Beyond the randomized controlled trial: Why our literature is often contradictory

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Overview

- Perioperative outcomes
- Research gold standard
- Efficacy vs effectiveness: Example I
- Observational research
- Multicenter collaboration

Disclosures

- No financial, consulting, contractual relationships with any vendor

Perioperative morbidity & mortality

- Anesthesia events
  - Mortality: 1 in 200,000
  - Difficult airway: 2-4%
  - Visual loss: 0.1 – 1%
- Organ system major morbidity
  - Acute kidney injury: 1 – 3%
  - Myocardial infarction: 1 – 3%
  - Stroke: 1%
  - Acute Lung Injury: ??

- We are focused on the needle in the haystack
**Perioperative period**

- Physically intrusive intervention
- Risky and expensive
- Very difficult to blind study individuals
- Challenging to ethically randomize
  - Difficult airway, Hypotension, Hypertension
- "Random" clinical decisions (RCDs) rampant
  - Wide variation in practice because of few guidelines
- Challenging to recruit "priority populations"
  - Pediatrics
  - Emergency surgery w/ non-optimized patient
  - Racial & Ethnic Minorities

**The Research Gold Standard**

- Prospective Randomized Controlled Trial (RCT)
  - Placebo
  - Blinded

- Strongest evidence
- Detailed protocols
- "Eliminate" alternate causality
- Power analysis $\rightarrow$ prospective study size

**Not so golden**

Infrequent events $\rightarrow$ large study

$\rightarrow$ small study

- *Controlled* trial is not *routine* clinical practice
- Specific, small study extrapolated to population at large

**Post release controversies**
**β blockers – small N**

**EFFECT OF ATENOLOL ON MORTALITY AND CARDIOVASCULAR MORBIDITY AFTER NON-CARDIAC SURGERY**

DENNIS T. MANDANG, PH.D., M.D., ELIZABETH L. LAVIG, M.D., APHEA WALLACE, PH.D., M.D., AND TIA TATHI, M.D., FOR THE MULTICENTER STUDY OF PERIOPERATIVE ISCHEMIA RESEARCH GROUP

- Published 1996, NEJM
- Total trial enrollment = 200 patients
- Non-cardiac surgery
  - IV β blocker preop, intraop
  - PO β blocker during hospitalization, no control after d/c
- Evaluated mortality, cardiac events
- Resting heart rate difference: 75 versus 87
- No in-hospital difference
- At 2 years mortality is 21 / 101 in placebo, 9 / 99 in treatment

**More evidence**

**THE EFFECT OF BISOPROLOL ON PERIOPERATIVE MORTALITY AND MYOCARDIAL INFARCTION IN HIGH-RISK PATIENTS UNDERGOING VASCULAR SURGERY**

DENIS POLAKOWSKI, PH.D., DAVE BENDER, PH.D., JEREMY J. BAY, PH.D., JAY R. THAXTON, PH.D., LOUIS L.M. VAN DE VEN, PH.D., JAN D. BLANKESTEIN, PH.D., HUBERT F. BAARS, M.D., TRIN N.Y. PH.D., ANDREAS RITZOS, M.D., CARLO VUOLTI, M.D., JOS T.C. ROLANDA, PH.D., AND PIERO VAN UN, PH.D., FOR THE DUTCH ECGOCARDIOGRAPHIC CARDIAC RISK EVALUATION APPLIED STRESS ECGOCARDIOGRAPHY STUDY GROUP

- 112 patients TOTAL
- Excluded patients
  - WITHOUT inducible ischemia
  - WITH left main disease

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**The difference is clear**

**Table 2. Results of Exercise ECGocardiography $^*$**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ECGocardiography (Exercise)</th>
<th>ECGocardiography (Rest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual affects</td>
<td>1.23</td>
<td>1.44</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>1.46 ± 0.18</td>
<td>1.46 ± 0.18</td>
</tr>
<tr>
<td>Right atrial dilation (%)</td>
<td>14 (24)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (%)</td>
<td>25 (42)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Non-obstructive angina (%)</td>
<td>28 (52)</td>
<td>24 (43)</td>
</tr>
<tr>
<td>Non-obstructive angina (%)</td>
<td>6 (11)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

$^*$: There were no significant differences between the two groups.

---

**The difference is clear**

- Extrapolated to become mainstay of optimization

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**Cardiac death or non-fatal MI**

- Standard care
- Bisoprolol

---

P < 0.001

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Days after Surgery

- 0
- 7
- 14
- 21
- 28

Percentage of Patients

- 0
- 10
- 20
- 30
- 40

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Cardiac death or non-fatal MI
Like most veterinary students, Doreen breezes through Chapter 9.

**β blockers – big N**

Perioperative Beta-Blocker Therapy and Mortality after Major Noncardiac Surgery

Peter K. Lindenaue, M.D., Penelope Pekow, Ph.D., Kaijun Wang, M.S., Dheeresh K. Mamidi, M.B., B.S., M.P.H., Benjamin Gutierrez, Ph.D., and Evan M. Benjamin, M.D.

- 663,635 patients in administrative database -- Premier®
- Outcome = in-hospital death
- Beta blocker = treatment within POD 2
- Created treatment and control groups

Odds Ratio for Death in the Hospital (95% confidence interval)

POISEd to make a change

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol (n=4174), n (%)</th>
<th>Placebo (n=4177), n (%)</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>151 (2.6)</td>
<td>215 (5.1)</td>
<td>0.70</td>
<td>0.0007</td>
</tr>
<tr>
<td>Revascularization</td>
<td>11 (0.3)</td>
<td>27 (0.6)</td>
<td>0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>91 (2.2)</td>
<td>120 (2.9)</td>
<td>0.76</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Outcome</th>
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<th>Placebo (n=4177), n (%)</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>125 (3.1)</td>
<td>97 (2.3)</td>
<td>1.33</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>41 (1.0)</td>
<td>19 (0.5)</td>
<td>2.17</td>
<td>0.005</td>
</tr>
<tr>
<td>Significant hypotension</td>
<td>626 (15.0)</td>
<td>404 (9.7)</td>
<td>1.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Significant bradycardia</td>
<td>274 (6.6)</td>
<td>101 (2.4)</td>
<td>2.71</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
But wait, there’s more . . .

Bisoprolol and Fluvastatin for the Reduction of Perioperative Cardiac Mortality and Myocardial Infarction in Intermediate-Risk Patients Undergoing Noncardiovascular Surgery

- Unblinded, titrated trial of bisoprolol and fluvastatin
- Started weeks before operation
- Focused on ASA 1, 2, and 3 patients
- Bisoprolol vs control: heart rate of 65 vs 78

- Primary end point: cardiac death or nonfatal MI
- Bisoprolol vs control: 2.1% vs 6.0% \( p = 0.002 \), \( OR = 0.34 \)

"Comparative Effectiveness"

- Efficacy: Can it work?
  - Under ideal circumstances

- Effectiveness: Does it work?
  - In real world patients treated in ordinary clinical settings

- Efficiency: Is it worth it?
  - Value of intervention in relation to resources it consumes

The circle of life

Abstract-based medicine  Have you noticed?

Small RCT  Broad Use  Large Retrospective Review

“Personalized” medicine  We need to study this

- Value of intervention in relation to resources it consumes

Efficacy: Can it work?
  - Under ideal circumstances

Effectiveness: Does it work?
  - In real world patients treated in ordinary clinical settings

Efficiency: Is it worth it?
  - Value of intervention in relation to resources it consumes
A new responsibility

The Value of Phase 4 Clinical Testing
Gus J. Vlahakes, M.D.

In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research
Jerry Avorn, M.D.

All RCTs are not the same

- Must evaluate
  - Background
  - Methods
  - Results
  - Discussion
- “CONsolidated Standards Of Reporting Trials” = CONSORT
- Group of Research Researchers
- Objective checklist for evaluation of an RCT
- Adopted by all major journals

Why isn’t efficacy enough?

- The “C” in RCT: control
  - The clinical process can’t be recreated
    - Intensive insulin therapy
  - The intervention is complex
    - Preoperative beta blockade
  - The patients are not your patients
    - Coronary revascularization for preop optimization
  - The intervention requires learning
    - Videolaryngoscopy for failed airway
Why isn’t efficacy enough?

• Risk and benefit must be considered
  – The adverse events are not observed due to rarity of the complication
    • Aprotinin
    • Vioxx
  – The adverse events are not observed due to inadequate follow-up period
    • Hormone replacement therapy
• Risk and benefit are not uniform
  – Lower benefit in some patients
  – Higher risk in some patients

Expanding the toolset

• Observational datasets to be considered
  – Administrative (eg NIS, Premier)
  – Clinical registries (eg STS, McSPI, NSQIP)
  – Clinical information systems – “chart review”
• Statistical tools
  – Covariate adjustment, propensity score matching & stratification
  – Hierarchical modelling
  – Bayesian analytics
• Data gathering
  – Objective outcomes (death, cost, laboratory values)
  – Clinical documentation
  – Understand data limitations

Chart review – Classic

• GIGO
  – Garbage In \(\rightarrow\) Garbage Out
• Impossible to do research on this

“Chart review” – Modern

“DIDO”

– Data In \(\rightarrow\) Decisions Out

“Chart review” – Modern

– Allows us to ask questions never asked before
We have 300+ Unsuspecting Data Collectors!!

Areas of conflict

- Outcomes with low incidence (i.e., < 2 or 3%)
- "Interventions" that are difficult to randomize or control
- Adverse events that are side effects of treatments
- Low frequency treatments
- Complex interventions that require learning

Bad data is worse than no data

- Data quality is a major issue
  - Variant EHR documentation practices by vendor and site
  - Investigators must evaluate data quality
- Be aware (and beware) of data limitations
- Specific, testable hypotheses are the starting point, not the data

Acute Kidney Injury (AKI)

- Very little success in renal preservation
- Outcomes similar to decades ago

- Prediction
  - Enables informed consent
  - Essential for prospective trials
  - Provides postoperative care surveillance guidance
  - Guides research resource allocation
Non-cardiac surgery

- 18 million non-cardiac procedures performed annually
- Some data on AKI in vascular surgery (high risk)
- No data regarding incidence, risk factors, or outcome after general surgery

An exploratory study

- Setting
  - Large, tertiary care university hospital – UMHS
  - Single center
- Study type
  - Prospective, observational
  - No clinical protocol, no interventions
  - Analysis of observational EHR dataset

Patient population

- Adult non-cardiac surgery patients
- “Major” surgery (LOS ≥ 2 days)
- Preoperative creatinine available within 30 days
  - Estimated CrCl ≥ 80 ml/min
  - Cockcroft-Gault formula (age, gender, weight)
- Excluded patients:
  - Urology
  - Nephrectomy or uretral manipulation
  - Supra-aortic clamping
  - Preoperative renal dysfunction (in H&P or by CrCl)

Outcome definitions

- Primary Outcome = CrCl <50 within POD 7
  - From laboratory interface
    - 40% decrease in renal function
    - Requires pharmacologic adjustment
- Secondary
  - RRT within 7 days
    - Hospital charge data
  - All cause mortality at 30 day, 60 day and 1 year
    - Social Security Death Master File
EHR data elements collected

- Preoperative comorbidities
  - Age, gender, CHF, CAD, COPD, BMI, liver dz, DM
- Operative considerations
  - Emergent surgery, “high risk” surgery, laparoscopic, etc
- Intraoperative management
  - Case length
  - PRBC administration
  - Intraoperative blood pressure variations
  - Urine output
  - Vasopressor boluses and infusion
  - Mannitol or furosemide administration

Automated Vital Sign Data

- Step #1
  - Create sequential 10 minute periods = epoch
- Step #2
  - Determine MEDIAN blood pressure (SBP or MAP)
- Step #3
  - Is this median value below a threshold
    - Absolute drop in BP:
      - SBP <80, <70, <60
      - MAP <60, <50, <40
    - Relative drop in BP (preoperative baseline)
      - SBP or MAP 30%, 40%, 50%
- Step #4
  - Count up the # of epochs below the threshold
- Allows evaluation of duration and severity

Statistical analysis

- Multivariate logistic regression for predictors of AKI
  - Full model fit \( \rightarrow \) independent predictors
  - Odds ratio for each predictor
  - Evaluate model using ROC curve
- Risk adjusted intraoperative analysis
  - Group patients into 4 preop risk categories
  - Evaluate intraoperative variables
  - Logistic regression within each risk quartile

Results -- Incidence

- 65,043 cases between 2003 and 2006
- 15,102 patients met the inclusion criteria
- 121 \( \rightarrow \) AKI (0.8%)
- 14 \( \rightarrow \) Dialysis (0.1%)
Results -- predictors

- Seven independent preoperative predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 59</td>
<td>4.2 (2.9 - 6.0)</td>
</tr>
<tr>
<td>BMI ≥ 32</td>
<td>1.9 (1.3 - 2.7)</td>
</tr>
<tr>
<td>High Risk Surgery</td>
<td>2.9 (2.0 - 4.3)</td>
</tr>
<tr>
<td>Emergent Surgery</td>
<td>1.9 (1.2 - 3.0)</td>
</tr>
<tr>
<td>PVOD</td>
<td>4.2 (2.5 - 7.1)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>2.4 (1.4 - 4.3)</td>
</tr>
<tr>
<td>COPD</td>
<td>3.0 (1.9 - 5.0)</td>
</tr>
</tbody>
</table>

Results – Increasing Risk

<table>
<thead>
<tr>
<th>Preoperative Risk Class</th>
<th>Acute Renal Failure, n (%)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (0 risk factors), n = 5,728</td>
<td>16 (0.3)</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Class II (1 risk factor), n = 5,841</td>
<td>32 (0.5)</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Class III (2 risk factors), n = 2,625</td>
<td>34 (1.3)</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Class IV (3+ risk factors), n = 908</td>
<td>39 (4.3)</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
</tbody>
</table>

Results -- Intraoperative management

- Identified predictors of AKI within each risk group
- Medium preoperative risk
  - Intraoperative risk factors: Diuretic administration
- High preoperative risk patients
  - Intraoperative risk factors: Vasopressor usage, diuretic, periods of hypotension
- Notable absence of association with
  - Case length, PRBC administration, urine output

Results -- Mortality

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Normal Preoperative Renal Function (n = 908)</th>
<th>Postoperative Acute Renal Failure (n = 116)</th>
<th>P Value</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent operation</td>
<td>61 (11)</td>
<td>33 (32)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>High-risk surgery</td>
<td>111 (20)</td>
<td>37 (31)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Intraoperative, high risk</td>
<td>2.0</td>
<td>1.0</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Blood loss, %</td>
<td>25.9</td>
<td>25.9</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Mean EBL, ml</td>
<td>50 (24)</td>
<td>50 (24)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Group therapy</td>
<td>59 (31)</td>
<td>81 (55)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>16 (8)</td>
<td>16 (8)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>39 (4.5)</td>
<td>19 (11)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Nonspecific chronic biliary/colonic disease</td>
<td>62 (20)</td>
<td>34 (20)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Perioperative vascular disease</td>
<td>47 (16)</td>
<td>19 (12)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>41 (20)</td>
<td>25 (12)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>All-case 30-day mortality</td>
<td>9 (2.2)</td>
<td>19 (6)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>All-case 90-day mortality</td>
<td>17 (5.6)</td>
<td>19 (5.7)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
<tr>
<td>All-case 1 yr mortality</td>
<td>11 (3.1)</td>
<td>39 (21)</td>
<td>NS</td>
<td>1.0 (1.0 - 1.0)</td>
</tr>
</tbody>
</table>

- Patients similar in terms of diseases and operative characteristics
- 30 day mortality hazard ratio of 6.5

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Multicenter Collaboration

• Essential to validate single center observations
• Provides broader patient population and provider pattern
• Challenged by
  – Disparate vendor & home grown IT systems
  – Variant implementations (preop, intraop, PACU, etc)
  – Absence of lexicon or failure to adopt
  – Idiosyncratic documentation patterns
• Prototypical failures
  – Vendor Driven Initiatives
  – Unequal access

50K foot view

• Automated process to extract cases at each site
• Transmit “valid” cases to central repository
• Every 3-6 months
• Socialized academia – “price” & “criteria” is the data

Multicenter Perioperative Outcomes Group

http://mpog.med.umich.edu

MPOG Members

• University of Michigan (Coordinating center)
• Columbia University
• Massachusetts General Hospital
• Fletcher Allen Healthcare
• OHSU
• University of Colorado
• University of Tennessee
• UCSF
• Washington University
• 25 others
MPOG status

- More than 1 million cases extracted, mapped, de-identified, and available for research
  - Medications / Infusions / Fluids / Outputs
  - Intraop notes
  - Patient Header
  - Staff in / out
  - Outcome record
  - Anesthesia billing
- Physiologic
- Laboratory values
- Preoperative H&P
- IV Access
- NSQIP (small subset)
- 7 institutions, 4 AIMS vendors
  - GE Centricity
  - iMDSoft Metavision
- In development: Epic and Innovian

Questions these data can address

- What is the variation in anesthetic management of common procedures?
- Describe clinical impact of national drug shortages
- Does anesthesiology variation explain part of risk adjusted outcome variation?
- Does hypotension matter to the brain, kidney, or heart?

Summary

- Advancing medicine is a process, not an event
- Must have multiple tools in the toolbox
- Many "conflicts" in the literature are different vantage points
- Multicenter collaboration is next

“Well, lemme think … You’ve stumped me, son. Most folks only wanna know how to go the other way.”