Pharmacological treatment in patients with aortic dissection

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ABSTRACT

Objectives To describe medical management in aortic dissection (AD) and to analyse the possible associations between antihypertensive, anti-thrombotic, anticoagulant and statin agents, respectively, and long-term survival.

Methods From Swedish medical registers, all patients diagnosed with AD in 2006–2015 were identified. Filled prescriptions prior to admission and within 1 year from discharge in patients discharged and alive at 30 days were registered. Associations between pharmacological treatment and long-term survival were analysed using Cox proportional hazards models.

Results Of 3951 patients hospitalised with acute AD, 3046 (77%) were discharged and alive at 30 days. In hospitalised patients, mean age was 66 years (SD 13), and 36% (n=1098) were women. Within 1 year from discharge, 96% (n=2939) had at least one antihypertensive drug. Beta blocker was the most commonly used drug type (90%, n=2741). Statin treatment (47%, n=1418) was associated with higher long-term survival; HR 0.74 (95% CI 0.63 to 0.87, p=0.001). The positive association between statins and long-term survival remained in subgroup analysis, in medically managed patients (HR 0.72 (95% CI 0.60 to 0.86, p=0.001)), but not in patients undergoing surgical repair (HR 0.82 (95% CI 0.58 to 1.14, p=0.230)). Beta blockers were associated with higher long-term survival in surgically managed patients (HR 0.58 (95% CI 0.35 to 0.97, p=0.038)) but not in medically managed patients (HR 0.93 (95% CI 0.72 to 1.12, p=0.057)). Neither antiplatelet therapy nor anticoagulants were associated with long-term survival.

Conclusions Statin treatment was associated with favourable long-term outcome in medically managed AD patients, whereas treatment with beta blocker was associated with higher survival only in surgically managed AD patients. Statin use as well as optimal antihypertensive treatment in the chronic stage of the disease need to be further analysed, preferably in randomised controlled trials.

INTRODUCTION

Early attempts to pharmacologically reduce the forces that propagate dissection in the aorta were described by Wheat et al in 1965. However, back then, no distinction was made between cases involving the ascending aorta, Stanford type A dissection (TAD), and those originating distal to the left subclavian artery ostium without involvement of the ascending aorta, type B dissection (TBD). The anatomical classifications of aortic dissection (AD) according to DeBakey and Stanford, respectively, were developed during the same era, more than five decades ago, and were put forward in 1965 and 1970, respectively, and surgical repair techniques were described. Since the first publication by the International Registry of acute Aortic Dissection (IRAD) consortium in the year 2000, the proportions of patients undergoing surgical management of TAD and thoracic endovascular aortic repair (TEVAR) for TBD, respectively, have increased.

The term best medical therapy (BMT) is widely used but rarely defined in studies of AD. In the European Society for Vascular
Surgery (ESVS) guidelines on the management of descending thoracic aortic diseases, no specific recommendations are given on pharmacological treatment in the chronic phase of AD. In acute AD, treatment with intravenous beta blockers is commonly initiated to reduce the heart rate and the systolic blood pressure. The combination of a beta blocker and one or more vasodilators has often been recommended. The effects on long-term survival in AD patients by statins and antiplatelet drugs, respectively, which play key roles in the management of ischaemic heart disease and stroke, remain to be determined. In the European Society of Cardiology guidelines for the management of arterial hypertension, AD is listed as a possible hypertensive emergency, but no guidelines for the management of arterial hypertension, determined. In the European Society of Cardiology guidelines for the management of arterial hypertension, AD is listed as a possible hypertensive emergency, but no guidelines for the management of arterial hypertension, determined. The possible associations between antihypertensive, anti-thrombotic, anticoagulant and statin agents, respectively, and long-term survival.

METHODS

National registers

The Swedish Board of Health and Welfare maintains 13 registers on healthcare and social services, six of which are medical registers. All Swedish inhabitants are identifiable in these registers by a unique 12-digit personal identity number (PIN). Data on hospitalisations and visits to specialist outpatient clinics are registered in the National Patient Register (NPR) containing information on age, sex, diagnoses according to the International Classification of Diseases (ICD-10) and surgical operations according to the Nomesco Classification of Surgical Procedures (NCSP). Results of laboratory tests or radiological examinations are not included in the registers. The Swedish Prescribed Drug Register (SPDR), launched in June 2005, holds data on all filled prescriptions in Sweden including Anatomical Therapeutic Chemical (ATC) Classification, specific drug and date of dispensing. Data on prescribed drugs that have not been dispensed are not included in the register. Data on all deaths in Sweden are registered in the Cause of Death Register, including the main cause of death and date of death. Reporting to this register is mandatory by Swedish law.

Study design and populations

This was a population-based retrospective cohort study. From the NPR, all patients diagnosed with AD (ICD-10 code I71.0) in Sweden from 1 January 2000 to 31 December 2015, were identified. Patients under the age of 18 years were excluded. As data were not available for the whole year 2005, pharmacological treatment in AD patients was analysed for the 10-year period 2006–2015, whereas data retrieved for the whole period 2000–2015 were used to analyse the incidence of acute AD in the Swedish population, sex differences and time trends. Data on relevant concomitant disorders at discharge and 90 days from discharge were registered. Surgical procedures for AD during hospitalisation were extracted from the NPR based on specific NCSP codes. Surgically managed patients were subdivided into TAD and TBD, respectively, by classifying the NCSP codes based on typical treatment differences. The dataset retrieved was cross-matched with the SPDR using the PINs, rendering a dataset comprising pharmacological treatment in all patients hospitalised for AD in Sweden during 10 years.

From the SPDR, data on filled prescriptions were extracted on a patient-specific level. Drugs were grouped based on ATC codes (online supplemental table 1). Patients that had filled a prescription of a specific drug within 1 year prior to the dissection event were regarded as having been treated with that drug on admission. Patients that had filled a prescription of a specific drug within 1 year after discharge from hospitalisation for AD were categorised as being treated with that drug at follow-up. The numbers and proportions of patients treated with drugs from specific drug groups were described. The patients were further subdivided into surgically or medically managed. In surgically managed patients, TAD and TBD were described separately. Date of death in every patient dying during the primary hospital stay or during the follow-up period was registered. Early mortality was defined as 30-day mortality and in-hospital mortality combined during the primary hospitalisation for AD. Last date of follow-up of survival and of filled prescriptions was 31 December 2016. Maximum follow-up was 11 years.

The Strengthening the Reporting of Observational Studies in Epidemiology Statement was used in the preparation of the analysis plan and of the manuscript.

Statistical analysis

Continuous variables are presented as means with SD. Categorical variables are presented with numbers and percentages. Differences between categorical variables were analysed with \( \chi^2 \) test, and differences between continuous variables were analysed with Mann-Whitney U test; \( p \) value of \(<0.05\) was considered statistically significant. The patients were divided into five different age groups (years): 18–49, 50–59, 60–69, 70–79 and 80–99. The patients were also divided into two different time periods based on the year of the index event: 2006–2010 was defined as the first time period and 2011–2015 as the second. Crude differences in long-term mortality between different treatment groups were analysed with Kaplan-Meier survival plot; log rank \( p \) <0.05 was considered statistically significant. The associations between pharmacological treatment after discharge and long-term survival were analysed, in patients discharged and alive at 30 days, using Cox proportional hazards models adjusting for age, sex, index year, concomitant disorders (hypertension, ischaemic heart disease, heart failure, atrial fibrillation, ischaemic stroke, peripheral arterial disease, kidney failure and diabetes) and all other listed pharmacological
groups in each specific analysis. Subgroup analyses were carried out in medically and surgically managed patients, respectively. Results are presented as HRs, with 95% CIs. P values <0.05 were considered statistically significant. The Statistical Package for the Social Sciences V.27.0 for Windows was used for statistical analyses.

Patients and public involvement
Patients and the public were not involved in the design, conduct, reporting or plans of this research.

RESULTS
Medication prior to admission
During the study period, 3951 patients were hospitalised and diagnosed with AD (figure 1). Mean age was 68 years (SD 13) and 38% (n=1480) were women. Pharmacological treatment prior to the AD event is described in table 1. Most of the patients were on antihypertensive medication prior to admission (60%, n=2367).

Early management
In total, 33% (n=1303) were subjected to acute aortic repair within 14 days from admission. A majority of these were TAD patients treated with OSR (n=1153/1303, 88%). Out of the 150 TBD patients managed with acute surgery, 88% (n=132/150) were managed with TEVAR and the rest with OSR. Surgically managed patients were younger than the patients who received only medical therapy (mean age 63 vs 71 years, p<0.001) (table 1). On admission, the patients who subsequently underwent acute aortic repair were to a lower degree on medication with antihypertensive agents, anticoagulants, antiplatelet agents and statins than patients managed medically (table 1). Out of the 905 deaths that occurred within 30 days or during primary hospital stay, 96% were from cardiovascular disease overall and 85% of these deaths were aortic related (aneurysm or dissection).

Medication in the chronic phase
A total of 3046 patients (77%) were discharged alive from the primary hospital stay for acute AD and eligible for follow-up (figure 1). Mean age was 66 years (SD 13) and 36% (n=1098) were women. Pharmacological treatment after the dissection event is described in table 2. The vast majority, 96% (n=2939/3046), were on antihypertensive medication. Almost half of the patients were treated with four or more antihypertensive drugs (n=1405, 46%). Beta blockers were the most commonly used drugs (90%, n=2741/3046) (table 2). The most common combination overall was treatment with a beta blocker, an ACE inhibitor, a calcium channel blocker (CCB) and a diuretic agent (21%, n=647/3046).

Among surgically managed patients, 85% (n=1114/1303) survived 30 days and were discharged alive, of whom 88% (n=981) had TAD and 12% (n=133) had TBD. Surgically managed patients were treated with beta blockers to a higher degree than medically managed patients (91% vs 88%, p=0.009). The proportion of patients on statins did not differ between medically managed and surgically managed patients; it amounted to 47% in both groups (table 2). Neither did the percentage
of patients with statins differ between surgically managed TAD and TBD patients (46% vs 50%, p=0.455).

Pharmacological treatment during the first and the second 5-year period, respectively, is described in table 3. The number of patients on any antihypertensive agent did not change between the periods. However, fewer patients were treated with ACE inhibitors in the second 5-year period, whereas during the same period, more patients were treated with angiotensin II receptor blockers (ARBs), CCBs and diuretics. Moreover, treatment with four or more antihypertensive agents was more common in the second 5-year period compared with the first. Likewise, treatment with statins became more common with time (table 3).

**Midterm and long-term survival**

In all patients discharged and alive at 30 days, 1-year survival was 95% (n=2896/3046). Mean follow-up was 4.8 years, SD 2.8. During follow-up, 25% (n=757/3046) of the patients died, 30% (n=585/1932) of patients managed medically and 15% (n=172/1114) of patients managed with surgical repair. In total, 56% of the deaths were from cardiovascular disease overall and 36% of these deaths were aortic related (aneurysm or dissection). The associations between different pharmacological regimens and long-term survival are described in figure 2 and table 4, respectively. Treatment with antihypertensive drugs was associated with higher long-term survival than no antihypertensive treatment, HR 0.56 (95% CI 0.43 to 0.84, p=0.003). Statin treatment was also associated with higher long-term survival (HR 0.74 (95% CI 0.63 to 0.87, p<0.001)). This association could be demonstrated both in women (HR 0.66 (95% CI 0.51 to 0.85, p=0.001)) and in men (HR 0.78 (95% CI 0.63 to 0.96, p=0.017)). Neither antiplatelet therapy nor treatment with anticoagulants associated with higher long-term survival (table 4A). An association with higher long-term survival was found for treatment with CCBs, ACE inhibitors and ARBs, respectively, whereas no association between treatment with beta blockers and long-term survival could be demonstrated (table 4B). Interestingly, statin use was likewise associated with higher long-term survival when looking at cardiovascular deaths (HR 0.71 (95% CI 0.58 to 0.88, p=0.002)) and aortic-related deaths (HR=0.62 (95% CI 0.43 to 0.89, p=0.009)). For treatment with any antihypertensive agent, there were no association with long-term cardiovascular mortality (HR 0.67 (95% CI 0.42 to 1.05, p=0.080)) or aneurysm related deaths (HR 0.58 (95% CI 0.30 to 1.12, p=0.104)).

Among surgically managed patients, both treatment with beta blockers, HR 0.58 (95% CI 0.35 to 0.97, p=0.038) and treatment with ARBs, HR 0.58 (95% CI 0.38 to 0.89, p=0.012), respectively, were associated with higher long-term survival. For treatment with CCBs, ACE inhibitors or diuretics, respectively, no association was found to long-term survival after surgical repair. Also, in subgroup analysis of the impact of statins, there was

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**Table 1** Pharmacological treatment in patients with aortic dissection in Sweden 2006–2015 prior to the first dissection event, described for the total cohort and subdivided into medically and surgically managed patients, respectively

| Variable, N (%) | Total (n=3951) | Medically managed (n=2648) | Surgery within 14 days (n=1303) | P value |
|----------------|----------------|--------------------------|-------------------------------|---------|
| Women          | 1480 (38)      | 1021 (39)                | 459 (35)                     | 0.42    |
| Age (years; mean±SD) | 68 (13)      | 71 (13)                  | 63 (12)                      | <0.001  |
| Any antihypertensive | 2367 (60%)    | 1693 (64%)               | 674 (52%)                    | <0.001  |
| Beta blocker   | 1409 (36%)     | 1042 (39%)               | 367 (28%)                    | <0.001  |
| Calcium channel blocker | 925 (23%)    | 646 (24%)                | 279 (21%)                    | 0.037   |
| ACE inhibitor  | 812 (21%)      | 567 (21%)                | 245 (19%)                    | 0.056   |
| ARB            | 487 (12%)      | 354 (13%)                | 133 (10%)                    | 0.004   |
| Diuretic       | 1228 (31%)     | 928 (35%)                | 300 (23%)                    | <0.001  |
| Statin         | 851 (22%)      | 625 (24%)                | 226 (17%)                    | <0.001  |
| Any anticoagulant* | 411 (10%)     | 306 (12%)                | 105 (8%)                     | <0.001  |
| Warfarin       | 393 (10%)      | 293 (11%)                | 100 (8%)                     | <0.001  |
| NOAC           | 20 (1%)        | 15 (1%)                  | 5 (0.4%)                     | 0.445   |
| Any antiplatelet therapy† | 1044 (26%) | 810 (31%)                | 234 (18%)                    | <0.001  |
| Acetylsalicylic acid | 987 (25%)    | 769 (29%)                | 218 (17%)                    | <0.001  |
| Clopidogrel    | 100 (3%)       | 73 (3%)                  | 27 (2%)                      | 0.198   |

P values refer to comparisons between the groups of medically and surgically managed patients, respectively.

*The sum of the number of patients on warfarin and on NOAC, respectively, may exceed the total number of patients on ‘Any anticoagulant’ as the patients may have switched from one drug to the other during the first year after discharge.

†This also applies for ‘Any antiplatelet therapy’; some patients were treated with dual antiplatelet therapy.

ARB, angiotensin II receptor blocker; NOAC, new oral anticoagulant.
no association between statins and long-term survival in surgically managed patients (HR 0.82 (95% CI 0.58 to 1.14, p=0.230)).

In medically managed patients, treatment with CCBs (HR 0.70 (95% CI 0.56 to 0.86, p=0.001)) and treatment with ACE inhibitors (HR 0.80 (95% CI 0.67 to 0.96, p=0.014)), respectively, were associated with higher long-term survival. Use of beta blockers, ARBs or diuretics, however, had no association to long-term survival in these patients. Statin use was associated with higher long-term survival in medical strategy patients (HR 0.72 (95% CI 0.60 to 0.86, p=0.001)), the results applied to both women (HR 0.66 (95% CI 0.50 to 0.89, p=0.006)) and men (HR 0.74 (95% CI 0.58 to 0.94, p=0.013)). The association for statins with better long-survival remained for cardiovascular mortality (HR 0.65 (95% CI 0.51–0.82, p<0.001)) as well as for aortic-related mortality (HR 0.51 (95% CI 0.34 to 0.77, p=0.002)).

**DISCUSSION**

This population-based nationwide study of nearly 4000 AD patients during a 10-year period demonstrated that 96% of the patients were on antihypertensive treatment within a year from discharge. The use of statins was associated with higher long-term survival in patients managed
medically, both in women and in men. The association between drug use and long-term survival for the various drugs differed between patients undergoing repair and those being managed only medically; ARBs and beta blockers were favourable in surgically managed patients, whereas ACE inhibitors and CCBs were favourable in medical management.

Aggressive lowering of systolic blood pressure has long been the mainstay in the acute management of AD. The best antihypertensive medication strategy and how to manage hypertension in patients with chronic AD, however, are still matters of debate. The ESVS guidelines recommend systolic blood pressure below 130 mm Hg and diastolic pressure below 85 mm Hg, with beta blockers as first-line treatment. The present study confirmed the wide use of antihypertensive medication in general and beta blockers in particular in AD patients, with 96% of the patients being on antihypertensive medication at discharge. In 90% of the cases a beta blocker was used, mostly combined with additional drugs. In the acute phase, resistant hypertension frequently requires multiple drugs, in contrast to the chronic stage of the disease, when the resistant hypertension tends to resolve. Nevertheless, within the first year, 46% of the patients were on ≥4 antihypertensives, which is in accordance with earlier reports.

Beta blockers and ARBs were associated with higher long-term survival in patients undergoing surgical repair, whereas in the medical strategy group, CCBs and ACE inhibitors were associated with better outcome. This finding is in agreement with an IRAD report demonstrating survival benefit of beta blockers in surgically treated TAD patients and an association between CCB use and higher survival in medically managed TBD patients. Similar to the IRAD data, it is most likely that the majority of patients subjected to medical treatment in the present report had uncomplicated TBD. Single-centre studies have shown reduction of aortic events in acute and chronic TBD by using beta blockers. A recent Taiwanese register study demonstrated lower risk of hospital readmission and all-cause mortality in acute AD patients receiving a beta blocker, ACE inhibitor or ARB after discharge from the primary hospitalisation. One potential weakness of the demonstrated favourable effect of beta blockers in surgically managed patients is that the study design does not allow further analysis of the mechanisms. Moreover, roughly 1 in 10 patients of both surgically and medically managed patients, respectively, did not receive beta blockers, but the reason for that decision is unknown. The role of beta blockers in chronic TBD needs to be evaluated in future studies. In TBD patients who experience side effects from beta blockers, one could consider shifting to other antihypertensive drugs, especially since the presumed superiority of beta blockers has not been confirmed in a randomised trial. The role of CCBs in patients with aortic dissection is uncertain. It was recently reported that in patients with Marfan syndrome, treatment with CCBs was associated with aortic dissection and aortic surgery during follow-up. In this report and in IRAD, medically managed patients did benefit from treatment with CCBs. The majority of these patients can be assumed to have had uncomplicated TBD and presumably very few of them had genetic disorders. Moreover, treatment with CCBs has been associated with decreased aortic expansion in patients with uncomplicated TBD. The diverging findings point at the need of further studies on the role of CCBs in AD patients with different aetiologies managed with different strategies.

Statins are recommended to all patients with peripheral arterial disease, according to the ESVS peripheral arterial diseases guidelines. The ESVS suggests treatment of hyperlipidaemia in patients with chronic AD but without further specific recommendations. Fairly recently, statin therapy was shown to improve long-term survival in patients undergoing abdominal aortic aneurysm (AAA) repair. To date, to our knowledge, no such evidence exists regarding patients with AD. In the JUPITER trial, 20 mg daily of the statin rosuvastatin was found to reduce the incidence of major cardiovascular events in patients without marked hyperlipidaemia but with elevated

| Table 3 | Pharmacological treatment within 1 year from discharge in patients hospitalised for acute aortic dissection in Sweden, comparing the two 5 year periods 2006–2010 and 2011–2015 |
|---------|--------------------------------------------------------------------------------|
| 2006–2010 (n=1416) | 2011–2015 (n=1630) | P value |
| Any antihypertensive drug | 1366 (97%) | 1573 (97%) | 0.959 |
| 0 antihypertensive | 50 (4%) | 57 (4%) | 0.959 |
| 1 antihypertensive | 92 (7%) | 93 (6%) | 0.362 |
| 2 antihypertensives | 259 (18%) | 259 (16%) | 0.078 |
| 3 antihypertensives | 397 (28%) | 430 (26%) | 0.305 |
| ≥4 antihypertensives | 615 (43%) | 790 (49%) | 0.005 |
| Beta blocker | 1285 (91%) | 1456 (89%) | 0.192 |
| Calcium channel blocker | 1035 (73%) | 1256 (77%) | 0.012 |
| ACE inhibitor | 755 (53%) | 797 (49%) | 0.015 |
| ARB | 366 (26%) | 527 (32%) | <0.001 |
| Diuretic | 950 (67%) | 1152 (71%) | 0.033 |
| Statin | 625 (44%) | 793 (49%) | 0.013 |
| Any anticoagulant† | 280 (20%) | 404 (25%) | <0.001 |
| Warfarin | 280 (20%) | 352 (22%) | 0.199 |
| NOAC | 0 | 62 (4%) | <0.001 |
| Any antiplatelet therapy† | 655 (46%) | 769 (47%) | 0.611 |
| Acetylsalicylic acid | 638 (45%) | 719 (44%) | 0.600 |
| Clopidogrel | 47 (3%) | 84 (5%) | 0.013 |

P values refer to comparisons between patients hospitalised during 2006–2010 and 2011–2015, respectively.
†The sum of the number of patients on warfarin and on NOAC, respectively, may exceed the total number of patients on ‘Any anticoagulant’ as the patients may have switched from one drug to the other during the first year after discharge.
†This also applies for ‘Any antiplatelet therapy’; some patients were treated with dual antiplatelet therapy.
ARB, angiotensin II receptor blocker; NOAC, new oral anticoagulant.
high-sensitivity C reactive protein (CRP) levels. Acute AD patients have been shown to exhibit an inflammatory reaction, manifested by elevated biomarkers, including CRP. A further meta-analysis indicated that the preventive effect of statins in men and women at equal cardiovascular disease risk was similar. In the present study, a minority were treated with statins prior to admission, whereas almost half of the patients were on statins within a year from discharge, pointing at the lack of evidence of statin use in AD patients. Treatment with statins after discharge from hospitalisation was associated with higher long-term survival. In subgroup analyses, the association was confirmed in medically managed patients, both in women and in men, but not in patients undergoing surgical repair. As statins have been shown to improve the long-term outcome of open and endovascular AAA repair, the absence of such an effect in association with AD surgery raises further questions.

We did observe some treatment strategy changes during the second 5-year study period, 2011–2015, compared with the first 5 years of the study. ACE inhibitors became less common, whereas ARBs, CCBs and diuretics were more commonly used in the later period. In comparison, during the period 2005–2016, except for decreased use of diuretics, antihypertensive treatment strategies in stroke survivors in the USA did not change. Since treatment with four or more antihypertensive agents became more common in the second 5-year period, it is possible that the increased use of ARBs, CCBs and diuretics was a result of multiple-drug use rather than just a shift from other drug types.

The aims of secondary preventive strategies in AD patients are to prevent dilatation and late aortic-related death as well as death from other cardiovascular diseases. In uncomplicated TBD, there is ongoing debate whether or not to prophylactically cover the entry site and adjacent aortic segment with a stent graft, in addition to providing the patients with BMT. An important factor to consider in assessment of the efficacy of medical management is adherence to antihypertensive medication. A study of patients with chronic TBD showed that less than half (43%) reported high degree of adherence and 21% reported low adherence. Analogously, in a study of 65-year-old Swedish men with screening-detected carotid plaque or asymptomatic carotid artery stenosis,
In part A, antihypertensive medication is presented as one single variable, whereas in part B, the different antihypertensive drugs were analysed separately. ARB, angiotensin II receptor blocker.

### Table 4: The association with long-term mortality of different pharmacological agents, age, sex and index year in patients discharged and alive at 30 days after hospitalisation for acute aortic dissection, analysed with Cox proportional hazards models

|                          | Total at start, n (%) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|-----------------------|-------------------|----------------------|
|                          |                       |                   |                      |
| **(A)**                  |                       |                   |                      |
| Men                      | 1948 (64)             | 1                 | 1                    |
| Women                    | 1098 (36)             | 1.31 (1.13 to 1.51)| 0.99 (0.86 to 1.15)  |
| Age categories           |                       |                   |                      |
| 18–49                    | 306 (10)              | 1                 | 1                    |
| 50–59                    | 532 (17)              | 1.54 (0.92 to 2.56)| 1.57 (0.94 to 2.64)  |
| 60–69                    | 932 (31)              | 3.10 (1.94 to 4.90)| 3.02 (1.89 to 4.92)  |
| 70–79                    | 803 (26)              | 6.32 (4.10 to 10.10)| 5.99 (3.77 to 9.51)  |
| 80–99                    | 473 (16)              | 16.40 (10.40 to 25.88)| 13.60 (8.54 to 21.66) |
| Index year               |                       |                   |                      |
| 2005–2010                | 1416 (47)             | 1                 | 1                    |
| 2011–2015                | 1630 (53)             | 0.87 (0.74 to 1.04)| 0.92 (0.78 to 1.10)  |
| Any antihypertensive     |                       |                   |                      |
| No                       | 107 (4)               | 1                 | 1                    |
| Yes                      | 2939 (96)             | 0.57 (0.41 to 0.79)| 0.56 (0.43 to 0.84)  |
| Statin                   |                       |                   |                      |
| No                       | 1628 (53)             | 1                 | 1                    |
| Yes                      | 1418 (47)             | 0.71 (0.61 to 0.82)| 0.74 (0.63 to 0.87)  |
| Antiplatelet therapy     |                       |                   |                      |
| No                       | 2362 (77)             | 1                 | 1                    |
| Yes                      | 684 (23)              | 0.80 (0.67 to 0.96)| 0.83 (0.68 to 1.03)  |
| Any antihypertensive     |                       |                   |                      |
| No                       | 1622 (53)             | 1                 | 1                    |
| Yes                      | 1424 (47)             | 1.07 (0.92 to 1.23)| 1.03 (0.87 to 1.20)  |
| **(B)**                  |                       |                   |                      |
| Beta blocker             |                       |                   |                      |
| No                       | 305 (10)              | 1                 | 1                    |
| Yes                      | 2741 (90)             | 0.60 (0.49 to 0.75)| 0.82 (0.66 to 1.03)  |
| Calcium channel blocker  |                       |                   |                      |
| No                       | 755 (25)              | 1                 | 1                    |
| Yes                      | 2291 (75)             | 0.73 (0.63 to 0.86)| 0.81 (0.68 to 0.96)  |
| ACE inhibitor            |                       |                   |                      |
| No                       | 1494 (49)             | 1                 | 1                    |
| Yes                      | 1552 (51)             | 0.81 (0.71 to 0.94)| 0.81 (0.70 to 0.95)  |
| ARB                      |                       |                   |                      |
| No                       | 2153 (71)             | 1                 | 1                    |
| Yes                      | 893 (29)              | 0.71 (0.61 to 0.85)| 0.76 (0.63 to 0.92)  |
| Diuretic                 |                       |                   |                      |
| No                       | 944 (31)              | 1                 | 1                    |
| Yes                      | 2102 (69)             | 1.13 (0.97 to 1.32)| 1.23 (1.03 to 1.47)  |

All multivariable Cox proportional hazards models were adjusted for age, sex, index year, concomitant disorders (hypertension, ischaemic heart disease, heart failure, atrial fibrillation, ischaemic stroke, peripheral arterial disease, kidney failure and diabetes) and all other listed pharmacological groups in each specific analysis.

In part A, antihypertensive medication is presented as one single variable, whereas in part B, the different antihypertensive drugs were analysed separately.

Acknowledgements We would like to thank Max Vikström, statistician at the Institute of Environmental medicine, Karolinska Institutet, and Hans Pettersson, statistician at the Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, for statistical advice.

Contributors All authors take full responsibility for data collection, analysis and interpretation, research conduct and manuscript submission. All authors contributed to study design and data collection. CS and JS performed statistical
analysis. CS and JS drafted the manuscript, and RH and KL critically revised the manuscript. CS accepts full responsibility for the work as guarantor.

Funding This work was supported by the Swedish Heart-Lung Foundation (grant numbers 20 180 506 and 20200645).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the Regional Board of Ethical Approval in Stockholm, DNR 2014/957-31 and DNR 2017/127-32. Only anonymised register data were used. Hence, the ethical review board of Stockholm, Sweden, decided that no informed consent was needed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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