Journal Club: What to Consider When Appraising an Article on Therapy

- Finding the evidence
    - Ex. Class II patient on lisinopril, wants spironolactone
    - Trial quoted uses class III and class IV heart failure patients
    - Therapy definition
        - Ameliorate sx or reduce morbidity and mortality
        - Prevent chronologically distant morbid or mortal events with known underlying pathology
        - Prevent morbidity and mortality at risk but no current illness
        - Improve outcome by improving process of care
        - Tests designed to reduce morbidity and mortality
        - Combo of test and therapy for screening programs

Are the Results Valid?

- Valid results?->review results>can results be applied?
- Were patients randomized?
    - Several studies have demonstrated randomized trials will often discredit trials where treatment decisions were not randomized
    - Observational studies tend to yield more bias->primarily 2/2 to prognostic factors->leads to unbalance between treatment and control groups
        - Will often show larger treatment effects than randomized trials
        - Randomized trials tend to balance known and unknown determinants of outcome

Was Randomization Concealed?

- If aware of arm, will allocate sicker patients to either treatment or control group->biased result

Were Patients Analyzed in Groups to Which they were Randomized?

- Randomization can be compromised if results are omitted for patients who do not take assigned treatment-> will lead to bias
- Ex. Patients not taking meds typically fair worse, if excluded will cause bias (control (no treatment) vs. treatment group)
    - Intention to treat Analysis: outcomes based on treatment arm to which patients randomized instead of treatment received
    - Preserves randomization

Were Patients in the Treatment and Control Groups Similar with Respect to Known Prognostic Factors?

- Randomization purpose: create groups who prognosis is similar split between groups
- Larger sample size=better
- Need balance of prognosis (ex. Poor) to be balanced between group
- Analysis options available to adjust for differences

Were Patients Aware of Group Allocation?

- Placebo Effect: pts who take tx they believe to be helpful may feel better-> can mislead clinicians as patients may answer or perform tasks dif if believe on med
    - Ensure treatment appears the same to patients so they are blind to treatment as well

Were Clinicians Aware of Group Allocation?

- Make sure other treatment interventions (not being studied) are equal between groups

Were Outcome Assessors Aware of Group Allocation?

- If not blinded, may offer closer follow up to one group or another and see dif in outcomes
- May bias borderline results in favor of one group or another

Was follow up complete?

- Ex. Patients lost to follow up (doing well vs. poorly). If not included vs. included may change rate of target event report
- If worst-case scenario does not change inferences from study results, no a problem.
- If it does change study results, validity if compromised

What are the Results?

How large was the Treatment Effect?

- Dichotomous Outcomes (yes vs. no) (did patient have outcome)
    - Ways to analyze
        - Absolute Difference (Absolute Risk Reduction->difference between the groups): x-y
        - Relative Risk->risk of events among patient on new treatment, relative to risk among control group: y/x
            - Most commonly used by pharma
        - Relative Risk Reduction (most common)->(1-y/x) X 100 (new treatment reduced the risk of X event by % relative to control group)
            - Higher RRR=more effective therapy
            - Survival Analysis (RRR over time)=hazard ratio

How Precise Was the Estimate of the Treatment Effect?

- Point Estimate: true risk can't be known, get an estimate of treat treatment effect
- Leverage Confidence Intervals-> range within which you can be confident population lies
    - 95% CI
        - More confident if range on + side of 0
    - Similar to $P<0.05$

- Larger sample size->larger # of events=greater confidence treat RRR is close to what was observed
- Values further from point estimate=less consistent with observed RRR
- Want a more narrow range of CI=stronger study, usually seen in larger sample sizes
- CI can assist with negative studies->study conclusion is that experimental therapy is no better than control therapy (look at upper range of interval)

When Authors Do Not Report the Confidence Interval

- If no CI reported, look at p-value
  - If p-value is 0.05 (lower bound has to lie at 0, RR=1) and can't exclude that treatment has no effect
  - If p-value <0.05 the lower bound limit rises above)
  - You can also calculate the CI yourself and then interrupt results

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How Can I apply the Results to Patient Care?

- If patient would have qualified for trial->can apply to patient with confidence
  - However, still possible won't be effective (everyone responds differently to tx)
  - For long term tx (can trial for a period of time vs. not on tx), ensure both physician and patient are blinded, have pt rate symptoms for both time periods and compare
  - Short term problems-> above option not helpful, but can trial treatment
- If patient doesn't meet criteria
  - May be able to generalize the results (ex. 2 years older than study requirement)
  - Applying based on subgroup analysis (works for some groups, not others, analyzed after study-.may over interpret data)-> be SKEPTICAL

Were All Clinically Important Outcomes Considered?

- Treat should improve outcome that is relevant/important to patients
  - Less likely to be hospitalized, able to perform ADL
- Surrogate endpoints or outcomes: Ex. Cardiac output, lipid profile, etc.
- Possible tx may improve one outcome but worsen another (ex. Antiarrythmics in MI, good short term, bad long term), chemo can increase life but decrease quality

Are the Likely Treatment Benefits Worth the Potential Harm and Costs?

- Number Need to Treat: # of patient who receive intervention during period of time to prevent one adverse outcome or produce positive event
  - If high, unlikely to be helpful, must way side effects, risks, etc.
  - ARR (1/NNT)
- Consider patient risk for adverse event if not tx vs. with tx (benefit vs. risk)

Clinical Resolution

- Example in paper with spironolactone

- Might be able to be applied to class II->can prevent progressive heart failure by reducing Na retention and myocardial fibrosis, can prevent sudden death by averting K loss and increasing uptake of NE, can block aldosterone->decrease collagen and fibrosis
- Other meds like ACEI are used in class III and IV heart failure
- Drug is cheap, easy to dc
- Can communicate to patient possible side effects and risk vs. benefit