Sham Controls in Evaluating Cardiac Procedures: A Pilot Systematic Review of RCTs

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ABSTRACT

Background: Blinding minimizes measurement bias, particularly when the outcome being assessed is patient-reported, since psychological measures of well-being and symptoms are influenced by expectations of the effectiveness of a treatment, which can come either from aspects of the intervention or from physician communication. Blinding of investigators collecting patient reported outcomes may be easy, but in surgery, blinding of the participant is impossible without a procedural control. A sham procedural control allows for participant blinding and serves to mimic the psychosocial context a patient will experience, which accounts for the placebo effect before analysis.

Purpose: To investigate the use and reporting of sham procedural controls in cardiac procedural randomized controlled trials (RCTs) assessing patient-reported outcomes.

Data Sources: Cardiac RCTs published in *The Lancet* and *The New England Journal of Medicine* from 1/2005 to 1/2016.

Study Selection: RCTs of adults (1) investigating an intervention that involved an invasive procedure for treating a cardiac disease, (2) with the potential to use a sham control, and (3) reporting patient-reported outcomes.

Data Extraction: A single reviewer extracted data from the full-text.

Data Synthesis: Of the 11 studies that could have used a sham procedural control, only 1 used a sham control and blinded both participants and research assessors to intervention group randomization. The remaining 10/11 surgery studies that assessed quality of life outcomes did not blind patients to their intervention group, leading to a high risk of measurement bias.

Limitations: Identification of published cardiac surgery RCTs was limited to two journals. A single reviewer completed all abstract reviews, full-text reviews, and data extraction.

Conclusions: Surgical research investigating the effect of a procedural intervention on patient-reported outcomes often do not use the ideal of a sham procedural control and often do not provide sufficient reporting about methods of collecting the patient reported outcome or the blinding status of the research assessor. The challenges of incorporating sham procedural controls in surgical studies include obtaining IRB approval, risk of low study enrollment, increased study costs, or fear of unavoidable ethical concerns. Nevertheless, these problems in weighing the benefits and risk of a study are not unique to surgical study design. More surgical studies that evaluate cardiac procedures using patient-reported outcomes should use sham controls to improve study result validity.

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My personal goal for a Master's Paper was to get experience with formulating a research question and developing a method to answer the question. Attending Dr. Sue Tolleson-Rinehart's Master's Paper group taught me how to formulate coherent research questions with my peers. In addition, the abstract assignment was an exercise that helped me to collect multiple study method ideas and decide which approach would be most feasible in the limited time available.

I would also like to thank Dr. Paul Mounsey, Dr. Randall Teal, and Dr. David Weber for helping me think about the logistics of studying sham surgery through a qualitative research approach. Though the logistics did not work out for me to conduct such a study, I appreciated learning about another method and process of research design.

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TABLE OF CONTENTS

LISTS OF TABLES, FIGURES, AND APPENDIX

INTRODUCTION

The gold standard of research design is a double-blinded randomized placebo-controlled trial. Although an Institutional Review Board must review all human subjects research proposal, the Food and Drug Administration (FDA) regulates the research and grants approval of drugs and devices for human use, while the Department of Health and Human Services (DHHS) regulates clinical trials of other therapies, such as surgeries.[1, 2] For approval of new drugs and new devices, placebo-controlled testing is nearly unavoidable and new drugs must undergo a four-phase evaluation process while new devices undergo a premarketing approval process.[3,4] Yet, new drugs and new devices can bypass the more stringent approval process by taking a fast-track evaluation route if the aim is to treat a serious or life-threatening medical condition or if the design and function is similar to a prior approved device.[4, 5] In contrast, innovations in surgical procedures do not require adherence to a predefined developmental pathway or to the gold standard of testing, because a randomized placebo-controlled trial in surgery would require a sham procedural control—a surgical placebo.

A placebo is an inert element administered to a control group so that participants in the control group have similar expectations about the effectiveness of treatment as those in the intervention group. This psychological expectation is important to equalize between groups, because it has the potential to create a placebo effect, which is a non-specific therapeutic effect that may be observed on neuroimaging or measurable through patient-reported outcomes.[6]

A placebo in a surgical study, also known as a "sham procedure", entails a skin incision and unawareness of the operative process to create the perception of having received a surgery in which the therapeutic intervention is not given. A sham procedural control is unnecessary for assessing outcomes not strongly influenced by a placebo effect on psychological state and

perception, such as mortality outcomes. Thus, a sham procedure control is only necessary to eliminate measurement bias in studies that assess patient-reported outcomes, because an individual's psychological state influences the patient's reported outcome.

This pilot systematic review aims to investigate the use and reporting of sham procedural controls in cardiac RCTs with patient-reported outcomes from 1/2005 to 1/2016 in *The Lancet* and *The New England Journal of Medicine.*

Definition of Placebo and Placebo Effect

The word placebo first came into vernacular use in the 1300s, when St. Jerome erroneously translated Psalm 116:9 from Hebrew into Latin.[7, 8] The Hebrew of "*I will walk* before the Lord in the land of the living" turned into the Latin "*I shall please* (Placebo) the Lord in the land of the living."[8] Mourners hoping to gain a reward from the family of the deceased or hired as stand-ins for members of the family sung the verse during funeral services, thus linking the word placebo with sycophancy and substitution.[7, 8]

It was not until 1785 that the word placebo gained a medical definition in A New Medical Dictionary as "a commonplace method or medicine".[7] Over time, placebos connoted an inert medicine that could not harm but could at least please or comfort a patient.[7, 9] Treatments such as bread pills, drops of colored water, and subcutaneous water were widespread into the 1890s.[7] In 1906, the passage of the first Pure Food and Drug Act led to a decrease in placebo remedies, but eventually, placebos reemerged as a presence in clinical trials.[9]

One of the earliest documented use of placebos in cardiac clinical research was by Gold and colleagues. Given conflicting research results on xanthine as a treatment for angina, they conducted a crossover study comparing the effect of a xanthine tablet to a placebo lactose table

for treating angina. The results showed that the proportion of people with worsened, stable, or improved perceived pain after using xanthine was similar to those using the lactose placebo, which concluded that xanthine was an ineffective treatment for angina. From these results, the researchers hypothesize that the supposedly inert lactose tablet may have led to a perceived improvement in chest pain through "confidence aroused in a treatment", "encouragement afforded by a new procedure", and "a change in medical advisor."[10]

Our twenty-first century understanding defines Gold and colleagues' observation as the placebo effect. Giving a placebo to participants in the control group creates a psychosocial context that attempts to mimic the psychosocial context experienced by participant receiving the study intervention. The psychosocial context is a combination of variables that include both individual and clinician characteristics and interaction among the patient, clinician, and the treatment environment. The hypothesis made by Gold and colleagues are associated with "expectancy" or the "patient-practitioner relationship" components of the placebo effect.[6] Kaptchuk et al found that various component parts combine in a graded dose escalation to create a placebo effect, of which the patient-practitioner relationship is the most substantial component.[11] Furthermore, the mode of intervention delivery influences a patient's expectations and makes a graded dose contribution to the placebo effect.[6] For example, in a systematic review of placebo effectiveness as migraine prophylaxis, more invasive treatment methods were associated with a greater reduction in migraine frequency. The proportion of responders was greatest for sham surgery (58%), followed by sham acupuncture (38%), and then oral pharmacological placebo (22%).[12] An implication of that review is double blinding of both participants and investigators to a participant's assigned treatment is imperative for equalizing expectancy and the patient-practitioner relationship experience across study groups. Lastly, the

psychosocial context that creates a placebo effect may work by activating various neurologic pathways that produce the experience of a therapeutic effect. Neuroimaging revealed release of endogenous opioids and dopamine, and this release can be to a specific body region.[6] Perhaps, this explains the targeted relief of chest pain in the Gold et al study.

Importance of Sham Placebos in Surgery Research

In 1959, Cobb et al published a surgical study on internal mammary artery ligation, a popular procedure for treating angina at the time. Since decreased blood flow to the myocardium causes chest pain, physicians thought tying sutures around two of the mammary arteries would redirect the collateral blood flow into the coronary artery. The study included 17 patients, in which 5 of 8 patients who received the ligation procedure and 5 of 9 patients who received a skin incision or sham surgery reported "significant subjective improvement." This suggested that the therapeutic effect was not from redirected blood flow but was a placebo effect.[13] One year later, Diamond et al published similar findings.[14] Thus, physicians stopped giving internal mammary ligation procedure to treat angina, but by then, a quarter of a million people had already received the ineffective procedure.[15] Other surgical studies that may not have used a sham procedural control but led to discontinuation of what were once well-established surgical practices include radical mastectomy and extracranial to intracranial bypass.[16, 17]

Likewise in 2002, when Moseley et al compared the effect of knee arthroscopy with debridement and lavage to either arthroscopic lavage alone or sham arthroscopy, the results showed similar improvement in symptoms across the three groups.[18] These arthroscopy procedures costed society over $3 billion dollars annually.[15] Other surgical RCTs that stimulated controversy about the importance of sham controls were fetal-tissue transplantation in treating

Parkinson's, vertebroplasty for compression fractures, and renal denervation for resistant hypertension.[19-22]

Few Studies on Procedural Innovations

Although RCTs can improve surgical practice and medicine is moving toward evidence-based practices, the frequency of surgical RCTs remains low at 9% in 1993 to 8% in 2006.[23] Even in August 2009, when there were 10,974 ongoing RCTs, the majority of trials was testing drugs (59%) and a small proportion tested procedure or devices (7% each).[24] These few published surgical RCTs received criticism for not meeting quality-reporting standards. Compared to general medicine RCTs, surgical RCTs received a significantly lower score when evaluated by the 2001 Consolidated Standards for Reporting of Trials (CONSORT) guidelines. The sample size was small, but for the 8 medical studies analyzed, the interquartile range of the CONSORT score was 81-86, whereas the range for the 61 surgical studies was 63-73. A maximum score of 90 corresponded to good quality reporting and methodology.[25]

With minimal regulatory oversight compared to the FDA regulations for drugs and devices, the lack of guidance and clear expectation may also contribute to lower rigor in surgical studies. The FDA regulates development of new drugs and new devices.[1, 3] New device approval for human use depends on a device's Class designation. Class I and Class II devices take a fast-track approval route that did not require a clinical trial for device approval before human use, because they are considered equivalent to prior approved devices. Class III devices must demonstrate safety and effectiveness prior to approval.[4] About 99% of new devices received approval via the fast-track route, but only 1% of all medical devices received approval for human use via premarketing clinical data.[26] Although the use or implantation of devices is a

fundamental part of surgical procedures, the FDA does not regulate surgical innovation, and the DHHS does not have specific regulatory rules or evaluation criteria for surgical research.[1,2,23]

Proposed reasons for the low number of RCTs in surgery are surgeons may be less tolerant of uncertainty about effectiveness of alternative treatment compared to other physicians, have insufficient methodological training in study design, and lack funding, support, and faculty development programs for surgical research.[27] Potential reason for less tolerance of uncertainty and less initiative to conduct procedural RCTs among researchers are surgical interventions cannot be tested on cells and are difficult to test in other mammal models as a first pass in assess safety. Surgical interventions are also not retractable, and there are no antidotes. Explaining and justifying these risks of surgical innovation research to the IRB and the public, especially when there is no national regulatory approval process, are likely a more arduous undertaking for surgical researchers.

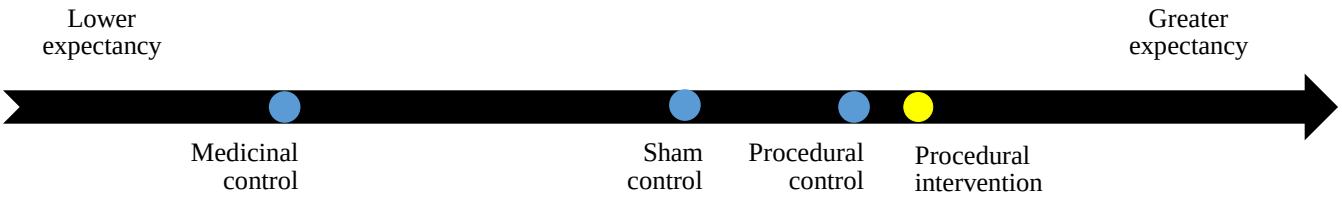
Literature often highlights other ethical concerns of placebo studies, such as physicians actively deceiving patients, patients developing an allergic or adverse response to elements of the placebo, and patients possibly forgoing conventional treatments that are available and delaying treatment.[2, 28, 29] Many of these ethical concerns seem unavoidable in both medical and surgical studies, but discussion of placebo controls in researcher attempts to define circumstances when study benefits may outweigh the risks and explain how to minimize these risks. Primarily, studies are only necessary when there is clinical equipoise, when there is uncertainty and no preferred intervention for treating patients with a specific set of medical characteristics.[30] This means studies that use placebo controls are investigating interventions for a specific group of patients where the current standard of care is not providing a therapeutic effect. London and Kadane provided 5 claims to aid in evaluating the ethical appropriateness of a sham control

trial.[31] Additionally, physician researchers can prevent deception by providing patients with appropriate information about the patient's health, discussing the detail of the study, and obtaining informed consent for the study.[30]

Blinding and Randomization in Surgical Research

Blinding is particularly challenging in surgery studies. A combination of surgeon-selected or physician-centered (eg mortality and morbidity) and patient-centered (eg social and functional status) clinical outcomes need to be measured when assessing medical treatment efficacy and effectiveness.[27] Patient-centered outcomes are often patient-reported and susceptible to the psychosocial context. To account for the potentially therapeutic effects of the psychosocial context, studies use placebo control and blind patient's to their intervention prior to outcome comparison and statistical analysis between groups. In a surgery study, only a sham procedural control can recreate a comparable psychosocial context and make blinding of the patient possible. Since surgeons operate on the patient, blinding of surgeons is not possible, but blinding of the clinician or data collector assessing outcomes is possible.[27] Blinding non-operative investigators and asking a standardized set of questions would prevent clinician measurement bias. Blinding would also minimize the potential that the physician would treat, counsel, or converse with patients differently across study groups. Inadequate blinding of patients can bias statistical analysis toward or away from detecting a significant difference in patient-reported outcomes, depending on the study control used. Thus, a sham procedural control is helpful in preventing overestimation and underestimation of a procedure's therapeutic effect on patient-reported outcomes (Figure 2).

Figure 1. Placebo Effect and Measuring Significant Difference



People who expect and receive a more invasive treatment tend to report greater improvement or placebo effect compared to less invasive treatments.[12] The magnitude of a placebo effect is associated with expectancy.[6] Patients who experience greater expectancy tend to report a greater therapeutic effect. The distance between a control and the intervention represent the difference in expectancy, which correlates with the magnitude of the difference in patient-reported outcomes. Without blinding, there is potential for the larger placebo effect of a procedural intervention to be mistaken as a significant therapeutic difference when compared to a medicinal control that has a small placebo effect. In contrast, the placebo effect of a procedural intervention compared to a procedural control is closer in magnitude, so comparison of therapeutic effect may result as an insignificant difference during analysis. Without a sham procedural control, surgical studies analyzing patient-reported outcomes can be misleading.

In addition to blinding, the complexity of creating an acceptable control and enrolling an adequate number of participants receptive to randomization in surgical studies is also challenging. The primary purpose of randomization is to minimize confounding. Even if patients adhere to their randomized treatment, large surgical research studies inherently possess additional confounders intrinsic to procedural interventions. The variability in skills, preferences, and experience of the anesthesia team, medical team, nursing team, and the

surgeons involved in patient care are part of the intervention, which may be difficult to allocate randomly. Furthermore, to create a "gold-standard" control of a surgical intervention, where a control patient receives a mirror experience of what a patient in the intervention group receives except that the treatment under investigation is not given, would require more medical staff per patient. Given the size of the patient care team, blinding all those involved up to the point of surgery and after the point of surgery may be necessary to decrease measurement bias and equalize pre- and post-surgical patient-practitioner interactions.

Standardizing the Process and Reporting of Surgical Innovation

The growing cost of health care has increased the pressure for proven effective medical and surgical treatments. As a greater volume of medical care involves treating slowly progressive diseases, it becomes more difficult to tell if a surgical intervention is effective.[15] Perhaps it is more difficult to distinguish or detect a true result from other confounding factors if a change in practice is subtle or the sought for outcomes are a long-term benefits rather than short-term improvements. Ergina et al argue that when advances are more subtle, the need for RCTs is greater.[27] When therapeutic outcomes are less apparent and detectable, well-designed randomized trials with sufficient initial investment of resources can lead to valid and reliable results faster.

Innovation is a core component of surgical practice that follow a standardized model of development. The American Society of University Surgeons describe surgeons as continuous innovators, because "surgeons are trained to perform continuous situational assessment, decision analysis, and improvisation, in preparation for the challenges and creativity required by nearly every clinical case." One could entertain the idea that because every encounter requires

innovation and innovation is a creative art, it would hinder surgical practice to place innovation within a formalized framework. Others may think without a clear regulating body, there is concern for accepting small advances overoptimistically.[32] In 2009, the Balliol Collaborative congregated to discuss how to advance and standardize surgical innovation and evaluation. They recommend a reporting framework of five stages in surgical innovation to encourage the quality improvement of surgical study design and reporting. They propose that published research should record and report surgeon experience, such that surgeons either receive specific training to participate in a study or complete an assessment of skill comparability and differences at the beginning of a study. Another recommendation was to create specialty specific postoperative outcomes classifications modeled after the Clavien-Dindo classification of surgical complications.[27] A graded classification establishes a common terminology, characterizes the degree of severity, and makes summarizing and comparing rates of clinical outcomes and complications easier. The 2009 Lancet "Surgical Innovation and Evaluation" IDEAL paradigm series make the call to adapt and improve the quality of surgical studies. The series did not explicitly encourage expanding the use of sham controls, but it acknowledges patient-reported outcomes are particularly susceptible to bias if participants are not masked.

Thus, this pilot systematic review aims to investigate the use and reporting of sham procedural controls in cardiac surgery RCTs with patient-reported outcomes from 1/2005 to 1/2016 in *The Lancet* and *The New England Journal of Medicine*.

METHODS

Cardiac RCTs published in *The Lancet* and *The New England Journal of Medicine* from 1/2005 to 1/2016 were systematically reviewed to investigate the use and reporting of sham

procedural controls and to assess if there were changes in reporting to reflect the 2009 IDEAL framework for surgical innovation and evaluation. These two journals were selected for their reputation of publishing influential peer-reviewed articles and wide readership, which implies studies of high quality are eligible for publication. Given the rich history and wide variety of cardiac procedures, cardiology RCTs were the focus of this pilot systematic review.

Study Identification

To identify randomized controlled trials in cardiology since 1/1/2005, the following search was conducting on PubMed: (cardiac[ti] OR heart[ti] OR coronary[ti] OR cardiovascular[ti] OR cardio*[ti] OR cardiol* OR mitral[ti] OR myocardial[ti] OR atrial[ti] OR aortic[ti]) AND (lancet[jour] OR nejm[jour]). Additional databases were not used to identify articles, because the search was limited to publication in two prominent journals, *The Lancet* or *The New England Journal of Medicine* from 1/1/2005-3/11/16, which would be up to date on PubMed. The PubMed searched for cardiology key words within abstracts to identify articles, because this method finds recently published articles that are awaiting MESH term coding.

Study Selection

Assessing Sham Procedural Control Relevance in Studies

A sham procedural control creates a circumstance where both patients and the investigator measuring outcomes are unable to tell which groups a patient is randomized to. The patient randomized to the sham group receives a procedure where a skin incision is made for the procedural intervention to be given, but ultimately, the therapeutic part of the intervention is not

given. For this review, I identified studies that could have used a sham procedural control regardless of the control a study actually used (Table 1).

Table 1. Deciding When Sham Procedure Controls are Relevant

The purpose of a sham control is similar to that of a placebo medication. That purpose is to blind both the patient and ideally the investigators collecting the data so that they do not know which study group the patient belongs to. Blinding helps to minimize measurement bias, particularly when the outcome assessed is a patient-reported outcome, since individual perception and style of clinical questioning influences assessment of psychological states such as well-being and pain symptoms.

	Intervention	**Control**	**Placebo or Sham Relevant Control**	**Example**
Medicinal Studies				
	M2	---	placebo	Antisense therapy to reduce apolipoprotein(a) synthesis[33]
	M2	M1	---blinding possible---	Bivalirudin vs heparin before PCI[34]
	M2 + M1	M1	M1 + placebo	Nebivolol and/or valsartan for hypertension[35]
Procedural Studies				
*	P2	---	Sham	Endovascular aneurysm repair[36]
	P2	P1	---blinding possible---	Mitral valve repair vs. replacement[37]
‡	P2 + P1	P1	P1 + Sham	Mitral valve repair + Coronary artery bypass graft (CABG) vs. CABG[38]
Mixed Medicinal and Procedural Studies				
	M2 + P1	P1	---blinding possible---	Stent studies[39]
	M2 + P1	P1 + M1	---blinding possible---	Stent studies[40]
‡	P2 + M1	M1	M1+sham	Coronary sinus reducing device in refractory angina[41]
√	P2	M1	P2 + placebo M1 + sham	Implantable cardioverter-defibrillator vs. standard medical therapy[42]

M1 = Standard medical or management therapy, P1=Standard procedural therapy, M2 = medicine or management method under investigation, P2=procedural strategy under investigation.

*Like placebo controls in drug studies, sham procedural controls are relevant when one is testing a new procedure against no known standard medication or procedure. ‡Sham controls are also relevant when the procedural intervention studied is a complement to and deliverable in conjunction with a known standard medicinal or procedural therapy. In many cases, there may be medications that are available, but the medications do not provide adequate treatment for a subgroup of patients. √Lastly, a sham control is relevant when the study compares outcomes of a new procedure to a standard medical treatment, because giving a sham procedural placebo with the standard medical therapy and a placebo medication in place of the standard medication makes blinding possible.

A sham procedure is neither relevant nor possible in new medication studies, but blinding may be possible with or without a placebo medication. A sham is also not possible when studying two separate procedures that cannot be given as complementary therapy. For example, a mitral valve repair compared to a mitral valve replacement. It would be unethical to perform a sham surgery when a therapeutic procedure already exists. Nevertheless, blinding of both the patients and investigator is possible. Lastly, studies that investigate a change in medication — whether administered before, during, or after the procedure —were classified as drug studies rather than procedural studies.

Inclusion and Exclusion Criteria

Randomized controlled trials of adults ≥ 18 years old were included if the study (1) investigated an intervention that involved an invasive procedure for treating a cardiac disease, (2) had the potential to use a sham control, whether it was actually used or not in the study (Table 1), and (3) assessed and reported patient-experienced and/or patient-reported outcomes (Table 2).

Studies were excluded if (1) they were not a randomized controlled trail, (2) participants were < 18 years old, (2) the intervention was not an invasive procedure, (3) there was no single standard control, and (4) if the outcome was measured by a device and not a patient reported outcome (Table 2).

Table 2. Inclusion and Exclusion Criteria

Inclusion	**Exclusion (with examples)**
Randomized controlled trial	Commentaries and letters
Participants ≥ 18 years old	Participants < 18 years old
Intervention was: • an invasive procedure that treats cardiac disease • included a strategy to address unexpected surgical situations during the operation	Intervention was: • A medicinal (oral, IV, infusion, stent coating) • Diet/lifestyle modification • An external equipment (CPR, CPAP, compression stocking) • Targeted lab or vital sign values (HbA1C, BP) • For diagnostic or management decisions (using FFR to determine operation given, timing of intervention) • Change in location of device implantation • Different use of implanted device (pacing, monitoring) • Organ transplant
Control: • could have been a sham procedure • was a single standard control with a strategy to address unexpected	Control is: • A procedure that is different from intervention (open vs. endovascular or repair vs. replace)

surgical situations during the operation	• Not a single standard control, (control that includes standard medical therapy with or without another specified procedure) • A procedure given in conjunction with the intervention procedure
Reported outcomes were patient-experienced and patient-reported	Outcomes measured: • with a device (ambulatory BP) • unclear human or device measurement (home BP) • not patient-reported (mortality)

The inclusion and exclusion criteria were determined in collaboration with Dr. Harris and Dr. Stouffer. I independently reviewed all abstracts and full-texts for inclusion or exclusion. When there was uncertainty, Dr. Harris was asked to guide the decision making process by either direct review or explanatory clarification of inclusion and exclusion criteria. I reviewed articles a maximum of 3-4 times before inclusion or exclusion was determined. Abstract review focused on inclusion criteria (1) and (2), because some studies analyzed patient-reported outcomes as a secondary outcome not mentioned in the abstract. Initial full-text review focused on screening for all inclusion criteria, before full-text reading for data extraction.

Data Extraction

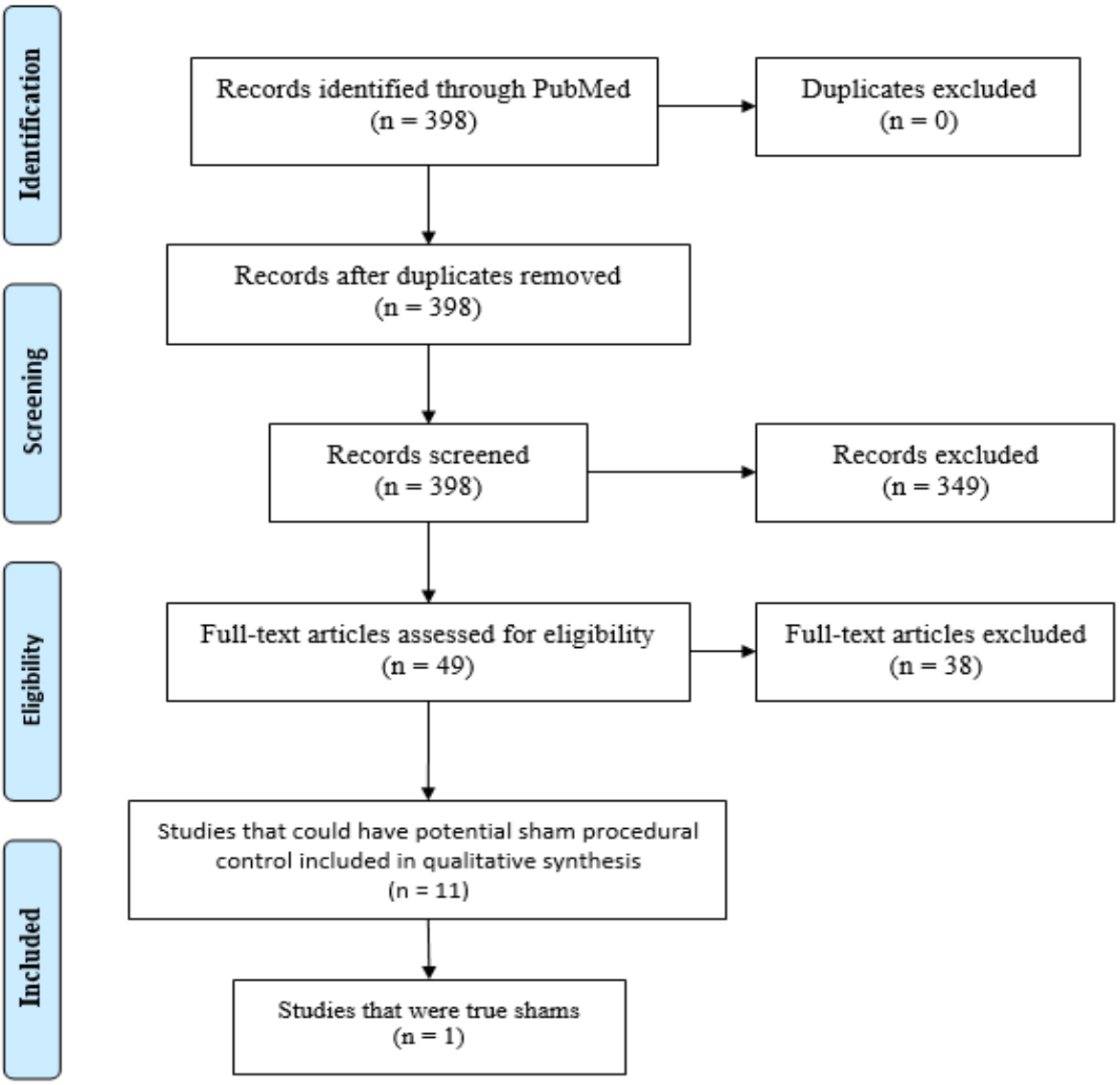
I extracted all the data from the full-text articles independently. For each article, I extracted information about the purpose of the study, blinding of the patient and investigator, the patient population, the intervention and control used, amount of crossover between groups, type of patient-reported outcome measured, reported results, adverse events, and regulating bodies involved.

RESULTS

Search Results

PubMed found 398 potential cardiology RCTs published in *The Lancet* and *The New England Journal of Medicine*. Of the 11 articles that fit inclusion criteria, only 1 article was a true sham study (Figure 1).

Figure 2. PRISMA diagram



Controls Used and Blinding

Of the 11 studies that could have used a sham procedural control, only 1 was a double-blinded sham RCT. In the remaining 10 studies, patients were not blinded to their randomization group assignment. Only 1 of the 10 studies explicitly stated blinding of the research assessor. In that study, research assessors conducted patient-reported outcomes through phone interviews. The other 9 studies did not report on blinding of the research assessor (Table 3). Both studies that blinded the research assessor were published after 2009. Patient-reported outcomes were the primary outcome of interest in 4 of the 11 studies.

Table 3. Controls used, Blinding, and Outcomes

Article	**Intervention**	**Control**	**Blinding (intervention: control)**	**Significant difference in patient reported outcomes between groups?**
[36]EVAR trial participants 2005	EVAR	no intervention	No : Unclear	No
[43]Hochman 2006	PCI with stent + control	OMT	No : Unclear	Yes
[44]Oral 2006	CPVA + control	amiodarone +2 cardioversions	No : Unclear	Did not compare.
[42]Mark 2008	shock only single lead/chamber ICD + SMT	1) amiodarone placebo + SMT 2) amiodarone + SMT	No : Unclear	Variable depending on measurement tool.
[45]Weintraub 2008	PCI + control	OMT	No : Unclear	Yes
[46]Jones 2009	ventricular reconstruction + control	CABG + medical therapy	Unclear : Unclear	No

[47]Kuck 2010	VT ablation followed by control	defibrillator implantation	No : Unclear	No
[48]Cosedis Nielson 2012	radiofrequency catheter ablation	class 1C or 3 antiarrhythmic drug	No : Unclear	Yes
[49]Thiele 2013	IABP + control	German/Austrian S3-Guideline on cardiogenic shock including early revascularization + OMT	No : Yes	No
[38]Smith 2014	MV repair + control	CABG alone	No : Unclear	No
[41]Verheye 2015	implantation of coronary-sins reducing device	sham: similar for all of procedure except device was not placed	Yes: Yes	Yes

CABG=coronary artery bypass graft, CPVA=circumferential pulmonary vein ablation, EVAR=endovascular aneurysm repair, IABP=intra-aortic balloon pump, ICD= implantable cardioverter-defibrillator, MV=mitral valve, OMT=optimal medical therapy, PCI=percutaneous coronary intervention, SMT=standard medical therapy, VT=ventricular tachycardia

Assessing Significance in Patient-Reported Outcomes

One study did not compare the patient reported outcomes between the study groups. When comparing patient reported outcomes between study groups, 4 of the 11 studies found a significant difference. Of those, 3 compared a procedural intervention to a medical control and 1 was a sham control. No significant difference or mixed results in patient-reported outcomes were found in 6 of the 11 studies, but 4 of the studies used a control that included a procedure with or without medicine, 1 study used a medicine only control, and 1 study had no intervention as the control (Table 3).

Reporting of Surgeon Experience, Adverse Events, and Regulatory Bodies

No studies reported or commented surgeon experience. 7 of 11 articles reported adverse events, but reporting of adverse events and outcomes was not on a graded classification scale,

not even the validated Clavien-Dindo classification of surgical complication. All 11 studies obtained institutional review board approval from the participating research center, but 7 received additional approval and support from national organizations.

DISCUSSION

RCTs should always strive to blind the outcome assessor. This means blinding the participant and the research assessor when the outcome is patient-reported, because both are providing a measure of the outcome. In this pilot review, I identified 11 cardiac RCTs that could have used a sham procedural control to blind participants, but 10/11 did not use a sham control. In 9 studies, participants were not blinded and blinding of the research assessor was not clearly stated. The studies did not describe the process of collecting patient-reported outcomes. Blinding of research assessors may be unnecessary if the patient-reported outcomes were collected by asking patients complete a questionnaire. One study only blinded the research assessor, who collected patient reported outcomes through a phone interview. Given that 10/11 studies did not blind the participants, the results for patient-reported outcomes in cardiac surgical studies are subject to high measurement bias.

The studies did not explain why sham procedural controls were not used. Studies may not have used sham procedural control, because it would have required the group of operating room staff to approximately double the participants they see, unless a study uses blocked randomization. This would mean seeing 100-1,000 more patients for sham operations, which may have been an unnecessary investment of human and material resources as well as time in studies where the primary outcome of interest was a physician-centered outcome, such as mortality and mechanically measurable labs. Patient-reported assessment was the secondary

outcome of interest in 7/11 of the studies reviewed. In these cases, patient-reported outcome should be published with clear statements of limitations and implications or not be reported at all, because the high potential of measurement bias makes the results difficult to interpret and inapplicable. As for the 3/11 studies and future surgical studies evaluating patient-reported outcomes as the primary outcome, sham procedural controls are recommended to minimize measurement bias and improve the validity and reliability of results. Even if ethical concerns prevent a sham procedural control from being used, reports should better explain the reasoning for the control chosen, how the patient reported outcome was measured, such as by phone interview or mailed questionnaire, and the blinding status of research assessors. Obstacles to including sham procedural controls in surgical studies may be due to challenges in obtaining IRB approval, risk of low study enrollment, cost, or fear of ethical dilemmas. For example at UNC, only 1 sham study was submitted to the IRB from 1990-2016, but it was not approved. These challenges are not unique to surgical studies. Therefore, using sham procedural controls when relevant to the research question of interest is worth the appropriate initial investment. Obtaining a precise, valid, and reliable answer during the initial investigation will prevent more people from having to enter future studies aimed to answer the same research question.

Investigators can make use of sham procedures and double-blinding to account for the placebo effect. Further, one can imagine that research may one-day result in a statistical calculation to account for placebo effect. In "The Powerful Placebo" article, Beecher concluded on average the magnitude of the placebo effect was 35.2% from reviewing 15 placebo control trials.[7, 50] Although this estimate did not represent all placebo types, it raises the question whether calculations can be performed to yield meaningful estimates of the magnitude of a placebo effect for study controls. For example, the true sensitivity and specificity of a test

remains unknown, but studies help to give the most likely estimate of the true sensitivity and specificity, or present a range of the potential values. If investigators can predictably account for the placebo effect during the analysis phase, this may prove useful for analyzing pilot studies before undertaking larger double-blinded sham procedural control studies. However, this all remains speculative and is impossible at present, but sham controls are an applicable method for blinding and accounting for the placebo effect.

A limitation of this study is that all abstract reviews, full-text reviews, and data extraction was completed by a single reviewer, but PRISMA recommends a double independent review. With a single review, there is the possibility articles that would have met the inclusion criteria may have been overlooked. Limited evidence source is another concern, because article searches were limited to *The Lancet* and *The New England Journal of Medicine*. It is possible that other journals may have different reporting standards for articles to be accepted for publication, but this does not change the finding that 10/11 of the surgery studies assessing quality of life outcomes for procedural interventions published in these two reputable journals were unreliable.

CONCLUSION

Surgical research that investigates the effect of a procedural intervention on patient-reported outcomes often do not use a sham procedural control and do not provide sufficient reporting about methods of collecting the patient reported outcomes or the blinding status of the research assessor. Future research should aim to use a sham control in surgical RCTs, where the primary outcome of interest is a patient reported outcome. Surgical RCTs that evaluate patient reported outcomes as a secondary outcome of interest should refrain from assessing and reporting these secondary outcomes when the control is not a sham procedure. The purpose of a

sham procedural control is to allow for participant and investigator blinding as a means of equalizing the psychosocial context experienced by participants—the placebo effect. Besides a sham procedural control, there are no additional research methods to account for the placebo effect in surgical studies, unless there is a way to accurately account for it during data analysis. The challenges of using sham procedural controls may include obtaining IRB approval, risk of low study enrollment, cost, or fear of unavoidable ethical concerns, but they are not unique to surgical studies. Therefore, surgical studies that plan to evaluate procedures using patient-reported outcomes should strongly consider sham controls to improve study validity. Publishers should refrain from publishing surgical RCTs that do not use sham controls when assessing patient-reported outcomes or at least request researchers to either clearly state limitations and implications of not using a sham procedural control or not include patient-report outcomes that are secondary outcomes of interest in the manuscript.

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APPENDIX

Appendix 1. Full Evidence Table

Table is organized by publication year.

Acronyms: AAA=abdominal aortic aneurysm, BARIS= Bypass Angioplasty Revascularization Investigation Substudy on Economics and Quality of Life, CCS= Canadian Cardiovascular Society, CPVA=circumferential pulmonary vein ablation, DASI= Duke Activity Status Index, EQ VAS= EQ Visual Analogue Scale, EQ-5D= EuroQoL descriptive quality of life assessment in 5 dimensions, EVAR=Endovascular Aneurysm Repair, IABP: intra-aortic balloon pump, ICD=implantable cardioverter-defibrillator, LV=left ventricle, LVESI= Left ventricular reverse remodeling, NHLBI=National Heart, Lung, and Blood Institute, NYHA=New York Heart Association, OMT=optimal medical therapy, MLHF= Minnesota Living with Heart Failure Scale, PAD=peripheral artery disease, SAQ=Seattle Angina Questionnaire, SF-12= 12-item Short From Health Survey, SF-36= 36-item Short From Mental Health Inventory, SMT= state-of-the-art medical therapy, VT=ventricular tachycardia

Article	Purpose	Patient population (location, inclusion and exclusion criteria)	Study arms and Blinding (received/ randomized)	Crossover (%)	Patient Reported Outcome (primary or secondary, assessment method)	Health Reported Outcome Results	Adverse Events	Regulating body
[36]EVAR trial participants 2005	To examine if EVAR compared with no intervention would reduce the risk of aneurysm-related death from rupture and improve the long-term survival and health-related quality of life for patients with AAA ≥5.5cm in diameter	31/41 eligible hospitals. **Inclusion:** ≥60yo, AAA≥5.5cm diameter, unit for open repair. **Exclusion:** reported in previous publication.	**Intervention:** 146/166 EVAR **Control:** 125/172 no intervention **Blinding:** No : Unclear	20% did not adhere to allocated treatment. 27% control to aneurysm exclusion, including 12 cases of open repair.	**Secondary:** SF36 and EQ-5D **Primary:** all-cause mortality.	**SF36 and EQ-5D:** EVAR vs control, physical component summary at 0-3mon compared to baseline -1.51 vs 0.48, p=0.04. Otherwise, no clear and consistent differences in QoL between the 2 groups at any time.	By 4 years, 43% of patients in EVAR group had at least 1 post-op complication compared to 18% in no intervention. HR 5.3 p<0.001. Considered whether the excess of respiratory deaths	North-West Multicenter Research Ethics Committee (UK).

	and unfit for open repair.						in EVAR group was attributable to use of general anesthesia, but analysis showed no significance p=0.45.	
[43]Hochman 2006	To evaluate a strategy of routine PCI for total occlusion of the infarct-related artery 3-28 days after acute MI in reducing the occurrence of composite end point of death, reinfarction, or NYHA class 4 heart failure.	US, New Zealand, and Canada. **Inclusion:** total occlusion of infarct-related artery w/ poor or absent antegrade flow (TIMI≤1) on coronary angiography 3-28days after MI + EF<50% +/- proximal occlusion of major epicardial vessel with large risk region. **Exclusion:** NYHA class 3/4 HF, shock, serum Cr>2.4mg/dL, angiographically sig Lt main or 3-vessel CAD, angina at rest, severe ischemia on stress testing.	**Intervention:** 1071/1082 PCI with stent + control **Control:** ---/1084 OMT **Blinding:** No : Unclear	3% control to PCI within 30 days of randomization. 6% control to PCI after 30 days. 0.4% control to CABG within 30 days.	**Secondary:** By phone, CCS and NYHA. **Primary:** death from any cause, nonfatal reinfection, and NYHA class 4 HF.	**CCS:** at 4 mon and 1 year significantly fewer patients with angina in the PCI group. Declined over time in both groups. Difference between the 2 groups also declined over time. No significant difference by 3 years. **NYHA:** at 4 years, no significant difference in NYHA class 3, 4, or 5 HF.	PCI group: death (0.2%), centrally adjudicated myocardial reinfarction (0.6%), NYHA class 4 HF (0.2%), cardiac tamponade (0.2%), stroke (0.1%)	NHLBI and IRB at centers.
[44]Oral 2006	To determine the long-term efficacy of CPVA in patients with chronic atrial fibrillation while taking into account the confounding variables of antiarrhythmic-drug therapy and cardioversion	1 hospital in Milan, 1 hospital in Michigan. **Inclusion:** Atrial fibrillation >6mon without intervening spontaneous episodes of sinus rhythm and recurred within 1wk after cardioversion. **Exclusion:** age <18 or >70, Left atrial diameter >55mm, LVEJ<30%, contraindication to amiodarone therapy or warfarin, presence of mechanical prosthetic valve, history of CVA, presence of left atrial thrombus on transesophageal	**Intervention:** 77/77 CPVA + control **Control:** 69/69 amiodarone +2 cardioversions **Blinding:** No : Unclear	77% control to intervention in whom recurrent atrial fibrillation developed more than 3mon after the 1st cardioversion.	**Secondary:** Severity of arrhythmia symptoms. **Primary:** freedom from atrial fibrillation or flutter in the absence of antiarrhythmic-drug therapy.	**Arrhythmia symptom**s: Patient in sinus rhythm had greater improvement in symptom severity score. Among patients in sinus rhythm, baseline=17 (SD 4), 12mon=6 (SD 2) after CPVA. Among patients with recurrent atrial fibrillation, baseline= 17 (SD 4), 12mon=12 (SD 4).	Atypical flutters in CPVA group. 1 intervention group, AV junction ablation and received pacemaker. 1 66yo died of pneumonia 6mon after CPVA. 2 had pacemaker placed or sick sinus syndrome unrelated to ablation or drug therapy.	IRB at centers.

		echocardiography, prior attempt at catheter or surgical ablation for atrial fibrillation						
[42]Mark 2008	To examine the effect of primary preventive ICD therapy on health-related quality of life compared to amiodarone and placebo in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)	US, Canada, and New Zealand. **Inclusion:** ≥18yo with NYHA class 3 or 4 due to ischemic or non-ischemic causes of LVEF ≤35%. **Exclusion:** none reported	**Intervention:** 814/829 shock only single lead/chamber ICD + SMT **Control:** 829/847 placebo + SMT. 825/845 amiodarone + SMT. **Blinding:** No : Unclear	14% ICD people received open-label amiodarone during some part of follow-up. 188 (11%) drug to some form of ICD therapy, median time 26.7mon. 44 amiodarone to open label amiodarone. 10% placebo to open label amiodarone.	**Primary:** Structured interview. DASI, SF-36, MLHF, time trade-off technique, rate health, total number of "bed days" and "disability days", driving status, financial management status, and employed status with BARIS	<u>Unadjusted</u> **DASI:** no significant difference between ICD vs placebo and amiodarone vs placebo at baseline, 3, 12, 30months. **SF-36:** ICD vs placebo, baseline 76 vs 76 p=0.17, 3months median 80 vs 76 p=0.01, 12months median 80 vs 76 p=0.003, 30month median 76 vs 76 p=0.79. Amiodarone vs placebo, no statistical difference at follow up. **Additional SF-36 scales:** ICD vs placebo, significant difference at 3months in all domain (physical function, emotional function, general health, social function, pain, vitality), significant difference at 6month for emotional function, general health, social function, and pain index. Amiodarone vs placebo, significantly higher score on pain index at baseline, 3, 12, and 30months. **MLHF:** ICD vs placebo, significantly better in ICD (median baseline 41 vs 43 p=0.77, 3mon 30 vs 36 p=0.006, 12mon 32 vs 36 p=0.07, 30mon 32 vs 36 p=0.05). Amiodarone vs placebo, no statistical difference. **Time trade-off utility:** ICD vs placebo, significant improvement in ICD at 3months median 75 vs 70 p=0.002. **Overall health rating:** ICD vs placebo, significantly higher in ICD	5% during implantation, 9% later in trail: clinical events requiring surgical correction, hospitalization, or new and otherwise unanticipated drug therapy.	NHLBI and IRB at center.

						group. 3months median 75 vs 70 p=0.002, 12months median 75 vs 70 p=0.05, 30months median 70 vs 70 p=0.18. Comparing within ICD group, shock vs no shock: Shocked within 1month group had significant decrease in general health perception, role function physical, role function emotional, social function, and self-rated health. Shocked within 2months shocked showed similar pattern but diminished magnitude of differences. By 12months NO significant difference. **"Bed days", "disability days", driving, manage finances, employment:** no detectable effect by ICD therapy. Survival-adjusted analysis showed similar results		
[45]Weintraub 2008	To assess the effect of PCI on relief of angina and effect on health status on a broader level as part of the COURAGE trial, since primary outcome of COURAGE trial.	50 centers in US and Canada. **Inclusion:** stenosis of >70% in at least 1 major epicardial coronary artery with objective evidence of myocardial ischemia or stenosis ≥80% in at least 1 coronary artery + classic angina without provocative testing. **Exclusion:** reported in previous publications	**Intervention:** 900s/1149 PCI + control **Control:** 900s/1138 OMT **Blinding:** No : Unclear	21% control to PCI within first 3mon.	**Primary:** SAQ and SF-36.	**SAQ:** Best summary statement: "A greater proportion of the PCI group had clinically significant improvements in the scores for physical function, angina frequency, and quality of life for the first 6 months after randomization, but these differences were no longer significant by 12 months." "There was an intermittent advantage of PCI w/ respect to the percentage of patients with clinically significant improvement in the lowest (most severe angina) and middle third for up to 2 years, depending on the domain." **SF-36:** improvement in all domains in both group up to 3 months. "The benefit across domains was less consistent than that seen in the	None reported	Department of VA Cooperative Studies Program and IRB at centers.

						results of the SAQ, with an advantage of PCI that was noted in most but not all domains and that had a shorter duration." At 6months, PCI group had greater clinically significant improvement in physical functioning and role limitations-physical. No advantage at 12months.		
[46]Jones 2009	To test if surgical ventricular reconstruction, when added to CABG, would decrease the rate of death or hospitalization for a cardiac event, as compared with CABG alone.	127 clinical sites in 26 countries. **Inclusion:** CAD amenable to CABG, LVEF≤35%. **Exclusion:** recent MI, need for aortic-valve replacement, planned PCI, or coexisting non-cardiac disease resulting in life expectancy <3yr.	**Intervention:** 454/501 ventricular reconstruction + control **Control:** 463/499 CABG + medical therapy **Blinding:** Unclear : Unclear	2% intervention to no surgery at all. 7% intervention to CABG alone. 2% CABG to no surgery. 5% CABG to also ventricular reconstruction.	**Secondary:** CCS and NYHA **Primary:** time to death from any cause or hospitalization for cardiac cause.	**CCS:** Proportion with no angina increased and proportion with CCS class 3/4 angina decreased. CCS improved average of 1.7 classes, but no difference between groups p=0.48. **NYHA:** class 1 heart failure (no symptom) increased and proportion with class 3/4 heart failure decreased. NYHA improved average of 1 class in both cohorts, but no for difference between groups p=0.70.	None reported	Duke Clinical Research Institute and IRB at centers.
[47]Kuck 2010	To assess prophylactic VT ablation followed by implantation of a cardioverter defibrillator in patients with previous MI, first episode of stable VT, and reduced LV function.	16 participating European centers. **Inclusions:** 18-80yo, indication for ICD as secondary prevention after documented stable clinical VT without any reversible cause, CAD, previous MI, LEVF ≤50%. **Exclusion:** acute MI within preceding month, cardiac surgery within preceding 2mon, protruding LV thrombus on echo before ablation, valvular heart disease, or a mechanical heart valve that precluded LV access, unstable angina, incessant ventricular tachycardia, bundle-branch re-entry tachycardia, contraindication to heparin,	**Intervention:** 52/54 VT ablation followed by control **Control:** 55/56 defibrillator implantation **Blinding:** No : Unclear	7% implant defibrillator before ablation, but these patients did not have any VT events before ablation. 1 control received ICD 64 days after randomization because of LV thrombus.	**Secondary:** SF-36 **Primary:** time from defibrillator implantation to recurrence of any sustained VT or VF.	**SF-36:** at 12months, obtained assessed in 54/94 (57%) of patients. At 24 months obtained from 30/54 (56%) patients. Baseline-adjusted SF-36 mean scores were higher in ablation group in 6/8 scales after 12mon and in 7/8 scores after 24mon. No significant different between groups.	None reported	IRB at centers.

		serum Cr>220, heart failure class 4, other medical condition likely to limit survival to <12mon.						
[48]Cosedis Nielson 2012	To compare long-term efficacy of an initial strategy of radiofrequency catheter ablation with an initial strategy of antiarrhythmic drug therapy in a larger population of patients with paroxysmal atrial fibrillation.	Denmark, Sweden, and Finland. **Inclusion:** symptomatic paroxysmal atrial fibrillation, candidate for rhythm-control therapy, ≥2 episodes of symptomatic atrial fibrillation within preceding 6mon but no episode of atrial fibrillation >7days. **Exclusion:** >70yo, previous or ongoing treatment with class 1C or 3 antiarrhythmic drugs, contraindication to both class 1C and 3 agents, previous ablation for atrial fibrillation, left atrial diameter of >50mm, LVEF<40%, contraindication to oral anticoagulant, moderate-severe MV disease, NYHA 3 or4 at time of enrollment, expected surgery for structural heart disease, secondary atrial fibrillation.	**Intervention:** 140/146 radiofrequency catheter ablation **Control:** 146/148 class 1C or 3 antiarrhythmic drug. If recurrent atrial fibrillation, then direct current cardioversion and other appropriate antiarrhythmic medication. If refractory, then offered ablation if appropriate. **Blinding:** No : Unclear	9% ablation with antiarrhythmic drug at 24mon 4% control to ablation.	**Secondary:** SF-36, freedom from symptomatic atrial fibrillation, and cumulative and per-visit burden of symptomatic atrial fibrillation. **Primary:** burden of atrial fibrillation on Holter monitor and cumulative burden of atrial fibrillation.	**SF36:** physical and mental component improved overtime in both groups. Physical-component improved more over time in ablation group than drug group (44.3+/-8.9 baseline to 50+/-8.8 24mon vs 45.2+/-8.9 baseline to 47.9+/-8.9) p=0.001 over time, p=0.01 interaction. **Free from symptomatic atrial fibrillation:** ablation vs drug, 93% vs 84%, p=0.01. **Symptomatic atrial fibrillation:** ablation vs drug, 95% v 84%, p=0.0006. Cumulative burden of symptomatic atrial fibrillation did not differ, p=0.12.	20 in ablation, 3 cardiac tamponade, 3 died in study where 1 was procedure related cerebral stroke 16 drug, 4 died in study. No significant difference between groups p=0.45.	Danish Data Protection Agency and IRB at centers.
[49]Thiele 2013	To assess long-term clinical and quality of life outcomes of IABP support compared to control in acute MI with cardiogenic shock.	37 German centers. **Inclusion:** cardiogenic shock (systemic hypotension, pulmonary congestions, and signs of impaired organ perfusion) w/ planned early revascularization preferably by PCI. **Exclusion:** no intrinsic heart action, resuscitations for >30min, severe cerebral	**Intervention:** 288/301 IABP + control **Control:** 199/269 German/Austrian S3-Guideline on cardiogenic shock including early revascularization + OMT **Blinding:**	15% control to IABP, only allowed if patient developed a mechanical complication	**Primary:** Structured phone interview. CCS, NYHA, EQ-5D, EQ VAS	**NYHA class I or II:** IABP vs control, at 12 months 115/127 (91%) vs 118/126 (94%), p=0.36. **CCS class I or II:** IABP vs control, at 12 months 125/127 (98%) vs 124/125 (99%, p=1.00. **EQ-5D and EQ VAS:** no significant difference between groups	None reported	National regulatory authorities and IRB at centers.

		deficit, mechanical causes of cardiogenic shock, onset of shock>12hr, severe PAD precluding IABP insertion, aortic regurgitation>grade 2 in severity, age >90yo, shock of other cause, other severe concomitant disease with life expectancy <6mon.	No : Yes			**Summary:** for survivors, self-reported QoL was moderate to good. There was no significant difference at 6 and 12months.		
[38]Smith 2014	To determine whether the potential benefits of mitral valve repair outweigh the increased risks of the procedure combined with CABG.	26 centers in the Cardiothoracic Surgical Trials Network. **Inclusion:** adults, multivessel CAD, moderate ischemic mitral regurgitation. **Exclusion:** not reported.	**Intervention:** 147/150 MV repair + control **Control:** 143/151 CABG alone **Blinding:** No : Unclear	2% CABG+MV to CABG alone, because surgeon's concern about risk associated with valve repair. 5% CABG alone to CABG + MV, mostly by increase severity in mitral regurgitation on intraoperative TEE.	**Secondary:** NYHA, MLHF, SF-12, and EQ-5D **Primary:** LVESVI.	**MLHF:** median reduction from baseline in heart failure symptom combined procedure vs CABG only 48.1% vs 44.8%. **SF-12:** physical subscale improved in combined procedure vs CABG only 14.3% vs 12.05%. **Summary:** No sig difference btw treatment groups with respect to any measurement of QoL or functional status amounting those surviving to 12months.	At 1year, 153 events in CABG alone, 185 in combined p=0.15. Serious neurologic adverse events, including stroke, TIA, metabolic encephalopathy, was significantly higher in combined group p=0.03, as was rate of supraventricular arrhythmia p=0.03. Mean length of stay after surgery was shorter with CABG alone 9.4 than with combined 11.3, p=0.002, as was mean length of stay in ICU 4.0 vs 4.8 p=0.006.	NIH and IRB at centers.
[41]Verheye 2015	Phase 2 study. To examine whether the implantation of the coronary-sinus reducing device could effectively improve angina symptoms in	11 clinical centers in Europe and Canada. **Inclusion:** >18yo, had CCS class 3 or 4 angina despite OMT for 30 days prior to screening, limited treatment options for revascularization by CABG or PCI, evidence	**Intervention:** 52 implantation of coronary-sins reducing device **Control:** 52	None	**Primary:** CCS and SAQ	**CCS:** intervention vs. sham, improvement of at least 2 CCS classes 35% vs 15% p=0.02; improvement of at least 1 CCS class 71% vs 42% p=0.003. **SAQ:** intervention vs. sham, improved by 17.6 points vs 7.6 points p=0.048, but no significant	Serious periprocedural events in… <u>Intervention group</u> 1 MI 1 unstable angina 1 Crohn's disease flare.	Relevant national authorities and IRB at centers.

	patients with obstructive coronary artery disease who had concomitant evidence of reversible myocardial ischemia and who were not considered to be candidates for revascularization.	of reversible ischemia that is attributable to left coronary arterial system, LVEF>25%, not pregnant. **Exclusion:** acute coronary syndrome <3mon ago, successful CABG or PCI <6mon ago, unstable angina <1mon ago, undergone placement of permanent pacemaker or defibrillator leads in the right heart.	sham: similar for all of procedure except device was not placed **Blinding:** Yes: Yes			difference between groups for angina stability or angina frequency.	<u>Sham group</u> 1 unstable angina 1 epigastric pain. Total adverse events reported… 76 in intervention group 93 in sham group. Total serious adverse events in trial… 10 in intervention group. 24 in sham group.	