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

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Aspirin use was associated with reduced cardiovascular events after a pneumonia episode in a large UK primary care cohort and is a promising avenue in managing cardiovascular risk in pneumonia https://bit.ly/2YBkPXJ

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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 years) 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 (PERR) analysis with propensity score matching (PSM), 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 MI. Secondary outcomes were ischaemic stroke and MI individually. Relevant confounders (smoking, comorbidities, age and gender) were included in the analysis.

Findings: 48 743 patients were eligible for matching. Of these, 9864 were aspirin users who were matched to 9864 non-users. Aspirin users had a reduced risk of the primary outcome (adjusted hazard ratio 0.64, 95% CI 0.52–0.79) in the PERR analysis. For both secondary outcomes, aspirin use was also associated with a reduced risk for MI (hazard ratio 0.46, 95% CI 0.30–0.72) and stroke (hazard ratio 0.70, 95% CI 0.55–0.91), 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.

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

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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 10% within patients who have been hospitalised with 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 each year in the UK alone [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. It 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]. As 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 diagnosed with pneumonia and a single, small randomised controlled trial (RCT) that likewise suggested promise [6–8].

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

Methods

Study design

This analysis was performed using data from the Clinical Practice Research Datalink (CPRD), a large database of coded, routine primary care health records considered representative of the wider UK population. This includes all diagnoses coded by primary care clinicians, as well as events occurring in hospital that are coded in the primary care record (*e.g. via* a discharge summary), but 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 the time between events. The study period started 12 months prior to pneumonia diagnosis and lasted for 6 months after diagnosis.

Outcomes

For all analyses, the primary outcome was the combined outcome of myocardial infarction (MI) or ischaemic stroke. The two secondary outcomes were MI and ischaemic stroke, individually.

Definitions

Codes for pneumonia were derived from the previous literature [9] and were updated to ensure current validity. There has been extensive use of the CPRD for studying pneumonia and coding in it is generally felt to be of good quality [9–13]. Specific explicit codes for pneumonia rather than simple lower respiratory tract infection were included (appendix 1) and these were again based on the 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 1. For MI in particular, the code list was edited to ensure that all events represented acute events, rather than chronic myocardial ischaemia. Mortality was based upon ONS mortality data, which was derived from death certificates. Time of death was taken from ONS data rather than CPRD date, as this was 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 MIs 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 two or more prescriptions for aspirin at a daily dose of <100 mg in the 6 months prior to study entry. This ensured chronic aspirin use at study entry and this requirement was then repeated in the next two, 6-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 6-month blocks. Patients who met the criteria in some but not all of the three blocks were censored. Other drugs examined in secondary analyses 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 (IHD), diabetes and peripheral vascular disease (PVD). 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 PERR analysis. In this analysis, confounding was taken into account in two ways. First, similar baseline characteristics were ensured across both groups by propensity score matching (PSM) of aspirin users to non-aspirin users. Propensity matching was performed with a 2:1 matching, using covariates that were likely to be relevant for aspirin prescription (age, smoking, gender, history of IHD, stroke, or PVD). An optimal, nearest neighbour approach was utilised using the MatchIt package in the R software environment (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Covariate imbalance was assessed using the standardised mean difference (SMD) with 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 more reliable effect size to be calculated [19–21].

In the 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.

For this analysis, patients were split into the two exposure groups (aspirin users and non-aspirin users) depending on their prescription records. For both groups a prior period was identified, starting 12 months prior to the pneumonia date and lasting for 6 months, as was 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. Bootstrapping was performed to generate confidence intervals (CIs). The resulting outcome then represents the estimated effect size of aspirin use on post-pneumonia events after

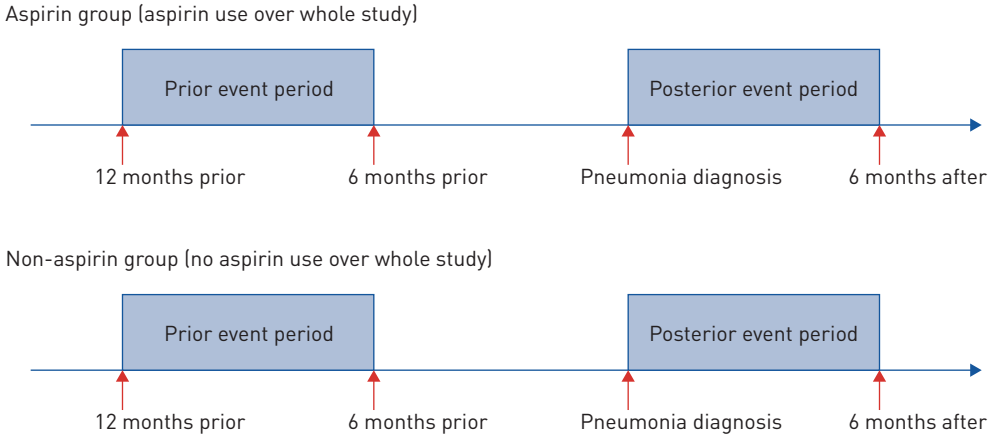

FIGURE 1 Schematic of the prior event rate ratio (PERR) analysis.

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, aimed at reducing any concern of bias that pneumonia events could be a consequence of MI 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 of 3%, with a crude sample size of around 17 112 participants required, which was easily achieved before PSM.

Data were extracted from the CPRD and processed using Stata software (StataCorp, College Station, TX, USA) with the CPRDUTIL package; however, all analyses were performed using R software versions 3.6.0 and 4.0.0 using the tidyverse, ggplot, matchit, broom, survival and rio packages.

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 thus not have coded events), there is a potential for a survival bias where one group has fewer posterior events as it has higher mortality and this 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 examined two alternative negative control outcomes: fracture (of any kind) and constipation, to ensure that any effect identified was specific to MI/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. First, paracetamol and levothyroxine were chosen, as these have no known cardiovascular effect and are not strongly correlated with aspirin prescription. Secondly, nonsteroidal anti-inflammatory drugs (NSAIDs, extracted by all NSAID drug codes in the CPRD) were compared as another potential drug class with an anti-inflammatory effect, albeit one known to have potential increased cardiovascular risk and which has been associated with increased events after pneumonia. Finally, proton pump inhibitors were compared as a commonly prescribed agent that is often co-prescribed with aspirin.

To compare with the PERR analysis, standard Cox regression (an analysis that accounts for measured confounders only) was undertaken 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 a consequence of administrative activity (*i.e.* 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 (limited to only 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 48 743 patients. Of these patients, 4731 were intermittent aspirin users and

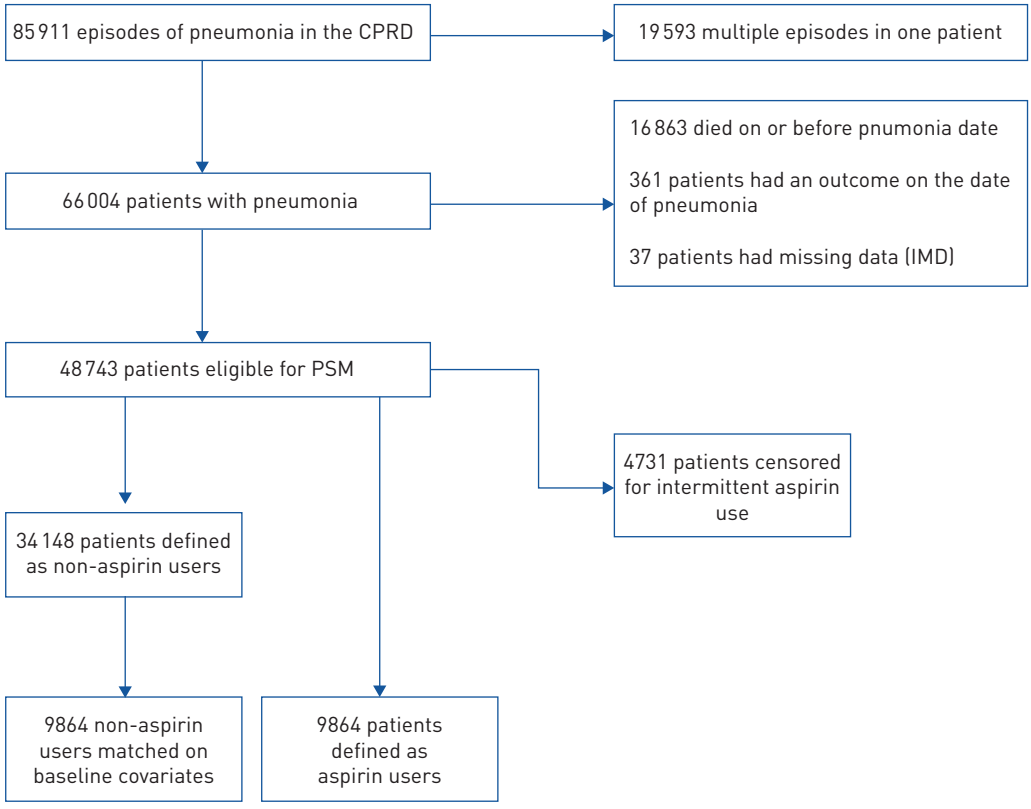

FIGURE 2 Flow of patients through the study. CPRD: Clinical Practice Research Datalink; PSM: propensity score matching; IMD: index of multiple deprivation.

were excluded. Aspirin users were then matched 1:1 with non-aspirin users. Pre-matching and post-matching group definitions are shown in table 1.

Basic demographic details are in given in table 1 and show the differences between groups and the impact of PSM. Before matching, aspirin users were older, more likely to be male, 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 IHD. For all subsequent analysis, the matched cohort was used.

TABLE 1 Demographics of study participants after propensity score matching

Characteristic	Aspirin users (n=9864)	Matched non-aspirin users (n=9864)	All non-aspirin users (n=34148)
Age years	81 (73–87)	82 (75–88)	74 (63–84)
Female	4512 (46)	4618 (47)	18 489 (54.1)
Diabetes	2245 (23)	2175 (22)	3514 (10.3)
PVD	1024 (10)	802 (8.1)	2737 (8.0)
Hypertension	5388 (55)	4239 (43)	11 350 (33.2)
Previous IHD	2631 (27)	2093 (21)	2737 (8.0)
Previous stroke	3425 (35)	3448 (35)	5528 (16.2)
Smoking status			
Former	4043 (41)	3937 (40)	3358 (9.8)
Current	1445 (15)	1401 (14)	12 029 (35.2)
Bottom decile of IMD	969 (9.8)	946 (9.6)	3005 (8.8)

Data are presented as median (interquartile range) or n (%). PVD: peripheral vascular disease; IHD: ischaemic heart disease; IMD: index of multiple deprivation.

TABLE 2 Number of events (percentage of total in that group) in matched aspirin and non-aspirin users

Characteristic	Non-aspirin users (n=9864)	Aspirin users (n=9864)
Stroke		
In prior period	175 (1.8)	193 (2.0)
In posterior period	307 (3.1)	234 (2.4)
Myocardial infarction		
In prior period	44 (0.4)	81 (0.8)
In posterior period	182 (1.8)	154 (1.6)
Died within 6 months	2028 (21)	2328 (24)

Data are presented as n (%).

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 MI events. There was clear evidence for an increase in both outcomes after pneumonia ($p<0.01$).

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 2, table S2.1), with a hazard ratio of 0.64 (95% CI 0.52–0.79) for the primary outcome, 0.70 (95% CI 0.55–0.91) for ischaemic stroke and 0.46 (95% CI 0.30–0.72) for MI.

Sensitivity and secondary analyses

The PERR analysis for other drugs is reported in appendix 2, 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 hazard ratio of 1.88 (95% CI 1.11–3.31).

The sensitivity analysis using a tighter definition of aspirin usage (appendix 2, table S2.3) found similar relationships to the main analysis, with a hazard ratio of 0.64 (95% CI 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 for the primary outcome, with a hazard ratio of 1.70 (95% CI 0.95–3.21).

When limiting consultations to those that were definitively primary care consultations (appendix 2, table S2.4), the results remained similar, with a hazard ratio of 0.60 (95% CI 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 hazard ratio of 0.63 (95% CI 0.30–1.24)

The Cox regression analysis supported the PERR approach and results are shown in appendix 2, table S3. 1. In particular, aspirin was associated with a reduced hazard for the primary outcome (hazard ratio 0.84, 95% CI 0.73–0.96) and stroke (hazard ratio 0.80, 95% CI 0.68–0.96), with weaker evidence of a reduction in MI (hazard ratio 0.82, 95% CI 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.

TABLE 3 Hazard ratios for aspirin use *versus* non-aspirin use

Outcome	Hazard ratio (95% CI)
Primary outcome	
Myocardial infarction or ischaemic stroke	0.64 (0.52–0.79)
Secondary outcome	
Ischaemic stroke	0.70 (0.55–0.91)
Myocardial infarction	0.47 (0.30–0.72)

Hazard ratio was based on prior event rate ratio analysis, adjusting for covariates, in a Cox regression model.

Strengths and limitations

This study has several important strengths. 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 PSM 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, whereas 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 MI and stroke, although the PSM substantially improved this. However, the limited (but generally supportive) empirical evidence and statistical modelling are supportive of a PERR approach being able to reduce bias in this setting [19–21].

Regarding censoring, one of the key requirements of a 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 users. 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 status is likely to be strongly related to the event that made them stop or start, 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 that this bias did not fundamentally alter the results.

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). However, in our study, 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.

Regarding 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. First, 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 (hazard ratio 0.64, 95% CI 0.52–0.79) and the sensitivity analysis (hazard ratio 0.60, 95% CI 0.42–0.87), suggesting that the manner in which pneumonia was diagnosed and recorded did not alter risk estimates or the effect of aspirin. Secondly, it is likely that there is under-reporting of MI and stroke across the dataset, as these often present primarily at hospital. Previous research has found that although CPRD coding of MI is accurate, it does not pick up all hospitalised events, with under-reporting 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 apparently reduced effect rate of ischaemic events. This was managed by death censoring in both the PERR and Cox analyses, 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 RCT from Turkey (n=185) [7], aspirin showed some promise (one event in the aspirin group, 10 in the control group); however, the numbers were too small to draw firm conclusions and 90% of potential participants were excluded, raising concern of bias or appropriate inclusion criteria (some key information was also not reported). The observational study [6] was performed in a single centre and showed a two-fifths reduction in the rate of cardiovascular events (4.9% *versus* 8.3%) with aspirin usage, a similar effect size to ours. 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 enroled patients who were 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 that approximately 100 000 cases of pneumonia occur every year in the UK alone [3] and based on our own findings of an absolute risk of around 2% for 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 MI risk 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.

Author contributions: F. Hamilton and D. Arnold conceived of the idea. F. Hamilton designed the study, did the majority of the analysis and wrote the first draft. D. Arnold helped with the analysis, editing and methodology. W. Henley did some analysis, and provided methodological support and editing. R.A. Payne was the senior supervisor, conceptualised the work and performed editing. 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.

Conflict of interest: F. Hamilton reports grants from the National Institute for Health Research (NIHR) (the Academic Clinical Fellowship Scheme), during the conduct of the study. D. Arnold has nothing to disclose. W. Henley has nothing to disclose. R.A. Payne has nothing to disclose.

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