家族性大動脈瘤・解離症例のDB登録へのscheme：JACVSD抽出dataからの解析・結果

結合織疾患（遺伝性素因を含む）を背景とした大動脈瘤・解離に対する外科治療成績の検討　表3

	非マルファン症候群	マルファン症候群	有意水準
術前大動脈性状			
上行大動脈不安定プラーク	3(1.7%)	0(0%)	0.039
弓部大動脈不安定プラーク	10(5.7%	4(1.2%)	0.007
下行大動脈不安定プラーク	18(10.3%)	5(1.5%)	<0.001
腹部大動脈不安定プラーク	7(4.0%)	3(0.9%)	0.036
腹部腸骨動脈不安定プラーク	5(2.9%)	1(0.3%)	0.019
手術適応			
解離性動脈瘤	57(32.6%)	187(54.8%)	<0.001
Stanford A型解離	40(22.9%)	100(29.3%)	0.071
仮性瘤	20(11.4%)	12(3.5%)	0.001
急性動脈瘤	30(17.1%)	74(21.7%)	0.247
大動脈瘤破裂	8(4.6%)	12(3.5%)	0.631
大動脈瘤拡張	112(64%)	227(66.6%)	0.559
手術部位			
大動脈基部	38(21.7%)	186(54.5%)	<0.001
上行大動脈	88(50.3%)	154(45.2%)	0.305
弓部大動脈	58(33.1%)	90(26.4%)	0.123
下行大動脈	38(21.7%)	61(17.9%)	0.345
腹部大動脈	2(1.1%)	6(1.8%)	0.722
胸腹部大動脈	11(6.3%)	50(14.7)	0.006

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	非マルファン症候群	マルファン症候群	有意水準
手術関連			
輸血有無	158(90.3%)	314(92.1%)	0.508
他家輸血	151(86.3%)	262(76.8%)	0.011
自己輸血	25(14.3%)	93(27.3%)	0.001
順行性脳循環	67(38.3%)	97(28.4)	0.028
逆行性脳循環	11(6.3%)	30(8.8%)	0.391
人工心肺使用	150(85.7%)	326(95.6%)	<0.001
心臓関連手術			
冠動脈バイパス術	17(9.7%)	26(7.6%)	0.406
予期しない冠動脈バイパス術	5(2.9%)	18(5.3%)	0.263
MAZE術	1(0.6%)	0(0%)	0.339
機械弁使用	35(20.1%)	116(34%)	0.001
生体弁使用	21(12.0%)	13(3.8%)	0.001
大動脈弁手術	61(34.9%)	180(52.8%)	<0.001
大動脈弁修復術	34(19.1%)	135(39.6%)	<0.001
大動脈弁置換	27(15.4%)	45(13.2%)	0.504
僧帽弁手術	6(3.4%)	12(3.5%)	1
僧帽弁修復術	4(2.3%)	4(1.2%)	0.453
僧帽弁置換	2(1.1%)	8(2.3%)	0.507
三尖弁手術	2(1.1%)	2(0.6%)	0.607
単弁手術	56(32.0%)	172(50.4%)	<0.001
複合弁手術	119(68.0%)	169(49.6%)	<0.001
3弁以上複合弁手術	1(0.6%)	0(0%)	0.339

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	非マルファン症候群	マルファン症候群	有意水準
ジギタリス製剤	7(4.0%)	15(4.4)	1
β遮断薬	45(25.7%)	110(32.3%)	0.13
硝酸薬	1(0.6%)	5(1.5%)	0.669
アスピリン製剤	17(9.7%)	17(5.0%)	0.059
抗凝固薬	11(6.3%)	15(4.4%)	0.397
ステロイド製剤	71(40.6%)	0(0%)	<0.001

研究成果の刊行に関する一覧表

雑誌

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家族性大動脈瘤・解離の実態解明・効果的な進行予防・治療を目的とした
レジストリー構築に関する研究班

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Type-Selective Benefits of Medications in Treatment of Acute Aortic Dissection (from the International Registry of Acute Aortic Dissection [IRAD])

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The effects of medications on the outcome of aortic dissection remain poorly understood. We sought to address this by analyzing the International Registry of Acute Aortic Dissection (IRAD) global registry database. A total of 1,301 patients with acute aortic dissection (722 with type A and 579 with type B) with information on their medications at discharge and followed for ≤5 years were analyzed for the effects of the medications on mortality. The initial univariate analysis showed that use of β blockers was associated with improved survival in all patients (p = 0.03), in patients with type A overall (p = 0.02), and in patients with type A who received surgery (p = 0.006). The analysis also showed that use of calcium channel blockers was associated with improved survival in patients with type B overall (p = 0.02) and in patients with type B receiving medical management (p = 0.03). Multivariate models also showed that the use of β blockers was associated with improved survival in those with type A undergoing surgery (odds ratio 0.47, 95% confidence interval 0.25 to 0.90, p = 0.02) and the use of calcium channel blockers was associated with improved survival in patients with type B medically treated patients (odds ratio 0.55, 95% confidence interval 0.35 to 0.88, p = 0.01). In conclusion, the present study showed that use of β blockers was associated with improved outcome in all patients and in type A patients (overall as well as in those managed surgically). In contrast, use of calcium channel blockers was associated with improved survival selectively in those with type B (overall and in those treated medically). The use of angiotensin-converting enzyme inhibitors did not show association with mortality. **(Am J Cardiol 2012;109:122–127)**

Medical management of aortic dissection is still mainly determined from personal experience, expert opinion, and historical observational studies.[1–8] β Blockers are thought to be the first-line medication,[9–14] and recent studies have suggested the benefit of inhibitors of the renin-angiotensin system,[15–19] although the effect of calcium channel blockers is poorly understood. Guidelines from the European Society of Cardiology,[2] Japanese Circulation Society,[3] and American College of Cardiology/American Heart Association[1] societies in the past decade have reaffirmed the lack of evidence for therapeutic approaches and targeted medical management. We, therefore, sought to understand the current approaches to medical management and the effects of medications on the outcomes by analyzing the International Registry of Acute Aortic Dissection (IRAD) database.[8]

Methods

IRAD is a multinational registry of 24 referral centers in 12 countries. The details of the IRAD structure and methods used have been previously published.[20–24]

Data from all patients with aortic dissection enrolled in IRAD from December 26, 1995 with follow-up to 5 years was examined, with a focus on patients discharged alive with medication and follow-up data that included the use of medications. The collected data included variables on clinical, imaging, and mortality data. Follow-up was monitored at each of the sites. Mortality data were obtained through the Social Security Death Index for American subjects when this information was missing. At each enrolling hospital, the study investigators worked with their ethics or institutional review board to obtain appropriate approval for participation.

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Table 1
Baseline demographics

Variable	All Patients (n = 1301)	Type A (n = 722)	Type B (n = 579)
Gender			
Male	918 (70.6%)	510 (70.6%)	408 (70.5%)
Female	383 (29.4%)	212 (29.4%)	171 (29.5%)
Admission status			
Hypertensive	622/1,240 (50.2%)	229/679 (33.7%)	393/561 (70.1%)
Normotensive	450/1,240 (36.3%)	298/679 (43.9%)	152/561 (27.1%)
Hypotensive/shock	149/1,240 (12.0%)	133/679 (19.6%)	16/561 (2.9%)
Medications			
Angiotensin-converting enzyme inhibitor	561/1,201 (46.7%)	272/667 (40.8%)	289/534 (54.1%)
Angiotensin receptor blocker	14/198 (7.1%)	8/93 (8.6%)	6/105 (5.7%)
β Blockers	1,100/1,242 (88.6%)	586/683 (85.8%)	514/559 (91.9%)
Calcium channel blocker	609/1,211 (50.3%)	258/670 (38.5%)	351/541 (64.9%)
Diuretic	58/201 (28.9%)	23/91 (25.3%)	35/110 (31.8%)
Vasodilator	259/1,179 (22.0%)	97/655 (14.8%)	162/524 (30.9%)
Discharge status			
Systolic blood pressure (mm Hg)	124.0 ± 17.9	124.1 ± 19.1	123.8 ± 16.3
Diastolic blood pressure (mm Hg)	71.0 ± 10.6	71.5 ± 10.3	70.4 ± 11.1
Heart rate (beats/min)	72.5 ± 11.5	75.0 ± 11.6	69.4 ± 10.6
Hypertensive	28/1,176 (2.4%)	13/651 (2.0%)	15/525 (2.9%)
Normotensive	1,056/1,176 (89.8%)	585/651 (89.9%)	471/525 (89.7%)
Data at 1-year follow-up			
Systolic blood pressure (mm Hg)	129.2 ± 20.0	129.6 ± 21.7	128.4 ± 17.0
Diastolic blood pressure (mm Hg)	76.4 ± 16.3	77.0 ± 19.1	75.4 ± 10.6
Heart rate (beats/min)	68.5 ± 12.4	69.0 ± 12.1	67.8 ± 12.9
Highest systolic blood pressure (mm Hg)	145.8 ± 27.7	146.2 ± 30.6	145.1 ± 22.0
Highest diastolic blood pressure (mm Hg)	85.6 ± 27.6	85.9 ± 28.0	85.0 ± 26.8
Mortality	78/1,274 (6.1%)	33/704 (4.7%)	45/570 (7.9%)

Data are presented as number of applicable patients/cases relative to number of recorded data points (%) or mean ± SD.

The summary statistics between groups are presented as frequencies for categorical variables and the mean ± SD for continuous variables. Missing data were not defaulted to negative, and denominators reflected only the cases reported. The relations with follow-up outcome were investigated using univariate Cox regression analysis. Multivariate analysis was used to identify the independent predictors of outcome using models previously determined to be predictive of follow-up mortality.[21,22] All-cause mortality was the examined end point. The variables tested for type A included history of atherosclerosis and previous cardiac surgery. For type B, female gender, a history of previous aortic aneurysm, a history of atherosclerosis, in-hospital renal failure, pleural effusion on chest radiograph, and in-hospital hypotension/shock were included. Stepwise selection of variables was performed sequentially with a default value for inclusion set at $p < 0.05$. SAS, version 8.2 (SAS Institute, Cary, North Carolina), was used for statistical analyses.

Results

For the 1,301 patients with acute aortic dissection who survived to discharge and had information on the medications at discharge and during follow-up (median 26.0 months, interquartile range 12.0 to 48.0), the blood pressure status on admission showed that a little >1/2 (50.2%) of all patients were hypertensive. Most of the patients with type B (70.1%) were hypertensive. In contrast, more of the patients with type A were normotensive (43.9%) than hypertensive (33.7%), with a significantly greater number of patients presenting with hypotension/shock than did those with type B (19.6% for type A vs 2.9% for type B), as would be expected for a typical patient population with aortic dissection.[23,24] The mortality rate for all patients at 1 year was 6.1% and was 4.7% for those with type A and 7.9% for those with type B.

At discharge, most patients (89.8%) were normotensive and hemodynamically stable, with a blood pressure of 124.0 ± 17.9/71.0 ± 10.6 mm Hg and a heart rate of 72.5 ± 11.5 beats/min. Those with type A tended to have a greater heart rate than those with type B (type A, 75.0 beats/min vs type B, 69.4 beats/min). Almost all patients received antihypertensive medications at discharge in our study population (96%), with 88.6% taking β blockers, 46.7% angiotensin-converting enzyme inhibitors, 50.3% calcium channel blockers, 28.9% diuretics, and 22.0% vasodilators. The demographic data are listed in Table 1.

The association of medications with all-cause mortality during follow-up was analyzed separately for the type A (n = 722) and type B (n = 579) groups. β Blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers were studies because the use of these agents, either alone or in combination, accounted for >80% of all medications. The initial univariate analysis showed β blockers to be associated with improved survival in all patients ($p = 0.03$), those with type A overall ($p = 0.02$),

Table 2
Univariate analysis of effects of medications on long-term survival

Medication	All Patients		Type A		Type B	
	n/Total	p Value	n/Total	p Value	n/Total	p Value
Angiotensin converting enzyme inhibitor	544/1,161	0.929	264/646	0.936	280/515	0.379
Angiotensin receptor blocker	14/195	0.654	8/92	0.421	6/103	0.887
β Blocker	1,066/1,201	0.035	567/661	0.024	499/540	0.204
Calcium channel blocker	592/1,171	0.853	253/649	0.223	339/522	0.015
Diuretic	57/198	0.107	22/90	0.427	35/108	0.185
Vasodilator	253/1,141	0.363	94/635	0.136	159/506	0.469

Data are presented as number of applicable patients/cases relative to number of recorded data points.

Table 3
Multivariate analysis on factors affecting long-term mortality

Variable	p Value	Hazard Ratio	95% CI
Type A			
Age ≥70 years	0.002	2.440	1.393–4.272
History of atherosclerosis	0.273	1.415	0.761–2.633
Previous cardiac surgery	0.498	1.330	0.582–3.040
Angiotensin-converting enzyme inhibitor at discharge	0.585	0.853	0.481–1.512
β Blocker at discharge	0.022	0.471	0.248–0.897
Calcium channel blocker at discharge	0.159	1.479	0.858–2.549
Type B			
Female gender	0.454	0.827	0.504–1.359
Age ≥70 years	0.001	2.321	1.383–3.897
Previous aortic aneurysm	0.183	1.418	0.848–2.371
History of atherosclerosis	0.380	1.248	0.761–2.046
Renal failure	0.611	0.841	0.431–1.640
Pleural effusion on chest radiograph	0.116	1.570	0.895–2.756
Hypotension	0.033	2.330	1.072–5.064
Angiotensin-converting enzyme inhibitor at discharge	0.378	0.813	0.513–1.289
β Blocker at discharge	0.375	0.719	0.347–1.491
Calcium channel blocker at discharge	0.012	0.554	0.348–0.880

and those with type A who had received surgery (p = 0.006). In contrast, calcium channel blockers were associated with improved survival in those with type B overall (p = 0.02) and in those with type B receiving medical management (p = 0.03). The univariate analysis results are listed in Table 2.

Multivariate analysis was used to determine whether the use of medications affected mortality. The medications were added to previously described mortality models using the IRAD database.[21,22] The analysis for type A used a model including a history of atherosclerosis and previous cardiac surgery.[21] Because the initial analysis of the 722 patients with type A dissections showed a robust association of surgery with survival (odds ratio [OR] 2.45, 95% confidence interval [CI] 1.47 to 4.11, p = 0.001), only surgically treated patients were studied (n = 654, 91% of patients). That analysis showed that the use of β blockers was significantly associated with improved survival (OR 0.47, 95% CI 0.25 to 0.90, p = 0.02) and that older age was associated with poor survival (OR 2.44, 95% CI 1.39 to 4.27, p = 0.002).

The patients with type B dissection were similarly analyzed using a previously described model that included female gender, a history of previous aortic aneurysm, a history of atherosclerosis, in-hospital renal failure, pleural effusion on the chest radiograph, and in-hospital hypotension/shock as parameters.[22] The analysis of the medically treated patients with type B dissection (n = 503, 87% of patients) showed the use of calcium channel blockers was associated with improved survival (OR 0.55, 95% CI 0.35 to 0.88, p = 0.01) and that in-hospital hypotension/shock (OR 2.33, 95% CI 1.07 to 5.06, p = 0.03) and old age (OR 2.32, 95% CI 1.38 to 3.90, p = 0.001) were associated with poor survival. The results from the multivariate model are listed in Table 3, the Kaplan-Meier survival curves are shown in Figure 1, and the effects of medications are shown in Figure 2.

Discussion

Acute aortic dissection involves blood flow through an intimal tear into the aortic media of an often weakened aortic wall resulting from degeneration (e.g., atherosclerosis, aging, hypertension) and/or genetic predisposition (e.g., Marfan syndrome). The underlying principle of treatment is to limit propagation of the false lumen and its negative consequences on end-organ perfusion by reducing and stabilizing the hemodynamic stress on the aortic wall.[1–8] Surgical repair is preferred for type A dissection, and medical therapy, centered on the use of antihypertensive agents, is generally used to achieve this goal in uncomplicated/stable type B dissection. Medical therapy is also used to maintain hemodynamic stability during follow-up to promote aortic stability and prevent aortic expansion with possible rupture and recurrent dissection.

The effects of medications on the outcomes in patients with aortic dissection were examined using the IRAD database. Almost all patients (96%) were discharged with antihypertensive medication. All patients, as well as those with type A overall and those with type A treated surgically, showed that β blockers, the most commonly used agent in patients with aortic dissection (88.6%), were associated with improved survival. In contrast, those with type B overall and those treated medically showed that calcium channel blockers were selectively associated with improved survival. Renin-angiotensin system inhibitors were not significantly associated with survival in our analysis.

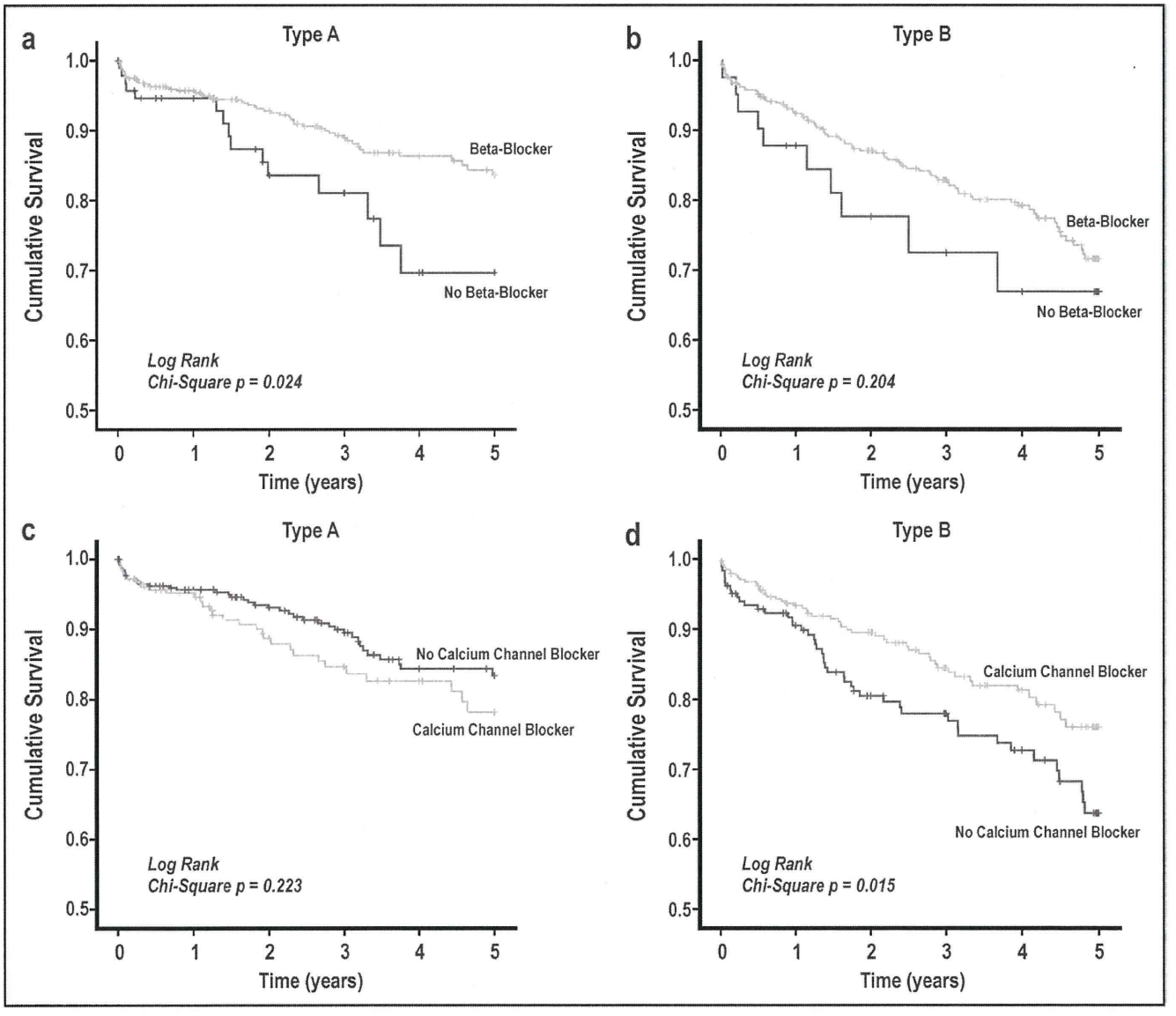

Figure 1. Kaplan-Meier survival curves for effects of medications on mortality. β Blockers in patients with *(A)* type A dissection and *(B)* type B dissection; and calcium channel blockers in those with *(C)* type A and *(D)* type B.

At discharge and during follow-up, the blood pressure was generally controlled at approximately 120/70 mm Hg, with a 15% deviation. The heart rate was approximately 70 beats/min at discharge, which was slightly lower, but similar, during follow-up. The most recent American guidelines (American College of Cardiology/American Heart Association)[1] recommend lower heart rate control, with a target of 60 beats/min; however, our study predated these recommendations.

β Blockers, because they reduce both the aortic blood pressure and heart rate and thus the hemodynamic stress to the arterial wall, have been considered the mainstay of medical management of aortic dissection in general for decades.[9–14] Our analysis has confirmed that β blockers are the most widely used class of medication in almost all patients with aortic dissection, in accordance with the guidelines,[1–3] and that not only are they beneficial for all patients but also for patients with type A overall and those treated surgically, in particular.

In contrast, calcium channel blockers, the second most commonly used agent, showed selective association with survival for the type B medically treated group. The type A surgical group, however, showed contrasting results, with calcium channel blockers showing an association with poor survival, albeit this result was not significant (Figure 2). The mechanisms of selective effect of calcium channel blockers are unclear. One possible explanation is that aortic remodeling in response to this agent is better when the descending aorta is primarily diseased. The role of calcium channel blockers in the management of aortic dissection, in general, remains poorly addressed. The present guidelines suggest that nondihydropyridine agents can be used as an alternative to β blockers.[1] A recent single-center study showed that calcium channel

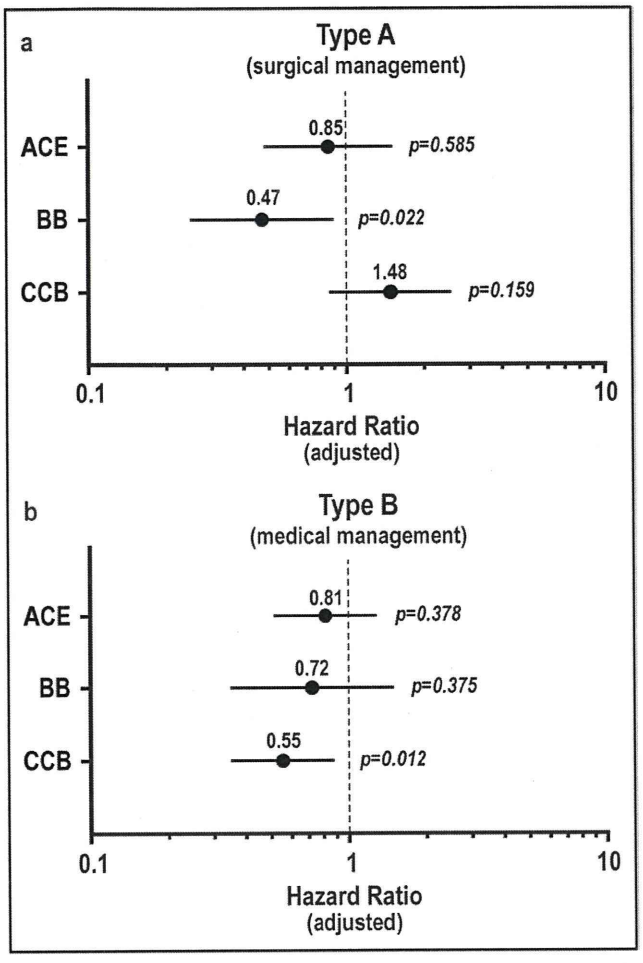

Figure 2. Effects of medications on outcomes. *(A)* Patients with type A who underwent surgery; and *(B)* those with type B treated medically. ACE = angiotensin-converting enzyme; BB = β blocker; CCB = calcium channel blocker.

blockers were associated with improved long-term survival (median follow-up 55 months) in those with type B aortic dissection.[25] Additional investigation of the role of calcium channel blockers in the management of aortic dissection is warranted.

Renin angiotensin system inhibitors (e.g., angiotensin-converting enzyme inhibitors) did not show an association with mortality in our cohort, although recent reports have suggested that renin angiotensin system inhibition might also play a pivotal role in the treatment of aortic disease.[15–20] Most of these studies focused on patients with Marfan syndrome; however, such patients differ from the conventional elderly adult patient included in IRAD. The renin angiotensin system and its inhibitors might affect the Marfan aorta differently from the diseased adult aorta. Also, we investigated the effects on mortality and not on aortic widening such as was done in these studies of patients with Marfan syndrome.

Our analyses of the medications used were limited to class effects and categorical/qualitative effects, because we did not monitor the use of individual drugs or their dosages. IRAD predates the current increased use of angiotensin receptor blockers, which were only used in 8% of patients, limiting our findings for this drug class. We were also unable to sufficiently test which combination of drugs showed the most beneficial effects owing to the statistical power limitations, given the cohort size. Other limitations included unknown adherence data for patients and the lack of information on the sequence of the addition of drugs because the medications were reported cross-sectionally only at discharge and follow-up. Furthermore, the present analysis was limited to all-cause mortality and did not include disease-specific mortality.

The present findings might help in selecting medications to treat patients with acute aortic dissection; however, any effects seen from these observational data from the registry format of IRAD must be considered preliminary and hypothesis generating. The optimal management needs to be confirmed in randomized controlled trials.

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