University Medical Center Groningen

Baseline imbalances in alirocumab and evolocumab trials: A meta-epidemiological study

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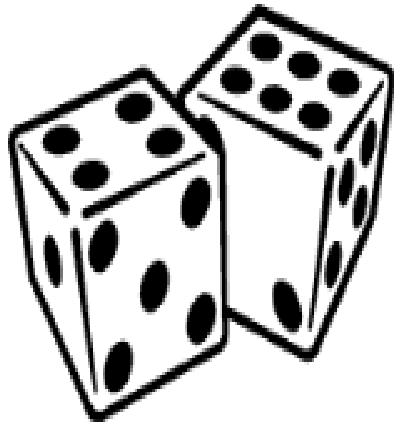
Critical assessment of randomisation

1. Randomness of allocation sequence?
2. Concealment of allocation?
3. Presence of baseline imbalances?



Higgins et al Cochrane Handbook 2023

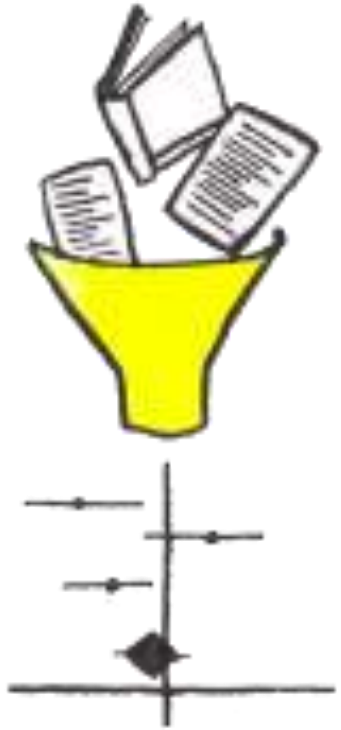
Critical assessment of baseline imbalances

Table 2. Clinical Characteristics of the Patients at Baseline.*

Characteristic	Evolocumab Group (N=2976)	Standard-Therapy Group (N=1489)
Mean age ±SD — yr	57.8±11.0	58.2±10.9
Male sex — no. (%)	1490 (50.1)	765 (51.4)
White race — no. (%)†	2559 (86.0)	1267 (85.1)

Sabatine et al NEJM 2015

Quantitative assessment of baseline imbalances



Search & selection: 43 studies

Data extracted per group:
- 7 baseline characteristics
- 5 clinical outcomes

Analysis

Range and direction of baseline differences

Patient characteristic	Range	Direction, n-/ n0/ n+	Sign test, p
Age, mean yearw	-3.1 to 4.1	20/5/18	.436
Male, %	-19.6 to 25.8	24/1/18	.220
LDL-cholesterol, mean mg/dl	-7.7 to 35.4	16/2/25	.106
BMI, mean	-1.5 to 1.7	15/1/15	.572
Diabetes mellitus, %	-12.6 to 17.4	18/2/17	.500
Smoking, %	-12.6 to 7.6	13/0/12	.500
Hypertension, %	-24.0 to 13.7	13/0/14	.500

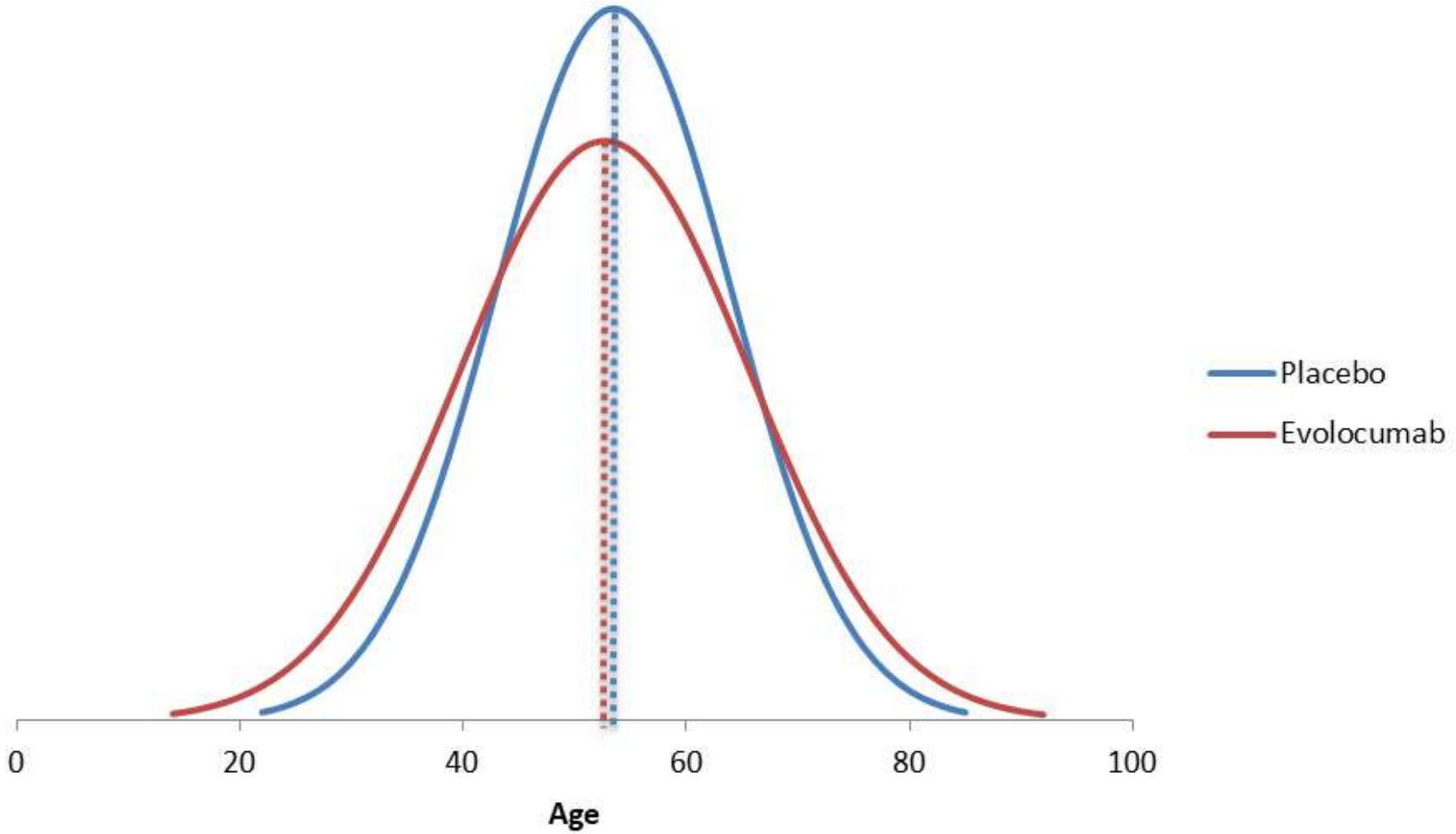
Pooled baseline differences & heterogeneity

Patient characteristic	Pooled difference, MD or RD (95%CI)	Heterogeneity, I^2 (95% CI); p
Age, mean	-0.03 (-0.18 to 0.12)	0 (0-35); .692
Male, %	0.00 (-0.01 to 0.01)	31 (0-53); .029
LDL-cholesterol, mean	0.07 (-0.34 to 0.47)	0 (0-35); .484
BMI, mean	-0.03 (-0.05 to -0.02)*	33 (0-57); .039
Diabetes mellitus, %	0.00 (-0.01 to 0.01)	32 (0-55); .035
Smoking, %	-0.00 (-0.01 to 0.00)	10 (0-43); .317
Hypertension, %	0.01 (0.00 to 0.02)#	36 (0-60); .033

* $p < .01$; # $p < .05$

Differences in standard deviations

Patient characteristics	Range	Direction, n-/n0/n+	Sign test, p	Average SD drug vs control; p
Age, SD	-2.1 to 3.0	13/2/28	.014	9.88 vs 9.54; .290
LDL-cholesterol, SD	-21.2 to 23.7	13/2/28	.014	34.30 vs 33.15; .806
BMI, SD	-1.5 to 1.7	10/1/20	.049	5.06 vs 4.83; .117



Koren et al JACC 2014

Association with effects on outcomes

Patient characteristic	Mortality, effect on OR (95% CI)
Age, per year older	0.16 (-0.25 to 0.58)
Male, per 1% more	-0.00 (-0.07 to 0.06)
LDL-cholesterol, per mg/dl more	-0.01 (-0.10 to 0.07)
BMI, per point more	-0.56 (-1.10 to -0.02)
Diabetes mellitus, per 1% more	-0.05 (-0.14 to 0.04)
Smoking, per 1% more	-0.09 (-0.24 to 0.07)
Hypertension, per 1% more	-0.05 (-0.13 to 0.04)

Limitations

- Missing baseline data
- No correction for multiple testing

Baseline differences in age: 12 reviews

Systematic review	Number of studies in meta-analysis	Difference in age (*P*-value)	I^2 value	Distribution of p-values	Distribution of standardized mean in control group	
Anothaisintawee et al. 2012	10	0.001	84.42		x	
Thangaratinam et al. 2012	20	0.113	50.11	x	x	
Umpierre et al. 2011	26	0.098	45.46		x	
Heneghan et al. 2011	7	0.223	40.13			
Neumann et al. 2012	9	0.821	33.46		x	
Palmer et al. 2012	11	0.173	29.03		x	
Rutjes et al. 2012	38	0.616	20.39	x	x	
Orrow et al. 2012	10	0.736	16.18			
Hemmingsen et al. 2012	13	0.347	0.00			✔
Coombes et al. 2010	18	0.362	0.00			✔
Leucht et al. 2012	21	0.008	0.00			
Hempel et al. 2012	26	0.818	0.00			✔

Clark et al JCE 2014

Conclusions

- Alirocumab and evolocumab trials showed biased randomisation
- Baseline imbalances in trials should be assessed quantitatively more often in reviews