Rival, P. M., Moore, T. H. M., McAleenan, A., Hamilton, H., Du Toit, Z., Akowuah, E., Angelini, G. D., & Vohra, H. A. (2019). Transthoracic clamp versus endoaortic balloon occlusion in minimally invasive mitral valve surgery: a systematic review and meta-analysis. *European Journal of Cardio-Thoracic Surgery*, *56*(4), 643-653. https://doi.org/10.1093/ejcts/ezy489

Transthoracic clamp versus endo-aortic balloon occlusion in minimally invasive mitral valve surgery: a systematic review and meta-analysis

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Word count: 6500

Visual abstract:

Key question: Is trans-thoracic clamping safer than endo-aortic balloon occlusion in minimally invasive mitral valve surgery?

Key findings: We found similar rates of cerebrovascular accident and survival between the two approaches.

Take home messages: At present there is little evidence to support one technique over another. A randomised controlled trial is needed.

Abstract

This systematic review and meta-analysis aims to determine outcomes following aortic occlusion with the transthoracic clamp (TTC) versus endoaortic balloon occlusion (EABO) in patients undergoing minimally invasive mitral valve surgery (MIMVS). A subgroup analysis compares TTC to EABO with femoral cannulation separately from EABO with aortic cannulation. We searched Medline and Embase up to December 2018. Two people independently and in duplicate screened title and abstracts, full-text reports, extracted data and assessed risk-of-bias (ROB) using the Cochrane ROB tool for non-randomised studies. We identified 1564 reports from which 11 observational studies with 4181 participants met the inclusion criteria. We found no evidence of difference in the risk of post-operative death or cerebrovascular accident (CVA) between the two techniques. Evidence for a reduction in aortic dissection with TTC was found: 4/1590 for the TTC group versus 19/2492 for the EABO group (RR, 0.33, 95% CI, [0.12] to [0.93], p=0.04). There was no difference in aortic cross-clamp (AoX) time between TTC and EABO (mean difference [-5.17] minutes, 95% CI, [-12.40] to [2.06], p=0.16). TTC was associated with a shorter AoX time compared to EABO with femoral cannulation (mean difference [-9.26] minutes, 95% CI, [-17.00] to [-1.52], p=0.02). EABO with aortic cannulation was associated with a shorter AoX time compared to TTC (mean difference [7.77] minutes, 95% CI, [3.29] to 12.26], p<0.001). There was no difference in cardio-pulmonary bypass (CPB) time between TTC and EABO with aortic cannulation (mean difference [-4.98] minutes, 95% CI, [-14.41] to [4.45], p=0.3). TTC was associated with a shorter CPB time compared to EABO with femoral cannulation (mean difference [-10.08] minutes, 95% CI, [-19.93] to [-0.22], p=0.05). Despite a higher risk of aortic dissection with EABO, the rates of survival and CVA across the two techniques are similar in MIMVS.

Background

Minimally invasive mitral valve surgery (MIMVS) is recognised as a safe surgical approach with patients reporting less pain, shorter hospital stay and better cosmetic results compared to other more invasive approaches.[1] To perform this, cardiopulmonary bypass (CPB) is needed and aortic occlusion is a critical step in its setup. This is achieved currently by two techniques available to surgeons: Transthoracic Clamp (TTC) and Endoaortic Balloon Occlusion (EABO). The TTC technique is simpler and involves inserting a clamp through the intercostal spaces to clamp the ascending aorta.[2] The EABO technique is associated with a longer learning curve as the procedure requires more monitoring and experience.[3] It involves accessing the aorta through a catheter inserted either in the femoral artery or directly through the ascending aorta with an inflatable balloon at its tip. This is guided by trans-oesophageal echocardiography (TOE), the balloon is inflated and the aorta occluded.

A previous meta-analysis of observational studies and abstracts reports that there was no significant difference in the occurrence of cerebrovascular accidents (CVA) and mortality when comparing TTC and EABO.[4] It however found that EABO was associated with significantly higher risk of iatrogenic aortic dissection as well as a trend towards increased CPB and aortic cross-clamp (AoX) times. In this review, we perform a subgroup analysis separating EABO with femoral cannulation to EABO with aortic cannulation to see if the cannulation approach in EABO has an impact on these clinical outcomes. In addition, we only include research published in full-text reports aiming to deliver a more comprehensive assessment of risk of bias.

Methods

To perform this research, we followed the review process as outlined by the *Cochrane Handbook for Systematic Reviews of Interventions.*[5]

Criteria for considering studies for this review

Types of studies

We searched for both observational and randomised studies that compared TTC and EABO in patients undergoing MIMVS. Studies included reported as full text and excluded those published as abstract only. No unpublished data was examined.

Types of participants

We included patients of any age, sex or ethnicity with mitral valve (MV) pathology and required MIMVS. Patients undergoing concomitant surgery alongside MV surgery were not excluded.

Types of interventions

We included studies comparing TTC (also called External Aortic Clamp or External Transthoracic Aortic Clamp) with EABO (also called Endoaortic Clamp Occlusion [EACO]) in MIMVS.

Types of outcome measures

- Primary outcomes
    1. All-cause mortality, within 3 months of MIMVS.
    2. CVA <30 days following MIMVS.
    3. Aortic dissection.
- Secondary outcomes
    1. AoX time (minutes).
    2. CPB time (minutes).

Search methods for identification of studies

Electronic search

We searched Medline and Embase on Ovid for published observational and randomised studies comparing TTC to EABO in MIMVS between January 2000 and December 2018. We decided to use the year 2000 as a cut off to target the latest reports only. The following keywords were used: Minimally Invasive Surgical Procedures, Mitral Valve, mini-MVS, mini-thoracotomy, ministernotomy,

hemisternotomy, endoclamp, endo-aortic, endoluminal, endo-balloon, Chitwood clamp, Intraclude clamp, Heartport clamp, ESTECH and flex clamp (Appendix 1).

Data collection and analysis

Statistical and data reporting guidelines for the European Journal of Cardiothoracic Surgery and the Interactive Cardiovascular and Thoracic Surgery[6] were consulted.

Selection of studies

Two reviewers (PR, ZDT) independently screened titles and abstracts for relevance. Any disagreements were resolved by conversation and consensus was reached with supervision of a third reviewer (HH). We retrieved the full-text reports and one reviewer (PR) screened these for inclusion or exclusion. We recorded the selection process and completed a PRISMA[7] flow diagram (Figure 1) and a "Characteristics of excluded studies table" (Appendix 2).

Data extraction and management

Three independent reviewers (PR, TM, AM) performed data collection, including assessment of bias, for each study and extracted information on the following:

1. Methods: date of study, country of origin, study design.
2. Patient characteristics: total number of patients; and number of patients, mean age, percentage of female patients and reported previous CVAs in each group.
3. Interventions: type of clamp used in the TTC technique, type of endoballoon used in the EABO technique, if the EABO approach was with femoral or aortic cannulation.
4. Outcomes: primary and secondary outcomes as reported in the earlier section.

The data was then transferred to Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre).[8]

Assessment of risk of bias in included studies

Three independent reviewers (PR, TM, AM) used the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool to assess risk of bias in the included studies.[9] This tool assesses risk of

bias by comparing each observational study with a hypothetical target randomized control trial (RCT) that addresses the same question as the observational study (Appendix 3). ROBINS-I assesses risk of bias in seven domains:

1. Bias due to confounding
2. Bias in selection of participants
3. Bias in classification of interventions
4. Bias due to departures from intended intervention
5. Bias due to missing data
6. Bias in measurement outcomes
7. Bias in selection of the reported results

Each domain was marked as having either a low; moderate; high; serious or critical risk of bias. ROBINS-I requires the pre-specification of confounders. Numerous confounding factors were identified and could be divided into the two following categories:

- Patient-based confounders: sex, diameter of femoral artery, age, NYHA class, history of previous CVA, history of previous vascular disease (HTN, diabetes), history of previous rheumatic heart disease, history of previous cardiac surgery.
- Technical confounders: type of surgery, complexity of the surgery, additional interventions during the surgery such as maze procedure or tricuspid surgery, use of robotics and surgeon experience or learning curve.

Surgeon learning curve was accounted for within the domain of “Bias due to confounding”. Studies which both accounted for this confounding factor and looked balanced for the main baseline confounders were judged to be at moderate risk of bias for this domain. Finally, in an attempt to investigate publication bias, we produced a funnel plot looking at the outcome of all cause mortality (Figure 2).

Measures of treatment effect

Continuous data was analysed as mean difference (MD) with 95% confidence intervals (CIs). We analysed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We chose RRs over odds ratios because they are considered easier to interpret.[5] Events are reported as a number per cohort and weighted using a random-effects model.

Unit of analysis issues

When collecting data for the CPB and AoX times, we converted any reports that were in "hours" to "minutes". In addition, for other outcomes, we converted any reports of "percentage of incidence" to a "number of events per group" by using the total number of patients in that group.

Assessment of heterogeneity

Chi^2 and I^2 statistics were used to measure the presence and extent of heterogeneity between the groups in each analysis. *p* values were considered statistically significant when ≤0.05.

Data analysis

We used the Mantel-Haenszel method for all meta-analyses with dichotomous outcomes and the Inverse Variance (IV) random effects model for continuous outcomes according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*.[5] Due to the heterogeneity of the interventions and comparators, we used a random-effects model in all instances. We performed all analyses using Review Manager 5 (RevMan 5) software,[8] following an intention-to-treat principle.

Subgroup analysis

Where there were sufficient numbers of events for a specific outcome we performed subgroup analyses investigating the effect of cannulation location for EABO.

Summary of findings' tables

We created 'Summary of findings' tables for each intervention type for primary and secondary outcomes. We used the five GRADE considerations to assess the quality of body of evidence as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions,*[5] employing GRADEpro GDT software.[10]

Results

Results of the search

We identified 11 papers with 4181 participants for inclusion in our review. We retrieved 1564 references from the electronic search of the literature. After removing studies that were clearly not eligible for inclusion we assessed 24 full-text articles. Of these we excluded 13 studies and recorded reasons for exclusion (Appendix 2).

Included studies with patient characteristics (Table 1)

Included studies were performed in Germany[11,12], Italy[14,15,16,17], Canada[18], the USA[19,20,21] and the Netherlands.[13] All studies were observational with 3 being prospective and 8 being retrospective in design (Table 1). These represented a total of 4181 patients undergoing MIMVS with cohort sizes ranging from 36 to 1064 patients. The total number of patients undergoing MIMVS with the TTC technique was 1606 (38%) as opposed to 2575 (62%) with the EABO technique. Of those, 2056 (80%) had EABO with femoral cannulation and 519 (20%) had EABO with direct aortic cannulation. Eight studies used the femoral cannulation technique for EABO.[11,12,13,16,17,18,19,20] Two studies used the direct aortic cannulation technique for EABO.[15,21] One study, Barbero et al. (2016),[14] offered 2 separate EABO cohorts, one with femoral cannulation and one with aortic cannulation (Table 1).

Risk of bias

Risk of bias is summarised in Table 2. Out of the eleven included studies, nine studies were deemed to be at an overall 'serious' risk of bias while the remaining two were deemed to be at an overall 'moderate' risk. The main source of bias was bias due to confounding.

1) Bias due to confounding:

Nine included studies[11,12,14,16,17,18,19,20,21] were rated as being at a 'serious' risk of bias due to confounding and two[13,15] were rated at a 'moderate' risk. Nine studies provided pre-operative patient characteristics tables. Of these, most reported unbalanced patient characteristics between TTC and EABO cohorts. All included studies were non-randomised and patient allocation to either TTC or EABO intervention groups was based on policy of surgical centre at the time of operation, patient characteristics and surgeon preference. Many studies compared two time periods, one when EABO was the technique of choice and one when TTC was the preferred technique. This introduces the possibility of differences in outcome due to differences in surgeon experience in MIMVS and due to changes in procedures over time which were not controlled for.

2) Bias in selection of participants:

All eleven included studies were at a 'low' risk of bias due to selection of participants because patient selection was not related to the intervention (or the effect of the intervention) and the outcome. Patients who underwent elective ventricular fibrillation were, for most outcomes, removed as part of the study designs.

3) Bias in classification of interventions:

All eleven studies were at a 'low' risk of bias due to classification of interventions, with both TTC and EABO interventions groups clearly defined before the start of the operation.

4) Bias due to departures from intended intervention:

All eleven studies were at a 'low' risk of bias due to departures from intended intervention.

5) Bias due to missing data:

Eight studies were at a 'low' risk of bias due to missing data. Three studies[14,16,21] were at a 'moderate' risk due to a very small number of patients having been allocated a group and then dropping out or being excluded from the intervention group due to conversion to full sternotomy or inadequate data reporting.

6) Bias in measurement of outcomes;

All eleven studies were at a 'low' risk of bias in measurement of outcomes as all outcomes were objective in nature.

7) Bias in selection of the reported results:

All eleven studies were at a 'moderate' risk of bias in selection of reported results because there was no protocol or pre-specified analysis plan.

8) Bias in publication:

A funnel plot was produced to investigate publication bias which showed that studies comparing TTC to EABO with aortic cannulation could be missing from the literature if they reported a higher risk of mortality than TTC. Overall however, there did not appear to be a publication bias when comparing TTC to EABO (Figure 2).

Summary of bias:

Overall, allocation bias seemed to favour TTC over EABO. Four studies[14,18,19,20] favoured TTC over EABO by having more patients with previous cardiac surgery allocated to their EABO cohorts compared to their TTC ones. With only two studies[13,20] specifically controlling for surgeon experience by stating that their surgeons had completed the learning curve for MIMVS, we can confidently say they were competent in both TTC and EABO techniques. All other studies are at risk of having surgeons experienced in TTC and not EABO; which is a serious potential confounder.

Primary outcomes

Summary of findings table:

All-cause mortality *(Figure 3)*

All studies reported all-cause mortality as post-operative mortality within 3 months following the surgery. In a random effects model, there was no difference in the risk of death between the two techniques or within any of the subgroups (overall RR, 1.52, 95% CI [0.86] to [2.66], p=0.15, I^2=0%).

Cerebrovascular accident *(Figure 3)*

Ten studies reported CVA either as stroke or transient ischaemic attack (TIA) within 30 days after surgery. Maselli et al. (2006)[15] did not report this outcome and therefore was not included in the analysis. There was no difference in the risk of CVA between the two techniques in a random effects model (RR, 0.83, 95% CI [0.48] to [1.44], p=0.5, I^2=6%).

Aortic dissection *(Figure 3)*

For studies comparing TTC to EABO with femoral cannulation there was a significantly lower risk of aortic dissection with TTC as opposed to the EABO with femoral cannulation (RR, 0.33, 95% CI, [0.12] to [0.93], p=0.04, I^2=0%). None of the studies that compared TTC to EABO with aortic cannulation found any events of aortic dissection in either group and therefore we did not include them in this analysis.

Secondary outcomes

Summary of findings table:

Aortic cross-clamp time (Aox-clamp time) *(Figure 4)*

Evidence for AoX time in MIMVS was very low (Table 4). The summary estimates for subgroups were significantly different (test for heterogeneity p<0.001, I^2=92%) therefore we focus on the subgroup summary estimates. AoX time for MIMVS using TTC was on average 9 minutes shorter than EABO

with femoral cannulation (mean difference -9.26 minutes, 95% CI, -17.00 to -1.52 minutes, p=0.02, I^2=84%). In contrast, AoX time for TTC was over 7 minutes longer than EABO with aortic cannulation (mean difference [7.77] minutes, 95% CI, 3.29 to 12.26 minutes, p<0.001, I^2=0%).

Cardiopulmonary Bypass time (CPB time) *(Figure 4)*

Evidence for CPB time was very low (see Table 4). The summary estimates for the subgroups were significantly different (test for heterogeneity p=0.02, I^2=82%) therefore we focus on the subgroup summary estimates. CPB time for MIMVS using TTC was on average 10 minutes faster than CPB using EABO with femoral cannulation (mean difference -10.08 minutes, 95% CI, -19.93 to -0.22 minutes, p=0.05, I^2=87%). The data were heterogeneous (Chi^2 test for heterogeneity <0.001; I^2 =87%). CPB time for MIMVS using EABO with aortic cannulation was ten minutes faster (mean difference 10.89 minutes, 95% CI, -3.37 to 25.15 minutes, p=0.13, I^2=79%) The data were heterogeneous (Chi^2 test for heterogeneity p<0.001; I^2 =79%) and the lower 95% CI indicates CPB could be 3 minutes longer than when using TTC.

Discussion

- **General summary of results**

All studies reported post-operative survival rates. Meta-analysis showed overall good survival rates with no difference between TTC and the two EABO techniques. However, there was weak evidence of no difference suggesting that both EABO techniques were associated with fewer post-operative deaths compared to TTC. The reasons for this were undetermined and most probably secondary to confounding. Several studies performed multivariable analyses to determine if there were any predictors of mortality[14,19]. They found that aortic clamping technique was not a predictor of mortality but patient pre-operative risk factors such as a NYHA class of III/IV, diabetes, renal failure, atrial fibrillation, age>70 years as well as prolonged CPB time were. These findings suggest that patient co-morbidities are more influential on survival rates than aortic occlusion technique.

Ten studies reported post-operative CVA. Meta-analysis showed no difference in risk of CVA with both techniques overall, and no difference when subgroup analyses were used to explore differences between TTC and EABO (femoral) and TTC and EABO (aortic). The mean summary estimates from the subgroup analysis indicate higher risk in the subgroup analysis of CVA with EABO (femoral) when compared to TTC but an opposite effect of a lower risk of EABO (aortic) when compared with TTC. However, the 95% CI for both these means cross the null. More evidence from additional studies would be helpful in determining if these trends persist and inform a hypothesis that EABO (aortic) is the occlusion approach with the least CVA risk. A previous meta-analysis[4] comparing TTC and EABO suggested several reasons for higher incidences of CVA with EABO (femoral): introduction of a guidewire along the aortic arch/ascending aorta, the balloon catheter being prone to migration during atrial wall retraction especially in patients with wide aortas and atheromatous disease and, finally, having to re-position the balloon intra-operatively with deflation and re-inflation of the balloon which can increase risk of embolization from the aorta. These reasons can explain why we found EABO (femoral) was associated with higher risk of CVA compared to TTC. On the other hand, the question still remains regarding how EABO (aortic) has the lowest risk of CVA. Two papers (Glower et al. (2010)[21] and Schmitz et al. (2002)[22]) have investigated this question and state that the advantages of the aortic cannulation approach over the femoral approach are a more direct and controlled placement of the balloon as well as the elimination of balloon migration because the balloon is pulled snuggly against the fixed aortic cannula and cannot move. In addition, we found EABO (aortic) was associated with the shortest AoX time and CPB times which suggests shorter extra-corporeal support times may be another reason for a low risk of CVA. Overall, both TTC and EABO are associated with similarly low risks of CVA; however EABO (aortic) seems the least risk prone for this outcome.

Ten studies reported AoX-clamp and CPB times. Meta-analysis showed no difference in length of AoX times and CPB times between TTC and the pooled EABO techniques. Overall, it showed weak

evidence of no difference between the two techniques suggesting TTC was associated with shorter AoX times and CPB times. However, upon subgroup analysis, we found that TTC was associated with shorter AoX times and CPB times compared to EABO (femoral) (p=0.02; p=0.05) but not EABO (aortic). EABO (aortic) was associated with shorter AoX times and CPB times compared to TTC (p<0.001; p=0.13). These results show that, out of all three approaches, EABO (aortic) is associated with the shortest AoX times and CPB times. Reasons for this may include an easier and more straightforward cannulation manoeuvre compared to femoral cannulation and a more reliable occlusion of the aorta than with TTC. In addition, surgeon learning curve is an important confounder to consider for this outcome. It is a difficult confounder to control for because in most cases the reports from operations performed at the early stages of the surgeon learning curve were not separated from those when surgeons had gained more experience. An example of bias caused by confounding due to changes over time is found in Mazine et al. (2013).[18] In this study, the experience from 2006 to 2009, when EABO was available, was compared with the experience from 2009 to 2011, when TTC was available. With the same surgeons operating, the potential for confounding due to surgeon learning curve suggests that these surgeons were less experienced both at MIMVS and EABO between 2006 and 2009 compared to when they started using TTC. We know that EABO is, by the nature of the technique, associated with a longer surgeon learning curve.[3] Surgeon experience not only has an impact on intra-operative times but also on clinical outcomes for patients. In Alturi et al. (2014)[20] for example, the authors noticed the learning curve associated with EABO had a significant impact on the number of iatrogenic aortic dissections in their patients. They reported a 3% rate of aortic dissection with EABO in their first 100 cases as opposed to only a 0.6% rate in their last 500. These two examples show how surgeon experience plays an important role in influencing these outcomes of interest.

Ten studies reported aortic dissection. Meta-analysis showed lower rates of aortic dissection with TTC compared to EABO: 4/1590 for the TTC group versus 19/2492 for the EABO group (RR, 0.33, 95%

CI, [0.12] to [0.93], p=0.04). This finding has been previously reported[4] and it is thought EABO is associated with higher rates of aortic dissection because of the need to insert a guidewire in the femoral artery which can damage the lining of the vessel as well as the need for higher perfusion pressures with this technique.[18] We were unable to perform a subgroup analysis for this outcome because all studies using EABO (aortic) found no incidence of aortic dissection to compare to TTC.

- **Quality of evidence and limitations of review**

The overall quality of the evidence was low. For AoX times and CPB times, we found substantial heterogeneity within the results (I^2 > 80%). We suspect the heterogeneity to be secondary to variations in surgeon experience, variations in recording technique of extracorporeal support times across studies, variations in the types of clamps used in TTC (Chitwood Clamp vs. Cygnet flexible clamp) as well as the balloons used in EABO (Heartport Endoaortic Clamp (Heartport) vs. EndoClamp Aortic Catheter (Edwards Lifesciences)) across the studies. Such high levels of heterogeneity (I^2 > 80%) suggest it is very difficult to infer anything from these findings because the variation in measurement technique is too influential. Based on the meta-analysis, the studies included did not report data on myocardial protection, acute right and/or left ventricular failure and need for post-operative ECMO to achieve a meaningful conclusion in this regard. The literature search, data collection and analysis have been performed in a transparent and reproducible form. This will have reduced any risk of bias in the review process.

Author's conclusions:

This systematic review and meta-analysis reports safe and similar rates of CVA and survival with both TTC and EABO in MIMVS. EABO was associated with a higher risk of aortic dissection. EABO with aortic cannulation offers the shortest extra-corporeal support times.

- **Implications for research**

To this day, all evidence for use of the two occlusion techniques are drawn from observational cohort studies. At present there is little evidence to support the adoption of one technique over another other than personal choice. In such a position of true equipoise we would therefore encourage the careful design of a randomised control trial comparing TTC and EABO, in specific participant subgroups. Adoption of a RCT design would remove the heavy bias of confounding factors. In our opinion, a threshold of 100 operations could be used to determine adequate surgeon experience in both techniques and would remove the confounding of surgeon learning curve.

Acknowledgements

We thank Sarah Dawson from the School of Social & Community Medicine (UOB) for her guidance on performing the literature search.

Sources of Funding: Theresa Moore's time was supported by NIHR CLAHRC West.

Disclosures: none

Affiliations

- This study was supported by the NIHR Biomedical Centre at the University Hospitals Bristol NHS Foundation Trust, the British Heart Foundation and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, the British Heart Foundation or the Department of Health.

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1 **Tables and figures:**

Figure 1: Study flow diagram according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysed) statement.

Figure 2: Funnel plot analysis of all-cause mortality for TTC vs EABO. On the horizontal axis is risk ratio (RR) and on the vertical axis is standard error.

Figure 3: Forest plot of primary outcomes with pooled risk ratios (diamonds) and 95% confidence intervals (CIs) (horizontal lines). Sizes of the squares are proportional to the weight of each study.

Figure 4: Forest plot for AoX-clamp and CPB times (min) with mean differences (diamonds) and 95% confidence intervals (CIs) (horizontal lines). Sizes of the squares are proportional to the weight of each study.

Study	Country	Study type	Type of Transthoracic Clamp (TTC)	Type of Endoaortic Balloon Occlusion (EABO) with cannulation approach	Patient characteristics								
					n = total	n = TTC group	n = EABO group	Age TTC group (years)	Age EABO group (years)	Female TTC group (%)	Female EABO group (%)	Previous CVA in TTC group (%)	Previous CVA in EABO group (%)
Aybek (2000)[11]	Germany	Prospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	Heartport Endoaortic Clamp (Heartport, Redwood City, CA) - Femoral cannulation	58	35	23	56.3 ± 12.9	58.3 ± 16.4	45.7	52.2	2.9	0
Reichenspurner (2005)[12]	Germany	Retrospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	EndoClamp (Cardiovation, Ethicon Inc Somerville, NJ) – Femoral cannulation	120	60	60	62.1 ± 10.5		70.8		NA	NA
Maselli (2006)[15]	Italy	Prospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	Cardiovations EndoClamp Aortic Catheter (Edwards LifeSciences Corporation, Irvine, CA) – Aortic cannulation	36	16	20	54.7 ± 5.4	56.5 ± 6.4	70	75	NA	NA
Ius (2009)[16]	Italy	Retrospective	Cygnet Flexible Clamp (Novare Surgical Systems Inc., Cupertino, CA)	EndoClamp Aortic Catheter (Edwards LifesSiences Corporation, Irvine, CA) – Femoral cannulation	127	95	32	62 ± 11	63 ± 9	50.5	40.6	NA	NA
Modi (2009)[19]	USA	Prospective	NA	NA – Femoral cannulation	1052	573	479	61.1 ± 13.9		51%		Not recorded	
Glower (2010)[21]	USA	Retrospective	Cosgrove Flexible Clamp (Cardinal Health V, Edwards LifeSciences Corporation, Irvine, CA)	EndoClamp Aortic Catheter (Edwards Lifesciences Corporation, Irvine, CA) – Aortic cannulation	671	235	436	58 ± 14	59 ± 13	59.1	52.5	NA	NA
Loforte (2010)[17]	Italy	Retrospective	Cygnet Flexible Clamp (Novare Surgical Systems Inc., Cupertino, CA)	EndoClamp Aortic Catheter (Edwards Lifesciences Corporation, Irvine, CA) – Femoral cannulation	138	93	45	58.8 ± 7.8	58.1 ± 11.4	73.1	77.7	NA	NA
Mazine (2013)[18]	Canada	Retrospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	Cardiovations EndoClamp Aortic Catheter (Edwards LifeSciences Corporation, Irvine, CA) – Femoral cannulation	243	103	140	61.9 ± 11	55.4 ± 1.9	38.8	40	5.8	6.4
Alturi (2014)[20]	USA	Retrospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	EndoClamp Aortic Catheter (Edwards Lifesciences Corporation, Irvine, CA) – Femoral cannulation	1064	189	875	58.9 ± 15.9	59.4 ± 12.6	52.4	42.5	NA	NA
Bentala (2015)[13]	Netherlands	Retrospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	EndoClamp Aortic Catheter, IntraClude Intra-Aortic Occlusion Device (Edwards LifeScience Corporation, Irvine, CA) – Femoral cannulation	221	57	164	62	66	43.9	43.9	7	1.9
Barbero (2016)[14]	Italy	Retrospective	Chitwood Clamp (Scanlan International, Inc, St Paul, MN)	Endoreturn/ IntraClude Intra-Aortic Occlusion Device (Edwards LifeScience Corporation, Irvine, CA) – one group (1) with femoral cannulation, the other (2) with aortic cannulation	451	150	238 (1)	67.1 ± 12.2	61.3 ± 13.9 (1)	42.7	51.7 (1)	11.3	6.3 (1)
							63 (2)		69.2 ± 9.4 (2)		23.8 (2)		9.5 (1)
TOTAL		3 Prospective 8 Retrospective	7 Chitwood Clamp 2 Cygnet Flexible Clamp 1 Cosgrove Flexible Clamp 1 not specified	1 Heartport Endoaortic Clamp 7 EndoClamp 2 IntraClude Intra-Aortic Occlusion Device 1 not specified	4181	1606	2575						

<u>Table 1</u>: Included studies with patient characteristics.

Study name	1. Bias due to confounding	2. Bias in selection of participants	3. Bias in classification of interventions	4. Bias due to departures from intended intervention	5. Bias due to missing data	6. Bias in measurement outcomes	7. Bias in selection of the reported result	Overall risk of bias
Aybek (2000)[11]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Reichenspurner (2005)[12]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Maselli (2006)[15]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Ius (2009)[16]	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
Modi (2009)[19]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Glower (2010)[21]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Loforte (2010)[17]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Mazine (2013)[18]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Alturi (2014)[20]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Bentala (2015)[13]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Barbero (2016)[14]	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious

Table 2: Assessment of risk of bias using ROBINS-I.

Summary of findings:

TTC compared to EABO for minimally invasive mitral valve surgery (MIMVS)

Patient or population: patients undergoing minimally invasive mitral valve surgery (MIMVS)

Setting: cardiac surgery

Intervention: TTC

Comparison: EABO

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EABO (with technical subgroups)	**Risk with TTC**				
Cerebrovascular Accident (CVA)	19 per 1,000	**16 per 1,000** (9 to 27)	**RR 0.83** (0.48 to 1.44)	4145 (11 observational studies)	⊕◯◯◯ VERY LOW	I^2 = 6%
All-cause mortality	11 per 1,000	**17 per 1,000** (9 to 29)	**RR 1.52** (0.86 to 2.66)	4181 (12 observational studies)	⊕◯◯◯ VERY LOW	I^2 = 0%
Aortic dissection	7 per 1,000	**2 per 1,000** (1 to 7)	**RR 0.33** (0.12 to 0.93)	4145 (11 observational studies)	⊕◯◯◯ VERY LOW	I^2 = 0%

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: The true effect may be substantially different from the estimate of the effect

Very low certainty: The true effect is likely to be substantially different from the estimate of effect

Table 3: Summary of findings table for primary outcomes.

Summary of findings:

TTC compared to EABO (with technical subgroups) for minimally invasive mitral valve surgery (MIMVS)

Patient or population: patients undergoing minimally invasive mitral valve surgery (MIMVS)
Setting: cardiac surgery
Intervention: TTC
Comparison: EABO (with technical subgroups)

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EABO (with technical subgroups)	**Risk with TTC**				
Cross Clamp Time (min) - TTC vs. Femoral cannulation EABO	The mean cross Clamp Time (min) - TTC vs. Femoral cannulation EABO was **0** minutes	The mean cross Clamp Time (min) - TTC vs. Femoral cannulation EABO in the intervention group was 9.26 minutes faster (17 to 1.52 minutes faster)	-	3336 (9 observational studies)	⨁◯◯◯ VERY LOW	I^2 = 84%
Cross Clamp Time (min) - TTC vs. Aortic cannulation EABO	The mean cross Clamp Time (min) - TTC vs. Aortic cannulation EABO was **0** minutes	The mean cross Clamp Time (min) - TTC vs. Aortic cannulation EABO in the intervention group was 7.77 minutes faster (3.29 to 12.26 minutes longer)	-	845 (3 observational studies)	⨁◯◯◯ VERY LOW	I^2 = 0%
Cardiopulmonary Bypass (CPB) time (min) - TTC vs. Femoral cannulation EABO	The mean cardiopulmonary Bypass (CPB) time (min) - TTC vs. Femoral cannulation EABO was **0** minutes	The mean cardiopulmonary Bypass (CPB) time (min) - TTC vs. Femoral cannulation EABO in the intervention group was 10.08 minutes faster (19.93 to 0.22 minutes faster)	-	3336 (9 observational studies)	⨁◯◯◯ VERY LOW	I^2 = 87%
Cardiopulmonary Bypass (CPB) time (min) - TTC vs. Aortic cannulation EABO	The mean cardiopulmonary Bypass (CPB) time (min) - TTC vs. Aortic cannulation EABO was **0** minutes	The mean cardiopulmonary Bypass (CPB) time (min) - TTC vs. Aortic cannulation EABO in the intervention group was 10.89 minutes longer (3.37 minutes faster to 25.15 minutes longer)	-	845 (3 observational studies)	⨁◯◯◯ VERY LOW	I^2 = 79%

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: The true effect may be substantially different from the estimate of the effect
Very low certainty: The true effect is likely to be substantially different from the estimate of effect

Table 4: Summary of findings table for secondary outcomes.