PALMER College of Chiropractic

THERAPY UNIT

Prevention of Diabetes with Lifestyle Modification or Metformin

Objectives:

In this session the learner will:

1. Assess the validity of a therapy paper.
2. Determine the clinical importance of the results of a valid therapy paper.
3. Compare and contrast the differences in clinical application of RRR and ARR.
4. Address how valid and important results from a therapy paper can be applied to our patient.
5. Consider the implications of terminating studies early for benefit.

Assignment:

Review the clinical scenario and the enclosed paper and decide:

1. Are the results of this therapy article valid?
2. Are the results of this therapy study important?
3. Can we apply this valid, important evidence about this therapy in caring for our patient?

Clinical Scenario:

A 48 year old female comes in for her annual exam. Her older brother was recently diagnosed with Type II diabetes and her father has Type II diabetes. She currently doesn't watch what she eats, and has at least 2 – 3 candy bars a day at work and doesn't pay attention to portion size. She eats cookies and dessert. She doesn't exercise. Otherwise, she is healthy. She is 5 foot 2 inches and weighs 158 pounds (BMI: 29.5). Her fasting blood sugar is 103 (normal <100). Her A1C is 6.0% (normal <5.7%). Her total cholesterol is 253(<200 desirable), HDL is 49, and LDL is 162 (>130 considered high), and triglycerides are 209 (<150 normal). She does not want to get diabetes and is wondering if intensive lifestyle modification (diet change, exercise and weight loss) or medication can prevent diabetes.

Enclosed Materials:

1. Worksheet for the evaluation of a therapy article.
2. Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. NEJM, Feb. 7, 2002. 346(6). P393 – 403.

Reference (Further Reading):

JAMA Evidence Webpage

Click on the 'book' *Users' Guides to the Medical Literature*

- Click Therapy
- Chapter 7 Therapy (Randomized Trials)
- Chapter 9, Does Treatment Lower Risk? Understanding the Results

FORMULAS

2x2 table	Event	No Event	N
Experimental	a	b	N for Experimental Group
Control	c	d	N for Control Group

CER = Control event rate. CER = c / c + d
EER = Experimental event rate. EER = a / a + b
ARR*: (Absolute Risk Reduction; difference in the event rates between control and experimental group, expressed over time)*
ARR or ABI= |CER – EER |.
ARR = |c/c+d - a/a+b|
RRR*: (Relative risk reduction (RRR) is the proportion of baseline risk reduced by the therapy, calculated by dividing the ARR by the absolute risk in the control group (CER), expressed over time. It is larger and more impressive. It is independent of baseline risk)*
RRR = |CER – EER | / CER x 100
RRR = [c/c+d – a/a+b] /c+d =
RRR = ARR / CER x 100
NNT (*Numbers needed to treat is the number of patients who need to be treated over a specific period of time to prevent one outcome)*
1/ ARR (Use fraction not %)
1/ = |c/c+d - a/a+b|
RR (Relative risk): EER/CER

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CRITICAL REVIEW FORM: THERAPY

Identify and outline your clinical question in plain language:

Build a PICO:

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Preferred Resource:

☐ Meta-analysis/Systematic Review ☐ RCT ☐ Cohort ☐ Case Control

Databases Searched:

Resource Acquired:

CRITICAL APPRAISAL - RCT

Did intervention and control groups start with the same prognosis?	
Were patients randomized?	
Was group allocation concealed?	

Adapted by John Stites DC and Amy Minkalis DC from : Walsh M, Perkovic V, Manns B, Srinathan S, Meade MO, Devereaux P, Guyatt G. Therapy (Randomized Trials). In: Guyatt G, Rennie D, Meade MO, Cook DJ. eds. *Users' Guides to the Medical Literature.* New York, NY: McGraw-Hill; 2014.

Were patients in the study groups similar with respect to known prognostic variables?	
Was prognostic balance maintained as the study progressed?	
To what extent was the study blinded?	
Were the groups prognostically balanced at the study's completion?	
Was follow-up complete?	
Were patients analyzed in the groups to which they were first allocated?	
How large was the treatment effect?	
What was the relative risk reduction and absolute risk reduction?	
How precise was the estimate of the treatment effect?	
What were the confidence intervals?	

Strength of Evidence:

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Low Quality High Quality

How does this apply to your patient?

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CRITICAL REVIEW FORM: THERAPY

1. Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. NEJM, 346(6). Feb. 2, 2002. P393 – 403.

2. Portions of online study protocol needed to answer some of the questions.

Guide		Comments
I	**Are the results of the study valid?**	
Did intervention and control groups start with the same prognosis?		
1. Were patients randomized?		See p. 394 "Interventions." Eligible patients were randomly assigned to one of three interventions: standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily, standard lifestyle recommendations plus placebo twice daily, or an intensive program of lifestyle modification. See online "Study Design" section 5.4.1 Randomization will be stratified by clinical center. This will ensure balance between the three treatment groups with respect to anticipated differences in the participant populations and possible differences in participant management.
2. Was group allocation concealed?		See online "Study Design" section 5.4.2 Randomization Method. The urn method of randomization provides a high probability of balance in treatment assignments, is unpredictable in unmasked studies, and allows an explicit randomization analysis to be conducted with relative ease (Wei and Lachin, 1988). For these reasons, the urn method will be used to randomly assign participants to the three treatment groups. The DPP Coordinating Center will prepare the master randomization list with assignments to the three treatment groups within a clinical center using the standard urn design. The sequence of pharmacological randomization numbers within a clinical center with the specific pharmacological treatment assignment (i.e., metformin or placebo) will be forwarded, in confidence, to the drug distribution center for drug labeling and distribution. Pharmacological treatment assignment to the sequence of pharmacological randomization numbers will be known only by the

	staff of the DPP Coordinating Center and the drug distribution center.
3. Were patients in the study groups similar with respect to known prognostic variables?	See Table 1 p. 395. There are no p values given, but on review the groups look very similar as would be expected in a large study. The authors state on p. 395 under Results: "Base-line characteristics, including all measured risk factors for diabetes were similar among study groups (Table 1)."
Was prognostic balance maintained as the study progressed?	
1. To what extent was the study blinded?	See online Study Design section 5.6 "Level of Masking." Section 5.6.1 "Treatment Groups." Pharmacological treatment assignment (metformin or placebo) will be double masked. Masking participants to the intensive lifestyle intervention versus pharmacological treatment is not possible and masking the investigators is not practical. Section 5.6.2 "Central Laboratory Outcomes." Primary outcome data (OGTT and FPG results) measured centrally will remain masked to the investigators and to the participants until confirmed progression from IGT to diabetes. Plasma lipid levels and HbA1c measured centrally will remain masked to the investigators and to the participants during the study. See Section 5.6.3.1 "Data Collectors." In order to promote objectivity of data collection and to minimize the opportunity for bias, the intent is to separate outcome measurement from the intensive lifestyle intervention case managers. This is particularly important for dietary intake data, blood pressure, interview questionnaires, and anthropomorphic measures, where the potential exists for subjectivity. Intensive lifestyle intervention case managers must not perform these outcome measures for participants with whom they are intervening.
Were the groups prognostically balanced at the study's completion?	
1. Was follow-up complete?	See p. 395 under "Results." The loss to follow up was very low. 92.5% of patients had attended a scheduled follow up within the previous 5 months, and 99.6% were known to be alive.
2. Were patients analyzed in the groups to which they were first allocated?	See p. 394 under "Statistical Analysis." The study design and analysis followed the intention-to-treat principle. See p. 395 under "Results." We randomly assigned

	3234 study participants to one of the three interventions 1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention. For the analysis see p. 398 Table 2 (Incidence of DM). Overall number of participants analyzed was 3234 as well. Despite no flow chart in this study, it can be inferred that the number randomized 3234 equaled the overall N in the "Incidence of Diabetes" results Table 2.
3. Was the trial stopped early?	See p. 394 under "Statistical analysis and Early closure." The blinded treatment phase was terminated one year early. By then, we had obtained evidence of efficacy on the basis of 65% of the planned person-years of observation. At that point they recalculated the power. There is controversy over whether studies should be stopped early for benefit, particularly if the benefits are not a life and death matter. These statistically significant highs could be random highs. Also important adverse events may be missed. Finally, a treatment may be effective early on and then lose its effectiveness as the trial proceeds. Studies stopped early for benefit often leave some unanswered questions. Interesting, that the drug portion was stopped early but the lifestyle was not, even though the lifestyle proved more beneficial at all points.
II **What are the results?**	
1. How large was the treatment effect (ARR, RRR, RR, and NNT)?	See p. 397 "Results" section under "Incidence of Diabetes." The estimated cumulative incidence of diabetes at three years was 28.9 percent, 21.7 percent and 14.4 percent in the placebo, metformin, and lifestyle-intervention groups, respectively. On the basis of these rates, the estimated number of persons who would need to be treated for 3 years to prevent one case of diabetes during this period is 6.9 (95%CI 5.4, 6.9), for the lifestyle intervention and 13.9 (95% CI 8.7, 33.9) for metformin. Calculations for Lifestyle: ARR= CER – EER = 28.9% - 14.4% RRR= (CER-EER) / CER 14.4 / 28.9 = 49.8% or 50% Numbers Needed to Treat= 1/ARR = 1/14.4 = 6.9 or 7. In other words: You need to treat 7 patients with impaired glucose tolerance for three years to prevent 1 person from developing diabetes. Development of DM by lab value can be viewed

	as a "surrogate outcome" for the adverse effects of DM. Calculations for Metformin. ARR = 28.9% - 21.7% = 7.7% RRR= 7.7% / 28.9% = 26.6% NNT = 12.9.
2. Is the treatment effect clinically important?	Development of diabetes is a surrogate outcome for morbidity and mortality associated with DM. The study didn't address patient important long term outcomes.
How precise was the estimate of the treatment effect?	
1. What were the confidence intervals?	See p. 398 Table 2 "Incidence of Diabetes: Reduction in Incidence (RRR)" Lifestyle vs. Placebo: 58% (95% CI 48%,66%) Metformin vs. Placebo: 31% (95% CI 17%, 43%) Lifestyle vs. Metformin: 39% (95% CI 24%, 51%) NNT: Lifestyle vs. Placebo: 6.9 (95%CI 5.4, 6.9) NNT: Metformin vs. Placebo: 13.9 (95% CI 8.7, 33.9) Looking at the lower limit of the CI, 48% for lifestyle would still be very important. It is more questionable for the lower limit of the CI for metformin which is 17%. The results are more precise for lifestyle than for metformin.
III	**How can I apply the results to patient care?**
Were the study patients similar to my population of interest?	
1. Does your population match the study inclusion criteria?	See p. 394 "Methods: Participants for eligibility criteria and exclusion criteria." Based on the inclusion and exclusion criteria, the patient in the clinical presentation would have been included in the trial (sex, age, race, fasting blood sugar, BMI, lack of severe comorbidities). The study participants were 55% white, 20% African Americans, 16% Hispanic and 5% American Indian and 4.5% Asian. 68% women, mean age was 50, and mean BMI was 34.
2. Was the duration of follow-up adequate?	See p. 395 "Results: Study cohort and Follow-up." The participants were followed for an average of 2.8 years (range 1. – 4.6). This was adequate follow up duration for the surrogate outcome of incidence of diabetes and short term medication adverse reactions, not for patient important outcomes. In addition, the reduction in glucose levels all occurred in year one. After that glucose

	levels rose at the same rate in all the groups, raising the question of whether there would be sustained benefit over a longer period of time.
3. Are the likely benefits worth the potential harms and costs?	See p. 394 under "Interventions." For lifestyle, there is little harm, and many benefits, and one can argue that even without patient important outcomes it may be worth it. On the other hand, it is an extremely intensive program with significant financial and logistic barriers to implementation, with a curriculum of 16 lessons taught by case managers one-on-one during the first 24 weeks, and was flexible, culturally sensitive and individualized. See p. 397, figure 2, both interventions lowered glucose in the first year, thereafter the rate of increase in fasting glucose for both interventions was similar to that in the control group, so the benefits may be short lived, whether due to compliance or other factors. Metformin may be easier to implement and sustain, but we currently have no direct evidence of improved outcome. Looking at a modeling exercise for Lifestyle and metformin, taking 10,000 patients over 3 yrs., 10,000 patients would take medication for 3 yrs. in the metformin group, while 2800 pts would take medication in the placebo group and 1400 pts would take medication daily in the lifestyle group. Many more patients would have GI symptoms in the metformin group.
Were all clinically important outcomes considered?	
1. What were the primary and secondary endpoints studied? Were all patient-important outcomes considered?	See p. 394 for outcome measures. The primary outcome was diabetes, diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual fasting plasma glucose test, according to the 1997 criteria of the American Diabetes Association. These values for diabetes are surrogates for the patient important outcome of CHD, stroke, renal failure, blindness, amputation and premature death. This study did not assess these patient important outcomes. The study did address adverse events. See Table 3, p. 401 including GI symptoms, musculoskeletal symptoms, hospitalization and death. Only increase risk of GI adverse events was statistically significant.