Internal and Emergency Medicine
https://doi.org/10.1007/s11739-026-04348-4

IM - ORIGINAL

Response to dual anti-impulse and lipid-lowering therapy is associated with clinical outcomes in chronic type B aortic syndrome

Paolo Bima[1] · Patrizia Ferrera[2] · Elvira Fanelli[3] · Francesco Revello[4] · Michele La Torre[5] · Emanuele Pivetta[1,2] · Mauro Rinaldi[5,6] · Fabio Verzini[6,7] · Enrico Lupia[1,2] · Fulvio Morello[1,2]

Received: 16 October 2025 / Accepted: 1 April 2026
© The Author(s) 2026

Abstract

Chronic type B aortic syndrome (cTBAS) is a rare condition characterized by persistent dissection, intramural hematoma or penetrating ulcer within the thoracic descending or thoraco-abdominal aorta. In cTBAS, pathological aortic remodeling leads to a high burden of morbidity and mortality. Guidelines recommend medical treatment with anti-impulse (AI) and lipid-lowering (LL) drugs to improve outcomes, but underlying evidence is sparse, trials are lacking, and feasibility is unknown. We performed a retrospective observational study on consecutive patients with cTBAS followed in a medical clinic from 2021 to 2025, while receiving dual AI/LL therapy with guideline-compliant targets. Response to medical therapy and occurrence of major aortic events (MAEs) were recorded. Thirty-five patients with cTBAS (23 with aortic dissection, 10 with intramural hematoma, and 2 with penetrating aortic ulcer) were followed for a median of 28 months. A MAE occurred in 11 (31%) patients. Demographic and clinical characteristics including systolic/diastolic blood pressure (SBP/DBP), heart rate and lipid levels at baseline were similar in patients who did or did not develop MAEs. During follow-up, patients without MAEs had significant reductions in SBP ($P=0.005$), total and LDL cholesterol ($P=0.002$, $P<0.001$), and increased achievement of SBP < 130 mmHg ($P=0.046$), and LDL cholesterol < 70 or < 55 mg/dL ($P<0.001$, $P=0.003$). All variables were statistically unchanged in patients who developed MAEs. On-target SBP at 6 months and LDL cholesterol at 12 months were associated with protection from MAEs (hazard ratio 0.19, $P=0.014$, and 0.15, $P=0.004$, respectively). In conclusion, results provide proof-of-concept that in cTBAS, strict dual AI/LL medical therapy is feasible and associated with favorable outcomes.

Keywords Aorta · Dissection · Chronic · Medical · Treatment · Outcome · Hypertension · Cholesterol

✉ Fulvio Morello
fulvio.morello@unito.it

1 Dipartimento di Scienze Mediche, Università Degli Studi di Torino, Corso Achille Mario Dogliotti 14, 10126 Turin, Italy

2 S.C. Medicina d'Urgenza U, Ospedale Molinette, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy

3 S.C. Medicina d'Emergenza e d'Urgenza 2, Ospedale S. Giovanni Bosco, Torino, Italy

4 Scuola di Medicina, Università degli Studi di Torino, Torino, Italy

5 S.C. Cardiochirurgia U, Ospedale Molinette, A.O.U. Città Della Salute e della Scienza di Torino, Torino, Italy

6 Dipartimento di Scienze Chirurgiche, Università degli Studi di Torino, Torino, Italy

7 S.C. Chirurgia Vascolare U, Ospedale Molinette, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy

Introduction

Acute aortic syndrome (AAS), including aortic dissection (AD), intramural aortic hematoma (IMH) and penetrating aortic ulcer (PAU), is a life-threatening disease category affecting 3 to 6 per 100,000 person-years [1–3]. Acute phase treatment of AAS differs based on anatomic involvement and clinical picture. Stanford type A AAS, characterized by ascending aorta involvement, is treated with emergency surgical intervention. Stanford type B AAS, which involves the thoracic descending or thoraco-abdominal aorta while sparing the ascending aorta, is treated with intensive medical therapy aiming at tight blood pressure (BP), heart rate (HR) and pain control, while emergency surgical or endovascular intervention is due only in complicated cases [4, 5].

In patients surviving > 14 days from AAS onset, persistence of AD, IMH or PAU within the descending thoracic or thoraco-abdominal aorta leads to development of chronic

Published online: 20 April 2026

Stanford type B aortic syndrome (cTBAS). This condition is characterized by incessant pathological aortic remodeling due to inflammation, extracellular matrix degradation, loss of vascular smooth muscle cells and thrombosis [6, 7]. Such processes pave the way for aneurysm formation, AAS recurrence, aortic rupture and therefore, subsequent interventions. Within 5 years, 63%–73% of patients with type B AD develop an aortic aneurysm. At 10 years, intervention rate is 20–50%, and mortality rate is 30–50%, with differences according to subtype [8–10]. Preventing this burden of morbidity and mortality is a clinically unmet need, with medical therapy, patient surveillance and patient selection for early thoracic endovascular repair (TEVAR) representing key albeit controversial elements [11, 12].

The mainstay therapeutic recommendation for cTBAS is represented by long-term anti-impulse pharmacological restraint of the rate of aortic pressure rise over time (dP/dT), representing the main cause of aortic wall shear stress [13]. This is obtained through coupling of both BP and HR reduction. For cTBAS, guidelines indicate targets of systolic BP (SBP) < 130 mmHg and HR of 60–70 beats per minute (bpm) [4, 5]. In clinical practice, this is usually obtained by an association therapy including a beta-blocker drug with other hypotensive drugs, as needed. In animal models of aortic dissection, blockade of beta-adrenergic or angiotensin II signaling has shown beneficial effects [14]. However, supporting evidence in humans from clinical studies is sparse and conflicting [15]. Randomized controlled trials are not available, and only few observational studies have reported that long-term therapy with beta-blockers, ACE inhibitors/ARBs or calcium channel blockers is associated with favorable outcomes in cTBAS [16–19]. In a recent survey across 7 countries, substantial variation in therapeutic targets, reporting standards, and management has been highlighted [20].

Another component of long-term medical treatment of cTBAS is represented by lipid-lowering (LL) therapy. In patients with underlying atherosclerotic aortic disease, LL drugs may promote favorable remodeling of atherosclerotic plaques. In addition, these drugs (especially statins) may provide pleiotropic benefits such as reduction of tissue inflammation, restraint of fibrotic remodeling and protection from vascular smooth muscle cell loss, even in non-atherosclerotic aortas [21, 22]. However, the benefits of LL therapy in human cTBAS have been shown only in few observational studies [23–26]. Furthermore, lipid-lowering targets tailored to cTBAS are not specified by guidelines. Assuming high or very-high cardiovascular risk for cTBAS, recommended LDL cholesterol targets are < 70 mg/dL (ACC/AHA and JAS guidelines) or < 55 mg/dL (ESC/EAS guidelines) [27–29].

Herein, we performed an observational proof-of-concept retrospective study, evaluating outpatients with cTBAS managed by a specialized clinic. All patients were treated with a best medical therapy bundle including anti-impulse and LL drugs, aimed at guideline-compliant targets for BP, HR and lipid levels. The working hypothesis was that favorable response to medical therapy is associated with better clinical outcomes.

Methods

Study design and setting

This was a single-center retrospective observational study conducted at the Molinette Hospital, A.O.U. Città della Salute e della Scienza di Torino, an interregional (Piemonte, Valle d'Aosta) referral hub for complex aortic diseases. The study protocol conformed to the Declaration of Helsinki and was approved by the local institutional Ethics Committee (42/2020, prot. 0029448). All participants provided informed consent, and data were collected anonymously, in compliance with data protection regulations.

Study patients

The study included consecutive outpatients affected by cTBAS, referred for best medical therapy to a specialized clinic of the Molinette Hospital (Torino, Italy) between March 2021 and May 2025. Referrals were decided based on clinical reasoning by physicians who were not involved in the study. Referred patients were considered eligible if they had a confirmed diagnosis of cTBAS, which included persisting dissection, intramural hematoma or penetrating ulcer within the descending thoracic or thoraco-abdominal aorta. Both primary and residual forms after a surgical repair of Stanford type A AAS were eligible. Chronicity of cTBAS was defined by more than 30 days from AAS onset.

The diagnosis of cTBAS was confirmed by a senior physician expert in cardiovascular medicine and by a vascular surgeon expert in aortic diseases, who had access to full medical data and imaging. Exclusion criteria were age < 18 years, traumatic etiology, AAS onset ≤ 30 days, patient's refusal to participate, unwillingness or impossibility to show up at follow-up visits and incomplete clinical data. All consecutive patients satisfying inclusion criteria and without exclusion criteria were enrolled in the study independent of previous medical prescriptions, current pharmacological treatment and response to therapy at day 0 in terms of BP, HR and lipid levels.

Clinical management

The clinic implemented a pre-defined structured outpatient surveillance program which included scheduled medical visits and serial multimodal vascular imaging, compliant with available guidelines. The clinical protocol involved

a first visit, which represented day 0 of patient's follow-up for the present analyses, subsequent visits scheduled after 6 and 12 months, and annually thereafter unless clinically needed. For patients enrolled after hospital admittance for AAS, the first outpatient visit was generally scheduled within 3 months from hospital discharge, based on feasibility and clinical reasoning. When in-person visits were not feasible, follow-up was conducted via telephone contact.

Overall clinical management of enrolled patients, including indications for surgical or endovascular interventions, was independent from patient enrollment in the present study. For medical therapy, however, the clinical policy of the surveillance program was to provide all patients with prescription of best medical therapy according to guidelines including anti-impulse therapy with target office BP values < 130/80 mmHg and HR < 60 beats per minute (bpm), and LL therapy aiming at LDL cholesterol < 55 mg/dL.

Data collection and variables

Clinical and outcome data were collected through manual review of all available hospital and clinic records by research personnel not involved in data analysis. Demographic, clinical and imaging data were collected anonymously in a structured dataset compiled using REDCap®. Demographic data included age, gender and body mass index. Clinical data included type of cTBAS diagnosis and previous AAS, "classic" cardiovascular risk factors (including hypertension, diabetes mellitus, dyslipidemia, smoking, drug use), risk factors for AAS (connective tissue disease, family history), history of aortic disease (aortic valve disease, previous aortic surgery or endovascular procedure, aortic aneurysm or aortic grafts), cardiovascular comorbidities (including coronary artery disease, peripheral artery disease, cerebrovascular disease), and other relevant comorbidities (chronic kidney disease, connective tissue disorder). Additional data included type and dose of pharmacological therapy.

The following clinical data were registered based on report by the treating physician at each time point: office SBP, diastolic BP (DBP) and HR values, and home self-reported BP control. Office BP was measured with a manual sphygmomanometer, following guideline indications. Per guidelines, office and self-reported home BP control was defined as optimal if < 130/80 mmHg. For HR, optimal control was defined if < 60 beats per minute (bpm). The patient's lipid profile registered in the study included total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Additional data included selected blood tests obtained within 3 months of patient enrollment (creatinine, C-reactive protein and D-dimer). All missing values were left as non-imputed.

Outcomes

The primary outcome was a composite of major aortic events (MAEs), defined as development of any of the following: death from any aortic cause, aortic rupture, new AAS, aortic dilatation defined as transverse diameter increase > 5 mm/year or maximal aortic diameter > 55 mm at any aortic level, new aortic intervention (either surgical or endovascular, at any level) or new aorta-related malperfusion or ischemic organ damage. In case of death from unknown cause after review of all available data, the case was considered as a MAE, applying worst-case-scenario. In case of repeated MAEs during the follow-up, the earliest was considered for all time-dependent analyses. The secondary outcome was a composite of major non-aortic cardiovascular events, defined as any of the following: death from cardiovascular non-aortic causes, acute coronary syndrome, cerebrovascular event (stroke or transient ischemic attack), new carotid revascularization, new coronary revascularization, limb ischemia or peripheral arterial revascularization. Overall mortality, including that resulting from non-aortic or cardiovascular conditions, was also annotated. Outcome adjudication was performed by two expert physicians who were not involved in data analysis and who had full access to the clinical data. In case of discordance, final adjudication was done after case discussion.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR, presented as 25th to 75th percentile value). Categorical variables were reported as counts and percentages. Statistical comparisons between groups were made using Wilcoxon rank-sum exact test for continuous variables, and Pearson's chi-square or Fisher's exact test for categorical values. Comparison of repeated measures in the same group was made using non-parametric Friedman's Two-Way Analysis of Variance by Ranks and Wilcoxon rank-sum exact test with Holm-Bonferroni correction for continuous variables, and Cochran's Q test and McNemar test with Holm-Bonferroni correction for categorical values.

Cox proportional hazards regression analysis (both univariate and bivariate adjusting for the presence of abdominal aortic aneurysm) was used to assess the association between selected variables and MAEs. Hazard ratios with corresponding 95% confidence intervals (CIs) were estimated. Kaplan–Meier survival curves were reported, evaluating the association between selected variables and MAEs.

Since this was an observational study performed on consecutive eligible patients with a rare condition and without an external control group, sample size calculations were not performed. Statistical analysis was performed using MedCalc® Statistical Software version 23.3.4 (MedCalc

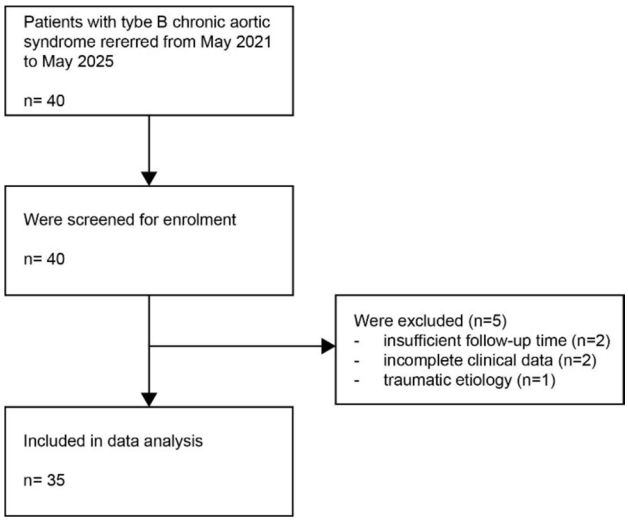


Fig. 1 Flow diagram of the study

Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2025), SPSS Statistics for Windows, ver. 27.0, (IBM Corp., Chicago, IL, USA), and R Software v4.3.1 for Mac OS (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Forty patients with cTBAS were screened for eligibility and 35 were further analyzed (Fig. 1). Nineteen (54.3%) developed primary AAS from January 2021 to January 2025, and the other 16 patients had earlier primary AAS. In the study period, 165 type A AASs and 41 type B AASs were admitted to the study hospital through the Emergency Department; 132 and 38 of them, respectively, were discharged alive. cTBAS subtypes included 23 (65.7%) ADs, 10 (28.6%) IMHs, and 2 (5.7%) of PAUs. The AAS leading to cTBAS was a primary type B AAS in 28 (80%) patients, and a previous surgically treated type A AAS in 7 (20%) patients (6 AD and 1 IMH). The median time from AAS diagnosis to study enrollment was 536 days. Sixty-three percent of patients were male, and the median age was 60 (53.5–66) years. Demographic and clinical characteristics of study patients are summarized in Table 1.

Response to medical therapy

The median follow-up time was 839 (640–1256) days. All patients were treated with anti-impulse and lipid-lowering drugs, as detailed in Table 2. Antihypertensive and LL regimens were intensified over time ($P = 0.032$ and $P < 0.001$, respectively). BP, HR, and lipid levels measured during follow-up are shown in Table 3. LDL cholesterol decreased over time, from a median value of 83 mg/dL at baseline to 56 mg/dL after 12 months ($P = 0.003$), corresponding to a median −32.5% reduction. Also triglycerides decreased from 95 mg/dL to 85 mg/dL, corresponding to a median −10.5% reduction ($P = 0.025$).

The proportions of patients at guideline targets during the study are detailed in Supplementary Table 1 (SBP, DBP, HR) and in Supplementary Table 2 (lipid levels). Individuals at target for SBP were 40% at baseline and 53.3% after 12 months ($P = 0.144$), for DBP 37.1% and 46.7% ($P = 0.050$), and for HR 25.7% and 36.7% ($P = 0.695$). Individuals at target for LDL cholesterol *per* ACC/AHA (< 70 mg/dL) or ESC/EAS guidelines (< 55 mg/dL) increased from 28.6% and 8.6% at baseline, to 75.8% ($P < 0.001$) and 42.4% ($P = 0.002$), respectively, after 12 months.

Outcomes

During follow-up, 11 (31.4%) patients had at least one MAE. Total MAEs, including multiple MAEs, were 3 (8.6%) deaths from aortic disease, 1 (2.9%) new AAS, 2 (5.7%) malperfusion syndromes, 5 (14.3%) aortic dilatations, and 5 (14.3%) aortic interventions. 1 patient (2.9%) had a non-aortic cardiovascular event, represented by new non-aorta-related peripheral artery disease.

Baseline demographic and clinical characteristics of patients with and without MAEs are shown in Table 1. All baseline variables, including SBP, DBP, HR and lipid levels, did not statistically differ between patients who subsequently developed or did not develop MAEs, except for abdominal aortic aneurysm at inclusion. This condition was more prevalent in patients who developed MAEs and was statistically associated with development of MAEs with a hazard ratio of 12.5 (95% CI, 2.7–58.2; $P = 0.001$).

Association with medical response

The distributions of SBP, DBP, HR and lipid levels during clinical follow-up, in patients with and without MAEs, are represented in Fig. 2. In patients who developed MAEs, SBP, DBP, HR and lipid levels were statistically unchanged over time. In this patient group, the proportions of individuals at target for SBP, DBP and HR were statistically unchanged during follow-up (Supplementary Table 1), whereas an increasing trend was observed in the proportion of patients reaching the LDL cholesterol target *per* ACC/AHA definition (18.2% to 40%, $P = 0.05$; Supplementary Table 2). Conversely, in patients without MAEs, significant changes were observed in SBP ($P = 0.005$), total cholesterol ($P < 0.001$) and LDL cholesterol ($P < 0.001$). Accordingly,

Table 1 Demographic and clinical characteristics of study patients at baseline

Variables	All patients $n=35$	Without MAE $n=24$	With MAEs $n=11$	*P*-value
Patient characteristics				
Age, years	60 (54–66)	59.5 (54–63)	63 (53–75)	0.534
Male sex	22 (62.9%)	15 (62.5%)	7 (63.6%)	0.948
BMI, kg/m^2	26.6 (24.2–31.5)	26.1 (23.6–30.7)	28.1 (25.8–32.3)	0.517
Hypertension	35 (100.0%)	24 (100.0%)	11 (100.0%)	1
Dyslipidemia	35 (100.0%)	24 (100.0%)	11 (100.0%)	1
Diabetes mellitus	1 (2.9%)	1 (4.2%)	0 (0.0%)	0.512
Active smoking	10 (28.6%)	6 (25.0%)	4 (36.4%)	0.489
Coronary artery disease	5 (14.7%)	3 (12.5%)	2 (20.0%)	0.574
Cerebrovascular disease	4 (11.4%)	3 (12.5%)	1 (9.1%)	0.768
Peripheral artery disease	4 (11.4%)	2 (8.3%)	2 (18.2%)	0.395
Chronic kidney disease	9 (25.7%)	5 (20.8%)	4 (36.4%)	0.329
Connective tissue disease	1 (2.9%)	1 (4.2%)	0 (0.0%)	0.492
Family history of acute aortic syndrome	2 (5.7%)	2 (8.3%)	0 (0.0%)	0.324
Aortic valve disease	4 (11.8%)	4 (16.7%)	0 (0.0%)	0.169
Thoracic aortic aneurysm	13 (37.1%)	7 (29.2%)	6 (54.5%)	0.149
Abdominal aortic aneurysm	3 (8.6%)	0 (0.0%)	3 (27.3%)	0.007
Time from acute aortic syndrome*, days	536 (66–1731)	550 (104–1459)	270 (38–2181)	0.612
Previous aortic intervention				
Thoracic aortic surgery	10 (29.4%)	7 (30.4%)	3 (27.3%)	0.850
Abdominal aortic surgery	1 (3.0%)	0 (0.0%)	1 (9.1%)	0.151
Thoracic endovascular aortic repair	8 (22.9%)	6 (25.0%)	2 (18.2%)	0.656
Abdominal endovascular aortic repair	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Vital parameters at baseline				
Systolic blood pressure, mmHg	130 (120–140)	130 (120–133)	130 (123–140)	0.588
Diastolic blood pressure, mmHg	80 (70–85)	80 (70–85)	80 (75–85)	0.420
Heart rate, bpm	60 (60–70)	60 (58–65)	70 (60–72)	0.117
Blood tests				
Creatinine (mg/dL)	1.04 (0.80–1.19)	1.03 (0.80–1.15)	1.07 (0.82–1.34)	0.594
C-reactive protein (mg/L)	4 (2.0–10.4)	4.4 (2.4–12.2)	3.5 (1.6–6.0)	0.662
D-dimer (ng/mL)	3410 (1766–5715)	3641 (2277–5632)	2519 (1766–6015)	0.799
Total cholesterol (mg/dL)	154 (132–181)	148.5 (132–205)	157 (132–165)	0.320
LDL cholesterol (mg/dL)	83 (69–119)	85 (68–130)	82 (73–92)	0.434
HDL cholesterol (mg/dL)	51 (41–55)	54 (44–58)	45 (38–52)	0.094
Triglycerides (mg/dL)	95 (80–127)	96 (77–135)	95 (81–111)	0.499

MAE(s) Major aortic event(s). Age, BMI and time from onset of acute aortic syndrome, are expressed as median (25th–75th percentile). The other variables are presented as n (%)

*Time from onset of the first acute aortic syndrome to enrollment in the present study, i.e. to follow-up

the proportions of patients at target for SBP (41.7% to 60%, $P=0.046$), DBP (41.7% to 65%, $P=0.050$) and LDL cholesterol < 70 mg/dL (33.3% to 91.3%, $P<0.001$) or < 55 mg/dL (8.3% to 56.5%, $P=0.003$), increased during the follow-up in patients without MAEs. The number of anti-impulse and LL drug classes at baseline, 6 and 12 months did not differ between patients with and without MAEs (Supplementary Table 3), while the number of LL drug classes increased significantly over time, in both groups.

After 6 months, in patients with and without MAEs, SBP was at target in 27.3% *vs* 80% individuals ($P=0.004$), and DBP was at target in 36.4% *vs* 75% ($P=0.035$), respectively. After 12 months, LDL cholesterol was at target < 70 mg/

Table 2 Antihypertensive and lipid-lowering therapy in study patients

Variable	Baseline $n=35$	6 months $n=33^{¶}$	12 months $n=34^{§}$	*P*-value
Antihypertensive drugs				
Number of drug classes/patient	3 (2–4)	3 (3–4)	3 (3–4)	0.032
Number of anti-impulse drugs/patient	2 (2–3)	3 (2–3)	3 (2–3)	0.171
Beta-blocker	32 (91.4%)	31 (93.9%)	29 (87.9%)	0.370
Calcium channel blocker	24 (68.6%)	25 (75.8%)	27 (81.8%)	0.115
RAS inhibitor (ACEi, ARBs)	27 (77.1%)	27 (81.8%)	27 (81.8%)	0.717
Diuretic	12 (34.3%)	13 (39.4%)	16 (48.5%)	0.417
Aldosterone receptor antagonist	9 (25.7%)	9 (27.3%)	11 (33.3%)	0.867
Alpha-blocker	8 (22.9%)	6 (18.2%)	6 (18.2%)	1
Other drugs	2 (5.7%)	1 (3%)	2 (6.1%)	0.370
Lipid lowering drugs				
Number of drug classes/patient	1 (0–1)	2 (1–2)	2 (1–2)	<0.001*†‡
Statin	21 (60%)	28 (84.8%)	29 (87.9%)	0.003*†
Ezetimibe	5 (14.3%)	17 (51.5%)	20 (60.6%)	<0.001*†
Bempedoic acid	0 (0%)	4 (12.1%)	6 (18.2%)	0.009*†
PCSK9 inhibitor	1 (2.9%)	1 (3%)	1 (3%)	0.368

The number of drug classes and of anti-impulse drugs per patient are presented as median and interquartile range (in parenthesis). The other variables are presented as n (%). ¶Data missing for 2 patients with data available at 12 months. §Data missing for 1 dead patient. Anti-impulse drugs include β-blockers, calcium channel blockers and renin-angiotensin system (RAS) inhibitors. *P*-value refers to Friedman rank sum test or Cochran's Q test. *$P<0.05$ for paired comparison between baseline and 6 months. †$P<0.05$ for paired comparison between baseline and 12 months. ‡$P<0.05$ for paired comparison between 6 and 12 months

Table 3 Blood pressure and lipid levels in study patients

Variable	Baseline	6 months	12 months	*P*-value
Systolic blood pressure, mmHg	130 (120–140) $N=35$	120 (115–130) $N=31$	125 (113–130) $N=30$	0.062
Diastolic blood pressure, mmHg	80 (70–85) $N=35$	70 (70–80) $N=31$	80 (70–80) $N=30$	0.069
Heart rate, bpm	60 (60–70) $N=35$	60 (55–68) $N=31$	60 (55–65) $N=30$	0.863
Total cholesterol, mg/dL	154 (132–181) $N=35$	134 (118–158) $N=27$	126 (110–136) $N=33$	0.010*†
LDL cholesterol, mg/dL	83 (69–119) $N=35$	61 (52–78) $N=26$	56 (46–66) $N=33$	0.003*†
HDL cholesterol, mg/dL	51 (41–55) $N=35$	50 (47–58) $N=26$	53 (44–59) $N=33$	0.388
Triglycerides, mg/dL	95 (80–127) $N=35$	96 (86–119) $N=27$	85 (70–110) $N=33$	0.025

Values are presented as median and interquartile range (in parenthesis). N indicates the number of patients with available data at each time point. *P*-value refers to Friedman rank sum test. *$P<0.05$ for paired comparison between baseline and 6 months; †$P<0.05$ for paired comparison between baseline and 12 months

dL in 40% *vs* 91.3% ($P=0.002$), and < 55 mg/dL in 10% *vs* 56.5% ($P=0.013$), respectively.

The results of Cox-regression analysis are summarized in Fig. 3. SBP < 130 mmHg at 6 months (hazard ratio 0.19, $P=0.014$) and LDL cholesterol < 70 mg/dL at 12 months (hazard ratio 0.15, $P=0.004$) were both associated with protection from MAEs. The association remained significant after adjustment for the presence of an abdominal aortic aneurysm (Supplementary Fig. 1). Event-free survival curves for patients classified according to achievement of SBP or LDL targets are shown in Fig. 4.

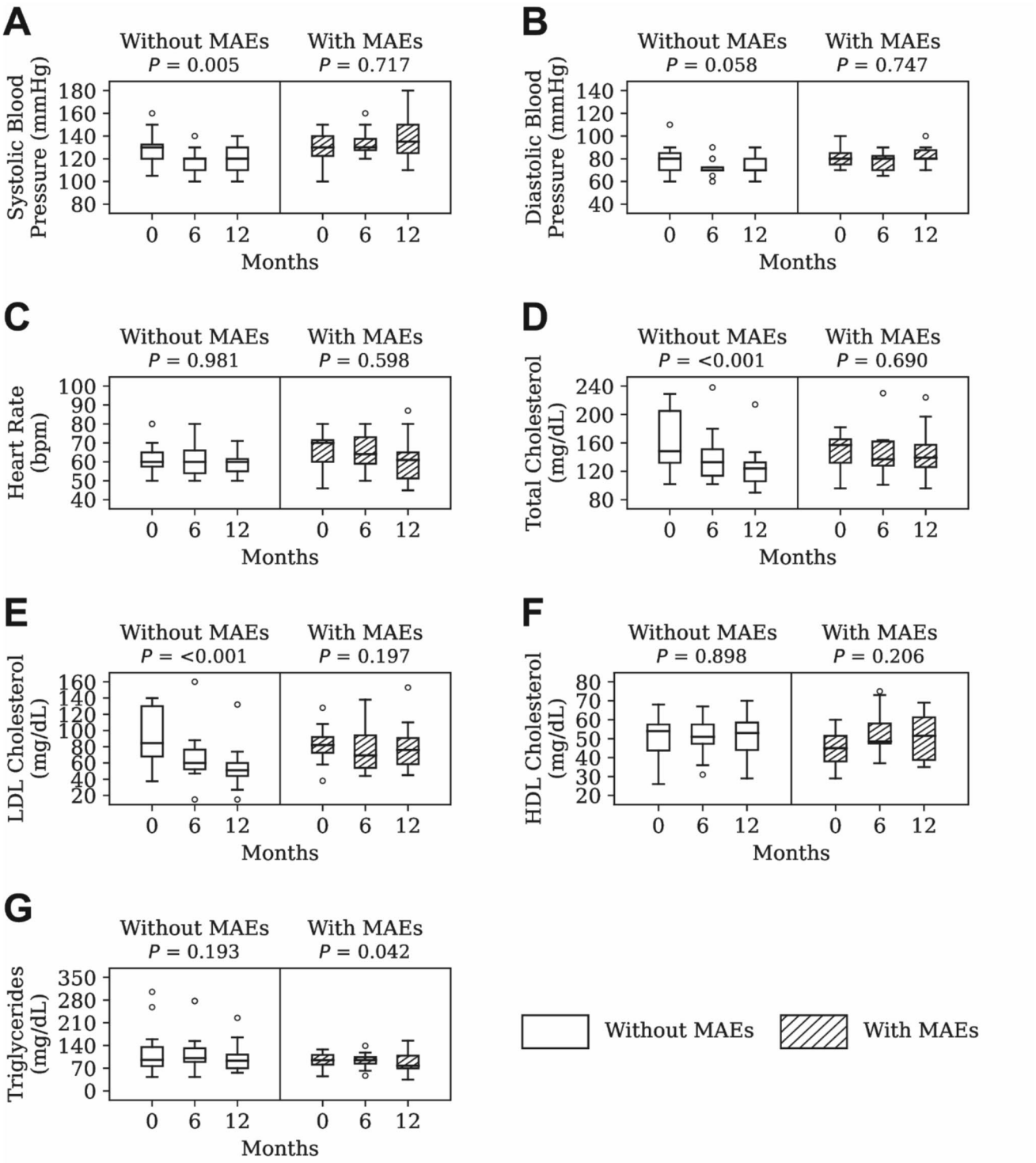


Fig. 2 Box-and-whisker plots representing levels of blood pressure (**A,B**), heart rate (**C**) and lipid levels (**D**, **E**, **F**, **G**) at baseline (0 months) and during follow-up (6 and 12 months), in study patients without and with major aortic events (MAEs). Boxes represent the 25th quartile, median, 75th quartile, and outlier values are presented. P-values in each patient group were obtained with Friedman two-way analysis of variance by ranks

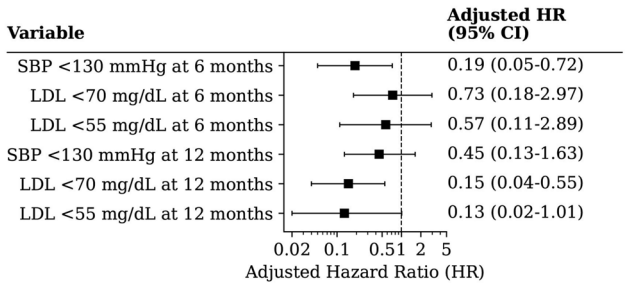


Fig. 3 Forest plot summarizing the adjusted hazard ratio for major aortic events, associated with the indicated medical response variables. The HR is presented in log scale. Values in brackets represent the lower and upper limits of the 95% confidence interval

Discussion

Current expert and guideline recommendations for long-term anti-impulse and LL therapies in cTBAS are poorly evidence-based, as observational studies have provided conflicting results. Furthermore, clinical trials are lacking, beneficial effects have mostly been described in animal or basic science studies, and heterogeneous reference, management and implementation standards have been reported [14, 20]. Herein, we provide a hypothesis-generating study suggesting that in cTBAS outpatients under supervision of a specialized medical clinic, pharmacological treatment strictly targeting BP, HR and LDL cholesterol may be associated with protection from MAEs. In patients who developed MAEs, BP, total and LDL cholesterol levels were unchanged during follow-up, indicating that conversely, failure to obtain satisfactory medical control may be associated with increased risk of MAEs. Since all patients received the same prescription and follow-up protocol, differences in outcomes appear related to individual response to medical therapy. Nonetheless, given the observational nature of the study, causality cannot be inferred, nor could adjustment for potential confounders be performed.

Results suggest that in current practice, optimal control of BP, HR and lipid levels in patients with cTBAS still represents a challenge and that improved awareness is warranted. At study enrollment, patients at target for BP, HR and LDL cholesterol were a net minority. In terms of feasibility, the study shows that an intensive medical program, implying a net increase in the number of drug prescriptions, can indeed improve response towards guideline-compliant targets and possibly be associated with favorable outcomes. However, the proportion of patients not at target was still significant after 12 months, especially for anti-impulse targets and for LDL cholesterol < 55 mg/dL.

Previous pilot translational and small observational studies in patients with cTBAS showed that anti-impulse and LL therapy seem to mitigate pathological aortic remodeling [14, 23–26]. In our study, the beneficial effects of this dual therapy seemed to develop within the first months, reaching statistical evidence within 6 to 12 months. Results reinforce the importance of early adoption or development for patients with cTBAS, of intensive programs dedicated to cardiovascular risk factor control and serial outpatient control, in the attempt to improve their clinical outcomes. In this study, however, the benefits of medical therapy were found also in patients with long-lasting cTBAS, as median time from AAS to study enrollment was 18 months. Unfortunately, a subgroup analysis by "chronicity" could not be performed given the low numbers in the groups. Considering the biology of aortic remodeling, we speculate that an earlier start of targeted medical therapy might lead to better outcomes. Nonetheless, whether these strict targets are beneficial for all cTBAS and should be applied regardless of the phenotype and amount of aortic atherosclerosis, remains to be understood in further studies.

Given the study design, causality cannot be unraveled, and results are hypothesis-generating, with two possible and potentially coexisting explanations. In line with translational studies, antihypertensive and LL therapies may protect from negative aortic wall remodeling following a dose–response relationship. Only in patients with a significant drop in BP and in LDL cholesterol levels, protective effects on the aortic wall are elicited, even after adjusting for the presence of an abdominal aortic aneurysm. An alternative explanation is that therapeutic response is underpinned by a combination of therapeutic adherence, additional lifestyle variables (*e.g.* dietary habits, metabolic phenotype) and genetic determinants (of both therapeutic response and aortic disease), which were not evaluated in our study.

Due to small sample size, the present study does not inform on the relative importance of therapeutic bundle components in MAE prevention. It is therefore unknown whether anti-impulse and LL therapy are both needed to boost aortic protection, or whether one of the two may be sufficient, or even superior. For the same reason, comparison between drug classes, or between medical therapy alone and medical therapy combined with aortic interventions, is not possible.

The current study has several limitations. First, this was an observational single-center study with a small sample size, which limits external validity and cannot assess causality. Since patients were selected based on their adequacy to attend an outpatient clinic, the cohort likely overrepresents younger and more motivated patients with reasonably high therapeutic compliance. We cannot exclude additional

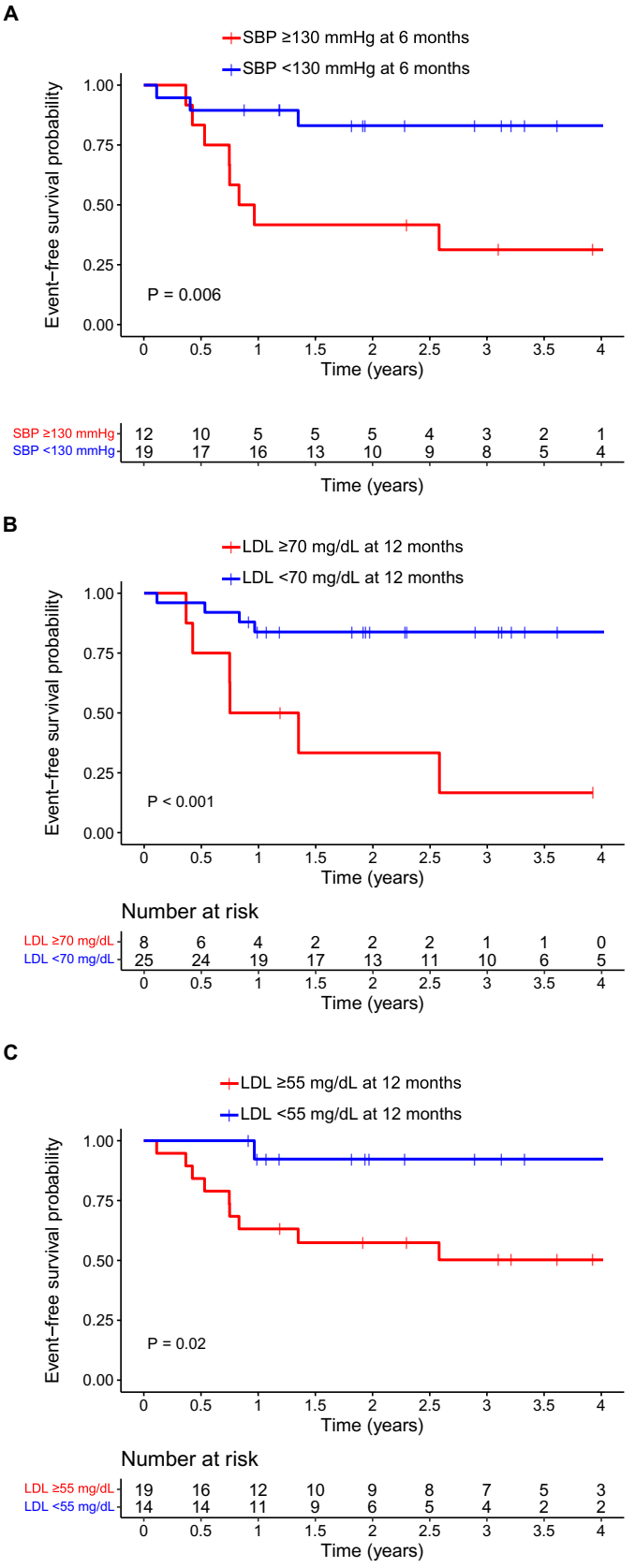


Fig. 4 Major aortic event-free survival curve of study patients classified according to achievement of pharmacological goals. **A** Therapeutic target: office systolic blood pressure (SBP) < 130 mmHg at 6 months. **B** Therapeutic target: LDL cholesterol < 70 mg/dL at 12 months. **C** Therapeutic target: LDL cholesterol < 55 mg/dL at 12 months. P-values were obtained with the Log-rank test

selection bias, since referrals were made by physicians not involved in the present study. Second, pharmacological compliance was not directly assessed through specific questionnaires or tests. It is possible that patients with reduced clinical response were less adherent to prescriptions. Third, BP and HR levels were only measured as office values, while more informative data from 24 h monitoring, which would account for daily variability and white-coat effect, was not available. Finally, the small sample size does not allow subgroup analyses to evaluate the impact of the different components of the therapeutic bundle and adjustment for confounders in multivariate analyses.

In conclusion, the present study provides proof-of-concept that in cTBAS, long-term combined medical therapy with anti-impulse and LL drugs applying ambitious guideline-compliant targets is feasible, and that medical response may be associated with favorable outcomes. Further multicenter studies are warranted to confirm these pilot results on larger patient cohorts.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11739-026-04348-4.

Acknowledgements FM received funding from the Università degli Studi di Torino (Dipartimento di Scienze Mediche). EL received funding from the Fondazione Ricerca Molinette.

Author contributions Conceptualization: FM; Methodology: FM, PB; Clinical data gathering: FR, PF; Formal analysis and investigation: FM, PB, FR, EF, EP; Writing—original draft preparation: FM; Writing—review and editing: FM, PB, EF; Clinical data review and adjudication: PF, MLT, FV; Supervision: EL. All authors read and approved the final manuscript.

Funding Open access funding provided by Università degli Studi di Torino within the CRUI-CARE Agreement. Dipartimento di Scienze Mediche, Università degli Studi di Torino, MORF_RILO_21_02, Fulvio Morello, MORF_RILO_23_03, Fulvio Morello, Fondazione Ricerca Molinette, 2023, Enrico Lupia

Data availability The datasets generated and analysed during the current study are not publicly available due to patient privacy and ethical restrictions. De-identified aggregate data are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None of the authors has any direct financial conflict of interest to disclose. FM received grants from the Università degli Studi di Torino (MORF_RILO_21_02, MORF_RILO_23_03). EL received a grant from Fondazione Ricerca Molinette (2023). PB received a grant from the Swiss Heart Foundation (FF23602) unrelated to the present work. FV receives scientific consultancy fees from WL Gore and Cook, unrelated to the present work.

Human and animal rights The study protocol conformed to the Declaration of Helsinki and was approved by the local institutional Ethics Committee (42/2020, prot. 0029448).

Informed consent All participants provided informed consent, and data were collected anonymously, in compliance with data protection regulations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Olsson C, Thelin S, Stahle E, Ekbom A, Granath F (2006) Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. Circulation 114:2611–2618. https://doi.org/10.1161/CIRCULATIONAHA.106.630400
2. Vilacosta I, Román JAS, di Bartolomeo R, Eagle K, Estrera AL, Ferrera C, Kaji S, Nienaber CA, Riambau V, Schäfers H-J, Serrano FJ, Song J-K, Maroto L (2021) Acute aortic syndrome revisited. JACC 78:2106–2125. https://doi.org/10.1016/j.jacc.2021.09.022
3. Morello F, Bima P, Castelli M, Nazerian P (2022) Acute aortic syndromes: an internist's guide to the galaxy. Eur J Intern Med 106:45–53. https://doi.org/10.1016/j.ejim.2022.10.003
4. Isselbacher EM, Preventza O, Hamilton Black J, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda A Jr, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ, M Peer Review Committee (2022) ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American heart association/American college of cardiology joint committee on clinical practice guidelines. Circulation 146:e334–e482. https://doi.org/10.1161/CIR.0000000000001106
5. Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, Bura-Rivière A, De Backer J, Deglise S, Della Corte A, Heiss C, Kałużna-Oleksy M, Kurpas D, McEniery CM, Mirault T, Pasquet AA, Pitcher A, Schaubroeck HAI, Schlager O, Sirnes PA, Sprynger MG, Stabile E, Steinbach F, Thielmann M, van Kimmenade RRJ, Venermo M, Rodriguez-Palomares JF (2024) 2024 ESC guidelines for the management of peripheral arterial and aortic diseases. Eur Heart J 45:3538–3700. https://doi.org/10.1093/eurheartj/ehae179
6. Peterss S, Mansour AM, Ross JA, Vaitkeviciute I, Charilaou P, Dumfarth J, Fang H, Ziganshin BA, Rizzo JA, Adeniran AJ, Elefteriades JA (2016) Changing pathology of the thoracic aorta from acute to chronic dissection: literature review and insights. J Am Coll Cardiol 68:1054–1065. https://doi.org/10.1016/j.jacc.2016.05.091
7. Kuzniar M, Wanhainen A, Tegler G, Hansen T, Mani K (2023) Longitudinal assessment of inflammatory activity in acute Type B aortic dissection with integrated fluorodeoxyglucose positron

emission tomography/magnetic resonance imaging. Eur J Vasc Endovasc Surg 66:323–331. https://doi.org/10.1016/j.ejvs.2023.05.039
8. Tsai TT, Trimarchi S, Nienaber CA (2009) Acute aortic dissection: perspectives from the International Registry of Acute Aortic Dissection (IRAD). Eur J Vasc Endovasc Surg 37:149–159. https://doi.org/10.1016/j.ejvs.2008.11.032
9. Fattori R, Montgomery D, Lovato L, Kische S, Di Eusanio M, Ince H, Eagle KA, Isselbacher EM, Nienaber CA (2013) Survival after endovascular therapy in patients with type B aortic dissection: a report from the International Registry of Acute Aortic Dissection (IRAD). JACC Cardiovasc Interv 6:876–882. https://doi.org/10.1016/j.jcin.2013.05.003
10. Demal TJ, Knochenhauer T, Weimann J, Juvonen T, Mäkikallio T, Fiore A, Perrotti A, Pettinari M, Peterss S, Buech J, Radner C, Dell'Aquila AM, Wisniewski K, Pol M, Kacer P, Onorati F, Francica A, Vendramin I, Piani D, Rinaldi M, Ferrante L, Quintana E, Pruna-Guillen R, Lega JR, Pinto AG, Acharya M, Field M, Kuduvalli M, Nappi F, Gerelli S, Di Perna D, Gatti G, Mazzaro E, Rosato S, D'Errigo P, Mariscalco G, El-Dean Z, Detter C, Reichenspurner H, Polvani G, Biancari F, Conradi L (2025) Outcome after day- and nighttime surgery for acute type A aortic dissection. Eur J Cardiothorac Surg 67:ezaf192. https://doi.org/10.1093/ejcts/ezaf192
11. Rahman T, Bicknell CD, Mussa FF, Björkman P (2025) Contemporary randomized controlled trials in uncomplicated type B aortic dissection: a comparative methodological analysis. J Cardiovasc Surg 66(5):405–415. https://doi.org/10.23736/s0021-9509.25.13339-9
12. Jubouri M, Surkhi AO, Alsarayrah AI, Alaraj R, Campbell D, Qaisi A, Andonie CR, Jubouri YF, Abdelhaliem A, Piffaretti G, Bailey DM, Williams IM, Bashir M (2025) TEVAR versus optimal medical therapy for uncomplicated Type B aortic dissection: a systematic review & meta-analysis. Ann Vasc Surg 120:272–284. https://doi.org/10.1016/j.avsg.2025.06.020
13. Papakonstantinou PE, Benia D, Polyzos D, Papakonstantinou K, Rorris FP, Toulgaridis F, Manousiadis K, Xydonas S, Sideris A (2022) Chronic thoracic aortic dissection: how to treat, when to intervene. Life 12:1511. https://doi.org/10.3390/life12101511
14. Milewicz DM, Ramirez F (2019) Therapies for Thoracic Aortic Aneurysms and Acute Aortic Dissections. Arteriosclerosis, Thrombosis, and Vascular Biology 39:126–136. https://doi.org/10.1161/ATVBAHA.118.310956
15. Chan KK, Lai P, Wright JM (2014) First-line beta-blockers versus other antihypertensive medications for chronic type B aortic dissection. Cochrane Database Syst Rev (2):CD010426. https://doi.org/10.1002/14651858.CD010426.pub2
16. Genoni M, Paul M, Jenni R, Graves K, Seifert B, Turina M (2001) Chronic beta-blocker therapy improves outcome and reduces treatment costs in chronic type B aortic dissection. Eur J Cardiothorac Surg 19:606–610. https://doi.org/10.1016/s1010-7940(01)00662-5
17. Suzuki T, Isselbacher EM, Nienaber CA, Pyeritz RE, Eagle KA, Tsai TT, Cooper JV, Januzzi JL Jr., Braverman AC, Montgomery DG, Fattori R, Pape L, Harris KM, Booher A, Oh JK, Peterson M, Ramanath VS, Froehlich JB (2012) Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol 109:122–127. https://doi.org/10.1016/j.amjcard.2011.08.012
18. Chen SW, Chan YH, Lin CP, Wu VC, Cheng YT, Chen DY, Chang SH, Hung KC, Chu PH, Chou AH (2021) Association of long-term use of antihypertensive medications with late outcomes among patients with aortic dissection. JAMA Netw Open 4:e210469. https://doi.org/10.1001/jamanetworkopen.2021.0469
19. Liisberg M, Lindholt JS, Larsen KL, Diederichsen ACP, Hallas J, Gerke O, Lasota AN, Jensen HK, Benhassen LL, Mørkved AL, Srinanthalogen R, Skovbo JS, Obel LM (2025) Beta blockers as primary and secondary prevention for aortic dissections in nonsyndromic patients with hypertension. J Am Heart Assoc 14:e040149. https://doi.org/10.1161/jaha.124.040149
20. Saricilar EC, Budtz-Lilly J, Biersteker B, van der Vorst J, Mani K (2025) SUNDAY trial insights: questionnaire of clinical perspectives on medical therapy in uncomplicated type B aortic dissections. J Cardiovasc Surg. 2025;66(5):395–404. https://doi.org/10.23736/s0021-9509.25.13363-6
21. Oesterle A, Laufs U, Liao JK (2017) Pleiotropic effects of statins on the cardiovascular system. Circ Res 120:229–243. https://doi.org/10.1161/circresaha.116.308537
22. Myasoedova VA, Rega S, Valerio V, Moschetta D, Massaiu I, Bonalumi G, Esposito G, Rusconi V, Bertolini F, Perrucci GL, Poggio P (2024) Exploiting the anti-fibrotic effects of statins on thoracic aortic aneurysm progression: results from a meta-analysis and experimental data. Front Pharmacol 15:1426982. https://doi.org/10.3389/fphar.2024.1426982
23. Tazaki J, Morimoto T, Sakata R, Okabayashi H, Yamazaki F, Nishiwaki N, Mitsudo K, Kimura T (2014) Impact of statin therapy on patients with coronary heart disease and aortic aneurysm or dissection. J Vasc Surg 60:604-612.e602. https://doi.org/10.1016/j.jvs.2014.03.280
24. Masaki N, Kumagai K, Sasaki K, Matsuo S, Motoyoshi N, Adachi O, Akiyama M, Kawamoto S, Tabayashi K, Saiki Y (2018) Suppressive effect of pitavastatin on aortic arch dilatation in acute Stanford type B aortic dissection: analysis of STANP trial. Gen Thorac Cardiovasc Surg 66:334–343. https://doi.org/10.1007/s11748-018-0916-z
25. Smedberg C, Hultgren R, Leander K, Steuer J (2022) Pharmacological treatment in patients with aortic dissection. Open Heart 9(2):e0002082. https://doi.org/10.1136/openhrt-2022-002082
26. Cheng J, Zhang Z, Wang Y, He H, Zhao T, Wang X (2024) Effect of statins on the prognosis after thoracic endovascular aortic repair for patients with acute type B aortic dissection. J Endovasc Ther. https://doi.org/10.1177/15266028241306356
27. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 139:1082–1143. https://doi.org/10.1161/CIR.0000000000000625
28. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O (2020) 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 41:111–188. https://doi.org/10.1093/eurheartj/ehz455
29. Okamura T, Tsukamoto K, Arai H, Fujioka Y, Ishigaki Y, Koba S, Ohmura H, Shoji T, Yokote K, Yoshida H, Yoshida M, Deguchi J, Dobashi K, Fujiyoshi A, Hamaguchi H, Hara M, Harada-Shiba M, Hirata T, Iida M, Ikeda Y, Ishibashi S, Kanda H, Kihara S, Kitagawa K, Kodama S, Koseki M, Maezawa Y, Masuda D, Miida T, Miyamoto Y, Nishimura R, Node K, Noguchi M, Ohishi M, Saito I, Sawada S, Sone H, Takemoto M, Wakatsuki A, Yanai H (2024) Japan Atherosclerosis Society (JAS) Guidelines for Prevention

of Atherosclerotic Cardiovascular Diseases 2022. J Atheroscler Thromb 31:641–853. https://doi.org/10.5551/jat.GL2022

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.