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Title: Pharmacist intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction.

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ABSTRACT

Background

Meta-analysis of small trials suggests that pharmacist-led collaborative review and revision of medical treatment may improve outcomes in heart failure.

Methods and results

We studied patients with left ventricular systolic dysfunction in a cluster-randomised controlled, event driven, trial in primary care. We allocated 87 practices (1090 patients) to pharmacist intervention and 87 practices (1074 patients) to usual care. The intervention was delivered by non-specialist pharmacists working with family doctors to optimise medical treatment. The primary outcome was a composite of death or hospital admission for worsening heart failure. This trial is registered, number ISRCTN70118765.

The median follow-up was 4.7 years. At baseline 86% of patients in both groups were treated with an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker. In patients not receiving one or other of these medications, or receiving less than the recommended dose, treatment was started, or the dose increased, in 33.1% of patients in the intervention group and in 18.5% of the usual care group (odds ratio [OR] 2.26, 95% CI 1.64-3.10; $p<0.001$). At baseline, 62% of each group were treated with a β-blocker and the proportions starting or having an increase in dose were 17.9% in the intervention group and 11.1% in the usual care group (OR 1.76, 95% CI 1.31-2.35; $p<0.001$). The primary outcome occurred in 35.8% of patients in the intervention group and 35.4% in the usual care group (hazard ratio 0.97, 95% CI 0.83-1.14; $p = 0.72$). There was no difference in any secondary outcome.

Conclusion

A low-intensity, pharmacist-led, collaborative intervention in primary care resulted in modest improvements in prescribing of disease-modifying medications but did not improve clinical outcomes in a population that was relatively well treated at baseline.

Keywords

Left ventricular systolic dysfunction

Primary care

ACE inhibitor

Beta-blocker

INTRODUCTION

Although angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) and β-blockers reduce morbidity and mortality in patients with heart failure due to left ventricular systolic dysfunction, there is evidence that these treatments are underused, particularly in primary care.[1-5] Some patients who should receive these medications do not and many receive less than evidence-based doses.[2-5] Pharmacists may play a role in improving treatment through "collaborative medication review", a process in which the pharmacist evaluates a patient's medications and suggests changes which are enacted with the agreement of the patient and the family doctor.[6-9] A meta-analysis of small, short-term, trials and observational data suggest that this intervention reduces the risk of hospital admission and possibly mortality in patients with heart failure studied in a secondary care setting.[6-10] We conducted a larger-scale, longer-term, prospective randomised controlled trial to test the hypothesis that a low-cost, low-intensity, pharmacist intervention to optimise medical treatments, particularly ACE inhibitors, ARBs, and β-blockers, in patients identified in primary care with left ventricular systolic dysfunction would reduce the composite outcome of hospital admission for worsening heart failure or death, as well as other clinically important outcomes.

METHODS

Study design and patients

The study was conducted within the National Health Service (NHS) which provides free health care to the population of the United Kingdom. The design of our trial has been published and was consistent with Consolidated Standards of Reporting Trials.[11-13] Consenting patients were eligible if aged 18 years or older and had left ventricular systolic dysfunction confirmed by cardiac imaging conducted at a local hospital (transthoracic echocardiography in 90% of cases). Patients did not have to have symptoms or signs of heart failure. Family doctors receive a semi-quantitative report of left ventricular systolic function (normal; mild, moderately or severely reduced) instead of ejection fraction. A key exclusion criterion was registration with the heart failure-nurse service which is provided to patients in our Health Board area recently admitted to hospital with heart failure. This criterion excluded higher risk patients with more severe symptoms. Other exclusion criteria included concurrent disease other than heart failure likely to reduce life-expectancy; severe cognitive impairment or psychiatric illness; dialysis, or a resident in a long-term care facility. The study was approved by the local ethics committee. All practices and patients gave written informed consent. The study is registered, number ISRCTN70118765.

Randomisation

We used a cluster-randomisation design as this provides protection against contamination across trial groups when trial patients are managed within the same setting as was the case in this study. Patients in practices in the UK are managed by all general practitioners within the practice; as the control intervention was mediated by general practitioners, this precluded

individual patient level randomisation. Family practices were randomly allocated using a third-party automated telephone interactive voice response system in a 1:1 ratio to receive intervention or usual care. Stratification was by socioeconomic deprivation (affluent, intermediate or deprived) at practice level, and practice-type (single-handed or group-practice).[11]

Study procedures

The intervention was delivered by 27 primary care-based pharmacists employed by the NHS to work with family doctors and directly with patients to promote rational, cost-effective prescribing.[14] All participating pharmacists had between three and 16 years of post-qualification experience. All had experience delivering primary care based medication review clinics for patients receiving multiple drug treatment. Seven pharmacists held postgraduate clinical pharmacy qualifications. Four pharmacists had hospital (ward-based) clinical pharmacy experience. Prior to commencing the intervention, all pharmacists attended one, in-house training day (contact time 7.5 hours) covering the aetiology, symptoms and evidence-based management of heart failure. The day was co-ordinated by three pharmacists who had a special interest in heart failure therapeutics, and a general practitioner with a special interest in heart failure. The day comprised of a mixture of didactic teaching and interactive role-play sessions. An additional mandatory three-hour session covered the methods of the trial. All pharmacists received an information pack with directed, heart failure-specific reading to supplement their training.

As part of routine continuing professional development, each pharmacist participated in a 3.5 hour peer-led session every month which involved group-discussion of cases encountered in their medication-review clinics. As the study pharmacists were embedded within primary

care practices, informal discussion on therapeutics occurred regularly between pharmacists, general practitioners and nurses within the practice. There was also regular telephone-contact between study pharmacists and the principal investigator or another pharmacist with a special interest in heart failure.

Patients from practices assigned to the intervention were offered a 30 minute appointment with a pharmacist. The main aim of this review was optimisation of medical treatment for left ventricular systolic dysfunction according to guidelines (see Supplementary data). If there was agreement between the pharmacist and patient during the consultation and subsequently with the family doctor, medications were initiated, discontinued or modified by the pharmacist during three to four subsequent weekly or fortnightly consultations. Family doctors provided usual care thereafter. No instructions were given to family doctors in the usual care practices. The study pharmacists did not collect information on symptoms or examine the patients as this was not part of their professional training. The cause of heart failure was established by scrutinising primary and secondary care (e.g. hospital letters and discharge summaries) clinical records.

Study outcomes

The primary outcome was the composite of death from any cause or hospital admission for worsening heart failure, analysed as time to first event. Secondary endpoints included the composites of death from any cause or hospital admission for pre-specified cardiovascular causes (see Supplementary data), death from any cause or hospital admission for any cause; total number of admissions (and patients admitted) for heart failure, cardiovascular causes and any cause; and days alive out of hospital. Outcome data were obtained from the Information Services Division (ISD) of the NHS in Scotland, which records all discharges from Scottish NHS hospitals (i.e. virtually all hospital admissions in Scotland) and the

General Register Office which records all deaths. Hospital discharge data are reported to ISD with discharge diagnoses coded according to the International Classification of Diseases (ICD) system, 10th revision.[15,16] This approach to patient follow-up has been compared favourably to traditional clinical trial methods.[17,18] Although the end-of-study date was January 31, 2011, data-extraction did not occur until July 25, 2011 in order to ensure that all deaths and hospital admissions were entered into the national database.

We also compared the prescribing of medications between the intervention and usual care groups and evaluated health-care utilisation, other than admissions, at one and two years of follow-up e.g. the number of primary care contacts and hospital emergency room visits.

Statistical analysis

The trial data were managed and analysed by the Robertson Centre for Biostatistics, University of Glasgow. The primary analysis compared the main outcomes between the intervention and control groups using a Cox proportional hazards frailty model, which accounted for the cluster-randomisation design.[11-13] These analyses were adjusted for the stratification variables and the following variables of prognostic importance: age, creatinine, grade of left ventricular systolic dysfunction, atrial fibrillation, respiratory disease, total number of medical treatments, and diuretic use.

We initially assumed the rate of the primary outcome would be 10% per year in the control group and pharmacist intervention would lead to a relative risk reduction of 26%, based upon the known benefits of initiating disease-modifying treatment and of higher doses of those therapies.[1, 19, 20] Due to the cluster-randomisation design, the sample size needed to be increased by a factor of 1.55.[11-13] Consequently 87 practices (1044 patients) were required in each group. Blinded review of patient data in September 2010 suggested that 750 patients

would experience a primary outcome event at follow-up, providing 80% power to detect a 19% relative risk reduction with the intervention.

Logistic regression models were used to examine secondary outcomes including whether patients started or stopped a medical treatment or had a change in dose.

Safety was evaluated by examining hospital admissions for: symptomatic hypotension, collapse or syncope; renal dysfunction, failure or impairment; hyperkalaemia; asthma or chronic obstructive pulmonary disease; and bradycardia, atrioventricular block or pacemaker implantation. Fisher's exact t-test was used to compare the intervention group with the usual care group.

RESULTS

Study patients

All general practices in our locality were approached and 174 of 220 (79%) practices (covering 790,421 of 998,402 i.e.79% of patients registered with a general practitioner in our Health Board area) took part in the trial. From October 25 2004, through September 6, 2007, 87 primary care practices (1090 patients) were randomly assigned to pharmacist intervention and 87 practices (1074 patients) to usual care (Figure 1). One patient had incomplete follow-up due to emigration. The median duration of follow-up was 4.7 years (range 6 days to 6.2 years; 9362 patient-years).

The two groups were balanced with respect to baseline characteristics (Table 1). Fifty five percent of patients were aged 70 years or older. There was a high prevalence of ischaemic heart disease (80%) and respiratory disease (30%). A semi-quantitative assessment of left ventricular function was recorded in 2023 (93%) patients, with most having either mild (41%) or moderate (42%) reduction in systolic function. In a small reasonably representative subset of patient records (n=256; 12%) there was documentation of a LVEF value along with a semi-quantitative assessment of systolic function. In these patients the mean ejection fraction was 36.8% (standard deviation 6.5%) in those with mildly reduced systolic function, 30.5% (7.5%) in those with moderately reduced function and 19.7% (7.7%) in patients with severely reduced function.

Although general practitioners do not routinely record New York Heart Association (NYHA) class in our area (and NYHA class was not recorded by the study pharmacists) this measure was documented in the records of 337 patients; 85 (25%) were NYHA class I; 219 (65%) were NYHA class II; 30 (9%) were NYHA class III and 3 (1%) were in NYHA class IV. Very few (1.7%) patients had been admitted to hospital for heart failure in the year prior to randomisation.

Medical treatment

In each treatment group, approximately 86% of patients were receiving an ACE inhibitor, ARB or both (Table 1) and of these patients, 55% received 100% or more of the recommended dose. The proportion of patients receiving a β-blocker was 62% in each treatment group. Of these, 21% were treated with 100% or more of the recommended dose (Table 1).

Patients not prescribed an ACE inhibitor, ARB or β-blocker, or not prescribed the recommended doses of these medications at baseline, were potentially eligible for treatment optimisation. Table 2 shows the effect of pharmacist intervention (patients who died during the first and second years of follow-up were excluded from this analysis - dead patients could not receive the intervention). Pharmacist intervention during the first year of the trial led to a greater frequency of initiation of an ACE inhibitor or ARB and a β-blocker, compared with usual care (Table 2). The same was true for increases in the dose of these treatments. By the end of year one, an ACE inhibitor or ARB was started or the dose was increased in 168/507 (33.1%) of patients in the intervention group and 95/514 (18.5%) of patients in the usual care group (odds ratio [OR] 2.26, 95% CI 1.64-3.10, p<0.001). The proportions starting or having an increase in dose of β-blocker were 153/854 (17.9%) of patients in the intervention group and 95/855 (11.1%) of patients in the usual care group (OR 1.76, 95% CI 1.31-2.35, p<0.001). The resultant proportion of patients receiving an ACE inhibitor, ACE inhibitor or ARB and beta-blocker at the end of year 1 and year two is shown in table 3, as well as the proportions of those patients receiving at least 50% and at least 100% of the recommended dose. ~~At the end of year one of follow-up the proportion of patients in the pharmacist intervention group receiving at least 100% of the recommended dose of ACE inhibitor was 66.4% compared with 61.5% in the usual care group; these proportions were 60.9% versus~~

~~55.3% for an ACE inhibitor or ARB and 26.2% versus 22.4% for a beta-blocker. The proportions at year 2 were 67.5% versus 59.5%, 61.4% versus 53.9% and 27.1 versus 22.5%, respectively.~~ These differences were sustained during the second year with no evidence of "catch-up" prescribing in the usual care group (see Supplementary data). There was no difference between treatment-groups regarding dose-reduction, or discontinuation of these drugs. The proportion of patients collecting 80% or more of prescriptions (from their general practice) was 99% in the pharmacist intervention group versus 99% in the usual care group for ACE inhibitors, 98% versus 98% for ARBs and 98% versus 99% for beta-blockers (no difference between treatment groups for any drug).

At the end of year 1, 5.0% of the pharmacist intervention group and 4.6% in the usual care group were prescribed an aldosterone antagonist. At the end of year 2 the proportions were 5.1% and 5.2%.

At baseline diltiazem or verapamil was used in 132 (6%) of patients, a non-steroidal anti-inflammatory drug in 144 (7%), an anti-depressant in 223 (10%) [a tricyclic in 73 (3%)] and a glitazone in 17 (1%). These drugs were discontinued more often in the pharmacist intervention group in the first year but the difference in rates of discontinuation between the two treatment groups were not statistically significant (see Supplementary data).

Study outcomes

Death from any cause or hospital admission for heart failure (the primary outcome) occurred in 390 patients (35.8%) in the intervention group and 380 patients (35.4%) in the usual care group (Figure 2 and Table 4). The adjusted hazard ratio [HR] for the primary outcome in the intervention group, as compared to the usual care group, was 0.97, 95% CI 0.83-1.14, p=0.72). The effect of the intervention on this outcome was consistent in an unadjusted analysis (Table 4) and across all pre-specified subgroups (Figure 3).

Death from any cause or hospital admission for a cardiovascular cause occurred in 487 patients (44.7%) in the intervention group as compared with 475 patients (44.2%) in the usual care group (HR 0.97, 95% CI 0.84-1.12, p = 0.70). A total of 337 patients (30.9%) in the intervention group and 331 patients (30.8%) in the usual care group died (HR 0.96, 95% CI 0.80-1.16, p=0.68). The number of deaths attributed to a non-cardiovascular cause was 155 in the intervention group and 169 in the usual care group.

The number of patients admitted to hospital for any reason, for a cardiovascular cause and for heart failure was similar in the two treatment groups (Table 4). The total numbers of hospital admissions (including second and subsequent hospital admissions) for any reason were 2205 versus 2191 (P=0.84), for cardiovascular causes 474 versus 517 (P=0.19) and for heart failure 149 versus 194 (P=0.08), in the intervention group and usual care group, respectively. Findings for the other pre-specified secondary outcomes and safety outcomes are reported in the Supplementary data.

DISCUSSION

Although a meta-analysis of small, short-term, studies suggested that pharmacist intervention improves clinical outcomes in patients with heart failure[7], we did not confirm this in a much larger and longer trial conducted in primary care, despite the intervention leading to improvements in the use of disease-modifying medications which persisted for at least two years.

There are a number of possible explanations for this finding. The frequency of use of ACE inhibitors and ARBs at baseline was greater than reported in previous studies in primary care, and even in our pilot study, with 86% of patients prescribed at least one of these medications.[2-5,21] The explanation for this unexpected finding is uncertain although in 2004, the year our trial started, the United Kingdom government introduced a new contract for family doctors linking pay to performance.[22,23]Prescribing of ACE inhibitors (but not β-blockers) in patients with left ventricular systolic dysfunction was one of the incentivised activities. As a consequence of the high baseline use of ACE inhibitors and ARBs, there was little scope to initiate these agents. There was also limited opportunity to increase the dose of these drugs as a high proportion (55%) of subjects was already receiving the recommended dose at baseline. Furthermore, dose was increased in only about a third of eligible patients in the intervention group (compared with 19% of those in the usual care group), presumably because of tolerability and safety considerations, perhaps indicating that the rate of use and dosing of these drugs may have already approached a ceiling level. Certainly, the rate of use of ACE inhibitors and ARBs and the doses that they were used at in our trial equal or exceed those in recent heart failure trials (despite our patients being more elderly than in these other trials)[24,25] and a national audit in the United Kingdom[26].

Although there was more scope to improve β-blocker prescribing, initiation of this type of medication and increase in dose of β-blocker was infrequent in both treatment groups. This lack of success may indicate that the brief period of tuition used to prepare the non-specialist pharmacists in our trial was insufficient. Unfamiliarity with the use of β-blockers, and persisting concerns about their tolerability and safety, in left ventricular systolic dysfunction amongst family doctors at the time our trial started, as well as the high prevalence of respiratory disease in our population may also have limited β-blocker use. Additionally, patients may also have been unwilling to take an additional medication given the high rate of multi-drug regimens in the population studied (47% were receiving more than 8 medications). Nevertheless, although the rate of use of beta-blockers was disappointing, the proportion of patients taking 100% or more of the recommended dose of beta-blocker by the end of the first year in the pharmacist intervention group (26%) compared favourably with the Systolic Heart failure treatment with I_f inhibitor ivabradine Trial (SHIFT) where this proportion was 26% at baseline.[24]

A second explanation for the lack of effect of our intervention was the relatively low frequency of hospital admission for heart failure which meant that the majority of events contributing to the primary composite outcome were fatal. In addition, only half of the deaths that occurred were attributed to cardiovascular causes. We excluded high-risk patients under the care of specialist heart failure nurses. Furthermore, falling hospital admission rates for heart failure have been reported in several countries[15,27-31] and, recently, cardiovascular deaths, as a proportion of overall deaths, have also been reported to be declining in patients with heart failure.[32] Consequently, there were fewer non-fatal and fatal events which might have been reduced through greater use of ACE inhibitors, ARBs and β-blockers. We believe that these two factors – only a modest improvement in use of disease-modifying treatment

coupled with a low rate of modifiable events – are the most likely explanation for a lack of improvement in clinical outcomes in our trial.

The low rate of use of aldosterone antagonists in our trial was due to the exclusion of more severely ill patients who were under the care of the specialist heart failure nurse service and hospital clinics. At the time of our trial aldosterone antagonists were only indicated in such patients.[1] Clearly, if such a trial were repeated today, use of aldosterone antagonists would be encouraged by pharmacists.

Potentially harmful medications e.g. rate-limiting calcium channel blockers, non-steroidal anti-inflammatory drugs, tricyclic antidepressants, oral corticosteroids and glitazones were prescribed in a very small proportion of patients at baseline and pharmacist intervention did not lead to any greater discontinuation of these medicines, as compared with usual care during follow-up.

As explained in the Methods section, we had to use a cluster randomisation design. We ensured good internal validity by accounting for the clustered nature of the data in our sample size calculations and ensuring blinding to allocation status of those recruiting individuals into the trial and good external validity by providing information on numbers approached, recruited and lost to follow-up. We therefore followed best practices in relation to this type of trial. Furthermore, although a major limitation of this design is lack of similarity of the study groups, our treatment groups were well matched.[12,13]

There were several limitations to our trial. The study pharmacists were not trained to elicit signs and symptoms of heart failure. We did not collect reasons why patients might have been ineligible for a specific treatment or unable to tolerate it (collecting this information on the control group might have caused contamination). Ejection fraction was not reported to general practitioners and natriuretic peptides measurements were not available in primary care at the time our patients were recruited. Although our trial did not achieve its goal of

improving clinical outcomes it did demonstrate that modest and sustained improvements in the prescribing of disease-modifying medications can be achieved by a brief, focused, collaborative intervention delivered by non-specialist pharmacists given only a short period of training. However, the short period of training and brevity of intervention may also have been limitations of our study. This was particularly true in relation to beta-blockers where our intervention had a disappointingly small effect on the use of these drugs. Lessons for future trials may be that more intense training, more patient visits and selective involvement of hospital specialists might be required to fully optimise treatment. It is also possible that modification of other treatments that we didn't target, such as diuretics may have improved outcome and this could also be examined in future studies. While this type of intervention may not benefit all patients, it might improve clinical outcomes if aimed at those in most need in terms of deficient background treatment or at those at higher risk of modifiable events. This is a question that may be considered in future comparative-effectiveness trials.

Contributors

All authors except PSJ designed the study and oversaw its conduct. All authors participated in interpretation of the data and writing of the report.

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The primary funder was the NHS in Greater Glasgow and Clyde. The funder played no role in data analysis or interpretation, writing of the report or the decision to submit for publication. The authors designed the trial and oversaw its conduct. The report was prepared by all authors who had unrestricted access to the data and made the decision to submit for publication.

Conflicts of interest

The authors have no conflict of interest

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FIGURE LEGENDS

Figure 1 Study Recruitment

Figure 2 Main Study Outcomes

Figure 3 Sub-group analysis for the primary outcome.

Table 1. Baseline characteristics of patients, according to study group.*

Characteristic	Pharmacist intervention (n=1092)**	Usual care (n=1077)**
Age (years)	70.6 (10.3)	70.6 (10.1)
Age ≥ 70 years	597 (55%)	597 (55%)
Sex (female)	320 (29%)	329 (31%)
Blood pressure [a]		
SBP (mm Hg)	127 (17.4)	128 (17.4)
DBP (mm Hg)	72 (10.1)	72 (10.2)
Left ventricular systolic function (%)[b]		
Mild reduction	433 (43%)	390 (39%)
Moderate reduction	416 (41%)	439 (44%)
Severe reduction	170 (17%)	175 (17%)
BMI (kg/m^2) [c]	28.0 (5.4)	28.0 (5.4)
Principal cause of heart failure (%)		
Ischaemic heart disease	874 (80%)	817 (76%)
Non ischaemic heart disease	197 (18%)	230 (21%)
Unknown	21 (2%)	30 (3%)
Duration of LVSD (years)[d]	3.31 (1.54, 5.85)	3.53 (1.76, 5.87)
Medical history		
Admission for heart failure in past year	19 (2%)	18 (2 %)
Hypertension	548 (50%)	495 (46%)
Myocardial infarction	722 (66%)	665 (62%)

PCI	161 (15%)	144 (13%)
CABG	266 (24%)	268 (25%)
Atrial fibrillation or flutter	292 (27%)	304 (28%)
Diabetes mellitus	234 (22%)	212 (20%)
Stroke	148 (14%)	162 (15%)
Respiratory disease	326 (30%)	318 (30%)
Asthma	72 (7%)	82 (8%)
Smoker	262 (24%)	260 (25%)
Serum creatinine (μmol/L)[e]	109 (33)	107 (30)
eGFR (mL/min per 1.73m^2) [f]	61.3 (17.5)	62.6 (23.2)
Device treatment (%)[g]		
Implantable cardioverter-defibrillator	19 (2%)	12 (1%)
Conventional pacemaker	22 (2%)	29 (3%)
Cardiac medicines at randomisation (%)		
ACE inhibitor	814 (75%)	768 (71%)
≥ 50% recommended dose[§]	695 (86%)	656 (86%)
≥ 100% recommended dose[§]	483 (60%)	472 (62%)
ARB	149 (14%)	181 (17%)
≥ 50% recommended dose[§]	102 (69%)	107 (59%)
≥ 100% recommended dose[§]	34 (23%)	35 (19%)
ACE inhibitor or ARB or both	944 (87%)	919 (85%)
B-blocker	674 (62%)	664 (62%)
≥ 50% recommended dose[§]	339 (51%)	339 (52%)
≥ 100% recommended dose[§]	146 (22%)	128 (20%)
Aldosterone antagonist	54 (5%)	56 (5%)

Digitalis glycoside	149 (14%)	124 (11%)
Diuretic	667 (61%)	654 (61%)
Aspirin	751 (69%)	691 (64%)
Antithrombotic (antiplatelet or oral anticoagulant)	990 (91%)	969 (90%)
Amiodarone	20 (2%)	32 (3%)
Lipid lowering agent	863 (79%)	841 (78%)
Number of medicines[†]	8.9 (4.0)	8.4 (3.5)

Data are numbers of patients (%) or mean (SD). Percentages may not total 100 because of rounding.

** 5 patients (2 intervention, 3 usual care) died before randomisation. SBP=systolic blood pressure. DBP = diastolic blood pressure. BMI = body mass index. PCI = percutaneous coronary intervention. CABG = coronary-artery bypass grafting. eGFR=estimated glomerular filtration rate. ACE = angiotensin-converting enzyme. ARB = angiotensin receptor blocker. [§] Percentage of those prescribed an ACE inhibitor, ARB or β-blocker and with dose recorded.

[†] Medicines on repeat prescription.

Data missing for [a]83; [b]146; [c]154; [d]36; [e]296; [f]302; [g]3 patients.

Table 2. Changes in key disease-modifying medicines between baseline and the end of the first year of follow-up.†

Medical treatment	Pharmacist Intervention	Usual Care	Odds Ratio (95% CI)	P value
	n (%)			
ACE inhibitor or ARB†				
Started*	39/131 (30%)	27/149 (18%)	2.03 (1.14-3.60)	0.02
Increased dose**	129/376 (34%)	68/365 (19%)	2.32 (1.57-3.44)	<0.001
Increased dose to ≥ 100% of target**	86/376 (23%)	40/365 (11%)	2.46 (1.51-3.99)	<0.001
Started or increased dose	168/507 (33%)	95/514 (19%)	2.26 (1.64-3.10)	<0.001
B-blocker†				
Started*	50/388 (13%)	35/388 (9%)	1.56 (0.98-2.47)	0.06
Increased dose**	103/466 (22%)	60/467 (13%)	1.90 (1.29-2.79)	0.001
Increased dose to ≥ 100% of target**	38/466 (8%)	22/467 (5%)	1.75 (0.99-3.09)	0.05
Started or increased dose	153/854 (18%)	95/855 (11%)	1.76 (1.31-2.35)	<0.001

* Of patients not taking this medicine at baseline ** Of patients taking this medicine at baseline but at < 100% of the target dose and had dose recorded (number with missing dose: ACE inhibitor ARB n=1; β-blocker n=12)

† Patients who died (n = 106) or were lost to follow-up (n = 2) during the first year of follow-up were not included in this analysis

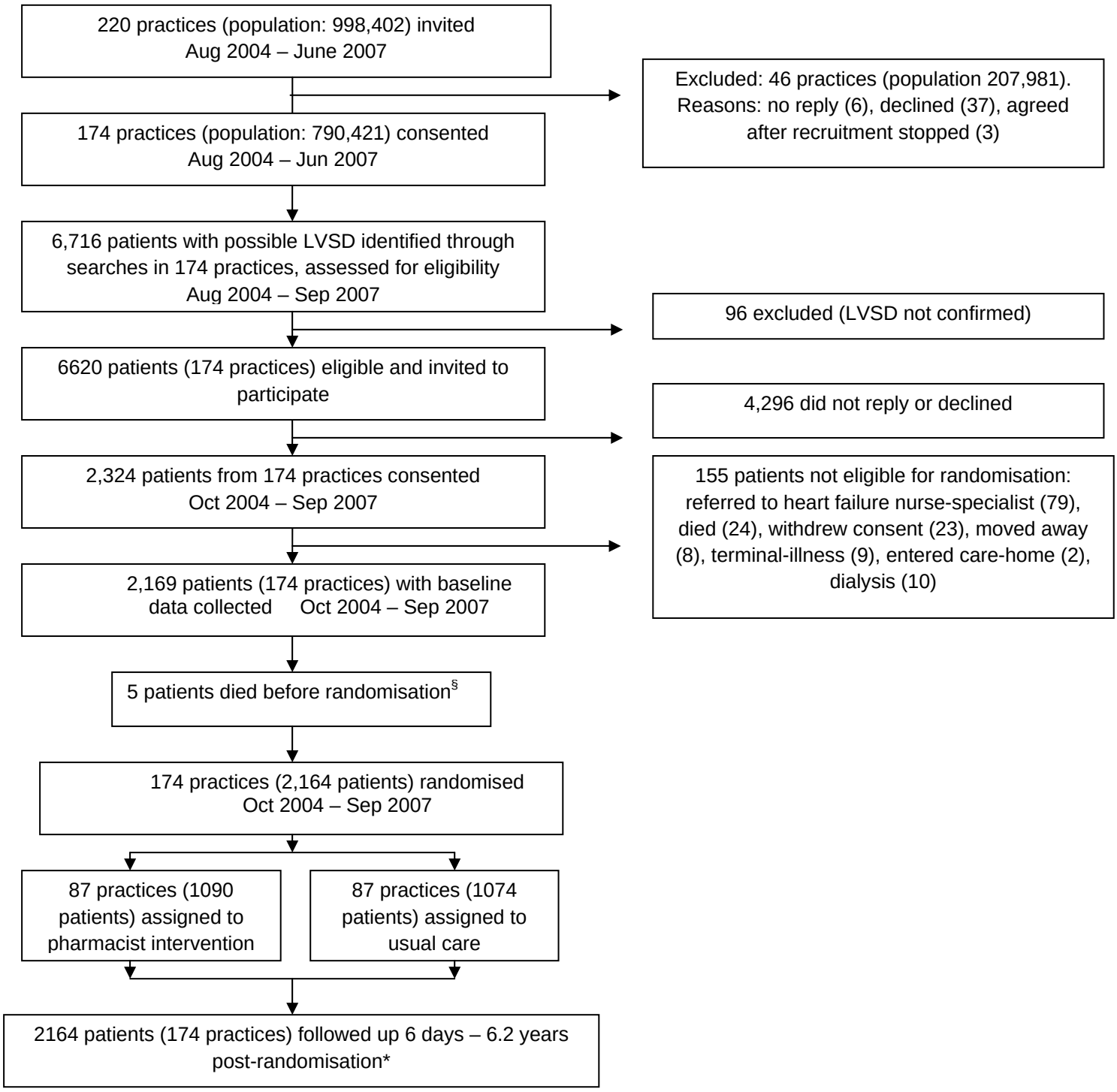
Table 4. Primary and Main Secondary Outcomes

Outcome	Pharmacist Intervention (n = 1090)		Usual care (n = 1074)		Adjusted Hazard Ratio (95% CI)	Adjusted P Value	Unadjusted Hazard Ratio (95% CI)	Unadjusted P Value
	Patients with Event	Event Rate *n/100 patient-yr*	Patients with Event	Event Rate *n/100 patient-yr*				
Primary outcome								
Death from any cause or admission for heart failure*	390 (36%)	8.53	380 (35%)	8.57	0.97 (0.83-1.14)	0.72	0.99 (0.87- 1.13)	0.91
Main secondary outcomes								
Death from any cause or admission for cardiovascular cause	487 (45%)	11.54	475 (44%)	11.67	0.97 (0.84-1.12)	0.70	0.98 (0.87-1.11)	0.81

Death from any cause or admission for any reason	758 (70%)	24.93	751 (70%)	25.46	0.96 (0.86-1.07)	0.41	0.97 (0.88-1.07)	0.55
Admissions								
Heart failure	107 (10%)	2.34	114 (11%)	2.57	0.88 (0.67-1.16)	0.36	0.90 (0.71-1.14)	0.38
Cardiovascular causes	292 (27%)	6.92	280 (26%)	6.88	0.98 (0.81-1.19)	0.83	0.99 (0.84-1.18)	0.94
Any reason	711 (65%)	23.38	695 (65%)	23.56	0.97 (0.87-1.09)	0.61	0.98 (0.89-1.08)	0.73
Death	337 (31%)	7.10	331 (31%)	7.18	0.96 (0.80-1.16)	0.68	0.99 (0.85-1.16)	0.92

* The number of events contributing to the primary composite in the intervention group was 283 deaths and 107 admissions for heart failure and in the usual care group 266 deaths and 114 admissions for heart failure.

Figure 1



§ 5 patients (from 5 practices; 2 intervention and 3 usual care) died in the period between baseline data collection and practice randomisation.
* Information on treatment unavailable for 2 patients between baseline year 1 and one additional patient between the end of year 1 and end of year 2
LVSD = left ventricular systolic dysfunction

Figure 2

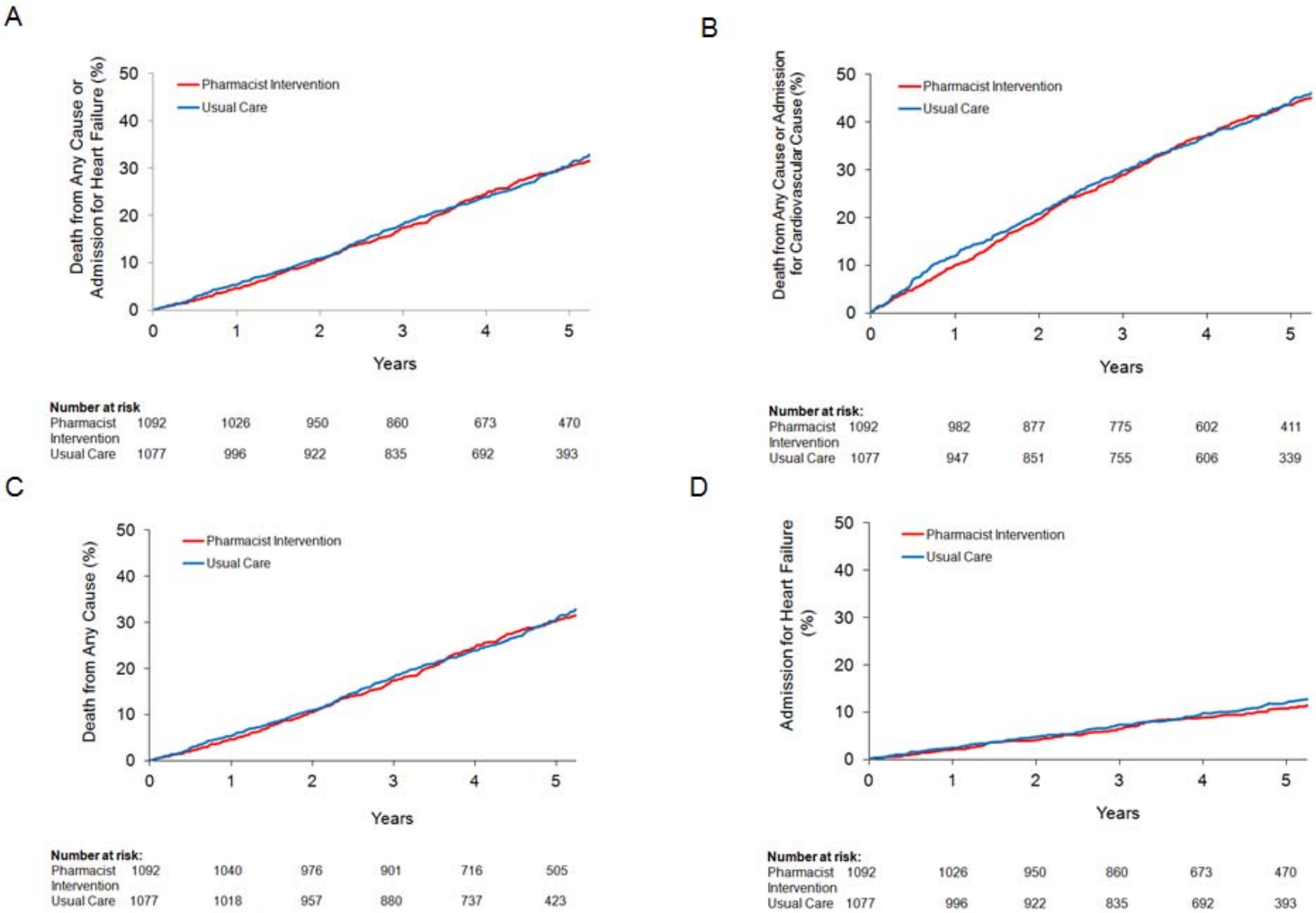
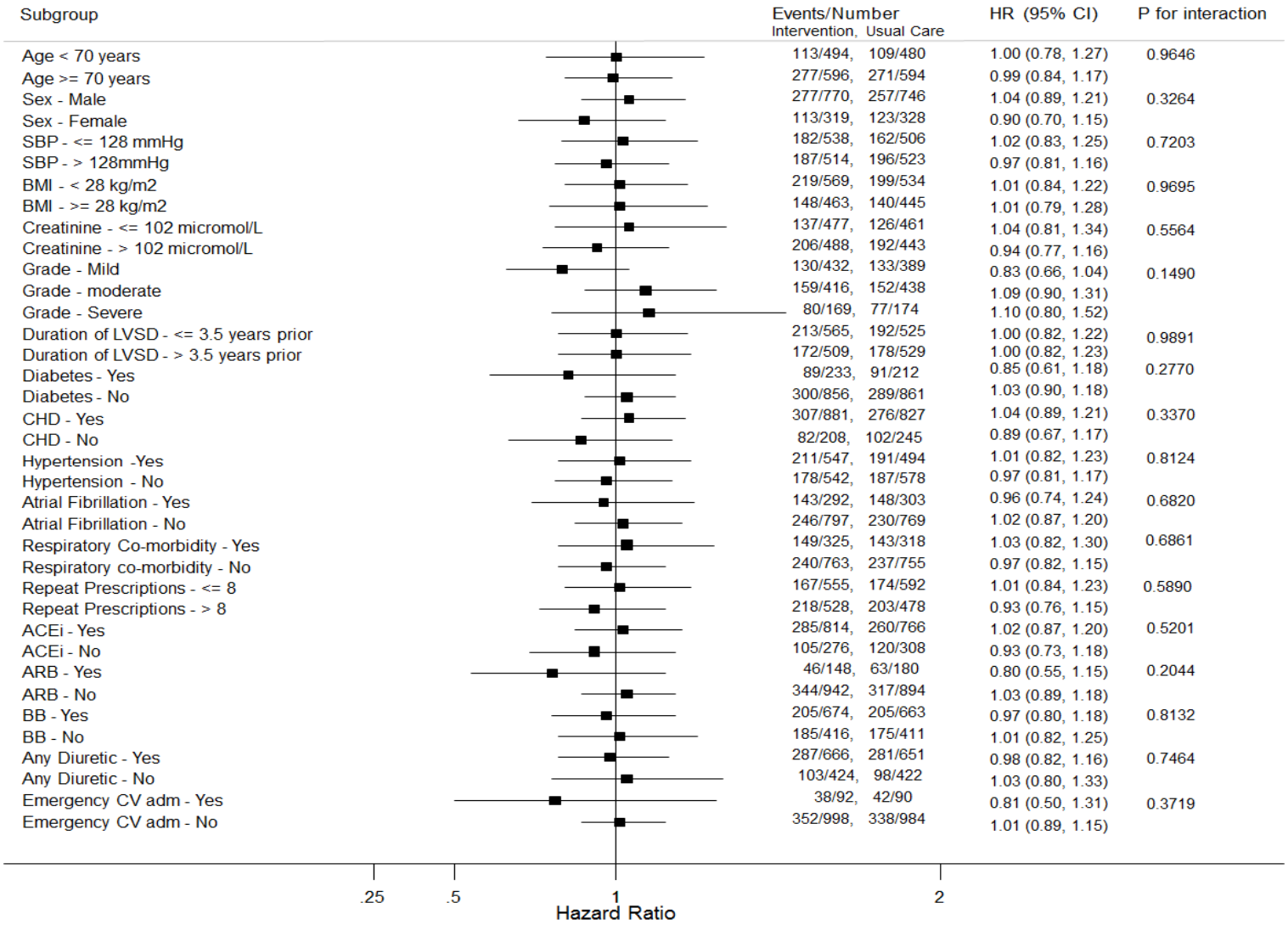

A
Death from Any Cause or Admission for Heart Failure (%)
Pharmacist Intervention
Usual Care
Years
Number at risk
Pharmacist Intervention 1092 1026 950 860 673 470
Usual Care 1077 996 922 835 692 393
B
Death from Any Cause or Admission for Cardiovascular Cause (%)
Pharmacist Intervention
Usual Care
Years
Number at risk:
Pharmacist Intervention 1092 982 877 775 602 411
Usual Care 1077 947 851 755 606 339
C
Death from Any Cause (%)
Pharmacist Intervention
Usual Care
Years
Number at risk:
Pharmacist Intervention 1092 1040 976 901 716 505
Usual Care 1077 1018 957 880 737 423
D
Admission for Heart Failure (%)
Pharmacist Intervention
Usual Care
Years
Number at risk:
Pharmacist Intervention 1092 1026 950 860 673 470
Usual Care 1077 996 922 835 692 393

Figure 3


Subgroup
Events/Number
Intervention, Usual Care
HR (95% CI)
P for interaction
Age < 70 years 113/494, 109/480 1.00 (0.78, 1.27) 0.9646
Age >= 70 years 277/596, 271/594 0.99 (0.84, 1.17)
Sex - Male 277/770, 257/746 1.04 (0.89, 1.21) 0.3264
Sex - Female 113/319, 123/328 0.90 (0.70, 1.15)
SBP - <= 128 mmHg 182/538, 162/506 1.02 (0.83, 1.25) 0.7203
SBP - > 128mmHg 187/514, 196/523 0.97 (0.81, 1.16)
BMI - < 28 kg/m2 219/569, 199/534 1.01 (0.84, 1.22) 0.9695
BMI - >= 28 kg/m2 148/463, 140/445 1.01 (0.79, 1.28)
Creatinine - <= 102 micromol/L 137/477, 126/461 1.04 (0.81, 1.34) 0.5564
Creatinine - > 102 micromol/L 206/488, 192/443 0.94 (0.77, 1.16)
Grade - Mild 130/432, 133/389 0.83 (0.66, 1.04) 0.1490
Grade - moderate 159/416, 152/438 1.09 (0.90, 1.31)
Grade - Severe 80/169, 77/174 1.10 (0.80, 1.52)
Duration of LVSD - <= 3.5 years prior 213/565, 192/525 1.00 (0.82, 1.22) 0.9891
Duration of LVSD - > 3.5 years prior 172/509, 178/529 1.00 (0.82, 1.23)
Diabetes - Yes 89/233, 91/212 0.85 (0.61, 1.18) 0.2770
Diabetes - No 300/856, 289/861 1.03 (0.90, 1.18)
CHD - Yes 307/881, 276/827 1.04 (0.89, 1.21) 0.3370
CHD - No 82/208, 102/245 0.89 (0.67, 1.17)
Hypertension -Yes 211/547, 191/494 1.01 (0.82, 1.23) 0.8124
Hypertension - No 178/542, 187/578 0.97 (0.81, 1.17)
Atrial Fibrillation - Yes 143/292, 148/303 0.96 (0.74, 1.24) 0.6820
Atrial Fibrillation - No 246/797, 230/769 1.02 (0.87, 1.20)
Respiratory Co-morbidity - Yes 149/325, 143/318 1.03 (0.82, 1.30) 0.6861
Respiratory co-morbidity - No 240/763, 237/755 0.97 (0.82, 1.15)
Repeat Prescriptions - <= 8 167/555, 174/592 1.01 (0.84, 1.23) 0.5890
Repeat Prescriptions - > 8 218/528, 203/478 0.93 (0.76, 1.15)
ACEi - Yes 285/814, 260/766 1.02 (0.87, 1.20) 0.5201
ACEi - No 105/276, 120/308 0.93 (0.73, 1.18)
ARB - Yes 46/148, 63/180 0.80 (0.55, 1.15) 0.2044
ARB - No 344/942, 317/894 1.03 (0.89, 1.18)
BB - Yes 205/674, 205/663 0.97 (0.80, 1.18) 0.8132
BB - No 185/416, 175/411 1.01 (0.82, 1.25)
Any Diuretic - Yes 287/666, 281/651 0.98 (0.82, 1.16) 0.7464
Any Diuretic - No 103/424, 98/422 1.03 (0.80, 1.33)
Emergency CV adm - Yes 38/92, 42/90 0.81 (0.50, 1.31) 0.3719
Emergency CV adm - No 352/998, 338/984 1.01 (0.89, 1.15)
.25
.5
1
2
Hazard Ratio