Summarizing the Evidence

Jane Gagliardi, MD, MHS
Megan von Isenburg, MSLS
The Evidence Cycle

**ASSESS**
**WHAT’S GOING ON?**
- History and Physical
- Initial Formulation

**ASK**
**PICOTT**
- Patient / Population
- Intervention
- Control
- Outcome
- Type of Question
- Type of Study

**ACQUIRE**
**LITERATURE SEARCH**

**EBM Cycle**

**APPLY**
**MUST CONSIDER:**
- Patient preference
- Access to care
- Quality of life
- Goals of care

**APPRAISE**
**VALIDITY CRITERIA**
- Methods
- Results
- Sources of Bias
- Strength of evidence
Objectives

• Recognize and use the evidence cycle
• Define a systematic review
• Define meta-analysis
  – Discuss what they can and can’t do for you
• Be able to explain:
  – Heterogeneity
  – Weighting
  – Publication Bias
• Draw and interpret a forest plot
• Critically appraise a systematic review
• Discuss teaching strategies and decision-points
The Evidence Pyramid

- Systematic Review/Meta-analysis
- RCT
- Observational Studies
- Case-Control
- Case Series
- Unsystematic Clinical Experience
Scenario: Rounding on Gen Med
Why Do We Need EBM? Consider…

- A study of steel mill workers identified by on-the-job screening program with hypertension
  - $\frac{1}{2}$ sent to primary care providers for specific treatment of hypertension
  - $\frac{1}{2}$ sent to on-the-job-site provider for algorithm-based treatment of hypertension

Adapted from Virginia Moyer, 1/14/2014
Why Do We Need EBM? Consider…

• A study of steel mill workers identified by on-the-job screening program with hypertension
• Unexpectedly low rates of treatment by primary care providers
Why Do We Need EBM? Consider...

Factors associated with likelihood of prescription of an antihypertensive agent:
• Diastolic blood pressure
• Age
• Target end-organ damage

Adapted from Virginia Moyer, 1/14/2014
Why Do We Need EBM? Consider…

Factors associated with likelihood of prescription of an antihypertensive agent:

• Diastolic blood pressure
• Age
• Target end-organ damage
• Time since graduation from medical school

Adapted from Virginia Moyer, 1/14/2014
Scenario: Rounding on Gen Med
Scenario: Pharmacy and Therapeutics

• For as long as anyone can remember, the formulary has included metoprolol.

• Carvedilol was reviewed for formulary status in 2003, at which time it was felt to provide no specific benefit (but cost more).
Scenario: Pharmacy and Therapeutics

- You now are the multidisciplinary health system Pharmacy and Therapeutics Committee.
Scenario: Pharmacy and Therapeutics

- Health system “nonformulary” report includes large increase in the utilization of carvedilol, particularly on the Gen Med services for patients with heart failure.

- The Chair of the committee tasks us with deciding which beta blocker will be preferred for formulary use: Metoprolol or Carvedilol? (Cost is now similar).
What Should the Health System Do?

A = Metoprolol

B = Carvedilol
What is the focused clinical question?

Among patients with heart failure, is carvedilol significantly different than metoprolol in preventing all-cause mortality?
Searching the Literature
Your Task

• The committee needs to decide.
• The Pharmacy administrator has a stack of journal articles.
• Is there any alternative to looking at each of 50 randomized controlled trials?
What is a Systematic Review?

- Answers one focused clinical question
- Summarizes evidence using methods to minimize the impact of bias
- The statistical method to combine data from different studies = meta-analysis
- Not all systematic reviews have meta-analysis (qualitative inferences only)
- Not all meta-analyses combine studies assembled through a systematic review
What systematic reviews can do for you

- Save time !!!
- Increase power to detect rare events
  - Obviate need for expensive mega-trials
  - Detect harm
- Increase the precision of the estimate of effect
- Enhance the generalizability of the results if samples from different populations are included
- Look for important differences in effectiveness among subgroups of patients
What systematic reviews can’t do for you

Random Error

Systematic Bias
What systematic reviews can’t do for you

...they also can’t tell you where TRUTH actually is
Exercise – Creating a Mini Meta-Analysis
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C+ | F: 81%  
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I: lost 14 in each group  
S: seems to be  
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<td>F: 81%&lt;br&gt;R: 1:1, CA?&lt;br&gt;I: lost 14 in each group&lt;br&gt;S: seems to be&lt;br&gt;B: yes, pts, clinicians&lt;br&gt;E: could modify if needed</td>
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<td>F: 10% loss to f/u&lt;br&gt;R: permuted blocks, CA&lt;br&gt;I: yes&lt;br&gt;S: more CABG, ischemia M&lt;br&gt;B: yes&lt;br&gt;E: yes</td>
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<td>1. Death&lt;br&gt;2. Hospitalization</td>
<td>M:   11%&lt;br&gt;C:   10%&lt;br&gt;HR= .72</td>
<td>Secondary analysis of RCT</td>
<td>Randomized for CRT-D or ICD, not M / C</td>
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<td>All-cause mortality</td>
<td>M:   40% (600/1518)&lt;br&gt;C:   34% (512/1511)</td>
<td>RCT&lt;br&gt;A</td>
<td>F: 10% loss to f/u&lt;br&gt;R: permuted blocks, CA&lt;br&gt;I: yes&lt;br&gt;S: more CABG, ischemia M&lt;br&gt;B: yes&lt;br&gt;E: yes</td>
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<td>HR= .71 unadj&lt;br&gt;HR = .78 adj</td>
<td>Retropective cohort&lt;br&gt;B</td>
<td>Study sponsor helped author&lt;br&gt;Cohort differences: M older, less males, more southern, more HTN, more arrhythmias, more renal</td>
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**Note:** The table above provides a summary of studies with the following details:

- **Author/year:** The name of the author(s) and the year of publication.
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- **Number of Subjects:** The number of subjects included in the study.
- **Intervention and control:** Details about the interventions and controls used in the study.
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- **Results: Mortality:** Results related to mortality.
- **Study Methodology:** Methodology used in the study.
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Does Combining *Studies* Make Sense?

- Determination (before proceeding to math) of whether or not it makes sense to combine
- Otherwise known as **The Common Sense Test**
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Cohort Study

Exposure Present

Exposure Absent

Outcome Yes

Outcome No

Measure HERE

TIME
Does Combining *Studies* Make Sense?

- Determination (*before* proceeding to math) of whether or not it makes sense to combine
- Otherwise known as
  The Common Sense Test

- Meta-analysis of all treatments for all heart disease?
- Meta-analysis of beta blockers for all heart disease?
- Meta-analysis of beta blockers for mortality in CHF?
- Meta-analysis of cohort studies and RCTs involving beta blockers for mortality in CHF?
We Need a Volunteer

Ooo! Ooo!
Me! I'll do it!
Pick me!
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<td>Italy • Outpatient • Ischemic or nonischemic cardiomyopathy • Class II, III, IV ≥ 6 months • EF ≤ 35% • Lasix + ACE consistent</td>
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<td>Metoprolol tartrate 115±56 mg/d Carvedilol 44±17 mg/d 23±12 months</td>
<td>1. LVEF 2. Hemodynamic variables at rest and peak exercise, exercise tolerance, QOL, NYHA fx class, death, urgent transplantation</td>
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<td>RCT</td>
<td>C+</td>
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<td>Europe • Multicenter (341 centers) • NYHA II, III, IV • EF ≤ 35% • diuretics + ACE</td>
<td>3029</td>
<td>Metoprolol tartrate 50 mg 2x/day Carvedilol 25 mg 2x/day 58 months mean duration</td>
<td>1. All-cause mortality</td>
<td>OR 0.78 (0.68, 0.91)</td>
<td>RCT</td>
<td>A</td>
</tr>
<tr>
<td>Delea, et al 2005</td>
<td>Constella database USA • CHF + C or M + age ≥ 35 • 1 outpt pharm claim for ACE + diuretic • ? NYHA • ?EF • Death rate?</td>
<td>1774</td>
<td>Metoprolol tartrate Carvedilol</td>
<td>1. Death 2. Hospitalization 3. Death or hospitalization</td>
<td>HR 0.78 (0.61, 1.00)</td>
<td>Retrospective cohort</td>
<td>B</td>
</tr>
<tr>
<td>Ruwald et al 2013</td>
<td>Patients enrolled in MADIT-CRT study on either M or C Europe, US, Canada Class I, II • EF ≤ 30% • Choice of BB left to treating physician</td>
<td>1515 who got M or C Out of 1820 total study pop</td>
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<td>Author/year</td>
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<td>Study Methodology</td>
<td>Grade of Evidence (A,B,C,D,F) &amp; Why</td>
</tr>
<tr>
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<td>C+&lt;br&gt;F: 81%&lt;br&gt;R: 1:1, CA?&lt;br&gt;I: lost 14 in each group&lt;br&gt;S: seems to be&lt;br&gt;B: yes, pts, clinicians&lt;br&gt;E: could modify if needed</td>
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<td>A&lt;br&gt;F: 10% loss to f/u&lt;br&gt;R: permuted blocks, CA&lt;br&gt;I: yes&lt;br&gt;S: more CABG, ischemia M&lt;br&gt;B: yes&lt;br&gt;E: yes</td>
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</tbody>
</table>

ANY OTHER DIFFERENCES TO CONSIDER?
Does Combining *Results* Make Sense?
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**Statistics:**

- **Test for Heterogeneity**
  - A statistical test asking if study results are more different than would be expected by chance alone.

- **I² Test**
  - A statistical test that describes the percentage of the variability due to *heterogeneity* rather than sampling error (chance).
Back to Pharmacy and Therapeutics

• Health system “nonformulary” report includes large increase in the utilization of carvedilol, particularly on the Gen Med services for patients with heart failure.

• The Chair of the committee tasks you with deciding which beta blocker will be preferred for formulary use: Metoprolol or Carvedilol? (Cost is now similar).
Meta-Analysis of the Effects of Carvedilol Versus Metoprolol on All-Cause Mortality and Hospitalizations in Patients With Heart Failure

Alexandros Briasoulis, MD, PhD*, Mohan Palla, MD, and Luis Afonso, MD

Long-term treatment with appropriate doses of carvedilol or metoprolol is currently recommended for patients with heart failure with reduced ejection fraction (HFrEF) to decrease the risk of death, hospitalizations, and patients’ symptoms. It remains unclear if the β-blockers used in patients with HFrEF are equal or carvedilol is superior to metoprolol types. We performed a meta-analysis of the comparative effects of carvedilol versus metoprolol in reducing all-cause mortality and/or hospitalization. We conducted an Embase and MEDLINE search for prospective controlled trials and cohort studies of patients with HFrEF who were randomized to treatment with carvedilol versus metoprolol. We identified 4 prospective controlled and 6 cohort studies with 30,943 patients who received carvedilol and 69,928 patients on metoprolol types (tartrate and succinate) with an average follow-up duration of 36.4 months. All-cause mortality was reduced in prospective studies with carvedilol versus metoprolol tartrate. Neither all-cause mortality nor hospitalizations were significantly different between carvedilol and metoprolol succinate in the cohort studies. In conclusion, in patients with HFrEF, carvedilol and metoprolol succinate have similar effects in reducing all-cause mortality. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:1111–1115)

Long-term treatment with appropriate doses of specific β blockers is currently recommended for patients with heart failure with reduced ejection fraction (HFrEF) to decrease the risk of death, hospitalizations, and patients’ symptoms independently of race, co-morbidities, and the presence of coronary artery disease. However, these are not class effects and have only been reported with 2 selective β-blocker blockers (sustained release metoprolol, bisoprolol, and carvedilol). Another selective β1 blocker, the short-acting metoprolol succinate, has been shown to be less effective in clinical trials. Several cohort studies and registries have reached to different conclusions regarding the comparative effects of different β blockers in patients with HFrEF. The pleiotropic actions of carvedilol (including vasodilating, antioxidant, metabolic, and antiarrhythmic actions) were hypothesized to confer additional benefit on cardiovascular outcomes compared to metoprolol. The present meta-analysis was designed to systematically evaluate prospective controlled trials and observational cohorts and assess the effects of carvedilol versus metoprolol types (succinate and tartrate) on all-cause mortality and hospitalization.

Methods

We systematically searched the electronic databases, MEDLINE, PubMed, Embase, and the Cochrane Library for Central Register of Clinical Trials, using the MESH terms, “β-blockers,” “heart failure with reduced ejection fraction,” “heart failures,” the names of individual β blockers (carvedilol, metoprolol succinate, metoprolol tartrate), “randomized trial,” “registry,” “cohort study.” We limited our search to studies in human subjects and English language in peer-reviewed journals published until November 2014. Additionally, a manual search of all relevant references from the screened articles and reviews of β blockers and heart failure (HF) was performed for additional clinical studies.

We included only prospective trials and cohort studies published as original articles in peer-reviewed scientific journals in English.1,2 We excluded those trials that did not include a detailed description of the cohort characteristics, concurrent therapy, and the end-of-treatment outcomes. We did not restrict eligibility according to left ventricular ejection fraction <40%.

The primary outcome measure was all-cause mortality. We also examined the difference in rehospitalization and the composite end point of all-cause mortality and rehospitalization if the latter was studied. Only 4 studies9,14,15 included rehospitalization as part of their secondary end points. Two studies11,12 used a composite outcome of death and rehospitalization.

The data were independently extracted by 2 authors (MP and AB) using standardized protocol. We extracted study characteristics (type of design with duration of intervention and methods), baseline demographics, ejection fraction and functional status at baseline and at the end of the study, and number of clinical outcomes from each trial. Cochrane risk-of-bias tool has been used to assess the individual risk of bias of each prospective randomized study.16 The Newcastle–Ottawa tool was used for the quality assessment of cohort studies. An intention-to-treat traditional meta-analysis was performed in line with recommendations from the Cochrane Collaboration.
Systematic Reviews: Validity

1. Did the review explicitly address a sensible clinical question?

The present meta-analysis was designed to systematically evaluate prospective controlled trials and observational cohorts and assess the effects of carvedilol versus metoprolol types (succinate and tartrate) on all-cause mortality and rehospitalization.
Systematic Reviews: Validity

2. Was the search for relevant studies detailed and exhaustive?
   - “Publication Bias”
   - “Funnel Plots”

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- "Publication Bias"
- "Funnel Plots"
Publication Bias

The small study effect, including publication bias, was tested using funnel plot, the Begg log-rank test, and the Egger test.
What is a Funnel Plot Anyway?

A.K.A, “Increasing Sample Size”

A.K.A, “The Results”

Remember: The “truth is out there” but we don’t actually know what it is
What is a Funnel Plot Anyway?

A.K.A, "Increasing Sample Size"

A.K.A, "The Results"
The funnel plot did not show asymmetry consistent with publication bias, and the Egger test was not significant for the outcomes studied (Egger test for cohort studies, \( p = 0.96 \) and for prospective studies, \( p = 0.48 \); Begg test for cohort studies, \( p = 0.77 \) and for prospective studies, \( p = 0.75 \).)
3. Were selection and assessment of studies reproducible?

We included only prospective trials and cohort studies published as original articles in peer-reviewed scientific journals in English.\textsuperscript{5,9-17} We excluded those trials that did not include a detailed description of the cohort characteristics, concomitant therapy, and end-of-treatment outcomes. We did restrict eligibility according to left ventricular ejection fraction <40%.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Mean age (years)</th>
<th>Average dose</th>
<th>Inclusion criteria</th>
<th>Primary end points</th>
<th>Secondary end points</th>
<th>Metoprolol type</th>
<th>Follow-up (months)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metra et al</td>
<td>RCT, double-blind</td>
<td>75</td>
<td>56.5</td>
<td>49</td>
<td>CHF ≥ 6 months, NYHA class II, III, or IV, LVEF ≤ 35%, peak VO2 ≤ 25 mL/kg/min, on diuretics, ACEi</td>
<td>LVEF</td>
<td>Mortality, exercise T tolerance, QOL, NYHA class</td>
<td>T</td>
<td>23</td>
<td>High</td>
</tr>
<tr>
<td>Piccirillo et al</td>
<td>RCT, single-blind</td>
<td>42</td>
<td>60</td>
<td>50</td>
<td>CHF ≥ 6 months, NYHA class II, III, or IV, LVEF ≤ 35%, peak VO2 ≤ 25 mL/kg/min, on diuretics, ACEi</td>
<td>QT variability index</td>
<td>T</td>
<td>12</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>COMET</td>
<td>RCT, double-blind</td>
<td>1511</td>
<td>62</td>
<td>41.8</td>
<td>CHF ≥ 6 months, NYHA class II, III, or IV, LVEF ≤ 35%, peak VO2 ≤ 25 mL/kg/min, on diuretics, ACEi</td>
<td>All-cause and cardiovascular mortality, re-hospitalization, stroke</td>
<td>Medication side-effects</td>
<td>T</td>
<td>58</td>
<td>Low</td>
</tr>
<tr>
<td>MADD-CRT</td>
<td>Post-hoc analysis of RCT</td>
<td>1077</td>
<td>64</td>
<td>18</td>
<td>CHF, NYHA class I or II, LVEF ≤ 30%, QRS duration ≥ 130 ms and GDMT</td>
<td>All-cause mortality or nonfatal CHF events</td>
<td>VT/VF</td>
<td>Mainly S (88%)</td>
<td>41</td>
<td>High</td>
</tr>
<tr>
<td>Pastemak et al</td>
<td>NROS</td>
<td>6026</td>
<td>69.3</td>
<td>50 (max dose reached by 52% of patients)</td>
<td>LVEF ≤ 40% and GDMT</td>
<td>All-cause mortality. Cardiovascular mortality</td>
<td>S</td>
<td>29</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Boiling et al</td>
<td>NROS</td>
<td>12363</td>
<td>73</td>
<td>10.2, 26.4 and 55</td>
<td>Age ≥5 years, with a primary discharge diagnosis of heart failure, CHF on carvedilol or metoprolol tartrate</td>
<td></td>
<td>-</td>
<td>S&amp;T</td>
<td>49</td>
<td>Low</td>
</tr>
<tr>
<td>Delea et al</td>
<td>NROS</td>
<td>887</td>
<td>71.4</td>
<td>14</td>
<td>CHF on carvedilol or metoprolol tartrate.</td>
<td>All-cause mortality and hospitalization</td>
<td>-</td>
<td>T</td>
<td>11</td>
<td>Low</td>
</tr>
<tr>
<td>Lazarus et al</td>
<td>NROS</td>
<td>2140</td>
<td>75</td>
<td>50</td>
<td>Hospitalized adult with a primary discharge diagnosis of heart failure, discharged on b-blockers</td>
<td>All-cause mortality</td>
<td>Mortality or HF readmission</td>
<td>S</td>
<td>21.6</td>
<td>Low</td>
</tr>
<tr>
<td>Rector et al</td>
<td>NROS</td>
<td>17429</td>
<td>74.5</td>
<td>12.5</td>
<td>Heart failure patients receiving carvedilol or metoprol tartrate</td>
<td>All-cause mortality and all-cause hospitalization</td>
<td>S</td>
<td>60</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Shore et al</td>
<td>NROS</td>
<td>1756</td>
<td>61</td>
<td>Doses &gt;12.5 and ≤12.5 used</td>
<td>LVEF &lt;40% on b-blockers and GDMT for ≥4 weeks</td>
<td>All-cause mortality and all-cause hospitalization, HF Readmissions</td>
<td>S</td>
<td>60</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitors; CHF = congestive heart failure; GDMT = guideline-directed medical therapy; LVEF = left ventricular ejection fraction; NROS = non-randomized observational study; NYHA = New York Heart Association class; RCT = randomized double-blind clinical trial; S = metoprolol succinate; T = metoprolol tartrate; VO2 = oxygen consumption.

* Patients in the study were divided into 3 groups according to the doses of medications (low, intermediate and high).
Systematic Reviews: Validity

4. Did the review address possible explanations of between-study differences in results?

Discussion

The main conclusion of our meta-analysis is that carvedilol does not seem to be superior compared to metoprolol in patients with HFrEF. The subanalysis of prospective trials confirmed the superiority of carvedilol over metoprolol tartrate with the results being driven mainly by the COMET study. In the subanalysis of cohort studies, no difference in all-cause mortality and/or hospitalization between carvedilol and metoprolol succinate or tartrate was found. In the subgroup of studies comparing carvedilol and metoprolol succinate, no difference in all-cause mortality was seen. The results were similar when studies that used low-dose blockers were excluded. Although the β blockers studied had similar effects on mortality and hospitalization, it is possible that carvedilol may be superior in reducing inappropriate shocks and maintaining favorable metabolic profile compared to metoprolol.

The largest randomized study (COMET), that showed a significant survival benefit with carvedilol, used low doses of metoprolol tartrate (50 mg twice daily). However, a recent analysis of a Danish registry with 58,634 patients hospitalized with a first admission for HFrEF suggested that patients receiving high-dose carvedilol (≥50 mg/day) had a significantly lower risk of all-cause mortality rehospitalization than patients receiving high-dose metoprolol (≥200 mg/day). The patients on high-dose carvedilol received more aggressive concomitant treatment had lower New York Heart Association class (NYHA) and thus had lower mortality risk. A subsequent cohort study of 6,026 patients on carvedilol and 5,638 patients on metoprolol succinate from the Danish HFrEF national registry showed similar efficacy of carvedilol and metoprolol succinate independently of dose achieved, NYHA class, cause of HF, and age. Metoprolol was associated with improved survival in a cohort of 3,716 patients with HFrEF, with the results driven by significant benefit in patients with ischemic HF. Other cohort studies post hoc analysis of randomized trials and small prospective controlled studies has reported either superiority of carvedilol or similar efficacy in reducing death rates and hospitalization. These discrepancies among studies should be attributed to differences in designs, co-morbidities, HF class severity, baseline HF medication regimens, and selection bias and confounding of the cohort studies.
Systematic Reviews: Validity

5. Did the review present results that are ready for clinical application?

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delea et al</td>
<td>-0.0834</td>
<td>0.118</td>
<td>11.7%</td>
<td>0.92 [0.73, 1.16]</td>
<td>2005</td>
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<tr>
<td>Bolling et al</td>
<td>-0.172</td>
<td>0.043</td>
<td>88.3%</td>
<td>0.84 [0.77, 0.92]</td>
<td>2014</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); i² = 0%
- Test for overall effect: Z = 4.00 (P < 0.0001)

Diagram: Favor of carvedilol vs metoprolol
Systematic Reviews: Validity

5. Did the review provide a rating for confidence in effect estimates or provide information needed to evaluate the confidence?

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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.85 [0.79, 0.92]</strong></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: $\chi^2 = 0.50$, df = 1 ($P = 0.48$); $I^2 = 0$
Test for overall effect: $Z = 4.00$ ($P < 0.0001$)

Favors carvedilol  Favors metoprolol
Table 1
Characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Mean age (years)</th>
<th>Average dose</th>
<th>Inclusion criteria</th>
<th>Primary end points</th>
<th>Secondary end points</th>
<th>Metoprolol type</th>
<th>Follow-up (months)</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metra et al</td>
<td>RCT, double-blind</td>
<td>75</td>
<td>56.5</td>
<td>49</td>
<td>CHF ≥ 6 months, NYHA class II, III, or IV, LVEF ≤ 35%, peak VO2 ≤ 25 mL/min, on diuretics, ACEi.</td>
<td>I.VEF</td>
<td>Mortality, exercise tolerance, QOL, NYHA class.</td>
<td></td>
<td>23</td>
<td>High</td>
</tr>
<tr>
<td>Piccirillo et al</td>
<td>RCT, single-blind</td>
<td>42</td>
<td>60</td>
<td>50</td>
<td>CHF ≥ 6 months, NYHA class II, III, or IV, LVEF ≤ 35%, peak VO2 ≤ 25 mL/min, on diuretics, ACEi.</td>
<td>QT variability index</td>
<td>T</td>
<td>12</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>COMET</td>
<td>RCT, double-blind</td>
<td>1511</td>
<td>62</td>
<td>41.8</td>
<td>CHF ≥ 6 months, NYHA class II, III, or IV, LVEF ≤ 35%, peak VO2 ≤ 25 mL/min, on diuretics, ACEi.</td>
<td>All-cause and cardiovascular mortality, re-hospitalization, stroke</td>
<td>Medication side-effects</td>
<td>T</td>
<td>58</td>
<td>Low</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>Post-hoc analysis of RCT</td>
<td>1077</td>
<td>64</td>
<td>18</td>
<td>CHF, NYHA class I or II, LVEF ≤ 30%, QRS duration ≥ 130 ms and GDMT.</td>
<td>All cause mortality or nonfatal CHF events.</td>
<td>VT/VF</td>
<td>Mainly S (88%)</td>
<td>41</td>
<td>High</td>
</tr>
<tr>
<td>Pasternak et al</td>
<td>NROS</td>
<td>6026</td>
<td>69.3</td>
<td>50 (max dose reached by 52% of patients)</td>
<td>LVEF ≤ 40% and GDMT.</td>
<td>All-cause mortality.</td>
<td>Cardiovascular mortality</td>
<td>S</td>
<td>29</td>
<td>Low</td>
</tr>
<tr>
<td>Boiling et al</td>
<td>NROS</td>
<td>12363</td>
<td>73</td>
<td>*10.2, 26.4 and 55 *64.4, 144.3, 200</td>
<td>Age ≥ 35 years, with a primary discharge diagnosis of heart failure.</td>
<td>All-cause mortality and hospitalization.</td>
<td>-</td>
<td>S&amp;T</td>
<td>49</td>
<td>Low</td>
</tr>
<tr>
<td>Delaun et al</td>
<td>NROS</td>
<td>887</td>
<td>71.4</td>
<td>14</td>
<td>CHF on carvedilol or metoprol tartrate.</td>
<td>All-cause mortality, hospitalization, and death or hospitalization.</td>
<td>-</td>
<td>T</td>
<td>11</td>
<td>Low</td>
</tr>
<tr>
<td>Lazarus et al</td>
<td>NROS</td>
<td>2140</td>
<td>75</td>
<td>50</td>
<td>Hospitalized adult with a primary discharge diagnosis of heart failure, discharged on b-blockers.</td>
<td>All-cause mortality</td>
<td>Mortality or HF readmission</td>
<td>S</td>
<td>21.6</td>
<td>Low</td>
</tr>
<tr>
<td>Rector et al</td>
<td>NROS</td>
<td>17429</td>
<td>74.5</td>
<td>12.5</td>
<td>Heart failure patients receiving carvedilol or metoprol tartrate.</td>
<td>All-cause mortality and all-cause hospitalization.</td>
<td>S</td>
<td>60</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Shore et al</td>
<td>NROS</td>
<td>1756</td>
<td>61</td>
<td>Doses &gt;12.5 and ≤12.5 used</td>
<td>LVEF &lt;40% on b-blockers and GDMT for ≥4 weeks</td>
<td>All-cause mortality and HF Readmissions</td>
<td>S</td>
<td>60</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1960</td>
<td></td>
<td>Doses &gt;100 and ≤100 used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitors; CHF = congestive heart failure; GDMT = guideline-directed medical therapy; LVEF = left ventricular ejection fraction; NROS = non-randomized observational study; NYHA = New York Heart Association class; RCT = randomized double-blind clinical trial; S = metoprolol succinate; T = metoprolol tartrate; VO2 = oxygen consumption.

* Patients in the study were divided into 3 groups according to the doses of medications (low, intermediate and high).
Systematic Review: Results

1. Were the results similar from study to study?

   • Clinical assessment of heterogeneity in population, intervention, outcomes
   • “Eyeball” test in Forest Plot
   • Statistical test or $I^2$
## Eyeball Test for Heterogeneity

### Statistical Tests for Heterogeneity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metra et al</td>
<td>17 75</td>
<td>21 75</td>
<td>0.75 [0.36, 1.58]</td>
<td>2000</td>
</tr>
<tr>
<td>Piccirillo et al</td>
<td>10 65</td>
<td>11 65</td>
<td>0.89 [0.35, 2.27]</td>
<td>2002</td>
</tr>
<tr>
<td>COMET</td>
<td>512 1511</td>
<td>600 1518</td>
<td>0.78 [0.68, 0.91]</td>
<td>2003</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>104 1077</td>
<td>48 438</td>
<td>0.87 [0.60, 1.25]</td>
<td>2013</td>
</tr>
</tbody>
</table>

Total (95% CI): 2728 2096 100.0% 0.80 [0.70, 0.91]

Heterogeneity: $\chi^2 = 0.34, df = 3 (P = 0.91); I^2 = 0$

Test for overall effect: $Z = 3.36 (P = 0.0008)$
Eyeball Test for Heterogeneity

Statistical Tests for Heterogeneity

Figure 1. (A) Fixed-effect meta-analysis for all-cause mortality in prospective controlled studies. The figure presents number of events; number of patients in treatment and control groups; OR and 95% CI for each trial; overall OR estimate with 95% CI, p value for association test, p value for heterogeneity test, and between-trial inconsistency ($I^2$) measurements. (B) Random-effect meta-analysis for all-cause mortality in cohort studies.
What are the Results?

2. What are the overall results of the review?
   – Forest plots and tables

3. How confident are you in the estimates?
   – Confidence intervals
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Metoprolol</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Metra et al</td>
<td>17</td>
<td>75</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
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<td>10</td>
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<td>104</td>
<td>1077</td>
<td>48</td>
<td>438</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2728</strong></td>
<td><strong>2096</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 643 680

Heterogeneity: Chi² = 0.34, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.36 (P = 0.0008)
What Should the Health System Do?

A = Metoprolol

B = Carvedilol
RECAP
How can you tell if an article is a “systematic review” rather than a “general review” article?

A. Top journals only publish systematic reviews
B. It will cover all known information about the topic (diagnosis, prognosis, treatment, etc)
C. It has a Methods Section
D. B and C
From which types of studies is it possible to combine data (do a “meta-analysis”)?

A. Randomized trials only
B. Randomized trials and cohort studies
C. Randomized trials, cohort studies, and case-control studies
D. Randomized trials, cohorts studies, case-control studies, and case series
You should assess for heterogeneity between studies in a systematic review by:

A. Deciding whether it makes sense to combine them based on your clinical knowledge
B. Seeing if a statistical test for heterogeneity among the results of the studies is non-significant, or an I² statistic is <20%
C. Looking for overlapping confidence intervals on a forest plot
D. A, B and C
“Weighting” refers to:

A. Eating too many snacks during your EBM workshop
B. A mathematical adjustment which makes larger studies contribute more to the combined result than smaller ones
C. A mathematical adjustment which makes better quality studies contribute more to the combined result than smaller ones
D. B or C
Objectives

- Define a systematic review
- Define meta-analysis
  - Discuss what they can and can’t do for you
- Be able to explain:
  - Heterogeneity
  - Weighting
  - Publication Bias
- Draw and interpret a forest plot
- Critically appraise a systematic review
Teaching Decisions

- Planning
- Process vs Content
- Working With What You’ve Got
  - (Play To Your Strengths)
  - Homo ridiculousness vs. Homo seriousness
- Knowing Your Audience
- To Mark or Not to Mark?
  - That is the Question
- Triage
Thanks!

- Evaluations
- https://www.youtube.com/watch?v=FqQ-JuRDKl8