Do patients have a worse outcome with heart failure than cancer? A primary care based cohort study with 10-year follow-up in Scotland

Short title: Outcomes in heart failure and cancer

Mamas A. Mamas[1,2], Matthew Sperrin[2], Margaret C. Watson[3], Alasdair Coutts[4], Katie Wilde[4], Christopher Burton[5], Umesh T. Kadam[6], Chun Shing Kwok[1,7], Allan B Clark[8], Peter Murchie[5], Iain Buchan[2], Philip C Hannaford[5], Phyo K. Myint[7]

1. Keele Cardiovascular Research Group, University of Keele, Stoke-on-Trent; Royal Stoke Hospital, University Hospital North Midlands, Stoke-on-Trent, UK.

2. Farr Institute, University of Manchester, Manchester, UK.

3. School of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY

4. Research Applications and Data Management Team, IT Services, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD.

5. Centre of Academic Primary Care, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, AB25 2ZD.

6. Institute of Science and Technology in Medicine, University of Keele, Stoke-on-Trent, UK.

7. Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, AB25 2ZD.

8. Norwich Medical School, University of East Anglia, Norfolk, UK.

Corresponding author:

Mamas A. Mamas

Professor of Cardiology

Keele Cardiovascular Research Group

University of Keele

Stoke-on-Trent, United Kingdom

Email: mamasmamas1@yahoo.co.uk

Abstract

Aims: To evaluate whether the survival rates of patients with heart failure (HF) in the community are better than those with a diagnosis of the 4 most common cancers in men and women in a contemporary primary care cohort in Scotland.

Methods and Results: The data were obtained from the Primary Care Clinical Informatics Unit from a database of 1.75 million people registered with 393 general practices in Scotland. Sex-specific survival modeling was undertaken using Cox proportional hazards models, adjusted for potential confounders. A total of 56,658 patients were eligible to be included in the study with 147,938 person years follow up (median follow up 2.04 years). In men, heart failure (reference group; 5yrs survival 37.7%) had worse mortality outcomes than patients with prostate cancer (HR 0.61, 95%CI 0.57-0.65; 5yrs survival 49.0%), and bladder cancer (HR 0.88, 95%CI 0.81-0.96; 5yrs survival 36.5%), but better than lung cancer (HR 3.86, 95%CI 3.65-4.07; 5yrs survival 2.8%) and colorectal cancer (HR 1.23 95%CI 1.16-1.31; 5 yrs survival 25.9%). In women, patients with HF (reference group; 5yrs survival 31.9%) had worse mortality outcomes than patients with breast cancer (HR 0.55 95%CI 0.51-0.59; 5yrs survival 61.0%), but better outcomes than lung cancer (HR 3.82, 95%CI 3.60-4.05; 5yrs survival 3.6%), ovarian cancer (HR 1.98, 95%CI 1.80-2.17; 5yrs survival 19%) and colorectal cancer (HR 1.21, 95%CI 1.13-1.29; 5yrs survival 28.4%).

Conclusions: Despite advances in management, heart failure remains as ‘malignant’ as some of the common cancers in both men and women.

Keywords:

- Heart failure
- Cancer
- Mortality

Introduction

Cardiovascular disease is the commonest cause of death globally, accounting for an estimated 17.5 million deaths in 2012 – around a third of all deaths worldwide.[1] Heart failure (HF) represents the end phenotype of many cardiovascular disorders and has a prevalence of around 1-2% in the general population, rising to >10% in individuals aged 70 years or older. HF is also the commonest cause of hospitalization in the over 65s.[2] Advances in pharmacological and intra-cardiac device based therapies have reduced mortality rates in patients with heart failure by as much as 50% over the past decade, but both short and long term mortality rates remain significant.[3-5] The adverse outcomes associated with heart failure have drawn comparisons to those of cancer amongst many commentators, including international cardiological societies.[7]

Collectively cancer is the second leading cause of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012.[8] As with cardiovascular disease, improved treatments over recent decades have reduced mortality rates from many cancers.[5,] A previous comparative analysis of patients with a first admission to Scottish hospitals in the UK in 1991 with HF and the four most common types of cancer specific to men and women, suggested that, with the exception of lung and ovarian cancer, HF had a similar or worse five-year survival rate than the remaining cancers.[9] A comparable analysis of over 1.1 million hospital admissions in Sweden from 1998-2004 reported similar findings.[5]

Important limitations of these findings include the observation that a first hospital admission for many cancers frequently relates to elective surgery or investigations [5], whilst that for HF often represents an acute heart failure syndrome. These differences will bias survival comparisons towards worse outcomes for HF. Furthermore, until now, there has been no attempt to adjusted for comorbid burden,[5,9] which has been increasingly recognised as important confounding factor in this patient population that could substantially affect survival.

Finally, whilst improved survival rates have been reported for patients diagnosed with HF and for many cancers over the past decade, that may have occurred at different rates in diagnostic groups, past comparisons, therefore, may no longer hold. In view of limitations of the previous studies highlighted above, it is possible that the survival rates of patients with heart failure in the community are significantly better than those with a diagnosis of cancer in contemporary practice,

particularly when differences in co-morbid burden are taken into account. We report here an analysis of outcome in patients in care cohorts derived from a national primary care database in Scotland to investigate whether the often quoted "HF is as malignant as cancer" still holds in contemporary practice.

Methods

Study Design and Setting

The data for this study were obtained from the Primary Care Clinical Informatics Unit (PCCIU).[10,11] In brief, PCCIU was founded in 1999 to feedback information to practices about aspects of clinical care as part of Royal College of General Practitioners Scotland Programme of Clinical Improvement and Effectiveness (SPICE). The work involved collecting anonymized clinical information bi-annually between 2000 and 2011 from 393 practices across Scotland caring for about a third of the Scottish population with data from 1.75 million patients and are representative of the Scottish population with a similar spread of age, gender, material deprivation and rurality.[12]

We carried out a retrospective analysis of PCCIU cohort; our population was all adults aged 16 years or older with an incident diagnosis of either heart failure or a cancer between 1 April 2002 and 31st March 2011 (the last update of the PCCIU dataset). The first three years of PCCIU (1 April 1999 – 30 March 2002) were used to mitigate the risk of including prevalent cases: patients with diagnosis codes for either heart failure or cancer in this period were excluded. Included cancers were restricted to the four most common by gender: prostate, lung, colorectal and bladder cancer for men; breast, colorectal, lung and ovarian cancer for women. The Read codes (the clinical coding system used in UK general practice to record patient diagnoses and procedures in health-care IT systems) for these diagnoses are given in Supplementary Tables 1A and 1B. The primary exposure was first entry of the diagnosis of HF or cancer type on the healthcare record, and date of diagnosis was the index date. Patients with both a HF and cancer diagnosis present were assigned to the cohort of patients with whichever diagnosis was made first. When possible, we based our morbidity definitions on Quality Outcomes Framework (QOF) (http://qof.digital.nhs.uk/) business rules[13] and read code groups for long-term disorders (as defined by NHS Scotland).[14] QOF is the world's largest pay-for-performance programme. It was introduced for all family practices in 2004, linking up

to 25% of family practitioners' income to performance for more than 100 publicly reported quality indicators relating to management of chronic disease, organisation of care, and patient experience. A significant proportion of a family practitioners income will depend on maintaining a register of patients with a particular diagnosis (such as HF and cancer diagnosis) and will also relate to the proportion of such patients that receive evidence based care.

The primary outcome was survival time to all-cause mortality. Potential confounders that we accounted for included: age at index diagnosis (continuous variable), material deprivation (Scottish index of material deprivation, in quintiles with 1= least deprived and 5 = most deprived), rurality (urban/rural index, 6 levels, with 1 representing most urban and 6 remote rural), smoking, comorbidities (before index date only). These confounders were treated as ever/never terms – i.e. they were not time-varying. Comorbidities were initially selected and derived from READ codes following Barnett et al.[10] A shortlist of these (Hypertension, Depression, Asthma, Coronary Heart Disease, Diabetes, Thyroid disease, Rheumatoid Arthritis, COPD, Stroke or TIA, Chronic Kidney Disease, Atrial Fibrillation, Peripheral Vascular Disease, Epilepsy, Dementia, Schizophrenia, Bronchiectasis, Parkinsons Disease, Multiple Sclerosis, Viral Hepatitis, Chronic Liver Disease, Previous Myocardial Infarction) was then used for subsequent modeling. Comorbidities diagnosed after the index date, and all medications for HF (diuretics, aldosterone receptor antagonists, beta blockers, ACE-inhibitors, angiotensin receptor blockers, anti-platelets and lipids) were not considered in multivariable models (Supplementary Table 2). Data cleaning included removal of patients with missing information on deprivation and rurality, and logical conflicts in dates of recorded events. Imputation of deprivation and rurality was considered but the proportion of patients missing these fields was low (1.94%) and it was felt reasonable to assume that these fields were missing completely at random. The majority of the clinical variables were binary indicators of presence of a clinical code; the associated condition or medication was assumed to be absent if the code was absent.

Statistical Methods

Descriptive statistics were presented as means with standard deviations, or proportions; these were stratified first by gender and then by primary exposure. These were compared between exposure groups using ANOVA (to compare means) or Chi

squared tests (to compare proportions), with the *P*-values reported. The number of comorbidities was compared between disease groups graphically; survival was compared between groups using Kaplan-Meier plots.

Sex-specific survival modeling was carried out using Cox proportional hazards models. Three models were considered: first a univariable model with the primary diagnosis only; second a model corrected for demographic variables of age and deprivation; and finally a fully adjusted model that corrected for all confounders described above - i.e. age, deprivation, rurality, smoking, and all of the comorbidities described above that were diagnosed before baseline. Many of these confounders described may be highly correlated, which may make their effect sizes and standard errors difficult to interpret. However, we do not make any inference about these. We did not correct for any medications, as these may act as mediators. Continuous variables such as age were treated as linear. The proportional hazards assumption was checked using Schoenfeld residuals.[15] All analyses were carried out using R version 3.0.2.[16]

Results

A total of 58,412 patients met the study inclusion criteria from a database of 1.75 million people registered with 393 medical practices in Scotland. Following exclusions of 1754 patients; 3.0% (1119 patients with missing deprivation data and 635 patients in which date of death was the date of diagnosis, or could not establish date of loss to follow up) the final dataset comprised 56,658 patients. There were 28,064 men and 28,594 women and mean age at first diagnosis was 69.16 (SD 12.76) years. Median follow-up was 2.04 years and there were 147,938 person years in total. There were 6,795 men with prostate, 4,693 lung, 4,239 colorectal and 2,028 bladder cancer, and 10,309 with heart failure. Among the women, 10,760 had breast, 3,610 colorectal, 3,859 lung and 1,234 ovary cancer, and 9,131 heart failure.

Descriptive sample characteristics are presented in Table 1 for men and Table 2 for women. In men, the age at cancer and heart failure diagnoses were similar whilst in women heart failure diagnosis occurred later in life than cancer. Patients with heart failure, both men and women, had more comorbidities than those with cancer; only 5.5% of heart failure patients of either gender, had no comorbidity, compared with 20 to 38% of patients with a diagnosis of cancer. The mean number of comorbid conditions was also greater in patients with heart failure compared to those patients

diagnosed with cancer. Male patients with heart failure had a mean number of comorbidities of 2.62 (SD 1.55), whilst in patients diagnosed with prostate cancer (mean 1.47, SD 1.38), lung (1.79, SD 1.56), colorectal (1.52, SD 1.49) and bladder cancer (mean 1.71, SD 1.52) mean number of comorbidities were less. Similar observations were recorded in women with mean comorbidity number greater in patients diagnosed with heart failure (2.8, SD 1.61) than breast (1.19, SD 1.31), colorectal (1.52, SD 1.46), lung (1.95, SD 1.6) and ovarian cancer (1.21, SD 1.32). The number of comorbidities at index date in each disease and gender group is shown in Figures 1a and 1b.

30-day, one-year and five-year crude mortality rates are also presented in Tables 1 and 2. The largest crude mortality rates occurred in patients with lung cancer, with 8.7% of men and 9.3% of women dying within 30 days. The lowest crude mortality rates were recorded in women diagnosed with breast cancer (0.5%) and men diagnosed with prostate cancer. 30 day mortality rates for men following diagnosis with heart failure were 1.5% and 2.2% for women whilst at 1 year mortality rates were 14.5% and 17.7% respectively.

Kaplan-Meier plots for overall survival in years since diagnosis are presented in Figure 2. The main Cox proportional hazards model results are presented in Table 3. Men with prostate (HR 0.61 95% CI 0.57-0.65, $P<0.001$) or bladder cancer (HR 0.88 95% CI 0.81-0.96), $P<=0.005$) had better survival than those with heart failure, while those with lung (HR 3.86 95% CI 3.65-4.07), $P<0.001$) or colorectal cancer (HR 1.23 95% CI 1.16-1.31, $P<0.001$) generally fared worse. Women with breast cancer (HR 0.55 95% CI 0.51-0.59, $P<0.001$) had better survival than those with heart failure, while those with lung (HR 3.82 95% CI 3.60-4.05, $P<0.001$), ovarian (HR 1.98 95% CI 1.80-2.17, $P<0.001$) or colorectal cancer (1.21 95% CI 1.13-1.29, $P<0.001$) fared worse.

All models showed some deviation from proportional hazards. Deviations still existed in the fully corrected models, but were minor and so should not affect the interpretation of the results (see Supplementary Table 3A and 3B).

Discussion

Our analysis is the first to compare survival outcomes in a primary care setting of patients with a diagnosis of heart failure and the 4 most common cancers in men and women in a contemporary cohort of patients treated with current evidence based practice that has changed dramatically over the two decades since the older studies first reported outcomes following first time hospital admission with a diagnosis of heart failure or cancer. Despite advances in care, we found that men and women with a diagnosis of heart failure continue to have a worse survival than patients with one of several common cancers. Our findings are particularly relevant given that the current analysis overcomes many of the limitations of previous work particularly around admission bias for different conditions and differences in co-morbid burden between the patients with HF and cancer.

Advances in both the medical and device based treatments, have been associated with improved survival rates in patients with HF in many[17-20] but not all national registry-based studies.[21] Age-standardized death rates from heart failure have been reported to decrease by 40% in seven European countries between 1987 and 2008.[4] An analysis of all patients in Scotland hospitalised with a first episode of heart failure between 1986 and 2003 demonstrated relative declines in short- and medium-term case-fatality rates of 40-50% in men and 20-25% in women; changes associated with significant increases in ACE inhibitor and beta blocker use over this period.[17]

There are limited data regarding longer-term outcomes of incident heart failure in the community. Our analysis suggests that mortality rates in patients with this condition remain significant. Our observed 1- and 5-year mortality rates of 13% and 35% respectively in males, and 15% and 40% in females from time of first recorded diagnosis of HF are lower than mortality rates recorded following an acute admission to hospital for HF,[22,23] probably because the latter population comprise a sicker cohort. Our mortality rates were similar to the 5-year mortality rate of 38% reported in a contemporary community cohort derived assembled in Ireland following a new diagnosis of HF.[24] Similarly, the ECHOES community based screening study, reported 5-year mortality rates of 38% for those with HF with preserved ejection fraction (HFPEF), and 47% with HF with reduced ejection fraction (HFREF)[25] although this was a cross sectional analysis and did not report on survival from time of diagnosis. Similarly data derived from Olmsted County reported a 5-year survival of 45%, but again was a cross-sectional survival analysis from the time of initiation of

the study rather than the time of diagnosis of HF introducing bias towards worse outcomes.[26]

HF survival rates, and that of many cancers, have improved over the past decade, but these improvements have occurred at different rates in HF and cancer populations. For example, an analysis by Stewart et al. of hospital admissions from Sweden[5] suggested that survival rates for heart failure admissions had improved by a greater margin each calendar year than those observed for the cancers studied. Whilst our analysis is not subject to many of the limitations of previous analyses such as admission bias and failure to adjust for type and number of comorbidities,[5,9] our findings are remarkably similar to those reported initially by Stewart et al[9] and subsequently from hospital admission data derived from Sweden.[5] This suggests that even in a more contemporaneous cohort (by at least a decade) a diagnosis of HF remains as 'malignant' as that of some cancers. Our findings were broadly consistent when the data were stratified by comorbid burden and age of diagnosis.

The burden of comorbidity among patients with HF is significant.[27] Only 3% of patients with HF have no recorded comorbidity whilst up to a third of patients with a cancer diagnosis had no comorbid conditions documented in their medical record. The number of comorbidities among patients with heart failure appeared to be similar in both sexes despite the average age at diagnosis for women with HF being 6 years older than that of men. Previous studies have also reported a significant comorbid burden in patients with HF and its presence is independently associated with increased mortality.[28,29] This burden appears to have increased over time.[29] In the cardiovascular network PRESERVE study undertaken between 2005-2008, less than 2% of HF patients had no comorbid conditions,[30] whilst data derived from the Spanish National Heart Failure Registry suggests that only 15% of patients with HF have no comorbidity[28] whilst only 4% individuals with HF in a Medicare dataset of 122,630 patients had no non-cardiac comorbid conditions and 40% had five or more such comorbidities.[31] It is not surprising that the burden of CV comorbidities is greatest in patients with HF given that many of them, such as diabetes mellitus, hypertension and coronary artery disease are risk factors for the future development of HF.[32] In contrast, studies of patients with cancer suggest that comorbid burden is significantly less. For instance, perhaps only half of all lung cancer patients have comorbidities[33] with even less in those with breast [34] ovarian or uterine cancers.[34]

Our data suggest that the burden of CV disease in patients with a diagnosis of cancer is also significant, with: 20% of men with a common cancer also having a diagnosis of coronary artery disease; 10-20% of either gender diagnosed with diabetes; significant rates of previous strokes or transient ischaemic attacks, particularly in men; and hypertension prevalence varying from between 30-45% in both genders. Previous registry-based studies have also reported significant CV comorbidity in patients with lung and prostate cancer.[35,36] CV comorbidity and estimated CV risk have been independently associated with worse outcomes in patients with lung and breast cancer.[35,37]

Our study also has several limitations. First, we relied on primary care coding to identify the study cohort, with no validation of the codes. Like all other observational research undertaken using data derived from electronic health care records, PCCIUR relies on clinicians' observations and entry of relevant codes into electronic healthcare records, which may be an incomplete or an inaccurate representation of patients' health. Whilst diagnoses of cancer are generally made by specialists based on imaging or biopsy information and hence robust, diagnoses of heart failure may be clinical in the first instance and may be less robust particularly in the presence of obesity or other conditions associated with dyspnea and edema. However the diagnosis of heart failure is well recorded in the United Kingdom primary care electronic healthcare records because it is an important part of the Quality and Outcomes Framework pay-for-performance scheme which includes maintenance of register of patients with a diagnosis of heart failure, and in such patients records the percentage of patients with a diagnosis of heart failure which has been confirmed by an echocardiogram or by specialist assessment 3 months before or 12 months after entry onto the register. In Scotland, the percentage of patients with a diagnosis of heart failure (diagnosed on or after 1 April 2006) which has been confirmed by an echocardiogram or by specialist assessment 3 months before or 12 months after entering on to the register is over 95%[38] suggesting that the diagnosis of heart failure is robust. Furthermore, the associated risk factor profile and survival rates among the heart failure and cancer cohort are in line with those reported in the literature for incident HF and cancer in the community. Second, whilst we were able to report on outcomes associated with a heart failure diagnosis we were unable to differentiate between heart failure with reduced ejection fraction (HFREF) or heart failure with preserved ejection fraction (HFPEF). Previous studies have suggested that

patients with HFREF have similar[39] or worse short- and long-term mortality outcomes compared to those patients with HFPEF[40] hence the comparative outcomes of HFREF or HFPEF with those of patients with a cancer diagnosis may be different. Third, whilst our analysis captures the diagnosis of cancer in the primary care health record, it does not provide information relating to the stage of cancer, whether the cancer is under remission, whether the cancer was "cured", or what cancer-related treatments were given. Finally, in order to reduce the risk of length time bias and exclude prevalent cases of HF or cancer, patients with diagnosis codes for either heart failure or cancer during the first three years of PCCIU (1 April 1999 – 30 March 2002) were excluded and only those patients registered with the practice for at least 3 months prior to their index diagnosis date were included. Nevertheless, we cannot exclude the possibility of non-incident cases of either HF or cancer included in the cohort studied, although numbers would be small.

In conclusion, the current report of over 147,938 person years of observation, is the first to compare survival outcomes in a primary care setting of patients with a diagnosis of heart failure and the four most common cancers in men and women separately. It has revealed that despite advances in management, heart failure remains as 'malignant' as some common cancers. Our results highlight the significant multi-morbidity associated with heart failure that will represent a significant challenge for delivery of healthcare in the future, particularly as the burden of heart failure continues to grow. Targeted management of the co-morbidities that are common in heart failure patient population may be associated with better survival and quality of life in this patient population.

Contributorship

MAM and PKM conceived the study and developed study protocol and analysis plan in collaboration with PCCIU Academic Team (MW, CB, PM, PH), Data management team of PCCIU (KW, AC), Medical Statistics Group at University of East Anglia (ABC) and the Farr Institute (MS, IB). Record linkage was performed by KW & AC. MS analysed the data. MAM drafted the paper. All authors contributed in interpretation of results and in making an important intellectual contribution to the manuscript. PKM and MAM are guarantors.

Acknowledgments

None.

Funding sources

MS and IB were supported by the University of Manchester's Health eResearch Centre (HeRC) funded by the Medical Research Council (MRC) Grant MR/K006665/1.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. World Health Organization. WHO Global status report on noncommunicable diseases 2014. 2014; Available from: http://www.who.int/nmh/publications/ncd-status-report-2014/en/.

2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-46.

3. Gabet A, Juilliere Y, Lamarche-Vadel A, Vernay M, Olie V. National trends in rate of patients hospitalized for heart failure and heart failure mortality in France, 2000-2012. Eur J Heart Fail 2015;17:583-90.

4. Laribi S, Aouba A, Nikolaou M, Lassus J, Cohen-Solal A, Plaisance P, Pavillion G, Jois P, Fonarow GC, Jougla E, Mebazza A. Trends in death attributed to heart failure over the past two decades in Europe. Eur J Heart Fail 2012;14:234-9.

5. Stewart S, Ekman I, Ekman T, Oden A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes. 2010;3:573-80.

6. Jaarsma T, Beattie JM, Ryder M, Rutten FH, McDonagh T, Mohacsi P, Murray SA, Grodzicki T, Bergh I, Metra M, Ekman I, Angermann C, Leventhal M, Pitsis A, Anker SD, Gavazzi A, Ponikowski P, Dickstein K, Delacretaz E, Blue L, Strasser F, McMurray J. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009;11:433-43.

7. World Health Organization. Cancer Fact sheet Nº 297. 2015; Available from: `http://www.who.int/mediacentre/factsheets/fs297/en/.

8. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunibyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015;385:977-1010.

9. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-22.

10. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380:37-43.

11. Macfarlane TV, Lefevre K, Watson MC. Aspirin and non-steroidal anti-inflammatory drug use and the risk of upper aerodigestive tract cancer. Br J Cancer 2014;111:1852-9.

12. Elder R, Kirkpatrick M, Ramsay W, Macleod M, Guthrie B, Sutton M, Watt G. Measuring Quality in Primary Medical Services Using Data from SPICE. NHS National Services Scotland: Edinburgh, Scotland; 2007.

13. NHS—Primary Care Commissioning. QOF implementation: business rules v 16.0, updated December 2009. http://www.pcc.nhs.uk/145/

14. Information Services Division, NHS National Services Scotland. Measuring long-term conditions in Scotland, June 2008. http://www.isdscotland.org/isd/5658.html

15. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika [Internet] 1994;81:515-526.

16. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: 2015. Available from: http://www.r-project.org.

17. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009;119:515-23.

18. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G, Kahan T. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. Eur J Heart Fail 2013;15:995-1002.

19. Christ M, Stork S, Dorr M, Heppner HJ, Muller C, Wachter R, Riemer U. Heart failure epidemiology 2000-2013: insight from the German Federal Health Monitoring System. Eur J Heart Fail 2016;18:1009-18.

20. Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Sorensen HT. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. Eur J Heart Fail 2016;18:490-9.

21. Teng TH, Katzenellenbogen JM, Hung J, Knuiman M, Sanfilippo FM, Geelhoed E, Bessarab D, Hobbs M, Thompson SC. A cohort study: temporal trends in prevalence of antecedents, comorbidities and mortality in Aboriginal and non-Aboriginal Australians with first heart failure hospitalization, 2000-2009. Int J Equity Health 2015;14:66.

22. Coles AH, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Darling CE, Golberg RJ. Magnitude of and Prognostic Factors Associated With 1-Year Mortality After Hospital Discharge for Acute Decompensated Heart Failure Based on Ejection Fraction Findings. J Am Heart Assoc 2015;4:e0002303.

23. Chang PP, Chambless LE, Shahar E, Bertoni AG, Russell SD, Ni H, He M, Mosley TH, Wagenknecht LE, Samadarshi TE, Wruck LM, Rosamond WD. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). Am J Cardiol 2014;113:504-10.

24. James S, Barton D, O'Connell E, Voon V, Murtagh G, Watson C, Murphy T, Prendiville B, Brennan D, Hensey M, O'Neill L, O'Hanlon R, Waterhouse D, Ledwidge M, Gallagher J, McDonald K. Life expectancy for community-based patients with heart failure from time of diagnosis. Int J Cardiol 2015;178:268-74.

25. Hobbs FD, Roalfe AK, Davis RC, Davies MK, Hare R, Midlands Research Practices C. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). Eur Heart J 2007;28:1128-34.

26. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail 2008;1:91-7.

27. Triposkiadis F, Giamouzis G, Parissis J, Starling RC, Boudoulas H, Skoulargis J, Butler J, Filippatos G. Reframing the association and significance of co-morbidities in heart failure. Eur J Heart Fail 2016;18:744-58.

28. Ruiz-Laiglesia FJ, Sanchez-Marteles M, Perez-Calvo JI, Formiga F, Bartolome-Satue JA, Armengou-Arxe A, Lopez-Quiros R, Perez-Silvestre J, Serrado-Iglesias A, Montero-Perez-Barguero M. Comorbidity in heart failure. Results of the Spanish RICA Registry. QJM 2014;107:989-94.

29. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure-associated hospitalizations in the United States. J Am Coll Cardiol 2013;61:1259-67.

30. Saczynski JS, Go AS, Magid DJ, Smith DH, McManus DD, Allen L, Ogarek J, Goldberg RJ, Gurwitz JH. Patterns of comorbidity in older adults with heart failure: the Cardiovascular Research Network PRESERVE study. J Am Geriatr Soc 2013;61:26-33.

31. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 2003;42:1226-33.

32. Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. Eur Heart J. 1987;8 Suppl F:23-6.

33. Kehl KL, Lamont EB, McNeil BJ, Bozeman SR, Kelley MJ, Keating NL. Comparing a medical records-based and a claims-based index for measuring comorbidity in patients with lung or colon cancer. J Geriatr Oncol 2015;6:202-10.

34. Sarfati D, Gurney J, Stanley J, Salmomd C, Crampton P, Dennett E, Koea J, Pearce N. Cancer-specific administrative data-based comorbidity indices provided valid alternative to Charlson and National Cancer Institute Indices. J Clin Epidemiol 2014;67:586-95.

35. Kravchenko J, Berry M, Arbeev K, Kim Lyerly H, Yashin A, Akushevich I. Cardiovascular comorbidities and survival of lung cancer patients: Medicare data based analysis. Lung Cancer 2015;88:85-93.

36. Gandaglia G, Sun M, Popa I, Schiffmann J, Trudeau V, Shariat SF, Trinh QD, Graefen M, Widmer H, Saad F, Briganti A, Montorsi F, Karakiewicz PI. Cardiovascular mortality in patients with metastatic prostate cancer exposed to androgen deprivation therapy: a population-based study. Clin Genitourin Cancer 2015;13:e123-30.

37. Onwudiwe NC, Kwok Y, Onukwugha E, Sorkin JD, Zuckerman IH, Shaya FT, Danial Mullins C. Cardiovascular event-free survival after adjuvant radiation therapy in breast cancer patients stratified by cardiovascular risk. Cancer Med 2014;3:1342-52.

38. QOF database. Data for HF002. Available at: https://www.gpcontract.co.uk/child/UK/HF002/15

39. Quiroz R, Doros G, Shaw P, Liang CS, Gauthier DF, Sam F. Comparison of characteristics and outcomes of patients with heart failure preserved ejection fraction versus reduced left ventricular ejection fraction in an urban cohort. Am J Cardiol 2014;113:691-6.

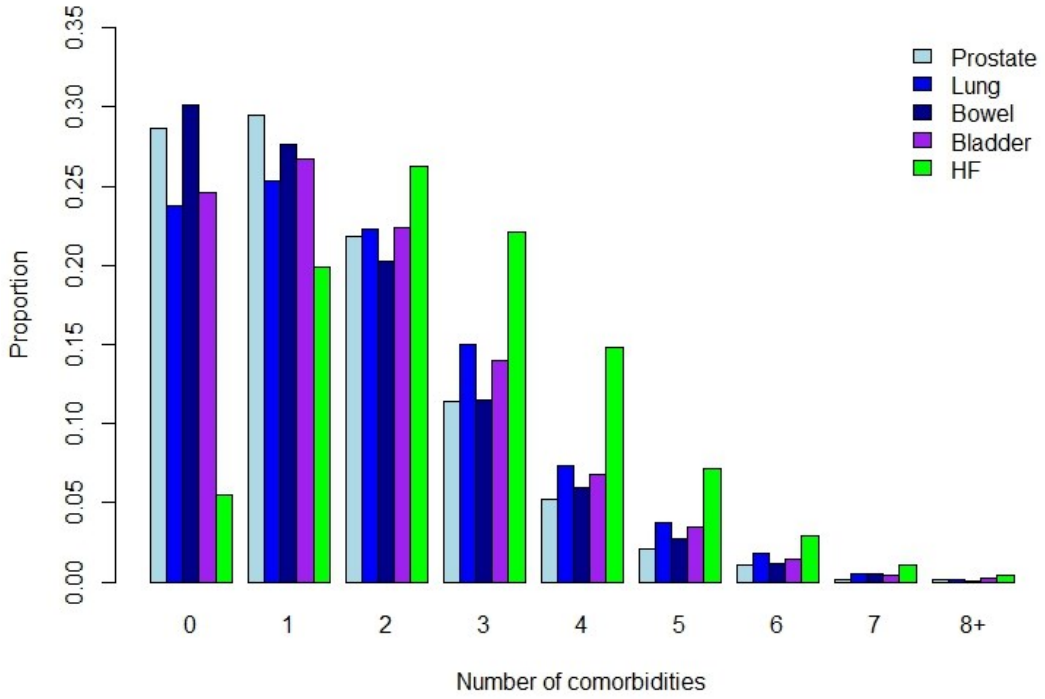
40. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750-7.

Figure Legends

Figure 1a and b: Number of comorbidities by disease group and gender.

Figure 2: Kaplan-Meier curves of overall survival, separated by gender.

Figure 1a and b: Number of comorbidities by disease group and gender.



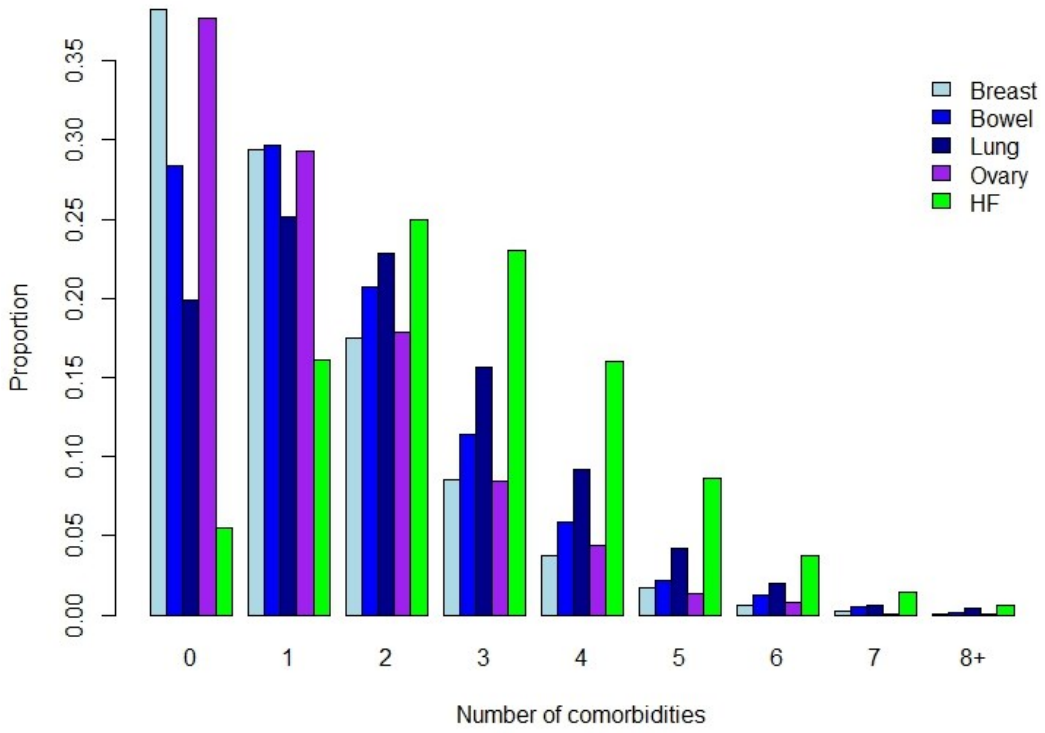


Figure 2: Kaplan-Meier curves of overall survival, separated by gender.

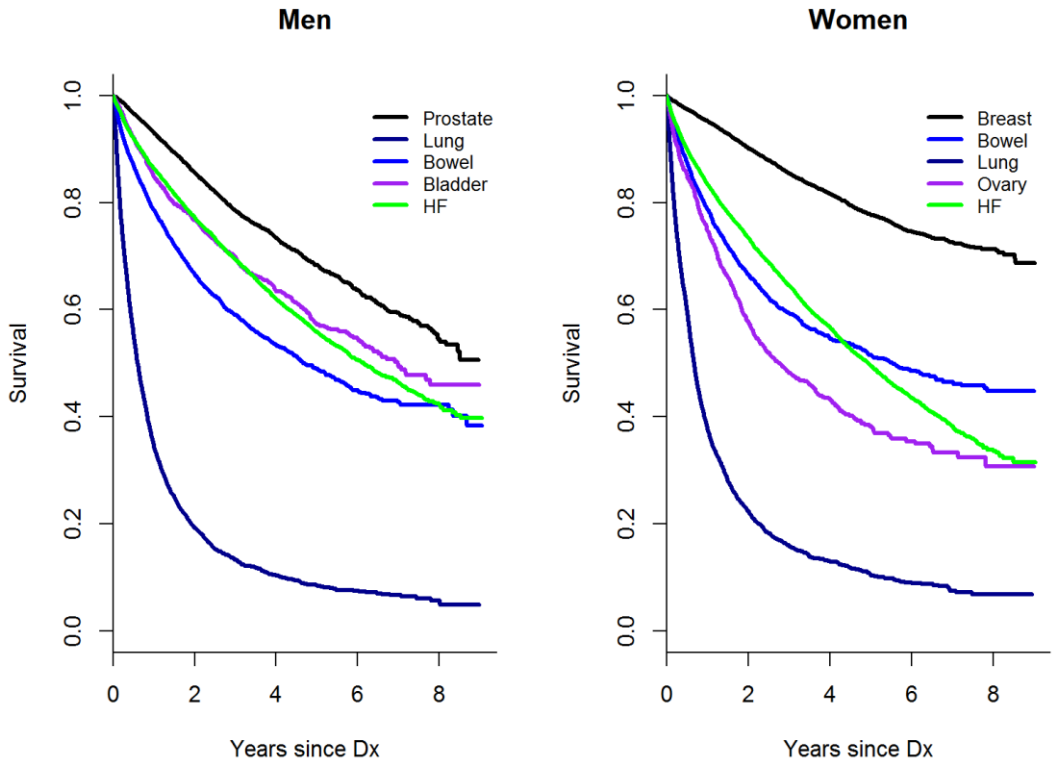


Table 1: Baseline and mortality characteristics for men.

	Prostate	Lung	Colorectal	Bladder	HF
Number of cases	6795	4693	4239	2082	10309
Age at diagnosis	70.4 (9.1)	69.1 (10.2)	68.3 (11.3)	70.2 (11.3)	70.5 (12.2)
Date of first diagnosis (median)	2005-12-22	2006-02-13	2006-01-13	2005-11-23	2005-01-05
Heart Failure	95 (1.4%)	97 (2.1%)	81 (1.9%)	41 (2%)	
Cancer					226 (2.2%)
Urban-rural index: 1 (most urban)	2151 (31.7%)	1749 (37.3%)	1429 (33.7%)	711 (35.1%)	3756 (36.4%)
2	2360 (34.7%)	1604 (34.2%)	1426 (33.6%)	722 (35.6%)	3255 (31.6%)
3	977 (14.4%)	654 (13.9%)	583 (13.8%)	288 (14.2%)	1374 (13.3%)
4	507 (7.5%)	269 (5.7%)	324 (7.6%)	100 (4.9%)	698 (6.8%)
5	481 (7.1%)	238 (5.1%)	278 (6.6%)	132 (6.5%)	686 (6.7%)
6 (most rural)	319 (4.7%)	179 (3.8%)	199 (4.7%)	75 (3.7%)	540 (5.2%)
Scottish index of multiple deprivation 1 (least deprived)	1165 (17.1%)	551 (11.7%)	608 (14.3%)	332 (16.4%)	1266 (12.3%)
2	1419 (20.9%)	712 (15.2%)	784 (18.5%)	379 (18.7%)	1732 (16.8%)
3	1401 (20.6%)	939 (20%)	862 (20.3%)	394 (19.4%)	2162 (21%)
4	1608 (23.7%)	1190 (25.4%)	1102 (26%)	516 (25.4%)	2708 (26.3%)
5 (most deprived)	1202 (17.7%)	1301 (27.7%)	883 (20.8%)	407 (20.1%)	2441 (23.7%)
non smoker	2085 (30.7%)	153 (3.3%)	942 (22.2%)	377 (18.6%)	2368 (23%)
smoker	913 (13.4%)	661 (14.1%)	430 (10.1%)	384 (18.9%)	1757 (17%)
ex-smoker	2283 (33.6%)	1033 (22%)	1345 (31.7%)	763 (37.6%)	4396 (42.6%)
smoking missing	1514 (22.3%)	2846 (60.6%)	1522 (35.9%)	504 (24.9%)	1788 (17.3%)
Number of	1.47 (1.38)	1.79 (1.56)	1.52 (1.49)	1.71 (1.52)	2.62 (1.55)

comorbidities					
No comorbidity	1949 (28.7%)	1116 (23.8%)	1278 (30.1%)	499 (24.6%)	562 (5.5%)
Hypertension	2614 (38.5%)	1515 (32.3%)	1596 (37.7%)	801 (39.5%)	4711 (45.7%)
Depression	603 (8.9%)	464 (9.9%)	358 (8.4%)	190 (9.4%)	1068 (10.4%)
Asthma	491 (7.2%)	355 (7.6%)	286 (6.7%)	124 (6.1%)	788 (7.6%)
Coronary Heart Disease	1303 (19.2%)	1091 (23.2%)	817 (19.3%)	488 (24.1%)	6295 (61.1%)
Diabetes	688 (10.1%)	562 (12%)	611 (14.4%)	314 (15.5%)	2234 (21.7%)
Thyroid Disease	202 (3%)	139 (3%)	109 (2.6%)	68 (3.4%)	480 (4.7%)
Rheumatoid Arthritis	584 (8.6%)	358 (7.6%)	382 (9%)	187 (9.2%)	1209 (11.7%)
COPD	611 (9%)	1241 (26.4%)	390 (9.2%)	237 (11.7%)	1707 (16.6%)
Stroke TIA	321 (4.7%)	445 (9.5%)	245 (5.8%)	112 (5.5%)	754 (7.3%)
CKD	550 (8.1%)	473 (10.1%)	381 (9%)	220 (10.8%)	1560 (15.1%)
AF	238 (3.5%)	168 (3.6%)	162 (3.8%)	106 (5.2%)	552 (5.4%)
PVD	388 (5.7%)	285 (6.1%)	250 (5.9%)	115 (5.7%)	2519 (24.4%)
Epilepsy	295 (4.3%)	508 (10.8%)	231 (5.4%)	149 (7.3%)	1153 (11.2%)
Dementia	78 (1.1%)	83 (1.8%)	57 (1.3%)	29 (1.4%)	172 (1.7%)
Schizophrenia	82 (1.2%)	72 (1.5%)	47 (1.1%)	46 (2.3%)	230 (2.2%)
Bronchiectasis	31 (0.5%)	60 (1.3%)	27 (0.6%)	14 (0.7%)	86 (0.8%)
Parkinsons Disease	32 (0.5%)	22 (0.5%)	15 (0.4%)	6 (0.3%)	54 (0.5%)
Multiple Sclerosis	50 (0.7%)	17 (0.4%)	22 (0.5%)	11 (0.5%)	100 (1%)
Viral Hepatitis	11 (0.2%)	3 (0.1%)	6 (0.1%)	2 (0.1%)	18 (0.2%)
Chronic Liver Disease	2 (0%)	4 (0.1%)	2 (0%)	0 (0%)	3 (0%)
Previous MI	657 (9.7%)	563 (12%)	442 (10.4%)	261	4448

				(12.9%)	(43.1%)
CABG	416 (6.1%)	239 (5.1%)	233 (5.5%)	127 (6.3%)	1956 (19%)
Diuretics	2406 (35.4%)	1279 (27.3%)	1402 (33.1%)	699 (34.5%)	8189 (79.4%)
Aldosterone receptor antagonist	464 (6.8%)	114 (2.4%)	218 (5.1%)	130 (6.4%)	741 (7.2%)
B-Blockers	1819 (26.8%)	733 (15.6%)	1048 (24.7%)	580 (28.6%)	6307 (61.2%)
ACE	1352 (19.9%)	451 (9.6%)	704 (16.6%)	396 (19.5%)	3634 (35.3%)
Angiotensin receptor antagonist	580 (8.5%)	165 (3.5%)	245 (5.8%)	149 (7.3%)	1727 (16.8%)
Anti-platelet agents	3014 (44.4%)	1565 (33.3%)	1600 (37.7%)	944 (46.5%)	7683 (74.5%)
Lipid lowering agents	2889 (42.5%)	1184 (25.2%)	1516 (35.8%)	903 (44.5%)	7143 (69.3%)
Dead 30 days after diagnosis	25/6759 (0.4%)	405/4647 (8.7%)	102/4196 (2.4%)	22/2017 (1.1%)	156/10254 (1.5%)
Dead 1 year after diagnosis	439/5862 (7.5%)	2879/4255 (67.7%)	850/3671 (23.2%)	290/1786 (16.2%)	1343/9322 (14.4%)
Dead 5 year after diagnosis	1442/2829 (51%)	3707/3812 (97.2%)	1616/2181 (74.1%)	621/978 (63.5%)	3430/5508 (62.3%)
Dead (ever recorded)	1586/6795 (23.3%)	3727/4693 (79.4%)	1671/4239 (39.4%)	655/2028 (32.3%)	3713/10309 (36%)

Categorical variables given as number (percentage); continuous variables given as mean (standard deviation), unless otherwise stated.

Table 2: Baseline and mortality characteristics for women.

	Breast	Colorectal	Lung	Ovary	HF
Number of cases	10760	3610	3859	1234	9131
Age at diagnosis	61.3 (14.0)	70.0 (13.1)	69.7 (10.7)	62.7 (14.3)	76.4 (11.5)
Date of first diagnosis (median)	30-11-2005	18-01-2006	20-04-2006	25-10-2005	25-01-2005
Heart Failure	85 (0.8%)	43 (1.2%)	61 (1.6%)	15 (1.2%)	
Cancer					364 (4%)
Urban-rural index: 1 (most urban)	3688 (34.3%)	1322 (36.6%)	1550 (40.2%)	432 (35%)	3354 (36.7%)
2	3694 (34.3%)	1162 (32.2%)	1311 (34%)	407 (33%)	2899 (31.7%)
3	1484 (13.8%)	475 (13.2%)	471 (12.2%)	168 (13.6%)	1168 (12.8%)
4	655 (6.1%)	256 (7.1%)	198 (5.1%)	83 (6.7%)	690 (7.6%)
5	727 (6.8%)	217 (6%)	199 (5.2%)	91 (7.4%)	573 (6.3%)
6 (most rural)	512 (4.8%)	178 (4.9%)	130 (3.4%)	53 (4.3%)	447 (4.9%)
Scottish index of multiple deprivation 1 (least deprived)	1542 (14.3%)	486 (13.5%)	431 (11.2%)	197 (16%)	1197 (13.1%)
2	2135 (19.8%)	700 (19.4%)	595 (15.4%)	242 (19.6%)	1453 (15.9%)
3	2270 (21.1%)	748 (20.7%)	750 (19.4%)	271 (22%)	2042 (22.4%)
4	2626 (24.4%)	866 (24%)	954 (24.7%)	274 (22.2%)	2293 (25.1%)
5	2187 (20.3%)	810 (22.4%)	1129 (29.3%)	250 (20.3%)	2146 (23.5%)
non smoker	4129 (38.4%)	1168 (32.4%)	140 (3.6%)	345 (28%)	3352 (36.7%)
Smoker	1646 (15.3%)	328 (9.1%)	617 (16%)	145 (11.8%)	1027 (11.2%)
ex-smoker	2264 (21%)	700 (19.4%)	760 (19.7%)	189 (15.3%)	2536 (27.8%)
smoking missing	2721 (25.3%)	1414 (39.2%)	2342 (60.7%)	555 (45%)	2216 (24.3%)

Number of comorbidities	1.19 (1.31)	1.52 (1.46)	1.95 (1.6)	1.21 (1.32)	2.8 (1.61)
No comorbidity	4115 (38.2%)	1024 (28.4%)	769 (19.9%)	465 (37.7%)	500 (5.5%)
Hypertension	3259 (30.3%)	1450 (40.2%)	1451 (37.6%)	364 (29.5%)	4984 (54.6%)
Depression	1863 (17.3%)	511 (14.2%)	776 (20.1%)	224 (18.2%)	1642 (18%)
Asthma	945 (8.8%)	296 (8.2%)	386 (10%)	95 (7.7%)	925 (10.1%)
Coronary Heart Disease	839 (7.8%)	499 (13.8%)	718 (18.6%)	108 (8.8%)	4367 (47.8%)
Diabetes	786 (7.3%)	425 (11.8%)	421 (10.9%)	89 (7.2%)	1708 (18.7%)
Thyroid Disease	1173 (10.9%)	465 (12.9%)	474 (12.3%)	133 (10.8%)	1532 (16.8%)
Rheumatoid Arthritis	613 (5.7%)	302 (8.4%)	392 (10.2%)	85 (6.9%)	1327 (14.5%)
COPD	583 (5.4%)	275 (7.6%)	1118 (29%)	74 (6%)	1455 (15.9%)
Stroke TIA	445 (4.1%)	237 (6.6%)	382 (9.9%)	58 (4.7%)	1404 (15.4%)
CKD	265 (2.5%)	179 (5%)	228 (5.9%)	37 (3%)	722 (7.9%)
AF	316 (2.9%)	158 (4.4%)	161 (4.2%)	25 (2%)	2370 (26%)
PVD	238 (2.2%)	130 (3.6%)	274 (7.1%)	30 (2.4%)	740 (8.1%)
Epilepsy	136 (1.3%)	39 (1.1%)	49 (1.3%)	23 (1.9%)	149 (1.6%)
Dementia	190 (1.8%)	75 (2.1%)	98 (2.5%)	13 (1.1%)	448 (4.9%)
Schizophrenia	96 (0.9%)	38 (1.1%)	36 (0.9%)	8 (0.6%)	103 (1.1%)
Bronchiectasis	34 (0.3%)	13 (0.4%)	26 (0.7%)	1 (0.1%)	73 (0.8%)
Parkinsons Disease	39 (0.4%)	12 (0.3%)	13 (0.3%)	4 (0.3%)	63 (0.7%)
Multiple Sclerosis	50 (0.5%)	10 (0.3%)	10 (0.3%)	6 (0.5%)	19 (0.2%)
Viral Hepatitis	6 (0.1%)	3 (0.1%)	0 (0%)	0 (0%)	3 (0%)
Chronic Liver Disease	597 (5.5%)	261 (7.2%)	258 (6.7%)	76 (6.2%)	984 (10.8%)
Previous MI	305 (2.8%)	207 (5.7%)	292 (7.6%)	48 (3.9%)	2665 (29.2%)
CABG	88 (0.8%)	62 (1.7%)	94 (2.4%)	13 (1.1%)	690 (7.6%)

Diuretics	3531 (32.8%)	1451 (40.2%)	1309 (33.9%)	422 (34.2%)	8010 (87.7%)
Aldosterone receptor blockers	320 (3%)	114 (3.2%)	79 (2%)	24 (1.9%)	566 (6.2%)
B-Blockers	2165 (20.1%)	840 (23.3%)	550 (14.3%)	228 (18.5%)	4480 (49.1%)
ACE	1358 (12.6%)	489 (13.5%)	337 (8.7%)	93 (7.5%)	2881 (31.6%)
Angiotensin receptor antagonist	805 (7.5%)	261 (7.2%)	174 (4.5%)	57 (4.6%)	1684 (18.4%)
Anti-platelet agents	2493 (23.2%)	1056 (29.3%)	1218 (31.6%)	225 (18.2%)	6326 (69.3%)
Lipid lowering agents	2547 (23.7%)	1061 (29.4%)	994 (25.8%)	223 (18.1%)	5149 (56.4%)
Dead 30 day post diagnosis	57/10666 (0.5%)	79/3577 (2.2%)	354/3826 (9.3%)	39/1224 (3.2%)	197/9065 (2.2%)
Dead 1 year post diagnosis	480/9235 (5.2%)	719/3101 (23.2%)	2241/3427 (65.4%)	295/1105 (26.7%)	1441/8121 (17.7%)
Dead 5 year post diagnosis	1582/4053 (39%)	1337/1867 (71.6%)	2920/3030 (96.4%)	596/736 (81%)	3448/5061 (68.1%)
Death (ever recorded)	1709/10760 (15.9%)	1376/3610 (38.1%)	2941/3859 (76.2%)	611/1234 (49.5%)	3747/3131 (41%)

Categorical variables given as number (proportion); continuous variables given as mean (standard deviation), unless otherwise stated.

Table 3: Results of Cox proportional hazards models, separated by gender.

Disease	Unadjusted HR (95% CI), *P*	HR adjusted for age, deprivation	HR, fully adjusted
Men			
HF	1.0 (ref)	1.0 (ref)	1.0 (ref)
Prostate	0.64 (0.60,0.68), *P*<0.001	0.64 (0.61,0.68), *P*<0.001	0.61 (0.57,0.65), *P*<0.001
Lung	5.72 (5.46,6.00), *P*<0.001	6.27 (5.98,6.58), *P*<0.001	3.86 (3.65,4.07), *P*<0.001
Colorectal	1.34 (1.26,1.42), *P*<0.001	1.45 (1.37,1.54), *P*<0.001	1.23 (1.16,1.31), *P*<0.001
Bladder	0.96 (0.88,1.04), *P*=0.28	0.97 (0.89,1.05), *P*=0.46	0.88 (0.81,0.96), *P*<0.005
Women			
HF	1.0 (ref)	1.0 (ref)	1.0 (ref)
Breast	0.34 (0.32,0.36), *P*<0.001	0.58 (0.55,0.62), *P*<0.001	0.55 (0.51,0.59), *P*<0.001
Colorectal	1.05 (0.99,1.12), *P*=0.12	1.31 (1.23,1.40), *P*<0.001	1.21 (1.13,1.29), *P*<0.001
Lung	4.22 (4.01,4.43), *P*<0.001	5.64 (5.36,5.94), *P*<0.001	3.82 (3.60,4.05), *P*<0.001
Ovary	1.46 (1.34,1.59), *P*<0.001	2.55 (2.33,2.78), *P*<0.001	1.98 (1.80,2.17), *P*<0.001

Supplementary Table 1A: Read Codes used for heart failure diagnosis.

Group Name	Read Code	Rubric
Heart failure	G58..	Heart failure
Heart failure	G580.	Congestive heart failure
Heart failure	G5800	Acute congestive heart failure
Heart failure	G5801	Chronic congestive heart failure
Heart failure	G5802	Decompensated cardiac failure
Heart failure	G5803	Compensated cardiac failure
Heart failure	G581.	Left ventricular failure
Heart failure	G5810	Acute left ventricular failure
Heart failure	G582.	Acute heart failure
Heart failure	G58z.	Heart failure NOS
Heart failure	G1yz1	Rheumatic left ventricular failure
Heart failure	662f.	New York Heart Association classification - class I
Heart failure	662g.	New York Heart Association classification - class II
Heart failure	662h.	New York Heart Association classification - class III
Heart failure	662i.	New York Heart Association classification - class IV

Supplementary Table 1B. Read code for cancer diagnosis.

Group Name	Read Code	Rubric
Cancer / Breast	B34..	Malignant neoplasm of female breast
Cancer / Breast	B340.	Malignant neoplasm of nipple and areola of female breast
Cancer / Breast	B3400	Malignant neoplasm of nipple of female breast
Cancer / Breast	B3401	Malignant neoplasm of areola of female breast
Cancer / Breast	B340z	Malignant neoplasm of nipple or areola of female breast NOS
Cancer / Breast	B341.	Malignant neoplasm of central part of female breast
Cancer / Breast	B342.	Malignant neoplasm of upper-inner quadrant of female breast
Cancer / Breast	B343.	Malignant neoplasm of lower-inner quadrant of female breast
Cancer / Breast	B344.	Malignant neoplasm of upper-outer quadrant of female breast
Cancer / Breast	B345.	Malignant neoplasm of lower-outer quadrant of female breast
Cancer / Breast	B346.	Malignant neoplasm of axillary tail of female breast
Cancer / Breast	B347.	Malignant neoplasm, overlapping lesion of breast
Cancer / Breast	B34y.	Malignant neoplasm of other site of female breast
Cancer / Breast	B34y0	Malignant neoplasm of ectopic site of female breast
Cancer / Breast	B34yz	Malignant neoplasm of other site of female breast NOS
Cancer / Breast	B34z.	Malignant neoplasm of female breast NOS
Cancer / Lung	B22..	Malignant neoplasm of trachea, bronchus and lung
Cancer / Lung	B220.	Malignant neoplasm of trachea
Cancer / Lung	B2200	Malignant neoplasm of cartilage of trachea
Cancer / Lung	B2201	Malignant neoplasm of mucosa of trachea
Cancer / Lung	B220z	Malignant neoplasm of trachea NOS
Cancer / Lung	B221.	Malignant neoplasm of main bronchus
Cancer / Lung	B2210	Malignant neoplasm of carina of bronchus
Cancer / Lung	B2211	Malignant neoplasm of hilus of lung
Cancer / Lung	B221z	Malignant neoplasm of main bronchus NOS
Cancer / Lung	B222.	Malignant neoplasm of upper lobe, bronchus or lung
Cancer / Lung	B2220	Malignant neoplasm of upper lobe bronchus
Cancer / Lung	B2221	Malignant neoplasm of upper lobe of lung
Cancer / Lung	B222z	Malignant neoplasm of upper lobe, bronchus or lung NOS
Cancer / Lung	B223.	Malignant neoplasm of middle lobe, bronchus or lung
Cancer / Lung	B2230	Malignant neoplasm of middle lobe bronchus
Cancer / Lung	B2231	Malignant neoplasm of middle lobe of lung
Cancer / Lung	B223z	Malignant neoplasm of middle lobe, bronchus or lung NOS
Cancer / Lung	B224.	Malignant neoplasm of lower lobe, bronchus or lung
Cancer / Lung	B2240	Malignant neoplasm of lower lobe bronchus
Cancer / Lung	B2241	Malignant neoplasm of lower lobe of lung
Cancer / Lung	B224z	Malignant neoplasm of lower lobe, bronchus or lung NOS
Cancer / Lung	B225.	Malignant neoplasm of overlapping lesion of bronchus and lung
Cancer / Lung	B226.	Mesothelioma

Cancer / Lung	B22y.	Malignant neoplasm of other sites of bronchus or lung
Cancer / Lung	B22z.	Malignant neoplasm of bronchus or lung NOS
Cancer / Prostate	B46..	Malignant neoplasm of prostate
Cancer / Bowel	B13..	Malignant neoplasm of colon
Cancer / Bowel	B130.	Malignant neoplasm of hepatic flexure of colon
Cancer / Bowel	B131.	Malignant neoplasm of transverse colon
Cancer / Bowel	B132.	Malignant neoplasm of descending colon
Cancer / Bowel	B133.	Malignant neoplasm of sigmoid colon
Cancer / Bowel	B134.	Malignant neoplasm of caecum
Cancer / Bowel	B135.	Malignant neoplasm of appendix
Cancer / Bowel	B136.	Malignant neoplasm of ascending colon
Cancer / Bowel	B137.	Malignant neoplasm of splenic flexure of colon
Cancer / Bowel	B138.	Malignant neoplasm, overlapping lesion of colon
Cancer / Bowel	B139.	Hereditary nonpolyposis colon cancer
Cancer / Bowel	B13y.	Malignant neoplasm of other specified sites of colon
Cancer / Bowel	B13z.	Malignant neoplasm of colon NOS
Cancer / Bowel	B14..	Malignant neoplasm of rectum, rectosigmoid junction and anus
Cancer / Bowel	B140.	Malignant neoplasm of rectosigmoid junction
Cancer / Bowel	B141.	Malignant neoplasm of rectum
Cancer / Bowel	B142.	Malignant neoplasm of anal canal
Cancer / Bowel	B1420	Malignant neoplasm of cloacogenic zone
Cancer / Bowel	B143.	Malignant neoplasm of anus unspecified
Cancer / Bowel	B14y.	Malignant neoplasm of other sites of rectum, rectosigmoid junction and anus
Cancer / Bowel	B14z.	Malignant neoplasm of rectum, rectosigmoid junction and anus NOS
Cancer / Ovary	B44..	Malignant neoplasm of ovary and other uterine adnexa
Cancer / Ovary	B440.	Malignant neoplasm of ovary
Cancer / Ovary	B441.	Malignant neoplasm of fallopian tube
Cancer / Ovary	B442.	Malignant neoplasm of broad ligament
Cancer / Ovary	B443.	Malignant neoplasm of parametrium
Cancer / Ovary	B444.	Malignant neoplasm of round ligament
Cancer / Ovary	B44y.	Malignant neoplasm of other site of uterine adnexa
Cancer / Ovary	B44z.	Malignant neoplasm of uterine adnexa NOS
Cancer / Bladder	B49..	Malignant neoplasm of urinary bladder
Cancer / Bladder	B490.	Malignant neoplasm of trigone of urinary bladder
Cancer / Bladder	B491.	Malignant neoplasm of dome of urinary bladder
Cancer / Bladder	B492.	Malignant neoplasm of lateral wall of urinary bladder
Cancer / Bladder	B493.	Malignant neoplasm of anterior wall of urinary bladder
Cancer /	B494.	Malignant neoplasm of posterior wall of urinary bladder

Bladder		
Cancer / Bladder	B495.	Malignant neoplasm of bladder neck
Cancer / Bladder	B496.	Malignant neoplasm of ureteric orifice
Cancer / Bladder	B497.	Malignant neoplasm of urachus
Cancer / Bladder	B498.	Local recurrence of malignant tumour of urinary bladder
Cancer / Bladder	B49y.	Malignant neoplasm of other site of urinary bladder
Cancer / Bladder	B49y0	Malignant neoplasm, overlapping lesion of bladder
Cancer / Bladder	B49z.	Malignant neoplasm of urinary bladder NOS

Supplementary Table 2. Drug group and search string.

Drug Group	Search String
Diuretic	Neo NaClex, Diumide K, Centyl K, Mannitol, aldactide, triam-co, burinex, aridil, moduretic, amil-co, co-amilofruse, burinex, frusene, lasilactone, co-flumactone, kalspare, dytide, dyazide, co-triamterzide, navispare, coamilozide, dytac, Amilamont, aldactone, spironolactone, inspra, eplerenone, triamterene, amiloride, Lasilactone, Frusene, Burinex A, Co-amilofruse, frusol, rusyde, frusid, froop, torem, torasemide, burinex, bumetanide, lasix, frusemide, furosemide, diurexan, xipamide, metenix, metolazone, natrilix, indapamide, navidrex, cyclopenthiazide, hygroton, chlorthalidone, chlortalidone, Neo-NaClex, Aprinox, bendroflumethiazide, bendrofluazide
ARA	slocinx, doxadura, rogitine, phentolamine, dibenyline, phenoxybenzamine, hytrin, terazosin, hypovase, prazosin, doralese, baratol, indoramin, doxazosin, cardura
Bblocker	Propranolol, Angilol, Syprol, Inderal, Half Inderal, Half Inderal, Bedranol, Beta Prograne, Slo-Pro, Acebutolol, Sectral, Atenix, Atenolol, Tenormin, Co tenidone, Kalten, Tenoret, Tenoretic, Beta Adalat, Tenif, Bisoprolol Fumarate, Bisoprolol, Vivacor, Cardicor, Emcor, Carvedilol, Eucardic, Celiprolol, Celectol, Esmolol Hydrochloride, Esmolol, Brevibloc, Labetalol Hydrochloride, Labetalol, Trandate, Metoprolol Tartrate, Metoprolol, Betaloc, Lopresor, Nadolol, Corgard, Nebivolol, Nebilet, Oxprenolol, Trasicor, Trasidrex, Pindolol, Visken, Viskaldix, Sotalol, Beta Cardone, Sotacor, Timolol, Betim, Prestim
ACE	tarka, gopten, trandolapril, triapin, tritace, lopace, rampril, accuretic, accupro, quinil, quinapril, coversyl, perindopril, perdix ,moexipril ,zestoretic ,lisicostad ,zestril ,carace ,lisinopril ,tanatril ,imidapril ,staril ,fosinopril ,innozide ,innovace, enalapril, vascace, cilazapril, capozide, capto co, co-zidocapt, capoten, tensopril, kaplon, Captopril, ecopace
ARB	co-diovan, diovan, valsartan, micardis, telmisartan, olmesartan, olmetec, cozaar, losartan, coaprovel, aprovel, irbesartan, teveten, eprosartan, candesartan, amias
Antiplatelet	acetylsalicylic, Aggrastat, Tirofiban, intergrilin, Eptifibatide, Asasantin, Persantin, Dipyridamole, Plavix, Clopidogrel, Nuseals, Nu-Seals, Caprin, Angettes, Micropirin, Gencardia, Aspirin, Abciximab, ReoPro
Lipid	Maxepa, Omega-3-Marine Triglycerides, Omacor, Omega-3-Acid Ethyl Esters, Niaspan, Nicotinic, Olbetam, Acipimox, Lopid, Gemfibrozil, Supralip, Lipantil, Fenofibrate, Modalim, Ciprofibrate, Bezalip, Bezafibrate, Ezetrol, Ezetimibe, Colestid, Colestipol, Questran, Cholestyramine, Colestyramine, Cholestagel, Colesevelam, Inegy, Zocor, simvador, Simvastatin, Crestor, Rosuvastatin, Lipostat, Pravastatin, Lescol, Fluvastatin, Atorvastatin, Lipitor

Supplementary Table 3A: Hazard non-proportionality (Rho=0 is perfect proportionality) for men.

Disease	Rho (p), uncorrected model	Rho (p) corrected for age, deprivation	Rho (p), fully adjusted
HF	Ref	Ref	Ref
Prostate	0.06 (<0.001)	0.05 (<0.001)	0.07 (<0.001)
Lung	-0.12 (<0.001)	-0.12 (<0.001)	0.01 (0.35)
Bowel	-0.08 (<0.001)	-0.08 (<0.001)	-0.02 (0.02)
Bladder	-0.02 (0.03)	-0.02 (0.02)	-0.003 (0.72)

Supplementary Table 3B: Hazard non-proportionality (Rho=0 is perfect proportionality) for women.

Disease	Rho (p), uncorrected model	Rho (p) corrected for age, deprivation	Rho (p), fully adjusted
HF	Ref	Ref	Ref
Breast	0.03 (<0.001)	0.04 (<0.001)	0.06 (<0.001)
Bowel	-0.10 (<0.001)	-0.09 (<0.001)	-0.04 (<0.001)
Lung	-0.12 (<0.001)	-0.11 (<0.001)	0.002 (0.81)
Ovary	-0.04 (<0.001)	-0.03 (0.004)	0.03 (0.004)