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BALLOON DILATATION AND STENTING FOR AORTIC COARCTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: There is no systematic assessment of available evidence on effectiveness and comparative effectiveness of balloon dilatation and stenting for aortic coarctation.

Methods and results: We systematically searched four online databases to identify and select relevant studies of balloon dilatation and stenting for aortic coarctation based on *a priori* criteria (PROSPERO 2014:CRD42014014418). We quantitatively synthesized results for each intervention from single-arm studies, and obtained pooled estimates for relative effectiveness from pair-wise and network meta-analysis of comparative studies.

Our primary analysis included 15 stenting (423 participants) and 12 balloon dilatation studies (361 participants) including patients ≥10 years of age. Post-treatment blood pressure gradient reduction to ≤20mm Hg and ≤10mm Hg was achieved in 89.5% [95%CI 83.7-95.3] and 66.5% [44.1-88.9%] of patients undergoing balloon dilatation and in 99.5% [97.5-100.0%] and 93.8% [88.5-99.1%] of patients undergoing stenting, respectively. Odds of achieving ≤20mm Hg were lower with balloon dilatation as compared to stenting (odds ratio [OR] 0.105 [0.010-0.886]). 30-day survival rates were comparable.

Numerically more patients undergoing balloon dilatation experienced severe complications during admission (6.4% [2.6-10.2%]) compared to stenting (2.6% [0.5-4.7%]). This was supported by meta-analysis of head-to-head studies (OR 9.617 [2.654-34.845]) and network meta-analysis (OR 16.23, 95% credible interval 4.27-62.77) in a secondary analysis in patients ≥1 month of age including 57 stenting (3,397 participants) and 62 balloon dilatation studies (4,331 participants).

Conclusions: Despite the limitations of the evidence base consisting predominantly of single-arm studies, our review indicates that stenting achieves superior immediate relief of a relevant pressure gradient compared to balloon dilatation.

Key words: coarctation; balloon; stents; heart defects, congenital; meta-analysis

Introduction

Coarctation of the aorta is a congenital heart disease (CHD) that significantly reduces life expectancy [1,2] and is associated with increased morbidity even years after successful repair.[3,4] With an incidence of 3 to 4 cases per 10,000 live births,[5,6] aortic coarctation accounts for 5-8% of all congenital heart defects and is frequently associated with other CHD such as bicuspid aortic valve disease.[7]

After the initial treatment, ongoing monitoring of patients is recommended by the American Heart Association (AHA) and European Society of Cardiology (ESC) to detect relapse of the disease, disease progression and late complications.[8,9] Key clinical challenges that may persist post-repair include re-coarctation, persisting arterial hypertension, exercise-induced hypertension and subsequent sequelae with atherosclerosis and coronary artery disease as major cause of death.[10–12]

Two transcatheter interventions exist for treatment of aortic coarctation, balloon dilatation and stenting. Balloon dilatation involves positioning the deflated balloon across the stenotic site and subsequent inflation, stretching the intimal and medial layers of the aorta.[13,14] This mechanism bears the risk of damaging the aortic wall and can lead to aneurysm formation. Implantation of a stent across the coarcted segment possesses theoretical advantages over balloon dilatation, including lower risk for aortic wall injuries and more sustained relief of the obstruction.[7,15] It is not clear whether these theoretical advantages hold true, particularly in the long term. Aortic wall injuries and restenosis were also seen in patients undergoing stent implantation,[16] highlighting the need to assess the comparative effectiveness of balloon dilatation and stenting. Guidelines on the management of patients with aortic coarctation from both AHA[17] and ESC[9] do not provide recommendations on the choice of transcatheter interventions. Considerations regarding the effectiveness and safety of the treatment options are largely based on C-level (expert consensus) and only rarely on B-level (non-randomized) evidence.

The evidence available on the effectiveness and comparative effectiveness of balloon dilatation and stenting for aortic coarctation has not yet been collected systematically. Furthermore, no systematic comparison of the effectiveness of these two transcatheter interventions exists.

Methods

Study identification and selection

A review protocol was developed and subsequently made publicly available on the PROSPERO website of the University of York Centre for Reviews and Dissemination at the onset of our work (http://goo.gl/ZhXomV).[18] The review was set up to assess the effectiveness of balloon dilatation and stenting as well as their comparative effectiveness in the treatment of patients with aortic coarctation. The main parameters of our systematic review are summarized in Table 1.

We searched online databases MEDLINE (via PubMed), CINAHL Plus, EMBASE, and the Cochrane Library with search strings containing word and phrase match terms as well as database specific subject headings. The search strategy was constructed to find relevant articles on balloon angioplasty and stenting in aortic coarctation and is available in the online supplement. We additionally searched reference lists of four review articles [7,19–21] and three clinical practice guidelines.[8,9,17] We did not distinguish between different types of stents (e.g. bare metal; covered; balloon- and self-expandable).

Pre-defined inclusion criteria included head-to-head comparisons of balloon angioplasty and stenting. Given the paucity of comparative studies, we also included single-arm studies which did not use any comparator (‘case series’), as well as studies comparing one of the two relevant procedures to a third comparator, surgical repair.

Studies were eligible for inclusion if they had a minimum of 15 patients with native or re-coarctation per relevant study arm. We thus excluded very small studies but were still able to systematically capture the vast majority of evidence on this topic. We included studies published from 1990 through 2014 to limit the potential bias in treatment results originating from outdated knowledge and other contextual differences before that date. Stenting and balloon dilatation are considered treatment options mainly in adolescents and adults. For our primary analysis, we restricted the sample to studies and study arms including patients aged ≥10 years to capture the patient population for which both interventions are appropriate. For our secondary analysis, we relaxed the age restriction and included all studies including patients ≥1 month of age. We subjected the results of all secondary analyses to extensive sensitivity testing with respect to patient age.

We excluded studies that were not in English; published before 1990; did not report any of our pre-specified outcomes; or that were conducted in animals. We further excluded comments; editorials; letters; and conference abstracts.

Search results from the database searches were merged and obvious duplicates were removed. One researcher scanned articles at the title and abstract level for eligibility according to pre-specified inclusion and exclusion criteria. Full texts of articles deemed eligible were then independently assessed for inclusion by two researchers. Deviating decisions on eligibility were resolved by discussion and consensus between the two researchers. Each eligible study was then re-examined and pre-specified data were extracted independently by two researchers.

For the few studies with overlapping populations, we included the report with the most detailed or relevant data, or the most recent publication in order to maximize follow-up time. For larger studies, we contacted corresponding authors to ascertain whether study participants were indeed from the same cohort and used the information provided to exclude duplicate patients.

Outcomes

We report pre-specified outcomes as proportions of the total number of patients in each study arm. Our primary measure of immediate treatment success was the proportion of patients achieving a post-treatment blood pressure gradient ≤20mm Hg. We adopted this cut-off value because of its widespread use in the literature and because it is the threshold below which patients are generally not considered candidates for intervention according to AHA and ESC guidelines.[9,17] In addition, we used a second cut-off value, ≤10mm Hg, as a stricter criterion for treatment success, reflecting some skepticism towards establishment of treatment success through a gradient threshold that is just below treatment indication. Adapting the categorization proposed by Vitiello et al.,[22] we report the proportion of patients with (1) severe complications during intervention or before discharge, and (2) minor complications. Severe complications were defined as life-threatening events requiring immediate therapy; permanent functional or anatomic lesion; any aortic wall injury (dissection/ acute aneurysm); and unexpected major drug side effects. Minor complications included balloon rupture; stent migration; bleeding at access site; loss of femoral pulse; and other complications that were not deemed severe by study investigators. We further report 30-day survival rates, and the proportion of patients with reinterventions for restenosis or vascular complications related to the initial intervention at follow-up. We standardized reintervention rates in our analysis of single-arm studies to represent annual reinterventions per 100 patient-years of follow-up. Linearized reintervention rates were calculated as [events/(sample size*mean follow-up time)]*100. We then obtained separate pooled estimates of linearized reintervention rates for studies with mean follow-up time ≤1 year; between 1 and 3 years; and >3 years.

Although our data extraction included additional outcomes, lack of data precluded meaningful analysis.

Statistical analysis

Our primary analysis focused on patients ≥10 years of age. Studies in this age group included very small numbers of patients. We therefore relaxed the age restriction and broadened the eligible evidence base in secondary analyses, allowing for more precise estimates of treatment effectiveness and safety.

For both primary and secondary analyses, we conducted three types of statistical analyses. First, using information from all case series and study arms within one intervention type, we computed overall estimates for proportions of participants with any given outcome. We assessed statistical heterogeneity between study results using the I^2 statistic.[23,24] A fixed-effect model was used for outcomes with low between-study heterogeneity (I^2 <25%) and a random-effects model for outcomes with moderate to high heterogeneity (I^2 ≥25%), as recommended by the Cochrane Collaboration. For studies with a proportion of 0 or 1 for any given outcome, we imputed the average of the variances of the other studies to obtain an estimate of the variance.[25]

Second, we synthesised the results from comparative studies using pair-wise meta-analysis. In a similar fashion to our analysis of single-arm studies, we first visually inspected heterogeneity of results and then assessed between-study heterogeneity using the I^2 statistic. Informed by this, a fixed-effect or random-effects model was used to obtain odds ratios (OR) for each outcome, comparing the odds for each outcome (number of patients with event compared to patients without event) in patients undergoing balloon dilatation with the odds in patients undergoing stenting. Meta-analyses of single-arm and comparative studies were carried out in STATA, version 13.

Finally, we conducted network meta-analyses for studies including one or both interventions of interest and a third intervention, surgery for aortic coarctation. Unlike traditional pair-wise meta-analysis, which pools the results of direct head-to-head studies between two treatment options, network meta-analysis allows for the combination of both direct and indirect sources

of evidence to compare multiple treatments that may not have been directly compared to each other in head-to-head studies.[26] It combines the results of studies that compare treatments A vs. C and the results of studies that compare treatments B vs. C to indirectly estimate the comparative effectiveness of treatments A vs. B.

In this analysis, we were able to widen the evidence base for comparisons of balloon dilatation and stenting by including studies comparing either one of the two transcatheter interventions with surgery. The primary assumption of network meta-analysis is that the pooled studies are comparable in terms of relative treatment effect modifiers (i.e., in terms of variables that have a known influence on the outcomes).[27–29] We qualitatively evaluated the comparability of the studies included in the network meta-analyses in terms of key baseline characteristics and visually inspected the influence of these baseline variables on outcomes.

Our network meta-analysis model combined study-level treatment effects using Bayesian methods in WinBUGS.[29] This was based on modelling the outcomes in every treatment group of every study, and specifying the relations among the relative effects across studies making different comparisons. The model adopted random-effects, which took into account potential heterogeneity by assuming that each treatment was drawn from the same distribution whose mean and variance were estimated from the data. We present the results from network meta-analysis as OR and 95% credible intervals (CrI). Credible intervals indicate a 95% probability that the true OR falls within the observed range of estimates. If a 95% CrI does not include the null value 1.00, this can be interpreted as indicating <5% probability that there is no difference between the two intervention groups.

We only report the findings of network meta-analyses for which history plots suggested successful convergence in WinBUGS. In all network meta-analyses, we qualitatively evaluated the consistency of relative treatment effects obtained from both the single-arm and comparative studies. The consistency of the relative treatment effects were visually inspected for potential differences between estimates obtained from three sets of analyses.

We checked for discrepancy in terms of the direction of effect, as well as its magnitude, and confirmed that all 95% intervals greatly overlapped, which suggested adequate consistency.

Results

The literature search process is presented in the PRISMA flow chart with the number of articles screened and excluded at every stage (Figure 1). None of the studies including both balloon dilatation and stenting patients was a randomized controlled trial. The evidence base therefore primarily consists of single-arm studies for both stenting and balloon dilatation, including all the participants of case series and respective study arms from multiple-arm studies. There was a limited number of multiple-arm studies directly comparing the interventions of interest.

For the primary analysis, we identified 15 stenting studies or study arms with 423 participants, 12 balloon dilatation studies or study arms with 361 participants, 2 studies comparing the two interventions,[30,31] and 1 study comparing stenting with surgery[32] (Figure 2, Panel A. Full list of included studies provided in the online supplement). Mean follow-up time ranged from 1 to 12 years in balloon dilatation studies and from 10 months to 4.7 years in stenting studies. Single-arm studies for balloon dilatation were published between 1992 and 2009, and single-arm studies for stenting between 2001 and 2013. Comparative studies including both balloon dilatation and stenting patients were published in 2003 and 2005.

For the secondary analysis, we identified 57 stenting studies (3,397 participants), 62 balloon dilatation studies (4,331 participants). 7 studies compared the two interventions (5 studies with patients undergoing stenting or balloon dilatation and 2 studies including surgery as common comparator. Figure 2, Panel B). We obtained additional unpublished data for one of the comparative studies included in the secondary analysis directly from the authors.[33]

Exploration of differences between patients undergoing balloon dilatation and stenting

Baseline characteristics for patients undergoing balloon dilatation and stenting are shown in Table 2. Statistically significant differences were found in pre-treatment blood pressure gradient and the proportion of patients with native/recurrent coarctation between groups.

For variables that were statistically significantly different between groups, and other variables that were considered to have a systematic effect on outcomes, we constructed forest plots to examine any potential effect on four key outcomes: proportion of patients achieving a gradient reduction ≤20mm Hg; proportion achieving a gradient reduction ≤10mm Hg; 30-day mortality; proportion of patients with severe complications before discharge. An example is Figure 3 [30,30,30,30,31,31,31,31,34,34,35,35,36,36,37,37,38,38,39,39,40,40,41,41–43,43,44,44,45,45,46,46,47,47,48,48,49,49,50,50], which demonstrates that for both interventions, average pre-treatment blood pressure gradient (Panel A) and proportion of patients with native coarctation (Panel B) do not systematically influence the proportion of patients with successful treatment. Further exploration of the effect of patient baseline characteristics on key outcomes is provided in the online supplement (Figures S1-S12). We also assessed the impact of mean age and found no discernible systematic effect on the four outcomes. We therefore pooled the results of individual studies.

Results from single-arm studies

Figure 4 shows pooled results and 95% CIs for each outcome in single-arm studies. Treatment success before discharge was more often achieved in patients undergoing stenting compared to balloon dilatation. The proportion of patients achieving post-treatment gradient ≤20mm Hg was 0.895 (95%CI 0.837-0.953; I^2 56.7%) in balloon dilatation studies vs 0.995 (95%CI 0.975-1.000; I^2 0.0%) in stenting studies, and proportion of patients achieving post-treatment gradient ≤10mm Hg was 0.665 (95%CI 0.441-0.889; I^2 93.2%) in balloon dilatation studies vs 0.938 (95%CI 0.885-0.991; I^2 0.0%) in stenting studies.

For the proportion of patients with severe complications before discharge we obtained a pooled estimate of 0.064 (95%CI 0.026-0.102; I^2 31.3%) for patients undergoing balloon dilatation and 0.026 (95%CI 0.005-0.047; I^2 0.0%) for patients undergoing stenting. Pooled estimates for the proportion with minor complications before discharge were 0.128 (95%CI 0.012-0.244; I^2 91.0%) for patients undergoing balloon dilatation and 0.073 (95%CI 0.041-0.106; I^2 7.8%) for patients receiving stents.

All patients undergoing balloon dilatation in the identified studies survived at 30 days and the pooled estimate for patients undergoing stenting was 0.999 (95%CI 0.988-1.000; I^2 0.0%).

At follow-up, the pooled estimates for the proportion of patients with reinterventions for re-coarctation or vascular complications related to the initial intervention were 0.061 (95%CI 0.026-0.096; I^2 0.0%) for patients undergoing balloon dilatation and 0.085 (95%CI 0.039-0.131; I^2 60.5%) for patients undergoing stenting. The pooled linearized reintervention rate was 0.9 (95% CI 0.3-1.4; I^2 0.0%) per 100 patient-years of follow-up for patients undergoing balloon dilatation and 3.3 (95% CI 1.6-5.0; I^2 37.5%) per 100 patient-years for patients undergoing stenting.

Results from comparative studies

Figure 5 shows pooled OR and 95% CIs for comparative studies. Patients undergoing balloon dilatation were significantly less likely to achieve treatment success compared to patients undergoing stenting as measured by the proportion of patients achieving a blood pressure gradient ≤20mm Hg (OR 0.105, 95%CI 0.010-0.886; I^2 0.0%).

No statistically significant difference was found for minor complications before discharge (OR 0.669, 95%CI 0.035-12.742; I^2 58.9%).

Focusing on the two main indications for reinterventions at follow-up the pooled OR included 1.00, but suggested a tendency towards increased risk after balloon dilatation. The OR for re-coarctation at follow-up in patients undergoing balloon dilatation vs. stenting was 7.010

(95%CI 0.794-61.92; I^2 0.0%), and the OR for aortic wall injuries at follow-up was 3.340 (95%CI 0.477-23.367; I^2 0.0%).

Secondary analysis

In the extended sample, including studies with patients <10 years of age, we found statistically significant differences in patient baseline age, weight, and pre-treatment gradient (Table S1 in online supplement). However, forest plots did not indicate a systematic impact of patient baseline characteristics on key outcomes (Figures S13-S24).

Compared to the primary analysis, pooled estimates of single-arm studies in the secondary analysis were generally more precise and showed less favorable results, but confirmed the overall direction of effect in stenting vs. balloon dilatation studies in all but two outcomes (Figure 4). The pooled linearized reintervention rate did not show a significant difference between balloon dilatation (3.8 events per 100 patient-years of follow-up, 95% CI 2.9-4.7; I^2 81.6%) and stenting (5.4 events, 95% CI 4.1-6.7; I^2 78.8%). A higher proportion of patients had re-coarctation at follow-up after balloon dilatation (0.165, 95% CI 0.136-0.194; I^2 77.1%) compared to stenting (0.048, 95% CI 0.029-0.067; I^2 54.2%).

For comparative studies, the secondary analysis confirmed the results of the primary analysis with more precise estimates (Figure 5). Due to data availability, we were also able to analyze additional outcomes. While the OR for the primary criterion of treatment success (blood pressure gradient ≤20mm Hg) included 1.00 (OR 0.663, 95%CI 0.358-1.229; I^2 40.3%), the stricter threshold of ≤10mm Hg was statistically significantly less likely to be achieved by patients undergoing balloon dilatation compared to patients undergoing stenting (OR 0.435, 95%CI 0.320-0.591; I^2 20.3%). The pooled OR of patients undergoing balloon dilatation with severe complications before discharge compared to patients undergoing stenting was 9.617 (95%CI 2.654-34.845; I^2 53.9%), indicating considerably higher rate of complications in balloon studies. Comparing the odds of reinterventions at follow-up in

patients after balloon dilatation to the odds after stenting, the OR was 0.65 (95%CI 0.38-1.10; I^2 0.0%).

Results from network meta-analysis

Network meta-analysis could only be conducted for the extended sample of studies because of limited data availability. We did not obtain precise estimates for the comparative effectiveness of balloon dilatation and stenting for all outcomes. We therefore only report the results for three outcomes for which our analyses achieved convergence.

Using surgery as a common comparator, we observed higher odds for experiencing severe complications before discharge in patients undergoing balloon dilatation compared to patients undergoing stenting (OR 16.23, 95%CrI 4.27-62.77). The majority of severe complications in balloon dilatation and stenting patients consisted of damages to the aortic wall.

In terms of minor complications, we found no statistically significant difference between the two interventions of interest: OR for patients undergoing balloon dilatation vs stenting 0.95 (95%CrI 0.23-4.16). Similarly, we found no statistically significant difference between the two transcatheter interventions for reinterventions at follow-up (OR patients undergoing balloon dilatation vs stenting 0.70, 95%CrI 0.35-1.28).

Sensitivity analysis

Results of sensitivity analyses are available in the online supplement.

To test the sensitivity of our comparative effectiveness results to potential overreporting of desirable and underreporting of undesirable events in case series, we obtained pooled estimates for each outcome excluding (1) the study reporting the most favorable results, and (2) the two studies reporting the most favorable results. We did not find materially different results for the comparative effectiveness of stenting and balloon dilatation (Figure S25 in the online supplement).

We plotted study publication year against the proportion of patients with post-treatment gradient ≤20mm Hg and linearized reintervention rate to study the potential impact of advanced technology and experience. We did not detect systematically better results in more recent studies (Figures S27 and S28 in the online supplement).

Discussion

Immediate and follow-up outcomes

The ultimate aim of coarctation treatment has traditionally been the complete relief of a pressure gradient.[51] While both treatments were capable of reducing the pressure gradient in patients aged ≥10 years, stenting was more frequently associated with a gradient reduction to ≤20mm Hg and ≤10mm Hg in our analyses and thus showed better immediate relief of the stenosis compared to balloon dilatation.

We observed a tendency towards higher risk of severe complications during intervention or before discharge after stenting compared to balloon dilatation in our primary analysis. This finding was amplified when we included patients below 10 years of age in our secondary analysis. Our results, which highlight the advantage of stenting with respect to patient safety, confirm and extend the findings reported by the studies of the Congenital Cardiovascular Interventional Study Consortium (CCISC).[51–53] Our results were consistent across the three types of statistical analysis conducted (meta-analysis of case series; pairwise meta-analysis; and network meta-analysis). Severe complications consisted of damages to the aortic wall in most cases. Other severe complications were rare.

Sustained relief of the obstruction and therefore the prevention of recurrent coarctation is an often-cited advantage of stenting.[31] Accordingly, a lower number of reinterventions for recurrent coarctation could be expected. Contradicting this theoretical advantage, we found no statistically significant difference in the proportion of patients with reinterventions at follow-up. The reason to re-intervene is not consistently reported across the studies, and

different arguments could lead to reintervention in the balloon dilatation group (e.g. restenosis due to growth in younger patients) than in the stenting group (e.g. neo-intimal proliferation). In comparison to balloon dilatation, less need for re-coarctation repair could be offset by the need for stent redilatation, which would only reflect a planned staged repair approach in very few patients with sub-atretic coarctation.

Even after successful stenting gradients frequently remain. The shape of the entire anatomical region as well as flow features can show an impact. While current guidelines recommend reintervention once gradient thresholds are reached, Computational Fluid Dynamic simulations carry the potential for more personalized decision making in the future.[54,55]

Overall, our results focusing on short and mid-term outcome may be seen as clear arguments towards stent placement. However, the issue of long term outcome has only incompletely been studied and remains more difficult to assess. Considering that most children undergo their first intervention at infancy or early childhood, long term consequences will be affected by placement of material that was originally planned for smaller vascular anatomy. Criteria for the decision of which treatment to use include patient age, history, and anatomy of the coarcted segment.[19,30] This suggests that a 'one treatment fits all' approach is not appropriate. Stent repair seems to be a preferred method in adults and older children, while its use in infants and younger children will be to bridge the time to surgical repair.

State of the evidence

There is widespread consensus that randomized controlled trials (RCTs) are the gold standard for establishing the effectiveness and safety of clinical interventions.[56] However, in our systematic review we found no RCT comparing balloon dilatation and stenting. We found that over 7,700 patients have been treated in the major clinical centers by either balloon dilatation or stenting for aortic coarctation over the last 25 years, and yet the evidence base

for interventional treatment for this condition is confined to mostly small case series and few large collaborative observational studies. Previous collaborative efforts such as the CCISC[51] and the Valvuloplasty and Angioplasty of Congenital Anomalies Registry (VACA)[57] have shown that pooling patient data from a considerable number of centers is feasible. Such future collaborations across centers, regions, and countries would significantly improve the current state of evidence on the effectiveness of treatment alternatives for aortic coarctation and generate much needed information regarding the comparative effectiveness of balloon dilatation and stenting in this patient population, ideally using more rigorous study designs such as RCTs.

Our systematic review and meta-analysis shares the limitations of the individual studies. Due to a clear lack of controlled studies in the literature, we included case series which rank low in the hierarchy of evidence.[58] Indeed, even when using control groups, observational study designs are susceptible to bias in several ways.[59] One particular area of concern in our review was potential selection bias, as allocation of patients to a given treatment was at the cardiologist's discretion. However, our extensive sensitivity studies suggested that, while there are some differences in patient characteristics between studies evaluating balloon dilatation and stenting, these do not seem to systematically affect the outcomes. Our exploration of the potential impact of patient characteristics on outcomes was limited to the study level and it is therefore possible that confounding effects at the individual patient level were concealed. In our secondary analysis, the lowest mean age in stenting studies was 8 years, while it was around 1 month in balloon dilatation studies. Although we did not find a detectable effect of mean age on key outcomes, we cannot fully rule out a confounding effect in stenting patients of very young age in these secondary analyses. The findings therefore cannot necessarily be applied to young patients.

In our network meta-analysis we made use of surgery as a common comparator between our two interventions of interest. Surgery for aortic coarctation may not be used in the same patients as balloon dilatation and stenting.[19] However, this is not necessarily a limitation of

our network meta-analysis. Similar characteristics of patients eligible for surgical intervention ensured that the common comparator was consistent across different studies included in the network meta-analysis. Nevertheless, we do not report the results of our network meta-analysis as the base-case. Rather, these findings support and extend the findings of our analyses based on single-arm and comparative studies.

Despite significant between-study heterogeneity in the evidence base, we decided to pool study results to gain insight about their comparative effectiveness. Applying narrative rather than quantitative synthesis can be misleading as it does not provide a clear approach towards heterogeneity.[60] Exploring heterogeneity in study results, we found that patient characteristics that could potentially impact on outcomes did not explain the observed variability.

Due to data availability, reporting limitations and inconsistencies, the list of outcomes reported in this paper does not include all outcomes that were prespecified in our review protocol.

In conclusion, our review suggests that stenting achieves better immediate relief of aortic coarctation. In addition, we found some evidence that patients undergoing stenting may experience fewer severe complications during their hospital admission compared to those undergoing balloon dilatation.

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Disclosures

None.

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Figures

Figure 1: PRISMA flow chart of study inclusion and exclusion

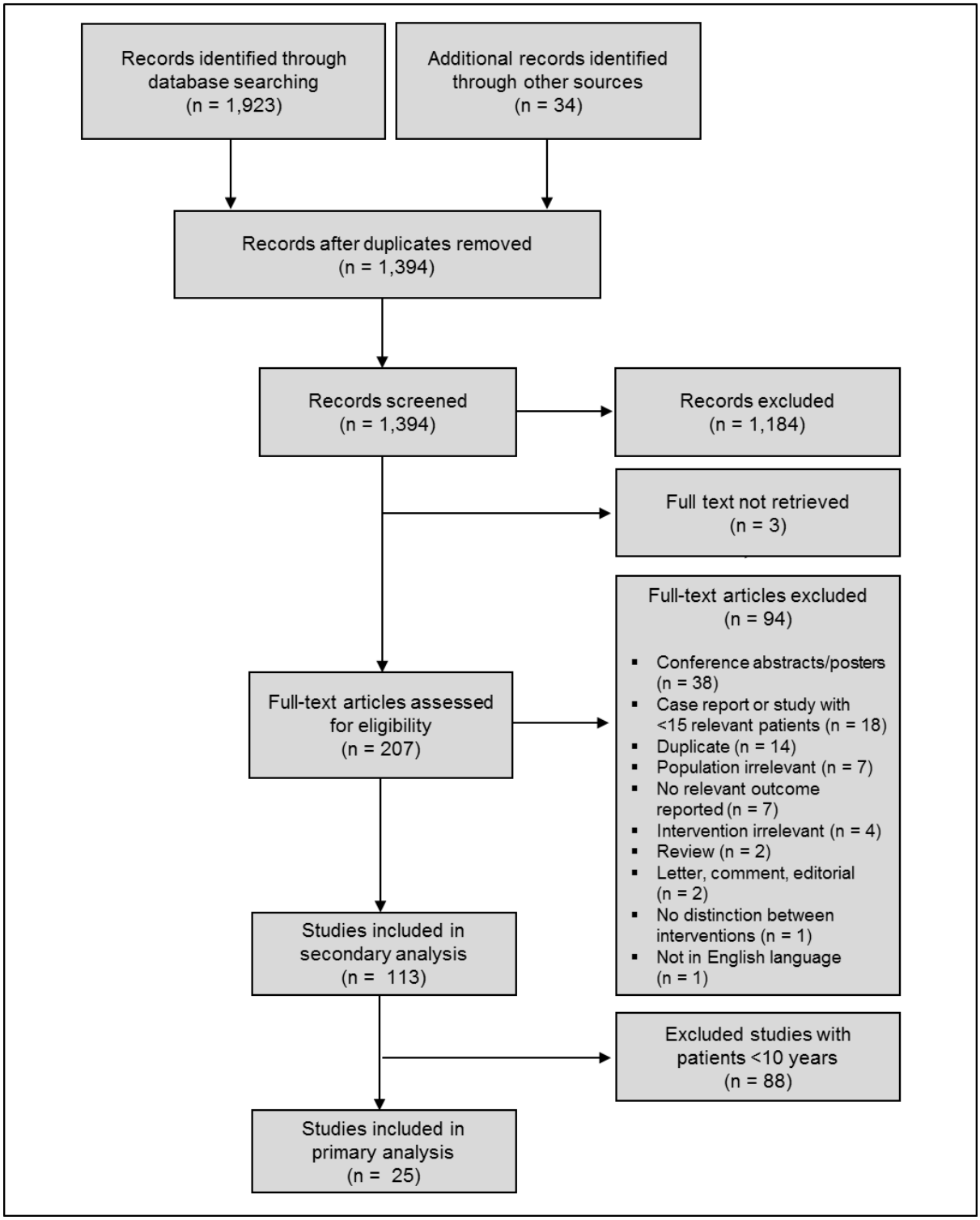
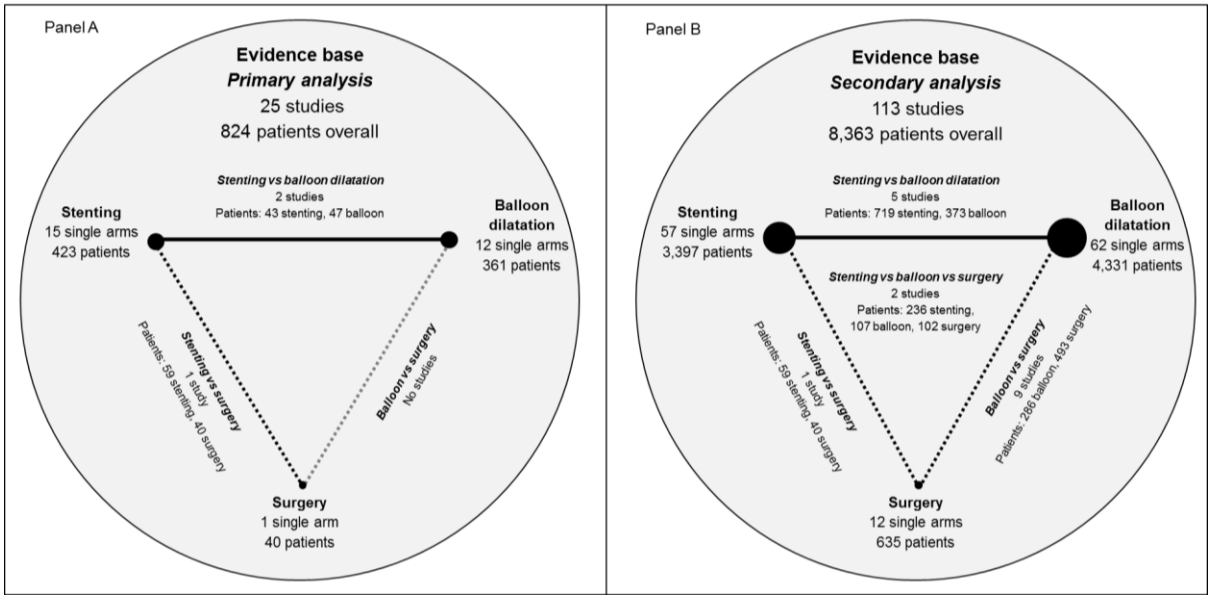


Figure 2: Network of evidence



The nodes show different treatment strategies (i.e., stenting, balloon dilatation, and surgery). The lines connecting the nodes indicate the few studies that directly compared two interventions to each other. The size of the nodes is proportional to the number of patients that received a particular treatment.

Panel A: network of evidence for primary analysis. Panel B: network of evidence for secondary analysis.

Figure 3: Effect of patient baseline characteristics on immediate treatment success

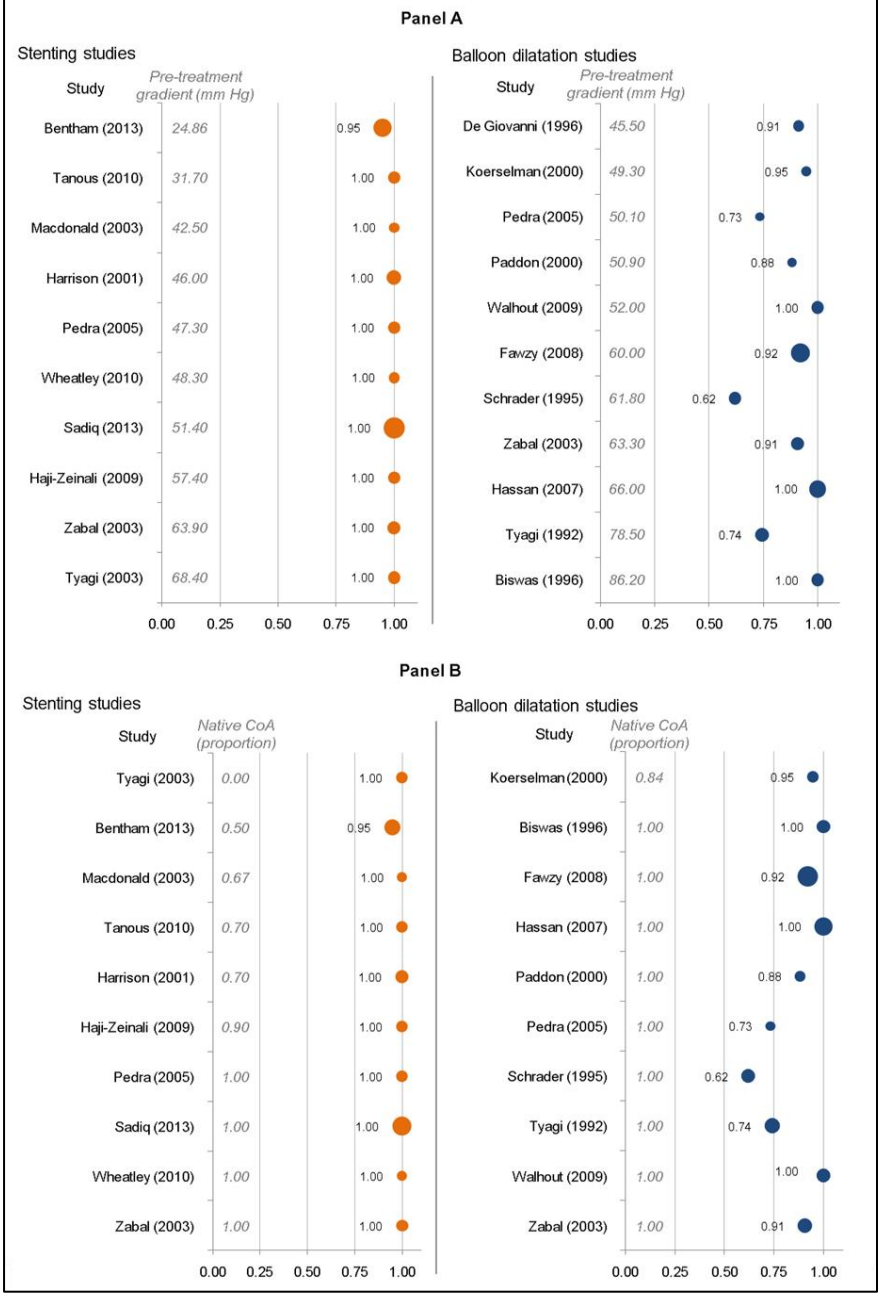


Figure shows the proportion of patients achieving blood pressure gradient ≤20mm Hg in single-arm studies (orange bubbles: stenting; blue bubbles: balloon dilatation). Each bubble represents one study, with bubble size representing study sample size.

Panel A: Studies are ranked by ascending peak pre-treatment blood pressure gradient.

Panel B: Studies ranked by ascending proportion of patients with native aortic coarctation.

Figure 4: Results from single-arm studies

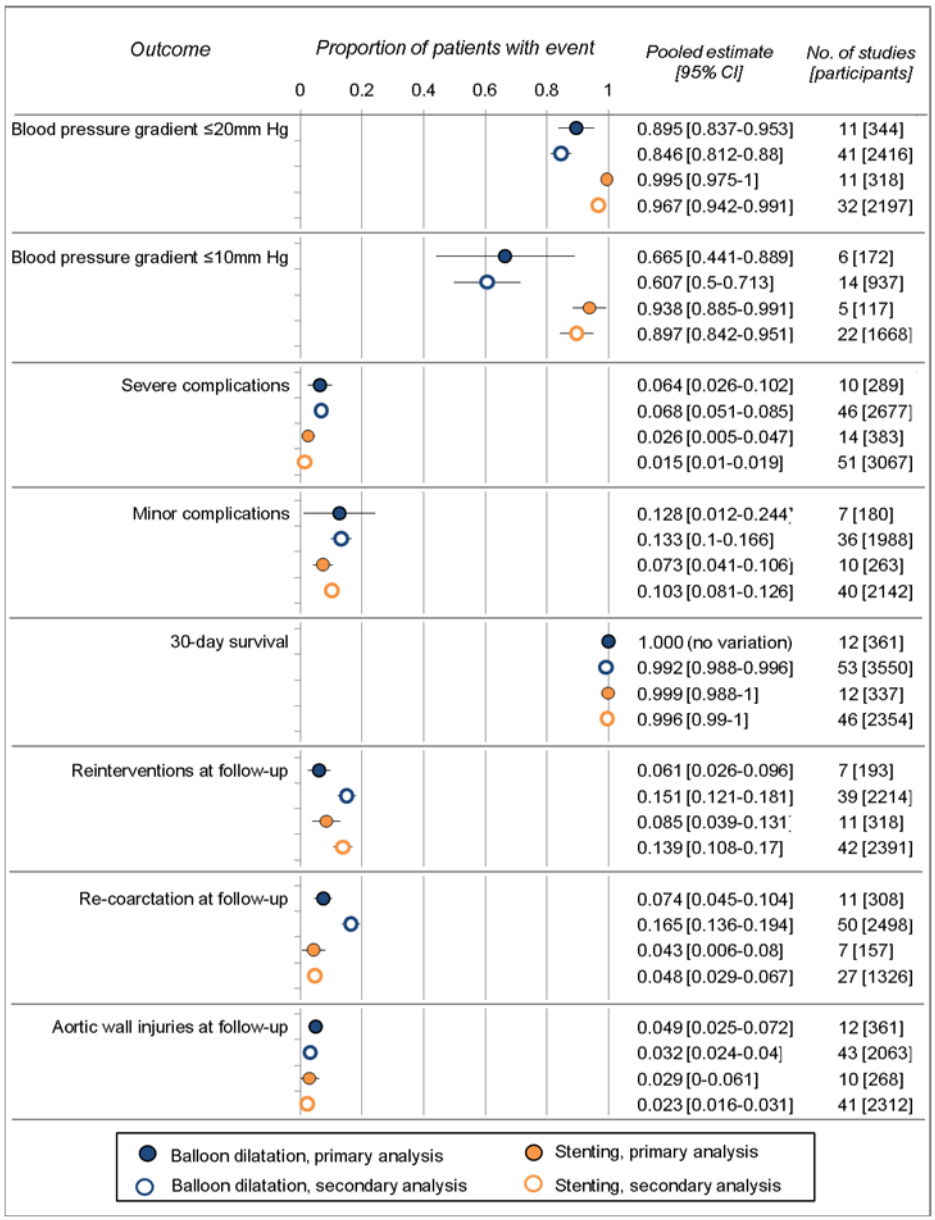
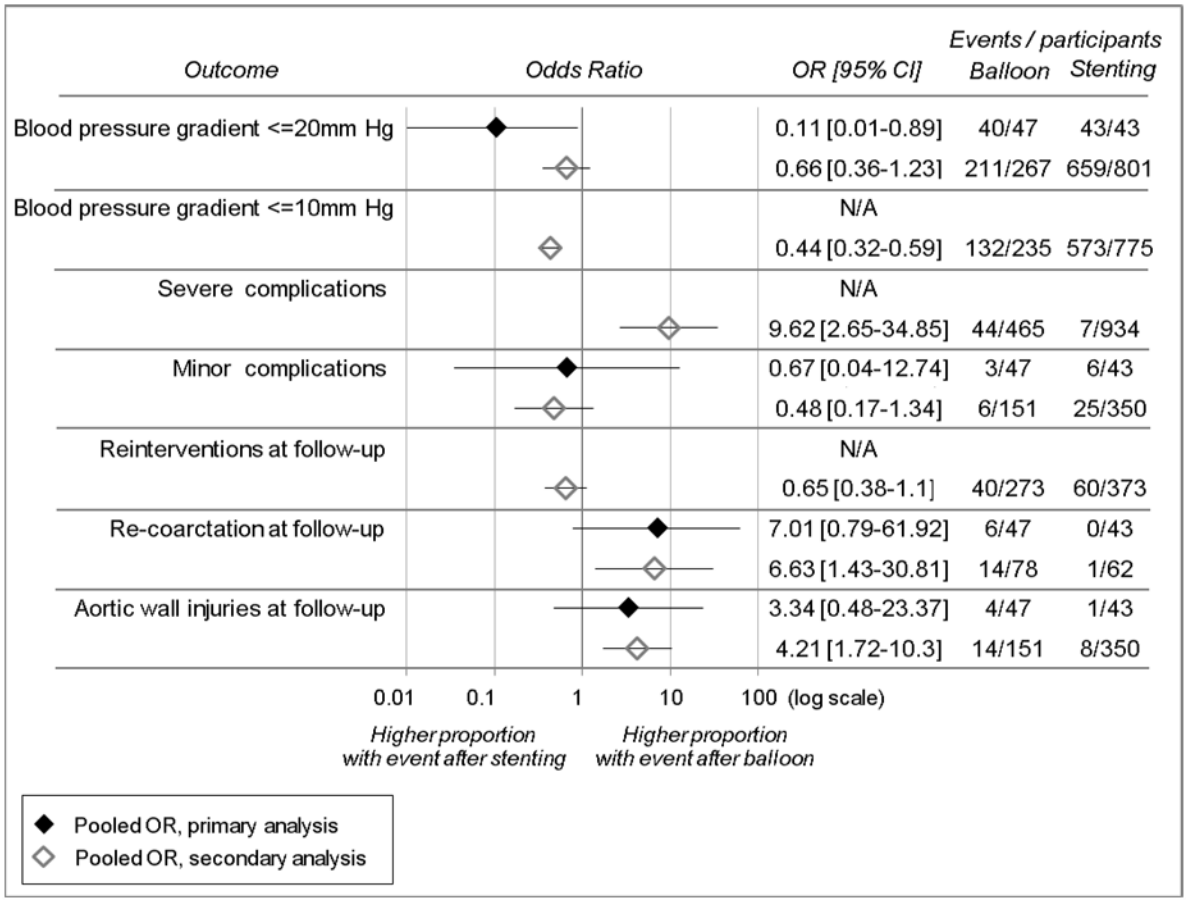


Figure shows pooled estimates and 95% CI of the proportion of patients with any given outcome for balloon dilatation and stenting studies obtained from primary (full circles) and secondary (empty circles) analysis.

Figure 5: Results from comparative studies



OR and 95% CI for comparative studies showing odds of patients with any given outcome in balloon dilatation vs. stenting study arms. Full diamonds represent estimates obtained from primary analysis, and empty diamonds estimates from secondary analysis.

Tables

Table 1: PICOS table

P I C O S	
Patient population	• Patients with native or recurrent coarctation of the aorta ≥10 years of age (primary analysis) • Patients with native or recurrent coarctation of the aorta ≥1 month of age (secondary analysis)
Interventions	• Balloon dilatation • Stenting
Comparators	• Any comparator
Outcomes	• Proportion of patients with post-treatment blood pressure gradient ≤20mm Hg • Proportion of patients with post-treatment blood pressure gradient ≤10mm Hg • Proportion of patients alive 30 days after treatment • Proportion of patients with severe complications during intervention or before discharge • Proportion of patients with minor complications during intervention or before discharge • Proportion of patients with reinterventions at follow-up • Proportion of patients with recurrent coarctation at follow-up • Proportion of patients with aortic wall injuries at follow-up
Study designs	• Any study design

Table 2: Patient baseline characteristics in all included studies

CoA: coarctation of the aorta; AVD: aortic valve disease; VSD: ventricular septal defect; PDA: patent ductus arteriosus
*** significant at the 1% level; ** 5% level; * 10% level

	Balloon dilatation		**Stenting**		*t-test for statistical difference*
		Studies reporting variable [participants]		*Studies reporting variable [participants]*	*p-value*
Patients overall	361		423		
Mean age (years)	26.65	*12 [361]*	28.82	*15 [423]*	0.355
Mean weight (kg)	51.80	*1 [15]*	59.37	*5 [163]*	0.480
Children patients	1.7%	*8 [181]*	1.6%	*8 [173]*	0.930
Adult patients	97.7%	*6 [134]*	97.9%	*6 [130]*	0.930
Gradient pre-treatment (mm Hg)	59.47	*12 [361]*	45.41	*13 [339]*	0.013**
Patients with native CoA	98.6%	*11 [338]*	75.6%	*14 [364]*	0.012**
Patients with recurrent CoA	1.4%	*11 [338]*	24.4%	*14 [364]*	0.012**
Patients receiving antihypertensive medication	60.7%	*9 [234]*	77.7%	*9 [198]*	0.103
Concomitant heart defects					
Patients with isolated CoA	64.2%	*4 [140]*	54.7%	*3 [60]*	0.579
Patients with AVD	37.2%	*9 [271]*	44.9%	*10 [256]*	0.616
Patients with VSD	8.7%	*7 [225]*	7.3%	*6 [157]*	0.734
Patients with PDA	4.2%	*4 [90]*	11.3%	*4 [117]*	0.177
Patients with other concomitant genetic heart defects	3.8%	*6 [218]*	20.9%	*8 [216]*	0.093*