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Comparison of Outcomes of Combined Thoracic Epidural Anesthesia with General Anesthesia Versus General Anesthesia During Coronary Artery Bypass Graft Surgery

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COMPARISON OF OUTCOMES OF COMBINED THORACIC EPIDURAL ANESTHESIA WITH GENERAL ANESTHESIA VERSUS GENERAL ANESTHESIA DURING CORONARY ARTERY BYPASS GRAFT SURGERY

A Major Paper Presented

by

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Abstract

Coronary artery bypass graft (CABG) surgery is the most common type of heart surgery in the United States. The main benefit of CABG surgery is a significant decrease in myocardial infarction rate, while the most common complications of CABG are myocardial damage and atrial fibrillation. The incorporation of epidural anesthesia occurred in order to decrease sympathetic nervous system response during CABG but has not been extensively studied. A systematic review was conducted to compare the cardiovascular outcomes of the addition of thoracic epidural anesthesia to the anesthetic plan versus general anesthesia as a solo technique during coronary artery bypass grafting surgery. The PubMed database was searched to identify randomized controlled trials in adult patients undergoing CABG with implementation of thoracic epidural anesthesia versus general anesthesia only. Seven studies involving 668 participants met the criteria. A previously published meta- analysis of randomized controlled trials was also included. The Preferred Reporting Items for Systematic Review (PRISMA) checklist was utilized to extrapolate and synthetize the data. The Critical Appraisal Sheet for Controlled Randomized Studies was adapted from the FRISBE tool in order to compare both within and across the studies. Two outcomes were measured: the degree of cardiac damage that was represented by troponin level and atrial fibrillation rate. The limited evidence suggested that thoracic epidural anesthesia does not provide cardioprotective benefits in adult patients undergoing CABG. The results of the study should be interpreted with caution due to the limited information available and heterogeneity of the studies. The question of whether thoracic epidural anesthesia provides cardioprotective functions requires further investigation. Taking into consideration the results of this study, it is not

recommended to use the epidural anesthesia as an adjunct technique on the routine basis during CABG until more information is available.

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Comparison of Outcomes of Combined Thoracic Epidural Anesthesia with General Anesthesia versus General Anesthesia during Coronary Artery Bypass Graft Surgery

Background/Statement of the Problem

The traditional approach to cardiothoracic surgery and specifically to coronary artery bypass grafting (CABG) surgery includes the administration of general anesthesia during the perioperative period. This includes the involvement of volatile anesthetic agents as a main anesthetic technique. All currently used volatile gases are known to produce significant cardiovascular side effects such as a negative inotropic effect and depression of the sinoatrial node that may have negative consequences on the cardiovascular system (De Hert, 2006).

Coronary artery bypass graft, also called bypass surgery, is the most common type of heart surgery in the United States ("Bypass surgery", 2012). A healthy artery or vein from elsewhere in the patient's body is used to bypass the blocked coronary artery and improve the blood supply to the heart. The CABG procedure significantly lowers the risk of heart attack and allows patients to remain symptom-free for as long as 10 to 15 years. The procedure itself has risks of infection, bleeding, reaction to anesthesia, long recovery time and small risk of stroke ("Bypass surgery").

The majority of patients who underwent coronary artery bypass graft surgery are Medicare patients 65 year of age or older with an average age of 75 years (Weintraub, Grau-Sepulveda, & Weiss, 2012). These patients usually present as complex patients with decreased functional capacity of all systems and multiple comorbidities. The comorbidities associated with aging and decreased functional capacity such as diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral

vascular disease, and renal dysfunction significantly increase postoperative complications after CABG procedure. Advanced age remains an independent predictor of mortality and morbidity in CABG procedures (Zawar et al., 2015). The administration of volatile anesthetics significantly increases the mortality risk of these patients during the intraoperative period (Van Allen et al., 2012).

All volatile anesthetics currently used in anesthetic practice produce negative inotropic, vasodilating and depressant effects on the sinoatrial node (De Hert, 2006). Volatile anesthetic administration is associated with myocardial depression and vasodilation that can contribute to intraoperative hypotension, potentially disturbing the balance between myocardial oxygen supply and demand and resulting in perioperative myocardial ischemia (Lee, 2008; Nakao, 2010). Besides the risk of myocardial infarction, the administration of volatile gases specifically during cardiothoracic surgery is associated with a high risk for arrhythmia development such as supraventricular and ventricular tachycardia. Also, the prolongation of the QT interval was reported during administration of volatile anesthetics, thus increasing the risk for Torsades de pointes ventricular fibrillation (Hanci, 2010; Thiruvenkatarajan, 2008).

Administration of general anesthesia during the intraoperative period provides not only amnesia, but also anesthesia for the patient. During the postoperative period, patients require a high amount of intravenous opioids in order to control postoperative pain. For patients 65 years of age and older, the administration of opioids is associated with increased risk for postoperative complications such as respiratory depression, restricted mobility and a prolonged recovery period (Kampe et al., 2014).

Implementation of regional anesthesia during CABG surgery has beneficial effects on the cardiovascular system such as reduction of the perioperative stress response and respiratory outcomes related to the improved pulmonary function (El-Morsy et al., 2012; Tenenbein et al., 2008). According to the study conducted by Kilickan (Kilickan et al., 2005), thoracic epidural anesthesia is associated with the preservation of myocardial function during intraoperative and postoperative period in patients after CABG surgery. However, Barrington reports no difference in biochemical markers of myocardial damage with implementation of thoracic anesthesia in comparison with traditionally used general anesthesia (Barrington et al., 2005). Since atrial fibrillation is the most common postoperative complication associated with CABG surgery (De Hert, 2006), many authors questioned if epidural anesthesia can be beneficial in reduction of the incidence of atrial fibrillation. The information related to the occurrence of postoperative atrial fibrillation with the implementation of thoracic anesthesia is controversial. Bakhiary (Bakhiary et al., 2007) reported significant reduction in the incidence of atrial fibrillation that is associated with the implementation of thoracic epidural anesthesia. However, Jideus (Jideus et al., 2001) reported no difference in the incidence or the time of onset of atrial fibrillation in the group where the thoracic epidural analgesia was implemented versus the group with general anesthesia only.

The purpose of this systematic review was to compare the cardiovascular outcomes of the addition of thoracic epidural anesthesia to the anesthetic plan versus general anesthesia as a solo technique during coronary artery bypass grafting surgery. The results of the review were used to determine the risk and benefit ratio of thoracic

epidural anesthesia in CABG surgery in comparison with the traditionally used general anesthesia.

Next, the review of the literature will be presented.

Literature Review

Overview

The literature review was conducted to collect available information about the topic of interest using the PubMed database. Keywords included regional anesthesia, thoracic epidural anesthesia, CABG, coronary bypass surgery, cardiovascular outcomes, myocardial markers, and atrial fibrillation. The search was restricted to articles published after the year of 1999. Forty four articles were retrieved initially.

Controlled randomized studies that compared the cardiovascular outcomes after implementation of thoracic epidural anesthesia versus general anesthesia alone were compared. Multiple studies have been conducted to assess different anesthetic approaches used during CABG surgery. Several randomized controlled studies that compared the implementation of thoracic epidural anesthesia with general anesthesia versus general anesthesia as a solo technique were identified

General Anesthesia during CABG

General anesthesia was identified as the most common anesthetic technique for cardiac surgery (Tenling et al., 1999). This anesthetic technique includes premedication, induction and neuromuscular blockade followed by tracheal intubation. Anesthesia is maintained with volatile agents (Zawar et al., 2015). All volatile anesthetics currently used in general anesthesia are associated with negative inotropic, vasodilating and depressing effects on the sinoatrial node (De Hert, 2006). Volatile anesthetic administration is associated with myocardial depression and vasodilation that can contribute to intraoperative hypotension, potentially disturbing the balance between myocardial oxygen supply and demand with resulting perioperative myocardial ischemia

(Nakao, 2010; Lee 2008). Moreover, general anesthesia is associated with prolonged postoperative recovery, higher complication rates, and increased stress hormones (Kiss & Castillo, 2015).

Thoracic Epidural Anesthesia during CABG

Multiple regional anesthesia techniques can be implemented during CABG surgery. Some of them are local wound infiltration, serratus anterior muscle plane block, selective intercostal nerve blockade, thoracic paravertebral blockade, thoracic epidural analgesia, and lidocaine administration in the pleural space (Kiss & Castillo, 2015). The thoracic epidural anesthesia should be the first choice for the thoracic surgeries because of its longer duration and the advantage of providing postoperative pain relief for a longer period of time (Kiss & Castillo).

Puncture level of the epidural block depends on the surgical incision site but is usually between T3 and T7. The volume of local anesthesia is titrated to achieve somatosensory anesthesia between T2 to T12, but depends on the size of the incision and varies with the patient's body size and weight (Kiss & Castillo, 2015). The administration of thoracic epidural requires testing to identify the degree of anesthesia. The quality of the epidural block should be tested either with ice cubes or with a maximal painful tetanic stimulus produced by a neuro stimulator before the operation. The surgery should be allowed only after the skin area defined for surgical incision is completely anesthetized (Kiss & Castillo).

The combination of thoracic epidural anesthesia with general anesthesia can provide multiple benefits to patients during the perioperative period. The main complications associated with CABG surgery are related to the cardiovascular and

pulmonary complications during the perioperative period and patients undergoing CABG have an increased risk of perioperative cardiac complications (Kilickan et al., 2005). Possible strategies to reduce the perioperative risk have been the focus of multiple studies (Kilichkan); one such strategy includes use of thoracic epidural anesthesia. Significant reduction of the incidence of perioperative arrhythmias such as atrial fibrillation was documented with implementation of thoracic epidural anesthesia during CABG procedure (Bakhiary et al., 2007). Also, the overall positive effects on coronary blood flow, left ventricular function, relief of the angina, hemodynamic stability and reduction of the stress response hormones have been reported (Kilickan et al., 2005). Sympathetic thoracic blockade that is produced by thoracic epidural block is associated with an improved ventricular wall movement during the surgical stress. Especially in cardiac surgery, thoracic epidural anesthesia provides inhibition of the surgically mediated catecholamine response and provides greater intraoperative hemodynamic stability (Kilickan). Epidural anesthesia administered in addition to general anesthesia is associated with reduced perioperative stress and myocardial ischemia, facilitated breathing and early mobilization. Although epidural anesthesia is expected to have similar beneficial effects in cardiac surgery, it is not a common procedure in clinical practice (Tenling et al., 1999). The advantageous effects of thoracic epidural anesthesia on the cardiovascular and pulmonary system of patients undergoing CABG surgery may be associated with faster recovery after the surgery (Tenling et al., 1999).

Thoracic Epidural during CABG and Outcomes Related to Cardiovascular System

Atrial fibrillation. According to De Hert (2006), the major factor that contributes to the high mortality during the CABG surgery is related to the cardiovascular system of

a patient and possible negative effects. Atrial fibrillation is a common complication associated with CABG surgery that significantly impairs mortality risks. Atrial wall stretch, ischemia, inflammation or imbalance in the autonomic nervous system of the heart during and after the CABG procedure may cause the changes in atrial conduction and contribute to atrial fibrillation (De Hert).

Several studies were conducted in order to assess the possibilities of reducing the incidence of atrial fibrillation to improve overall outcomes after the procedure. The impact of thoracic epidural anesthesia on the sympathetic and parasympathetic activity through the level of neuropeptides, catecholamines, heart rate and incidence of atrial fibrillation were assessed in a study conducted by Jideus and colleagues (2001). The study was performed in the University Hospital in Uppsala, Sweden. The study group consisted of 41 patients that received thoracic epidural anesthesia with general anesthesia for CABG surgery. The control group included 80 patients that underwent the procedure under general anesthesia alone.

The measured outcomes included the incidence of postoperative atrial fibrillation and sympathetic and parasympathetic activity which were evaluated by analysis of neuropeptides, catecholamines and heart rate variability preoperatively and postoperatively. The result of the study revealed that thoracic epidural block effectively suppressed the sympathetic activity resulting in a dominating vagotonic status in comparison to patients under general anesthesia. However, there was no significant difference between those patients developing atrial fibrillation and patients remaining in sinus rhythm. A similar percentage of atrial fibrillation occurred in both groups: 31.7% in the thoracic epidural anesthesia group and 36.3% in the control group with general

anesthesia (p=0.77). The administration of thoracic epidural was associated with significantly suppressed sympathetic activity, which was indicated by a less pronounced increase in norepinephrine and epinephrine and a significant decrease in neuropeptide. The authors concluded that thoracic epidural anesthesia had no effect on the incidence of postoperative sustained atrial fibrillation, despite a significant reduction in sympathetic activity (Jideus et al.).

Another study with the goal to investigate the impact of thoracic epidural anesthesia on reduction of perioperative atrial fibrillation was conducted by Bakhtiary and colleagues (2007) at the Johann Wolfgang Geothe University Hospital in Frankfurt on Main, Germany. One hundred and thirty-two subjects undergoing elective CABG surgery were randomized in groups receiving general anesthesia (66 participants) or combined general and thoracic epidural anesthesia group (also 66 participants). The incidence of perioperative arrhythmias such as atrial fibrillation, as well as serum epinephrine level and heart rate variability, were measured during the study. According to the results, thoracic epidural anesthesia in combination with general anesthesia reduced significantly the incidence of perioperative atrial fibrillation and epinephrine serum levels. The incidence of perioperative arrhythmias was significantly lower ($p<0.01$) in the group where thoracic epidural technique was implemented (3%) versus the general anesthesia group (23.7%). Also, serum epinephrine levels were significantly lower in the group with implementation of epidural anesthesia (69+/- 11 to 35 +/- 7 ng/dL) than in the group under general anesthesia (72+/- 9 to 70 +/- 9 ng/dl)($p=0.001$). The author stressed that the results of the study supported a combination of thoracic epidural anesthesia with

general anesthesia as a multidisciplinary approach that may lead to a reduction of perioperative complications and a better patient outcome (Bakhiary et al.).

Myocardial cell damage. A study conducted by Barrington and colleagues (2005) assessed if thoracic epidural anesthesia had myocardial protective effects. The study included 120 subjects that were randomly assigned to thoracic and general anesthesia group or general anesthesia only during CABG surgery. The measured outcomes consisted of troponin I level, time to extubation and postoperative analgesia. According to the results, the troponin levels were increased in both groups at 12 and 24 hours, but there no significant differences between the groups (17.2 mcg/L in 12 hours and 9.1 mcg/L for thoracic anesthesia group versus 17.0mcg/L in 12 hours and 9.1 mcg/L in 24 hours for the general anesthesia group). The author concluded that thoracic epidural anesthesia had no protective myocardial effect (Barrington et al.).

The impact of thoracic epidural anesthesia on myocardial cell damage, inflammatory and stress response in patients undergoing CABG surgery was measured by Caputo and colleagues (2009). The study included 74 patients that were randomly assigned to the study group with implementation of thoracic epidural anesthesia and the control group that received the procedure under general anesthesia only. The outcomes measured included the level of troponin I, 8-isoprostane, cortisol, C3alpha, and interleukin preoperatively, at 30 minutes, and 4, 12, 24, and 48 hours postoperatively. According to the results, baseline characteristics were similar in the two groups. The interleukin 6 and interleukin 8 levels were lower in the group with thoracic epidural (ratio 0.83) versus the general anesthesia group (ratio 0.90). The difference in levels of interleukin 10 varied over time between the thoracic epidural and general anesthesia

group. The C3alpha, troponin I, 8-isoprostane, and cortisol levels were similar in the two groups throughout. The authors concluded that thoracic epidural anesthesia did not provide any additional benefits in terms of reducing myocardial damage, inflammatory or stress response (Caputo et al.).

Cardiac index and cardiac arrhythmias. A study that measured the impact of thoracic epidural anesthesia on myocardial function conducted by Klickan and colleagues (2005) demonstrated conflicting results. The study included 80 subjects that were assigned into four groups. There was no randomization during the assignment and patients were placed in groups according to the degree of ventricular function. The assignment into groups was as follows: patients with poor ventricular function and general anesthesia; patients with good ventricular function and general anesthesia, patients with poor ventricular function and thoracic epidural and general anesthesia; patients with good ventricular function and thoracic epidural and general anesthesia. The level of ventricular function was determined by the ejection fraction, with ejection fraction of above 40% identified as good. The measured outcomes consisted of cardiac index, incidence of arrhythmias after the release of the aortic clamp and ionotropic requirements.

The results of the study demonstrated that patients that received thoracic epidural during CABG procedure showed improved cardiac index, reduced number of arrhythmias, and decreased ionotropic requirements. The cardiac index values in thoracic anesthesia with general anesthesia group were significantly higher than baseline values ($P<0.05$), but no difference was found in the group with general anesthesia. The number of patients with ventricular fibrillation, atrial fibrillation or heart block during intra-

operative period was 25 - 30% in the groups with thoracic anesthesia versus 60-65% in the groups where thoracic anesthesia was not implemented. The requirement for ionotropic support was also lower in the groups with thoracic epidural (20-35%) versus the groups without epidural block (45-65%; $p<0.05$). Moreover, the group of patients with poor ventricular function benefitted the most from thoracic epidural anesthesia which was demonstrated by the lower number of ventricular fibrillation associated with reperfusion (20 % versus 55% in the group with general anesthesia and poor ventricular function) (Kilickan et al.).

According to the reviewed literature, the thoracic epidural anesthesia provides some benefits related to the cardiovascular system, such as decreased incidence of cardiac arrhythmias, improvement in cardiac index, decreased inflammatory and stress response by myocardium. However, contradictory results are also reported and further critical analysis is warranted.

Next, the theoretical framework will be presented.

Theoretical Framework

A systematic review was conducted to identify studies that evaluated the benefits, complications, and outcomes of thoracic epidural anesthesia in patients undergoing coronary artery bypass grafting surgery. A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research. The systematic review collects and analyzes data from the studies that are included in the review (Moher, Liberati, Tetzlaff, & Altman, 2009).

Systematic reviews have become increasingly important in the health care industry. They are identified as one of the fundamental tools for the generation of reliable summaries of health care information for clinicians, decision makers and patients. Clinicians use systematic reviews to stay updated in a specialty and they are often used as a starting point in developing clinical practice guidelines. Agencies that provide grants often require a systematic review to ensure that there is justification for further research. Systematic reviews provide valuable information on clinical benefits and harms of interventions and help identify future research needs (Moher at et al., 2009).

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed in conducting this systematic review. The PRISMA statement is a guideline designed to improve the completeness of reporting of systematic reviews and meta-analyses. Many authors worldwide have used this guideline to prepare systematic reviews and meta-analyses for publication. The PRISMA guideline includes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (Hutton et al., 2015).

The PRISMA statement consists of a 27-item checklist and a four-phase flow diagram which will be used for identification, screening and determination of eligibility and inclusion of the literature. The checklist of items to include when conducting a systematic review is included in Appendix A. The checklist was designed to help with analyzing and organizing a systematic review. For each check list item, the PRISMA guideline provides an explanatory document which serves as an example of good reporting, a rationale for its inclusion and supporting evidence. This explanatory document served as a useful resource for assessment and documentation of the reviewed studies. The checklist identified the items that must be included in a systematic review. The largest portion of the checklist is designated to the methods such as assessment of eligibility criteria, search, study selection, data collection process, and risk of bias in individual studies and across the studies. All studies included in a systematic review require study-level and outcome-level assessment of the risk of bias. An outcome-level of assessment involves evaluation of reliability and validity of the data for each important outcome by determining if the methods used to assess are reliable and free of bias (Moher et al., 2009).

The flow diagram included in the PRISMA guideline was used to guide the process of screening and determination of studies that were included in the review. Table 1 illustrates the process for the selection of the studies included in the systematic review.

Table 1

Flow of Information through the Different Phases of a Systematic Review

Number of studies	Description of action
	Number of records identified through initial database searching
	Number of records of additional records identified outside the initial search
	Number of records after duplicates removed
	Number of records excluded
	Number of full-text articles assessed for eligibility
	Number of full text articles excluded after full text was reviewed
	Number of studies included in the study

Note: Table was adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

The table was adapted and modified from the PRISMA statement to better suit the specificity of the systematic review. Some items were excluded due to repetition and the specificity of the original search.

The Critical Appraisal Sheet for Controlled Randomized Studies was adapted from the FRISBE tool in order to compare both within and across the studies. The FRISBE criteria stands for patient follow up, randomization, intention to treat analysis, assessment of characteristics of patients to ensure that compared groups had similar baseline characteristics, blinding of studies and equal treatment. The FRISBEE tool was created by Duke University's psychiatry residency program in order to help to

incorporate evidence-based medicine into patient care (Xiong & Adams, 2007). The main purpose of the tool is to examine the validity of clinical trials before translating the results into clinical practice. Even though randomized controlled studies are considered as a gold standard, their validity should be careful examined (Xiong & Adams, 2007). The FRISBE Expanded Critical Appraisal Worksheet with Key Learning Points was used to conduct the critical appraisal.

The original tool was modified to accommodate for the specifications of the individual studies. The assessment included the number of participants, the degree of the treatment effect, the importance of clinical outcomes, and the comparison of benefit/harm for the study. All studies were classified as met the criteria, not completely met; or did not meet the criteria. The FRISBE Expanded Critical Appraisal Worksheet was also used for cross study assessment of the studies.

Next, the methods used to conduct this systematic review will be presented.

Method

Purpose/ Clinical question

The purpose of the systematic review was to compare selected cardiovascular outcomes of combined thoracic epidural technique with general anesthesia versus general anesthesia as a solo technique during CABG surgery. The examined cardiovascular outcomes included the incidence of atrial fibrillation and cardiac cell damage

Search Strategy

An extensive literature review was conducted using the PubMed database. Keywords searched included regional anesthesia, thoracic epidural anesthesia, CABG, coronary artery bypass grafting, coronary bypass surgery, atrial fibrillation, cardiac arrhythmia, myocardial stress response, myocardial damage, troponin level to identify suitable publications.

The PRISMA framework was used to establish the criteria for the selection of the studies suitable for the review. The flow of information during the search process was guided by the PRISMA framework. The PRISMA establishes the stages of the search process in order to provide complete and accurate information for the review. Each stage was utilized to assess available articles in detailed and organized manner. It helped to identify the additional articles that were retrieved through the collateral sources and the articles that had a duplicate information. This step is very important because the duplication of the information can greatly affect the results of the review.

The search of the literature resulted in studies that were screened for eligibility for inclusion in the review. The studies were assessed by title and abstract in order to identify if the topic of the study matched with the intent of the systematic review. All studies

identified as potential studies for inclusion were organized and divided into specific categories such as arrhythmias and myocardial cell damage. The value of a systematic review depends on what is done, what was found, and the clarity of reporting (Moher et al., 2009).

The function of "see related articles" in PubMed was implemented in order to complement additional citations. The search was restricted to the articles published after the year of 1999. The controlled randomized studies related to the proposed topic were accessed in full text. A conducted meta-analysis of randomized controlled trials describing the outcomes related to thoracic anesthesia in preventing atrial fibrillation after coronary artery bypass surgery was included into the systematic review and was used for supplementation. Four studies included in the meta-analysis were already identified through the PubMed search and included in the study. The majority of studies included in the meta-analysis did not meet the criteria for the inclusion in the systematic review due to the outdated publication. Some of the articles were dated as old as the year of 1995 which was an exclusion criteria in the search. One article (Tenenbein et al., 2008) was not directly related to the topic of the systematic review, but was used for supplemental information. One article (Zawar et al., 2015) was retrieved during the process of reviewing information for any additional publications after the initial search was done. A total of eight studies were included: one meta-analysis and seven randomized controlled studies.

Inclusion/Exclusion Criteria

The inclusion criteria included: the language of publication in English; controlled randomized studies that compared thoracic epidural anesthesia alone or with general

anesthesia versus general anesthesia alone during CABG surgery; publication year after 1999; ages of subjects not less than 18; outcomes assessed included incidence of atrial fibrillation and degree of myocardial cell damage represented by troponin release. Surgeries performed in both general anesthesia techniques such as volatile anesthetics as well as total intravenous anesthesia were included in the review.

The exclusion criteria included: non-randomized control trials; insufficient or limited provided data; identified outcomes measured in mixed groups of surgical procedures such as CABG and another surgical intervention.

Data Collection

Data collection was performed using the data collection forms that were independently created by the author in order to organize the information from the studies. First, a data collection table was created specifically for the recording of key data specific to meta-analysis of randomized controlled studies that was included in this review. The table described the number of studies included in the meta-analysis, types of interventions used in the studies, outcome measures, and findings of all included studies. The example of the table is included on the next page.

Table 2

Data collection for the meta-analysis of randomized controlled studies

Title	

Study eligibility

Type of study	
#of studies included	
Types of intervention	
Types of comparison	
Outcome measures	
Findings	
Conclusions	
Limitations	

A data collection form was also created for each randomized controlled trial that was included in the systematic review as illustrated in Table 3 on the next page.

Table 3

Data collection of the randomized controlled trial

Title	

Study eligibility

Type of study	
Participants	
Types of intervention	
Exclusion criteria	
Types of comparison	
Outcome measures	
Assessment method	
Findings	
Recommendations	
Notes	
Limitations	

All studies were introduced with a brief description of the study, the outcomes that were measured, and the results of the study. The measured outcomes included two categories: atrial fibrillation and the degree of damage to the myocardium.

Each study was individually appraised in order to evaluate the scientific integrity of the study. The appraisal of each individual study was conducted using the Critical Appraisal Worksheet for Controlled Randomized Studies as illustrated in Table 5 on the next page.

Table 5

Critical Appraisal Worksheet for Individual and Cross Study Comparisons

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes: Not completely: No:
Was follow-up complete?	Yes: Not completely: No:
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes: Not completely: No:
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Yes: Not completely: No:
Were all randomized patient data analyzed?	Yes: Not completely: No:
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes: Not completely: No:
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	Yes: Not completely: No:
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes: Not completely: No:
Summary of Article's validity	
Results	
How large was the treatment effect?	Yes: Not completely: No:
Were all clinically important outcomes considered?	Yes: Not completely: No:

Are the likely treatment benefits worth the potential harms and costs?	Yes: Not completely: No:

The comparison across the studies were also conducted using The Critical Appraisal Sheet for Controlled Randomized Studies. All studies were classified as: met the criteria, not completely met; or did not meet the criteria.

Next, the results will be presented.

Results

The search process used is illustrated below in Table 4.

Table 4

Flow of Information through the Different Phases of a Systematic Review

Number of studies	Description of action
42	Number of records identified through initial database searching
1	Number of records of additional records identified outside the initial search
0	Number of records after duplicates removed
33	Number of records excluded
10	Number of full-text articles assessed for eligibility
2	Number of full text articles excluded after full text was reviewed
8	Number of studies included in the study

Adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

The original search resulted in 42 studies with one additional study added during the process of reviewing the current literature. Thirty five studies were eliminated at different points of the assessment with eight studies remaining. One of the included articles was a meta-analysis, with the remaining seven being randomized controlled studies.

Meta-Analysis

The meta-analysis of randomized controlled trials (Gu et al., 2012; Appendix B) evaluated the efficacy of thoracic epidural anesthesia in preventing postoperative atrial

fibrillation in patients undergoing CABG surgery. The quantitative synthesis included five controlled randomized studies. The size of each study ranged from 50 to 163 participants. The total number of participants in the meta-analysis was 540 with 247 patients in the group with the thoracic epidural combined with general anesthesia and 293 patients in the general anesthesia group. Four studies assessed the elective CABG procedure and only one study assessed elective and semi-elective CABG surgery. Two studies out of five were conducted using the off-bypass surgical technique. The outcome that was assessed during the meta-analysis was the rate of postoperative atrial fibrillation.

The rate of atrial fibrillation in the groups with thoracic epidural was similar to the group with general anesthesia approach in three studies: 32% (13 out of 41 patients) versus 36% (29 out of 80 patients) (Jideus, 2001); 35% (28 out of 79) versus 30% (25 out of 84) (Nygard as cited in Gu)(Gu et al., 2012); 24% (6 out of 25) versus 36% (9 out of 25) (Tenenbein, 2008). In the studies conducted by Bakhtiary (2007) and Caputo (2009), there was a significant difference in the rate of atrial fibrillation between the groups with thoracic epidural versus general anesthesia: 3% (2 out of 66 studies) versus 27% (18 out of 66 patients) (Bakhtiary) and 19% (7 out of 36) versus 47% (18 out of 38) (Caputo). Gu and colleagues explained the heterogeneity in the results due to the fact that all CABG surgeries performed in these two studies were performed without cardiopulmonary bypass. Also, in the study conducted by Bakhtiary, the patients in the epidural group received ropivacaine, which has an inti-inflammatory effect and could contribute to the lower incidence of atrial fibrillation.

The authors of the meta-analysis concluded that the thoracic epidural anesthesia has no beneficial efficacy in preventing post-operative atrial fibrillation in patients undergoing CABG surgery.

The critical appraisal of the meta-analysis is included in Appendix C. The PRISMA format (Appendix A) was described earlier in this text and was used for the critical appraisal of the meta-analysis. The critical appraisal assessed the presence of the main components that determine the degree of scientific integrity. Based on the assessment, the meta-analysis has strong scientific integrity. All major factors were included in the study. The search for the studies, the study selection and data collection processes were described in detail. The results of the individual studies within the summary of evidence are provided. Unfortunately, the risk of bias for the separate studies as well as across the studies was not provided, but it was not identified as impacting the results of the study. The summary of evidence with limitations of the study as well as conclusions were also provided.

Studies that Assessed Atrial Fibrillation

The study of 121 patients conducted by Jideus (Jideus et al., 2001; Appendix D#1) assessed the incidence of postoperative atrial fibrillation in the group of patients that received thoracic epidural anesthesia for CABG surgery and in the group that underwent the surgery under general anesthesia. The assessment of atrial fibrillation was recorded by using 24 hour Holter recording monitor. Postoperative sustained atrial fibrillation occurred with equal frequency (31.7% or 13 patients in the TEA group and 36.3% or 29 patients in the control group). The study compared not only the incidence of atrial fibrillation, but also the time after surgery at which atrial fibrillation occurred. Both

groups had no significant difference in the time of onset of atrial fibrillation. The time of onset of atrial fibrillation in the TEA group was 1.9 days (44.47+/- 20.5 hours) versus 2.2 days (52.84+/-20.8 hours) after the surgical procedure in the group with general anesthesia.

According to the critical appraisal assessment (Appendix E#1), the study has demonstrated scientific integrity. The number of participants is sufficient for the study to have definitive results (121 patients); all patients that participated in the study were accounted for and the follow up was complete. The allocation of patients to groups was randomized and the patients were analyzed in the same groups that they were assigned to. The study was not blinded, which is expected for this type of treatment. The groups of patients were treated equally; however, some patients were moved to another group due to inability to perform the selected treatment. All clinical outcomes in the study were considered.

The randomized controlled trial by Bakhiatry and colleagues (Bakhiatry et al., 2007; Appendix D#2) compared two groups of patients (N = 133) on the incidence of perioperative atrial fibrillation in patients with CABG. The first group of patients received a combination of general anesthesia (total intravenous anesthesia) and thoracic epidural anesthesia. The second group of patients received only total intravenous general anesthesia. Each group consisted of 66 patients. The incidence of atrial fibrillation was assessed with continuous automated ECG analysis for leads I, II, and V5 using intra-atrial ECG lead.

The group that used thoracic epidural anesthesia as a part of anesthetic management had a significantly lower incidence of perioperative atrial fibrillation (3%;

n=2). The incidence of atrial fibrillation in the group with general anesthesia was 23.7% (n =18). The critical appraisal of this study (Appendix E#2) revealed that the study had a full inclusion of patients with complete follow up. However, the randomization of the study was modified. The study was not blinded which was expected. The groups were similar at the start of the study. The groups of participants were treated equally during the study and all clinical outcomes were considered.

Another study that measured the incidence of atrial fibrillation was conducted by Yashiki and assessed 55 patients (Yashiki et al., 2005, Appendix D#3). The study assessed three groups of patients: the first group received only thoracic epidural anesthesia, the second group was managed with the combination of general and thoracic epidural anesthesia, and the third group received only general anesthesia. The incidence of atrial fibrillation was recorded with 24-hour Holter electrocardiograms before and during the surgery, as well as for four days after the surgery continuously and on the postoperative day 7. On the day of surgery the atrial fibrillation was noted only in the group with thoracic epidural anesthesia (about 5% of the patients). There was no significant difference between the incidences of atrial fibrillation between the groups with thoracic epidural and combined anesthesia noted on the postoperative day 1. No incidence of atrial fibrillation was recorded in the group with general anesthesia on the postoperative day 1. The thoracic epidural catheter was discontinued on the postoperative day 2 and any incidences of atrial fibrillation are not included in the study since there is no comparison between groups.

According to the critical appraisal (Appendix E#3), the validity of this study was significantly affected by the lack of randomization which can affect the homogeneity of

groups and the results of the study. The study had a small number of participants (n=55) with distribution between 3 groups. Otherwise, the groups were treated equally with complete follow-up. All data were utilized and the patients were analyzed in the same groups that they were assigned.

A study that included 80 patients undergoing CABG surgery under general versus general with thoracic epidural anesthesia was conducted by Kilickan (Kilickan et al., Appendix D#4). The study assessed cardiac arrhythmias including atrial fibrillation and troponin level at 24, 48, and 72 hours after the surgery. The patients were divided in groups not only based on the method of anesthesia used during the procedure, but also based on the degree of the left ventricular function. The poor left ventricular function was defined as ejection fraction equal or less than 40%. Thus, the patients were divided into four groups: patients with poor left ventricular function and general anesthesia, patients with poor left ventricular function and general with epidural anesthesia, patients with good left ventricular function and general anesthesia, and patients with good left ventricular function and general with thoracic epidural anesthesia. The results of the study revealed that at 24 and 48 hour period the troponin level was slightly higher in participants received general anesthesia, but the 72 hour period there was no difference in the troponin level between groups. At the 24 hour the troponin level in the groups with general anesthesia was 6.55 – 10.1 ng/ml; in the groups with general and thoracic epidural anesthesia the troponin level was ranging from 6.25 – 6.43 ng/ml. At 48 hour mark, the troponin level in the groups with general anesthesia was 1.44-1.87 ng/ml, in the groups with the combined anesthesia it was ranging from 0.96 to 1.52 ng/ml. The difference in troponin level at 72 hours was insignificant with number ranging from 0.85-

1.58 ng/ml for the groups with general anesthesia and from 0.74-1.46 for the groups with thoracic anesthesia. The study assessed the number of cardiac arrhythmias in general and included ventricular fibrillation, atrial fibrillation, and heart block in the same group. It is very difficult to assess the impact of thoracic epidural anesthesia on the incidence of atrial fibrillation from the general arrhythmia group. The authors made their recommendations based on results from other assessed outcomes such as cardiac index and general number of arrhythmias. The recommendations stated that thoracic epidural anesthesia was effective especially in patients with poor left ventricular function in reducing the number of arrhythmias after the release of the aortic clamp.

According to the critical appraisal, the study has good scientific integrity (Appendix E#4). All patients were accounted for in the study with the complete follow-up. The patients were randomized for the treatment and were analyzed in the same groups that they were assigned. The groups were similar at the start of the trial and were treated equally. All randomized patient data were analyzed. Similar to previously mentioned studies, the study is not blinded which was expected.

A study that assessed both the occurrence of atrial fibrillation and the troponin release was the randomized controlled study conducted by Caputo on 74 patients (Caputo et al., 2009, Appendix D#5). The study compared two groups of patients with similar characteristics. The primary outcome of the study was the release of troponin as a marker for cardiac stress, but the incidence of atrial fibrillation was also noted. The incidence of atrial fibrillation was recorded by continuous monitoring of all hemodynamic measurements including heart rate in the operating room. Samples of blood to determine the troponin level were collected preoperatively, at the end of the operation, and 4, 12,

24, and 48 hours after the surgery. Troponin levels remained constant in both groups over the time of the study with the ratios of geometric means ranging from 1.22 to 1.62. However the incidence of atrial fibrillation was lower in the group receiving general and thoracic anesthesia with 19% versus 47% in the group with only general anesthesia.

According to the critical appraisal, the study has reasonable scientific integrity (Appendix E#5). The study has a small number of participants (n=74).The assessment of a larger number of participants might identify more clinically and statistically significant differences in myocardial response to the type of anesthesia. The information about the incidence of atrial fibrillation among the groups is lacking details such as the time of occurrence. Since patients remained on the constant hemodynamic observation and the study was looking at the general occurrence of atrial fibrillation, this fact should not affect the results. All patients participated in the study were properly accounted for and contributed to the conclusion. The study is randomized with the full follow-up of the patients in the same groups that they were assigned. The groups were similar at the beginning of the study and treated equally.

The troponin level as an indication of the stress response of the heart was also assessed by the study conducted by Barrington and colleagues (Barrington et al., 2005, Appendix D#6). The study measured troponin levels in 120 patients on preinduction, 12 and 24 hours after the aortic cross-clamp release. The groups consisted of 60 patients each that were randomly assigned to the group that provided general anesthesia or combined general and epidural anesthesia for the operation. The troponin level was increased in both groups at 12 and 24 hours with no significant differences between groups with a median number of 17.2 in the group with general and 17.0 in the group

with general and thoracic epidural anesthesia at 12 hours after cross-clamp release. The similar results were at 24 hour with a median number of 9.1 in the general anesthesia group and 9.1 in the group where the thoracic epidural was implemented.

According to the critical appraisal, the scientific integrity of the study was diminished (Appendix D#6). The patients were randomly assigned to the treatment, with full follow-up, but later some patients were moved to a different group which affected the equality of the groups. The groups were treated equally and all clinically important outcomes were considered.

Zawar et al. (2015, Appendix D #7) compared troponin levels in 86 patients that were randomly assigned to the general anesthesia group or the group with general with thoracic epidural anesthesia group. Both groups had similar troponin level that was obtained post induction. Also both groups had similar levels in troponin on the postoperative day 2, but the significantly lower levels on the postoperative day 5 (0.12 mcg/L in the thoracic anesthesia group versus 0.64 mcg/L in the control group). It should be noted that the epidural anesthesia was discontinued on the postoperative day 3.

According to the critical appraisal, the study has excellent scientific integrity (Appendix E#7). The groups were randomly assigned to the treatment options and were analyzed in the same groups. The groups appear to be similar at the start of the trial with a complete follow-up. The study is not blind which was expected for this type of treatment. The groups were treated equally and all clinically important outcomes were considered in the study.

Across Studies Assessment

The across study assessment was conducted in order to identify the weaknesses of the studies included in the review and to compare the data across the studies (Appendix F). The main problem related to the validity of the data was related to the design of the studies. Some studies had a small sample size of participants (Yashiki et al., 2005) or unequal distribution of participants between the groups (Jideus et al., 2001); other studies had a modified randomization where patients were pre-selected by an anesthesiologist for eligibility to receive an epidural catheter before randomization (Bakhiatry et al., 2007). Some data were partially excluded from the systematic review because authors combined all observed arrhythmias in one group without the differentiation (Kilickan et al., 2005). The same study also had a very complicated differentiation of groups with a small number of participants (Kilickan et al., 2005). Since the studies were completed in different countries, it is difficult to compare the numbers of troponin level across the studies due to different measurement standards.

The outcomes related to atrial fibrillation can be divided into intraoperative and postoperative periods. The intraoperative incidence of atrial fibrillation was assessed by Bakhtiary (2007). The authors found a significant difference in the incidence of atrial fibrillation in the group with thoracic epidural anesthesia (3% or 2 cases). The incidence of atrial fibrillation in the group with general anesthesia consisted of 23.7% or 18 cases. The authors proposed that the significant difference is contributed to a balance within the autonomous nervous system due to epidural anesthesia. These results were confirmed by the study conducted by Caputo (2009). The study did not differentiate between the periods of the surgery and recorded all incidents of atrial fibrillation up to 48 hours postoperatively. According to the study, the incidence of atrial fibrillation was

significantly lower in the epidural anesthesia group (19%) versus 47% in the general anesthesia group. The authors did not make any assumptions about the mechanism that could contribute to the results of the study.

The study that assessed the rate of atrial fibrillation in the postoperative period demonstrated no difference between the epidural anesthesia and general anesthesia groups (Jideus et al., 2001). Postoperative atrial fibrillation occurred in 31.7% in the thoracic epidural group versus 36.3% in the general anesthesia group. Also, the time of onset of atrial fibrillation was not significantly different in both groups: 1.9 days in the TEA group and 2.2 days in the GA group. Yashiki et al. (2005) assessed the incidence of atrial fibrillation intra and postoperatively up to day 4 and on postoperative day 7. The highest incidence of atrial fibrillation was noted on the postoperative day 2 when the epidural catheters were discontinued. The authors explained this sudden increase with the sympathetic activity dominance due to discontinuation of thoracic epidural anesthesia. The meta-analysis of randomized controlled studies that assessed the efficacy of thoracic epidural anesthesia across five studies (Gu et al., 2012) found no significant difference in the incidence of postoperative atrial fibrillation between the group with general anesthesia and implementation of thoracic epidural anesthesia.

Troponin release was the other variable that was used as indication of the myocardial function. Several studies were assessing cardiac markers in order to determine if the thoracic epidural anesthesia has benefits in preservation of cardiac function. According to the following studies, thoracic epidural anesthesia has no significant benefit in preserving myocardial function. Barrington et al. (2005) observed the increase in troponin level in both groups. No difference was noted between two

groups with the following distribution of numbers: the medial number of Troponin level was 17.2 in the GA group and 17.0 in the TEA at 12 hour mark and 9.1 in both groups at the 24 hour mark. Kilickan and colleagues (2005) supported the above mentioned findings by assessing troponin level at 24, 48 and 72 hours after the surgery. The distribution of troponin concentration consisted of 6.55 to 10.1ng/ml in the general anesthesia group and 6.25 to 6.43 in thoracic epidural group for 24 hour assessment and 1.44 to 1.87 for the general anesthesia group versus 0.96 to 1.52 for the epidural anesthesia group for 48 hour assessment. No significant difference was recorded at the 72 hour period. The study conducted by Caputo also supported the above stated findings. Zawar et al. (2015) also noted the similar distribution of troponin in both groups throughout the study with the exclusion of postoperative day 5 where the thoracic epidural group had a significantly lower level of troponin (0.12 mcg/L versus 0.64 mcg/L). It should be noted that the epidural anesthesia was discontinued on the postoperative day 3. All authors that assessed the role of epidural anesthesia on the myocardial cell damage which was indicated by release of troponin level agreed that regional anesthesia does not provide any significant reduction in cardiac damage.

Next, summary and conclusions will be presented.

Summary and Conclusions

Currently, the traditional approach to CABG surgery includes the administration of general anesthesia as a solo anesthetic technique. Volatile agents, total intravenous anesthesia or a combination of both can be used in providing general anesthesia. General anesthesia can be associated with significant adverse reactions especially in an older population that requires coronary artery bypass surgery. The CABG procedure itself is associated with a significant stress on the heart that results in high incidence of cardiac arrhythmias, especially atrial fibrillation. Atrial fibrillation has a strong association with CABG surgery and remains the most common complication (Gu, 2012). Increased sympathetic activation related to the general anesthesia administration is the main concern and pathogenesis of cardiac stress response and cardiac arrhythmia (Gu). Some authors proposed that thoracic epidural anesthesia may attenuate the cardiac stress response and promote preservation of myocardial function during intraoperative and postoperative period (El-Morsy, 2012). The implementation of thoracic epidural anesthesia may not only attenuate the cardiac stress response, but also decrease the incidence of atrial fibrillation during intraoperative as well as postoperative period (Gu, 2012).

The purpose of this systematic review was to assess the benefits of thoracic epidural anesthesia during CABG surgery to determine if it will provide a significant reduction in cardiac stress response as well as reduction in the atrial fibrillation rate. Studies were selected through a comprehensive literature review using selected key terms. The initial search yielded 42 articles. After inclusion and exclusion criteria were applied, only five articles met criteria. An additional three articles were selected through

the related search option. A final total of seven controlled randomized trials and one meta-analysis were included in the systematic review. The main observed outcomes included the incidence of atrial fibrillation and troponin release as markers for cardiac stress.

The main findings of the systematic review do not support the use of thoracic epidural anesthesia during the CABG surgery as a supplementation to the traditional approach of general anesthesia. The main concern during the CABG surgery is related to the maintaining and preserving the cardiac function of the patient. The stress of the heart can be assessed by two main parameters: troponin level and the rate of cardiac arrhythmias. These parameters were assessed during this systematic review in order to identify if the addition of epidural anesthesia would decrease the sympathetic response of the heart and subsequently the level of the stress. The results of the study did not support this proposition. No significant difference in the level of the troponin and the rate of atrial fibrillation between the groups with thoracic epidural and general anesthesia were identified. Taking into consideration the possible complications related to the coagulation status of patients, inconsistent positive results cannot be used as a guideline in the anesthesia practice.

There were certain limitations in conducting this systematic review. The main limitation is related to the small amount of available studies. Also, the fact that the studies were conducted in different settings and countries made the comparison of the numeric data such as a troponin level, difficult to cross compare. Another limitation is related to the inadequate randomization of the patients in some studies. For this reason, the limited positive results should be interpreted with caution.

In conclusion, this systematic review determined that thoracic epidural anesthesia does not improve the incidence of atrial fibrillation and does not provide the decrease in troponin level in the patients undergoing CABG surgery.

The recommendations and implications for advanced practice nurses will be discussed in the next section.

Recommendations and Implications for Advanced Nursing Practice

The systematic review yielded some valuable information for nurse anesthesia practice. Currently in anesthesia practice, there is significant opposition and controversy related to implementation of thoracic epidural anesthesia for CABG. The primary reason for this hesitation is the fact that the majority of patients requiring CABG surgery are treated with thrombolytic therapy. Nurse anesthetists as anesthesia providers are aware of the sympathectomy effect of epidural anesthesia and its correlation with myocardial stress response. Regardless, there is a lack of evidence-based knowledge related to the impact of thoracic epidural technique during CABG surgery.

The current policies related to the administration of epidural anesthesia are only related to the level of anticoagulation of patients in order to provide safe epidural anesthesia and avoid complications related to bleeding. The ultimate choice of the type of anesthesia for the surgery depends on the anesthesia provider, including the certified nurse anesthetist. The risks and benefits for a specific patient and specific surgery are the major determinants of the type of anesthesia. There is not a set policy or recommendations related to what type of anesthesia will be used during CABG surgery. Nurse anesthetists could be instrumental in creating some guidelines related to the utilization of thoracic anesthesia based on the evidence provided in this review. Nurse anesthetists can take the lead in providing safe anesthesia by promoting and adhering to evidence based practice.

Nurse anesthetists are leaders in utilizing evidence-based practice in order to provide the best surgical conditions for surgeons and safest conditions for patients. Nurse

anesthetists can also provide education to their colleagues within anesthesia departments or during anesthesia conferences about evidence-based approaches.

The American Association of Nurse Anesthetists (AANA) provides multiple resources in order to support education among CRNAs. After additional research, the AANA could provide valuable information about neuraxial anesthesia during cardiac surgeries on their website in order to keep CRNAs informed about the latest anesthesia techniques for CABG surgery. By being involved in this professional organization, the CRNA can potentially impact practice on a national level.

Taking into consideration the current evidence and the high risk for complications, the author of this review does not recommend to use epidural anesthesia as an adjunct technique for general anesthesia during CABG. More research needs to be conducted on the influence of thoracic anesthesia on cardiac performance. The research could be designed to isolate one variable at the time in one specific group of patients (patients with previous history of atrial fibrillation or myocardial impairment) in order to provide more detailed data on the effect of thoracic epidural. A study that stratified patients based on age would provide valuable information on age-related responses to thoracic epidural. Studies that include a larger number of participants are needed to confirm the current findings and establish the recommendations for anesthesia provider practice.

In conclusion, the results of this systematic review revealed that epidural anesthesia does not provide a significant difference in atrial fibrillation rate or cardiac stress and is not recommended for routine use for CABG surgeries. CRNAs should implement anesthesia techniques that provide the safest conditions for a patient and continue seeking new evidence to improve patient care.

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Appendix A

PRISMA Systematic Review Check List

Table 1. **Checklist of Items to Include When Reporting a Systematic Review (With or Without Meta-Analysis)**

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Note. Adapted from the PRISMA statement of reporting the systematic reviews and meta-analyses.

Appendix B

Title	Gu et al. Meta-analysis of randomized controlled trials on the efficacy of thoracic epidural anesthesia in preventing atrial fibrillation after coronary artery bypass grafting, BioMedCentral Cardiovascular Disorder, 2012,12:67

Study eligibility

Type of study	Meta-analysis
#of studies included	5 randomized controlled studies with 540 patients total
Types of intervention	Elective CABG
Types of comparison	TEA+GA group (n=247), GA group (n=293)
Outcome measures	The occurrence of atrial fibrillation in postoperative period
Findings	No significant difference in the incidence of postoperative atrial fibrillation between two groups.

Conclusions	TEA shows no beneficial efficacy in the incidence of postoperative atrial fibrillation in adult patients undergoing CABG.
Limitations	Significant heterogeneity of the studies included

Appendix C

Critical appraisal of the meta-analysis

Gu et al. Meta-analysis of randomized controlled trials on the efficacy of thoracic epidural anesthesia in preventing atrial fibrillation after coronary artery bypass grafting. BMC Cardiovascular Disorder. 2012, 12:67.

Title	Systematic review
ABSTRACT	
Structured summary	The following items are provided: the background, data sources, study eligibility criteria, participants, interventions, methods, results, limitations, conclusion.
INTRODUCTION	
Rationale	Provided
Objectives	Statement of questions being addressed provided
METHODS	
Protocol and registration	Not available
Eligibility criteria	Included
Information sources	Databases with data coverage provided
Search	Full electronic search strategy provided
Study selection	The process for selecting studies described
Data collection process	Method of data extraction provided
Data items	Not included
Risk of bias in individual studies	Not included
Summary measures	Risk ratio
Synthesis of results	Provided
Risk of bias across studies	Not provided
Additional analyses	Not provided
RESULTS	
Study selection	Provided
Study characteristics	Not provided
Risk of bias within studies	Not provided
Results of individual studies	Provided
Synthesis of results	Not provided
Risk of bias across studies	Not provided
Additional analysis	Not provided
DISCUSSION	
Summary of evidence	Provided
Limitations	Provided
Conclusions	Provided
FUNDING	
Funding	Not provided

Appendix D

Data collection form D#1

Title	Jideus et al. Thoracic epidural anesthesia does not influence the occurrence of postoperative sustained atrial fibrillation. Annals of Thoracic Surgery, 2001;72:65-71.

Study eligibility

Type of study	Randomised controlled trial
Participants	121 participants
Types of intervention	Elective CABG
Exclusion criteria	Disorders associated with an increased incidence of atrial fibrillation, anticoagulation medication or disorders that are associated with increased risk with TEA, health related conditions that could compromise results of the study, TEA did not function properly.
Types of comparison	TEA group (n=45), GA group (n=96)
Outcome measures	The occurrence of atrial fibrillation in postoperative period
Assessment method	24 hour Holter recording monitor
Findings	The incidence of postoperative sustained AF was the same in the TEA group as in the control with GA. There was no significant difference in the average time after surgery at which AF occurred. Postoperative sustained AF occurred with equal frequency (31.7% (13 patients) in the TEA group compared with 36.3% (29 patients) in the control group. The time of onset of AF was 1.9 days (44.47+/-20.5 hours) in the TEA group versus 2.2

	days (52.84+/- 20.8 hours) in the control group after the surgical procedure. The secondary outcome that was measured was the sympathetic activity.
Recommendations	TEA has no effect on the incidence of postoperative sustained AF.
Notes	The proposed mechanism that TEA administered in addition to GA reduces sympathetic stress to sternotomy will result in improved hemodynamic stability was not supported by the study. Reduced NE did not reduce incidence of AF. The new assumption of the triggering mechanism of postoperative AF is mechanical, such as distention of the pulmonary veins after surgery was made. The author recommends further studies to identify The mechanism and patients at risk in order to target patients with intensive prophylactic measures to reduce the incidence of postoperative AF.
Limitations	Small groups, unequal distribution of patients in groups (45 vs 96), one setting, no data about AF occurrence during the case, time of operation, EBL, no indication what kind of GA was implemented

Data collection form D#2

Title	Bakhtiary et al. Impact of high thoracic epidural anesthesia on incidence of perioperative atrial fibrillation in off-pump coronary bypass grafting: a prospective randomized study. The Journal of Thoracic and Cardiovascular Surgery, 2007; 134: 460-4
Type of study	Randomised controlled trial
Participants	132 patients
Intervention	Elective off-pump CABG
Exclusion criteria	History of atrial arrhythmias, those undergoing emergent operations, and patients requiring intraoperative inotropic support were excluded from the study.
Comparison	GA group (n=66) and group with combined GA and TEA (n=66)
Outcome measures	Incidence of perioperative atrial fibrillation
Assessment method	Intra-atrial ECG lead, continuous automated ECG analysis for leads I, II, and V5.
Findings	Patients in the GA+TEA group had a significantly lower incidence of perioperative AF (3% or n=2) than in the GA group (23.7% or n=18).
Recommendations	The authors propose TEA as a significant factor in reduction of AF due to sympatholytic properties of TEA. The TEA promotes the balance within the autonomous nervous system as a major mechanism responsible for reduction of AF incidence.
Notes	There was no significant difference between the operation time, blood loss, ventilation time, and number of distal anastomoses. TIVA was used as GA.

Limitations	A small number of participants, all patients were preselected by an anesthesiologist for eligibility to receive an epidural catheter before randomization. Patients with contraindications for TEA were excluded from the study.

Data collection form D#3

Title	Yashiki et al. Thoracic epidural anesthesia for coronary bypass surgery affects autonomic neural function and arrhythmias. Innovations, 2005; 1:83-87
Type of study	Randomised controlled trial
Participants	55 patients (group A, n=17 ; group B, n=21; group C, n=17).
Intervention	Elective coronary artery bypass surgery
Exclusion criteria	Patients with acute myocardial infarction or perioperative atrial fibrillation, receiving antiarrhythmic drugs other than beta-blockers, patients having emergency operation or minimally invasive direct coronary artery bypass surgery.
Comparison	3 groups: A group: high TEA alone; group B: GA combined with TEA; group C: GA alone.
Outcome measures	Atrial fibrillation
Assessment method	24-hourHolter electrocardiograms were recorded before, during, and after surgery over 4 consecutive days and on postoperative day 7.
Findings	Sympathetic inhibition was observed in both group that TEA was used. After discontinuation of TEA, sympathetic activity was recovered. The incidence of postoperative atrial fibrillation was the highest in group B (TEA+GA) on the postoperative day 2.

Recommendations	TEA can be used to decrease GA. Further studies are necessary to evaluate its effect on the incidence of postoperative atrial fibrillation.
Notes	The postoperative atrial fibrillation was the highest in group B (TEA and GA) because sympathetic activity rapidly became dominant on this day due to the discontinuation of TEA.
Limitations	Modified randomization (groups were formed on patients wish, length of surgery, coagulation status).

Data collection form D# 4

Title	Kilickan et al. Thoracic epidural anesthesia preserves myocardial function during intraoperative and postoperative period in coronary artery bypass grafting operation. The Journal of Cardiovascular Surgery,2005;46,6:559-567
Type of study	Randomized controlled trial
Participants	80 participants
Intervention	Elective CABG with pulmonary bypass
Exclusion criteria	Patients with compromised coagulation were excluded. 4 patients were excluded during the study due to intraoperative acute myocardial infarction.
Comparison	4 groups: 1- pts with poor ventricular function (VF) with GA, 2- good VF patients with GA, 3- poor VF patients with TEA, 4- good VF patients with TEA. The poor VF was defined as EF</= 40%, good VF was defined as EF>/=40% by echocardiography
Outcome measures	Hemodynamic data such as cardiac output (CO) and cardiac index (CI) and systemic vascular resistance index (SVRI). Cardiac arrhythmias (VF, AF, HB) after release of the aortic cross-clamp

Assessment method	Hemodynamic data were measured before CPB as a baseline (preCPB), 4 hours after the end of CPB (postCPB) and at 24 hours after operation. The continuous cardiac output was monitored continuously during the surgery. Postoperative myocardial ischemia was assessed by measuring troponin I. The exact methods are not indicated.
Findings	The cardiac index values were significantly higher than baseline values at 4 hrs after the end of CPB in the group TEA+GA+PV and TEA+GA+GV. No difference was found in the group GA+PV and group GA+GV. Patients in groups GA+PV and GA+GV had higher incidence of VF, AF or HB after release of the aortic cross-clamping (GA+PV 65% or 13/20; GA+GV 60% or 12/20 versus 30% or 6/20 in TEA+GA+PV group and 25% or 5/20 in TEA+GA+GV group). Cardiac troponin values I (TnI) values were higher in GA+PV group at 24 hours (10.1+/- 8.35) versus 6.55 in GA+GV, 6.25 in TEA+GA+PV, and 6.43 in TEA+GA+GV groups. TnI values were lower in TEA+GA+GV group at 48 hrs (0.96+/- 1.63) versus 1.87+/-2.38 in GA+PV group, 1.44+/- 2.07 in GA+GV group, and 1.52+/-2.03 in TEA+GA+PV group. No significant difference was recorded in baseline TnI or at 72 hours.
Recommendations	TEA seems to be effective in patients with poor left ventricular function in improving cardiac index, reducing the number of arrhythmias after release of aortic clamp.
Notes	Very confusing study, poorly worded, the methods and assessment are not clear.
Limitations	No indication of the specific arrhythmia that was measured as one of the outcomes, but combined all in one group (VF, AF, HB). The data are provided only on the incidence of FV in all 4 groups. We consider not to include the data about the arrhythmias in the systematic review since the provided data are not clear enough.

Data collection form D #5

Title	Caputo et al. Myocardial, Inflammatory, and Stress Responses in Off-Pump Coronary Artery Bypass Graft Surgery With Thoracic Epidural Anesthesia. Annals of Thoracic Surgery 2009;87:1119-26
Type of study	Randomised controlled trial

Participants	74 patients (males, mean age 63.8 in GAE and 66.5 in GA group), patients characteristics were similar between the two groups
Intervention	Off-pump CABG
Exclusion criteria	Patients with salvage CABG, with cardiogenic shock, heart valve pathologies were excluded. Patients on intravenous heparin, warfarin, or clopidogrel or who suffered from bleeding diathesis were also excluded. Patients with previous Q-wave MI or CHF were not excluded.
Comparison	GA group and GA+EA
Outcome measures	Release of troponin I as measurement of myocardial reperfusion injury. Atrial fibrillation
Assessment method	Samples of blood were collected preoperatively, at the end of the operation, and 4, 12, 24, and 48 hours postoperatively.
Findings	No significant difference in Tn I release between the two groups. Troponin levels remained constant over the time of the study. Atrial fibrillation- the incidence of atrial fibrillation was lower in the GA +EA group (19%) versus 47% in the GA group.
Recommendations	Regional anesthesia does not provide any significant reduction in the release of markers of myocardial cell damage
Notes	No significant difference in TnI release between the two groups, but TnI release is reduced in OCPB in comparison with on bypass surgery.
Limitations	The main limitations – not blinded, a small sample size, missing data for some blood markers (the authors did not indicate the markers and the group).. Alarger study may have identified more clinically and statistically significant differences in myocardial response in two groups.

Data collection form D# 6

Title	Barrington et al. Epidural anesthesia for coronary artery bypass surgery compared with general anesthesia alone does not reduce biochemical markers of myocardial damage. Anesthesia Analgesia 2005; 100:921-8
Type of study	Randomised controlled trial
Participants	120 patients
Intervention	Elective CABG
Exclusion criteria	Emergency or repeat CABG surgery, combined valve and CABG surgery, platelet or other coagulation abnormalities, or aspirin administration within 6 days of surgery or active neurological disease
Comparison	GA group (n=60) and GA+TEA group (n=60)
Outcome measures	TnI level and EKG changes such as new persistent Q wave and new ST segment depression or elevation in at least 2 contiguous leads of the same vascular territory. Transmural infarction was defined as new Q waves and TnI>15 mcg/L at 24 hours.
Assessment method	Samples of blood preinduction, 12 and 24 hours after aortic cross-clamp release for TnI levels. 12 lead EKG before surgery and on postoperative days 1 and 5 for Q wave and ST segment changes.
Findings	The TnI levels were increased in both groups at 12 and 24 hours, but there were no significant differences between groups with a median number in GA group 17.2 (10.7-26.4) and 17.0 (10.4-27.9) in the group with GA and TEA at 12 hours and 9.1 (4.9-25.9) in GA group and 9.1 (6.0-21.0) in GA and TEA group at 24 hrs. Eight patients (6.7%) developed new persistent Q waves by day 5 (GA group, n=5; GA+TEA group, n=3. However only 3 (2.5%) patients has a transmural myocardial infarction based on TnI and ECG criteria.

Recommendations	TEA for elective CABG surgery had no effect on biochemical or ECG markers of myocardial ischemia or infarction.
Notes	GA group received TIVA (Fentanyl and Morphine infusion), TEA group received Fentanyl infusion and epidural with Ropivacaine 0.2% and Fentanyl.
Limitations	Epidural blockade was successful in 58 of 60 patients. The 2 patients with nonfunctioning epidural catheters were analyzed as in the epidural group, but received GA only. Also as authors indicated, the prevalence of peripheral and cerebrovascular disease in the TEA group was more frequent that also can influence the results of the study.

Data collection form D#7

Title	Zawar et al. Nonanalgesic benefits of combined thoracic epidural analgesia with general anesthesia in high risk elderly off pump coronary artery bypass patients. Annals of Cardiac Anaesthesia
Type of study	Randomised controlled trial
Participants	86 patients, age>= 70 years with distribution between groups: study group: 40 patients, mean age – 74.9 years, 89.1 % males. Control group -46 patients, mean age - 74.2 years, 88.6% - males.
Intervention	Primary OPCAB surgery without the use of CPB and cardioplegic arrest.
Exclusion criteria	Infection over the spine, coagulation disorders, emergency cases, unstable agina, left main stem disease, patients with dysrhythmias, undergoing combined procedures, patients on intra-aortic balloon pulsation, patients on antiplatelet agent, low molecular weight heparin or heparin infusion.
Comparison	GA + TEA (study group) and GA (control group)

Outcome measures	Primary outcomes are postoperative complications, total intensive care unit stay and hospital stay. Secondary outcomes: stress response (measures by interlukin, TNF, troponin I, decreased total hospital stay.
Assessment method	Samples of venous blood were collected at postanesthesia induction and on the day 2 and 5
Findings	Secondary outcomes: the baseline levels of troponin I were comparable between groups at postinduction, but was significantly lower in study group at day 5 (0.64 mcg/L in control group vs. 0.12 mcg/L in the study group). The patients in the study group and control group had no significant difference in postoperative complication such as atrial and ventricular arrhythmias.
Recommendations	The addition of TEA to GA results in a significant reduction in the stress (troponin level) and inflammatory response to surgery.
Notes	TPN level is measured as a secondary outcome at day 2,5. Primary outcomes are postoperative complications, total intensive care unit stay and hospital stay. Secondary outcomes: stress response (measures by interlukin, TNF, troponin I, decreased total hospital stay.
Limitations	The study is not blinded. The study was slow in recruiting because large number of patients were on intravenous heparin or antiplatelet agents. This may represent a significant limitation to the application of epidural anesthesia.

Appendix E

Critical Appraisal Worksheet E # 1

Jideus et al. Thoracic epidural anesthesia does not influence the occurrence of postoperative sustained atrial fibrillation. Annals of Thoracic Surgery, 2001;72:65-71.

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Yes
Were all randomized patient data analyzed?	Yes
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Not completely
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	No
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article's validity	
Results	
How large was the treatment effect?	No
Were all clinically important outcomes considered?	Yes
Are the likely treatment benefits worth the potential harms and costs?	No

Critical Appraisal Worksheet E# 2

Bakhtiary et al. Impact of high thoracic epidural anesthesia on incidence of perioperative atrial fibrillation in off-pump coronary bypass grafting: a prospective randomized study. The Journal of Thoracic and Cardiovascular Surgery, 2007; 134: 460-4

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	No
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Not completely
Were all randomized patient data analyzed?	Yes
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	No
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article's validity	
Results	
How large was the treatment effect?	Not completely
Were all clinically important outcomes considered?	Yes
Are the likely treatment benefits worth the potential harms and costs?	Not completely

Critical Appraisal Worksheet E# 3

Yashiki et al. Thoracic epidural anesthesia for coronary bypass surgery affects autonomic neural function and arrhythmias. Innovations, 2005; 1:83-87

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Yes
Were all randomized patient data analyzed?	Yes
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	No
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article's validity	
Results	
How large was the treatment effect?	No
Were all clinically important outcomes considered?	Yes
Are the likely treatment benefits worth the potential harms and costs?	No

Critical Appraisal Worksheet E# 4

Kilickan et al. Thoracic epidural anesthesia preserves myocardial function during intraoperative and postoperative period in coronary artery bypass grafting operation. The Journal of Cardiovascular Surgery,2005;46,6:559-567

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Yes
Were all randomized patient data analyzed?	Not completely
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	No
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article's validity	
Results	
How large was the treatment effect?	Not completely
Were all clinically important outcomes considered?	No
Are the likely treatment benefits worth the potential harms and costs?	Not completely

Critical Appraisal Worksheet E#5

Caputo et al. Myocardial, inflammatory, and stress responses in off-pump coronary artery bypass graft surgery with thoracic epidural anesthesia. Annals of Thoracic Surgery 2009;87:1119-26

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Yes
Were all randomized patient data analyzed?	No
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	No
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article's validity	
Results	
How large was the treatment effect?	No
Were all clinically important outcomes considered?	Not completely
Are the likely treatment benefits worth the potential harms and costs?	No

Critical Appraisal Worksheet E# 6

Barrington et al. Epidural anesthesia for coronary artery bypass surgery compared with general anesthesia alone does not reduce biochemical markers of myocardial damage. Anesthesia Analgesia 2005; 100:921-8

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	No
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Yes
Were all randomized patient data analyzed?	Yes
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	No
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article's validity	
Results	
How large was the treatment effect?	Yes
Were all clinically important outcomes considered?	Yes
Are the likely treatment benefits worth the potential harms and costs?	Yes

Critical Appraisal Worksheet E# 7

Zawar et al. Nonanalgesic benefits of combined thoracic epidural analgesia with general anesthesia in high risk elderly off pump coronary artery bypass patients. Annals of Cardiac Anaesthesia

Question	Assessment:
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes
Was follow-up complete?	Yes
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were randomized?	Not completely
Were all randomized patient data analyzed?	Yes
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Not completely
B = Blinding	
Were patients, health workers, and study personnel “blind” to treatment?	Not completely
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes
Summary of Article’s validity	
Results	
How large was the treatment effect?	No
Were all clinically important outcomes considered?	Yes
Are the likely treatment benefits worth the potential harms and costs?	No

Appendix F

Critical appraisal across the studies

Question	Assessment: studies
FRISBE	
F= Patient Follow-Up	
Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes: 1, 2, 3, 4, 5, 6, 7 Not completely: No:
Was follow-up complete?	Yes: 1, 2, 3, 4, 5, 6, 7 Not completely: No:
R= Randomization	
Was the allocation of patients to treatment randomized?	Yes: 1, 4, 5, 6, 7 Not completely: No: 2, 3
I = Intention-to-Treat Analysis	
Were patients analyzed in the groups to which they were assigned?	Yes: 1, 2, 4, 5, 7 Not completely: 3, 6 No:
Were all randomized patient data analyzed?	Yes: 1, 2, 3, 5, 6, 7 Not completely: 4 No: 5
S = Similar Baseline, Characteristics of Patients	
Were groups similar at the start of the trial?	Yes: 2, 3, 4 , 5, 7 Not completely: 1, 6 No:
B = Blinding	
Were patients, health workers, and study personnel "blind" to treatment?	Yes: Not completely: 6 No: 1, 2, 3, 4, 5, 7
E = Equal Treatment	
Aside from experimental intervention, were the groups treated equally?	Yes: 1, 2, 3, 4, 5, 6, 7 Not completely: No:
Summary of Article's validity	
Results	
How large was the treatment effect?	Yes: 2 Not completely: 3, 4 No:1, 5, 6, 7
Were all clinically important outcomes considered?	Yes: 1, 2, 3, 6, 7 Not completely: 5 No: 4

Are the likely treatment benefits worth the potential harms and costs?	Yes: 2 Not completely: 3, 4 No:1, 5, 6, 7