THERAPY

Daniella Zipkin MD
Duke

Ken Goldberg MD
Orlando VA
University of Central Florida

Teaching and Leading Evidence-Based Medicine
Duke University Medical Center
March 12, 2013

Objectives

- State validity criteria for randomized controlled trials (RCTs) and the reasoning behind them

- Critically appraise an article about an intervention

- Define absolute and relative risk reductions

- Model large group teaching

ACQUIRE

ASK

APPRAISE

APPLY

ASSESS

A Clinical Question

- Has this ever happened to you?

- Your buddy, we'll call him "Ken", is back in town from Florida. You're excited to go out for some Carolina barbecue to celebrate – pulled pork and hush puppies!

- Ken was thinking along the lines of seafood and veggies…

- Sad face ☹

About Olive Oil

- **Extra Virgin Olive Oil** - The acidity of Extra Virgin olive oil can be no more than 1%, or 1 gram acid per 100 grams oil. The IOOC (International Olive Oil Council states that Extra Virgin Olive Oil must not contain more than .8% acidity.)

- **Virgin Olive Oil** - Virgin olive oil can have an acidity of no more than 2%.

- **Ordinary Virgin Olive Oil** – Ordinary Virgin olive oil can have an acidity of no more than 3.3%. Only sold in Spain to wholesalers.

The Food Crisis

- Let's frame that in PICO format!
- P = population
- I = intervention/exposure
- C = comparison/control
- O = outcome
- TT = type of question, type of study

What kind of study do we want?

P

I

C

O

For EBM enthusiasts, how does a Mediterranean diet compare to a North Carolina diet for overall happiness, inner peace, and perhaps cardiovascular health?
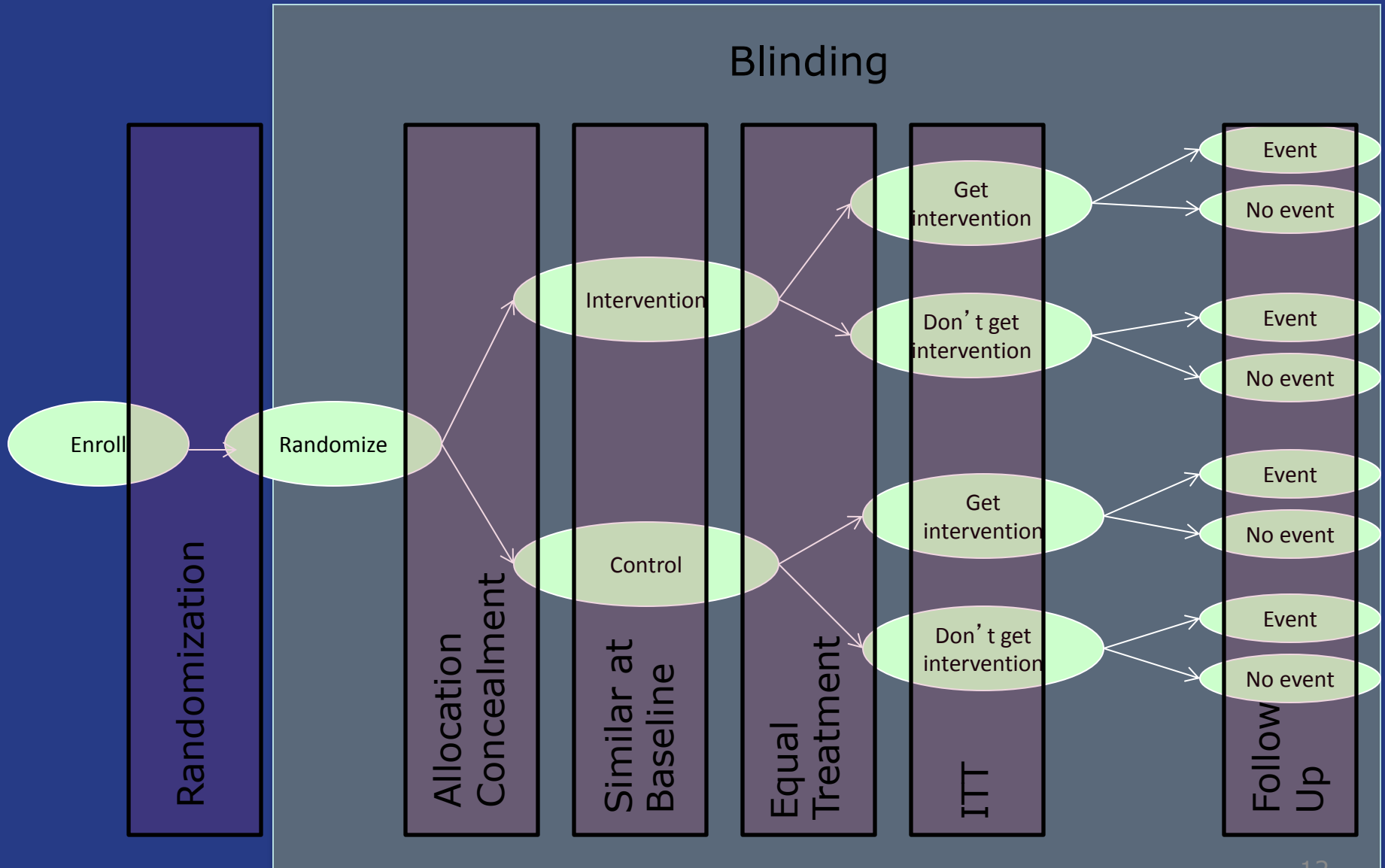
Anatomy of an RCT

Denise Campbell-Scherer, Tom Owens

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Validity Criteria

User's Guides for an Article About Therapy:
Are the Results Valid?

1. Did the intervention and control groups start with the same prognosis?
   - a. Were patients randomized?
   - b. Was randomization concealed?
   - c. Were patients in the study groups similar with respect to known prognostic factors?
2. Was prognostic balance maintained as the study progressed?
   - a. To what extent was the study blinded?
   - b. Aside from the experimental intervention, were the groups treated equally?
3. Were the groups prognostically balanced at the study's completion?
   - a. Was follow up complete?
   - b. Were patients analyzed in the groups to which they were randomized? (i.e., was it an intention-to-treat analysis?)
   - c. Was the trial stopped early?

Validity Criteria, cont.

What are the results?

    1. How large was the treatment effect?

    2. How precise was the estimate of the treatment effect?

How can I apply the results to patient care?

    3. Were the study patients similar to my patient?

    4. Were all patient-important outcomes considered?

    5. Are the likely treatment benefits worth the potential harms and costs?

Prognosis at the beginning

- Randomization

- Allocation concealment

- Similar at baseline

Randomization

- Spread confounding variables evenly across the groups

- Increase likelihood that the intervention is the only difference between groups

Allocation Concealment

- Investigator cannot influence the allocation at the time of study entry

- RCTs lacking a statement about allocation concealment are associated with larger effect-size bias (33% if unclear, 41% if not done)

- Not typically done (55% of RCTs in "best" journals, 7% of RCTs in "poorer" journals)

JAMA 1995;273:408-412.   Lancet 1998; 352:609-13.
BMJ 2004 3;328:22-4. ACP J Club. 2000 Mar-Apr;132:A11

Similar at Baseline

- Known prognostic factors should be balanced between groups.
  - ➢ Typically "Table 1"

- Bonus point: Does Table 1 need to have p values?
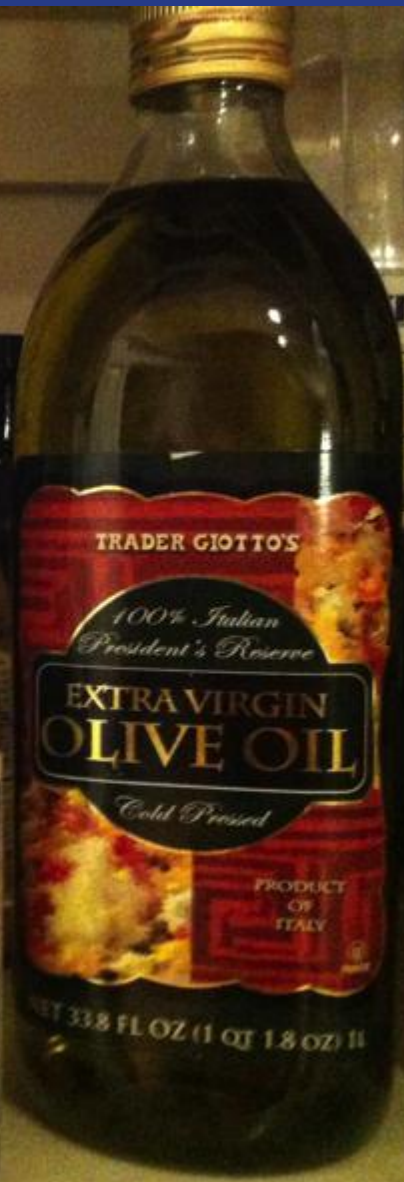
Prognosis in the middle

- Blinding

- Equal treatment

Blinding

- Prevents biased outcomes
- Whom shall we blind?
  - ➢ Subjects
  - ➢ Clinicians
  - ➢ Data collectors
  - ➢ Outcome adjudicators
  - ➢ Data analysts

Equal Treatment

- The experimental intervention should be the only thing that differs between groups.

- Any other factor which differs systematically between groups is called a "co-intervention", and may obscure true results.

What if…

- The Mediterranean diet group receives 30 minute massages right after the nutrition visits?

- Was it the diet itself, or the pampering that helped people change?

Prognosis at the end

- Follow up complete

- INTENTION TO TREAT!

- Trials stopped early

Follow-up Complete

- Loss of subjects creates missing data, which threatens the balance of randomization

- Those lost may have different prognosis than those who stayed

- Methods for managing missing data vary in strength

Food for thought…

- What can we say about the people who don't stick around?

Intention to Treat

- **Analyzed in the groups to which they were randomized**

- **Even if they didn't get the intervention!!**

- Don't allow cross-over

  ➢ It introduces bias – why did some crossover? Why did others not?

- "Effectiveness"

- Euphemisms for breaking ITT: "per protocol analysis", "as treated analysis", "efficacy analysis"
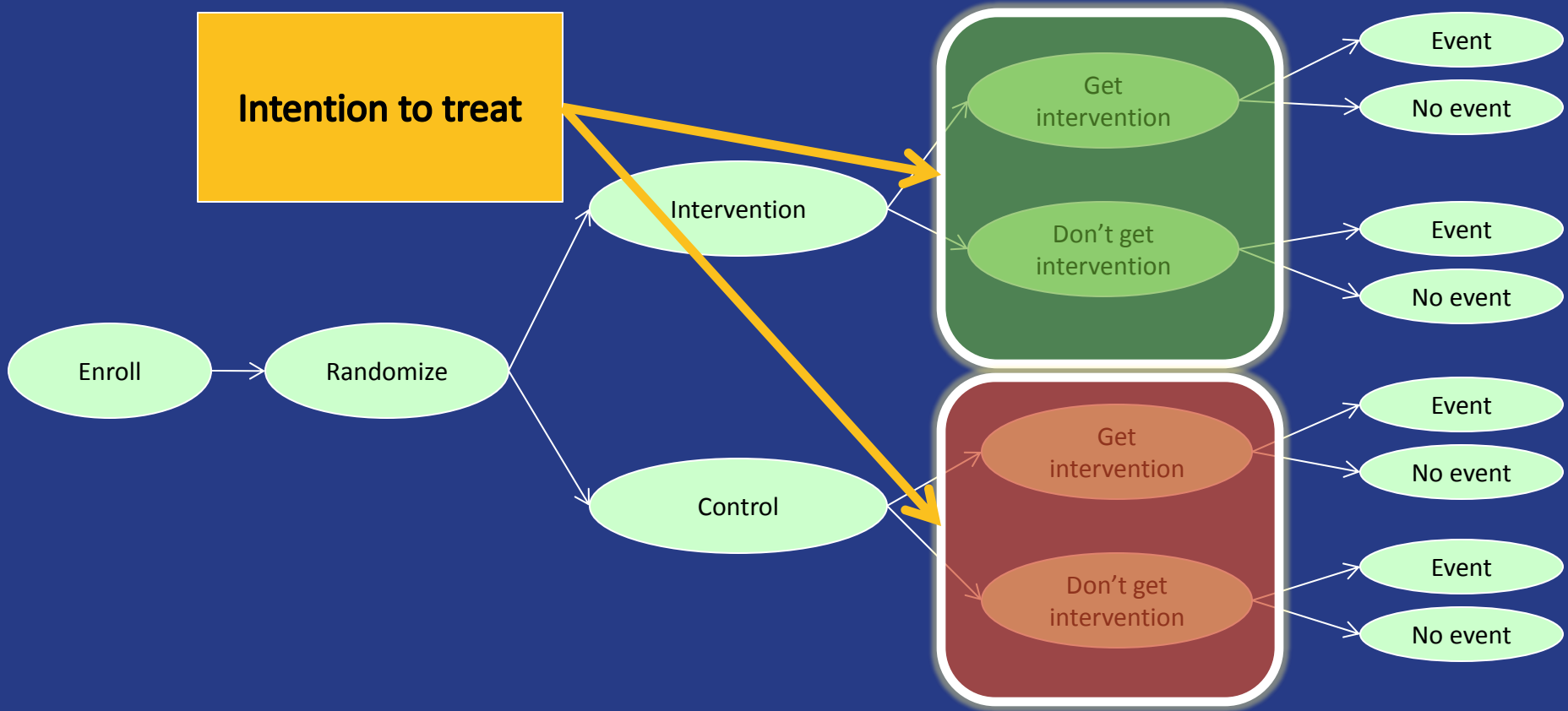
Intention to Treat
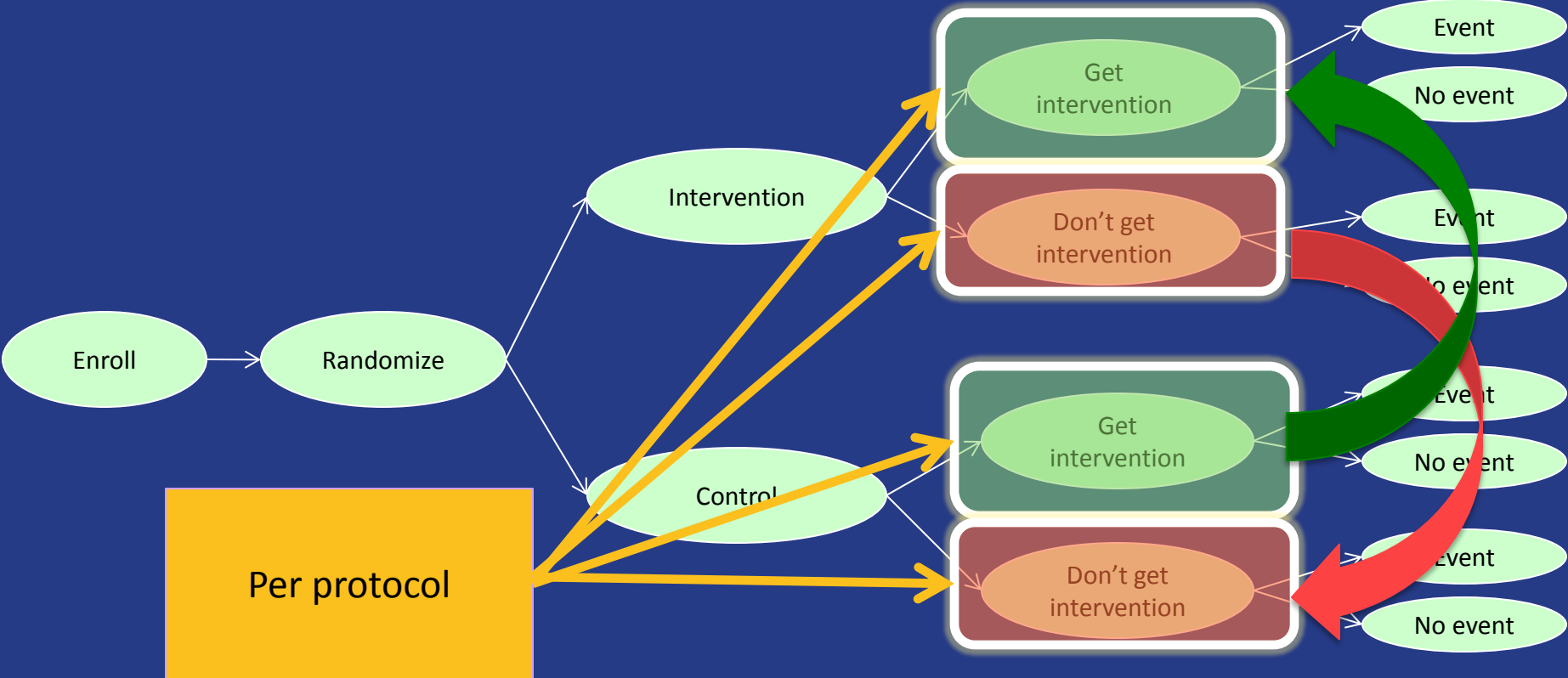
- What ca[n]   [e]rs" who
  crash the
  randomi

- How doe   [if] you
  analyze t   group?

Trials Stopped Early

- Fewer observed outcomes

- Greater chance of random error

- Truncating RCTs accounts for differences in effect size, in a systematic review

- Magnitude is greatest with fewer than 500 outcome events

Bassler et al. JAMA 2010;303(12):1180-1187

You are now leaving Validity and entering….

THERAPY MATH!!!

How are results presented?

- **RISK** = events or outcomes
- **Absolute Risk** = proportion of group with an outcome = event rate
- For example:
  - ➢ *100 pre-schoolers were randomized to drug A for prevention of nose picking. 15 kids still pick their noses.*
  - ➢ *100 pre-schoolers were randomized to new drug B. 10 kids are still digging for gold.*

Absolute Risk

- Drug A: event rate is 15%

- Drug B: event rate is 10%

- **There are only two things we can do to these numbers: (1) <u>Subtract</u>, or (2) <u>Divide</u>**

Subtract

- 15% **-** 10% = 5%

- What is this number?

- **Absolute Risk Reduction (ARR)**

Divide

- 10% ÷ 15% = 0.67

- What do we call this number?

- **Relative Risk (RR)**
- **Synonym = Risk Ratio**

Relative Risk *Reduction (1)*

- **RRR = 1 − RR**
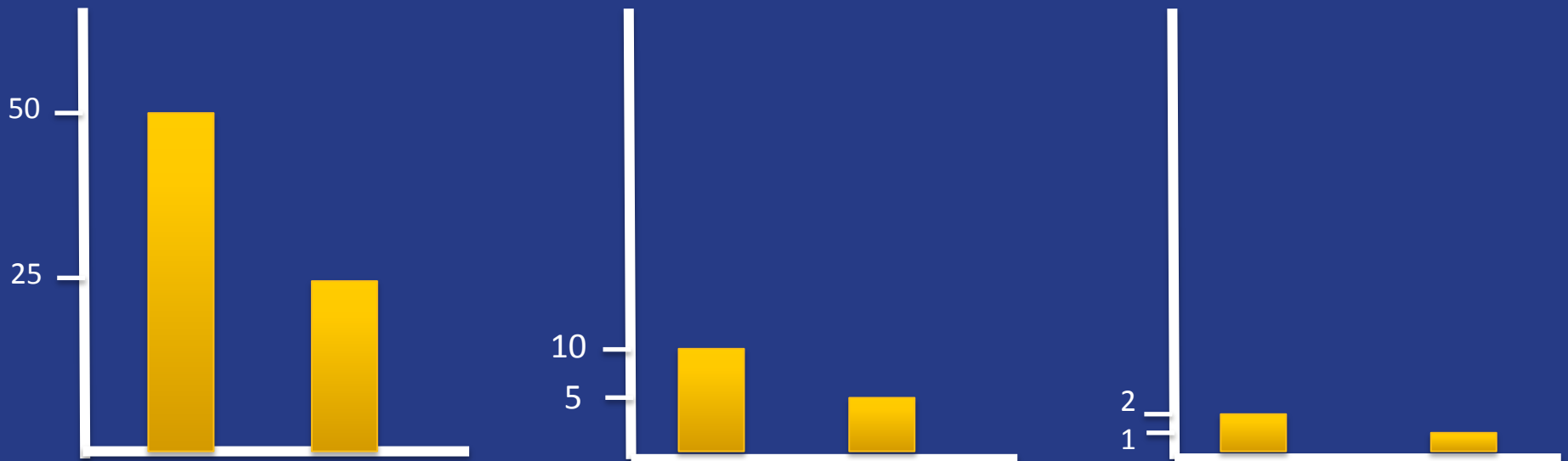

- RRR = 1 − 0.67 = 0.33 = 33%

Relative Risk *Reduction (2)*

- **"What proportion of our baseline risk have we reduced?"**
- **RRR = ARR/baseline risk**

- RRR = 5%/15% = 33%
- Remember, the ARR was 5%
- Which one is more impressive?

Relative Risk *Reduction (3)*

- Did you catch that?

- RRR = 1 − RR

- And...

- RRR = ARR/baseline risk

ARR vs. RRR

ARR:	**25%**	**5%**	**1%**
RRR:	**50%**	**50%**	**50%**

Number Needed to Treat (NNT)

NNT = 1/ARR   **(why?)**

If ARR = 5%...

Treating 100
people reduces
outcome in 5;
How many do I
treat to help 1?

| 100 | ⟶ | 5 |

| ? | ⟶ | 1 |

Answer: 20

So, where should Dani and Ken eat?

Show of hands:

A: "The Pit" NC barbecue, Raleigh
   (whole hog, "from the snooter to the tooter")

B: "Parizade", a lovely Mediterranean restaurant in Durham

Let's look at the paper…
20 min

- See the pre-marked article in your binder (disclaimer: no RCTs use the NC diet! ☹)

- What is the PICO-TT?

- Three groups:

  (1) Prognosis at the beginning

  (2) Prognosis in the middle

  (3) Prognosis at the end

- All: calculate the ARR, and compare to RRR (for diet #1, extra virgin olive oil - EVOO)

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**Let's calculate the Absolute
Risk Reduction...**

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
Person-yr of follow-up	11,852	10,365	9763
Primary end point‡			
No. of events	96	83	109
Crude rate/1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)

	CV event	No event	
Mediterranean Diet with EVOO	96	2447	2543
Control	109	2341	2450

Absolute Risk (AR) medi diet = 96/2543 = 3.78%
Absolute Risk (AR) control diet = 109/2450 = 4.45%

ARR = $\boxed{\text{AR1} - \text{AR2}}$ **= 4.5% - 3.8% = 0.7%**

RR (Relative Risk) = $\boxed{\text{AR2/AR1}}$ **= 3.8%/4.5% = 0.84**

Baseline risk was 4.5%

RRR = ARR/baseline risk = 1 − RR = 0.7%/4.5% = 1 − 0.84 = 16%

Hey, dudes, your numbers do not match what they got in the paper…

It's ok! They used patient years, and we are just using….. patients.

And, there are hazard ratios – discussion of these is best left to the small groups.

RESULTS

A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.

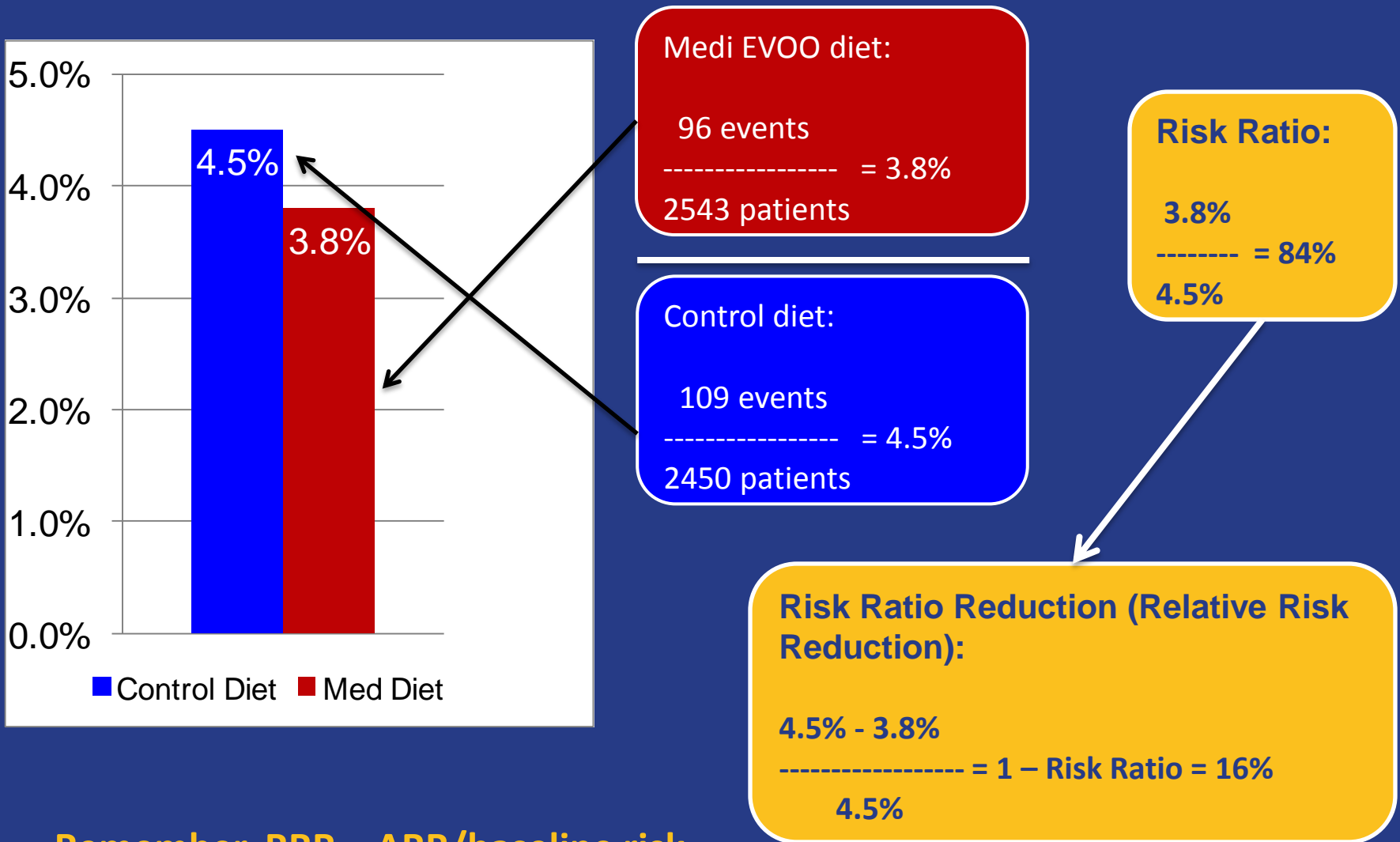# So, how powerful is this intervention?

Absolute Risk Reduction= 0.7%

Number Needed to Treat (NNT) = 1/ARR = 1/0.007 = 143 people

"We need to give 143 high-risk people the Mediterranean diet with extra virgin olive oil for five years to prevent one of the cardiovascular events"

Pssssst…….

By the way, the outcome was a composite of multiple cardiovascular events, but the numbers were driven mostly by strokes….

Risk of Cardiovascular Events

5.0%
4.0%
3.0%
2.0%
1.0%
0.0%

4.5%   3.8%

■ Control Diet ■ Med Diet

Medi EVOO diet:

96 events
----------------- = 3.8%
2543 patients

Control diet:

109 events
----------------- = 4.5%
2450 patients

Risk Ratio:

3.8%
-------- = 84%
4.5%

Risk Ratio Reduction (Relative Risk Reduction):

4.5% - 3.8%
----------------- = 1 – Risk Ratio = 16%
      4.5%

Remember, RRR = ARR/baseline risk

Absolute vs. Relative Risk
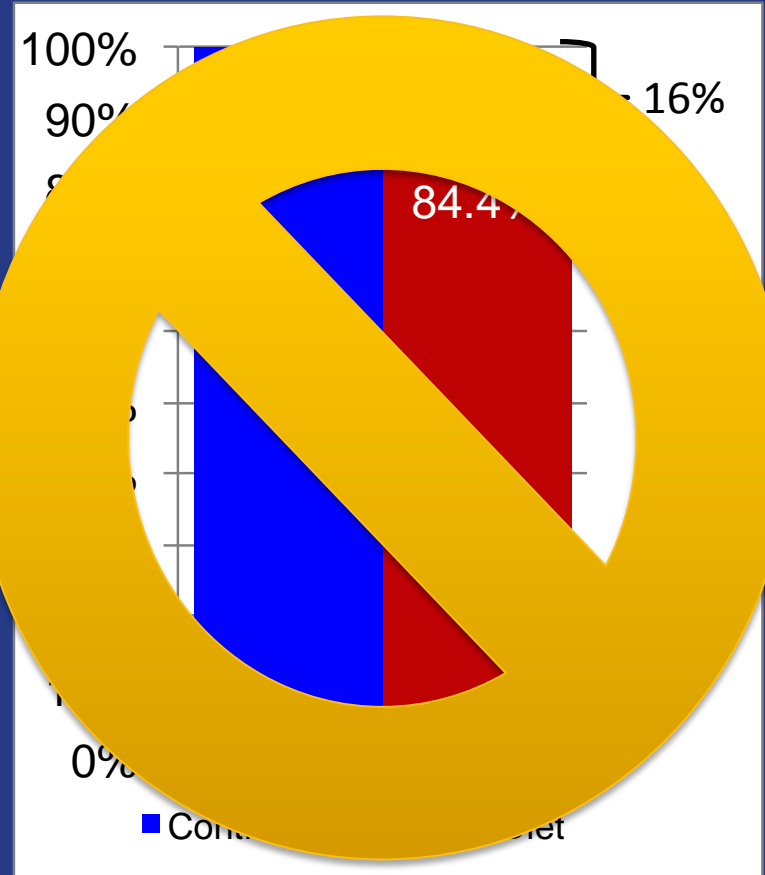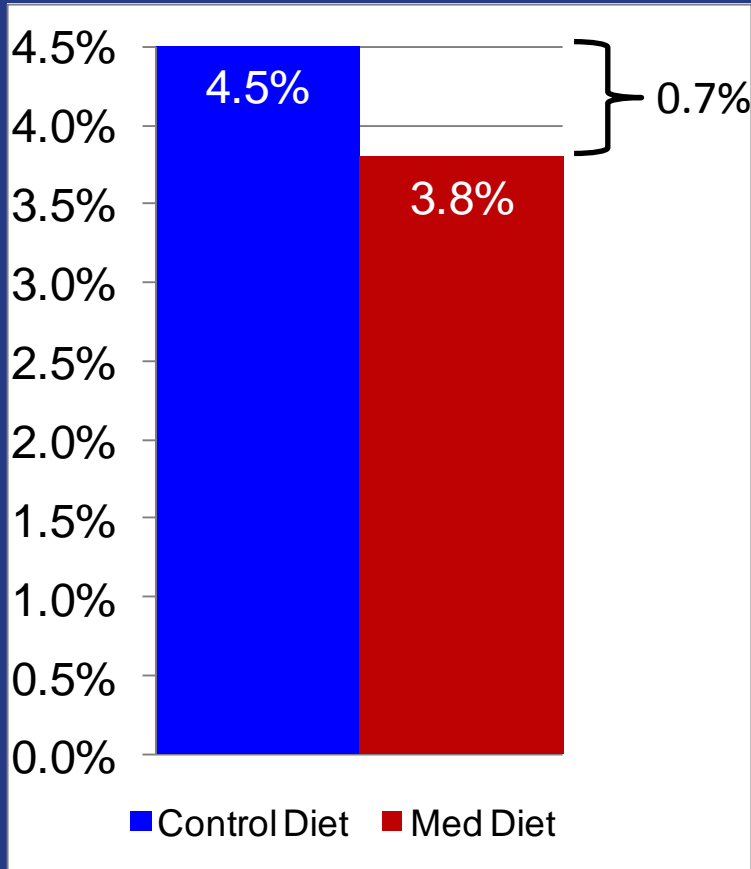
So…..

- Will this evidence change what you recommend to patients?

Debrief/Questions

- Concepts
  - ➤ RCT Validity
  - ➤ Risk reduction/Number needed to treat
- Teaching Techniques:
  - ➤ Funny examples
  - ➤ Real-time validity review
  - ➤ Small groups
  - ➤ Multiple methods for expressing a concept

Other topics….

- Inappropriate comparators

- Surrogate outcomes

- Composite outcomes

- Sub-group analysis

- Clinical vs. statistical significance

- Non-inferiority designs