Temporal trends in the incidence, treatment patterns, and outcomes of coronary artery disease and peripheral artery disease in the United Kingdom, 2006-2015

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Abstract

Aims: Most reports estimating national incidence rates of coronary (CAD) and peripheral arterial disease (PAD) have focused on stable outpatients or acute or elective hospital admissions, but not on the overall burden of disease. In this study, we report the changing trends in the population level incidence of CAD and PAD respectively from 2006 to 2015, statin utilisation for secondary prevention and survival outcomes using multiple nationally representative data sources from the UK (primary care encounters, hospital admissions and procedure level data).

Methods and results: A nationally representative study of linked primary and secondary care electronic health records of 4.6 million individuals from the UK. We calculated crude and standardised annual incidence rates separately for CAD and PAD. Statin use for secondary prevention, trends in annual major vascular event rates, and mortality between 2006 and 2015, were estimated for CAD and PAD respectively. We identified 160,376 and 70,753 patients with incident CAD and PAD respectively. The age and sex-standardised incidence of CAD was similar in 2006 (443 per 100,000 person years [pyrs]) and 2015 (436 per 100,000 pyrs; adjusted incidence rate ratio [IRR] 0.98, 95%CI 0.96-1.00). By contrast, there was a 15% decline in the standardised incidence of PAD (236 per 100,000 pyrs in 2006 to 202 per 100,000 pyrs in 2015; adjusted IRR 0.85, 95%CI 0.82-0.88). The proportion of incident CAD and PAD patients prescribed long-term statins, was only 66% and 55% respectively and was less common amongst women, patients aged >70 years, with heart failure, chronic lung disease or depression. CV mortality declined by 43% for incident CAD (adjusted IRR: 0.57, 95%CI: 0.50-0.64) between 2006 and 2015 but did not decline for incident PAD (adjusted IRR: 0.84, 95%CI: 0.70-1.00).

Conclusion and Relevance: In the UK, the standardised incidence of CAD appears stable but mortality rates are falling whereas the standardised incidence of PAD is falling but mortality rates are not.

Introduction

For the past four decades, high-income countries have experienced a tremendous decline in the standardised incidence rates of atherosclerotic cardiovascular disease (ASCVD) and cardiovascular (CV) mortality.[1–6] Nevertheless, ASCVD remains one of the leading causes of death and disability-adjusted life-years.[7–9] The clinical spectrum of ASCVD is wide and can be broadly categorised into those involving the coronary arteries (CAD), other vascular beds (e.g., peripheral arterial disease-PAD) or both.[10,11] Estimating the population level incidence of ASCVD stratified by the involvement of vascular beds may help inform health policy, as resource utilisation and economic burden related to management may be influenced by the type of vascular beds involved.[12,13]

Most previous studies estimating the incidence of CAD have included either chronic ischemic heart disease from general practice (GP) consultations or acute myocardial infarction (AMI) from hospital admissions. [8, 12–14] Previous studies have shown that failure to use linked primary and secondary care data can lead to a substantial (25-50%) underestimate of the burden of CAD.[17] Therefore, analyses of clinical encounters across the entire spectrum of health care services (both inpatient and outpatient) are required to capture the full burden of CAD.

Peripheral arterial disease (PAD) is reported to affect about 13% of people aged greater than 50 years in Western Europe and North America.[10,18,19] In spite of its high prevalence and poor prognosis, PAD attracts less attention in terms of research, early detection, and treatment. [20,21] There is a paucity of PAD data in terms of geographic and secular trends in the incidence, patient characteristics, treatment patterns, and survival.

Accordingly, we investigated the changing incidence of CAD and PAD respectively from 2006 to 2015, using multiple data sources (GP consultations, hospital admissions and procedure level data) that are representative of the UK population. We also investigated the regional variations in the incidence, trends in cardiovascular (CV) risk factors, statin use for secondary prevention, trends in annual major

vascular event rates and mortality among patients with incident CAD and PAD respectively, from 2006 to 2015.

Methods

Data source

Primary care records from general practitioners (GPs) caring for about 9% of the UK population (about 6 million people) were obtained from the Clinical Practice Research Datalink (CPRD) covering the period between January 1st, 1986 to December 31st, 2016.[22] Data from CPRD were linked to the hospital episode statistics (HES), which contains in-patient diagnostic and procedural records, and to the Office of National Statistics (ONS) for information on the date and cause of death.

Study population

People aged at least 18 years old with CAD or PAD were identified from CPRD using READ codes, from HES using International Classification of Diseases, tenth revision (ICD-10) codes and from Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) revision 4.6 for codes for coronary and peripheral revascularisations (Supplementary Appendix; Tables S4-S5). READ codes used in CPRD are the standard clinical terminology system used in General Practice in the UK. READ codes gives detailed clinical coding of multiple patient features such as occupation; social circumstances; ethnicity and religion; clinical signs, symptoms and observations; laboratory tests and results, medications and diagnoses.[23] Patients with a prior diagnosis (before 1st January, 2006) of CAD or PAD (prevalent disease) were excluded for incidence calculation of CAD or PAD respectively. The incident diagnosis was defined as the first record of diagnosis in the primary care or hospital admission records. Incident cases (for both CAD and PAD) formed the base cohort for analyses of statin prescribing (Statin cohort) and HES linkage (Complications cohort) (Supplementary Figures S1 and S2)

The investigation of statin use and its predictors was restricted to patients with incident CAD and PAD aged greater than 40 years who had complete follow-up data for at least one year from the date of diagnosis. Those transferring out of a CPRD participating GP practice or whose last collection date was

within a year of diagnosis were excluded (Supplementary Figure S1 and S2). Patients who could be linked to HES and ONS (~ 60% of patients in CPRD) were used to evaluate trends in the annual rates of major vascular events and mortality between 2006 and 2015.

Patient characteristics

Common co-morbidities were identified using CPRD READ codes. Socioeconomic status was reported using Index of Multiple Deprivation (IMD) 2015 quintiles, with quintile 1 being the least and quintile 5 the most deprived. Information on geographic region, ethnicity, other relevant clinical variables such as body mass index and baseline medications (prior to incident diagnosis) including antiplatelet therapy, statins, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB), beta-blockers, calcium channel blockers and other vasodilators were also analysed.

Outcomes

The individual trends in the incidence of CAD and PAD between 2006 and 2015 were the primary outcomes of interest. The overall proportion of patients on a stable treatment regimen of statins, stratified by the type of vascular disease (CAD and PAD) and co-morbidities are described. A stable treatment regimen of statins was defined as prescriptions for more than 75% (273.75/365.25 days) of the first year after incident diagnosis. Finally, we present trends (from 2006 to 2015) in the annual age and sex adjusted event rates of complications including, myocardial infarction, stroke, hospitalisation for bleeding, CV hospitalisation (planned and unplanned), premature CV mortality (defined as death <75 years), CV mortality and all-cause mortality among patients with incident CAD and incident PAD.

Statistical analyses

Baseline characteristics were expressed using mean ± standard deviation for continuous variables and percentages for categorical variables. Baseline characteristics were stratified by sex and three time periods of diagnosis (2006-07, 2010-11 & 2014-2015). We calculated sex and age specific (5 year intervals) incidence rates per 100,000 person years for each year. For the denominator the total person years in each year was calculated in 5 year age intervals. Standardised incidence rates were

computed individually for CAD and PAD on the basis of 2013 European standard population distribution of age and sex.[24] We employed Poisson regression models to estimate adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for quantifying the change in the incidence rates between 2006 and 2015. [25]

The proportion of incident CAD and incident PAD patients on statins, stratified by baseline co-morbidities were analysed. Logistic regression model was used to investigate the predictors of statin use (or non-use) after an incident diagnosis, separately for patients with incident CAD and patients with incident PAD. We adjusted the model for age, sex, year of diagnosis, and relevant co-morbidities including, diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), depression, dementia, history of malignancy, chronic liver disease (CLD), prior history of PAD or CAD, and prior history of ischemic stroke.

The event rates of complications were defined as the annual rate of occurrence (per 100 person years) of the complications during the first year of follow up. Total follow-up was calculated from the time of incident CAD or PAD diagnosis in CPRD or HES and the date of the outcome (i.e. first event for each outcome of interest), death (when it is not the outcome), date of disenrollment in the practice or of the practice in CPRD, or the end of follow up (one year from the date of incident diagnosis). Rates were age and sex standardised to 2013 European Standard Population. For all the complications, we computed adjusted IRR and 95% CI to estimate changes in the event rates over time (2006 to 2015), separately for incident CAD and incident PAD patients. We performed sensitivity analyses for event rates and mortality in incident PAD patients by excluding those with history of concomitant CAD (Please see Supplementary Appendix for details).

Ethics approval

The study was approved by the Independent Scientific Advisory Committee of the Medicine and Healthcare Products Regulatory Agency (MHRA) for database research (protocol number: 18_057R). The data are anonymous, and the requirement for informed consent was therefore waived.

Role of funding source

The present work was funded by a research grant from Bayer. VS and JKQ had full access to all the data and all authors made the final decision to publish. We had two Bayer representatives that were engaged in the project: KB and JBB. Both representatives participated to the funding of the study. KB and JBB were not involved in the data analyses and the results interpretations. No Bayer drug was involved in the study limiting risk of potential conflict of interest.

Results

From 15.4 million patient records, 4,618,735 people who were alive on Jan 1, 2006 were identified of whom 184,814 had prevalent CAD and 52,667 had prevalent PAD (Supplementary Figure S1 and S2). Between 2006 and 2015, 160,376 incident cases of CAD (base-cohort for CAD) and 70,753 incident cases of PAD (base-cohort for PAD) were identified. Using multiple data sources, compared to using primary care encounters only, we identified an additional 38,207 cases of incident CAD (25% increase) and 4,500 incident cases of PAD (7% increase) (Supplementary Figure S3).

Incidence of CAD and PAD

Across the UK, there was no change in the age- and sex-standased incidence of CAD between 2006 and 2015 [443 per 100,000 person years in 2006 and 436 per 100,000 person years in 2015; adjusted IRR 0.98, 95% CI 0.96 - 1.00] (Figure 1). Similarly, there was no change in the crude incidence for CAD from 439 per 100,000 person years in 2006 to 450 per 100,000 person years in 2015 (IRR 1.02, 95% CI 1.00 - 1.05) (Figure 2). The age-standardised incidence of CAD was higher amongst men (650 per 100,000 person years) than women (370 per 100,000 person years) (Supplementary Figure S3 and S4). The trends in standardised incidence of CAD among men and women remained relatively stable from 2006 to 2015 (adjusted IRR for men 1.00, 95% CI 0.96 – 1.03; adjusted IRR for women 0.97, 95% CI 0.93 – 1.00) (Supplementary Figures S4 and S5). In keeping with the overall trend for CAD (which included chronic ischemic heart disease and AMI), the age- and sex-adjusted incidence rates for AMI were similar in 2006 and 2015 (adjusted IRR 0.99, 95% CI 0.95 – 1.03). We observed a transient

increase in the age- and sex-standardised incidence of CAD peaking in 2008, similar to an earlier report on AMI in the UK (please see supplementary appendix for details).[14]

There was a 15% decline in the age- and sex-standardised incidence of PAD from 236 per 100,000 person years in 2006 to 202 per 100,000 person years in 2015 (adjusted IRR 0.85, 95% CI 0.82 - 0.88) (Figure 1). In line with the standardised rates, there was 10% decline in the crude incidence of PAD – falling from 234 per 100,000 person years in 2006 to 211 per 100,000 person years in 2015 (IRR 0.90, 95% CI 0.87 - 0.93) (Figure 2). The decrease in the standardised incidence of PAD over time was consistent across most of the age groups. Age-standardised PAD incidence was higher in men (300 per 100,000 person years) than women (156 per 100,000 person years). Reductions in the age-standardised incidence of PAD in women from 2006 to 2015 (adjusted IRR for women 0.86, 95% CI 0.81 – 0.91) exceeded those for men (adjusted IRR for men 0.93, 95% CI 0.89 – 0.97) (Supplementary Figures S4 and S5).

Regional variations in the standardised incidence of CAD in England which were apparent in 2006, particularly the difference between the north and south, were lower in 2015 (Supplementary Figure S6). There was a substantial decline in the age and sex standardised incidence of PAD in the Northwest and North-eastern regions of England between 2006 and 2015 (>30% reduction in the standardised incidence of PAD) (Supplementary Figure S7).

Patient characteristics stratified by sex and time period

The mean age at diagnosis for CAD and PAD was similar and did not change between 2006 and 2015 (Tables 1 and 2). Patients diagnosed in more recent years were more likely to be obese, have DM, CKD, dyslipidaemia and a history of cancer. Women were slightly older and had more co-morbidities than men. The use of statins and ACE inhibitors (for primary prevention) prior to an incident diagnosis increased substantially from 2006 to 2015 in both CAD and PAD (Table 1 and Table 2).

Predictors of statin non-use for secondary prevention

After applying the eligibility criteria for statin analyses, we included 121,011 incident cases of CAD and 49,426 incident cases of PAD (Statin cohort) (Supplementary Figures S1 and S2, Supplementary Table S3). The proportion of incident cases of CAD and PAD who qualified as receiving a stable statin treatment regimen were 66% and 55% respectively. Notably, over 40% of women and 50% of elderly (age > 70 years) with established ASCVD (CAD and PAD), were not on a stable statin regimen (Table 3 and Supplementary Table S2). In a multivariable logistic regression model, for patients with CAD, failure was associated with female sex (odds ratio [OR] 0.67, 95% CI 0.65 - 0.69), heart failure (OR 0.73, 95% CI 0.69 – 0.78), age >70 years (OR 0.87, 95% CI 0.84 - 0.90), COPD (OR 0.82, 95% CI 0.78 – 0.86) and depression (OR 0.86, 95% CI 0.81 – 0.90) and was similar for PAD (Figure 3). Statin uptake did not increase significantly between 2006 and 2015 (Supplementary appendix Figure S7).

Trends in the annual event rates of major vascular events and mortality from 2006 to 2015

The overall annual age- and sex-standardised rates for MI were higher for CAD than for PAD but the reverse was true for ischemic stroke (Table 4). The age- and sex-standardised annual CV mortality was similar for CAD and PAD. However all-cause mortality was higher for PAD (9.2 per 100 person years, 95% CI 9.0-9.5) compared to incident CAD (8.2 per 100 person years, 95% CI 8.1-8.4). Age-adjusted rates of MI and bleeding requiring hospitalisation were higher in men than in women for both CAD and PAD, whereas the rate of ischemic stroke for those with incident CAD group was higher in women (Table 4). Morbidity and mortality were similar for patients with PAD whether or not they had CAD (Supplementary Figure S10 and Supplementary Table S4).

Comparing 2006 vs 2015, the annual age- and sex-adjusted rate of MI fell by 48% in those with incident CAD (adjusted IRR 0.52, 95% CI 0.43 - 0.63) and 56% in those with incident PAD (adjusted IRR 0.44, 95% CI 0.32 – 0.61) (Figure 4). The greatest reduction in the annual event rates of stroke were observed in incident PAD patients [PAD: adjusted IRR 0.63 (0.45 - 0.89); CAD adjusted IRR 0.84 (0.66 - 1.07)]. A marked decline in CV mortality (43%) was observed amongst cases of incident CAD from 2006 to 2015 (adjusted IRR 0.57, 95% CI 0.50 – 0.64) which was less obvious amongst cases of incident PAD

(adjusted IRR 0.86, 95% CI 0.70 – 1.00), with or without concomitant CAD (Figure 4, Supplementary Figure S10-S13). The rate of all-cause mortality fell amongst cases of incident CAD but rose amongst cases of PAD even after adjusting for age and sex.

Discussion

This study of a large nationally representative population in the UK over one decade provides vital insights into the trends in incidence, risk factors, statin use, major vascular complications and mortality of two important clinical spectrums of ASCVD – CAD and PAD.

In contrast to previous studies that have reported a decline until 2010, the incidence of CAD in models standardised for age and sex, in our study, has remained relatively stable between 2006 and 2015.[8,14] The absence of decline in our study versus the findings of previous studies could have been caused by myriad reasons. To begin with, unlike previous studies, we included the entire spectrum of patients with CAD from all possible clinical encounters within the UK health system including chronic ischemic heart disease from GP encounters (READ codes), hospitalisations for AMI (HES codes) and from procedural records for coronary revascularisations (OPCS 4.6 codes). By this process, we identified an additional 38,207 incident CAD patients, a 25% increase (Figure 1), utilizing multiple nationally representative data sources in comparison to conventional case ascertainment using one data source only. Secondly, whilst improvements in primary prevention measures were expected to decrease the incidence of CAD, offsetting trends such as an increase in the prevalence of obesity, dyslipidaemia, diabetes and CKD may have attenuated the decline. Thirdly, previous studies on the incidence of AMI included patients with prior history of chronic ischemic heart disease.[14,16,26] As result of this, some of those patients could have been on CV prevention medications, which in turn may have contributed to the decline in the incidence rates of AMI. Finally, there could have been an increase in the detection of non-ST elevation MI (NSTEMI), attributable to the introduction of high sensitivity troponin (hsTnT) as a diagnostic marker. The European Society Cardiology Study Group on Biomarkers in Cardiology recommended the routine use of hsTnT as a diagnostic biomarker for AMI in 2012,[27] possibly leading

to additional identification of cases since. Data from the other European countries and the United States also have reported an increase in the incidence of NSTEMI.[28–32] Contrary to the trends in CAD, there was a 15% reduction in the standardised incidence of PAD during the study period. The fall in the incidence rates of PAD could be due to policy measures incorporating primary prevention of ASCVD. Moreover, a significant proportion (30 - 50%) of PAD patients have CAD prior to their diagnosis[33], which could have led to an increased uptake of CV medications.

There was a notable shift in the co-morbidity burden over the last decade, especially in patients with incident PAD. Patients diagnosed with PAD in the more recent years (2014-15) were sicker, with a significantly higher proportion of patients with obesity, DM, HLD, CKD, COPD and malignancy, compared to those diagnosed in 2006-07. It is plausible that the rising trends in the CV and non CV co-morbidities from 2006-07 to 2010-11 may be partly related to the differences in coding practices, due to the introduction of new indicators to Quality and Outcomes framework in 2008, a system for the performance management and payment of general practitioners in the National Health service.[34,35] However, it is unlikely that the changes observed in the later part of the study period (2010-11 to 2014-15) are related to a change in coding practice.

Our findings suggest, in spite of consistent evidence from multiple RCTs that statins reduce recurrent CV events in patients with established ASCVD, statins remain underutilized in clinical practice in the UK. A substantial segment of incident CAD (~ 1 out of every 3 CAD patients) and incident PAD (~ 1 out of every 2 PAD patients) patients were not receiving long term statin therapy. These findings are in line with the results of other large studies such as the PURE study and the SHARE study, where 30-40% of patients with established ASCVD in the developed countries were not prescribed with statin.[25, 39, 40] We observed the phenomenon of *"risk treatment paradox"* [39] in our study population i.e*.,* ASCVD patients at higher risk (elderly, female, CHF, COPD and depression) for CV outcomes were less likely to have been prescribed persistent statin therapy by their physicians. Meta-analysis of individual data of 174,000 patients by the Cholesterol Treatment Trialists' (CTT) collaboration, showed significant

reductions in recurrent CV events with statin among elderly patients with pre-existing vascular disease.[40,41] However, we observed an inverse relationship between treatment propensity and age with regard to statins. Among all the variables, female sex was the most significant predictor to have negatively influenced physician prescribing pattern with statins, after accounting for important confounders. Despite compelling evidence of the benefits of statin in women, [42] the reasons for the barriers in clinical practice remains unclear. Female gender has been shown to be a risk factor for statin induced myalgias, which could have led to an early discontinuation. [43]It has also been shown that intense media publicity of exaggerated side effects of statins may have had a negative impact on continuation of statins, with more profound effects on women.[44,45] Our findings shine a spotlight on the necessity to highlight sex specific disparities in the utilisation of statins in clinical practice to patients and physicians, and the imperative to implement additional sex specific strategies to improve CV outcomes for women.

The trends in outcomes from 2006 to 2015 suggest that the reduction in the annual CV event rates and CV mortality in patients with incident CAD outpaced their PAD counterparts (even after excluding patients with concomitant CAD) (Figure 4 and Supplementary Figures S10-S13). The significant decline in recurrent CV events, recurrent CV hospitalisation and CV mortality among patients with incident CAD in the latter part of our study could be a consequence of improvements in treatment, particularly the health care policy measures related to early revascularisation in AMI, and secondary prevention with the introduction of newer pharmacological agents (e.g., newer antiplatelet therapy).[46–48] However, this could also be related to an increase in the frequency of detecting smaller infarcts with less severity after the widespread utilisation of hsTnT. Conversely, in patients with incident PAD, there was no significant reduction in CV mortality over time. There are several potential explanations for this. Our study shows that the prevalence of smoking, one of the most important risk factors for PAD, has not changed over time. In addition to increasing the risk of incident PAD, cigarette smoking has shown to negatively impact functional capacity and increase CV mortality among patients with prevalent PAD. [49]In the UK, a primary care service network was established for evaluation of

symptomatic PAD in primary care in 2009. However, the onset of symptoms in PAD indicates advanced systemic atherosclerosis and the effect of disease modifying CV medications might be less than what is observed in patients with CAD alone. A significant proportion of patients with PAD have established atherosclerosis in other vascular beds which could have an additive or multiplicative effect on CV mortality. However, sensitivity analyses of incident PAD patients excluding those with concomitant CAD demonstrated results comparable to the overall incident PAD patients (Supplementary Figure S10).

Limitations

Our study has several strengths but some limitations. While we hypothesize that the introduction of hsTnT could have led to an overestimation in the incidence of CAD after 2012 (due to an increase in NSTEMI cases), we were not able to perform a stratified analyses by AMI type, as it has been shown that ICD10 subcategory codes, are insufficient to distinguish AMI type. [50]CPRD captures medications that are prescribed to patients. The fact that the patient received a prescription for a medication does not ensure that the patient actually filled or even took the medication. In addition, over-the-counter medication use or medications administered during hospitalisations were not captured. Our analyses was also restricted to the use of statin and not the dosage of statins (high potency statins) which is clinically relevant with the recent changes in guidelines. [51] Only 60% of the CPRD patients eligible for HES and ONS linkage were included for the vascular events and mortality analyses. Another limitation of research using electronic health records includes the potential for misclassification of diseases and of the outcomes. Wherever possible, definitions and algorithms that have been validated in these data sources were preferentially used to identify both the diseases of interest as well as complications. [52–54]

Conclusion

In conclusion, the standardised incidence of CAD appears stable but mortality rates are falling, whereas the standardised incidence of PAD is falling but mortality rates are not. The stable incidence of CAD, despite primary prevention measures, remains an important concern for healthcare policy

planning for an aging population. In the general population, statin use for secondary prevention remains suboptimal and the uptake has not increased in the past decade, necessitating measures to address this gap. Our findings also highlight the importance of identification of PAD early in the course of the disease where disease modifying interventions (e.g., counselling and therapies targeting smoking cessation) may improve CV outcomes.

References

1. Murray CJL, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet. 2013;381:997–1020.

2. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. Heart. 2016;102:1945–52.

3. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980-2009. Eur Heart J. 2013;34:3017–27.

4. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459–544.

5. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. Circ Res. 2017;120:366–80.

6. Editorial: A decline in coronary mortality. Br Med J. 1976;1:58.

7. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70:1–25.

8. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;37:3232–45.

9. Roth GA, Johnson CO, Abate KH, Abd-Allah F, Ahmed M, Alam K, et al. The Burden of Cardiovascular Diseases Among US States, 1990-2016. JAMA Cardiol. 2018;3:375–89.

10. Fowkes FGR, Aboyans V, Fowkes FJI, McDermott MM, Sampson UKA, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol. 2017;14:156–70.

11. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. Heart. 2018;104:284–92.

12. Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. Am J Cardiol. 1998;81:1110–5.

13. Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. Circ Cardiovasc Qual Outcomes. 2010;3:642–51.

14. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. BMJ. 2012;344:d8059.

15. Tran J, Norton R, Conrad N, Rahimian F, Canoy D, Nazarzadeh M, et al. Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. PLoS Med. 2018;15:e1002513.

16. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010;362:2155–65.

17. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013;346:f2350.

18. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116:1509–26.

19. Kalbaugh Corey A., Kucharska-Newton Anna, Wruck Lisa, Lund Jennifer L., Selvin Elizabeth, Matsushita Kunihiro, et al. Peripheral Artery Disease Prevalence and Incidence Estimated From Both Outpatient and Inpatient Settings Among Medicare Fee-for-Service Beneficiaries in the Atherosclerosis Risk in Communities (ARIC) Study. Journal of the American Heart Association. 6:e003796.

20. Moxon JV, Golledge J. The Need for Translational Research to Advance Peripheral Artery Disease Management. Int J Mol Sci. 2015;16:11125–30.

21. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39:763–816.

22. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44:827–36.

23. Metcalfe D, Masters J, Delmestri A, Judge A, Perry D, Zogg C, et al. Coding algorithms for defining Charlson and Elixhauser co-morbidities in Read-coded databases. BMC Med Res Methodol. 2019;19:115.

24. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet. 2018;391:572–80.

25. Frome EL, Checkoway H. USE OF POISSON REGRESSION MODELS IN ESTIMATING INCIDENCE RATES AND RATIOS. Am J Epidemiol. 1985;121:309–23.

26. Wong CX, Sun MT, Lau DH, Brooks AG, Sullivan T, Worthley MI, et al. Nationwide trends in the incidence of acute myocardial infarction in Australia, 1993-2010. Am J Cardiol. 2013;112:169–73.

27. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012;33:2252–7.

28. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008;156:1026–34.

29. Khera S, Kolte D, Aronow WS, Palaniswamy C, Subramanian KS, Hashim T, et al. Non-ST-Elevation Myocardial Infarction in the United States: Contemporary Trends in Incidence, Utilization of the Early Invasive Strategy, and In-Hospital Outcomes. J Am Heart Assoc [Internet]. 2014 [cited 2019 Feb 26];3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4310389/

30. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med. 2011;124:40–7.

31. Jennings SM, Bennett K, Lonergan M, Shelley E. Trends in hospitalisation for acute myocardial infarction in Ireland, 1997-2008. Heart. 2012;98:1285–9.

32. Gierlotka M, Gąsior M, Wilczek K, Wasilewski J, Hawranek M, Tajstra M, et al. Temporal trends in the treatment and outcomes of patients With non-ST-segment elevation myocardial infarction in Poland from 2004-2010 (from the Polish Registry of Acute Coronary Syndromes). Am J Cardiol. 2012;109:779–86.

33. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas J-L, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295:180–9.

34. Doran T, Fullwood C, Gravelle H, Reeves D, Kontopantelis E, Hiroeh U, et al. Pay-for-performance programs in family practices in the United Kingdom. N Engl J Med. 2006;355:375–84.

35. Campbell SM, Reeves D, Kontopantelis E, Sibbald B, Roland M. Effects of pay for performance on the quality of primary care in England. N Engl J Med. 2009;361:368–78.

36. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet. 2011;378:1231–43.

37. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ. 2016;353:i3283.

38. Börsch-Supan A, Brandt M, Hunkler C, Kneip T, Korbmacher J, Malter F, et al. Data Resource Profile: the Survey of Health, Ageing and Retirement in Europe (SHARE). Int J Epidemiol. 2013;42:992–1001.

39. Weiss CO, Varadhan R. Risk-Treatment Paradox in Use of Statins. JAMA. 2004;292:169–169.

40. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

41. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393:407–15.

42. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385:1397–405.

43. Feng Q, Wilke RA, Baye TM. Individualized risk for statin-induced myopathy. Pharmacogenomics. 2012;13:579–94.

44. Schaffer AL, Buckley NA, Dobbins TA, Banks E, Pearson S-A. The crux of the matter: Did the ABC's Catalyst program change statin use in Australia? Med J Aust. 2015;202:591–5.

45. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J. 2016;37:908–16.

46. Hall M, Bebb OJ, Dondo TB, Yan AT, Goodman SG, Bueno H, et al. Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. Eur Heart J. 2018;39:3798–806.

47. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.

48. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–15.

49. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. Rev Cardiovasc Med. 2004;5:189–93.

50. Alexandrescu R, Bottle A, Jarman B, Aylin P. Current ICD10 codes are insufficient to clearly distinguish acute myocardial infarction type: a descriptive study. BMC Health Services Research. 2013;13:468.

51. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation. 2018;CIR0000000000000625.

52. Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). BMJ Open. 2014;4:e005540.

53. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010;60:e128-136.

54. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69:4–14.

Table 1: Baseline characteristics of patients with incident CAD (2006 -2015)

	All patients	Sex		Time period		
		Male (n=91,668)	Female (n=68,708)	2006-2007 (n=28,591)	2010-2011 (n=35,287)	2014-2015 (n=25,269)
Age						
Age (years) (SD)	69·1 (13·7)	66·6 (13·2)	72·6 (13·7)	69·2 (13·5)	69·2 (13·7)	68·8 (13·8)
Age > 75 years	60,977 (38·0%)	27,232 (29·7%)	33,744 (49·1%)	11,016 (38·5%)	13,361 (37·9%)	9,407 (37·3%)
Sex						
Women	68,708 (42·8%)	N/A	N/A	12,366 (43·2%)	15,191 (43·1%)	10,530 (41·7%)
Men	91,668 (57·2%)	N/A	N/A	16,225 (56·8%)	20,096 (56·9%)	14,739 (58·3%)
Ethnicity						
White	43,298 (52·1%)	24,668 (56·9%)	18,629 (43·0%)	6,457 (14·1%)	10,141 (23·4%)	7,281 (16·8%)
Missing data	48·80%	48·80%	48·80%	59·70%	47·20%	43·70%
Socio economic quintile*						
Quintile 1	23,010 (20·0%)	13,389 (20·8%)	9,621 (19·0%)	4,319 (19·5%)	5,197 (20·4%)	3,475 (20·9%)
Quintile 2	26,128 (22·8%)	14,808 (23·1%)	11,320 (22·4%)	5,174 (23·4%)	5,842 (22·9%)	3,749 (22·6%)
Quintile 3	24,173 (21·1%)	13,574 (21·1%)	10,599 (21·0%)	4,586 (20·7%)	5,304 (20·8%)	3,483 (30·0%)
Quintile 4	22,569 (19·7%)	12,294 (19·1%)	10,275 (20·3%)	4,293 (19·4%)	4,895 (19·2%)	3,274 (19·7%)
Quintile 5 (most deprived)	18,927 (16·5%)	10,189 (15·9%)	8,738 (17·3%)	3,780 (17·1%)	4,261 (16·7%)	2,638 (15·9%)
Body Mass Index						
Mean kg/m2 (SD)	27·2 (5·9)	27·9 (5·3)	27·7 (6·5)	27·4 (5·7)	27·9 (5·9)	28·1 (6·0)
Underweight	2,710 (2·9%)	851 (1·7%)	1,859 (4·5%)	542 (3·0%)	615 (3·0%)	340 (2·6%)
Normal	27,096 (29·2%)	13,877 (26·9%)	13,218 (32·2%)	5,605 (31·2%)	5,890 (28·7%)	3,713 (28·5%)
Overweight	34,722 (37·4%)	21,615 (41·8%)	13,107 (31·9%)	6,793 (37·9%)	7,736 (37·6%)	4,748 (36·4%)
Obesity	25,054 (27·0%)	14,003 (27·1%)	11,050 (26·9%)	4,512 (25·1%)	5,562 (27·1%)	3,753 (28·8%)
Morbid obesity	3,200 (3·5%)	1,329 (2·6%)	1,871 (4·6%)	495 (2·8%)	749 (3·6%)	494 (3·8%)
Missing data	42·00%	43·00%	40·00%	37·00%	42·00%	48·00%
Smoking						
Current smoker	38,335 (23·9%)	21,323 (23·3%)	17,009 (24·8%)	6,702 (23·4%)	8,537 (24·2%)	6,051 (24·0%)
Ex-smoker	43,431 (26·5%)	27,524 (30·0%)	15,817 (23·0%)	8,565 (30·0%)	9,558 (27·1%)	5,955 (23·6%)
No	74,136 (46·2%)	40,512 (44·2%)	33,624 (48·9%)	12,742 (44·6%)	16,170 (45·8%)	12,400 (49·1%)
Missing data	4,564 (2·9%)	2,309 (2·5%)	2,255 (3·3%)	582 (2·0%)	1,023 (2·9%)	863 (3·4%)
Co-morbidities						
Diabetes Mellitus	30,611 (19·0%)	17,668 (19·3%)	12,941 (18·8%)	4,552 (15·9%)	6,658 (18·8%)	5,684 (22·5%)
Hypertension	100,037 (62·4%)	52,187 (56·9%)	47,847 (69·6%)	17,567 (61·4%)	21,812 (61·9%)	15,779 (62·4%)
Dyslipidaemia	33,358 (20·8%)	18,379 (20·0%)	14,979 (21·8%)	5,278 (18·5%)	7,451 (21·4%)	5,849 (23·1%)
Atrial fibrillation	18,398 (11·5%)	9,949 (10·9%)	8,449 (12·3%)	2,984 (10·4%)	4,023 (11·4%)	3,011 (11·9%)
Chronic Heart Failure	11,818 (7·4%)	6,218 (6·8%)	5,600 (8·2%)	2,297 (8·0%)	2,484 (7·0%)	1,851(7·3%)
Stroke	13,279 (8·3%)	6,967 (7·6%)	6,312 (9·2%)	2,033 (7·1%)	3,067 (8·7%)	2,201 (8·7%)
Peripheral arterial disease	10,810 (6·7%)	6,747 (7·4%)	4,063 (5·9%)	1,890 (6·6%)	2,499 (7·1%)	1,561 (6·2%)
Chronic Kidney Disease	26,001 (16·2%)	11,616 (12·7%)	14,385 (20·9%)	2,852 (10·0%)	6,351 (18·0%)	4,311 (17·1%)
Chronic Obstructive Pulmonary Disease	14,848 (9·3%)	8,352 (9·1%)	6,494 (9·5%)	2,431 (8·5%)	3,340 (9·5%)	2,479 (9·8%)
Depression	13,034 (8·1%)	5,966 (6·5%)	7,068 (10·3%)	2,485 (8·7%)	2,822 (8·0%)	1,952 (7·7%)
Cancer	13,715 (8·6%)	7,402 (8·1%)	6,312 (9·2%)	2,109 (7·4%)	3,164 (9·0%)	2,437 (9·6%)
High bleeding risk	12,558 (12·2%)	7,169(7·8%)	5,389 (7·8%)	2,044 (7·1%)	2,712 (7·7%)	2,173 (8·6%)
Baseline Medications						
Statins	62,571 (39·0%)	35,608 (38·8%)	26,963 (39·2%)	9,838 (34·4%)	14,265 (40·4%)	10,526 (41·7%)
At least one antiplatelet therapy	52,439 (32·7%)	28,108 (30·7%)	24,331 (35·4%)	9,871 (34·5%)	11,904 (33·7%)	7,103 (28·1%)
ACEI/ARB	60,419 (37·8%)	32,900 (35·9%)	27,518 (40·1%)	9,627 (33·7%)	13,572 (38·5%)	9,822 (38·7%)
Diuretics	49,773 (31·0%)	22,207 (24·2%)	27,566 (40·1%)	10,016 (35·0%)	10,841 (30·7%)	6,678 (26·4%)
Beta-blockers	34,567 (21·5%)	17,725 (19·3%)	16,841 (24·5%)	6,463 (22·6%)	7,366 (20·9%)	3,756 (21·9%)
Calcium channel blockers	17,911 (11·1%)	8,887 (9·7%)	9,024 (13·1%)	3,632 (12·7%)	3,916 (11·7%)	2,294 (9·1%)
Vasodilators	14,894 (9·3%)	7,708 (8·4%)	7,186 (10·5%)	3,008 (10·5%)	3,138 (8·9%)	2,121 (8·4%)

**Data available on socioeconomic status was available only for patients eligible for HES linkage n=114,807; BMI: Underweight: <18·5 kg/m2; Normal: 18·5-24·9 kg/m2, Overweight: 25-29·9 kg/m2, Obesity: 30-39·9 kg/m2, Morbid obesity: > 40 kg/m2; ACEI/ARB; Angiotensin Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker*

Table 2 Baseline characteristics of patients with incident PAD (2006 -2015)

	All patients	Sex		Time period		
		Male (n=42,663)	Female (n=28,090)	2006-2007 (n=15,359)	2010-2011 (n=14,812)	2014-2015 (n=11,132)
Age						
Age, mean in years (SD)	70·4 (13·8)	69·5 (12·5)	71·8 (15·5)	71·0 (13·5)	70·0 (14·0)	70·3 (13·8)
Elderly (age > 75)	30,126 (42·6%)	15,930 (37·3%)	14,196 (50·5%)	8,493 (55·3%)	6,035 (40·7%)	4,584 (41·2%)
Sex						
Women	28,090 (39·7%)	N/A	N/A	6,190 (40·3%)	5,926 (40·0%)	4,228 (38·0%)
Men	42,663 (60·3%)	N/A	N/A	9,169 (59·7%)	8,886 (60·0%)	6,904 (62·0%)
Ethnicity						
White	19,848 (57·0%)	12,105 (57·1%)	7,743 (56·4%)	3,269 (57·3%)	4,380 (57·0%)	3,527 (56·8%)
Missing data	51%	51%	51%	61%	48%	45%
Socioeconomic quintile						
Quintile 1	8,441 (18·5%)	5,059 (18·6%)	3,382 (18·4%)	1,827 (18·0%)	1,850 (19·4%)	1,219 (18·1%)
Quintile 2	10,195 (22·4%)	6,142 (22·6%)	4,053 (22·1%)	2,248 (22·1%)	2,117 (22·2%)	1,512 (22·5%)
Quintile 3	9,591 (21·0%)	5,716 (21·0%)	3,875 (21·1%)	2,085 (20·5%)	2,054 (21·5%)	1,419 (21·1%)
Quintile 4	9,537 (20·9%)	5,686 (20·9%)	3,851 (21·0%)	2,141 (21·1%)	1,901 (19·9%)	1,529 (22·7%)
Quintile 5 (most deprived)	7,815 (17·2%)	4,611 (16·9%)	3,201 (17·5%)	1,867 (18·4%)	1,618 (17·0%)	1,057 (15·7%)
Body Mass Index						
Mean, kg/m2 (SD)	26·9 (5·7)	27·1 (5·2)	26·5 (6·3)	26·6 (5·5)	26·9 (5·7)	27·4 (6·0)
Underweight	1,737 (4·1%)	643 (2·5%)	1,094 (6·4%)	376 (3·8%)	345 (3·9%)	233 (4·0%)
Normal	14,859 (34·9%)	8,382 (32·7%)	6,477 (38·1%)	3,589 (36·6%)	3,073 (34·6%)	1,863 (32·0%)
Overweight	15,321 (36·0%)	10,147 (39·6%)	5,174 (30·4%)	3,530 (36·0%)	3,190 (35·9%)	2,090 (35·9%)
Obesity	9,653 (22·7%)	5,941 (23·2%)	3,712 (21·8%)	2,124 (21·7%)	2,066 (23·3%)	1,420 (24·4%)
Morbid obesity	1,737 (4·1%)	489 (1·9%)	561 (3·3%)	191 (2·0%)	204 (2·3%)	209 (3·6%)
Missing data	40%	40%	40%	36%	40%	48%
Smoking						
Current smoker	21,835 (29·9%)	12,433 (29·1%)	8,751 (31·2%)	4,269 (27·8%)	4,708 (31·8%)	3,338 (30·0%)
Ex-smoker	19,632 (27·8%)	13,367 (31·3%)	6,265 (22·3%)	4,465 (29·1%)	4,128 (27·9%)	2,770 (24·9%)
Never smoked	129,437 (41·6%)	16,611 (38·9%)	12,826 (45·7%)	6,457 (42·0%)	5,884 (39·7%)	4,959 (44·6%)
Missing data	499 (0·7%)	251 (0·6%)	248 (0·9%)	168 (1·1%)	92 (0·6%)	65 (0·6%)
Co-morbidities						
Diabetes Mellitus	17,561 (24·8%)	11,309 (26·5%)	6,251 (22·3%)	3,389 (22·1%)	3,455 (23·3%)	3,368 (30·3%)
Hypertension	46,129 (65·2%)	27,321 (64·0%)	18,807 (67·0%)	10,164 (66·2%)	9,368 (63·2%)	7,312 (65·7%)
Dyslipidaemia	16,642 (23·5%)	10,151 (23·8%)	6,491 (23·1%)	3,211 (20·9%)	3,455 (23·3%)	2,966 (26·6%)
Atrial fibrillation	8,614 (12·2%)	5,163 (12·1%)	3,451 (12·3%)	1,718 (11·2%)	1,845 (12·5%)	1405 (12·6%)
Chronic Heart Failure	6,047 (8·5%)	3,799 (8·9%)	2,248 (8·0%)	1,480 (9·6%)	1,196 (8·1%)	939 (8·4%)
Stroke	6,353 (9·0%)	3,857 (9·0%)	2,496 (8·9%)	1,466 (9·5%)	1,318 (8·9%)	999 (9·0%)
Coronary artery disease	17,971 (25·1%)	12,521 (29·3%)	5,450 (19·4%)	4,378 (28·5%)	3,590 (24·2%)	2,534 (22·8%)
Chronic Kidney Disease	14,026 (19·8%)	7,467 (17·5%)	6,559 (23·3%)	2,147 (14·0%)	3,127 (21·1%)	2,293 (20·6%)
Chronic Obstructive Pulmonary Disease	8,582 (12·1%)	5,453 (12·8%)	3,128 (11·1%)	1,680 (10·9%)	1,757 (12·4%)	1,528 (13·7%)
Depression	5,625 (8·0%)	2,694 (6·3%)	2,930 (10·4%)	1,288 (8·3%)	1,240 (8·7%)	829 (7·4%)
Malignancy	6,791 (9·6%)	4,153 (9·7%)	2,637 (9·4%)	1,299 (8·5%)	1,480 (10·0%)	1,208 (10·9%)
High bleeding risk	5,452 (7·7%)	3,318 (7·8%)	2,134 (7·6%)	1,186 (7·7%)	1,115 (7·5%)	903 (8·1%)
Baseline Medications						
Statins	31,844 (45·0%)	20,842 (48·9%)	11,002 (39·2%)	6,399 (41·2%)	6,668 (45·0%)	5,337 (47·9%)
At least one antiplatelet therapy	27,059 (38·2%)	17,296 (40·5%)	9,763 (34·8%)	6,396 (41·7%)	5,593 (37·8%)	3,802 (34·2%)
ACEI/ARB	30,241 (42·7%)	18,664 (43·7%)	11,337 (40·4%)	6,313 (41·1%)	6,269 (42·3%)	4,817 (43·3%)
Diuretics	23,610 (33·4%)	12,413 (29·1%)	11,197 (39·9%)	6,033 (39·3%)	4,663 (31·5%)	3,204 (28·9%)
Beta-blockers	18,421 (26·0%)	11,460 (26·7%)	6,961 (24·8%)	4,156 (27·1%)	3,734 (25·2%)	2,909 (26·1%)
Calcium channel blockers	8,629 (12·2%)	5,112 (12·0%)	3,517 (12·5%)	2,303 (15·0%)	1,698 (11·5%)	1,050 (9·4%)
Vasodilators	8,721 (12·3%)	5,410 (12·7%)	3,311 (11·8%)	2,320 (15·1%)	1,672 (11·3%)	1,159 (10·4%)

**Data available on socioeconomic status was available only for patients eligible for HES linkage n=114,807;*
BMI: Underweight: <18·5 kg/m2; Normal: 18·5-24·9 kg/m2, Overweight: 25-29·9 kg/m2, Obesity: 30-39·9 kg/m2,

Morbid obesity: > 40 kg/m2; *ACEI/ARB; Angiotensin Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker*

Table3: Baseline characteristics of CAD and PAD patients with and without statins

	Statin prescriptions (CAD)		Statin prescriptions (PAD)	
	Yes (n=79,641)	**No (n=41,370)**	**Yes (n=27,150)**	**No (n=22,276)**
Age (years), mean (SD)	***67·3(11·6)***	***69·2(13·5)***	***70·7 (10·1)***	***70·4 (12·5)***
Age 40-49 years	5,590 (7·0%)	3,789 (9·2%)	664 (2·4%)	1,228 (5·5%)
Age 50-59 years	15,170 (19·0%)	7,031 (17·0%)	3170 (11·7%)	3,496 (15·7%)
Age 60-69 years	23,800 (29·9%)	9,474 (22·9%)	7,989 (29·4%)	5,480 (24·6%)
Age 70-79 years	22,254 (27·9%)	10,295 (24·9%)	9,716 (35·8%)	5,995 (26·9%)
Age > 80 years	12,820 (16·1%)	10,873 (26·3%)	5,611 (20·7%)	6,077 (27·3%)
Sex				
Women	29,687 (37·3%)	20,713 (50·1%)	9,143 (33·7%)	9,086 (40·8%)
Men	49,960 (62·7%)	20,744 (50·1%)	18,007 (66·3%)	13,189 (59·2%)
Socioeconomic quintile				
Quintile 1	10,873 (21·4%)	6,009 (19·5%)	3,001 (18·4%)	2,490 (18·2%)
Quintile 2	11,776 (23·2%)	6,874 (22·3%)	3,665 (22·4%)	3,001 (22·0%)
Quintile 3	10,459 (20·6%)	6,711 (21·8%)	3,315 (20·4%)	2,926 (21·4%)
Quintile 4	9,670 (19·2%)	6,132 (19·9%)	3,523 (21·6%)	2,913 (21·3%)
Quintile 5	8,053 (15·8%)	5,111 (16·6%)	2,796 (17·2%)	2,322 (17·0%)
Smoking				
Current smoker	19,946 (25·7%)	9,993 (24·7%)	8,265 (30·4%)	7,713 (34·6%)
Co-morbidities				
Diabetes Mellitus	16,276 (20·4%)	6,076 (14·7%)	8,578 (31·6%)	4,108 (18·4%)
Hypertension	48,789 (61·3%)	24,748 (59·8%)	20,553 (75·7%)	12,768 (57·3%)
Prior acute coronary syndrome	29,660 (37·2%)	6,104 (14·8%)	4,906 (18·1%)	1,613 (7·2%)
Stroke	6,179 (7·8%)	2,997 (7·2%)	2,824 (10·4%)	1,305 (5·9%)
Peripheral arterial disease/Coronary artery disease	5,418 (6·8%)	2,327 (5·6%)	9,641 (35·5%)	3,598 (16·1%)
Chronic Kidney Disease	10,760 (13·5%)	6,428 (15·5%)	5,603 (20·6%)	3,617 (16·2%)
Heart Failure	4,143 (5·2%)	3,418 (8·3%)	2,289 (8·2%)	1,454 (6·5%)
Dementia	2,296 (2·9%)	1,610 (3·9%)	1,035 (3·8%)	806 (3·6%)
COPD	6,221 (7·8%)	4,132 (10·0%)	3,318 (12·2%)	2,882 (12·9%)
Chronic Liver Disease	880 (1·1%)	647 (1·6%)	348 (1·2%)	383 (1·7%)
Depression	6,071 (7·6%)	3,754 (9·1%)	2,088 (7·7%)	1,782 (8·0%)
Malignancy	5,610 (7·0%)	3,635 (8·8%)	2,326 (8·6%)	2,106 (9·5%)
Management				
Mean number of medications during follow up, mean (SD)	5·5 (4·0)	5·4 (4·1)	5·9 (4·4)	5·6 (4·3)

COPD: Chronic Obstructive Pulmonary Disease

Table 4 Complications of patients with incident CAD and PAD

	Annual crude incidence rate per 100-person years, 95% CI	Standardized annual incidence rate per 100-person years, 95% CI		
		Age and sex standardized	Male (age standardized)	Female (age standardized)
Incident CAD				
MI	3·1 (3·0 - 3·2)	2·4 (2·3 - 2·5)	2·8 (2·6 - 2·9)	1·7 (1·6 - 1·8)
Ischemic Stroke	2·1 (2·0 - 2·2)	1·4 (1·3 - 1·4)	1·2 (1·1 - 1·3)	1·6 (1·5 - 1·7)
Hospitalization for bleeding	2·5 (2·4 - 2·6)	1·7 (1·6 - 1·8)	1·9 (1·8 - 2·0)	1·5 (1·4 - 1·6)
CV hospitalization	11·8 (11·6 - 12·0)	9·7 (9·5 - 9·9)	10·1 (9·8 - 10·4)	9·1 (8·8 - 9·3)
Premature CV death	2·2 (2·1 - 2·4)	2·0 (1·9 - 2·1)	2·2 (2·1 - 2·3)	1·7 (1·5 - 1·8)
Premature death from any cause	6·1 (5·9 - 6·3)	4·5 (4·4 - 4·6)	4·5 (4·4 - 4·6)	4·4 (4·2 - 4·7)
CV death	7·8 (7·6 - 8·0)	3·7 (3·6 - 3·8)	3·8 (3·7 - 3·9)	3·5 (3·4 - 3·6)
Death from any cause	17·1 (16·8 - 17·4)	8·2 (8·1 - 8·4)	8·3 (8·1 - 8·4)	8·2 (8·0 - 8·4)
Incident PAD				
MI	2·9 (2·7 - 3·1)	1·9 (1·8 - 2·0)	2·3 (2·1 - 2·4)	1·4 (1·3 - 1·5)
Ischemic Stroke	2·6 (2·4 - 2·7)	1·6 (1·5 - 1·7)	1·7 (1·5 - 1·8)	1·4 (1·3 - 1·6)
Hospitalization for bleeding	2·1 (2·0 - 2·3)	1·4 (1·3 - 1·5)	1·6 (1·4 - 1·7)	1·2 (1·1 - 1·2)
CV hospitalization	10·3 (10·0 - 10·6)	6·6 (6·4 - 6·7)	7·8 (7·5 - 8·1)	4·9 (4·7 - 5·2)
Premature CV death	2·5 (2·3 - 2·8)	2·1 (1·9 - 2·3)	2·3 (2·1 - 2·5)	1·9 (1·6 - 2·1)
Premature death from any cause	8·3 (8·0 - 8·7)	6·2 (5·8 - 6·4)	7·3 (6·9 - 7·8)	7·2 (6·5 - 7·9)
CV death	7·6 (7·3 - 7·8)	3·5 (3·3 -3·6)	3·7 (3·5 - 3·9)	3·5 (3·3 - 3·6)
Death from any cause	18·5 (18·1 - 18·9)	9·2 (9·0 - 9·5)	9·1 (8·7 - 9·4)	9·6 (9·3 - 9·9)

MI: Myocardial infarction, CV hospitalization: cardiovascular hospitalization (planned and unplanned), Premature CV death: Death <75 years of age due to cardiovascular cause, CV death: Death due to cardiovascular cause

Figure 1 A) Age and sex standardized incidence rates (per 100,000 person years) of CAD in the UK in 2006 vs 2015; 1 B) Age and sex standardized incidence rates (per 100,000 person years) of PAD in the UK in 2006 vs 2015

*** IRR: incidence rate ratio adjusted for age and sex; CAD: coronary artery disease; PAD: peripheral artery disease*

*** Figure 1A shows stable standardized incidence rates of CAD between 2006 and 2015; Figure 1B shows a decline in the standardized incidence of PAD between 2006 and 2015*

Figure 2 A) Number of cases stratified by age group (per total person years of follow in each age category) of CAD in the UK in 2006 vs 2015; 2 B) Number of cases stratified by age group (per total person years of follow in each age category) of PAD in the UK in 2006 vs 2015

*** IRR: incidence rate ratio adjusted for age and sex; CAD: coronary artery disease; PAD: peripheral artery disease*

*** Figure 2A shows no significant change in the crude incidence of CAD between 2006 and 2015; Figure 2B shows a decline in the crude incidence of PAD between 2006 and 2015*

Figure 3; Predictors of statin use for secondary prevention among patients with incident CAD and incident PAD

***Statin analyses was performed separately for incident CAD and incident PAD patients. The model was adjusted for age, sex, and relevant co-morbidities including, diabetes mellitus,, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, depression, dementia, history of malignancy, chronic liver disease, and prior history of stroke; additionally, prior history of PAD was included in the model for incident CAD patients and prior history of CAD was included the model for incident PAD patients*

Figure 4; Trends in the annual age and sex adjusted event rates of major vascular events, bleeding, hospitalization and mortality among patients with incident CAD and incident PAD in 2006 vs 2015

*** MI: Myocardial infarction, CV hospitalization: cardiovascular hospitalization (planned and unplanned), Premature CV death: Death <75 years of age due to cardiovascular cause, CV death: Death due to cardiovascular cause*