

Comparative Effectiveness of SGLT2i, GLP-1, and Metformin on Cardiovascular Outcomes in Adults with Severe Mental Illness

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Background

- Individuals with severe mental illness (SMI) face disproportionately high cardiovascular (CV) and metabolic risk, leading to excess CV mortality.^{1,2}
- SGLT2 inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP-1s) provide established CV benefits in the general population.³
- However, their CV benefits in individuals with SMI—particularly as first-line treatment options—remain unclear.

Objective

- To assess first-line treatment with SGLT2i/GLP-1 versus metformin on major adverse cardiovascular events (MACE) risk in individuals with SMI and type 2 diabetes (T2D)

Methods

Study Design

Active comparator new-user design

Data Source

20% random sample of Medicare beneficiaries 2017–2022

Study Cohort

- Initiated SGLT2i, GLP-1, or metformin monotherapy 1/1/2018 – 12/31/2021
 - Index date [Day 0] = first RX claim for SGLT2i, GLP-1, or metformin
 - No prior use of metformin / 2nd-line agents during baseline [Days -365, -1]
- Inclusion criteria:
 - Continuous Medicare enrollment (Parts A, B, & D) during baseline
 - Age ≥18 on index date
 - SMI + T2D diagnosis during baseline [Days -365, 0]
 - SMI = schizophrenia, bipolar disorder, or major depressive disorder
- Exclusion criteria:
 - Initiated ≥2 antihyperglycemic classes on index date
 - Baseline diagnosis of type 1/gestational diabetes, polycystic ovary syndrome, organ transplant, ESRD, or HIV/AIDS
- Baseline confounding adjustment: overlap weighting
- Outcomes
 - ICD-10 codes in 1st or 2nd diagnosis position on inpatient claims
 - Primary: Composite of hospitalization for myocardial infarction, stroke, and all-cause mortality (3-point MACE)
 - Secondary: Individual MACE components; hospitalization for heart failure
- Follow-up
 - Began on [Day 1] and continued until the earliest of: outcome occurrence, treatment discontinuation or switch/add-on (per-protocol analyses only), Medicare disenrollment, end of study (Dec 31, 2022), 3 years of follow-up

Statistical Analysis

- Estimated intention-to-treat (ITT) and per-protocol (PP) effects
- PP analyses used inverse probability of censoring weights
- Outcomes model: pooled logistic regression
- Competing risk of death handled using the Aalen-Johansen estimator
- 95% CI obtained from 200 nonparametric bootstrap resamples

Results

- Among individuals with SMI and T2D, we identified new users of SGLT2i (n=1,322), GLP-1 (n=2,306), and metformin (n=21,144) as first-line treatment.
- Comparators were significantly different for most comorbidities (**Table 1**).

Table 1. Baseline characteristics of the study cohort by index treatment

No. (%)	SGLT2i n=1,322	GLP-1 n=2,306	Metformin n=21,144	P-Value
Demographics				
Age, mean (SD), y	67.1 (12.1)	65.0 (12.1)	66.3 (13.0)	<.001
Sex, Female	785 (59.4)	1,594 (69.1)	12,877 (60.9)	<.001
Original entitlement reason				
Age-based	602 (45.5)	889 (38.6)	9,437 (44.6)	<.001
Disability-based	720 (54.5)	1,417 (61.4)	11,707 (55.4)	<.001
Schizophrenia	142 (10.7)	267 (11.6)	4,283 (20.3)	<.001
Bipolar disorder	211 (16.0)	426 (18.5)	4,445 (21.0)	<.001
Major depressive disorder	1,169 (88.4)	2,023 (87.7)	17,295 (81.8)	<.001
Comorbidities				
Obesity	769 (58.2)	1,573 (68.2)	10,795 (51.1)	<.001
Diabetic nephropathy	675 (51.1)	1,090 (47.3)	6,456 (30.5)	<.001
Cardiovascular disease	977 (73.9)	1,487 (64.5)	12,460 (58.9)	<.001
Hyperlipidemia	1,190 (90.0)	1,968 (85.3)	17,293 (81.8)	<.001
Hypertension	1,236 (93.5)	2,143 (92.9)	18,798 (88.9)	<.001
Chronic kidney disease	601 (45.5)	1,000 (43.4)	5,200 (24.6)	<.001

Figure 3. 3-year risk difference and risk ratio (ITT): SGLT2i vs. Metformin

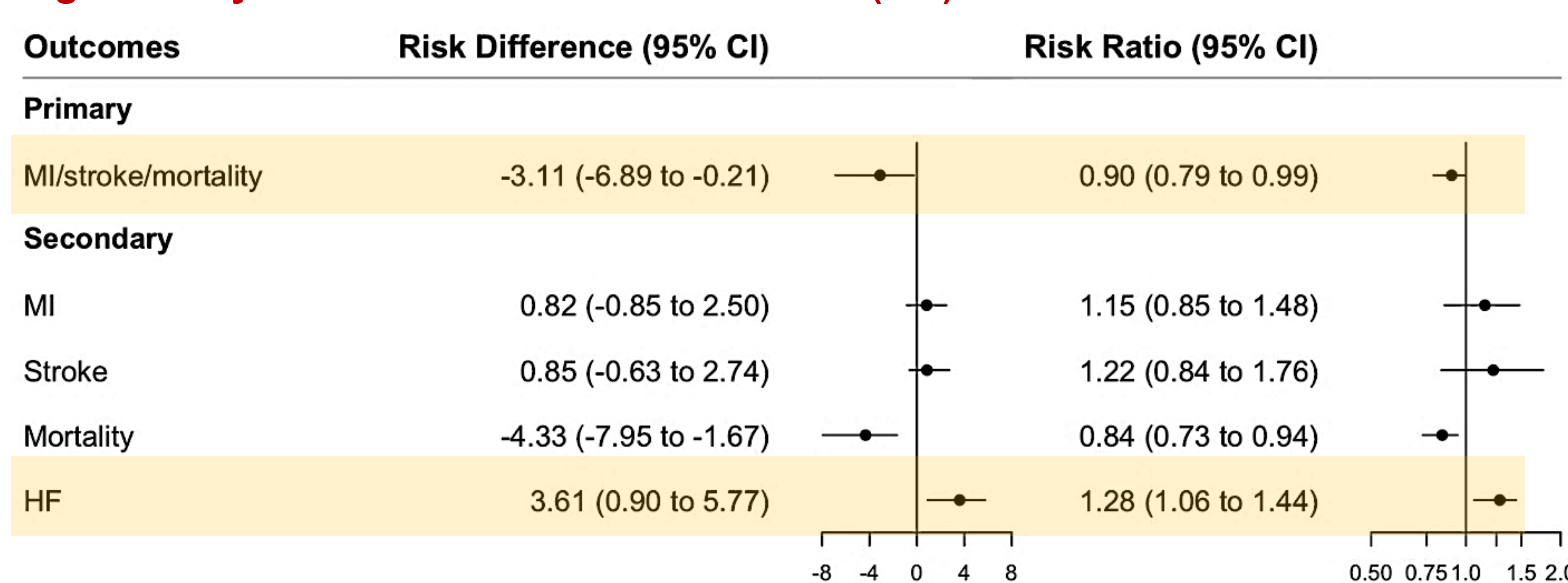


Figure 4. 3-year risk difference and risk ratio (ITT): GLP-1 vs. Metformin

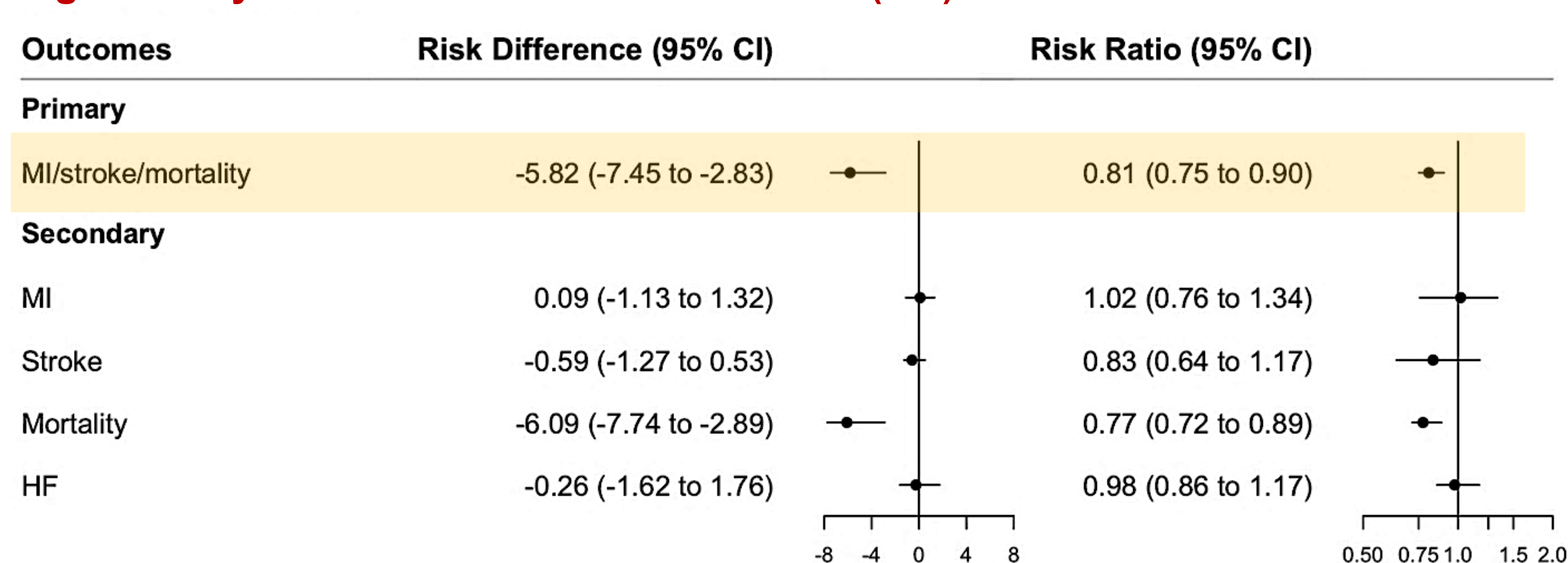


Figure 1. Cumulative incidence of MACE (ITT): SGLT2i vs. Metformin

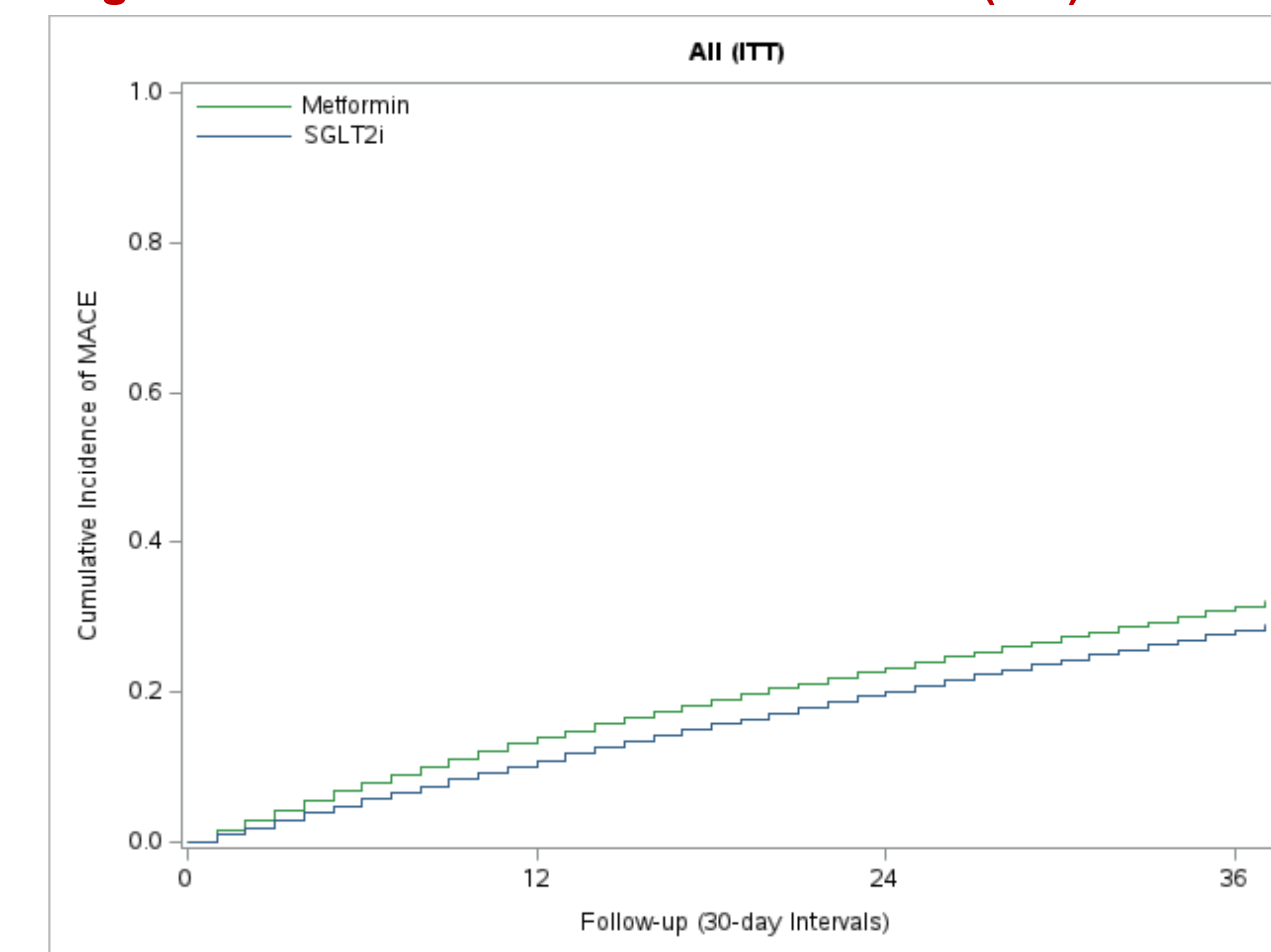
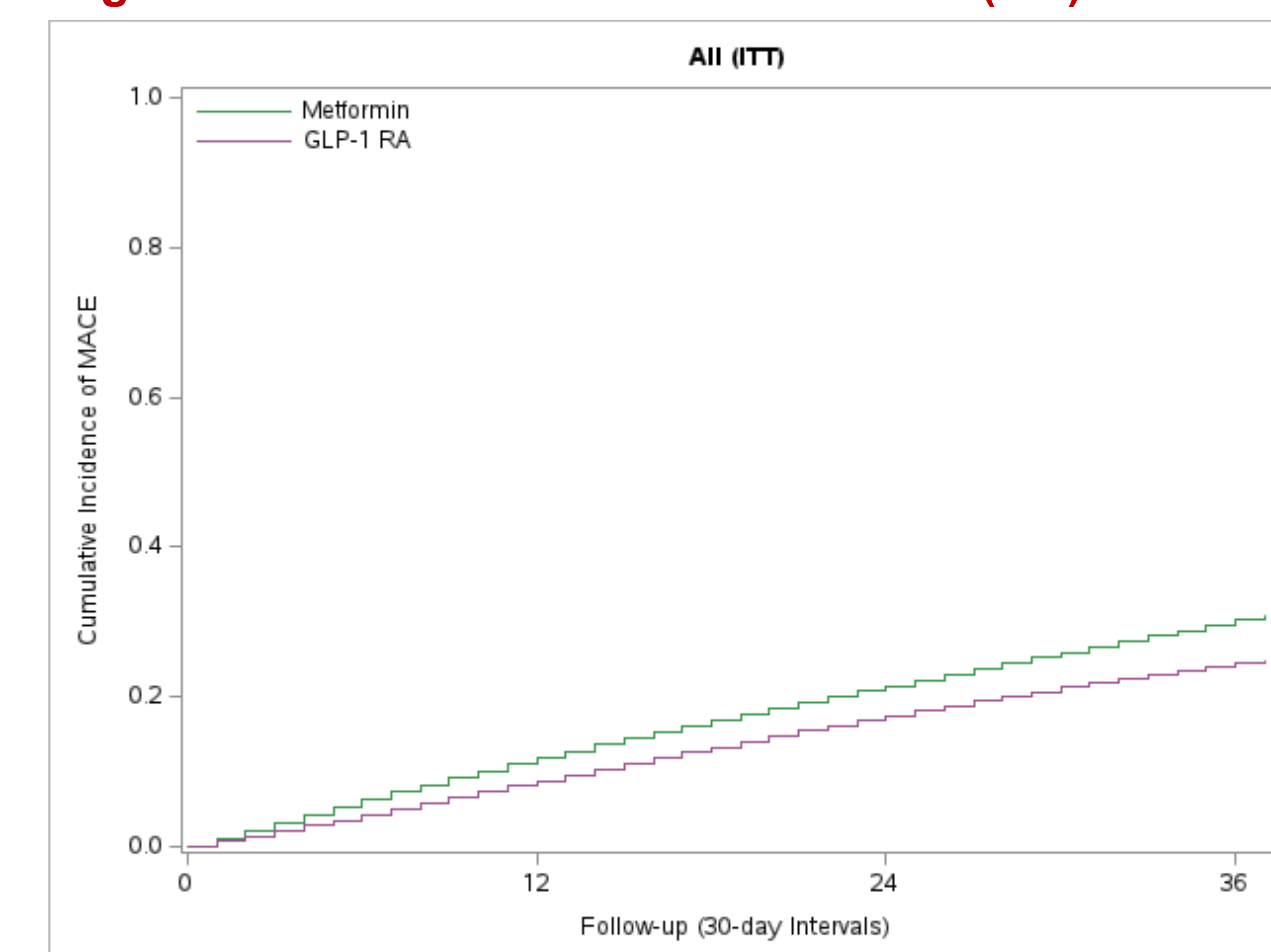


Figure 2. Cumulative incidence of MACE (ITT): GLP-1 vs. Metformin



Key Takeaways

- ✓ Among adults with SMI and T2D, SGLT2i and GLP-1 were associated with lower all-cause mortality, consistent with the broader T2D population.
- ✓ Higher HF risk with SGLT2i contrasts prior evidence, highlighting the need for studies with richer clinical data.
- ✓ PP estimates were directionally consistent with ITT estimates; suboptimal adherence and treatment changes were common.

References

1. Goldfarb et al. Severe mental illness and cardiovascular disease. J Am Coll Cardiol. 2022.
2. Polcwiartek et al. Severe mental illness: CV risk assessment and management. Eur Heart J. 2024.
3. Cardiovascular benefits of SGLT2i and GLP-1 RA in T2D. JAMA. 2019.

