

ORIGINAL ARTICLE

EVOLVING CONCEPTS AND TREATMENT  
OF AORTIC DISSECTIONS

# SUNDAY trial insights: questionnaire of clinical perspectives on medical therapy in uncomplicated type B aortic dissections

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## ABSTRACT

**Background:** Medical therapy is the cornerstone of managing uncomplicated type B aortic dissections (uTBAD), however there are limited guidelines on its implementation. This study aimed to investigate variations in the interpretation and implementation of medical therapy among principal investigators of an ongoing international randomized clinical trial on uTBAD management.

**Methods:** A cross-sectional questionnaire-based study was conducted among all principal investigators participating in the Scandinavian trial of Uncomplicated Aortic Dissection Therapy (SUNDAY) trial across seven countries. A secure online survey was distributed and entered into Research Electronic Data Capture (REDCap), collecting categorical data on different aspects of medical therapy, including therapy targets, reporting standards, medical management and investigations.

**Results:** A total of 34 of 46 investigators responded (74%). While 31 (91%) agreed upon blood pressure targets of less than 120 mmHg, refractory hypertension was defined as blood pressure exceeding 140 mmHg by 12 (35%), with 17 (50%) considering the number of antihypertensives used to determine refractory hypertension of which eight (24%) set this at >3, and nine (27%) at >5. The upper limit for heart rate was agreed as 60 bpm by 20 (59%). There was no agreement on the definition of refractory pain, with seven (21%) not even considering it in decision-making. There was notable variation in reporting standards regarding chronicity, with 11 (32%) deeming hyperacute to be <24 hours, 13 (38%) deeming it <48 hours and five (15%) not considering it at all. 29 (85%) stated that they have a standardized hospital protocol for medical therapy for acute uTBAD. There was general agreement on escalation of anti-hypertensives in acute uTBAD with 30 (88%) starting with IV labetalol as first line, followed by calcium channel antagonists by 13 (38%) as second- and third-line treatments. Adjunctive medications were used consistently with 20 (59%) commenced statins as part of medical therapy and 22 (65%) commenced life-long single antiplatelets.

**Conclusions:** These findings highlight variation and possibly reflect a lack of high-level evidence for medical therapy for uTBAD. Variations in therapeutic targets, reporting standards, medical management and adjunctive therapies between clinicians are evident.

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**Key words:** Aortic dissection; Vascular surgical procedures; Therapeutics.

Stanford type-B aortic dissections (TBAD) have an incidence of 3.9-6.0 per 100,000 persons per year.<sup>1, 2</sup> Complicated TBAD (cTBAD) represents between 40-50% of cases and require surgical intervention, most often with thoracic endovascular aortic repair (TEVAR). For uncomplicated dissections (uTBAD), in-hospital survival is cited at nearly 90% with conservative medical therapy.<sup>3</sup> The role of surgical intervention in uTBAD is less definitive, since relevant societal guidelines recommend that TEVAR can be considered selectively.<sup>4-6</sup>

Medical therapy is recommended (Class I) for all uTBAD patients with Level C evidence.<sup>4</sup> Most notably, there are no high-level clinical trials determining the specifics of medical therapy to establish standards of management although randomised controlled trial protocols have been developed to answer some aspects of medical therapy.<sup>7</sup> Strict blood pressure targets are set at 120/80 mmHg with first-line beta-blocker treatment.<sup>4, 8</sup> There is no unanimous guideline set for heart rate control, however an upper limit of 60 or 70 beats per minute (bpm) is often iterated.<sup>4, 6</sup> Second line antihypertensive treatment includes calcium channel antagonists and/or renin-angiotensin inhibitors.<sup>4</sup>

Classification of cTBAD has historically regarded refractory hypertension and pain as diagnostic criteria which was categorized at the same level as end-organ ischemia and aortic rupture.<sup>4</sup> Recent guidelines and reporting standards have included refractory hypertension and pain as high-risk features combined with other clinical and anatomical features.<sup>5, 6, 9</sup> The term refractory was recently defined in the 2020 SVS/STS reporting standards for TBAD as the symptom occurring more than 12 hours.<sup>9</sup> While this definition is arbitrary, its prognostic predictive power should not be understated, as a review of the IRAD dataset demonstrated that refractory hypertension and pain significantly increase mortality risk in medical therapy alone and may benefit from TEVAR.<sup>9, 10</sup> Additionally, the chronicity

of the dissection is important in management, as it has often been stated that as a patient transitions to the subacute stage of the disease, the aorta has stabilized and is safer for stenting to permit better aortic remodelling.<sup>11</sup> Again there are differences in the definitions of the hyperacute, acute, subacute and chronic stages of the disease, all of which affect management.

The Scandinavian trial of Uncomplicated Aortic Dissection Therapy (SUNDAY) trial is an international, randomized, open-label, two-armed controlled study that aims to determine the impact of TEVAR on five-year survival of patients with uTBAD.<sup>12</sup> During protocol design, a review of literature and international input found that there was no clear and standardized medical therapy (SMT) protocol. The trial is pragmatic and investigator-driven, with no industry involvement, allowing sites to follow local protocols, thus the use of SMT. Included subjects are randomized to either SMT alone or SMT with TEVAR in the subacute period of the disease.<sup>13</sup> In addition to the primary endpoint of five-year survival, there are secondary outcomes, looking at aortic-related mortality, neurological events, quality of life, costs, reinterventions and readmissions.

While the medical strategy for SMT is decided at each center in the SUNDAY trial based on local routines, therapeutic goals are set within the study protocol. In line with guidelines, target blood pressure level of less than 120/80 mmHg and target heart rate of less than 60 bpm are underlined in the study protocol. Recruited subjects receive blood pressure monitors and logbooks to control and report this data regularly. This allows for analysis of the quality of blood pressure regulation relating to outcomes regardless of local SMT protocol implemented and controlling for SMT variations behaving as a potential confounder.<sup>12</sup>

Aspects of SMT that may vary between centers and lead to heterogeneity in the management of patients can be separated into therapy targets, definitions of chronicity,

medications for blood pressure and pain management, and investigations. The purpose of this study is to investigate variations in medical therapy between principal investigators of the SUNDAY trial to establish patterns of treatment across regions. A complete list of the SUNDAY collaborators is provided in Supplementary Digital Material 1 (Supplementary Text File 1).

## Materials and methods

### Study design

This questionnaire was performed as part of the broader SUNDAY trial. It includes principal investigators from sites from seven countries including Sweden, Denmark, Finland, Norway, Iceland, the Netherlands and New Zealand. A cross-sectional questionnaire study was conducted using a secure multi-factor authentication protected online Research Electronic Data Capture (REDCap) (Vanderbilt University, Nashville, TN, USA) survey hosted by the SUNDAY trial coordinators.

### Study population

All principal investigators of the SUNDAY trial were emailed unique and personalized links to an online REDCap survey. This included a total of 45 potential participants. The period of time for the survey to be completed was 4 weeks, involving a comprehensive onboarding email followed by a total of 4 reminder emails being sent weekly to participants yet to have completed the questionnaire. Participants could only provide their response once using the unique link created for them.

### Questionnaire design

The questionnaire was developed by the author through several rounds of review. This involved an initial round to make a decision on the scope of each questionnaire topic, then to agree, expand or remove questions, and finally to clarify potential answers. The contents of the questionnaire were kept hidden from any external researchers regardless of involvement in the SUNDAY trial in order to maintain impartiality of the questionnaire and prevent influence outside of the scope of the SUNDAY trial.

The questionnaire was divided into three major topics: therapy targets and reporting standards, medical therapy, and diagnostic investigations. All questions were then based on key societal guideline recommendations and reporting guidelines. The questions were prepared as categorical variables with each section having a single free-text section.

A copy of the questionnaire is provided as Supplementary Digital Material 2 (Supplementary Table I).

### Data collection and statistical analysis

All collected data were securely stored in the REDCap database behind multi-factor authentication. All potential participants were reminded weekly for four weeks via email if they had not yet registered their responses. At the conclusion of the questionnaire time period, access was locked to all that had not submitted their answers, and the results were de-identified. The only remaining identifying factor was the country of the participant which was considered an important factor to assess regional differences in potential variations or patterns that may emerge from the questionnaire.

Any collected data were codified for use in SPSS 30 (IBM, Armonk, NY, USA) prior to analysis. Frequency analyses were performed on categorical data (no assumptions of ordinal data were made). All free-text questions were independently analyzed by two researchers and conflicts reviewed separately by another author for inclusion as either a quantitative outcome in the dataset or was into the discussion of this report. Any investigations for significance were performed using the Pearson's Chi-squared Test, assuming two-sided asymptotic significance as a contingency table between categorical variables. A P value of less than 0.05 was assumed to be significant. When multiple covariates were included, multinomial regression was performed, assessing significance with a Chi-squared likelihood ratio test. Only where significance was achieved is stated in the results.

## Results

### Demographics

A total of 34 of a potential 44 (73.9%) participants responded to the survey within the time period. At least one participant from each country included in the SUNDAY trial responded to the survey. There were a total of ten respondents from Sweden, four from Denmark, three from Finland, thirteen from the Netherlands, one from New Zealand, two from Norway and one from Iceland (Figure 1).

### Therapy targets and reporting standards

The participants were asked about the blood pressure, heart rate and pain management targets that are used to guide SMT at their respective center (Table I, Figure 2). Thirty-one (91.2%) respondents defined the target blood pressure for patients with uTBAD in the acute period at <120

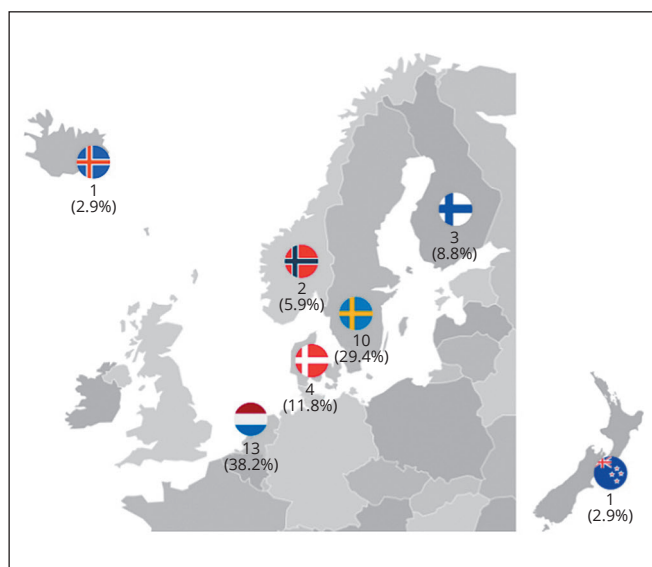


Figure 1.—Map of the count and percentage of respondents as part of the SUNDAY trial. There was at least one respondent from each participating site of the trial.

mmHg. Two (5.9%) respondents set this at <130 mmHg and one (2.9%) at <140 mmHg. There were significant regional differences with Finland and New Zealand as outliers ( $P=0.023$ ) both of which set this limit as <130 mmHg.

The definition of refractory hypertension was variable in the group. Twelve (35.3%) respondents regarded a persistent blood pressure >140 mmHg as refractory hypertension. Five (14.7%) respondents set the limit at 150 mmHg, while four (11.8%) set this at 160 mmHg. Five (14.7%) respondents did not assess refractory hypertension at all. Seventeen (50.0%) respondents did not consider the number of antihypertensives at maximal dosage as affecting assessment of refractory hypertension, while the other seventeen (50.0%) referred to >3 or >5 medications as criteria for refractory hypertension (Figure 2).

Regarding heart rate, twenty (58.5%) respondents agreed that the upper limit was 60 bpm. Three (8.8%) set this limit at 70 bpm, seven (20.6%) at 80 bpm, and four (11.8%) at >80 bpm. Again, there were significant regional differences, with Denmark, Finland, Iceland, the Nether-

TABLE 1.—Summary of therapy targets and reporting standards in the acute presentation of uTBAD with count and percentage based on question. If participants ( $N=34$ ) could select more than one option, a total count is not presented.

Item	N. (%)
<b>Hypertension</b>	
1. What is your upper limit for systolic blood pressure in the acute period?	
120 mmHg	31 (91.2%)
130 mmHg	2 (5.9%)
140 mmHg	1 (2.9%)
2. How do you define a patient that has refractory hypertension in the acute period?	
Not assessed	5 (14.7%)
>120 mmHg	6 (17.6%)
>130 mmHg	2 (6.3%)
>140 mmHg	12 (35.3%)
>150 mmHg	5 (14.7%)
>160 mmHg	4 (11.8%)
3. Does number of antihypertensives at maximal dosage used affect your assessment of refractory hypertension?	
No	17 (50.0%)
>3 antihypertensives	8 (23.5%)
>5 antihypertensives	9 (26.5%)
<b>Heart rate</b>	
1. What is your upper limit for heart rate in the acute period?	
50 bpm	0 (0.0%)
60 bpm	20 (58.8%)
70 bpm	3 (8.8%)
80 bpm	7 (20.6%)
>80 bpm	4 (11.8%)
<b>Pain</b>	
1. How do you define a patient that has refractory pain?	
Not assessed	7 (20.6%)
>12 h of pain on maximum analgesia	9 (26.5%)
>24 h of pain on maximum analgesia	6 (17.6%)
>48 h of pain on maximum analgesia	9 (26.5%)
>1 week of pain on maximum analgesia	3 (8.8%)

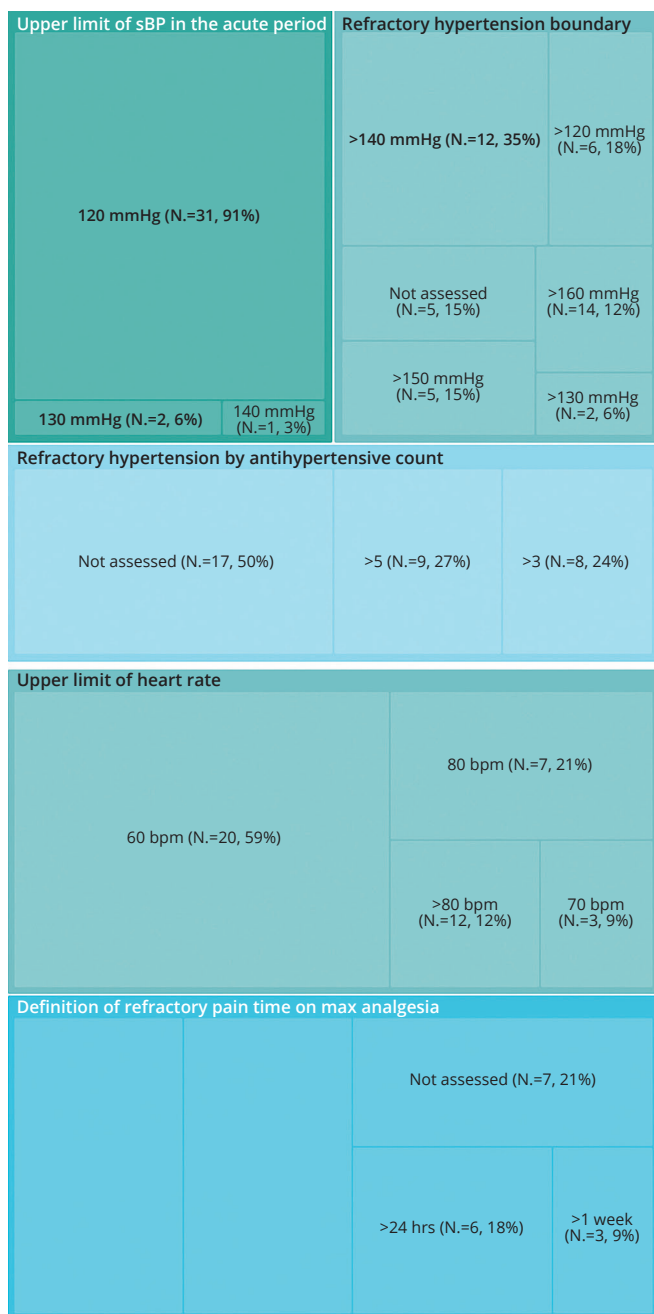


Figure 2.—Summary of the count and percentages of therapy targets using proportional box-map.

lands and Norway acting as outliers with fewer counts at 60 bpm (P=0.047) when compared to Sweden and New Zealand.

There was no consistent agreement on what constitutes refractory pain. Seven (20.6%) respondents did not assess

for refractory pain. Among the remaining participants, refractory pain was defined as anything from pain on maximum analgesia for >12 hours to >1 week (Table I, Figure 2). When considering regional differences, Finland and the Netherlands generally considered refractory pain for a longer period of time of >24 hours than Sweden which typically assessed at as >12 hours of pain on maximum analgesia (P=0.028).

A combined analysis of therapy targets of the upper limit of blood pressure and heart rate showed significance

TABLE II.—Summary of definitions of chronicity in the presentation of uT-BAD with count and percentage based on question. If participants could select more than one option, a total count is not presented.

Item	N. (%)
What is your definition of the hyperacute period?	
Not considered	5 (14.7%)
<24 h	11 (32.4%)
<48 h	13 (38.2%)
<72 h	5 (14.7%)
What is your definition of the acute period?	
<14 days	31 (91.2%)
<1 month	3 (8.8%)
What is your definition of the subacute period?	
Not considered	1 (2.9%)
14 days to 3 months	28 (82.4%)
1 month to 3 months	4 (11.8%)
>3 months	1 (2.9%)
What is your definition of the chronic period?	
>3 months	33 (97.1%)
>12 months	1 (2.9%)

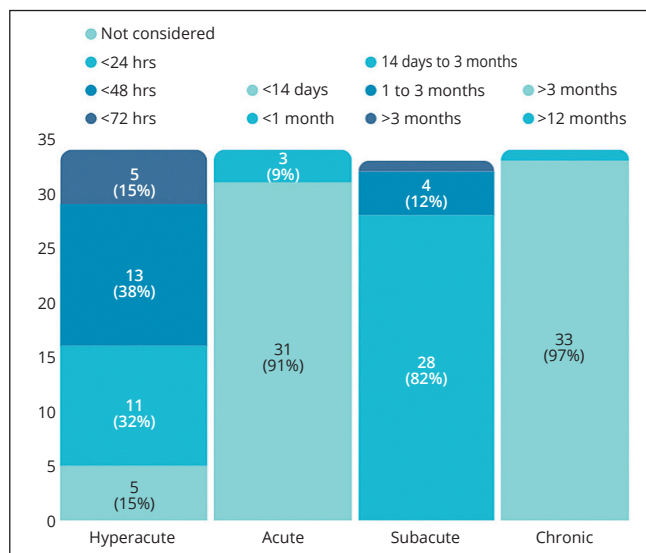


Figure 3.—Reporting standards of chronicity with a stacked column chart.

TABLE III.—Standard medical therapy of uTBAD in the acute period with count and percentage based on question. If participants could select more than one option, a total count is not presented.

Item	N. (%)
<i>Adjunctive medications</i>	
1. Do you regard an uncomplicated type B dissection alone indicates use of antiplatelet or anticoagulant therapy?	
None	9 (26.5%)
1-6 months single anti-platelet	2 (5.9%)
Life-long single anti-platelet	22 (64.7%)
Life-long anticoagulant	1 (2.9%)
2. Do you regard an uncomplicated type B dissection alone indicates use of statin therapy?	
None	14 (41.2%)
Standard dose statin	15 (44.1%)
Statin with LDL target	5 (14.7%)
<i>Standard medications (general)</i>	
1. Is there a standardized medical management protocol in place at your institution?	
Yes	29 (85.3%)
No	5 (14.7%)
2. For patients with acute uTBAD, which wards are utilized for monitoring purposes?	
Surgical/vascular ward	6 (17.6%)
General medicine ward	0 (0.0%)
ICU	14 (41.2%)
HDU	16 (47.1%)
CCU	13 (38.2%)
Cardiology	8 (23.5%)
<i>Standard medications (hypertension)</i>	
1. Do you involve a multidisciplinary team in management and titration of antihypertensives?	
None	1 (2.9%)
ICU	13 (38.2%)
Cardiology	18 (52.9%)
Renal	4 (11.8%)
Internal medicine or angiologist	21 (61.8%)
2. What is the trigger to transition to oral medications?	
Initially start with oral beta-blocker	6 (17.6%)
>24 h of control with IV beta-blocker	24 (70.6%)
>48 h of control with IV beta-blocker	4 (11.8%)
3. Acute management - first line antihypertensive	
IV labetalol	30 (88.2%)
Oral beta-blocker	4 (11.8%)
4. Acute management - second line antihypertensive	
Calcium channel blockers	13 (38.2%)
ACE inhibitors	7 (20.6%)
ARBs	1 (2.9%)
Sodium nitroprusside	7 (20.6%)
Oral beta-blocker	4 (11.8%)
Nitrate (IV)	1 (2.9%)
All of the above considered	1 (2.9%)
5. Acute management - third line antihypertensive	
Calcium channel blockers	13 (38.2%)
ACE inhibitors	6 (17.6%)
ARBs	2 (5.9%)
Alpha blockers	2 (5.9%)
Sodium nitroprusside	6 (17.6%)
Oral beta-blocker	1 (2.9%)
Clonidine	1 (2.9%)
Methyldopa	1 (2.9%)
All of the above considered	1 (2.9%)
<i>Standard medications (pain)</i>	
1. Do you involve a multidisciplinary team in management pain and analgesics?	
None	4 (11.8%)
Anesthetics	23 (67.6%)
Acute pain service	11 (32.4%)
General medicine or angiologist	2 (5.9%)
Cardiologist	1 (2.9%)
ICU	1 (2.9%)
2. Are opioids used routinely for first-line management of pain in acute uTBAD?	
Only if required	26 (76.5%)
Are opioids used routinely for first-line management of pain in acute uTBAD?	
Yes	7 (20.6%)

based on the region of the respondent which agrees with the above findings (P=0.015).

With regards to definitions of chronicity and time limits for hyperacute/acute/subacute and chronic dissection, data are summarized in Table II and Figure 3. There is discord in the definition of the hyperacute period of dissection, while 31 (91.2%) respondents defined the acute period as <14 days. Similarly, 28 (82%) respondents agreed on subacute being defined as 1-3 months after initial symptoms, and 33 (97.1%) stated that the chronic period was >3 months.

**Medical therapy**

The responds regarding first- and second-line medical treatment strategies are presented in Table III. In acute management, thirty (88.2%) respondents preferred intravenous (IV) labetalol as the first-line antihypertensive. There was general agreement across respondents on the use of second- and third-line antihypertensives in an acute setting (Table III, Figure 4). Twenty-four (70.6%) respondents transitioned from IV beta-blocker to oral beta-blocker after more than 24 hours of adequate control with IV beta-blocker. Six (17.6%) respondents initially started therapy with oral beta-blocker (Figure 4).

Twenty-nine (85.3%) respondents stated that their institution has a protocol for standardized medical management. For monitoring purposes, a high-intensity unit was used in majority of centers among other higher level monitoring wards (Table III).

A multidisciplinary team (MDT) is used by most respondents for management of blood pressure and pain,

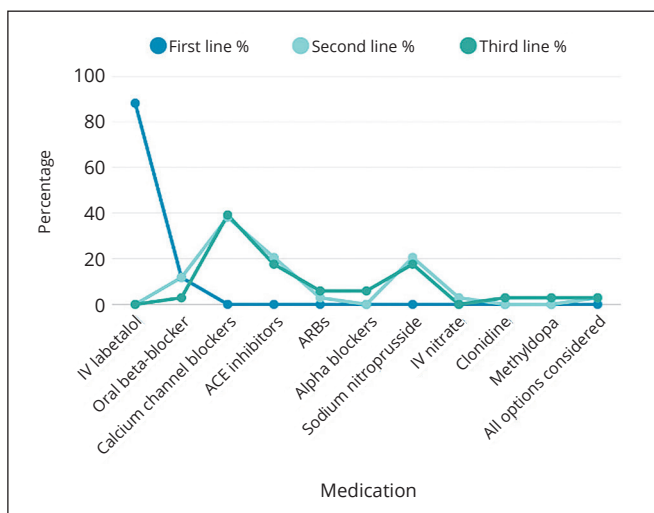


Figure 4.—Acute blood pressure management for first line, second line and third line therapies.

with the different components of the MDT being presented in Table III.

Adjunctive medical therapies included anti-thrombotic therapy and statins. Twenty-five (73.5%) respondents consider commencing an anti-thrombotic agent, while nine (26.5%) did not routinely administer anti-thrombotics for uTBAD. Twenty-two (64.7%) respondents would consider life-long single anti-platelet therapy, whilst two (5.9%) respondents administer 1-6 months of a single anti-platelet agent, and one (2.9%) respondent administers life-long anticoagulation.

There is little agreement regarding statin therapy. Fourteen (41.2%) respondents do not routinely initiate statin therapy. Fifteen (44.1%) respondents indicated that standard doses were initiated, while five (14.7%) initiate statins with an LDL target (Figure 5).

**Investigations**

Thirty-two (94.1%) respondents reserved genetic testing for young patients. While the questionnaire did not set an upper limit for a young patient, free-text answers set this as either less than 50 or 60 years of age. Other indications

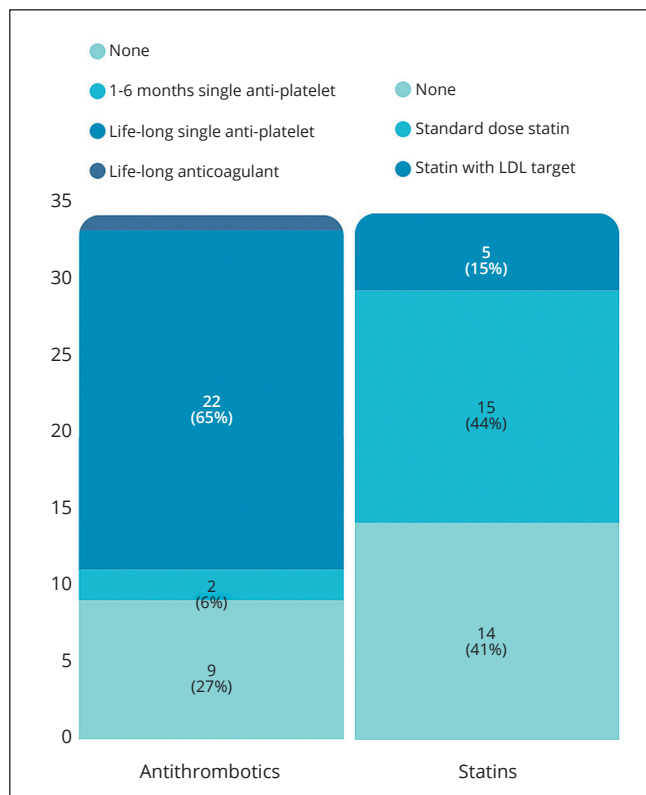


Figure 5.—Adjunctive medical therapy using a stacked column chart.

TABLE IV.—Investigations of the acute uTBAD with count and percentage based on question. Totals are not included since participants were given the option to select multiple options.

Item	N. (%)
1. When do you perform genetic testing?	
Not performed	1 (2.9%)
All patients	1 (2.9%)
Young patient	32 (94.1%)
Identified characteristic features	18 (52.9%)
Family history	25 (73.5%)
Indigenous heritage	6 (17.6%)
2. Do you routinely perform an ancillary investigation to investigate vascular risk factors?	
Not performed	17 (50.0%)
Lipid profile	16 (47.1%)
Coagulation profile	8 (23.5%)
Vasculitis screen	0 (0.0%)
3. Do you use adjuncts to assess for potential causes of hypertension?	
Not performed	27 (79.4%)
CT brain	0 (0.0%)
Renal duplex	6 (17.6%)
MAG3 scan	0 (0.0%)
Other – based on the suggestion of general medicine	1 (2.9%)

for genetic testing included identifiable characteristic features, family history and indigenous heritage (Table IV).

Ancillary investigations for vascular risk factors are not often performed (Table IV) with seventeen (50.0%) respondents not performing any investigations such as lipid profile and coagulation profile.

Twenty-seven (79.4%) respondents stated that they did not routinely perform additional adjuncts to assess for potential causes of hypertension. However, six (17.6%) respondents utilize renal duplex while one (2.9%) respondent stated that they are guided by general medicine.

## Discussion

All of the relevant societal guidelines recommend medical therapy for both short- and long-term treatment of aortic dissections.<sup>4-6</sup> Because of the limited evidence in these recommendations, the present analysis aimed to query the interpretation and implementation of medical therapy in the ongoing SUNDAY trial. The results indicate variation between centers, and it is presumed that this heterogeneity reflects real world practice in an area where evidence is scarce. It also reflects the pragmatic nature of the SUNDAY trial that intentionally does not mandate a specific medical therapy regimen as part of the trial but rather relies on therapeutic targets that are monitored through patient-driven reporting of blood pressure and heart rate.

In general, the upper limit of blood pressure was agreed by the respondents to be 120 mmHg, and heart rate at 60 bpm, which is in line with guideline recommendations. Whilst it is intuitive to reduce the stress on the dissected

aortic wall with blood pressure lowering, there is little clinical data to clarify targets or strategies. Lederle and Powell have also raised concerns of the potential harm in rapidly lowering the blood pressure of patients and the risk of organ malperfusion.<sup>14</sup> Interestingly, one prospective cohort study demonstrated no survival benefit in intensive target-directed therapy when compared to more liberal regimens. It was further observed that the intensive regimens were associated with nephrologic injury.<sup>15</sup>

The role of refractory hypertension has changed with recent guidelines and reporting standards. Whilst the 2017 ESVS guidelines regarded patients with refractory hypertension or pain to suffer from a complicated dissection, recent guidelines and reporting standards rather regard these entities as “high risk features.”<sup>4, 6, 9</sup> Still, refractory hypertension and pain reflect when therapeutic targets are not adequately met, leading to an escalation in therapy and potential intervention with TEVAR. Most practitioners relax their definitions of the upper limit of systolic blood pressure, which goes from 120 mmHg to 140 mmHg, at which point the pathology can be considered a high risk uTBAD. Also, the number of antihypertensives used can have an impact on decision making, as some clinicians believe that requiring more than 5 antihypertensives with adequate blood pressure control still constitutes refractory hypertension. These relaxed targets may protect from kidney injury while not affecting survival.<sup>15</sup> There is no consensus amongst the respondents for the definition of the term “refractory” – clearly, more substantial research performed on the clinical validity or utility of this defini-

tion would be of value in order to develop clear definitions or a consensus.

There is consensus regarding the types of antihypertensives to use as part of SMT. It is likely that most SMT strategies are based on low-level and small-scale cohort studies with limited generalizability.<sup>16, 17</sup> In fact, there is very limited evidence to demonstrate the benefit of beta-blockers specifically as first-line anti-impulse measures even though all respondents follow this recommendation as set out by relevant societal guidelines.<sup>14, 18</sup>

There is currently no high-level evidence to support antiplatelet therapies nor anticoagulation as part of the medical management of TBAD, although several experts maintain there is a need.<sup>19</sup> One study from the American Vascular Quality Initiative, including 1210 patients, showed no benefit or risk of antiplatelet therapy in aortic remodeling or survival.<sup>20</sup> The majority of principal investigators in the SUNDAY trial choose to commence an antiplatelet agent in uTBAD, and this may reflect a broader vascular surgical practice in patients with arterial disease. For the use of statins, it appears to decrease mortality risk and aorta-related adverse events following TEVAR, particularly for patients with high low-density lipoprotein cholesterol (LDL-C) levels based on a retrospective single-center study.<sup>21</sup> Critically, a multicenter, prospective and randomized comparative trial found that pitavastatin specifically had a significant protective effect on aortic arch dilatation in uTBAD treated with medical therapy alone.<sup>22</sup>

The current study underlines that, even in a contemporary dissection RCT, there are areas where strategies for management varies. Centres that participate in the SUNDAY trial have a joint commitment to study the effect of TEVAR on long-term survival after uncomplicated type B dissection and are assumed to have overlap in management strategies for TBAD with the same therapeutic goal. Heterogeneity in practice can be problematic in multicenter trials. It may not result biases, because of the randomization, but it may limit generalizability because of treatment heterogeneity. The pragmatic design of the SUNDAY compensates for the lack of standardized regimens by careful registration of blood pressure readings.

### Limitations of the study

There are inherent limitations associated with questionnaire-based research. Notably, response bias, or the interpretation or processing of the question with the sample size may influence the generalizability of results, particularly across regions. Relying on self-reported data, responses may not reflect actual clinical practice. Additionally, the

questionnaire primarily used categorical responses, restricting insights if compared to open-ended qualitative methods. This may be more relevant in considerations of adjunctive medical therapy.

### Conclusions

This questionnaire study, as part of the SUNDAY trial, highlights the presence of variation in medical management of patients with uTBAD. These variations reflect the lack of high-level evidence that can guide local practice. Whilst the lack of consistent therapeutic strategies across sites in the SUNDAY trial can be problematic, the pragmatic design of the study does consider this aspect. The differences in medical management between centers underlines the importance of the goal-directed therapy target for medical management in the SUNDAY trial, which is monitored as part of trial outcome with patient reported blood pressure and heart rate in all included subjects. Future trial results, which will include data on medical treatment, may shed further light on how well different medical strategies reach pre-defined targets.

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#### Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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#### Authors' contributions

Erin C. Saricilar: conception and design, data collection, data analysis and interpretation, manuscript writing, critical revision, statistical analysis. Bianca Biersteker, Joost van der Vorst, Jacob Budtz-Lilly: conception and design, data analysis and interpretation, manuscript writing, critical revision. Kevin Mani: conception and design, data collection, data analysis and interpretation, manuscript writing, critical revision. All authors read and approved the final version of the manuscript.

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## SUPPLEMENTARY DIGITAL MATERIAL 1

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SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table I.—Questionnaire presented to all SUNDAY trial principal investigators which was separated into sections labelled Definitions, Standard Medical Therapy and Investigations. All questions marked with an asterisk required a response. Any selection of “Other” permitted free-text to be entered.

<i>Definitions</i>	
What is your upper limit for systolic blood pressure in the acute period? *	<ul style="list-style-type: none"> <li>• 110mmHg</li> <li>• 120mmHg</li> <li>• 130mmHg</li> <li>• 140mmHg</li> <li>• &gt;140mmHg</li> </ul>
What is your upper limit for heart rate in the acute period? *	<ul style="list-style-type: none"> <li>• 50</li> <li>• 60</li> <li>• 70</li> <li>• 80</li> <li>• &gt;80</li> </ul>
How do you define a patient that has refractory hypertension in the acute period? *	<ul style="list-style-type: none"> <li>• Not assessed</li> <li>• &gt; 120mmHg</li> <li>• &gt; 130mmHg</li> <li>• &gt; 140mmHg</li> <li>• &gt; 150mmHg</li> <li>• &gt; 160mmHg</li> </ul>
Does number of antihypertensives at maximal dosage used affect your assessment of refractory hypertension? *	<ul style="list-style-type: none"> <li>• No</li> <li>• &gt;3</li> <li>• &gt;5</li> </ul>
How do you define a patient that has refractory pain? *	<ul style="list-style-type: none"> <li>• Not assessed</li> <li>• &gt; 12hrs of pain on maximum analgesia</li> <li>• &gt; 24hrs of pain on maximum analgesia</li> <li>• &gt; 48hrs of pain on maximum analgesia</li> <li>• &gt;1 week of pain on maximum analgesia</li> </ul>
What is your definition of the hyperacute period? *	<ul style="list-style-type: none"> <li>• Not considered</li> <li>• &lt;24hrs</li> <li>• &lt;48hrs</li> <li>• &lt;72hrs</li> </ul>
What is your definition of the acute period? *	<ul style="list-style-type: none"> <li>• &lt; 14 days</li> <li>• &lt; 1 month</li> <li>• &lt; 3 months</li> </ul>
What is your definition of the subacute period? *	<ul style="list-style-type: none"> <li>• 14 days to 3 months</li> <li>• 1 month to 3 months</li> <li>• &gt; 3 months</li> </ul>
What is your definition of the chronic period? *	<ul style="list-style-type: none"> <li>• Not considered</li> <li>• &gt; 3 months</li> <li>• &gt; 6 months</li> </ul>

	<ul style="list-style-type: none"> <li>• &gt; 12 months</li> </ul>
Does the chronicity of the disease affect your management of blood pressure and heart rate control? *	<ul style="list-style-type: none"> <li>• None</li> <li>• Relaxed after the hyperacute period</li> <li>• Relaxed after the acute period</li> <li>• Relaxed after the subacute period</li> </ul>
General comments regarding definitions in uTBAD.	
<i>Standard medical management</i>	
Do you regard an uncomplicated type B dissection alone indicates use of antiplatelet or anticoagulant therapy? *	<ul style="list-style-type: none"> <li>• None</li> <li>• 1-6 months single anti-platelet</li> <li>• Life-long single anti-platelet</li> <li>• 1-6 months DAPT</li> <li>• Life-long DAPT</li> <li>• 1-6 months anticoagulant</li> <li>• Life-long anticoagulant</li> </ul>
Do you regard an uncomplicated type B dissection alone indicates use of statin therapy? *	<ul style="list-style-type: none"> <li>• None</li> <li>• Yes, standard dose statin</li> <li>• Yes, high dose statin</li> <li>• Yes, statin with LDL target</li> </ul>
Do you involve a multidisciplinary team in management and titration of antihypertensives? Select all relevant. *	<ul style="list-style-type: none"> <li>• None</li> <li>• ICU</li> <li>• Cardiology</li> <li>• Renal</li> <li>• General medicine/internal medicine/angiologist</li> <li>• Other</li> </ul>
Do you involve a multidisciplinary team in management pain and analgesics? Select all relevant. *	<ul style="list-style-type: none"> <li>• None</li> <li>• Anaesthetics</li> <li>• Acute pain service (APS)</li> <li>• General medicine</li> <li>• Other</li> </ul>
Are opioids used routinely for first-line management of pain in acute uTBAD? *	<ul style="list-style-type: none"> <li>• Yes</li> <li>• No</li> <li>• Only if required</li> </ul>
For patients with acute uTBAD, which wards are utilised for monitoring purposes? Select all relevant. *	<ul style="list-style-type: none"> <li>• Surgical/vascular ward</li> <li>• General medical ward</li> <li>• Intensive care unit (ICU)</li> <li>• High dependency unit (HDU)</li> <li>• Coronary care unit (CCU)</li> <li>• Cardiology ward</li> <li>• Other</li> </ul>
Is there a standardised medical management protocol in place at your institution? *	<ul style="list-style-type: none"> <li>• Yes</li> <li>• No</li> <li>• In review</li> </ul>
Acute management:	
- First line*	<ul style="list-style-type: none"> <li>• IV esmolol</li> <li>• IV labetalol</li> <li>• Oral beta-blocker</li> <li>• Other</li> </ul>

- Second line*	<ul style="list-style-type: none"> <li>• Calcium channel blockers</li> <li>• ACE inhibitors</li> <li>• ARBs</li> <li>• Non-Dihydropyridine Calcium Channel Blockers</li> <li>• Alpha blockers</li> <li>• Sodium nitroprusside</li> <li>• Hydralazine</li> <li>• Beta-blocker (IV/Oral)</li> <li>• Other</li> </ul>
- Third line*	<ul style="list-style-type: none"> <li>• Calcium channel blockers</li> <li>• ACE inhibitors</li> <li>• ARBs</li> <li>• Non-Dihydropyridine Calcium Channel Blockers</li> <li>• Alpha blockers</li> <li>• Sodium nitroprusside</li> <li>• Hydralazine</li> <li>• Beta-blocker (IV/Oral)</li> <li>• Other</li> </ul>
Out of hospital management	
- First line	<ul style="list-style-type: none"> <li>• Oral beta-blocker</li> <li>• Calcium channel blocker</li> <li>• Alpha blocker</li> <li>• Hydralazine</li> <li>• Other</li> </ul>
- Second line	<ul style="list-style-type: none"> <li>• Calcium channel blockers</li> <li>• ACE inhibitors</li> <li>• ARBs</li> <li>• Non-Dihydropyridine Calcium Channel Blockers</li> <li>• Alpha blockers</li> <li>• Hydralazine</li> <li>• Oral beta-blocker</li> <li>• Other</li> </ul>
- Third line	<ul style="list-style-type: none"> <li>• Calcium channel blockers</li> <li>• ACE inhibitors</li> <li>• ARBs</li> <li>• Non-Dihydropyridine Calcium Channel Blockers</li> <li>• Alpha blockers</li> <li>• Hydralazine</li> <li>• Oral beta-blocker</li> <li>• Other</li> </ul>
What is the trigger to transition to oral medications? *	<ul style="list-style-type: none"> <li>• Initially start with oral beta-blocker</li> <li>• &gt; 24hrs of control with IV beta-blocker</li> <li>• &gt; 48hrs of control with IV beta-blocker</li> </ul>

<b><i>Investigations</i></b>	
When do you perform genetic testing? *	<ul style="list-style-type: none"> <li>• Not performed</li> <li>• All patients</li> <li>• Young patient (no specific age cut off and dependent on surgeon)</li> <li>• Identified characteristic features</li> <li>• Family history</li> <li>• Indigenous heritage</li> <li>• Other</li> </ul>
Do you routinely perform an ancillary investigations to investigate vascular risk factors? *	<ul style="list-style-type: none"> <li>• Not performed</li> <li>• Lipid profile</li> <li>• Coagulation profile</li> <li>• Vasculitis screen</li> <li>• Other</li> </ul>
Do you use adjuncts to assess for potential causes of hypertension? *	<ul style="list-style-type: none"> <li>• CT Brain</li> <li>• Renal duplex</li> <li>• MAG3 scan</li> <li>• Other</li> </ul>