Journal Club – May 24, 2018

Drs. Ryan Iverach, Rebecca Schonnop, Amanda Schouten

Achieving ventricular rate control in patients taking chronic beta-blocker therapy

Feeney, M., et. al. *American Journal of Emergency Medicine,* 2018

P: Adult patients taking chronic beta-blocker therapy, who present with atrial fibrillation with RVR
I: IV Diltiazem
C: IV Metoprolol
O_1: Successful response to ventricular rate control
O_2: Treatment failure, hospital admission, adverse events
D: Single-center retrospective chart review

What we already know:

- Atrial fibrillation (AF) is one of the most commonly seen tachyarrhythmias in the ED
- When chemical cardioversion is selected, and in the absence of contraindications, IV beta-blockers and IV nondihydropyridine calcium channel blockers are often the agents of choice
- A recent study showed that beta-blocker naïve patients were more likely to achieve rate control with IV metoprolol compared to patients on chronic beta-blocker therapy
- No other studies have reviewed if patients on chronic beta-blocker therapy would have improved response with medications other than beta-blockers, such as IV calcium channel blockers

Methods:

- Single center retrospective chart review
- Adult patients presenting between January 2007 and August 2014
- Outcome measures and statistical methods were defined *a priori*
- Fixed dosing regimens of metoprolol and diltiazem
- Primary outcome: Successful response to ventricular rate control
    - Successful response = ventricular rate <100bpm or to <120bpm if the decrease was at least 20% from initial presentation
    - Lowest achieved rate within 6 hrs of last dose of metoprolol or diltiazem was recorded
- Secondary outcome: Treatment failure, hospital admission, adverse events (sBP <90 or HR <50 requiring pharmacologic intervention or pacing) within 6hrs of either drug
    - Treatment failure = need for cardiac ablation, alternative medication therapy, electrical cardioversion, total doses of metoprolol >15mg, total doses of diltiazem >0.6 mg/kg or a continuous infusion of diltiazem started within 24h of an initial dose
- Statistical analysis:
    - Power calculated assuming clinical significance of 15%, alpha of 5%, and beta of 20%, with a total of 374 patients required to achieve significance (187 per group)

Inclusion Criteria:

- 18 years or older
- Presented in AF with RVR with a ventricular rate ≥120 bpm
- Chronic beta-blocker therapy (Prescribed and taking PO metoprolol within 5 days of study)

Exclusion Criteria:

- Prescribed PO diltiazem or any beta-blocker other than metoprolol
- Known hypersensitivity to metoprolol or diltiazem
- Contraindications to metoprolol or diltiazem (acute decompensated HF, CHF, sick sinus syndrome, AV block, or pre-excitation syndrome)
- Acute MI
- Pregnant
- SBP <90 mmHg
- Recurrent ED visit within 24 hrs

Results:
- 398 patients received IV metoprolol in the ED for AF with RVR
    - 316 met inclusion criteria as they were chronically taking PO metoprolol
- 317 patients received IV diltiazem in the ED for AF with RVR
    - Only 16 met inclusion criteria (excluded for not taking chronic PO metoprolol (n=282), duplicate encounters (n=12), presenting HR <120 (n=6), PO diltiazem given (n=1)).
- No significant differences in treatment arms in regards to age, sex, CHADS2 score, comorbidities
    - Metoprolol arm had a significantly greater number of patients with history of digoxin use
- Primary outcome: successful rate control
    - 11 patients (68.8%) in diltiazem arm vs. 134 patients (42.4%) in metoprolol arm (p = 0.067)
- Treatment failure occurred in 5 patients (31.25%) in the diltiazem arm
- 34 patients (10.8%) in the metoprolol arm required >15mg metoprolol (treatment failure)
- Subsequent hospitalization was required for 58% of patients in metoprolol arm, compared to 6.25% of patients in diltiazem arm (p <0.001)
- No difference in incidence of hypotension between groups
- No bradycardia in the metoprolol arm, while 2 (13%) patients in the diltiazem arm had a recorded HR <50bpm (p = 0.002)

Limitations:
- Retrospective chart review
- Underpowered and unbalanced study, with very small sample size for the diltiazem arm
- Patient medications were based on their current medication list, thus compliance of their home therapy was not verified
- ED did not have continuous cardiac monitoring, so response rate for each group may have missing documentation
- Unable to differentiate spontaneous cardioversion vs rate control with IV medication
- Single individual for data entry, who was not blinded to the study question. Possibility for bias.
- Not applicable to patients taking other beta-blocker agents
- No comment on treatment failure in metoprolol arm besides 10.8% who required higher dose

Strengths:
- Outcome measures and statistical methods defined apriori
- Clinically relevant question

Study Conclusions:
- In patients taking chronic beta-blocker therapy who present to the ED with AF with RVR, the use of diltiazem was associated with a higher successful response compared to the IV metoprolol group. However, the difference was not statically significant.

Presenter's Clinical Bottom Line:
- IV diltiazem is a safe and effective agent to consider in the treatment of patients with AF with RVR, who were previously on chronic beta-blocker therapy.

Necrotizing Soft Tissue Infection: Diagnostic Accuracy of Physical Examination, Imaging, and LRINEC Score

Fernando, S., et. al. *Annals of Surgery,* 2018

Background:

- Necrotizing fasciitis is a life-threatening skin and soft tissue infection, and delay to diagnosis and surgical management is associated with increased mortality.
- Despite advances in care, mortality remains between 20-30%
- LRINEC score is a diagnostic clinical decision tool that uses 6 lab values (WBC, Hb, Na, glucose, Cr, and CRP). A score ≥6 is moderate risk (50-75% probability) of NSTI, ≥8 indicates high risk (>75% probability).
- Clinicians rely on physical exam, diagnostic imaging, and clinical instruments to make the diagnosis, however, little evidence validates the utility of these assessments.

Methods:

- Systematic reviews was structured according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), the Cochrane Handbook for Diagnostic Test Accuracy, and other guidelines for reviews of diagnostic accuracy
- Six databases were searched, from inception to November 13, 2017
- Diagnosis of NSTI is defined by any of the following: operative findings, histo-pathologic tissue exam, or death from suspected NSTI
- Disagreements in citation inclusion were resolved by consensus without third party assistance.
- Each study had to have a 2x2 table either in the original article or calculated from sensitivity and specificity
- Variables collected included: author and publication info, inclusion criteria, CT imaging details, number of patients, age of patients, number of deaths, true positive, false positive, false negative, true negative, total number of diagnosed NSTI cases, SN and SP of diagnostic tests.
- QUADAS-2 tool was used to assess the risk of bias of the included studies.
- Statistical analysis:
    - Results were presented graphically with one-dimensional forest plots of sensitivity and specificity estimates, as well as the Receiver Operating Characteristics (ROC).
    - HSROC model (Hierarchical Summary Receiver Operating Characteristic) was applied to the pooled results to get summary point estimates of the pairs of SN and SP, the odds ratios, likelihood ratios and the confidence intervals.
- Overall confidence in pooled diagnostic effect was estimated using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach. The overall confidence in effect evidence was grouped into 1 of 4 levels: high, moderate, low or very low.

Inclusion Criteria:

- Enrolled adult patients (≥16 years) with suspected NSTI
- Conducted in the ED, hospital wards, or ICU
- Evaluated the test characteristics of: physical examination, imaging modalities, or LRINEC score for the diagnosis of NSTI

Exclusion Criteria:

- Case reports
- Case series
- Animal studies
- Pediatric studies

- Observational studies evaluating prognosis in cohorts of patients with confirmed NSTI only (i.e. no controls)

Results:

- 2290 citations were identified through the relevant searches, 1661 studies were screened, and 30 studies underwent full-text review.
- 24 cohorts from 23 studies (n=5982) were included in the meta-analysis.
- **Demographics/Risk Factors**
  - Comparison between NSTI and non-NSTI patients for each study found the following to be significant risk factors:
    - Diabetes (in 4 of 8 studies)
    - Immunocompromised status (in 4 of 6 studies)
    - IVDU (in 2 of 3 studies)
- Table 3 below provides the summary estimates of the SN and SP for each of the exam, imaging, and clinical scores for diagnosis of NSTI.
- **Physical Exam**
  - Only 3 physical exam findings had at least 3 relevant studies allowing for meta-analyses
    - 4 studies evaluated accuracy of fever
    - 5 studies evaluated for hemorrhagic bullae
    - 6 studies evaluated for hypotension
  - A patient with a 50% pre-test probability of NSTI, but the absence of fever, hemorrhagic bullae, or hypotension still retains a post-test probability of 41.3%, 43.9%, and 44.7%, respectively.
- **Imaging**
  - 4 studies investigated the accuracy of plain radiography
  - 7 studies evaluated the presence of fascial gas on CT
  - In a patient with a 50% pre-test probability of NSTI, the presence of fascial gas on CT increases the post-test probability to 93%, while the absence of fascial enhancement, edema, or gas decreases the post-test probability to 7%.
- **Clinical tool (LRINEC)**
  - 14 studies evaluated the accuracy of LRINEC ≥6, and 9 studies evaluated the LRINEC ≥8
  - Of the variables in the LRINEC score, WBC count was most commonly found to be a significant predictor.
  - A patient with a 50% pre-test probability of NSTI, but a LRINEC score < 6, would still retain a 27.3% risk

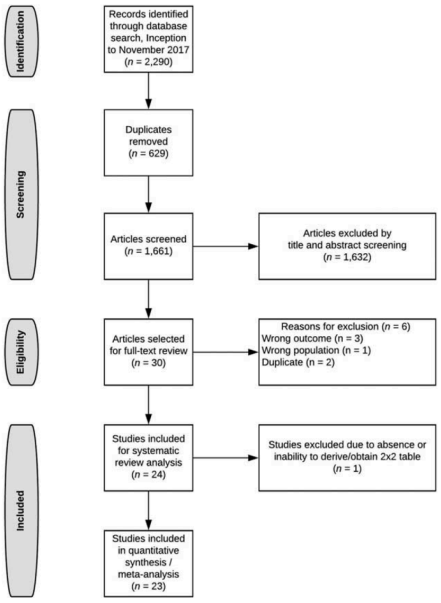

FIGURE 1. Flow chart summarizing evidence search and study selection.

TABLE 3. Summary Estimates of the Performance of Physical Examination Features, Imaging, and LRINEC Score in Diagnosing Necrotizing Soft Tissue Infection

	No. of Cohorts (No. of Patients)	Sensitivity (%)	Specificity (%)	Diagnostic Odds Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio
Physical examination						
Fever	4 (647)	46.0 (38.9 to 53.2)	77.0 (59.7 to 88.1)	2.81 (1.34 to 5.88)	1.98 (1.12 to 3.51)	0.70 (0.59 to 0.84)
Hemorrhagic bullae	5 (951)	25.2 (12.8 to 43.7)	95.8 (87.3 to 98.7)	7.64 (3.81 to 15.32)	5.97 (2.89 to 12.32)	0.78 (0.66 to 0.93)
Hypotension	6 (1014)	21.0 (9.4 to 40.4)	97.7 (91.4 to 99.4)	11.38 (5.00 to 25.90)	9.20 (3.87 to 21.86)	0.81 (0.68 to 0.96)
Imaging						
Plain Radiography	4 (478)	48.9 (24.9 to 73.4)	94.0 (63.8 to 99.3)	15.03 (3.69 to 61.22)	8.17 (1.61 to 41.47)	0.54 (0.36 to 0.82)
Computed tomography (fascial gas only)	7 (787)	88.5 (55.5 to 97.9)	93.3 (80.8 to 97.9)	107.64 (12.32 to 940.18)	13.27 (4.24 to 41.50)	0.12 (0.03 to 0.62)
Computed tomography (fascial edema OR fascial enhancement OR fascial gas)	6 (700)	94.3 (81.2 to 98.5)	76.6 (21.3 to 97.5)	54.29 (5.51 to 534.73)	4.04 (0.62 to 26.47)	0.07 (0.02 to 0.24)
LRINEC Score						
≥6	14 (4339)	68.2 (51.4 to 81.3)	84.8 (75.8 to 90.9)	11.95 (5.32 to 26.83)	4.49 (2.74 to 7.35)	0.38 (0.24 to 0.60)
≥8	9 (1905)	40.8 (28.6 to 54.2)	94.9 (89.4 to 97.6)	12.71 (4.71 to 34.28)	7.94 (3.44 to 18.32)	0.62 (0.50 to 0.78)

LRINEC indicates laboratory risk indicator for necrotizing fasciitis.

- In the sensitivity analysis which excluded high risk-of-bias studies, only CT with facial gas, LRINEC ≥6, and LRINEC ≥8 had at least 3 studies for meta-analysis:
  - CT has pooled SN of 93.3% (95%CI 48.7-99.5%), SP of 93.1% (95%CI 80.9-98.2%)
  - LRINEC ≥6 had SN of 62.6% (95%CI 43.7-78.3%), SP of 78.7% (95%CI 67.0-87.1%)
  - LRINEC ≥8 had SN of 32.4% (95%CI 22.0-45.1%), SP of 93.9% (95%CI 80.9-98.2%)

Strengths:
- Meta-analysis
- Comprehensive review of available literature
- Given high morbidity and mortality, which increases with delays to care, this is a clinically important question, no existing good screening tool

Limitations:
- Overall quality of the studies was poor. Potential high risk-of-bias for many of the included studies.
- Clinical heterogeneity of the included studies. Three articles looked at cervical NSTI, and the other studies were not specific to a body site. Body site or total body surface area is a known indicator of prognosis.
- Inclusion criteria required control patients, and thus all patients were relatively high-risk, as they needed imaging or surgery to rule out NSTI. As a result, studies selected may be biased toward prioritizing tests that are linked with more advanced disease as opposed to tests that could be used for screening.

Study Conclusions:
- Individual physical exam findings and the LRINEC score are poorly sensitive for the diagnosis of NSTI.
- CT had superior sensitivity and specificity to plain radiography.

Presenter's Clinical Bottom Line:
- Despite the availability of physical exam findings, LRINEC score, and imaging, their utility in the diagnosis of NSTI is poor. It is the combination of findings that often make the diagnosis, however combinations were not studied in the literature.
- A high clinical suspicion warrants early surgical consultation for definitive diagnosis and management.

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Early Recurrence of First Unprovoked Seizures in Children

Golgberg, et. al. *Society for Academic Emergency Medicine*

P: Pediatric patients age 29d – 18 years with first unprovoked seizures
I: None
C: None, compared groups that were/were not started on AED's prior to 14d
O_1: Seizure recurrence within 14 days of the incident seizure
O_2: Seizure recurrence within 48h and 4m, independent risk factors for seizure recurrence at 14d

What we already know:

- Pediatric patients often present to ER following first time seizures that lack a clear precipitant such as head trauma, fever, or meningitis – termed "unprovoked" seizures
- These can present a disposition dilemma with respect to when follow up visits and investigations should be scheduled, and who to involve
- There is a paucity of evidence for seizure recurrence in pediatric patients at 14d and <6m after the initial seizure (most studies look at 6m or longer)

Methods:

- Setting: 6 urban, university affiliated pediatric ER centers between March 2005 and September 2007
- A clinician (multidisciplinary) performed a detailed patient history and physical exam and recorded the findings - this was from a study the assessed the risk of intracranial abnormalities in children with first unprovoked seizures
- In the secondary analysis, charts were retrospectively reviewed, and follow up phone calls were made at 14d-2m, and at 4-6m time periods. Mail surveys sent if unable to reach by phone
- More detail was recorded about Hx of febrile seizures, and the nature of the original event
- An epileptologist or the lead investigator, who were blinded to patient outcomes, evaluated the initial seizure description to see if a seizure had indeed occurred, if there was a clear precipitant, and whether it was an index seizure
- Backward elimination multivariable logistic regression analysis to identify independent risk factors of seizure recurrence at 14 days was performed
- Risk factors selected based on previous literature suggestion of potential association. Excluded abnormal findings on EEG or MRI as these are not available in the ED

Inclusion Criteria:

- Pediatric patients aged 29d – 18 years who presented to the ED for evaluation following first seemingly unprovoked seizures

Exclusion Criteria:

- Patients with head trauma or fever in the 24 hours prior to presentation or known metabolic disorders predisposing to seizures
- Patients with any of: syncope, presumed breath-holding episode, altered mental status without seizure symptoms, neurologic disorders that inhibited the ability to conduct a neurologic examination, and absence seizures
- Those who had been started on AED prior to recurrences and those lost to follow up
- 48h Group – any who received a one time bolus of phenobarbital or phenytoin or valproic acid
- 4m Group – any who did not have a 4 month follow up completed and had not had a recurrence noted on prior follow up
- Any who, at the time of follow up, became clear that the event was not a seizure, they had an absence seizure or a clear seizure precipitant, or it was not the index event

Results:

- 475 enrolled, 27 excluded (precipitant, not a seizure, absence or prevalent seizure)
- Risk of recurrence at 48h was between 5.4-6.6% (low-high estimate)
- Only factor associated with recurrence at 48h was having had more than one seizure within 24h at the time of presentation
- 82 excluded for 14d high estimate due to loss to follow up, unknown seizure timing, and AED initiated prior to 14d follow up
- Risk of recurrence at 14d was between 14.2-15.8% (high estimate varied 9.5-19.8% across sites) Risk of recurrence at 4m was between 30.4-31.5%
- When they added in those who were started on AEDs in first 14d and assumed they would have had a seizure they reached a 14d recurrence of 24.5%
- Compared the patients for whom chronic AEDs were started prior to the 14d recurrence and those for whom they were not – most of these were younger, had and had abnormal presentations (longer seizures, more than one in 24h, focal neuro deficits, and more often had a neuro consult in ER)
- Risk factors associated with 14 day recurrence were younger age (median 33.6 mo), and more than one seizure within 24h at the time of ED presentation – on multi-variable analysis only younger age (<36mo) remained associated, with an odds ratio of 2.1

Strengths:

- Multicenter study
- Addresses a question that is important for clinicians and parents
- Attempted to address ambiguity in seizure recurrence times with high and low risk estimates

Limitations:

- Those started on AEDs were excluded, so 14 day recurrence may be higher than reported
- Study was completed >10 years ago – but risk has likely not changed
- Didn't collect EEGs, but the results of these may have driven the decision to start AEDs
- Didn't include an assessment of parental anxiety or other factors that may have influenced the choice to start AEDs
- No data on FMHx of epilepsy to see how/if that influenced the risk of recurrence
- Dates were not exact for when recurrence happened
- Some patients were lost to follow up
- Secondary analysis

Validity:

- Performed across 6 centers – likely gave generalizable results
- Some risk factors may give a higher risk of recurrence, but they excluded these patients from the study as many of them had already been started on AEDs

Study Conclusions:

- Risk of seizure recurrence at 14 days is substantial after a first unprovoked seizure in children, with younger children being at higher risk. Prompt EEG and Neuro consultation is appropriate for these children.

Presenter's Clinical Bottom Line:

- Useful study to provide anticipatory guidance to parents about possible recurrence risk and guide urgency of referral.
- Local practice varies. For GTC seizure in normal child, there is NP run seizure clinic, or rapid access neuro clinic with outpatient EEG requisition +/- MRI requisition. If more unusual presentation (ie. patients in this study who were started on AED's), young, more than one seizure, abnormal neurologic exam, focality etc. it is appropriate to request more urgent consultation in the department.
- Overall, 14 day risk of recurrence may be higher than we think.

Eliminating In-Hospital Fecal Occult Blood Testing: Our Experience with Disinvestment

Gupta et. al. *American Journal of Medicine* 2018; Article In Press

P: In-hospital use of FOBT
I: Educational campaign regarding appropriate use of FOBT, followed by elimination of test
C: Pre-intervention ordering practices
O_1: Post-intervention ordering practices

What we already know:

- Fecal occult blood testing was introduced as a screen for colorectal cancer about 50 years ago
- Soon after that, it was introduced for workup of melena and anemia
- Guaic-based tests test for heme, and Immunochemical tests measure globin
- Both are plagued by false positives and negatives – nose bleeds, foods, drugs, toxins – and false positives can occur with slow or intermittent bleeds
- Inappropriate testing and interpretation leads to increased costs and potential harm through interventions
- Current practice for colorectal cancer screening is the Fecal Immunochemical Test, not FOBT

Methods:

- Setting: Parkland Health and Hospital System – an 870 bed safety net hospital in Dallas, Texas
- Retrospectively reviewed 31,790 medical records from Jan. 1, 2011 to Dec. 31, 2014, plus 400 randomly selected patient files with a positive FOBT to determine the indication for testing
- Weekly 2 minute announcements and weekly e-mails over a 2 month period (after discussions with leadership from Internal Medicine, ER, General Surgery, Pathology and Lab Services), plus having the GI fellow and Attending contact the ordering provider about proper use of FOBT after any consult where results of an FOBT were presented. In addition, house staff interested in GI gave noon lectures on appropriate use of FOBT
- Impact of intervention was monitored during 2015 and 2016
- Authors attempted to appeal to physicians sense of non-maleficence by presenting data on patients in whom a false positive had led to an unnecessary procedure, and those in which a patients with a false negative did not get an urgent colonoscopy, and how, in the majority of all cases, the FOBT did not alter care but did delay appropriate care
- Other strategies employed along with eliminating availability of the test included establishing consensus within the gastroenterology department (based on available evidence), communicating

with non specialist colleagues who were ordering the test, and engaging multidisciplinary stakeholders.
- Overall, they employed a top-down approach contrasted to 'Choosing Wisely' and other initiatives which are bottom up

Inclusion Criteria:
- In-hospital use of FOBT from 2011 to 2017

Exclusion Criteria:
- No exclusion criteria were listed

Results:
- 31,790 FOBT over initial 4 year period
- 71% were performed in the ER, 29% on inpatients
- 76% were performed as point of care, and 24% were sent to the lab
- 17% of FOBT were positive
- Indications for performing FOBT were Hx of dark stool (33%), anemia (24%), overt GI bleeding (12%) nonbloody diarrhea (6%), colon cancer screening (0.5%), unknown (25%, with 82% of these being sent reflexively after DRE)
- In all 400 instances, the FOBT testing was not evidence based or recommended by guidelines
- After their education campaign, there was a 16% drop in FOBT ordering
- In the months after abolishing the test, FOBT ordering rates dropped by 98%

Strengths:
- Limited statistical strengths, however a very detailed narrative of top-down change and disinvestment

Limitations:
- Performed at a safety net hospital (legal obligation to provide healthcare for individuals regardless of insurance status), and change is multifactorial based on political, clinical, and cultural environments, so results and methods may not be generalizable to other settings

Study Conclusions:

- Reasons for inappropriate use of FOBT tests are to evaluate dark-colored stools, anemia, diarrhea, or routinely during a DRE, but results are irrelevant in almost all cases to the next steps of management (melena is a clinical Dx, and FOBT may confound the Dx, and anemia workup without another clear source of bleeding needs endoscopy regardless of FOBT results).
- If they are not iron deficient, then chronic GI bleeding is much less likely and other anemia sources should be sought
- Despite overwhelming evidence, de-adoption of unnecessary medical tests continues to be a vexing problem internationally
- Changing established low-value hospital practices is difficult, and different approaches, including education, peer review, and feedback have been attempted, but are insufficient to significantly modify ingrained ordering practices
- Top-Down approaches that involve informed, educated directives from subject matter experts may be more helpful than grass roots approaches
- When sufficient medical evidence exists, modifying the opportunity to order a test such as elimination or restriction, along with education and support from hospital leadership becomes necessary.

Presenter's Clinical Bottom Line:

- Helpful narrative to illustrate one hospitals experience with disinvestment of an unnecessary test
- As emergency physicians it is important for us to communicate with our specialist colleagues about opportunities for evidence based practice change
- Staying up to date on the latest and greatest literature is important, but means very little if we don't have the infrastructure to adopt change within our institutions

EBM PEARL

Assessing Risk of Bias

- *Bias*: systematic error leading to underestimation or overestimation of the true intervention effect. Not to be confused with imprecision as bias is often a systematic error in design, meaning multiple replications of the same study would reach the same 'wrong' conclusion.
- *Selection bias*: systematic differences between baseline characteristics of the groups that are compared (prevent this with randomization and allocation concealment).
- *Performance bias*: systematic differences between groups in care provided or exposure to factors other than interventions of interest (prevent this by blinding or masking participants and personnel).
- *Detection bias*: differences between groups in how outcomes are determined (prevent this by blinding or masking of outcome assessors).
- *Attrition bias*: differences between groups in withdrawals from the study (prevent this by minimizing lost to follow up, and analyzing all available data without exclusions).
- *Reporting bias*: differences between reported and unreported findings (prevent by reporting all outcomes of interest even if not statistically significant or positive).