Importanța clinică şi legătura cu semnificația statistică (mărimea efectului)

Cristian Băicuş
Medicină Internă Colentina
www.baicus.ro

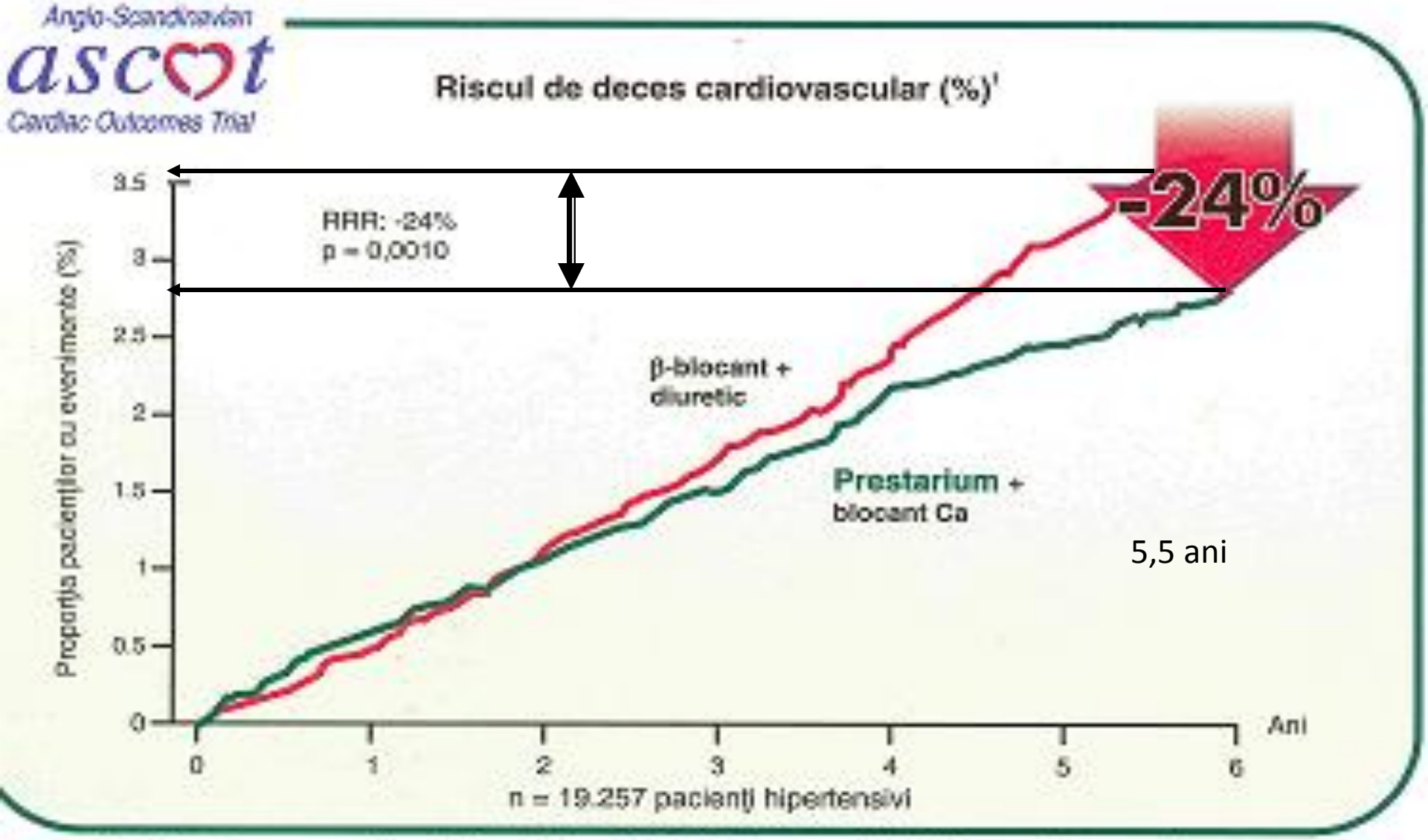
- Placebo: supraviețuire: 10 ani
- Tratament: supraviețuire 10 ani + 1h
- p= 0,0001.

- Tratamentul îmbunătățeşte semnificativ supraviețuirea (p= 0,0001)

1. **Uitați-vă întotdeauna după mărimea efectului!**

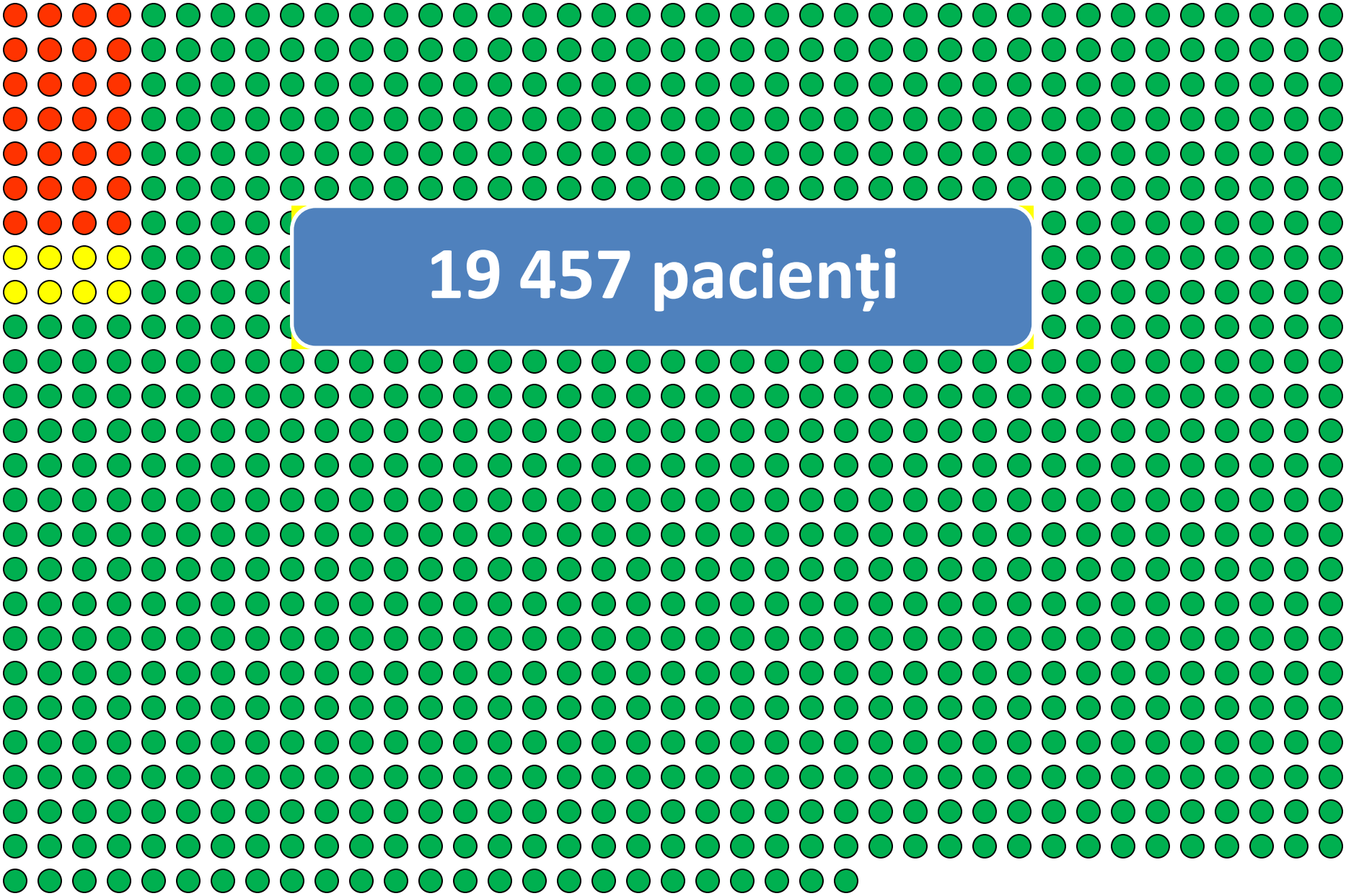
- Tratamentul îmbunătățeşte *semnificativ* supraviețuirea (p= 0,0001)
  - CI dau mai multe informații decât p, aşadar sunt de preferat
  - p-urile amestecă mărimea efectului cu mărimea eşantionului
  - p-urile nu au ce căuta în medicină

    Schulz, Grimes. The Lancet Handbook of Clinical Research, 2006
  - 1986: Ken Rothman a interzis p-urile în *Epidemiology*



RRA=3,6-2,8 = 0,8%

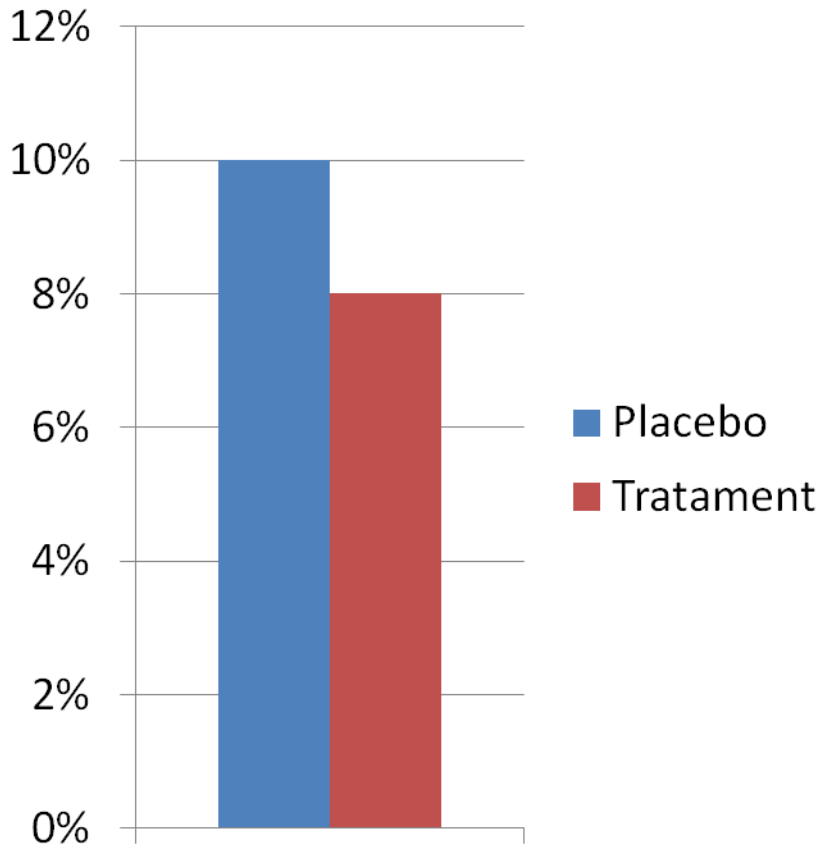
NNT=100:0,8 = 125

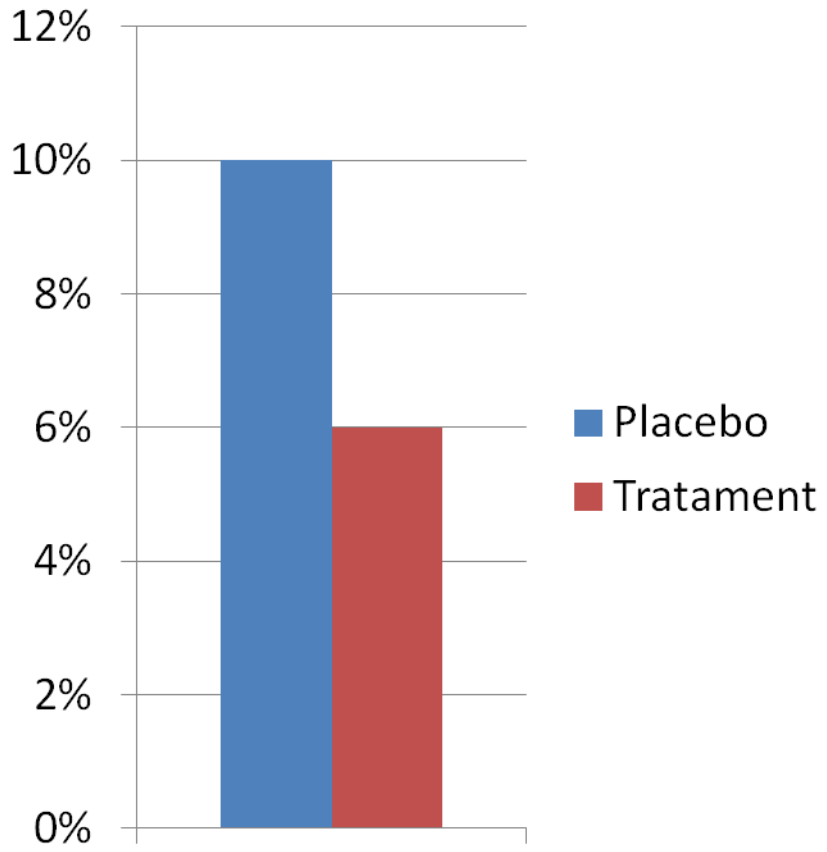


ASCOT-BPLA: mortalit. cv.

RAR = 0,8%, p=0.001

p=0.01, putere=80%





2. Dacă eşantionul este foarte mare, efectul este mic.

9762 pts

2246 pts

3. Este efectul important?

Ce inseamnă efect important?

ARTICLE IN PRESS

EJINME-01683; No of Pages 2

European Journal of Internal Medicine xxx (2008) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Editorial

Effect measure for quantitative endpoints: Statistical versus clinical significance, or "how large the scale is?"

Cristian Baicus *, Simona Caraiola

Clinica de Medicina Interna, and Réseau d'Epidémiologie Clinique International Francophone (RECIF), Spitalul Colentina, Soseaua Stefan cel Mare 19–21, Sector 2, 21125 Bucharest, Romania

Table X.1. Topical diclofenac local (DLO) versus vehicle control (VC) or placebo solution (PLA) for osteoarthritis (OA) of the knee at 28 days (modified, from 3).

Outcomes*	Mean change from baseline			Difference in mean change from baseline (95%CI)	Size of the scale
	DLO	VC	PLA		
Pain	-3.9	-2.5		1.4 (1.2 to 1.5)	50
	-3.9		-2.5	1.4 (1.2 to 1.5)	50
Physical function	-11.6	-5.7		5,9 (5,1 la 6,4)	170
	-11.6		-7.1	4.5 (4.0 to 5.4)	170
Stiffness	-1.5	-0.7		0.8 (0.7 to 0.8)	20
	-1.5		-0.6	0.9 (0.9 to 0.9)	20
Pain in walking	-0.8	-0.4		0.4 (0.4 to 0.5)	
	-0.8		-0.6	0.2 (0.2 to 0.3)	

* Measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale.

"The 4 week blinded RCT by Bookman et al in patients with primary OA of the knee found that topical diclofenac was *significantly* better than both vehicle controlled and placebo solutions in reducing WOMAC pain, physical dysfunction, and stiffness"

Cranney, O'Donnell. *EBM 2005*

Tabelul X.2. Effect of 52 weeks treatment on health status and symptoms (from 6).

SGRQ* total score	Placebo	Salmeterol	Fluticasone	Combination
Mean	46,3	45,2	45,5	44,1
Difference (95%CI) §	-2,2 (-3,3 to -1)	-1,1	-1,4	
p§	0,0003	0,071	0,021	

* St George's Respiratory Questionnaire
§ versus combination

- Tratamentul combinat a produs o îmbunătățire *semnificativă clinic*: modificarea medie a scorului SGRQ a fost de –4.5 (SD 12.9) în grupul tratat cu combinația
- Modificarea medie a scorului SGRQ în grupul tratat cu combinația a fost *semnificativ mai mare* decât în grupurile placebo şi fluticazonă.

Calverley et al. TRISTAN. *Lancet 2003*

3. Este efectul important?

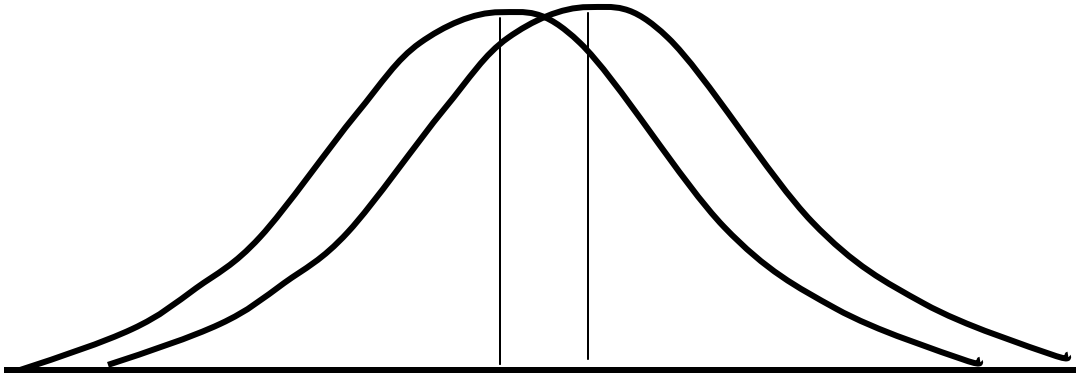
Ce inseamnă efect important?

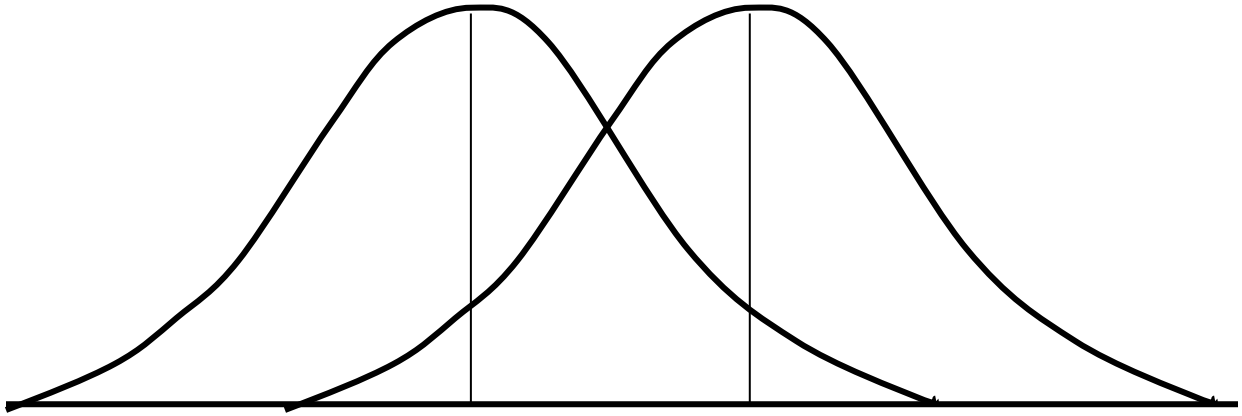
1. Criteriu statistic

2. Criteriu clinic (modificarea scorului corespunde unei modificări validate de pacient însuşi)

3. Este efectul important?

- **Criteriul statistic**
  - Cohen (1988): diferența medie/SD
    - 0,2-0,5 (mic); 0,5-0,8 (moderat); >0,8 (mare)
  - Norman (2003): **0.5 SD**
  - Rosenthal (1996)
    - OR: 1,5 (mică); 2,5 (medie); 4 (mare); >10 (f mare)
      (OR: 0,66 0,4 0,25 <0,10)
    - RAR: 7% (mică); 18% (medie); 30% (mare); [15-85%]
      - 12%-2%=10% (0,88SD); 50%-40%=10% (0,25SD).
  - Sackett et al. (1991): RRR>25% (importantă)
  - Pearson (1905) corelații
    - <0,25 (mică); 0,25-0,50 (moderată); 0,51-0,75 (considerabilă); >0,75 (mare)





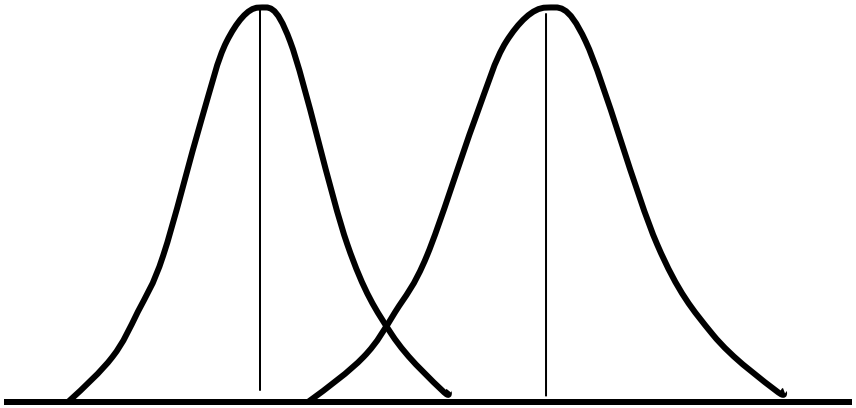


Table 2.1 Cohen's effect size benchmarks

Test	Relevant effect size	Effect size classes		
		Small	Medium	Large
Comparison of independent means	d, Δ, Hedges' g	.20	.50	.80
Comparison of two correlations	q	.10	.30	.50
Difference between proportions	Cohen's g	.05	.15	.25
Correlation	r	.10	.30	.50
	r^2	.01	.09	.25
Crosstabulation	w, φ, V, C	.10	.30	.50
ANOVA	f	.10	.25	.40
	η^2	.01	.06	.14
Multiple regression	R^2	.02	.13	.26
	f^2	.02	.15	.35

Cohen, 1988

3. Este efectul important?

- Criteriul clinic
  - modificarea scorului corespunde unei modificări validate de pacient însuşi
  - *“anchor method”* G Guyatt (scale Likert)
  - fiecare scală trebuie să primească, în timpul procesului de validare, şi valoarea MID/ MCID
  - MID = “cea mai mică diferență a scorurilor pe care pacientul o percepe ca benefică şi care permite, în lipsa unor efecte adverse importante şi a costului excesiv, o schimbare în mangementul pacientului”

Tabelul X.2. Effect of 52 weeks treatment on health status and symptoms (from 6).

SGRQ* total score	Placebo	Salmeterol	Fluticasone	Combination
Mean	46,3	45,2	45,5	44,1
Difference (95%CI) §	-2,2 (-3,3 to -1)	-1,1	-1,4	
p§	0,0003	0,071	0,021	

* St George's Respiratory Questionnaire
§ versus combination

- Tratamentul combinat a produs o îmbunătățire *semnificativă clinic*: modificarea medie a scorului SGRQ a fost de –4.5 (SD 12.9) în grupul tratat cu combinația **4,5:12,9=0,34**
- Modificarea medie a scorului SGRQ în grupul tratat cu combinația a fost *semnificativ mai mare* decât în grupurile placebo şi fluticazonă.

SGRQ: 100 p; Δ=4 (mică); 8 (medie); 12 (mare)

Table 2. *Primary and secondary efficacy variables*

	Placebo	50 mg Mirabegron
	Co-primary end points: change from baseline to final visit	
Incontinence episodes/24 hrs:*		
Mean ± SE	−1.13 ± 0.11	−1.47 ± 0.11*
95% CI	(−1.35, −0.91)	(−1.69, −1.25)
Micturitions/24 hrs:		
Mean ± SE	−1.05 ± 0.13	−1.66 ± 0.13*
95% CI	(−1.31, −0.79)	(−1.92, −1.40)
	Key secondary endpoints: change from baseline to final visit	
Vol voided (ml)/micturition:		
Mean ± SE	7.0 ± 2.41	18.2 ± 2.44*
95% CI	(2.3, 11.7)	(13.4, 22.9)
Mean ± SD micturitions/24 hrs	11.5 ± 3.3	11.8 ± 3.5
Mean ± SD ml voided/micturition	157.5 ± 58.7	156.0 ± 58.7
Mean ± SD urgency episodes (grade 3 or 4)/24 hrs	5.6 ± 3.2	5.9 ± 3.8
Mean ± SD nocturia episodes/24 hrs	1.9 ± 1.6	1.9 ± 1.6
	OAB parameters: FAS-I‖	
No. pts	325	312
Mean ± SD incontinence episodes/24 hrs	3.0 ± 3.1	2.8 ± 2.7
Mean ± SD urgency incontinence episodes/24 hrs	2.5 ± 2.5	2.3 ± 2.4

Benefits

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
We found one systematic review comparing acetylcholinesterase inhibitors as a group versus placebo;[20] one systematic review comparing the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine individually versus placebo;[21] one systematic review of rivastigmine versus placebo;[22] and one subsequent RCT comparing galantamine versus placebo.[23] There was widespread overlap of RCTs between the reviews. The first review (search date 2005; 13 multicentre double-blind RCTs; people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company.[20] It performed an intention-to-treat analysis, and where full data were not available, it performed an analysis with the last observation carried forward (LOCF). The review found that people leaving before the end of studies ranged from 16% to 43% in the treatment group and 0% to 30% in the placebo group. The review found that acetylcholinesterase inhibitors significantly improved cognitive outcomes compared with placebo at 6 months or later (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 10 RCTs, 4236 people; WMD –2.4, 95% CI –2.7 to –2.0; Mini Mental State Examination [MMSE]: 9 RCTs, 3118 people; WMD 1.4, 95% CI 1.1 to 1.6).[20] There was significant heterogeneity among RCTs included in both analyses. The review reported that in one analysis (MMSE), this resulted from one RCT (466 people) that found a larger treatment effect than other RCTs. It also found that acetylcholinesterase inhibitors significantly improved global assessment compared with placebo at 6 months (Clinician's Interview-Based Impression of Change-Plus [CIBIC-Plus] scale; number of people improved: 8 RCTs;

Google ADAS-cog MID

Web Images Videos More Search tools

About 1,290,000 r **70p; MID=4**

The ADAS-cog and clinically meaningful change in the VISTA...
www.ncbi.nlm.nih.gov/pubmed/19548273
by K Rockwood - 2010 - Cited by 13 - Related articles
BACKGROUND: A minimum 4-point change at 6 months on the Alzheimer's disease assessment scale-cognitive subscale (**ADAS-cog**) is deemed clinically ...

The ADAS-Cog revisited: novel composite scales based on A...
www.ncbi.nlm.nih.gov/pubmed/23127469
by N Raghavan - 2013 - Cited by 1 - Related articles
Nov 2, 2012 - BACKGROUND: The Alzheimer's Disease Assessment Scale-Cognitive (**ADAS-Cog**) has been used widely as a cognitive end point in ...

[PDF] **ADAS – Cognitive Behavior SAMPLE FORM – Page 1 of 4**
www.dementia-assessment.com.au/**cognitive**/**ADAS**_Packet.pdf
Middle Alzheimer's Disease Cooperative Study: ADAS Cognitive Behavior of

Benefits

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
We found one systematic review comparing acetylcholinesterase inhibitors as a group versus placebo;[20] one systematic review comparing the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine individually versus placebo;[21] one systematic review of rivastigmine versus placebo;[22] and one subsequent RCT comparing galantamine versus placebo.[23] There was widespread overlap of RCTs between the reviews. The first review (search date 2005; 13 multicentre double-blind RCTs; people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company.[20] It performed an intention-to-treat analysis, and where full data were not available, it performed an analysis with the last observation carried forward (LOCF). The review found that people leaving before the end of studies ranged from 16% to 43% in the treatment group and 0% to 30% in the placebo group. The review found that acetylcholinesterase inhibitors significantly improved cognitive outcomes compared with placebo at 6 months or later (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 10 RCTs, 4236 people; WMD –2.4, 95% CI –2.7 to –2.0; Mini Mental State Examination [MMSE]: 9 RCTs, 3118 people; WMD 1.4, 95% CI 1.1 to 1.6).[20] There was significant heterogeneity among RCTs included in both analyses. The review reported that in one analysis (MMSE), this resulted from one RCT (466 people) that found a larger treatment effect than other RCTs. It also found that acetylcholinesterase inhibitors significantly improved global assessment compared with placebo at 6 months (Clinician's Interview-Based Impression of Change-Plus [CIBIC-Plus] scale; number of people improved: 8 RCTs;

minimum important difference for MMSE

About 26,200 results (0.07 sec)

MMSE: 1,4 p

Did you mean: ***minimal*** important difference for MMSE

Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline
P Raina, P Santaguida, A Ismaila... - Annals of Internal ..., 2008 - Am Coll Physicians
1.
Cited by 356 Related articles All 20 versions Cite Save

Minimal detectable change and clinically **important difference** of the Wolf Motor Function Test in stroke patients
K Lin, Y Hsieh, C Wu, C Chen, Y Jang... - ... and neural repair, 2009 - nnr.sagepub.com
... there is concern over the **differences** between group and individual clinical **importance**.40 Average **...**
Understanding the **minimum** clinically **important difference**: a review of concepts and methods. **...**
Responsiveness and minimal **important differences** for patient reported outcomes. **...**
Cited by 41 Related articles All 8 versions Cite Save

Determining the **minimum** clinically **important differences** for outcomes in the DOMINO trial
R Howard, P Phillips, T Johnson... - ... journal of geriatric ..., 2011 - Wiley Online Library
... Despite a large clinical trial base, the **importance** and cost-effectiveness of drug treatments for **...**
The **minimum** change that would constitute a clinically significant behavioural response in AD2000
was **...** and memantine in the treatment of people with dementia it is **important** that the **...**
Cited by 14 Related articles All 9 versions Cite Save

Benefits

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
We found one systematic review comparing acetylcholinesterase inhibitors as a group versus placebo;[20] one systematic review comparing the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine individually versus placebo;[21] one systematic review of rivastigmine versus placebo;[22] and one subsequent RCT comparing galantamine versus placebo.[23] There was widespread overlap of RCTs between the reviews. The first review (search date 2005; 13 multicentre double-blind RCTs; people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company.[20] It performed an intention-to-treat analysis, and where full data were not available, it performed an analysis with the last observation carried forward (LOCF). The review found that people leaving before the end of studies ranged from 16% to 43% in the treatment group and 0% to 30% in the placebo group. The review found that acetylcholinesterase inhibitors significantly improved cognitive outcomes compared with placebo at 6 months or later (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 10 RCTs, 4236 people; WMD –2.4, 95% CI –2.7 to –2.0; Mini Mental State Examination [MMSE]: 9 RCTs, 3118 people; WMD 1.4, 95% CI 1.1 to 1.6).[20] There was significant heterogeneity among RCTs included in both analyses. The review reported that in one analysis (MMSE), this resulted from one RCT (466 people) that found a larger treatment effect than other RCTs. It also found that acetylcholinesterase inhibitors significantly improved global assessment compared with placebo at 6 months (Clinician's Interview-Based Impression of Change-Plus [CIBIC-Plus] scale; number of people improved: 8 RCTs;

[21] The review also found that donepezil, galantamine, and rivastigmine significantly improved functional outcomes compared with placebo (SMD in functional outcome change from baseline: donepezil 5 mg or 10 mg: 7 RCTs; SMD 0.31, 95% CI 0.21 to 0.40; galantamine 16–32 mg: 4 RCTs; SMD 0.27, 95% CI 0.18 to 0.36; rivastigmine 6–12 mg: 3 RCTs; SMD 0.26, 95% CI 0.11 to 0.40; numbers of people not reported for any of the pooled analyses).[21] There was significant heterogeneity among RCTs included in the rivastigmine comparison. The review found that rivastigmine and donepezil significantly improved global assessment of change scores compared with placebo at 3 to 6 months (CIBIC-Plus scale: donepezil 5 mg or 10 mg: 3 RCTs; RR 1.88, 95% CI 1.50 to 2.34; rivastigmine 6 mg or 12 mg: 2 RCTs; RR 1.64, 95% CI 1.29 to 2.09), but that galantamine did not significantly improve CIBIC-Plus scores (galantamine 16–32 mg: 4 RCTs; RR 1.15, 95% CI 0.96 to 1.39; numbers

Therapeutics

Review: Antispasmodic and antidepressant drugs were each effective in the irritable bowel syndrome; bulking agents were not

Ruepert L, Quartero AO, de Wit NJ, et al. ***Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome.*** *Cochrane Database Syst Rev. 2011;(8):CD003460.*

Clinical impact ratings: GM ★★★★★★☆ GI ★★★★★☆☆

Antispasmodic drugs, antidepressant drugs, or bulking agents vs placebo in patients with the irritable bowel syndrome*

Treatment type	Outcomes	Number of trials (*n*)	Weighted event rates	RBI (95% CI)	NNT (CI)
				Standardized mean difference (CI)‡	
Bulking agents	Improved abdominal pain	2 (116)§		0.03 (–0.34 to 0.40)	
	Improved symptom score	2 (84)§		0.00 (–0.43 to 0.43)†	

http://annals.org/article.aspx?articleid=1033249&resultClick=3

In addition, the effect of antidepressants might not be clinically important because the lower margins of the confidence intervals are <0.5 standardized mean differences for continuous measures of abdominal pain and symptom scores.

Cristian Baicus, MD
Theodor Voiosu, MD
Colentina University Hospital
Bucharest, Romania

1. **Uitați-vă întotdeauna după mărimea efectului!**
2. **Dacă eşantionul este foarte mare, efectul este mic.**
3. **Este efectul important?**
4. **Care este intervalul de încredere?**
5. **Cum a răspuns acest pacient?**