Framework for Effective Use of CED (Coverage with Evidence Development) To Inform Decision Making

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CMS Rationale for CED

The purpose of CED is to generate data on the utilization and impact of the item or service evaluated in the NCD, so that Medicare can a) document the appropriateness of use of that item or service in Medicare beneficiaries under current coverage; b) consider future changes in coverage for the item or service; c) generate clinical information that will improve the evidence base on which providers base their recommendations to Medicare beneficiaries regarding the item or service.

CMS Guidance issued July 12, 2006

Principles Governing the Application of Coverage with Evidence Development

Principle 1. Transparent NCDs requiring CED will occur within the NCD processes, which is transparent and open to public comment.

Principle 2. Provide needed evidence CED will not be used when other forms of coverage are justified by the available evidence.

Principle 3. Increase access CED will in general expand access to technologies and treatments for Medicare beneficiaries.

Principle 4. Use seldom CMS expects to use CED infrequently.

Principle 5. Information complementary CED will lead to the production of evidence complementary to existing medical evidence.

Principle 6. Complement FDA CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices.

Principle 7. Complement NIH CED will not assume the NIH's role in fostering, managing, or prioritizing clinical trials.

Principle 8. Compliant with law Any application of CED will be consistent with federal laws, regulations, and patient protections.

CMS Evidentiary Priorities in Medicare

Importance of question

- Which diseases represent the greatest burden to Medicare beneficiaries?
- Which diseases and their treatments are the costliest to the Medicare Program?

Value of incremental information

- Where are our greatest deficits in knowledge about the most important diseases and their treatments in the Medicare population as discussed in Questions 1 and 2?

Next steps

- How do we approach the problem of increasing the evidence base for the most important diseases and their treatments in the Medicare population as discussed in Questions 1 and 2?
- Please provide a priority list of diseases and their treatments that are most critical to increasing the evidence base for making coverage decisions that affect the Medicare population based on your discussions of the above questions.

Central Question: What Value Will CED Add?

- Absent CED, will evidence ever be developed?
  - Is technology a monopoly product?
  - Are there special reasons to subsidize adoption of the technology?

    Who should bear the costs?
- Will the information generated by CED lead to better health care decisions?

Subsidiary Questions

- Is intervention sufficiently promising?
- Can efficacy be determined from CED data?
- Are methods sufficiently robust and convincing for purposes of coverage determination?

Use of CED

- Complement to randomized clinical trials (RCTs)
  - Effectiveness in included subgroups
  - Effectiveness in excluded populations
  - Effectiveness in “real world” treatment settings
  - Larger sample size

- Substitute for privately sponsored RCTs
  - CED could be used to evaluate off-label uses of approved drugs
  - CED can include Medicare-sponsored RCTs
  - Observational data in lieu of RCT
    - RCT may be too difficult to conduct

Will CED Data be Good Enough?

CED-Generated Data: Options

- RCT
- Registry
  - How designed?
  - How administered?
  - Special purpose data?
- Routinely collected clinical data
- Claims files and other administrative databases

Central methodological challenge: can you draw causal inferences about treatments and other health interventions from observational data?

Observational data can be refined at a cost

Common Criticisms of Observational Data

- Intervention may not be standardized
- No blinding
- Tests of statistical significance often misleading

Selection Effects

- Can they be eliminated?

  More detailed information about patient characteristics only partially mitigates

Inference Techniques

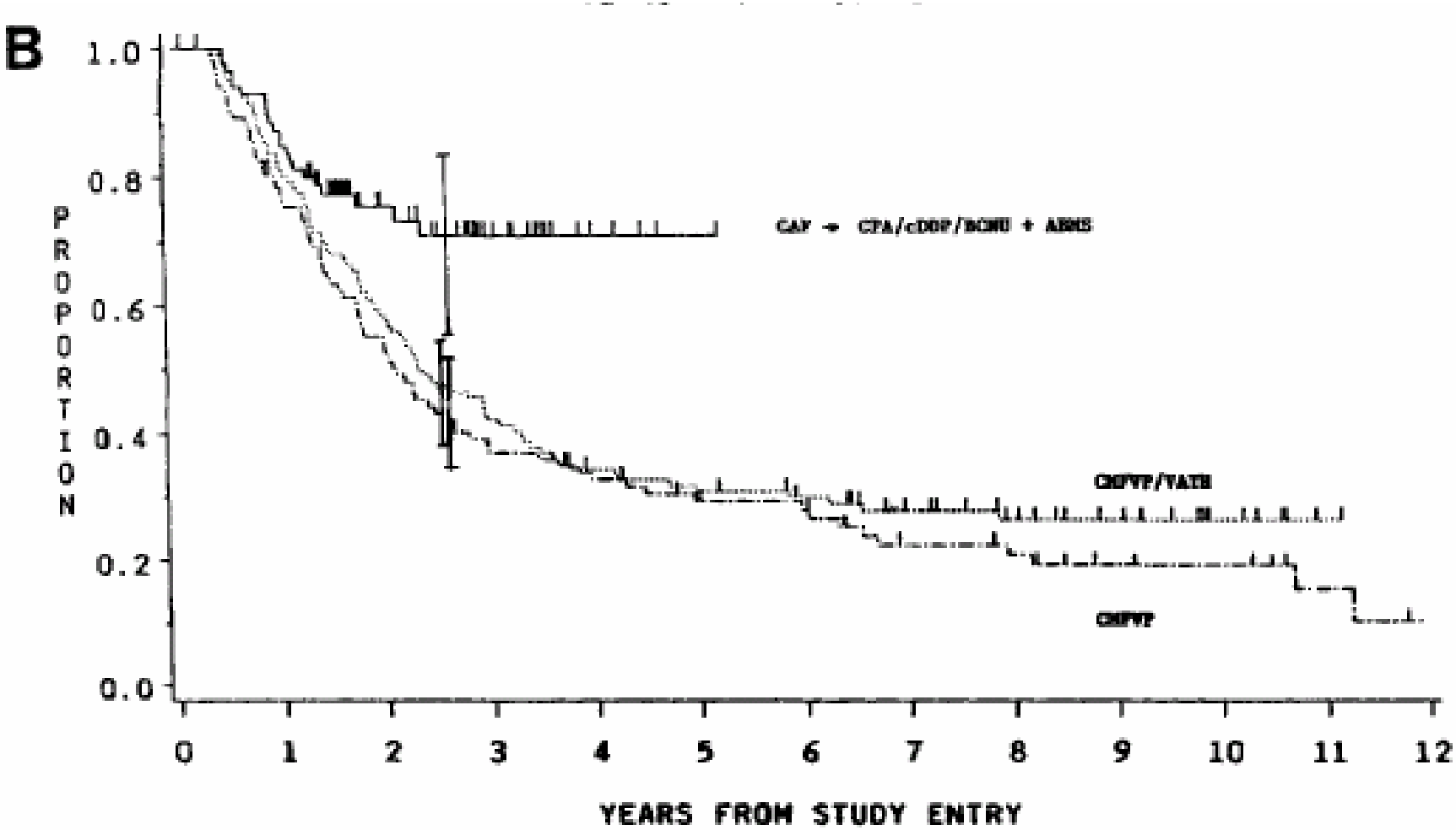
- Exploit natural experiments
  - Geographic characteristics as instrumental variables
- Matched controls without randomization
  - Constructed: propensity scores
  - “Natural”: Intervention for disease whose outcome has little variability under alternative intervention

How do Results of RCTs and Observational Studies Compare?

- What is direction of bias, if any, in observational studies?
- Are differences between results of RCTs and of observational studies larger than differences between results of different RCTs?

High-Dose Chemotherapy for Breast Cancer

Event-Free Survival, High Dose (BMT) vs. Conventional Chemotherapy



Source: Peters et al., JCO 11:1132-43, 1993

Sometimes observational studies predict results of RCTs, especially when there are multiple studies of both types

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[13]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[13]	418,343	0.77 (0.75–0.80)

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.

†CI denotes confidence interval.

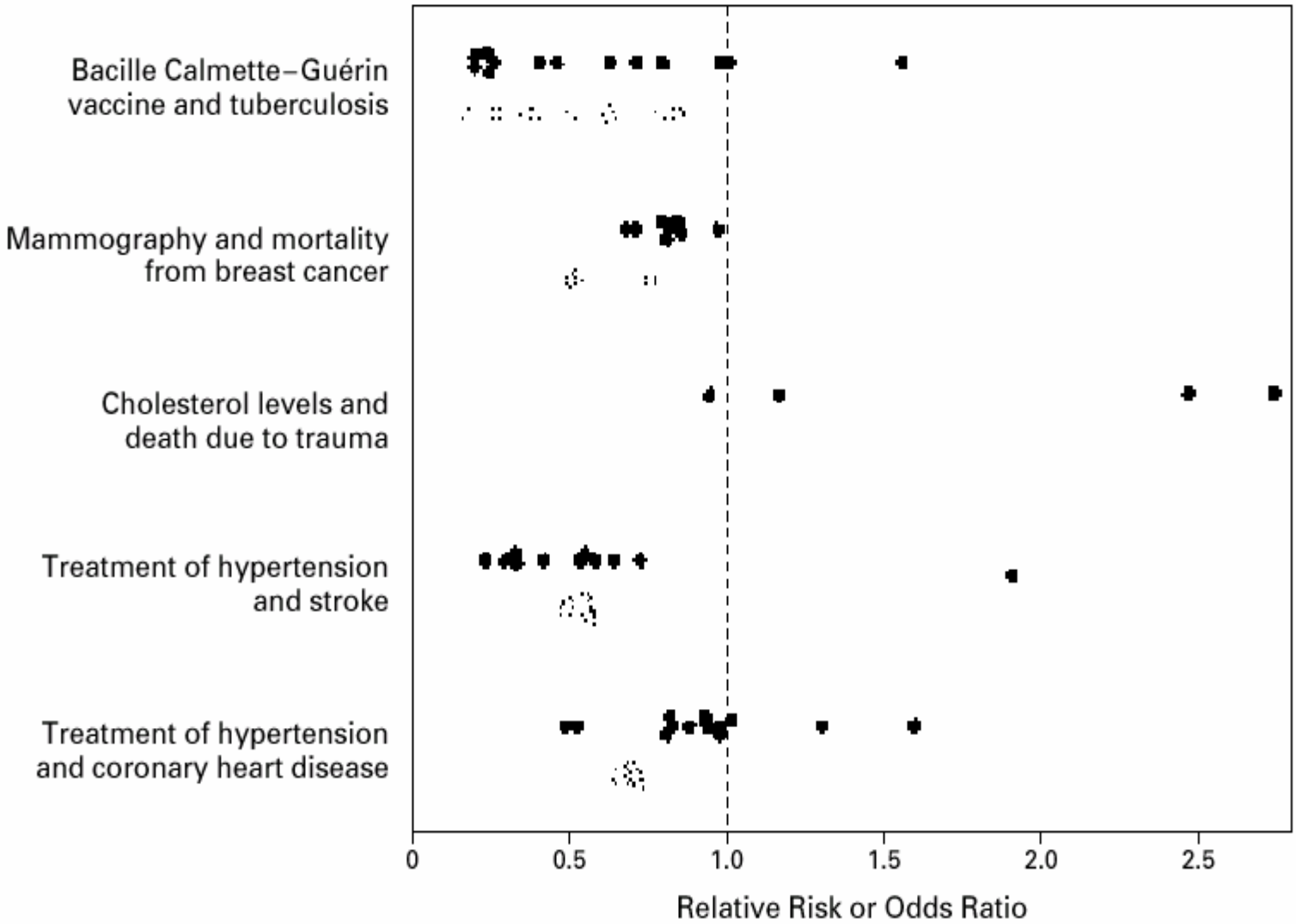


Figure 1. Range of Point Estimates According to Type of Research Design.

Dark spots represent RCTs, light spots represent observational studies

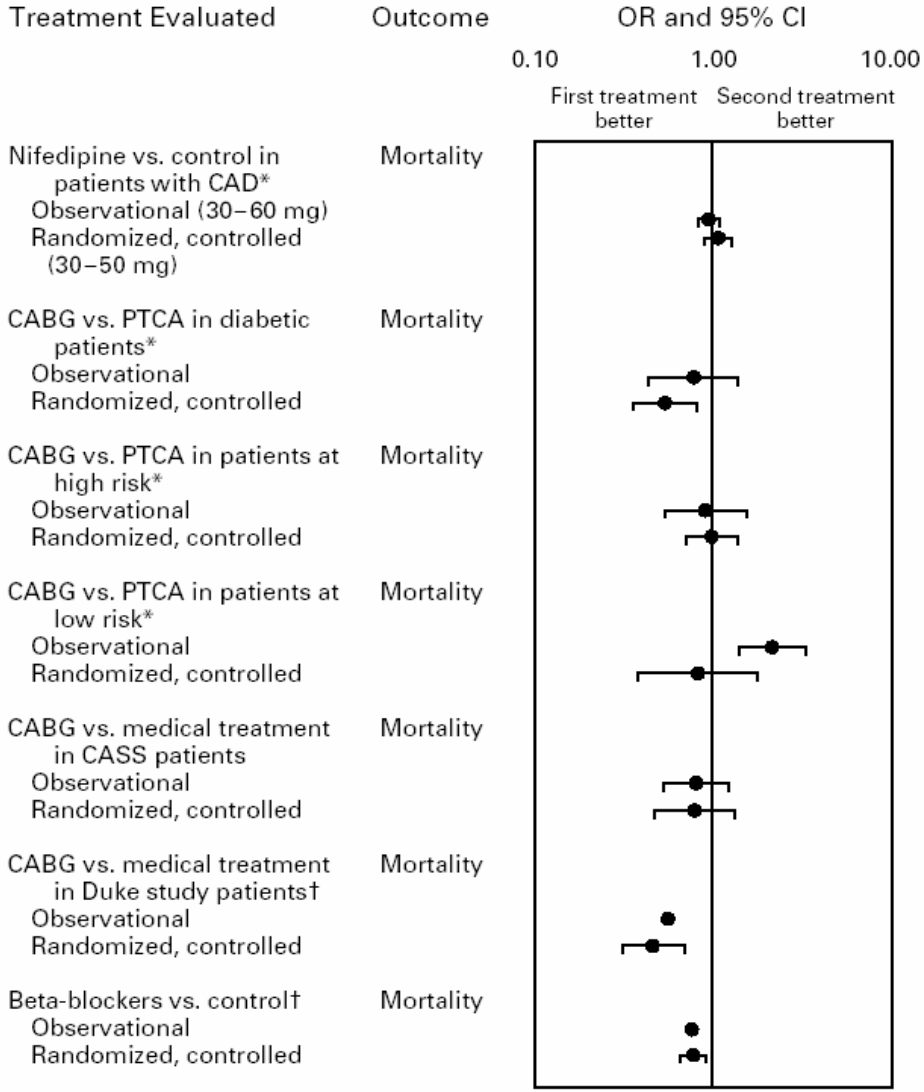
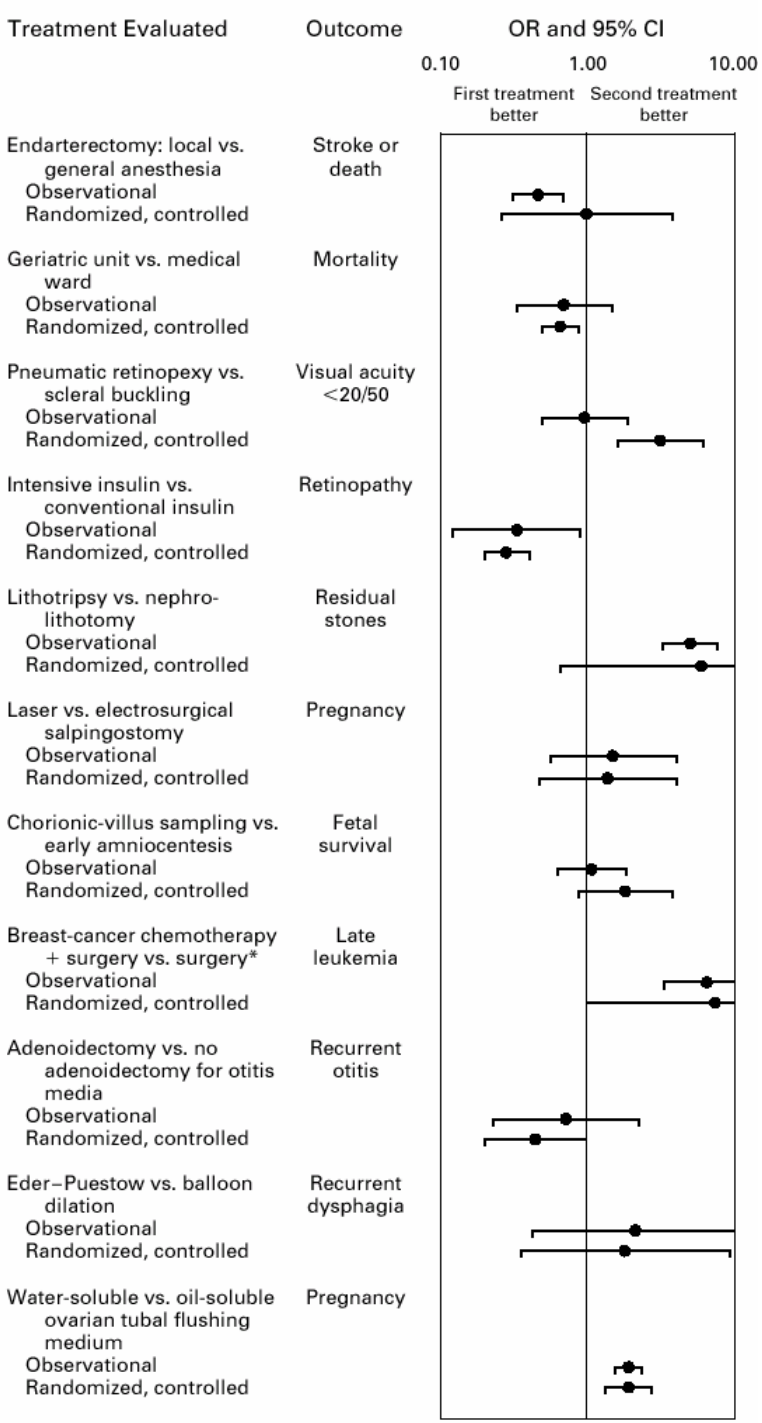


Figure 1. Results of Observational Studies and Randomized, Controlled Trials of Cardiologic Treatments.

The figure is based on data from eight articles.[13-20] Some articles contain data from more than one study. OR denotes odds ratio, CI confidence interval, CAD coronary artery disease, CABG coronary-artery bypass graft surgery, PTCA percutaneous transluminal coronary angioplasty, CASS Coronary Artery Surgery Study, and Duke the Duke University Cardiovascular Disease Databank. Asterisks indicate studies that reported relative risks rather than odds ratios. Daggers indicate studies that reported neither a confidence interval nor a P value for the odds ratio.


Treatment Evaluated
Outcome
OR and 95% CI
0.10
1.00
10.00
First treatment better
Second treatment better
Endarterectomy: local vs. general anesthesia
Observational
Randomized, controlled
Stroke or death
Geriatric unit vs. medical ward
Observational
Randomized, controlled
Mortality
Pneumatic retinopexy vs. scleral buckling
Observational
Randomized, controlled
Visual acuity <20/50
Intensive insulin vs. conventional insulin
Observational
Randomized, controlled
Retinopathy
Lithotripsy vs. nephrolithotomy
Observational
Randomized, controlled
Residual stones
Laser vs. electrosurgical salpingostomy
Observational
Randomized, controlled
Pregnancy
Chorionic-villus sampling vs. early amniocentesis
Observational
Randomized, controlled
Fetal survival
Breast-cancer chemotherapy + surgery vs. surgery*
Observational
Randomized, controlled
Late leukemia
Adenoidectomy vs. no adenoidectomy for otitis media
Observational
Randomized, controlled
Recurrent otitis
Eder–Puestow vs. balloon dilation
Observational
Randomized, controlled
Recurrent dysphagia
Water-soluble vs. oil-soluble ovarian tubal flushing medium
Observational
Randomized, controlled
Pregnancy

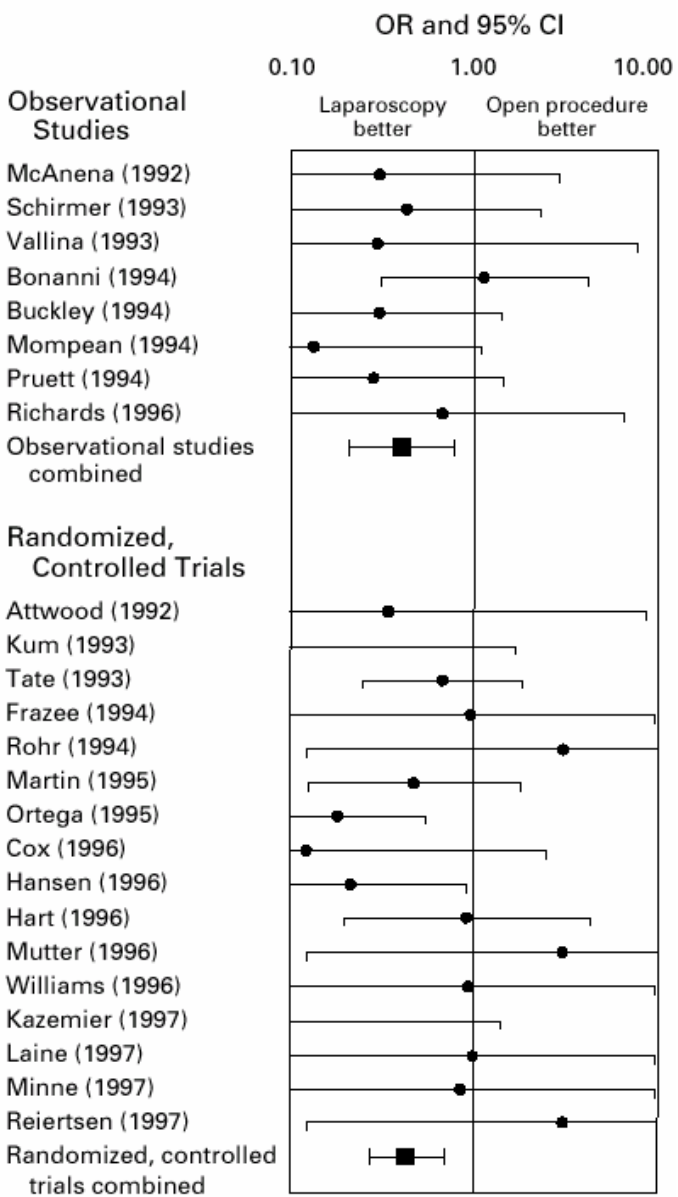
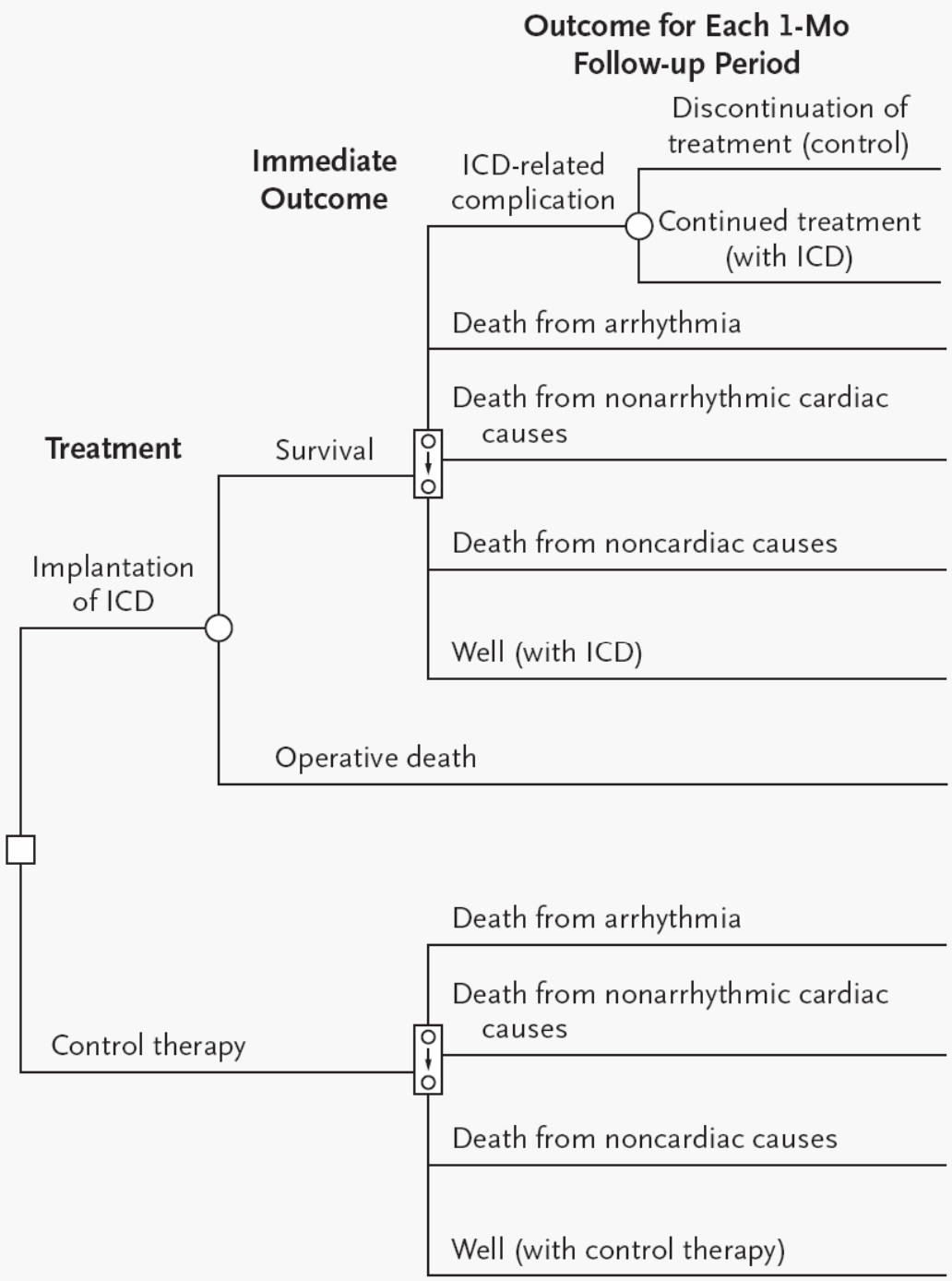


Figure 5. Odds Ratio for Infection after Laparoscopic as Compared with Open Appendectomy.

The figure is based on data from nine articles.[64-72] The 16 randomized, controlled trials were analyzed by Golub et al.[72] Trials that reported rates of all complications rather than rates of infection have been excluded. OR denotes odds ratio, and CI confidence interval.

Claims and Conjectures

- Observational data can facilitate formal modeling to extend results of RCTs
- Quantify effect size – not just a yes/no answer


Outcome for Each 1-Mo Follow-up Period
Immediate Outcome
Discontinuation of treatment (control)
ICD-related complication
Continued treatment (with ICD)
Death from arrhythmia
Death from nonarrhythmic cardiac causes
Treatment
Survival
Death from noncardiac causes
Implantation of ICD
Well (with ICD)
Operative death
Death from arrhythmia
Death from nonarrhythmic cardiac causes
Control therapy
Death from noncardiac causes
Well (with control therapy)

- Consider “randomization” by geography
- Declining costs of clinically detailed data will increase viability of observational approaches and decrease costs of RCTs

The Best Candidates for CED

- Predictable outcomes (low unexplained variance)
- Sources of natural variation in use of procedure uncorrelated with outcomes
- Effects observed in RCTs unlikely to be representative of effects obtained in community
- RCT complement rather than substitute