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# Risk of Glioblastoma Multiforme in Patients Taking Ion Channel Blockers

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# Abstract

#### Background

Ion channels play a role in the development and progression of glioblastoma multiforme. This study investigates the association between the risk of developing glioblastoma multiforme in patients taking these medications.

#### Methods

A retrospective propensity score-matched analysis was performed using the TriNetX multinational electronic health record database for patients taking verapamil, digoxin, amiodarone, or diltiazem versus those not taking these medications. The outcome of interest was the incidence of glioblastoma multiforme.

#### Results

Verapamil users had an OR of 0.494 (p < 0.0001) of developing glioblastoma versus verapamil non-users. Patients on digoxin had an OR of 0.793 (p = 0.2393), patients on amiodarone had an OR of 0.600 (p = 0.0035), patients on diltiazem had an OR of 0.584 (p < 0.0001), and patients on verapamil, digoxin, amiodarone, or diltiazem had an OR of 0.641 (p < 0.0001) of developing glioblastoma versus patients not taking these medications.

#### Conclusion

In patients taking the ion channel blockers diltiazem, amiodarone, or verapamil, the odds of developing glioblastoma multiforme were lower than in patients not taking these medications.

Categories: Neurosurgery

Keywords: ion channel blockers, glioblastoma multiforme, gbm, database, ion channel, neurosurgery, glioblastoma

#### Introduction

Glioblastoma multiforme (GBM) is a primary central nervous system (CNS) tumor that accounts for approximately 16% of all CNS neoplasms and causes approximately 15,000 deaths yearly in the United States [1,2]. The current school of thought suggests that this malignancy originates from the supporting cells of the CNS, known as glial cells. This tumor exhibits a particularly high affinity for invasion and spread into the surrounding brain parenchyma. Although current surgical and medical therapy is available for managing this tumor, the prognosis for patients remains dismal [3]. Only two factors have been shown to increase the risk of developing gliomas: high doses of ionizing radiation and certain inherited mutations [4]. However, several factors have been shown to worsen the prognosis of GBM, one of them being mutations in ion channels, specifically sodium, potassium, and calcium transporters, as well as the sodium/potassium-ATPase. Recent studies have shown that gliomas use these ion channels to foster their growth and invasion of the brain [5]. As such, it is possible to hypothesize that ion channel blockers could play a role in the development and progression of GBM.

This study investigates the association between the risk of developing GBM in patients taking ion channel blockers, specifically verapamil, diltiazem, digoxin, and amiodarone.

## **Materials And Methods**

This study is a retrospective case-control study model using a multi-institutional healthcare database, the TriNetX research network, to collect data on patients diagnosed with GBM while taking verapamil, digoxin, diltiazem, or amiodarone. The TriNetX research network is a database that houses de-identified electronic medical records from several healthcare organizations spanning 57 academic medical institutions, and the information in this database is updated daily. This database contains information regarding patient demographics, diagnoses, medications, and outcomes. Since the database is federated, an Institutional Review Board approval for this study has been waived.

The TriNetX database was interrogated for patients who took the ion channel blockers verapamil, digoxin, amiodarone, or diltiazem. These were stratified into four different groups. The primary outcome of interest was the risk of GBM development in patients taking one of these drugs compared to patients who were not taking the drug. An analysis was performed for each of the drugs individually without patients taking any other ion channel blockers, as well as in a combined cohort where patients could be on any ion channel blocker. Chi-square analysis was used for categorical variables. The significance level was set as p-value ≤ 0.05.

# **Results**

Tables 1, 2 show the baseline characteristics and measures of association for our patients taking verapamil. After matching, of the 512,098 patients using verapamil, 45 patients (0.009%) subsequently developed a glioblastoma. This is in comparison to the 512,098 patients not taking verapamil, of which 91 patients (0.018%) developed a glioblastoma (p = <0.0001, odds ratio (OR) = 0.494, 95% confidence interval (CI) = 0.346, 0.707).

oho	ort 1 (N = 522,713) and cohort 2 (N = 6,437,822) characteristics before propensity score matching								
De	emographi	CS							
	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.	
	1	Δ١	Age at index	60.1 ± 15.8	512,098	100%	<0.001	0.822	
	2			44.0 ± 22.8	6,437,658	100%	40.001	0.022	
	1	2106-3	White		360,872	70.50%	<0.001	0.067	
	2	2.000			4,335,933	67.40%	0.001	01001	
	1	2054-5	Black or African American		77,336	15.10%	<0.001	0.079	
	2				1,161,646	18.00%			
	1	М	Male		243,685	47.60%	<0.001	0.126	
	2	2			2,662,613	41.40%			
Diagnosis									
	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.	
	1	K74	Fibrosis and cirrhosis of the liver		8,621	1.70%	<0.001	0.066	
	2	2			60,006	0.90%	0.001	0.000	
	1	110-116	Hypertensive diseases		248,178	48.50%	<0.001	0.476	
	2		,-		1,677,156	26.10%			
	1	E08-E13	Diabatas mallitus	105 780	105,204	20.50%	<0.001	0.229	
	2				780,400	12.10%			
	1	N17-N19	Acute kidnev failure and chronic kidnev disease		71,413	13.90%	<0.001	0.281	
	2		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		364,519	5.70%			
	1	F17	Nicotine dependence		62,388	12.20%	<0.001	0.154	
	2				488,350	7.60%			
	1	F10.1	Alcohol abuse		11,819	2.30%	<0.001	0.067	
	2				90,056	1.40%			
	1	J40-J47	Chronic lower respiratory diseases		94,392	18.40%	<0.001	0.132	
	2				876,601	13.60%			
	1	148	Atrial fibrillation and flutter		57,620	11.30%	<0.001	0.304	
	2				220,156	3.40%	<0.001		
	1	150	Heart failure		71,447	14.00%	<0.001	0.371	

2					233,409	3.60%		
1		100 105			157,034	30.70%	-0.001	0.640
2		120-125	ischemic heart diseases		438,602	6.80%	<0.001	0.642
phort 1	(N = 5	12,098) and	cohort 2 (N = 512,098) characteristics after propensity s	core matching				
Demo	graphi	cs						
Co	hort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff
1		A1	Ago at index	60.1 ± 15.8	512,098	100%	<0.001	0.012
2		AI	Age at much	60.3 ± 15.8	512,098	100%	<0.001	0.013
1		2106-3	White		360,872	70.50%	0.061	0.004
2		2100-3	White		361,736	70.60%	0.001	0.004
1		2054 5	Plack or African Amorican		77,336	15.10%	0.755	0.001
2		2034-3	black of Affican Affician		77,449	15.10%		
1		м	Male		243,685	47.60%		0.001
2		171	ividio		243,336	47.50%	0.43	0.001
Diagno	osis							
Co	hort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. dif
1		K71	Fibrosis and cirrhosis of the liver		8,621	1.70%	0.812	<0.001
2		1(14			8,590	1.70%		<0.001
1		110-116	Hypertensive diseases		248,178	48.50%	0.28	0.002
2		110-110			248,724	48.60%		
1		E08-E13	Disk step melliture		105,204	20.50%	0.365	0.002
2		L00-L13			105,575	20.60%		
1		N17-N19	Acute kidney failure and chronic kidney disease		71,413	13.90%	0.677	0.004
2		117-1113			71,267	13.90%	0.077	0.001
1		E17	Nicotino dopondopos		62,388	12.20%	0.022	0.005
2		/			61,633	12.00%	0.022	0.000
1		F10 1	Alcohol abuse		11,819	2.30%	<0.001	0 011
2		. 10.1			11,023	2.20%	-0.001	0.011
1		140- 147	Chronic lower respiratory diseases		94,392	18.40%	986 0	<0 001
2		510-011	enterno tomor roopiratory algoageg		94,399	18.40%	0.000	-0.001
1		148	Atrial fibrillation and flutter		57,620	11.30%	0.026	0 004
2		. 10			56,912	11.10%	0.020	0.004
1		150	Heart failure		71,447	14.00%	<0.001	0.011
2	2			69,468	13.60%	<0.001	0.011	
1		120-125	lechamic haart disaasas		157,034	30.70%	0.001	0.006
2		120-120	ושטוטוויט ווכמוג עושבמשבש		155,516	30.40%	0.001	

TABLE 1: Baseline characteristics for patients taking verapamil

Cohort	Cohort		Patients in cohort	Patients with outcome	Risk
1	Verapamil		512,098	45	0.01%
2	No verapamil		512,098	91	0.02%
			95% CI	Z	р
Risk difference		-0.01%	(-0.013, -0.005)	-3.945	<0.0001
Risk ratio		0.495	(0.346, 0.707)		
Odds ratio		0.494	(0.346, 0.707)		

#### TABLE 2: Measures of association for patients taking verapamil and glioblastoma development

Tables *3*, *4* show the baseline characteristics and measures of association for our patients taking digoxin. Of the 400,800 patients using digoxin, 46 patients (0.011%) developed a glioblastoma, while of the 400,800 patients not taking digoxin, 58 patients (0.014%) did (p = 0.2393, OR = 0.793, 95% CI = 0.539, 1.168).

Cohort 1 (N = 4	141,710) and	cohort 2 (N = 6,488,498) characteristics before prop	ensity score r	natching			
Demographi	CS						
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.
1	A1	Ago ot index	67.8 ± 17.3	424,025	100%	<0.001	1 170
2	AI	Age at muex	44.0 ± 22.7	6,488,324	100%	<0.001	1.170
1	2106-3	White		301,763	71.20%	<0.001	0.083
2	2100-3	White		4,368,586	67.30%	<0.001	0.005
1	2054-5	Black or African American		43,147	10.20%	10.001	0.23
2	2004-0	Black of Anton Antonican		1,175,846	18.10%	40.001	0.20
1	М	Male		228,788	54.00%	<0.001	0 255
2		indio		2,679,748	41.30%		0.200
Diagnosis	Diagnosis						
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.
1	K74	Fibrosis and cirrhosis of the liver		6,821	1.60%	<0.001	0.059
2				61,241	0.90%		0.000
1	110-116	Hypertensive diseases		178,905	42.20%	<0.001	0.337
2		,		1,714,988	26.40%		
1	E08-E13	Diabetes mellitus		129,006	30.40%	<0.001	0.23
2				1,328,705	20.50%		
1	N17-N19	Acute kidney failure and chronic kidney disease		81,736	19.30%	<0.001	0.192
2		. ,		797,676	12.30%		
1	F17	Nicotine dependence		78,807	18.60%	<0.001	0.404
2				367,245	5.70%		
1	F10.1	Alcohol abuse		33,130	7.80%	0.026	0.004
2				500,814	7.70%		

1 J40-J47 Chronic lower respiratory of	0.077 0.400/	
2	diseases <	0.054
-	91,540 1.40%	
1 I48 Atrial fibrillation and flutter	78,837 18.60%	0.133
2	889,710 13.70%	
1 I50 Heart failure	169,820 40.00%	1 1.008
2	197,088 3.00%	
1	123,790 29.20%	0 744
2	222,074 3.40%	0.744
ohort 1 (N = 400,800) and cohort 2 (N = 400,800) char	acteristics after propensity score matching	
Demographics		
Cohort Code	Mean ± SD Patients % of cohort P-value	e Std. diff.
1	67.1 ± 17.4 400,800 100%	
Al Age at index	<0.00 68.0 ± 16.8 400,800 100%	0.053
1	285,025 71.10%	
2106-3 White	<0.00 286,563 71.50%	0.008
1	41,969 10.50%	
2054-5 Black or African American	<0.00 43,428 10.80%	0.012
1	215.191 53.70%	
M Male	<0.00	0.017
Diagnosis		
Cobort Code	Mean + SD Patients % of cohort Puval	
1	6.405 1.60%	e Sta. diff.
1 K74 Fibrosis and cirrhosis of th	e liver 0.245	e Sta. diff. 0.003
1 K74 Fibrosis and cirrhosis of th	e liver 6,405 1.60% 0.245 6,275 1.60% 140.00%	e Sta. diff.
1     K74     Fibrosis and cirrhosis of th       2     1       1     I10-I16     Hypertensive diseases	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% <0.00	e Sta. diff. 0.003
1     K74     Fibrosis and cirrhosis of th       1     Interview     Interview       1     Interview     Interview       2     Interview     Interview	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70%	e Sta. dm. 0.003
1     K74     Fibrosis and cirrhosis of th       1     Illo-II6     Hypertensive diseases       1     E08-E13     Diabetes mellitus	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 70.00 171,031 42.70% 30.10% <0.00	e Sta. am. 0.003 I 0.03 I 0.033
1     K74     Fibrosis and cirrhosis of th       1     1       1     110-116       2     1       1     E08-E13       2     Diabetes mellitus	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70% 30.10% 0.00 126,550 31.60% 0.00	e Sta. am. 0.003 1 0.03 1 0.033
1     K74     Fibrosis and cirrhosis of th       1     I10-I16     Hypertensive diseases       2     I     E08-E13       1     Diabetes mellitus       1     N17-N19	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70% 30.10% 0.00 126,550 31.60% 10.00% 0.00 76,156 19.00% 0.000	e Sta. am. 0.003 1 0.03 1 0.033
1     K74     Fibrosis and cirrhosis of the       1     10-116     Hypertensive diseases       1     10-116     Hypertensive diseases       1     E08-E13     Diabetes mellitus       1     N17-N19     Acute kidney failure and che	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70% 42.70% 0.00 120,504 30.10% 0.00% 126,550 31.60% 19.00% 0.00% 76,156 19.00% 0.00% 0.00%	e Sta. am. 0.003 1 0.03 1 0.033 1 0.03
1     K74     Fibrosis and cirrhosis of th       1     1       1     110-116       2     1       1     E08-E13       1     Diabetes mellitus       1     N17-N19       2     Acute kidney failure and ch       1     F17	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70% 42.70% 0.00 120,504 30.10% 0.00 126,550 31.60% 0.00 76,156 19.00% 0.00 81,008 20.20% 17.60% 0.005	<ul> <li>e Sta. am.</li> <li>0.003</li> <li>1 0.03</li> <li>1 0.033</li> <li>1 0.03</li> <li>0.006</li> </ul>
1     K74     Fibrosis and cirrhosis of the       1     1       2     110-116       1     Hypertensive diseases       1     E08-E13       1     Diabetes mellitus       1     N17-N19       2     F17       1     F17	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70% 30.10% 0.00 120,504 30.10% 30.10% 0.00 126,550 31.60% 0.00 76,156 19.00% 0.00 81,008 20.20% 17.60% 0.00 71,325 17.80% 0.005	e Sta. am. 0.003 1 0.03 1 0.033 1 0.03 0.006
1     K74     Fibrosis and cirrhosis of the       1     10-116     Hypertensive diseases       1     10-116     Hypertensive diseases       1     E08-E13     Diabetes mellitus       1     N17-N19     Acute kidney failure and cl       1     F17     Nicotine dependence       1     E10.1     Alcohol abuse	e liver 6,405 1.60% 0.245 6,275 1.60% 0.245 165,032 41.20% 41.20% 0.00 171,031 42.70% 0.00 120,504 30.10% 42.70% 0.00 126,550 31.60% 0.00 126,550 19.00% 0.00 126,550 16.00% 0.00\% 0.00\% 0.00\% 0.00\% 0.0	e Sta. dm. 0.003 0.03 0.033 0.03 0.006 0.007
1     K74     Fibrosis and cirrhosis of the       1     1       1     110-116       2     1       2     1       1     E08-E13       1     Diabetes mellitus       1     N17-N19       2     6       1     F17       1     F17       1     F10.1       2     F10.1	e liver 6,405 1.60% 1.60% 0.245 6,275 1.60% 1.60% 0.245 6,275 1.60% 1.60% 1.60% 1.60% 0.245 6,275 1.60% 1.60% 1.60% 1.60% 1.60% 0.245 1.60\% 0.245 1.60\% 0.25	<ul> <li>e Sta. dm.</li> <li>0.003</li> <li>1 0.03</li> <li>1 0.033</li> <li>1 0.03</li> <li>0.006</li> <li>0.007</li> </ul>
1       K74       Fibrosis and cirrhosis of th         1       11       Hypertensive diseases         1       10-116       Hypertensive diseases         1       E08-E13       Diabetes mellitus         1       N17-N19       Acute kidney failure and ch         1       F17       Nicotine dependence         1       F10.1       Alcohol abuse         1       K10-147       Chronic luver sceningtory	e liver e liver hronic kidney disease hronic kidney disease hron	e Sta. am. 0.003 0.03 0.033 0.03 0.006 0.007
$\begin{array}{c} \text{construction} \\ con$	e liver 6,405 1.60% 1.60\% 1.60	<ul> <li>e Sta. dir.</li> <li>0.003</li> <li>0.03</li> <li>0.033</li> <li>0.03</li> <li>0.03</li> <li>0.006</li> <li>0.007</li> <li>0.01</li> </ul>
1       K74       Fibrosis and cirrhosis of the         1       10-116       Hypertensive diseases         1       10-116       Hypertensive diseases         1       E08-E13       Diabetes mellitus         1       N17-N19       Acute kidney failure and cl         1       F17       Nicotine dependence         1       F10.1       Alcohol abuse         1       J40-J47       Chronic lower respiratory of	e liver e liver 6,405 1.60% 1.60\%	<ul> <li>e Std. diff.</li> <li>0.003</li> <li>0.03</li> <li>0.033</li> <li>0.033</li> <li>0.033</li> <li>0.006</li> <li>0.007</li> <li>0.01</li> </ul>
1       K74       Fibrosis and cirrhosis of the         1       10-116       Hypertensive diseases         1       10-116       Hypertensive diseases         1       E08-E13       Diabetes mellitus         1       N17-N19       Acute kidney failure and cheet         1       F17       Nicotine dependence         1       F10.1       Alcohol abuse         1       J40-J47       Chronic lower respiratory of         1       I48       Atrial fibrillation and flutter	e liver e liver 6,405 1.60% 1.60\%	<ul> <li>e Sta. dir.</li> <li>0.003</li> <li>0.03</li> <li>0.033</li> <li>0.033</li> <li>0.03</li> <li>0.006</li> <li>0.007</li> <li>0.01</li> <li>&lt;0.001</li> </ul>
1       K74       Fibrosis and cirrhosis of the         1       10-116       Hypertensive diseases         1       10-116       Hypertensive diseases         1       E08-E13       Diabetes mellitus         1       N17-N19       Acute kidney failure and classes         1       F17       Nicotine dependence         1       F10.1       Alcohol abuse         1       J40-J47       Chronic lower respiratory of         1       I48       Atrial fibrillation and flutter	e liver 6,405 1.60%	<ul> <li>e Sta. an.</li> <li>0.003</li> <li>0.03</li> <li>0.033</li> <li>0.03</li> <li>0.03</li> <li>0.006</li> <li>0.007</li> <li>0.01</li> <li>&lt;0.001</li> </ul>
1       K74       Fibrosis and cirrhosis of the         1       10-116       Hypertensive diseases         1       10-116       Hypertensive diseases         1       E08-E13       Diabetes mellitus         1       N17-N19       Acute kidney failure and cl         1       F17       Nicotine dependence         1       F10.1       Alcohol abuse         1       J40-J47       Chronic lower respiratory of         1       I48       Atrial fibrillation and flutter         1       I50       Heart failure	e liver       6,405       1.60%       -245         6,275       1.60%       -245         165,032       41.20%       -400         165,032       41.20%       -400         171,031       42.70%       -400         120,504       30.10%       -400         126,550       31.60%       -400         126,550       31.60%       -400         126,550       31.60%       -400         126,550       31.60%       -400         126,550       19.00%       -400         126,550       19.00%       -400         126,550       19.00%       -400         126,550       19.00%       -400         126,550       19.00%       -400         126,550       19.00%       -400         126,550       19.00%       -400         13,030       17.60%       -400         13,294       7.80%       -400         13,294       1.90%       -400         140,834       1.90%       -400         146,884       36.60%       -400         144,007       35.90%       -400	<ul> <li>e Sta. ant.</li> <li>0.003</li> <li>0.03</li> <li>0.033</li> <li>0.03</li> <li>0.03</li> <li>0.03</li> <li>0.03</li> <li>0.03</li> <li>0.006</li> <li>0.007</li> <li>0.001</li> <li>&lt;0.001</li> <li>&lt;0.015</li> </ul>

Risk ratio

Odds ratio

2 120-12	25 Ischemic heart of	liseases		102,127 25.50%	<0.001 0.015
TABLE 3: Base	line characteris	tics for pat	ients taking digoxi	n	
Cohort			Patients in cohort	Patients with outcome	Risk
1	Digoxin		400,800	46	0.01%
2	No digoxin		400,800	58	0.01%
			95% CI	z	р
Risk difference		-0.003%	(-0.008, 0.002)	-1.177	0.239

## TABLE 4: Measures of association for patients taking digoxin and glioblastoma development

(0.539, 1.168)

(0.539, 1.168)

0.793

0.793

Tables *5*, *6* show the baseline characteristics and measures of association for our patients taking amiodarone. A total of 543,288 patients were taking amiodarone; of this number, 51 patients (0.009%) developed a glioblastoma. A matched group of 543,288 patients not taking amiodarone was identified and, in this cohort, 85 patients (0.016%) developed a glioblastoma (p = 0.0035, OR = 0.6, 95% CI = 0.424, 0.849).

ohort 1 (N =	646,598) and	d cohort 2 (N = 6,413,181) characteristics before pr	opensity score r	matching			
Demograph	ics						
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.
1	ΔΙ	Ago at index	68.2 ± 13.9	642,771	100%	<0.001	1 201
2	AI	Age at muex	43.7 ± 22.7	6,413,010	100%	~0.001	
1	2106.2	White		458,481	71.30%	<0.001	0.080
2	2100-3	White		4,311,815	67.20%	~0.001	0.000
1	2054 5	Plack or African American		71,752	11.20%	<0.001	0.199
2	2004-0	Diack of American		1,164,000	18.20%	<0.001	
1	м	lale		398,131	61.90%	<0.001	0.420
2			2,628,514	41.00%	<0.001	0.120	
Diagnosis							
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.
1	1/74	Fiberaia and simbosis of the lives		12,352	1.90%	-0.001	0.004
2	K/4	Fibrosis and cirmosis of the liver		59,755	0.90%	<0.001	0.084
1	140.140			329,918	51.30%	-0.001	0.507
2	110-116	Hypertensive diseases		1,670,564	26.00%	<0.001	0.537
1	E08-E13	Diskatos mellitus		152,108	23.70%	-0.001	0.200
2		Diabetes mellitus		774,882	12.10%	<0.001	0.306
1				166,302	25.90%		
	N17-N19	Acute kidney failure and chronic kidney disease				<0.001	0.587

1     P1     Automagnetic problem     P1	2				346,303	5.40%		
1     Nonline dependence     491.40     7.0%     20.00     0.000       1     10.1     Head     Abold abuse     1.0%     4.0%     0.0%       1     Head     Abold abuse     1.0%     1.0%     0.0%     0.0%       1     Head     Head     1.0%     0.0%     0.0%     0.0%       1     Head     Abold abuse     Mean 100     0.0%     0.0%     0.0%       1     Head     Mean 100     Mean 100     0.0%     0.0%     0.0%       1     Head     Mean 100     Mean 100     0.0%     0.0%     0.0%       1     Head     Mean 100     Mean 100     Mean 100     0.0%     0.0%       1     Head     Mean 100     Mean 100     Mean 100     Mean 100     0.0%       1     Head     Mean 100     Mean 100     Mean 100     Mean 100     Mean 100   <	1	F 4 7	Niceline descedance		64,200	10.00%	-0.001	0.000
1     1 </td <td>2</td> <td>F1/</td> <td>Nicotine dependence</td> <td></td> <td>491,406</td> <td>7.70%</td> <td>&lt;0.001</td> <td>0.082</td>	2	F1/	Nicotine dependence		491,406	7.70%	<0.001	0.082
1     10.1     Addrian and source segmentation diseases     1	1	<b>E</b> 40 4			15,383	2.40%		0.070
1     Auguar bases     144.54     144.54     144.54     144.54     144.54     144.54     144.54     147.55<	2	F10.1	Alconol abuse		89,828	1.40%	<0.001	0.073
2     340-44     Contractional power respiratory descesses     10     876.330     1.3.70%     40.00     0.134       1     H     H     Heiral fibrillation and fluter     10.00     200%     20.00%     20	1	140 147			124,451	19.40%	10.001	0.454
1     And any organization and fluter     2117.33     2.00%     3.0	2	J40-J47	Chronic lower respiratory diseases		876,350	13.70%	<0.001	0.154
1     No.     No.     No.     No.     No.     No.       1	1	140	Atrial fibrillation and futtor		271,736	42.30%	<0.001	1 072
1         300         Hertalure         10,000         20,000         30	2	140			177,783	2.80%	<0.001	1.073
2     00     Part and a part of	1	150	Heart foilure		190,200	29.60%	<0.001	0.700
1     20-25     Behamic heart disease     2007     38.90%     -0.08       2     100-25     6.0%     -0.0%     0.08       2     0     0.0%     0.0%     0.0%       2     0     0     0.0%     0.0%     0.0%       2     0     0     0     0.0%     0.0%     0.0%       1     0     0     0     0.0%     0.0%     0.0%       1     0     0     0     0.0%     0.0%     0.0%       1     0     0     0.0%     0.0%     0.0%     0.0%       1     0     0     0.0%     0.0%     0.0%     0.0%       1     0     0     0.0%     0.0%     0.0%     0.0%       1     0     0     0.0%     0.0%     0.0%     0.0%       1     0     0     0.0%     0.0%     0.0%     0.0%       1     0     0     0.0%     0.0%     0.0%     0.0%       1     0     0     0     0     0.0%     0.0%       1     0     0     0     0     0     0.0%       1     0     0     0     0     0     0       1     0	2	150	neart lailure		206,561	3.20%	<0.001	0.762
2     2013     istantin leaf diseases     42,319     6,60%     40,00     0.03       42,319     6,60%     42,319     6,60%     42,319     6,60%     0.03       intermediation of the second of the sec	1	100,105			250,057	38.90%	-0.001	0.025
value view view view view view view view vie	2	120-125	Ischemic heart diseases		423,919	6.60%	<0.001	0.835
image	ort 1 (N = 5	43,288) and	cohort 2 (N = 543,288) characteristics after propensity s	core matching				
Coded     Idea     Main ± SD     Patients     % of cohon     P-value     % of cohon       1     A     A     Age at index     67.1 ± 14.2     543.288     10%       2     1     543.288     10%     -0.06       1     A     66.6 ± 14.1     543.288     10%     -0.06       2     1     443.288     10%     -0.06     -0.06       2     1     68.6 ± 14.1     543.288     10%     -0.06       2     1     443.288     10%     -0.06     -0.06       2     1     -0.06     56.07     1.06%     -0.06       2     2     1     1.06%     -0.06     -0.06       3     30.895     60.09%     -0.06     -0.06       3     30.895     60.09%     -0.06     -0.06       3     30.895     60.09%     -0.06     -0.06       3     1     -0.06     50.06     -0.06     -0.06       2     1     -0.06     -0.06     -0.06     -0.06       3     1     1     -0.06     -0.06     -0.06       2     1     -0.06     -0.06     -0.06     -0.06       3     1     1     -0.06     -0.06	emographi	ics						
1         A         Agg at index         67.1 ± 14.2         54.3.28         10%         -0.00         -1.1           2         10%-3         10%-3         10%-3         68.6 ± 14.1         54.3.28         10%-3         -0.00 <td>Cohort</td> <td>Code</td> <td></td> <td>Mean ± SD</td> <td>Patients</td> <td>% of cohort</td> <td>P-value</td> <td>Std. d</td>	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. d
A     Age at index     66.6 ± 14.1     54.32.80     10%     -0.00     1.1       1     206-3     White     384.058     7.70%     -0.00     -0.00       1     384.058     7.10%     68.6 ± 14.1     586.072     71.10%     -0.00       1     206-3     Multe     68.6 ± 14.1     586.072     71.10%     -0.00       2     20-45-5     Black or African American     68.6 ± 14.1     58.6 0.0%     -0.00     -0.00       2     20-45-5     Black or African American     59.00%     60.0%     -0.00     -0.00       2     0     Mae     Mae     50.06%     0.0%     -0.00     0.00       3     0.05     0.00%     0.00%     0.00%     0.00     0.00       3     Mae     Mae     Mae     10     10     -0.00     0.00       1     Mae     Mae     Mae     10     10     0.00     0.00       1     Mae     Mae     Mae     10     10     0.00     0.00       1     Mae     Mae     Mae     10     10     0.00     0.00       1     Mae     Mae     Mae     10     10     10     0.00       1     Mae     Mae </td <td>1</td> <td></td> <td></td> <td>67.1 ± 14.2</td> <td>543,288</td> <td>100%</td> <td></td> <td></td>	1			67.1 ± 14.2	543,288	100%		
1       206-3       White       384,058       7.0%       386,072       71.10%       360,072       71.10%       360,072       71.10%       360,072       71.10%       360,072       71.10%       360,072       71.10%       360,072       71.10%       360,072       71.10%       360,072       71.10%       360,074	2	AI	Age at index	68.6 ± 14.1	543,288	100%	<0.001	0.11
2       200-3       White       386.072       71.10%       0.005         1       2014-5       Black or African American       62,661       11.50%       0.219       0.007         2       0       63,071       11.60%       0.219       0.007         1       0       30,885       60,60%       0.219       0.007         2       0       Male       308,85       60,60%       0.001       0.006         1       0       0       0.001       0.001       0.001       0.001       0.001         1       0       0       0       0       0.001       0.001       0.001       0.001         1       0       0       0       0       0       0.001 </td <td rowspan="2">1 2</td> <td></td> <td></td> <td></td> <td>384,058</td> <td>70.70%</td> <td></td> <td rowspan="2">0.008</td>	1 2				384,058	70.70%		0.008
1         203-5         Black or African American         62,61         11.50%         2.19         2.19         62,61         11.60%         2.19         0.002           1         A         A         A         30,85         60.60%         0.014         0.002           1         A         A         A         30,855         60.60%         0.014         0.002           1         A         A         A         30,855         60.60%         0.014         0.016         0.014         0.016         0.014<		2106-3	White		386,072	71.10%	<0.001	
$ \begin{array}{c c c c c c } \hline 2 \\ \hline 2 \\ \hline 2 \\ \hline 3 \\ \hline 1 \\ \hline 4 \\ \hline 4 \\ \hline 4 \\ \hline 4 \\ \hline 1 \\ \hline 4 \\ \hline 4 \\ \hline 4 \\ \hline 4 \\ \hline 5 \\$	1		Black or African American		62,661	11.50%	0.219 0.001	0.002
1         32,165         60.60%         30,085         60.90%         30,007         30	2	2054-5			63,071	11.60%		
$ \begin{array}{c c c c c c } & \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ $	1				329,165	60.60%		0.006
kinematic	2	М	Male		330,885	60.90%		
Code         Code         Image: Code         State of the liver         Peralue         State of the liver           1         The second of the liver         9,713         1.80%         9,974         1.80%           2         9,974         1.80%         9,974         1.80%         9,974         1.80%           1         House and cirrhosis of the liver         9,974         1.80%         9,974         1.80%         9,004           1         House and cirrhosis of the liver         25,101         47.00%         9,974         48.50%         9,001         0.00         9,001         0.00 <td>iagnosis</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	iagnosis							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. d
K74       Fibrosis and cirrhosis of the liver       9,974       1.80%       0.06       0.004         1       1.80%       255,101       47.00%       2.001       0.032         2       10-116       Hypertensive diseases       263,759       48.50%       20.01       0.026         1       263,759       48.50%       263,759       48.50%       20.01       0.026         1       E08-E13       Diabetes mellitus       118,383       21.80%       20.001       0.026         1       M17-N19       Acute kidney failure and chronic kidney disease       116,493       21.40%       20.001       0.016         1       M17-N19       Acute kidney failure and chronic kidney disease       116,493       21.40%       20.001       0.016         1       M17-N19       Acute kidney failure and chronic kidney disease       116,493       21.40%       20.001       0.016         1       M12,833       20.80%       12.059       2.00%       2.001       0.009         1       M16,493       2.20%       0.001       2.001       0.009         1       M16,493       2.20%       0.001       2.001       0.009         1       M10,104       M10,004       9.004       18.	1				9,713	1.80%		
1       10-116       Hypertensive diseases       255,101       47.00%       20.01       20.0	2	K74	Fibrosis and cirrhosis of the liver		9,974	1.80%	0.06	0.004
10-116       Hypertensive diseases       <0.001	1				255,101	47.00%		
1       I18,383       21.80%       2.001       0.026         2       124,236       22.90%       124,236       22.90%       0.016         1       N17-N19       Acute kidney failure and chronic kidney disease       116,493       21.40%       0.001       0.016         2       112,883       20.80%       20.80%       0.001       0.016         1       F17       Nicotine dependence       51,538       9.50%       0.001         1       F10.1       Alcohol abuse       12,059       2.20%       0.001         1       F10.1       Alcohol abuse       12,139       2.20%       0.603       0.001         1       J40-J47       Chronic lower respiratory diseases       95,383       17.60%       0.001	2	110-116	Hypertensive diseases		263,759	48.50%	<0.001	0.032
2       E08-E13       Diabetes mellitus       124,236       22.90%       0.001       0.026         1       124,236       21.40%       116,493       21.40%       0.001       0.016         2       112,883       20.80%       112,883       20.80%       0.016       0.016         1       F17       Nicotine dependence       51,538       9.50%       0.001       0.009         1       F10.1       Alcohol abuse       12,059       2.20%       0.001       0.001         1       F10.1       Alcohol abuse       12,139       2.20%       0.001       0.001         1       J40-J47       Chronic lower respiratory diseases       95,383       17.60%       0.001       0.013	1				118,383	21.80%		
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	2	E08-E13	Diabetes mellitus		124,236	22.90%	<0.001	0.026
N17-N19       Acute kidney failure and chronic kidney disease       <0.001	1				116,493	21.40%		
1       F17       Nicotine dependence       51,538       9.50%       9.001       0.009         2       50,106       9.20%       12,059       2.20%       0.603       0.001         1       F10.1       Alcohol abuse       12,139       2.20%       0.603       0.001         1       J40-J47       Chronic lower respiratory diseases       95,383       17.60%       0.001       0.013	2	N17-N19	Acute kidney failure and chronic kidney disease		112,883	20.80%	<0.001	0.016
2       F17       Nicotine dependence       <0.001	1				51,538	9.50%		
1     F10.1     Alcohol abuse     12,059     2.20%       2     12,139     2.20%     0.603     0.001       1     J40-J47     Chronic lower respiratory diseases     95,383     17.60%       2     98,004     18.00%     0.001	2	F17	Nicotine dependence		50,106	9.20%	<0.001	0.009
2     F10.1     Alcohol abuse     0.603     0.001       1     12,139     2.20%     95,383     17.60%       2     98,004     18.00%     0.011	1				12,059	2.20%		
1       95,383       17.60%         2       98,004       18.00%	2	F10.1	Alcohol abuse		12,139	2.20%	0.603	0.001
2 J40-J47 Chronic lower respiratory diseases <	1				95,383	17.60%		
	2	J40-J47	Chronic lower respiratory diseases		98,004	18.00%	<0.001	0.013

1	148	Atrial fibrillation and flutter	176,728	32.50%	<0.001	0.063
2			160,853	29.60%	01001	0.000
1	150	Heart failure	125,441	23.10%	<0.001	0.014
2	150 Heart failure		122,234	22.50%	<0.001	0.014
1	120-125	Ischemic heart diseases	177,864	32.70%	<0.001	0.014
2	Ischemic heart diseases	181,496	33.40%	-0.001	0.017	

#### TABLE 5: Baseline characteristics for patients taking amiodarone

Cohort		Patients in cohort	Patients with outcome	Risk
				0.040/
1	Amiodarone	543,288	51	0.01%
2	No amiodarone	543,288	85	0.02%
		95% CI	Z	р
Risk difference	-0.01%	(-0.01, -0.002)	-2.916	0.0035
Risk ratio	0.6	(0.424, 0.849)		
Odds ratio	0.6	(0.424, 0.849)		

#### TABLE 6: Measures of association for patients taking amiodarone and glioblastoma development

Tables 7, 8 show the baseline characteristics and measures of association for our patients taking diltiazem. A total of 828,618 patients were identified to have been taking diltiazem, and of this number, 94 patients (0.011%) developed a glioblastoma. In a matched group of 828,618 patients not taking diltiazem, 161 patients (0.019%) developed a glioblastoma (p < 0.0001, OR = 0.584, 95% CI = 0.453, 0.753).

ohc	ort 1 (N = 8	395,591) and	I cohort 2 (N = 6,361,272) characteristics before prop	pensity score r	natching			
D	emographi	ics						
	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff
	1	AI	Age at index	66.4 ± 14.7	879,921	100%	<0.001	1 10
	2		Age at index	43.6 ± 22.7	6,361,111	100%	<0.001	
	1	2106-3	White		640,364	72.80%	<0.001	0 121
	2	2100-3		4,276,040	67.20%	40.001	0.121	
	1		Black of African American		110,409	12.50%	<0.001	0.155
	2	2004-0	2054-5 Black of African American		1,151,481	18.10%	0.001	
	1	м			405,529	46.10%	<0.001	0.095
	2	IVI	male		2,630,906	41.40%		
Di	Diagnosis							
	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. dif
	1		Ethernia and simbools of the lives		10,925	1.20%	-0.001	0.00
	2	N/4	Fibrosis and cirmosis of the liver		59,209	0.90%	<0.001	0.03

1	110-116	Hypertensive diseases		388,689	44.20%	<0.001	0 395
2	110-110	Trypertensive diseases		1,633,614	25.70%	<0.001	0.395
1				156,196	17.80%		
2	E08-E13	Diabetes mellitus		762,610	12.00%	<0.001	0.162
1				128,695	14.60%		
2	N17-N19	Acute kidney failure and chronic kidney disease		345,520	5.40%	<0.001	0.31
1				73,433	8.30%		
2	F17	Nicotine dependence		484,719	7.60%	<0.001	0.027
1				17,819	2.00%		0.05
2	F10.1	Alcohol abuse		87,952	1.40%	<0.001	
1	140			165,911	18.90%	10.004	0.440
2	148	Atrial fibrillation and flutter		854,137	13.40%	<0.001	0.148
1	120			230,044	26.10%		
2	150	Heart failure		171,025	2.70%	<0.001	0.708
1				112,697	12.80%		
2	120-125	Ischemic heart diseases		216,558	3.40%	<0.001	0.35
rt 1 (N = 8	328,618) and	cohort 2 (N = 828,618) characteristics after propensity	core matching				
emograph	ics						
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. d
1	AI Age at index		65.6 ± 14.7	828,618	100%		
2		66.3 ± 14.8	828,618	100%	<0.001	0.044	
1				599,855	72.40%		
2	2106-3	White		595,428	71.90%	<0.001	0.012
1				107,250	12.90%		
2	2054-5	Black or African American		111,823	13.50%	<0.001	0.016
1				381,608	46.10%		
2	М	Male		394,062	47.60%	<0.001	0.03
iagnosis							
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. d
1				10,269	1.20%		
2	K74	Fibrosis and cirrhosis of the liver		10,133	1.20%	0.338	0.001
1				350,863	42.30%		
2	110-116	Hypertensive diseases		357,943	43.20%	<0.001	0.017
1				143,869	17.40%		
2	E08-E13	Diabetes mellitus		150,221	18.10%	<0.001	0.02
	1						
1				112,067	13.50%		0.016
1 2	N17-N19	Acute kidney failure and chronic kidney disease		112,067 116,736	13.50% 14.10%	<0.001	0.016
1 2 1	N17-N19	Acute kidney failure and chronic kidney disease		112,067 116,736 68,443	13.50% 14.10% 8.30%	<0.001	0.016
1 2 1 2	N17-N19 F17	Acute kidney failure and chronic kidney disease Nicotine dependence		112,067 116,736 68,443 65,296	13.50% 14.10% 8.30% 7.90%	<0.001	0.016

2	F10.1	Alcohol abuse	15,310	1.80%	<0.001	0.009
1	149	Atrial fibrillation and flutter	148,156	17.90%	<0.001	0.007
2	140		145,875	17.60%	<0.001	0.007
1	150	Heart failure	179,559	21.70%	<0.001	0 044
2	100		164,661	19.90%	0.001	0.011
1	120-125	Ischemic heart diseases	94,800	11.40%	<0.001	0.026
2			101,848	12.30%		

#### TABLE 7: Baseline characteristics for patients taking diltiazem

Cohort		Patients in cohort	Patients with outcome	Risk
1	Diltiazem	828,618	94	0.01%
2	No diltiazem	828,618	161	0.02%
		95% CI	Z	р
Risk difference	-0.008	(-0.012, -0.004)	-4.196	<0.0001
Risk ratio	0.584	(0.453, 0.753)		
Odds ratio	0.584	(0.453, 0.753)		

### TABLE 8: Measures of association for patients taking diltiazem and glioblastoma development

Tables *9*, *10* show the baseline characteristics and measures of association for our patients taking any of the aforementioned ion channel blockers. The combined cohort consisted of 1,576,042 patients; in this group, 184 patients (0.012%) developed glioblastoma. In a matched cohort of 1,576,042 patients not on any of these ion channel blockers, 287 patients (0.018%) developed a glioblastoma (p < 0.0001, OR = 0.641, 95% CI = 0.533, 0.771).

hort 1 (N = 2,035,921) and cohort 2 (N = 6,089,750) characteristics before propensity score matching								
Demographics								
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. di	
1	AI	Age at index	65.0 ± 15.9	1,998,460	100%	<0.001	1 1 /	
2			42.7 ± 22.6	6,089,598	100%	<0.001	1.14	
1	2106.2	White		1,415,666	70.80%	<0.001	0.083	
2	2106-3			4,078,606	67.00%	~0.001	0.005	
1	2054 5	I-5 Black or African American		252,945	12.70%	<0.001	0.150	
2	2004-0			1,102,736	18.10%	<0.001	0.152	
1	14	M Male		1,023,976	51.20%	10.004	0.01	
2	М			2,485,621	40.80%	<0.001	0.21	
Diagnosis								
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. d	
1				27,381	1.40%			

	2	K74	Fibrosis and cirrhosis of the liver		52,695	0.90%	<0.001	0.048
	1	110 116	Huportopolya disassas		849,956	42.50%	<0.001	0.206
	2	110-110	Typertensive useases		1,474,384	24.20%	<b>\0.001</b>	0.590
	1	E09 E12	Diskatas mellitus		361,253	18.10%	<0.001	0.105
	2	E00-E13			682,224	11.20%	<b>\0.001</b>	0.195
	1	N17 N10	Aguta kidney failure and chronic kidney disease		298,367	14.90%	<0.001	0.246
	2	1117-1113	Acute Nulley failure and chronic Nulley disease		290,013	4.80%	<b>\0.001</b>	0.340
	1	<b>E</b> 17	Nigotino dopondonoo		171,097	8.60%	<0.001	0.044
	2	Γ1/			448,607	7.40%	<b>\0.001</b>	0.044
	1	E10.1	Alashal abusa		37,767	1.90%	<0.001	0.045
	2	F 10.1	Alconor abuse		80,852	1.30%	<0.001	0.045
	1	140	Atrial fibrillation and futtor		450,002	22.50%	<0.001	0.666
	2	140			113,082	1.90%	<0.001	0.000
	1	120 125	lashomia hast diagooo		486,062	24.30%	<0.001	0.546
	2	120-125	Ischemic heart diseases		338,211	5.60%	<0.001	0.546
Coho	ort 1 (N = 1	,576,042) an	d cohort 2 (N = 1,576,042) characteristics after propensi	ty score match	ing			
D	emographi	ics						
	Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.
	1	AI	Aze et index	62.3 ± 16.0	1,576,042	100%	<0.001	0.043
		/ 11	Ago at maox				.0.001	0.010

1	A.I.	Age of index	62.3 ± 16.0	1,576,042	100%	<0.001	0.042
2	AI	Age at index	63.0 ± 16.0	1,576,042	100%	<0.001	0.043
1	2106.2	White		1,104,941	70.10%	0.041	0.002
2	2100-5	White		1,103,278	70.00%	0.041	0.002
1	2054 5	Plack or African Amorican		219,752	13.90%	<0.001	0.022
2	2004-0	Black of Affican Affendan		232,607	14.80%	<0.001	0.025
1	м	Molo		773,458	49.10%	<0.001	0.01
2	IVI	Wale		781,452	49.60%	<0.001	0.01
Diagnosis							
Cohort	Code		Mean ± SD	Patients	% of cohort	P-value	Std. diff.
1	K71	Fibrosis and cirrhosis of the liver		19,910	1.30%	<0.001	0.013
2	IXI 4			22,233	1.40%	40.001	0.010
1	110-116	Hunartansiva disaasas		582,928	37.00%	<0.001	0.063
2	110-110	Hito Hypertensive diseases		631,448	40.10%		0.005
1	E08-E13	Diabatas mallitus		253,554	16.10%		0.022
2	L00-L13	Diabetes meintus		272,736	17.30%	<0.001	0.000
1	N17-N10			173,596	11.00%	<0.001	0.027
2	N17-N15			192,279	12.20%	40.001	0.007
1	E17	Nicotine dependence		130,924	8.30%	<0.001	0.013
2	1 17			136,818	8.70%	<0.001	0.013
1	F10 1			27,412	1.70%	<0.001	0.013
2	F10.1			30,199	1.90%	<0.001	0.013

1	148	Atrial fibrillation and flutter	145,984	9.30%	<0.001	0.077
2	140		112,626	7.10%	<0.001	0.077
1	120 125	loohamia haart disaasaa	279,011	17.70%	<0.001	0.05
2	120-125		309,580	19.60%	<0.001	0.05

# TABLE 9: Baseline characteristics for patients taking any of the ion channel blockers (verapamil, digoxin, amiodarone, or diltiazem)

Cohort		Patients in cohort	Patients with outcome	Risk
1	lon channel blockers (verapamil, digoxin, amiodarone, or diltiazem)	1,576,042	184	0.01%
2	No ion channel blockers (verapamil, digoxin, amiodarone, or diltiazem)	1,576,042	287	0.02%
		95% CI	z	р
Risk difference	-0.01%	(-0.009, -0.004)	-4.746	<0.0001
Risk ratio	0.641	(0.533, 0.771)		
Odds ratio	0.641	(0.533, 0.771)		

TABLE 10: Measures of association for patients taking any of the ion channel blockers(verapamil, digoxin, amiodarone, or diltiazem) and glioblastoma development

## Discussion

These results suggest that in patients using the ion channel blockers verapamil, amiodarone, or diltiazem, the odds of developing GBM were lower than in patients not taking these drugs. These results suggest a similar pattern for digoxin, albeit statistically insignificant. Furthermore, this association persisted when all patients were analyzed in a general group.

GBM originates from the brain's supporting cells, and these cells express a myriad of ion channels, including sodium, potassium, and anion channels [6]. Genomic analysis of mutations present in GBM has shown the presence of mutations in the genes encoding these ion channels in 90% of the glioblastoma samples examined [7]. Research suggests that mutations in these ion channels harbor a poor prognostic factor for patients by promoting proliferation, migration, and invasion of normal brain tissue by GBM. This effect is primarily believed to be mediated by the action of ion channels in promoting progression through the cell cycle [8].

Studies have shown that different types of Ca2+ selective ion channels are upregulated in GBM, where they confer a host of pro-survival benefits to the tumor, including promoting tumor invasiveness, proliferation, and resistance to apoptosis [9]. For example, diltiazem and verapamil primarily block the L-type voltage-gated calcium channels. This specific Ca2+ channel is expressed in several tumor cells, and blockage of this channel inhibits cancer cell invasion. This effect is primarily mediated by inhibiting the role of these channels in the development of filopodia, thereby preventing tumor cell migration and invasion of nearby healthy tissue [10]. Furthermore, verapamil has been shown to inhibit the T-type Ca2+ channels, and inhibition of this channel has been shown to induce apoptosis in glioblastoma cells [11]. As such, these Ca2+ channel blockers may prevent tumorigenesis via myriad mechanisms, including prevention of cell cycle progression, induction of apoptosis, and prevention of aberrant migration of malignant cells.

The anti-tumorigenic effects of cardiac glycosides have been previously established [12]. In addition, in vitro studies have shown that digoxin can exhibit antiproliferative and pro-apoptotic effects in GBM [13]. Although the mechanism of action has not yet been elucidated, the current school of thought suggests that inhibition of sodium currents might be a mechanism by which digoxin exerts its anti-tumor effects. Digoxin primarily acts by inhibiting the Na+/K+ ATPase, an energy-dependent transporter that plays a role in maintaining homeostatic levels of potassium and sodium in cells. Inhibition of this channel has been shown to independently induce cell death in GBM and increase tumor cells' sensitivity to chemotherapy [14]. As

such, it is plausible that digoxin can play a role in preventing the development and progression of GBM.

K+ channels also contribute to the proliferation and apoptosis resistance exhibited by GBM. Specifically, GBM overexpresses certain voltage-dependent K+ channels, which are reportedly involved in signaling pathways that promote proliferation and inhibit apoptosis [15]. Some of these effects are caused by the role of K+ channels in establishing the resting membrane potential. Changes to this baseline can alter cell-cycle progression, promoting a pro-tumorigenic profile. Clinical studies have shown that the use of inhibitors of these channels is associated with better survival in patients with GBM, again emphasizing the role of these channels in the development and progression of GBM [16]. High expression of a specific subtype of the potassium channel (Kv10.1) in GBM cells is associated with a more dismal prognosis [17]. Amiodarone is an anti-arrhythmic that can block voltage-gated potassium, calcium, and sodium channels. This drug has also been shown to reduce glioblastoma growth in vivo by exhibiting direct anti-cancer effects and anti-angiogenic activity [18,19]. As such, some anti-tumorigenic effects of amiodarone are likely due to its inhibition of ion channels, which inhibit tumor cell proliferation and migration and its effect on angiogenesis.

Thus, the effect of these drugs on the development of GBM is probably due to a mixture of the various mechanisms aforementioned, including delayed progression across the cell cycle, inhibition of cell proliferation, and induction of apoptosis in de-novo malignant cells.

Several limitations exist in this study. Firstly, and most importantly, this analysis was primarily retrospective; hence, this investigation is limited to the constraints of such studies. Secondly, some information about the medication history could not be obtained from the TriNetX database. Specifically, the dosage of each medication, the indication in each patient, and the duration of usage of these medications could not be obtained. Furthermore, information about the stage and grade of each patient's GBM diagnosis could not be retrieved. The isocitrate dehydrogenase (IDH) mutation status and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status of the tumors were unknown. The International Classification of Diseases, Tenth Revision (ICD-10) codes are primarily used for billing purposes. Finally, due to the nature of database studies, some misidentification is always present.

## Conclusions

These findings suggest that in patients taking the ion channel blockers diltiazem, amiodarone, or verapamil, the odds of developing GBM were lower than in patients not taking these drugs. The same relationship was seen in patients taking digoxin; however, this association was not statistically significant. Ion channels play a fundamental role in the development and progression of GBM. Therefore, inhibition of these channels could serve as a therapeutic target for the management of GBM.

## **Additional Information**

#### Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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