# 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
  - $X_i \sim$ Bernoulli(p)
  - Y= $\sum_{i=1}^{n} X_i$

$$Y \sim Bin(n, p)$$

- 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?

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$$E(Y)=np=?$$

# 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:

$$Var(Y)=np(1-p)$$

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

# 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:

$$Var(Y)=np(1-p)=100 \times 0.5 \times 0.5=25$$

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

# 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*?

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- 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 $\overline{Y}$:

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

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

# Which of These Variables Would Have a Binomial Distribution?

- Number of female students in this class given the total number of students

- BMI of 100 people

- Number of people with BMI ≥ 30 kg/m2

# 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

- Number of people with BMI ≥ 30 kg/m2

# 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

# 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

# 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)
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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 | No | |
| Treatment | 14 | 113 | 127 |
| Placebo | 57 | 71 | 128 |
| Total | 71 | 184 | 255 |

# 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:

$$H_0\colon\ p_1 = p_2$$

Vs.

$$H_A\colon\ p_1 \neq p_2$$

# 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

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

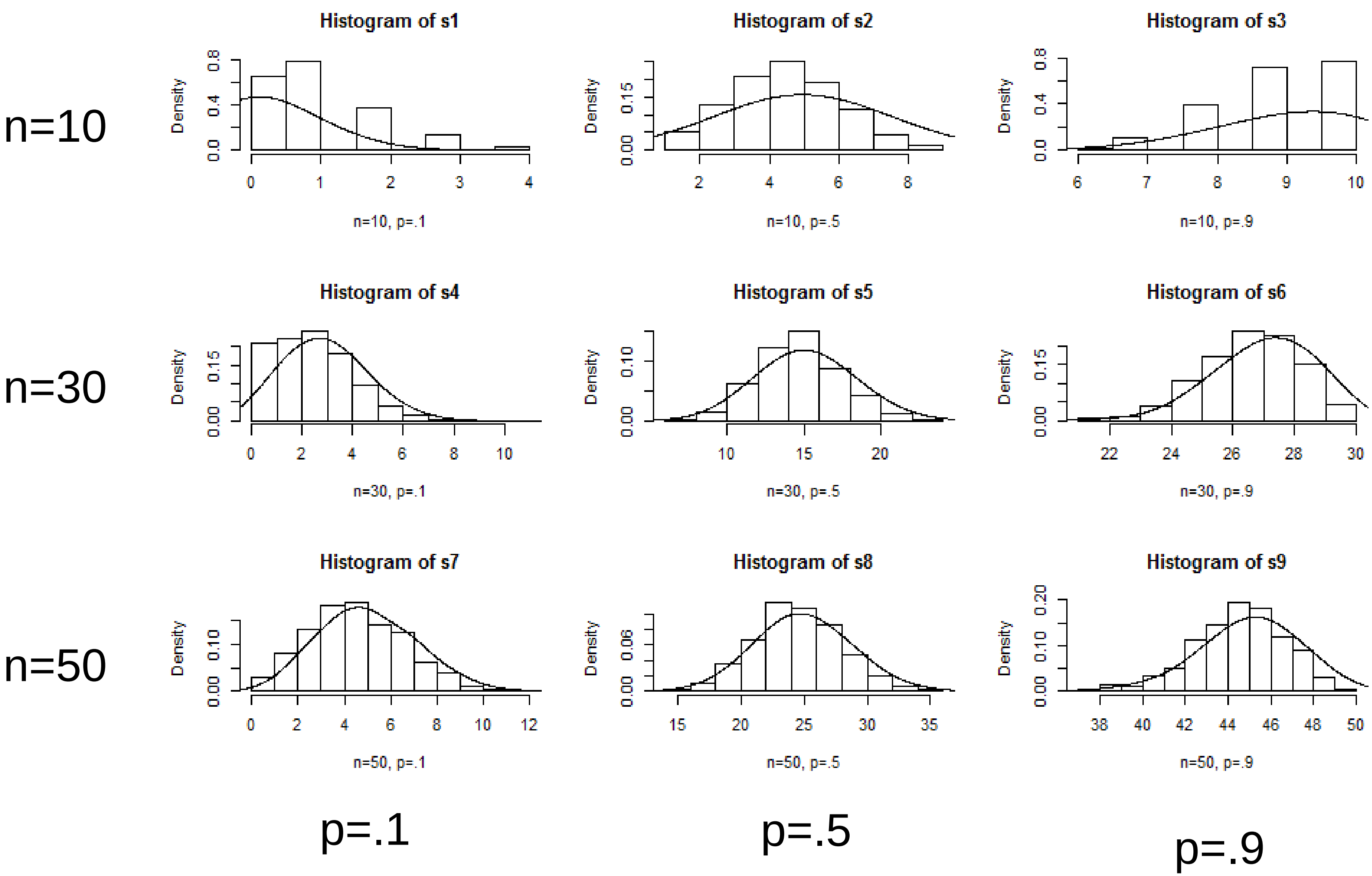
- Chi-Square test

  - 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)

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

p-value=2.52 x $10^{-9}$, 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 | 113 | 127 |
| Placebo | 57 | 71 | 128 |
| Total | 71 | 184 | 255 |

Cell % relative to the overall n=255

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

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

| | Hypertension | | Total |
|---|---|---|---|
| | Yes | No | |
| Treatment | 14(5.5%) | 113(44.3%) | 127 |
| Placebo | 57(22.4%) | 71(27.8%) | 128 |
| Total | 71 | 184 | 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 | ? | | 49.8% |
| Placebo | ? | | 50.2% |
| Total | 27.8% | 72.2% | 255(100%) |

Marginal proportions are fixed.

Q: What proportion of the total sample is expected in each cell (when $H_0$ is true)?

# 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% | 255(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?

# 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 | | | 128 |
| Total | 71 | 184 | 255 |

# 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 |

# 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

# 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

# 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 | | | 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 |

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

# 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 <u>same or less likely</u> 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 |

# 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 |

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

Treatment row: 1 combination
Placebo row: ? combinations

Total: 1*?=? Tables

# 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 |

| 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 |

Treatment row: 1 combination
Placebo row: 4 combinations

Total: 1*4=4 Tables

| 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

# 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

# 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 (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)

| 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 Reduction (RRR)

| 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?

# 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)

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| | | |
|---|---|---|
| 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) |

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| 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-p*

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

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- 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 <u>or more</u> 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 $\beta_3$?

# 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**

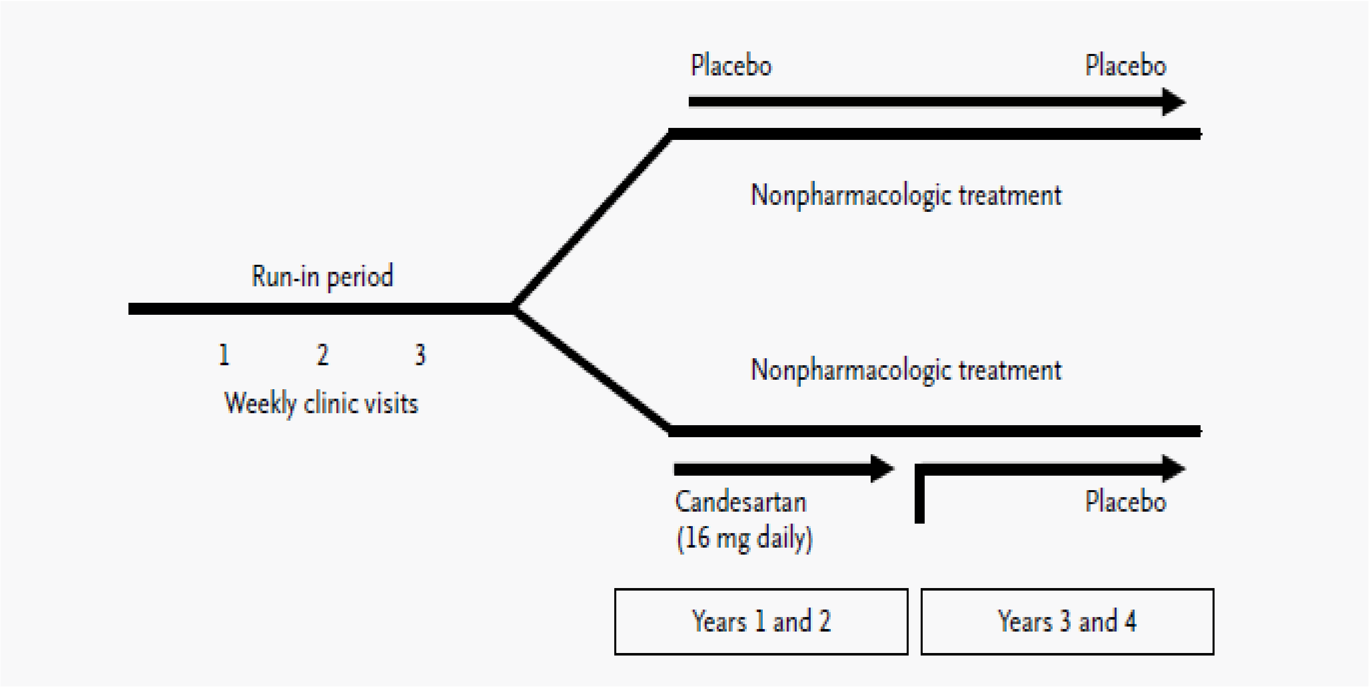
# Application and Discussion of a Research Article*

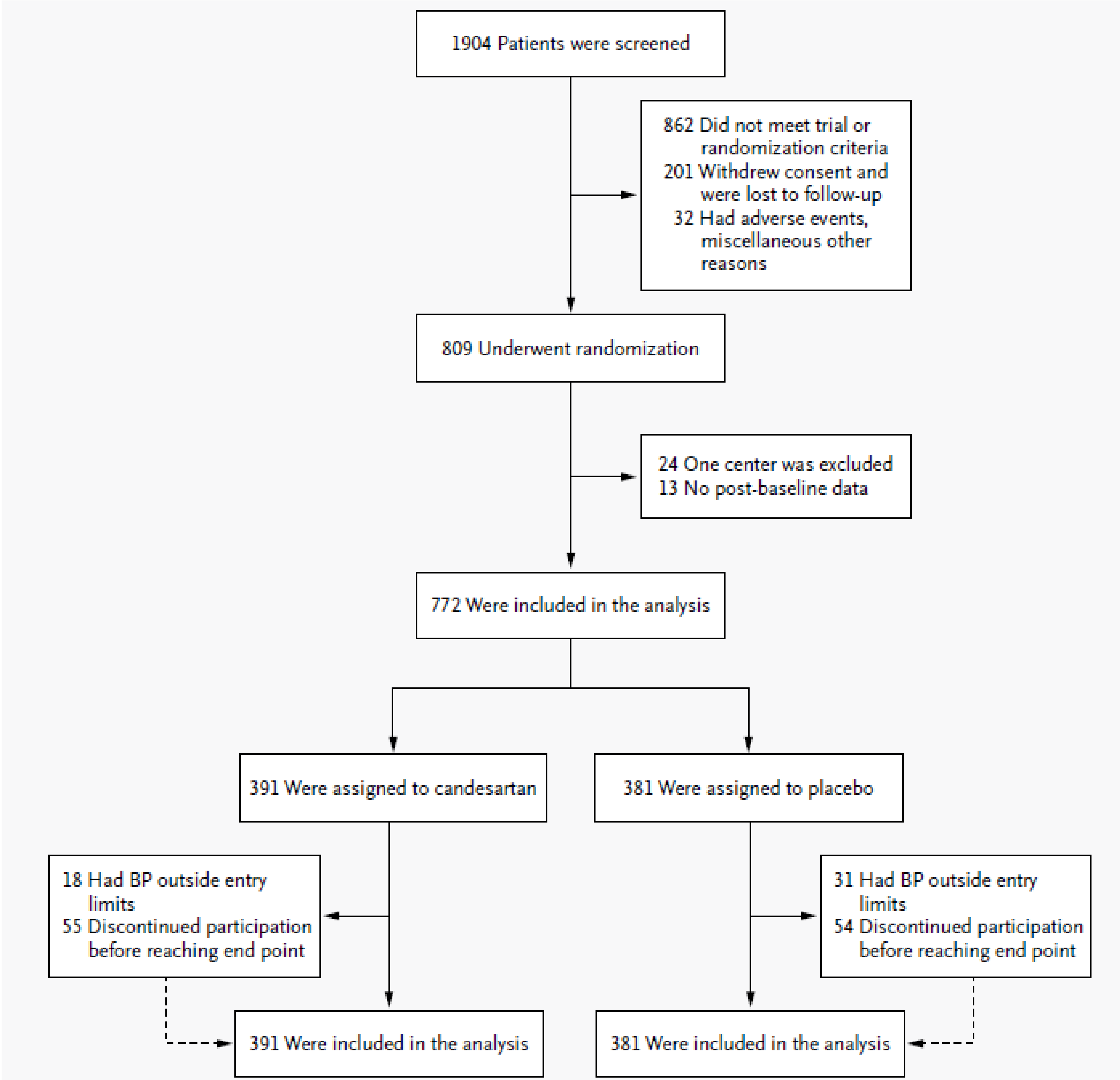
- **Tr**ial **of P**reventing **Hy**pertension (TROPHY Study)
  - **Background:** Hypertension is a strong predictor of excessive cardiovascular risk. TROPHY study investigated whether pharmacologic treatment of prehypertension prevents or postpones hypertension, thus reducing the CV risk.

*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 <u>and</u> 2 years <u>after discontinuation</u> of treatment.




1904 Patients were screened
862 Did not meet trial or randomization criteria
201 Withdrew consent and were lost to follow-up
32 Had adverse events, miscellaneous other reasons
809 Underwent randomization
24 One center was excluded
13 No post-baseline data
772 Were included in the analysis
391 Were assigned to candesartan
381 Were assigned to placebo
18 Had BP outside entry limits
55 Discontinued participation before reaching end point
31 Had BP outside entry limits
54 Discontinued participation before reaching end point
391 Were included in the analysis
381 Were included in the analysis

# 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) |

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| At 2 Years | Hypertension | | Total |
|---|---|---|---|
| | Yes(row %) | No | |
| Candesartan | 13.6% | | 391 |
| Placebo | 40.4% | | 381 |
| Total | | | 772 |

ARR at 2 years: 40.4-13.6=26.8%

RR at 2 years: .136/.404=.34

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| 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%

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# Main Results of the Study

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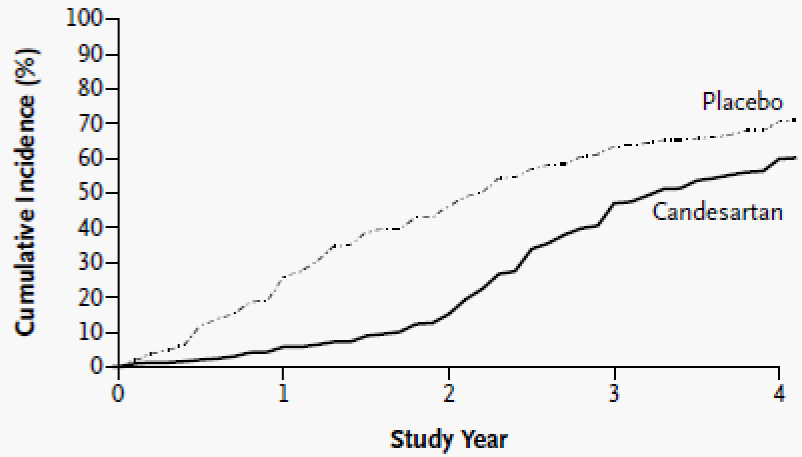
| At 4 Years | Hypertension | | Total |
|---|---|---|---|
| | Yes(row %) | No | |
| Candesartan | 208 (53.2%) | 183 | 391 |
| Placebo | 240(63.0%) | 141 | 381 |
| Total | 448 | 324 | 772 |

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




**No. of Patients without Hypertension**

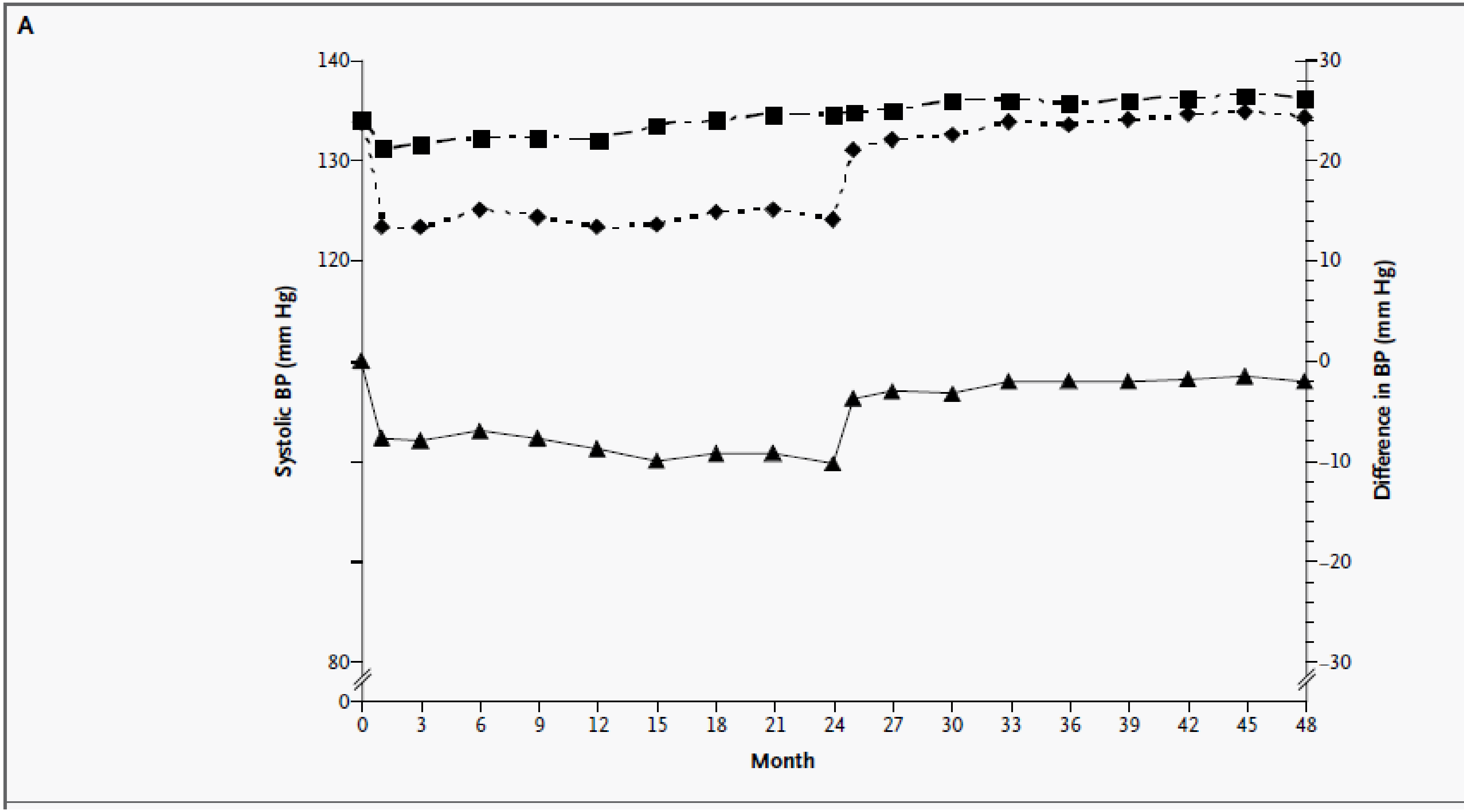
| | | | | | |
|---|---|---|---|---|---|
| Candesartan group | 391 | 356 | 309 | 191 | 127 |
| Placebo group | 381 | 269 | 184 | 118 | 85 |

**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 <u>over time</u>. 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

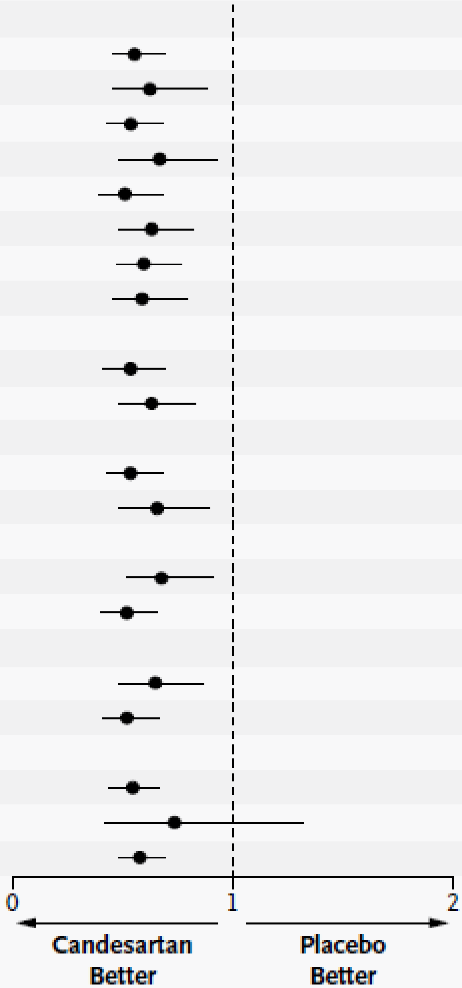



SBP curve (mean of SBP at each visit) over 4 years

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*)*

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