# Module 2: Introduction to Statistics

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## Topic

- Dichotomous Variables
- Compare Proportions
  - Two sample test (Normal approximation theory)
  - Chi-square test
  - Fisher Exact test
- Measuring Treatment Effect on Binary Outcomes
  - Absolute Risk Reduction (ARR)
  - Relative Risk (RR)
  - Odds Ratio (OR)
- Application and Discussion of a Research Article
  - Feasibility of treating prehypertension with an angiotensin-receptor blocker. Julius S. *et al. N Engl J Med*. 2006; 354:1685-97

## Dichotomous Variables: Binary Data

- Binary variables indicate two different states
  - Presence or absence of a characteristic: X=1 (Yes)/ 0(No)
    - Tossing a Coin: *Pr(Tail)=0.5*
    - *Pr*(Carrying Gene G)=*p*

$$X_i \sim \text{Bernoulli}(p)$$

  - Choose a cutoff point in continuous measure
    - Obesity: BMI ≥ 30 kg/m2
    - Hypertension: SBP ≥ 140 or DBP ≥ 90 mmHg
  - Assign status based on a checklist
    - Depressed: (If 16 or more items from the checklist are checked)
    - Control: (If < 16 items from the checklist are checked)

## Binomial Distribution

- Y is the number of successes in a fixed number (n) of independent Bernoulli trials ($X_i$) with the same probability of success in each trial
  - $X_i \sim \text{Bernoulli}(p)$
  - $Y = \sum_{i=1}^{n} X_i$

$$Y \sim \text{Bin}(n, p)$$

- Requirements
  1. Each trial has one of two possible outcomes (1=success/0=fail)
  2. The trials are independent
  3. Probability of success (event) is the same in all trials
  4. A fixed number of trials (i.e. n=100)

## Mean and Standard Deviation of Number of Successes: Y ~ Bin(n,p)

- Mean of Y:
  - If a coin is tossed n=100, what is the expected number of Tails?

    E(Y)=np=50

  - n is the number of trials
  - p is the probability of success
- Variance and Standard Deviation:

  Var(Y)=np(1-p)=100 x 0.5 x 0.5=25

  SD(Y)=$\sqrt{np(1-p)}$

## Mean and Standard Deviation of Proportion Y ~ Bin(n,p)

- Estimate of Proportion:
  - If an unfair coin is tossed 100 times and the result is 25 Tails, what is the expected value of *p*?

    $\hat{p}=\frac{Y}{n}=\overline{Y}=\frac{25}{100}=.25$

    E($\overline{Y}$)=p

  - Y number of successes
  - n number of trials
  - p probability of success
- Variance and Standard Deviation of $\overline{Y}$:

  Var($\overline{Y}$)= p(1-p)/n $\approx \hat{p}(1-\hat{p})/100$

  SD($\overline{Y}$)=$\sqrt{p(1-p)/n}$

## Which of These Variables Would Have a Binomial Distribution?

- Number of female students in this class given the total number of students
  - ✓ Yes
- BMI of 100 people
  - X No
- Number of people with BMI ≥ 30 kg/m2
  - ✓ Yes

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  - **Fisher Exact test**
- Measuring Treatment Effect on Binary Outcomes
  - Absolute Risk Reduction (ARR)
  - Relative Risk (RR)
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## Examples of Testing for Differences Between Two Proportions

- Does the proportion of patients with hypertension differ between two groups?
  - Treatment vs. Control
  - Smoker vs. Non smoker

## Notation and Display of Categorical Data 2 x 2 Contingency Tables

| | Hypertension | | |
|---|---|---|---|
| | Yes | No | Total |
| Treatment | $n_{11}$ | $n_{12}$ | $n_{1.}$ |
| Placebo | $n_{21}$ | $n_{22}$ | $n_{2.}$ |
| Total | $n_{.1}$ | $n_{.2}$ | n |

$n_{ij}$ are referred to as cell frequencies.
$n_{.j}$ and $n_{i.}$ are refereed to as marginal frequencies
n is the total sample size

## Example: 2 x 2 Tables

| TROPHY data | Hypertension | | Total |
|---|---|---|---|
| | Yes (% of row) | No | |
| Treatment | 14(11%) | 113 | 127 |
| Placebo | 57(44.5%) | 71 | 128 |
| Total | 71(27.8%) | 184 | 255 |

Proportion of HT in Treatment group: $p_1$ =14/127 =11%
Proportion of HT at Placebo group: $p_2$ =57/128=44.5%
Proportion of HT in both groups: p =71/255=27.8%

Q: What is the number of subjects with HT from the Treated group?

## Test for Differences in Proportions Between Two Groups

- Testing whether the proportions for some outcome (e.g. HT) are different between two groups:

$$H_0: p_1 = p_2$$

Vs.

$$H_A: p_1 \neq p_2$$

## Three Tests for Differences in Proportions Between Two Groups

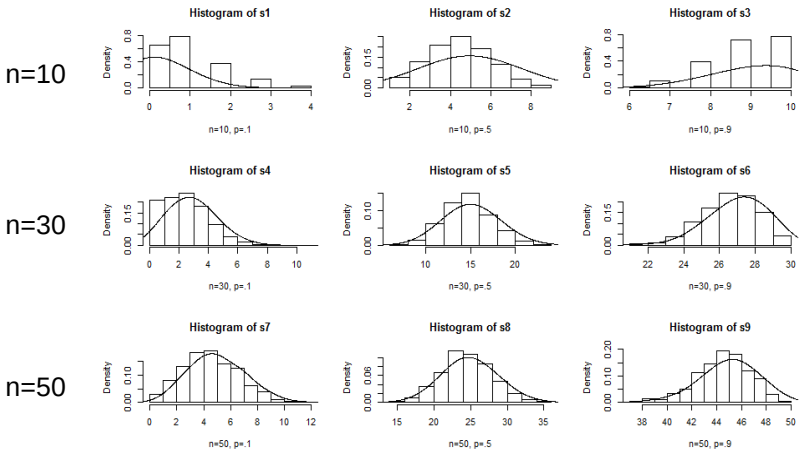
- Two-sample test for differences in two proportions
  - Normal theory test, works for large *n* due to CLT

$$Y = \sum_{i=1}^{n} X_i$$

- Chi-Square test
  - Works when $n > 5$ in all cells

- Fisher's Exact test
  - Works for any *n*, but computationally intensive when *n* is large
  - Used when *n* is not large, otherwise use the Chi-Square test

## Normal theory test: Y ~ Bin(n, p) is approximate normal for large n (CLT)



## Test Statistics for Difference in Two Binomial Proportions (Normal theory test)

$\hat{p}_1$: proportion in group 1 with outcome (sample size is $n_1$)

$\hat{p}_2$: proportion in group 2 with outcome (sample size is $n_2$)

$\hat{p}$: Overall proportion for group 1 and 2 combined

$$z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}\,(1-\hat{p})(\frac{1}{n_1}+\frac{1}{n_2})}}$$

Can be used only if

$n_1\hat{p}_1(1-\hat{p}_1) > 5$

$n_2\hat{p}_2(1-\hat{p}_2) > 5$

*e.g. p=.5 and n > 20*

*p=.1 and n > 56*

## TROPHY Data test for Binomial Proportions (Normal theory test)

| TROPHY data | Hypertension | | Total |
|---|---|---|---|
| | Yes (% of row) | No | |
| Treatment | 14(11%) | 113 | 127 ($n_1$) |
| Placebo | 57(44.5%) | 71 | 128 ($n_2$) |
| Total | 71(27.8%) | 184 | 255 |

$$z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}(1-\hat{p})(\frac{1}{n_1}+\frac{1}{n_2})}}$$

$\hat{p}_1$ =14/127 =11%

$\hat{p}_2$ =57/128=44.5%

$\hat{p}$=71/255=27.8%

## TROPHY Data test for Binomial Proportions (Normal theory test)

$$z = \frac{.11 - .445}{\sqrt{.278 * (1 - .278)\left(\frac{1}{127} + \frac{1}{128}\right)}} = \frac{-.335}{\sqrt{.207 * .01569}} = -5.96$$

p-value=$2.52 \times 10^{-9}$, Reject $H_0$: $p_1 = p_2$

## Chi-Square ($\chi^2$) Test

The Chi-Square test is the most commonly used test for categorical data analysis

- Can be used for 2 x 2 tables
- Can be used for n x m tables (for any n and m)

## Observed Cell Proportions
### (Deriving $\chi^2$ Test)

| | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 14(5.5%) | 113(44.3%) | 127(49.8%) |
| Placebo | 57(22.4%) | 71(27.8%) | 128(50.2%) |
| Total | 71(27.8%) | 184(72.2%) | 255 |

Cell % relative to the overall n=255

E.g. What proportion of the total sample is from the treatment group and has HT?

14/255 =5.5%

## Expected Cell Proportions
### (Deriving $\chi^2$ Test)

| TROPHY data | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 14 | 113 | 127(49.8%) |
| Placebo | 57 | 71 | 128(50.2%) |
| Total | 71(27.8%) | 184(72.2%) | 255 |

Marginal Proportions:

- Marginal Row %: What proportion is in the Treatment (Placebo) group?
  127/255 =49.2%
- Marginal Column %: What proportion is HT (Not HT)?
  71/255=27.8%

## Expected Cell Proportions
### (Deriving $\chi^2$ Test)

| TROPHY Data | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 13.8% | 36% | 49.8% |
| Placebo | 14% | 36.2% | 50.2% |
| Total | 27.8% | 72.2% | 100% |

Marginal proportion are fixed.
Q: What proportion of the total sample is expected in each cell (when $H_0$ is true)?
Multiply the row percent with column percent:
27.8% x 49.8% = 13.8%

## Expected Cell Frequency
### (Deriving $\chi^2$ Test)

| TROPHY Data | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 35.2(13.8%) | 91.8 | 127 |
| Placebo | 35.7 | 92.3 | 128 |
| Total | 71 | 184 | 255 |

What number from the total sample is expected in each cell?

13.8% x 255=35.2

## Compare Observed vs. Expected Frequencies
### (Deriving $\chi^2$ Test)

| TROPHY Data | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 14/35.2 | 113/91.8 | 127 |
| Placebo | 57/35.7 | 71/92.3 | 128 |
| Total | 71 | 184 | 255 |

Observed frequencies: $O_{11} = 14$

Expected frequency: $E_{11} = 35.2$

If $H_0$ is true then $O_{11}$ should be close to $E_{11}$

## Chi-Square Test

- Chi-Square test, with Yate's correction , is based on:

$$\chi^2 = \frac{(|O_{11}-E_{11}|-.5)^2}{E_{11}} + \frac{(|O_{12}-E_{12}|-.5)^2}{E_{12}} + \frac{(|O_{21}-E_{21}|-.5)^2}{E_{21}} + \frac{(|O_{22}-E_{22}|-.5)^2}{E_{22}}$$

- $\chi^2$ has a Chi-Square distribution with *df* = *k*(?)
- Calculate the p-value based on the Chi-Square distribution with k *df*
  - If p-value < 0.05 reject $H_0$

## Chi-Square Test: Calculating Degrees of Freedom

| TROPHY Data | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 14 | | 127 |
| Placebo | | | 128 |
| Total | 71 | 184 | 255 |

For 2 x 2 tables, the frequency number in only one cell is free to vary. Frequencies in the remaining 3 cell are constrained and can be derived.

What is the frequency for non HT in the Treated group?

## Chi-Square Test: Calculating Degrees of Freedom

| TROPHY Data | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 14 | 113(127-14) | 127 |
| Placebo | 57 (71-14) | 71(128-57) | 128 |
| Total | 71 | 184 | 255 |

- df=(Rows-1) x (Columns-1)=1
- Then, use the Chi-Square with 1 *df* to derive the p-value.
  If p-value < .05, then reject $H_0$: $p_1 = p_2$

## Chi-Square Test in R

- In R: chisq.test(HT,Trt)
- Output:

Pearson's Chi-squared test with Yates' continuity correction

data: HT and Trt

X-squared = 33.9775, df = 1, p-value = 5.575e-09 ⟶ Reject $H_0$ of no treatment effect

## Fisher's Exact Test

- Fisher's exact test is not based on the normal approximation theory. It is an exact test
- It calculates the exact probability (under $H_0$) that one would observe a 2 x 2 table same or more extreme than the one observed (if < .05 reject $H_0$)
- It is used when n is small, and the Chi-square test or the normal approximation theory might not apply

## Example: 2 x 2 Contingency Table Fisher's Exact Test (Small Sample)

| Example | Not HT | HT | Total |
|---|---|---|---|
| Treated | 4 | 0 | 4 |
| Placebo | 1 | 3 | 4 |
| Total | 5 | 3 | 8 |

Marginal counts (are fixed)

- Under the $H_0$ of no difference on HT between two groups, calculate the probability of each table with the same marginal counts
- How many Tables with these given margins are possible?

| Example | Not HT | HT | Total |
|---|---|---|---|
| Treated | ? | | 4 |
| Placebo | | | 4 |
| Total | 5 | 3 | 8 |

## All Tables With Same Marginal Counts

| Table 1 | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 | | 4 |
| Placebo | | | 4 |
| Total | 5 | 3 | 8 |

| Table 2 | No HT | HT | Total |
|---|---|---|---|
| Treated | 3 | | 4 |
| Placebo | | | 4 |
| Total | 5 | 3 | 8 |

| Table 3 | No HT | HT | Total |
|---|---|---|---|
| Treated | 2 | | 4 |
| Placebo | | | 4 |
| Total | 5 | 3 | 8 |

| Table 4 | No HT | HT | Total |
|---|---|---|---|
| Treated | 1 | | 4 |
| Placebo | | | 4 |
| Total | 5 | 3 | 8 |

| Table 5 | No HT | HT | Total |
|---|---|---|---|
| Treated | 0 | | 4 |
| Placebo | 5(?) | | 4 |
| Total | 5 | 3 | 8 |

## All Tables With Same Marginal Counts

| Table 1 | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 | 0 | 4 |
| Placebo | 1 | 3 | 4 |
| Total | 5 | 3 | 8 |

| Table 2 | No HT | HT | Total |
|---|---|---|---|
| Treated | 3 | 1 | 4 |
| Placebo | 2 | 2 | 4 |
| Total | 5 | 3 | 8 |

| Table 3 | No HT | HT | Total |
|---|---|---|---|
| Treated | 2 | 2 | 4 |
| Placebo | 3 | 1 | 4 |
| Total | 5 | 3 | 8 |

| Table 4 | No HT | HT | Total |
|---|---|---|---|
| Treated | 1 | 3 | 4 |
| Placebo | 4 | 0 | 4 |
| Total | 5 | 3 | 8 |

Tables (1 and 4) are same or less likely than the observed data (Table 1)

Total Probabilities: Table 1 = 0.071
Table 2 = 0.429
Table 3 = 0.429
Table 4 = 0.071

The p-value for Fisher exact test is: p=.071+.071=.142

## Table1: How Many Combinations Can Have This Result?

| Table 1 | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 | 0 | 4(A,B,C,D) |
| Placebo | 1 | 3 | 4(a,b,c,d) |
| Total | 5 | 3 | 8 |

Treatment row: 1 combination
Placebo row: 4 combinations

Total: 1*4=4 Tables

| Table 1a | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 (A,B,C,D) | 0 | 4 |
| Placebo | 1 (a) | 3 (b,c,d) | 4 |
| Total | 5 | 3 | 8 |

| Table 1b | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 (A,B,C,D) | 0 | 4 |
| Placebo | 1 (b) | 3 (a,c,d) | 4 |
| Total | 5 | 3 | 8 |

| Table 1d | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 (A,B,C,D) | 0 | 4 |
| Placebo | 1 (d) | 3 (a,b,c) | 4 |
| Total | 5 | 3 | 8 |

| Table 1c | No HT | HT | Total |
|---|---|---|---|
| Treated | 4 (A,B,C,D) | | 4 |
| Placebo | 1 (c) | 3 (a,b,d) | 4 |
| Total | 5 | 3 | 8 |

## How Many Total Tables are Possible?

| Table 1 | Not HT | HT | # Tables | Proportion |
|---|---|---|---|---|
| Treatment | 4 | 0 | 1*4=4 | 4/56=.071 |
| Placebo | 1 | 3 | | |
| **Table 2** | | | | |
| Treatment | 3 | 1 | 4*6=24 | 24/56=.429 |
| Placebo | 2 | 2 | | |
| **Table 3** | | | | |
| Treatment | 2 | 2 | 6*4=24 | 24=56=.429 |
| Placebo | 3 | 1 | | |
| **Table 4** | | | | |
| Treatment | 1 | 3 | 4*1=4 | 4/56=.071 |
| Placebo | 4 | 0 | | |
| **Total** | | | 56 | 1.00 |

## Fisher's Exact Test in R

- In R: fisher.test(HT,Trt)

- R output:

Fisher's Exact Test for Count Data

data: HT and Trt
p-value = 0.1429
alternative hypothesis: true odds ratio is not equal to 1

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- **Measuring Treatment Effect on Binary Outcomes**
  - **Absolute Risk Reduction (ARR)**
  - **Relative Risk (RR)**
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- Application and Discussion of a Research Article
  - Feasibility of treating prehypertension with an angiotensin-receptor blocker. Julius S. *et al. N Engl J Med*. 2006; 354:1685-97

## How to Measure Treatment Effect for Binary Data

There are several measures of a treatment effect (or associations) for binary data. Three most commonly used are:

- Absolute Risk Reduction (ARR)
- Relative Risk Reduction (RR)
- Odds Ratio (OR)

## Absolute Risk Reduction (ARR)

| TROPHY data | Hypertension | | Total |
|---|---|---|---|
| | Yes (% of row) | No | |
| Treatment | 14(11%) | 113 | 127 |
| Placebo | 57(44.5%) | 71 | 128 |
| Total | 71(27.8%) | 184 | 255 |

- Risk of HT is measured by the probability of developing HT: *Pr(HT=Yes).*

  *Pr(HT=Yes|Treated)=11%* *Pr(HT=Yes|Placebo)=44.5%*

- Absolute risk reduction (ARR) measures how much the risk is reduced due to Treatment?

  ARR=44.5% - 11%=33.5%

- If ARR=0, no Trt effect

## Relative Risk (RR)

| TROPHY data | Hypertension | | Total |
|---|---|---|---|
| | Yes (% of row) | No | |
| Treatment | 14(11%) | 113 | 127 |
| Placebo | 57(44.5%) | 71 | 128 |
| Total | 71(27.8%) | 184 | 255 |

- Relative risk (RR) measures how much the risk is reduced due to Treatment relative to Placebo?

$$\text{RR} = \frac{0.11}{0.445} = 0.25$$

- If RR=1, no Trt effect

## Which is a Better Measure: ARR or RR?

- The ARR and RR are sensitive to the magnitude of the proportions:

  Ex 1: ARR=2%-1%=1% (small effect)
  RR=1%/2%=0.5 (big effect)

  Ex 2: ARR=95%-80%=15% (big effect)
  RR=.95/.8=0.84 (small effect)

- Always report both the ARR and the RR

## Odds Ratio(OR)

| TROPHY data | Hypertension | | Total |
|---|---|---|---|
| | Yes (% of row) | No | |
| Treatment | 14(11%) | 113 | 127 |
| Placebo | 57(44.5%) | 71 | 128 |
| Total | 71(27.8%) | 184 | 255 |

- Odds of developing HT are: $ODD = \frac{\Pr(HT=Yes)}{\Pr(HT=No)} = p/1\text{-}p$

  *ODD(Treated)=.11/.89=.124* *ODD(Placebo)=.445/.556=.80*

- Odds Ratio (OR) measures how much the Odds are reduced due to Treatment compared to Placebo.

  $OR = \frac{.124}{.80} = 0.16$ (If OR=1, no Trt effect)

## Odds Ratio(OR)

- OR are useful for measuring the relationship of any variable (Age, Trt) with a binary outcome (HT). They are usually derived using logistic regression
- In short, logistic regression is a statistical modeling technique used to predict the ODDs of HT (or any binary outcome) based on one or more variables

## Modeling OR (log-OR) as a function of other predictors

- Logistic regression model is:

$$\log\left(\frac{\Pr(HT=1)}{1-Pt(HT=1)}\right)= \beta_0+ \beta_1*Trt+ \beta_2*BMI+ \beta_3*X+\ldots$$

- OR(Trt)=$e^{\beta_1}$
  Compares the ODDs of HT between Treatment and Placebo
- OR(BMI)=$e^{\beta_2}$
  How much the ODDs of HT change if BMI increases by 1 (e.g. BMI=27 vs. BMI=26)
- OR(X)=$e^{\beta_3}$=1, implies no relationship between X and Y.

  Q: If X does not relate to Y, what is $\beta_3$?

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  - Relative Risk (RR)
  - Odds Ratio (OR)
- **Application and Discussion of a Research Article**
  - **Feasibility of treating prehypertension with an angiotensin-receptor blocker. Julius S. *et al. N Engl J Med*. 2006; 354:1685-97**

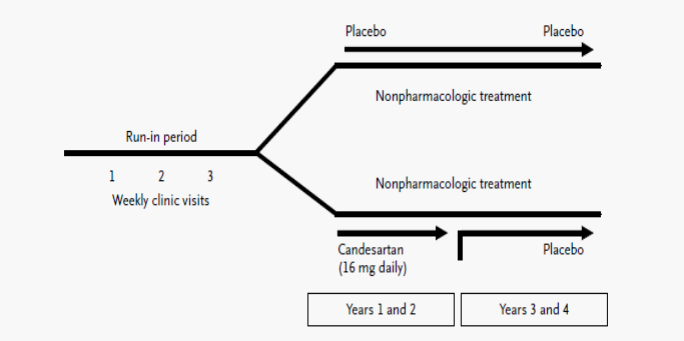
## Application and Discussion of a Research Article*

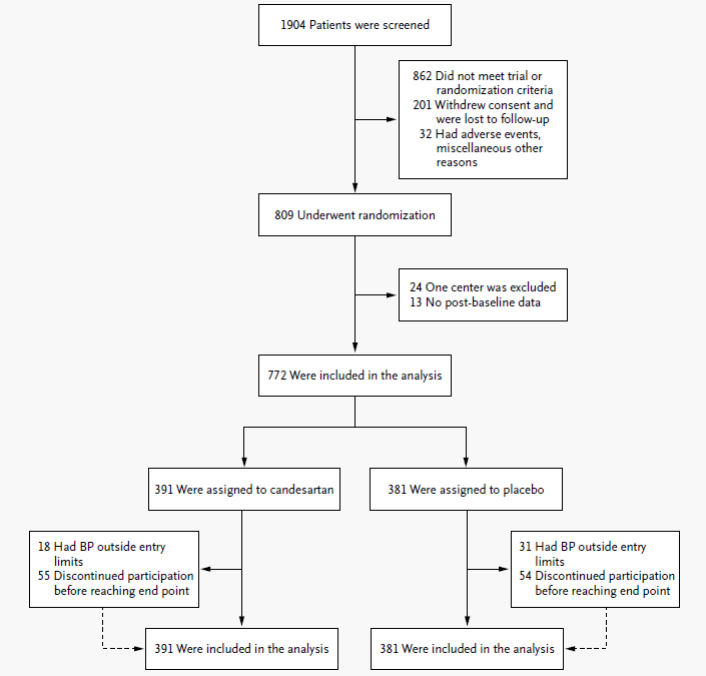
- **Tr**ial **o**f **P**reventing **Hy**pertension (TROPHY Study)
  - **Background:** Hypertension is a strong predictor of excessive cardiovascular risk. TROPHY study investigated whether pharmacologic treatment of prehypertension prevents or postpones hypertension, thus reducing the CV risk.

*Feasibility of treating prehypertension with an angiotensin-receptor blocker. Julius S. *et. al. N Engl J Med*. 2006; 354:1685-97

# TROPHY Study

- **Objective:** The primary hypothesis of the study was to determine whether two years of treatment with candesartan reduces the incidence of hypertension two years after treatment and 2 years after discontinuation of treatment.



# Characteristics of the Study Population

**Table 1. Baseline Characteristics of the Study Participants.***

| | Candesartan Group (N=391) | Placebo Group (N=381) |
|---|---|---|
| Age — yr | 48.6±7.9 | 48.3±8.2 |
| Male sex — no. (%) | 231 (59.1) | 229 (60.1) |
| Race — no. (%)† | | |
| White | 312 (79.8) | 321 (84.3) |
| Black | 48 (12.3) | 31 (8.1) |
| Other | 31 (7.9) | 29 (7.6) |
| Weight — kg | 89.0±17 | 88.8±17.7 |
| Body-mass index‡ | 29.9±5.1 | 30.0±5.5 |
| Blood pressure — mm Hg | | |
| Measured at clinic visit with automated device§ | 133.9±4.3/84.8±3.8 | 134.1±4.2/84.8±4.1 |

# Main Results of the Study

**Table 2. Incident Hypertension and Incidence of Serious Adverse Events.***

| | Candesartan Group (N=391) | Placebo Group (N=381) | P Value | Relative Risk (95% CI) |
|---|---|---|---|---|
| **New-onset hypertension** | | | | |
| No. of participants in whom hypertension developed | 208 | 240 | | |
| Hypertension at year 2 visit — % | 13.6 | 40.4 | <0.001† | 0.34 (0.25–0.44) |
| Hypertension at year 4 visit — % | 53.2 | 63.0 | 0.007† | 0.84 (0.75–0.95) |
| Hypertension during study period | | | <0.001‡ | 0.58 (0.49–0.70) |
| Clinical criteria for end-point determination | | | | |
| BP at three clinic visits, ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%) | 142 (36) | 168 (44) | 0.03† | 0.82 (0.69–0.98) |
| BP at any clinic visit ≥160 mm Hg systolic, ≥100 mm Hg diastolic, or both — no. (%) | 15 (3.8) | 19 (5.0) | 0.49† | 0.77 (0.40–1.49) |
| BP requiring pharmacologic treatment — no. (%) | 45 (12) | 48 (13) | 0.66† | 0.91 (0.62–1.34) |
| BP at month 48 clinic visit ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%) | 6 (1.5) | 5 (1.3) | >0.99† | 1.17 (0.36–3.80) |

# Main Results of the Study

| | Candesartan Group (N=391) | Placebo Group (N=381) | P Value | Relative Risk (95% CI) |
|---|---|---|---|---|
| **New-onset hypertension** | | | | |
| No. of participants in whom hypertension developed | 208 | 240 | | |
| Hypertension at year 2 visit — % | 13.6 | 40.4 | <0.001† | 0.34 (0.25–0.44) |
| Hypertension at year 4 visit — % | 53.2 | 63.0 | 0.007† | 0.84 (0.75–0.95) |

| At 2 Years | Hypertension | | Total |
|---|---|---|---|
| | Yes(row %) | No | |
| Candesartan | 53(13.6%) | 338 | 391 |
| Placebo | 154(40.4%) | 227 | 381 |
| Total | 207 | 565 | 772 |

ARR at 2 years: 40.4-13.6=26.8%  RR at 2 years: .136/.404=.34

# Main Results of the Study

| | Candesartan Group (N=391) | Placebo Group (N=381) | P Value | Relative Risk (95% CI) |
|---|---|---|---|---|
| **New-onset hypertension** | | | | |
| No. of participants in whom hypertension developed | 208 | 240 | | |
| Hypertension at year 2 visit — % | 13.6 | 40.4 | <0.001† | 0.34 (0.25–0.44) |
| Hypertension at year 4 visit — % | 53.2 | 63.0 | 0.007† | 0.84 (0.75–0.95) |

| At 4 Years | Hypertension | | Total |
|---|---|---|---|
| | Yes(row %) | No | |
| Candesartan | 208 (53.2%) | 183 | 391 |
| Placebo | 240(63.0%) | 141 | 381 |
| Total | 448 | 324 | 772 |

ARR at 4 years: 63.0-53.2=9.8%  RR at 4 years: 53.2/63.0=.84

## Cumulative Incidence of HT by Treatment Group

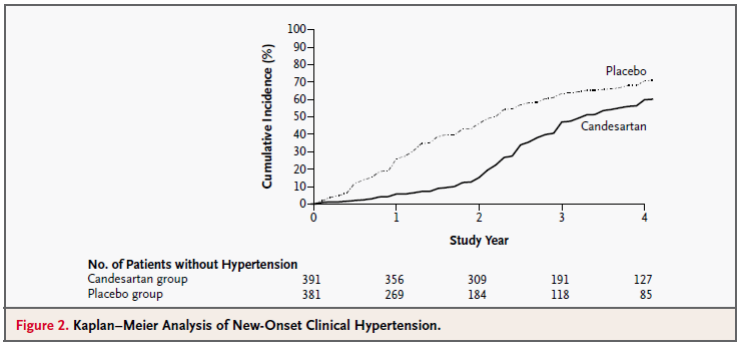
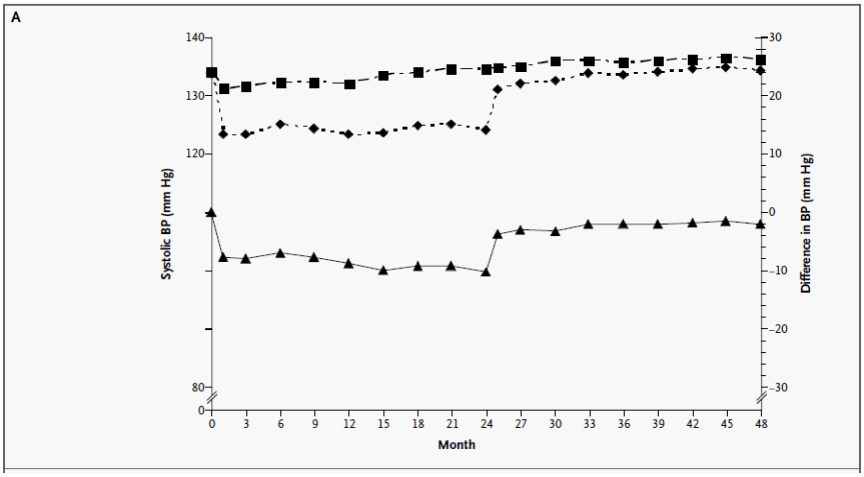



Figure 2. Kaplan–Meier Analysis of New-Onset Clinical Hypertension.

Kaplan-Meier Analysis shows if the overall cumulative incidence of HT is different between groups over time. It gives the full picture on the development of HT over the 4 year follow-up.

Note: Cumulative incidence is calculated as 100% - K-M curve

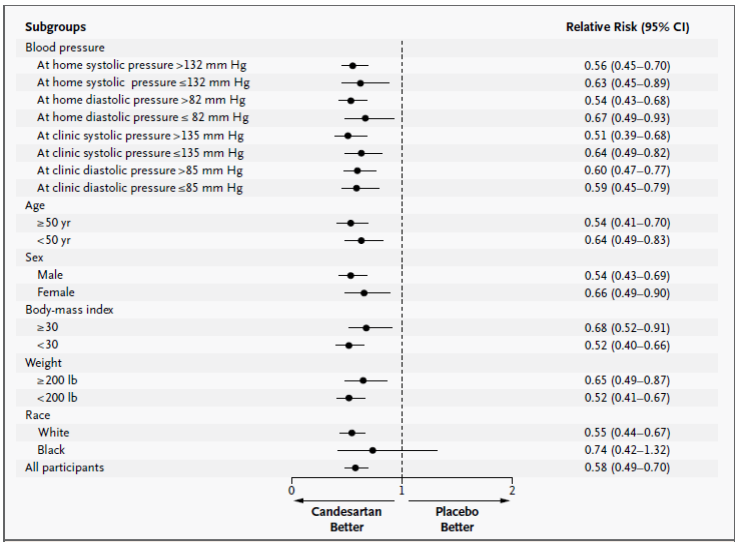
## SBP Values Over 4 Years




SBP curve (mean of SBP at each visit) over 4 years

Two-ample t-test: Showed 2.0 mm Hg (p=0.037) decrease in SBP at year 4 due to Candesartan

## Subgroup Analysis: Does Candesartan work the same way for different subgroups



| Subgroups | Relative Risk (95% CI) |
|---|---|
| Blood pressure | |
| At home systolic pressure >132 mm Hg | 0.56 (0.45–0.70) |
| At home systolic pressure ≤132 mm Hg | 0.63 (0.45–0.89) |
| At home diastolic pressure >82 mm Hg | 0.54 (0.43–0.68) |
| At home diastolic pressure ≤ 82 mm Hg | 0.67 (0.49–0.93) |
| At clinic systolic pressure >135 mm Hg | 0.51 (0.39–0.68) |
| At clinic systolic pressure ≤135 mm Hg | 0.64 (0.49–0.82) |
| At clinic diastolic pressure >85 mm Hg | 0.60 (0.47–0.77) |
| At clinic diastolic pressure ≤85 mm Hg | 0.59 (0.45–0.79) |
| Age | |
| ≥50 yr | 0.54 (0.41–0.70) |
| <50 yr | 0.64 (0.49–0.83) |
| Sex | |
| Male | 0.54 (0.43–0.69) |
| Female | 0.66 (0.49–0.90) |
| Body-mass index | |
| ≥30 | 0.68 (0.52–0.91) |
| <30 | 0.52 (0.40–0.66) |
| Weight | |
| ≥200 lb | 0.65 (0.49–0.87) |
| <200 lb | 0.52 (0.41–0.67) |
| Race | |
| White | 0.55 (0.44–0.67) |
| Black | 0.74 (0.42–1.32) |
| All participants | 0.58 (0.49–0.70) |



## Summary Points

Tests for Comparing Proportions: $H_0$: $p_1 = p_2$ vs. $H_A$: $p_1 \neq p_2$

| Statistical test | Used when |
|---|---|
| • Two-sample normal theory test<br>– $z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}\,(1-\hat{p})(\frac{1}{n_1}+\frac{1}{n_2})}}$ | $n_1\hat{p}_1(1-\hat{p}_1) > 5$<br>$n_2\hat{p}_2(1-\hat{p}_2) > 5$ |
| • Chi-square test<br>– Use $\chi^2_k$ where k=(nrow-1) x (ncol-1) | n > 5 in all cells |
| • Fisher's exact test<br>– Calculates the exact p-value | n is small and the other two tests does not apply |

## Summary Points

Measure of association (treatment effect) for Dichotomous Outcomes.
"Risk" is defined as: *Pr(Y=Yes)=p, ($p_1$ is for treatment, $p_2$ is for control)*

| Measure of association | Interpretation |
|---|---|
| • Absolute Risk Reduction (ARR) | |
| – ARR $= p_2 - p_1$ | (ARR=0 do not reject $H_0$: $p_1 = p_2$) |
| • Relative Risk (RR) | |
| – RR $= \frac{p_1}{p_2}$ | (RR=1 do not reject $H_0$: $p_1 = p_2$) |
| • Odds Ratio (OR) | |
| – ODDs $= \frac{\Pr(Y=1)}{\Pr(Y=0)} = \frac{p}{1-p}$ | |
| – OR $= \frac{ODDs(Trt)}{ODDS(Control)} = \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$ | (OR=1 do not reject $H_0$: $p_1 = p_2$ |