Standard of Care for the Management of Thoracic Aortic Disease: a Systematic Review and Meta-analysis

PROTOCOL INFORMATION

Protocol title and version

Protocol title: “Standard of care for the management of thoracic aortic disease: a systematic review and meta-analysis”

Protocol version: 1.3 Date: 01/12/2014

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CONFLICT OF INTEREST
None

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DATES
Anticipated or actual start date
01 December 2014

Anticipated completion date
31 August 2015

TYPE OF REVIEW
Epidemiologic; Intervention

LANGUAGE
English

COUNTRY
United Kingdom

KEYWORDS
Aorta, thoracic; Aortic aneurysm; Aortic dissection; Standard of care; Health care; Treatment outcome; Hospital volume; Hospital mortality.
PROTOCOL

INTRODUCTION

Rationale
Recent guidelines on diagnosis and management of thoracic aorta disease (TAD) have identified a knowledge gap with respect to the safest and most effective referral model/organisation of services for the management of TAD. Previous research has defined best quality care for many similar cardiovascular diseases, including abdominal aortic aneurysm. Considering the incidence of TAD and likely impact on patients, the public and the health service from variation in the level and quality of care, we attempted to analyse the existing evidence that relates to organisation of health services relating to TAD.

Key points
Thoracic aortic disease is term that refers to an interrelated collection of pathologies that include aneurysms, aortic dissections and atherosclerosis. These diseases are often silent and commonly present as life-threatening emergencies, referred to as acute aortic syndromes. In the United Kingdom (UK) the number of deaths attributable to TAD is increasing. Attempts to formulate consensus statements and relevant guidelines have identified significant gaps in knowledge with respect to the pathogenesis, appropriate management of, and configuration of clinical services for aortic disease. This results in high variability in the management of these patients, and presumably variation in the quality of care and outcomes. To address this knowledge gap, we propose to undertake a systematic review of the existing literature that relates to the organisation of thoracic aortic services and the impact this may have on clinical outcomes. A secondary aim is also to summarise the existing evidence as to the relationship between service configuration and outcome, identify areas of uncertainty or gaps in knowledge and highlight key areas for further research.

Description of the condition and the intervention
The term “thoracic aortic disease” includes a wide range of aortic diseases with variable clinical presentations and prognosis. The Global Burden Disease 2010 project demonstrated that the overall global death rate from aortic aneurysms and aortic dissection increased from 2.49 per 100000 to 2.78 per 100000 inhabitants between 1990 and 2010, with higher rates for men. At the same time, admissions for thoracic aortic aneurysms have increased from 4.4 to 9.0 per 100000 in the UK, mainly due to an increase in elderly patients, over 75 years of age.

The epidemiology of TAD is difficult to establish since aortic diseases may be diagnosed after a long period of subclinical development or they may have an acute fatal presentation. In addition, the natural history of TAD remains poorly understood, and errors in the diagnostic process may account for deaths otherwise attributed to other diseases such as myocardial infarction or pulmonary embolism. TADs are usually asymptomatic until an acute complication occurs, requiring a prompt diagnosis and treatment in specialized centres.

Management of TAD is complex and dictated by the size, extent and location of the disease condition as well as the underlying pathology (aneurysm or dissection). Options include conservative medical therapy (oral hypotensive agents such as beta blockers, ace-inhibitors, diuretics or statins) open surgical intervention, thoracic endovascular aortic repair (TEVAR), or hybrid procedures including epiaortic vessel debranching.
Early and late results also vary across centres and countries. In Europe and the wider world, mortality for operated type A dissection ranges from 19% to 42%. However, in some high-volume USA centers the mortality rate is lower, ranging from to 2 to 13%. On the other hand, hospital mortality from elective nondissection surgery on the thoracic aorta ranges from 5% to 10%. For patients suffering from acute type B aortic dissection, mortality for medical treatment approach, endovascular and open surgical repair ranges from 3% to 20%.

The knowledge gap
The 2010 American Heart Association (AHA) guidelines for the management of TAD include a level I recommendation for the “evidence-based referral” of TAD patients, limiting their care to large volume centres, with experienced physicians, and supporting teams. However, the evidence to support this recommendation is level C, based on the consensus of opinion of the experts and small studies, retrospective studies and registries. Similarly, the European Society of Cardiology (ESC) 2014 guidelines on TAD primarily consist of recommendations based on level C evidence. This contrasts with the evidence base for the management of other cardiovascular conditions.

There are several plausible reasons why service configuration may affect outcomes in TAD. The first of these relates to the volume or experience of centres or surgeons with the treatment of these complex patients. Operations on the thoracic aorta (mainly on the aortic arch and descending thoracic aorta) are challenging surgical procedures, with prolonged learning curves, for individuals and surgical teams. The availability and coordination of critical care, imaging and other treatment modalities are additional important considerations. Specifically it has been suggested that the availability of a specialist ‘aortic team’ to deal with TAD patients will result in better clinical outcomes. Previous data on patients with an abdominal aortic aneurysm, a complex pathology with subsequent morbidity and mortality similar to TAD, have indicated that volume and centre-experience are of crucial importance to subsequent outcomes, with a 13% estimated reduction in the odds of mortality for each additional 20 cases performed.

OBJECTIVE
The overarching aim of this review is to assess the interaction between the health service organisation and clinical outcomes in patients with TAD.

Primary objective
The primary aim of this review is to assess the interaction between center/unit volume (major thoracic aortic cases) and clinical outcomes in patients affected by TAD. The relationship between provider volume and operative outcomes (especially 30 days/in-hospital mortality) has been adopted as surrogate of healthcare quality in other cardiac areas including mitral valve reconstruction and off-pump myocardial revascularization.

Secondary objective
The secondary objective is to assess whether additional organisational aspects of care including: a) centralised emergency care for TAD (especially for acute aortic syndromes), b) integrated endovascular and surgical procedures, b) aortic teams or multidisciplinary thoracic aortic surgery programs, may influence clinical outcome in patients with TAD.
METHODS

Criteria for selecting studies for this review

Types of studies

Studies with quantitative, qualitative and mixed-methods approaches in order to obtain a comprehensive overview of the existing literature will be included (clinical randomized trials, observational prospective and retrospective cohort studies, case control studies, and cross sectional studies).

Study exclusion criteria

Exclusion criteria included:

• conference abstracts;
• books or grey literature.

Types of participants

The population of interest will include adult patients (age ≥16 years old) diagnosed with one of the following diseases:

• Thoracic/thoraco-abdominal aortic aneurysms (i.e. atherosclerotic and degenerative);
• Thoracic/thoraco-abdominal Aortic Dissection;
• Acute aortic syndromes (i.e. aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer, pseudoaneurysms of the thoracic aorta, traumatic rupture of the thoracic aorta);
• Thoracic aortic aneurysms and dissections associated with genetic syndromes (i.e. Marfan Syndrome, Loeys-Dietz Syndrome, Ehlers-Danlos Syndrome, Turner Syndrome).
• Thoracic aortic diseases associated with inflammatory syndromes (i.e. Takayasu arteritis and giant cell arteritis, Behçet disease, ankylosing spondylitis (Spondyloarthropathies), infective thoracic aortic aneurysms);
• Thoracic aortic diseases associated with other cardiovascular conditions (i.e. bicuspid aortic valve and associated congenital variants in adults, aberrant right subclavian artery, coarctation of the aorta, right aortic arch).

Exposures of Interest

Primary exposure of interest:

• High-volume hospital vs. low-volume hospital;

Secondary exposures of interest:

• High-volume surgeon vs. low-volume surgeon;
• Teaching hospital vs. non-teaching hospital;
• Urban hospital vs. rural hospital;
• Aortic team vs. no aortic team;
• Multidisciplinary thoracic aortic surgery program vs no program;
• Presence of cardiothoracic unit along with hybrid room;
• Open surgery vs. thoracic endovascular aneurysm repair (TEVAR) vs. medical therapy;

Types of outcome measures

A. Primary outcome measure: (all-cause) in-hospital/30-day mortality.
B. Secondary outcome measures:
• Neurologic complications (ischemic or haemorrhagic stroke, paraplegia, delirium);
• Renal dysfunction (acute renal failure, renal replacement therapy);
• Clinically significant bleeding defined as re-exploration for bleeding/tamponade;
• Length of stay in intensive care unit and/or in hospital.

**Search methods for identification of studies**

**Electronic searches**

The following databases (from inception to 31st December 2014) were explored:

• Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2014).
• MEDLINE (OvidSP, 1946 to December 2014).
• Embase (OvidSP, 1974 to December 2014).
• PubMed (e-publications only: searched December 2014).
• SCOPUS (1960 to December 2014)

No language restriction will be applied.

**Searching other resources**

The references of all identified trials, relevant review articles, and current treatment guidelines for further literature were also considered. These searches will be limited to the ‘first generation’ reference lists.

**Results of the scoping search**

A preliminary scoping search (PUBMED) using the terms [Aorta, thoracic] AND ([aortic aneurysm] or [aortic dissection]) AND ([Standard of care) or [health care] or [treatment outcome] or [hospital mortality]) accounted for 3,032 sources.

**Data collection**

**Selection of studies**

Three authors (GM, SM, AS) will screen all titles and abstracts of papers relevant to the review aims. Studies clearly not meeting the eligibility criteria will be excluded at that stage. Remaining studies will be assessed on the basis of their full text for inclusion or exclusion using the criteria indicated above. At this stage, three authors independently will assess eligibility. Disagreements will be resolved by consensus in discussion with a fourth reviewer (GJM). Numbers of studies assessed, included and excluded will be recorded. Duplicate reporting of studies will be assessed and documented.

**Assessment of Study Quality**

Three authors (GM, SM, AS) will independently assess the risk of bias in included studies by considering the following:

• Randomised trials (if any) will be assessed using the Cochrane Collaboration’s Risk of Bias tool, assessing randomization, sequence generation, concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors; incomplete outcome data, selective reporting of outcomes, and reporting of adherence to study protocol.
• Observational studies will be assessed using the Newcastle-Ottawa Scales (NOS) for cohort and case-control studies, which consist of 3 parameters for: selection (maximum 4 points), comparability (2 points), and exposure/outcome assessment (3 points). A maximum score of 9 points thus reflects the lowest risk of bias (highest quality). In addition, because of the quality scoring is controversial in reviews/meta-analyses of observational studies, all observational articles will be appraised according to the critical review checklist of the Dutch Cochrane Centre proposed by MOOSE.
Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a fourth review (GJM) author.

**Analysis of subgroups**

Subgroup analyses will be conducted to examine whether the effect of the health service and referral model varies by different diagnosis, group of patients, and type of surgery:
- Thoracic aortic aneurysms;
- Thoraco-abdominal aneurysms;
- Acute aortic syndromes;
- Teaching hospital vs. non-teaching hospital;
- Urban hospital vs. rural hospital;
- Aortic team vs. no aortic team;
- Multidisciplinary thoracic aortic surgery program vs no program;
- TEVAR vs. open surgical repair (OAR) procedures.

**Data synthesis and analysis**

A narrative synthesis of the included studies will be provided, focusing on the impact of center/unit volume to the hospital outcomes in order to identify the optimal service configuration/delivery for patients affected by TAD. Detailed tables of the findings from the included studies will be provided, with reference to the type of study (i.e. randomized, cohort studies, case control studies...), the study period, the inclusion/exclusion criteria, type of analysed outcomes, the presence of a specific thoracic program/protocol or project, and threshold definition for high vs low volume units. In addition, additional tables will be provided listing salient characteristics of each study, with reference to population age, gender proportions (male vs. female), comorbidity proportions (i.e. diabetes), number of treatment or control subjects, proportions of postoperative complications (i.e. stroke, re-exploration for bleeding, renal dysfunction, perioperative myocardial infarction, respiratory failure...), and length of hospital stay. Additional tables will summarize the attributable study (randomized or observational) points obtained by the Cochrane Collaboration’s Risk of Bias tool, Newcastle-Ottawa Scales (NOS) for cohort and case-control studies, and the checklist of the Dutch Cochrane Centre proposed by MOOSE. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes). Pooled adjusted odds ratios (OR) and (95% CI) will be estimated using both fixed-effects and random-effects models. Separate analyses for observational studies and/or randomized controlled trials will be conducted. Subgroup analyses will be performed by study design and type of outcomes. Heterogeneity will be assessed by Cochrane Q statistic, which will give a qualitative value and will be considered statistically significant for heterogeneity if a P value of less than 0.10 is obtained, and the I² statistic, which gives a quantitative measurement; I² values higher than 50% will be considered a reflection of severe heterogeneity.

Sensitivity analyses will be conducted to explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we will perform an exclusion sensitivity analysis where studies will be deleted one at a time. Results obtained with a fixed-effects model will be compared with those obtained with a random effects model. All calculations and graphs will be performed with the meta-analysis software Review Manager version 5.
REFERENCES

APPENDIX

Data extraction form

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## Intervention/Comparator

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## Outcomes/Results

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## Conclusions

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## Bias

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