



# Pharmacological Interventions to Treat Antipsychotic-Induced Dyslipidemia in Schizophrenia Patients: A Systematic Review and Meta Analysis

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**Introduction:** Antipsychotic-induced dyslipidemia represents a common adverse effect faced by patients with schizophrenia that increases risk for developing further metabolic complications and cardiovascular disease. Despite its burden, antipsychotic-induced dyslipidemia is often left untreated, and the effectiveness of pharmacological interventions for mitigating dyslipidemia has not been well-addressed. This review aims to assess the effectiveness of pharmacological interventions in alleviating dyslipidemia in patients with schizophrenia.

**Methods:** Medline, Psychlnfo, and EMBASE were searched for all relevant English articles from 1950 to November 2020. Randomized placebo-controlled trials were included. Differences in changes in triglycerides, HDL cholesterol, LDL cholesterol, and VLDL cholesterol levels between treatment and placebo groups were meta-analyzed as primary outcomes.

**Results:** Our review identified 48 randomized controlled trials that comprised a total of 3,128 patients and investigated 29 pharmacological interventions. Overall, pharmacological interventions were effective in lowering LDL cholesterol, triglycerides, and total cholesterol levels while increasing the levels of HDL cholesterol. Within the intervention subgroups, approved lipid-lowering agents did not reduce lipid parameters other than total cholesterol level, while antipsychotic switching and antipsychotic add-on interventions improved multiple lipid parameters, including triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol. Off label lipid lowering agents improved triglycerides and total cholesterol levels, with statistically significant changes seen with metformin.

**Conclusion:** Currently available lipid lowering agents may not work as well in patients with schizophrenia who are being treated with antipsychotics. Additionally, antipsychotic switching, antipsychotic add-ons, and certain off label interventions might be more

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effective in improving some but not all associated lipid parameters. Future studies should explore novel interventions for effectively managing antipsychotic-induced dyslipidemia.

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# INTRODUCTION

Dyslipidemia refers to abnormalities in lipid levels such as increases in total and low-density lipoprotein (LDL) cholesterols, low concentrations of high-density lipoprotein (HDL) cholesterols, and high triglyceride levels. This metabolic abnormality causes almost a third of ischemic heart disease and a fifth of global cerebrovascular disease (1). Patients with schizophrenia are at an increased risk of developing cardiovascular disease in part due to the illness itself (2-7), as well as a higher prevalence of well-known lifestyle factors that promote cardiovascular disease risk, namely sedentary lifestyle, poor diet, and smoking (8, 9). Antipsychotics are the cornerstone of treatment in schizophrenia and are widely prescribed across other psychiatric conditions (10). However, their use is associated with severe metabolic adverse effects, including weight gain, dyslipidemia, insulin resistance, and risk of type 2 diabetes mellitus (T2D) in a population burdened with premature cardiovascular mortality.

While the prevalence of dyslipidemia and consequent effects on morbidity and mortality are high worldwide among the general population, particular subgroups may be at a greater risk. In particular, patients with schizophrenia are at an increased risk of dyslipidemia and its associated influence on cardiovascular disease and metabolic dysfunction (11, 12). Despite its high prevalence and associated cardiovascular risk, dyslipidemia often goes untreated among patients with schizophrenia. Reported rates for non-treatment are almost 90% (13-15), and patients with schizophrenia are often medically underserved and disadvantaged in their physical health care (16-18). As shown by results from a study by the National Institute of Mental Health, namely the Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP), at baseline more than half of patients (161/394 or 56.5%) had dyslipidemia and only 0.5% were receiving treatment (16).

Previous discussions addressing antipsychotic-induced metabolic abnormalities in patients with schizophrenia have largely focused on weight gain or metabolic syndrome, and not dyslipidemia *per se* (19–21). Only a few studies have investigated approved lipid lowering agents for treating dyslipidemia in schizophrenia (22–30). More commonly, as reported in a 2014 review by Tse et al. a wide variety of pharmacological agents have been investigated to treat dyslipidemia in patients with schizophrenia, including treatment with omega-3 fatty acids, fluvoxamine, topiramate, metformin, sibutramine, telmisartan, ramelteon, and valsartan (31). Antipsychotic switching and adding aripiprazole have also been evaluated as strategies to improve lipid outcomes in patients with schizophrenia (32–38).

Given the variety of approaches used to address dyslipidemia in this patient population, as well as the absence of clear clinical guidelines, it is important to summarize the available evidence and guide clinical decision making. Hence, we performed a systematic review and meta-analysis of randomized controlled trials to compare the effects of pharmacological interventions vs. placebo treatment in antipsychotic-induced dyslipidemia in patients with schizophrenia.

## **METHODS**

The protocol for the review is registered on PROSPERO (PROSPERO 2020 CRD42020219982; https://www.crd.york. ac.uk/prospero/display\_record.php?ID=CRD42020219982). PRISMA guidelines were used for study design and reporting.

#### Search

We searched for studies published between 1950 and November 2020 using Medline, PsychInfo and EMBASE databases, with the following search string: *psychotic disorder* OR *schizophrenia* OR *schizoaffective* OR *schizophreniform* OR *psychosis* OR *first episode* AND *hyperlipidemia* OR *triglycerides* OR *cholesterol* OR *lipid* OR *LDL cholesterol* OR *VLDL cholesterol* OR *HDL cholesterol*. The search was limited to studies conducted in human participants and published in English. References cited in previously published literature reviews and meta-analyses pertaining to interventions for metabolic disturbances in the schizophrenia population were reviewed for additional studies.

### **Inclusion Criteria**

Articles were initially screened using title and abstract, based on the study's relevance to our meta-analysis. Thereafter, articles were further screened to ensure that studies met the following inclusion criteria: (a) randomized placebo-controlled trial; (b) diagnosis of schizophrenia spectrum disorders comprising the majority (>50%) of study populations; (c) patients with current metabolic abnormalities; (d) an active pharmacological intervention used to improve metabolic abnormalities or an antipsychotic switching/add-on method if the antipsychotic change is aimed to improve metabolic parameters; and (e) primary outcome listed as lipids or other metabolic measures if lipid outcomes were included in the list of metabolic measures.

Studies were excluded from analysis during the final screening stage if (a) not aimed at improving metabolic measures; (b) comparing different modes of antipsychotic administration (i.e., deltoid, sublingual, gluteal etc.); (c) comparing effectiveness between different antipsychotics; (d) evaluating non-pharmacological intervention (e.g., behavioral interventions, dietary modulations etc.); or, (e) evaluating strategies to prevent dyslipidemia (i.e., patients did not have metabolic abnormalities or dyslipidemia at baseline).

# **Outcomes Extracted**

The primary outcomes included the following lipid parameters: total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and very low-density lipoprotein cholesterol (VLDL) cholesterol. Additional secondary outcome data were also extracted including body weight, body mass index (BMI), waist circumference, waist to hip ratio, fasting blood glucose, fasting insulin, hemoglobin A1c (HbA1c), diastolic blood pressure, systolic blood pressure, the homeostatic model assessment of insulin resistance (HOMA-IR), and total positive and negative symptom scale (total PANSS). Outcomes were extracted for both the intervention and placebo groups, where the placebo groups were used as comparators. Outcomes were extracted by two authors (PK and KC-D) and were checked by authors, FP and JL. For studies that examined multiple doses of the same intervention, the data pertaining to the higher dose were extracted.

### **Data Analysis**

Review Manager 5.4 (Revman 5.4.0 (Mac Version) Cochrane Collaboration, Oxford) was used to analyze the data extracted from the final list of included articles. Continuous outcomes were reported using mean differences (MD) with 95% confidence intervals (CIs), following the inverse variance statistical method and random effects model to account for study heterogeneity. Missing standard deviations (SDs) were calculated using other available statistics that were reported. Endpoint data were primarily used unless not available, in which case mean change data were used. Endpoint and change data were combined during the analysis, as we used mean difference rather than standardized mean difference (39). For Emsley et al. which was a double-blind trial with an open-label extension (27), data were extracted at the endpoint of the double-blind phase. Study heterogeneity was calculated using the  $I^2$  statistic, with significant heterogeneity being classified as  $I^2 \ge 50\%$ . Significant statistical differences were classified as p < 0.05. Changes in lipid profiles (i.e., HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, and total cholesterol) were assessed for all interventions pooled and for the following 4 subgroups: lipid lowering agents; antipsychotic switching or antipsychotic add-on interventions; the off-label lipid lowering agent metformin; and other off-label lipid lowering agents.

All included studies were judged for risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias using the Cochrane Risk of Bias tool (40). Studies were judged to have either a low, high, or unclear risk of bias. Sensitivity analyses were conducted after removing studies found to be at high risk of bias to examine their impact on findings.

# RESULTS

Of the 244 full-text articles screened, 48 articles (n = 3,128) met criteria for inclusion (Figure 1, Supplementary Table 1). Fortythree studies were double-blind, 2 were open-label, one had blinding but did not specify level, and the remaining 2 studies did not provide information on blinding. All studies included adult populations (18 years or older). The average age ( $\pm$ SD) of participants receiving interventions was 40.1 (±12.8) years, vs. 40.6 ( $\pm$ 9.6) for those receiving placebo. A total of 74% of participants in both the intervention and placebo groups were male, with 89.2% diagnosed with schizophrenia. Trials were 4-24 weeks long, with a mean duration ( $\pm$ SD) of 13.1 ( $\pm$ 5.7) weeks. Studies comprised a total of 29 interventions. Lipid lowering agents included omega-3 fatty acids [(26-28, 30), N = 4, n = 250]and pravastatin [(29), N = 1, n = 49]. Antipsychotic switching or add-on interventions included the following: switching to quetiapine [(41), N = 1, n = 133]; adding aripiprazole [(33, 34, 38), N = 3, n = 322]; and, switching to aripiprazole [(35–37), N = 3, n = 390]. Off label lipid modulating agents included the following: metformin [(42-47), N = 6, n = 565], reboxetine [(48), n = 565]N = 1, n = 54], nizatidine [(49), N = 1, n = 54], atomoxetine [(50), N = 1, n = 29], combination of metformin and sibutramine [(51), N = 1, n = 28], rosiglitazone [(52, 53), N = 2, n = 47], ramelteon [(54), N = 1, n = 20], telmisartan [(55), N = 1, n =43], vitamin D and probiotic combination [(56), N = 1, n = 60], sibutramine [(17, 57), N = 2, n = 55]; dehydroepiandrosterone [DHEA; (58), N = 1, n = 43], exenatide [(59), N = 1, n = 40], orlistat [(60), N = 1, n = 63], vitamin D [(61), N = 1, n = 47], liraglutide [(62), N = 1, n = 97], intranasal insulin [(63), N = 1, n= 39], minocycline [(64), *N* = 1, *n* = 55], fluvoxamine [(65, 66), N = 2, n = 153], naltrexone and bupropion combination [(67), N = 1, n = 21], melatonin [(68, 69), N = 2, n = 80], pioglitazone [(70), N = 1, n = 52], Liuyu decoction, traditional Chinese medicine [(71), N = 1, n = 154], a combination of celery, dill, and green tea [(72), N = 1, n = 60], naltrexone [(73, 74), N = 2, n = 47], Konjac powder [(75), N = 1, n = 59], and resveratrol [(76), N = 1, n = 19]. Baseline antipsychotic use by participants included olanzapine (N = 27), clozapine (N = 25), risperidone (N = 11), quetiapine (N = 8), aripiprazole (N = 5), ziprasidone (N = 2), paliperidone (N = 2), haloperidol (N = 1), fluphenazine (N = 1), flupenthixol (N = 1), clopenthixol (N =1), and sulpiride (N = 1), chlorpromazine (N = 1), perphenazine (N = 1), zuclopenthixol (N = 1), chlorprothixene (N = 1), amisulpride (N = 1), sertindole (N = 1), and sulpiride (N = 1).

## **Primary Outcomes: Lipid Profile**

Compared to placebo, pharmacological interventions were associated with a pooled mean difference of -13.08 mg/dL (CI: -20.82, -5.33; p = 0.0009) for triglycerides (**Figure 2**), 0.43 mg/dL (CI: -0.85, 1.70; p = 0.51) for HDL (**Figure 3**), -4.19 mg/dL (CI: -7.71, -0.67; p = 0.02) for LDL cholesterol (**Figure 4**), -3.27 mg/dL (CI: -7.38, 0.84; p = 0.12) for VLDL cholesterol (**Figure 5**), and -7.96 mg/dL (CI: -11.14, -4.77; p < 0.00001) for total cholesterol (**Figure 6**). Heterogeneity was low to moderate for most outcomes:  $I^2 = 71\%$  for HDL,  $I^2 = 60\%$ 



for LDL cholesterol,  $I^2 = 0\%$  for VLDL cholesterol,  $I^2 = 52\%$  for triglycerides,  $I^2 = 37\%$  for total cholesterol.

#### Lipid Lowering Agents

Lipid lowering agents were associated with significant reductions in total cholesterol compared to placebo (**Figure 6**; N = 4, n = 227; WMD = -11.52 mg/dL, CI: -15.51, -7.53; p < 0.00001;  $I^2 = 0$ ). There were no significant differences in triglycerides

(**Figure 2**; N = 4, n = 243;  $l^2 = 56$ ), HDL cholesterol (**Figure 3**; N = 5, n = 299;  $l^2 = 81$ ), and LDL cholesterol (**Figure 4**; N = 4, n = 227;  $l^2 = 56$ ) levels. None of the lipid lowering agent studies examined VLDL cholesterol.

#### Antipsychotic Switching/Add-on Interventions

Antipsychotic switch/add-on strategies were associated with significant decreases in triglycerides (Figure 2; N = 7, n = 800;

tudy or Subgroup Mean	n [mg/dL] S	D [mg/dL]	Total	Mean [mg/dL]	SD [mg/dL]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	ABCDEFG
U.2.1 Lipid Lowering Agents		<b>C1 A</b> <sup>2</sup>	20				3 50	0.001.00.00.00.00		
nsley 2008	115.14	61.99	39	115.14	53.14	33	3.5%	0.00 [-26.59, 26.59]		<b>***</b> ****
obinson 2019	104.62	13.66	25	97.43	11.97	25	5.6%	7.19 [0.07, 14.31]	-	
incenzi 2014	134.33	92.47	24	135.39	81.44	25	1.8%	-1.06 [-49.92, 47.80]		??? 🛡 🖶 🕂
u 2019	145.25	69.97	37	196.63	114.26	35	2.0%	-51.38 [-95.44, -7.32]		<b> </b>
ubtotal (95% CI)			125			118	12.8%	-4.60 [-25.22, 16.02]	<b>•</b>	
eterogeneity: Tau <sup>2</sup> = 230.87; C est for overall effect: Z = 0.44	$Chi^2 = 6.85,$ (P = 0.66)	df = 3 (P = 0	0.08); I <sup>2</sup>	= 56%						
0.2.2 Antipsychotic Switch/A	dd-on Inter	ventions								
eberdt 2008	6.2	79.7	65	-9.74	86.8	68	3.3%	15.94 [-12.36, 44.24]		<b>Q</b> 77 <b>0Q</b> 7
n 2013	-5.9	75.1	16	-7.3	100.3	14	1.2%	1 40 [-62 74 65 54]		2020000
eischhacker 2010	-12	79.06	96	-1.2	64 53	85	4 1%	-10.80 [-31.74 10.14]		
aucomar 2008	25 72	52.2	54	11.06	70.8	61	2 7%	-26 70 [ 61 22 -12 25]		2220000
2011	-23.75	76.42	34	11.00	79.0	01	J.7/0	-30.79 [-01.35, -12.25]		
roup 2011	-25.7	76.42	89	/	/1.28	98	4.1%	-32.70 [-53.94, -11.46]		
ani 2015	196.35	44.46	21	223.61	72.89	26	2.8%	-27.26 [-61.12, 6.60]		
ao 2015	134.6	61.1	54	148.8	61.99	53	3.8%	-14.20 [-37.53, 9.13]		<b>? ? ? <del>9</del> <del>9</del> <del>9</del> <del>9</del></b>
ibtotal (95% CI) eterogeneity: Tau <sup>2</sup> = 146.25; C	$chi^2 = 10.81$	, df = 6 (P =	<b>395</b> 0.09);	$l^2 = 44\%$		405	22.9%	-17.32 [-31.07, -3.56]	•	
est for overall effect: Z = 2.47	(P = 0.01)									
J.2.3 Off Label Lipid Lowerin	g Agent: Me	ttormin								
ptista 2007	111.1	41	36	138.5	79.4	36	3.2%	-27.40 [-56.59, 1.79]		
arrizo 2009	-4.1	80	24	2.9	82.4	30	2.1%	-7.00 [-50.52, 36.52]		<b>~~~</b>
1en 2013	126.8	47.4	28	126.9	79.4	27	2.7%	-0.10 [-34.82, 34.62]		<b>666666</b> 6
niu 2016	140.6	70.4	19	145.3	66.8	18	2.0%	-4.70 [-48.91, 39.51]		<b>GGGGGG</b> ?
rskog 2013	-7	58.24	75	13.2	57.03	71	4.4%	-20.20 [-38.90, -1.50]		9999994
u 2016	185.99	69.97	103	222.31	96.54	98	3.8%	-36.32 [-59.73 -12 91]	I	220000
btotal (95% CI)	105.55	05.57	285	222.31	50.54	280	18.1%	-21.01 [-32.39, -9.64]	•	
terogeneity: Tau <sup>2</sup> - 0.00: Chi	2 = 4 15 45	= 5 (P - 0 F	3). 12 -	0%		200	10.1/0	LIGE [ JEIJS, -3.04]	•	
est for overall effect: $Z = 3.62$	(P = 0.0003)	)	5), 1 =	0.20						
.2.4 Off Label Lipid Lowerin	g Agents: O	thers								
nrami-Weizman 2013	140.8	84.3	29	124.7	61.6	25	2.4%	16.10 [-22.94, 55.14]		
suncao 2006	179.4	112.7	27	152.7	75.1	27	1.7%	26.70 [-24.38, 77.78]		2 2 2 9 2 9 4
II 2011	134.3	64.9	14	236.8	178.3	15	0.6%	-102.50 [-198.92, -6.08]	·	???
ptista 2008	121.6	27.2	13	160.2	68.4	15	2.5%	-38.60 [-76.24, -0.96]		999979999
ptista 2009	163	52.7	14	161.5	76.7	15	1.8%	1.50 [-46.13, 49.13]		979999
rba 2011	186.43	100.22	14	157.83	79 35	6	0.8%	28 60 [-53 78 110 98]		2266666
n 2019	-26	76	22	-10	81	21	1 9%	-16 00 [-63 00 31 00]		<b>A</b> 222 <b>AAA</b>
adari 2019	124.0	40.7	20	165	62.2	20	2 2%	-20 10 [ 58 50 -1 61]		
aden 2019	134.9	49.7	30	274.7	101	10	0.3%	-50.10 [-58.59, -1.01]		
anderson 2003	200.0	12.2	19	2/4./	67.22	10	0.2%	27 20 [ 110 61 65 21]		
enderson 2007	-01.1	120.7	10	-33.9	07.52	10	0.0%	-27.20 [-119.01, 03.21]		
enderson 2009	152	109	0	200	100	10	0.4%	-134.00 [-233.23, -12.77]		
olka–Pokorska 2015	137.62	76.19	23	110.86	43.23	22	2.6%	26.76 [-9.24, 62.76]		<b></b>
hoy 2017	212.57	88.57	20	185.98	97.43	20	1.4%	26.59 [-31.12, 84.30]		
ivoy 2017	11.5	44	23	-43.9	130.8	24	1.5%	55.40 [0.07, 110.73]		
rsen 2017	141.71	60.32	47	177.14	186.98	50	1.5%	-35.43 [-90.05, 19.19]		????
2013	-8	67	18	-0.5	43	21	2.6%	-7.50 [-43.50, 28.50]		<b></b>
u 2018	43.4	111.6	27	48.7	85	28	1.6%	-5.30 [-57.87, 47.27]		9799999
2004	109.8	46.2	34	132.5	45.9	34	4 0%	-22 70 [-44 59 -0.81]		2220000
2018	155 3	55 7	43	185 2	62.2	42	3.6%	-29.90 [-55.02 -4.78]		
2019	- 99 57	70 71	45	25 42	52.2	42	1.40	-29.90 [-35.02, -4.78]		
u 2016	-00.57	/9./1	11	-35.43	53.14	10	1.4%	-55.14 [-110.62, 4.34]		
boabbernia 2014	168.2	82.86	18	217.5	114	18	1.1%	-49.30 [-114.41, 15.81]		444444
mo-Nava 2014	186.13	98.22	20	160.29	119.14	24	1.2%	25.84 [-38.39, 90.07]		
nith 2013	124.8	141.52	29	217.09	139.41	23	0.9%	-92.29 [-169.10, -15.48]	· · · · · · · · · · · · · · · · · · ·	7799999
n 2020	496.87	1,013.24	102	337.45	193.96	52	0.1%	159.42 [-44.16, 363.00]		→ <b>@@??@@</b> @
vakoli 2014	158.9	59.4	30	168	61.3	30	3.1%	-9.10 [-39.64, 21.44]		?
veira 2014	157.5	169.15	11	171.4	113.57	13	0.4%	-13.90 [-131.39, 103.59]		0700000
k 2014	121.22	49.7	10	121.44	57.1	11	1.9%	-0.22 [-45.91. 45.47]		9999994
ang 2020	241.8	102.74	30	235.6	116.91	29	1.4%	6.20 [-50.03, 62 43]		6667666
btotal (95% CI)	2.110	101.74	696	200.0	110.01	641	46.2%	-11.06 [-23.08, 0.97]	•	
terogeneity: $Tau^2 = 346.53$ ; C st for overall effect: $Z = 1.80$	$Chi^2 = 44.09$ (P = 0.07)	, df = 27 (P	= 0.02)	; l <sup>2</sup> = 39%						
otal (95% CI)			1501			1444	100.0%	-13.08 [-20.825.33]	•	
eterogeneity: $Tau^2 = 267.21 \cdot C$	$hi^2 = 91.07$	df = 44 (P)	< 0.000	(1): $I^2 = 52\%$						_
eterogeneity. rau = 267.21, c	n = 91.07	, ui = 44 (P	< 0.000	(1), 1 = 52%					–100 –50 0 50 100	
ist for overall effect: $z = 3.31$	r = 0.0009	16 2 12 -	10.0	00/					Favours [intervention] Favours [placebo]	
est for subgroup differences: C	$m^2 = 2.56, n^2$	$u_1 = 3 (P = 0)$	,40), l <sup>e</sup>	= 0%						
sk of bias legend										
) Random sequence generatio	n (selection	bias)								
Allocation concealment (sele	ction bias)									
) Blinding of participants and	personnel (p	erformance	bias)							
) Blinding of outcome assess	nent (detecti	on bias)								
	trition bias)									
) Incomplete outcome data (at										
) Incomplete outcome data (at	(hiac)									
Incomplete outcome data (at Selective reporting (reporting	bias)									

analyses and Risk of Bias assessments.

WMD = -17.32 mg/dL, CI: -31.07, -3.56; p = 0.01;  $l^2 = 44$ ), LDL cholesterol (**Figure 4**; N = 5, n = 689; WMD = -6.45 mg/dL, CI: -12.83, -0.07; p = 0.05;  $l^2 = 55$ ), and total cholesterol levels (**Figure 6**; N = 6, n = 798; WMD = -8.83 mg/dL; CI: -13.91, -3.74; p = 0.0007;  $l^2 = 32$ ) in comparison to placebo. A significant increase was noted for HDL cholesterol level (**Figure 3**; N = 7, n = 844; WMD = 1.72 mg/dL; CI: 0.06,

3.39; p = 0.04;  $I^2 = 58$ ). None of the antipsychotic switching/addon studies examined VLDL cholesterol.

#### Off Label Lipid Lowering Agent: Metformin

Metformin was associated with significant reductions in triglycerides (**Figure 2**; N = 6, n = 565; WMD = -21.01 mg/dL, CI: -32.39, -9.64; p = 0.0003;  $I^2 = 0$ ) and total cholesterol

U.3.1. Lipid Lowering Agents           ehdani 2018         -0.28           msley 2008         50.27           obinson 2019         50.7           incenzi 2014         47.91           u 2019         37.51           ubtotal (95% CD)         est for overall effect: Z = 0.60 (P = 0.55)           0.3.2 Antipsychotic Switch/Add-on Interver           Deberdt 2008         -0.77           an 2013         -0.4           leischhacker 2010         -1.85           lewcomer 2008         0.77           froup 2011         0.6           Ani 2015         54.52           ubtotal (95% CI)         leterogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 14.20, df =           leetrogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 14.20, df =           est for overall effect: Z = 2.03 (P = 0.04)           0.3.3 Off Label Lipid lowering Agent: Metfor           aptista 2007         44.6           arrizo 2009         3.8           hen 2013         44.2           hubtal (95% CI)         stersogenetiv: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df a           leterogenetiv: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df a           est for overall effect: Z = 1.34 (P = 0.18)           0.3.4 Off Label Lipid Lowering Agents: Othe           marka 2011         48.1 <th>10.94 <math display="block">11.6</math> <math display="block">3.31</math> <math display="block">12.04</math> <math display="block">15.08</math> = 4 (P = 0) <b>ntions</b> 6.96 5.6 6.46 7.24 7.17 7.73 16.6 (P = 0.0) <b>rmin</b> 9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0) <b>ers</b></th> <th>28 39 25 24 37 153 .0003);  <sup>2</sup> 65 16 96 80 89 21 54 421 54 421 53 .12 54 421 54 421 54 421 54 421 54 421 54 421 54 55 54 421 54 55 55 56 56 56 56 56 56 56 56</th> <th>-0.78 50.27 58.69 47.3 36.35 = 81% -1.16 -2.7 -0.99 -2.46 -0.1 38.03 49.5 %</th> <th>12.02 15.47 3.14 10.59 12.76 8.12 6.2 7.31 6.19 6.73 8.18 13.5</th> <th>28 33 25 35 146 68 14 88 76 98 26 53 423</th> <th>2.0% 1.9% 3.5% 1.9% 1.3% 3.3% 2.6% 3.4% 3.4% 2.5% 2.1% 20.8%</th> <th>0.50 [-5.52, 6.52] 0.00 [-6.41, 6.41] -7.99 [-9.78, -6.20] 0.61 [-5.75, 6.97] 1.16 [-5.28, 7.60] -1.59 [-6.74, 3.57] 0.39 [-2.18, 2.96] 2.30 [-1.95, 6.55] -0.86 [-2.86, 1.14] 3.23 [1.12, 5.34] 0.70 [-1.30, 2.70] 5.87 [1.31, 10.43] 5.02 [-0.71, 10.75] 1.72 [0.06, 3.39]</th> <th>*</th> <th></th>	10.94 $11.6$ $3.31$ $12.04$ $15.08$ = 4 (P = 0) <b>ntions</b> 6.96 5.6 6.46 7.24 7.17 7.73 16.6 (P = 0.0) <b>rmin</b> 9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0) <b>ers</b>	28 39 25 24 37 153 .0003);   <sup>2</sup> 65 16 96 80 89 21 54 421 54 421 53 .12 54 421 54 421 54 421 54 421 54 421 54 421 54 55 54 421 54 55 55 56 56 56 56 56 56 56 56	-0.78 50.27 58.69 47.3 36.35 = 81% -1.16 -2.7 -0.99 -2.46 -0.1 38.03 49.5 %	12.02 15.47 3.14 10.59 12.76 8.12 6.2 7.31 6.19 6.73 8.18 13.5	28 33 25 35 146 68 14 88 76 98 26 53 423	2.0% 1.9% 3.5% 1.9% 1.3% 3.3% 2.6% 3.4% 3.4% 2.5% 2.1% 20.8%	0.50 [-5.52, 6.52] 0.00 [-6.41, 6.41] -7.99 [-9.78, -6.20] 0.61 [-5.75, 6.97] 1.16 [-5.28, 7.60] -1.59 [-6.74, 3.57] 0.39 [-2.18, 2.96] 2.30 [-1.95, 6.55] -0.86 [-2.86, 1.14] 3.23 [1.12, 5.34] 0.70 [-1.30, 2.70] 5.87 [1.31, 10.43] 5.02 [-0.71, 10.75] 1.72 [0.06, 3.39]	*	
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lab 2015       54.52         lab 2015       54.52         terogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 14.20, df =         est for overall effect: Z = 2.03 (P = 0.04) <b>D.3.3 Off Label Lipid lowering Agent: Metfor</b> publista 2007       44.6         atrizo 2009       3.8         terogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 14.20, df =         strizo 2009       3.8         terogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 23.95, df =         viz 2016       52.6         rskog 2013       -0.6         u 2016       38.28         bibtotal (95% CI)       1         tetrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df =         tetrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df =         tetrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df =         ssuncao 2006       45.8         ll 2011       48.1         usincao 2006       45.8         ull 2011       40.71         n 2019       0         anderson 2005       38.1         enderson 2005       38.1         enderson 2007       -1.2         enderson 2007       -1.2         enderson 2007       -1.2         enderson 2007       -1.2         senderson 2007       -1.2	16.63 rmin 9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0	34 <b>421</b> $33); I^2 = 58$ 36 24 28 19 75	49.5 % 47.4 -1.8	13.5	423	2.1% 20.8%	1.72 [0.06, 3.39]		
Introduct (95% Cl)           sterogeneity: Tau <sup>2</sup> = 2.64; Chi <sup>2</sup> = 14.20, df =           est for overall effect: Z = 2.03 (P = 0.04) <b>D.3.3 Off Label Lipid lowering Agent: Metfor</b> up to the sterogeneity: Tau <sup>2</sup> = 2.03; (P = 0.04) <b>D.3.3 Off Label Lipid lowering Agent: Metfor</b> up to the sterogeneity: Tau <sup>2</sup> = 2.03; (P = 0.04) <b>D.3.3 Off Label Lipid lowering Agent: Metfor</b> vitz 2009         3.8           ten 2013         44.2           vitz 2016         52.6           stodo 1         38.8           biotal (95% Cl)         tetrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -           tetrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -           stof or overall effect: Z = 1.34 (P = 0.18) <b>D.3.4 Off Label Lipid Lowering Agents: Othe</b> mrami-Weizman 2013         38.8           ssuncao 2006         45.8           II 2011         48.1           up tista 2008         49.5           ptista 2008         49.5           ptista 2009         38.1           enderson 2007         -1.2           enderson 2007         -1.2           enderson 2007         -1.2           enderson 2007         42.54           ffe 2008         -0	e 6 (P = 0.0 rmin 9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0 ers	421 D3); I <sup>2</sup> = 58 36 24 28 19 75	47.4 -1.8		423	20.8%	1.72 [0.06, 3.39]		<u></u>
est for overall effect: Z = 2.03 (P = 0.04) <b>D.3.3 Off Label Lipid lowering Agent: Metfor</b> Aptista 2007 44.6 arrizo 2009 3.8 hen 2013 44.2 hiu 2016 52.6 rskog 2013 -0.6 u 2016 38.28 <b>ibtotal (95% CI)</b> eterogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df = est for overall effect: Z = 1.34 (P = 0.18) <b>D.3.4 Off Label Lipid Lowering Agents: Othe</b> mrami-Weizman 2013 38.8 suncao 2006 45.8 all 2011 48.1 aptista 2008 49.5 aptista 2009 38.7 rba 2011 40.71 nt 2019 0 haderi 2019 38.2 enderson 2005 38.1 enderson 2007 -1.2 enderson 2007 38.0 hoy 2017 7 tive 2017 42.54 hoy 2017 42.54 hoy 2017 -7 rsten 2017 38.67 2013 1 u 2018 5.03 i 2018 40.6 u 2018 5.03 i 2018 40.6 u 2018 3.1 mith 2013 36.63 i 2018 40.6 i 2018 5.03 i 2018 40.6 i 2018 5.03 i 2018 5.03 i 2018 40.6 i 2018 5.03 i 2018 5.03	rmin 9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0	36 24 28 19 75	47.4 -1.8					•	
3.3.3 Off Label Lipid lowering Agent: Metfor         upitsta 2007       44.6         upitsta 2009       3.8         sen 2013       44.2         ui 2016       52.6         rskog 2013       -0.6         u 2016       38.28         bitotal (95% CI)       38.28         terogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -         est for overall effect: Z = 1.34 (P = 0.18) <b>D.3.4 Off Label Lipid Lowering Agents: Othe</b> mami—Weizman 2013       38.8         issuncao 2006       45.8         ill 2011       48.1         upitsta 2009       38.7         ribitsta 2009       38.7         orbitsta 2009       38.1         enderson 2005       38.1         enderson 2005       38.1         enderson 2007       -1.2         enderson 2007       -1.2         enderson 2007       -3.9         ivoy 2017       -7         rsce       0         obdabernia 2014       40.6         u 2018       0         obdabernia 2014       40.6         u 2018       0         obdabernia 2014       43.4         weira 2014       39.7	9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0	36 24 28 19 75	47.4 -1.8						
aprista 2007       44.6         arrizo 2009       3.8         arrizo 2009       3.8         arrizo 2009       3.8         arrizo 2009       3.8         arrizo 2013       -0.6         u 2016       38.28         abtotal (95% CI)       38.28         abtotal (95% CI)       38.28         sterogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -         sst for overall effect: Z = 1.34 (P = 0.18) <b>D.3.4 Off Label Lipid Lowering Agents: Othe</b> mrami-Weizman 2013       38.8         ssuncao 2006       45.8         ull 2011       48.1         uptista 2008       49.5         putista 2009       38.7         rba 2011       40.71         un 2019       0         haderi 2019       38.2         enderson 2007       -1.2         enderson 2007       -1.2         enderson 2007       42.54         ffe 2008       -0.39         ivoy 2017       -7         rsen 2017       38.67         2018       0         odabbernia 2014       40.9         u 2018       0         odabbernia 2014       40.5         <	9.2 7.5 14.6 19.2 7.82 7.73 = 5 (P = 0	36 24 28 19 75	47.4 -1.8						
arrizo 2009       3.8         hen 2013       44.2         hen 2013       44.2         hui 2016       52.6         rskog 2013       -0.6         u 2016       38.28         hbtotal (95% CI)       138.28         betrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -         st for overall effect: Z = 1.34 (P = 0.18) <b>0.3.4 Off Label Lipid Lowering Agents: Othe</b> mrami-Weizman 2013       38.8         ssunca 2006       45.8         till 2011       48.1         uptista 2008       49.5         ustaerizon 2007       -1.2         enderson 2007       -1.2         enderson 2007       -1.2         ife 2008       -0.39         ivoy 2017       -7         uz 2018       0         odabbernia 2014       40.6         uz 2018       0	7.5 14.6 19.2 7.82 7.73 = 5 (P = 0	24 28 19 75	-1.8	10.1	36	2.6%	-2.80 [-7.26, 1.66]	+	<b>99?999</b>
hen 2013       44.2         hill 2016       52.6         skog 2013       -0.6         a 2016       38.28         bibotal (95% Cl)       38.28         setorgeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -         st for overall effect: Z = 1.34 (P = 0.18) <b>Diate Coll Charles Clip Conversiones</b> mrami-Weizman 2013       38.8         sisuncao 2006       45.8         ill 2011       48.1         uptista 2008       49.5         pitista 2009       38.7         vrba 2011       40.71         n 2019       0         naderi 2019       38.2         enderson 2007       -1.2         index - Pokorska 2015       45.59         hoxy 2017       -7         rsen 2017       38.67         2018       0         odabbernia 2014       40.9         u 2018       0         odabbernia 2014       40.5         u 2018       0         odabbernia 2014       43.15	14.6 19.2 7.82 7.73 = 5 (P = 0	28 19 75		3.7	30	3.0%	5.60 [2.32, 8.88]		9997999
hiu 2016       52.6         rskog 2013       -0.6         u 2016       38.28         bbtotal (95% Cl)       38.28         bbtotal (95% Cl)       23.95, df -         eterogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -       38.28         bstat (95% Cl)       38.28         b.3.4 Off Label Lipid Lowering Agents: Othermami-Weizman 2013       38.8         ssuncao 2006       45.8         uil 2011       48.1         uptista 2008       49.5         proba 2011       40.71         anderi 2019       38.2         enderson 2005       38.1         enderson 2007       -1.2         enderson 2007       42.54         ffe 2008       -0.39         rivoy 2017       -7         rsen 2017       38.67         2013       1         u 2018       0         odabbernia 2014       40.9         ymmo-Nava 2014       43.15         inth 2013       36.63         uz 2018       0         odabberdia 2014       40.9         ymmo-Nava 2014       33.7         sk 2014       43.4         uz 2018       6.34         tetrogeneity: T	19.2 7.82 7.73 = 5 (P = 0	19 75	46.4	14.2	27	1.6%	-2.20 [-9.81, 5.41]		9999999
rskog 2013       -0.6         u 2016       38.28         bibtotal (95% CI)       38.28         terogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df -       st for overall effect: Z = 1.34 (P = 0.18)         D.3.4 Off Label Lipid Lowering Agents: Othe       mrami-Weizman 2013       38.8         ssuncao 2006       45.8       45.8         ill 2011       48.1       48.1         pitista 2008       49.5       5         pitista 2009       38.7       7         nrba 2011       40.71       0         naderi 2019       0       0         naderison 2007       -1.2       enderson 2007         enderson 2007       -1.2       enderson 2007         Jika-Pokorska 2015       45.59       10         hoty 2017       -7       7         rsen 2017       38.67       2013       1         u 2018       0       0       0         odabbernia 2014       40.9       1       0         u 2018       0       0       0         odabbernia 2014       43.15       1       1         u 2018       0       0       0       0         odabbernia 2014       43.4       40.6	7.82 7.73 = 5 (P = 0	75	43	10.7	18	1.1%	9.60 [-0.35, 19.55]	<u> </u>	99999997
u 2016       38.28         u 2016       38.28         ubtotal (95% CI)       38.28         ubtotal (95% CI)       38.28         eterogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df =       est for overall effect: Z = 1.34 (P = 0.18)         0.3.4 Off Label Lipid Lowering Agents: Othe       mrami-Weizman 2013         ssumcao 2006       45.8         all 2011       48.1         uptista 2009       38.7         yrba 2011       40.71         un 2019       0         adderi 2019       38.2         enderson 2005       38.1         enderson 2007       -1.2         enderson 2007       42.54         ffe 2008       -0.39         vitoy 2017       -7         ursen 2017       38.67         2013       1         u 2018       0         odabbernia 2014       40.9         yomo-Nava 2014       43.15         uith 2013       36.63         uz 2018       0         vodabbernia 2014       40.9         yomo-Nava 2014       43.4         vaeira 2014       39.7         ek 2014       49.22         anang 2020       36.74	7.73 = 5 (P = 0		-0.4	8.03	71	3.3%	-0.20 [-2.77. 2.37]	-	
30.20         30.20           bibotal (95% Cl)         21.41; Chi <sup>2</sup> = 23.95, df =           eterogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df =         sst for overall effect: Z = 1.34 (P = 0.18)           0.3.4 Off Label Lipid Lowering Agents: Othe         mrami-Weizman 2013         38.8           ssuncao 2006         45.8         11           urrami-Weizman 2013         38.8         ssuncao 2006         45.8           ull 2011         48.1         14.1         14.1           uptista 2009         38.7         orba 2011         40.71           na 2019         0         naderi 2019         38.2           enderson 2005         38.1         anderson 2007         -1.2           enderson 2007         -1.2         sunderson 2007         -2.3           ioy 2017         42.54         ffe 2008         -0.39           ioy 2017         -7         rsrsen 2017         38.67           12 018         40.6         0         odabbernia 2014         40.9           ur 2018         0         odabbernia 2014         43.15           inth 2013         36.63         10         2020         76.7           vakoli 2014         43.4         40.92         39.7         38.2	= 5 (P = 0 ers	103	32 1	10.82	0.8	3.3%	6 18 [3 57 8 70]		220000
terrogeneity: Tau <sup>2</sup> = 14.14; Chi <sup>2</sup> = 23.95, df + est for overall effect: Z = $1.34$ (P = $0.18$ ) <b>0.3.4 Off Label Lipid Lowering Agents: Othe</b> mrami-Weizman 2013 38.8 suncao 2006 45.8 ull 2011 48.1 aptista 2008 49.5 aptista 2009 38.7 rba 2011 40.71 un 2019 0 haderi 2019 38.2 enderson 2009 38.1 enderson 2007 -1.2 enderson 2007 38.1 enderson 2007 42.54 ffe 2008 -0.39 rivay 2017 42.54 ffe 2008 -0.39 trivoy 2017 -7 rusen 2017 38.67 2013 1 u 2018 5.03 a 2018 40.6 u 2018 40.6 u 2018 0 odabbernia 2014 43.15 mith 2013 36.63 a m 2020 76.17 avakoli 2014 43.4 aveira 2014 43.25 aveira 2014 39.7 ek 2014 49.22 anag 2020 36.74 ortea 2016 3	= 5 (P = 0	285	52.1	10.05	280	14.8%	2.46 [-1.15, 6.06]		
3.3.4 Off Label Lipid Lowering Agents: Other mani—Weizman 2013       38.8         ssuncao 2006       45.8         li 2011       48.1         pista 2006       45.8         li 2011       48.1         pista 2009       38.7         rba 2011       40.71         n 2019       0         naderi 2019       38.2         enderson 2005       38.1         enderson 2007       -1.2         inderson 2017       42.54         ffe 2018       -0.39         ivoy 2017       -7         rssen 2017       38.67         2018       40.6         u 2018       0         obdebernia 2014       43.15         inth 2013       36.63         in 2020       76.17         vakoli 2014       43.4         weira 2014       39.7         k	ers	.0002); l <sup>2</sup> :	= 79%		200	1110/0	2.10 [ 1.25, 0.00]		
3.4 Off Label Lipid Lowering Agents: Other analysis of the constraint well and the constraint of the constr	ers								
nram-Weizman 2013 38.8 suncao 2006 45.8 II 2011 48.1 ptista 2008 49.5 ptista 2009 38.7 rba 2011 40.71 n 2019 0 aderi 2019 38.2 inderson 2005 38.1 inderson 2007 -1.2 inderson 2007 -1.2 inderson 2007 42.54 fe 2008 -0.39 ika-Pokorska 2015 45.59 ioy 2017 42.54 fe 2008 -0.39 ika-2017 38.67 2013 1 i 2018 5.03 2018 40.6 u 2018 0 o odabbernia 2014 40.9 idabbernia 2014 43.15 ith 2013 36.63 n 2020 76.17 vakoli 2014 39.7 k 2015 39.7 k 2015 39.7 k 2015 39.7 k 2015 39.7 k 2016 39.7 k 2017 39.7 k 2017 39.7 k 2017 39.7 k 2017 39.7 k 2018 39.7		26					1 201 5 20		
suncao 2006         45.8           II 2011         48.1           ptista 2008         49.5           ptista 2009         38.7           rba 2011         40.71           n 2019         0           adderi 2019         38.2           inderson 2005         38.1           inderson 2007         -1.2           inderson 2007         42.54           fc 2008         -0.39           ivay 2017         42.54           fc 2008         -0.39           ivay 2017         38.67           2013         1           i 2018         0           odabernia 2014         40.9           u 2018         0           odabernia 2014         43.15           nith 2013         36.63           n 2020         76.17           vakoli 2014         43.4           veira 2014         39.7           k 2014         49.22           ang 2020         36.74           terogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df = st for overall effect: Z = 0.55 (P = 0.58)	13.2	29	37.6	11.1	25	1.9%	1.20 [-5.28, 7.68]		4444444
II 2011 48.1 II 2011 48.1 ptista 2008 49.5 ptista 2009 38.7 rba 2011 40.71 40.71 n 2019 0 naderi 2019 38.2 enderson 2005 38.1 inderson 2007 -1.2 enderson 2009 38 Nka-Pokorska 2015 45.59 noy 2017 42.54 ffe 2008 -0.39 tivoy 2017 -7 rsen 2017 38.67 2013 1 a 2018 5.03 2018 40.6 u 2018 0 obdabbernia 2014 43.15 nith 2013 36.63 n 2020 76.17 vakoli 2014 43.4 veira 2014 39.7 k 2015 39.7 k 2016 30.7 k 2016 30.7 k 2016 30.7 k 2017 30.7 k 2016 30.7 k 2017 30.7 k	10.6	27	46.5	12.7	27	2.0%	-0.70 [-6.94, 5.54]		<b>2224244</b>
ptista 2008 49.5 ptista 2009 38.7 rba 2011 40.71 n 2019 0 ataderi 2019 38.2 enderson 2005 38.1 enderson 2007 -1.2 enderson 2009 38 ytka-Pokorska 2015 45.59 ytka-Pokorska 2015 45.59 ytka-Pokorska 2015 45.59 ytka-Pokorska 2015 45.59 yta 2017 -7 rsen 2017 38.67 2013 1 2018 5.03 2018 5.03 2018 40.6 u 2018 5.03 2018 40.6 u 2018 0 0 dababernia 2014 40.9 ytmo-Nava 2014 43.15 ni 2020 76.17 vakoli 2014 43.4 u 2014 39.7 k 2015 30.7 k 2015 30.7	13.3	14	44.1	10.5	15	1.4%	4.00 [-4.76, 12.76]		<b>? ? ? 9 9 9 9</b>
ptista 2009 38.7 pha 2011 40.71 n 2019 0 naderi 2019 38.2 enderson 2005 38.1 enderson 2007 -1.2 sinderson 2009 38 kla-Pokorska 2015 45.59 noy 2017 42.54 ffe 2008 -0.39 kvoy 2017 -7 rsen 2017 38.67 2013 1 1 2018 5.03 2018 40.6 u 2018 0 0 dabbernia 2014 40.9 umo-Nava 2014 43.15 nith 2013 36.63 n 2020 76.17 vakoli 2014 49.22 ang 2020 36.74 rtea 2016 36.8 btotal (95% CI)	8.6	13	45.3	10.4	15	1.7%	4.20 [-2.84, 11.24]		<b></b>
what 2011     40.71       na 2019     0       naderi 2019     38.2       enderson 2005     38.1       enderson 2007     -1.2       enderson 2007     -1.2       enderson 2007     42.54       ffe 2008     -0.39       ivoy 2017     -7       rsen 2017     38.67       2013     1       i 2018     5.03       i 2018     0       oddabernia 2014     40.9       ymo-Nava 2014     43.15       inith 2013     36.63       in 2020     76.17       vakoli 2014     49.22       anag 2020     36.74       wreta 2016     36.8       bibtotal (95% CI)     50.5       est or overall effect: Z = 0.55 (P = 0.58)	11.1	14	44.4	12.8	15	1.4%	-5.70 [-14.40, 3.00]		9799999
In 2019 0 naderi 2019 38.2 enderson 2005 38.1 enderson 2007 -1.2 enderson 2009 38 blka-Pokorska 2015 45.59 hoty 2017 42.54 ffe 2008 -0.39 ivoy 2017 -7 rsen 2017 38.67 2013 1 a 2018 5.03 to 2018 40.6 u 2018 0 odabbernia 2014 40.9 odabbernia 2014 43.15 nith 2013 36.63 in 2020 76.17 vakoli 2014 43.4 viera 2014 39.7 ik 2014 43.4 viera 2014 39.7 ik 2014 36.7 ibtotal (95% CI)	6.79	14	38.83	3.54	6	2.5%	1.88 [-2.67, 6.43]		??
naderi 2019       38.2         enderson 2005       38.1         inderson 2007       -1.2         enderson 2009       38         jka-Pokorska 2015       45.59         hory 2017       42.54         ffe 2008       -0.39         ivoy 2017       -7         rsen 2017       38.67         2013       1         i 2018       40.6         i 2018       0         odabbernia 2014       40.9         inith 2013       36.63         inith 2014       43.4         veria 2014       39.7         isk 2014       49.22         inang 2020       36.74         isterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =         ist for overall effect: Z = 0.55 (P = 0.58)         obtal (95% CI)       20.55	6	22	0	8	21	2.6%	0.00 [-4.24, 4.24]		<b>977999</b>
enderson 2005 38.1 enderson 2007 -1.2 enderson 2009 38 3)ka-Pokorska 2015 45.59 hoy 2017 42.54 ffc 2008 -0.39 ivoy 2017 -7 rsen 2017 38.67 2013 1 a 2018 5.03 a 2018 00 odabbernia 2014 40.9 odabbernia 2014 43.15 nith 2013 36.63 nith 2013 36.63 nith 2013 36.63 nith 2014 43.4 veira 2014 39.7 ek 2014 49.22 ang 2020 36.74 ortea 2016 36.8 biotal (95% CI)	9.2	30	39.3	6.3	30	2.7%	-1.10 [-5.09, 2.89]		99??999
enderson 2007       -1.2         enderson 2009       38         blka-Pokorska 2015       45.59         hoty 2017       42.54         ffe 2008       -0.39         ivoy 2017       -7         arsen 2017       38.67         2013       1         u 2018       5.03         u 2018       0         odabbernia 2014       40.9         ormo-Nava 2014       43.15         inth 2013       36.63         un 2020       76.17         vakoli 2014       49.22         anag 2020       36.74         brotal (95% CI)       36.8         brotal (95% CI)       est for overall effect: Z = 0.55 (P = 0.58)	13.1	19	36.8	10.1	18	1.6%	1.30 [-6.21, 8.81]		9999999
enderson 2009         38           olka-Pokorska 2015         45.59           oky 2017         42.54           ffe 2008         -0.39           vivoy 2017         -7           rsren 2017         38.67           2013         1           u 2018         5.03           n 2018         0           odabbernia 2014         40.9           omo-Nava 2014         43.15           ninth 2013         36.63           un 2020         76.17           vakeira 2014         49.22           anag 2020         36.74           ortera 2016         36.8           ubtotal (95% CI)         etcrogeneity: Tau <sup>2</sup> = 0.05; (Pi = 0.58)           otal (95% CI)         50.51	6.32	10	-0.8	3.11	8	2.6%	-0.40 [-4.87, 4.07]		9977999
bika-Pokorska 2015         45.59           hoy 2017         42.54           ffe 2008         -0.39           rivoy 2017         -7           rsen 2017         38.67           2013         1           u 2018         5.03           a 2018         40.6           u 2018         0           odabbernia 2014         40.9           mono-Nava 2014         43.15           nith 2013         36.63           nu 2020         76.17           vakoli 2014         43.4           viera 2014         39.7           sk 2014         49.22           anag 2020         36.74           vieterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)           otal (95% Cl)	11	8	35	7	10	1.4%	3.00 [-5.77, 11.77]		2220444
hoy 2017         42.54           ffe 2008         -0.39           vison 2017         -7           zrsen 2017         38.67           2013         1           u 2018         5.03           u 2018         40.6           u 2018         0           odabbernia 2014         40.9           omo-Nava 2014         43.15           ninth 2013         36.63           un 2020         76.17           avakoli 2014         43.4           vavira 2014         39.7           ek 2014         49.22           anag 2020         36.74           ortera 2016         36.8           ubtotal (95% CI)         est for overall effect: Z = 0.55 (P = 0.58)           otal (95% CI)         56.74	11.8	23	46 42	8 45	22	2 1%	-0.83[-6.81 5.15]		A 2 2 A A A A
101 J J J         42.34           162 2008         -0.39           vivoy 2017         -7           2013         1           u 2018         5.03           j 2018         40.6           vu 2018         0           odabbernia 2014         43.15           mith 2013         36.63           j 2020         76.17           avakoli 2014         43.4           aveira 2014         39.7           ek 2014         49.22           anag 2020         36.74           pritea 2016         36.8           ubtotal (95% CI)         eterogeneity: Tau <sup>2</sup> = 0.05; (Pi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)         otal (95% CI)	7 73	20	42 54	11.6	20	2.0%	0.00[-6.11.6.11]		
1000         1000           10000         1000           10000         1000           10000         1000           10000         1000           10000         1000           10000         1000           10000         1000           10000         1000           10000         1000           100000         10000	6.57	31	0.77	4 64	32	3 2%	-1 16 [-3 98 1 66]	_	2220000
No. J. 2017         38.67           2013         1           u 2018         5.03           u 2018         40.6           u 2018         0           odabbernia 2014         40.9           omo-Nava 2014         43.15           nith 2013         36.63           un 2020         76.17           avakira 2014         43.4           variar 2014         49.22           anang 2020         36.74           portea 2016         36.8           abbotal (95% CI)         est for overall effect: Z = 0.55 (P = 0.58)           otal (95% CI)         21.83, df =	273	23	-3.1	173	24	0.8%	-3 90 [-17 03 9 23]		
arsen 2017       36.87         2013       1         u 2018       5.03         u 2018       40.6         u 2018       0         lodabbernia 2014       40.9         momo-Nava 2014       43.15         mith 2013       36.63         un 2020       76.17         avakoli 2014       43.4         aveira 2014       39.7         ek 2014       49.22         hang 2020       36.74         ortea 2016       36.8         ubtotal (95% CI)       eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =         est for overall effect: Z = 0.55 (P = 0.58)       otal (95% CI)	12 19	23	42.42	26.95	50	1 40/	3.50 [-17.03, 5.25]		
2013       1         2013       1         u 2018       5.03         u 2018       0         odabbernia 2014       40.9         omo-Nava 2014       43.15         mith 2013       36.63         un 2020       76.17         avakoli 2014       43.4         aveira 2014       39.7         ek 2014       49.22         anag 2020       36.74         ortea 2016       36.8         abbotal (95% CI)       est for overall effect: Z = 0.55 (P = 0.58)         otal (95% CI)       9.00	15.10	47	42.45	20.05	50	1.4%	-3.76 [-12.10, 4.38]		
u 2010         5.03           u 2018         40.6           vu 2018         0           odabbernia 2014         40.9           mono-Nava 2014         43.15           nith 2013         36.63           un 2020         76.17           avakoli 2014         43.4           aveira 2014         39.7           ek 2014         49.22           anag 2020         36.74           ortea 2016         36.8           ubtotal (95% CI)         eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)         otal (95% CI)	8	10	-1	4	21	2.7%	2.00 [-2.07, 6.07]		
1 2018         40.6           1 2018         0           odabbernia 2014         40.9           omo-Nava 2014         43.15           inth 2013         36.63           un 2020         76.17           avakoli 2014         43.4           aveira 2014         39.7           sk 2014         49.22           anag 2020         36.74           ortea 2016         36.8           bbtotal (95% CI)         eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)         otal (95% CI)	29	27	8.9	33.6	28	0.5%	-5.87 [-20.44, 12.70]		444444
uu 2018         0           odabbernia 2014         40.9           owno-Nava 2014         43.15           nich 2013         36.63           nich 2013         36.61           un 2020         76.17           vaxakoli 2014         43.4           vaveira 2014         39.7           sk 2014         49.22           nang 2020         36.74           ortea 2016         36.8           bibotal (95% CI)         eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)         otal (95% CI)	13.3	43	38.1	11.4	42	2.3%	2.50 [-2.76, 7.76]		444444
odabbernia 2014         40.9           mon-Nava 2014         43.15           nith 2013         36.63           un 2020         76.17           vakoli 2014         43.4           tveira 2014         39.7           sk 2014         49.22           tang 2020         36.74           tottal (95% CI)         36.8           tetrogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)           otal (95% CI)	42.54	11	0	3.87	10	0.2%	0.00 [-25.25, 25.25]		<b>7799999</b>
>mmo-Nava 2014         43.15           nith 2013         36.63           nin 2020         76.17           vakoli 2014         43.4           aveira 2014         39.7           sk 2014         49.22           ang 2020         36.74           ortea 2016         36.8           bibtotal (05% CI)         36.8           eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =         est for overall effect: Z = 0.55 (P = 0.58)           otal (95% CI)         9.55	10.31	18	42.7	10.18	18	1.8%	-1.80 [-8.49, 4.89]		444444
nith 2013 36.63 In 2020 76.17 vaxali 2014 43.4 varia 2014 39.7 sk 2014 49.22 ang 2020 36.74 ortea 2016 36.8 bitotal (95% Cl) terogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df = est for overall effect: Z = 0.55 (P = 0.58) botal (95% Cl)	9.97	20	44.78	10.56	24	2.0%	-1.63 [-7.71, 4.45]		
in 2020       76.17         ivakoli 2014       43.4         veria 2014       39.7         sk 2014       49.22         anag 2020       36.74         brotea 2016       36.8         bibtotal (95% CI)       61.2         est for overall effect: Z = 0.55 (P = 0.58)       0.58	16.59	29	34.99	16.16	23	1.3%	1.64 [-7.31, 10.59]		??
wakoli 2014         43.4           weira 2014         39.7           sk 2014         49.22           hang 2020         36.74           bytte 2016         36.8           bytte 2016         36.8           bytte 2016         36.8           bytte 2016         36.8           bytte 105% CI)         eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)         btal (95% CI)	42.92	102	77.72	61.48	52	0.4%	-1.55 [-20.22, 17.12]		99??999
viveira 2014         39.7           ik 2014         49.22           anga 2020         36.74           virtea 2016         36.8           ibitotal (95% CI)         isterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =           est for overall effect: Z = 0.55 (P = 0.58)         otal (95% CI)	10.1	30	37	10	30	2.3%	6.40 [1.31, 11.49]	——	?
ek 2014         49.22           nang 2020         36.74           preta 2016         36.8           bibtotal (95% CI)         36.8           eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df =         36.8           est for overall effect: Z = 0.55 (P = 0.58)         36.8           btal (95% CI)         36.8	6.63	11	44.1	14.42	13	1.4%	-4.40 [-13.16, 4.36]		
hang 2020 36.74 Jortea 2016 36.8 Jubotal (95% CI) eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df = est for overall effect: Z = 0.55 (P = 0.58) botal (95% CI)	8	10	53.56	10.1	11	1.6%	-4.34 [-12.10, 3.42]		9999999
vitea 2016 36.8 Jbtotal (95% CI) eterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df = est for overall effect: Z = 0.55 (P = 0.58) otal (95% CI)	5.8	30	40.6	8.89	29	2.8%	-3.86 [-7.70 -0.02]		0002000
lbtotal (95% Cl) terogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 23.83, df = tst for overall effect: Z = 0.55 (P = 0.58) tal (95% Cl)	3.29	10	40.33	7	9	2.4%	-3.53 [-8.54, 1.48]	+	2200000
eterogeneity: Tau <sup>4</sup> = 0.00; Chi <sup>4</sup> = 23.83, df = est for overall effect: Z = 0.55 (P = 0.58) otal (95% Cl)		703		,	648	53.0%	-0.30 [-1.36, 0.76]	•	
stal (95% CI)	28 (P = 0	.69); I <sup>2</sup> = 0	1%						
		1562			1497	100.0%	0.43 [-0.85, 1.70]	▲	
$atorogonolity: Tauf = 11.26 \cdot Chif = 150.00 \cdot 16$	f - 46 /D	0.00001	12 - 710		1.57	100.070			
eterogeneity. rau = 11.20; $CH = 159.80$ , dr		. 0.00001)	- / 176					-20 -10 0 10 20	
est for overall effect. $z = 0.65$ (P = 0.51)	2 /0 0	12) 12	0.1%					Favours [placebo] Favours [intervention]	
est for subgroup afferences: Chi* = 5.90, df =	= 3 (P = 0)	$(12), \Gamma = 4$	9.1%						
isk of blas legend									
A) Random sequence generation (selection bias	s)								
<ol> <li>Allocation concealment (selection bias)</li> </ol>									
C) Blinding of participants and personnel (perfe	ormance b	oias)							
D) Blinding of outcome assessment (detection									
E) Incomplete outcome data (attrition bias)	bias)								
) Selective reporting (reporting bias)	bias)								
) Other bias	bias)								
	bias)								
<b>PE 2</b>   Export plot abouting the second	bias)		non in char	ann in h'-	h de	noiti i li-	protoin obclasterel	(ma/dl) for all interventions	poored to alc

(**Figure 6**; N = 3, n = 419; WMD = -14.40 mg/dL; CI: -26.51, -2.28; p = 0.02;  $I^2 = 47$ ) compared to placebo. No significant changes were noted for HDL cholesterol (**Figure 3**; N = 6, n = 565;  $I^2 = 79$ ) and LDL cholesterol (**Figure 4**; N = 3, n = 419;  $I^2 = 89$ ). None of the metformin studies examined VLDL cholesterol.

#### Off Label Lipid Lowering Agents: Others

For other off label lipid lowering agents, there was a statistically significant reduction in total cholesterol levels (**Figure 6**; N = 27, n = 1,322; WMD = -5.18 mg/dL, CI: -10.31, -0.05; p = 0.05;  $I^2 = 41$ ) along with a decreasing trend in levels of triglycerides

udy or Subgroup	Mean [mg/dL]	SD [mg/dL]	Total	Mean [mg/dL] S	D [mg/dL]	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	ABCDEF
.4.1 Lipid Lowering	Agents									
hdani 2018	-15.42	49.78	28	0.5	62.18	28	1.1%	-15.92 [-45.42, 13.58]		<b></b>
nsley 2008	131.48	38.67	39	123.74	34.8	33	2.4%	7.74 [-9.24, 24.72]		?
binson 2019	91.18	6.95	25	97.71	6.11	25	5.1%	-6.53 [-10.16, -2.90]	-	6666666
ncenzi 2014	85.13	25.38	24	104.21	19.34	25	3.2%	-19.08 [-31.75, -6.41]		2 2 2 0 0 0 0
btotal (95% CI)			116			111	11.8%	-7.90 [-17.56, 1.76]	•	
eterogeneity: Tau <sup>2</sup> = ! st for overall effect: 2	50.15; Chi <sup>2</sup> = 6.80, Z = 1.60 (P = 0.11)	df = 3 (P = 0)	.08); l <sup>2</sup> =	= 56%						
.4.2 Antipsychotic S	witch/Add-on Int	erventions								
berdt 2008	-2.7	19.72	65	-5.41	31.71	68	4.0%	2.71 [-6.22, 11.64]	- <del>-</del>	
n 2013	-15.1	19.8	16	4.4	22.5	14	2.7%	-19.50 [-34.77, -4.23]		<b>? <del>?</del> <b>? <del>9 0</del> <del>9</del> <del>0</del></b></b>
ischhacker 2010	-12.64	26.02	95	0	43.62	88	3.6%	-12.64 [-23.15, -2.13]		676666
wcomer 2008	-12.7	25.4	80	-5.52	27.64	76	4.1%	-7.18 [-15.52, 1.16]		222444
oup 2011	-15.4	26.04	89	-12.5	25.14	98	4.4%	-2.90 [-10.25, 4.45]		
btotal (95% CI)			345			344	18.8%	-6.45 [-12.83, -0.07]	•	
terogeneity: Tau <sup>2</sup> = 2 st for overall effect: 2	28.24; Chi <sup>2</sup> = 8.89, 2 = 1.98 (P = 0.05)	df = 4 (P = 0.1)	.06); I <sup>2</sup> =	= 55%						
4.3 Off Label Lipid	Lowering Agent: M	Metformin								
ptista 2007	134.5	64.3	36	126.9	63.9	36	1.1%	7.60 [-22.01, 37.21]	<del></del>	
skog 2013	-7.1	23.9	75	-2	24.08	71	4.3%	-5.10 [-12.89, 2.69]	+	
2016	116.8	31.32	103	150.43	47.95	98	3.5%	-33.63 [-44.8922.37]		??
btotal (95% CI)	1010		214			205	8.8%	-12.52 [-35.86, 10.82]		
terogeneity: Tau <sup>2</sup> = 3 st for overall effect: 2	851.30; Chi <sup>2</sup> = 18.2 Z = 1.05 (P = 0.29)	70, df = 2 (P <	0.0001	l); I <sup>2</sup> = 89%						
.4.4 Off Label Lipid	Lowering Agents:	Others								
rami-Weizman 2013	125.6	40	29	133.6	38.7	25	1.8%	-8.00 [-29.03, 13.03]		
suncao 2006	198.8	46	27	180.3	34.1	27	1.8%	18.50 [-3.10, 40.10]	+	777979
II 2011	97.9	35.3	14	88.3	29.3	12	1.5%	9.60 [-15.23, 34.43]		???
ptista 2008	110.1	31.9	13	113.8	31.4	15	1.6%	-3.70 [-27.22, 19.82]	<b>.</b>	
otista 2009	108.5	19.9	14	124.5	20.9	15	2.7%	-16.00 [-30.85, -1.15]		A 7 B A A A
rba 2011	117.07	31.1	14	104.83	31.8	6	1.1%	12 24 [-17 97 42 45]		220000
2019	-1	25	22	4.5	15	21	3.3%	-5.50 [-17.76.6.76]		A 2 2 2 A A
aderi 2019	96.6	31.1	30	106.2	32.5	30	2.5%	-9.60 [-25.70, 6.50]		AA22AA
nderson 2005	112.6	38.9	19	146.4	43.4	18	1 3%	-33.80 [-60.41 -7.19]		
nderson 2007	12.0	86.01	10	7.9	32.81	8	0.3%	4 10 [-53 85 62 05]		
nderson 2009	124	25	10	2.5	52.01	10	2.3%	24 00 [15 80 52 20]		
lka Bokorska 2015	120 42	25 26	22	120.28	24.26	22	2.2%	-9.06 [-22.40 5.57]		
2017	120.42	23.50	20	110.99	24.30	20	2.0%	7 73 [ 11 59 37 05]		
10y 2017	127.01	34.0	20	12.33	27.07	20	2.1/0	0.00 [ 12.00 13.00]		
10 2008	-12.57	27.07	51	-12.57	23.32	52	5.1%	0.00 [-13.00, 13.00]		
2017	-15.4	21.25	4/	-2.5	13.44	50	4.470	-13.10 [-20.23, -3.97]		
2015	-3	20	10	-0.06	23	21	2.0%	-4.94 [-20.47, 10.39]		
2018	0.10	32.48	27	11.6	21.05	20	2.8%	-5.42 [-20.06, 9.22]		44444
2018	105.3	28.1	43	99	32.7	42	3.1%	6.30 [-6.67, 19.27]		444444
u 2018	-15.47	27.07	11	-7.73	27.07	10	1.6%	-7.74 [-30.92, 15.44]		
odabbernia 2014	123.9	30.17	18	116.3	22.189	18	2.3%	7.60 [-9.70, 24.90]		444444
mo-Nava 2014	112.93	32.33	20	94.69	23.4	24	2.4%	18.24 [1.26, 35.22]		444444
hith 2013	95.44	38.88	29	96.85	39.81	23	1.8%	-1.41 [-22.97, 20.15]		7799999
n 2020	178.26	37.5	102	183.29	34.02	52	3.4%	-5.03 [-16.80, 6.74]		<b></b>
vakoli 2014	112.8	35.5	30	103.8	36.7	30	2.2%	9.00 [-9.27, 27.27]		<b>799999</b>
veira 2014	100.9	37.15	11	100.4	64.18	13	0.6%	0.50 [-40.72, 41.72]		
k 2014	104.11	39.9	10	111.22	33.5	11	1.0%	-7.11 [-38.79, 24.57]		
ang 2020	105.18	29	30	112.14	28.62	29	2.8%	-6.96 [-21.66, 7.74]		
btotal (95% CI)	118.4	28.18	10 680	117.8	26.73	9 621	1.5% 60.6%	0.60 [-24.10, 25.30] -1.03 [-5.69, 3.62]	•	<u></u>
terogeneity: Tau <sup>2</sup> = 6 st for overall effect: 2	57.76; Chi <sup>2</sup> = 52.57 Z = 0.43 (P = 0.66)	7, df = 27 (P =	= 0.002);	; $I^2 = 49\%$						
tal (95% CI)			1355			1281	100.0%	-4.19 [-7.71, -0.67]	•	
terogeneity: Tau <sup>2</sup> = 6 st for overall effect: 2	50.05; Chi <sup>2</sup> = 96.34 Z = 2.33 (P = 0.02)	4, df = 39 (P <	0.0000	()1); $I^{z} = 60\%$					-50 -25 0 25 50 Favours [intervention] Favours [placebo]	_
k of bias legend	rences: Chi <sup>+</sup> = 3.25	$a_{1} = 3 (P = 0)$	0.35), l*	= 7.7%						
Random sequence g Allocation concealm Blinding of participa	eneration (selectio ent (selection bias) ents and personnel	n bias) (performance	hias)							
) Blinding of outcome	assessment (deter	ction bias)	unas)							
	reporting hise)									

that was nonsignificant (**Figure 2**; N = 28, n = 1,337; WMD = -11.06, CI: -23.08, 0.97; p = 0.07;  $l^2 = 39$ ). There were no significant differences for LDL cholesterol (**Figure 4**; N = 28, n = 1,301;  $l^2 = 49$ ), HDL cholesterol (**Figure 3**; N = 29, n = 1,351;  $l^2 = 0$ ), and VLDL cholesterol (**Figure 5**; N = 4; n = 223;  $l^2 = 0$ ).

### Secondary Outcomes: Additional Metabolic Measures

Cumulatively, the pharmacological interventions reviewed in this paper were associated with significant reductions in body weight (Supplementary Figure 1; N = 38, n = 2,380; WMD = -1.13 kg, CI: -2.18, -0.08; p = 0.03), BMI (Supplementary Figure 2; N = 36, n = 2,174; WMD = -0.42 kg/m<sup>2</sup>, CI: -0.85, 0.01; p = 0.05), and waist circumference (Supplementary Figure 3; N = 29, n = 1,532; WMD = -1.34 cm, CI: -2.34, -0.34; p = 0.009) compared to placebo. As for glucose-related parameters, interventions led to significant decreases in blood insulin (Supplementary Figure 4; N = 24, n = 1,636; WMD = -1.64 mIU/mL, CI: -2.76, -0.52; p = 0.004) and HOMA-IR (Supplementary Figure 5; N = 16, n = 867; WMD = -0.52, CI:



-0.89, -0.15; p = 0.005) compared to placebo. Blood glucose levels showed a decreasing trend, but the difference was not significant (**Supplementary Figure 6**; N = 46, n = 3,048; WMD = -1.17 mg/dL, CI: -2.44, -0.11; p = 0.07). Differences in HbA1c levels were also not significant (**Supplementary Figure 7**; N = 19, n = 1,097). Total PANSS scores showed a trend toward improvement in the intervention group, but the difference again was not statistically significant (**Supplementary Figure 8**; N =13, n = 1,005, WMD = -2.15; CI: -4.45, 0.16; p = 0.07). Finally, there were no significant differences in systolic blood pressure (**Supplementary Figure 9**; N = 16, n = 892) and diastolic blood pressure (**Supplementary Figure 10**; N = 15, n = 845).

#### **Risk of Bias**

Risk of bias in random sequence generation was deemed to be low in 29 studies, high in 1, and unclear in 18 (**Supplementary Figure 11**). Outcomes did not change significantly after the study with high risk of bias was removed.

## DISCUSSION

In this systematic review and meta-analysis, we examined different pharmacological interventions used to treat antipsychotic-induced dyslipidemia in schizophrenia spectrum disorders. The 29 pharmacological interventions analyzed were cumulatively effective in lowering total cholesterol, LDL cholesterol, and triglycerides, while increasing HDL cholesterol. However, improvements were not significant with VLDL cholesterol. Amongst the subgroups analyzed, we found that antipsychotic switching/add-on proved most effective in improving lipid parameters commonly dysregulated in schizophrenia, namely triglycerides and HDL cholesterol (77). Notably, the off-label lipid lowering agent metformin was more promising than approved lipid lowering agents in decreasing triglycerides and total cholesterol levels. However, other off label agents only showed a trend in improving lipid parameters.

Our findings suggest that off label strategies can be effectively employed to ameliorate antipsychotic-induced dyslipidemia. In

particular, metformin shows considerable promise, improving lipid parameters and showing consistent association with a decrease in triglycerides and total cholesterol levels. Similar findings for triglycerides and total cholesterol levels were previously demonstrated in a review by Jiang et al. (78), and in the context of schizophrenia would benefit through evidence specific to long-term outcomes. Prior studies indicate that a 40 mg/dL reduction in LDL cholesterol and triglycerides translates into a 20% and 4-5% decrease in risk for developing cardiovascular disease, respectively, independent of baseline risk (79). Given this, our review suggests that the available strategies for targeting dyslipidemia are inadequate, reinforcing the need for novel, more effective interventions. Furthermore, while our findings provide strong evidence for antipsychotic switch/add-on interventions, study duration ranged from 6 to 24 weeks, which does not provide adequate time to assess the long-term effects of these treatments on dyslipidemia. While aripiprazole and quetiapine are both second generation antipsychotics with less severe metabolic side-effects compared to others like olanzapine and clozapine, they have their own metabolic burden that cannot be ignored and needs to be better understood over the longer term (80, 81). Similarly, while our findings suggest that lipid lowering agents are not effective in improving dyslipidemia, these results may have been limited by the short duration of the included studies. The small number of studies also did not permit examination of the possible effects of dose of lipid-lowering agents.

Current studies provide general support for the potential effectiveness of pharmacological interventions, but further research is warranted to refining recommendations pertaining to individual treatments. Currently in many studies, lipid management was not a primary focus; of the 48 reviewed studies, only 26 identified lipid profile as a primary outcome measure, in contrast to 22 where it was positioned as a secondary outcome. More studies focused on this area of research sets the stage for additional insights and the increased power necessary to detect not only beneficial outcomes, but also the elucidation of specific variables contributing to effective

0.1.1 Lipid Lowering Agents	n [mg/dL] SI	ition [mg/dL]	Total M	Place ean [mg/dL] SD	bo [mg/dL]	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl	A B C D E F (
nana anpia aonaning riganto										
hdani 2018	-5.2	73.63	28	4.14	81.54	28	0.6%	-9.34 [-50.03, 31.35]		<b></b>
nsley 2008	204.95	42.54	39	201.08	46.4	33	1.9%	3.87 [-16.84, 24.58]		?
obinson 2019	163.91	8.22	25	175.75	6.88	25	7.7%	-11.84 [-16.04, -7.64]	+	6666666
ncenzi 2014	161.04	34.18	24	178.56	28.4	25	2.4%	-17.52 [-35.15, 0.11]		???
btotal (95% CI)			116			111	12.5%	-11.52 [-15.51, -7.53]	•	
terogeneity: Tau <sup>2</sup> = 0.00; Ch	i <sup>2</sup> = 2.60, df =	3 (P = 0.4)	6); $I^2 = 0\%$	5					•	
st for overall effect: Z = 5.66	(P < 0.00001)									
.1.2 Antipsychotic Switch/A	dd-on Interv	entions								
berdt 2008	-4.25	26.3	65	-7.73	35.96	68	4.5%	3.48 [-7.19, 14.15]		•??•••
n 2013	-15.3	33.3	16	5.6	34	14	1.5%	-20.90 [-45.05, 3.25]		? - ?
eischhacker 2010	-14.61	25.01	97	-2.43	26.64	88	6.0%	-12.18 [-19.65, -4.71]		$\Theta$
wcomer 2008	-18.44	26.03	80	-6.52	27.55	76	5.5%	-11.92 [-20.34, -3.50]		<b>????~~~</b> ~
oup 2011	-19.6	28.21	89	-10.8	26.63	98	5.8%	-8.80 [-16.68, -0.92]		
ao 2015	167.1	35.6	54	175.6	42.9	53	3.0%	-8.50 [-23.45, 6.45]		????
btotal (95% Cl) terogeneity: Tau <sup>2</sup> = 12.44; C	hi² = 7.35, df	= 5 (P = 0.	401 20); l <sup>2</sup> = 3	2%		397	26.1%	-8.83 [-13.91, -3.74]	•	
st for overall effect: Z = 3.40	(P = 0.0007)									
1.3 Off Label Lipid Lowerin	ng Agent: Met	formin								
ptista 2007	199.6	70	36	204.7	59.5	36	1.0%	-5.10 [-35.11, 24.91]		
skog 2013	-8.9	29.12	75	0.2	28.31	71	5.1%	-9.10 [-18.42. 0.22]		999999
2016	187.94	38.28	103	213.07	60.71	98	3.2%	-25.13 [-39.2411.02]		224444
ototal (95% CI)			214			205	9.3%	-14.40 [-26.51, -2.28]	•	
erogeneity: Tau <sup>2</sup> = 53.25; C t for overall effect: Z = 2.33	$hi^2 = 3.77, df$ (P = 0.02)	= 2 (P = 0.	15); I <sup>2</sup> = 4	7%						
1.4 Off Label Linid Loweria	a Agents: Ot	iers								
rami_Weizman 2012	211.0	527	20	202.2	51 5	25	1 1%	9 60 [-18 50 27 70]		
irami-weizman 2013	211.9	53.7	29	202.3	51.5	25	1.1%	9.60 [-18.50, 37.70]	-	444444
suncao 2006	198.8	46	27	180.3	34.1	27	1.7%	18.50 [-3.10, 40.10]		
ptista 2008	184	29.1	13	191.1	41.1	15	1.3%	-7.10 [-33.23, 19.03]		444,444
otista 2009	179.9	22.6	14	201.2	26.02	15	2.4%	-21.30 [-39.01, -3.59]		
ba 2011	195.21	42.07	14	175.17	35.81	6	0.7%	20.04 [-16.11, 56.19]		?? 🕊 🖶 🗣
2019	-6	23	22	-3	27	21	3.0%	-3.00 [-18.02, 12.02]		$\Theta$ $O$
aderi 2019	161.8	36.7	30	178.5	35.8	30	2.3%	-16.70 [-35.05, 1.65]		<b></b>
nderson 2005	202.7	52.5	19	232.8	41.6	18	1.0%	-30.10 [-60.54, 0.34]		999999
nderson 2007	-7.7	16.76	10	-2	31.4	8	1.5%	-5.70 [-29.81, 18.41]		<b></b>
nderson 2009	188	36	8	178	15	10	1.2%	10.00 [-16.62, 36.62]		222000
lka-Pokorska 2015	192.92	34.62	23	201.4	26.85	22	2.3%	-8.48 [-26.54, 9.58]		977999
lov 2017	201.08	42.54	20	193.35	34.8	20	1.5%	7.73 [-16.36, 31.82]		
fe 2008	-4.25	29.78	31	-8.51	25.52	32	3.4%	4.26 [-9.45, 17.97]		777444
rsen 2017	-19.3	23.99	47	3.5	21.92	50	5.1%	-22.80 [-31.96, -13.64]		224444
2013	-1	39	18	0	21	21	2.0%	-1 00 [-21 13 19 13]		007000
2018	-27 1	201.9	27	14 3	24.6	28	0.2%	-41 40 [-118 10 35 30]	<b>←</b>	020000
2004	180.2	23.0	34	190.4	21.5	34	1 194	-10.20 [-21.01.0.61]		222000
2018	172.2	34.8	43	177.5	34.7	42	3 1%	-5 30 [-20.08 9 48]		
debberrie 2014	102.2	34.0	45	177.5	34.7	42	1. 20/	-3.30 [-20.08, 9.48]		
Naus 2014	198.5	45.05	10	202.5	53.09	18	1.5%	-4.00 [-30.05, 22.05]		
mo-Nava 2014	198.4	51.84	20	170.83	27.46	24	1.4%	27.57 [2.33, 52.81]		444444
ith 2013	157.02	45.61	29	171.11	40.05	23	1.5%	-14.09 [-37.40, 9.22]		44444
1 2020	178.26	38.5	102	183.29	34.02	52	4.0%	-5.03 [-16.92, 6.86]		<b>HHSSSSSSSSSSSSS</b>
vakoli 2014	181	48.8	30	168.7	48.6	30	1.4%	12.30 [-12.35, 36.95]		<b>799999</b>
veira 2014	170.5	43.45	11	178.4	55.89	13	0.6%	-7.90 [-47.68, 31.88]		
k 2014	175.33	41.3	10	189.78	41.2	11	0.7%	-14.45 [-49.78, 20.88]		
ang 2020	177.88	37.12	30	192.58	32.1	29	2.4%	-14.70 [-32.39, 2.99]	+	<b>GGG?GG</b>
tea 2016	195.6	37.64	10	201.78	40.12	9	0.8%	-6.18 [-41.27, 28.91]		<b>??@@@@</b>
terogeneity: Tau <sup>2</sup> = 66.63; C	hi² = 44.43, d	f = 26 (P =	689 0.01); l <sup>2</sup> :	= 41%		633	52.0%	-5.18 [-10.31, -0.05]	•	
st for overall effect: Z = 1.98	(P = 0.05)									
tal (95% CI)	hi² c1 77 .	- 20 /2	1420	2.7%		1346	100.0%	-7.96 [-11.14, -4.77]	• •	
terogeneity: Tau* = 29.68; C	nr = 61.77, d	r = 39 (P =	0.01); 1* :	= 37%					-100 -50 0 50 100	
st for subgroup differences:	(P < 0.00001)	F _ 2 (P _ C	22) 12 -	21 69/					Favours [intervention] Favours [placebo]	
st for subgroup differences: (	- 4.36, di		.22), 1" =	51.0%						
sk of blas legend										
) kandom sequence generatio	on (selection bi	ias)								
	ection bias)									
) Allocation concealment (sele	personnel (pe	rformance	bias)							
<ul> <li>Allocation concealment (seld)</li> <li>Blinding of participants and</li> </ul>	ment (detectio	n bias)								
<ul> <li>Allocation concealment (sele ) Blinding of participants and</li> <li>Blinding of outcome assess</li> </ul>	ttrition hias)									
) Allocation concealment (seli ) Blinding of participants and ) Blinding of outcome assessi ) Incomplete outcome data (at	tintion bidby									
<ul> <li>Allocation concealment (seli)</li> <li>Blinding of participants and</li> <li>Blinding of outcome assessiin incomplete outcome data (at Selective reporting (reporting)</li> </ul>	g bias)									
Allocation concealment (sel Blinding of participants and Blinding of outcome assessi Incomplete outcome data (at Selective reporting (reporting Other bias	g bias)									
Allocation concealment (sel Blinding of participants and Blinding of outcome assess Incomplete outcome data (a Selective reporting (reporting Other bias	g bias)									
Allocation concealment (sel: Blinding of participants and Blinding of outcome assessi ncomplete outcome data (al Selective reporting (reporting Other bias	g bias)	oled me	an differ	ence in char	aes in tr	otal ch	olester	ol (ma/dl.) for all inte	eventions as compared to placebo	along with sub

treatment. At present, the significant heterogeneity among studies within intervention categories limit generalizations that can be made with respect to mechanisms or interacting variables. Factors affecting outcomes may include specific antipsychotic treatment, diagnosis and stage of illness, co-morbid health conditions, concomitant medications, and duration of antipsychotic and/or lipid intervention treatment. Differential pharmacological interventions may, in fact, vary as a function of patient population. Moreover, to date, many interventions are confined to a single study, precluding pooled data or comparisons between interventions. Our review restricted the population to schizophrenia patients, even though antipsychotics are used to treat patients with other psychiatric illnesses such as affective disorders who also share the metabolic burden (82) and may benefit from the reviewed interventions. Finally, while behavioral and lifestyle interventions remain first-line treatments for dyslipidemia, our review restricted the search to pharmacological interventions.

Given the prevalence of dyslipidemia in schizophrenia, along with the associated increased risk of metabolic complications

and cardiovascular disease, it is imperative that such studies be undertaken. At present, dyslipidemia is often left untreated (13– 15); indeed, the physical health of this population is generally overlooked while the focus is directed to managing psychotic symptoms (83, 84). The integration of psychiatric and medical care falls short at present (85); however, this overview of dyslipidemia, its prevalence and current treatment underscores the need to ensure a more comprehensive model of care be implemented.

# DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

# **AUTHOR CONTRIBUTIONS**

PK, SMA, and MKH contributed to developing the original protocol. PK and KC-D contributed to the original screening, data extraction, risk of bias assessments, and writing the first draft of the manuscript (introduction, methods, and results). FP and JL wrote and registered the protocol with PROSPERO, re-ran the search, updated study selection and risk of bias, and contributed to final data extraction and synthesis prior to manuscript submission, as well as updating the first draft. LH assisted with editing and writing the final draft. SMA was

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involved in supervising all aspects of the review. GR and MKH contributed to editing the final draft. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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