Impact of diabetes on long-term mortality following major lower limb amputation: A population-based cohort study in Wales

Jennifer Hayes [a c], James M Rafferty [d], Wai-Yee Cheung [a], Ashley Akbari [b], Rebecca L Thomas [a], Steve Bain [a c], Claire Topliss [c], Jeffery W Stephens [a c]

Abstract

Background: Major lower limb amputation is associated with high morbidity and mortality, particularly among patients with diabetes. Previous studies suggest variable mortality rates, but none have investigated the impact of diabetes in Wales.

Methods: A population-based cohort study was conducted using anonymised data from the Secure Anonymised Information Linkage Databank. Survival from all incident major amputations in persons ≥18 years from 2006–2013 in Wales was assessed over 5-year follow-up. Kaplan-Meier survival curves and Cox regression models, stratified by amputation level, were used to examine the time-dependent effect of diabetes on mortality while adjusting for confounding factors.

Results: 2542 individuals underwent major amputation, 48.4% had diabetes. Mortality at 30 days was 9.2% and 61.9% within 5 years. Patients with diabetes had higher 5-year mortality (67.0%) compared to those without diabetes (57.1%). Diabetes was associated with an increased risk of long-term mortality (hazard ratio 1.62, $p<0.001$), but a reduced risk of death in the first 30 days post-amputation. A history of peripheral vascular disease and above-knee amputation were strong predictors of mortality.

Conclusion: Time-stratified analysis demonstrates lower short-term but higher long-term mortality risk for persons with diabetes following major amputation. Further research is required to explore interventions aimed at improving survival.

KeyWords

1. Diabetes
2. Major lower extremity amputation
3. Mortality
4. Peripheral vascular disease
5. Population-based study
6. Survival analysis

Introduction

Current literature on morbidity and mortality related to major lower limb amputations demonstrate exceptionally poor outcomes. In hospital mortality for major amputation is reported to be as high as 8.3% [1] and 5-year mortality reported to be between 53% and 80% [2]. There is evidence that outcomes following major amputation are worse in persons with diabetes. In England, the median survival after amputation of any cause has been reported to be 20 months shorter in persons with diabetes compared to the population without [3]. However, the influence of diabetes on survival after major amputation in the current literature is contentious. Several studies examining mortality following major amputation report no associated increased risk of death with a history of diabetes [1,4], and some

demonstrate equivocal [5,6,7] or reduced risk [8,9] on mortality in the short-term but an increased risk of mortality in the long-term. However, methods used to analyse the effect of diabetes are varied and many of these studies are not stratified by time or population base. No recent study has investigated the effect of diabetes on mortality over time in a large population, with the last in a German population looking at the period until 2007. Advances in diabetes and arterial disease management, post operative care and rehabilitation may mean that mortality rates and the effect of diabetes on mortality in the literature may not reflect the current landscape.

A high mortality rate is to be expected, as the population undergoing amputation are often frail, multi-morbid, and because a low predicted life expectancy can be used as an indication for major amputation by operating physicians when management is being considered [2]. However, even with acceptance of considerable expected mortality there is variance in reported mortality rates between geographic locations [10, 4, 11]. Direct comparison of mortality rates following amputation can be difficult due to differences in population, amputation definitions and reporting, and at present there has been no data published about amputation related mortality in the population with or without diabetes in Wales. With variability in mortality between populations previously reported, and as there is no recent literature reflective of the effect of diabetes on mortality, it is also important to investigate mortality within Wales. The aims of this study were to: (i) Determine the 30 day, 1-year and 5-year mortality rates following incident major amputation in the Welsh diabetes and non-diabetes population between 2006-2013. (ii) Explore the time dependent impact of diabetes on mortality rate while controlling for other risk factors for death. (iii) Describe the main

causes of death for the diabetes and non-diabetes population in those people who have undergone amputation.

Methods

1.1 Ethical approval

Approval for the use of anonymised data in this study, provisioned within the Secure Anonymised Information Linkage (SAIL) Databank was granted by an independent Information Governance Review Panel (IGRP) under project 0716. The IGRP has a membership comprised of senior representatives from the British Medical Association (BMA), the National Research Ethics Service (NRES), Public Health Wales and Digital Health and Care Wales (DHCW). The SAIL Databank follows the General Data Protection Regulations (GDPR) and is UK Data Protection Act compliant.

1.2 Study population and data assessment

As described in previous publication from the research group, data were extracted from SAIL, a repository of routine medical data primarily focused on the residents of, or people receiving services in Wales from primary, secondary and outpatient settings [12]. Description of the maintenance of data within SAIL and datasets used are described in detail in a previous publication [12]. Patient Episode Database for Wales (PEDW) within SAIL was used to identify major amputations, defined as amputation above the ankle [13], using relevant classification of Office of Population, Census and Surveys interventions and procedures version 4 (OPCS4) codes (OPCS4 codes: X09:X095, X098, X099) [13]. All incident major amputations in persons aged over 17 years between 2006-2013 were identified. Amputations were defined as incident

if no record of amputation was found within the 5 years prior to the amputation of interest [14]. All amputations were included in the analysis, regardless of cause in line with other national papers and Public Health England (PHE) analysis [15, 16, 17]. The index date of entry into the study was the date of incident major amputation during the study period. All incident major amputations between 2006-2013 were assessed and subjects followed until 2018-12-31 to give a minimum 5-year observation following amputation.

People with diabetes were identified using an established algorithm [18,19] utilising linked data from several clinical sources. People were considered to have diabetes from first registration of diabetes and those with gestational diabetes were excluded unless subsequent development of another diabetes type occurred.

1.3 Data collection and analysis

The primary variable of interest was time to death from date of incident amputation. This date was classified as the index date. The date of death was taken from Office of national statistics (ONS) Annual district death extract (ADDE). The ONS ADDE provides the date of death as recorded on the death certificate for all registered deaths in Wales, along with the recorded cause of death including underlying cause of death. Time to death, in months, was calculated from index date to date of death. Records were censored at date of death or at the end of the follow-up period (31-12-2018) whichever occurred first.

Different socio-demographic factors and comorbidities that could reliably be sampled from hospital records were investigated as potential confounding factors. The factors included have been demonstrated to be associated with mortality in people with diabetes or associated with amputation within the diabetes and non-diabetes populations [20,21].

Independent characteristic variables included;- age at amputation, gender, Welsh Index of multiple deprivation (WIMD) quintile and health board at admission. Age was categorised into the age groups <65years, 65-75 years, 75-85 years and 85+ years as previous studies have demonstrated that mortality risk begins to increase in the population above the age of 65 years [22,23]. Primary medical risk factors were selected as they were previously identified to be associated with the most frequent causes of death in the diabetes and peripheral vascular disease (PVD) populations. Medical comorbidities included were:- Charlson comorbidity index, a history of limb salvage procedures, hypertension (HTN), end stage renal disease (ESRD), myocardial infarction (MI), cerebrovascular accident (CVA), congestive cardiac failure (CCF) and PVD. Surgical history included amputation level; determined as above knee amputation (AKA) or below knee amputation (BKA), and previous limb salvage attempt. The updated Royal College of Surgeons (RCS) Charlson score [24] is a marker of general frailty. Codes pertaining to diabetes were not used in the score in this study as this was the variable defining the population not a co-morbidity. HIV/AIDS status is considered sensitive information and therefore diagnosis codes were not available within the data set and were not included in the analysis. IDC10 codes for comorbidities within the index were identified from PEDW data up to one year prior to the index date and from the index admission (Appendix 1). Information about the rational, International Classification of Diseases, Tenth Revision (ICD-10) codes and the look back period for each variable can be found in appendix 1.

A person's health board at entry into the study was derived from their registered home address at time of admission using 2011 lower super output areas (LSOA) unitary authorities. WIMD was derived from LSOA information derived from the patient's home address. [25].

The WIMD score was split into quintiles from the most to the least deprived groups. Cause of death is presented from codes in the ADDE of the underlying cause of death in each case.

1.4 Statistical Analysis

All analysis was undertaken in R (R version 3.6.1 2019) and figures were produced using the package ggplot2 [26]. For comparison of baseline variables between groups chi- squared and rank biserial correlation were used for categorical variables and the student t-test and Mann-Whitney U test for normally and non-normally distributed continuous variables respectively. For all analyses, a $p \leq 0.05$ was considered statistically significant. Characteristics of patients that died at 30 days, 1 year and 5 years were compared to those that survived at 5 years using chi-squared tests for categorical variables and t-test for continuous variables. Missing data was not imputed, the numbers included in analysis are noted throughout.

Survival was assessed with Kaplan-Meier curves and stratified log-rank tests were used to analyse differences in survival associated with independent variables. Crude differences between the diabetes and non-diabetes population for major amputation violated the proportional hazard assumption as the survival curves crossed, therefore, proportional hazards could not be assumed [27]. This was confirmed using the Schoenfeld test for proportional hazards. To allow for this, Cox regression with a step function was performed using discrete time intervals to model the time dependency of diabetes whilst assessing for other predictors of death in the population.

In all models, death was the primary outcome and diabetes was the primary exposure variable. Hazard ratios are presented individually for all variables with respect to mortality and then adjusted within each model. The first model included diabetes interaction with

discrete time intervals (30 and 60 days, 6 months, and 1-, 2-, 3-, and 5 years), age and gender. The second model included Charlson index and surgical history, the third included medical risk factors for death and the fourth included geographical variance and socioeconomic deprivation.

Results

Of the 2542 individuals who underwent incident major amputation between 2006-2013, 67.7% were men (n=1720), the mean age at amputation was 69 ±14.2 years and there was an even split of amputation level between AKA and BKA (AKA:BKA 49.3:50.7%) (Table 1). Marginally, more amputations were performed in patients without diabetes (51.6%). A greater proportion of the population with diabetes were men and were more likely to have undergone a BKA, have a history of HTN, ESRD, MI, CCF and PVD compared to the population without diabetes. Despite a higher rate of PVD they did not have a significantly greater history of a prior limb salvage procedure (diabetes 433 (35.2%): non-diabetes 432 (33.0%), p=0.24). When examining the population with PVD in isolation, a higher percentage of persons in the non-diabetes population underwent a revascularisation procedure (diabetes 41.1%: non diabetes 44.0%) but this difference was not statistically significant. Persons with diabetes were also significantly more likely to have undergone more than 1 major amputation within the study period.

Overall, 1934 (76.1%) people died over the follow-up period, 235 (9.2%) within 30 days, 817 (32.1%) within 1 year and 1573 (61.9%) within 5 years. Of those who died, 52.5% (n=1015) had a diagnosis of diabetes. The median survival time was 36.5 [IQR 35.9-39.0] months (Table 2). People undergoing AKA had a significantly shorter survival time of 23.2 [19.6-27.8] months

compared to those undergoing BKA (52.2 [47.4-58.4] months, p<0.001) (Figure 1). Significant differences in survival time were seen by gender, age, and when amputation level was stratified by age. The greatest difference in survival time between AKA and BKA was seen in those under 65 years of age at time of amputation. Persons in the under 65 years age group who required an AKA had a 31.5 months shorter average survival time compared to those that underwent a BKA (BKA 101.1 [84.2-121] months: AKA 69.9 [46.2-87.4] months).

Figure 2 shows the Kaplan-Meier curves demonstrating the difference in survival following amputation stratified by diabetes diagnosis. The population without diabetes had a median survival of 43.8 [37.3-48.0] months, over 10 months longer than those with diabetes (31.3 months [29.0-35.7]). In the first 30 days a smaller percentage of people with diabetes died (7.9%). This trend then reversed just prior to 1-year following amputation where the survival curves for the two populations crossed. At five years a greater proportion of the population with diabetes had died. The relative mortality risk associated with diabetes in univariate analysis was time dependent with greater survival for those with diabetes for the first year after major amputation. There was no difference in mortality at 365 days, with a mortality of 32% in both populations.

The results of all unadjusted and final Cox regression analysis models are shown in Table 3. In the unadjusted model there was a significant relative mortality risk associated with diabetes in all time periods except for between 31 days and 6 months. The risk of mortality associated with diabetes was highest at 3-5 years following amputation with a hazard ratio of 1.62 [95% Confidence interval 1.29-2.02] after having a reduced risk with a hazard ratio of 0.72 [0.58-0.97] in the initial 0-30 days. The most parsimonious model for incident major amputation was model 3 which included diabetes status, gender, Charlson index, surgical history, and the

other medical risk factors. In the fully adjusted model the hazard ratios associated with diabetes were as in the univariate analysis; an increased risk of mortality seen after the first 6 month following amputation. The reduction of risk of mortality associated with diabetes in the time period between 0 and 30 days remained statistically significant; HR 0-30 days: 0.74 [0.57-0.96]. There was no association between diabetes and mortality in the time period between 30 days and 6 months after amputation. Increasing age remained significantly associated with an increase in the risk of mortality (HR 1.04 [1.03-1.04] per year), as did increasing Charlson index score (score 1, 1.39 [1.25- 1.55]; 2, 1.76 [1.50-2.07]; 3+, 2.30[1.66-3.18]), a history of ESRD (2.35[1.92-2.87]), MI (1.21[1.07-1.37]), CCF (1.17[1.03-1.32]) and PVD (1.42[1.24-1.63]) and requiring an AKA versus a BKA (1.24[1.13-1.37]). The only variable associated with a reduced risk of mortality was a history of a limb salvage procedure within the 2 years prior to LEA admission; associated with a reduction in risk of mortality with a hazard ratio of 0.83 [0.76- 0.92].

When the analysis was stratified by level of amputation, diabetes was not shown to be significantly associated with an increased risk of mortality after AKA in any time period. There was a trend towards an increased risk of mortality over time but this was not statistically significant. All other independent variables that had associations with mortality in the unstratified analysis remained significant apart from history of MI. Again, a history of limb salvage procedure was the only variable associated with a reduction in the risk of mortality (HR 0.85 [0.74-0.97]). For BKA there was an association between diabetes and mortality. There was a statistically significant reduction in the risk of mortality for the population with diabetes in the time period between 0 and 30 days (HR 0.61 [0.38-0.99]). There was an increased risk of mortality seen for the time periods over 1 year, with the greatest risk of

mortality associated with diabetes seen between 3 to 5 years (HR 1.73 [1.24-2.43]). All other independent variables that had associations with mortality in the unstratified analysis remained significant apart from history of CCF. A history of a prior limb salvage procedure again was the only variable associated with a reduction in risk of mortality (HR of 0.81 [0.70-0.93]). Increasing WIMD quintile was associated a decreasing risk of mortality when controlling for other variables. Compared to the most deprived quintile, patients in the least deprived quintile (WIMD quintile 5) were 21% less likely to die at any time point within the follow up period (HR 0.79 [0.63-0.99]).

For the population with diabetes the leading cause of death as reported following major amputation was coronary heart disease (n=269, 26.5%). The second leading cause of death for the population was recorded as 'diabetes mellitus' (n=189, 18.6%) and the third cause was 'other circulatory causes', recorded for 10% (n=102) of patients. For this population the main disease within the 'other circulatory causes' category was PVD (n=33) recorded for 32.4% of the deaths. For the population without diabetes the leading cause of death following major amputation was other circulatory causes (n=236, 25.7%). The majority of deaths were attributed to PVD, recorded as the underlying cause in 175 cases, 74.2% of the deaths in the other circulatory cause category and 19% of all deaths. PVD was recorded for more deaths than the secondary leading cause of death, coronary heart disease, resulting in 131 deaths (14.3%).

Discussion

This population-based study examined mortality following incident amputation in the Welsh population between 2006-2013 with a minimum 5-year follow-up period. The analysis was

stratified by amputation level with the main focus to examine the effect of diabetes as a predictor of mortality. This is the first study investigating mortality following incident amputation secondary to diabetes within the Welsh population.

As expected, the mortality following major amputation was high. The mortality rate was 61.9% at 5 years in the total population and 67% in the population with diabetes. Direct comparison of mortality rates following amputation can be difficult due to differences in population, amputations definition and reporting. However, the findings were congruent with a global systematic review of mortality following amputation [2] where an estimated 5-year mortality rate post major amputation of between 52% and 80% was reported.

A mortality rate of 9.2% at 30 days highlights the frailty of the study population. This finding was comparable with an estimated mortality rate of 10% presented in studies from other western populations [8, 28, 29] and lower than that seen in Scandinavian studies with a reported rate of between 19-30% [4, 30, 31]. Differences in health service provision and clinical decision making may explain some of this variation. It is suggested that in Scandinavian populations major amputation is utilised more frequently within a palliative setting for pain relief in critical limb ischaemia than within the UK [2].

The main dependant variable of interest within the study was the effect of diabetes status on mortality risk over time. When controlling for other variables in the first time period after incident major amputation, mortality was lower in the population with diabetes compared to those without. Subsequently, this risk reversed and at 1 year the mortality risk for persons with diabetes was significantly increased compared to those without. The influence of diabetes on survival after major amputation has previously been described as time

dependent, with diabetes showing a similar [5,6,7] or reduced risk [8,9] of mortality in the short-term but an increased risk of mortality in the long-term. It has been postulated that the initial decrease in mortality risk is due to a greater frequency of monitoring by multiple specialists over the initial period. As demonstrated in this study, the population with diabetes often have a greater number of co- morbid conditions [8]. However, it would be expected that as the population with diabetes have a greater number of co-morbidities, they would be frailer at the time of procedure and the burden of the operation would be greater, increasing the risk of post- operative mortality [32]. This is suggestive that the decreased risk of mortality in the initial time period is in relation to care provision rather than due to patient characteristics. People with diabetes are more likely to undergo BKA due to the pattern of vascular involvement in PVD in diabetes [33]. This was demonstrated in this population with BKA occurring as the incident major amputation in 61.7% of the population with diabetes and only 40.4% in the population without. Patients who undergo BKA are often younger, as was found in this study, and have been shown to have a longer survival than those undergoing AKA [7] which could explain some of the short term variance in survival for the population with diabetes in the unadjusted model. However, this variance held true after adjusting for amputation level. It is also possible that death was a competing risk factor and more patients with diabetes and disease severe enough to require major amputation may have been palliated or died prior to procedure. This is an area that requires further research.

There is some disagreement within the literature regarding mortality within the population with diabetes. Several studies examining mortality following major amputation reported no associated increased risk of death with a history of diabetes [2]. The majority of these studies were not stratified by time and were not population based. Icks et al, reported similar findings

of an intial decreased risk of mortality and subsequent increase [8] in their time-stratified study of the German population between 2004-2007. The trend was again reflected in the findings of Subaramaniam et al [7] in an American population. Other authors found no association with diabetes and mortality in time-stratified analysis, but the methods used for assessing time-trend varied. Fortington et al [4] used logistic regression to compare the characteristics of those who died with those who did not at different time points rather than utilising a time dependent analysis which may explain some of the variance in findings, along with variance in study populations and definitions of amputation.

When the analysis was stratified for level, the effect of diabetes on the risk of death was only significant for BKA. For those patients undergoing AKA there was no significant difference in mortality risk associated with diabetes during any follow-up period. There is no other stratified analysis in the literature to compare with, but these findings suggest that these procedures occur in the most morbid patients in both populations, mitigating the effect of diabetes. The highest level of amputation is chosen as the priority for the procedure is post-operative wound healing reducing the risk of further procedure [34]. When the results were stratified by age and amputation level, survival time was considerably shorter for all age categories in both populations with and without diabetes undergoing AKA, again suggesting that these individuals are frailer at the time of procedure.

A history of PVD increased the risk of post-operative mortality. For those undergoing incident major amputation, 80% of patients had a history of PVD. Despite this, only 34% had undergone a limb salvage procedure in the two years prior to amputation and the percentage of patients undergoing a limb salvage procedure in the diabetes population compared to the number of patients with PVD in the non-diabetes population was even lower. This is

concerning as a history of limb salvage procedure was the only factor associated with a reduced the risk of mortality in this analysis. Patients undergoing limb revascularization will have had access to secondary care services prior to the requirement for amputation and are often more often optimized regarding medical therapy, which partly may explain this finding. NICE guidance [35] recommends attempting limb salvage procedures prior to amputation for PVD when possible, therefore the number of procedures performed within this population seems low. This may reflect that many patients were admitted with critical limb ischaemia without revascularisation option. People with diabetes are more likely to have asymptomatic PVD [36] and thresholds for limb salvage procedures may not be met as readily as the diagnosis is often dependent on rest pain [35] which may explain the lower number of procedures performed. This was not evaluated within this study.

The main strength of the study was that it was a population analysis; not only had this population not been investigated before, it is one of the few studies of amputation mortality that has examined an entire population. The long study period, with a minimum of 5-year follow-up for all persons allowed a large sample size to be maintained to the end analysis point of 5-year mortality. As the data were analysed in SAIL, it was also possible to assess cause of death from the national ADDE, which had not previously been reviewed in other studies.

Several limitations must be considered. As with any analysis using hospital data, the findings are only as reliable as the coding. Although smoking status was available for some patients through PEDW data this coding has been shown to be unreliable. For a subset of patients, it was possible to assess smoking status more reliably using GP records but as there is not full GP coverage for the entire Welsh population within SAIL, these data could not be used in the

entire population analysis. This was also true of other clinical variables such as HbA1c, cholesterol or a history of ulceration prior to amputation. These variables would have helped to further assess disease severity and may have increased the predictive value of the Cox regression models.

As discussed in the methodology a decision was made to include all amputation types. This is in line with other national studies and PHE analysis [15, 16, 17] as diabetes is associated with an increase in the incidence of [37, 38] and association with poorer outcomes of traumatic lower limb injuries [39]. As well as an increase in the incidence of [40] and association with poorer outcomes such as mortality of soft tissue and bone cancers such as sarcoma [41]. However, despite the incidence of these amputations contributing a small percentage to the overall burden of amputation in similar populations [34, 38,42], as there is variance in the pathogenesis and prognosis of these amputations this will affect the generalisability of the study.

Diabetes was associated with an increased risk of mortality in the five years following major amputation. This finding is concerning as diabetes is the leading cause of non-traumatic amputation within the UK and within Wales [12]. With limb salvage procedures the only modifiable risk factor within the analysis to infer a survival benefit, this could be an area for further research within this population along with other aspects of preoperative and preventative care.

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Appendix 1

All primary medical risk factors listed above, excluding ESRD, were identified from a 5 year look back period from the index date using ICD 10 codes (Table 2). ESRD was identified from inpatient admission codes using the standards described by the UK BIOBANK(UK Biobank, 2017a). Again, a 5 year look back period from index date was applied.

A previous limb salvage attempt by arterial bypass, angioplasty or a combination of both procedures was identified for each patient using coding methods described in previous papers examining PVD outcomes (P. W. Moxey et al., 2011b). A history of limb salvage was recorded if the procedures had occurred within a 2-year look-back period from the index date. The length of the look back period was adopted as the risk of amputation following attempted limb salvage and mortality associated with limb salvage has been shown to plateau at two years (Darling et al., 2018). Progression to amputation or any effect on mortality associated with the procedure would less likely be related to the limb salvage attempt after that point.

Table 1. RCS Charlson morbidity index disease categories and ICD 10 codes (Armitage & van der Meulen, 2010)

Disease category	ICD-10 codes
AIDS/HIV infection	B20–B24
Any malignancy	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C80–C85, C88, C90–C97
Cerebrovascular disease	G45, G46, I60–I69
Chronic pulmonary disease	I26, I27, J40–J45, J46*, J47, J60–J67, J684, J701, J703
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Dementia	A810, F00–F03, F051, G30, G31
Diabetes mellitus	E10–E14
Hemiplegia or paraplegia	G114, G81–G83
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Metastatic solid tumour	C77–C79

Myocardial infarction	I21*, I22*, I23*, I252
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959
Renal disease	I12, I13, N01, N03, N05, N07, N08, N171*, N172*, N18, N19*, N25, Z49, Z940, Z992
Rheumatological disease	M05, M06, M09, M120, M315, M32–M36

*Indicates acute condition included only if present within hospital admission record within preceding year

Table 2. ICD 10 codes
history of limb salvage procedures, HTN, ESRD, MI, CVA, congestive cardiac failure (CCF), PVD
(i) History of limb salvage procedures

Anatomical subgroup	OPCS-4 codes
Extra-anatomical bypass	L16
Iliac bypass	L20.6, L21.6, L50, L51, L52, L65.2
Iliac angioplasty	L54
Femoroproximal bypass	L58.1, L58.2, L58.3, L59.1, L59.2, L59.3, L60
Femorodistal bypass	L58.4, L58.5, L58.6, L58.7, L59.4, L59.5, L59.6, L59.7
Femoral angioplasty	L63.1, L63.5, L63.8, L63.9
Unspecified lower limb angioplasty	L66.2, L66.5, L66.7, L66.8, L66.9, L71.1, L71.5, L97.2

(ii) Comorbidities other than ESRD

Comorbidity	ICD-10 codes
Cerebrovascular accident	G45, G46, I60–I69
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Hypertension	I10, I11, I12,I13,I15
Myocardial infarction	I21*, I22*, I23*, I252
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959

(iii) ESRD - End Stage Renal Disease Detected in Hospital Admission as per UK Biobank protocol (UK Biobank, 2017b)

Step 1:

ICD 10 and OPCS 4 codes from hospital admissions are used to create variable categories that identify participants who received any RRT (and within this category those who received a kidney transplant or peritoneal dialysis which was assumed to be for maintenance RRT), and those with indicators of CKD stage 5:

Indicator	ICD-10/OPCS-4 codes
Renal replacement therapy	E85.3, N16.5, T82.4, T86.1, Y60.2, Y61.2, Y62.2, Y84.1 , Z49.0, Z49.1 ,Z49.2, Z94.0, Z99.2, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M08.4, M17.4, M17.8, M17.9, X40.1, X40.2, X40.3, X40.4, X40.5, X40.6, X40.7, X40.8, X40.9, X41.1,X41.2, X41.8, X41.9, X42.1, X42.8, X42.9, X43.1
Renal replacement therapy maintenance	N16.5, T86.1, Z49.2, Z94.0, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M08.4, M17.4, M17.8, M17.9, X40.2, X40.5, X40.6, X41.1,X41.2
CKD 5 indicator	E85.3, N16.5, N18.0, N18.5, T86.1, Z94.0, L74.1, L74.2, L74.3, L74.4, L74.5, L74.6, L74.8, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M02.3, M08.4, M17.2, M17.4, M17.8, M17.9, X40.2, X40.5, X40.6, X41.1,X41.2

Step 2: ICD 10 and OPCS 4 codes are combined to create the following Derived Phenotypic Variables (DPVs).

DPV Category	Description	Rules
DPV_COMPOSITE_ANY_RRT	Any renal replacement therapy (RRT: dialysis or transplantation), i.e. includes both acute or maintenance RRT	Any participant with RRT =1 should be considered DPV_COMPOSITE_ANY_RRT=1. For this outcome, first and any subsequent records need to be recorded with all the relevant dates.
DPV_COMPOSITE_ESRD_TX_OR_PD	CKD stage 5 treated by transplantation or peritoneal dialysis	Any participant with MAINTENANCE_RRT=1 should be considered DPV_COMPOSITE_ESRD_TX_OR_PD=1. Use the earliest date of these records as the date.
DPV_COMPOSITE_CKD5_INDICATOR	Any CKD stage 5 indicator	Any participant with CKD5_INDICATOR=1; should be considered DPV_COMPOSITE_ CKD5_INDICATOR = 1. For this outcome, first and any subsequent records need to be recorded with all the relevant dates.

Step 3: Participants without evidence of a CKD stage indicator are excluded (i.e. those with acute kidney injury are excluded).

DPV Category	Description	Rules
DPV_COMPOSITE_ESRD_ONRRT	CKD stage 5 treated with renal replacement therapy identified using CKD stage 5 indicators	A record of DPV_COMPOSITE_ANY_RRT = 1 with (a) a record in DPV_COMPOSITE_CKD5_INDICATOR = 1 before the record in DPV_COMPOSITE_ANY_RRT=1, OR (b) a record in DPV_COMPOSITE_CKD5_INDICATOR = 1 on or within 365 days of the record in DPV_COMPOSITE_ANY_RRT = 1. - Use the earliest date of a record in DPV_COMPOSITE_ANY_RRT = 1 that fulfills one of these criteria as the date.
DPV_COMPOSITE_ESRD_ONRRT_COMBINED	Combined CKD stage 5 treated with RRT	Any participant with DPV_COMPOSITE_ESRD_TX_OR_PD = 1 or DPV_COMPOSITE_ESRD_ONRRT = 1. Use the earliest date of these records as the assigned case date.

Step 4: Any participant with DPV_COMPOSITE_ESRD_ONRRT_COMBINED=1 after implementation of the above algorithm steps is deemed to be an ESRD case detected by hospital admission EHRs.