Role of SGLT2 Inhibitor Use in Patients With Myelodysplastic Syndromes and Type 2 Diabetes: A TriNetX-Based Retrospective Analysis

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BACKGROUND

Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders characterized by ineffective hematopoiesis, immune dysregulation, and chronic marrow inflammation. By acting on overlapping metabolic, inflammatory, and hypoxia-related pathways (AMPK, PI3K/AKT/mTOR, NLRP3, oxidative stress, mitochondrial function, HIF-1α), SGLT2 inhibitors may influence infection risk, cardiovascular (CV) mortality, and survival in MDS. Real-world clinical evidence, however, remains limited.

METHOD

Design & data source: Retrospective cohort study using the TriNetX Analytics Network

Population: Adults with MDS and type 2 diabetes

Cohorts: SGLT2 inhibitor-exposed vs. nonexposed

Outcomes: Infectious complications, hematologic outcomes, CV events, and all-cause mortality

Confounding control: Propensity score matching (PSM) on baseline demographics, comorbidities, and contemporary MDS therapies

Analysis: Kaplan-Meier and Cox proportional hazards models for time-to-event outcomes, excluding preexisting events

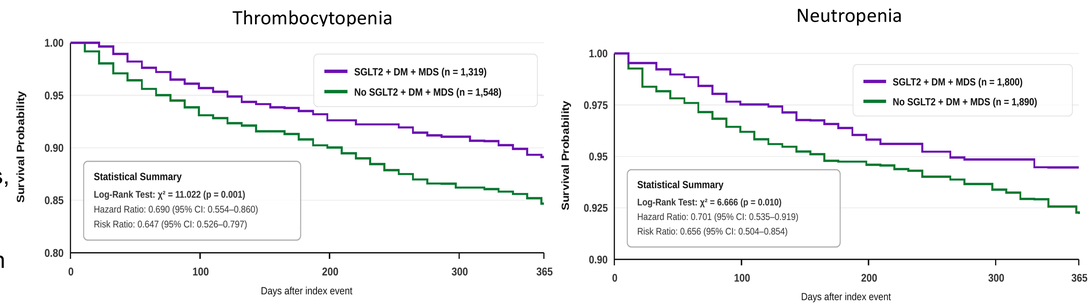
Baseline Characteristics of the Propensity-Score-Matched Cohorts

Characteristic	SGLT2i (n=2,297)	No SGLT2i (n=2,297)	P-value	Std. diff.
Demographics				
Age at index, mean ± SD (yr)	71.7 ± 11.2	71.2 ± 11.3	0.135	**0.044**
Female	888 (38.7%)	869 (37.8%)	0.564	**0.017**
Male	1,408 (61.3%)	1,428 (62.2%)	0.544	**0.018**
White	1,586 (69.0%)	1,588 (69.1%)	0.949	**0.002**
Black or African American	314 (13.7%)	315 (13.7%)	0.966	**0.001**
Not Hispanic or Latino	1,795 (78.1%)	1,808 (78.7%)	0.641	**0.014**
Comorbidities				
Type 2 diabetes	2,151 (93.6%)	2,190 (95.3%)	0.012	**0.074**
Chronic kidney disease	1,158 (50.4%)	1,158 (50.4%)	1.000	**<0.001**
Heart failure	1,144 (49.8%)	1,099 (47.8%)	0.184	**0.039**
MDS-directed & concomitant therapy				
Systemic corticosteroids	1,786 (77.8%)	1,794 (78.1%)	0.776	**0.008**
Azacitidine	133 (5.8%)	106 (4.6%)	0.073	**0.053**
Lenalidomide	62 (2.7%)	43 (1.9%)	0.061	**0.055**

Values are n (%) unless otherwise indicated. P-values from chi-square or t-test; standardized differences <0.1 indicate good covariate balance.

Table 1. Baseline characteristics of the propensity-score-matched cohorts. SGLT2 inhibitor-exposed (n = 2,297) and unexposed (n = 2,297) adults with myelodysplastic syndromes and type 2 diabetes, after 1:1 propensity-score matching. Values are n (%) unless otherwise indicated; age is mean ± SD. Standardized differences <0.1 indicate good balance across all measured covariates.

Kaplan-Meier Event-Free Survival



Kaplan-Meier Survival Summary

Cohort	Patients in cohort	Patients with outcome	Median survival (days)	Survival prob. at 365 days
SGLT2	1,319	123	—	89.12%
No SGLT2	1,548	223	—	84.68%

— median survival not reached (>50% event-free at 365 days). Excludes patients with the outcome before the index date.

Kaplan-Meier Survival Summary

Cohort	Patients in cohort	Patients with outcome	Median survival (days)	Survival prob. at 365 days
SGLT2	1,800	85	—	94.47%
No SGLT2	1,890	136	—	92.21%

— median survival not reached (>50% event-free at 365 days). Excludes patients with the outcome before the index date.

Figure 1. Kaplan-Meier event-free survival for thrombocytopenia (left) and neutropenia (right) over 365 days, comparing SGLT2 inhibitor-exposed and unexposed cohorts after propensity-score matching. Curves show the probability of remaining free of each outcome; patients with the outcome before the index date were excluded (incident events only). n = patients at risk per arm; hazard ratios are from Cox proportional-hazards models and p-values from the log-rank test. The y-axis is truncated at 0.80 to display curve separation.

RESULTS

- **Follow-up (post-PSM):** Short-term 289 vs 316 days; long-term 578 vs 791 days
- **Thrombocytopenia:** Significantly reduced with SGLT2i: 9.3% vs 14.4% (HR 0.69; 95% CI 0.55-0.86)
- **Neutropenia:** Significantly reduced: 4.7% vs 7.2% (HR 0.70; 95% CI 0.53-0.91)
- **Sepsis, pneumonia, CV mortality:** Numerically lower with SGLT2i; not statistically significant
- **Progression to AML:** No significant difference (HR 0.90; 95% CI 0.65-1.25), likely underpowered given cohort size
- **All-cause mortality (long-term, incident events):** No difference in time to death (HR 0.98; 95% CI 0.87-1.10)

CONCLUSION

SGLT2 inhibitors might have biologically plausible metabolic and immunomodulatory effects that may improve hematologic and survival outcomes in MDSs. Longer follow-up and prospective studies are needed to define the clinical relevance of SGLT2 inhibitors in patients with MDSs and type 2 diabetes, and their impact on survival.

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AKT, protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; HIF-1α, hypoxia-inducible factor 1-alpha; mTOR, mechanistic target of rapamycin; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain–containing 3; PI3K, phosphoinositide 3-kinase; SGLT2, sodium-glucose cotransporter 2.