Glucagon-like Peptide-1 Agonists and Clinical Outcomes in Polycythemia Vera: A Large-Scale Propensity-Matched Cohort Study

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Introduction

- Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by an elevated risk of venous thromboembolism (VTE), stroke/TIA, and progression to myelofibrosis in 10–25% of patients.
- Glucagon-like peptide-1 agonists (GLP-1a), initially developed for glycemic control, exhibit antineoplastic properties by inhibiting PI3K/AKT/mTOR and ERK/MAPK pathways, inducing G2/M cell cycle arrest, modulating JAK/STAT pathway and reducing glucose uptake in neoplastic cells. Furthermore, activation of GLP1 receptor in monocytes, macrophages, and neutrophils has been shown to suppress NF-κβ signaling, limit NLRP3 inflammasome priming, and mitigate oxidative stress.
- Despite these properties, their impact on PV, particularly on thrombotic risk and clinical outcomes, remains underexplored. This study investigates the effect of GLP-1a in PV patients, in a large global cohort study.

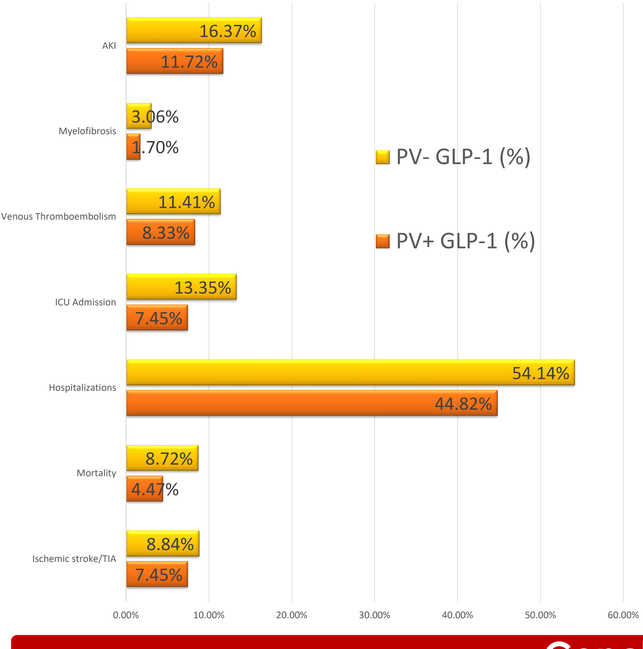
Methods

- We performed a retrospective propensity score-matched (PSM) cohort study using the TriNetX Analytics Network database, including patients with PV treated with GLP-1a (n=5,291) and controls without GLP-1a (n=79,027) from 2010 to 2022 from **147 Healthcare organizations**.
- PSM (1:1) was applied using a greedy nearest-neighbor method with a caliper of 0.1 pooled standard deviations, adjusting for demographics, PV-directed therapy, comorbidities, laboratory values, and cardiovascular medications.
- Primary outcomes were all-cause mortality, myelofibrosis, and VTE. Secondary outcomes included hospitalizations, ICU admissions, acute kidney injury (AKI), and ischemic stroke/TIA.
- Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated over a **3-year follow-up**.

Results

- After PSM, 4,119 matched pairs were analyzed in both cohorts.
- Mean time for patients on GLP-1 a therapy was 297.603 ± 162.423 days

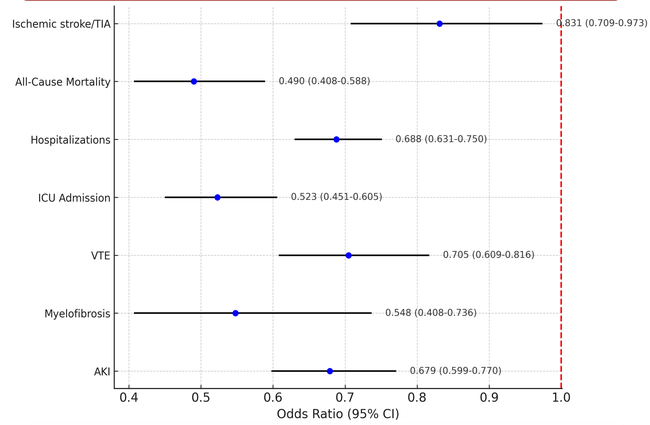
Number of Events %



Patient Characteristics

Characteristics	GLP-1a User Cohort, n = 4,119	GLP-1a Non-Users Cohort, n = 4,119	Standardized Difference
Demographics			
Age (yrs), mean ± SD	63.4 ± 12.1	63.8 ± 15.0	0.025
Age at Index,	59.8 ± 11.9	60.2 ± 15.1	0.03
White	2956 (71.8)	2981 (72.4)	0.014
African American	271 (6.6)	266 (6.5)	0.005
Asian	112 (2.7)	120 (2.9)	0.012
Hispanic or Latino	236 (5.7)	236 (5.7)	<0.001
Female	1494 (36.3)	1480 (35.9)	0.007
Male	2244 (54.5)	2263 (54.9)	0.009
Unknown Race,	608 (14.8)	590 (14.3)	0.012
AIAN	15 (0.4)	18 (0.4)	0.012
Pacific Islander,	40 (1.0)	36 (0.9)	0.01
Diagnosis			
Hypertension,	3192 (77.5)	3196 (77.6)	0.002
Cardiomyopathy	306 (7.4)	301 (7.3)	0.005
Lipid disorders	3052 (74.1)	3066 (74.4)	0.008
CAD	1330 (32.3)	1323 (32.1)	0.004
Obesity	2386 (57.9)	2343 (56.9)	0.021
Heart failure	748 (18.2)	725 (17.6)	0.015
CKD stage 3	580 (14.1)	597 (14.5)	0.012
COPD	646 (15.7)	638 (15.5)	0.005
Cerebral infarction	295 (7.2)	292 (7.1)	0.003
Hepatic fibrosis	91 (2.2)	90 (2.2)	0.002
PAD	455 (11.0)	439 (10.7)	0.012
ESRD	132 (3.2)	135 (3.3)	0.004
Coagulation disorders	625 (15.2)	626 (15.2)	0.001
OSA	1552 (37.7)	1498 (36.4)	0.027
A-Fib/Flutter	555 (13.5)	571 (13.9)	0.011
Nicotine dependence	1129 (27.4)	1128 (27.4)	0.001
Alcohol disorders	259 (6.3)	262 (6.4)	0.003
Diabetes mellitus	2790 (67.7)	2823 (68.5)	0.017
Medications			
Antilipemic agents	2915 (70.8)	2941 (71.4)	0.014
Insulin,	1660 (40.3)	1680 (40.8)	0.01
Aspirin,	2027 (49.2)	1999 (48.5)	0.014
Hydroxyurea,	258 (6.3)	259 (6.3)	0.001
Busulfan,	10 (0.2)	10 (0.2)	<0.001
Ruxolitinib,	49 (1.2)	54 (1.3)	0.011
Interferon alfa-2a,	10 (0.2)	10 (0.2)	<0.001
Laboratory			
LDL cholesterol,	91.1 ± 38.1	93.2 ± 39.4	0.053
Hemoglobin A1c	7.3 ± 2.0	6.7 ± 1.8	0.251

Forest Plot



Outcomes

Outcomes	OR	95% CI	p-value
Ischemic stroke/TIA	0.831	0.709–0.973	0.022
All-Cause Mortality	0.490	0.408–0.588	<0.001
Hospitalizations	0.688	0.631–0.750	<0.001
ICU Admission	0.523	0.451–0.605	<0.001
VTE	0.705	0.609–0.816	<0.001
Myelofibrosis	0.548	0.408–0.736	<0.001
AKI	0.679	0.599–0.770	<0.001

Conclusion

- GLP-1a therapy in patients with PV was associated with significantly reduced risks of **all-cause mortality, myelofibrosis, VTE, and health care utilization including All-cause hospitalization and All-cause ICU Admissions.**
- Despite limitations such as limited detailed clinical granularity and observational design precluding causality, these findings suggest GLP-1a has therapeutic benefits for this high-risk population, requiring urgent randomized controlled trials to confirm GLP-1a efficacy and safety in PV.

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