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).

| Cohort 1 (N = 522,713) and cohort 2 (N = 6,437,822) characteristics before propensity score matching |
|---------------------------------------------------------------|
| **Demographics**                                              |
| Cohort | Code | Age at index | Patients | % of cohort | P-value | Std. diff. |
|--------|------|--------------|----------|-------------|---------|------------|
| 1      | Al   | 60.1 ± 15.8  | 512,098  | 100%        | <0.001  | 0.822      |
| 2      |      | 44.0 ± 22.8  | 6,437,658| 100%        |         |            |
| 1      | 2106-3| White       | 360,872  | 70.50%     | <0.001  | 0.067      |
| 2      |      | 4,335,933   | 67.40%   |            |         |            |
| 1      | 2054-5| Black or African American | 77,336 | 15.10% | <0.001 | 0.079 |
| 2      |      | 1,161,646   | 18.00%   |            |         |            |
| 1      | M    | Male       | 243,685  | 47.60%     | <0.001  | 0.126      |
| 2      |      | 2,662,613   | 41.40%   |            |         |            |
| **Diagnosis**                                                 |
| Cohort | Code | Fibrosis and cirrhosis of the liver | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-------------------------------------|----------|-------------|---------|------------|
| 1      | K74  | 8,621                               | 1.70%    | <0.001      | 0.066   |
| 2      |      | 60,006                              | 0.90%    |            |         |            |
| 1      | I10-I16| Hypertensive diseases               | 248,178  | 48.50%     | <0.001  | 0.476      |
| 2      |      | 1,677,156                            | 26.10%   |            |         |            |
| 1      | E08-E13| Diabetes mellitus                   | 105,204  | 20.50%     | <0.001  | 0.229      |
| 2      |      | 780,400                              | 12.10%   |            |         |            |
| 1      | N17-N19| Acute kidney failure and chronic kidney 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      | I48  | Atrial fibrillation and flutter     | 57,620   | 11.30%     | <0.001  | 0.304      |
| 2      |      | 220,156                              | 3.40%    |            |         |            |
| 1      | I50  | Heart failure                       | 71,447   | 14.00%     | <0.001  | 0.371      |

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Cohort 1 (N = 512,098) and cohort 2 (N = 512,098) characteristics after propensity score matching

### Demographics

| Cohort Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|-------------|-----------|----------|-------------|---------|------------|
| 1 AI        | 60.1 ± 15.8 | 512,098  | 100%        | <0.001  | 0.013      |
| 2           | 60.3 ± 15.8 | 512,098  | 100%        |         |            |
| 1 2106-3    | 360,872    | 70.50%   |             | 0.061   | 0.004      |
| 2           | 361,736    | 70.60%   |             |         |            |
| 1 2054-5    | 77,336     | 15.10%   |             | 0.755   | 0.001      |
| 2           | 77,449     | 15.10%   |             |         |            |
| 1 M         | 243,685    | 47.60%   |             | 0.49    | 0.001      |
| 2           | 243,336    | 47.50%   |             |         |            |

### Diagnosis

| Cohort Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|-------------|-----------|----------|-------------|---------|------------|
| 1 K74       | 8,621     | 1.70%    |             | 0.812   | <0.001     |
| 2           | 8,590     | 1.70%    |             |         |            |
| 1 I10-I16   | 248,178   | 48.50%   |             | 0.28    | 0.002      |
| 2           | 248,724   | 48.60%   |             |         |            |
| 1 E08-E13   | 105,204   | 20.50%   |             | 0.365   | 0.002      |
| 2           | 105,575   | 20.60%   |             |         |            |
| 1 N17-N19   | 71,413    | 13.90%   |             | 0.677   | 0.001      |
| 2           | 71,267    | 13.90%   |             |         |            |
| 1 F17       | 62,388    | 12.20%   |             | 0.022   | 0.005      |
| 2           | 61,633    | 12.00%   |             |         |            |
| 1 F10.1     | 11,819    | 2.30%    |             | <0.001  | 0.011      |
| 2           | 11,023    | 2.20%    |             |         |            |
| 1 J40-J47   | 94,392    | 18.40%   |             | 0.986   | <0.001     |
| 2           | 94,399    | 18.40%   |             |         |            |
| 1 I48       | 57,620    | 11.30%   |             | 0.026   | 0.004      |
| 2           | 56,912    | 11.10%   |             |         |            |
| 1 I50       | 71,447    | 14.00%   |             | <0.001  | 0.011      |
| 2           | 69,468    | 13.60%   |             |         |            |
| 1 I20-I25   | 157,034   | 30.70%   |             | 0.001   | 0.006      |
| 2           | 155,516   | 30.40%   |             |         |            |

**TABLE 1: Baseline characteristics for patients taking verapamil**
### TABLE 2: Measures of association for patients taking verapamil and glioblastoma development

| 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       | p      |
|------------------|----------------|---------|--------|
| Risk difference  | -0.01%          | -3.945  | <0.0001|
| Risk ratio       | 0.495           | (0.346, 0.707) |
| Odds ratio       | 0.494           | (0.346, 0.707) |

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 = 400,800) and cohort 2 (N = 400,800) characteristics after propensity score matching

#### Demographics

| Cohort | Code  | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|-------|-----------|----------|-------------|---------|------------|
| 1      | AI    | 67.1 ± 17.4 | 400,800  | 100%        | <0.001  | 0.053      |
| 2      |       | 68.0 ± 16.8 | 400,800  | 100%        |         |            |
| 1      | 2106-3| 285,025   | 71.10%   |             | <0.001  | 0.008      |
| 2      |       | 286,563   | 71.50%   |             |         |            |
| 1      | 2054-5| 41,969    | 10.50%   |             | <0.001  | 0.012      |
| 2      |       | 43,428    | 10.80%   |             |         |            |
| 1      | M     | 215,191   | 53.70%   |             | <0.001  | 0.017      |
| 2      |       | 218,660   | 54.60%   |             |         |            |

#### Diagnosis

| Cohort | Code           | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|----------------|-----------|----------|-------------|---------|------------|
| 1      | K74            | 6,405     | 1.60%    | 0.245       | 0.003   |
| 2      |                | 6,275     | 1.60%    |             |         |            |
| 1      | I10-I16        | 165,032   | 41.20%   | <0.001      | 0.03    |
| 2      |                | 171,031   | 42.70%   |             |         |            |
| 1      | E08-E13        | 120,504   | 30.10%   | <0.001      | 0.033   |
| 2      |                | 126,550   | 31.60%   |             |         |            |
| 1      | N17-N19        | 6,156     | 19.00%   | <0.001      | 0.03    |
| 2      |                | 81,008    | 20.20%   |             |         |            |
| 1      | F17            | 70,372    | 17.60%   | 0.005       | 0.006   |
| 2      |                | 71,325    | 17.80%   |             |         |            |
| 1      | F10.1          | 31,294    | 7.80%    | 0.003       | 0.007   |
| 2      |                | 30,582    | 7.60%    |             |         |            |
| 1      | J40-J47        | 8,977     | 2.10%    | <0.001      | 0.01    |
| 2      |                | 91,540    | 1.40%    |             |         |            |
| 1      | I48            | 78,837    | 18.60%   | <0.001      | 0.133   |
| 2      |                | 889,710   | 13.70%   |             |         |            |
| 1      | I50            | 169,820   | 40.00%   | <0.001      | 1.008   |
| 2      |                | 197,088   | 3.00%    |             |         |            |
| 1      | I20-I25        | 123,790   | 29.20%   |             | <0.001  | 0.744      |
| 2      |                | 222,074   | 3.40%    |             |         |            |
I20-I25 Ischemic heart diseases

<0.001 0.015

2 102,127 25.50%

TABLE 3: Baseline characteristics for patients taking digoxin

| Cohort | Patients in cohort | Patients with outcome | Risk |
|--------|-------------------|-----------------------|------|
| 1      | Digoxin           | 400,800               | 46   | 0.01% |
| 2      | No digoxin        | 400,800               | 58   | 0.01% |

| Risk difference | 95% CI | z    | p    |
|-----------------|-------|------|------|
| -0.003%         | (-0.008, 0.002) | -1.177 | 0.239 |

Risk ratio 0.793 (0.539, 1.168)
Odds ratio 0.793 (0.539, 1.168)

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

Tables 5, 6 show the baseline characteristics and measures of association for our patients taking amiodarone. A total of 345,288 patients were taking amiodarone; of this number, 51 patients (0.009%) developed a glioblastoma. A matched group of 345,288 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).

Co  hen 1 (N = 646,598) and cohort 2 (N = 6,413,181) characteristics before propensity score matching

Demographics

| Cohort | Code | Demographic | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-------------|-----------|----------|-------------|---------|------------|
| 1      | AI   | Age at index| 68.2 ± 13.9 | 642,771 | 100%        | <0.001  | 1.301      |
| 2      |      |             | 43.7 ± 22.7 | 6,413,010 | 100%       |         |            |
| 1      | 2106-3 | White      | 458,481 | 71.30% | <0.001 | 0.089 |
| 2      |      |             | 4,311,815 | 67.20% |         |       |
| 1      | 2054-5 | Black or African American | 71,752 | 11.20% | <0.001 | 0.199 |
| 2      |      |             | 1,164,000 | 18.20% |         |       |
| 1      | M     | Male        | 396,131 | 61.90% | <0.001 | 0.429 |
| 2      |      |             | 2,628,514 | 41.00% |         |       |

Diagnosis

| Cohort | Code | Diagnosis | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-----------|-----------|----------|-------------|---------|------------|
| 1      | K74  | Fibrosis and cirrhosis of the liver | 12,352 | 1.90% | <0.001 | 0.084 |
| 2      |      |           | 59,755 | 0.90% |         |       |
| 1      | I10-I16 | Hypertensive diseases | 329,918 | 51.30% | <0.001 | 0.537 |
| 2      |      |           | 1,670,564 | 26.00% |         |       |
| 1      | E08-E13 | Diabetes mellitus | 152,108 | 23.70% | <0.001 | 0.306 |
| 2      |      |           | 744,882 | 12.10% |         |       |
| 1      | N17-N19 | Acute kidney failure and chronic kidney disease | 166,302 | 25.90% | <0.001 | 0.587 |
### Demographics

| Cohort Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|-------------|-----------|----------|-------------|---------|------------|
| AI          | 67.1 ± 14.2 | 543,288  | 100%        | <0.001  | 0.11       |
| 2           | 68.6 ± 14.1 | 543,288  | 100%        |         |            |
| 2106-3      | 384,058   | 70.70%   |             | <0.001  | 0.008      |
| 2           | 386,072   | 71.10%   |             |         |            |
| 2054-5      | 62,661    | 11.50%   |             | 0.219   | 0.002      |
| 2           | 63,071    | 11.60%   |             |         |            |
| M           | 329,165   | 60.60%   |             | 0.001   | 0.006      |
| 2           | 330,885   | 60.90%   |             |         |            |

### Diagnosis

| Cohort Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|-------------|-----------|----------|-------------|---------|------------|
| K74         | 9,713     | 1.80%    | 0.06        | 0.004   |
| 2           | 9,974     | 1.80%    |             |         |            |
| I10-I16     | 255,101   | 47.00%   |             | <0.001  | 0.032      |
| 2           | 263,759   | 48.50%   |             |         |            |
| E08-E13     | 118,383   | 21.80%   |             | <0.001  | 0.026      |
| 2           | 124,236   | 22.90%   |             |         |            |
| N17-N19     | 116,493   | 21.40%   |             | <0.001  | 0.016      |
| 2           | 112,883   | 20.80%   |             |         |            |
| F17         | 51,538    | 9.50%    |             | <0.001  | 0.009      |
| 2           | 50,106    | 9.20%    |             |         |            |
| F10.1       | 12,059    | 2.20%    |             | 0.603   | 0.001      |
| 2           | 12,139    | 2.20%    |             |         |            |
| J40-J47     | 95,383    | 17.60%   |             | <0.001  | 0.013      |
| 2           | 98,004    | 18.00%   |             |         |            |
### TABLE 5: Baseline characteristics for patients taking amiodarone

| Cohort | Patients in cohort | Patients with outcome | Risk |
|--------|-------------------|-----------------------|------|
| 1      | Amiodarone        | 543,288               | 51   | 0.01% |
| 2      | No amiodarone     | 543,288               | 85   | 0.02% |

Risk difference: -0.01% (95% CI: -0.01, -0.002)  
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).
| Code     | Description                                           | Patients | % of cohort | P-value | Std. diff. |
|----------|-------------------------------------------------------|----------|-------------|---------|------------|
| I10-I16  | Hypertensive diseases                                 | 388,689  | 44.20%      | <0.001 | 0.395      |
| E08-E13  | Diabetes mellitus                                     | 156,196  | 17.80%      | <0.001 | 0.162      |
| N17-N19  | Acute kidney failure and chronic kidney disease       | 128,695  | 14.60%      | <0.001 | 0.31       |
| F17      | Nicotine dependence                                   | 73,433   | 8.30%       | <0.001 | 0.027      |
| F10.1    | Alcohol abuse                                         | 17,819   | 2.00%       | <0.001 | 0.05       |
| I48      | Atrial fibrillation and flutter                       | 165,911  | 18.90%      | <0.001 | 0.148      |
| I50      | Heart failure                                         | 230,044  | 26.10%      | <0.001 | 0.708      |
| I20-I25  | Ischemic heart diseases                               | 112,691  | 13.00%      | <0.001 | 0.35       |

Cohort 1 (N = 828,618) and cohort 2 (N = 828,618) characteristics after propensity score matching

### Demographics

| Cohort | Code | Description   | Mean ± SD  | Patients | % of cohort | P-value | Std. diff. |
|--------|------|---------------|------------|----------|-------------|---------|------------|
| 1      | AI   | Age index     | 65.6 ± 14.7| 828,618  | 100%        | <0.001 | 0.044      |
| 2      |      |               | 66.3 ± 14.8| 828,618  | 100%        |         |            |
| 1      | 2106-3 | White      | 599,855   | 72.40%   | <0.001       | 0.012   |
| 2      |      |               | 595,428   | 71.90%   |             |         |
| 1      | 2054-5 | Black or African American | 107,250 | 12.90%   | <0.001       | 0.016   |
| 2      |      |               | 111,823   | 13.50%   |             |         |
| 1      | M    | Male          | 381,608   | 46.10%   | <0.001       | 0.03    |
| 2      |      |               | 394,062   | 47.60%   |             |         |

### Diagnosis

| Cohort | Code | Description                                           | Mean ± SD  | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-------------------------------------------------------|------------|----------|-------------|---------|------------|
| 1      | K74  | Fibrosis and cirrhosis of the liver                   | 10,269     | 1.20%    | 0.338       | 0.001   |
| 2      |      |                                                       | 10,133     | 1.20%    |             |         |
| 1      | I10-I16 | Hypertensive diseases      | 350,863    | 42.30%   | <0.001       | 0.017   |
| 2      |      |                                                       | 357,943    | 43.20%   |             |         |
| 1      | E08-E13 | Diabetes mellitus     | 143,869    | 17.00%   | <0.001       | 0.02    |
| 2      |      |                                                       | 150,221    | 18.10%   |             |         |
| 1      | N17-N19 | Acute kidney failure and chronic kidney disease | 112,691    | 13.00%   | <0.001       | 0.016   |
| 2      |      |                                                       | 116,736    | 14.10%   |             |         |
| 1      | F17  | Nicotine dependence                                   | 68,443     | 8.30%    | <0.001       | 0.014   |
| 2      |      |                                                       | 65,296     | 7.90%    |             |         |
| 1      |      |                                                       | 16,283     | 2.00%    |             |         |
### 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% |

| Risk difference | 95% CI | z     | p    |
|-----------------|--------|-------|------|
| -0.008          | (-0.012, -0.004) | -4.196| <0.0001 |

| Risk ratio | 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).

### Cohort 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. diff. |
|--------|------|-----------|----------|-------------|---------|------------|
| 1      | A    | 65.0 ± 15.9 | 1,998,460 | 100%        | <0.001  | 1.14       |
| 2      | B    | 42.7 ± 22.6 | 6,089,598 | 100%        |         |            |

| Cohort | Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-----------|----------|-------------|---------|------------|
| 1      | 2016-3 | 1,415,666 | 70.80%   | <0.001     | 0.083   |
| 2      | 2054-5 | 252,945  | 12.70%   | <0.001     | 0.152   |

| Cohort | Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-----------|----------|-------------|---------|------------|
| 1      | 2022 | 2,485,621 | 40.80%   | <0.001     | 0.21    |

#### Diagnosis

| Cohort | Code | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|--------|------|-----------|----------|-------------|---------|------------|
| 1      | 27,381 | 1.40%     |          |             |         |            |
| Code    | Description                                      | Mean ± SD | Patients | % of cohort | P-value | Std. diff. |
|---------|--------------------------------------------------|-----------|----------|-------------|---------|------------|
| K74     | Fibrosis and cirrhosis of the liver              | 52,695    | 0.90%    | <0.001      | 0.048   |
| I10-I16 | Hypertensive diseases                            | 849,956   | 42.50%   | <0.001      | 0.396   |
|         |                                                  | 1,474,384 | 24.20%   |             |         |
| E08-E13 | Diabetes mellitus                                | 361,253   | 18.10%   | <0.001      | 0.195   |
|         |                                                  | 682,224   | 11.20%   |             |         |
| N17-N19 | Acute kidney failure and chronic kidney disease  | 298,367   | 14.90%   | <0.001      | 0.346   |
|         |                                                  | 290,013   | 4.80%    |             |         |
| F17     | Nicotine dependence                              | 171,097   | 8.60%    | <0.001      | 0.044   |
|         |                                                  | 448,607   | 7.40%    |             |         |
| F10.1   | Alcohol abuse                                    | 37,677    | 1.90%    | <0.001      | 0.045   |
|         |                                                  | 80,852    | 1.30%    |             |         |
| I48     | Atrial fibrillation and flutter                  | 450,002   | 22.50%   | <0.001      | 0.666   |
|         |                                                  | 113,082   | 1.90%    |             |         |
| I20-I25 | Ischemic heart diseases                          | 486,062   | 24.30%   | <0.001      | 0.546   |
|         |                                                  | 338,211   | 5.60%    |             |         |
Atrial fibrillation and flutter

| Cohort | Patients in cohort | Patients with outcome | Risk |
|--------|-------------------|-----------------------|------|
| 1      | 148               | 145,964               | 9.30%<0.001 0.077 |
| 2      | 120-125           | 112,626               | 7.10%<0.001 0.05 |

Ischemic heart diseases

| Cohort | Patients in cohort | Patients with outcome | Risk |
|--------|-------------------|-----------------------|------|
| 1      | 120-125           | 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)**

**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. Second, 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.

References

1. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, Villano JL: Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev. 2014, 23:1985-96. 10.1158/1055-9965.EPI-14-0275
2. Ogaki H, Kleihues P: The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013, 19:764-72. 10.1158/1078-0432.CCR-12-3002
3. Alexander BM, Cloughesy TF: Adult glioblastoma. J Clin Oncol. 2017, 35:2402-9. 10.1200/JCO.2017.73.0119
4. Schwartzbaum JA, Fisher JL, Aldape KD, Wrench M: Epidemiology and molecular pathology of glioma. Nat Clin Pract Neurol. 2006, 2:494-505. 10.1038/ncpneuro0289
5. Ransomb CB, O’Neal JT, Sontheimer H: Volume-activated chloride currents contribute to the resting conductance and invasive migration of human glioma cells. J Neurosci. 2001, 21:7674-85. 10.1525/JNEUROSCI.21-19-07674.2001
6. Verkhratsky A, Steinhauser C: Ion channels in glial cells. Brain Res Rev. 2000, 32:580-412. 10.1016/S0165-0171(99)00093-4
7. Parsons DW, Jones S, Zhang X, et al.: An integrated genomic analysis of human glioblastoma multiforme. Science. 2008, 321:1807-12. 10.1126/science.1164382
8. Joshi AD, Parsons DW, Velculescu VE, Riggins GI: Sodium ion channel mutations in glioblastoma patients correlate with shorter survival. Mol Cancer. 2011, 10:17. 10.1186/1476-4598-10-17
9. Santoni G, Santoni M, Nabissi M: Functional role of T-type calcium channels in tumour growth and
10. Jacquier G, Baghirov H, Georgiadou M, et al.: L-type calcium channels regulate filopodia stability and cancer cell invasion downstream of integrin signalling. Nat Commun. 2016, 7:13297. 10.1038/ncomms13297
11. Kuga T, Sadoshima J, Tomoike H, Kanaide H, Akaike N, Nakamura M: Actions of Ca2+ antagonists on two types of Ca2+ channels in rat aorta smooth muscle cells in primary culture. Circ Res. 1990, 67:469-80. 10.1161/01.res.67.2.469
12. Goldin AG, Safa AR: Digitalis and cancer. Lancet. 1984, 325:1154. 10.1016/S0140-6736(84)92556-X
13. Molenaar RJ: Ion channels in glioblastoma. ISRN Neurol. 2011, 2011:1-7. 10.5402/2011/590249
14. Turner KL, Sontheimer H: Cl- and K+ channels and their role in primary brain tumour biology. Philos Trans R Soc Lond B. 2014, 369:20130095. 10.1098/rstb.2013.0095
15. Pointer KB, Clark PA, Elieeiri KW, Salamat MS, Robertson GA, Kuo JS: Administration of non-torsadogenic human ether-a-go-go-related gene inhibitors is associated with better survival for high hERG-expressing glioblastoma patients. Clin Cancer Res. 2017, 23:73-80. 10.1158/1078-0432.CCR-15-5169
16. Chen D, Song M, Mohamad O, Yu SP: Inhibition of Na+/K+-ATPase induces hybrid cell death and enhanced sensitivity to chemotherapy in human glioblastoma cells. BMC Cancer. 2014, 14:716. 10.1186/1471-2407-14-716
17. Martínez R, Stühmer W, Martin S, Schell J, Reichmann A, Rohde V, Pardo L: Analysis of the expression of Kv10.1 potassium channel in patients with brain metastases and glioblastoma multiforme: impact on survival. BMC Cancer. 2015, 15:839. 10.1186/s12885-015-1848-y
18. Kim IY, Kang YJ, Yoon MJ, et al.: Amiodarone sensitizes human glioma cells but not astrocytes to TRAIL-induced apoptosis via CHOP-mediated DR5 upregulation. Neuro Oncol. 2011, 13:267-79. 10.1093/neuonc/noq195
19. Steinberg E, Flukman A, Zemmour C, et al.: Low dose amiodarone reduces tumor growth and angiogenesis. Sci Rep. 2020, 10:18034. 10.1038/s41598-020-75142-1