

Statistical and Clinical Differences
Understanding and Applying These
Concepts in P&T Decision Making

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Essential Components of a Drug Review (Clinical)

1. Understand disease state being treated
2. Determine which treatments are already available
3. Research best practice guidelines
4. Evaluate safety and efficacy of new drug
5. Make recommendations to P&T committee

1. Understand disease state being treated

The screenshot shows a Windows Internet Explorer browser window. The address bar contains the URL: http://www.uptodate.com/contents/overview-of-medical-care-in-adults-with-diabetes-mellitus?source=search_result&search=type+2+diabetes&selectedTitle=7%7E150. The browser's menu bar includes File, Edit, View, Favorites, Tools, and Help. The Favorites bar shows links to Google, HN Connect, Wellness Reimbursement, and desktop.ini. The page title is "Overview of medical care in adults with diabetes mellitus".

At the top right of the page, there is a navigation bar with the text "Welcome, Cathrine Misquitta" and links for "My Account" and "C". Below this is a search bar containing "type 2 diabetes" and a search icon. To the right of the search bar are links for "All Topics", "Contents", "Patient Info", "What's New", "PCUs", and "Calculators".

The main content area features the title "Overview of medical care in adults with diabetes mellitus" and a search box with "type 2 diabetes" and a "Find" button. On the left side, there is a "Topic Outline" sidebar with a green button labeled "SUMMARY & RECOMMENDATIONS" and a right-pointing arrow. Below this, the word "INTRODUCTION" is visible.

The main content area also displays the title "Overview of medical care in adults with diabetes mellitus" followed by three columns of text:

Author David K McCulloch, MD	Section Editor David M Nathan, MD	Deputy Editor Jean E Mulder, MD
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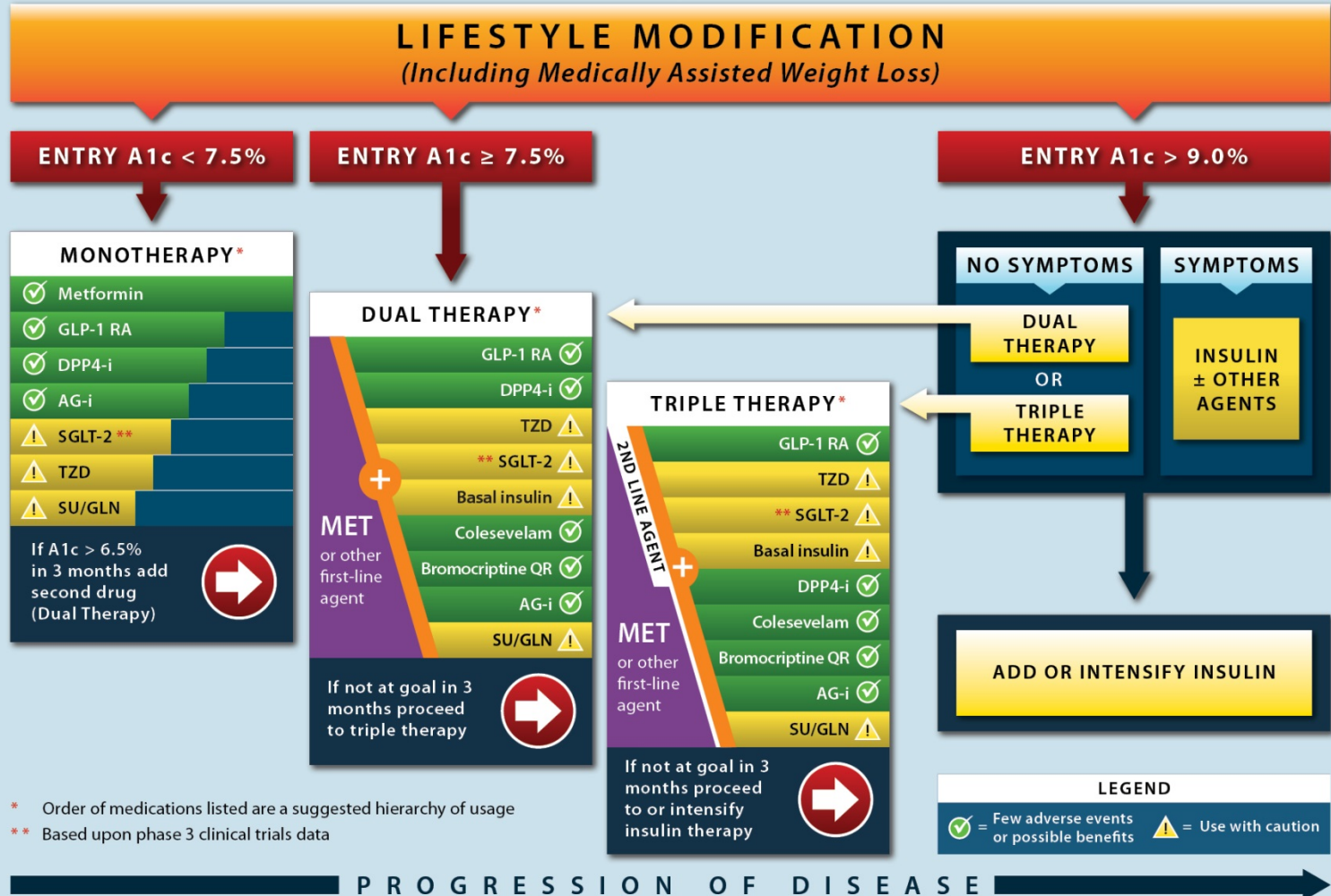
2. Determine which treatments are already available



3. Research Best Practice Guidelines



GLYCEMIC CONTROL ALGORITHM



LEGEND

✓ = Few adverse events or possible benefits ⚠ = Use with caution

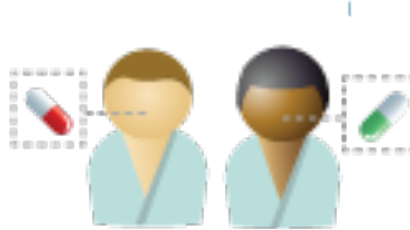
PROGRESSION OF DISEASE →

* Order of medications listed are a suggested hierarchy of usage
 ** Based upon phase 3 clinical trials data

4. Evaluate safety and efficacy of the new drug



Phase 1 Testing



Phase 2 Testing



Phase 3 Testing

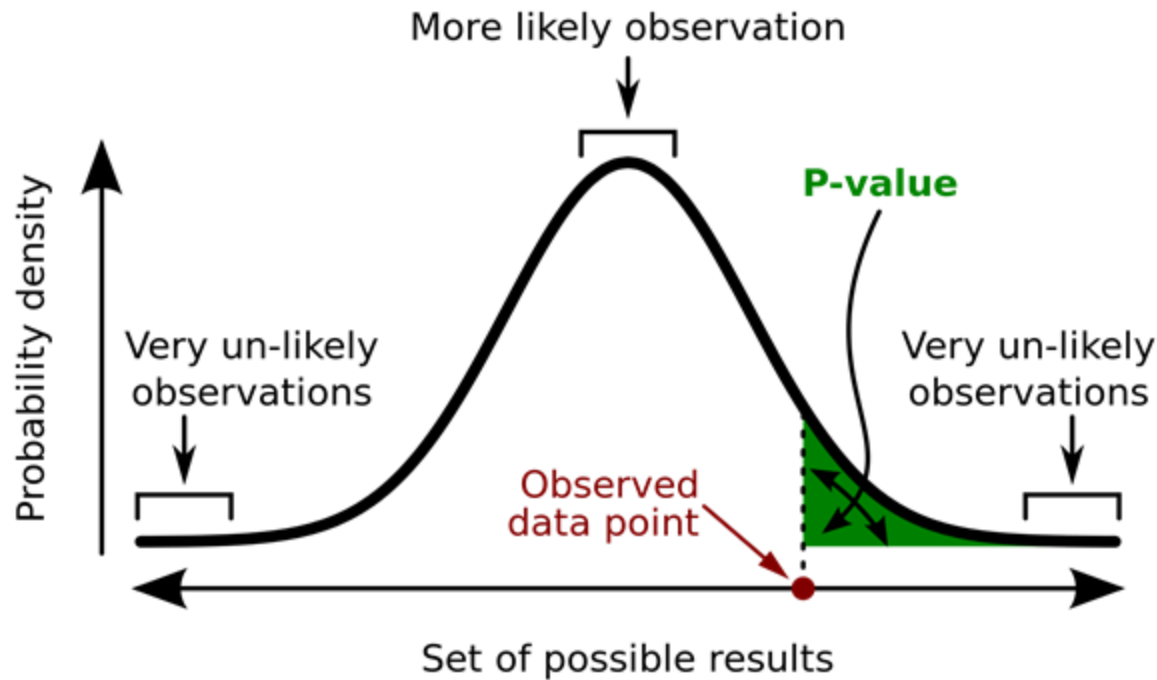
Brief overview of analyzing clinical trials (PP-ICONS)

- Problem
- Population
- Intervention
- Comparison (or Controls)
- Outcome (DOEs vs. POEMs)
- Number
- Statistics

Statistical Significance

- Part 1 – The p-value
- Part 2 – Odds ratios
- Part 3 – Confidence intervals

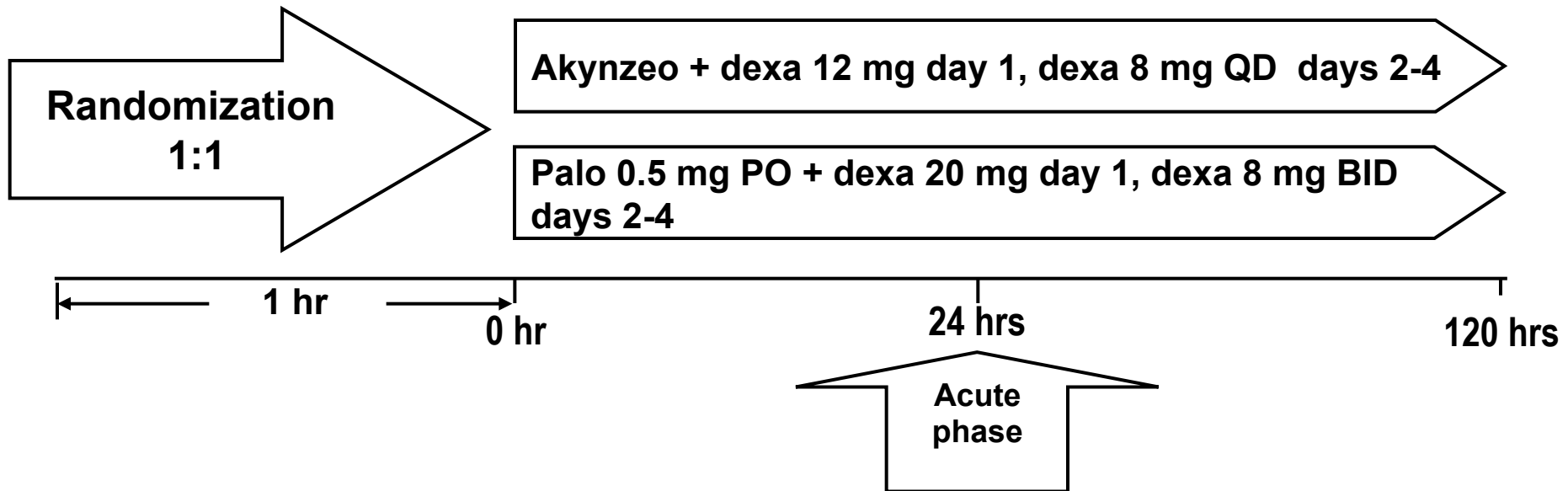
Statistical Significance (p-values)



A **p-value** (shaded green area) is the probability of an observed (or more extreme) result assuming that the null hypothesis is true.

Putting it into practice – Example 1

Multicenter, randomized, parallel, DB, Controlled Trial



Patient eligibility criteria:

- adult patients
- chemo regimen that included cisplatin

- Primary endpoint – complete response (CR, defined as no emetic episode and no use of rescue medication)

Response to therapy – Example 1

	AKYNZEO 300 mg netupitant/ 0.5 mg palonosetron N=135	Palonosetron 0.5 mg N=136	
	%	%	p-value*
COMPLETE RESPONSE			
Delayed Phase†	90.4	80.1	0.032
Acute Phase‡	98.5	89.7	0.002
Overall Phase§	89.6	76.5	0.003

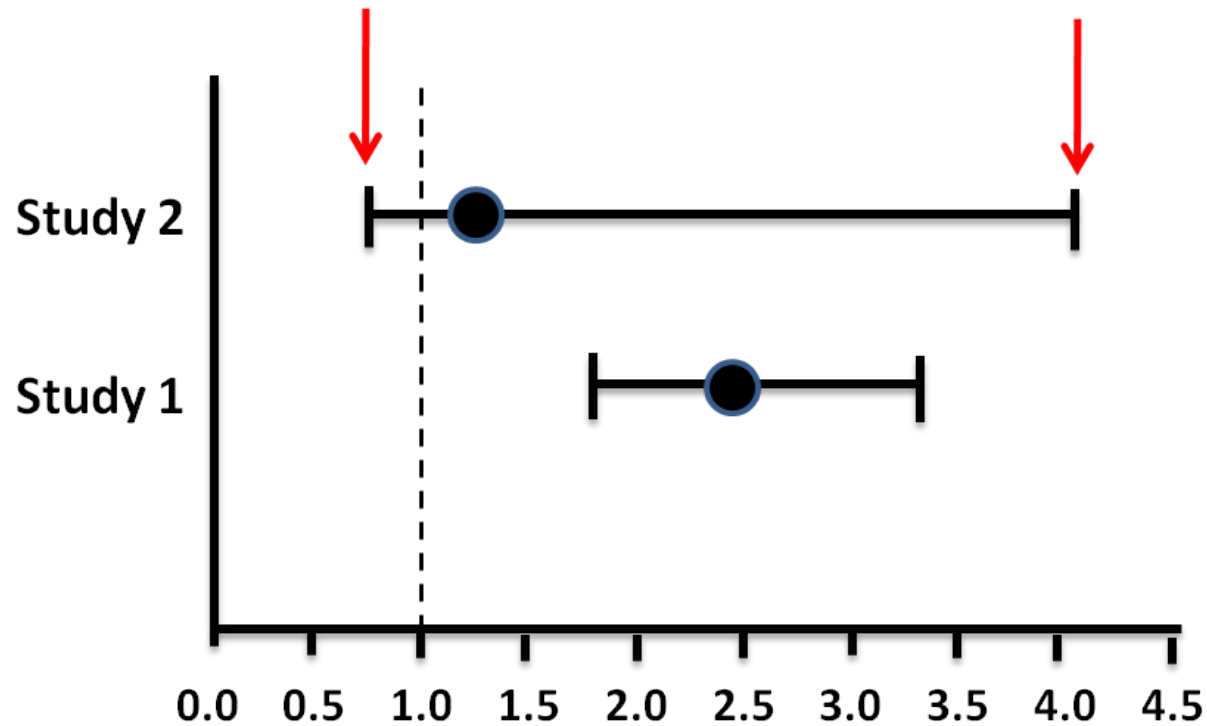
*Adjusted p-values for multiple comparisons using Cochran-Mantel-Haenszel test, stratified by gender.

†Delayed phase: 25 to 120 hours post-cisplatin treatment.

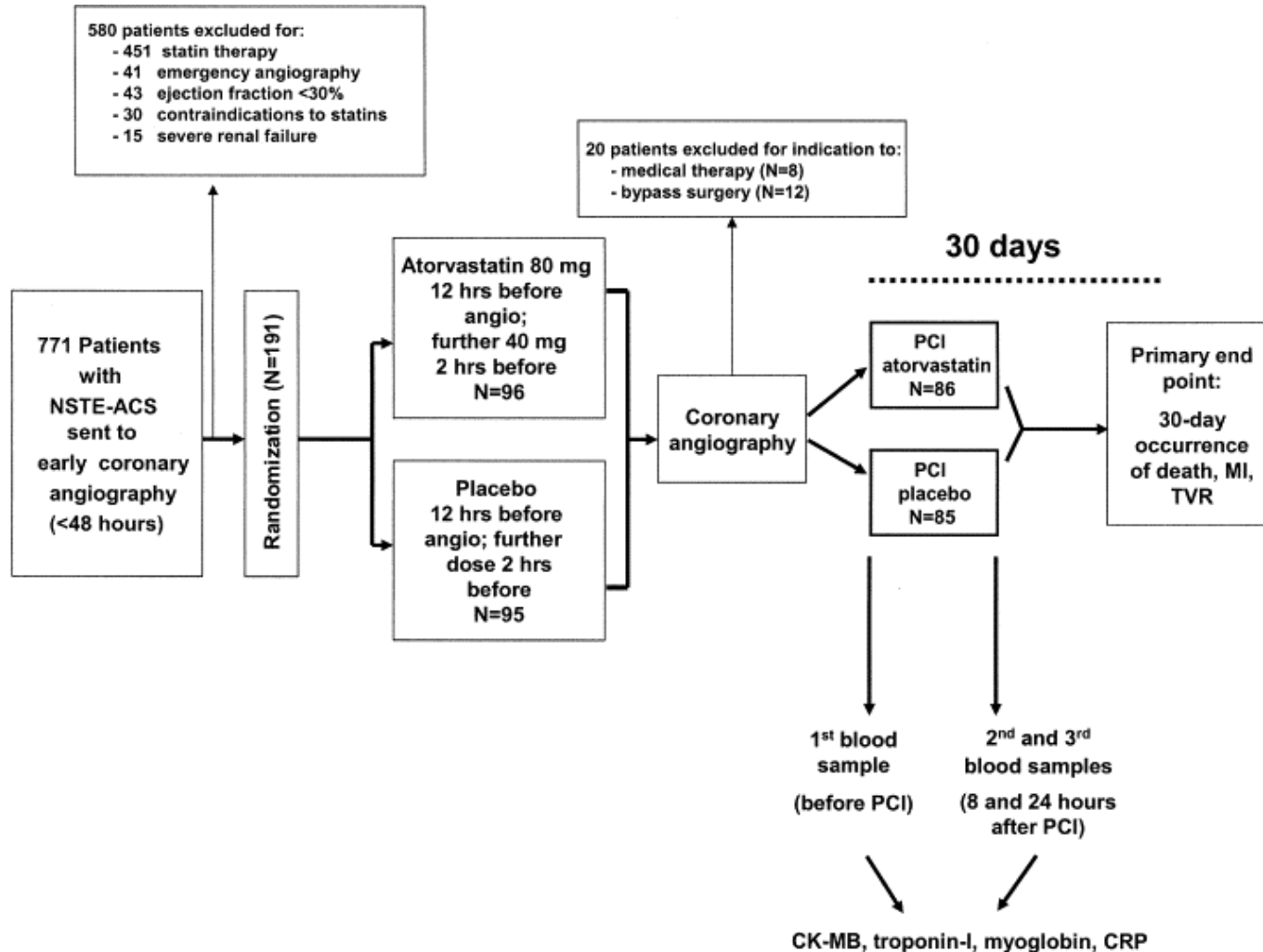
‡Acute phase: 0 to 24 hours post-cisplatin treatment.

§Overall: 0 to 120 hours post-cisplatin treatment.

Statistical Significance (Odds ratios)



Putting it into practice – Example 2



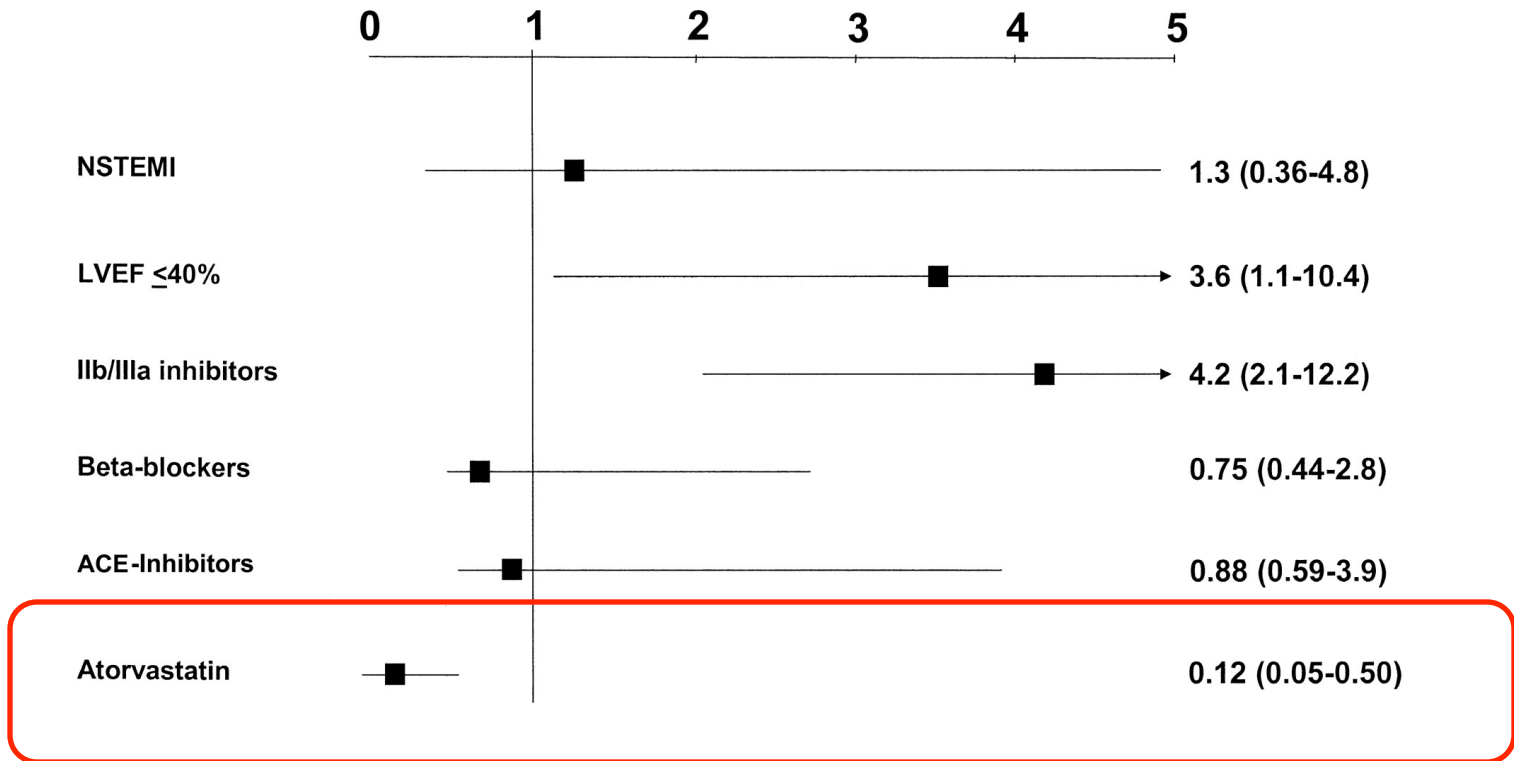
Giuseppe Patti , Vincenzo Pasceri , Giuseppe Colonna , Marco Miglionico , Dionigi Fischetti , Gennaro Sardella , A...

Atorvastatin Pretreatment Improves Outcomes in Patients With Acute Coronary Syndromes Undergoing Early Percutaneous Coronary Intervention : Results of the ARMYDA-ACS Randomized Trial

Journal of the American College of Cardiology, Volume 49, Issue 12, 2007, 1272 - 1278

<http://dx.doi.org/10.1016/j.jacc.2007.02.025>

Response to therapy – Example 2

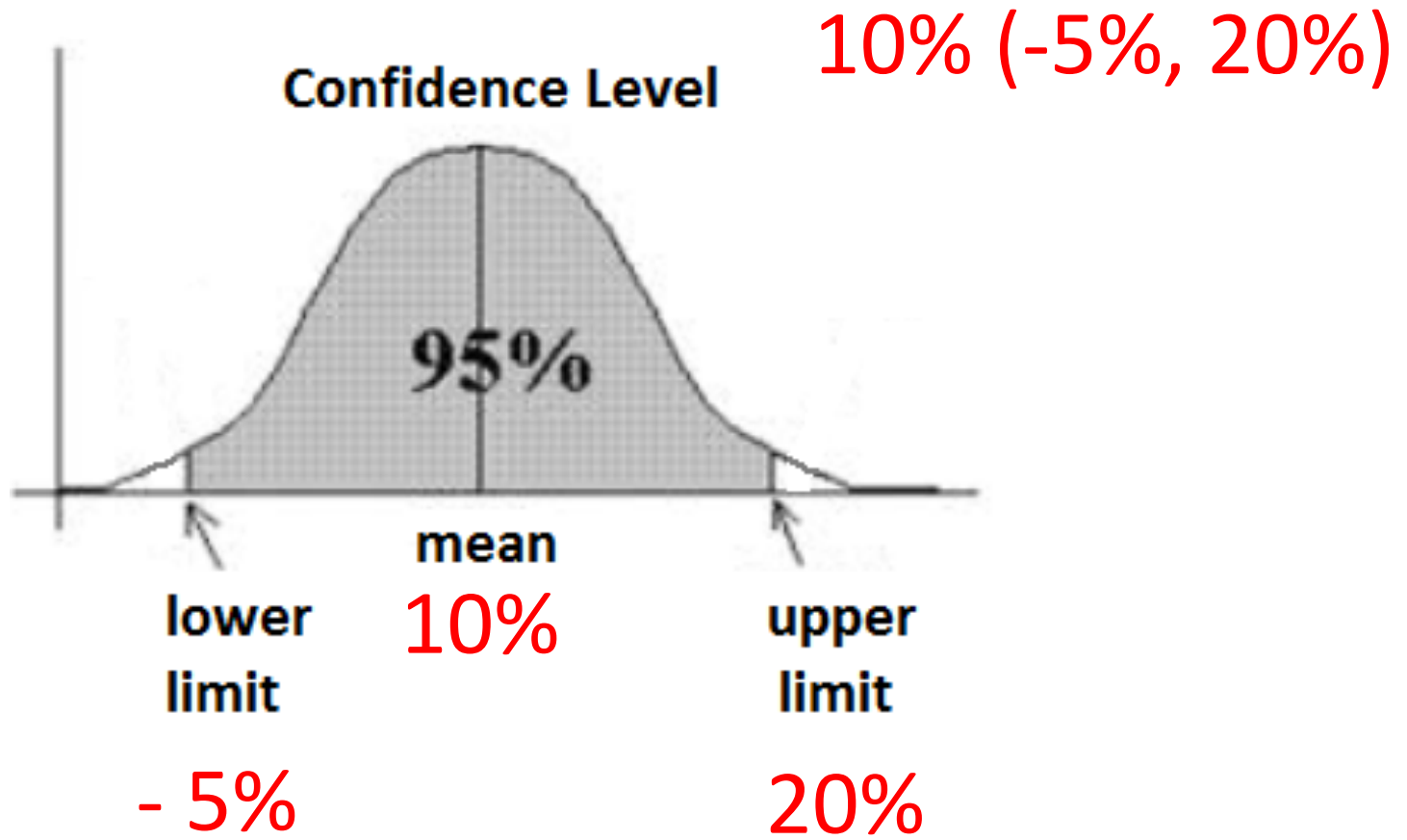


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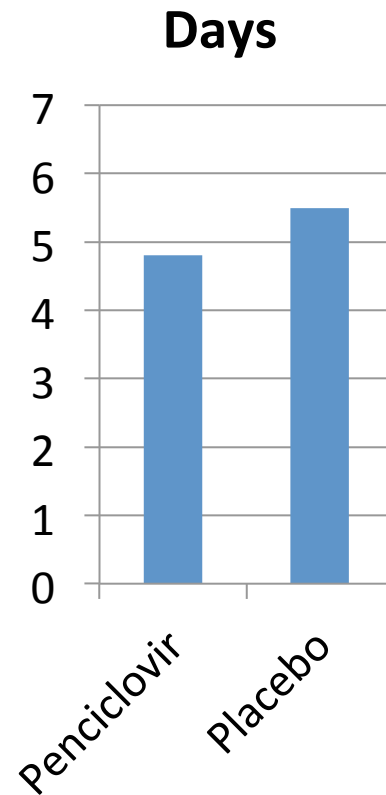
Statistical Significance (Confidence Intervals)



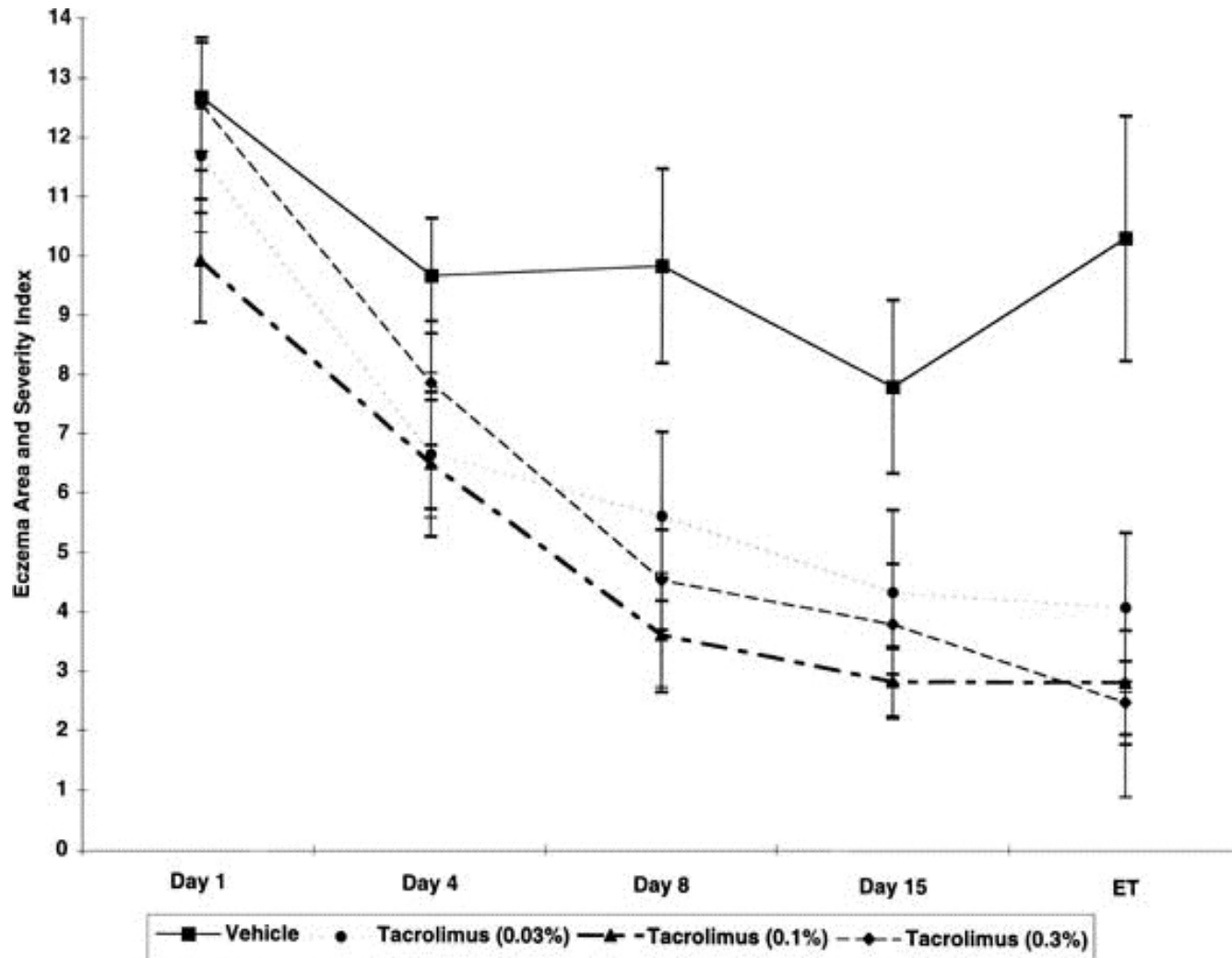
Clinical Significance

- Part 1 – Understanding the descriptive side of statistics
- Part 2 – Understanding the studies and the primary outcomes

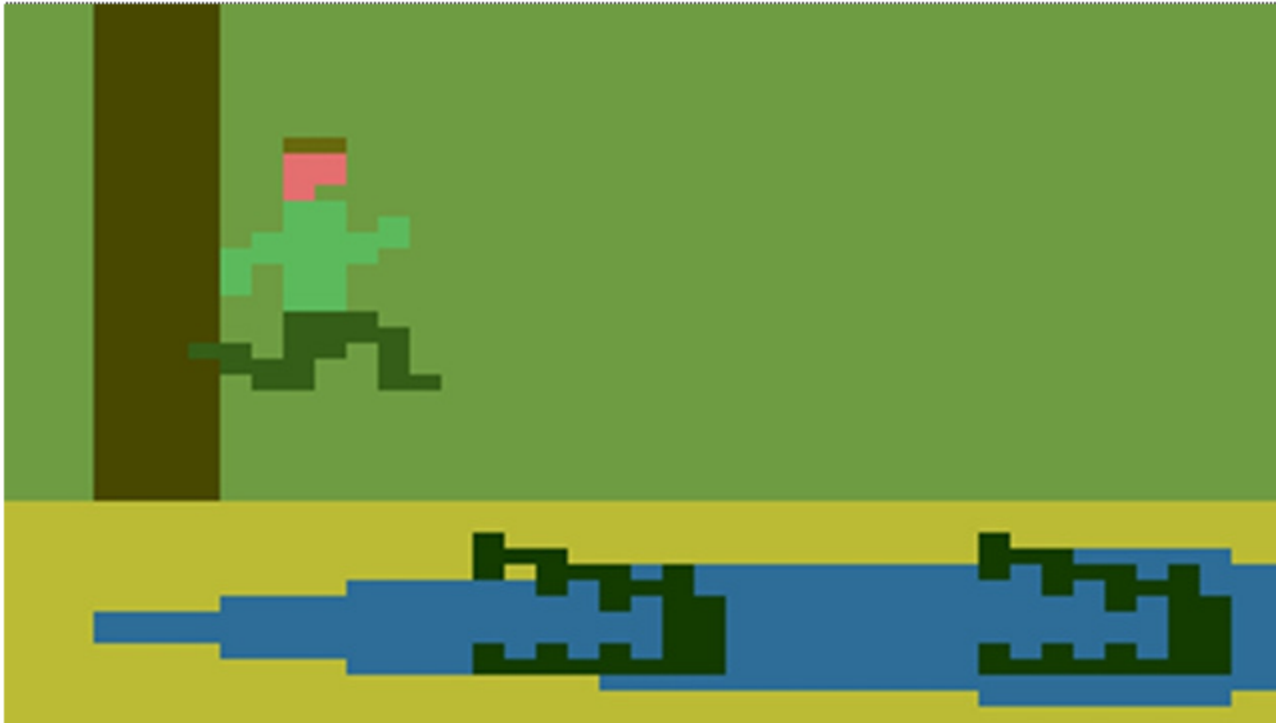
Clinical Significance (Confidence Intervals) – Example 3



Clinical Significance (Confidence Intervals) – Example 4



Avoid Pitfalls and Look for Useful Stats



RRR vs. ARR vs. NNT

First: Ignore the RRR

Long-Term Effects of Mammography Screening: Updated Overview of the Swedish Randomised Trials

“There were **511** breast cancer deaths in 1,864,770 women-years in the invited groups and **584** breast cancer deaths in 1,688,440 women-years in the control groups, a **significant 21 percent reduction** in breast cancer mortality.”

	When the experimental treatment reduces the risk of a bad event	Reduction in breast cancer mortality
Relative risk reduction (ARR)	$CER - EER / CER$	$(0.00035 - 0.00027) / 0.00035$

CER = Control Event Rate

EER = Experimental Event Rate

A better statistic: The ARR

	When the experimental treatment reduces the risk of a bad event	Beta-blockers to prevent deaths in high-risk patients with recent myocardial infarction
Absolute risk reduction (ARR)	CER-EER	$(0.66-0.50) = .16$ or 16%

CER = Control Event Rate

EER = Experimental Event Rate

A really helpful statistic: NNT

Therapy	NNT
Triple antibiotic therapy to eradicate <i>H. pylori</i>	1.1
Isosorbide dinitrate for prevention of exercise-induced angina	5
Short course of antibiotics for otitis media in children	7
Statins for secondary prevention of adverse cardiovascular outcomes	11
Statins for primary prevention of adverse cardiovascular outcomes	35
Finasteride to prevent one operation for benign prostatic hyperplasia	39
Misoprostol to prevent any gastrointestinal complication in nonsteroidal anti-inflammatory drug users	166

How they RRR, ARR, and NNT relate

<i>% Control with poor outcomes</i>	<i>% <u>intervention</u> with poor outcomes</i>	<u>RR</u>	<u>RRR</u>	<i>ARR (%)</i>	<u>NNT</u>
60	40	0.67	0.33	20	5
30	20	0.6	0.33	10	10
15	10	0.67	0.33	5	20
3	1	0.67	0.33	2	50

Smart Health Choices: Making Sense of Health Advice.
Irwig L, Irwig J, Trevena L, et al.
London: [Hammersmith Press](#); 2008.

Understanding the Outcomes

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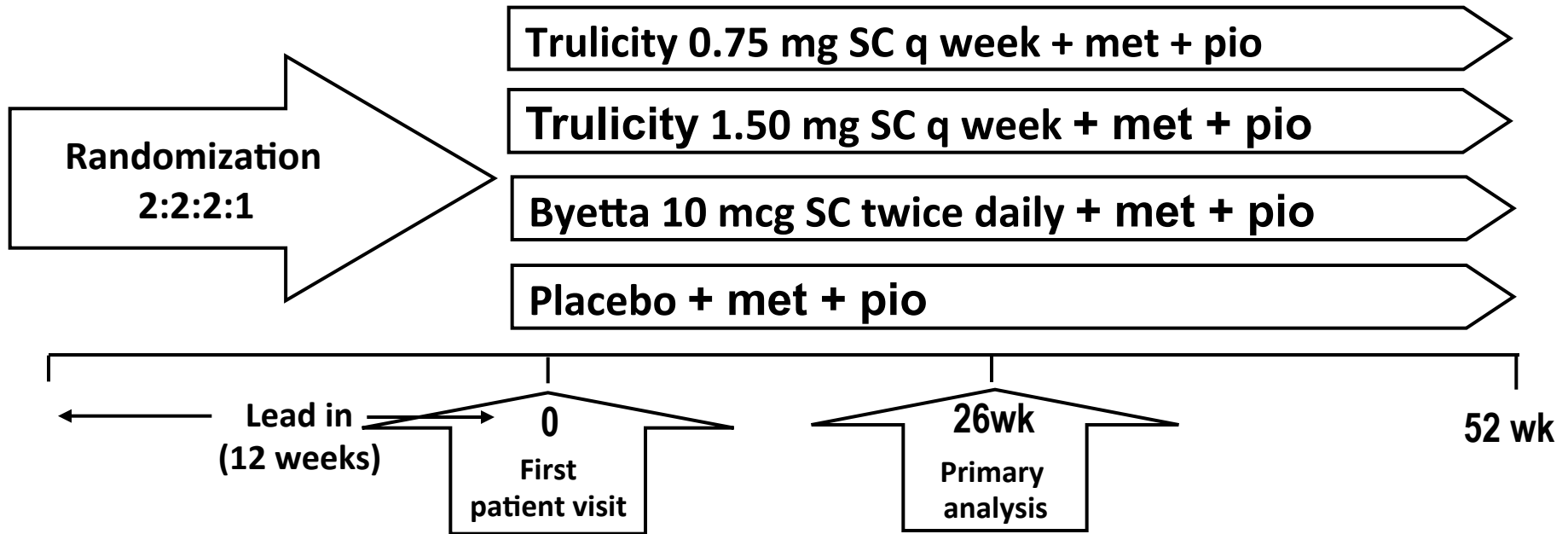
Revisit
Step #1



The DOEs (a.k.a. surrogate markers)



Putting it into Practice – Example 5



Eligibility criteria:

- $n = 976$
- Age ≥ 18 years
- BMI 23- 45 kg/m²
- HbA1C 7-11% on oral anti-diabetic monotherapy
- HbA1C 7-10% on oral anti-diabetic dual therapy

Exclusion criteria:

- GLP-1 agonist therapy within the last 3 months
- Long term insulin users

Primary end-point

- HbA1C change at baseline at 26 weeks

Secondary end-point

- HbA1C change at baseline at 52 weeks
- Change in body weight from baseline

Putting it into Practice - Example 5

The results demonstrate superiority of Trulicity compared to Byetta

Outcome Week 26	Trulicity 0.75mg + Met + Pio n=280	Trulicity 1.50 mg + Met + Pio n=279	Byetta (Exenatide) + Met + Pio n=276	Placebo + Met + Pio n =141
HbA1C (%)				
Baseline (mean)	8.1	8.1	8.1	8.1
Mean change from baseline	-1.30 ± 0.06	-1.51 ± 0.06	-0.99 ± 0.06	-0.46 ± 0.08
Difference vs placebo 95% CI P<0.001	-0.84 (-1.01 to -0.67)	-1.05 (-1.22 to -0.88)		

Putting it into Practice – Example 6

Evaluating the impact of new antihypertensives

(mmHg)	Aliskiren results (placebo subtracted)		
Placebo (mean change)	75 mg	150 mg	300 mg
2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*

* p-value <0.05 vs. placebo



Prescribing information

Putting it into Practice – Example 7

Percent Change in LDL-C From Baseline to Week 6

Treatment	10mg/day	20mg/day	40mg/day	80mg/day
Rosuvastatin	-46	-52	-55	--
Atorvastatin	-37	-43	-48	-51
Simvastatin	-28	-35	-39	-46
Pravastatin	-20	-24	-30	--
Treatment	10mg/day	20mg/day	40mg/day	80mg/day
Rosuvastatin	-46	-52	-55	--
Atorvastatin	-37	-43	-48	-51
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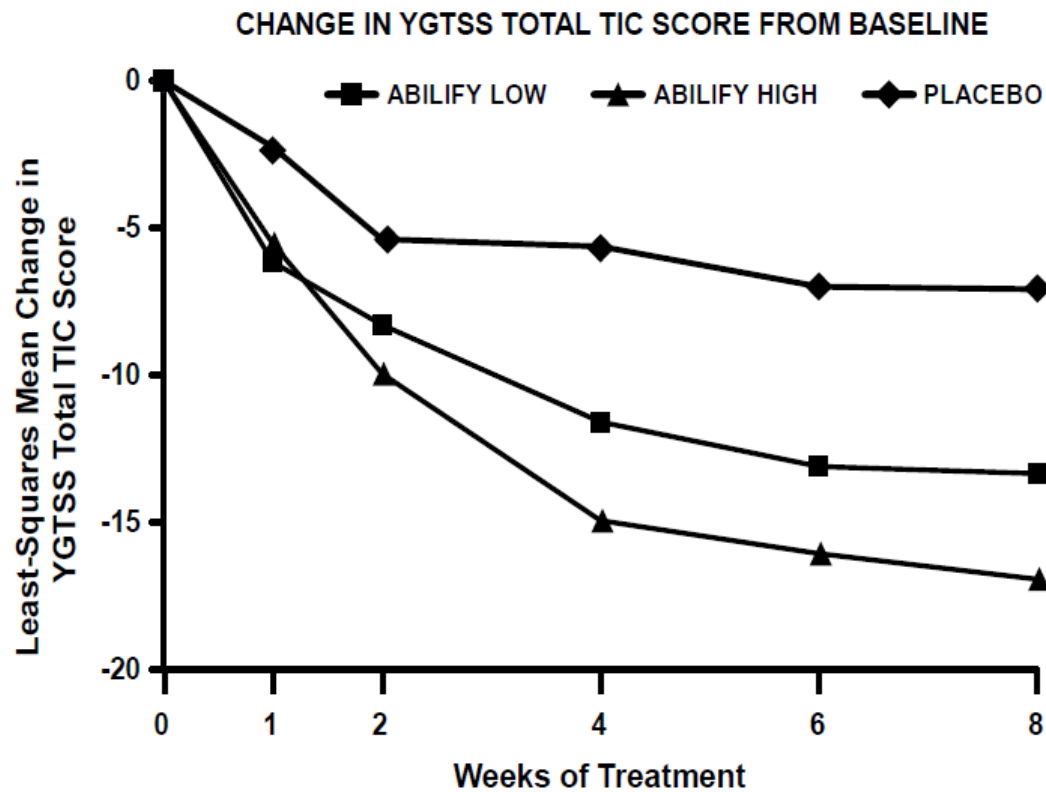
POEMs

(Patient-Oriented Evidence that Matters)



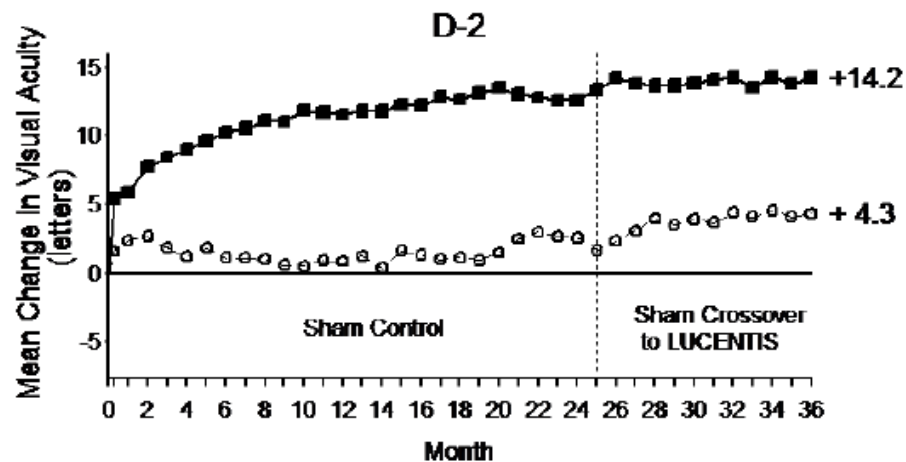
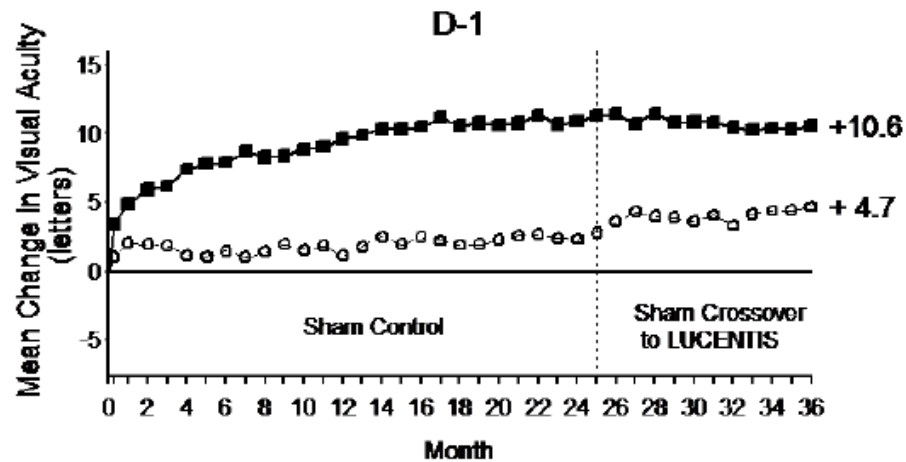
Putting it in practice – Example 8

Figure 9: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1)



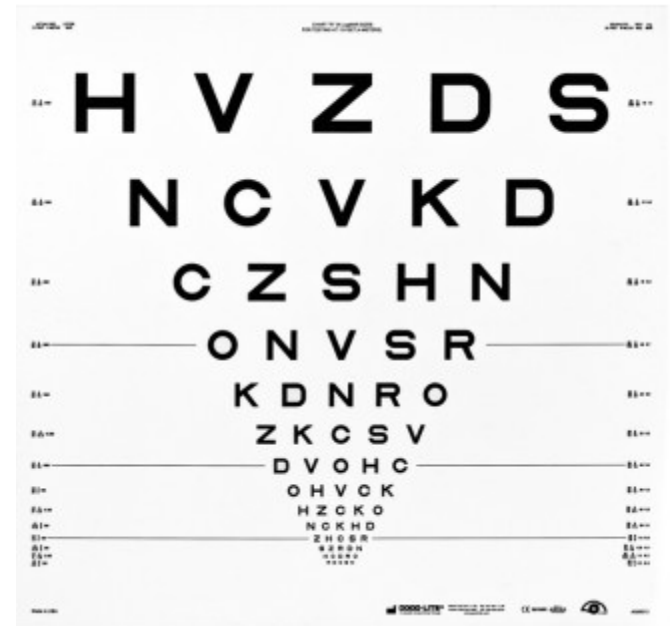
Putting it into Practice – Example 9

Mean Change in Visual Acuity from Baseline to Month 36 in Study D-1 and Study D-2



Putting it in practice – Example 9

E	1	20/200
F P	2	20/100
T O Z	3	20/70
L P E D	4	20/50
P E C F D	5	20/40
E D F C Z P	6	20/30
F E L O P Z D	7	20/25
D E F P O T E C	8	20/20
L E F O D P C T	9	
F D P L T C E O	10	
F E Z O L C P T D	11	

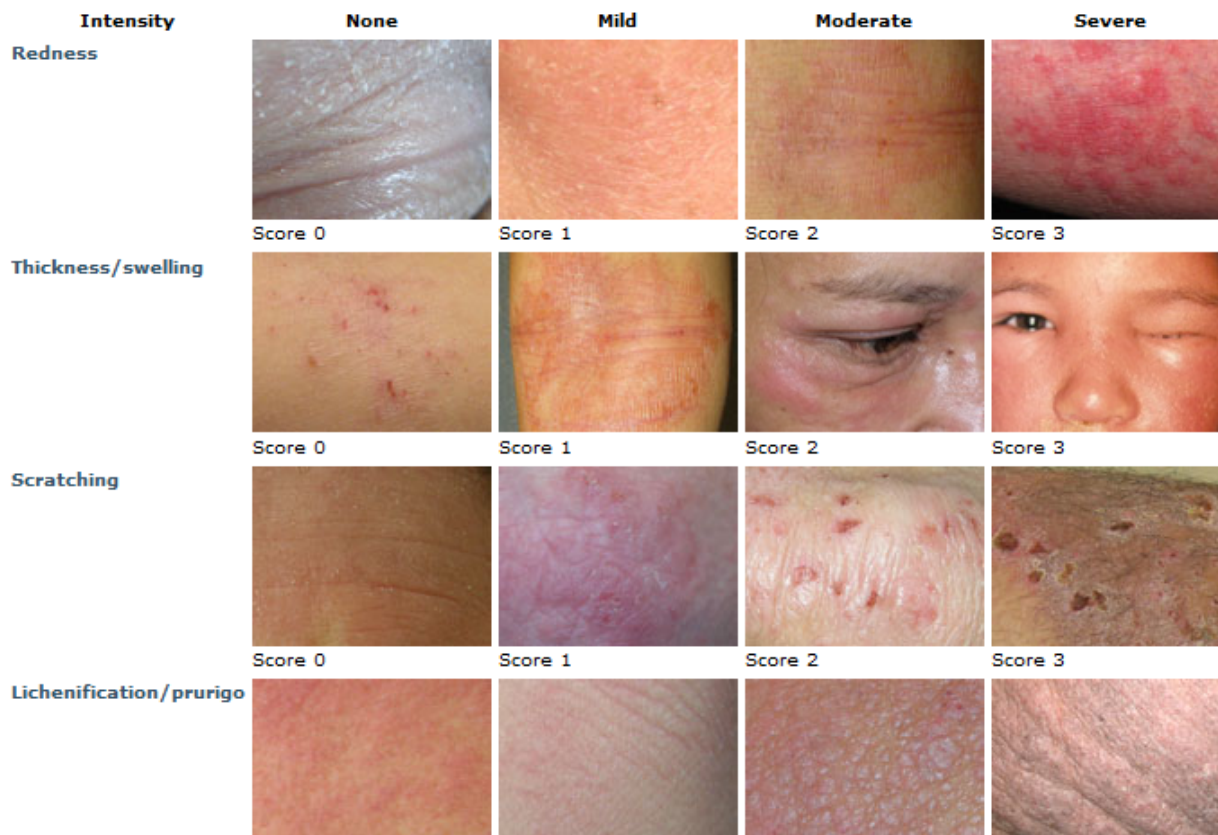


Putting it into practice – Example 10



	Baseline	After Treatment
Soolantra	100% moderate or severe (3 or 4)	40% clear or almost clear (0 or 1)
Vehicle	100% moderate or severe (3 or 4)	19% clear or almost clear (0 or 1)

Putting it into practice – Example 4

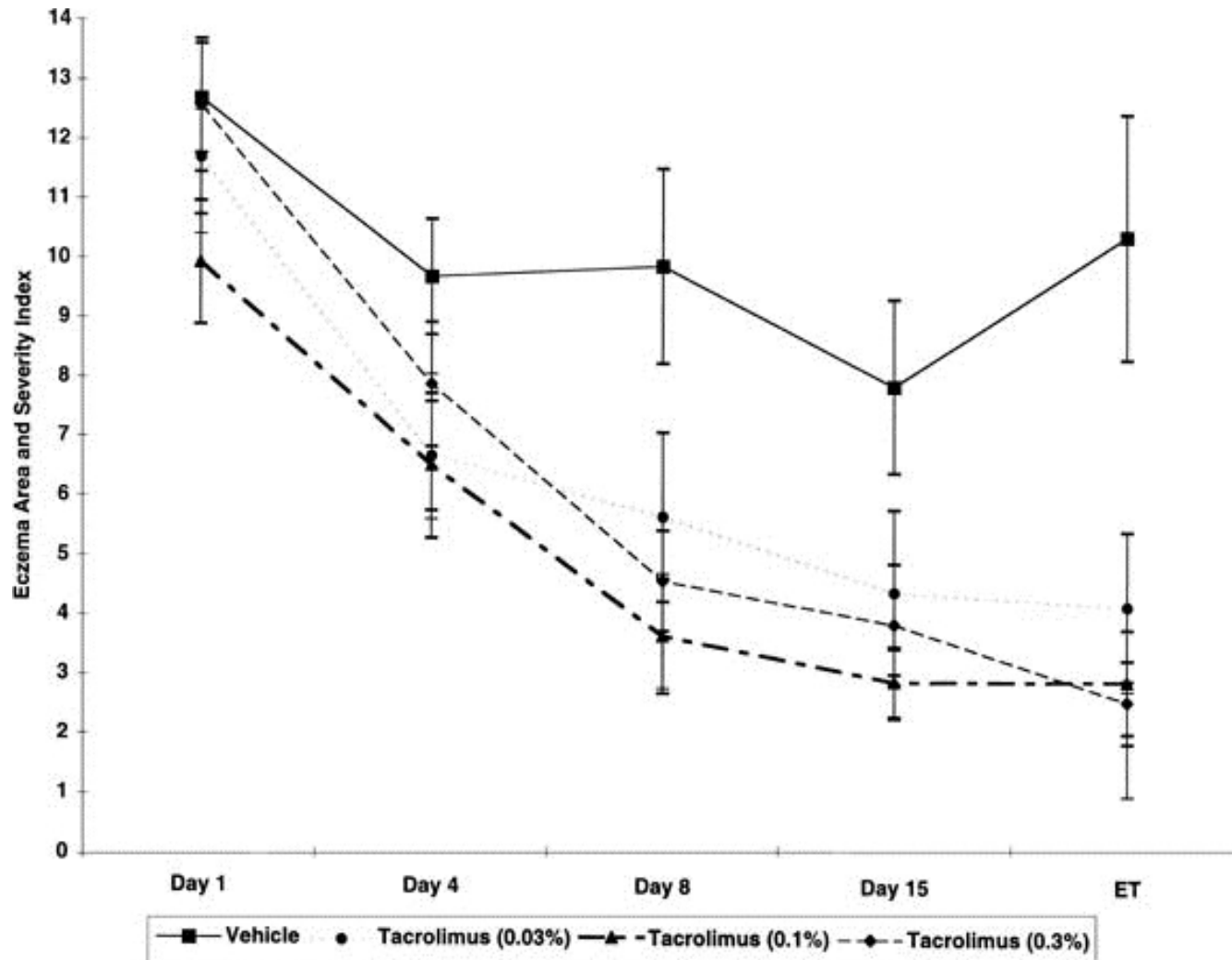


Recording the EASI score

Recording the EASI score

Body region	Redness	Thickness	Scratching	Lichenification	Severity score	Area score	Multiplier	Region score
Head/neck	_____	+_____	+_____	+_____	=_____	X_____	X 0.1 (If ≤7 yrs, X 0.2)	=_____
Trunk	_____	+_____	+_____	+_____	=_____	X_____	X 0.3	=_____
Upper limbs	_____	+_____	+_____	+_____	=_____	X_____	X 0.2	=_____
Lower limbs	_____	+_____	+_____	+_____	=_____	X_____	X 0.4 (If ≤7 yrs, X 0.3)	=_____
The final EASI score: add up the 4 region scores								=_____ (0-72)

Putting it into practice – Example 4



Making a formulary recommendation

Efficacy

Safety

Administration

Frequency

Long-term effects

Indications

Cost

Operational considerations

+ Impact on health plan's population

Final Recommendation

Questions?