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Aspirin reduces cardiovascular events in patients with pneumonia: a prior event rate ratio analysis in a large primary care database.

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Abstract

Background

Ischaemic stroke and myocardial infarction (MI) are common after pneumonia and are associated with long-term mortality. Aspirin may attenuate this risk and should be explored as a therapeutic option.

Methods

We extracted all patients with pneumonia, aged over 50, from the Clinical Practice Research Datalink (CPRD), a large UK primary care database, from inception until January 2019. We then performed a prior event rate ratio analysis (PERR) with propensity score matching, an approach that allows for control of measured and unmeasured confounding, with aspirin usage as the exposure, and ischaemic events as the outcome. The primary outcome was the combined outcome of ischaemic stroke and myocardial infarction. Secondary outcomes were ischaemic stroke and myocardial infarction individually. Relevant confounders were included in the analysis (smoking, comorbidities, age, gender).

Findings

48,743 patients were eligible for matching. 8,099 of these were aspirin users who were matched to 8,099 non-users. Aspirin users had a reduced risk of the primary outcome (adjusted hazard ratio, HR 0.64; 95% confidence interval 0.52 - 0.79) in the PERR analysis. For both secondary outcomes, aspirin use was also associated with a reduced risk HR 0.46 (0.30 – 0.72) and HR 0.70 (0.55 – 0.91) for myocardial infarction and stroke respectively).

Interpretation

This study provides supporting evidence that aspirin use is associated with reduced ischaemic events after pneumonia in a primary care setting. This drug may have a future clinical role in preventing this important complication.

Introduction:

It is well established that infections predispose to cardiovascular events, with data supporting this from both primary and secondary care. The risk appears to vary, but some reports suggest that the risk is as high as ten percent within patients who have hospitalised pneumococcal pneumonia.[1] These cardiovascular events are also associated with an increased short-term mortality.[2] The mechanism of this risk is not completely clear, although it appears to be mediated through a pro-inflammatory cascade. Given that pneumonia is very common, with around 100,000 cases in the UK alone each year,[3] any potential reduction of that risk is likely to lead to significant public health benefit.

Aspirin has been suggested as a potential therapeutic option to try and attenuate this risk. Aspirin has an excellent track record in secondary prevention of cardiovascular disease[4], although recent studies have confirmed the lack of benefit in primary prevention[5]. Because aspirin has both an anti-platelet and anti-inflammatory effect, it has been suggested this may reduce the risk of cardiovascular events.[5] Some limited secondary care evidence supports this, with small observational trials showing a reduction in cardiovascular events in patients taking aspirin when they are diagnosed with pneumonia, and a single, small RCT suggesting promise [6–8].

The aim of the current study was to establish whether aspirin reduced the risk of cardiovascular events in patients who had experienced a recent pneumonia, in a large observational cohort of UK primary care patients.

Methods:

Study design

This analysis was performed using data from the Clinical Practice Research Datalink (CPRD), a large database of routine coded primary care health records considered representative of the wider UK population. This includes all diagnoses coded by primary care clinicians. This also includes events occurring in hospital that are coded in the primary care record (e.g. via discharge summary), but this does not necessarily include all hospitalised events. We included all patients who had a coded diagnosis of pneumonia from inception of the database until January 2019. Primary care records were linked to Office for National Statistics (ONS) mortality data. If patients had multiple episodes of pneumonia, the first was taken, irrespective of time between events. The study period started 12 months prior to pneumonia diagnosis and lasted for 6 months after.

Outcomes

For all analyses, the primary outcome was the combined outcome of myocardial infarction or ischaemic stroke.

The two secondary outcomes were myocardial infarction and ischaemic stroke, individually.

Definitions

Codes for pneumonia were derived from previous literature[9] and were updated to ensure current validity. There has been extensive use of the CPRD for studying pneumonia, and coding in the CPRD is generally felt to be good quality.[9–13] Specific explicit codes for pneumonia rather than simple lower respiratory tract infection were included (see Appendix S1); these were again based on previous literature. As this is a primary care dataset, all presentations are those coded from primary care records.

Codes for outcomes and comorbidity were derived from the Manchester ClinicalCodes repository.[14] Code lists are also presented in Appendix S1. For myocardial infarction in particular, the codelist was edited to ensure that all events represented acute events, rather than chronic myocardial ischaemia. Mortality was based upon ONS mortality data, which is derived from death certificates. Timing of death was taken from ONS data rather than CPRD date, as this is more reliable.[15,16]

Patients who had outcomes on the same day as the pneumonia diagnosis were excluded. This was to ensure reliable data on which event happened first, and to limit reverse confounding (pneumonia as a consequence of myocardial infarctions or stroke).

Aspirin use was defined in relation to study entry (12 months prior to pneumonia diagnosis). Aspirin users were defined as patients who had received 2 or more prescriptions of aspirin at a daily dose of less than 100mg in the 6 months prior to study entry. This ensured chronic aspirin use at study entry use. This requirement was then repeated in the next two, six month blocks, to ensure a continued prescription of low dose aspirin over the whole 12-month period prior to pneumonia diagnosis.

Aspirin non-users were defined as patients who did not meet this criterion in all three six-month blocks. Patients who met the criteria in some, but not all of the three blocks, were censored, as explained below. Other drugs examined in secondary analyses (see below) were defined similarly. Age, gender, and index of multiple deprivation (IMD, an area-based measure of socioeconomic deprivation) were included as covariates in the analysis, alongside medical comorbidities.

Comorbidity data were collected on smoking status, hypertension, stroke, ischaemic heart disease, diabetes and peripheral vascular disease. All comorbidities were defined by codes derived from the ClinicalCodes repository and must have occurred prior to the whole study period (i.e. 12 months prior to the pneumonia diagnosis). The absence of a comorbidity was taken to mean the absence of that condition. Smoking was defined as a categorical variable based on the most recent smoking code (current, former, never, or missing).

Statistical methodology

Our primary analysis methodology was a propensity matched, prior event rate ratio (PERR) analysis.

In this analysis, confounding is taken account for in two ways; firstly by propensity score matching (PSM) aspirin users to non-aspirin users, to ensure similar baseline characteristics across both groups. Propensity matching was performed with 2:1 matching, using covariates that were likely to be relevant for aspirin prescription (age, smoking, gender, history of ischaemic heart disease, stroke, or peripheral vascular disease). An optimal, nearest neighbour approach was utilised, using the MatchIt package in R. Covariate imbalance was assessed using the standardised mean difference (SMD) using a detection threshold of 0.1.[17] Secondly, PERR analysis was used to account for

unmeasured confounders. Double adjustment was carried out for any covariates that remained imbalanced after PSM.[18]

PERR analysis uses a form of self-controlled design in which participants act as their own controls to reduce confounding. In a standard PERR analysis, the rate of events (in this case, cardiovascular events) prior to and after a discrete exposure are compared within the same population group, allowing for unmeasured confounders to be taken account of, and a calculation of a more reliable effect size. [19–21]

In this current analysis, the standard PERR methodology has been adapted to address the question of interest. Usually exposed and unexposed groups are defined based on incident exposure to a treatment at an index date (time origin). We define the index date as the date of pneumonia diagnosis. The incident exposure is defined to be experiencing the pneumonia diagnosis when a current aspirin user. The unexposed group are selected from non-aspirin users who also experience the pneumonia diagnosis. This allows calculation of an adjusted effect of aspirin use on post-pneumonia events.

Figure 1: Schematic of the PERR analysis.

For this analysis, patients were split into the two exposure groups (aspirin users and non-aspirin users), depending on their prescription records (defined above). For both groups, a prior period was identified, starting 12 months prior to the pneumonia date, and lasting for 6 months, and a posterior period, the 6 months directly after diagnosis of the pneumonia (Figure 1).

Cardiovascular events occurring during these periods were recorded and used to estimate a PERR ratio of hazards for prior events to posterior events. The hazards for the prior and study periods were calculated using a Cox proportional hazards model with group membership as the independent variable, adjusted for relevant covariates (see above). Bootstrapping was performed to generate confidence intervals. The resulting outcome then represents the estimated effect size of the aspirin use on post-pneumonia events after accounting for the effect of time-invariant confounding. Any patients who died in the posterior period were right-censored.

To avoid the possibility of patients switching from being non-aspirin users to aspirin users, which would violate the assumptions of the PERR methodology, patients were required to be either on or off aspirin throughout the whole reference period (12 months prior, until diagnosis of pneumonia). Patients who started aspirin between the prior period and diagnosis of pneumonia were censored.

The prior period deliberately ended 6 months prior to the pneumonia diagnosis. This was to ensure there was complete washout between periods. This was a pragmatic choice and aimed to reduce any concern of bias that pneumonia events could be as a consequence of myocardial infarction hospitalisation episodes.

Missing data for smoking status was coded as such, whereas other missing data was removed (complete case analysis), as this was rare (43 patients). We estimated a hazard ratio of 0.8, a prevalence of routine aspirin usage of 33%, and incidence of events at 6 months at 3%, with a crude sample size required of around 17,112 participants, which was easily achieved before propensity score matching.

Data were extracted from the CPRD and processed using Stata (StataCorp, TX, US), with the package *CPRDUTIL*, but all analyses were performed using R version 3.6.0 and 4.0.0 (R foundation for Statistical Computing, Vienna), using packages: *tidyverse, ggplot, matchit, broom, survival* and *rio*.

Sensitivity and secondary analyses

For the main analysis, it was possible for aspirin prescription not to overlap the pneumonia diagnosis index date (the precise timing of prescriptions can be subject to uncertainty in the CPRD). To determine whether findings were robust to the timing of aspirin use, a sensitivity analysis was performed restricting aspirin patients to those in receipt of the drug on the index date.

As participants might die in the posterior period and hence not have coded events, there is a potential for a survival bias (one group has fewer posterior events, as they have a higher mortality), which should be accounted for by right censoring. Death represents a competing risk and our chosen approach is to use a proportional cause-specific hazards model, as recommended for aetiological research in the presence of competing risks[22].

As a test for robustness, we also examined two alternative negative control outcomes: fracture (of any kind), and constipation, to ensure that any effect identified was specific to myocardial infarction/stroke, and to identify evidence of survival bias.

To look for possible evidence of residual confounding after PERR analysis, the analysis was replicated with four other drug classes, three of which were negative control exposures. Firstly, paracetamol and levothyroxine were chosen, as these have no known cardiovascular effect, and are not strongly correlated with aspirin prescription. NSAIDs were compared as another potential drug with anti-inflammatory effect, but known to have potential increased cardiovascular risk and which have been associated with increased events after pneumonia. Proton pump inhibitors were compared as a final, commonly prescribed agent, which is often co-prescribed with aspirin.

Standard Cox regression was undertaken as an analysis that accounts for measured confounders only, to compare with the PERR analysis, using the same outcome variables. This analysis was performed on the same population used in the PERR analysis, equivalent to simply performing the analysis on the posterior period only, without adjusting for the prior period events. These models were then tested for the proportional hazards assumption (using the Therneau and Grambsch approach), to look for evidence of a time varying-effect which might have impacted the PERR analysis.[23]

As coding in CPRD could be as a consequence of administrative activity (e.g. recording information from a hospital discharge summary or clinic letter) rather than direct clinical care provided by the GP, we undertook a subsequent sensitivity analysis only including consultations that were definitively performed by the primary care clinician, by limiting only to consultation types that were in the GP practice, at a home-visit, or over the telephone. This was achieved using the *constype* variable in CPRD.

Results:

Figure 2 describes the flow of patients through the study. Data for 66,004 patients, accounting for 85,911 episodes of pneumonia, were extracted from the CPRD. Patients with missing data, those who died on or before the index date (i.e. retrospective coding), and those where the primary outcome fell on the index date, were excluded, leaving 48,260 patients. Of those, 4,964 patients were intermittent aspirin users and excluded. Aspirin users were then matched one-to-one with non-aspirin users. Pre and post match group definitions are shown in Table 1.

Figure 2: Flow of patients through the study.

Basic demographic details are in Table 1 showing differences between groups and the impact of propensity score matching. Before matching, aspirin users were older, more likely to be male, and more comorbid than non-aspirin users, and were imbalanced on many covariates. We considered matching to be successful as it limited baseline differences (SMD < 0.1) in all covariates except age (SMD = -0.1035), although aspirin users still had an increased history of hypertension and ischaemic heart disease . For all subsequent analysis, the matched cohort was used.

Characteristic	Aspirin users, N = 9,864	Matched non-aspirin users, N = 9,864	All non-aspirin users N = 35,197
Age[1]	81 (73, 87)	82 (75, 88)	74 (63, 84)
Female	4512 (46%)	4618 (47%)	18,489 (52.5%)
Diabetes	2245 (23%)	2175 (22%)	3,514 (10.0%)
PVD	1024 (10%)	802 (8.1%)	2,737 (7.8%)
Hypertension	5388 (55%)	4239 (43%)	11,350 (32.2%)
Previous IHD	2631 (27%)	2093 (21%)	2,737 (7.7%
Previous stroke	3425 (35%)	3448 (35%)	5,528 (15.7%)
Smoking status			
Former	4043 (41%)	3937 (40%)	3,358 (9.53%)
Current	1445 (15%)	1401 (14%)	12,029 (34.2%)
Bottom decile of IMD	969 (9.8%)	946 (9.6%)	3,005 (8.5%

1. Brackets represent interquartile range

Table 1: Demographics of study participants after propensity score matching

Numbers and rates of the primary outcome are presented in Table 2. Both groups had similar prior stroke events, although aspirin users had more prior myocardial infarction events. There was clear evidence for an increase in both outcomes after pneumonia ($p < 0.01$).

Table 2: Number of events (% of total in that group) in matched aspirin and non-aspirin users

Characteristic	Non-aspirin users (n = 9,468)	Aspirin users (n = 9,468)
Stroke in prior period:	175 (1.8%)	193 (2.0%)
Stroke in posterior period:	307 (3.1%)	234 (2.4%)
MI in prior period:	44 (0.4%)	81 (0.8%)
MI in posterior period:	182 (1.8%)	154 (1.6%)
Dead within 6 months:	2028 (21%)	2328 (24%)
Statistics presented: n (%), *MI = Myocardial Infarction*		

Results of the PERR analysis are shown in Table 3. Aspirin use was strongly associated with reduced MI and stroke, but had no effect on the two comparator outcomes (Appendix Table S2.1), with a hazard ratio of 0.64 (0.52 – 0.79) for the primary outcome, 0.70 (0.55 – 0.91) for ischaemic stroke, and 0.46 (0.30 – 0.72) for myocardial infarction.

Table 3: Hazard ratios for aspirin use vs. no aspirin use

	Hazard ratio (95% confidence interval)
Primary outcome (MI or ischaemic stroke)	0.64 (0.52 - 0.79)
Ischaemic stroke	0.70 (0.55 – 0.91)
Myocardial Infarction	0.47 (0.30 – 0.72)

Hazard ratio based on PERR analysis, adjusting for covariates in a Cox regression model. MI, myocardial infarction.

Sensitivity and secondary analyses

The PERR analysis for the other drugs is reported in the supplementary appendix (table S2.2). No significant association was found for paracetamol, levothyroxine or proton-pump inhibitors with either the primary, secondary or composite outcome. In comparison, NSAIDS were associated with an increased risk of the primary outcome with a HR of 1.88 (1.11 – 3.31).

The sensitivity analysis using a tighter definition of aspirin usage (Table S2.3) found similar relationships to the main analysis, with a HR of 0.64 (0.50-0.84) for aspirin users and the primary outcome. Again, no association was found with any other control drugs except NSAIDs, which were associated with increased hazard of the primary outcome, with a HR of 1.70 (0.95 – 3.21). When limiting consultations to those that were definitively primary care consultations(Table S2.4), the results remained similar, with a HR of 0.60 (0.42 – 0.87) for the primary outcome. However, due to the subsequent reduction in power, this did not meet significance for MI, with a HR of 0.63 (0.30 – 1.24)

The Cox regression analysis supported the PERR approach, with results in Table S3.1. In particular, aspirin was associated with a reduced hazard of the primary outcome (HR 0.84, 0.73 – 0.96) and stroke (HR 0.80, 0.68-0.96), with weaker evidence of a reduction in myocardial infarction (HR 0.82, 0.66 – 1.02).

Discussion

This is the first large-scale study to show that aspirin prescription is associated with a substantial reduction in risk of cardiovascular complications following pneumonia.

Strengths and limitations

This study has several important strengths. Firstly, a large observational dataset with high quality coding was used, comprising a significantly larger sample size than the previous study.[8] The analytical approach combining propensity score matching with a PERR approach helps strengthen causal inference, and a number of additional analyses were conducted which support the main findings. The analysis used data from primary care, where the majority of pneumonia is encountered; previous research has largely focused on secondary care.

There are several limitations of this study, most importantly with respect to confounding by indication and censoring. Although the PERR methodology aims to reduce confounding, the populations compared were still different across a range of demographics and had different absolute risks of myocardial infarction and stroke, although the propensity score matching substantially improved this. However, the limited (but generally supportive) empirical evidence, and statistical modelling are supportive that PERR can reduce bias in this setting.[19–21]

A second limitation regards censoring. One of the key requirements of PERR analysis is self-control of patients, so it was necessary to censor patients who were intermittent aspirin users and did not consistently use or not use aspirin over the whole study period. This censored population comprised around 10% of the whole population and was more similar to the aspirin user population than the non-aspirin user. Some of the censored patients may have started (or stopped) aspirin because they had ischaemic events across the study period, and the exclusion of these patients could bias the results. It is difficult to assess the direction of this bias, as the risk of post-pneumonia events in patients who switch aspirin is likely to be strongly related to the event that made them stop or start aspirin, rather than their underlying risk. This censoring bias is much less likely to occur in stroke (where aspirin is not commonly chronically prescribed, in the UK) than MI, and it is reassuring that the beneficial effect of aspirin was found in both groups, suggesting this bias did not fundamentally alter the results.

Thirdly, although the PERR method and Cox regression rely on time-invariant effects the risk of MI is felt to be highest in the few days just after pneumonia, so these assumptions may not apply. Also, the PERR approach requires hidden confounders not to vary with time, which may not be true after a significant medical event (e.g. lifestyle change after pneumonia).In our study, however, we found no evidence of time-varying effects of any agent, and all three Cox models did not violate the proportional hazards adjustment, supporting our statistical approach. As most events happened early, it is unlikely that change in hidden confounders such as lifestyle would substantially alter the risk of subsequent events.

A fourth limitation regards the lack of hospital linkage and coding accuracy. This study did not include individual hospital linkage, relying on accurate coding of hospital events in the primary care record. This has two implications. Firstly, pneumonia events could represent true primary care pneumonia events, or coded secondary care events (e.g. from discharge summaries). Importantly, in our sensitivity analyses restricting to definitive primary care events, the hazard ratios for the primary outcomes were similar in the main analysis (HR 0.64; 0.52 – 0.79) and the sensitivity analysis (HR 0.60; 0.42 – 0.87), suggesting that manner in which pneumonia was diagnosed and recorded did not alter risk estimates, or the effect of aspirin. Secondly, it is likely there is under-reporting of MI and stroke across the dataset, as these often present primarily to hospital. Previous research has found that although CPRD coding of MI is accurate, it does not pick up all hospitalised events, with underreporting compared to registry data.[24] However, we would not expect this to be biased with

respect to aspirin use, and therefore this would not alter the relative risk of events between aspirin users and non-aspirin users, which is our reported outcome.

A final limitation is potential survival bias, with patients in the aspirin group dying more frequently, and therefore having an apparent reduced effect rate of ischaemic events. This was managed by death censoring in both the PERR and Cox analysis, which is supported by the literature.[22,25]

Comparison with previous work

There have been two previous studies on this specific topic, one observational and one randomised. In the randomised controlled trial (n = 185) from Turkey, aspirin showed some promise (1 event in the aspirin group, 10 in the control group), but the numbers were too small to draw firm conclusions; and 90% of potential participants were excluded, raising concern of bias or appropriate inclusion criteria, and some key information was not reported.[7] The observational study was performed in a single centre, and showed a two-fifths reduction in the rate of cardiovascular events (4.9% vs 8.3%) with aspirin usage, a similar effect size to ours.[6] Other observational data has identified a reduced mortality with aspirin usage, and one study has shown reduced mortality with clopidogrel usage.[8,26]

Implications for practice and research

Our study provides supporting evidence of an association between aspirin usage in community acquired pneumonia and preventing cardiovascular complications, and sets the foundation for a prospective, randomised trial. However, it is important to note this study enrolled patients on aspirin already, and any randomised trial would initiate therapy at diagnosis.

Future research should thus focus on the potential initiation of aspirin in patients with newly diagnosed pneumonia, and whether the risk-benefit balance is shifted in the short-term in favour of aspirin prophylaxis. Inflammation may be apparent early in the disease process, so the importance of the timeliness of aspirin initiation in preventing ischaemic complications must also be established.

The potential benefits of aspirin prescription in pneumonia are significant. Given approximately 100,000 cases of pneumonia occur every year in the U.K. alone,[3] and based on our own findings of an absolute risk of around 2% of MI or stroke, our observed 30% reduction in ischaemic events would lead to 600 fewer cases a year in primary care. In secondary care, with the absolute risk of MI and stroke approaching 10% in some studies, there could be even more benefit.

Conclusion

Aspirin usage is associated with reduced short-term ischaemic stroke and myocardial infarction, in primary care participants who develop pneumonia. Further work should explore this promising approach to preventing cardiovascular complications after pneumonia, in a prospective, randomised fashion.

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Competing Interests

FH, DA, and RP have nothing to declare. WH has previously received conference fees from Eisai, and grant funding from IQVIA, unrelated to this work.

Ethics:

Ethical approval for this study was given by the CPRD, who safeguard patient information in this database (https://www.cprd.com/safeguarding-patient-data), application ISAC 18_310R.

Data sharing and dissemination:

Unfortunately, CPRD does not allow direct data-sharing due to patient confidentiality issues. The lead author would welcome informal and formal contact if required. It is not feasible to disseminate results back to individual patients within the CPRD.

Contributions

FH and DA conceived of the idea. FH designed the study, did the majority of the analysis, and wrote the first draft. DA helped with the analysis, editing, and methodology. WH did some analysis, and provided methodological support and editing. RP was the senior supervisor, conceptualised the work, and performed editing

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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