Outcomes of type A intramural hematoma: Influence of Diabetes Mellitus

Zhonggui Shan[1], Qu Chen[2], Dandan Jiang[2], Feng Kuang[2], and Fan Yang[3]

[1]Affiliation not available
[2]The First Affiliated Hospital of Xiamen University
[3]Xiamen University and Fujian Medical University Affiliated First Hospital

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Abstract

Objectives We aimed to investigate whether uncomplicated type A intramural hematoma (IMHA) patients with type 2 diabetes mellitus (DM) who underwent a "wait-and-watch strategy" and tight glycemic control had similar clinical outcomes as patients without DM who received the same treatment strategy. Methods Between January 2010 and December 2016, uncomplicated IMHA patients with and without diabetes mellitus were included and were propensity score matched to improve balance between the two groups. Cox proportional hazard models were constructed to identify the specific factors associated with aorta-related mortality. The Fine-Gray model for the competing risk analysis was used to estimate the aorta-related and non-aorta-related mortality in different groups during the follow-up period. Results 109 IMHA patients were included in this study, and 66 patients were included after matching. Patients without DM experienced significantly more aorta-related adverse events (51.6% vs 13.3%, P=0.001) and reinterventions than patients in the DM group (29.0% vs 6.7%, P=0.023). Cox regression analysis revealed that a higher matrix metalloproteinase-9 level (hazard ratio [HR], 1.70; 95% confidence interval [CI], 1.39-2.09, P<0.001) and larger maximum aortic diameter (HR, 1.41; 95% CI, 1.11-1.80, P=0.005) were associated with higher aorta-related mortality. The competing risk analysis revealed a significantly higher aorta-related mortality during the follow-up period in the no DM group than in the DM group (36.4%; 95% CI, 11.6%-82.3%, P=0.0294). Conclusions Uncomplicated IMHA patients with DM (receiving the "wait-and-watch strategy" and tight glycemic control) may have a lower aorta-related mortality, and rates of aorta-related adverse events and reinterventions than the no DM group.

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Authors:

Qu Chen, MD[ad], Dandan Jiang, MD[bd], Feng Kuang, MD, PhD[a], Fan Yang, MD[c], Zhonggui Shan, MD, PhD[a],

[a]: Department of Cardiovascular Surgery, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen, Fujian Province, People's Republic of China.

[b]: Department of Internal Medicine, Xinglin Branch of The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen, Fujian Province, People's Republic of China.

[c]: Department of Radiology, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, Xiamen, Fujian Province, People's Republic of China.

[d]: The first two authors contributed equally to this work.

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Email:

Qu Chen: cmuchenqu@163.com

Dandan Jiang: jddcmu@163.com

Feng Kuang: tysonf@sina.com

Fan Yang : buyiwangdao@126.com

Zhonggui Shan: xmchenqu@163.com

Email: xmchenqu@163.com

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Corresponding author

Zhonggui Shan, MD, PhD

Department of Cardiovascular Surgery, The First Affiliated Hospital of Xiamen University, Teaching Hospital of Fujian Medical University, No. 55 Zhenhai Road, Siming District, Xiamen City, Fujian Province, 36100, People's Republic of China

Tel.: +86 15805911864

Abstract

Objectives

We aimed to investigate whether uncomplicated type A intramural hematoma (IMHA) patients with type 2 diabetes mellitus (DM) who underwent a "wait-and-watch strategy" and tight glycemic control had similar clinical outcomes as patients without DM who received the same treatment strategy.

Methods

Between January 2010 and December 2016, uncomplicated IMHA patients with and without diabetes mellitus were included and were propensity score matched to improve balance between the two groups. Cox proportional hazard models were constructed to identify the specific factors associated with aorta-related mortality. The Fine-Gray model for the competing risk analysis was used to estimate the aorta-related and non-aorta-related mortality in different groups during the follow-up period.

Results

109 IMHA patients were included in this study, and 66 patients were included after matching. Patients without DM experienced significantly more aorta-related adverse events (51.6% vs 13.3%, P=0.001) and reinterventions than patients in the DM group (29.0% vs 6.7%, P=0.023). Cox regression analysis revealed that a higher matrix metalloproteinase-9 level (hazard ratio [HR], 1.70; 95% confidence interval [CI], 1.39-2.09, P <0.001) and larger maximum aortic diameter (HR, 1.41; 95% CI, 1.11-1.80, P =0.005) were associated with higher aorta-related mortality. The competing risk analysis revealed a significantly higher aorta-related mortality during the follow-up period in the no DM group than in the DM group (36.4%; 95% CI, 11.6%-82.3%, P =0.0294).

Conclusions

Uncomplicated IMHA patients with DM (receiving the "wait-and-watch strategy" and tight glycemic control) may have a lower aorta-related mortality, and rates of aorta-related adverse events and reinterventions than the no DM group.

Abbreviations:

CTA: Computed tomography angiography

CRP: C-reactive protein

DM: Diabetes mellitus

MMP: Matrix metalloproteinase

IMH: Intramural hematoma

TEVAR: Thoracic endovascular aortic repair

Key words : IMH, Diabetes mellitus, Outcome

Introduction

The prevalence of diabetes mellitus (DM) in patients requiring cardiac surgery is significantly increasing and achieving tight perioperative glycemic control in DM patients could decrease perioperative morbidity and improve survival [**1-3**] . Regarding aortic diseases, current studies have demonstrated a negative correlation between DM and the occurrence of aortic diseases [**4-7**] . However, previous studies are contradictory in that patients with DM were found to have poorer outcomes after abdominal aortic aneurysm repair [**8**],whereas mortality and clinical complications in type B aortic dissection patients after thoracic endovascular aortic repair (TEVAR) were significantly reduced in DM patients [**9**] . Whether patients with aortic diseases may benefit from the tight glycemic control remains unclear [**10-11**] .

DM has been shown to reduce the progression of aortic disease and the pathophysiological explanation of these phenomena include: 1) increasing the matrix of the aortic wall (suppression of plasmin and decreased levels/activity of matrix metalloproteinase [MMP]) and 2) reducing aortic mural macrophage infiltration and neovascularization[**12**] . The anti-inflammatory effect of oral antidiabetic medication drugs (including metformin, sulfonylurea, and thiazolidinedione) can also lower the risk of aortic aneurysm development [**13**] . However, insulin treatment may diminish this protective effect of hyperglycemia in preventing the aortic aneurysm development process [**14**] . Therefore, it seems that tight glycemic control (especially insulin treatment) is probably unnecessary and harmful for DM patients with aortic diseases.

Acute aortic syndromes consist of three interrelated diseases: aortic dissection, penetrating aortic ulcer and intramural hematoma (IMH). According to the analysis from the International Registry of Acute Aortic Dissection, fewer than 10% IMHA cases will resolve spontaneously whereas 16% to 47% will progress to aortic dissection[**15**] . Complicated IMHA is defined as the presence of rapid aortic expansion, signs of aortic rupture, fatal organ ischemia, recurrent or refractory pain, and refractory hypertension despite adequate medical therapy in the acute phase ([?]14 days); immediate open surgery is the first choice for these patients. However, for uncomplicated IMHA patients, the 'wait-and-watch strategy' (optimal medical therapy with blood pressure and pain control, serial imaging and necessary TEVAR/surgery) is appropriate, particularly in the absence of aortic dilation (>50 mm) and hematoma thickness less than 11 mm [**16-17**] . In Asian countries, the "wait-and-watch strategy" is the first-line treatment for uncomplicated IMHA patients with a maximum aortic diameter less than 50 mm and a hematoma thickness less than 11 mm [**18-20**] . However, adverse clinical events (development of aortic dissection, delayed surgery or death) that develop within 6 months after medical treatment of uncomplicated IMHA can reach a prevalence of 36.5% [**18**] which means that not all uncomplicated IMHA patients may benefit from the "wait-and-watch strategy".

In sum, we hypothesized that in uncomplicated type A IMH patients who received the "wait-and-watch strategy" (combined with tight glucose management), patients with DM (compared with patients without DM) would not benefit from such a treatment strategy because the anti-hyperglycemia treatment would

probably diminish the protective effect of hyperglycemia in preventing aortic disease progression and the obviously high adverse clinical events that develop within 6 months after medical treatment of uncomplicated IMHA [**1**][**18**] . To answer this question, we compared the clinical outcomes in uncomplicated IMHA patients who received the "wait-and-watch strategy" (with and without DM) during the first hospitalization and later follow-up period.

Methods

This study was conducted after obtaining ethical clearance from the Institutional Ethical Committee of Xiamen University (Xiamen, China) and written informed consent was obtained from each patient.

Patient Characteristics

A total of 219 uncomplicated IMHA patients who initially received the "wait-and-watch strategy" (initial medical treatment with TEVAR/open surgery for aortic complication**s**) from January 2010 to December 2016 were included and followed for at least three years. The diagnosis of IMHA was confirmed by electrocardiographic-triggered computed tomography angiography (CTA) examination on admission. Uncomplicated IMHA patients are defined as those without the presence of rapid aortic expansion, signs of aortic rupture, fatal organ ischemia, recurrent or refractory pain, and refractory hypertension despite adequate medical therapy[**10**][**16**] . Patients with traumatic aortic injury, aortic valvular diseases (including bicuspid aortic valve [**21**]) and genetic disease (diagnosed by pathology or genetic test) were excluded. The definition of missing data was as follows: patients who refused any medical therapy on admission, those without CTA images to estimate the evolution of IMHA, those without complete data and those lost to follow-up (see the details of the CONSORT diagram in**Figure 1**).

Blood Glucose Management

Newly diagnosed type 2 DM patients without standard antidiabetic treatments before the onset of IMHA were identified (diagnostic criteria of type 2 DM included: hemoglobin A1c [HbA1c] [?]6.5%, fasting plasma glucose [?]126 mg/dL, and 2 hour plasma glucose[?]200 mg/dL)[**22**] . The insulin therapy for these patients included the insulin pump with and without long-acting and short-acting subcutaneous insulin to achieve efficient rapid glycemic control during the acute phase (with the help of a physician, **D.J.**). The target blood glucose level included proper blood glucose levels of fasting and premeal states (80-130 mg/dL) and the postprandial state (less than 180 mg/dL) [**1**][**11**][**22**] . After achieving target glucose control, type 2 DM patients were transitioned to scheduled subcutaneous insulin therapy combined with the admission of oral antidiabetic medication drugs. After TEVAR or open surgery, patients with persistently elevated serum glucose ($>$ 180 mg/dL) received continuous intravenous insulin perfusion to maintain serum glucose $<$ 180 mg/dL during their stay in the intensive care unit and then were transitioned to their preoperative scheduled insulin therapy combined with oral antidiabetic drugs [**1**][**11**][**22**] . The HA1c level was measured every 3 months to determine whether glycemic targets were reached and maintained. A near-normal HbA1c ($<$7%) was considered reasonable for the majority of patients[**11**][**23**] .

General Management Strategy

It was important to obtain control of pain (intravenous opiate analgesia), heart rate ($<$60 beats per minute), and blood pressure (systolic blood pressure between 100 and 120 mmHg)[**10**][**16**] . The timing of CTA was as follows: on admission and every 14 days until the absorption of the ascending aortic hematoma, CTA examinations were adjusted accordingly in eventful cases. Hematoma thickening, ulcer-like projection, aortic dissection and aortic aneurysm development and aortic rupture were defined as aorta-related adverse events. The indications of necessary TEVAR were as follows: after the complete absorption of the ascending aorta hematoma, the intimal lesion could be visualized with CTA (which indicated the evolution of the IMHA to an ulcer-like projection, a type B aortic dissection, and an aortic aneurysm). Before TEVAR, all patients received at least one week of medical treatment (if not, these patients were excluded) **[24].** The concomitant arch reconstruction methods included the arch debranching procedure, chimney technique and in situ laser fenestration technology. By measuring the diameter of the proximal attachment site, the stent was not

oversized by more than 10%. The proximal portion of the stent graft was implanted in the healthy aorta (arch reconstructive methods were utilized to create sufficient landing zones), and the landing zone had to be greater than 2 centimeters in length without a substantial hematoma or circumferential calcification. In our institution, two stent devices with proximal bare spring designs were available (Valiant [Medtronic, Inc, Minneapolis, Minn] and Ankura [Lifetechmed, Inc, Shenzhen, China]) and we avoided balloon dilation**[25][26]** . The indications for necessary open surgery were as follows: uncontrollable symptoms (pericardial effusion, periaortic hematoma and signs of aortic rupture) and CTA imaging indicating the evolution of type A aortic dissection.

Detection of Serum Matrix Metalloproteinase-9

Matrix metalloproteinase-9 (MMP-9) is an important diagnostic biomarker in aortic pathophysiology in which MMP-9 can weaken the aortic media by degrading multiple extracellular components and DM patients have a 2-fold decreased level of MMP-9, which could restrict the degradation of the aortic wall **[12]** . Plasma MMP-9 was measured by using an enzyme-linked immunosorbent assay (ELISA), designed by R&D Systems (Minneapolis, MN, USA), according to the manufacturer's instructions and protocols. Venous blood was drawn from all patients at admission (within 24 hours of symptom onset) and plasma samples were obtained after centrifugation at 3500 rpm at 4 °C for 15 min immediately after collection and then stored at -80 degC for further analysis. The MMP-9 level was measured on admission, at day 14 (after the acute phase) and day 90 (after the subacute phase), at 6 and 12 months and then annually during follow-up.

Follow-up and Study Endpoints

Patients were discharged (with oral medications to maintain systolic blood pressure [< 120 mmHg]) after receiving necessary open surgery or until the complete absorption of the ascending aortic hematoma with or without necessary TEVAR. The surveillance included clinical examinations and imaging re-examinations at 1, 3, 6, and 12 months and then annually. All imaging studies were independently evaluated by one radiologist (F.Y.) and two cardiac surgeons (Q. C. and F.K.) who specialized in cardiac imaging techniques. The criteria for further reintervention were as follows: complications after TEVAR (endo-leak, ascending aortic pseudoaneurysm retrograding, retrograde type A aortic dissection), signs of aortic rupture, rapid growth of aortic diameters (>5 mm/year), or a maximum aorta diameter > 55 mm **[10][16]** . The primary outcome was aorta-related mortality (confirmed by autopsy or CTA examination). Secondary outcomes included all-cause mortality and aortic remodeling.

Statistical Analysis

Comparisons among the groups were performed using the t -test or Mann-Whitney U test when necessary. Categorical variables are expressed as frequencies and percentages and were compared using the $\chi 2$ test and Fisher's exact test when appropriate. We used the Kolmogorov− Smirnov test to evaluate the normality of the continuous variables. Patients with DM were propensity score matched to patients without DM. A logistic model was used to create propensity scores that included the following covariates (including known risk factors for aortic diseases and known factors that could influence the progression and long-term outcomes of aortic diseases): age, gender, body mass index, hypertension, smoking, atherosclerosis, drug abuse, maximum aortic diameter, hematoma thickness, C-reactive protein level and administration of the β-blocker**[10][16][17]** . A caliper of 0.2 propensity score standard deviations was used to match patients. All further analyses used propensity score-matched patients. Cox proportional hazard models were constructed to evaluate the specific factors associated with aorta-related mortality. Those variables for which the P value < 0.20 in univariate analyses were included in the multivariate analyses. The Fine-Gray model for the competing risk analysis of death was used to estimate the aorta-related and non-aorta-related mortality in different groups during the follow-up period. IBM SPSS Statistics for Windows Version 26.0 (IBM Corp., Armonk, New York) was used for statistical analysis. Differences of $P<0.05$ were considered statistically significant.

Results

Patient characteristics after matching

A total of 114 uncomplicated IMHA patients who received the "wait-and-watch strategy" and had complete follow-up data in a single institution from January 2010 to December 2016 were included in this study (DM group [n=42], no DM group [n=67]). These two groups differed significantly in several covariables (including known risk factors for aortic diseases and known factors that could influence the progression and long-term outcomes of aortic diseases, **Table 1**) and became balanced after propensity score matching (**Table 1**and **Supplement 1**). Demographic characteristics after matching are shown in **Table 2** . The median follow-up times for each group after matching were as follows: DM group (49.0 months, 95% confidence interval [CI], 45.5-52.5 months) and no-DM group (45.0 months, 95% CI, 42.2-47.8 months). The hyperglycemia was poorly controlled before hospitalization in DM group (**Table 2**). There were no statistically significant differences in the medical treatment strategy between the two groups (additional details in **Table 2**). In the DM group, the MMP-9 level was lower than no DM group ($P< 0.\ 001$, **Figure 2**) and reached the highest level (day 14) early than that in the no DM group (day 90).

Clinical outcomes and follow-up results after matching

In the DM group, ten patients received TEVAR treatment, including two patients with ulcer-like projection development, seven patients with type B aortic dissection development, and one patient with aortic pseudoaneurysm. Two patients developed a type A aortic dissection in the DM group and received open surgery; one patient died after the surgery (**Table 2** and **Figure 3**). In the no DM group, nine patients with intramural hematoma evolution and unstable syndromes underwent TEVAR (including one case of ulcer-like projection development, seven cases of type B aortic dissection and one case of aortic pseudoaneurysm, **Figure 3**). There were no statistically significant different in the procedural details between the two groups, and the stent was successfully deployed in all nineteen patients (**Table 2**). The aorta-related mortality during the first hospital stay was similar among two groups (9.1% vs 6.1%,P =1.000, **Table 2**). The indications and outcomes of surgery/TEVAR are summarized in **Figure 3.** There were no statistically significant differences in the procedural details between the two groups (**Table 2**). All 61 patients survived the in-hospital had follow-up after discharge. In the no DM group, two non-aorta-related death cases involved patients who died of renal failure at 40 months and 39 months and the only non-aorta-related death case in the DM group involved a patient who died of lung cancer at 37 months. The Fine-Gray model for the competing risk analysis revealed a significantly higher aorta-related mortality during the follow-up period in the no DM groups than in the DM group (36.4%; 95% CI, 11.6%-82.3%, P= 0.0294). The cumulative incidence curves for the two groups were significantly different for aorta-related death (P =0.0294) and not significantly different for non-aorta-related death (P =0.567) (**Figure 4A-C**). In the no DM group, more aorta-related deaths occurred during the 3 to 6 months after the onset of intramural hematoma (P =0.011) (**Figure 4D**). Patients without DM experienced significantly more aorta-related adverse events (51.6% vs 13.3%, P =0.001) and reinterventions than patients in the DM group (29.0% vs 6.7%, P =0.023) (**Table 2**). In the no DM group, the development of aortic dissection was the most common reason for TEVAR/surgery reinterventions (n=10), and the majority of aorta-related death cases (six patients) occurred during the 3 to 6 months after the onset of intramural hematoma (**Figure 4D**). Five of these six patients (Patients 5, 6, 8, 9 and 10**, Supplement 2**) in the no DM group suffered from chest/back pain after TEVAR during the subacute phase (14-90 days)(P <0.014) (**Table 2**) and died of retrograde type A aortic dissection or ascending aortic pseudoaneurysm rupture(**Supplement 2**). During follow-up, eight in ten deaths were caused by rupture of a retrograde type A aortic dissection (n=5) and ascending aortic pseudoaneurysm (n=3) after receiving TEVAR (**Patients D -G** , **Supplement 3**).

Predictors of aorta-related mortality after matching

Cox regression analysis (c statistic=0.952) revealed that a higher MMP-9 level (hazard ratio [HR], 1.70; 95% CI, 1.39-2.09,P <0.001) and larger maximum aortic diameter (HR, 1.41; 95% CI, 1.11-1.80, P =0.005) (**Table 3**) were associated with higher aorta-related mortality. More details of univariate and multivariate

analyses for the predictors of aorta-related mortality are shown in **Table 3** .

Discussion

The evolution of IMHA is very dynamic from complete resolution to aortic dissection **[10][16][17][27].** However, for patients with uncomplicated IMHA, which is significantly more common in Asian countries, the "wait-and-watch strategy" is the first-line treatment because of the lower mortality with early medical therapy than with type A aortic dissection **[18-20]** . However, the development of classic aortic dissection (19%) and retrograde type A aortic dissection (27%) are very common fatal evolutions after medical treatment, and the need for delayed further interventions rises up to 30% within the first 6 months **[18][28]** . In our study, the hospital aorta-related mortality in both groups (**Table 2**) was similar to that reported by Song et al. **[18]** (7.9%) and lower than that reported by Sandhu et al **[28]** (12%).

Newly diagnosed type 2 DM patients with IMHA probably benefit from antidiabetic treatments and DM is possibly a protective factor for IMHA during the chronic phase (>90 days) whereas tight glycemic control may influence the evolution of IMHA at the acute phase (<14 days) (**Figure 4D**). The potentially protective value of DM has been well described [4**-7],** and the possible explanations included the increasing matrix of the aortic wall (suppression of plasmin and decreased levels/activity of MMP-2 and MMP-9), and decreased aortic mural macrophage infiltration and neovascularization **[12]** . MMP-9 is involved in tissue degradation and remodeling in aortic dissection and is significantly increased in aortic dissection patients, and a higher level of MMP-9 can weaken the aortic media by degrading multiple extracellular components; DM patients have a 2-fold decreased level of MMP-9, which may restrict the degradation of the aortic wall **[12].** Tan et al**[29]** demonstrated that MMP-9 may be a useful biomarker for aortic dissection. In our study, the MMP-9 level in the DM group was lower than that in the no DM group ($P<$ 0. 001,**Figure 2**) especially one year after the onset of IMHA. However, all three deaths during the acute phase occurred in the DM group (although there were no significant differences) even though the MMP-9 level was obviously lower (**Figure 2** , **Figure 4D**) than that in the no DM group. The probable explanation is that insulin treatment may diminish this protective effect of hyperglycemia that prevent the aortic aneurysm development process (under laboratory conditions) **[14];** after receiving tight glycemic control recommended by guidelines **[1][11][22],** the**DM group had an** MMP-9 level that was dramatically increased (reached the highest value) during the acute phase, which probably indicated the potentially decreased protective effect of hyperglycemia.

Rupture of retrograde type A aortic dissection and ascending aortic pseudoaneurysm after receiving TEVAR were the main causes of death in our study. The explanation for these complications is the choice of TEVAR devices, stent graft landing zones and commitment arch reconstruction surgery which can probably influence the outcomes after TEVAR. Although we avoided balloon dilatation because of the potential risk of retrograde type A aortic dissection **[25]** , we did have one patient who probably died of retrograde type A aortic dissection after balloon dilation (Patient 4, **Supplement 2**). Additionally, we employed only stent grafts with a proximal bare spring design. Although non-proximal bare-spring stent grafts yield a similar incidence of retrograde type A aortic dissection **[25],**proximal bare-spring stent grafts have long been regarded as a risk factor and may injure the fragile aortic wall, resulting in the development of retrograde type A aortic dissection **[26]** . Moreover, in our study, intramural hematomas that affected the aortic arch without obvious entry tears characterized as aortic dissection always required arch revascularization. However, the partial occlusion clamp may injure the fragile aortic wall (during the debranching procedure) and cause further damage that results in lethal complications**[29] (** Patient 16, **Supplement 2).** In addition, a dilated ascending aorta (> 4 cm) (Patients 6,8,9 and 12,**Supplement 2**) and TEVAR in the chronic phase are potential risk factors for fatal complications after TEVAR **[30][31].**Additionally, five patients died of aorta-related complications complaining of refractory pain after TEVAR (Patients 5, 6, 8, 9 and 10,**Supplement 2**). Juvonen, et al **[32]** reported that chest or back pain is predictive of aortic rupture, and that patients with uncharacteristic or atypical pain have a higher risk of rupture over time, and that medical management is unwarranted for these patients**[33]** . In sum, for IMHA, it seems logical to recommend prophylactic replacement of the aortic wall that presented the intramural hemorrhage, because of the risk of fatal complications especially for those with a dilated aorta, intramural hematomas that affect the aortic

arch, and refractory pain after TEVAR.

In the "wait-and-watch strategy" the interval of the imaging evaluation is also important. Kitai, et al recommended careful serial imaging because conventional 5-mm axial images may not completely identify ulcer-like projections (ULPs) smaller than 5 mm[**34**] . Thus, with low-resolution computed tomography scan results, simply equating the lack of a ULP with a favorable prognosis is probably unjustified, and a more precise CTA scan and closer monitoring for the development of a ULP are necessary. Moreover, intravascular ultrasonography [**16**] is another meaningful examination method that permits a dynamic real-time evaluation of the aorta and can detect the origin of side branches, evaluate adequate expansion after the deployment of the stent graft and exclude potential complications (such as retrograde type A aortic dissection occurring intraoperatively).

There are several limitations of this study. First, future longitudinal prospective investigations with a multicenter cooperation focusing on more patients are necessary. Second, techniques (such as TEVAR devices and arch reconstruction methods) probably affect patient outcomes, and further studies are required for a more standardized and uniform management strategy. Third, the anti-inflammatory effect of oral antidiabetic medication drugs could lower the risk of fatal progression[**13**], and the enrollment of more patients with different medical treatment strategies (insulin with/without oral antidiabetic medication drugs) may provide more meaningful insight into this question.

Summary

In conclusion, uncomplicated type A intramural hematoma patients with type 2 diabetes mellitus (receiving the "wait-and-watch strategy" and tight glycemic control) may have a lower aorta-related mortality, rates of aorta-related adverse events and reinterventions during the follow-up period than patients without diabetes mellitus. Moreover, in patients without diabetes mellitus, it seems logical to recommend prophylactic replacement of an aortic wall that presents the intramural hemorrhage, since the rates of aorta-related adverse events and reinterventions during the follow-up period were found to be obviously higher than those in patients with diabetes mellitus.

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Figure 1 CONSORT Diagram of Patient Selection

The CONSORT diagram of the patient selection process is shown in this figure. Thirteen individuals among the eligible uncomplicated type A intramural hematoma patients who refused further medical treatments or those without complete imaging records, laboratory test results and follow-up data were regarded as missing data. In our study, 5 of 114 patients who refused further medical treatment, lacked authentic laboratory/imaging data or were loss to follow-up were identified as missing data regarding eligible uncomplicated Type A IMH. The probability of these missing data did not depend on any factors that we considered, and such data were classified as missing completely at random; while the percentage of data missing was less than 10%, specifically, only 5.6% (5/114). For these reasons, we used the method of complete-case analysis in which we discarded these 13 cases with incomplete information. In total, 109 uncomplicated type A IMH patients with complete data were included in the study.

Figure 2 Levels of Plasma Matrix Metalloproteinase-9 in the Two Groups After Matching

***:** result of the longitudinal mixed models

Plasma matrix metalloproteinase-9 (MMP-9) was measured by using enzyme-linked immunosorbent assay technique, designed by R&D Systems (Minneapolis, MN, USA), according to the manufacturer's instructions and protocols. The levels of MMP-9 were measured at day 14 (after the acute phase), at day 90 (after the subacute phase), at 6 and 12 months and then annually during the follow-up. In the diabetes mellitus (DM) group, the level of MMP-9 was lower at each time point ($P< 0.\ 001$) and reached the highest level earlier than that of the no DM group, specifically, at day 14.

Figure 3 Clinical Outcomes of Uncomplicated Type B Intramural Hematoma after Matching

A total of 66 patients diagnosed with uncomplicated acute type A intramural hematoma were included after matching. An ulcer-like projection was defined as an intimal disruption with contrast material-filled pouching from the aortic lumen and with a communicating orifice more than 3 mm in size without atherosclerotic plaque. In the diabetes mellitus (DM) group, two patients received surgery and ten patients underwent thoracic endovascular aortic repair (TEVAR). The indications for surgery/TEVAR were also summarized. In the DM group, during the acute phase (<14 days), two patients died of sudden aortic rupture and one patient who developed type A aortic dissection died of heart failure after emergency open surgery. In the no DM group, two patients received surgery and nine patients underwent TEVAR. Two patients died of sudden aortic rupture during the subacute phase (15-90 days) of the first hospitalization.

In the no DM group, two non-aorta-related death cases involved patients who died of renal failure at 40 months and 39 months and the only non-aorta-related death case in the DM group involved a patient who died of lung cancer at 37 months. Only one patient with aorta-related death was noted in the DM group and the nine aorta-related death deaths were noted in the no DM group. In the no DM group, nine patients underwent reintervention during the follow-up period including two cases of surgical treatment (three cases of type A aortic dissection [AD]) and six cases of TEVAR, In the no DM group, the development of aortic dissection was the most common reason for TEVAR/surgery reinterventions (n=10) and the majority of aorta-related death cases (six patients) occurred during the 3 to 6 months after the onset of intramural hematoma (**Figure 4D**). Five of these six patients (Patients 5, 6, 8, 9 and 10**, Supplement 2**) in the no DM group suffered from chest/back pain after TEVAR during the subacute phase (14-90 days)(P <0.014) (**Table 2**) and died of retrograde type A aortic dissection or ascending aortic pseudoaneurysm rupture. During the follow-up, eight in ten death cases involved patients who died of a ruptured retrograde type A aortic dissection (n=5) or ascending aortic pseudoaneurysm (n=3) after receiving TEVAR (**Patients D -G** , **Supplement 3**).

Figure 4Competing Risk Analysis Results

A) The cumulative incidence of aorta-related and non-aorta-related mortality in the diabetes mellitus (DM) group and no DM group.

B-C) These two pictures show the results of Fine-Gray's test for equality of cumulative incidence functions across the DM and no DM groups. In **Picture B** , the cumulative incidence curve for the two groups was significantly different for aorta-related death (P =0.0294). The no DM group had a significantly higher aorta-related mortality during the follow-up period than the DM group (36.4%; 95% confidence interval, 11.6%-82.3%, P= 0.0294).In**Picture C,** the cumulative incidence curve for the two groups is not significantly different for non-aorta-related death (P =0.567).

D) In the no DM group, more aorta-related deaths occurred during the 3 to 6 months after the onset of intramural hematoma (P =0.011). There were no significantly differences in the aorta-related death among the DM and no DM groups at the other time points. Although there was no significant difference in the acute phase, all three death cases appeared during the acute phase (first 14 days after the onset of uncomplicated type A intramural hematoma [IMH]) in the DM group. All 12 deaths in the no DM group appeared during the first two years after the onset of uncomplicated type A IMH.

Supplement 1 Jitter Plot of Propensity Score Matching Analysis

Jitter plot demonstrating the distribution of propensity scores for the diabetes mellitus group and the no diabetes mellitus group.

Supplement 2 Aorta-related Death Cases

Ascending aortic pseudoaneurysms are ruptured areas of the aorta in which the majority of the aortic wall has been breached and the luminal blood is held in place only by a thin rim of the remaining wall or adventitia. On computed tomography aortography, the typical finding is a contrast-filled, out-pouching of the wall of the aorta or into the thickened aortic wall in the absence of an intimal flap or a false lumen. Retrograde type A aortic dissection is defined as a new tear (adjacent to the proximal stent graft) caused by manipulation or by the stent graft itself.

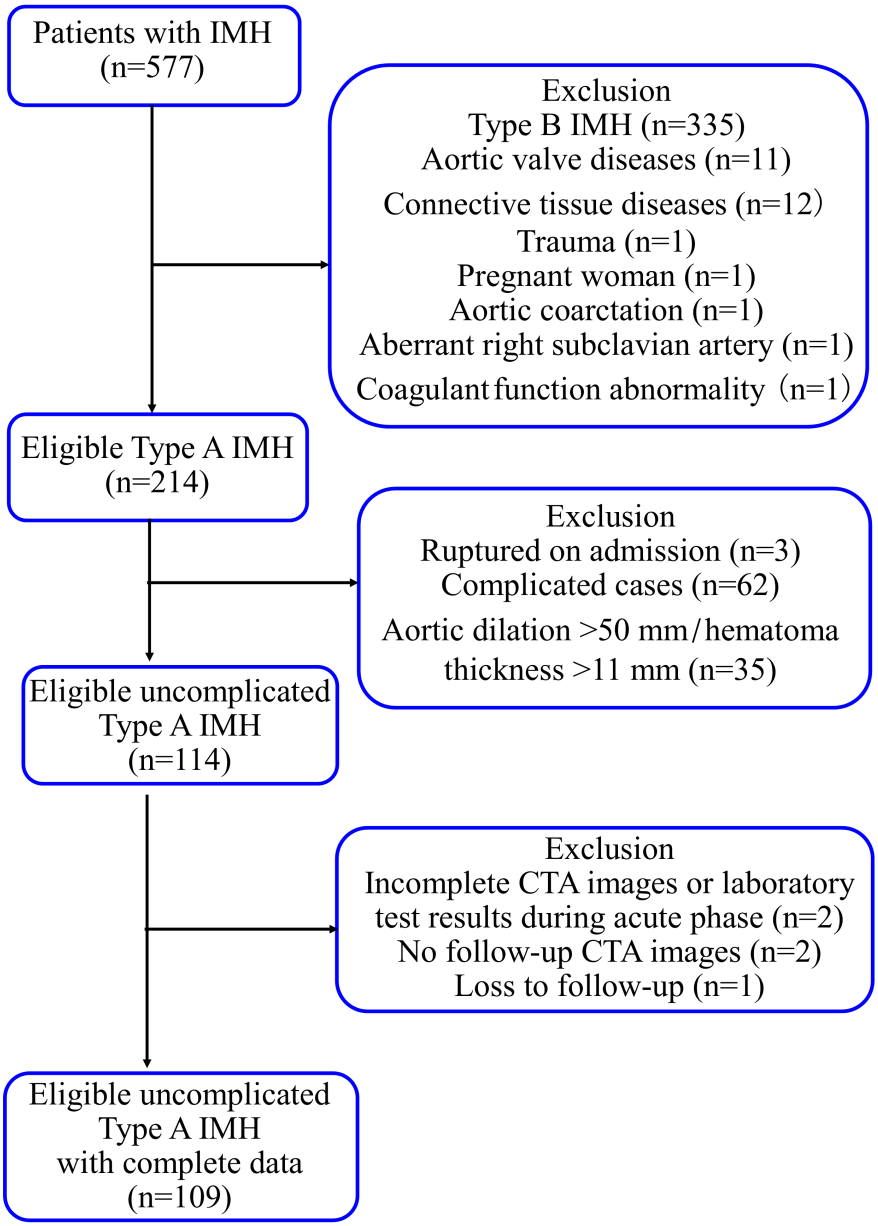
In the diabetes mellitus (DM) group, during the acute phase (<14 days), two patients (Patients 13 and 14) died of sudden aortic rupture and one patient (Patient 15) with development of type A aortic dissection died of heart failure after emergency open surgery. In the no DM group, three patients (Patients 1, 2 and 3) died of sudden aortic rupture during the subacute phase (15-90 days). Two patients (#1, #3) had a new-onset entry tear (autopsy finding) at the ascending aorta and developed classic type A aortic dissection. By computed tomography angiography (CTA) examinations, the development of ascending aortic pseudoaneurysm and retrograde type A aortic dissection were identified in Patients 2, 13 and 14.

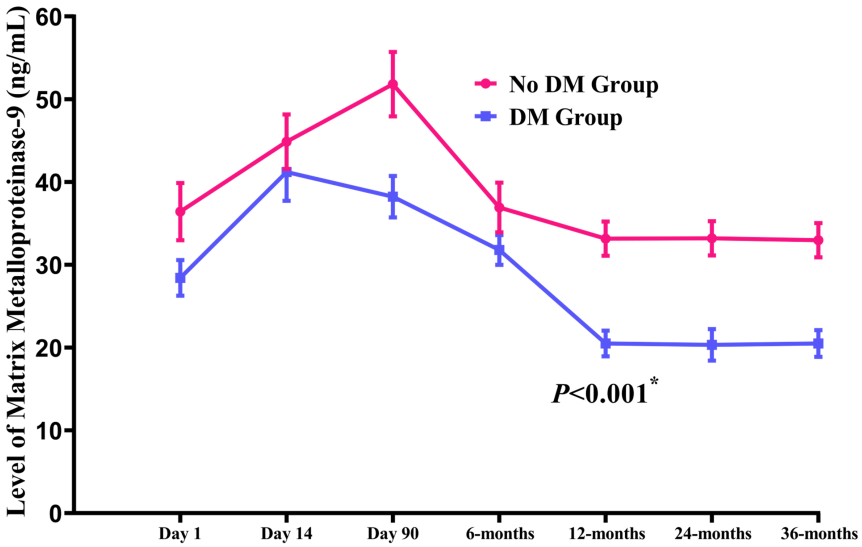
During the follow-up period, only one patient (#16) with aorta-related death was noted in the DM group, and in this patient, the new-onset entry tear adjacent to the inflow anastomosis of the bypass graft used for the arch debranching operation (presumed to be related to the injury of the aortic wall after partial occlusion clamping) was confirmed by autopsy findings.

The majority of aortic sudden death cases occurred during the 3 to 6 months after the onset of an intramural hematoma, and six patients (Patients 4 to 9) in the no DM group received thoracic endovascular aortic repair (TEVAR) treatment during the subacute phase. Five of these six patients (Patients 5, 6, 8, 9 and 10**,** in the no DM group suffered from chest/back pain after TEVAR during the subacute phase (14-90 days) and died of retrograde type A aortic dissection or ascending aortic pseudoaneurysm rupture. During follow-up, eight in ten death cases involved patients who died of a ruptured retrograde type A aortic dissection (n=5) and ascending aortic pseudoaneurysm (n=3) after receiving TEVAR.

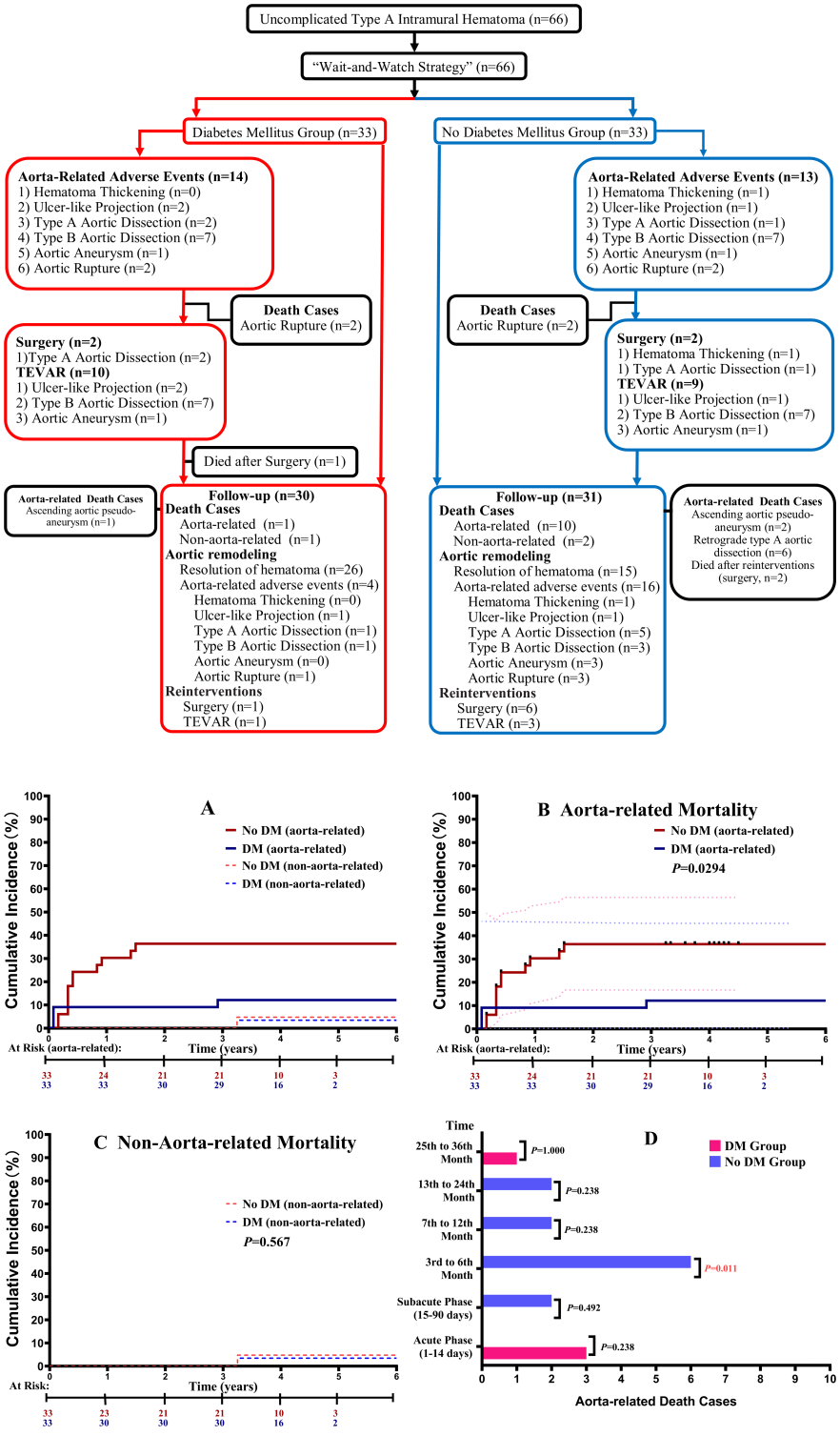
Supplement 3 Evolutions of Type A Intramural Hematoma

The orange arrows indicate the process of evolution, and the red arrows indicate the lesion.**A)** In the diabetes mellitus (DM) group, the hematoma could be completely absorbed after medical treatment; **B)** The development of an ulcer-like projection (ULP) was identified during the acute phase and the ULP disappeared in the chronic phase, indicating that this patient was free from receiving thoracic endovascular aortic repair (TEVAR) treatment. **C)** This patient received open surgery during the follow-up period because of hematoma thickening during the chronic phase ($>$ 90 days) and ULPs appeared in different areas of the aortic wall combined with refractory back pain. **D-G)** In the no DM group, four patients died of a ruptured ascending aortic pseudoaneurysm (D, E and G) or retrograde type A aortic dissection (F) after receiving TEVAR in the subacute phase (15-90 days).





	DM Group	No DM Group
MMP-9 (ng/mL)		
Day 1	28.5±2.5	36.5±3.4
Day 14	40.5±3.5	45.2±3.2
Day 90	38.1±2.5	50.4±3.3
6-months	31.8±2.0	36.2±2.7
12-months	20.9±1.5	33.0±2.2
24-months	20.4±1.7	33.3±2.6
36-months	20.7±1.6	32.7±2.3



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