Aortic valve preservation and repair in acute Type A aortic dissection†

Richard Saczkowski, Tarek Malas, Thierry Mesana, Laurent de Kerchove, Gebrine El Khoury and Munir Boodhwani

Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, ON, Canada
Department of Thoracic and Cardiovascular Surgery, Cliniques Universitaires St. Luc, Brussels, Belgium

Abstract

OBJECTIVES: Repair and preservation of the aortic valve in Type A aortic dissection (AAD) remains controversial. We performed a meta-analysis of outcomes for aortic valve (AV) repair and preservation in AAD focusing on long-term valve-related events.

METHODS: Structured searches were performed in Embase (1980–2013) and PubMed (1966–2013) for studies reporting AV repair or preservation in AAD. Early mortality and linearized rates for late mortality and valve-related events were derived. Outcome data were pooled with an inverse-variance-weighted random-effects model.

RESULTS: Of 5325 screened articles, 19 observational studies met the eligibility criteria consisting of 2402 patients with a median follow-up of 4.1 [range: 3.1–12.6 years, total 13 733 patient-years (pt-yr)]. The cohort was principally male (median = 68.1%, range: 39–89) with a median age of 59 (range: 55–68) years and Marfan’s syndrome was present in 2.5%. AV resuspension was performed in 95% of the patients and the remainder underwent valve-sparing root replacement (reimplantation = 2.5% and remodelling = 2.5%). Pooled early mortality rate was 18.7% [95% confidence interval (95% CI): 12.2–26.2%], and linearized late mortality rate was 4.7%/pt-yr (95% CI: 3.4–6.3). Linearized rate for AV reintervention was 2.1%/pt-yr (95% CI: 1.0–3.6), recurrent aortic insufficiency (>2+) was 0.9%/pt-yr (95% CI: 0.3–2.2) and endocarditis was 0.2%/pt-yr (95% CI: 0.1–0.5). The composite rate of thromboembolism and bleeding was 1.4%/pt-yr (95% CI: 0.7–2.2).

CONCLUSIONS: Patients surviving an AAD have a limited long-term survival. Preservation and repair of the aortic valve is associated with a moderate risk of reoperation, but a low risk of thromboembolism, bleeding and endocarditis.

Keywords: Aortic valve repair • Type A aortic dissection • Valve-sparing root replacement • Meta-analysis

INTRODUCTION

Patients with acute Type A aortic dissection (AAD) frequently present with varying degrees of associated aortic insufficiency (AI). In this setting, AI may be due to dilatation of the functional aortic annulus (typically the sinotubular junction) leading to leaflet malcoaptation, commissural disruption causing cusp prolapse or impingement of the leaflet by the dissection flap. In the majority of cases, the cusp tissue is normal and associated cusp pathology is observed infrequently.

Despite this, the decision to repair or replace the aortic valve can be a complex one and requires consideration of numerous factors. The primary objective of the operation is to save the patient’s life by eliminating the potentially fatal complications of rupture, coronary, cerebral and systemic malperfusion, and restoration of a functioning aortic valve. Attempts at aortic valve repair that significantly prolong myocardial ischaemic time, fail and require aortic valve (AV) re-exploration and increase the bleeding risk are therefore undesirable. On the other hand, these patients are often young and the vast majority will have to live with complex residual aortopathy. The risk of prosthetic valve-related events and lifelong anticoagulation may unnecessarily complicate their future management. Whether repair of the aortic valve reduces these risks is unclear. On the other hand, from a long-term perspective, many of these patients have competing risks of mortality and morbidity related to their aortopathy and therefore, the longevity of the AV repair may be a lesser concern.

In order to better inform this decision-making, we performed a systematic review and meta-analysis to determine early and late outcomes following aortic valve repair in the context of AAD. We focused on early mortality and morbidity, late mortality and valve-related events during follow-up.

MATERIALS AND METHODS

The systematic review and meta-analysis were performed using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.
Search strategy

One reviewer (Richard Saczkowski) performed structured searches of PubMed (1966–2013) and Embase (1980–2013) on 25 January 2013 using (aortic valve repair) OR (aortic valve reconstruction) OR (aortic valve preservation) OR (valve-sparing root replacement). The search results from each database were restricted to display human, adult and English language manuscripts prior to initial screening. A study was eligible for inclusion if it reported morbidity or mortality for aortic valve preservation or repair in AAD. An article was excluded if it had <100 patient-years (pt-yr) of follow-up or reported the results from a paediatric cohort. Two reviewers (Richard Saczkowski and Tarek Malas) screened title and abstract to identify articles for full-text review. The reference list of the included articles was screened to aid in the identification of relevant studies. No authors required contact for clarification of published data.

Data extraction and analysis

A standardized data extraction form was used and data were electronically captured using Microsoft Excel for Windows. One reviewer (Richard Saczkowski) transcribed data into the standardized collection form and a second reviewer (Tarek Malas) verified data accuracy. The Cohen’s Kappa statistic was used to assess inter-annotator data agreement and discrepancies were rectified through consensus.

Each study underwent methodological assessment with the Downs and Black checklist and assigned a study quality score [1]. Studies were awarded points according to a 27-question checklist focusing on specific methodological characteristics. The possible scores range from 0 to 32, where an increased score coincides with studies embodying enhanced methodological attributes.

Outcome events were catalogued according to prescribed definitions [2]. Patient-years were calculated for each study by multiplying the number of patients by the mean follow-up time. Institutions publishing multiple reports of the same patient population had a single article selected based on the largest number of pt-yr follow-up. Thromboembolic and bleeding events were infrequently reported separately in the manuscripts; therefore, the two outcomes were combined into a composite end point. Early mortality was expressed as a per cent. Late mortality and valve-related outcomes were linearized ([number of events/number of pt-yr] × 100). Studies reporting an outcome event rate of zero were approximated [1/(4 × sample size)]. Studies not reporting a specific outcome measure were excluded from that particular pooled estimate. Prior to meta-analytical pooling, data underwent the Freeman–Tukey double arcsine variance-stabilizing transform [3]. The DerSimonian–Laird inverse-variance-weighted random-effects model was used to derive pooled summary estimates [4]. This model was chosen because of anticipated heterogeneity and the between-study variance adjustment used during pooled calculations. Outcome measures were reported with a 95% confidence interval (95% CI). Heterogeneity was assessed with the Cochrane Q and I² statistics and was deemed present when I² > 50%.

Meta-regression was undertaken to ascertain study level predictors of early and late mortality. In addition, sensitivity analysis was also performed to determine whether the Downs and Black quality score altered the estimates of these two outcome measures. Recalculated early and late mortality pooled estimates were compared after allocating studies to ‘lower’ (≤20) and ‘higher’ (>20) quality score groups. Comparisons were performed with an unpaired t-test. Statistical significance was considered present with P < 0.05. Data extraction agreement between the two reviewers was 99.5% (Cohen-Kappa statistic 0.96, 95% CI: 0.89–1.00). Statistical analyses were performed with Stata 11 (College Station, TX, USA).

RESULTS

Identification of studies

The keyword search results of PubMed and Embase produced 5325 potential articles (Fig. 1). After removal of duplicate studies present in both search engines, 3507 unique articles remained. Further screening for relevance by title and abstract eliminated an additional 3299 papers. Two reviewers (Richard Saczkowski and Munir Boodhwani) performed a full-text review of the remaining 208 articles, which resulted in additional exclusions based on the following reasons: not an AAD cohort, publications of the same cohort from the same institution and <100 pt-yr of follow-up.

Study population

There were no randomized trials identified comparing aortic valve repair with replacement in the setting of AAD. Nineteen unique observational studies involving 2402 patients with a total of 13 733 pt-yr follow-up met the eligibility criteria and were included in the meta-analysis (Table 1). These studies reported a median follow-up time of 4.1 (range: 3–12.6 years) with a median follow-up completion rate of 97% (range: 74–100%). The majority of the population reviewed were male (median: 68%, range: 39–89%) and in their fifth decade of life (median: 59, range: 55–68 years). Marfan’s syndrome was present in 2.5% (range: 0–6.3%) of the population. Reoperative surgery was required in 3.2% (range: 0.7–7.7%) of patients, while 6.3% (range: 2–21%) of the population needed concomitant cardiac procedures (Table 2). Preoperative neurological deficits were reported at a rate of 9.3% (range: 1.4–31.7%).

Analysis of the procedure-related data revealed that the median cardiopulmonary bypass and cross-clamp times were 179 (range: 111–238) min and 101 (range: 44–171) min, respectively. AV resuspension was used exclusively in 100% of patients in 17 studies [5, 6, 8–11, 13–23]. The remaining two trials utilized a combination of resuspension, reimplantation and remodelling [7, 12]. As a result, AV resuspension was performed in 95% of patients, while the remainder underwent valve-sparing root replacement (reimplantation = 2.5% and remodelling = 2.5%). Intraoperative conversion to AV replacement occurred at a rate of 3.9% (range: 0–7.3%).

Mortality

Early mortality was reported in all 19 studies [5–23] with the definition varying among papers from 30, 60 and 90 days postoperatively up to hospital discharge. The pooled early mortality rate was 18.7% (95% CI: 12.2–26.2%, I² = 93%, P < 0.001). Late mortality was universally defined in the studies reviewed as death occurring after hospital discharge. The estimated pooled rate was 4.7%/pt-yr (95% CI: 3.4–6.3%, I² = 87%, P < 0.001), representing 1350 patients with 4928 pt-yr follow-up [5, 6, 8, 10–12, 14–23] (Fig. 2). Based on these rates, survival estimates at 5 and 10 years were 58 and 34%, respectively.

Meta-regression to determine whether study quality, population size, mean age and year of publication were predictive of
early or late mortality rates did not reveal any significant predictors (all \( P > 0.150 \)). A sensitivity analysis was undertaken to compare pooled early and late mortality estimates based on study quality. The recalculated early mortality estimates for studies with quality scores of \( \leq 20 \) (19.8\%, 95\% CI: 14.2–26.1) and \( >20 \) (18.2\%, 95\% CI: 13.2–23.7) were not significantly different \( (P = 0.758) \). Similar results were obtained for late mortality that were also not significantly different \( (P = 0.192) \) between quality scores of \( \leq 20 \) (5.4%/pt-yr, 95\% CI: 3.4–7.9) and \( >20 \) (3.2%/pt-yr, 95\% CI: 1.9–4.8).

### Valve-related events

Data for AV reintervention were categorized separately as early reintervention (≤30 days) and late reintervention (>30 days) based
Table 2: Surgical technique and valve-related outcomes

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Reoperation (%)</th>
<th>Concomitant cardiac surgery (%)</th>
<th>VSRR technique (%)</th>
<th>Early mortality (%)</th>
<th>Late mortality (%/pt-yr)</th>
<th>TE/BL (%/pt-yr)</th>
<th>AV reintervention (%/pt-yr)</th>
<th>OVE (%/pt-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dell'Aquila et al. [5]</td>
<td>2.2</td>
<td>6.9</td>
<td>100</td>
<td>34</td>
<td>2.4</td>
<td>-</td>
<td>5.9</td>
<td>-</td>
</tr>
<tr>
<td>Ro et al. [6]</td>
<td>-</td>
<td>6.6</td>
<td>100</td>
<td>5</td>
<td>3.9</td>
<td>-</td>
<td>1.7</td>
<td>-</td>
</tr>
<tr>
<td>Subramanian et al. [7]</td>
<td>7.7</td>
<td>-</td>
<td>100</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yamanaka et al. [8]</td>
<td>0.7</td>
<td>2.9</td>
<td>100</td>
<td>9.3</td>
<td>1.6</td>
<td>0.2</td>
<td>-</td>
<td>0.2</td>
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<tr>
<td>Piccardo et al. [9]</td>
<td>2.0</td>
<td>6.7</td>
<td>100</td>
<td>27.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Immer et al. [10]</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>17.1</td>
<td>4.9</td>
<td>-</td>
<td>1.6</td>
<td>-</td>
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<tr>
<td>Mastroprisco et al. [11]</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>19.6</td>
<td>2.4</td>
<td>1.3</td>
<td>-</td>
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<tr>
<td>Garibaldi et al. [12]</td>
<td>3.4</td>
<td>-</td>
<td>100</td>
<td>26.1</td>
<td>6.1</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
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<tr>
<td>Geirsson et al. [13]</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>8.1</td>
<td>-</td>
<td>-</td>
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<td>1.5</td>
<td>-</td>
<td>0.4</td>
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<tr>
<td>Westaby et al. [15]</td>
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<td>-</td>
<td>100</td>
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<td>-</td>
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<tr>
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<td>21</td>
<td>2.9</td>
<td>0.8</td>
<td>-</td>
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<tr>
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<td>13</td>
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<td>-</td>
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<td>21.5</td>
<td>100</td>
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<td>5.8</td>
<td>2.9</td>
<td>3.7</td>
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<td>13.5</td>
<td>100</td>
<td>25</td>
<td>10.9</td>
<td>-</td>
<td>8.4</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>100</td>
<td>21</td>
<td>8</td>
<td>-</td>
<td>3.1</td>
<td>-</td>
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<tr>
<td>von Segesser et al. [21]</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>24.8</td>
<td>7.7</td>
<td>1.5</td>
<td>4.4</td>
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<tr>
<td>Mazzucchi et al. [22]</td>
<td>4.3</td>
<td>-</td>
<td>100</td>
<td>30</td>
<td>3.7</td>
<td>0.3</td>
<td>2.7</td>
<td>-</td>
</tr>
<tr>
<td>Fann et al. [23]</td>
<td>-</td>
<td>6</td>
<td>100</td>
<td>13</td>
<td>6.8</td>
<td>3.4</td>
<td>1.7</td>
<td>0</td>
</tr>
</tbody>
</table>

OVE: operated valve endocarditis; TE/BL: thromboembolism and bleeding; VSRR: valve-sparing root replacement.
on the time from initial repair. Only a single study reported the early AV reintervention rate (0%) [17]. However, the 13 studies reporting late AV reintervention after initial repair had a pooled rate of 2.1%/pt-yr (95% CI: 1.0–3.6%, I² = 83%, P < 0.001) (Fig. 3) [5, 6, 10, 12, 13, 15, 17–23]. Based on these data, the freedom from AV reintervention was 89 and 79% at 5 and 10 years, respectively. The recurrence of significant AI (>2+) was reported in seven studies with an occurrence of 0.9%/pt-yr (95% CI: 0.3–2.2%, I² = 80%, P < 0.001) [8, 10, 11, 17, 18, 20, 22]. The estimated freedom from recurrent AI (>2+) was 95 and 86% at 5 and 10 years, respectively. The composite outcome of thromboembolism and bleeding had a pooled rate of 1.4%/pt-yr (95% CI: 0.7–2.2%, I² = 58%, P = 0.031) (Fig. 4) [8, 11, 14, 16, 18, 21–23]. The pooled rate of operated valve endocarditis was 0.2%/pt-yr (95% CI: 0.1–0.5%, I² = 79%, P < 0.001) [8, 9, 13, 14, 18, 21, 23]. None of the studies reviewed reported all of the recommended reporting categories for morbidity and mortality according to the described guidelines [3]; however, all of the studies reported at least one category.

**DISCUSSION**

Preservation and repair of regurgitant aortic valves in the setting of Type A dissection is controversial. There is a paucity of data on late survival and valve-related complications in these patients. In this meta-analysis, including 2402 patients and 13,733 pt-yr of follow-up, we observed an early mortality rate of 19% and a linearized late mortality rate of 4.7%/pt-yr, confirming that these patients have a
poor long-term survival. The incidence of thromboembolism and bleeding was low (1.4%/pt-yr). Linearized risk of AV reoperation was moderate at 2.1%/pt-yr, suggesting a 10-year freedom from reoperation rate of 78%. In summary, patients who survive following repair of a Type A aortic dissection and a preserved aortic valve have a limited long-term survival, moderate risk of reoperation and a low risk of valve-related complications. Decision-making related to the aortic valve in AAD needs to factor in the perioperative risks of mortality and morbidity, which may be affected by procedural complexity, as well as competing risks of late mortality related to residual aortopathy or other comorbid conditions. Other important considerations include the incidence of valve-related events and the risk of late aortic valve reoperation. A quick review of the surgical techniques reveals that a relatively simple surgical manoeuvre of AV resuspension was utilized as the only technique in the majority of studies and was effective in the short term in the majority of patients. There was, however, a moderate risk of reoperation of 20–25% at 10 years in these patients with a median time to reoperation of approximately 4 years. More complex valve-sparing root replacement procedures were only utilized to varying degrees in two studies. While it is plausible that valve preserving intervention on the aortic root, when performed by experienced teams, could improve the rate of AV reoperation, this would have to be carefully balanced with the risks of increasing surgical complexity and potentially increased myocardial ischaemic time. It is also likely that patients who had significant aortic root pathology selectively underwent composite aortic valve and root replacement and were, therefore, not eligible for inclusion in this meta-analysis.

A reassuring finding in this study is that the risk of valve-related events of thromboembolism, bleeding and endocarditis is low. This is consistent with and comparable to studies of elective AV repair patients [24, 25] and lower than what would be expected with mechanical aortic valve replacement. Furthermore, in those patients who do not require AV reoperation, the risk of recurrent AI is relatively low at 0.9%/pt-yr. Given the high competing risk of long-term mortality in these patients, a strategy of bioprosthetic aortic valve replacement would be justifiable, despite the young age of the patients. With a 10-year mortality risk of 66%, it is likely that the reoperation risk of prosthetic valve dysfunction would be acceptably low. However, a decision to replace or repair the aortic valve is an individually tailored one and should incorporate patient and disease factors, patient’s choice and the clinical context into the decision-making process.

Limitations

There are several limitations of this study. First, this meta-analysis combines the results of the selected cohort of patients in whom AV preservation and repair was deemed feasible. The results may, therefore, not apply to unselected patient cohorts. Secondly, the data included in this meta-analysis span over two decades of publications and evolution of surgical technique and medical management of these patients may affect the reported outcomes. Thirdly, data on valve-related outcomes were not consistently reported according to guidelines in all studies, leading to exclusion of some studies for certain end points. Finally, despite having a combined follow-up of over 13 000 pt-yr, median follow-up was 4.1 years and data beyond 10 years were available only in a small number of studies.

CONCLUSIONS

Aortic valve repair in AAD can be performed in most patients using aortic valve resuspension. Aortic valve repair is associated with a low risk of valve-related events and a moderate risk of reoperation. The high competing risks of long-term mortality in this patient population may be an important factor to consider selecting prosthesis type, should valve replacement be required. Longer-term data in this population are required to better inform decision-making.

Conflict of interest: none declared.
REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr M. Pocar (Milan, Italy): In the title of this presentation the term ‘valve repair’ sounds somewhat provocative since actually the population consists of root repairs with valve cusp preservation, obviously in acute type A dissection.

Two points. One of the limitations, as you partially pointed out, is that 95% of these patients received simple valve resuspension, and two studies actually included root replacement with valve-sparing, either reimplantation or remodelling. However, these represent only 5% of the population. So with this nonhomogeneous population I don’t know if you would have obtained different results if you removed from your analysis this 5% of patients. Actually the patients can be treated with simple resuspension. Obviously the first objective is to save the patient’s life, and more complex procedures are technically more demanding. However, especially the valve-related complications are extremely low in these two studies including the root replacement. So, might this relate to the technique, or to the surgical period? It is difficult to understand this from the data. And so at your institution what are the current indications and eventually the surgeon dependency of the indications in case of these life-threatening emergencies? Also, the degree of aortic regurgitation and root anatomy could not be extracted from the analysis of the data, and in this respect, what are your eventual indications for more aggressive root surgery with or without valve-sparing?

Question two. This was the main message of the paper: overall survival is quite poor, with roughly 60% at five years and 35% survival at 10 years. For this reason you suggest bioprosthetic devices in case you choose to replace the valve. Do you have any age cut-off to modify this? What do you do in very young patients? Might this possibly be dictated by the distal extension of the dissection? So if you anticoagulate the patients, what is the residual false lumen and so on?

Dr Boodhwani: To address your first question, the indication to perform a more complex repair than just a sinotubular junction remodelling is really the extension of dissection into the aortic root, number one, or pre-existing aortic root pathology, and these would be intuitive to any surgeon. I would reiterate that the primary objective in this type of situation is to save the patient’s life, and if your surgical technique is going to increase the myocardial ischaemic time or the bleeding risk, then you would be less likely to perform it. So I think there is an element of patient disease but also an element of surgeon comfort with application of these techniques, and this is a general algorithm that we would use.

The second question is use of a bioprosthetic valve. What is obvious, and it is sort of humbling, from this review is that the 10-year survival is only 34%. For any other patient in whom the 10-year survival was 34%, you would probably be leaning towards a bioprosthetic approach. So en masse you could say that that’s an appropriate approach for the patient. However, you may subselect certain groups who are very young, who have no significant comorbidities, and in whom you expect to have a longer survival, or those who have a very limited extension of their dissection in whom you would make the decision for a mechanical valve replacement.

Dr Pocar: But age per se is probably one of the determinants of late survival. So this might not be so homogeneous in the various ages.

Dr Boodhwani: I would just point out that the mean age in this population was 58. So we can use that as a guide.

Dr J. Bavaria (Philadelphia, PA, USA): First of all, congratulations on a very well done meta-analysis on a specific question, which is preserving the aortic valve during type A aortic dissection repair. Based on the fact that there are many groups out there now kind of advocating for aortic root replacement, whether it is a bioprosthesis or mechanical aortic root valve, as a definitive sort of proximal strategy for type A dissection, what is your comment on that based on your data that you have right there?

Dr Boodhwani: I would say that the piece of information that guides us most is that 2.1% per year risk of aortic valve or root intervention. So that’s the risk that you are accepting by leaving your aortic root intact and alone. As long as you don’t see any major pathology in the root, this is the risk that you are taking on. I think that’s what someone has to judge. Now, if your intervention, whether it be a Bentall procedure, a bioprosthesis or valve-sparing, increases your operative risk, then I don’t think it is worth taking on that risk for only a 2% per year risk of late reintervention.

Dr Bavaria: I tend to totally agree with that.