Kaplan-Meier Curves, Hazard Ratios & Composite Endpoints

Objectives – 2 (00:46)
1. Interpret survival curves
2. Determine medium time to endpoint for survival curves = median survival time
3. Interpret hazard ratios (HR)
4. State the meaning of HR
5. Explain advantages of using composite endpoint(s)
6. Explain drawbacks with composite endpoint(s)
7. Determine when composite endpoint is valid
8. Determine if treatment decisions should be based on composite endpoint(s)
9. Determine when the individual components of composite endpoint(s) should be used

1. Commonly used in drug studies
2. Survival curves are used with time to event analysis
3. **Time to event analysis**
   - Study of pts until certain # of events occur
   - Plots the # of pts. that experience the endpoint over the entire length of the study period; this is how you get survival curve
   - Plot of: # pts. with the endpoint ÷ entire study duration
4. Can be any endpoint
   - i.e. death; MI; time to breast cancer recurrence; stroke
   - can be any type of endpoint
5. Kaplan-Meier most common survival curve
6. Survival curve permits median survival time determination

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**Simple Survival Curve**
X-Axis → Time in months
Y-Axis → % pts. still alive
Time “0” → 100 % pts. alive
As time progresses curve declines → fewer pts. living

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**Survival Time Determination**
1. Choose a percentile on Y-Axis
   - Draw line from this point over to the Curve.
2. Draw line down to the X-Axis
   - to see what the timeframe is for that % of pts. to still be alive.
3. Can look @ various percentiles &
   - determine the amount of time it took to get @ that % of survival (can calculate % that died).

**Median Survival Time**
Y-Axis = 50 % → Draw line over to curve then down to the X-Axis.
Censoring of Patients in Survival Studies – 6 (3:57)

1. Censoring accounts for patients not enrolled for total study duration
   - Censoring accounts for some statistical manipulations needed when pts. enrolled for different periods of time.

Example:
Time to Event study:
1. Enrollment Period: is over time i.e. 1-2 yrs.
2. Patients followed: until a certain # of events occur
3. Patient enrolled on day 1 → in the study longer than the pt. enrolled @ the 2 yr. mark.

Typical Study (not Time to Event Study):
1. Patients followed:
   - Over time period specified regardless of when they are enrolled.
     Average ≈ 4.5 – 5 yrs.
2. Censoring accounts for:
   - Pts. not experiencing endpoint @ study conclusion & were not enrolled for total study duration
   - Study Dropouts
     - Pts. lost to follow up
     - Competing risks

Example: Competing Risks:
1. Endpoint: MI
2. Problem: Pt. dies
3. Conclusion: That pt. can’t have an MI just because they died.

By censoring, can used data for duration pt. was alive & didn’t have an MI.
Censoring allows you to still use the data.

Important assumption:
Prognosis for endpoint occurring - remains the same over time.
1. Above Kaplan-Meier curve looking @:
   **Composite Endpoint:** Breast cancer recurrence or death.
   **HR:** 0.68.

2. Along the bottom:
   Event # that have occurred by year
   Total # of pts. at risk for the event.

3. At time = 0:
   N= 2,362 pts. Exemestane study arm vs
   N= 2,380 pts. Tamoxifen arm.

4. At time = yr. 3:
   N=757 pts. Exemestane study arm vs
   N= 730 pts. Tamoxifen arm.
   It’s easy to see how many pts. were followed for the different yrs.

5. Survival curve benefit:
   You can see when the 2 study arms (survival curves) begin to separate.

6. Statistical significance achieved, not noted in this study.
   Example:
   After 2 yrs. see benefit from i.e. Exemestane.

7. Typical study:
   Relative Risk at a given # of yrs. will be given.
   You don’t know what happened between time = 0 to time = 5 yrs.
   However, you do know what happened @ 5 yrs.

**Advantage of survival curve** → you can see how the survival or the endpoint was effected throughout the length of the study because of the way it is plotted.
Hazard Ratios (HR) – 7 (7:53)
Hazard ratios are used to describe the differences between study arms when you’re looking @ survival curves.
1. **Hazard Ratios = relative risk that compares to survival curves**
2. HR definition
   - Estimate of the hazard rate in the treatment group compared to the hazard rate in the control group
3. HR measures the probability that if the endpoint has not already occurred it will occur in the next time interval.
   - Time interval is usually very short, it’s like a continuous time
   - Hazard Rate = probability ÷ time frame

HR Interpretation – 9 (8:47)
1. HR → similar to Relative Risks & Odds Ratio
   - = no difference between groups
   - > 1 endpoint is happening faster in the treatment group
   - < 1 endpoint is happening slower in treatment group
   - **HR → should be given a 95 % confidence interval (CI)**
      For statistically significant finding → CI should not cross 1
HR interpretation – 10, 11 (9:18; 10:58)

1. **HR = 0.68 →** for the Composite Endpoint (above study)
2. **CI = 0.56 – 0.82**
3. **P Value < 0.001 →** provided
4. **IF Confidence Interval (CI) does NOT cross “1.0”:**
   - P Value not needed (for statistical significance)
   - You WILL have a statistically significant finding(s)
     - whether all values:
       1. Lay to the left → so they are < 1
       2. Lay to the right → so they are > 1.
5. **HR = 0.68 →** authors found for this study → **applies to pts. in this study.**
6. With 95 % CI, 0.56-0.62, this means:
   - As we apply the study results to the entire population →
     1. 95 % sure that the true value lies within that CI
     2. It’s just as likely to be anywhere in that range of that CI
     3. We can say confidently:
        - Exemestane compared to Tamoxifen ↓ recurrence risk of contralateral breast recurrence or death
        - Anywhere from 44 % (which is 0.56) to 18 % (which is 0.82) more likely to have a + benefit from Exemestane vs Tamoxifen.
   - As long as the CI does not cross 1, you’ll have a statistically significant finding.
7. **If CI > 1 (crosses 1), we might say**
   - Sometimes Exemestane is better but it could be just as likely that Tamoxifen is better.
Non-significant HR Example

1. Same study looking @ overall survival for one component of the Composite Endpoint (CE) → death.
2. **HR death** = 0.88 → favors Exemestane because it is < 1
   - We want death to occur slower rather than faster.
3. CI = 0.67-1.16 means:
   - 1 – 0.67 = 0.33 (33 % ↓); 1.16 – 1 = 0.16 (16 % ↑)
   - Exemestane causes either a 33 % less likely chance that you are going to die
   OR
   - Exemestane could ↑ death risk by 16 %.
   - If you look @ that whole range of the CI it sometimes risk ↓ but sometimes risk ↑
   - Important to remember → true value lies within that range.
   - So we cannot confidently say that Exemestane ALWAYS ↓ or ↑ survival.
HR Interpretation – 12 (12:00)
1. HR → easy to misinterpret
   Example:
   HR = 2 for resolution of pneumonia
   HR Interpretation:
   HR means:
   • Pts. will have faster pneumonia resolution if they receive treatment
   • Treated pts. → 2x as likely to have pneumonia resolve @
     any given point in time compared to the control or no treatment
   HR does NOT mean:
   • Treated pts. will have resolution 2 x as fast;
     You know pneumonia resolves faster;
     You DO NOT KNOW HOW FAST it resolve with TX.

2. Calculation of resolution probability
   • Probability = HR ÷ (1 + HR)
     = 2 ÷ (1 + 2) = 2/3 = 0.67 or 67 %
   • For HR = 2 → Interpretation → compared to not receiving treatment
     If you take the TX, there is 67 % chance that resolution → faster.

Statistical Analysis – 13 (13:32)
For survival curves i.e. Kaplan-Meier, there are 3 statistical tests used to
determine that curve. Look in “methods” section of clinical trial for test used.
1. Kaplan-Meier Curves (Survival Curves)
   • Cox Proportional hazards regression → most often used
     It will say “We determined the Kaplan-Meier Curve using
     Cox-Proportional Hazards Regression”.
   • Log – rank
   • Wilcoxon 2- sample test

2. Time to event analysis
   In Methods/ Statistics / Description section/ Time to Event Analysis
   you still want the following:
   • Power/ alpha
   • Estimated effect on 1° endpoint
     Example:
     Study N=4,000
     Expected Result:
     20 % ↓ in the 1° endpoint by using this treatment.
   • # of patients → this is how you will know you can achieve Power
   • # of events
     Example:
     Study N= 4,000 pts., see an estimated
     Expected Result:
     20 % ↓ in the 1° endpoint by using this treatment.
     Time to follow pt.: 500 events. → At that point we will censor pts.”.
   • Estimated length of study (not always included)
Composite Endpoints (CE) – 14 (15:04)
Composite endpoints often described as a Hazard Ratio (HR) using a Kaplan-Meier Curve.

1. CE Definition:
   Multiple endpoints of interest, grouped together to form 1 endpoint.
   - Can be a 1st or 2nd endpoint
   - Studies are statistically Powered to look @ the 1st endpoint
   - Studies usually > 1 endpoint of interest
     **Examples:**
     - Death; effect of TX on morbidity/mortality
     **Example:**
     - Studying antiplatelet drug → want to study effect on:
       Death; MI; Stroke → multiple endpoints
   - **CE allows you to power a study to look @ multiple 1st endpoints.**

2. CE Advantages:
   - **CE allows you to power a study to look @ multiple 1st endpoints.**
   - CE provides statistical advantage → ↑ study efficacy
     **Example:**
     - 3 possible endpoints as 1st endpoint
       - Larger # pts. achieve 1st endpoint
         1. Need fewer pts. enrolled to achieve statistical power
         More options for the pt. to have as the 1st endpoint
         2. Usually, < time to complete study
   - Net clinical benefit of intervention can be estimated
     **Example:**
     - Studying antiplatelet drug
     Endpoints evaluated: Death; MI; Intracranial hemorrhage
     Endpoints looking @: Morbidity/Mortality; Does it ↑ bleed risk
     If bleed risk ↑ → want to capture
     If i.e. bleed risk evaluated → can determine net clinical benefit of intervention.
   - Useful for rare events
     - Many times death is endpoint – hopefully death is a rare event in a study.
     - It will give you more power to determine if there is an effect on death.
Ideal Composite Endpoint (CE) – 15 (17:30)

1. 2-4 individual endpoints maximum
   - > 4 individual endpoints → difficult to achieve other characteristics
     of an ideal composite endpoint (listed below)

2. Individual Endpoints are biologically related
   
   Example 1:
   Provide intervention
   
   Endpoints: Want endpoints related or intervention needs to be able to
   affect those endpoints
   
   Example 2:
   Intervention: Antiplatelet
   
   Endpoints: MI; Stroke; Death → all 3 related; expect antiplatelet would affect all
   
   Endpoints: Add hospitalization for CV related disease →? Whether anti-platelet
   will affect this new endpoint.
   
   Might have differences in the rates of endpoints or relative risks (RR)
   
   Endpoints biologically related → Helps keep rates & events similar for all individual endpoints

3. Want event rates & relative risk similar for all individual endpoints
   
   - Helps ↑ endpoint validity
   
   - Event rates & RR have better similarity if endpoints biologically
     Related (# 2 above discussed)

4. Individual Endpoints should carry similar importance to pt.
   
   Example:
   
   Intervention: anticoagulant / antiplatelet
   
   Endpoints: Death; MI; Stroke (all 3 are related)
   
   Pt. Perspective: All important endpoints for pt. NOT to have
   
   Add Endpoint: Hospitalization for CV related reason
   
   Pt. Perspective: Pts. don’t want to be hospitalized;
   
   Pts. would opt for hospitalization over death
   
   Death prevention > importance than hospitalization

5. Individual endpoints move in same direction for valid Composite Endpoint / good characteristic
   
   - All endpoints provide benefit /harm to the pt. to prevent conflict in results
   
   - Overall impact of Composite Endpoint is diminished without the
     Individual Endpoints moving in the same direction

6. Individual endpoints: either ALL clinician driven or none
   
   Examples:
   
   Deciding to hospitalize a pt. is a clinician driven decision.
   
   Revascularization procedure is a clinician driven decision.
   
   Pt. death is not a clinician driven decision.
   
   Results can be skewed combining clinician driven decisions with non-clinician driven
   decisions.

   Studies need to provide results for all the individual components, independently, so we evaluate:
   
   - Whether or not they occurred @ the same rate;
   
   - If they have the same relative risk;
   
   - How they affected the overall composite endpoint.
**Composite Endpoints:**

1. Individual components of a composite endpoint are equal in determining the Composite Endpoint.
2. If one of the components of a Composite Endpoint occurs more frequently or is statistically significant & the other components are not, this can affect the overall Composite Endpoint.
3. All individual components of a Composite Endpoint are statistically considered equal parts. When you do the numbers, all individual components are put into the overall composite endpoint equally.
4. It is important to be able to review and see how each individual component, of the CE, affects the overall results.

**Composite Endpoint (CE) Challenges – 16 (21:32)**

1. CEs are difficult to interpret if:
   - Individual components differ in pt. importance
   - Individual components differ a lot in the event rates; relative risk rates (RRR); direction
2. May mask harmful effect
3. May hide beneficial effect

**Composite Endpoint (CE) Interpretation – 17 (22:13)**

1. Ask 3 questions:
   - Are all endpoints similar importance to pt.?
   - Do all endpoints occur at similar rates / RRR reductions?
   - Do all endpoints move in the same direction?
2. If answers to all three questions are YES → composite endpoint:
   - is valid
   - can be interpreted as presented
3. If NO to @ least 1 question above → must review individual components to see which component the TX effects.
Composite Endpoint (CE) Example 1 Tirofiban (PRISM Trial) – 18, 19 (23:04; 23:51)

1. Tirofiban (Aggrastat®) prescribing info

**INDICATIONS AND USAGE**
AGGRASTAT, in combination with heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PCI or atherectomy. In this setting, AGGRASTAT has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure (for discussion of trial results and for definition of acute coronary syndrome, see CLINICAL PHARMACOLOGY, Clinical Trials).

AGGRASTAT has been studied in a setting, as described in Clinical Trials, that included aspirin and heparin.

**PRISM TRIAL**
N > 3,000 pts.

**Pt. Characteristic:** Unstable angina

**Intervention:** Randomized to Tirofiban or Heparin

**Composite Endpoint @ 48 hrs.:**
Death; MI; Refractory Ischemia

**Results:**
Composite Endpoint Tirofiban: 3.8% had Composite Endpoint
Composite Endpoint Heparin: 5.6% had Composite Endpoint

Risk Ratio: 0.67
Confidence Interval (CI) 95% (0.48-0.92) → this is statistically significant ↓
Endpoint for Tirofiban b/c CI DOES NOT cross “0”. CI all lies to the left of “1.0”.

**Tirofiban appears to have benefit.**

Composite Endpoint (CE) Example 1 Tirofiban – 20 (27:02)

1. Are all endpoints similar importance to pt.? YES
   • Death; nonfatal MI; refractory ischemia

2. Do all endpoints occur at similar rates / RRR reductions? NO / NO; Esp. NOT rates
   • Rates: Majority of pts. had refractory ischemia; very few pts. had MI or Death.
     o Refractory Ischemia: 3.5% Tirofiban vs 5.3% Heparin arm
     o MI: 0.9% Tirofiban vs 1.4% Heparin
     o Death: 0.4% Tirofiban vs 0.2% Heparin
   • Relative Risks: RR of Death > 1; RR of Refractory ischemia & MI were ≈ 0.65; All NOT similar
     o Refractory Ischemia: Risk Ratio: 0.65 (0.46-0.91) → statistically significant CI did NOT cross 1.
     o MI: Risk Ratio: 0.64 (0.33-1.25) → look @ upper limit → NOT statistically significant
     o Death: Risk Ratio: 1.48 (0.42-5.27) → Looks like Tirofiban causes death; Not statistically significant b/c CI crossed 1.

3. Do all endpoints move in the same direction? NO
   • Refractory Ischemia significantly ↓; MI ↓ but CI crossed 1
   • → so not statistically significant;
   • MI & Death → NO benefit from Tirofiban

4. This is not a valid CE →
   • 1 endpoint dominated (Refractory Ischemia) → results may mask ↑ death risk or a negative outcome.
Death as a component of a Composite Endpoint (Death is a rare Endpoint)

1. In a review of cardiovascular (CV) studies that had:
   - A Composite Endpoint (CE) that was positive (showed reduction as a composite).
   - One component of the CE = death,

2. Finding: Death was only statistically significant, on its own < 25 %, when reviewed individually.
   - Reason for finding: death is rare
   - Need to make sure you don’t have an ↑ risk in any components of the CE when you are looking @ them.
**Kaplan-Meier Curves, Hazard Ratios & Composite Endpoints**

**Composite Endpoint (CE) Example 2 Proactive Study**

Primary CE = HR 0.90 95% CI 0.8-1.02, p=0.095

**N > 5200 pts.**

**Pt. Characteristic:**
DM; Macro Vasc. Heart Disease → MI, Stroke, CAGB Procedure

**Intervention:**
Randomized Pioglitazone or Placebo

**Composite Endpoint:** 7 components
Death; Non-Fatal MI; Stroke;
Major Leg Amputation; ACS; Coronary Revascularization; Leg revascularization;
1<sup>st</sup> Composite Endpoint not shown in slide

**HR Composite:** 0.9; 95% CI (0.8-1.02)

**Not statistically significant; CI crossed 1.**
May have reached statistical significance if:
↑ # pts. with the Composite Endpoint; or a component of the composite endpoint.
→ May have pulled it into statistical significance.

**Frequency similar:** Death; nonfatal MI; coronary revascularization similar;
Major leg amputation occurred least

**All endpoints contributed to CE:** not 1-2 endpoints going to pull the majority of the patients & affect the overall result (Composite Endpoint).

**HR:** All 0.75 or ↑; although 2 are > 1 → means pioglitazone no effect on major leg Amputation; might ↑ risk of Leg revascularization

1. **Are all endpoints similar importance to pt.? NO**
   - Death, Non-Fatal MI, stroke → VERY important; possibly major leg amputation too
   - Coronary or leg revascularization does NOT carry same importance as i.e. death

2. **Do all endpoints occur at similar rates / RRR reductions? Yes**
   - Individual endpoints did not all occur @ same rate BUT all did effect the 1<sup>st</sup> Endpoint.
   - There wasn’t one that occurred in the majority of pts. that left the other individual endpoints @ small #s. Major leg amputation not common, but there wasn’t one other endpoint that predominated. None of the endpoints statistically significant
   → All CI crossed 1. All HR were 0.75 or greater.

3. **Do all endpoints move in the same direction? NO**
   - 1 endpoint that was ↑; one endpoint was neutral; 2 showed benefit with pioglitazone

4. **Is this a valid CE? NO**
   **Study demonstrates why:**
   - Use endpoints of equal importance to pts.
   - 7 endpoints makes it hard to show everything is related, important to the pt.
   - Procedure / clinician-driven endpoints may skew results when mixed with non-clinician driven endpoints; 3 of last 4 were procedure or clinician-driven in this study
Composite Endpoint (CE) – 23, 24 (33:35; 34:18)

Example 2 Proactive Study 2

Secondary CE (death, nonfatal MI, or stroke)
- Found statistically significant finding.

HR 0.84; 95% CI (0.72-0.98); P Value = 0.027
- HR in favor of pioglitazone.
- Found statistical significance (CI did not cross 1) of pioglitazone benefit in ↓ endpoints.

Evaluation Questions

1. **Do all endpoints occur at similar rates / RRR reductions? YES**
   - Rates Similar – almost down the middle: 1/3rd; 1/3rd; 1/3rd
   - HR Similar: 0.8 or ↑; none are statistically significant (CI crosses 1.0 for all)

2. **Are all 2^st endpoints similar importance to pt.? YES**
   - death; nonfatal MI; stroke

3. **Do all endpoints occur at similar rates / RRR reductions? YES**
   - Occurred at similar rates & relative risks

4. **Do all endpoints move in the same direction? YES**

5. **Is this a valid CE? YES**
   - Used a valid Composite Endpoint in this example
   - Used 3 endpoints that are not common in frequency
   - Example shows Composite Endpoint(s) for RARE EVENTS
     1. On their own, not significant
     2. Combining these 3 endpoints, significant finding is found → Effect of pioglitazone on the three components
Composite Endpoint (CE) Example 3 – HOPE Trial – 25, 26 (35:00; 36:24)

Looking @ Composite Endpoint:

CE Ramipril: 14% incidence of CE;
CE Placebo: 17.8% incidence of CE

Looking @ RR of Composite Endpoint:

RR = 0.78, 95% CI (0.70-0.86) → statistically significant → CI did NOT cross 1.0

Individual components: Death; MI; Stroke →
- All 3 occurred in pts.
- One did not dominate in affecting overall CE

RR: Similar → 0.74/0.8/0.68 → all statistically significant; none of them cross 1

1. Are all endpoints similar importance to pt.? YES
   - Death from CV causes; nonfatal MI; stroke
2. Do all occur @ similar rates & RR? Yes
3. Do all endpoints move in the same direction? YES
   - All showed benefits
4. Is this a valid CE? YES

Conclusion:
- Ramipril DOES affect the Combined Endpoint of:
  - Death from CV causes; Non-fatal MI; Stroke
- Ramipril has a + effect on each of these individually

\[ N = 9300 \text{ pts.} \]

Pt. characteristics: Vascular Disease → CVD; Stroke HX; PVD; OR Diabetes
Plus 1 other risk factor i.e. HTN, ↑ lipids, smoker. @ high risk for CVD.

Intervention:
Randomized to Ramipril 10 mg daily vs Placebo.

Duration: 5 yrs.

1º Composite Endpoint:
MI; Stroke; Death
Composite Endpoint (CE) Example 4 – CAPRICORN Study – 27, 28 (36:56; 39:22)

Articles

N > 1900 pts.
Pt. Characteristics:
Acute MI + Ejection Fraction < 40 %
(Heart Failure)
Intervention:
Randomized to Carvedilol or Placebo
Composite Endpoint:
All-cause mortality; CV hospitalization

Composite Endpoint:
All-cause mortality + CV hospitalization:
Carvedilol CE: 35% incidence; Placebo CE: 37% incidence
HR: 0.92, CI crosses 1 → NOT statistically significant

All-cause mortality:
Carvedilol CE: 12% incidence; Placebo CE: 15% incidence
HR: 0.77, 95%, CI (0.6-0.98) → statistically significant? → see below; yes for academic purposes
Study Endpoint was initially: All-cause mortality
Enough people weren’t dying so CE Δ’d mid study to include CV related hospitalization
By adding second endpoint → had to manipulate the statistics → chose arbitrary P Value < 0.005
needed to be demonstrated for all-cause mortality to be statistically significant.
Because of this addition, they cannot claim ↓ mortality with carvedilol.

1. Are all endpoints of the CE similar importance to pt.? NO
   • All-cause mortality; CV related hospital admission
   • Endpoints are 2 ends of the spectrum for significance

2. Do all endpoints of the CE occur at similar rates / RRR reductions? NO
   • Rate for CV related hospitalizations not given.
     o Carvedilol group: 23%; Placebo group: 22%
   • Both occurred: about 2 x as many pts. were admitted compared to those that died.
   • Hospitalizations affected the Composite Endpoint → it took a significant finding and diluted it as the Composite Endpoint → this MUST have affected RR & Rates.

3. Do all endpoints move in the same direction? NO; Hospitalizations >> Death for carvedilol

4. Is this a valid CE? NO
   • Study power was diluted → survival benefit masked by adding hospitalizations as endpoint
   • Non biologically – related endpoints
   • Clinician driven endpoint → 1 → CV hospitalization; Death → Non-Clinician driven

5. Mixing clinician / non-clinician driven → ↑ likelihood for 1⁰ CE to show significant result / positive outcome in the treatment arm. Can affect your results.
**Composite Endpoint (CE) Example 5 Diabetic Neuropathy Study – 29, 30, 31 (41:59; 43:03; 44:34)**

**TABLE 2. OUTCOMES ACCORDING TO STUDY GROUP.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>IRBESARTAN GROUP (N=578)</th>
<th>AMLODIPINE GROUP (N=567)</th>
<th>PLACEBO GROUP (N=569)</th>
<th>ALL PATIENTS (N=1715)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome no. (%)</td>
<td>189 (32.6)</td>
<td>233 (41.1)</td>
<td>222 (39.0)</td>
<td>644 (37.6)</td>
</tr>
<tr>
<td>Doubling of serum creatinine concentration</td>
<td>98 (16.9)</td>
<td>144 (25.4)</td>
<td>135 (23.7)</td>
<td>377 (22.0)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>83 (14.2)</td>
<td>104 (18.3)</td>
<td>101 (17.8)</td>
<td>287 (16.7)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>87 (15.0)</td>
<td>83 (14.6)</td>
<td>93 (16.3)</td>
<td>263 (15.3)</td>
</tr>
<tr>
<td>Secondary composite outcome no. (%)</td>
<td>138 (23.8)</td>
<td>128 (22.6)</td>
<td>144 (25.3)</td>
<td>410 (23.9)</td>
</tr>
<tr>
<td>Never received study medication — no. (%)</td>
<td>2 (0.3)</td>
<td>8 (1.4)</td>
<td>6 (1.1)</td>
<td>16 (0.9)</td>
</tr>
<tr>
<td>Lost to follow-up — no. (%)</td>
<td>5 (0.9)</td>
<td>2 (0.4)</td>
<td>4 (0.7)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Completed study without primary outcome — no. (%)</td>
<td>385 (66.5)</td>
<td>332 (58.6)</td>
<td>343 (60.3)</td>
<td>1060 (61.8)</td>
</tr>
<tr>
<td>Mean duration of follow-up — days</td>
<td>952</td>
<td>924</td>
<td>921</td>
<td>932</td>
</tr>
</tbody>
</table>

*The numbers of patients with the composite end points are lower than the sums of those with the various components because some patients reached more than one component.

**TABLE 3. RELATIVE RISKS OF OUTCOMES.**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>UNADJUSTED RELATIVE RISK (95% CI)</th>
<th>P VALUE</th>
<th>ADJUSTED RELATIVE RISK (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan vs. placebo</td>
<td>0.80 (0.66-0.97)</td>
<td>0.02</td>
<td>0.81 (0.67-0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Amloprimine vs. placebo</td>
<td>1.04 (0.86-1.25)</td>
<td>0.69</td>
<td>1.07 (0.89-1.29)</td>
<td>0.47</td>
</tr>
<tr>
<td>Irbesartan vs. amloprimine</td>
<td>0.77 (0.63-0.93)</td>
<td>0.006</td>
<td>0.76 (0.63-0.92)</td>
<td>0.005</td>
</tr>
<tr>
<td>Doubling of serum creatine concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan vs. placebo</td>
<td>0.67 (0.52-0.87)</td>
<td>0.003</td>
<td>0.71 (0.54-0.92)</td>
<td>0.009</td>
</tr>
<tr>
<td>Amlodipine vs. placebo</td>
<td>1.06 (0.84-1.35)</td>
<td>0.60</td>
<td>1.15 (0.91-1.46)</td>
<td>0.24</td>
</tr>
<tr>
<td>Irbesartan vs. amloprimine</td>
<td>0.63 (0.48-0.81)</td>
<td>&lt;0.001</td>
<td>0.61 (0.48-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan vs. placebo</td>
<td>0.77 (0.57-1.03)</td>
<td>0.07</td>
<td>0.83 (0.62-1.11)</td>
<td>0.19</td>
</tr>
<tr>
<td>Amlodipine vs. placebo</td>
<td>1.00 (0.76-1.32)</td>
<td>0.99</td>
<td>1.09 (0.82-1.43)</td>
<td>0.56</td>
</tr>
<tr>
<td>Irbesartan vs. amloprimine</td>
<td>0.77 (0.57-1.03)</td>
<td>0.07</td>
<td>0.76 (0.57-1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan vs. placebo</td>
<td>0.92 (0.69-1.23)</td>
<td>0.57</td>
<td>0.94 (0.76-1.17)</td>
<td>0.69</td>
</tr>
<tr>
<td>Amlodipine vs. placebo</td>
<td>0.88 (0.66-1.19)</td>
<td>0.40</td>
<td>0.90 (0.68-1.21)</td>
<td>0.47</td>
</tr>
<tr>
<td>Irbesartan vs. amloprimine</td>
<td>1.04 (0.77-1.40)</td>
<td>0.80</td>
<td>1.05 (0.78-1.42)</td>
<td>0.75</td>
</tr>
<tr>
<td>Secondary, cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>composite end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irbesartan vs. placebo</td>
<td>0.91 (0.72-1.14)</td>
<td>0.40</td>
<td>0.91 (0.72-1.14)</td>
<td>0.40</td>
</tr>
<tr>
<td>Amlodipine vs. placebo</td>
<td>0.88 (0.69-1.12)</td>
<td>0.29</td>
<td>0.88 (0.69-1.11)</td>
<td>0.27</td>
</tr>
<tr>
<td>Irbesartan vs. amloprimine</td>
<td>1.03 (0.81-1.34)</td>
<td>0.79</td>
<td>1.03 (0.81-1.32)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.

The relative risks were adjusted for the mean arterial blood pressure during follow-up.

**N > 1700 pts.**
**Pt. Characteristics:**
Nephropathy 2° to DM
**Intervention:**
Randomized to Irbesartan or Amlodipine or placebo.
Titrated to goal BP < 135/85
1° Endpoint: Death; doubling of base SrCr; End Stage Renal disease.

Endpoints were well distributed.
Irbesartan: Equally distributed
SrCr ↑ 2x: 17% incidence
End Stage Renal: 14.2%
Death any cause: 15%
Consistent across groups
Amlodipine: generally well distributed
SrCr ↑ 2x: 25.4% (a few more pts.)
End Stage Renal: 18.3%
Death any cause: 14.%
SrCr was higher in this group than the other 2 endpoints.

**Relative Risks Unadjusted**
CE Irbesartan vs Placebo:
Statistically significant finding that
Irbesartan ↓ risk of Composite Endpt. 0.8; 95% CI (0.66 - 0.97) that does NOT Cross 1.
CE Amlodipine vs Placebo:
Results are neutral
1.04; 95% CI (0.86-1.25)
CE Irbesartan vs Amlodipine
0.77; 95% CI (0.623 - 0.93)
CI did not cross 1.
Statistically significant finding that
Irbesartan superior to amlodipine @ ↓ risk of composite endpoint.
Individual Endpoint Evaluation

Doubling of SrCr:
Irbesartan vs Placebo:
Statistically significant finding - CI did NOT cross 1.
RR: 0.67; 95% CI (0.52-0.87)
Amlodipine vs Placebo:
RR: 1.06; 95% CI (0.84-1.25)
- Not statistically significant
- CI crossed 1.
Irbesartan vs Amlodipine
RR: 0.63; 95% CI (0.48-0.81)
- Statistically significant finding – CI did not cross 1.
- Irbesartan ↓ incidence of doubling SrCr

End-Stage Renal Disease:
Irbesartan vs placebo
Irbesartan vs amlodipine
- Looks like irbesartan ↓ incidence End-Stage Renal disease
- However, NOT statistically significant because CI crosses 1.

Death from any cause:
Fairly neutral overall – No effect on death
Irbesartan vs Placebo
RR: 0.92; 95% CI (0.69-1.23)
- NOT statistically significant. CI is wide & crosses over 1.

Even though no effect on death;
End-Stage renal disease was not statistically significant
Overall Composite Endpoint is positive for Irbesartan.

1. Are all endpoints similar importance to pt.? NO
- SrCr doubling; end stage renal disease; mortality
2. Do all endpoints occur at similar rates / RRR reductions? NO
- Did occur @ similar rates;
- RR similar for End-Stage Renal disease & for doubling of SrCr
- RR for mortality, were increased or neutral.
3. Do all endpoints move in the same direction? NO
- Death endpoint – neutral;
- SrCr doubling & End-Stage renal disease → looked like irbesartan would improve them.
4. Is this a valid CE? NO
Study was good example showing:
- 1-2 endpoints carried the Composite Endpoint making it a positive when several of the individual components were not
- Unrelated biological endpoint represented Doubling of SrCr then All-Cause Mortality – would not think irbesartan & amlodipine would affect them in the same manor.
Take Home Message – 32 (45:56)

1. Common statistical concepts
   - Kaplan-Meier curves;
   - Hazard Ratios (HR);
   - Composite Endpoints (CE)

2. Hazard Ratios (HR) are often misinterpreted
   - Carefully interpret HRs
   - Carefully state results if HRs
     - make sure NOT to pin a time to the outcome i.e. 2-3x as fast
     - State it correctly i.e. as: “It will occur faster” or “Less fast” if it’s < 1

3. Composite Endpoints are valid if:
   - Endpoints are of = importance to pt.
   - Endpoints similarly affect overall results (Composite Endpoints)

4. Interpret individual components of CE if # 3 above is not met:
   - To see which ones are truly affected by the treatment