Observational Results Versus RCT Results

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Introduction

- I already showed through simulation how selection bias can cause observational analyses to give the "wrong" answer.
- This presentation will describe an actual instance of exactly this phenomenon.

NASCET

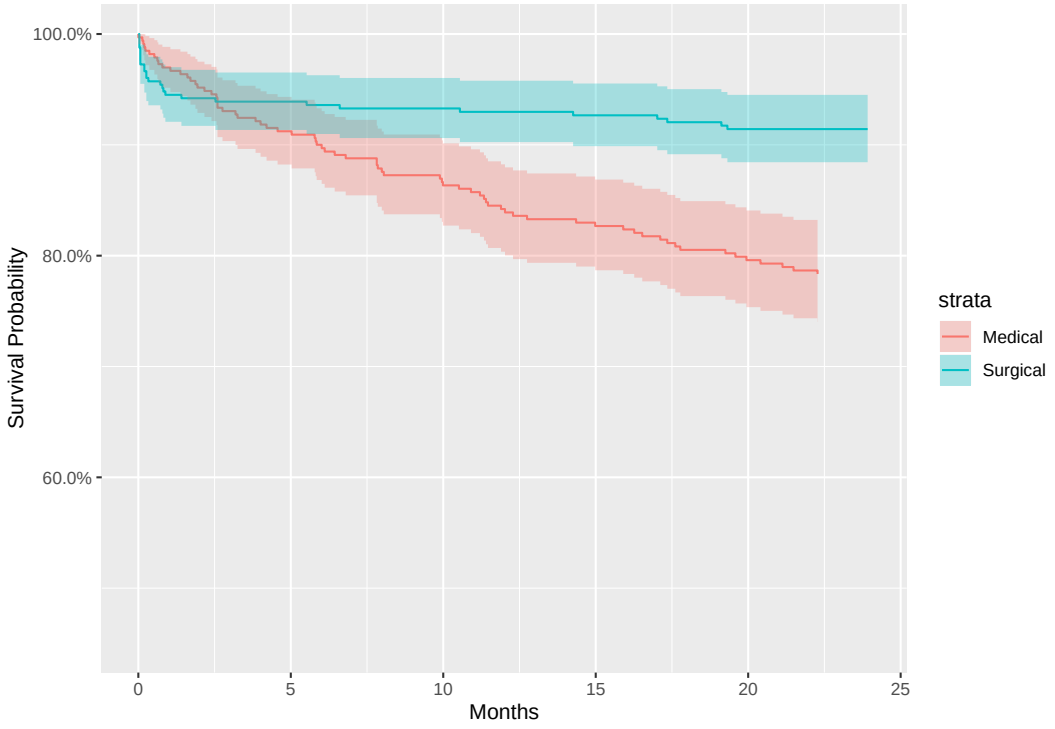
Overview

- The North American Symptomatic Carotid Endarterectomy Trial (NASCET) randomized patients with a recent minor stroke or TIA and carotid artery stenosis to receive either best medical care alone or best medical care plus carotid endarterectomy.
- The primary outcome was time to ipsilateral stroke.

NASCET

Results — 1

- First patient was enrolled in December 1987.
- Randomization was stratified by severity of stenosis ($\geq 70\%$ versus $< 70\%$) and these two strata were monitored separately for the possibility of early stopping.
- In 1991, recruitment to the severe stenosis stratum was halted due to profound benefit of surgery.



NASCET

Results — 1

- Given the importance of reducing perioperative risk, various exploratory analyses were conducted.
- ASA dose was a strong predictor of perioperative risk. Specifically, patients receiving 0–325 mg/day experienced a perioperative risk of 6.9% compared to a risk of 1.8% for patients receiving 650–1300 mg/day. This 5.1% reduction is clinically meaningful and statistically compelling ($p = 0.02$).
- Since this result was observational, the investigators were uncomfortable recommending a dose without confirmatory results from a RCT. These data were, however, compelling enough to obtain funding to run such a trial.

ACE

Overview

- The ASA and Carotid Endarterectomy (ACE) trial enrolled patients undergoing a carotid endarterectomy and randomized them to one of four doses of ASA: 81, 325, 650 or 1300 mg/day, started before surgery and continued for three months.
- The primary outcome was the occurrence of any stroke or death within 30 days of surgery. Secondary outcomes expanded the time window to three months, restricted to ipsilateral stroke and added MI to the original primary.
- The primary comparison combined the two low dose groups and compared them to the two high dose groups.

ACE

Results — ITT

Outcome	Low Dose $N = 1395$	High Dose $N = 1409$	Risk Difference ($L - H$) and 95% CI	p
Any stroke or death	66 (4.7%)	86 (6.1%)	−1.4% (−3.0% to 0.3%)	0.109
Ipsilateral stroke or death	58 (4.2%)	81 (5.7%)	−1.6% (−3.2% to 0%)	0.052

ACE

Results — Efficacy

There was also a pre-planned *efficacy* analysis that was restricted to patients who started taking the study medication two or more days prior to surgery and who were taking less than 650 mg/day prior to randomization.

Outcome	Low Dose $N = 566$	High Dose $N = 550$	Risk Difference ($L - H$) and 95% CI	p
Any stroke or death	19 (3.4%)	38 (6.9%)	−3.6% (−6.1% to −1.0%)	0.007
Ipsilateral stroke or death	17 (3.0%)	36 (6.5%)	−3.5% (−6.0% to −1.0%)	0.005

Discussion

- The ACE (RCT) results did not confirm the NASCET (observational) results. If anything, they show the opposite of the observational analysis.
- The two most likely explanations that people would suggest are:
  1. The sample size for the NASCET observation was too small.
  2. Selection bias that you could correct for through adjustment.

Discussion

Sample Size

- The original observation in NASCET was based on 327 patients so maybe it just wasn't a robust finding.
- When NASCET finished, the analysis was repeated on 1415 patients. The perioperative risks were 8.3% and 3.9% for patients taking < 650 and ≥ 650 mg/day of ASA ($p = 0.001$). This was a 4.4% reduction for high dose (OR is 0.45) which is comparable to the 5.1% reduction in the original analysis.
- Therefore, we can probably not blame the sample size.

Discussion

Selection Bias

- This is something we considered and carried out some analyses to investigate.
- The analyses involved identifying predictors of ASA dose and then using those predictors in a logistic regression model for perioperative event and then assessing the incremental effect of ASA dose on perioperative risk. The odds ratios remained essentially unchanged and p-values remained small.
- Selection bias is still the most likely explanation, however, I have not been able to model the mechanism. It is also possible that I may never be able to if the right data were not collected.