Can the principles of evidence-based medicine be applied to the treatment of aortic dissections?

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Summary

Surgical treatment of patients with acute type A aortic dissections has improved early survival from 10–20 to approximately 80%. Data supporting several other treatment recommendations in patients with aortic dissection, however, are less convincing. We hypothesized that applying strict principles of evidence-based medicine would invalidate most of the recommendations in these published papers. We conducted a literature search asking three questions: (1) Is the use of routine circulatory arrest and an ‘open distal’ anastomosis technique better than traditional aortic cross clamping? (2) Does a persistent false lumen in the distal aorta wall have an adverse influence on long-term event-free survival? and (3) Is primary surgical or medical treatment of patients with Stanford acute type B dissections preferable in terms of long-term event-free survival? We searched Entrez Pubmed (National Library of Medicine) for all papers on these topics from 1980 to January 2003. Screening 3164 papers identified using the search terms ‘aortic dissection’ and ‘treatment’ yielded 15 papers fulfilling a set of a priori inclusion criteria. No study had a design that allowed unequivocal conclusions; moreover, the heterogeneity in study design and patient populations precluded formal meta-analysis. The difficulties inherent in conducting stringent clinical studies addressing various treatment strategies for patients with aortic dissection hamper their quality and weaken their recommendations for different treatment options. Specifically, no conclusive evidence exists favoring use of an open distal anastomosis in patients with acute type A dissections or complete elimination of flow in the distal aortic false lumen; similarly, medical therapy of patients with acute type B aortic dissections has no proven advantage over surgical treatment.

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1. Introduction

An increasing demand for rigorous documentation of treatment effectiveness is emerging in the medical community, and the concept of a quality hierarchy of medical data has evolved [1,2]. Studies are ranked from the strong prospective randomized trial to case-matched observational studies to the lowest-ranked observational studies based on historical controls [3]. The traditional presentation of retrospective clinical series has been assigned low merit, associated with numerous potential flaws thus making conclusions suspect [4]. Large, carefully conducted, prospective, randomized studies, on the other hand, are rare in most surgical specialties [5]. The demand for more rigorous documentation has mainly come from the fields of internal medicine and epidemiology [2], but, paradoxically, coronary artery bypass surgery is one of the best-documented treatments in all of medicine [6]. To what extent this development can and should be applied to other aspects of thoracic and cardiac surgery continues to be hotly debated.

We conducted a literature search based on guidelines from the American Medical Association [7,8] to answer three questions related to the treatment of aortic dissections. First, we asked whether the routine use of an open distal anastomosis using circulatory arrest is better than aortic cross clamping only, reserving profound hypothermic circulatory arrest for selected patients with acute type A aortic dissections? Second, for these same patients does a persistently patent distal aortic false lumen postoperatively adversely influence long-term outcome? Third, is primary
surgical or medical treatment of patients with acute Stanford type B dissections preferable in terms of long-term ‘event-free’ survival? In this review we assessed the documented support for these various treatment options and factors traditionally thought to influence long-term outcome and survival.

2. Methods

The study was conducted as a structured literature review [7,8]. The three questions constituting the aims were formulated before the literature search, and all three were constructed in a manner comparing two clearly defined factors. The first was a comparison between use of circulatory arrest and an ‘open distal’ aortic anastomosis (i.e. no aortic cross clamp) in patients with acute Stanford type A dissections versus routine use of aortic cross clamping reserving circulatory arrest only for dissections where transverse arch repair was necessary. The second was a comparison between the effects on long-term outcome of a thrombosed or closed versus a persistently patent distal aortic false lumen. Lastly, we addressed the question of whether surgical or medical treatment of patients with uncomplicated acute Stanford type B dissections provided the best event-free outcome (i.e. no aortic dilatation, rupture, reoperation or death). These questions were selected as being clinically important—yet widely debated—treatment principles which lend themselves to direct comparison. Thus, the supportive evidence for accepting one treatment method or the other potentially could be evaluated.

The literature search was conducted by searching PubMed (National Library of Medicine) using the words ‘aortic dissection’ and ‘treatment’. Predefined criteria for study inclusions were: studies containing 20 or more patients with the desired two-group comparisons published after 1980 with at least the abstract if not the entire paper in the English language; fewer than 20 patients in one study was accepted if a clear interventional and control group were found. The reference lists in the papers found were searched for additional papers matching the same inclusion criteria. No abstract, unpublished data, or personal communications were included. Papers were excluded if the average follow-up was shorter than 1 year or the specific end points (e.g. rupture, reoperation or death) could not be clearly defined. Patient follow-up studies were excluded if they contained selected cases only or had incomplete follow-up, unequal observation periods between groups, and/or lacked adequate definition of treatment-to-patient links. Series were also excluded if they did not single out one of the three main questions under analysis, or a surrogate for one of the aims could be deduced. No case reports were included. Studies were classified as randomized trials or case-control studies or retrospective patient series (follow-up studies). A meta-analysis was planned if four homogenous studies with the same treatments and equal end points were identified in any of the main groups [9]. The titles and studies were evaluated in a screening process by the first author. The results of such selection or rejection of studies were reviewed by the other authors.

3. Results

The complete search provided 3164 ‘hits’ using the words aortic dissection or aortic dissection and treatment. The papers were initially screened by evaluating title only; when fulfillment of inclusion criteria was deemed possible, the abstracts or the full papers were then reviewed. Also, the reference lists of these papers were assessed. A total number of 1566 titles were reviewed.

No randomized trials were found for any aspect of the treatment of patients with aortic dissections. A total of six studies fulfilling the inclusion criteria was found addressing the question of a treatment benefit for an open distal anastomosis (Table 1). These included one patient series (follow-up study) and five studies using a case-control design, all using historical controls from the same institution. The patient series (study 1 in Table 1) did not specifically address the question of a treatment benefit for an open distal anastomosis, but ‘circulatory arrest’ was substituted for this technique as an approximation. The use of circulatory arrest did not significantly affect outcome. No randomized trials were found for any aspect of the treatment of patients with aortic dissections. A total of six studies fulfilling the inclusion criteria was found addressing the question of a treatment benefit for an open distal anastomosis (Table 1). These included one patient series (follow-up study) and five studies using a case-control design, all using historical controls from the same institution. The patient series (study 1 in Table 1) did not specifically address the question of a treatment benefit for an open distal anastomosis, but ‘circulatory arrest’ was substituted for this technique as an approximation. The use of circulatory arrest did not significantly affect outcome. Four of the remaining five studies had defects in study design as mentioned under ‘Comments’ in Table 1. A lower 60-day mortality rate was reported in one of these five studies using the open distal technique. No long-term results (beyond 5 years) were found in the literature review. The heterogeneity of the patient samples in the studies [15] precluded a meaningful meta-analysis.

Studies addressing the effect of a persistent false lumen on long-term outcome are presented in Table 2. We found three studies using a case-control design and two retrospective patient series which addressed this issue, but all had defects in study design as explained in ‘Comments’ in Table 2. Two reports found a connection between a persistently patent false lumen and increased diameter of some segment of the downstream aorta. No studies demonstrated a connection between persistent false lumen and a higher likelihood of rupture or reoperation. One study reported an adverse influence of a persistently patent false lumen on long-term survival.

Comparative studies between primary surgical and medical treatment of patients with uncomplicated acute type B dissections are presented in Table 3. Only four reports fulfilling our criteria were found, again with inadequate study designs (see Comments in Table 3). No differences in survival were demonstrated between the two treatments.
Table 1
Effect of an open distal technique on surgical outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor College of Medicine</td>
<td>Retrospective patient series Multivariable risk factor analysis. Open distal not entered in analysis (circulatory arrest serve as substitute)</td>
<td>$N = 82$ (1968–1992)</td>
<td>Circulatory arrest not significant factor in predicting surgical outcome</td>
<td>Continuing improvement of results during the period with no direct evidence of benefit of open distal technique. Multiple factors altered during the period</td>
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<tr>
<td>(Crawford) 1992</td>
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<tr>
<td>University of Philadelphia</td>
<td>Retrospective case-control design (historical controls) Comparing selective HCA* (group 1) with routine open distal technique (group 2)</td>
<td>$N = 41$ (group 1) (1987–1995); $N = 19$ (group 2) (1993–1995)</td>
<td>60-day mortality: group 1, 29% (12/41); group 2, 5% (1/19); $P = 0.04$ CVA: group 1, 6% (10/178); group 2, 0% (0/19); $P = 0.02$</td>
<td>Selection criteria unclear. Multiple alterations in protocol concomitant with open distal (use of retrograde cerebral perfusion, EEG, TEE, drug alterations, more use of composite grafts)</td>
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<tr>
<td>(Bavaria) 1996</td>
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<tr>
<td>University of Kobe (Yamashita)</td>
<td>Retrospective case-control design (historical controls) Comparing cross-clamped ascending repair (group 1) with routine open distal technique (group 2)</td>
<td>$N = 27$ (group 1) (1986–1991); $N = 16$ (group 2) (1991–1996)</td>
<td>Operative mortality: group 1, 19% (5/27); group 2, 19% (3/16) Persistent false lumen: group 1, 50% (9/18); group 2, 13% (2/13); $P &lt; 0.05$</td>
<td>Unequal graft techniques between groups. Most persistent false lumens found in patients operated with ring grafts (16/18 ring grafts used in group 1). Short follow-up in group 2. Effect on long-term survival uncertain</td>
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<tr>
<td>1997</td>
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<tr>
<td>University of Berne (Nguyen)</td>
<td>Retrospective case-control design (historical controls) Comparing cross-clamped ascending repair (group 1) with routine open distal without (group 2) or with (group 3) use of glue</td>
<td>$N = 20$ (group 1); $N = 16$ (group 2); $N = 18$ (group 3)</td>
<td>Operative mortality: group 1, 13% (3/23); group 2, 15% (3/20); group 3, 18% (4/22) Long-term distal aneurysm: group 1, 20% (4/20); group 2, 13% (2/16); group 3, 11% (2/18); $P &lt; 0.05$ (1 vs. 3)</td>
<td>No information on exact year of operation or whether or not the follow-up time was different in the three groups (probable difference, deduced from discussion). No details of aneurysmal development (diameter, rupture, survival effect)</td>
</tr>
<tr>
<td>1999</td>
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<tr>
<td>University of Toronto (David)</td>
<td>Retrospective case-control design (historical controls) Comparing selective HCA (group 1) with routine open distal technique (group 2)</td>
<td>$N = 55$ (group 1); $N = 54$ (group 2) (1979–1996, time period separating the two groups not given)</td>
<td>Operative mortality: group 1, 20% (11/55); group 2, 9% (5/54); $P = 0.1$ Strokes: group 1, 15% (8/55); group 2, 4% (2/54); $P = 0.05$ A non-significant tendency towards less persistent false lumens and longer survival was observed in group 2</td>
<td>Time point discriminating the two groups and detailed operative protocols (including other potentially altered factors) not given</td>
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<tr>
<td>1999</td>
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<tr>
<td>Stanford University (Lai)</td>
<td>Retrospective case-control design (historical controls); subgroup analysis using propensity scoring Comparing profound hypothermic circulatory arrest (PHCA; group 1) with patients were no PHCA was used (group 2)</td>
<td>$N = 121$ (group 1); $N = 186$ (group 2) (1967–1999) Subgroup propensity: $N = 113$, PHCA; $N = 39$, no PHCA</td>
<td>Survival overall: 30-day, 81% ± 2%; 1-year, 74% ± 3%; 5-year, 63% ± 3% No difference between PHCA and no-PHCA in any groups</td>
<td>Long time period with concomitant time-related changes in surgical methods (historical controls) Large series of patients with careful statistical approach, but unequal and small numbers in propensity-matched groups</td>
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<tr>
<td>2002</td>
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Table includes studies found in the literature where this has been addressed as a separate issue. Open distal technique, the use of routinely hypothermic circulatory arrest and construction of the distal anastomosis without aortic clamp. CVA, cerebrovascular accident; EEG, electro-encephalogram; TEE, transesophageal echocardiogram.

* Selective HCA (hypothermic circulatory arrest), HCA used when intimal tear extended to arch (20 of 41 patients in group 1).
Table 2
Effect of a persistent false lumen on surgical outcome (rupture, reoperation and death)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Mount Sinai Medical Center</td>
<td>Retrospective case-control design</td>
<td>N = 18 (group 1); N = 20 (group 2)</td>
<td>5-year survival: group 1, 76%; group 2, 95%; n.s.</td>
<td>Two different surgical techniques were used; 25 suture anastomosis and 13 intra-luminal grafts. Persistent false lumen was observed in 30% of the intra-luminal grafts (4/13) and 56% of sutures (14/25)</td>
</tr>
<tr>
<td>(Ergin) 1994 [16]</td>
<td>Comparing survival in patients with persistent (group 1) and occluded (group 2) false lumen after surgery for acute type A dissection</td>
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<tr>
<td>Southampton General Hospital</td>
<td>Retrospective case-control design</td>
<td>N = 29 (group 1); N = 11 (group 2); 20 years Subgroup of all patients (40/87) with surgically treated acute type A dissection eligible for follow-up MRI</td>
<td>Diameter of the aorta, at hiatus: group 1, 4.4 cm; group 2, 3.4 cm; P &lt; 0.02 In abdomen: group 1, 4.4 cm; group 2, 3.3 cm; P &lt; 0.01</td>
<td>Complete follow-up of patients eligible for MRI. No difference in the ascending aorta and arch</td>
</tr>
<tr>
<td>(Barron) 1997 [17]</td>
<td>Comparing aortic diameter in patients with (group 1) or without (group 2) persisting false lumen after surgery for acute type A</td>
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</tr>
<tr>
<td>National Cardiovascular Center, Osaka</td>
<td>Retrospective case-control design</td>
<td>N = 67 (group 1); N = 19 (group 2); 1978–1998 Subgroup analysis of surviving patients (86/119) after surgical treatment of acute type B dissections</td>
<td>Time-related increase in aortic diameter (hiatus): group 1, 4.5 mm; group 2, 10.1 mm; P = 0.04 Persistent false lumen: group 1, ~25%; group 2, ~95%; P &lt; 0.001; No difference in aortic-related events</td>
<td>Selection and eligibility criteria for different treatment choices not defined</td>
</tr>
<tr>
<td>(Okita) 1999 [18]</td>
<td>Comparing aortic diameter, persistent false lumen and aortic events in surgically treated acute type B dissections with the anastomosis to the true lumen (group 1) or both lumens (group 2)</td>
<td></td>
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</tr>
<tr>
<td>The Mount Sinai Medical Center</td>
<td>Retrospective patient series</td>
<td>N = 50 Subgroup of acute type B dissections (50/120) with at least two follow-up CT scans</td>
<td>Persistent false lumen not a risk factor for rupture</td>
<td>Highly selected subgroup of patients in an environment of aggressive prophylactic surgery</td>
</tr>
<tr>
<td>(Juvonen) 1999 [19]</td>
<td>Risk factor analysis for rupture in patients with medically treated acute type B dissection</td>
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<tr>
<td>University Hospital Jean-Minjoz (Bernard)</td>
<td>Retrospective patient series</td>
<td>N = 109, 1984–1996 Average follow-up, 57 ± 43 months Both acute type A and B dissection in a follow-up study using different (echo, CT and MRI) imaging techniques</td>
<td>Persistent false lumen relative risk factor for late death (RR, 3.2; 95% CI, 1.17–8.8)</td>
<td>Not stated whether the group of patients is consecutive. Unclear number lost to follow-up Medical treatment criteria and success in follow-up unknown (i.e. hypertension)</td>
</tr>
</tbody>
</table>

4. Discussion

In a landmark paper on aortic dissections [10] Crawford and coworkers stated: “Ideally, a randomized trial should be conducted to determine the indications for including the arch in all replacement operations for acute DeBakey type I aortic dissections. However, because of the variability that can be expected among patients with acute dissections involving the ascending aorta, a large group of patients would be required, and a very long-term follow-up would be necessary to determine the probability of freedom from unfavorable outcome events. Such a study will probably not be done”. This statement points directly to the problems connected with statistical evaluation of different treatments options in patients with aortic dissections. Due to the acuity, life-threatening nature, relative rarity, and treatment difficulties related to this serious disease, the best methods to evaluate treatment outcomes, viz. randomized trials and rigorously matched cohort or case-control observational studies are hard to conduct, if not impossible. Therefore, the majority of papers published in this field are purely descriptive outcome studies or case reports. As surgical techniques and postoperative care have been evolved, clinical results have improved [10]. There is no doubt that aggressive surgical treatment has saved a large number of lives compared to medical therapy only; the ‘natural
such results are reproducible[4]. On the other hand, to prove other than documentation from multiple patient series that effect of this magnitude does not need further validation dissection.

efficacy studies have not yet been satisfied for aortic criteria). Thus, the demand for rigorously designed clinical tables represent the closest to fulfilling the inclusion questions in the affirmative (the studies presented in the provide unequivocal support to answer any of the three studies revealed that no high quality studies exist which standing controversy. Strict assessment of published principles of surgical treatment and surrounded by long analysis. The three questions addressed are central prin-

cipal follow-up are other limitations. Thus, despite the fact that five of the six studies did not demonstrate a statistically significant beneficial effect on survival of the open technique, this could easily have been due to a type II statistical error (lack of significance due to a small patient sample).

Whether or not an open distal technique should be routinely used could not be answered conclusively from the presently available publications. The six studies comparing the two most commonly applied techniques all have major structural weaknesses, and all used historical controls. The substantial advances that have occurred in cardiac surgery during this period [27] make the validity of using historical controls dubious, at best. Most available reports also lack necessary information related to patient selection and specific treatment methods; patient sample size, lack of truly long-term (10–15 years) outcome data, and incomplete follow-up are other limitations. Thus, despite the fact that five of the six studies did not demonstrate a statistically significant beneficial effect on survival of the open technique, this could easily have been due to a type II statistical error (lack of significance due to a small patient sample).

Likewise, whether or not a persistently patent down-
stream aortic false lumen adversely influences long-term outcome cannot be determined convincingly from existing data. The three studies which did include a control group could not demonstrate an adverse effect of a patent false

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### Table 3
Comparison between medical and surgical treatment of acute type B dissections

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke University Medical Center and Stanford University [21]</td>
<td>Retrospective case-control design Comparison of long-term outcome in selected surgically (group 1) and medically (group 2) treated type B dissections (both acute and chronic)</td>
<td>$N = 23$ (group 1); $N = 33$ (group 2); 1975–1988 subgroup of good risk patients (56/136)</td>
<td>5-year survival: group 1, 80%; group 2, 87%; 10-year survival: group 1, 50%; group 1, 32%; n.s. No difference within other subgroups with more general organ disease</td>
<td>No randomization. Selection at the discretion of the surgeon</td>
</tr>
<tr>
<td>The Mount Sinai Medical Center (Schor) 1996 [22]</td>
<td>Retrospective case-control design Comparison of long-term outcome in selected surgically (group 1) and medically (group 2) treated type B dissections</td>
<td>$N = 17$ (group 1); $N = 48$ (group 2); 1985–1995</td>
<td>1-year survival: group 1, 93%; group 2, 90%; 5 year survival: group 1, 68%; group 2, 87%; n.s.</td>
<td>No randomization. Selection at the discretion of the surgeon</td>
</tr>
<tr>
<td>University of Berne (Gysi) 1997 [23]</td>
<td>Retrospective case-control design Comparison of long-term outcome in selected surgically (group 1) and medically (group 2) treated type B dissections</td>
<td>$N = 38$ (group 1); $N = 187$ (group 2); 1980–1995 All patients</td>
<td>5-year survival: group 1, 85%; group 2, 76%; 10-year survival: group 1, 67%; group 2, 50%; $P &lt; 0.001$</td>
<td>No randomization. Selection at the discretion of the surgeon. Unequal group size in the comparison</td>
</tr>
<tr>
<td>Stanford University (Umana) 2002 [24]</td>
<td>Retrospective case-control design. Subgroup analysis using propensity scoring Comparing long-term outcome in selected surgically (group 1) and medically treated patients (group 2) with acute type B dissections</td>
<td>$N = 67$ (group 1); $N = 122$ (group 2); 1963–1999 Subgroup propensity: $N = 31$, surgical; $N = 111$, medical</td>
<td>Survival overall: 1 year, 71%; 5 years, 60%; 10 years, 35%; 15 years, 17%. No difference in survival, freedom from reoperation or freedom from aortic complications overall or in propensity matched groups</td>
<td>No randomization. Large time span. Small number of surgical patients eligible for propensity matching</td>
</tr>
</tbody>
</table>
lumen. These studies, however, either had unequal matching, were too small and/or included follow-up which was too short to address the question in a statistically sound manner. The notion of striving to eliminate flow in the distal aortic false lumen has been a mainstay of surgical treatment for acute aortic dissection for decades, and its potential merit has been mentioned in three papers published during the 1970s [28–30]; however, these papers were excluded from the screening process because they were published before 1980. Nonetheless, deficiencies in the design of these studies cannot answer conclusively whether or not a thrombosed false lumen significantly influences long-term outcome. Since it is intuitive that rigorous blood-pressure control and negative inotropic therapy might protect the distal aorta from dilating postoperatively, this important question still needs to be answered. Such information is even more important given that stent-grafting of patients with both acute type B [31] or chronic type B [32] aortic dissections is now being performed; in the chronic dissection cases especially, it is almost a certainty that the distal aortic false lumen will remain patent after stent-grafting due to mixing of blood through numerous flap fenestrations between the true and false lumens.

Lastly, only four studies were found that met our inclusion criteria which compared primary surgical and medical treatment of patients with acute type B aortic dissections, another long-standing controversy. Conservative medical treatment of most patients with uncomplicated acute type B dissections is the treatment of choice at most institutions around the world. The studies here are relatively small with no proper randomization; however, clear support for surgical treatment was not found in either. The natural history of patients with acute type B dissections is not quite as dismal as for those with acute type A dissections [25,26], and the surgical results are not better either [25,26]. Therefore, primary medical therapy for patients with uncomplicated acute type B aortic dissections probably has merit despite the lack of sound scientific proof. Improvement in surgical results [24,33] could well alter this.

Treatment of patients with aortic dissection has evolved to a refined surgical approach to replace the most life-threatening portions of the aorta, modulated by seasoned surgical judgment and Kirklin’s ‘plight-to-treat’ [34] in a disease with a grave natural prognosis. Future treatment refinements, including more prophylactic surgical and more less-invasive stent-graft-based interventions [31,32], will demand more rigorous documentation based on prospective multi-center registries [26] and, hopefully, multi-center, prospective randomized trials. The tremendous difficulties surrounding documentation of the efficacy of treatments in an uncommon and life-threatening disease, such as acute aortic dissection, should not prevent investigators in the field from refining clinical study designs in order to enhance scientific validity. The use of evidence-based principles in medicine is sadly not possible today based on the extant literature. It is our responsibility to improve data collection, study design, and statistical methodology; it can be accomplished.

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