SURROGATE OUTCOME MEASURES; SUPERIORITY, EQUIVALENCE, AND NON-INFERIORITY TRIALS

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“SURROGATE”

Latin: Surrogatus- Put in Another’s Place

Definition: Deputy or Substitute

Connotation: Less Than Equivalent Substitute
SOME CHARACTERISTICS OF A SURROGATE ENDPOINT

- Directly related to major clinical outcome (e.g., mortality, stroke)
- Ascertainment is reliable and valid
- Alteration in surrogate endpoint produces alteration in major clinical outcome
- Safe and acceptable to participants
- Persuasive to scientific and medical colleagues
- Cost effective
POSSIBLE ADVANTAGES OF TRIALS USING SURROGATE ENDPOINTS

• Fewer Patients
  Shorter Trial

• Pathophysiologic
  Orientation

Less Cost
Reduced Total Risk

? More Persuasive
POTENTIAL DISADVANTAGES OF TRIALS USING SURROGATE ENDPOINTS

- Surrogate endpoint and outcome variable, e.g., mortality, may not correlate well.
- Change in surrogate and change in outcome variable may not correlate well.
- Technical difficulties (e.g., lack of standardization)
- Missing data
- Cost and safety of measuring surrogate endpoint
- Loss of information on net effect of drug (e.g., unexpected toxicity)
Examples of Potential Surrogate Endpoints in Cardiovascular Disease Clinical Trials

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>Stroke, CHD, Total Mortality</td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td>CHD</td>
</tr>
<tr>
<td>“Infarct Size”</td>
<td>CHD</td>
</tr>
<tr>
<td>Holter Monitoring</td>
<td>Ventricular Arrhythmia</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>LVH</td>
</tr>
<tr>
<td>Radionuclide Angiography</td>
<td>LVH or EF</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Peripheral Vascular Progression</td>
</tr>
<tr>
<td>Plasma Cholesterol</td>
<td>CHD</td>
</tr>
</tbody>
</table>
Purpose of Workshop:

To discuss in broad epidermiologic, biostatistical and clinical terms the use of surrogate endpoints in cardiovascular clinical trials using the examples of blood pressure, coronary angiography, infarct size and holter monitoring. To identify, if possible, essential characteristics of the surrogate endpoints.
BLOOD PRESSURE

• Death
• Coronary Heart Disease
• Stroke
Randomized Design of ALLHAT

High-risk hypertensive patients

Consent / Randomize

Eligible for lipid-lowering

Consent / Randomize

Pravastatin

Usual care

Not eligible for lipid-lowering

Amlodipine
Chlorthalidone
Doxazosin
Lisinopril

Follow until death or end of study (4-8 yr, ave 6 yr).
Decision to Drop an ALLHAT Arm

• January 24, 2000 – NHLBI Director accepts recommendation of independent review to terminate doxazosin arm
  – Futility of finding a significant difference for primary outcome
  – Statistically significant 25 percent higher rate of major secondary endpoint, combined CVD outcomes
SBP Results by Treatment Group

Chlorthalidone
Doxazosin

mm Hg BP

0 6 12 18 24 30 36 42 48

Months
Coronary Heart Disease

Cumulative Event Rate

Doxazosin

Rel Risk: 1.03
95% CL: 0.90-1.17
z = 0.38, p = 0.71

Chlorthalidone

C: 15,268
D: 9,067

ALLHAT
Cardiovascular Disease

Rel Risk  95% CL
1.25  1.17-1.33

z = 6.77,  \( p < 0.0001 \)

C: 15,268  D:  9,067

ALLHAT
Stroke

Cumulative Event Rate

Rel Risk  95% CL
1.19  1.01-1.40

z = 2.05,  p = 0.04

ALLHAT
Cumulative Event Rate

Years of Follow-up

C: 15,268
D: 9,067

Rel Risk 95% CL
2.04 1.79-2.32

z = 10.95, p < 0.0001

ALLHAT

Congestive Heart Failure

Doxazosin

Chlorthalidone

C: 15,268
D: 9,067

C: 9,541
D: 5,457

C: 5,531
D: 3,089

C: 2,427
D: 1,351

Years of Follow-up
Cumulative Event Rate

Non-CHF Cardiovascular Disease

Rel Risk 95% CL
1.13 1.06-1.21

z = 3.53, p < 0.001

ALLHAT

C: 15,268
D: 9,067

Years of Follow-up

C: 15,268
D: 9,067
Relative Risks and 95% CI
Combined CVD
Doxazosin/Chlorthalidone
Relative Risks and 95% CI
Congestive Heart Failure
Doxazosin/Chlorthalidone
On Step 1 or Equivalent Treatment by Antihypertensive Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Chlor</th>
<th>Dox</th>
</tr>
</thead>
<tbody>
<tr>
<td>12M</td>
<td>88.4</td>
<td>81.6</td>
</tr>
<tr>
<td>24M</td>
<td>87.3</td>
<td>78.8</td>
</tr>
<tr>
<td>36M</td>
<td>86.5</td>
<td>76.1</td>
</tr>
<tr>
<td>48M</td>
<td>85.8</td>
<td>74.7</td>
</tr>
</tbody>
</table>
# Full Crossovers by Antihypertensive Treatment Group

**Chlorthalidone:** not on assigned medicine or open-label diuretic, but on open-label alpha-blocker

**Doxazosin:** not on assigned medicine or open-label alpha-blocker, but on open-label diuretic

<table>
<thead>
<tr>
<th></th>
<th>12M</th>
<th>24M</th>
<th>36M</th>
<th>48M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlor</td>
<td>0.4</td>
<td>0.6</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Dox</td>
<td>4.8</td>
<td>6.6</td>
<td>9.2</td>
<td>9.7</td>
</tr>
</tbody>
</table>
VENTRICULAR PREMATURE BEATS

SUDDEN CARDIAC DEATH
CHARACTERISTICS OF VENTRICULAR ARRHYTHMIAS IN MAN

- They are common
- They increase with age
- They increase with ventricular scarring
  - Infarction
  - Hypertrophy
  - Infection
- They do not increase with coronary atherosclerosis per se
- They can be precipitated/aggrivated by exercise
  - Ischemia
  - Increased Sympathetic Activity
  - Increased Heart Rate
- Electrocardiographically similar arrhythmias may have different causes and significance
Mortality rate as a function of average hourly frequency of ventricular premature depolarizations (VPDs).

![Graph showing the relationship between one-year mortality percent and VPD per hour.](image)
Relation Between Repetitive Ventricular Premature Complexes and Mortality, Adjusted for the Effects of Frequency of Ventricular Premature Complexes

<table>
<thead>
<tr>
<th>VPC Frequency (Per Hour)</th>
<th>Repetitive VPCs</th>
<th>Status</th>
<th>Total</th>
<th>Mortality</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dead</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Absent</td>
<td>31</td>
<td>349</td>
<td>380</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>16</td>
<td>68</td>
<td>84</td>
<td>19%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>Absent</td>
<td>6</td>
<td>36</td>
<td>42</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>31</td>
<td>79</td>
<td>110</td>
<td>28%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>84</td>
<td>532</td>
<td>616</td>
<td>14%</td>
</tr>
</tbody>
</table>
# Mortality 1 Year After Infarction as a Function of Left Ventricular Ejection Fraction and Repetitive Ventricular Premature Complexes

<table>
<thead>
<tr>
<th>Ejection Fraction (%)</th>
<th>Repetitive VPCs</th>
<th>Status</th>
<th>Total</th>
<th>Mortality</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dead</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Absent</td>
<td>3</td>
<td>196</td>
<td>199</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>4</td>
<td>51</td>
<td>55</td>
<td>7%</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Absent</td>
<td>6</td>
<td>81</td>
<td>87</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>12</td>
<td>35</td>
<td>47</td>
<td>25%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>25</td>
<td>363</td>
<td>388</td>
<td>6%</td>
</tr>
</tbody>
</table>
CARDIAC ARRHYTHMIA SUPPRESSION TRIAL (CAST)

• Double Blind
• 6 days to 2 years post-myocardial infarct
• 6 or more VPD on an 18-hour Holter recording
• Open titration, evidence of suppressibility
• Randomization
  - Encainide
  - Flecainide
  - Moricizine (Alternative)
• Primary endpoint – arrhythmic death
• Power – 4000, \( \alpha_1 = 0.025 \), \( 1- \beta = 0.85 \)
ACTUARIAL PROBABILITIES OF FREEDOM FROM DEATH OR CARDIAC ARREST DUE TO ARRHYTHMIA

<table>
<thead>
<tr>
<th>Days after Randomization</th>
<th>Placebo (n = 743)</th>
<th>Encainide or Flecaïnide (n = 755)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>743</td>
<td></td>
</tr>
<tr>
<td></td>
<td>632</td>
<td></td>
</tr>
<tr>
<td></td>
<td>516</td>
<td></td>
</tr>
<tr>
<td></td>
<td>412</td>
<td></td>
</tr>
<tr>
<td></td>
<td>292</td>
<td></td>
</tr>
<tr>
<td></td>
<td>201</td>
<td></td>
</tr>
</tbody>
</table>

Patients without Event (%)
## Cause of Death and Cardiac Arrest (with Resuscitation) in CAST, According to Treatment Group

<table>
<thead>
<tr>
<th>Cause</th>
<th>Encainide Group</th>
<th>Flecainide Group</th>
<th>Both Groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Drug</td>
<td>Placebo</td>
<td>Active Drug</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients in group</td>
<td>432</td>
<td>425</td>
<td>323</td>
<td>319</td>
</tr>
<tr>
<td>All deaths and cardiac arrests</td>
<td>44</td>
<td>19</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac death or cardiac arrest</td>
<td>42</td>
<td>15</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Arrest with resuscitation</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Noncardiac death</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
EJECTION FRACTION

CARDIAC DEATH
OR
TOTAL MORTALITY
% PATIENTS FREE OF CHF

PERCENT SURVIVAL

YEAR

- EJECFA < 35 (721)
- EJECFA 35-49 (2336)
- EJECFA > 50 (9249)
Comparison of Ejection Fraction Determinations and Events by Treatment Group

<table>
<thead>
<tr>
<th>Ejection Fraction (%)</th>
<th>T Mortality (%)</th>
<th>CV Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>28.7</td>
<td>28.5</td>
</tr>
<tr>
<td>Echo</td>
<td>26.9</td>
<td>27.1</td>
</tr>
<tr>
<td>Radionuclide</td>
<td>26.7</td>
<td>26.6</td>
</tr>
</tbody>
</table>
To test whether or not captopril at a dose of up to 150 mg/d could improve total mortality and/or prevent reduction in EF by 9 units or more in those having had an MI within 3 to 17 days with EF < 40.
SAVE

All-Cause Mortality

Mortality rate

Placebo

Captopril

Risk reduction = 19%
P = 0.019

Years

SOLVD TRIALS

- TREATMENT AND PREVENTION TRIALS
- TREATMENT-OVERT HEART FAILURE
- PREVENTION-REDUCED EF (<40%)
- PRIMARY OUTCOME-ALL CAUSE MORTALITY
- SUBSTUDY- EFFECT ON EF
- T=2569, P=4228 PARTICIPANTS
# PROMISE

<table>
<thead>
<tr>
<th></th>
<th>Milrinone (n = 561)</th>
<th>Placebo (n = 527)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Deaths</strong></td>
<td>168 (30%)</td>
<td>127 (24%)</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>No. CV Deaths</strong></td>
<td>165 (29.4%)</td>
<td>119 (22.6%)</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>No. Hospitalizations</strong></td>
<td>247 (44%)</td>
<td>205 (30%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>No. Improved Functional Capacity</strong></td>
<td>191 (34%)</td>
<td>163 (31%)</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>No. Worsening CHF</strong></td>
<td>168 (30%)</td>
<td>153 (29%)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
CREATINE KINASE-MB

MYOCARDIAL INFARCT SIZE
COMPARISON OF ACCURACY, SENSITIVITY AND SPECIFICITY OF TOTAL CREATINE KINASE (CK), PYROPHOSPHATE, AND ELECTROCARDIOGRAPHIC CRITERIA FOR DETECTION OF ACUTE MYOCARDIAL INFARCTION

[Bar chart showing comparison of Accuracy, Sensitivity, and Specificity for Total CK, Pyrophosphate, and ECG]
COMPARISON OF MEAN CREATINE KINASE (CK)-MB INFARCT SIZE INDEX FOR TRUE-POSITIVE VS FALSE-NEGATIVE DETERMINATIONS OF ACUTE MYOCARDIAL INFARCTION BY TOTAL CK, PYROPHOSPHATE AND ELECTROCARDIOGRAPHIC CRITERIA

\[ p < 0.01 \]

\[ p < 0.03 \]
\[ p < 0.01 \]

- Total CK
- ECG
- Pyrophosphate

\[ * \ p < 0.01 \]
\[ \uparrow \ p < 0.02 \]

Compared to

True Positive

False Negative
# Accuracy and Sensitivity of Total CK and Pyrophosphate Imaging in Q-Wave and Non-Q-Wave Infarction by Electocardiography

<table>
<thead>
<tr>
<th></th>
<th>Total CK</th>
<th></th>
<th>Pyrophosphate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q-Wave MI</td>
<td>Non-Q Wave MI</td>
<td>Q-Wave MI</td>
<td>Non-Q Wave MI</td>
</tr>
<tr>
<td>True Positive</td>
<td>379</td>
<td>169</td>
<td>361</td>
<td>156</td>
</tr>
<tr>
<td>True Negative</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>False Positive</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>False Negative</td>
<td>2</td>
<td>6</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>99</td>
<td>94*</td>
<td>93</td>
<td>84*</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>99</td>
<td>97*</td>
<td>95</td>
<td>89*</td>
</tr>
</tbody>
</table>

* P< 0.01;   * P< 0.05
SUMMARY

Appropriately selected and validated surrogate endpoints can reduce size, duration, and perhaps costs of clinical trials.

• Caution: Trials of surrogate endpoints may sometimes be misleading as to the true net worth of an intervention

• They must be meticulously defined apriori and blindly evaluated
SUPERIORITY, EQUIVALENCE, AND NON-INFERIORITY TRIALS

DIFFERENT KINDS OF TRIALS WITH DIFFERENT PURPOSES
EFFICACY OF A NEW AGENT

ESTABLISH IF ITS TREATMENT/EFFECTS PROVE TO BE AT LEAST EQUIVALENT TO THOSE OBSERVED FROM STANDARD OF CARE- R/O EQUIVALENCE.

OTHER ISSUES: TOXICITY, COST EASE OF ADMINISTRATION
EQUIVALENCE TRIALS

“PROVIDE AN IMPORTANT FRAMEWORK FOR DETERMINING WHETHER AN EXPERIMENTAL THERAPY CAN BE ACCEPTED AS A STANDARD OF CARE.”

POINT ESTIMATE AND CONFIDENCE INTERVALS- NOT P-VALUES
AIM EQUVALENCE TRIAL

ESTABLISH: “CLINICALLY IMPORTANT DIFFERENCE”

R/O ALL DIFFERENCES OF CLINICAL IMPORTANCE BETWEEN TWO TREATMENTS

REJECT NULL HYPOTHESIS THAT THE SMALLEST DIFFERENCE OF CLINICAL IMPORTANCE EXISTS IN FAVOR OF THE STANDARD OF CARE (SOC).
SMALLEST CLINICALLY IMPORTANT DIFFERENCE

1. DETERMINED BY TEAM OF CLINICAL AND BIOSTATISTICAL RESEARCH EXPERTS
2. ADOPT PROSPECTIVE OF PARTICIPANT
3. NOT DETERMINED BY SSE
Statistical Considerations

In HOPE the hazard ratio for ramipril vs placebo : 0.77
40\textsuperscript{th} percentile : 0.794
Excess risk of placebo/ramipril : 1.26
Half of above : 1.13

For non-inferiority (Telmisartan vs ramipril) the one-sided 97.5\% CI should be below 1.13
Assuming an annual event rate of 3.97\%, 7800 patients per group followed for 4.5 yrs provided :
- 89\% power for NI (T v R)
- 93\% power superiority (T + R v R)

Total randomized: 25,620 in 18 months
ADVANTAGES EQUIVALENCE
TRIAL

1. COMPARE NEW TREATMENT VS SOC
2. EVERYONE RECEIVES ACTIVE TREATMENT
3. SETTING: PLACEBO UNETHICAL
Figure 2

Point Estimates and 95% CI: (t-PA—r-PA)

A, Hypothetical comparison of reteplase (rPA) and alteplase (tPA) showing data consistent with but not establishing the equivalence of rPA with tPA (point estimate [*] and 95% confidence interval for 30-day mortality rate). B, Hypothetical comparison of rPA and tPA showing data that establishes rPA is at least equivalent to tPA (point estimate [*] and 95% confidence interval for 30-day mortality rate).
Figure 3

Point Estimate and 95% CI: (t-PA—r-PA)

<table>
<thead>
<tr>
<th>t-PA: 7.24% vs r-PA: 7.47%</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-PA Better</td>
</tr>
<tr>
<td>-1.11%</td>
</tr>
<tr>
<td>-0.23%</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.66%</td>
</tr>
<tr>
<td>r-PA Better</td>
</tr>
</tbody>
</table>

Percent reduction in 30-day mortality rate with accelerated infusion of alteplase (tPA) vs double-bolus infusion of reteplase (rPA) in the GUSTO III trial (point estimate [*] and 95% confidence interval). Shaded region on the x-axis represents the region where the increase in mortality rate with rPA is clinically important.
EQUIVALENCE TRIAL
SAMPLE SIZE ESTIMATES

• ALWAYS LARGER THAN SUPERIORITY TRIAL !?

• USUALLY SAME ORDER OF MAGNITUDE IF:
  1. 10% EVENT RATE
  2. 1% IMPROVEMENT
  3. 0.5% CLINICALLY IMPORTANT DIFFERENCE
AIM SUPERIORITY TRIAL

-R/O EQUALITY BETWEEN TREATMENTS BY REJECTING THE NULL HYPOTHESIS

IF NULL NOT REJECTED, EQUIVALENCE CAN NOT BE ASSUMED

“LACK OF EVIDENCE OF A DIFFERENCE” ≠ “EVIDENCE OF A LACK OF DIFFERENCE”
Figure 1

Point Estimates and 95% CI: (SK—t-PA)

A. Consistent With Superiority
   SK: 8/100 vs t-PA: 7/100: 1% ± 7%

   SK Better                      t-PA Better

   -6%                              0       1%       8%

B. Establishing Superiority
   SK: 800/10,000 vs t-PA: 700/10,000: 1% ± 0.7%

   SK Better                      t-PA Better

   0       1%

A, Hypothetical comparison of streptokinase and alteplase (a recombinant tissue plasminogen activator; tPA) showing data consistent with but not establishing the superiority of tPA over streptokinase (point estimate [*] and 95% confidence interval for 30-day mortality rate). B, Hypothetical comparison of streptokinase and tPA showing data that establishes the superiority of tPA over streptokinase (point estimate [*] and 95% confidence interval for 30-day mortality rate).
**Figure 4**

**A**
95% Confidence Intervals of Percent CR (IDR minus DNR)

<table>
<thead>
<tr>
<th>-30</th>
<th>-20</th>
<th>-10</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
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</tr>
<tr>
<td>MSKCC</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SEG</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adria</td>
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</tr>
</tbody>
</table>

**B**
95% Confidence Intervals of Hazard Ratio (DNR:IDR)

<table>
<thead>
<tr>
<th>0.1</th>
<th>0.8</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>MSKCC</td>
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<tr>
<td>SEG</td>
<td></td>
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<tr>
<td>Adria</td>
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**A**, Overall summary of complete response (CR) rates in three clinical trials of daunorubicin (DNR) vs idarubicin (IDR) for treatment of acute nonlymphocytic leukemia (point estimates [*] and 95% confidence intervals). **B**, Overall summary of hazard ratios for patient survival in three clinical trials of DNR versus IDR for treatment of acute nonlymphocytic leukemia (point estimates [*] and 95% confidence intervals). Adria, Adria Laboratories study (unpublished data); MSKCC, Memorial Sloan Kettering Cancer Center study; SEG, Southeastern Cancer Group study.\(^{11}\)\(^{12}\)
NON-INFERIORITY TRIALS

• “ONE-SIDED COMPARISON”
• TREATMENT NOT SUBSTANTIALLY WORSE THAN CONTROL (SOC)
• SUFFICIENCY TRIAL- TO SUPPORT AN EXPERT RECOMMENDATION FOR REGULATORY APPROVAL
Potential outcomes in an active-control trial. Plots A and I represent the active-control effect estimated from historic trials; plots B through H display point estimates and confidence intervals for the difference between study drug and active control (see text).
Main Study
ONTARGET: The ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

Parallel Study
TRANSCEND: Telmisartan Randomized Assessment Study in aCE iNtolerant Subjects with Cardiovascular Disease
• ACE-inhibitors (e.g. ramipril in the HOPE trial) reduces CV death, MI, stroke and HF hosp in those with CVD or DM in the absence of ventricular dysfunction or heart failure
• ACE-inhibitors are not tolerated by 15% to 25% of patients
• Will an ARB (telmisartan) be as effective (or superior) and better tolerated?
• Is the combination superior?
ONTARGET/TRANSCEND trials: RAAS modulation after HOPE—the next chapter


ONTARGET

730 centers, 40 countries

N = 25,620

Telmisartan + placebo

Ramipril + placebo

Telmisartan + Ramipril

Non-inferiority

Primary outcome: CV death, MI, stroke, hospitalization for HF

Superiority

TRANSCEND

N = 5926

Telmisartan

Placebo

Superiority

Primary outcome: CV death, MI, stroke, hospitalization for HF

Follow-up 5.5 years
Study Organization

**Study Population:** Large Randomized Double Blind Controlled Clinical Trial, enrolling subjects at high risk for developing cardiovascular disease. (Approximately 35% diabetics).

**Participating Centers:** 733 from 40 countries, every inhabited continent globally.

**Organization:** Coordinated by PHRI/CCC at McMaster University (Hamilton, Ontario) in conjunction with two regional centres (Oxford and Auckland)

**Sponsor:** Boehringer-Ingelheim, Germany
Possible results for the end of the Trial for ONTARGET Non-Inferiority Comparison

Case (1) - point estimate with 95% CI proves T is 'non-inferior' than R
Case (2) - point estimate with 95% CI fails to prove T is 'non-inferior' to R
Case (3) - point estimate with 95% CI proves T is 'inferior to R
## Primary Outcome & HOPE Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Ram</th>
<th>Tel</th>
<th>Tel vs Ram</th>
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<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>RR (95% CI)</td>
<td>P (non-inf)</td>
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<tr>
<td>N</td>
<td>8576</td>
<td>8542</td>
<td></td>
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<tr>
<td>Primary Outcome</td>
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<tr>
<td>CV Death, MI, Stroke, CHF Hosp</td>
<td>1412 (16.46%)</td>
<td>1423 (16.66%)</td>
<td>1.01 (0.94-1.09)</td>
<td>0.0038</td>
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<tr>
<td>(Adjusted for SBP)</td>
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<td>1.02 (0.95-1.10)</td>
<td>0.0055</td>
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<tr>
<td>HOPE Primary Outcome</td>
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<tr>
<td>CV Death, MI, Stroke</td>
<td>1210 (14.11%)</td>
<td>1190 (13.93%)</td>
<td>0.99 (0.91-1.07)</td>
<td>0.0009</td>
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<tr>
<td>(Adjusted for SBP)</td>
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<td>0.99 (0.91-1.07)</td>
<td>0.0012</td>
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</table>
Note that the outcomes are presented as point estimates with confidence intervals. The solid line is the 95% CI representing 1.96 SD and the dashed line is the 97.5% CI representing the adjusted CI for each outcome.
Statistical Analysis

Intent-to-treat (ITT) principle for all randomized patients

Per-protocol set (PPS) – sensitivity analysis
-all patients taken study medication >50% of their time
<table>
<thead>
<tr>
<th></th>
<th>Ram (n=6913)</th>
<th>Tel (n=7077)</th>
<th>Tel v Ram</th>
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<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
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<tr>
<td>CV Death, MI, Stroke, CHF Hosp</td>
<td>1000 (14.47%)</td>
<td>1025 (14.48%)</td>
<td>1.00 (0.92-1.09)</td>
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<td><em>(Adjusted for SBP)</em></td>
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<td>1.01 (0.92-1.10)</td>
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<tr>
<td><strong>HOPE Primary Outcome</strong></td>
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<td></td>
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<tr>
<td>CV Death, MI, Stroke</td>
<td>861 (12.45%)</td>
<td>869 (12.28%)</td>
<td>0.98 (0.90-1.08)</td>
</tr>
<tr>
<td><em>(Adjusted for SBP)</em></td>
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<td>0.99 (0.90-1.09)</td>
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ISSUES: VALIDITY EQUVALENCE TRAILS

1. CHOICE ACTIVE CONTROL
2. DETERMINATION OF ACCEPTABLE MARGIN
3. CHOICE PERAMETERS OF COMPARISON
   - WHICH VARIABLES
   - BLIND DETERMINATION
   - SECONDARY OUTCOME IMPORTANT
4. QUALITY OF TRIAL CONDUCT
   - BEWARE FALSE POSITIVES
   - ABSOLUTE RATES VS RATIOS
SUPERIORITY, EQUIVALENCE, AND NON-INFERIORITY TRIALS

DIFFERENT KINDS OF TRIALS WITH DIFFERENT PURPOSES

BE CAREFUL WITH INTERPRETATION OF A TRIAL RESULTS