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

Varun Sundaram MD, FRCP [1, 2], Chloe Bloom MBChB, Ph.D. [2], Rosita Zakeri MBChB, Ph.D. [2,3], Prof Julian Halcox MD [4], Alexander Cohen MD[8], Kevin Bowrin Msc [6], Jean-Baptiste-Briere PharmD[7], Amitava Banerjee MBChB, D.Phil [5], Prof Daniel I. Simon MD, FAHA [1], Prof John GF Cleland MD, FRCP [2,9], Prof Sanjay Rajagopalan MD, FAHA [2], Jennifer K. Quint MBChB, Ph.D [2,10]

1. Department of Cardiovascular Medicine, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

2. Department of Population Health, National Heart and Lung Institute, Imperial College London, London, UK

3. Department of Cardiovascular Medicine, Royal Brompton and Harefield Hospitals NHS Foundation Trust, London, UK

4. Department of Cardiovascular Medicine, Swansea University Medical School, UK

5. Department of Hematological Medicine, Guy's & St Thomas' NHS Foundation Trust, King's College London, Westminster Bridge Road, London, UK.

6. Bayer plc, Reading UK.

7. Bayer AG, Berlin, Germany

8. Institute of Health Informatics, University College London, London, UK

9. Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow

10. Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

Word count: 5,375 words (including references)

Corresponding author

Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Centre, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, Ohio, 44106, USA; Emmanuel Kaye Building, Manresa Road, National Heart and Lung Institute, Imperial College, London, SW3 6LR, UK

Tel: +12168447690; +44 (0) 207 594 882; Fax; +12168448954

Email: varun.sundaram@uhhospitals.org; varun.sundaram@imperial.ac.uk

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.[1–5] Nevertheless, ASCVD remains one of the leading causes of death and disability-adjusted life-years.[1,6] The age standardised prevalence of CAD in the in the UK and Europe in 2015 has been reported to be 2.5 % and 3.7% respectively. [6] 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.[7,8] 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.[9,10]

Most 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. [1,11–13] 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.[14] 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.[7,15] In spite of its high prevalence and poor prognosis, PAD attracts less attention in terms of research, early detection, and treatment. [16,17] 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), including prescription data, caring for about 9% of the UK population were obtained from the Clinical Practice Research Datalink (CPRD) covering the period between January 1st, 1986 to December 31st, 2016.[18] 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 S6). 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. READ codes used in CPRD are the standard clinical terminology system used in General Practice across the UK. READ codes gives detailed clinical coding of multiple patient features such as clinical signs, symptoms and observations; laboratory tests and results, medications and diagnoses.[18] 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 obtained from the CPRD records.

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 were 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. The complication rates were analysed only for patients whose data from CPRD could be linked to HES and ONS data-sets.

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.[19] 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.

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), and prior history of ischemic stroke; in addition to these, the model was also adjusted for prior history of PAD for incident CAD patients and prior history of CAD for incident PAD patients.

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 Figures 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-standardised 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 and Take home figure). 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 Figures S4 and S5). 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).[11]

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 and Take home figure). 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 an overall decline in the age and sex standardised incidence of PAD, which was substantial in some regions (e.g.:- >30% in north-west and north-east England) (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

We included 121,011 incident cases of CAD and 49,426 incident cases of PAD (Statin cohort) (Supplementary Figures S1 and S2). 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 S3). 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 S8).

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

We included 114,807 incident cases of CAD and 45,503 incident cases of PAD (those eligible for HES-ONS linkage; Complication cohort). 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 and Supplementary Table S4). Morbidity and mortality were similar for patients with PAD whether or not they had CAD (Supplementary Table S4). The annual crude incidence rates of amputation and acute limb ischemia in the overall PAD population were 2.2 (95 % CI, 2.0-2.4) and 0.6 (95 % CI, 0.5-0.7) per 100 person years of follow up respectively (Supplementary Table S5).

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)]. Between 2006 and 2015, there were no significant changes in the annual crude and adjusted rates of lower extremity amputations [crude incidence rate ratio (IRR): 1.2, 95% CI, 0.9 - 1.7; adjusted IRR: 1.2, 95% CI 0.9 – 1.7] and acute limb ischemia [crude IRR: 1.1, 95% CI, 0.3 - 3.3; adjusted IRR: 1.2, 95% CI 0.4 - 3.0] (Supplementary Table S5). 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) (Figure 4), with or without concomitant CAD (Supplementary Figure S10). 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.[2,11] The absence of a decline in CAD incidence in our study versus the findings of previous studies could have been caused by myriad reasons. Whilst improvements in primary prevention measures were expected to decrease the incidence of CAD[16], offsetting trends such as an increase in the prevalence of obesity, dyslipidaemia, diabetes and CKD may have attenuated the decline. Secondly, previous studies on the incidence of AMI included patients with prior history of chronic ischemic heart disease.[11,13,20] 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,[20] 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.[22–25]

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[26], 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 among patients with incident PAD. Patients diagnosed with incident PAD in the more recent years (2014-15) were

sicker, with a significantly higher proportion of patients with co-morbidities including obesity, DM, HLD, CKD, COPD and malignancy, compared to those diagnosed in 2006-07. In the UK National Health Service (NHS), the Quality and Outcomes Framework (QOF) introduced a pay for performance program in 2004. [27] Further changes were brought to the QOF reporting system in 2008, including the introduction of new indicators such as COPD and smoking cessation. [28] Given our study time frame begins in 2006, the 2004 QOF changes would have been assimilated in the data analysed. The rising trends in the CV and non-CV co-morbidities from 2006-07 to 2010-11 observed in our analyses may, in part, correspond to the differences in coding practices resulting from the QOF changes in 2008. However, changes observed in the later part of the study period (from 2010-11 to 2014-15) are unlikely to be related to coding practice changes.

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. Our analyses also revealed that in addition to statins, dual and single antiplatelet therapy was also less often prescribed for those with incident PAD than those with CAD (Supplementary Figure S9). 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.[29–31] We observed the phenomenon of *"risk treatment paradox"* [32] 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.[33] 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, [34] the reasons for the barriers in clinical practice remains unclear. Women may be more prone to statin induced myalgias, which could have led to more early discontinuations.[35] It has 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.[36,37] 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.

Previous studies have demonstrated an increased bleeding risk after MI and PCI in women than men.[38,39] Conversely, we observed a higher age-adjusted bleeding rates requiring hospitalisation in men than women. This could be related to the higher annual age adjusted event rates of MI and subsequent use of DAPT during follow up in men (Table 4 and Supplementary Figure S9). While, these can partly explain the increased bleeding rates among men compared to women, unmeasured confounders (such as undisclosed bleeding risk etc.) might be a plausible reason for this observed difference. A single reason for this disparity is not clear from this data.

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. Furthermore, changes in guidelines and clinical practice, including the duration of antiplatelet therapy and the introduction of potent newer antiplatelet therapy agents (prasugrel and ticagrelor) could have influenced the adjusted incident rate ratio (2015 vs 2006) of CV outcomes (both ischemic events and bleeding).[40–43] 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. Although the prevalence of smoking in the overall UK population has declined, contributing to the falling incidence of PAD, the prevalence of smoking amongst those who develop PAD has not changed over time. In addition to increasing the risk of incident PAD, cigarette smoking reduces exercise capacity and increases CV mortality among patients with prevalent PAD.[44] 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).

Strengths and limitations

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 (Supplementary Figure S3), utilizing multiple nationally representative data sources in comparison to conventional case ascertainment using one data source only.

Our study has several strengths but some limitations. While we hypothesise that the introduction of hsTnT could have led to an increase 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 ICD10 subcategory codes,

do not reliably distinguish AMI type.[45] 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. 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. [46,47]

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 early identification of PAD so that disease modifying interventions (e.g., smoking cessation and statins) to improve CV outcomes can be implemented in a timely fashion.

Conflict of interest

V.S.: has none conflict of interest to declare. C.B.: has none conflict of interest to declare. R.Z.: has none conflict of interest to declare. J.H. has received personal fees from Bayer AG. A.C. has received personal fees from Bayer AG, Bristol_Myers Squibb, Daiichi-Sankyo and Pfizer; A.C. has been a

consultant to Janssen and ONOP pharmaceuticals. K.B. and J.B.B. are employees of Bayer. A.B. has received honoraria/personal fees from BI, Pfizer, GSK, Novo-Nordisk, and AstraZeneca. D.S. has none conflict of interest to declare. JGFC has received honoraria/personal fees from Amgen, AstraZeneca, Bayer, Bristol-Meyer-Squibb, GSK, Medtronic, PharmaNord, Pharmacosmos, Philips, Myokardia, Torrent Pharmaceuticals, Sanofi, Vifor, Stealth Biopharmaceuticals, Servier and Novartis. S.R. has been a consultant for Takeda Pharmaceuticals, Janssen, Astra Zeneca, and Glenmark. J.K.Q. has received honoraria/personal fees from AstraZeneca, Bayer, GSK, Ins med, Chiesa and BI.

1. 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.

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, Mussolino ME, Hsu LL, Addou E, Engelgau MM, Gordon D. Decline in Cardiovascular Mortality: Possible Causes and Implications. *Circ Res* 2017; 120:366–80.

6. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Ärnlöv J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Bärnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castañeda-Orjuela CA, Castillo-Rivas J, Catalá-López F, Choi JY, Christensen H, Cirillo M, Cooper L Jr, Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C,

Kasaeian A, Khader Y, Khan A, Khang YH, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin MJ, Shishehbor M, Shore H, Silva DAS, Sobngwi E, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol* 2017; 70:1–25.

7. 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.

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

9. 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.

10. Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, Steg G, Bhatt DL, Hirsch AT; Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes*. 2010; 3:642–51.

11. 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.

12. Tran J, Norton R, Conrad N, Rahimian F, Canoy D, Nazarzadeh M, Rahimi K. 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.

13. 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.

14. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, Timmis A, Hemingway H.. 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.

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

16. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37:2315–81.

17. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, Collet J-P, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, Widimsky P, Kolh P, Agewall S, Bueno H, Coca A, De Borst GJ, Delgado V, Dick F, Erol C, Ferrini M, Kakkos S, Katus HA, Knuuti J, Lindholt J, Mattle H, Pieniazek P, Piepoli MF, Scheinert D, Sievert H, Simpson I, Sulzenko J, Tamargo J, Tokgozoglu L, Torbicki A, Tsakountakis N, Tuñón J, de Ceniga MV, Windecker S, Zamorano JL, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Juni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Zelveian PH, Haumer M, Isachkin D, De Backer T, Dilic M, Petrov I, Kirhmajer MV, Karetova D, Prescott E, Soliman H, Paapstel A, Makinen K, Tosev S, Messas E, Pagava Z, Müller OJ, Naka KK, Járai Z, Gudjonsson T, Jonas M, Novo S, Ibrahimi P, Lunegova O, Dzerve V, Misonis N, Beissel J, Pllaha E, Taberkant M, Bakken T, Teles R, Lighezan D, Konradi A, Zavatta M, Madaric J, Fras Z, Melchor LS, Näslund U, Amann-Vesti B, Obiekezie A. 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(9):763–816.

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

19. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018; 391:572–80.

20. Wong CX, Sun MT, Lau DH, Brooks AG, Sullivan T, Worthley MI, Roberts-Thomson KC, Sanders P. Nationwide trends in the incidence of acute myocardial infarction in Australia, 1993-2010. *Am J Cardiol* 2013; 112:169–73.

21. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM, Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H, Jaffe AS; Study Group on Biomarkers in Cardiology of ESC Working Group on Acute Cardiac Care.. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012; 33:2252–7.

22. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, Pollack CV Jr, Gore JM, Chandra-Strobos N, Peterson ED, French WJ. 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.

23. Khera S, Kolte D, Aronow WS, Palaniswamy C, Subramanian KS, Hashim T, Mujib M, Jain D, Paudel R, Ahmed A, Frishman WH, Bhatt DL, Panza JA, Fonarow GC. 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* 2014; 3: pii: e000995

24. 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.

25. Gierlotka M, Gąsior M, Wilczek K, Wasilewski J, Hawranek M, Tajstra M, Osadnik T, Banasiak W, Poloński L.. 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.

26. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Röther J, Wilson PW; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295:180–9.

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

28. 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.

29. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, Kruger A, Kutty R, Lanas F, Lisheng L, Wei L, Lopez-Jaramillo P, Oguz A, Rahman O, Swidan H, Yusoff K, Zatonski W, Rosengren A, Teo KK; Prospective Urban Rural Epidemiology (PURE) Study Investigators. *Lancet* 2011; 378:1231–43.

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

31. Börsch-Supan A, Brandt M, Hunkler C, Kneip T, Korbmacher J, Malter F, Schaan B, Stuck S, Zuber S; SHARE Central Coordination Team. Data Resource Profile: the Survey of Health, Ageing and Retirement in Europe (SHARE). *Int J Epidemiol* 2013; 42:992–1001.

32. Weiss CO, Varadhan R. Risk-Treatment Paradox in Use of Statins. *JAMA* 2004; 292(2):169–169.

33. 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.

34. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. 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.

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

36. 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.

37. 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.

38. Ahmed B, Dauerman HL. Women, bleeding, and coronary intervention. *Circulation* 2013; 127:641–9.

39. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. *Circulation* 2016; 133:916–47.

40. Hall M, Bebb OJ, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP, Brieger D, Batin PD, Farkouh ME, Hemingway H, Timmis A, Fox KAA, Gale CP. Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. *Eur Heart J* 2018; 39:3798–806.

41. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361:1045–57.

42. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; 35:2541–619.

43. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; 40:87–165.

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

45. 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.

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

47. 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.

Figure legends

Figure 1 A) Age and sex standardised incidence rates (per 100,000 person years) of CAD in the UK in 2006 vs 2015; 1 B) Age and sex standardised 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 standardised incidence rates of CAD between 2006 and 2015; Figure 1B shows a decline in the standardised 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 individually 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. In addition to these, the model was also adjusted for prior history of PAD for incident CAD patients and prior history of CAD for incident PAD patients.*

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

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

Take home figure: Temporal trends in the standardised incidence and CV mortality of CAD and PAD in the UK, 2006-2015