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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, antithrombotic, 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 favourable 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 therapy in the chronic stage of the disease need to be further analysed, preferably in randomised controlled trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antihypertensive therapy is a key pillar in the treatment arsenal in all patients with aortic dissection. Beta blockers are suggested as first-line treatment, but there is actually not much evidence supporting this statement. Whether or not statins, anticoagulants or antiplatelet agents influence long term outcome is not known.

WHAT THIS STUDY ADDS

⇒ In this 10-year nationwide retrospective cohort study, it was found that in patients discharged alive after hospitalisation for acute aortic dissection, treatment with statins was associated with higher long-term survival, both in women and in men. In further subgroup analyses, the association remained only in patients subjected to medical therapy alone. Beta blockers were associated with higher survival in surgically managed patients but not in medically managed patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Improved individualisation of the pharmaceutical strategy in patients with aortic dissection is likely to benefit the outcome. Future research should be devoted to individualised antihypertensive treatment, both in the acute and the chronic phases, and to optimal cardiovascular protective medication in the chronic phase in patients with aortic dissection.

INTRODUCTION

Early attempts to pharmacologically reduce the forces that propagate dissection in the aorta were described by Wheat *et al*[1] 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).[1] 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.[2 3] 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.[4 5]

The term best medical therapy (BMT) is widely used but rarely defined in studies of AD.[6] 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.[7] 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.[8 9] 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.[10 11] In the European Society of Cardiology guidelines for the management of arterial hypertension, AD is listed as a possible hypertensive emergency, but no disease-specific advice is given regarding blood pressure management in chronic AD.[12]

The aims of the study were to describe medical management in AD in a population-based setting and to analyse the possible associations between antihypertensive, antithrombotic, 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.[13] 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.[14]

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 χ^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

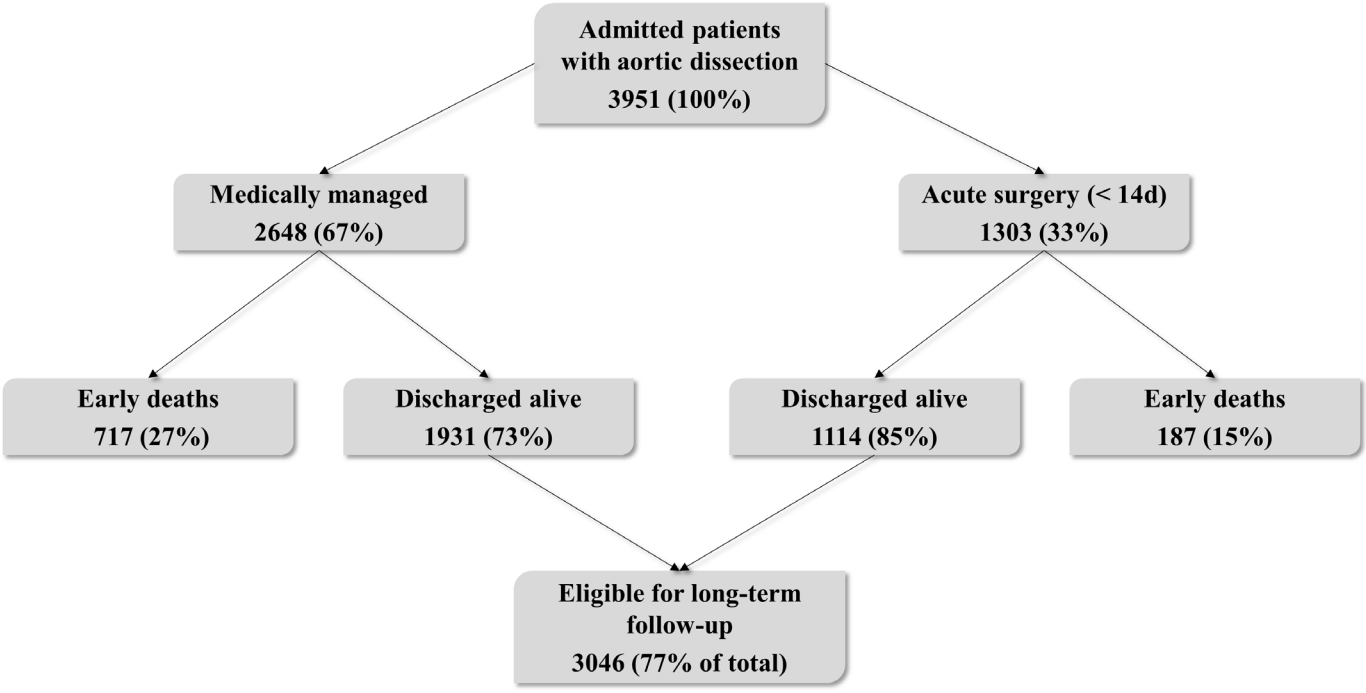

Figure 1 Flow chart of included patients. all patients hospitalised for acute aortic dissection in Sweden 2006–2015 were identified from the National Patient Register. The proportions of patients managed medically and by means of surgical repair, respectively, are described as well as early deaths in each group. Patients discharged and alive at 30 days were eligible for long-term follow-up.

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

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.

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 was associated with 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

Table 2 Pharmacological treatment, concomitant diagnoses and demographic data of all patients with acute aortic dissection in Sweden 2006–2015 registered after discharge from the primary hospitalisation

	Total (n=3046)	Medically managed (n=1932)	Surgically managed <14 days (n=1114)	P value
Women	1098 (36%)	719 (37%)	379 (34%)	0.077
Age (mean, SD)	66 (13)	69 (12)	62 (12)	<0.001
Hypertension	1561 (51%)	937 (49%)	624 (56%)	<0.001
Heart failure	158 (5%)	94 (5%)	64 (6%)	0.291
Atrial fibrillation	537 (18%)	267 (14%)	270 (24%)	<0.001
Ischaemic heart disease	123 (4%)	77 (4%)	46 (4%)	0.846
Stroke	235 (8%)	80 (4%)	155 (14%)	<0.001
Kidney failure	183 (6%)	106 (6%)	77 (7%)	0.111
Diabetes	142 (5%)	84 (4%)	58 (5%)	0.279
Any antihypertensive	2939 (96%)	1852 (96%)	1087 (98%)	0.013
0 antihypertensive	111 (4%)	84 (4%)	27 (2%)	0.006
1 antihypertensive	185 (6%)	106 (6%)	79 (7%)	0.076
2 antihypertensives	518 (17%)	299 (16%)	219 (20%)	0.003
3 antihypertensives	827 (27%)	488 (25%)	339 (30%)	0.002
≥4 antihypertensives	1405 (46%)	955 (49%)	450 (41%)	<0.001
Beta blocker	2741 (90%)	1714 (89%)	1027 (92%)	0.002
Calcium channel blocker	2291 (75%)	1525 (79%)	766 (69%)	<0.001
ACE inhibitor	1552 (51%)	975 (51%)	577 (52%)	0.480
ARB	893 (29%)	579 (30%)	314 (28%)	0.268
Diuretic	2102 (69%)	1366 (71%)	736 (66%)	0.008
Statin	1418 (47%)	899 (47%)	519 (47%)	0.976
Any anticoagulant*	684 (23%)	323 (17%)	361 (32%)	<0.001
Warfarin	631 (21%)	293 (15%)	338 (30%)	<0.001
NOAC	62 (2%)	32 (2%)	30 (3%)	0.051
Any antiplatelet therapy†	1424 (47%)	869 (45%)	555 (50%)	0.010
Acetylsalicylic acid	1357 (44%)	829 (43%)	528 (47%)	0.016
Clopidogrel	131 (4%)	86 (5%)	45 (4%)	0.589

P values refer to comparisons between the groups of medically and surgically managed patients.
Data are presented for all patients and subdivided into 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% 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

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.

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.[15] 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.[7] 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.[16 17]

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.[18] 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.[13] Single-centre studies have shown reduction of aortic events in acute and chronic TBD by using beta blockers.[9 19] 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.[20] One potential weakness of the demonstrated favourable effect of beta blockers in surgically manged 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.[15 21] 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.[22] 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.[23] 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.[24] The ESVS suggests treatment of hyperlipidaemia in patients with chronic AD but without further specific recommendations.[7] Fairly recently, statin therapy was shown to improve long-term survival in patients undergoing abdominal aortic aneurysm (AAA) repair.[25] 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

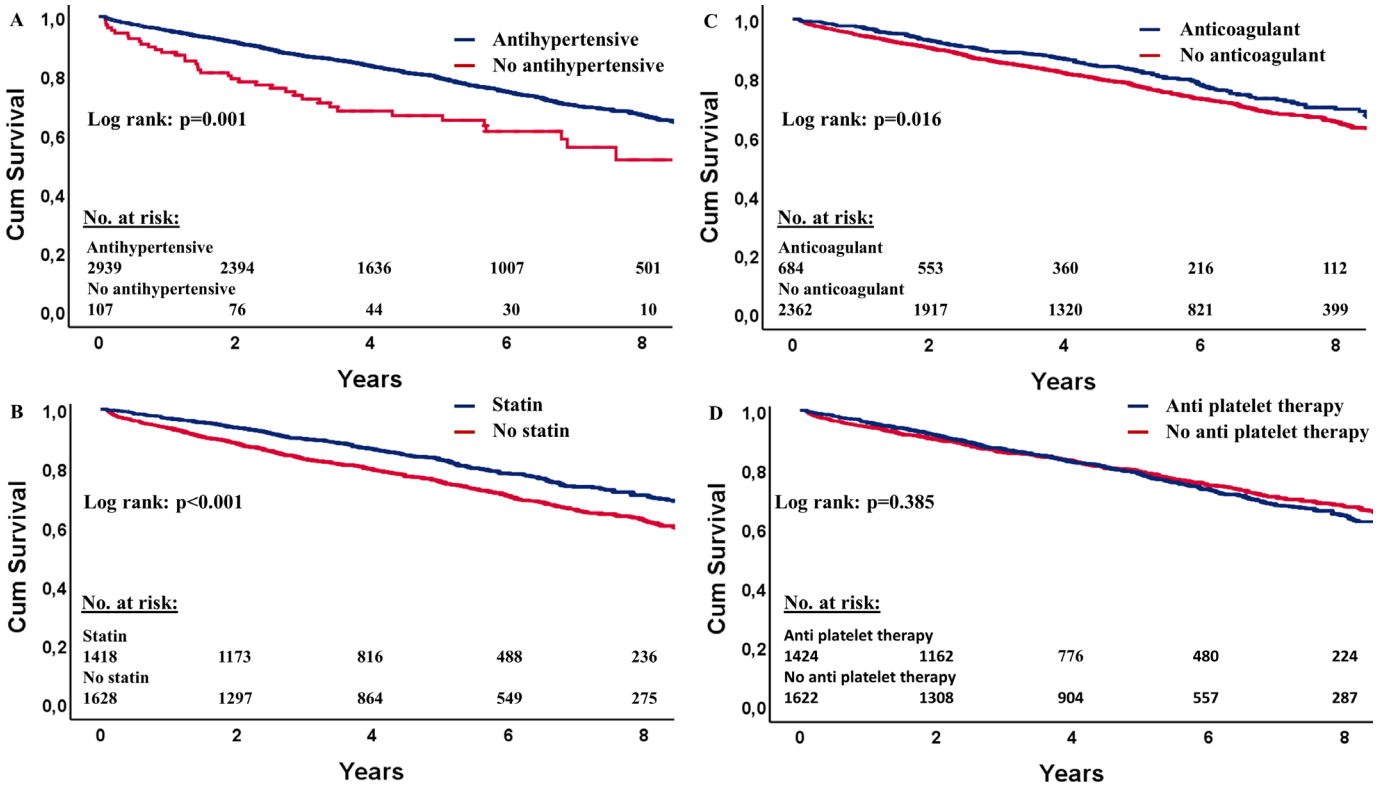

Figure 2 Kaplan-Meier survival plots comparing patients with and without specific pharmacological agents. Long-term survival analysed in patients with and without treatment with antihypertensive drugs (A), statins (B), anticoagulants (C) and antiplatelet agents (D), respectively, within a year from discharge after hospitalisation for acute aortic dissection. Comparisons were done with log rank test, p<0.05 was considered statistically significant. Numbers at risk at 2, 4, 6 and 8 years, respectively, are presented.

high-sensitivity C reactive protein (CRP) levels.[26] Acute AD patients have been shown to exhibit an inflammatory reaction, manifested by elevated biomarkers, including CRP.[27] A further meta-analysis indicated that the preventive effect of statins in men and women at equal cardiovascular disease risk was similar.[28] 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.[25] It is plausible that lower degree of atherosclerosis in AD patients than in aneurysm patients influenced the importance of statins, mainly in patients with TAD who constitute the absolute majority of surgically managed patients in the present study. The pivotal role of antiplatelet therapy in coronary heart disease and stroke and in AAA repair was not exhibited in this large group of AD patients, possibly further suggesting that acute AD is not primarily an atherosclerotic disease.[29]

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.[30] 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.[31] Analogously, in a study of 65-year-old Swedish men with screening-detected carotid plaque or asymptomatic carotid artery stenosis,

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)
Anticoagulant			
No	2362 (77)	1	1
Yes	684 (23)	0.80 (0.67 to 0.96)	0.83 (0.68 to 1.03)
Antiplatelet therapy			
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
ARB, angiotensin II receptor blocker.

the majority were neither treated with statins nor antiplatelet agents at follow-up 5 years later.[32]

In the present study, there are no data on blood pressure levels or medication adherence. Nevertheless, 96% of all the discharged patients had filled prescriptions of one or more antihypertensive drugs, which is highly encouraging in terms of adherence. The study is further limited by the absence of data on lipid levels, renal function, haemoglobin, platelet count and liver function as well as information on the main indication for each drug; for example, an ACE inhibitor could be prescribed for either hypertension or heart failure or both, that is, confounding by indication may be present. Details on drug types and doses from each drug group were not available. The retrospective register-based design and dependence on valid ICD coding of AD are also potential limitations, including the inability to distinguish between TAD and TBD among medically managed patients and the incapacity to differentiate between various dissection aetiologies.[13] As treatment strategies, including medical management, of AD patients may vary based on aetiology, the lack of information on aetiology is a limitation to the generalisability of the findings. The SPDR includes only dispensed prescription drugs; it is unique in that PINs are included, enabling linkage with other registers. The SPDR has undergone thorough scrutiny.[33] It would be of great interest to link drug dispensing data from the register to patient-reported intake to learn more about adherence to medication and the overall quality of drug treatment.

A strength of this study is the population-based design with inclusion of nearly 4000 patients over a 10-year period. The analysis of filled prescriptions is likely to provide a good marker of drug intake as it is probable that once drugs are dispensed, they are to a high degree also taken by the patients.

In summary, this large population-based study demonstrated two key perspectives on pharmacological treatment of patients with AD. First, the beneficial effects of beta blockers in the chronic stage of the disease are challenged by the lack of positive association with long-term survival in medically managed patients in this study. Second, it is striking that previously established positive effects of statins on survival in other cardiovascular patient groups seem to be true also for patients with AD, and statins should perhaps be recommended to all medically managed AD patients. Several results may be hypothesis generating for future randomised controlled trials further assessing the impact of statins in surgically managed patients as well as optimal antihypertensive therapy in the chronic stage of the disease.

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Supplement table 1: Drugs included in the study described as groups, subgroups and at specific drug level including ATC codes.

Groups	Subgroups	Specific drugs	ATC codes
Anticoagulants + antiplatelet drugs			B01
	Any anticoagulants		B01AA + B01AE + B01AF
		Warfarin	B01AA03
	New oral anticoagulants		B01AE + B01AF
		Dabigatran	B01AE07
		Rivaroxaban	B01AF01
		Apixaban	B01AF02
		Edoxaban	B01AF03
	Any antiplatelet drugs		B01AC
		Acetylsalicylic acid	B01AC06
		Clopidogrel	B01AC04
		Ticagrelor	B01AC24
		Dipyridamol	B01AC07
Antihypertensives			C02 + C03 + C04 + C07 + C08 + C09
	Beta blockers (all)		C07
	Beta blockers, non-selective		C07AA
	Beta blockers, selective		C07AB
	Beta/alfa blockers		C07AG
	Calcium channel blockers		C08
	ACE inhibitors		C09A + C09B
	Angiotensin II receptor blockers		C09C + C09D
	Diuretics		C03 + C09B + C09D
Lipid lowering drugs			C10
	Statins		C10AA + C10BA + C10BX
	Other lipid lowering drugs		C10AB + C10AC + C10AD + C10AX