Use of dipyridamole is associated with lower risk of lymphoid neoplasms: a propensity score-matched cohort study

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Summary

The anti-cancer potential of dipyridamole has been suggested from experiments, but evidence from population-based studies is still lacking. We aimed to explore if dipyridamole use was related to a lower risk of lymphoid neoplasms. We identified individuals with prescription of aspirin after diagnosis of ischaemic cerebrovascular disease since 2006 by linking several Swedish registers. In these aspirin users, those with dipyridamole prescription were further identified as the study group and patients without dipyridamole were randomly selected as reference group with 1:1 ratio using a propensity score-matching approach. After a median of 6.67 years of follow-up, a total of 46 patients with dipyridamole use developed lymphoid neoplasms with an incidence rate of 0.49 per 1 000 person-years, while the rate in the matched group was 0.74 per 1 000 person-years. As compared to non-users, dipyridamole users were associated with a significantly decreased risk of lymphoid neoplasms [hazard ratio (HR) = 0.65; 95% confidence interval (CI) = 0.43-0.98]. Specifically, the reduced risk was observed for non-Hodgkin lymphomas (HR = 0.64; 95% CI 0.42-0.94), especially B-cell lymphomas (HR = 0.56; 95% CI 0.35-0.88). Dipyridamole use was related to a lower risk of lymphoid neoplasms, indicating a clinical potential of dipyridamole to be an adjunct anti-tumour agent against lymphoid neoplasms.

Keywords: dipyridamole, lymphoid neoplasms, cohort study, drug repurposing.

Introduction

Dipyridamole is an FDA-approved platelet inhibitor. Although the underlying mechanisms of dipyridamole have not been completely clarified, its anti-platelet effect is related to the inhibition of phosphodiesterase (PDE) and the blockade of nucleoside transportation. Emerging data have demonstrated the extra anti-inflammatory and anti-oxidant potential of dipyridamole, which is independent of its classical anti-platelet action. These classical and pleiotropic actions of dipyridamole have been suggested to play a role in inhibiting tumourigenesis and progression. Recently, a growing amount of evidence from preclinical research indicated the anti-cancer activity of dipyridamole on several types of malignancies, including colorectal, breast, prostate, or haematological malignancies. Dipyridamole was recently found to prevent Epstein–Barr virus (EBV) re-activation, indicating a possibility to be repurposed as a non-toxic anti-viral drug to prevent EBV-related diseases. It is known that EBV was originally discovered in cells from Burkitt’s lymphoma, and the re-activation has been demonstrated to directly and indirectly associate with lymphomagenesis. Based on the available preclinical evidence, it is reasonable to put forward the hypothesis that dipyridamole has the potential to be repurposed as an adjunct anti-tumour drug against lymphoid neoplasms. However, population-based evidence is still lacking.

We aimed to explore the chemo-preventive potential of dipyridamole against lymphoid neoplasms in the Swedish population. In Sweden, the majority of dipyridamole prescriptions are dispensed concurrently with aspirin for patients diagnosed with ischaemic cerebrovascular diseases, which shows a stronger anti-platelet efficacy over aspirin monotherapy. By linking several Swedish national...
registers, we identified patients who were newly prescribed with aspirin after diagnosis of ischaemic cerebrovascular disease and stratified them by dipyridamole use or non-use. We compared the incidence of lymphoid neoplasms between individuals with a prescription of dipyridamole and those without in aspirin users. Next, we investigated the association of dipyridamole use with types of lymphoid neoplasms.

Methods

Study population

The Swedish Prescribed Drug Register was created in July 2005 by the National Board of Health and Welfare and includes information on the date of prescription, date of dispensation, and cumulative defined daily doses (DDDs).

The use of low-dose aspirin was identified by the use of Anatomical Therapeutic Chemical (ATC) codes of B01AC06 from the Swedish Prescribed Drug Register. Low-dose aspirin is available only by prescription in Sweden, which accounts for more than 95% of all aspirin used. The use of dipyridamole must be prescribed in Sweden, which was identified by ATC code B01AC07. To ensure an active comparator, new user study design, we firstly identified individuals who were diagnosed with ischaemic cerebrovascular disease since January 2006 from the National Patient Register, thus a washout period of up to six months was applied between July 2005 and the date of ischaemic cerebrovascular disease diagnosis. To prevent secondary ischaemic stroke and transient ischaemic attacks, individuals with ischaemic stroke and transient ischaemic attacks would be prescribed with either aspirin monotherapy or aspirin combined with dipyridamole. We thus compared the incidence of lymphoid neoplasms among patients treated with aspirin combined with dipyridamole (study group) and patients with aspirin monotherapy (active comparator). To improve comparability, a propensity score-matched cohort design was used in this study with a 1:1 ratio. The flowchart is presented in Fig. S1. We restricted the age of the study population to 30–85 years old. Individuals were excluded if they were followed for less than six months.

Assessment of outcome

By accessing the Swedish Cancer Registry, we identified patients who had a lymphoid neoplasms diagnosis through the 10th version of the International Classification of Diseases (ICD-10) codes: C81–88, C90, C91.1, C91.4, C96, and D76.0. We further classified lymphoid neoplasms into subtypes by using the International Classification of Diseases-Oncology, Second Edition (ICD-O-2) based on the recommendations that were developed by the Pathology Working Group of the International Lymphoma Epidemiology Consortium (Inter-Lymph). The details of codes are described elsewhere. Information on death, including date and cause, was identified from the Cause of Death Register during the study period.

Assessment of covariates

Socioeconomic information was obtained from the Swedish Total Population Register, including sex, birth year, birth country, the region of residence, and highest education. We further retrieved clinical information about chronic conditions, alcohol or tobacco use disorder, obesity and gastrointestinal bleeding by linking to the National Patient Register with ICD codes (Table SI). We calculated the Charlson Comorbidity Index (CCI) based on 19 chronic conditions at baseline. Information of co-medications was obtained from the Swedish Prescribed Drug Register by using ATC codes, including non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), statins, metformin, angiotensin-converting enzyme (ACE) inhibitors and other anti-platelet drugs (Table SII). Cumulative DDDs of dipyridamole were defined as the sum of DDDs for all prescriptions during the follow-up.

All the links between the different registers were made based on the unique identification number which is assigned to all residents staying in Sweden longer than three months. To preserve persons’ integrity, the identification number was replaced with serial numbers.

Statistical analysis

Propensity scores were calculated by using a multivariable logistic regression model, where the dependent variable was dipyridamole use or non-use. Covariates used to calculate propensity scores are listed in Table I. Greedy matching within a ‘caliper’ of 0.05 was used to select matched comparisons. Standardized mean difference was used to test the balance of distribution of several demographic and clinical factors between dipyridamole users and the matched comparisons (shown in Table I). Cumulative incidence of lymphoid neoplasms was calculated by using the Kaplan–Meier curve and the log rank test was used to test the difference between groups. Conditional Cox regression was used to evaluate the association of dipyridamole use and lymphoid neoplasms risk. Follow-up started at the date of the first dispensation of aspirin and ended at the date of diagnosis of lymphoid neoplasms, the date of death, or the end of the follow-up period (December 2016), whichever came first. Dipyridamole use was modelled as time-varying, which meant that individuals moved from a follow-up period of non-exposure (from the date of the first dispensation of aspirin to the date of the first dispensation of dipyridamole) to a period of exposure (from the date of the first dispensation of dipyridamole and thereafter of the follow-up). Stratified analyses were further performed for the association between dipyridamole use and the risk of lymphoid neoplasms based on sex, age at baseline, cumulative doses of aspirin and CCI score. Interactive effect was further investigated by adding the interaction term in the model. The outcome was assessed at five years or after five years of follow-up to evaluate the difference between the short-term and
long-term effect of dipyridamole use on the risk of lymphoid neoplasms. The dose–response relationship of dipyridamole with lymphoid neoplasms was assessed by using restricted cubic splines (RCS) regression with three knots. Several sensitivity analyses were performed to explore the possibility of chance findings. First, instead of comparing with propensity score matched comparisons, we tested the association in the overall aspirin cohort by using inverse probability of treatment weighting. Second, regarding the potential of competing risk from death, we examined the association by using a competing risk model in Cox regression. Third, to take into account the potential biological latency, we investigated the association by lagging one year for dipyridamole use, meaning that individuals moved from a follow-up period of non-exposure (from the date of the first dispensation of aspirin to the date of one year after the first dispensation of dipyridamole) to a period of exposure (from the date of one year after the first dispensation of dipyridamole and thereafter of the follow-up). Fourth, as 98% of patients were prescribed dipyridamole within 12 months after baseline in the exposed group, landmark analysis was thus used to examine the association by selecting 12 months as the landmark point. Fifth, it is known that gastrointestinal haemorrhage is the major serious side effect of anti-platelet drugs. By linking to the National Patient Register, we further explored whether individuals with a

### Table I. Comparison of baseline characteristics between dipyridamole users and non-users.

| Characteristics                      | Overall cohort | Propensity score-matched cohort |
|--------------------------------------|----------------|---------------------------------|
|                                      | Users, n (%)   | Non-users, n (%)                | Users, n (%) | Non-users, n (%) |
|                                      |                |                                 |              |                  |
| Overall                              | 14 121 (100)   | 60 775 (100)                    | 14 119 (100) | 14 119 (100)     |
| Sex                                  |                |                                 |              |                  |
| Male                                 | 8 237 (58.3)   | 31 376 (51.6)                   | 8 235 (58.3) | 8 193 (58.0)     |
| Female                               | 5 884 (41.7)   | 29 399 (48.4)                   | 5 884 (41.7) | 5 926 (42.0)     |
| Birth year                           |                |                                 |              |                  |
| <1940                                | 6 312 (44.7)   | 29 152 (48.0)                   | 6 312 (44.7) | 6 402 (45.3)     |
| ≥1940                                | 7 809 (55.3)   | 31 623 (52.0)                   | 7 807 (55.3) | 7 717 (54.7)     |
| Birth country                        |                |                                 |              |                  |
| Sweden                               | 12 298 (87.1)  | 52 613 (86.6)                   | 12 296 (87.1)| 12 409 (87.9)    |
| Others                               | 1 823 (12.9)   | 8 162 (13.4)                    | 1 823 (12.9) | 1 710 (12.1)     |
| Residence area                       |                |                                 |              |                  |
| Big cities                           | 5 551 (39.3)   | 20 359 (35.5)                   | 5 549 (39.3) | 5 652 (40.0)     |
| South Sweden                         | 5 712 (40.5)   | 28 177 (46.4)                   | 5 712 (40.5) | 5 771 (40.9)     |
| North Sweden                         | 2 858 (20.2)   | 12 399 (20.1)                   | 2 858 (20.2) | 2 696 (19.1)     |
| Highest education, years             |                |                                 |              |                  |
| 1-9                                  | 5 029 (35.6)   | 22 187 (36.5)                   | 5 029 (35.6) | 5 129 (36.3)     |
| 10-11                                | 5 659 (40.1)   | 24 110 (39.7)                   | 5 659 (40.1) | 5 644 (40.0)     |
| 12+                                  | 3 433 (24.3)   | 14 478 (23.8)                   | 3 431 (24.3) | 3 346 (23.7)     |
| Charlson Comorbidity Index           |                |                                 |              |                  |
| 1                                    | 8 674 (61.4)   | 35 624 (58.6)                   | 8 673 (61.4) | 8 900 (63.0)     |
| 2                                    | 1 734 (12.3)   | 8 470 (13.9)                    | 1 734 (12.3) | 1 695 (12.0)     |
| 3                                    | 2 535 (18.0)   | 10 288 (16.9)                   | 2 534 (17.9) | 2 397 (17.0)     |
| >3                                   | 1 178 (8.3)    | 6 393 (10.6)                    | 1 178 (8.4)  | 1 127 (8.4)      |
| Alcohol use disorder                 | 651 (4.6)      | 3 088 (5.1)                     | 651 (4.6)    | 541 (3.8)        |
| Tobacco use disorder                 | 398 (2.8)      | 1 271 (2.1)                     | 396 (2.8)    | 327 (2.3)        |
| Obesity                              | 259 (1.8)      | 1 177 (1.9)                     | 259 (1.8)    | 187 (1.3)        |
| Comedications                        |                |                                 |              |                  |
| Non-aspirin NSAIDs                   | 6 473 (45.8)   | 27 383 (45-1)                   | 6 471 (45.8) | 6 449 (45.7)     |
| Statins                              | 11 147 (79.0)  | 38 525 (63-4)                   | 11 145 (78.9)| 11 155 (79.0)    |
| Metformin                            | 1 102 (7.8)    | 4 698 (7.7)                     | 1 102 (7.8) | 980 (6.9)        |
| ACE inhibitors                       | 5 886 (41.7)   | 22 223 (36-6)                   | 5 884 (41.7) | 5 840 (41.4)     |
| Other anti-platelet drugs            | 575 (4.1)      | 5 136 (8.5)                     | 575 (4.1)    | 506 (3.6)        |
| Cumulative DDDs of aspirin use       | 0.316          |                                 | 0.316        | 0.028            |

ACE, angiotensin-converting enzyme; DDD, defined daily dose; NSAIDs, non-steroidal anti-inflammatory drugs.
prescription of dipyridamole were at higher risk of gastrointestinal bleeding as compared to their matched comparisons. Sixth, a negative control study was conducted to increase the confidence of the observed association by exploring the association of dipyridamole use with the risk of accidents. It is assumed that the occurrence of accidents is random, which is thus not related to dipyridamole use. Information on accidents was available until December 2012 in the National Patient Register. Furthermore, the E-value was calculated to investigate the role of unmeasured confounders. The value is defined as the minimal association that an unmeasured factor should have with both dipyridamole and lymphoid neoplasms to fully explain the observed association.30

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) or R (3.6.2).

Results

Among 74,896 patients with cerebrovascular disease, a total of 14,121 individuals were prescribed aspirin combined with dipyridamole, whereas others were prescribed aspirin monotherapy. There were 14,119 dipyridamole users with eligible comparisons after propensity score matching (Table I). After propensity score matching, the distributions of baseline characteristics were comparable between dipyridamole and lymphoid neoplasms to fully explain the observed association.30

In Fig. 1, we found that patients with dipyridamole use had a lower cumulative incidence of lymphoid neoplasms than those without use ($P$ value = 0.029). As shown in Table II, after a median of 6-67 years of follow-up, a total of 46 individuals with dipyridamole use developed lymphoid neoplasms with an incidence rate of 0.49 per 1,000 person-years, while the rate in matched comparisons is 0.74 per 1,000 person-years. The hazard ratio (HR) of lymphoid neoplasms was 0.65 with a 95% confidence interval (CI) of 0.43–0.98 among dipyridamole users when compared with non-users. The reduced risk was significant for non-Hodgkin lymphoma (NHL; HR = 0.64; 95% CI = 0.42–0.94), rather than Hodgkin lymphoma (HR = 1.00; 95% CI = 0.14–7.10). The observed association varied between different types of NHL with a HR of 0.56 (95% CI = 0.35–0.88) for B-cell lymphoma and a HR of 1.00 (95% CI = 0.14–7.10) for T-cell lymphoma. A dose–response association was observed between dipyridamole use and risk of lymphoid neoplasms but without statistical significance (Fig 2, $P = 0.142$). Stratified analyses for the association between dipyridamole use and lymphoid neoplasms risk are presented in Table III. The observed association was more pronounced in males (HR = 0.49), individuals with high cumulative DDDs of aspirin (HR = 0.39), or individuals with a better health condition (HR = 0.58). However, no statistical difference was found between these subgroups. Besides, a protective effect of dipyridamole was found against lymphoid neoplasms with a HR of 0.32 (95% CI = 0.13–0.79) after being followed up for more than five years, but not at up to five years of follow-up (HR = 0.85; 95% CI = 0.38–1.89).

We present the results of the sensitivity analyses in Table IV. The association remained stable when using different methods or study designs, including inverse probability of treatment weighting in the overall cohort (HR = 0.80; 95% CI = 0.68–0.94), competing risk model (HR = 0.64, 95% CI = 0.48–0.86), lagging one year model (HR = 0.64, 95% CI = 0.42–0.99) and landmark analysis model (HR = 0.72, 95% CI = 0.60–0.86). Furthermore, the risk of
gastrointestinal bleeding was comparable between patients with dipyridamole and their corresponding comparisons (HR = 0.91, 95% CI = 0.79-1.04). Additionally, as assumed, no association was found between dipyridamole use and accident risk in the study population (HR = 0.98, 95% CI = 0.92–1.04). The E-value was 2.45 with a confidence limit of 1.16, suggesting that the observed association between dipyridamole use and risk of lymphoid neoplasms could be explained by an unmeasured confounder when the confounding factor was associated with both dipyridamole and lymphoid neoplasms with a relative risk > 2.45 or < 0.40. It indicated moderate robustness of the observed association in our study (Fig. S2).

**Discussion**

To our best knowledge, this is the first population-based study to explore the preventive role of dipyridamole against lymphoid neoplasms by accessing nationwide databases, which guarantees reliable risk estimates and generalizations.
A protective effect of dipyridamole was observed against lymphoid neoplasms, especially for NHL arising from B cells, whereas the association with T-cell NHL did not show a chemopreventive effect. The association was more pronounced among individuals being followed for more than five years, suggesting a biological plausibility. The incidence of gastrointestinal bleeding was comparable among dipyridamole users and non-users, which suggests the side effects of the clinical utilization of dipyridamole against lymphoid neoplasms might be negligible.

Dipyridamole was originally developed as an anti-anginal agent in 1959, then re-purposed as an anti-thrombotic medication, and was recently reported to possess anti-oxidant and anti-inflammatory properties. Emerging evidence, in vitro and in vivo, has shown an anti-cancer effect of dipyridamole via its anti-viral activity, immunoregulation, autophagic flux blockade, anti-proliferative activity, inhibiting tumour cell metastasis, and its enhancing the cytotoxicity of anti-cancer drugs. The anti-cancer effects of dipyridamole are mainly involved in PDE inhibitions, including PDE10, PDE8, PDE5, and PDE4. Growing evidence suggests that PDEs play an important role in carcinogenesis via influencing the level of cAMP and/or cGMP; thus, PDEs have the potential to be a novel target for inhibiting tumour cell growth. A few PDEs were overexpressed in lymphoma cells and inhibition of PDEs contributed to enhanced apoptosis of lymphoma. Dipyridamole showed its ability as a PDE inhibitor in potentiating statin-induced apoptosis in haematologic malignant cells. Furthermore, a preclinical study observed that the anti-tumour efficacy of bortezomib against lymphoma/leukaemia cells could be markedly enhanced when combined with dipyridamole which contributed to abrogate

| Characteristics | No. of individuals | No. of person-years | No. of outcome | IR, per 1 000 person-years | HR | 95% CI | P value | P interaction |
|-----------------|--------------------|---------------------|----------------|-----------------------------|----|--------|---------|--------------|
| Sex             |                    |                     |                |                             |    |        |         |              |
| Male            |                    |                     |                |                             |    |        |         |              |
| Non-users       | 8 193              | 52 668              | 41             | 0.78                        | Ref|        |         |              |
| Users           | 8 235              | 54 506              | 23             | 0.42                        | 0.27–0.88 | 0.018 |
| Female          |                    |                     |                |                             |    |        |         |              |
| Non-users       | 5 926              | 37 786              | 26             | 0.69                        | Ref|        |         |              |
| Users           | 5 884              | 38 735              | 23             | 0.59                        | 0.48–1.70 | 0.746 |
| Age at aspirin use |                |                     |                |                             |    |        |         |              |
| <75             |                    |                     |                |                             |    |        |         |              |
| Non-users       | 9 901              | 66 743              | 50             | 0.75                        | Ref|        |         |              |
| Users           | 10 071             | 69 241              | 33             | 0.48                        | 0.39–1.11 | 0.118 |
| ≥75             |                    |                     |                |                             |    |        |         |              |
| Non-users       | 4 218              | 23 710              | 17             | 0.72                        | Ref|        |         |              |
| Users           | 4 048              | 24 000              | 13             | 0.54                        | 0.37–2.22 | 0.819 |
| Cumulative DDDs of aspirin |        |                     |                |                             |    |        |         |              |
| Low             |                    |                     |                |                             |    |        |         |              |
| Non-users       | 7 642              | 37 948              | 36             | 0.95                        | Ref|        |         |              |
| Users           | 7 577              | 40 708              | 33             | 0.81                        | 0.49–1.49 | 0.572 |
| High            |                    |                     |                |                             |    |        |         |              |
| Non-users       | 6 477              | 52 505              | 31             | 0.59                        | Ref|        |         |              |
| Users           | 6 542              | 52 533              | 13             | 0.25                        | 0.19–0.80 | 0.010 |
| Charlson Comorbidity Index |                    |                     |                |                             |    |        |         |              |
| ≤1              |                    |                     |                |                             |    |        |         |              |
| Non-users       | 8 900              | 59 709              | 54             | 0.90                        | Ref|        |         |              |
| Users           | 8 673              | 59 294              | 33             | 0.56                        | 0.36–0.95 | 0.031 |
| >1              |                    |                     |                |                             |    |        |         |              |
| Non-users       | 5 219              | 30 744              | 13             | 0.42                        | Ref|        |         |              |
| Users           | 5 446              | 33 947              | 13             | 0.38                        | 0.43–2.91 | 0.809 |
| Follow-up       |                    |                     |                |                             |    |        |         |              |
| < 5 years       |                    |                     |                |                             |    |        |         |              |
| Non-users       | 14 119             | 19 944              | 43             | 2.16                        | Ref|        |         |              |
| Users           | 14 119             | 17 026              | 32             | 1.88                        | 0.38–1.89 | 0.683 |
| ≥5 years        |                    |                     |                |                             |    |        |         |              |
| Non-users       | 9 746              | 75 383              | 24             | 0.32                        | Ref|        |         |              |
| Users           | 10 730             | 81 580              | 14             | 0.17                        | 0.13–0.79 | 0.014 |

CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; IR, incidence rate.
Association of dipyridamole use and risk of accident in propensity score-matched cohort.

Association of dipyridamole use and risk of gastrointestinal haemorrhage in propensity score-matched cohort.

aspirin use.

birth country, the region of residence, highest education, CCI, tobacco use disorder, alcohol use disorder, obesity, comedications and cDDDs of aspirin use.

Association of dipyridamole use and risk of lymphoid neoplasms by using 12-months landmark analysis. HR was adjusted for sex, birth year, birth country, the region of residence, highest education, CCI, tobacco use disorder, alcohol use disorder, obesity, comedications and cDDDs of aspirin use.

**Association of dipyridamole use and risk of lymphoid neoplasms in propensity score-matched cohort by using a competing risk model.

#Association of dipyridamole use and risk of lymphoid neoplasms in the overall cohort. HR was adjusted for sex, birth year, birth country, the region of residence, highest education, CCI, tobacco use disorder, alcohol use disorder, obesity, comedinations and cDDDs of aspirin use.

Association of dipyridamole use and risk of lymphoid neoplasms in propensity score-matched cohort by lagging one year.

##Association of dipyridamole use and risk of lymphoid neoplasms by using 12-months landmark analysis.

Abbreviations: CCI, Charlson Comorbidity Index; cDDD, cumulative defined daily dose; CI, confidence interval; HR, hazard ratio; IR, incidence rate.

*Association of dipyridamole use and risk of lymphoid neoplasms in the overall cohort. HR was adjusted for sex, birth year, birth country, the region of residence, highest education, CCI, tobacco use disorder, alcohol use disorder, obesity, comedinations and cDDDs of aspirin use.

**Association of dipyridamole use and risk of lymphoid neoplasms in propensity score-matched cohort by using a competing risk model.

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$Association of dipyridamole use and risk of gastrointestinal haemorrhage in propensity score-matched cohort.

$Association of dipyridamole use and risk of accident in propensity score-matched coh.

JAK2 phosphorylation in tumour cells, indicating a novel therapeutic modality of the bortezomib/dipyridamole combination against haematologic malignancies.

In this study, dipyridamole users were at a significantly lower risk of lymphoid neoplasms, especially B-cell NHL. It is known that most EBV-associated lymphoid neoplasms are of a B-cell lineage. Accumulating population-based studies have investigated the role of the EBV antibody profile in NHL risk, which is a marker reflective of viral reactivation. A positive association was observed in several studies between EBV antibody level and risk of overall NHL or subtype of NHL. A recent study found that dipyridamole could prevent EBV re-activation from B-cell lines via a multifactorial process. EBV infection could be persistent for life following primary infection while the human immune system usually tightly controls its reactivation. Nevertheless, EBV re-activation would increase the viral load, further promote B-cell re-infection and lymphomagenesis. Dipyridamole can inhibit protein Zta expression which plays a critical role in initiating viral reactivation. The mechanisms behind the inhibition of Zta expression include blocking the signalling pathways of BZLF1 activation, inhibiting the regulation of BZLF1 promoter, blocking nucleoside import, and inhibiting RNA synthesis. The evidence discussed above provides some clues for the underlying mechanisms of the observed association between dipyridamole use and risk of lymphoid neoplasms. More study is needed to confirm our research findings and explore the underlying mechanisms of the antitumour effect of dipyridamole against lymphoid neoplasms, especially against B-cell lymphoma.

The mechanisms of dipyridamole for the prevention of vascular events are different from and complementary to aspirin. In current clinical practice in Sweden, dipyridamole is rarely prescribed alone but almost always prescribed together with aspirin. To minimize the potential effect of aspirin, we limited the study population to aspirin users with a diagnosis of ischaemic cerebrovascular disease and included the cumulative doses of aspirin as a confounding factor for calculation of the propensity score. Besides, it is reported that the combination of aspirin and dipyridamole does not affect the kinetics of each, which suggests the co-administration of aspirin and dipyridamole may exert its effect through complementary mechanisms, while a
A stronger association was found in patients with a high dose of aspirin in this study. Thus, further studies are needed to explore whether dipyridamole plays a potential anti-tumour effect individually or through an interactive effect with aspirin.

Although numerous studies have investigated the anti-cancer effect of aspirin, the protective effect of aspirin against lymphoid neoplasms is still controversial and the side effects of long-term use of aspirin are an issue. Thus, there is still a high priority to identify agents that may have chemo-preventive properties. The most common adverse events related to anti-platelet drugs range from a vasodilating effect and hypotension, headache, and gastrointestinal disorders to serious bleeding events. Dipyridamole-related PDE inhibition was suggested to be safer than aspirin-related COX inhibition in terms of bleeding complications.45 In this study, we found a similar risk of gastrointestinal bleeding between dipyridamole users and non-users after taking aspirin doses into account, which is in line with evidence from previous randomized controlled trials.19,20 Such evidence minimizes the worries of its serious side effects and supports the clinical utilization of dipyridamole against lymphoid neoplasms.

There are several strengths in support of our study. The nationwide coverage of data sets and the complete follow-up excluded selection bias and ensured external validity. The high-quality and validated data regarding drug prescriptions and cancer diagnosis minimized misclassification. Propensity score matching allowed us to control the impact of potential confounders. Immortal time bias was controlled by modelling dipyridamole as a time-varying variable. All patients in this study were prescribed aspirin after being diagnosed with cerebrovascular disease, which eliminated indication bias by underlying diseases. Several limitations should be noted. Firstly, as few individuals were prescribed with dipyridamole alone, it is not permissible to explore the anti-cancer effect of dipyridamole monotherapy in this study. Secondly, due to the limited cases regarding specific types of lymphoid neoplasms in the study population, false negatives cannot be fully removed. Thus, the results in terms of types of lymphoid neoplasms should be interpreted with caution. Studies with a larger sample size are necessary to examine the associations of dipyridamole with different types of lymphoid neoplasms. Thirdly, we have no information on EBV status, and thus we are unable to do stratified analysis based on EBV infection, which would provide more information regarding the role of EBV in the observed association. Fourthly, we lacked individual-level information about lifestyles, such as dietary factors, smoking, and alcohol use. However, information of tobacco or alcohol use disorder and obesity could be obtained from the National Patient Register and taken into consideration, thus minimizing their confounding effect.

To sum up, dipyridamole use was associated with a significantly reduced risk of lymphoid neoplasms, especially B-cell lymphoma. Furthermore, dipyridamole use did not increase the incidence of gastrointestinal bleeding.

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Author contributions

WH, JJ, KS and JS were responsible for the study concept and design. JS, KS, and JJ obtained funding. KS and JS acquired the data. WH did the statistical analysis and drafted the manuscript, and all authors revised it for important intellectual content.

Conflicts of Interest

None.

Data availability statement

The data, which are not publicly available due to Swedish law and to protect patient privacy, can only be made available from the appropriate Swedish authorities (the Swedish National Board of Health and Welfare, https://www.sjukvardsstyrelsen.se/en, and Statistics Sweden, https://www.scb.se/en), for researchers who meet the criteria for access to confidential material.

Ethics approval and consent to participate

The Ethics Committee in Lund, Scania, Sweden approved (6 February 2013) this nationwide cohort study (Dnr 2012/795).
Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Flowchart of this population-based study in Sweden.

Fig S2. Value of the joint minimal strength of association that an unmeasured confounder must associate with dipyridamole use and risk of lymphoid neoplasms to fully explain the observed hazard ratio in our study.

Table SII. International Classification of Disease (ICD) codes for diseases retrieved by linking to the Swedish Prescribed Drug Register.

Table SIII. Distribution of the Propensity Score within each decile according to the exposed group.

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