Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study*†
Tobias Gerhard, D. P. Devanand, Cecilia Huang, Stephen Crystal and Mark Olfson

Background
Lithium inhibits glycogen synthase kinase-3, an enzyme implicated in the pathogenesis of dementia.

Aims
To examine the association of lithium and dementia risk in a large claims-based US cohort of publicly insured older adults with bipolar disorder.

Method
The cohort included individuals ≥50 years diagnosed with bipolar disorder who did not receive dementia-related services during the prior year. Each follow-up day was classified by past-year cumulative duration of lithium use (0, 1–60, 61–300 and 301–365 days). Dementia diagnosis was the study outcome. Anticonvulsants commonly used as mood stabilisers served as a negative control.

Results
Compared with non-use, 301–365 days of lithium exposure was associated with significantly reduced dementia risk (hazard ratio (HR) = 0.77, 95% CI 0.60–0.99). No corresponding association was observed for shorter lithium exposures (HR = 1.07, 95% CI 0.67–1.71 for 1–60 days) or for any exposure to anticonvulsants.

Conclusions
Continuous lithium treatment may reduce dementia risk in older adults with bipolar disorder.

Declaration of interest
D.P.D. is a consultant for Abbvie and Lundbeck.

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Lithium is a well-established and highly effective treatment for patients with bipolar disorder. Lithium use has steadily declined since the early 1990s, partly because newer, branded, alternative treatments became available.1–3 Glycogen synthase kinase-3 (GSK3) is an enzyme with a multitude of effects on neurotrophic response, autophagy, oxidative stress, inflammation and mitochondrial function, and it has been implicated in the pathogenesis of neurodegenerative disorders including Alzheimer’s disease.4 Lithium inhibits GSK3 and has been hypothesised to protect against the development of Alzheimer’s disease, which is the most common cause of dementia.5,6 Empirical evidence regarding the hypothesised protective effect has been promising but mixed.7 After small observational studies in the mid-2000s produced contradictory findings,8,9 reports from a large Danish population-based registry data-set reported a significant protective effect of lithium against dementia.10,11 Two studies, the first inclusive of all patients prescribed lithium in Denmark, the other restricted to the subset with psychiatric hospital services for bipolar disorder, reported strong protective effects (as large as a 62% reduction in relative risk) of continued lithium use among lithium users. Two randomised controlled trials of adults with mild to moderate Alzheimer’s disease did not observe a protective lithium effect,12,13 whereas another trial of adults with mild to moderate Alzheimer’s disease did

*An earlier version of this research was, in part, presented at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2014 Annual Meeting, 18–22 March 2014, Atlanta, Georgia, USA.
†See invited commentary, pp. 52–54, this issue.

Method
We conducted a retrospective, population-based, observational cohort study among people ≥50 years of age who had been diagnosed with bipolar disorder. As bipolar disorder has been linked with increased dementia risk and lithium is predominantly used to treat bipolar disorder, we restricted the study population to those diagnosed with bipolar disorder to reduce confounding by indication.17–19

Data sources and study cohort
Our study used combined service and pharmacy claims (Medicaid Analytic Extract, Medicare Parts A and B) from 1 January 2001 to 31 December 2004 from eight large US states (California, Florida, Georgia, Illinois, New Jersey, New York, Ohio, Texas). These data include over 44 million individuals and represent approximately 40% of the Medicaid insured US population. Medicaid is a social healthcare programme for US residents with low incomes or...
various disabilities. Because Medicare is the primary payer for physician and hospital services for most individuals ages ≥ 65 years in the USA, Medicare Part A and B data were matched for all Medicaid insured individuals who were dually eligible for Medicare. People entered the study upon meeting the following criteria at the index date: (a) continuous Medicaid eligibility during the previous 395 days, (b) a diagnosis of bipolar disorder (one in-patient or two out-patient claims with ICD-9-CM codes 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x in any position) during the pre-index period, and (c) age ≥ 50 years. Because our lithium exposure definition is calculated based on the medication supply during the preceding 365 days, we required a 395-day period of prior eligibility to facilitate the calculation of exposure from day 1 of follow-up (365 days plus 30 days to capture prescription claims in the month prior to the 1-year exposure period). Patients with a diagnosis of dementia or mild cognitive impairment (any claim with ICD-9-CM 290.0x-290.4x, 294.1x, 331.0x, 331.1x-331.2x, 331.82-3, 331.9x), treatment for dementia (any prescription claim for donepezil, galantamine, rivastigmine or memantine) or a diagnosis of schizophrenia or other psychoses (any claim with ICD-9-CM 295.xx, 290.8x, 290.9x, 297.xx-299.xx, 780.1x) during the 12-month pre-index period were excluded.

**Exposure and outcome**

Lithium was the primary exposure. Because the hypothesised protective effects require prolonged exposure, we examined cumulative exposure over a 1-year period. Specifically, exposure to lithium was defined time-dependently for each day of follow-up as the cumulative number of days of medication supply over the previous 365 days in 4 categories: none (0 days), sporadic (1–60 days), intermittent (61–300 days) and continuous (301–365 days). Anticonvulsants that may be used in this population as mood stabilisers served as a negative control and were operationalised in a manner analogous to lithium (online Table DS1).

Anticonvulsants were selected as a negative control because among available pharmacological treatments for bipolar disorder (i.e. lithium, anticonvulsants, antidepressants, antipsychotics), anticonvulsants are most comparable with lithium in anti-manic and antidepressant properties,\(^{21,22}\) thus reducing the potential for confounding.\(^{23}\) Study outcome was incident dementia, defined as one in-patient or two out-patient claims for any listed ICD-9-CM diagnosis of 290.0x-290.4x, 294.1x, 331.0x, 331.1x-331.2x, 331.82-3, 331.9x, treatment for dementia (any prescription claim for donepezil, galantamine, rivastigmine or memantine) or a diagnosis of schizophrenia or other psychoses (any claim with ICD-9-CM 295.xx, 290.8x, 290.9x, 297.xx-299.xx, 780.1x) during the 12-month pre-index period were excluded.

**Covariates**

Demographic variables included age, gender, ethnicity and reason for Medicaid eligibility (disability, poverty, other). In addition, we included residency in a long-term care facility, psychiatric comorbidity (depression, anxiety, alcohol-related, and drug-related disorders), cardiovascular comorbidity (arrhythmias, heart failure, myocardial infarction, other acute ischemic heart disease, other chronic ischemic heart disease, and hypertension), cerebrovascular disease, diabetes mellitus and Parkinson's disease (online Table DS2). Medication classes included antidepressants, antipsychotics and anti-anxiety medications (online Table DS1).

**Statistical analysis**

We calculated sociodemographic and clinical characteristics at baseline for the full cohort and stratified by use of lithium and anticonvulsants at any point during the study period. We then calculated event rates and 95% confidence intervals for the full cohort as well as for non-use (referent), sporadic use, intermediate use, and continuous use of lithium and anticonvulsants. Cox proportional hazard models with time-dependent exposure were then fit to estimate the hazard ratios for prior year exposure (sporadic use, intermediate use and continuous use) to (a) lithium and (b) anticonvulsants (negative control) compared with non-use. Follow-up began on the index date and ended at loss of service eligibility, death, end of the study period or occurrence of the study outcome, whichever came first. We fit an unadjusted model, a model adjusted for gender, age and ethnicity; and a fully adjusted model. The fully adjusted model controlled for all covariates presented in online supplement DS1. Age was categorised into 5-year age bands beginning with age 50–54. Age categories and medication treatments for bipolar disorder were included as time-dependent variables and updated for each day of follow-up.

**Results**

The study cohort included 41,931 people ≥ 50 years of age who had been diagnosed with bipolar disorder. Figure 1 depicts the cohort assembly process. The cohort was predominantly female and White with a mean age of 60.4 years at index date. Three-quarters were eligible for Medicaid through disability and 18% resided in long-term care. Table 1 presents detailed demographic and clinical characteristics of the cohort overall and stratified by exposure to lithium and to anticonvulsants at any point over follow-up.

Compared with non-users of any mood stabilisers, lithium users were younger, less likely to reside in long-term care or have diagnosed psychiatric, cardiovascular or other somatic comorbidities, and more likely to receive other classes of psychotropic medications. Characteristics of users of anticonvulsants generally fell between those of lithium users and mood stabiliser non-users. Alcohol and substance-related disorders, and use of antidepressants or anxiolytics/hypnotics, were more common in users of anticonvulsants than in the other two groups.

The study cohort accrued a total of 66,258 person-years of follow-up (mean follow-up of 19 months). End of study period was the most common reason for censoring followed by loss of Medicaid eligibility and death (online Table DS3). Lithium use...
Discussion

Main findings and comparison with findings from other studies

We demonstrate that continued lithium use in older adults with bipolar disorder is associated with a reduced incidence of dementia diagnosis. This finding contrasts with the result for the negative control (use of anticonvulsants) for which no such effect was observed. Our cohort is broadly representative of publicly insured older patients with bipolar disorder in the USA.
and is one of the largest to date to examine the association between lithium use and dementia risk in bipolar disorder. These results are consistent with previous reports from Danish population-based registry data. The magnitude of the observed protective lithium effect in our study is smaller than that observed in the Danish registry data, possibly because the US cohort was older and restricted to individuals on Medicaid.10,11 Particularly, the incidence of dementia was higher in the US cohort than in the Danish cohort (2.3% vs. 1.0%), possibly because the US cohort was older and restricted to individuals on Medicaid.

In contrast, our finding of a lithium protective effect limited to continuous use over the previous year reduces concerns regarding patient characteristics associated with lithium tolerability. By reverse for use of anticonvulsants with higher use rates in the USA (53.2% over 4 years) compared with Denmark (36.7% over 10 years). Antidepressants and antipsychotics were used in a majority of patients in both countries. The incidence of dementia was higher in the US cohort than in the Danish cohort (2.3% vs. 1.0%), possibly because the US cohort was older and restricted to individuals on Medicaid.

As this is a non-randomised study from administrative claims data, our findings are open to alternative explanations. We employed multiple time-dependent exposure categories for lithium as well as a carefully chosen negative control exposure to examine the plausibility of the most pertinent potential sources of bias. First, the observed protective lithium effect could be attributed to channelling bias; i.e. the preferential selection of lithium over anticonvulsants for patients at lower risk for dementia.

This possibility is supported by the fact that lithium-treated patients had lower baseline rates of cerebrovascular disease and diabetes than those treated with anticonvulsants, both of which have been associated with increased rates of dementia.26–28 However, if channelling were the cause for the observed protective effect associated with lithium, then this protective effect would be expected to be present in all treatment durations relative to anticonvulsants rather than limited to continuous use as observed. Second, previous studies reported a protective lithium effect after only two prescriptions, which is suggestive of confounding by patient characteristics associated with lithium tolerability. By contrast, our finding of a lithium protective effect limited to continuous use over the previous year reduces concerns regarding such confounding. Third, a protective effect of maintenance medication treatment with lithium could reasonably be attributed to what has been described as the ‘healthy adherer effect’, in other words, confounding by healthy behaviours that correlate with medication adherence.29 Our finding of an absence of a beneficial effect for continued use of anticonvulsants reduces this concern.

Patients with bipolar disorder are at increased risk of developing dementia.37–39 Because several medication options exist for managing bipolar disorder,31 it is important to evaluate whether they differ with respect to risk of dementia. Although consistent treatment with lithium appears to lower the risk of dementia, a similar protective association was not observed following treatment with mood stabilising anticonvulsants considered as a group. In practice, clinicians often make medical decisions not only on the basis of individual patient considerations such as treatment history, current presentation, patient preferences and known drug sensitivities, but also on the basis of comparative safety and effectiveness research.30 In this context, the present findings add to the accumulating clinically relevant evidence that

### Table 2 Dementia diagnosis during follow-up period for baseline cohort of patients with bipolar disorder a

<table>
<thead>
<tr>
<th></th>
<th>n b</th>
<th>Person-years</th>
<th>Event</th>
<th>Incidence rate (95% CI) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cohort</td>
<td>41,931</td>
<td>66,258</td>
<td>1,538</td>
<td>2.32 (2.21–2.44)</td>
</tr>
<tr>
<td>Lithium, cumulative exposure b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 day</td>
<td>37,485</td>
<td>56,164</td>
<td>1,377</td>
<td>2.45 (2.32–2.58)</td>
</tr>
<tr>
<td>1–60 days</td>
<td>2,925</td>
<td>990</td>
<td>18</td>
<td>1.82 (1.98–2.66)</td>
</tr>
<tr>
<td>61–300 days</td>
<td>4,808</td>
<td>4,460</td>
<td>79</td>
<td>1.77 (1.38–2.16)</td>
</tr>
<tr>
<td>301–365 days</td>
<td>3,766</td>
<td>4,644</td>
<td>64</td>
<td>1.38 (1.04–1.72)</td>
</tr>
<tr>
<td>Anticonvulsants, cumulative exposure b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 day</td>
<td>28,046</td>
<td>37,656</td>
<td>925</td>
<td>2.46 (2.30–2.61)</td>
</tr>
<tr>
<td>1–60 days</td>
<td>8,604</td>
<td>3,344</td>
<td>78</td>
<td>2.33 (1.82–2.85)</td>
</tr>
<tr>
<td>61–300 days</td>
<td>13,920</td>
<td>12,114</td>
<td>251</td>
<td>2.07 (1.82–2.33)</td>
</tr>
<tr>
<td>301–365 days</td>
<td>11,014</td>
<td>13,145</td>
<td>284</td>
<td>2.16 (1.91–2.41)</td>
</tr>
</tbody>
</table>

a. Data from eight states of Medicaid claims.

b. Not mutually exclusive. As a result of the time-dependent specification of exposure, one individual can appear in multiple exposure categories.

c. Rate expressed per 100 person-years.

d. Cumulative exposure in past 365 days for each day in the follow-up period beginning on the index date and ending at end of study period; occurrence of outcome, death or loss of eligibility, whichever comes first.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI), unadjusted</th>
<th>HR (95% CI), gender, age, ethnicity adjusted</th>
<th>HR (95% CI), fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative 365 day exposure</td>
<td>Lithium</td>
<td>Anticonvulsants</td>
<td>Lithium</td>
</tr>
<tr>
<td>0 days (referent) (non-use)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1–60 days (sporadic)</td>
<td>0.74 (0.47–1.18)</td>
<td>0.95 (0.76–1.20)</td>
<td>1.16 (0.73–1.86)</td>
</tr>
<tr>
<td>61–300 days (intermittent)</td>
<td>0.72 (0.58–0.91)</td>
<td>0.85 (0.74–0.97)</td>
<td>0.98 (0.78–1.23)</td>
</tr>
<tr>
<td>301–365 days (continuous)</td>
<td>0.56 (0.44–0.72)</td>
<td>0.88 (0.77–1.01)</td>
<td>0.70 (0.54–0.93)</td>
</tr>
</tbody>
</table>

a. Data from eight states of Medicaid claims. Results presented as hazard ratios (HR) with 95% confidence intervals in parentheses.

b. The fully adjusted model includes the following covariates: gender, ethnicity (Black, White, Hispanic, other), age (time-dependent, years, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90+), Medicaid eligibility (disability, poverty, other), long-term care residency, depression, anxiety, alcohol-related disorders, drug-related disorders, arthritis, heart failure, myocardial infarction, other acute ischemic heart disease, other chronic ischemic heart disease, hypertension, cerebrovascular disease, diabetes mellitus, Parkinson’s disease, antipsychotic use (time-dependent), antidepressant use (time-dependent), use of anti-anxiety medications (time-dependent).

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The table below shows the risk of dementia in patients with bipolar disorder by cumulative exposure to lithium and anticonvulsants.

<table>
<thead>
<tr>
<th>Cumulative 365 day exposure</th>
<th>HR (95% CI), unadjusted</th>
<th>HR (95% CI), gender, age, ethnicity adjusted</th>
<th>HR (95% CI), fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Anticonvulsants</td>
<td>Lithium</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>0 days (referent) (non-use)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1–60 days (sporadic)</td>
<td>0.74 (0.47–1.18)</td>
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</tr>
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</tr>
</tbody>
</table>

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The table shows the risk of dementia in patients with bipolar disorder by cumulative exposure to lithium and anticonvulsants.
maintenance lithium treatment may delay or reduce the risk of dementia onset in older patients with bipolar disorder.

Limitations

Our study is also subject to limitations related to the use of automated claims data. First, dementia is underdiagnosed and undercoded in clinical practice, which raises concerns regarding the accuracy of our claims-based outcome definition. Furthermore, non-differential misclassification of the outcome from under- or delayed diagnosis or undercoding is expected to result in a conservative bias towards the null hypothesis. Similar claims-based definitions have been used in previous research and shown acceptable measurement characteristics. In addition, the fact that established dementia risk factors, including age, alcohol use, cerebrovascular disease and diabetes, were associated with increased dementia in our sample provides empirical face validity to our claims-based dementia definition. Second, as with all claims-based studies, prescription fills only indicate medications dispensed, not those ingested. This could result in exposure misclassification and would, again, probably introduce a conservative bias towards the null hypothesis. Third, because of concerns regarding the accuracy of medical claims records in establishing dementia subtype, we did not differentiate between Alzheimer’s disease and other types of dementia. Fourth, with a maximum follow-up of less than 3 years, our study duration is relatively short compared with the lifetime duration of bipolar disorder and gradual onset of dementia. Similarly, lifetime exposure to lithium and anticonvulsants cannot be established from the data. Fifth, our study does not address the mechanism of the observed lithium-associated protective effects on dementia. Sixth, despite statistical methods to lessen concerns regarding confounding, we cannot completely rule out confounding in this non-randomised study.

Implications

The present findings support and strengthen the hypothesis that lithium exerts a protective effect on the development of dementia in patients with bipolar disorder. Because dementia has a devastating impact on the lives of patients, families and caregivers, and no curative or preventive treatments exist, our findings strengthen the rationale for extending clinical research on the potentially neuroprotective effects of lithium, including studies in patients who do not necessarily have bipolar disorder. The clinical trials with lithium in patients with mild cognitive impairment and dementia have been limited, and whether lithium exerts its protective effect through reduction in affective episodes, inhibition of GSFK, or some other mechanism remains unknown. Systematic prevention or treatment trials to investigate the neuroprotective effects of lithium may be warranted.

References


Funding

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Lithium treatment and risk for dementia in adults with bipolar disorder


28 Skoog I. Risk factors for vascular dementia: a review. Dementia 1994; **5**: 137–44.


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### Extra Content Online

**poem**

**Careful**

Kathleen M. Kelley

There is a man I almost know, an orderly in green scrubs I see in the elevator, pass in the halls at the hospital where we are careful to look down, knowing our patients deserve their privacy, and we are strangers.

Elevators are full of strangers. They see without even looking and know more than you’d think about the patients on gurneys. The door opens. I look to see who’s getting off, and it’s him, being careful with his gurney as it takes the bump into halls where everyone is in a hurry, uneven halls clumsily connected, painted by strangers in colors that sicken. Always, he is careful with the bumps, I’ve been behind him, know the set of his shoulders, his grey pony tail. I see some others who transport patients with tumors or wounds or dementia, patients who are helpless, but leave them in the halls alone while they hurry off on break to see if the coffee’s ready yet. Professional strangers, we avert our eyes because we know too much about the system’s failures. Careful about privacy means we protect our own, careful to forget that sometimes we are the patients. We all take a turn being human, should know better than to walk along these halls as if we shared nothing with the strangers we take care of, like the ones I’m here to see today, who carry code words I never like to see: metastatic, bipolar, morbidly obese. ‘Careful,’ what’s implied. Extraordinary strangers often, for I have much in common with my patients, whose bedside can remind me of familial halls that bore the exact same misery. Good thing I know enough as I start to chart on patients who would all rather be cured than healed, to be careful not to write about everything I know.

Kathleen M. Kelley is a social worker. The poem was selected by Femi Oyebode. Published in *The Hippocrates Prize Anthology*, Hippocrates Press, 2012. ©Kathleen M. Kelley. Reprinted with permission.

**Table DS1 Drug Classes (generic names)**

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>carbamazepine, lamotrigine, valproic acid, divalproex, acetazolamide, felbamate, gabapentin, levetiracetam, oxcarbazepine, pregabalin, topiramate, zonisamide</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, thioridazine, thiothixene, trifluoperazine, triflupromazine, chlorprothixene, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, mirtazapine, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, phenerzine, tranylcypromine, isocarboxazid, nefazodone, trazodone, bupropion</td>
</tr>
<tr>
<td>Anxiolytics/Hypnotics</td>
<td>alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, oxazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplon, zolpidem, zopiclone, ramelteon, buspirone, chloral hydrate, ethchlorvynol, meprobamate, amobarbital, butabarbital, mephobarbital, secobarbital</td>
</tr>
</tbody>
</table>

**Table DS2 Diagnostic covariates (ICD 9-CM)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia*</td>
<td>295.xx</td>
</tr>
<tr>
<td>Other psychosis*</td>
<td>290.8x, 290.9x, 297.xx-299.xx, 780.1x</td>
</tr>
<tr>
<td>Depression</td>
<td>293.83, 296.2x, 296.3x, 296.9x, 298.0x, 300.4x, 311.xx</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>300.0x, 300.2x, 300.3x</td>
</tr>
<tr>
<td>Alcohol related disorders</td>
<td>291.xx, 303.xx, 305.0x</td>
</tr>
<tr>
<td>Substance related disorders</td>
<td>292.xx, 304.xx, 305.xx, except 305.0x</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>427.1x, 427.2x, 427.5x, 427.9x, 785.0x, 427.41, 427.42, 427.60, 427.69, 427.89</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>430.xx-438.xx</td>
</tr>
</tbody>
</table>
Heart failure 428.xx
Myocardial infarction 410.xx, 412.xx
Other acute ischemic heart disease 411.xx, 413.xx
Other chronic ischemic heart disease 414.0x, 414.2x, 414.8x, 414.9x, 429.2x
Parkinson 332.xx, 333.82
Hypertension 401.xx-405.xx
Diabetes 250.xx

* Exclusion criteria

<table>
<thead>
<tr>
<th>Reason</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Censoring</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2,616</td>
<td>6.2</td>
</tr>
<tr>
<td>Loss of eligibility</td>
<td>4,111</td>
<td>9.8</td>
</tr>
<tr>
<td>End of observation period</td>
<td>33,666</td>
<td>80.3</td>
</tr>
<tr>
<td>Outcome</td>
<td>1,538</td>
<td>3.7</td>
</tr>
<tr>
<td>Total</td>
<td>41,931</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Online supplement DS1
**Covariates included in the multivariate Cox model**
Sex, race/ethnicity (black, white, Hispanic, other), age [time-dependent, years] (50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90+), Medicaid eligibility (disability, poverty, other), long term care residency, depression, anxiety, alcohol-related disorders, drug-related disorders, arrhythmia, heart failure, myocardial infarction, other acute ischemic heart disease, other chronic ischemic heart disease, hypertension, cerebrovascular disease, diabetes mellitus, Parkinson’s disease, antidepressant use [time-dependent], antipsychotic use [time-dependent], use of anti-anxiety medications [time-dependent].
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Supplementary material can be found at:
http://bjp.rcpsych.org/content/suppl/2015/01/14/bjp.bp.114.154047.DC1

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