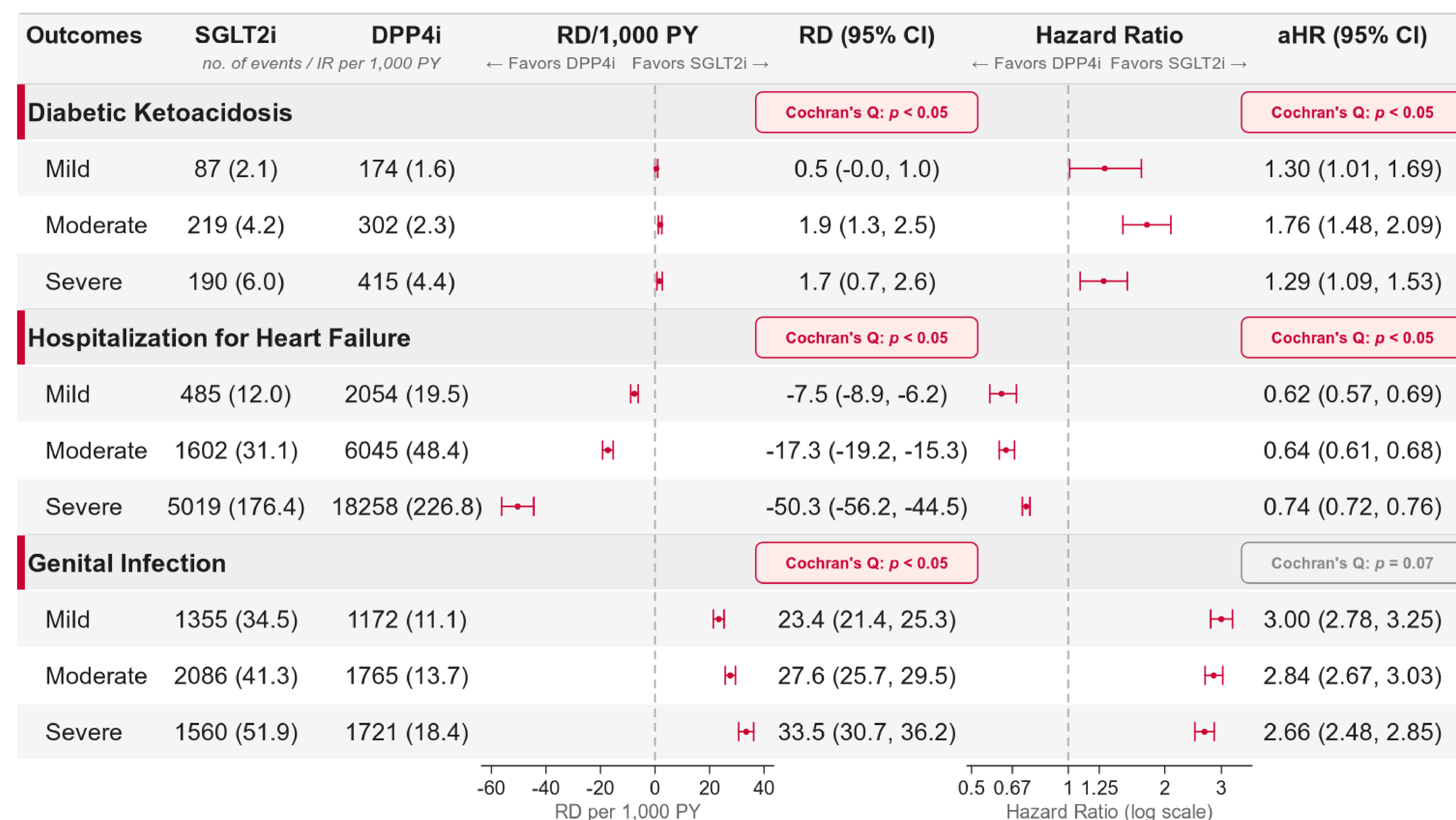
Results

Table 1. Selected baseline characteristics of antidiabetic users between SGLT2i and DPP4i before and after IPTW.

Characteristics	Unweighted			Weighted		
	SGLT2i (N = 117,519)	DPP4i (N = 258,008)	SMD	SGLT2i (N = 116,224)	DPP4i (N = 260,512)	SMD
Age, mean (SD), yr	73.0 (5.7)	75.3 (7.2)	35.4	74.4 (6.6)	74.5 (6.9)	1.5
Female	57,334 (48.8)	152,089 (58.9)	20.5	66,150 (56.9)	66,568 (56.1)	1.6
Race						
White	85,537 (72.8)	172,598 (66.9)	12.9	80,361 (69.1)	81,799 (68.9)	0.4
Black	9,741 (8.3)	28,896 (11.2)	9.8	11,809 (10.2)	12,109 (10.2)	0.1
Hispanic	11,087 (9.4)	30,938 (12.0)	8.3	13,000 (11.2)	13,262 (11.2)	0.0
Other	11,154 (9.5)	25,576 (9.9)	1.4	11,054 (9.5)	11,490 (9.7)	0.6
No., inpatient visits	0.1 (0.5)	0.4 (0.9)	41.2	0.3 (1.0)	0.3 (0.8)	0.0
CCI terciles						
Mild	33,945 (28.9)	76,383 (29.6)	1.6	34,404 (29.6)	34,919 (29.4)	0.4
Moderate	49,812 (42.4)	99,479 (38.6)	7.8	46,455 (40.0)	47,068 (39.7)	0.6
Severe	33,762 (28.7)	82,146 (31.8)	6.8	35,365 (30.4)	36,672 (30.9)	1.0
DKA	24,594 (20.9)	45,526 (17.6)	8.3	21,051 (18.1)	22,004 (18.5)	1.1
CKD	18,635 (15.9)	50,511 (19.6)	9.8	21,735 (18.7)	21,965 (18.5)	0.5
Heart failure	103,960 (88.5)	221,705 (85.9)	7.6	100,615 (86.6)	102,935 (86.7)	0.5
Genital infection	2,873 (2.4)	7,345 (2.8)	2.5	3,602 (3.1)	3,312 (2.8)	1.8
Polypharmacy	61,281 (52.1)	211,960 (82.2)	67.4	84,595 (72.8)	85,762 (72.3)	1.1

Abbreviations: CCI, combined comorbidity index; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; DPP4i, dipeptidyl peptidase-4 inhibitors; IPTW, inverse probability of treatment weighting; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standard mean difference.

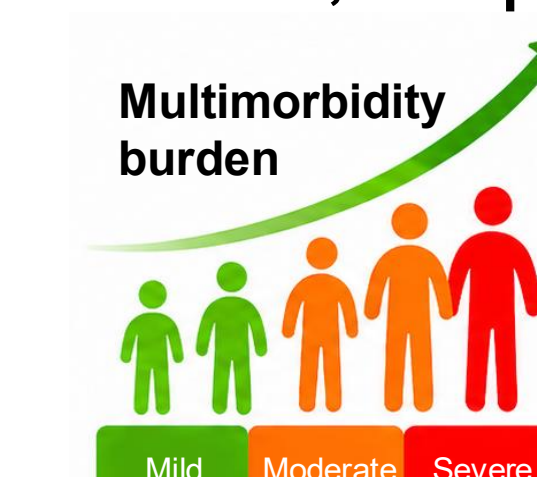
Figure 1. RD & aHR comparing SGLT2i and DPP4i after IPTW for primary outcomes stratified by CCI.



Abbreviations: aHR, adjusted hazard ratio; CCI, combined comorbidity index; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; IPTW, inverse probability of treatment weighting; MWI, multimorbidity weighted index; PY, person-year; RD, risk difference; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standard mean difference.

Conclusions

- Among older Medicare beneficiaries with T2D, SGLT2i initiation was associated with lower HHF risk but higher risks of DKA and genital infection compared with DPP4i, as previously validated.



- Greater multimorbidity burden was associated with larger absolute HHF benefit and greater excess risk of genital infection.

- DKA risk was increased overall but showed less consistent variation across multimorbidity strata.

Multimorbidity burden should be carefully considered when evaluating the benefit-risk profile of SGLT2i in older adults with T2D.

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