Chapter Five: Aspirin use and health outcomes in COPD populations

5.1 Background

5.1.1 Aspirin for chronic obstructive pulmonary disease treatment

COPD patients are at disproportionate risk of CVD but often do not receive the same treatments as patients with CVD alone (1, 195). This is a major problem as an exacerbation in COPD patients can cause or worsen underlying CVD and increase risk of mortality. Existing treatments for COPD exacerbations such as corticosteroids and beta-agonists are inadequate for reducing mortality from CVD and improving quality of life. Therefore, it is essential that treatment regimens for COPD are developed that are compatible with underlying CVD.

One promising avenue of treatment is the repurposing of existing CVD drugs to treat COPD, which may have ameliorative effects on exacerbations and survival in COPD patients, in addition to their beneficial effects for cardiovascular health. Aspirin is one such CVD drug that is widely prescribed and cheaply available. It is an anti-platelet that irreversibly inhibits the COX enzymes by acetylating the serine residue, which prevents thromboxane A_2 (promotes platelet aggregation) production in platelets (119). Aspirin is also known to promote the production of epimers of SPMs that have been shown to have anti-inflammatory effects in COPD and CVD animal models, as well as human *in vitro* studies (176, 196, 197). Furthermore, stable COPD patients have been shown to have elevated platelet levels compared to controls, which increase further during an exacerbation, which could be the cause of increased risk of CVD in COPD populations (117). The anti-platelet properties of aspirin suggests a potential to target this pathway.

5.1.2 Data analysis of aspirin and chronic obstructive pulmonary disease outcomes

While there have been no randomised control trials of aspirin for COPD treatment, previous observational studies of COPD patients have found that aspirin use was associated with fewer exacerbations, slower disease progression and lower mortality after exacerbations (122, 123, 198, 199).

However, these observational studies vary greatly in data quality and collection methods, follow up time and cohort demographics. There are large, high quality datasets available from published clinical trials involving thousands of COPD patients, which provide a wealth of information such as concomitant medications and CVD history/risk. These datasets are highly valued for their clear and consistent data entry and detailed records on the large populations of COPD patients involved, which can provide insights into the relationship between aspirin and outcomes such as risk of mortality and exacerbations.

COPD and CVD are still major causes of mortality and reduced quality of life worldwide, and constitute heavy economic burdens to health systems. While there is a need for novel drugs, the long development process for new therapeutics suggests that it is prudent to identify commonly used drugs such as aspirin that can be repurposed for treating COPD and are compatible with underlying CVD.

Taking into account previous reports of the beneficial effects of aspirin in COPD, there is a need to comprehensively investigate, using large high quality datasets, the potential of aspirin for reducing the risk of exacerbations and all-cause mortality in COPD patients with varying severity of disease and with a history/risk of CVD.

5.2 Hypothesis

Aspirin use is associated with decreased risk of mortality and exacerbations over follow up in COPD patients from the SUMMIT and IMPACT trials.

5.3 Aims

Evaluating the association of aspirin use in COPD populations with risk of all-cause mortality, exacerbations and cardiovascular composite events during follow up.

5.4 Methods

5.4.1 Study design

Despite the increased risk of mortality for COPD patients with CVD, there is currently a lack of CVD compatible therapeutics that reduces the risk of exacerbations and mortality for these patients. Considering the complex discovery process associated with developing new therapeutics, a cost and time effective method would be to repurpose existing drugs, such as aspirin, which is widely used in CVD populations and has been reported in observational studies to be associated with reduced exacerbations and mortality. I carried out all statistical analysis, coding and data presentation.

To further explore the potential of aspirin for improved health outcomes in COPD patients, I analysed using statistical methods, large datasets consisting of COPD patients from the SUMMIT (n=16485, moderate COPD with risk/history of CVD defined as CAD, PAD, stroke, MI and diabetes with target organ disease, median follow up 1.8 years, published 2016) and IMPACT (n=10355, severe COPD, 52 weeks follow up, published 2018) studies, to evaluate the effects of aspirin on risk of mortality, exacerbations and cardiovascular composite events (200, 201).

5.4.2 Datasets

The SUMMIT and IMPACT datasets were provided by Clinical Study Data Request (https://www.clinicalstudydatarequest.com). Dr Marie Fisk wrote the proposal for using the patient level datasets for analysis described in this chapter.

The SUMMIT study was a clinical trial assessing the effectiveness of fluticasone furoate (FF), vilanterol (VI) and FF/VI combination treatment on the primary outcome of all-cause mortality. The inclusion criteria for the study population included current or former smokers with minimum of ten-pack-year history, 40-80 years old, moderate COPD (FEV1% 50-70% of predicted value), history or increased risk (60 years or older using medication for more than two of hypercholesterolemia, hypertension, diabetes, PAD) of CVD (CAD, PAD, stroke, MI, diabetes with target organ disease) (200). The exclusion criteria were non-COPD respiratory disease, lung reduction surgery, oral corticosteroid use, on long term oxygen, severe heart failure, life expectancy below three years, end stage chronic renal disease (200). The SUMMIT study researchers found that the treatments did not have a significant effect on all-cause mortality or cardiovascular events, but did reduce exacerbations (200).

The IMPACT study was a clinical trial assessing the effectiveness of FF/VI/umeclidinium triple therapy, FF/VI dual therapy and VI/umeclidinium dual therapy on the primary outcome of exacerbation rate. The inclusion criteria for participants included severe COPD (FEV1% below 50% of predicted value and history of at least one moderate/severe exacerbation one year prior to study entry) and to be 40 years or older (201). The IMPACT study researchers found that triple therapy was significantly more effective in reducing exacerbation rate compared to the dual therapies, and therapies including FF were associated with lower mortality than VI/umeclidinium (201).

The datasets included detailed records of the concomitant medications (including aspirin) that the study participants were using at baseline. It is unknown how long the participants had been using reported concomitant medications or if they stopped using them during the course of the clinical study and follow up period. Only the intention to treat population will be used in data analysis.

5.4.3 Statistical analysis

The primary outcomes of this analysis were hazard ratios for time to first event occurrence of ACM, moderate and severe exacerbations (moderate defined as requiring antibiotics/glucocorticoid treatment, severe defined as requiring hospitalisation) and cardiovascular events, calculated using multivariate Cox Proportional Hazards models. The hazard ratios are presented using forest plots. Sensitivity analyses were carried out for the covariates of age (oldest strata), sex (M/F), race (white) and country (top five sources of participants), and the results were compared to those from the main population. Additionally, for bias analysis, E-values were calculated, which represent the minimum strength of association an unmeasured confounder would need to have with the treatment (aspirin) and the outcome to explain away an observed association between aspirin and the outcome (125). Propensity score matching was carried out on the SUMMIT and IMPACT datasets using covariates that predict for being on/off aspirin. In the SUMMIT dataset, 5038 matched pairs (of aspirin users and non-users) were selected. In the IMPACT dataset, 2037 matched pairs of aspirin users and non-users were selected. The scores were calculated with logistic regression and the matching method used was ‘nearest neighbour matching’, with a caliper of 0.2. The adjustment factors of the logistic regression for SUMMIT were history of PAD, stroke, CAD, MI and percutaneous coronary intervention, and for IMPACT were history of PAD, stroke, CAD, MI and angina. Hazard ratios for health outcomes were then calculated using the propensity score matched groups.

All analysis (except for E-values which were determined manually) was carried out with RStudio Desktop, R version 4.2.0. The full code used for this analysis is available in Appendix A.

5.5 Results

Datasets consisting of COPD patients from the SUMMIT and IMPACT studies were analysed to assess the association between aspirin use and risk of mortality, exacerbations and cardiovascular events over the follow up period.

From the SUMMIT and IMPACT studies, 16,485 moderate COPD patients with a history/risk of CVD and 10355 severe COPD patients were included respectively.

The demographics and clinical history/events of the populations are shown in Table 4. All subjects were from the intention to treat population. The SUMMIT and IMPACT populations had similar age, sex, BMI and ethnic backgrounds. The main difference is that the IMPACT subjects had more severe COPD (% FEV1 less than 50% of predicted value) and were not specifically recruited from a CVD risk/history population. SUMMIT had a median follow up time of 1.8 years and IMPACT had a follow up time of 52 weeks. Reported events were those that took place on treatment (trial drugs or placebo), except for ACM in SUMMIT, which included all deaths before the common end date.

Cardiovascular events for SUMMIT was defined as CV death, MI, stroke, unstable angina, transient ischaemic attack, and for IMPACT as CV death, acute MI Preferred Term (PT), CNS haemorrhage, heart disease Standardised MedDRA Queries (SMQ), MI PT, MI SMQ. For heart disease, definition for SUMMIT is myocardial infarction and/or coronary artery disease and/or percutaneous coronary intervention, and definition for IMPACT is myocardial infarction and/or coronary artery disease and/or angina.

Table 4: Demographics and clinical history of the SUMMIT and IMPACT populations.

Variable	**SUMMIT (n=16485)**	**IMPACT (n=10355)**
Age (mean years)	65	65.3
Sex	12289 (75%) male	6870 (66%) male
BMI (mean)	28.0	26.6
Race	13357 (81%) white	8083 (78%) white
Smoking Status	7678 (47%) current smoker	3587 (35%) current smoker
Pack Years (smoking)	41	47
FEV1%	59.1	45.5
Previous exacerbations prior to study entry (0, 1, >=2)	0 (61%) 1 (24%) >=2 (15%)	0 (<1%) 1 (45%) >=2 (55%)
Aspirin use (monotherapy)	6844 (41.5%)	2318 (22.4%)
Reported events (first time occurrence)		
All-cause mortality	1037 (6%)	138 (1%)
Moderate exacerbations	2858 (17%)	4401 (43%)
Severe exacerbations	1293 (8%)	1180 (11%)
Cardiovascular events	688 (4%)	299 (3%)
Clinical History (Yes)		
Diabetes	4376 (27%)	1599 (16%)
Hypercholesterolemia	10190 (62%)	3367 (33%)
Hypertension	14265 (87%)	5446 (53%)
Heart Disease	8599 (52%)	1684 (16%)
Arrhythmia	NA	816 (8%)
Stroke	1595 (10%)	458 (4%)
HF	3456 (21%)	539 (5%)
Peripheral Artery Disease	3145 (19%)	342 (3%)

5.5.1 All-cause mortality

Aspirin use in the SUMMIT study was associated with an increased risk of ACM before the common end date (January 25th 2015, date by which there would be at least 1000 deaths), HR of [1.15 (1.00-1.33), p=0.048], with 1037 deaths and 15448 survivors before the common end date. In the IMPACT dataset, aspirin use was also associated with increased risk of ACM, although the effect was not significant, HR of [1.45 (0.95-2.19), p=0.082] (Figure 18), with 138 deaths and 10217 survivors. SUMMIT multivariate HRs were adjusted for covariates of age, sex, BMI, smoking status, smoking pack years, FEV1% and history of stroke, HF, hypercholesterolemia, hypertension, heart disease, diabetes and PAD. IMPACT multivariate HRs were adjusted for covariates of age, sex, BMI, trial treatment arm, smoking status, smoking pack years, FEV1% and history of arrhythmia, stroke, HF, hypercholesterolemia, hypertension, heart disease, diabetes and PAD.

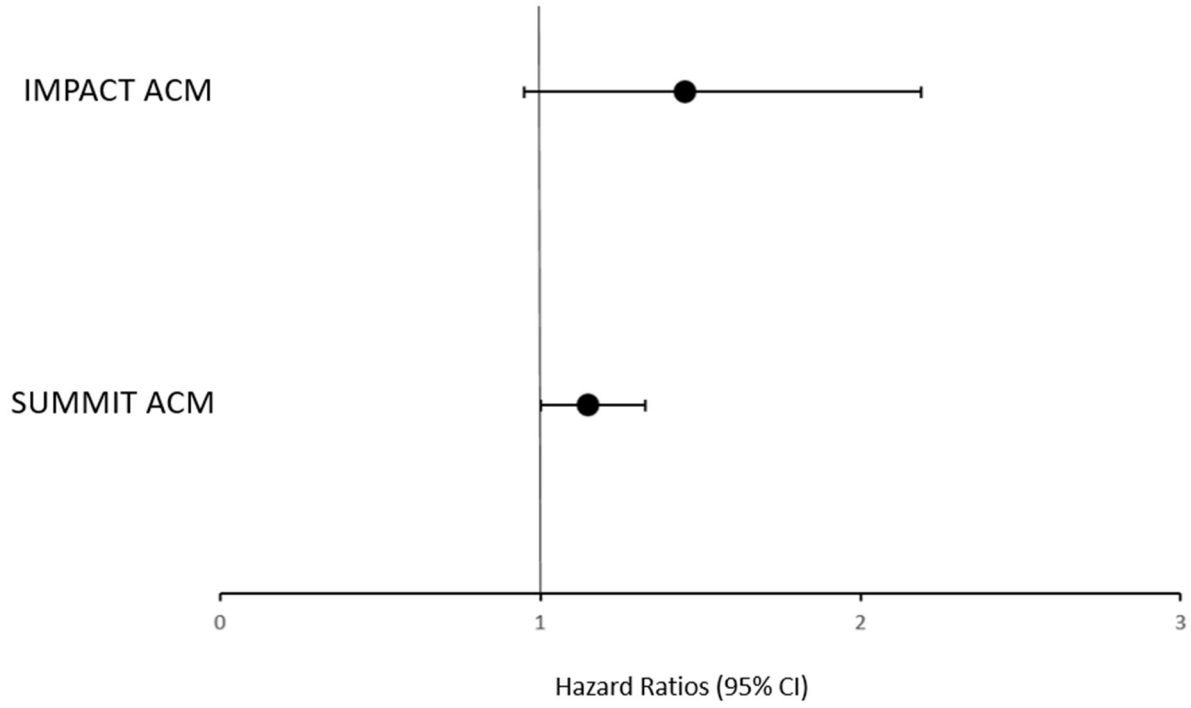

Figure 18: Forest plot showing multivariate adjusted HR and 95% CI for aspirin use and its relationship with ACM. ACM=All-cause mortality. SUMMIT multivariate HRs were adjusted for covariates of age, sex, BMI, smoking status, smoking pack years, FEV1% and history of stroke, HF, hypercholesterolemia, hypertension, heart disease, diabetes and PAD. IMPACT multivariate HRs were adjusted for covariates of age, sex, BMI, trial treatment arm, smoking status, smoking pack years, FEV1% and history of arrhythmia, stroke, HF, hypercholesterolemia, hypertension, heart disease, diabetes and PAD.

5.5.2 Exacerbations

Aspirin use was associated with increased risk of moderate exacerbations in the SUMMIT [HR=1.17 (1.08-1.27), p<0.001] and IMPACT [HR=1.10 (1.02-1.18), p=0.012] populations. There were 2858 patients who experienced a moderate exacerbation in the SUMMIT trial and 4401 patients who did so in the IMPACT trial. For severe exacerbations, aspirin use was also associated with an increased risk in the SUMMIT [HR=1.35 (1.19-1.52), p<0.001] trial with 1293 patients reporting a severe exacerbation, and in the IMPACT [HR=1.30 (1.14-1.49), p<0.001] trial with 1180 patients reporting a severe exacerbation (Figure 19). SUMMIT and

IMPACT multivariate HRs were adjusted for covariates of age, sex, BMI, trial treatment arm, smoking status, smoking pack years, FEV1% and previous exacerbations.

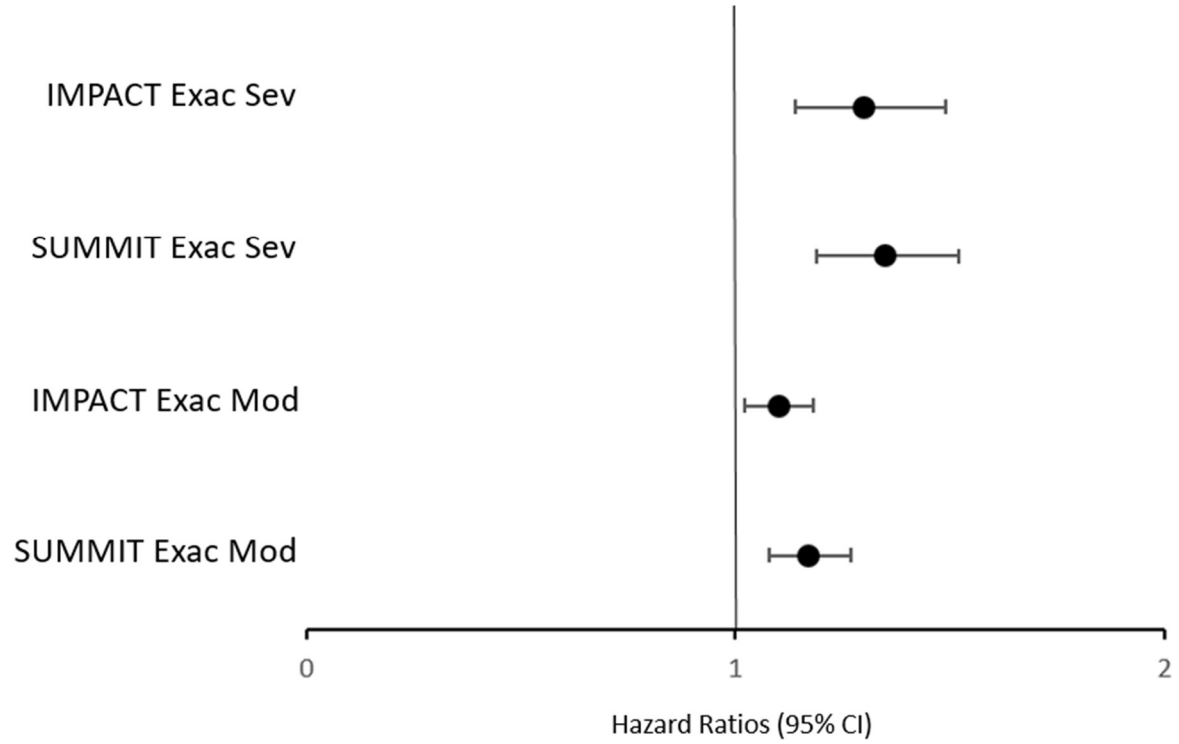

Figure 19: Forest plot showing multivariate adjusted HR and 95% CI for aspirin use and its relationship with moderate and severe exacerbations. Exac Sev= Severe exacerbation, Exac Mod= Moderate exacerbation. SUMMIT and IMPACT multivariate HRs were adjusted for covariates of age, sex, BMI, trial treatment arm, smoking status, smoking pack years, FEV1% and previous exacerbations.

5.5.3 Cardiovascular events

In the SUMMIT dataset, aspirin use was associated with an increased risk of cardiovascular events (688 patients experienced an event), with an adjusted HR of 1.65 (1.33-2.05), $p<0.001$. The adjustment factors were age, sex, BMI, trial treatment arm, smoking status, smoking pack years, history of stroke, HF, hypercholesterolemia, hypertension, heart disease, PAD, diabetes, previous exacerbations. For the IMPACT dataset, aspirin use was associated with an increased rate (adjusted) of cardiovascular events (rate ratio=2.22), with 299 patients experiencing an event. The adjustment factors were age, sex, BMI, trial treatment arm, smoking status, smoking

pack years, history of arrhythmia, stroke, HF, hypercholesterolemia, hypertension, heart disease, PAD, diabetes, previous exacerbations.

5.5.4 Sensitivity analysis

In sensitivity analysis, the subgroups of age (>=75), sex (M/F), race (white) and country (top five sources of patients) were analysed. Sensitivity analysis did not show any major differences from the main group, on aspirin use and association with increased risk of ACM, exacerbation and cardiovascular events. Subgroup analysis by race (white) found for moderate exacerbations a HR of [1.27 (1.15-1.40), p<0.001] in SUMMIT and a HR of [1.08 (1-1.17), p=0.049] in IMPACT. The same subgroup analysis for severe exacerbations found a HR of [1.33 (1.15-1.55), p<0.001] in SUMMIT and a HR of [1.31 (1.12-1.53), p<0.001] in IMPACT.

5.5.5 Bias analysis

Whilst many potential confounders were included as covariates in the Cox Models, E-values were also calculated (for the HR estimate and the lower estimate of the 95% CI) to identify the minimum association with aspirin and outcomes an unknown confounder would need to have to explain away the observed association of aspirin use and increased risk of ACM, exacerbations and cardiovascular events. For the outcome of ACM in the SUMMIT dataset, the E-value was 1 (for the lower estimate of CI), and for the outcome of moderate exacerbation, the E-values were 1.37 (SUMMIT) and 1.16 (IMPACT). For the outcome of severe exacerbation, the E-values for the lower estimate of CI were 1.67 (SUMMIT) and 1.54 (IMPACT). A low E-value (1-2) indicates an unknown confounding factor can credibly explain away observed associations of aspirin with COPD health outcomes.

5.5.6 Propensity score matched groups

After matching, there were 5038 pairs from the SUMMIT study and 2037 pairs from the IMPACT study. The analysis results of the propensity score matched groups were similar to the findings of the main group. For the matched pairs from the SUMMIT study, association of aspirin use with ACM risk was HR [1.22 (1.04-1.43), p=0.015], [1.19 (1.09-1.31), p<0.001] for moderate exacerbation risk and [1.32 (1.14-1.53), p<0.001] for severe exacerbation risk. For the matched pairs from the IMPACT study, association of aspirin use with risk of ACM, moderate exacerbation and severe exacerbation was [1.32 (0.79-2.19), p=0.3], [1.11 (1.01-1.23), p=0.031] and [1.16 (0.97-1.39), p=0.11] respectively. The demographics tables for the new matched SUMMIT and IMPACT groups are available in Appendix D. Risk of bleeding analysis (adjusted for age, sex, BMI and trial treatment arm) was also carried out, with aspirin use being associated (as expected) with increased risk of bleeding in SUMMIT [HR 1.25 (0.88-1.78), p=0.2] and IMPACT [HR 2.19 (1.09-4.41), p=0.028] populations.

5.5.7 Absolute Risk

In the SUMMIT population, the absolute risk of ACM in aspirin users was 6.9% compared to 5.3% in non-users. For risk of moderate exacerbations, aspirin users were also at increased risk compared to non-users, at 18.2% and 15.4% respectively. Aspirin users had an absolute risk of 8.4% for severe exacerbations, while non-users were at 6.2%.

In the IMPACT population, the absolute risk of ACM in aspirin users and non-users was 1.8% versus 1.2%. For risk of moderate exacerbations, aspirin users were at 44.2% risk compared to 41.5% for non-users. Additionally, aspirin users had 13.4% risk of severe exacerbations, while non-users were at 10.3% risk.

5.6 Discussion

Findings from previous observational studies had suggested a potential association of aspirin use with reduced risk of mortality and exacerbations in COPD patients. Those findings, in addition to aspirin's well known cardiovascular benefits, suggested a potential for aspirin as a well-tolerated and accessible treatment for COPD patients with a CVD background. In this project, two large high quality datasets from the SUMMIT (n=16485) and IMPACT (n=10355) trials were analysed, and the multivariate Cox models showed an association of aspirin use with increased risk of ACM, exacerbations (moderate and severe) and cardiovascular events. These associations were significant for outcomes in both datasets, with the exception of ACM in the IMPACT trial. These results are different to previous studies that suggested aspirin use was associated with ameliorative effects in COPD populations, and further investigation is needed to identify the causes of this (122).

Relative risk measures such as hazard ratios can overestimate an observed effect, so absolute risk of events was also calculated (202). When considering absolute risk of ACM, moderate and severe exacerbations, aspirin users were also at higher risk of an event compared to non-users, supporting the results of the hazard ratio analysis. Sensitivity analysis focusing on age (oldest group), sex, race (white) and country did not reveal major differences from the findings of the main group, nor did it find any association of aspirin use with reduced risk of ACM, exacerbations or cardiovascular events.

A previous observational study by Fawzy *et al* involving 503 propensity score matched participant pairs had suggested that aspirin use in COPD patients was associated with reduced exacerbation rate (122). The contrasting findings of this study could be due to the heterogeneity in methods and population clinical history of previous studies, as well as varied data quality. The study by Fawzy *et al* analysed a population which also included non-smokers and excluded

those with unstable CVD (122, 203). This analysis used high quality trial data from populations inclusive of moderate and severe COPD and those with a history/risk of CVD. The SUMMIT and IMPACT datasets had consistent data entry and well defined clinical conditions. Additionally, it has been noted by Bakshi *et al* 2021 that many previous observational studies investigating aspirin use in COPD were affected by biases such as collider-stratification bias (shows non-existent association between exposure and outcome) and exposure misclassification (204).

Additionally, considering aspirin's indication for CVD treatment regimens, patients who are prescribed aspirin have more CVD risk factors such as increased platelet count or have already been diagnosed with CVD. These risk factors such as increased platelet count have been implicated in COPD pathogenesis (including acute exacerbations) and are also associated with poor health outcomes. Potentially, the findings of this study that aspirin use is associated with worse outcomes in COPD patients could be due to confounding factors such as aspirin users having poorer health, more risk factors for mortality, and acute exacerbations at baseline, compared to non-users of aspirin.

However, even after creating new propensity score matched groups based on covariates that predict for aspirin use (e.g. CAD, MI and stroke), to reduce potential bias caused by confounding factors, aspirin was still associated with increased risk of ACM, moderate and severe exacerbations over follow up. Nevertheless, matching cannot fully exclude bias such as disease severity.

Bias analysis showed that E-values calculated using the lower estimate of the outcome HRs were relatively low, with values being between 1-2. This suggests that an unknown confounding factor could credibly explain away the observed association of aspirin use with negative health outcomes.

Dysregulated SPM pathways could also have contributed to the observed effects. It has been previously reported that T cells sourced from chronic heart failure patients were unresponsive to treatment with RvD1 and Resolvin D2 (76). Considering the systemic inflammation involved in COPD and the significant presence of CVD and CVD risk factors in the SUMMIT and IMPACT populations, it is possible that dysregulated SPM pathways in these patients prevented them from benefiting from the immunomodulatory effects of aspirin (production of aspirin triggered SPMs).

Additionally, the use of bronchodilators among significant portions of the study population could have increased the risk of mortality and development of CVD (which is a reported negative effect of bronchodilators), potentially masking the beneficial effects of aspirin (94).

Given the association of aspirin use with negative health outcomes shown in this study, and the high level of aspirin use in the COPD population (22.4% for IMPACT and 41.5% for SUMMIT), it is essential to investigate the causes of these findings. This is particularly important considering aspirin's status as a commonly prescribed CVD drug and the elevated risk of concurrent CVD in COPD patients. To identify potential molecular mechanisms that could explain the observed harmful effects of aspirin use in this study, levels of platelets and aspirin triggered SPMs should be measured in aspirin users and non-users, to assess if aspirin directed pathways are functioning as expected.

5.6.1 Limitations

There are several limitations to this analysis. For analysis of populations with the demographic characteristics seen in this study, it is difficult to find patients in statistically viable numbers who are only using the medication of interest, such as aspirin. While aspirin users were defined as patients who were only using one type of anti-platelet medication (aspirin), the other medications they were using such as statins, beta-blockers and ACEI/ARBs were not included

in the analysis. These medications could have an effect on health outcomes, including mortality and exacerbations. Particularly, statins have been shown to decrease mortality risk and beta-blockers are of increasing interest in treating COPD patients with concurrent CVD (101, 205).

Another limitation is the variation in aspirin dosages amongst the analysis population. The regularity of use, dosage and administrative route varied in the included population, which could have an influence on the health outcomes of interest. Additionally, while the trial drugs were included in the Cox Models if they were found to have had an effect on study outcomes (ACM, exacerbations and cardiovascular events), their potential interactions with aspirin and other CVD medications have not been assessed. To investigate this further, sensitivity analysis by trial drug subgroup could be carried out and compared with the designated placebo group from the SUMMIT study.

5.6.2 Impact and future work

The findings of this study that aspirin use is associated with increased risk of exacerbations and all-cause mortality are highly significant given the high proportion of COPD patients using aspirin and will be directly followed by the ASPIRE clinical study, which has already been approved. The ASPIRE study will involve randomised groups of 24 COPD patients/smokers and 24 controls given omega-3 and aspirin supplementation or placebo, over the course of 12 weeks. Plasma SPM levels and lung/cardiovascular function will be regularly measured during the study to assess the effects of aspirin use on production of SPMs as well as pulmonary and cardiovascular health.

5.6.3 Summary

This study comprehensively analysed large high quality datasets, comprised of moderate and severe COPD patients, including those with a history/risk of CVD. These demographic and clinical characteristics made the SUMMIT and IMPACT datasets ideal for assessing the

potential of aspirin use in reducing mortality and exacerbations in COPD patients, particularly those with CVD. Contrary to previous reports from observational studies, the findings of this study show that aspirin is associated with increased risk of ACM, exacerbations and cardiovascular events. In contrast to previous observational studies which observed beneficial effects of aspirin (smaller cohorts), at best, this work suggests no benefit and possible increased risk of harm. Although these data may simply reflect that patients prescribed aspirin have increased cardiovascular risk and poorer health than those that do not, and statistical adjustment for confounders (despite propensity score matching and other methodology) is not sufficient to mitigate this inherent association. Given these data, a randomised controlled trial would be the useful methodology to assess the effect of aspirin on exacerbations and mortality in patients with COPD.