Prescription of Pharmacotherapy and the Incidence of Stroke in Patients with Symptoms of Peripheral Artery Disease

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Background and purpose: Current guidelines recommend prescription of a number of medications to prevent cardiovascular events in patients with peripheral artery disease (PAD). The impact that these medications have on the incidence of stroke in PAD patients has not been thoroughly investigated. This study aimed to investigate the association of prescription of antihypertensive drugs, antiplatelet medications and statins, as well as cardiovascular disease risk factors, with stroke incidence in patients with symptoms of PAD.

Methods: A database search was completed to identify studies reporting the incidence of stroke and prescription of antihypertensive drugs, antiplatelet medications and statins in patients with PAD symptoms. A random-effects model was used to meta-analyse the incidence of stroke in patients with symptoms of PAD and in subgroups with intermittent claudication (IC) and critical limb ischaemia (CLI). Meta-regression was performed to explore the association between the incidence of stroke and the prescription of medications and the presence of cardiovascular disease risk factors.

Results: Twelve studies including 67 915 patients with symptoms of PAD were included. A meta-analysis of data from seven studies demonstrated an incidence of stroke of 1.31 per 100 patient-years. Patients with CLI experienced stroke 2.3 times more frequently than those with IC (95% CI 1.58-3.36, $p<0.01$). The reported prescription of anti-hypertensive agents varied between 10% and 71%, anti-platelet drugs between 49% and 90% and statins between 11% and 79% in different studies. Meta-regression suggested an association between a lower incidence of stroke and the prescription of anti-platelet drugs ($R^2=0.81$, $p<0.01$) and statins ($R^2=0.86$, $p<0.01$) but not antihypertensive agents. A prior history of cerebrovascular events was associated with a higher incidence of stroke ($R^2=0.58$, $p<0.05$).

Conclusion: This review supports previous research which suggests the need for more effective means of ensuring more widespread prescription of preventative medications in patients with PAD.

Introduction

Peripheral artery disease (PAD) is an athero-occlusive condition which results in lower limb ischaemia and is usually diagnosed by an ankle brachial pressure index (ABPI) of <0.9.[1] The most well recognised symptom of PAD is pain in the muscles of the leg upon exertion, known as intermittent claudication (IC). Less commonly PAD presents as rest pain, ischaemic ulceration or gangrene, referred to as critical limb ischemia (CLI).[1, 2]

Population studies suggest the prevalence of IC increases from about 3% in people aged 40 years to >6% in people aged >60 years.[2] No recent population studies have reported the prevalence of CLI, but data from Medicare suggests this to be between 0.2 and 1.3% in those aged >40 years.[2, 3] Whilst the focus of PAD management is frequently on the limbs much of the disease burden is the result of other major cardiovascular events which occur at a frequency 3-5 times greater than the age-matched general population.[1, 4] While ischaemic stroke is an important cause of cardiovascular mortality in PAD patients, a relatively low frequency of events means that individual studies are often inadequately powered to assess this outcome independently. Thus, the impact that preventative interventions have on the incidence of stroke in PAD patients is infrequently reported.

Current guidelines recommend medical management to reduce the incidence of cardiovascular events in PAD patients through antiplatelet therapy, lowering low density lipoprotein-cholesterol (LDL-C) using statins, and blood pressure (BP) control using medications such as angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB).[5, 6] These recommendations for medical management are predominantly based on large randomised control trials (RCTs) where PAD patients were included as a small and frequently unreported subgroup.[5, 6,] Antiplatelet monotherapy is the intervention with the strongest evidence base in the prevention of stroke in PAD patients. Meta-analyses[7, 8] have suggested that aspirin and clopidogrel are both effective in reducing

the relative risk of stroke by 29-36%. The evidence for the use of lipid lowering and anti-hypertensive therapy is not as well defined. The UK heart protection study (UKHPS) and the Heart Outcomes Prevention Evaluation (HOPE) study are the only RCTs to report the effect of statin and anti-hypertensive prescription, respectively, on the incidence of stroke in PAD patients.[9,10] The allocation of 40mg of simvastatin, as compared to placebo, reduced the incidence of stroke by 25% (relative risk, RR, 0.75, 95% CI 0.66-0.85).[9] While the allocation of 10 mg of ramipril resulted in a 25% relative reduction in the incidence of stroke (RR 0.75, 95% CI 0.58-0.98) by comparison to placebo.[10]

Overall, these data provide limited level 1 evidence on the benefit of medical management in the prevention of stroke in PAD patients. Furthermore, it has been reported that the prescription of these medications is low amongst those with PAD.[11] Previous cohort studies report that the incidence of stroke in PAD patients ranges from 0.8 to 4.7 events per 100 patient years (PY)[12, 13] and it is possible that this variation may be due to differences in the prescription of anti-hypertensive drugs, anti-platelet medication and statins.[12] The aim of this study was to systematically review the incidence of stroke in patients with symptoms of PAD and investigate the reported prescription of preventative medications and the association of this and other cardiovascular disease risk factors with stroke incidence.

Methods

The authors declare that all supporting data are available within the article and its supplements.

Search strategy

This meta-analysis was conducted in line with the preferred reporting items for systematic review and meta-analysis (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines. A detailed protocol was published in the PROSPERO database before commencing the study, in accordance with the PRISMA protocol (CRD42017076193). A systematic literature search was conducted using Scopus (1966), MEDLINE/PubMed (US National Library of Medicine, Bethesda, MD, USA), CINAHL and the Cochrane Library. Databases were searched on two separate occasions (September, 2017 and July, 2018) to ensure that potentially eligible papers which were published whilst this manuscript was under preparation were also included. Databases were searched using the search terms in appendix A. Manual searches were performed using the related articles function in PubMed, and hand searching the reference lists of included studies.

Study selection

This review included prospective or retrospective observational studies or RCTs involving participants with IC or CLI. A study was included if the following criteria were met:

1. Presence of PAD was confirmed using a validated diagnostic method, including one or more of the following: clinical history and examination, ABPI, duplex ultrasound or angiography;
2. The incidence of stroke was reported for symptomatic PAD patients and was consistent with the definition of a focal neurological deficit persisting >24 hours,

confirmed by either clinical history and examination or imaging (computed tomography, CT, or magnetic resonance imaging, MRI).

Studies were excluded if:

1. Only fatal strokes were recorded;
2. Data specific to patients with symptoms of PAD alone could not be obtained;
3. They were not published in the English language.

Studies were included in the quantitative analysis if the above criteria were met and the incidence of stroke was recorded, or able to be calculated, in events per PY either from data reported in the paper or obtained from the authors. Relevant articles were identified and systematically screened against the inclusion and exclusion criteria by two authors (DRN and JS).

Data extraction

Data extraction was performed independently by three authors (DRN, JVM and JRS) using a pre-defined excel spreadsheet. Extracted data included details related to study design, participant demographics, definitions of PAD and stroke, cardiovascular disease risk factors and prescribed medications. The proportion of patients prescribed anti-hypertensive and anti-platelet therapy was calculated from the number prescribed ACEI or ARBs, and aspirin or clopidogrel at baseline. These medications were combined for this review as they share a similar mechanism of action and were frequently reported together by included studies. All definitions of diabetes, hypertension, current smoking and prior cerebrovascular disease were accepted. Data on the length of follow-up was extracted as either mean or median years or the total number of patient years. Authors of studies with missing data of interest were contacted via email. One author[12] was able to provide further information including the total patient years of follow up and cumulative event rate of stroke in their study population.

Study quality assessment

Quality assessment was conducted using a set of 18 questions specifically developed for this study and relevant for PAD and stroke research. The quality assessment tool was developed and scored based on the Evidence Based Library and Information Practice and Newcastle Ottawa scale. The tool assessed the study methodology, definition of PAD and diagnosis and reporting of stroke. The questions were first trialled on excluded articles to assess the tools validity. Two authors (DRN and JRS) who were blinded from study identifiers (i.e. authors, journal and institute) conducted the quality assessment. A difference of two or more points triggered a consensus meeting where the papers were discussed and discrepancies resolved. All 18 questions were equally weighted and individual scores were calculated based on the proportion of yes answers. Studies that scored <50%, 50-75% and >75% were deemed of low, moderate and high quality, respectively.

Quantitative data synthesis

The quantitative analysis was conducted using comprehensive meta-analysis 3 software and a random-effects model given that significant inter-study heterogeneity was expected. The primary analysis utilised the meta-analysis of incidence model to calculate the pooled incidence of stroke in those with symptoms of PAD. A subgroup analysis calculating the incidence of stroke in patients with IC or CLI was also performed. Results were presented as events per 100 PY with 95% confidence intervals (CI) and heterogeneity was assessed using I^2. I^2 values of 25%, 50% and 75% were acknowledged to represent low, moderate and high heterogeneity respectively. A rate ratio comparing the risk of stroke for patients with IC and CLI was calculated from three studies which reported results for patients with both of these presenting symptoms. The secondary analysis utilised a meta-regression model to investigate the association between the incidence of stroke and the prescription of anti-hypertensive,

anti-platelet or statin therapy as well as the presence of hypertension, diabetes, prior cerebrovascular events or current smoking. Given the substantial difference in the incidence of stroke between patients with IC and CLI the meta-regression was performed by separating patients with these presenting symptoms and considering them as individual cohorts in the analysis. Therefore, only studies which reported results separately for patients with IC or CLI were included. Results were presented in a bubble plot with a regression equation and the proportion of between study variance explained by the model (R^2). Prescribed medications and risk factors were deemed to be associated with the incidence of stroke if the p value for the regression equation was <0.05.

Results

Selection of included studies

A systematic search identified 3500 articles (Supplementary figure I). After duplicates were removed the titles and abstracts of 2354 articles were screened with the majority excluded as they were not original investigations of patients with PAD. Fifty-six full-text articles were reviewed, of which 44 were excluded; 17 because they did not report stroke as an independent outcome, 14 because PAD cases did not meet the study definition, six because they investigated the incidence of PAD in those with stroke and seven because they were from a duplicate study population. The remaining 12 studies were included in this review.

Description of included studies

A total of 67 915 patients with symptoms of PAD were investigated in the 12 included studies. Eight studies included patients presenting with both IC and CLI, three included only patients with IC and one included only patients with CLI. Six studies [12-17] recruited patients after diagnostic or interventional procedures (e.g. lower limb angiography), four [18-21] recruited newly referred patients to vascular surgery services and two [22, 23] recruited patients from a general practice setting. Nine studies[12-15, 18, 19, 21-23] confirmed PAD diagnosis using ABPI whilst three [14, 16, 17] used lower limb angiography.

Supplementary table I details the design and patient characteristics for each included study. Of note 42% of the total population were derived from the study reported by Cea Soriano et al.[22] Mean age of the population ranged from 60 to 79 years.

Quality of the included studies

Supplementary table II details the quality assessment results for each included study. Inter-observer agreement ranged from 90-100%. All studies reported their method of patient

sampling, inclusion criteria and statistical analysis technique. For two studies[19, 20] further information on the diagnosis of PAD and definitions of stroke was obtained from protocol papers. Sigvant et al.[12] were contacted to confirm the definitions of IC and CLI used in their study. Out of the 12 studies included in this review 10 were considered to be of high quality, and two[16, 19] were considered to be of moderate quality.

Incidence of stroke

The incidence of stroke and follow up periods for each study are presented in supplementary table I.

Seven studies[12-15, 18, 21, 22] reported ischaemic stroke alone, one[17] reported ischaemic stroke combined with transient ischaemic attack (TIA) and three[16, 19, 23] did not define whether stroke was ischaemic or haemorrhagic. Dormandy et al.[20] reported major strokes defined as acute neurological deficits lasting >1 week. In nine studies[12, 13, 15-18, 21-23] stroke diagnosis was confirmed by either CT or MRI whilst in three studies[14, 19, 20] stroke was diagnosed on the basis of clinical history and examination alone. Five studies[14-17, 19] reported the incidence of stroke as the proportion of the starting population who experienced the event over the follow-up period. As there was high heterogeneity in follow-up periods, comparison of the incidence of stroke between these studies was not possible. Seven studies[12, 13, 18, 20-23] reported the incidence of stroke as number of events per 100 PY of follow up (for one of these studies[12] information used to calculate the incidence of stroke was obtained from the author). The reported incidence of stroke varied from 0.84 to 4.7 events per 100 PY with three studies reporting a higher incidence in patients with CLI compared to IC. Quantitative analysis revealed an overall incidence of stroke in those with symptoms of PAD of 1.31 per 100 PY (95% CI 0.91-1.71, I^2 97.89%, figure 1). The incidences of stroke in patients with CLI and IC (supplementary figure II) were 2.50 per 100 PY (95% CI 1.94- 3.07, I^2 77.21%) and 1.12 per

100 PY (95% CI 0.74-1.51, I^2 91.95%) respectively. Rate ratio analysis suggested that patients with CLI were 2.3 times more likely to have a stroke than those with IC (95% CI 1.58-3.36, p<0.01, supplementary figure III).

Association between prescribed medications and the incidence of stroke

The proportions of the study populations prescribed anti-hypertensive, anti-platelet and statin medications at baseline is shown in table 1. Eight studies[12-14, 16, 18, 19, 21, 22] reported on ACEI and ARB prescriptions, nine[12, 14, 15, 17-19, 21, 22] reported on aspirin and clopidogrel prescriptions, and eight[12-16, 19, 21, 22] reported on statin prescription. Three studies[13, 18, 20] reported on anti-hypertensive, anti-platelet or lipid lowering therapy in general with no further explanation. Dormandy et al.[20] excluded all patients prescribed anti-platelet therapy and Diehm et al.[23] did not report on any of these medications. The reported prescription of anti-hypertensive agents varied between 10% and 71%, anti-platelet drug prescription varied between 49% and 90% and statin prescription varied between 11% and 79%. Three studies[12, 13, 21] reported a higher frequency of prescription of these medications in patients with IC compared to those with CLI.

Meta-regression demonstrated a statistically significant association between a lower incidence of stroke and a higher prescription of anti-platelet agents (R^2=0.81, p<0.01 Figure 2b) and statins (R^2=0.86, p<0.01, Figure 2c). No statistically significant association was demonstrated between the incidence of stroke and the prescription of antihypertensive drugs (Figure 2a). Of the studies included in the meta-regression, patients with CLI reported by Sigvant et al.[12] had the lowest prescription of statins, anti-hypertensive drugs and anti-platelet agents. The patients with IC reported by Sanclemente et al.[13] had the highest prescription of these drugs. For all of the analyses, the patients with CLI reported by Sanclemente et al.[13]

were the only cohort which did not fall within the 95% confidence intervals of the regression equation.

Association between cardiovascular risk factors and the incidence of stroke

The proportion of patients with hypertension, diabetes, a prior cerebrovascular event and current smoking at baseline is shown in table 1. Six studies[13-17, 21] reported these risk factors based on assessment of medical records, two[12, 22] through national electronic records and four[18-20, 23] from baseline history and examination. Three studies[12, 18, 19] defined hypertension as a BP of >140/90mmHg, one[13] as >130/90mmHg, one[20] as >160/90mmHg and seven[14-17, 21-23] provided no definition. Two studies[12, 22] reported the proportion of patients with previous ischaemic stroke, the remaining 10 did not differentiate between previous ischaemic or haemorrhagic stroke or TIA. Meta-regression demonstrated that studies which included higher proportions of patients with prior cerebrovascular events reported higher incidences of stroke during follow-up (R^2=0.58, $p<0.05$, Figure 3d). Patients with CLI reported by Sanclemente et al.[13] and Sigvant et al.[12] reported the highest proportion of patients with prior cerebrovascular disease. No statistically significant association was demonstrated between the incidence of stroke and the proportion of patients with hypertension, diabetes and current smoking (Figure 3).

Assessment of publication bias

Given the small number of included studies assessment of publication bias was not possible.

Discussion

This review found that the mean incidence of stroke amongst patients with symptoms of PAD in previously reported studies was 1.31 per 100 PY and that patients with CLI experienced stroke at a rate 2.3 times greater than those with IC. The proportion of patients prescribed anti-hypertensive drugs, antiplatelet medication and statins was low. There was marked variation in the reported incidence of stroke in the included studies. A large proportion of this variation was likely the result of significant inter-study variation in the definitions and diagnosis of stroke and length of study follow-up. Whilst most studies reported ischaemic strokes only, some reported a composite of ischaemic stroke, haemorrhagic stroke and TIA which likely resulted in higher reported number of events. The primary analysis included two studies that reported this composite outcome and after removal from the model there was no significant change in results. Varying follow-up periods were adjusted for by comparing the incidence of stroke between studies in events per 100 PY. Any study in which the incidence of stroke could not be expressed as events per 100 PY was excluded from the primary analysis. Despite use of this standardized outcome, the primary analysis still found a high degree of heterogeneity in the reported incidence of stroke between studies.

There may be a number of reasons for this heterogeneity. Firstly, the proportion of patients with modifiable cardiovascular risk factors varied between patient cohorts. Meta-regression suggested that a history of cerebrovascular events was associated with a higher incidence of stroke during follow-up. This finding was not unexpected since history of previous stroke or TIA is an established risk factor for subsequent stroke.[24] Interestingly, meta-regression did not demonstrate associations between hypertension, diabetes or current smoking with the incidence of stroke. This might be interpreted as being unexpected given that these are well recognised risk factors for ischaemic stroke in the general population.[24] It should be noted that these analyses were unable to consider the degree of control of these risk factors and

therefore do not account for the response of the risk factors to the treatment patients received. It is also possible that as a result of aggregation bias any possible association between cardiovascular risk factors and stroke within study cohorts may not be reflected by meta-regression. Heterogeneity in how these risk factors were defined may have also contributed to these findings.

Secondly, variation in the incidence of stroke may be explained by differences in the age of patients and geographical regions they were recruited from. The reported average age of patient cohorts varied by 18 years. After removal of one study[12] this variation reduced to less than 10 years with no significant change in the results. Thus, although age may explain some of the observed variation it is unlikely to have been a major contributor. Geographic factors may have also contributed to some variation although this was difficult to assess given that this review included studies from more than seven countries.

Finally, variation in the incidence of stroke may be explained by variation in the prescription of components of medical management. Meta-regression suggested that a higher prescription of anti-platelet medications and statins was associated with a lower incidence of stroke. These findings are consistent with results from previous RCTs which have demonstrated reductions in the risk of stroke with the prescription of these medications.[8-10] Meta-regression did not show a statistically significant correlation between the prescription of antihypertensive drugs and the incidence of stroke. Previous RCTs have demonstrated clear reductions in the incidence of stroke with the prescription of ACEI and ARBs and thus it is possible that the results of this analysis were impacted by the confounding factors discussed above and the small number of studies able to be included.[8-10] Variation in the prescription of cardiovascular medications may also partially explain the higher incidence of stroke reported in patients with CLI compared to those with IC. Three studies reported a lower prescription of anti-hypertensive drugs, anti-platelet medications and statins in patients with CLI than in

those with IC. Prior cerebrovascular events were also more common in patients with CLI than those with IC which also likely contributed to the higher incidence of stroke in these patients.

It has been reported that PAD patients have suboptimal prescription of cardiovascular medications and this is supported by the findings of this review.[11] Half of all studies reported a baseline prescription of anti-hypertensive drugs of <50%, whilst rates of hypertension were reported to be as high as 89%. This discrepancy suggests potential barriers in the prescription of preventative medications. Two national surveys[25, 26] have suggested that awareness about the high risk of cardiovascular events amongst PAD patients and the benefits of prescribing medical management are generally low amongst both patients and clinicians. Although current PAD guidelines emphasize the importance of prescribing these medications, there may be a lack of widespread adoption of these guidelines outside the specialist domain and lack of effective means to implement evidence based practice. PAD patients usually present at an advanced age and suffer a high burden of co-morbid disease, hence concerns about polypharmacy may also contribute to the low prescription of preventative medications.[12]

The findings of this review should be considered in the context of several limitations. Firstly, there was qualitative heterogeneity in the methods of patient recruitment, population demographics and definitions of cardiovascular risk factors. Secondly, as a result of varying periods of follow-up, only studies reporting the incidence of stroke as events per PY were included in the quantitative analyses. This limited the quantitative analysis to six studies and meta-regression to three. A larger number of studies would have provided greater confidence in the findings. Finally, as this review predominantly analyzed cohort studies using meta-regression, all findings are observational, not adjusted for potential confounders and possibly subject to aggregation bias.

In conclusion this review suggests that low prescription of cardiovascular medications, particularly antiplatelet agents and statins, contributes to the high reported incidence of stroke in PAD patients. Effective, evidence based methods are needed to achieve better implementation of medical management amongst PAD patients. This may include encouraging patients to take a more active role in their self-management[25, 27] and further encouraging physicians to implement guideline recommended medical management.[26, 28] Further studies are required to assess which techniques can best achieve effective implementation of medical management in PAD patients.

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None.

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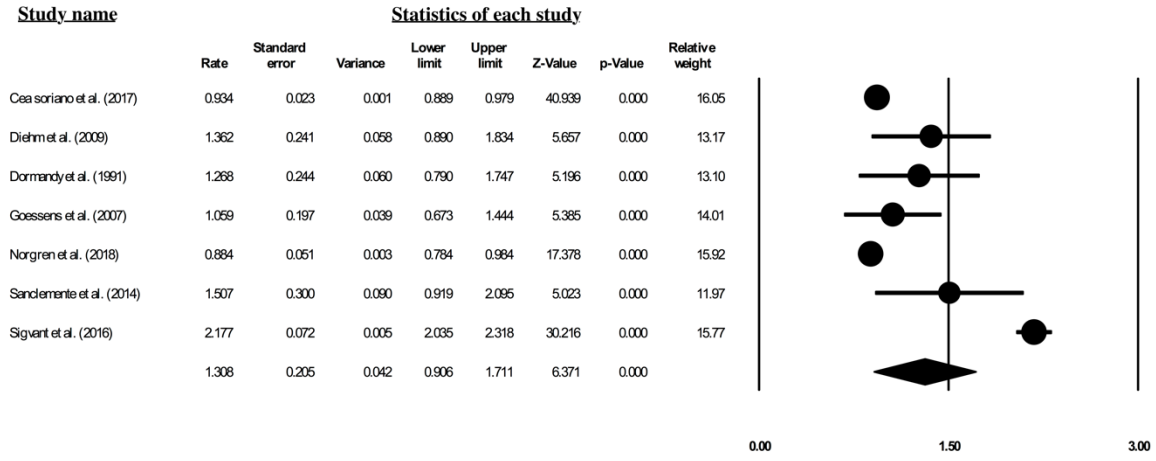

Figure 1: Incidence of stroke for patients with symptoms of PAD. Circles indicate the incidence of stroke in events per 100 PY and horizontal lines indicate the 95% CI for each study. The diamond represents the incidence of stroke for patients with PAD symptoms (Incidence 1.31 per 100 PY, 95% CI 0.91-1.71, I^2 97.89%) calculated with random effects meta-analyses after combining the patients with IC or CLI alone in each study.

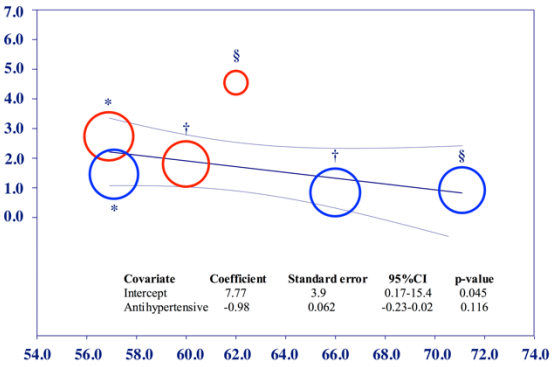

Figure 2A

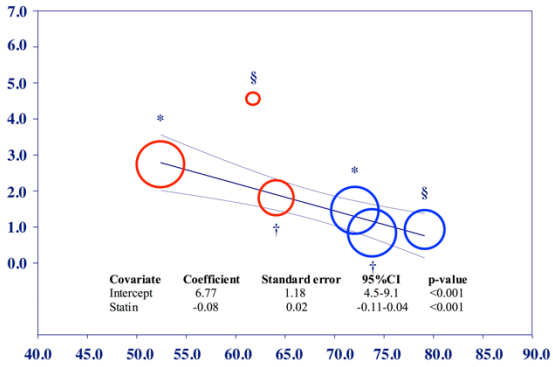

Figure 2B

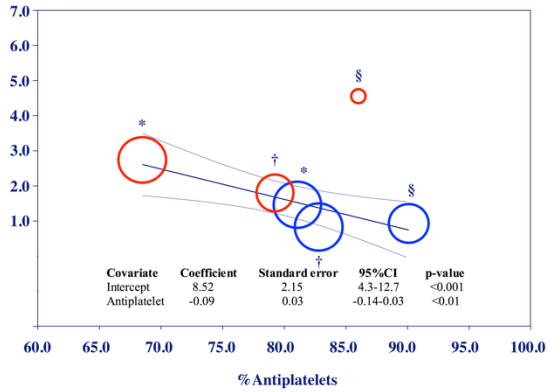

Figure 2C

Figure 2: Meta-regression examining the association of antihypertensive drugs (2A), antiplatelet medication (2B) and statin (2C) prescription with the incidence of stroke. Y-axis is the incidence of stroke in events per 100 PY, X-axis is the proportion of patients prescribed medications at baseline. Circles represent individual study subgroups. Blue circles represent cohorts with IC alone and red circles represent cohorts with CLI alone. Size of the circle is representative of the relative weighting of each cohort. Central line represents the linear regression equation and outer lines represent the 95% CI.

*Sigvant et al.; †Norgren et al.; §Sanclemente et al.

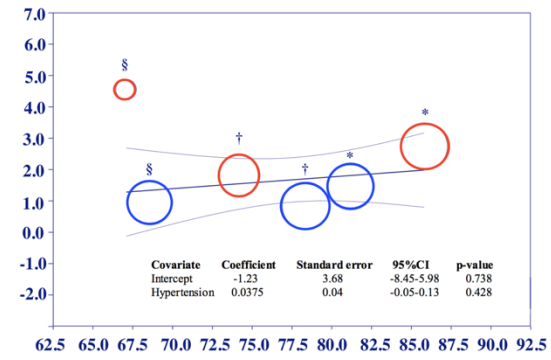

Figure 3A %Hypertension

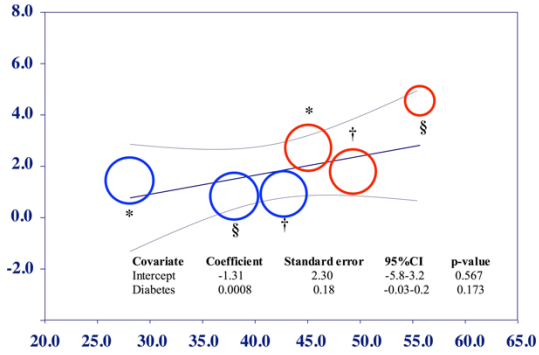

Figure 3B %Diabetes

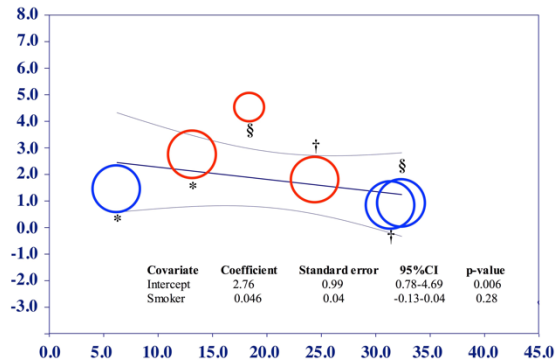

Figure 3C %Current smoking

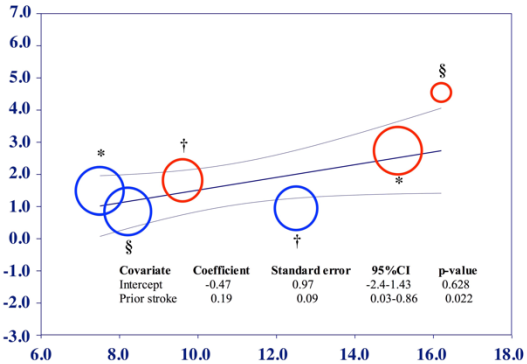

Figure 3D %Prior cerebrovascular event

Figure 3: Meta-regression examining the association of hypertension (3A), diabetes (3B), current smoking (3C) and prior cerebrovascular event (3D) with incidence of stroke. Y-axis is the incidence of stroke in events per 100 PY, X-axis is the proportion of patients with the risk factor at baseline. Circles represent individual study subgroups. Blue circles represent cohorts with IC and red circles represent cohorts with CLI. Size of the circle is representative of the relative weighting of each cohort. Central line represents the linear regression equation and outer lines represent the 95% CI.

*Sigvant et al.; †Norgren et al.; §Sanclemente et al

Table 1: Proportion of patients with cardiovascular risk factors and proportion prescribed anti-hypertensive, anti-platelet and statin medications within included studies.

Study	PAD subgroup	%DM	%HTN	%Prior CVE	%Current smoker	%Anti-hypertensive	%Anti-platelet	%statin
Sigvant et al.(2016)[12]	IC	28.1	81.2	7.5	6.2	57.1	81.1	72.5
	CLI	45.1	85.8	15.1	13.1	56.9	68.5	52.4
Sanclemente et al.(2014)[13]	IC	42.7	68.6	12.5	32.4	71.1	90.1§	79.1
	CLI	55.7	67.1	16.2	18.4	62.0	86.0§	61.8
Norgren et al.(2018)[21]	IC	38.0	78.4	8.2	31.4	66.0	82.8	73.8
	CLI	49.3	74.2	9.6	24.4	60.0	79.3	64.1
Stansby et al.(2011)[19]	IC	20.0	73.8	7.0	38.7	32.4	70.1	44.4
Soga et al.(2010)[14]	IC	38.0	57.0	17.0	NR	10.0	92.0†	11.0
Dormandy et al.(1991) [20]	IC	14.1	56.5	8.5	70.1	13.0§	NR‡	NR
Westin et al.(2014) [15]	CLI	60.0	83.0	19.0	NR	NR	87.0	65.0
Goessens et al.(2007)[18]	IC/CLI	8.0	51.0	12.0	59.0	21.0*	53.0§	25.0§
Cea Soriano et al.(2017)[22]	IC/CLI	18.9	NR	9.1	31.8	27.4	48.7	31.0
Jones et al.(2015)[16]	IC/CLI	40.6	89.3	25.2	30.6	NR	NR	74.4
Wisman et al.(2012)[17]	IC/CLI	22.6	38.6	10.2	60.0	NR	50.40†	NR
Diehm et al.(2009)[23]	IC/CLI	38.3	82.1	NR	18.2	NR	NR	NR

The number of decimal places in the included studies varied. Where possible data has been reported consistently in the table with rounding up of numbers where appropriate. *ACEI only; †Aspirin only; ‡Excluded all patients on antiplatelet therapy; §Did not define which medications constituted antihypertensive, anti-platelet or lipid lowering therapy.

Abbreviations: NR-not reported DM-diabetes, HTN-hypertension, CVE-cerebrovascular event, PAD-peripheral artery disease, IC-intermittent claudication, CLI-critical limb ischemia.