SAFETY AND CARDIOVASCULAR EFFICACY OF ANTI-PCSK9 MONOCLONAL ANTIBODIES: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

With thanks to the EAS for support
in the form of a Young Investigator Fellowship

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BACKGROUND

Proprotein convertase subtilisin-kexin type 9 (**PCSK9**) is a serine protease crucially **involved in lipid metabolism** by mediating LDL receptor clearance.

Since the role of PCSK9 in LDLR degradation and LDL-cholesterol metabolism was discovered, different pharmacological approaches to inhibit this protein and lower plasma LDL-C have been developed. Among the monoclonal antibodies (**mAbs**) developed against PCSK9, clinical trial results are available for **alirocumab** (SAR236553/REGN727) and **evolocumab** (AMG145).

Data from randomized controlled trials (RCTs) assessing the impact of PCSK9 mAbs on cardiovascular (CV) outcomes have indicated a clear **clinical benefit** in subjects at high CV risk.

AIM

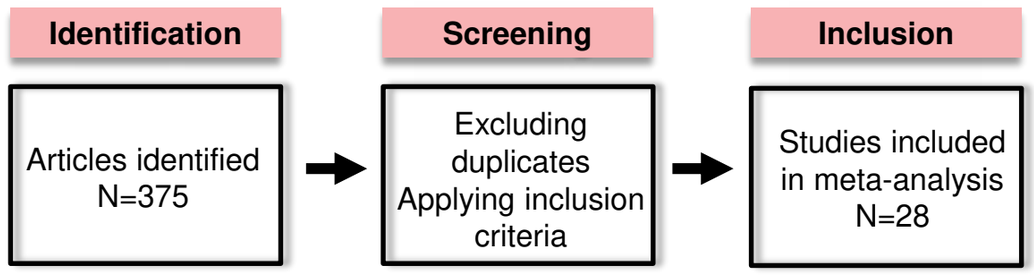
Aim of this meta-analysis was to investigate the safety and efficacy of treatment with PCSK9 antibodies, particularly with respect to their effect on clinical outcomes, in all published RCTs, updating the available results.

METHODS

Pubmed, MEDLINE, and EMBASE were searched from inception until November 2018.
The search strategy included keywords and MeSH terms relating to the PCSK9 inhibitors evolocumab and alirocumab.
The inclusion criteria were:
(1) English language;
(2) phase 2 or 3 RCTs;
(3) comparing PCSK9 antibodies with placebo;
(4) reporting data on CV outcomes;
(5) treatment duration longer than 8 weeks.

Primary clinical end points were all-cause mortality and cardiovascular mortality; secondary end points were CV events (myocardial infarction, unstable angina, revascularization, heart failure, cerebrovascular events, stroke), and serious adverse events (as reported in each RCT).

Odds ratios (ORs) with 95% CIs were used as summary statistics. Between-study heterogeneity was measured with the I^2 statistics.



CONCLUSIONS

We observed a significant reduction in the risk of CV events, a small but significant reduction of serious adverse events, and no differences in either all-cause or cardiovascular mortality.

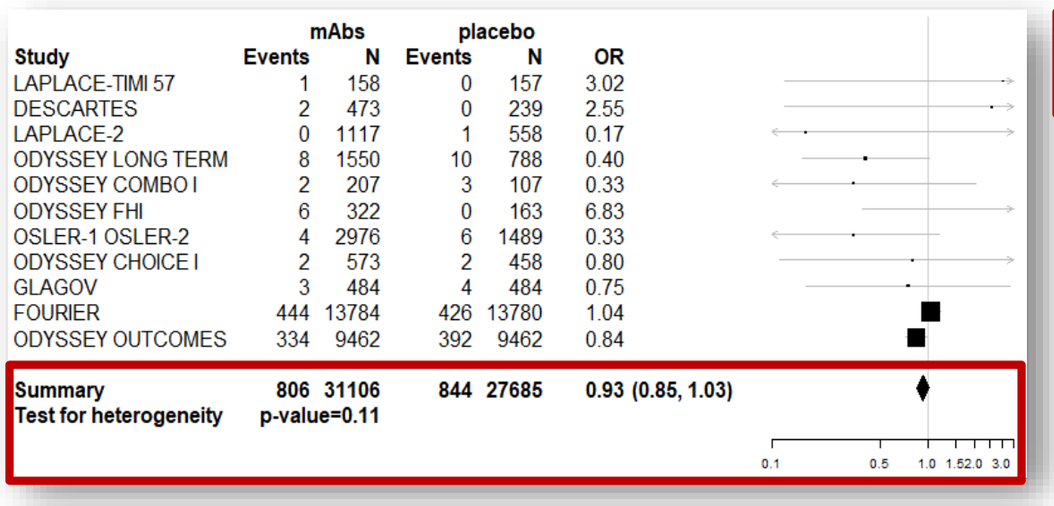
These results suggest that:
(1) the inhibition of PCSK9 significantly improves cardiovascular outcomes
(2) the treatment with PCSK9-mAbs appears to be safe.

Despite that, no significant cardiovascular mortality benefit seems to be associated with PCSK9 mAb treatment. It might be achievable with a longer observation period, since translation of cholesterol lowering into a cardiovascular benefit requires time.

RESULTS

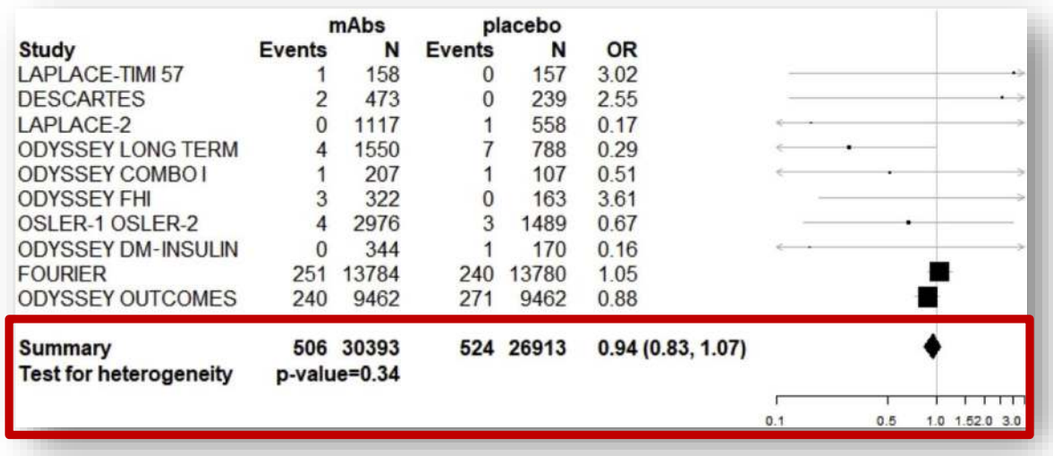
The 28 selected studies included 62,281 participants (33,204 in the mAb arm, 29,077 in the placebo arm); all of them were RCTs comparing evolocumab or alirocumab with placebo (mainly on top of a statin). The treatment follow-up ranged from 8 weeks up to 208 weeks.

All-cause mortality



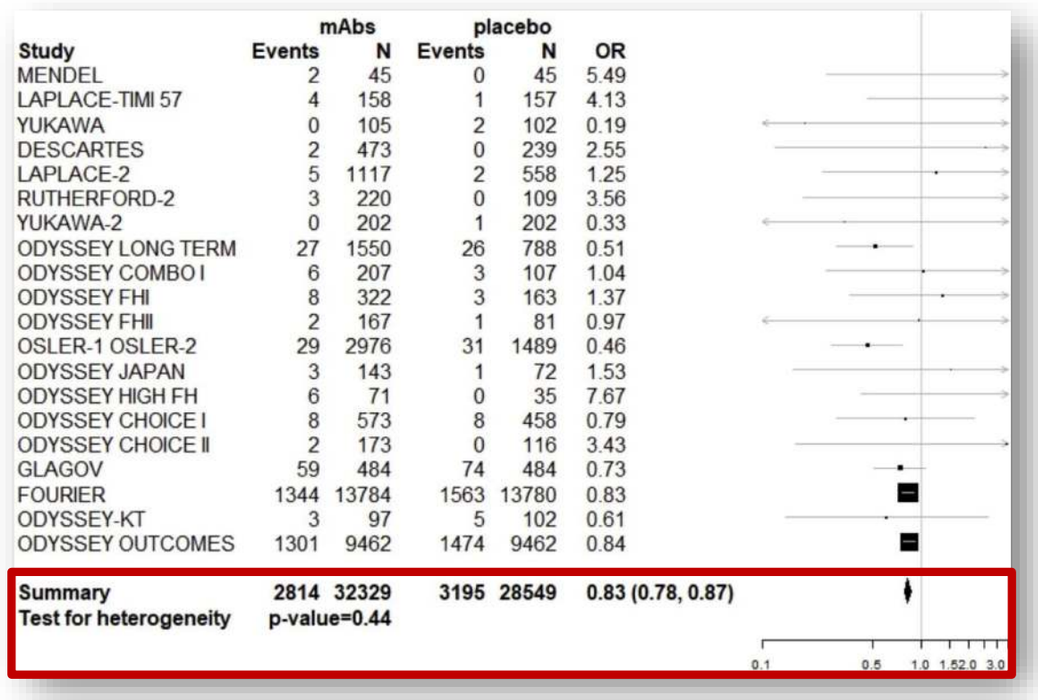
Study	mAbs Events	mAbs N	placebo Events	placebo N	OR
LAPLACE-TIMI 57	1	158	0	157	3.02
DESCARTES	2	473	0	239	2.55
LAPLACE-2	0	1117	1	558	0.17
ODYSSEY LONG TERM	8	1550	10	788	0.40
ODYSSEY COMBO I	2	207	3	107	0.33
ODYSSEY FHI	6	322	0	163	6.83
OSLER-1 OSLER-2	4	2976	6	1489	0.33
ODYSSEY CHOICE I	2	573	2	458	0.80
GLAGOV	3	484	4	484	0.75
FOURIER	444	13784	426	13780	1.04
ODYSSEY OUTCOMES	334	9462	392	9462	0.84
Summary	**806**	**31106**	**844**	**27685**	**0.93 (0.85, 1.03)**
Test for heterogeneity	**p-value=0.11**				

CV mortality



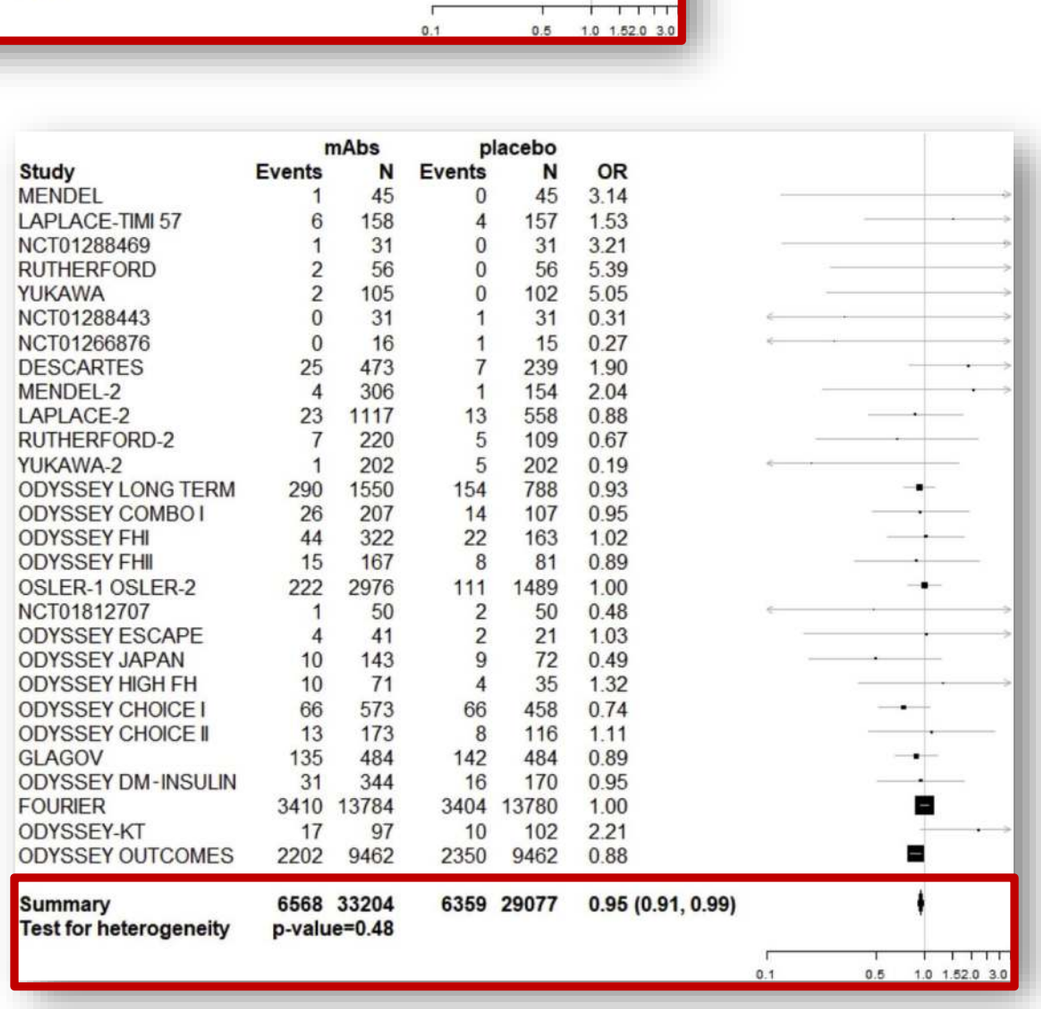
Study	mAbs Events	mAbs N	placebo Events	placebo N	OR
LAPLACE-TIMI 57	1	158	0	157	3.02
DESCARTES	2	473	0	239	2.55
LAPLACE-2	0	1117	1	558	0.17
ODYSSEY LONG TERM	4	1550	7	788	0.29
ODYSSEY COMBO I	1	207	1	107	0.51
ODYSSEY FHI	3	322	0	163	3.61
OSLER-1 OSLER-2	4	2976	3	1489	0.67
ODYSSEY DM-INSULIN	0	344	1	170	0.16
FOURIER	251	13784	240	13780	1.05
ODYSSEY OUTCOMES	240	9462	271	9462	0.88
Summary	**506**	**30393**	**524**	**26913**	**0.94 (0.83, 1.07)**
Test for heterogeneity	**p-value=0.34**				

CV events



Study	mAbs Events	mAbs N	placebo Events	placebo N	OR
MENDEL	2	45	0	45	5.49
LAPLACE-TIMI 57	4	158	1	157	4.13
YUKAWA	0	105	2	102	0.19
DESCARTES	2	473	0	239	2.55
LAPLACE-2	5	1117	2	558	1.25
RUTHERFORD-2	3	220	0	109	3.56
YUKAWA-2	0	202	1	202	0.33
ODYSSEY LONG TERM	27	1550	26	788	0.51
ODYSSEY COMBO I	6	207	3	107	1.04
ODYSSEY FHI	8	322	3	163	1.37
ODYSSEY FHII	2	167	1	81	0.97
OSLER-1 OSLER-2	29	2976	31	1489	0.46
ODYSSEY JAPAN	3	143	1	72	1.53
ODYSSEY HIGH FH	6	71	0	35	7.67
ODYSSEY CHOICE I	8	573	8	458	0.79
ODYSSEY CHOICE II	2	173	0	116	3.43
GLAGOV	59	484	74	484	0.73
FOURIER	1344	13784	1563	13780	0.83
ODYSSEY-KT	3	97	5	102	0.61
ODYSSEY OUTCOMES	1301	9462	1474	9462	0.84
Summary	**2814**	**32329**	**3195**	**28549**	**0.83 (0.78, 0.87)**
Test for heterogeneity	**p-value=0.44**				

Serious adverse events



Study	mAbs Events	mAbs N	placebo Events	placebo N	OR
MENDEL	1	45	0	45	3.14
LAPLACE-TIMI 57	6	158	4	157	1.53
NCT01288469	1	31	0	31	3.21
RUTHERFORD	2	56	0	56	5.39
YUKAWA	2	105	0	102	5.05
NCT01288443	0	31	1	31	0.31
NCT01266876	0	16	1	15	0.27
DESCARTES	25	473	7	239	1.90
MENDEL-2	4	306	1	154	2.04
LAPLACE-2	23	1117	13	558	0.88
RUTHERFORD-2	7	220	5	109	0.67
YUKAWA-2	1	202	5	202	0.19
ODYSSEY LONG TERM	290	1550	154	788	0.93
ODYSSEY COMBO I	26	207	14	107	0.95
ODYSSEY FHI	44	322	22	163	1.02
ODYSSEY FHII	15	167	8	81	0.89
OSLER-1 OSLER-2	222	2976	111	1489	1.00
NCT01812707	1	50	2	50	0.48
ODYSSEY ESCAPE	4	41	2	21	1.03
ODYSSEY JAPAN	10	143	9	72	0.49
ODYSSEY HIGH FH	10	71	4	35	1.32
ODYSSEY CHOICE I	66	573	66	458	0.74
ODYSSEY CHOICE II	13	173	8	116	1.11
GLAGOV	135	484	142	484	0.89
ODYSSEY DM-INSULIN	31	344	16	170	0.95
FOURIER	3410	13784	3404	13780	1.00
ODYSSEY-KT	17	97	10	102	2.21
ODYSSEY OUTCOMES	2202	9462	2350	9462	0.88
Summary	**6568**	**33204**	**6359**	**29077**	**0.95 (0.91, 0.99)**
Test for heterogeneity	**p-value=0.48**				