REVIEW

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Efficacy and safety of different doses of alirocumab in reducing low-density lipoprotein cholesterol levels: a network meta-analysis

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This study aimed to conduct a network meta-analysis of the efficacy and safety of different doses of alirocumab in reducing low-density lipoprotein cholesterol levels. In the present study, a total of 16 studies were selected, published between January 2012 and October 2016. Pair-wise and network meta-analyses was used to carry out a direct and indirect comparison of the three treatment strategies of alirocumab in patients with hypercholesterolemia. The efficacy and safety of these different treatment strategies were analyzed. Results revealed that alirocumab could significantly reduce LDL-c levels, compared with placebo (relative effect 95 % CI: -71.45 [-91.16, -50.44], -74.32 [-90.40, -58.63] and -77.28 [-92.21, -61.90]) and ezetimibe (EZE) (relative effect 95 % CI: -37.2 [-61.21, -12.41], -40.07 [-56.92, -24.22] and -43.00 [-68.39, -17.91]). The comparison of the three treatment strategies of alirocumab indicated no significant differences in reducing the levels of LDL-c, TGs, TC, Lp (a), Apo B and SAEs, LTTD, IST, ACE, MD and NC. For the probabilities of 75 mg, 75-150 mg and 150 mg of alirocumab, the best treatment for EZE and placebo were 50 %, 68 %, 82 %, 1 % and 0 %, according to LDL-c level. The results of the benefit-risk analysis of efficacy and safety revealed that the logarithmic scale was 0.016 for 75 mg *vs.* 75-150 mg of alirocumab and 0.125 for 75-150 mg *vs.* 150 mg of alirocumab. The PCSK9 inhibitor alirocumab presents a significantly greater reducing effect on the levels of LDL-c compared with EZE, and the different doses of alirocumab exhibited no significant difference in the efficacy of LDL-c for hypercholesterolemia. An alirocumab dose of 75-150 mg *Q2W* might be the best choice due to its most favorable balance between efficacy and safety.

1. Introduction

The reduction in low-density lipoprotein cholesterol (LDL-c) levels has been included in practice guidelines as a fundamental method of reducing cardiovascular events and mortality. Based on previous studies, statins have been confirmed to reduce cardiovascular disease (CVD) events, and recommended as the first-line therapy for CVD management (Stone et al. 2013). However, a necessity for other lipid-lowering (especially LDL-c) agents still exists, because some patients cannot tolerate statins due to adverse events, or cannot achieve an intensive LDL-c target level (Dadu and Ballantyne 2014). Therefore, non-statin therapy for LDL-c reduction has been considered as a novel effective medication and treatment strategy for reducing LDL-c levels, and has become a focus of research.

Monoclonal antibodies to proprotein convertase subtilisin-kexin type 9 (PCSK9) have been shown up as a novel class of therapeutic agent that targets LDL-c (Noto et al. 2014). The efficacy and safety of the PCSK9 inhibitor alirocumab were assessed in randomized, controlled trials (RCTs) (Huynh 2015). Alirocumab, a fully human monoclonal antibody, can effectively reduce LDL-c levels, and has been investigated in phase-3 trials (Stone et al. 2014; Roth et al. 2014; Moriarty et al. 2015; Cannon et al. 2015; Roth et al. 2016; Teramoto et al. 2016a; Robinson et al. 2015; McKenney et al. 2012; Ginsberg et al. 2016; Koren et al. 2015; Kereiakes et al. 2015; Farnier et al. 2016a; Kastelein et al. 2015; Bays et al. 2015; Farnier et al. 2016b; Teramoto et al. 2016b;). In 2014, pharmaceutical companies submitted a biologics license application to obtain approval from the U.S. Food and Drug Administration for the use of the PCSK9 inhibitor alirocumab (SAR236553/REGN727) in the treatment of high cholesterol levels (Bays et al. 2015). Most RCTs of alirocumab contain three treatment strategies: alirocumab 75-mg Q2W throughout (alirocumab 75-mg Q2W), alirocumab 150-mg Q2W throughout (alirocumab 150-mg Q2W), and alirocumab 75-mg Q2W with a dose adjustment to 150 mg Q2W when the W8 predefined LDL-C levels were not less than 70 mg/dL (alirocumab 75-150 mg Q2W). The sample sizes of each trial were small and limited, which may have decreased their reliability. A meta-analysis, which is a means of summarizing and combining the quantitative results of research or a method used to reach the quantitative effect size based on individual studies, uses many quantitative approaches and calculation formulas when compiling multiple research findings (Çoğaltay and Karadağ 2015). Although traditional meta-analytical methods pertain to pair-wise comparisons between two interventions, network meta-analysis can be used for all possible comparisons in a body of evidence, regardless of whether there have been direct head-to-head comparisons in clinical trials (Panagiotou 2015). A network meta-analysis can statistically compare mixed treatments and obtain relative scientific comparison results (Lipinski et al. 2016). However, to the best of our knowledge, a comprehensive analysis of the efficacy and safety of the above mentioned three treatments strategies of alirocumab have not been evaluated.

Therefore, in the present study, we compared the regular treatment strategies of alirocumab for hypercholesterolemia, and aimed to determine the best treatment through the network meta-analysis of RCTs, in order to address the efficacy (to determine the exact extent of lipid changing effect) and safety (to provide the exact rates of common adverse events).

2. Search strategy

Using an OVID interface, two independent reviewers systematically searched the EMBASE, MEDLINE/PubMed, Cochrane CENTRAL and ClinicalTrials.gov electronic databases for published studies between August 2004 and October 2016. Relevant RCTs were identified by a combination of medical subject headings without subheading and language restrictions and key words including the following terms: (Randomized trial OR clinical trial) AND blind OR random AND control (placebos OR ezetimibe) NOT (comment OR editorial OR meta-analysis OR letter) AND (proprotein convertases subtilisin/kexin type 9 OR PCSK9) inhibitor (alirocumab OR REGN727 OR SAR236553) AND (75 mg Q2W OR 150 mg Q2W) AND efficacy (LDL-c level OR LDL-c concentration) OR safety OR tolerability.

3. Inclusion/exclusion criteria and study selection

Inclusion criteria comprised RCTs that enrolled patients scheduled for any of the following treatments: placebo, ezetimibe, A, B and C. When different studies reported on the same population, the study that had a larger sample size and performed the evaluation using more comprehensive methods was included.

4. Data extraction and quality assessment

The following data elements were extracted from each report, according to a fixed protocol: author, publication year, study design, characteristics of the trial participants, median follow up, mean age, the ratio of males, females, diabetes cases, smokers and hypertension cases, and data on the efficacy and safety outcomes of the intervention. Data were extracted directly from the manuscripts, compared with the data included in the Cochrane review, and entered into the ADDIS software. Methodological quality assessment was performed using the Cochrane Collaboration's tool for assessing risk of bias, addressing the adequacy of randomization and allocation concealment, blinding (participants/personnel and outcome assessment), the completeness of outcome data, selective reporting and the presence of any other bias (Cochrane Handbook for Systematic Reviews of Interventions).

5. End-points and definition

The primary efficacy end-point was patients who achieved LDL-c concentrations <70 mg/dl (1.8 mmol/l). The secondary efficacy end-point were TC, TGs, HDL-c, Lp(a), Apo A1, Apo B, and non-HDL-c. The safety end-point (more than 10%) included serious adverse events (SAEs) that led to treatment discontinuation, injection-site reactions, adjudicated cardiovascular events, and musculoskeletal disorders.

6. Statistical analysis

Continuous data were expressed as mean±standard deviation (SD) or median with interquartile range. The relative effects were estimated in terms of odds ratio (OR) with 95% confidence intervals (CI). The results were considered to show no significant inconsistency when 95% CIs of inconsistency factors included zero. A large *P*-value (>0.05) for the comparison between direct and indirect effects in the node splitting analysis also indicates a lack of significant inconsistency. The ranking probability was estimated for each treatment strategy, that is, the overall ranks were interpreted by the surface under the cumulative ranking (SUCRA) technique (Salanti et al. 2011). A difference between active treatments and placebo was assumed to be statistically significant when the lower limit of 95 % CIs of the OR was not equal to 1. In the logistic regression model, if OR of a variable is >1, this means that this factor is a risk factor. Otherwise, an OR of <1 means that this factor is a protect factor. Network meta-analyses are often conducted in a Bayesian framework, and estimated using the Markov chain Monte Carlo methods, which is the approach recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Documents on evidence synthesis (TSD2 General meta analysis). If there was no significant inconsistency, the relative effects of the interventions were analyzed using a consistency model based on the random-effects Bayesian model provided by the ADDIS software. A network meta-analysis was performed in ADDIS Version 1.16.1, which is the software that uses Bayesian Markov chain Monte Carlo methods.

7. Eligible studies and its characteristics

The preferred reporting items for the meta-analysis flow diagram is presented in Fig. 1. Sixteen trials (Roth et al. 2014; Moriarty et al. 2015; Cannon et al. 2015; Roth et al. 2016; Teramoto et al. 2016a; Robinson et al. 2015; McKenney et al. 2012; Ginsberg et al. 2016; Koren et al. 2015; Kereiakes et al. 2015; Farnier et al. 2016a; Kastelein et al. 2015; Bays et al. 2015; Farnier et al. 2016b; Teramoto et al. 2016b; Stroes et al. 2016; Moriarty et al. 2014) with 7,042 randomized participants were included in the network meta-analysis. The duration of the trials ranged from 12 to 24 weeks. Four studies compared B with both placebo (Roth et al. 2016; Teramoto et al. 2016a; Kereiakes et al. 2015; Kastelein et al. 2015;) and ezetimibe (Roth et al. 2014; Cannon et al. 2015; Teramoto et al. 2016b; Stroes et al. 2016; Moriarty et al. 2014),

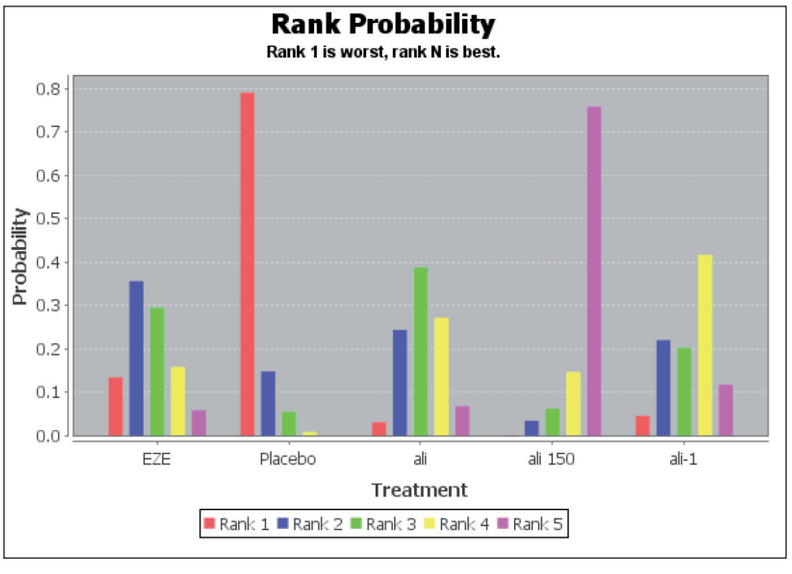

Fig. 1: Rank scores providing probability rank of therapy providing the greatest reduction in lipid following therapy with the different treatment groups where the closer to one equates to the probability the therapy leads to the greatest reduction, probability of the best treatment for TG.

five studies (Robinson et al. 2015; McKenney et al. 2012; Ginsberg et al. 2016; Koren et al. 2015; Salanti et al. 2011; TSD2 General meta analysis) compared C with placebo, and one study compared A with ezetimibe (Moriarty et al. 2015). The details are presented in Fig. 2. All included studies had a low risk of bias, as assessed by the Cochrane Collaboration tool for assessing risk of bias 24 in Fig. 3, and all studies were considered of high quality according to the GRADE system (Guyat et al. 2008). Tables 1, 2 and 3 provide the details on the characteristics of the included studies. All trials reported the change in the mean of LDL-c levels.

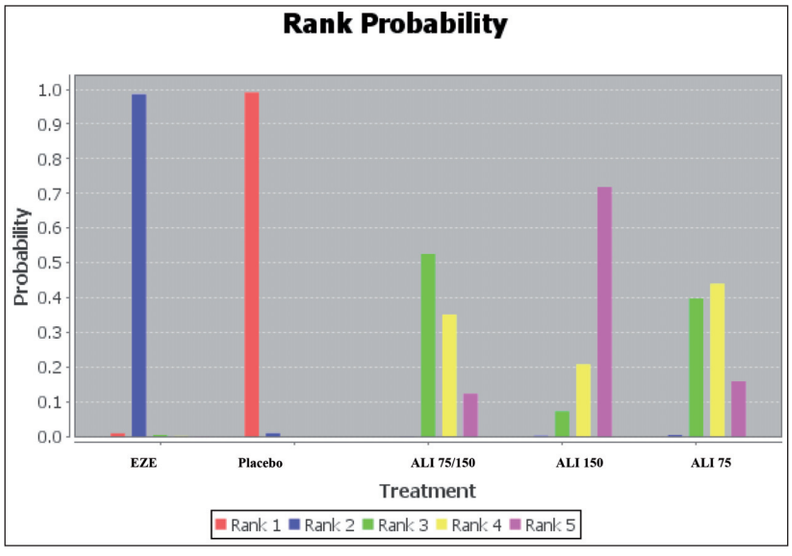

Fig. 2: Rank scores providing probability rank of therapy providing the greatest reduction in lipid following therapy with the different treatment groups where the closer to one equates to the probability the therapy leads to the greatest reduction, shows the probability analysis of the best treatment for LDL-c.

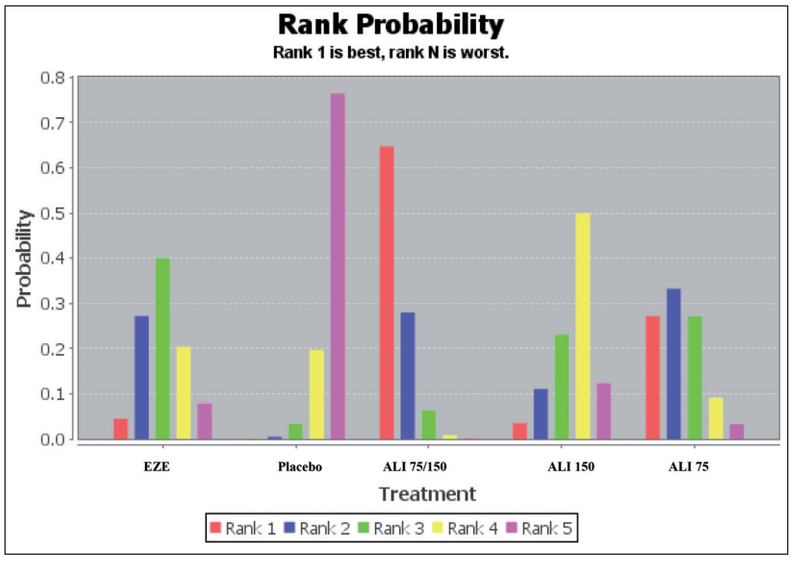

Fig. 3: Rank scores providing probability rank of therapy providing the greatest reduction in lipid following therapy with the different treatment groups where the closer to one equates to the probability the therapy leads to the greatest reduction, probability of the best treatment for HDL-c.

Table 1: Study characteristics of included trials

First Author	Publication year	Study type	Included patients	Patient groups	Groups for Analysis	Followup length	Stain intolerance
Roth EM	2014	Phase 3	103	51 ezetimible(10mg), 52 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	NR
Moriarty PM	2015		251	126 ezetimible(10mg), 125 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	NR
Cannon CP	2015		720	479 ezetimible(10mg), 241 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	No
Roth EM	2016	Phase 3	345	230 Placebo, 115 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Placebo Alirocumab	24W	No
Teramoto T	2016	Phase 1, 2	75	25 Placebo, 50 Alirocumab(25, 150mg Q2W, 25:75mg Q2W)	Placebo Alirocumab	12W	No
Robinson J	2015	Phase 3	2341	780 Placebo, 1530 Alirocumab(150mg Q2W)	Placebo Alirocumab	24W	No
Mckenney JM	2012		62	31 Placebo, 29 Alirocumab(150mg Q2W)	Placebo Alirocumab	12W	No

First Author	Publication year	Study type	Included patients	Patient groups	Groups for Analysis	Followup length	Stain intolerance
Ginsbery HN	2016	Phase 3	107	35 Placebo, 72 Alirocumab(150mg Q2W)	Placebo Alirocumab	24W	No
Koren MJ	2015	Phase 2	57	31 Placebo, 26 Alirocumab(150mg Q2W)	Placebo Alirocumab	12W	Yes
Kereiakes DJ	2015	Phase 3	316	107 Placebo, 209 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Placebo Alirocumab	24W	No
Farnier M	2016	Phase 3	1130	686 ezetimible(10mg), 444 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	No
Kastelein JJP	2015	Phase 3	735	490 ezetimible(10mg), 245 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	No
Bays H	2015	Phase 3	206	102 ezetimible(10mg), 104 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	Yes
Farnier M	2015	Phase 3	204	101 ezetimible(10mg), 103 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Ezetimible Alirocumab	24W	Yes
Teramoto T	2016	Phase 3	216	72 Placebo, 144 alirocumab(started 75mg Q2W and increased to 150mg Q2W if not at goal)	Placebo Alirocumab	24W	No
Stroes E	2016	Phase 3	174	58 Placebo, 116 Alirocumab(75mg Q2W)	Placebo Alirocumab	24W	

Q2W,every 2 weeks;Q4W,every 4 weeks. NR, not reported.

Table 2: Patient characteristics of included randomized controlled trials

First Author	Age (year)	Male gender (%)	Caucasian (%)	Black (%)	known CAD (%)	Hypertension (%)	Diabetes mellitus (%)	Smoking (%)	Family history of CAD(%)	Baseline statins(%)
Roth EM	60.2±5.0	53.4	90.3	9.7	NR	NR	3.9	NR	NR	NR
Moriarty PM	63.5±9.6	54.6	92.8	4.8	47.0	64.5	23.9	6.4	NR	59.4
Cannon CP	61.6±9.3	73.6	84.7	3.9	90.1	NR	34.9	NR	NR	99.7
Roth EM	60.7±9.9	46.4	86.7	11.3	NR	NR	40.3	NR	NR	68.1
Teramoto T	57.7±10.0	48.0	NR	NR	0.0	34.7	14.7	NR	NR	NR
Robinson J	60.5±10.4	62.2	92.7	NR	68.6	NR	34.6	20.7	NR	99.9
Mckenney JM	56.6±10.4	41.9	83.9	14.5	6.5	40.3	6.5	27.4	NR	NR
Ginsbery HN	50.6±13.3	53.3	87.9	NR	49.5	57.0	23.4	19.6	NR	100.0
Koren MJ	56.3±10.0	45.6	NR	NR	NR	NR	7.0	29.8	NR	NR
Kereiakes DJ	63.0±9.4	65.8	81.6	16.1	78.2	NR	43.0	NR	NR	99.7
Farnier M	61.9±9.7	68.8	85.6	NR	78.1	NR	36.2	NR	NR	99.9
Kastelein JJP	52.4±12.7	55.1	93.6	NR	42.7	39.6	9.1	16.1	NR	100.0
Bays H	64.0±9.9	63.6	88.3	NR	57.3	78.6	50.0	NR	NR	NR
Farnier M	60.9±10.3	56.9	85.8	7.8	56.9	71.1	39.7	NR	NR	78.9
Teramoto T	60.8±9.5	60.6	NR	NR	12.0	NR	68.5	NR	8.8	85.6
Stroes E	62.7±10.1	57.5	94.3	2.3	48.3	60.9	17.8	NR	NR	29.3

Data presented as mean ± SD. CAD, coronary artery disease; NR, not reported.

8. Network meta-analysis

Alirocumab 75 mg Q2W, alirocumab 75-150 mg Q2W, alirocumab 150-mg Q2W and ezetimibe have significant superior relative effects, compared to placebo, with OR and 95 % CIs of -71.45 (-91.16,-50.44), -74.32(-90.40,-58.63), -77.28 (-92.21,-61.90), and -34.31 (-54.84, -12.95), respectively, as shown in Table 4. A (OR: -37.2, 95 % CI: -61.21, -12.41), B (OR: -40.07, 95 % CI: -56.92, -24.22) and C (OR: -43.00, 95 % CI: -68.39, -17.91) were shown to be more efficacious than ezetimibe, and the change in mean LDL-c levels in A, B and C was statistically not significant.

The probabilities of the five drugs for TGs, LDL-c, and HDL-c are shown in Figures 1, 2 and 3. The results for LDL-c were shown to be consistent from the inconsistency model analysis.

9. Pairwise meta-analysis results

The pair-wise meta-analysis pooling implied that alirocumab markedly reduced the LDL-c level to <70 mg/dl (1.8 mmol/L) when compared with placebo (OR_A = -79.33, 95% CI = -97.42 to -61.24, P(Z)<0.01, P(Q)=15.52, I^2=93.6%; OR_B = -71.45, 95% CI = -88.22 to -54.68, P(Z)<0.01, P(Q)=137.13, I^2=97.8%; OR_C = -75.34, 95% CI, -80.92 to -69.76, P(Z)<0.01, P(Q) = 25.37, I^2=84.2%)

10. Safety

Various serious adverse effects (SAEs) could be observed after administration of alirocumab partly leading to treatment discontinuation. In our study, we collected the data based on a side-effect greater than 10%.

Alirocumab 75-150 mg Q2W had the greatest probability of being the safest treatment option in terms of the risk of any SAEs, leading to treatment discontinuation, injection-site reactions, adjudicated cardiovascular events, and musculoskeletal disorders (the probability of being in the top ranking positions were 5 %, 6 %, 1 %, 13 % and 0 %, respectively). Alirocumab 150-mg Q2W caused the most patient withdrawals, because this led to treatment discontinuation, and was followed by ezetimibe, alirocumab 75-mg Q2W, alirocumab 75-150mg Q2W and placebo. Alirocumab 150-mg Q2W was probably the safest option (74 %). The rank probabilities are presented in Table 5.

Table 3: Baseline lipid levels of included patients from the included randomized controlled trials

First Author	LDL-C(mg/dl)	TC(mg/dl)	TGs(mg/dl)	HDL(mg/dl)	ApoB(mg/dl)	LPa(mg/dl)	ApoA1(mg/dl)	non-HDL(mg/dl)
Roth EM	139.7±25.8	222.8±31.9	118±16.3	57.1±17.8	104.3±18.7	14.5±8	158.4±31.7	165.7±29.9
Moriarty PM	192.3±71.7	279.7±81.3	152±32.5	49.8±14.7	140±38.4	16±9.6	149.7±24.6	229.9±83.4
Cannon CP	106.8±34.7	186±42.6	106.2±29.8	46.5±13	90±20	NR	NR	NR
Roth EM	124.3±37.5	200.9±44.5	129±22.1	50.8±15.4	101.9±24.9	23.2±13.9	151.1±29.4	149±41.9
Teramoto T	120.9±18.7	210.9±23.3	120.6±18.1	60±13.8	100±19.7	13.8±6.3	157.5±26.4	146.2±21.8
Robinson J	122.4±42.2	NR	133±22.8	49.9±12.3	101.7±27.6	21.8±14.9	146.8±25.9	152.4±46.3
Mckenney JM	127.2±27	207.2±28.6	132±23.9	51.1±13.5	105.1±23.2	24.8±17.4	144.8±26.3	156±31.8
Ginsbery HN	197.9±53.4	274.4±54	128.4±20.9	48.1±13.3	140.9±31	24.6±10.4	NR	226.4±55.3
Koren MJ	127.2±27	NR	132±20.4	51.1±13.5	NR	NR	NR	NR
Kereiakes DJ	102.2±31.6	NR	127.6±23.3	48.5±13.8	91±22.3	33.4±17.5	NR	131.2±36
Farnier M	107.7±32.3	NR	131±22.5	48.1±13.2	93.5±23.2	25.2±15.2	142.3±26.9	137.8±40.6
Kastelein JJP	104.9±33.5	NR	NR	NR	NR	NR	NR	NR
Bays H	141.2±5.9	NR	NR	NR	NR	NR	NR	NR
Farnier M	112.1±38.5	NR	125.6±25.8	51.1±12.6	95.5±24	36.7±21.7	NR	141.4±43.7
Teramoto T	142.9±26.9	226.1±32.3	126.8±21.8	54.3±13	110±20	16.1±6.5	NR	NR
Stroes E	155.6±44.7	241±50.3	149.8±29.2	51.7±15.6	120.2±27.2	14.2±9.6	150.7±27.4	189.3±50.2

Data presented as mean ± SD.LDL-C, Low-density lipoprotein cholesterol;TGs,Triglycerides;TC,Total cholesterol;HDL-C,igh-density lipoprotein cholesterol;LPa ,Lipoprotein(a);ApoB,apolipoprotein B;Apo A1,apolipoprotein A1;NR,not reported.

Table 4: Network meta-analysis of relative effects of efficacy

LDL-C, Non-HDL (95% CI)				
ALI 75	13.28(-13.93,41.64)	-8.75(-34.98,17.78)	52.36(23.77,80.23)	75.37(53.44,98.07)
2.75(-19.61,26.01)	**ALI 75/150**	-22.03(-50.24,6.61)	38.85(19.65,58.77)	62.28(39.08,85.80)
5.86(-17.46,29.81)	2.96(-18.44,24.46)	**ALI 150**	61.09(29.41,92.20)	84.10(66.19,102.60)
-37.20(-61.21,-12.41)	-40.07(-56.92,-24.22)	-43.00(-68.39,-17.91)	**EZE**	22.94(-3.41,51.22)
-71.45(-91.16,-50.44)	-74.32(-90.40,-58.63)	-77.28(-92.21,-61.90)	-34.31(-54.84,-12.95)	**Placebo**
TGs, Apo B (95% CI)				
ALI 75	1.21(-15.98,17.49)	-6.72(-23.35,10.18)	26.77(9.01,43.91)	47.29(33.05,61.02)
-2.07(-20.90,18.44)	**ALI 75/150**	-7.81(-24.51,8.75)	25.56(13.39,38.16)	46.13(33.93,58.29)
9.65(-10.22,30.63)	11.59(-8.79,32.43)	**ALI 150**	33.41(13.96,53.09)	53.93(42.15,65.87)
-4.04(-25.33,17.16)	-2.20(-15.43,11.39)	-13.67(-36.94,9.27)	**EZE**	20.56(4.26,36.18)
-13.27(-30.99,3.98)	-11.26(-26.87,3.79)	-22.75(-37.06,9.62)	-9.02(-28.02,9.70)	**Placebo**
TC, LPa (95% CI)				
ALI 75	7.39(-2.46,15.65)	5.71(-5.77,15.90)	13.26(3.37,21.53)	11.34(2.08,19.39)
-1.46(-39.92,36.28)	**ALI 75/150**	-1.79(-10.51,7.42)	5.79(0.23,11.57)	4.09(-1.71,9.50)
5.64(-25.16,35.44)	6.74(-28.05,41.92)	**ALI 150**	7.67(-2.51,17.50)	5.78(-1.26,12.54)
-43.40(-87.61,0.93)	-41.96(-64.55,-18.93)	-48.91(-90.80,-7.90)	**EZE**	-1.78(-9.28,5.51)
-80.32(-107.51,-53.24)	-79.03(-150.94,-52.13)	-85.89(-108.50,-63.06)	-37.02(-72.35,-1.95)	**Placebo**
HDL-C, Apo A1 (95% CI)				
ALI 75	-0.01(-13.72,14.12)	-3.58(-16.37,8.36)	-6.84(-21.65,8.55)	-7.19(-17.00,2.77)
-1.81(-9.49,5.19)	**ALI 75/150**	-3.59(-16.44,8.09)	-6.79(-12.43,-1.05)	-7.18(-17.02,2.75)
3.08(-4.53,10.37)	4.90(-1.83,12.34)	**ALI 150**	-3.27(-16.05,10.95)	-3.64(-10.45,4.20)
1.45(-6.42,8.60)	3.24(-1.40,8.00)	-1.62(-9.99,6.17)	**EZE**	-0.32(-12.16,10.79)
5.44(-1.06,11.83)	7.24(2.16,13.05)	2.37(-2.28,7.31)	3.99(-2.30,11.05)	**Placebo**

ALI 75, Alirocumab 75mg every 2 weeks; ALI 75/150, Alirocumab 75mg every 2 weeks with dose adjustment to 150mg every 2 weeks if predefined LDL-C target levels were not met; ALI 150, Alirocumab 150mg every 2 weeks; EZE, ezetimibe 10mg per day.
How to read the table: Treat one as target, then read the row of the target; the higher the median, the greater the treatment. (e.g.,in the median of LDL-c, treat placebo as the target; then read the row of LDL-C, the median is -77.28 for placebo, which is the highest; thus, Ali 150mg has the greatest treatment).
LDL-c, Low-density lipoprotein cholesterol; TGs, Triglycerides; HDL-c,High-density lipoprotein cholesterol; TC, Total cholesterol; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Lp (a), lipoprotein(a)

11. Conclusion

The present analysis revealed that alirocumab presented a significantly greater LDL reduction than ezetimibe, and different doses of alirocumab have no significant differences in LDL-c reduction for hypercholesterolemia treatment. In the safety analysis, alirocumab 75-150 mg Q2W had a reduced risk of SAEs and muscle-associated events. Furthermore, treatment with alirocumab 150-mg Q2W was a better choice with respect to efficacy and safety.

As far as we know, previous studies have performed pair-wise comparisons between alirocumab, ezetimibe and placebo (Jones et al. 2016), and the present study is the first network meta-analysis conducted for the mixed treatment of hypercholesterolemia. This was performed to compare the change in different lipids from baseline to follow-up with different doses of alirocumab. All different doses of alirocumab can reduce LDL-c, TC, Apo B, Lp (a) and TGs, compared with both placebo and ezetimibe. These also led to

Table 5: Network meta-analysis of safety (number of patient withdrawals due to adverse events) of drugs

	SAEs OR (95% CI)	LTTD OR (95% CI)	IST OR (95% CI)	ACE OR (95% CI)	MD OR (95% CI)	NC OR (95% CI)
ALI 75 VS ALI 75/150	1.12(0.46,2.85)	0.68(0.20,2.01)	6.19(1.03,38.26)	1.23(0.02,63.57)	6.07(0.69,15.69)	8.91(0.27,641.32)
VS ALI 150	0.98(0.35,2.82)	0.42(0.11,1.46)	5.26(0.84,31.81)	0.90(0.01,58.15)	2.46(0.53,6.42)	1.56(0.03,212.60)
VS EZE	1.20(0.51,3.05)	0.79(0.24,2.34)	10.45(1.61,74.32)	1.14(0.02,47.42)	5.40(1.37,16.24)	3.50(0.16,176.03)
VS Placebo	0.98(0.41,2.49)	0.56(0.16,1.74)	8.88(1.61,52.87)	1.54(0.03,83.71)	5.27(1.70,12.00)	2.65(0.08,208.25)
ALI 75/150 VS ALI 150	0.88(0.44,1.62)	0.65(0.25,1.52)	0.89(0.28,2.20)	0.85(0.05,4.80)	0.40(0.13,1.05)	0.18(0.01,4.18)
VS EZE	1.11(0.71,1.55)	1.14(0.76,1.96)	1.70(0.79,3.82)	0.97(0.12,4.50)	0.92(0.51,1.51)	0.42(0.03,4.00)
VS Placebo	0.87(0.60,1.33)	0.86(0.48,1.50)	1.44(1.79,2.72)	1.28(0.36,5.36)	0.86(0.53,1.55)	0.31(0.03,2.94)
Ali150 VS EZE	1.28(0.58,2.57)	1.77(0.73,5.42)	1.94(0.61-7.65)	1.14(0.07,23.87)	2.32(0.74,7.28)	4.47(0.04,78.72)
VS Placebo	1.00(0.63,1.79)	1.34(0.68,2.89)	1.63(1.81,4.33)	1.45(0.42,18.64)	2.17(0.95,6.17)	1.76(0.21,11.82)
EZE VS Placebo	0.79(0.48,1.45)	0.73(0.35,1.46)	0.85(0.31,2.32)	1.30(0.20,17.77)	0.94(0.49,2.19)	0.72(0.04,19.84)

ALI 75, Alirocumab 75mg every 2 weeks; ALI 75/150, Alirocumab 75mg every 2 weeks with dose adjustment to 150mg every 2 weeks if predefined LDL-C target levels were not met; ALI 150, Alirocumab 150mg every 2 weeks; EZE, ezetimibe 10mg per day; SAEs, Serious adverse Events; LTTD, Leading to treatment discontinuation; IST, Injection-site reactions; ACE, Adjudicated cardiovascular events; M D,Musculoskeletal disorders .OR: odds ratio. OR > 1 means treatment has more AEs. Significant associations are in bold.

a tendency towards the increase in HDL and Apo A1, but without statistical significance.

These outcomes reveal that the PCSK9 inhibitor alirocumab at most led to a 77.28 mg/dl reduction in LDL-c, a 85.89 mg/dl reduction in TC, a 53.95 mg/dl reduction in Apo B, a 11.34 mg/dl reduction in Lp(a) and a 7.24mg/dl increase in HDL-c, compared with placebo, and a 43 mg/dl reduction in LDL-c, a 48.91 mg/dl reduction in TC, a 13.26 mg/dl reduction in Lp(a), a 33.41 mg/dl reduction in Apo B and a 6.79 mg/dl increase in Apo A1, compared with ezetimibe. As a fully human monoclonal antibody, the PCSK9 inhibitor offers promising therapeutic applications in the control of PCSK9-regulated pathologies. This inhibits the direct binding of PCSK9 and LDL receptors, reduces the degradation of the receptor, increases LDL receptor activity on the hepatocyte surface, and ultimately, improves the uptake of plasma lipoprotein (DeVay et al. 2015).

A single study revealed that there were no obvious relationships between the lipid-lowering effect and doses of alirocumab. McKenney et al. (2012) suggested that alirocumab doses of 200 or 300 mg every four weeks resulted in cholesterol reductions of 43 % and 48 %, respectively (McKenney et al. 2012). Its subcutaneous administration (doses within 50–150 mg) significantly (P<0.001 *vs.* placebo) reduced cholesterol levels by 41%-58% in patients with FH and by 38–65% in patients in the study of Stein et al. (2012). The present study indirectly compared three doses of alirocumab by network meta-analysis, and also found no significant difference in reducing blood lipids, especially for LDL-c levels.

The rates of local IST occurred at a higher rate with alirocumab *vs.* placebo and ezetimibe. IST could represent local intolerability due to the device or drug, and the viscosity, volume, or other aspects that may have contributed to the symptoms, such as pain, stinging, and redness. However, the precise mechanism for the increased rate of pruritus with alirocumab remains unknown.

These results imply that alirocumab 75-mg Q2W was sufficient for a majority of patients to achieve LDL-c <70 mg/dl without the need for subsequent dose increase to 150 mg. These findings provide support for initiating alirocumab therapy at 75 mg in patients on maximized standard of care, who have suboptimally controlled hypercholesterolemia with a dose increase to 150 mg in these patients with higher incidences of side-effects.

However, the network meta-analysis has theoretical limitations due to the incorporation of data from the direct and indirect comparisons of different drugs and dosages. Furthermore, it has several limitations inherent to the meta-analysis, including the lack of raw or uniform data. Finally, meta-regression techniques are limited given the lack of raw patient information, and these were not powered to assess outcomes. Therefore, caution should be given in conducting hypothesis–generating approaches.

In conclusion, the PCSK9 inhibitor alirocumab presents with a significantly greater lipid level reduction than ezetimibe, and different doses of alirocumab have no significance for the efficacy of LDL-c reduction in hypercholesterolemia. However, in the safety analysis, alirocumab 75-150 mg Q2W had a reduced risk of SAEs and muscle-associated events, while alirocumab 150-mg Q2W had a high risk of leading to treatment discontinuation, when compared with other doses of alirocumab. Therefore, treatment with alirocumab 75-150 mg Q2W is better with respect to efficacy and safety.

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TSD2 General meta analysis.