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The effects of statin use on inflammatory markers among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Current evidence suggests that statin use decreases the incidence of cardiovascular diseases (CVD) through reducing LDL cholesterol and decreasing inflammation. Metabolic syndrome (MetS) is usually associated with increased inflammatory markers and increased risk of CVD. We conducted a systematic review and meta-analysis to determine the effect of statin use on inflammatory markers including C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1 (IL-1) among patients with MetS and related disorders. PubMed, EMBASE, Web of Science databases, and Cochrane Library were searched for randomized controlled trials (RCTs) through April 2018. Three independent investigators evaluated study eligibilities, extracted data, and assessed study quality using the Cochrane Collaboration risk of bias tool and Jadad's quality scales. Heterogeneity was determined using Cochran's Q statistic and I-square (I^2) test. Based on the heterogeneity results, we pooled data using random-effect or fixed effect models presented as standardized mean differences (SMD) and corresponding 95% confidence intervals (CI). One hundred thirteen RCTs (19,644 patients) were included in our meta-analysis. The pooled results using random effects model showed that statin use statistically significantly decreased CRP level (SMD = -0.97; 95% CI, -1.10, -0.85; $P < 0.001$; I^2: 95.1%), TNF-α (SMD = -1.88; 95% CI, -2.40, -1.38; $P < 0.001$; I^2: 97.2%), IL-6 (SMD = -1.67; 95% CI, -1.98, -1.34; $P < 0.001$; I^2: 96.5%), and IL-1 concentrations (SMD = -8.35; 95% CI, -10.49, -6.22; $P < 0.001$; I^2: 98.4%) among patients with MetS and related disorders. Our meta-analysis showed beneficial effects of statin use on reducing inflammatory markers in patients with MetS and related disorders.

1. Introduction

Increased inflammatory cytokines have had a major contribution to atherosclerosis and cardiovascular disease (CVD) events [1]. Statins are known to affect certain inflammatory factors [2], though the dose-response effect is mostly unknown. Moreover, chronic inflammation increases the risk of metabolic disorders including type 2 diabetes mellitus (T2DM) [3]. Reduced adiponectin levels occur in patients with T2DM

Abbreviations: CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interlokin-6; IL-1, interlokin-1; SMD, standardized mean differences

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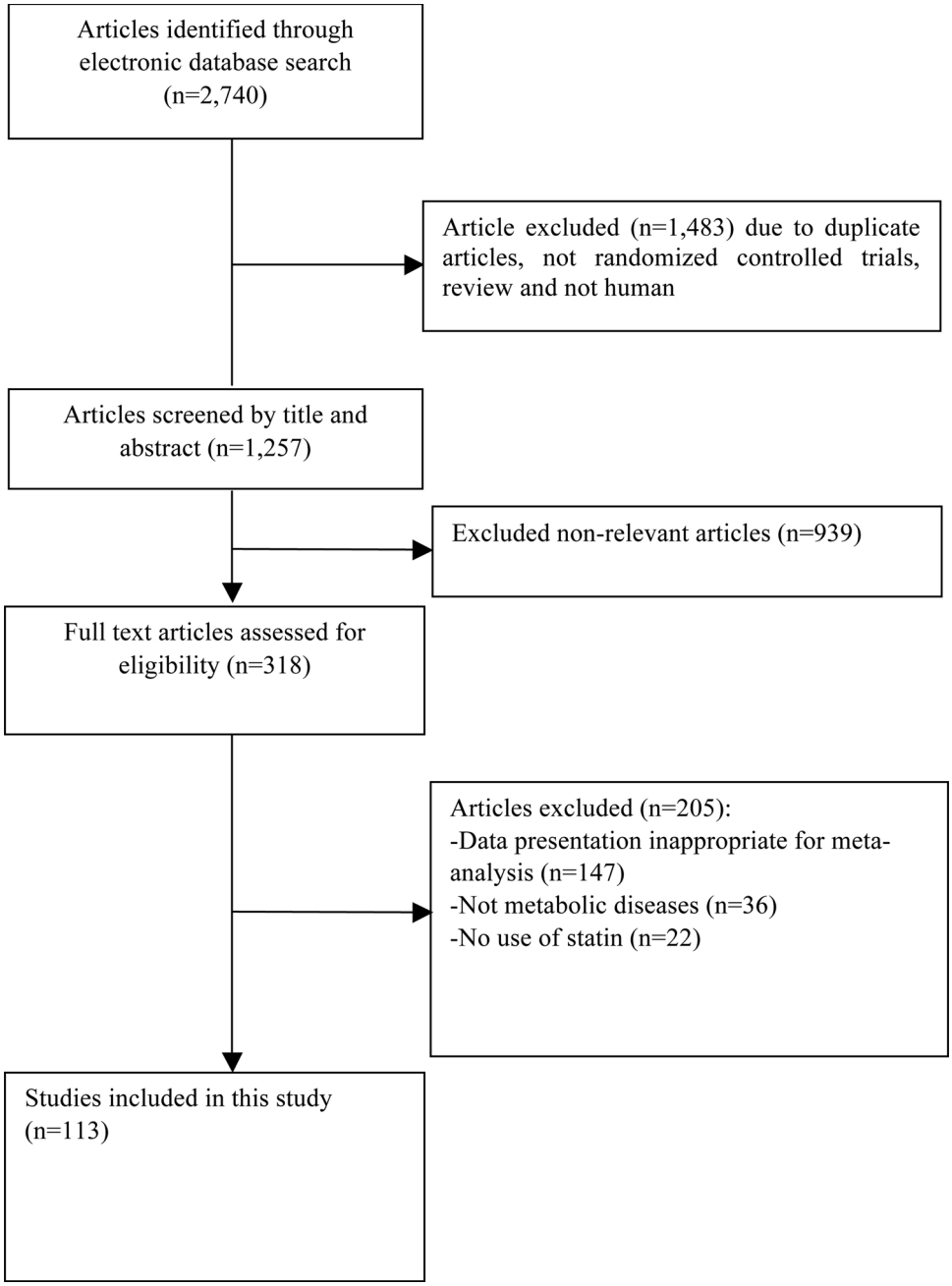

Fig. 1. Literature search and review flowchart for selection of studies.

and metabolic syndrome (MetS) [4] has been associated with increased levels of inflammatory markers, such as C-reactive protein (CRP) [5]. Study participants were considered to have MetS according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III when 3 or more of the following criteria were present: fasting hyperglycemia ≥100 mg/dl or under drug treatment for diabetes mellitus; systolic arterial blood pressure (SBP) ≥130 mmHg and/or diastolic arterial blood pressure (DBP) ≥85 mmHg or under drug treatment for arterial hypertension; serum triglycerides ≥150 mg/dl or receiving drug treatment for dyslipidemia; serum HDL-cholesterol < 40 mg/dl in men and < 50 mg/dl in women or under drug treatment for dyslipidemia; waist circumference > 102 cm in men and > 88 cm in women [6]. Decreased adiponectin levels has also been shown to be correlated with impaired lipid profile in diabetes and metabolic disorders [7]. Current evidence suggest that statin use may result in increased adiponectin levels [8], and decreased inflammatory markers.

Several studies have evaluated the effects of statins on inflammatory markers, yet, the results are inconclusive. In a study by Gruzdeva et al. [9], atorvastatin use improved adipokines levels and decreased pro-inflammatory markers in patients diagnosed with myocardial

Table 1
Characteristics of included studies.

First Author	Publication year	Sample size (control/ intervention)	Country/Population	Intervention (name and daily dose)	Duration	Age (control, intervention)	Presented data
Jiao et al. [39]	2015	64/62	China/acute coronary syndromes	Rosuvastatin 20 mg	24 h after PCI	75.6 ± 7.8, 74.9 ± 8.7	CRP
Wang et al. [40]	2013	63/62	China/acute coronary syndromes	Rosuvastatin 20 mg	6 h after PCI	65.4 ± 10.2, 64.8 ± 11.6	CRP, IL-6
Kinlay et al. [23]	2003	1186/1216	USA/acute coronary syndromes	Atorvastatin 80 mg	16 weeks	64 ± 11, 64 ± 12	CRP, IL-6
Patti et al. [41]	2007	85/86	Italy/acute coronary syndromes	Atorvastatin 80 mg	24 h after PCI	64 ± 11, 67 ± 10	CRP
Lewandowski et al. [42]	2008	39/39	Poland/acute coronary syndromes	Atorvastatin 20-40 mg	5 day	54 ± 8.86, 55 ± 9.42	CRP, TNF-α, IL-6
Correia et al. [43]	2003	18/18	Brazil/acute coronary syndromes	Atorvastatin 80 mg	6 days	65 ± 12, 66 ± 9	CRP
Dohi et al. [44]	2010	84/85	Japan/acute coronary syndromes	Atorvastatin 20 mg	48 weeks	62.3 ± 10.4, 62.8 ± 10.4	CRP
Yun et al. (2009) [45]	2009	220/225	Korea/acute coronary syndromes	Rosuvastatin 40 mg	24 h after PCI	64 ± 10, 63 ± 11	CRP
Yun et al. (2011) [46]	2011	242/237	Korea/acute coronary syndromes	Statins	24 h	63 ± 11, 63 ± 11	CRP
Macin et al. [47]	2004	46/44	Argentina/acute coronary syndromes	Atorvastatin 40 mg	1 month	59.3 ± 13.4, 61.1 ± 11.5	CRP
Vasilieva et al. [48]	2008	20/19	Russia/acute coronary syndromes	Atorvastatin 40-80 mg + Aspirin	8 days	70.1 ± 2.4, 72.1 ± 1.9	CRP
Wassmann et al. [49]	2003	14/13	Germany/stable angina	Pravastatin 40 mg	24 hours after treatment	66.4 ± 2.6, 63.7 ± 2.5	CRP
Li et al. (2007) [50]	2007	16/18	China/unstable angina	Simvastatin 10 mg after admission	48 h	57 ± 6, 58 ± 8	CRP
Li et al. (2005) [51]	2005	17/19	China/unstable angina	Atorvastatin 20 mg	4 weeks	NR	CRP
Sawara Y. [52]	2008	16/22	Japan/chronic kidney disease	Rosuvastatin 2.5 mg	12 weeks	63.8 ± 9.1, 67 ± 7.9	CRP, TNF-α
Fassett et al. [53]	2014	17/24	Australia/chronic kidney disease	Atorvastatin 10 mg	3 years	59.6 ± 15.1, 60.2 ± 15.6	CRP, TNF-α, IL-6
Verma et al. [54]	2005	39/44	USA/chronic kidney disease	Rosuvastatin 10 mg/day	20 weeks	73 ± 10, 74 ± 19	CRP
Jo et al. [55]	2008	99/90	South Korea/chronic kidney disease	Simvastatin 80 mg	2 days	65 ± 9.3, 66.1 ± 8.2	CRP
Marschang et al. [56]	2006	16/47	Austria/coronary artery disease	Statins	24 weeks	59 ± 2, 61 ± 2	CRP
Chan et al. [57]	2008	30/30	Taiwan/coronary artery disease	Atorvastatin 10 mg	24 weeks	66.13 ± 11.50, 63.77 ± 12.73	CRP
Suzuki et al. [58]	2008	9/10	Japan/coronary artery disease	Fluvastatin + Atorvastatin 5 or 10 mg	12 weeks	68 ± 7, 71 ± 8	CRP
Azar et al. [59]	2005	26/44	Lebanon/coronary artery disease	Statins	48 h after PCI	59 ± 1, 63 ± 8	CRP, TNF-α
Karaca et al. [60]	2003	32/46	Turkey/coronary artery disease	Atorvastatin 20 mg	4 weeks	52	CRP
Abe et al. [61]	2011	52/52	Japan/diabetic nephropathy	2.5 mg/day rosuvastatin, increased to 10 mg/day	24 weeks	64.5 ± 9.6, 64.9 ± 9.2	CRP
Dornbrook-Lavender et al. [62]	2005	8/5	USA/dialysis	Atorvastatin 10	20 weeks	70 ± 15, 62 ± 15	CRP
Sezer et al. [63]	2007	20/25	Turkey/dialysis	Simvastatin 20 mg/day	4 weeks	51.2 ± 13.1, 57.4 ± 11.6	CRP, TNF-α, IL-6
Arabul et al. [64]	2008	18/22	Turkey/end-stage renal disease	Fluvastatin 40 mg	8 weeks	48.7 ± 11.3, 43.6 ± 14.4	CRP
Abulhul et al. [65]	2012	28/28	Ireland/heart failure	Atorvastatin titrated from 10 to 40 mg/d over 3 months and maintained at 40 mg/d for a further 3 months	24 weeks	72 ± 14, 72 ± 9	CRP, TNF-α, IL-6
Kirmizis et al. [66]	2010	25/25	Greece/hemodialysis	Simvastatin 10 mg/day	24 weeks	63 ± 11, 62 ± 13	CRP, IL-6
Chang et al. [67]	2002	30/28	Korea/hemodialysis	Simvastatin, 20 mg	8 weeks	63 ± 11, 60 ± 12	CRP
Burmeister et al. [68]	2009	31/28	Brazil/hemodialysis	Rosuvastatin 10 mg/day	1 month	60.1 ± 13.8, 53.7 ± 16.6	CRP
Ichihara et al. [69]	2002	10/12	Japan/hemodialysis with type 2 diabetes	Fluvastatin 20	12 weeks	65.8 ± 3, 64.3 ± 3.7	CRP
Ge et al. [70]	2008	65/61	China/hypercholesterolemic	Atorvastatin 20 mg + amlodipine 10 mg	4 month	64 ± 10, 65 ± 12	CRP

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Table 1 (*continued*)

First Author	Publication year	Sample size (control/ intervention)	Country/Population	Intervention (name and daily dose)	Duration	Age (control, intervention)	Presented data
Yamagami et al. [71]	2008	41/40	Japan/hypercholesterolemic	Statins	48 weeks	63.4 ± 8.3, 65.4 ± 6.9	CRP, IL-6
Koh et al. (2004) [72]	2004	31/32	South Korea/hypercholesterolemic	Diet + simvastatin 20 mg	14 weeks	60	CRP, TNF-α
Koh et al. (2008) [73]	2008	30/32	Korea/hypercholesterolemic	Simvastatin 10 mg/day	8 weeks	57 ± 2, 59 ± 2	CRP
Koh et al. (2010) [74]	2010	44/42	Korea/hypercholesterolemic	Atorvastatin 10 mg	8 weeks	56 ± 10, 54 ± 11	CRP
Koh et al. (2009) [75]	2009	42/43	Korea/hypercholesterolemic	Simvastatin 20 mg/day	8 weeks	58 ± 2, 59 ± 1	CRP
Koh et al. (2011) [76]	2011	44/45	Korea/hypercholesterolemic	Simvastatin 20 mg/day	8 weeks	61 ± 2, 57 ± 2	CRP
Koh et al. (2015) [77]	2015	51/51	Korea/hypercholesterolemic	Simvastatin 20 mg/day	8 weeks	57 ± 8, 59 ± 6	CRP
Nilsson et al. [78]	2010	39/37	Sweden/hypercholesterolemic	Simvastatin 40 mg/day	6 weeks	51 ± 5, 50 ± 6	CRP, TNF-α, IL-6, IL-1
Ascer et al. [79]	2004	23/45	Brazil/hypercholesterolemic	Atorvastatin 20 mg	8 weeks	18-71	CRP, TNF-α, IL-6, IL-1
Kuklinska et al. [80]	2010	60/39	Poland/hypertension	Atorvastatin 80 mg	12 weeks	53.66 ± 0.14	CRP
McMurray et al. [81]	2009	779/777	UK/ischemic systolic heart failure with baseline CRP < 2.0 mg/L	Rosuvastatin 10 mg	12 weeks	73.2 ± 7.2, 72 ± 7	CRP
Zhang et al. [82]	2015	41/43	China/metabolic syndrome	Simvastatin 40 mg	48 weeks	75.19 ± 8.56, 77.17 ± 8.42	CRP, IL-6
Singh et al. [83]	2008	24/23	USA/metabolic syndrome	Atorvastatin 10 mg	12 weeks	51 ± 11, 51 ± 12	CRP, TNF-α
Oguz et al. [84]	2008	43/42	Turkey/metabolic syndrome	Fluvastatin 80 mg	6 weeks	55.5 ± 10.46, 56.16 ± 7.56	CRP
Devaraj et al. [85]	2007	25/25	USA/metabolic syndrome	Simvastatin 40 mg/day	8 weeks	51 ± 12	CRP, TNF-α, IL-6, IL-1
Krysiak et al. [24]	2010	56/61	Poland/metabolic syndrome with pre-diabetes	Atorvastatin 40 mg	90 days	NR	CRP, TNF-α, IL-6, IL-1
Nafasi et al. [86]	2014	95/95	Iran/myocardial infarction	Atorvastatin 80 mg	6 h after PCI	56.48 ± 10.97, 58.56 ± 8.7	CRP
Chan et al. [87]	2002	12/13	Australia/obesity	Atorvastatin 40 mg	6 weeks	53.5 ± 9	CRP, TNF-α, IL-6
Puurunen et al. [88]	2013	13/15	Finland/polycystic ovary syndrome	Atorvastatin 20 mg	12 weeks	40.5 ± 5.9, 38.5 ± 4.8	CRP
Sathyapalan et al. [89]	2010	18/19	UK/polycystic ovary syndrome	Atorvastatin 20 mg	12 weeks	26.6 ± 1.2, 28.8 ± 1.8	CRP
Raja-Khan et al. [90]	2011	11/9	USA/polycystic ovary syndrome	Atorvastatin 40 mg	6 weeks	33.8 ± 4.3, 29.4 ± 5.8	CRP
Guo et al. [91]	2012	54/47	China/stable atherosclerotic plaques	Atorvastatin 10 mg	24 weeks	62.64 ± 12.00, 62.07 ± 8.51	CRP
Lunder et al. [92]	2017	22/22	Slovenia/type 1 diabetes mellitus	Fluvastatin 10 mg + Valsartan 20 mg	30 days	36.3 ± 1.7, 35.6 ± 2.1	CRP
Fegan et al. [93]	2005	12/20	UK/type 2 diabetes	Cerivastatin 0.4 mg	12 weeks	63.3 ± 8.1, 61 ± 9.6	CRP
Konduracka et al. [94]	2008	50/154	Poland/type 2 diabetes	Atorvastatin 40 mg + hyperlipidemic diet	24 weeks	36.3 ± 8.3	CRP
van de Ree et al. [95]	2003	55/67	Netherlands/type 2 diabetes mellitus	Atorvastatin 10 mg	30 weeks	59.8 ± 7.5, 58.8 ± 7.4	CRP, IL-6
Economides et al. [96]	2004	18/19	USA/type 2 diabetes mellitus	Atorvastatin 20 mg	12 weeks	51 ± 14, 55 ± 11	CRP, TNF-α
Jialal et al. [25]	2007	26/26	USA/type 1 Diabetes	Simvastatin 20 mg/day	12 weeks	23.4 ± 9.1, 26.6 ± 13.3	CRP, TNF-α, IL-6, IL-1
Ghanim et al. [97]	2017	10/10	USA/obesity	Ezetimibe 10 mg + simvastatin 40 mg	6 weeks	51 ± 3, 49 ± 4	CRP, IL-1
Joy et al. [98]	2008	26/19	USA/hemodialysis	Atorvastatin 10 mg	36 week	63 ± 15, 61 ± 14	CRP
luo et al. [99]	2004	9/11	China/acute myocardial infarction	Simvastatin 20 mg	3 weeks	65.7 ± 3.6, 67.4 ± 4.5	CRP, IL-6

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Table 1 (*continued*)

First Author	Publication year	Sample size (control/ intervention)	Country/Population	Intervention (name and daily dose)	Duration	Age (control, intervention)	Presented data
Goicoechea et al. [100]	2006	19/44	Spain/chronic kidney disease	Atorvastatin 20 mg	6 months	66.2 ± 13.6, 70.0 ± 14.3	CRP, TNF-α, IL-6, IL-1
Strazhesko et al. [101]	2016	38/44	Italy/atherosclerotic	Atorvastatin 20 mg	12 month	59.2 ± 1.2, 51.4 ± 1.2	CRP, IL-6
Sola et al. [20]	2006	191/255	USA/heart failure	Statins	24-month	55.4 ± 6.4, 53.8 ± 5.7	CRP, TNF-α
Li et al. [102]	2009	13/13	China/end-stage renal disease	Simvastatin 20 mg	8 week	49.9 ± 14.4, 32.5 ± 7	CRP, IL-6
Doo et al. [103]	2005	30/20	Korea/unstable angina	Statins	24 h after stenting	62 ± 9, 60 ± 9	CRP, IL-6
Gruzdeva et al. [104]	2016	66/60	Russia/myocardial infarction	Atorvastatin 20 mg	12 days	60.4, 56.5	CRP, IL-6
Andreou et al. [105]	2010	18/21	Greece/heart failure	Rosuvastatin 10 mg	1 month	65 ± 11, 66 ± 11	CRP, IL-6
Nakagom et al. [106]	2012	83/63	Japan/heart failure	Statins	6 month	64.3 ± 9.9, 66.2 ± 11.9	CRP, TNF-α, IL-6
Doh et al. [107]	2012	35/35	Korea/dialysis	Rosuvastatin10 mg	6 month	48.9 ± 11.7, 48.5 ± 11.3	CRP, IL-6
Gonalves et al. [108]	2009	39/37	Sweden/hypercholestrolemic	Simvastatin 40 mg	6 weeks	NR	CRP, IL-6
Ostadal et al. [109]	2003	17/13	Czech Republic/myocardial infarction	Cerivastatin 0.3 mg	24 h	NR	CRP, IL-6
Link et al. [110]	2006	17/18	Germany/acute coronary syndromes	Rosuvastatin 20 mg	1 day	60 (51.0, 69.5), 55.5 (48.0, 69.0)	CRP, TNF-α
Yang et al. [111]	2006	20/40	China/acute coronary syndromes	Fluvastatin 40 mg	1 week	63.0 ± 10.5, 63.5 ± 9.4	CRP, TNF-α
Kishimoto et al. [112]	2010	9/14	Japan/hemodialysis	Simvastatin 5 mg	1weeks	61.2 ± 8.6, 61.5 ± 5.2	TNF-α, IL-6
Krysiak et al. [22]	2011	30/32	Poland/hypercholesterolemia	Simvastatin 40 mg	30 days	54.3 ± 3.4, 52.3 ± 2.4	TNF-α, IL-6, IL-1
Stefanadi et al. [113]	2009	12/12	Greece/myocardial infarction	Atorvastatin 10 mg	6weeks	58.8 ± 1.8, 59.0 ± 2.5	IL-6
Pereira et al. [114]	2014	30/162	Brazil/cardiovascular disease	Statins	12 months	NR	IL-6
Tousoulis et al. [115]	2006	23/24	Greece/unstable angina	Atorvastatin 10 mg	1weeks	60.1 ± 2.8, 62.1 ± 1.8	TNF-α, IL-6
Nawawi et al. [116]	2003	14/41	Malaysia/hypercholesterolemic	Atorvastatin 10 mg	2 weeks	48.5 ± 1.3, 46 ± 2.9	CRP, IL-6
Gomez-Garcla et al. [117]	2007	16/16	México/hypertension	Rosuvastatin10 mg	12 weeks	56 ± 8.8, 54 ± 8.01	TNF-α, IL-6
Tousoulis et al. (2005) [118]	2005	19/19	Greece/heart failure	Atorvastatin 10 mg	4 weeks	64, 70	TNF-α, IL-6
Tousoulis et al. (2005) [119]	2005	12/14	Greece/heart failure	Atorvastatin 10 mg	4 week	67.2 ± 5.53, 70.6 ± 6.02	TNF-α, IL-6
Tousoulis et al. (2006) [120]	2005	13/15	Greece/type 2 diabetes	Atorvastatin 10 mg	4 weeks	58.1, 60.9	TNF-α, IL-6
Usharani et al. [121]	2008	21/23	India/type 2 diabetes	Atorvastatin 10 mg	8 weeks	50.47 ± 10.35, 49.75 ± 8.18	TNF-α, IL-6
KrysiaK et al. [122]	2014	18/22	Poland/hypercholesterolemia	Simvastatin 40 mg	30 days	35–60	TNF-α
Xie et al. [123]	2014	109/109	China/acute coronary syndromes	Rosuvastatin 20 mg	1 month	59.8 ± 10.5, 61.5 ± 11.4	TNF-α, IL-6
Koh et al. [124]	2002	31/32	Korea/coronary artery disease	Simvastatin 20 mg	14 weeks	62 ± 8, 62 ± 7	TNF-α
Sola et al. [20]	2006	54/54	USA/heart failure	Atorvastatin 20 mg	12-month	54.1 ± 6.9, 53.3 ± 6.2	CRP, TNF-α
Zhao et al. [125]	2004	12/12	China/hypertension	Simvastatin 40 mg + valsartan 80 mg	1 week	67.3 ± 8.0, 66.1 ± 14	IL-1
Huptas et al. [126]	2006	10/10	Germany/metabolic syndrome	Atorvastatin 10 mg/day	6 weeks	40 ± 12	CRP, IL-6
Hu et al. [21]	2009	20/23	China/type 2 diabetic patients with atherosclerosis	Simvastatin 40 mg/daily	12 weeks	55.2 ± 2.3, 58.5 ± 1.6	CRP, TNF-α, IL-6
Banaszewska et al. [127]	2007	24/24	Poland/polycystic ovary syndrome	Simvastatin + OCP	12 weeks	24 ± 3.5, 23.8 ± 3.7	CRP
Cueto-Manzano et a.l. [128]	2013	76/76	Mexico/continuous ambulatory peritoneal dialysis (CAPD).	Pravastatin 20 mg/day	8 weeks	55.5 ± 10.7, 53.4 ± 13.8	CRP

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Table 1 (*continued*)

First Author	Publication year	Sample size (control/ intervention)	Country/Population	Intervention (name and daily dose)	Duration	Age (control, intervention)	Presented data
Wagner et al. [129]	2011	71/72	Spain/type 2 diabetes	Atorvastatin 10 mg/day	12 weeks	57 ± 9	CRP, TNF-α
Dogra et al. [130]	2004	16/16	Australia/type 1 diabetes mellitus patients	Atorvastatin 40 mg/day	6 weeks	46.6 ± 13.0	CRP
Moohebati et al. [131]	2010	51/51	Iran/who were not originally taking lipid lowering agents	Simvastatin (40 mg/day)	4 weeks	44.18 ± 12.07, 46.00 ± 14.83	CRP
Bays et al. (2002) [132]	2002	91/85	Ohio/subjects with mixed hyperlipidemia	Simvastatin 40 mg/day	6 weeks	52	CRP, IL-6
Bays et al. (2004) [133]	2004	148/622	USA + multicenter/hypercholesterolemic patients	Simvastatin 80 mg/day	12 weeks	56 ± 10.8, 54.9 ± 11.2	CRP
Farnier et al. [134]	2006	60/179	Spain/patients with mixed hyperlipidemia	Ezetimibe/Simvastatin 10/ 20 mg	12 weeks	53.7 ± 11.0, 55.0 ± 10.7	CRP
Goldberg et al. [135]	2004	52/204	USA + multicenter/hypercholesterolemia	Simvastatin 80 mg/day	12 weeks	54.69,	CRP
Lu et al. [136]	2004	23/23	Multicenter/hypercholesterolemia	Rosuvastatin 10 mg/day	6 weeks	59.8 ± 11.8, 62.8 ± 11.2	CRP
Tousoulis et al. (2007) [120]	2007	13/15	Greece/type 2 diabetes mellitus	Atorvastatin-treated (10 mg/ day)	4 weeks	60.9 ± 3.1, 58.1 ± 2.6	CRP, TNF-α, IL-6
Tan et al. [137]	2002	41/39	Hong Kong/patients with diabetes	Atorvastatin (10 mg/day)	3 months	55.0 ± 8.1	CRP
Strom et al. [138]	2012	44/45	Germany/type 1 diabetes and detectable islet autoantibodies	Aorvastatin (80 mg/day)	3 months	0.36 ± 0.42, 0.53 ± 0.39	CRP
Ridker et al. [19]	2001	2834/2885	Texas/who had average levels of total and LDL cholesterol	Lovastatin (20 mg/day)	12 weeks	Men 45 to 73 years old and women 55 to 73 years old	CRP
Rudofsky et al. [139]	2012	9/10	Germany/type 2 diabetes	Simvastatin 80 mg	8 weeks	64 ± 9, 56 ± 10	CRP, IL-6
Vernaglione et al. [140]	2004	17/16	Italy/hemodialysis	Atorvastatin (10 mg/day)	6 months	65.47 ± 10.22, 65.19 ± 11.79	CRP
Almquist et al. [141]	2013	21/21	Sweden/diabetes mellitus	Simvastatin was 40 mg/day	10 weeks	64 ± 7	TNF-α
Folkeringa et al. [142]	2010	71/71	Netherlands/hypertension	Rosuvastatin 20 mg/day	6 months	63 ± 10, 63 ± 11	CRP

CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interlokin-6; IL-1, interlokin-1.

infarction. In addition, atorvastatin use immediately after an atherosclerotic ischemic stroke attenuated the immune-inflammatory activation in an acute phase of stroke [10]. In a meta-analysis conducted by Tuttolomondo et al. [11], statin use in patients with chronic heart failure significantly decreased high-sensitivity CRP (hs-CRP) and soluble vascular cell adhesion molecule-1, though did not affect interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels. In a systematic review by Balk et al. [12], statin use decreased CRP levels, not in a dose-response manner. Discrepancies in current evidences may be related to the differences in study design, characteristics of study populations and comorbid conditions, dosage and type of statin used and statin duration of use.

In this study, we aimed to systematically review and quantify the effect of statin use on inflammatory markers among patients with MetS and related disorders in randomized controlled trials (RCTs).

2. Materials and methods

2.1. Search strategy and study selection

To identify RCTs reporting the effects of statin use on inflammatory markers, two independent authors (O-RT and MA) electronically conducted the searches in PubMed, EMBASE, Web of Science databases, Cochrane Library, and www.clinicaltrial.gov for ongoing projects through April 2018. The keywords used for database search were; patients, including "MetS" and related disorders with metabolic diseases. These related disorders consisted of "acute coronary syndromes" or "coronary artery disease" or "CVD" or "diabetic" or "T1DM" or "T2DM" or "overweight" or "obese" or "chronic kidney disease" or "end-stage renal disease" or "dialysis" or "heart failure" or "myocardial infarction" or "atherosclerotic" or "hypercholesterolemic" or "hypertension" or "high blood pressure" or "dyslipidemia" or "hyperlipidemia" or "polycystic ovary syndrome" or "stable angina or "unstable angina" or "diabetic nephropathy" or "obesity or "stable atherosclerotic plaques" or "atherosclerotic", intervention, including "statins" or "rosuvastatin" or "atorvastatin" or "pravastatin" or "simvastatin" or "fluvastatin" or "cerivastatin" or "lovastatin" and "supplementation" or "intake", and outcomes, including "CRP" or "TNF-α" or "IL-6" or "IL-1". To avoid missing any related study, authors checked reference lists of eligible articles as an additional search. Searches were limited to RCTs published in English.

2.2. Inclusion and exclusion criteria

Studies with the following inclusion criteria were included in this meta-analysis: RCTs conducted on human, provided proper data for the

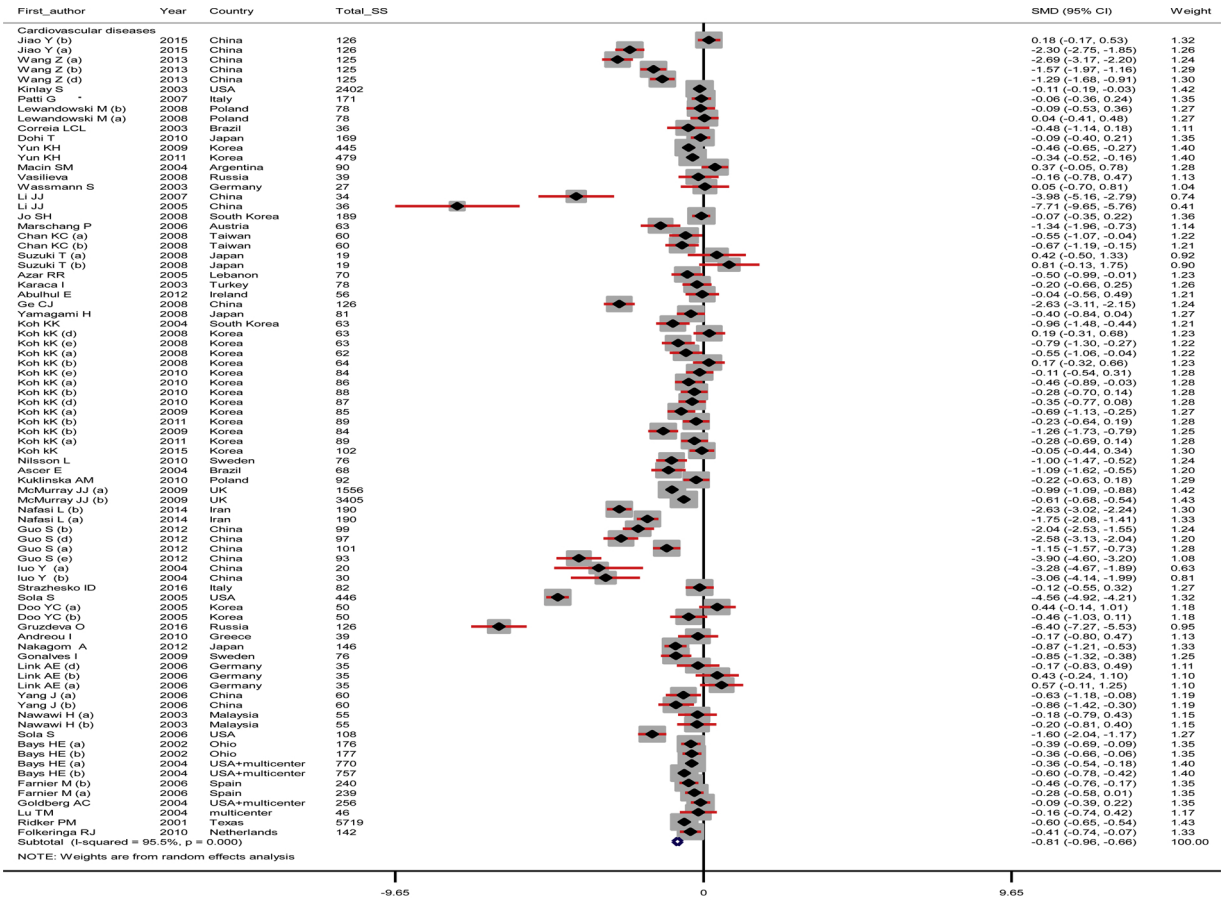
mean changes of CRP, TNF-α, IL-6, and IL-1 over time with standard deviation (SD) for both intervention and placebo groups, RCTs conducted among patients with MetS and other related disorders. Other studies including animal experiments, in vitro studies, observational studies, study protocols without findings, or congress abstracts without full texts, non- placebo-controlled trials were excluded from our meta-analysis.

2.3. Data extraction and quality assessment

Two authors (O-RT and MA) independently extracted data from each selected RCTs using a standard abstraction excel sheet. The extracted data included the name of first author, year of publication, study setting, the characteristics of participants, study design, sample size in both treatment and placebo groups, dosage of statin, duration of statin, type of disease, and outcomes of interest including the mean and SD for CRP, TNF-α, IL-6, and IL-1. The methodological quality of the selected RCTs was evaluated by two independent investigators (MA and RT) using the Cochrane Collaboration risk of bias tool. Also, Jadad's quality scales were determined to assess internal validity of clinical trials. The Cochrane Collaboration risk of bias tool used the following criteria for quality assessment: "randomization generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias". Jadad's total score lower than 3 represented the low quality and ≥3 showed the high quality of included trials reporting. Any disagreement between authors was resolved by discussion and final consensus between authors or a third author (ZA) approved the findings.

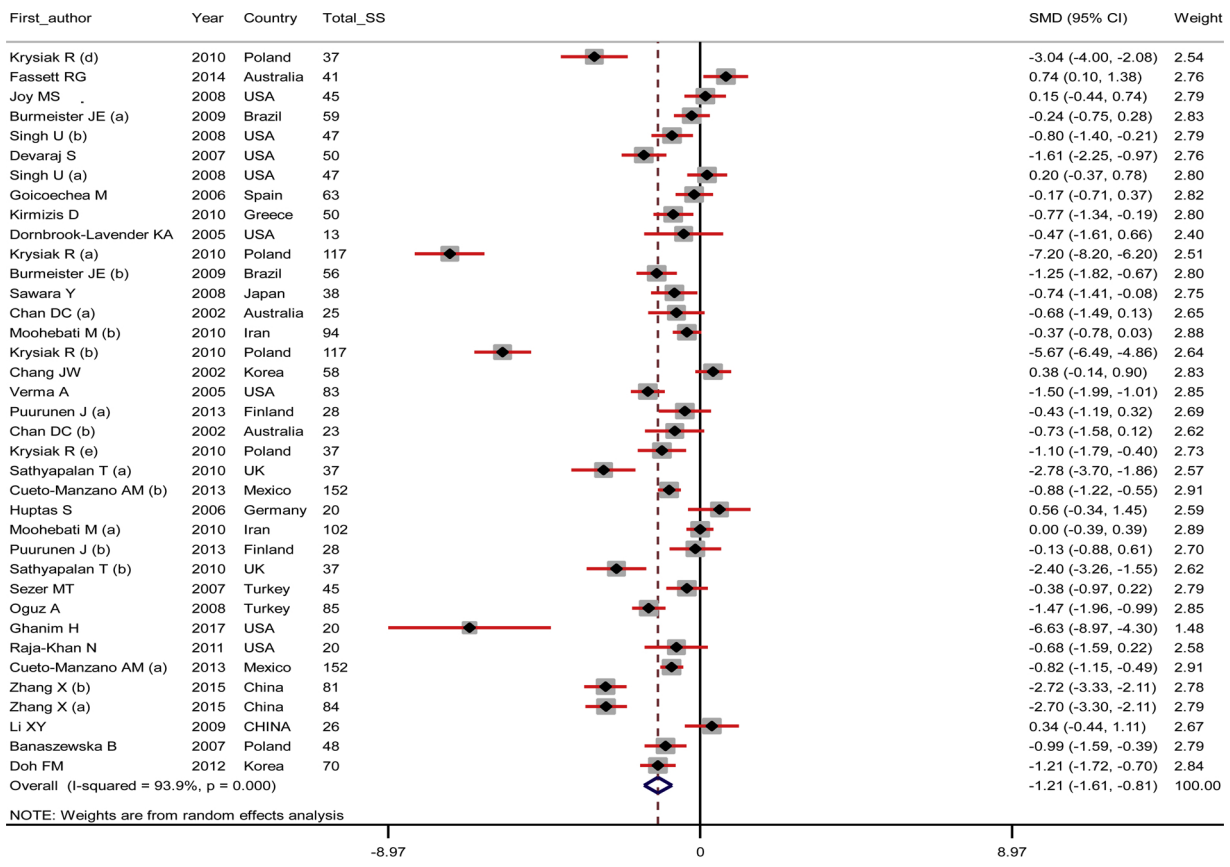
2.4. Data synthesis and statistical analysis

The mean differences with SD of inflammatory markers between intervention and placebo groups were used to pool data. The standardized mean differences (SMDs) with corresponding 95% CI were calculated as effect sizes using the fixed effect model (with inverse variance method) or random effect model (Dersimonian–Lairdmethod method). Heterogeneity was assessed using Cochran's Q test and I-square (I^2) test with an $I^2 > 50\%$ ($P < 0.05$) was considered to be a significant heterogeneity. Sensitivity analyses were conducted using



A1

Fig. 2. A–D. Random effects meta analysis of randomized controlled trials that examined the effect of statins intake on inflammatory markers including (A1) strata cardiovascular for CRP levels, (A2) strata other disease for CRP levels, (A3) strata diabetic for CRP levels (B) for TNF-α, (C) for IL-6, (D) for IL-1 in intervention and control groups with 95% CI.



A2

Fig. 2. (*continued*)

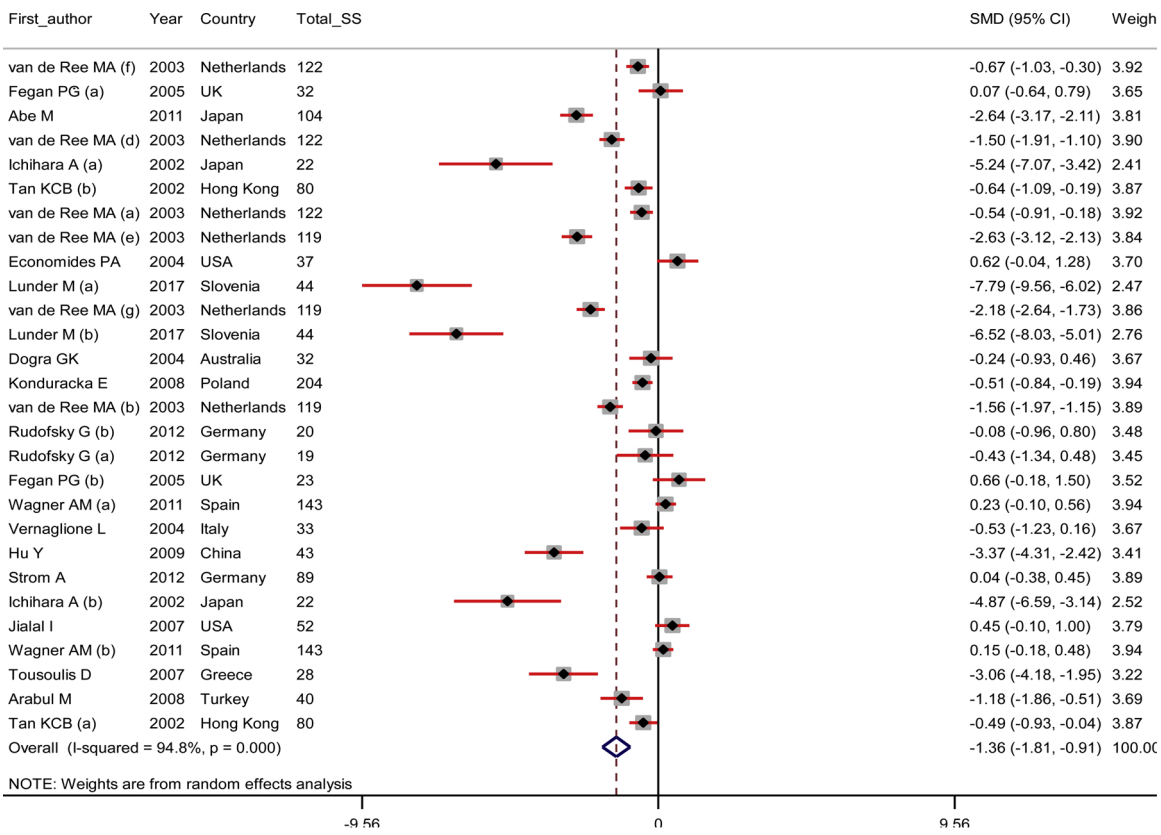
leave-one-out method to determine the effect of each individual trial on reliability of the overall pooled SMDs. Further, subgroup analyses were carried out to determine the source of heterogeneity according to the potential moderator variables. The subgroup analyses were conducted according to the following variables: dosage of statins (< 40 vs. ≥40 mg/day), type of statin used (rosuvastatin vs. atorvastatin vs. simvastatin vs. statins plus other drugs vs. statins plus nutrients vs. other statins), type of disease (CVD vs. diabetic vs. other disease), duration of study (≤8 vs. > 8 weeks), and Jadad's overall scores (high risk vs. low risk). Egger's regression tests and funnel plot symmetry tests were used to evaluate any possible publication bias in our meta-analysis. All statistical analyses were conducted using STATA software version 12.0 (Stata Corp., College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). $P < 0.05$ was considered statistically significant.

3. Results

Overall, 113 articles, out of 2740 citations, met our inclusion criteria. One hundred thirteen articles included 19,644 participants which were randomly assigned to 10,460 individuals in treatment group and 9190 in placebo group. One hundred forty-seven RCTs have reported the impact of statin use on CRP, 56 RCTs on TNF-α, 68 RCTs on IL-6, and 15 RCTs on IL-1 levels. The step by step screening process has been illustrated in Fig. 1. The sample size varied from 13 to 5719 individuals among included articles in our meta-analysis. Dosage of statin use ranged from 0.3 to 80 mg/day. Duration of statin use ranged from 4 weeks to 3 years. The selected RCTs were published between 2001 and 2017. Diagnosis of MetS in the included studies was conducted based on the criteria of the NCEP-Adult Treatment Panel III [13–18]. The detailed characteristics of included RCTs have been summarized in Table 1.

3.1. The association between statin use and inflammatory markers

Forest plots demonstrating the effects of statin use on inflammatory markers are shown in Fig. 2. Our results showed that statin use in patients with MetS and related disorders significantly decreased CRP (SMD = -0.97; 95% CI, -1.10, -0.85; $P < 0.001$; I^2: 95.1%), TNF-α (SMD = -1.88; 95% CI, -2.40, -1.38; P < 0.001; I^2: 97.2%), IL-6 (SMD = -1.67; 95% CI, -1.98, -1.34; P < 0.001; I^2: 96.5%), and IL-1 levels (SMD = -8.35; 95% CI, -10.49, -6.22; P < 0.001; I^2: 98.4%). Pooled effect sizes, calculated based on the baseline and end of trial information in treatment and placebo groups are summarized in Table 2.



A3

Fig. 2. (*continued*)

3.2. Sensitivity/subgroup analyses

We did not find any statistical significant difference between pre- and post-sensitivity pooled SMDs for all inflammatory markers. However, the lower and higher pooled SMDs for CRP were -0.99 (95% CI: -1.13, - 0.84) after excluding Ridkar et al. [19] study and -0.92 (95% CI: -1.04, -0.80) after removing Sola et al. [20] study. For TNF-α, the lower pooled SMDs in was -2.01 (95% CI: -2.51, -1.51) after excluding Hu Y et al. [21] study and the higher was -1.64 (95% CI: -2.13, -1.15) after excluding Krysiak (a) et al. [22] study. The lower and higher pooled SMDs for IL-6 were -1.74 (95% CI: -2.10, -1.38) after excluding Kinlay et al. [23] study and -1.50 (95% CI: -1.81, -1.20) after removing Krysiak (a) et al. [24] study, respectively. For IL-1, the lower pooled SMD in the sensitivity analysis was -9.01 (95% CI: -11.40, -6.62) after excluding Jialal et al. [25] study and the higher was -7.13 (95% CI: -9.29, -5.33) after removing Krysiak (a) et al. [22] study (Table 3).

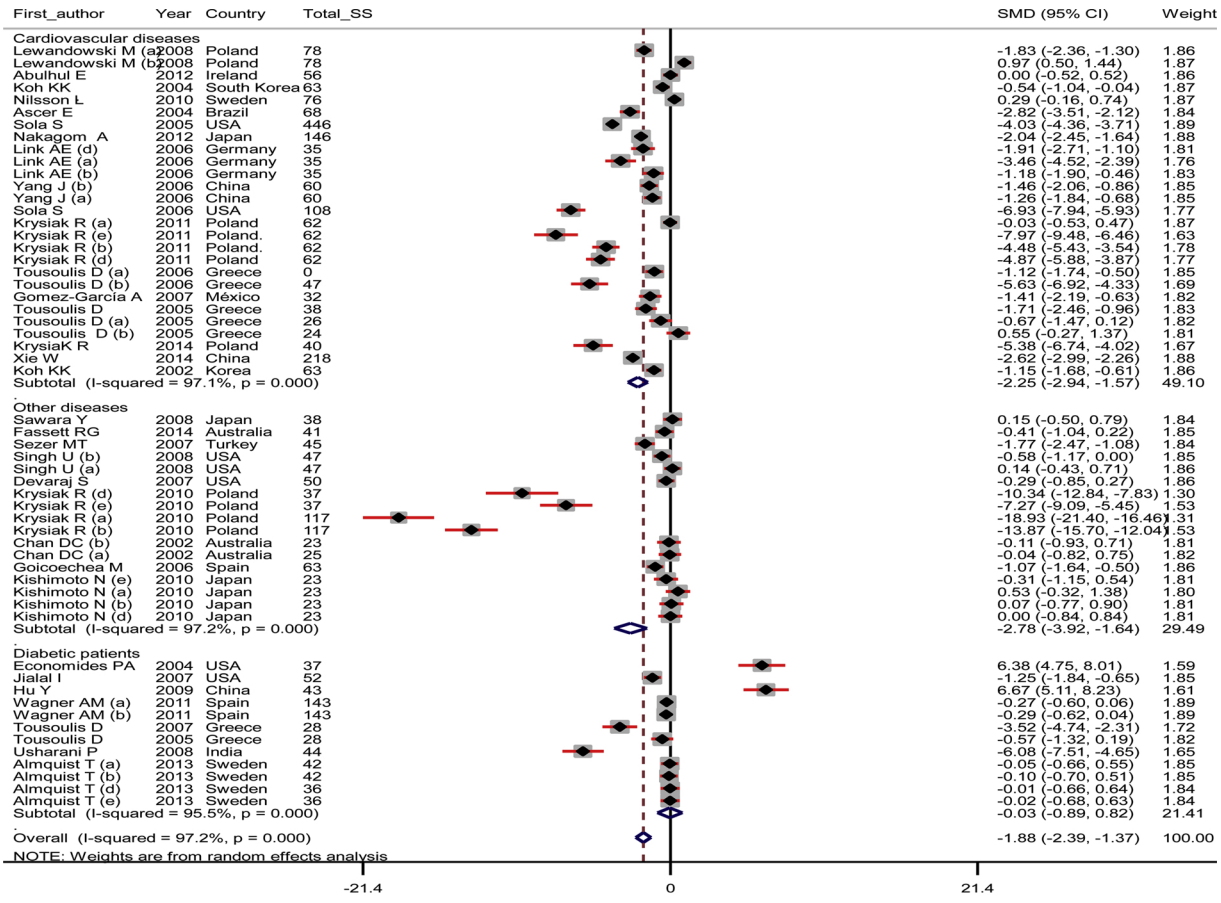
Following subgroup analyses, heterogeneity was changed among some of the strata of subgroups, however there was no significant difference between before and after subgroup analysis. The detailed findings of subgroups analyses are presented in Table 4.

3.3. Publication bias and quality assessment

As presented in Fig. 3, there was potential publication bias for inflammatory markers including CRP (B = -1.84, $P = 0.001$), TNF-α (B = -4.02, $P = 0.04$), IL-6 (B = -4.73, $P = 0.001$), and IL-1 (B = -12.57, $P = 0.001$). Non-parametric method (Duval and Tweedie) was used to compute the results of censored articles. Pooled effect sizes for inflammatory markers did not significantly change after Duval and Tweedie test.

The pooled SMD before and after including censored articles were -0.97 (95% CI, -1.10, -0.84) and -1.21 (95% CI, -1.34, -1.07) for CRP, -1.88 (95% CI, -2.40, -1.38) and -2.60 (95% CI, -3.19, -2.01) for TNF-α levels, respectively. Pooled SMD for IL-6 levels before including censored articles was -1.67 (95% CI, -1.98, -1.34) compared with -2.35 (95% CI, -2.79, -1.91) after including censored articles. For IL-1, SMD before including articles was -8.35 (95% CI, -10.49, -6.21) which changed to -8.35 (95% CI, -10.48, -6.22) after including censored articles.

The methodological qualities of RCTs was assessed using Cochrane Collaboration risk of bias tool and Jadad's overall scores and are



B

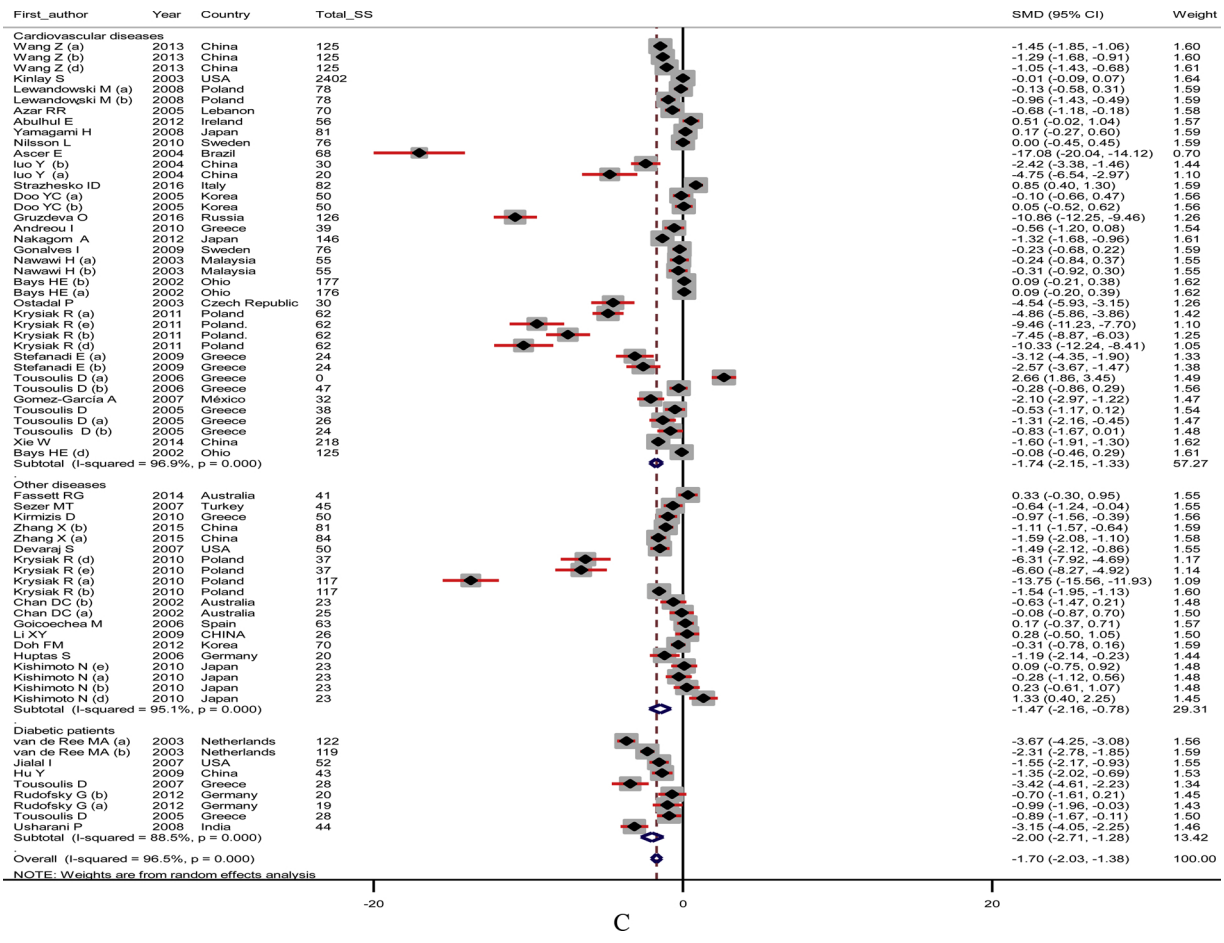
Fig. 2. (*continued*)

summarized in Table 5.

4. Discussion

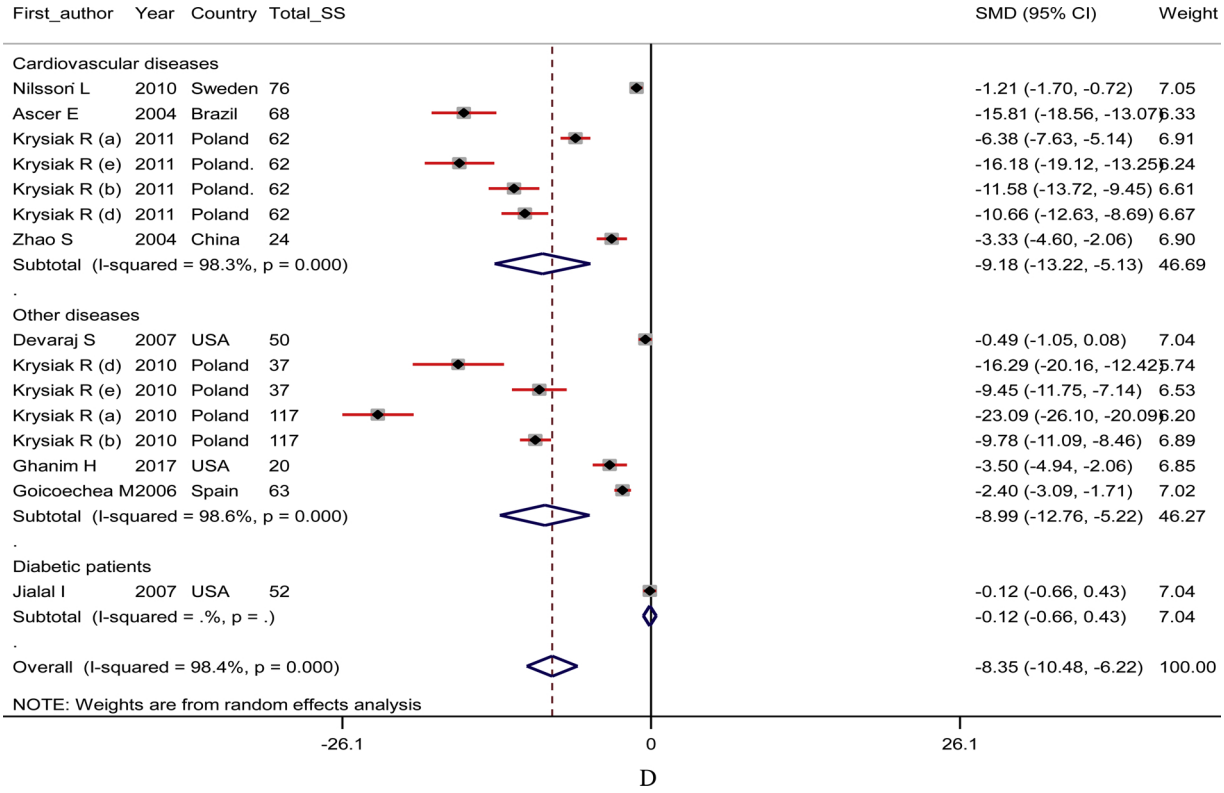
To our best knowledge, this is the first systematic review and meta-analyses of RCTs evaluating the effect of statin use on inflammatory markers among patients with MetS and related disorders. Our meta-analysis (including 113 RCTs and 19,644 patients) showed the beneficial impact of statin use on reducing inflammatory markers in patients suffering from MetS and related disorders. Increased inflammatory markers are one of the main pathophysiological causes of diseases related to metabolic disorders, which include different chronic, conditions such as obesity, T2DM, CVD, stroke, fatty liver, and other metabolic diseases. Therefore, due to similar metabolic status, we included a broad range of chronic diseases in the current meta-analysis. However, the effectiveness of statin use might vary with the type of metabolic abnormalities. To address this limitation, we have conducted subgroup analysis based on the type of metabolic diseases (e.g. cardiovascular vs. diabetes vs. other related disorders).

MetS and other related disorders especially heart failure are considered as inflammatory diseases [26,27]. Different inflammatory markers including IL-6 and TNF-α may contribute to endothelial dysfunction, cardiac myocyte apoptosis, structural deterioration and left ventricular dysfunction [28,29]. Furthermore, hs-CRP is one of the common inflammatory markers to assess inflammation. It is an independent predictor for MetS prognosis and other related disorders, therefore, it can provide additional prognostic information for the risk stratification and treatment of patients with CVD [30]. In a meta-analysis conducted by Zhang et al, statin use significantly decreased hs-CRP and soluble vascular cell adhesion molecule-1 in patients with chronic heart failure, though it did not influence IL-6 and TNF-α [11]. Further, in a systematic review assessing the effect of different statins, they were



C

Fig. 2. (*continued*)



D

Fig. 2. (*continued*)

Table 2
Standardized mean difference of related indictors between the intervention and placebo groups.

Variables		Number of study	Standardized mean difference	CI 95%	P-value	Heterogeneity		
						I^2 (%)	Q	P- value heterogeneity
CRP	Intervention group (after vs. before)	146	−0.51	−0.62, -0.41	< 0.001	93.5	2216.18	< 0.001
	Placebo group (after vs. before)	146	0.06	−0.03, 0.14	0.200	88.6	1270.14	< 0.001
	Change intervention group vs. placebo group	147	−0.97	−1.10, -0.84	< 0.001	95.1	2966.70	< 0.001
TNF-α	Intervention group (after vs. before)	56	−1.11	−1.57, -0.65	< 0.001	97.1	1920.65	< 0.001
	Placebo group (after vs. before)	56	0.03	−0.17, 0.24	0.750	87.4	436.16	< 0.001
	Change intervention group vs. placebo group	56	−1.88	−2.40, -1.38	< 0.001	97.2	1931.96	< 0.001
IL-6	Intervention group (after vs. before)	65	−1.05	−1.38, -0.73	< 0.001	96.8	1974.22	< 0.001
	Placebo group (after vs. before)	65	−0.20	−0.45, 0.06	0.129	94.3	1130.47	< 0.001
	Change intervention group vs. placebo group	69	−1.67	−1.98, -1.34	< 0.001	96.5	1926.58	< 0.001
IL-1	Intervention group (after vs. before)	15	−4.09	−5.41, -2.75	< 0.001	97.8	628.66	< 0.001
	Placebo group (after vs. before)	15	−0.16	−0.30, -0.03	0.019	9.0	15.38	0.352
	Change intervention group vs. placebo group	15	−8.35	−10.49, -6.21	< 0.001	98.4	881.22	< 0.001

SMD, standardized mean differences; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interlokin-6; IL-1, interlokin-1.

Table 3
The association between statin use and inflammatory markers followed by sensitivity analysis.

Variables	Pre-sensitivity analysis			Upper & lower of effect size	Post-sensitivity analysis		
	No. of studies included	Pooled SMD (random effect)	95% CI		Pooled SMD (random effect)	95% CI	Excluded studies
CRP	147	−0.97	−1.10, -0.84	Upper	−0.92	−1.04, -0.80	Sola (2005)
				Lower	−0.99	−1.13, -0.84	Ridker (2001)
TNF-α	56	−1.88	−2.40, -1.38	Upper	−1.64	−2.13, -1.15	Krysiak(a) (2010)
				Lower	−2.01	−2.51, -1.51	Hu Y (2009)
IL-6	69	−1.67	−1.98, -1.34	Upper	−1.50	−1.81, -1.20	Krysiak(a) (2010)
				Lower	−1.74	−2.10, -1.38	Kinlay (2003)
IL-1	15	−8.35	−10.49, -6.21	Upper	−7.13	−9.29, -5.33	Krysiak(a) (2010)
				Lower	−9.01	−11.40, -6.62	Jialal (2007)

CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interlokin-6; IL-1, interlokin-1; SMD, standardized mean differences.

effective to reduce CRP levels, though dose-independent [12]. In another meta-analysis, statin use elevated left ventricular ejection fraction and reduced hospitalization due to worsening heart failure. Using atorvastatin, all-cause mortality also significantly decreased [31]. Among statin pre-treated patients, the risk of increasing CRP post-operatively was significantly lower [32]. However, in another meta-analysis conducted by Artola et al, there was no significant impact of statin use on serum levels of hs-CRP in patients with systemic lupus erythematosus [33]. Discrepant results might be related to differences in study design, characteristics of study populations, dosage, type and duration of statin use.

Previous studies have documented the drug-specific effects of statins [34]. Atorvastatin may reduce hs-CRP-induced inflammatory response by inhibiting nuclear factor-kB pathway [35]. Statin use can also decrease stimulating activator protein-1 (AP-1), a transcription factor which in turn might decrease inflammatory markers [36]. Further, the Rho-Rho kinase pathway, which is a negative regulator of endothelial nitric oxide synthase (eNOS) activity, is usually activated in inflammatory status and might reduce nitric oxide (NO) availability. Statin use causes a remarkable increase in eNOS activity by decreasing prenylation of Rho [37]. Furthermore, post-translational activation of eNOS involves phosphatidyl inositol 3-kinase (PI3K) and the serine/threonine kinase, Akt (PI3K-Akt) signaling pathway, which is the other mechanism by which statin use might decrease inflammation [38].

There are several strengths for this study. Large numbers of studies included in this meta-analysis and longer period of intervention in included RCTs have increased the value of this meta-analysis. All included studies were placebo-controlled randomized trials with acceptable methodological quality. Further, we relied on independent judgment in which different reviewers independently performed the systematic review process. The current meta-analysis had a few limitations. Different doses of statins were used for intervention in the included RCTs. Considerable heterogeneity across studies made us to interpret our results cautiously.

In summary, our meta-analysis demonstrated that statin use in patients with MetS and related disorders appeared to significantly decrease inflammatory markers, such as CRP, TNF-α, IL-6 and IL-1 levels.

Table 4
The association between statin use and inflammatory markers following subgroup analysis.

Variables		K*	I^2 (%)	Q test	SMD (95% CI)	*P*-value
CRP						
Total		147	95.1	2966.70	−0.97 (-1.10, -0.85)	< 0.001
Dosage of statins (mg/day)						
	< 40	93	95.1	1860.83	−0.96 (-1.12, -0.79)	< 0.001
	≥40	54	94.9	1044.44	−0.99 (-1.22, -0.78)	< 0.001
Type of intervention						
	Rosuvastatin	20	93.9	311.31	−0.88 (-1.14, -0.62)	< 0.001
	Atorvastatin	61	96.0	1482.42	−1.14 (-1.41, -0.86)	< 0.001
	Statins plus other drugs	12	95.7	255.89	−1.57 (-2.21, -0.92)	< 0.001
	Other statins	22	96.5	599.23	−0.97 (-1.37, -0.57)	< 0.001
	Simvastatin	29	88.8	249.38	−0.68 (-0.93, -0.43)	< 0.001
	Statins plus nutrient	3	3.5	2.07	−0.65 (-0.92, -0.38)	< 0.001
Type of disease						
	Cardiovascular	82	95.5	1812.29	−0.81(-0.96, -0.66)	< 0.001
	Diabetic	28	94.8	518.16	−1.35 (-1.80, -0.91)	< 0.001
	Other	37	93.9	588.16	−1.21 (-1.61, -0.81)	< 0.001
Duration of study						
	> 8 weeks	71	96.2	1836.25	−1.07 (-1.24, -0.89)	< 0.001
	≤8 weeks	76	93.4	1130.07	−0.90 (-1.14, -0.69)	< 0.001
Jadad's overall scores						
	High risk	31	94.3	529.92	−0.87 (-1.27, -0.47)	< 0.001
	Low risk	115	95.3	2436.70	−0.40 (-0.73, -0.07)	< 0.001
TNF-α						
Total		56	97.2	1931.96	−1.88 (-2.40, -1.38)	< 0.001
Dosage of statins (mg/day)						
	< 40	32	96.4	857.80	−1.42 (-1.99, -0.86)	< 0.001
	≥40	24	97.7	1002.45	−2.63 (-3.60, -1.68)	< 0.001
Type of intervention						
	Rosuvastatin	6	92.6	67.60	−1.72 (-2.72, -0.71)	0.001
	Atorvastatin	23	97.8	985.95	−3.04 (-4.05, -2.04)	< 0.001
	Statins plus other drugs	5	97.2	141.90	−1.89 (-3.59, -0.19)	0.030
	Other statins	4	97.4	114.39	−2.21 (-3.61, -0.81)	0.002
	Simvastatin	15	94.9	276.70	−0.68 (-1.48, 0.11)	0.093
	Statins plus nutrient	3	60.4	5.06	−0.09 (-0.74, 0.55)	0.775
Type of disease						
	Cardiovascular	27	97.1	902.40	−2.25 (-2.94, -1.57)	< 0.001
	Diabetic	12	95.5	243.67	−0.03 (-0.90, 0.82)	0.93
	Other	17	97.2	562.88	−2.78 (-3.91, -1.64)	< 0.001
Duration of study						
	> 8 weeks	27	97.8	1188.16	−1.60 (-2.38, -0.82)	< 0.001
	≤8 weeks	29	96.2	740.97	−2.15 (-2.82, -1.47)	< 0.001
Jadad's overall scores						
	High risk	8	95.0	139.81	−0.89 (-1.70, -0.10)	0.02
	Low risk	48	97.3	1762.52	−2.08 (-2.68, -1.47)	< 0.001
IL-6						
Total		69	96.5	1926.58	−1.67 (-1.98, -1.34)	< 0.001
Dosage of statins (mg/day)						
	< 40	46	95.1	918.26	−1.25 (-1.65, -0.85)	< 0.001
	≥40	23	97.7	939.86	−2.60 (-3.23, -1.98)	< 0.001
Type of intervention						
	Rosuvastatin	7	80.3	30.52	−1.17 (-1.55, -0.78)	< 0.001
	Atorvastatin	29	97.6	1172.66	−2.25 (-2.87, -1.62)	< 0.001
	Statins plus other drugs	3	98.3	114.57	−6.12 (-12.09, -0.15)	0.045
	Other statins	7	93.4	91.17	−4.67 (-1.41, 0.07)	0.076
	Simvastatin	21	93.8	323.59	−1.15 (-1.67, -0.64)	0.016
	Statins plus nutrient	2	0.0	0.11	−0.73 (-1.32, -0.14)	< 0.001
Type of disease						
	Cardiovascular	40	96.8	1229.95	−1.67 (-2.07, -1.28)	< 0.001
	Diabetic	9	88.5	69.54	−2.0 (-2.71, -1.29)	< 0.001
	Other	20	95.1	387.60	−1.48 (-2.16, -0.78)	< 0.001
Duration of study						
	> 8 weeks	23	97.5	894.36	−1.95 (-2.57, -1.33)	< 0.001
	≤8 weeks	46	95.3	965.30	−1.56 (-1.96, -1.17)	< 0.001
Jadad's overall scores						
	High risk	16	95.8	359.59	−1.36 (-2.07, -0.64)	< 0.001
	Low risk	53	96.7	1564.45	−1.77 (-2.14, -1.40)	< 0.001
IL-1						
Total		15	98.4	881.22	−8.35 (-10.48, -6.22)	< 0.001
Dosage of statins (mg/day)						
	< 40	3	98.5	135.45	−5.67 (-9.76, -1.58)	0.007
	≥40	12	98.4	703.17	−9.09 (-11.86, -6.32)	< 0.001
Type of intervention						
	Rosuvastatin	–	–	–	–	–
	Atorvastatin	6	98.6	345.42	−12.69 (-18.62, -6.76)	< 0.001

(*continued on next page*)

Table 4 (*continued*)

Variables		K*	I^2 (%)	Q test	SMD (95% CI)	*P*-value
	Statins plus other drugs	4	96.1	76.00	−7.20 (-11.33, -3.07)	0.001
	Other statins					
	Simvastatin	5	97.9	187.60	−4.22 (-6.44, -2.00)	0.001
	Statins plus nutrient	–	–	–	–	–
Type of disease						
	Cardiovascular	7	98.3	358.47	−9.18 (-13.22, -5.13)	< 0.001
	Diabetic	1	–	–	−0.12 (-0.66, 0.43)	0.67
	Other	7	98.6	428.78	−8.99 (-12.76, -5.22)	< 0.001
Duration of study						
	> 8 weeks	6	98.9	450.73	−11.20 (-15.98, -6.43)	< 0.001
	≤8 weeks	9	98.1	428.88	−6.67 (-9.25, -4.09)	< 0.001
Jadad's overall scores						
	High risk	–	–	–	–	–
	Low risk	15	98.4	881.22	−8.35 (-10.49, -6.22)	< 0.001

* K, Number of SMD Included; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interlokin-6; IL-1, interlokin-1; SMD, standardized mean differences

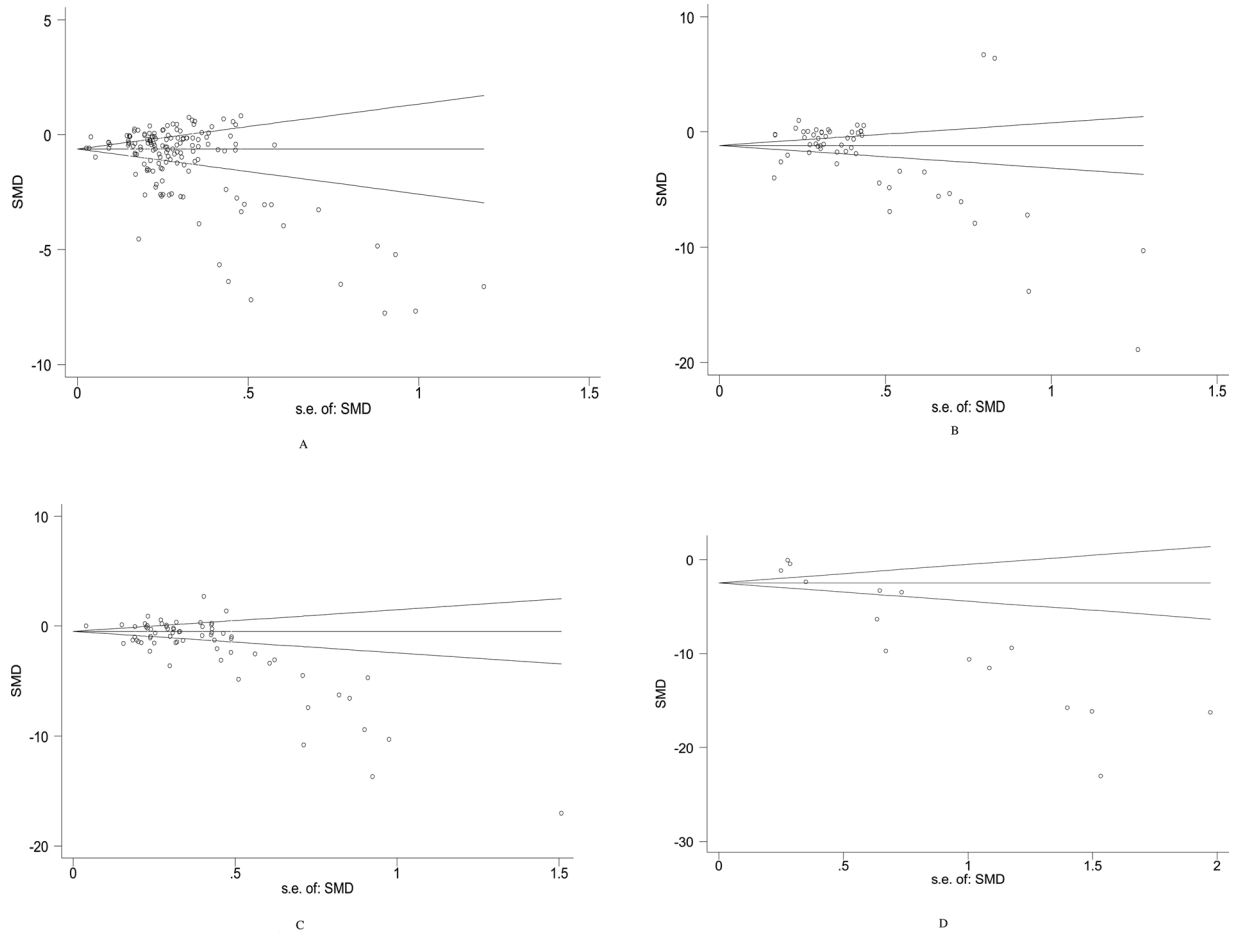


Fig. 3. A–D. Begg's funnel plot for assessing the publication bias (A) CRP, (B) for TNF-α, (C) for IL-6, and (D) for IL-1.

Table 5
Quality assessment of included clinical trials using Cochrane's risk of bias tool and Jadad's scale.

First Author	Cochrane's risk of bias tool							Jadad's scores
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome	Selective reporting	other sources of bias	
Jiao et al	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	4
Wang et al	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	3
Kinlay et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	4
Patti et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Lewandowski et al	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk	2
Correia et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	3
Dohi et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	3
Yun et al (2009)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk	3
Yun et al (2011)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk	3
Macin et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	4
Vasilieva et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk	3
Wassmann et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Li et al (2007)	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	3
Li et al (2005)	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	2
Sawara Y	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	4
Fassett et al	Low risk	Unclear risk	High risk	High risk	High risk	Low risk	Unclear risk	2
Verma et al	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	High risk	2
Jo et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	5
Marschang et al	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	2
Chan et al	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk	2
Suzuki et al	High risk	High risk	High risk	High risk	Low risk	Low risk	Unclear risk	1
Azar et al	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk	2
Karaca et al	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk	2
Abe et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Dornbrook-Lavender et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Sezer et al	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	2
Arabul et al	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	Unclear risk	2
Abulhul et al	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	2
Kirmizis et al	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk	2
Chang et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	3
Burmeister et al	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Ichihara et al	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Ge et al	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	4
Yamagami et al	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	3
Koh et al (2004)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Koh (2008)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Koh et al (2009)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	3
Koh et al (2009)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	3
Koh et al (2010)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	3
Koh et al (2015)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	3
Nilsson et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	4
Ascer et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	3
Kuklinska et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	3
McMurray et al	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	5
Zhang et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	3
Singh et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	3
Oguz et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	3
Devaraj et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	3
Krysiak et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	4
Nafasi et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Chan et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	4
Puurunen et al	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Unclear risk	5
Sathyapalan et al	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	3
Raja-Khan et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	3
Guo et al	Low risk	Unclear risk	High risk	High risk	High risk	Low risk	High risk	2
Lunder et al	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Fegan et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	4
Konduracka et al	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk	1
van de Ree et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	3
Economides et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	5
Jialal et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	3
Ghanim et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	3
Joy et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	2
luo et al	Low risk	Unclear risk	Low risk	High risk	Unclear risk	Low risk	High risk	3
Goicoechea et al	Low risk	Low risk	High risk	High risk	High risk	Low risk	High risk	3
Strazhesko et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk	3
Sola et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Li et al	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk	2
Doo et al	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk	1

(*continued on next page*)

Table 5 (*continued*)

First Author	Cochrane's risk of bias tool							Jadad's scores
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome	Selective reporting	other sources of bias	
Gruzdeva et al	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk	1
Andreou et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	5
Nakagom et al	High risk	High risk	Low risk	Low risk	High risk	Low risk	High risk	2
Doh et al	Low risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	Low risk	3
Gonalves et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	4
Ostadal et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	2
Link et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Yang et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Kishimoto et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	3
Krysiak et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Stefanadi et al	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	2
Pereira et al	High risk	High risk	High risk	High risk	Unclear risk	Low risk	High risk	1
Tousoulis et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Nawawi et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk	4
Gomez-Garcla et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Tousoulis et al (2005)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	3
Tousoulis et al (2005)	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	3
Tousoulis et al (2006)	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	3
Usharani et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	5
KrysiaK et al	High risk	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	2
Xie et al	Low risk	Low risk	High risk	High risk	High risk	Low risk	Low risk	3
Koh et al	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk	3
Sola et al	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	4
Zhao et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	3
Huptas et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	4
Hu et al	Low risk	Low risk	Low risk	High risk	Unclear risk	Low risk	High risk	4
Banaszewska et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	3
Cueto-Manzano et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Wagner et al	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	4
Dogra et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Moohebati et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Bays et al(2002)	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	High risk	3
Bays et al (2004)	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	4
Farnier et al	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk	4
Goldberg et al	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	4
Lu et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	4
Tousoulis et al (2007)	Low risk	Unclear risk	Low risk	High risk	Unclear risk	Low risk	Unclear risk	3
Tan et al	Low risk	Unclear risk	Low risk	Low risk	High risk	Low risk	Unclear risk	3
Strom et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Unclear risk	3
Ridker et al	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	4
Rudofsky et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	4
Vernaglione et al	Low risk	Low risk	High risk	High risk	Unclear risk	Low risk	Low risk	3
Almquist et al	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	5
Folkeringa et al	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	3

Author contributions

ZA, RT, NM and MA contributed in conception, design, statistical analysis and drafting of the manuscript. O-RT, NM, KB-L, ED and PP contributed in conception, data collection and manuscript drafting. FA, A-BH, MM and MC contributed in revised version. The final version was confirmed by all authors for submission.

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Availability of data and material

The primary data for this study is available from the authors on direct request.

Ethics approval and consent to participate

This study was considered exempt by the SUMS Institutional Review Board.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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References

[1] P. Libby, Y. Okamoto, V.Z. Rocha, E. Folco, Inflammation in atherosclerosis: transition from theory to practice, Circ. J. 74 (2010) 213–220.
[2] A.S. Antonopoulos, M. Margaritis, R. Lee, K. Channon, C. Antoniades, Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials, Curr. Pharm. Des. 18 (2012) 1519–1530.
[3] C. Liu, X. Feng, Q. Li, Y. Wang, M. Hua, Adiponectin, TNF-alpha and inflammatory cytokines and risk of type 2 diabetes: a systematic review and meta-analysis, Cytokine 86 (2016) 100–109.
[4] G. Yuan, L. Zhou, J. Tang, Y. Yang, W. Gu, F. Li, et al., Serum CRP levels are equally elevated in newly diagnosed type 2 diabetes and impaired glucose tolerance and related to adiponectin levels and insulin sensitivity, Diabetes Res. Clin. Pract. 72 (2006) 244–250.
[5] S. Devaraj, N. Torok, M.R. Dasu, D. Samols, I. Jialal, Adiponectin decreases C-reactive protein synthesis and secretion from endothelial cells: evidence for an adipose tissue-vascular loop, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1368–1374.
[6] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III), Jama 285 (2001) 2486–2497.
[7] S.N. Magge, N. Stettler, D. Koren, L.E. Levitt Katz, P.R. Gallagher, E.R. Mohler 3rdet al., Adiponectin is associated with favorable lipoprotein profile, independent of BMI and insulin resistance, in adolescents, J. Clin. Endocrinol. Metab. 96 (2011) 1549–1554.
[8] S.H. Han, M.J. Quon, J.A. Kim, K.K. Koh, Adiponectin and cardiovascular disease: response to therapeutic interventions, J. Am. Coll. Cardiol. 49 (2007) 531–538.
[9] O. Gruzdeva, E. Uchasova, Y. Dyleva, O. Akbasheva, V. Karetnikova, O. Barbarash, Early effects of treatment low-dose atorvastatin on markers of insulin resistance and inflammation in patients with myocardial infarction, Front. Pharmacol. 7 (2016) 324.
[10] A. Tuttolomondo, D. Di Raimondo, R. Pecoraro, C. Maida, V. Arnao, V. Della Corte, et al., Early high-dosage atorvastatin treatment improved serum immune-inflammatory markers and functional outcome in acute ischemic strokes classified as large artery atherosclerotic stroke: a randomized trial, Medicine (Baltimore) 95 (2016) e3186.
[11] L. Zhang, S. Zhang, H. Jiang, A. Sun, Y. Wang, Y. Zou, et al., Effects of statin therapy on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials, Arch. Med. Res. 41 (2010) 464–471.
[12] E.M. Balk, J. Lau, L.C. Goudas, H.S. Jordan, B. Kupelnick, L.U. Kim, et al., Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review, Ann. Intern. Med. 139 (2003) 670–682.
[13] S. Devaraj, D. Siegel, I. Jialal, Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome, Am. J. Cardiol. 100 (2007) 1397–1399.
[14] R. Krysiak, A. Gdula-Dymek, R. Bachowski, B. Okopien, Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes, Diabetes Care 33 (2010) 2266–2270.
[15] X. Zhang, X. Zeng, L. Dong, X. Zhao, X. Qu, The effects of statins on benign prostatic hyperplasia in elderly patients with metabolic syndrome, World J. Urol. 33 (2015) 2071–2077.
[16] A. Oguz, M. Uzunlulu, Short term fluvastatin treatment lowers serum asymmetric dimethylarginine levels in patients with metabolic syndrome, Int. Heart J. 49 (2008) 303–311.
[17] S. Huptas, H.C. Geiss, C. Otto, K.G. Parhofer, Effect of atorvastatin (10 mg/day) on glucose metabolism in patients with the metabolic syndrome, Am. J. Cardiol. 98 (2006) 66–69.
[18] U. Singh, S. Devaraj, I. Jialal, D. Siegel, Comparison effect of atorvastatin (10 versus 80 mg) on biomarkers of inflammation and oxidative stress in subjects with metabolic syndrome, Am. J. Cardiol. 102 (2008) 321–325.
[19] P.M.R.N. Ridker, M. Clearfield, J.R. Downs, S.E. Weis, J.S. Miles, A.M. Gotto Jr, Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events, N. Engl. J. Med. 28 (June(344)) (2001) 1959–1965.
[20] S. Sola, M.Q. Mir, B.V. Khan, S. Lerakis, N. Tandon, Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure, J. Am. Coll. Cardiol. 17 (47) (2006 Jan) 332–337.
[21] Y. Hu, G. Tong, W. Xu, J. Pan, K. Ryan, R. Yang, et al., Anti-inflammatory effects of simvastatin on adipokines in type 2 diabetic patients with carotid atherosclerosis, Diab. Vasc. Dis. Res. 6 (October) (2009) 262–268.
[22] R. Krysiak, B. Okopien, The effect of ezetimibe and simvastatin on monocyte cytokine release in patients with isolated hypercholesterolemia, J. Cardiovasc. Pharmacol. 57 (2011) 505–512.
[23] S. Kinlay, G.G. Schwartz, A.G. Olsson, N. Rifai, S.J. Leslie, W.J. Sasiela, et al., High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study, Circulation 108 (2003) 1560–1566.
[24] R. Krysiak, A. Gdula-Dymek, R. Bachowski, B. Okopień, Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes, Diabetes Care 33 (2010) 2266–2270.
[25] I. Jialal, E. Miguelino, S.C. Griffen, S. Devaraj, Concomitant reduction of low-density lipoprotein-cholesterol and biomarkers of inflammation with low-dose simvastatin therapy in patients with type 1 diabetes, J. Clin. Endocrinol. Metab. 1 (August(92)) (2007) 3136–3140.
[26] S. Adamopoulos, J.T. Parissis, D.T. Kremastinos, A glossary of circulating cytokines in chronic heart failure, Eur. J. Heart Fail. 3 (2001) 517–526.
[27] K. Ma, X. Jin, X. Liang, Q. Zhao, X. Zhang, Inflammatory mediators involved in the progression of the metabolic syndrome, Diabetes Metab. Res. Rev. 28 (2012) 388–394.
[28] D.J. Pinsky, B. Cai, X. Yang, C. Rodriguez, R.R. Sciacca, P.J. Cannon, The lethal effects of cytokine-induced nitric oxide on cardiac myocytes are blocked by nitric oxide synthase antagonism or transforming growth factor beta, J. Clin. Invest. 95 (1995) 677–685.
[29] D.L. Mann, Inflammatory mediators and the failing heart: past, present, and the foreseeable future, Circ. Res. 91 (2002) 988–998.
[30] W.H. Yin, J.W. Chen, H.L. Jen, M.C. Chiang, W.P. Huang, A.N. Feng, et al., Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure, Am. Heart J. 147 (2004) 931–938.
[31] M.J. Lipinski, C.A. Cauthen, G.G. Biondi-Zoccai, A. Abbate, B. Vrtovec, B.V. Khan, et al., Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure, Am. J. Cardiol. 104 (2009) 1708–1716.
[32] J. An, F. Shi, S. Liu, J. Ma, Q. Ma, Preoperative statins as modifiers of cardiac and inflammatory outcomes following coronary artery bypass graft surgery: a meta-analysis, Interact. Cardiovasc. Thorac. Surg. 25 (2017) 958–965.
[33] R.T. Artola, C.G. Mihos, O. Santana, Effects of statin therapy in patients with systemic lupus erythematosus, South. Med. J. 109 (2016) 705–711.
[34] R. Hurks, I.E. Hoefer, A. Vink, G. Pasterkamp, A. Schoneveld, M. Kerver, et al., Different effects of commonly prescribed statins on abdominal aortic aneurysm wall biology, Eur. J. Vasc. Endovasc. Surg. 39 (2010) 569–576.
[35] J. Li, J.J. Li, J.G. He, J.L. Nan, Y.L. Guo, C.M. Xiong, Atorvastatin decreases C-reactive protein-induced inflammatory response in pulmonary artery smooth muscle cells by inhibiting nuclear factor-kappaB pathway, Cardiovasc. Ther. 28 (2010) 8–14.
[36] W. Dichtl, J. Dulak, M. Frick, H.F. Alber, S.P. Schwarzacher, M.P. Ares, et al., HMG-CoA reductase inhibitors regulate inflammatory transcription factors in human endothelial and vascular smooth muscle cells, Arterioscler. Thromb. Vasc. Biol. 23 (2003) 58–63.
[37] W. Ni, K. Egashira, C. Kataoka, S. Kitamoto, M. Koyanagi, S. Inoue, et al., Antiinflammatory and antiarteriosclerotic actions of HMG-CoA reductase inhibitors in a rat model of chronic inhibition of nitric oxide synthesis, Circ. Res. 89 (2001) 415–421.
[38] R.M. Bell, D.M. Yellon, Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway, J. Am. Coll. Cardiol. 41 (2003) 508–515.
[39] Y. Jiao, F. Hu, Z. Zhang, K. Gong, X. Sun, A. Li, et al., Efficacy and safety of Loading-Dose rosuvastatin therapy in elderly patients with acute coronary syndromes undergoing elective percutaneous coronary intervention, Clin. Drug Investig. 35 (2015) 777–784.
[40] Z. Wang, H. Dai, M. Xing, Z. Yu, X. Lin, S. Wang, et al., Effect of a single high loading dose of rosuvastatin on percutaneous coronary intervention for acute coronary syndromes, J. Cardiovasc. Pharmacol. Ther. 18 (2013) 327–333.
[41] G. Patti, V. Pasceri, G. Colonna, M. Miglionico, D. Fischetti, G. Sardella, et al., Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial, J. Am. Coll. Cardiol. 49 (2007) 1272–1278.
[42] M. Lewandowski, Z. Kornacewicz-Jach, B. Millo, J. Zielonka, M. Czechowska, R. Kaliszczak, et al., The influence of low dose atorvastatin on inflammatory marker levels in patients with acute coronary syndrome and its potential clinical value, Cardiol. J. 15 (2008) 357–364.
[43] L.C. Correia, A.C. Spósito, J.C. Lima, L.P. Magalhães, L.C. Passos, M.S. Rocha, et al., Anti-inflammatory effect of atorvastatin (80 mg) in unstable angina pectoris and non–Q-wave acute myocardial infarction, Am. J. Cardiol. 92 (2003) 298–301.
[44] T. Dohi, K. Miyauchi, S. Okazaki, T. Yokoyama, N. Yanagisawa, H. Tamura, et al., Early intensive statin treatment for six months improves long-term clinical outcomes in patients with acute coronary syndrome (Extended-ESTABLISH trial): a follow-up study, Atherosclerosis 210 (2010) 497–502.
[45] K.H. Yun, M.H. Jeong, S.K. Oh, S.J. Rhee, E.M. Park, E.M. Lee, et al., The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome, Int. J. Cardiol. 137 (2009) 246–251.
[46] K.H. Yun, I.-S. Shin, S.-N. Shin, J.-H. Choi, S.H. Kim, S.J. Rhee, et al., Effect of previous statin therapy in patients with acute coronary syndrome and percutaneous coronary intervention, Korean Circ. J. 41 (2011) 458–463.
[47] S.M. Macin, E.R. Perna, E.F. Farías, V. Franciosi, J.R. Cialzeta, M. Brizuela, et al., Atorvastatin has an important acute anti-inflammatory effect in patients with acute coronary syndrome: results of a randomized, double-blind, placebo-controlled study, Am. Heart J. 149 (2005) 451–457.
[48] E. Vasilieva, O. Kasyanova, A. Shpektor, The antiplatelet effect of atorvastatin in patients with acute coronary syndrome depends on the hs-CRP level, Acute Card. Care 10 (2008) 181–184.
[49] S. Wassmann, A. Faul, B. Hennen, B. Scheller, M. Böhm, G. Nickenig, Rapid effect of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition on coronary endothelial function, Circ. Res. 93 (2003) e98–e103.
[50] J.-J. Li, Y. Wang, S.-P. Nie, C.-Y. Zhang, Y.-S. Li, R.-T. Hui, et al., Reduction of C-

reactive protein by a single 80 mg of simvastatin in patients with unstable angina, Clin. Chim. Acta 376 (2007) 163–167.
[51] J.-J. Li, C.-H. Fang, Effects of 4 weeks of atorvastatin administration on the anti-inflammatory cytokine interleukin-10 in patients with unstable angina, Clin. Chem. 51 (2005) 1735–1738.
[52] Y. Sawara, T. Takei, K. Uchida, T. Ogawa, T. Yoshida, K. Tsuchiya, et al., Effects of lipid-lowering therapy with rosuvastatin on atherosclerotic burden in patients with chronic kidney disease, Intern. Med. 47 (2008) 1505–1510.
[53] R.G. Fassett, I.K. Robertson, M.J. Ball, D.P. Geraghty, J.S. Coombes, Effects of atorvastatin on biomarkers of inflammation in chronic kidney disease, Clin. Nephrol. 81 (2014) 75–85.
[54] A. Verma, K.M. Ranganna, R.S. Reddy, M. Verma, N.F. Gordon, Effect of rosuvastatin on C-reactive protein and renal function in patients with chronic kidney disease, Am. J. Cardiol. 96 (2005) 1290–1292.
[55] S.-H. Jo, B.-K. Koo, J.-S. Park, H.-J. Kang, Y.-S. Cho, Y.-J. Kim, et al., Prevention of radiocontrast medium–induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study, Am. Heart J. 155 (499) (2008) e1–e8.
[56] P. Marschang, G.J. Friedrich, H. Ditlbacher, A. Stoeger, D. zur Nedden, R. Kirchmair, et al., Reduction of soluble P-selectin by statins is inversely correlated with the progression of coronary artery disease, Int. J. Cardiol. 106 (2006) 183–190.
[57] K.C. Chan, H.H. Chou, C.N. Huang, M.C. Chou, Atorvastatin administration after percutaneous coronary intervention in patients with coronary artery disease and normal lipid profiles: impact on plasma adiponectin level, Clin. Cardiol. 31 (2008) 253–258.
[58] T. Suzuki, T. Nozawa, M. Sobajima, N. Igarashi, A. Matsuki, N. Fujii, et al., Atorvastatin-induced changes in plasma coenzyme Q10 and brain natriuretic peptide in patients with coronary artery disease, Int. Heart J. 49 (2008) 423–433.
[59] R.R. Azar, G. Badaoui, A. Sarkis, R. Kassab, E. Salamé, S. Klaymé, et al., Effects of tirofiban and statins on high-sensitivity C-reactive protein, interleukin-6, and soluble CD40 ligand following percutaneous coronary interventions in patients with stable coronary artery disease, Am. J. Cardiol. 95 (2005) 236–240.
[60] I. Karaca, E. Ilkay, M. Akbulut, M. Yavuzkır, M. Pekdemir, H. Akbulut, et al., Atorvastatin affects C-reactive protein levels in patients with coronary artery disease, Curr. Med. Res. Opin. 19 (2003) 187–191.
[61] M. Abe, N. Maruyama, K. Okada, S. Matsumoto, K. Matsumoto, M. Soma, Effects of lipid-lowering therapy with rosuvastatin on kidney function and oxidative stress in patients with diabetic nephropathy, J. Atheroscler. Thromb. 18 (2011) 1018–1028.
[62] K.A. Dornbrook-Lavender, M.S. Joy, C.J. Denu-Ciocca, H. Chin, S.L. Hogan, J.A. Pieper, Effects of atorvastatin on low-density lipoprotein cholesterol phenotype and C-Reactive protein levels in patients undergoing long-term Dialysis, Pharmacotherapy 25 (2005) 335–344.
[63] M. Tugrul Sezer, S. Katirci, M. Demir, J. Erturk, S. Adana, S. Kaya, Short-term effect of simvastatin treatment on inflammatory parameters in peritoneal dialysis patients, Scand. J. Urol. Nephrol. 41 (2007) 436–441.
[64] M. Arabul, M. Gullulu, Y. Yilmaz, I. Akdag, S. Kahvecioglu, M.A. Eren, et al., Effect of fluvastatin on serum prohepcidin levels in patients with end-stage renal disease, Clin. Biochem. 41 (2008) 1055–1058.
[65] E. Abulhul, K. McDonald, R. Martos, D. Phelan, J.P. Spiers, M. Hennessy, et al., Long-term statin therapy in patients with systolic heart failure and normal cholesterol: effects on elevated serum markers of collagen turnover, inflammation, and B-type natriuretic peptide, Clin. Ther. 34 (2012) 91–100.
[66] D. Kirmizis, A. Papagianni, F. Dogrammatzi, L. Skoura, A.-M. Belechri, E. Alexopoulos, et al., Effects of simvastatin on markers of inflammation, oxidative stress and endothelial cell apoptosis in patients on chronic hemodialysis, J. Atheroscler. Thromb. 17 (2010) 1256–1265.
[67] J.W. Chang, W.S. Yang, W.K. Min, S.K. Lee, J.S. Park, S.B. Kim, Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients, Am. J. Kidney Dis. 39 (2002) 1213–1217.
[68] J.E. Burmeister, D.R. Miltersteiner, B.M. Campos, Rosuvastatin in hemodialysis: short-term effects on lipids and C-reactive protein, J. Nephrol. 22 (2009) 83.
[69] A. Ichihara, M. Hayashi, M. Ryuzaki, M. Handa, T. Furukawa, T. Saruta, Fluvastatin prevents development of arterial stiffness in haemodialysis patients with type 2 diabetes mellitus, Nephrol. Dial. Transplant. 17 (2002) 1513–1517.
[70] C.-J. Ge, S.-Z. Lu, Y.-D. Chen, X.-F. Wu, S.-J. Hu, Y. Ji, Synergistic effect of amlodipine and atorvastatin on blood pressure, left ventricular remodeling, and C-reactive protein in hypertensive patients with primary hypercholesterolemia, Heart Vessels 23 (2008) 91–95.
[71] H. Yamagami, M. Sakaguchi, S. Furukado, T. Hoshi, Y. Abe, H. Hougaku, et al., Statin therapy increases carotid plaque echogenicity in hypercholesterolemic patients, Ultrasound Med. Biol. 34 (2008) 1353–1359.
[72] K.K. Koh, J.W. Son, J.Y. Ahn, D.K. Jin, H.S. Kim, Y.M. Choi, et al., Vascular effects of diet and statin in hypercholesterolemic patients, Int. J. Cardiol. 95 (2004) 185–191.
[73] K.K. Koh, M.J. Quon, S.H. Han, Y. Lee, J.Y. Ahn, S.J. Kim, et al., Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients, Diabetes Care 31 (2008) 776–782.
[74] K.K. Koh, M.J. Quon, S.H. Han, Y. Lee, S.J. Kim, E.K. Shin, Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients, J. Am. Coll. Cardiol. 55 (2010) 1209–1216.
[75] K.K. Koh, M.J. Quon, S.H. Han, Y. Lee, S.J. Kim, J.B. Park, et al., Differential metabolic effects of pravastatin and simvastatin in hypercholesterolemic patients, Atherosclerosis 204 (2009) 483–490.
[76] K.K. Koh, M.J. Quon, I. Sakuma, Y. Lee, S. Lim, S.H. Han, et al., Effects of simvastatin therapy on circulating adipocytokines in patients with hypercholesterolemia, Int. J. Cardiol. 146 (2011) 434–437.
[77] K.K. Koh, P.C. Oh, I. Sakuma, E.Y. Kim, Y. Lee, T. Hayashi, et al., Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia, Int. J. Cardiol. 199 (2015) 126–131.
[78] L. Nilsson, P. Eriksson, P. Cherfan, L. Jonasson, Effects of simvastatin on proinflammatory cytokines and matrix metalloproteinases in hypercholesterolemic individuals, Inflammation 34 (2011) 225–230.
[79] E. Ascer, M.C. Bertolami, M.L. Venturinelli, V. Buccheri, J. Souza, J.C. Nicolau, et al., Atorvastatin reduces proinflammatory markers in hypercholesterolemic patients, Atherosclerosis 177 (2004) 161–166.
[80] A.M. Kuklińska, B. Mroczko, W.J. Musiał, R. Sawicki, A. Kozieradzka, M. Usowicz-Szaryńska, et al., Hypotensive effect of atorvastatin is not related to changes in inflammation and oxidative stress, Pharmacol. Rep. 62 (2010) 883–890.
[81] J.J. McMurray, J. Kjekshus, L. Gullestad, P. Dunselman, Å Hjalmarson, H. Wedel, et al., Effects of statin therapy according to plasma high-sensitivity C-reactive protein concentration in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): a retrospective analysis, Circulation 120 (2009) 2188–2196.
[82] X. Zhang, X. Zeng, L. Dong, X. Zhao, X. Qu, The effects of statins on benign prostatic hyperplasia in elderly patients with metabolic syndrome, World J. Urol. 33 (2015) 2071–2077.
[83] U. Singh, S. Devaraj, I. Jialal, D. Siegel, Comparison effect of atorvastatin (10 versus 80 mg) on biomarkers of inflammation and oxidative stress in subjects with metabolic syndrome, Am. J. Cardiol. 102 (2008) 321–325.
[84] A. Oguz, M. Uzunlulu, Short term fluvastatin treatment lowers serum asymmetric dimethylarginine levels in patients with metabolic syndrome, Int. Heart J. 49 (2008) 303–311.
[85] S. Devaraj, D. Siegel, I. Jialal, Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome, Am. J. Cardiol. 100 (2007) 1397–1399.
[86] L. Nafasi, R. Rahmani, A. Shafiee, A. Salari, A. Abdollahi, A. Meysamie, Can a high reloading dose of atorvastatin prior to percutaneous coronary intervention reduce periprocedural myocardial infarction? Curr. Med. Res. Opin. 30 (2014) 381–386.
[87] D.C. Chan, G.F. Watts, P.H.R. Barrett, L.J. Beilin, T.A. Mori, Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity, Clin. Chem. 48 (2002) 877–883.
[88] J. Puurunen, T. Piltonen, K. Puukka, A. Ruokonen, M.J. Savolainen, R. Bloigu, et al., Statin therapy worsens insulin sensitivity in women with polycystic ovary syndrome (PCOS): a prospective, randomized, double-blind, placebo-controlled study, J. Clin. Endocrinol. Metab. 98 (2013) 4798–4807.
[89] T. Sathyapalan, J. Shepherd, C. Arnett, A.M. Coady, E.S. Kilpatrick, S.L. Atkin, Atorvastatin increases 25-hydroxy vitamin D concentrations in patients with polycystic ovary syndrome, Clin. Chem. 56 (2010 Nov) 1696–1700.
[90] N. Raja-Khan, A.R. Kunselman, C.S. Hogeman, C.M. Stetter, L.M. Demers, R.S. Legro, Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial, Fertil. Steril. 95 (April) (2011) 1849–1852.
[91] S. Guo, R. Wang, Z. Yang, K. Li, Q. Wang, Effects of atorvastatin on serum lipids, serum inflammation and plaque morphology in patients with stable atherosclerotic plaques, Exp. Ther. Med. 1 (December(4)) (2012) 1069–1074.
[92] M. Lunder, M. Janić, V. Savić, A. Janež, K. Kanc, M. Šabovič, Very low-dose fluvastatin-valsartan combination decreases parameters of inflammation and oxidative stress in patients with type 1 diabetes mellitus, Diabetes Res. Clin. Pract. 1 (May (127)) (2017) 181–186.
[93] P.G. Fegan, A.C. Shore, D. Mawson, J.E. Tooke, K.M. MacLeod, Microvascular endothelial function in subjects with Type 2 diabetes and the effect of lipid-lowering therapy, Diabet. Med. 1 (December (22)) (2005) 1670–1676.
[94] E. Konduracka, D. Galicka-Latala, G. Cieslik, P. Rostoff, D. Fedak, J. Sieradzki, et al., Effect of atorvastatin on endothelial function and inflammation in long--duration type 1 diabetic patients without coronary heart disease and arterial hypertension, Diabetes Obes. Metab. 1 (September (10)) (2008) 719–725.
[95] M.A. Van de Ree, M.V. Huisman, H.M. Princen, A.E. Meinders, C. Kluft, Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus, Atherosclerosis. 1 (January (166)) (2003) 129–135.
[96] P.A. Economides, A. Caselli, E. Tiani, L. Khaodhiar, E.S. Horton, A. Veves, The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes, J. Clin. Endocrinol. Metab. 1 (February (89)) (2004) 740–747.
[97] H. Ghanim, K. Green, S. Abuaysheh, R. Patel, M. Batra, A. Chaudhuri, et al., Ezetimibe and simvastatin combination inhibits and reverses the pro-inflammatory and pro-atherogenic effects of cream in obese patients, Atherosclerosis. 1 (August (263)) (2017) 278–286.
[98] M.S. Joy, K.A. Dornbrook-Lavender, H. Chin, S.L. Hogan, C. Denu-Ciocca, Effects of atorvastatin on Lp (a) and lipoprotein profiles in hemodialysis patients, Ann. Pharmacother. 42 (January) (2008) 9–15.
[99] Y. Luo, D. Jiang, D. Wen, J. Yang, L. Li, Changes in serum interleukin-6 and high-sensitivity C-reactive protein levels in patients with acute coronary syndrome and their responses to simvastatin, Heart Vessels 1 (November (19)) (2004) 257–262.
[100] M. Goicoechea, S.G. de Vinuesa, V. Lahera, V. Cachofeiro, F. Gómez-Campderá, A. Vega, et al., Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease, J. Am. Soc. Nephrol. 1 (December) (2006) S231–S235.
[101] I.D. Strazhesko, O.N. Tkacheva, D.U. Akasheva, E.N. Dudinskaya, E.V. Plokhova, V.S. Pykhtina, et al., Atorvastatin therapy modulates telomerase activity in

patients free of atherosclerotic cardiovascular diseases, Front. Pharmacol. 30 (September) (2016) 347.
[102] X.Y. Li, J.P. Chang, Z.W. Su, J.H. Li, B.S. Peng, S.L. Zhu, et al., How does short--term low-dose simvastatin influence serum prohepcidin levels in patients with end-stage renal disease? A pilot study, Ther. Apher. Dial. 1 (June (14)) (2010) 308–314.
[103] Y.C. Doo, S.J. Han, S.W. Han, W.J. Park, S.H. Choi, G.Y. Cho, et al., Effect of preexisting statin use on expression of C-reactive protein, adhesion molecules, interleukin-6, and antioxidized low-density lipoprotein antibody in patients with unstable angina undergoing coronary stenting, Clin. Cardiol. 1 (February (28)) (2005) 72–76.
[104] O. Gruzdeva, E. Uchasova, Y. Dyleva, O. Akbasheva, V. Karetnikova, O. Barbarash, Early effects of treatment low-dose atorvastatin on markers of insulin resistance and inflammation in patients with myocardial infarction, Front. Pharmacol. 7 (2016) 324.
[105] I. Andreou, D. Tousoulis, A. Miliou, C. Tentolouris, K. Zisimos, P. Gounari, et al., Effects of rosuvastatin on myeloperoxidase levels in patients with chronic heart failure: a randomized placebo-controlled study, Atherosclerosis 210 (2010) 194–198.
[106] A. Nakagomi, Y. Seino, K. Kohashi, M. Kosugi, Y. Endoh, Y. Kusama, et al., Effects of statin therapy on the production of monocyte pro-inflammatory cytokines, cardiac function, and long-term prognosis in chronic heart failure patients with dyslipidemia, Circ. J. 76 (2012) 2130–2138.
[107] F.M. Doh, T.-I. Chang, H.M. Koo, M.J. Lee, D.H. Shin, C.H. Kim, et al., The effect of HMG-CoA reductase inhibitor on insulin resistance in patients undergoing peritoneal dialysis, Cardiovasc. Drugs Ther. 26 (2012) 501–509.
[108] I. Goncalves, P. Cherfan, I. Söderberg, G. Nordin Fredrikson, L. Jonasson, Effects of simvastatin on circulating autoantibodies to oxidized LDL antigens: relation with immune stimulation markers, Autoimmunity. 42 (2009) 203–208.
[109] P. Ostadal, D. Alan, P. Hajek, D. Horak, J. Vejvoda, J. Trefanec, et al., The effect of early treatment by cerivastatin on the serum level of C-reactive protein, interleukin-6, and interleukin-8 in the patients with unstable angina and non-Q-wave myocardial infarction, Vascular Biochemistry, Springer, 2003, pp. 45–50.
[110] A. Link, T. Ayadhi, M. Böhm, G. Nickenig, Rapid immunomodulation by rosuvastatin in patients with acute coronary syndrome, Eur. Heart J. 27 (2006) 2945–2955.
[111] J. Yang, X.-P. Li, S.-P. Zhao, J. Li, J.-D. Li, X.-M. Xie, The effect of different doses of fluvastatin on inflammatory markers in the early phase of acute coronary syndrome, Clin. Chim. Acta 368 (2006) 183–187.
[112] N. Kishimoto, T. Hayashi, I. Sakuma, H. Kano-Hayashi, T. Tsunekawa, M. Osawa, et al., A hydroxymethylglutaryl coenzyme a reductase inhibitor improves endothelial function within 7 days in patients with chronic hemodialysis, Int. J. Cardiol. 145 (2010) 21–26.
[113] E. Stefanadi, D. Tousoulis, C. Antoniades, V. Katsi, E. Bosinakou, E. Vavuranakis, et al., Early initiation of low-dose atorvastatin treatment after an acute ST-elevated myocardial infarction, decreases inflammatory process and prevents endothelial injury and activation, Int. J. Cardiol. 133 (2009) 266–268.
[114] M.M. Pereira, T.P.S.A. Santos, R. Aras, R.D. Couto, M.L.B.S. Atta, A.M. Atta, Serum levels of cytokines and chemokines associated with cardiovascular disease in Brazilian patients treated with statins for dyslipidemia, Int. Immunopharmacol. 18 (2014) 66–70.
[115] D. Tousoulis, C. Antoniades, V. Katsi, E. Bosinakou, M. Kotsopoulou, C. Tsioufis, et al., The impact of early administration of low-dose atorvastatin treatment on inflammatory process, in patients with unstable angina and low cholesterol level, Int. J. Cardiol. 109 (2006) 48–52.
[116] H. Nawawi, N. Osman, K. Yusoff, B. Khalid, Reduction in serum levels of adhesion molecules, interleukin-6 and C-reactive protein following short-term low-dose atorvastatin treatment in patients with non-familial hypercholesterolemia, Horm. Metab. Res. 35 (2003) 479–485.
[117] A. Gómez-García, G.M. Torres, L.E. Ortega-Pierres, E. Rodríguez-Ayala, C. Álvarez-Aguilar, Rosuvastatin and metformin decrease inflammation and oxidative stress in patients with hypertension and dyslipidemia, Rev. Esp. Cardiol. 60 (2007) 1242–1249.
[118] D. Tousoulis, C. Antoniades, E. Bosinakou, M. Kotsopoulou, C. Pitsavos, C. Vlachopoulos, et al., Effects of atorvastatin on reactive hyperemia and inflammatory process in patients with congestive heart failure, Atherosclerosis 178 (2005) 359–363.
[119] D. Tousoulis, C. Antoniades, C. Vassiliadou, M. Toutouza, C. Pitsavos, C. Tentolouris, et al., Effects of combined administration of low dose atorvastatin and vitamin E on inflammatory markers and endothelial function in patients with heart failure, Eur. J. Heart Fail. 7 (2005) 1126–1132.
[120] D. Tousoulis, C. Antoniades, C. Vasiliadou, P. Kourtellaris, K. Koniari, K. Marinou, et al., Effects of atorvastatin and vitamin C on forearm hyperaemic blood flow, asymmentrical dimethylarginine levels and the inflammatory process in patients with type 2 diabetes mellitus, Heart 93 (2007) 244–246.
[121] P. Usharani, A. Mateen, M. Naidu, Y. Raju, N. Chandra, Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus, Drugs in R & D 9 (2008) 243–250.
[122] R. Krysiak, W. Żmuda, B. Okopień, The effect of short-term simvastatin treatment on plasma adipokine levels in patients with isolated hypercholesterolemia: a preliminary report, Pharmacol. Rep. 66 (2014) 880–884.
[123] W. Xie, P. Li, Z. Wang, J. Chen, Z. Lin, X. Liang, et al., Rosuvastatin may reduce the incidence of cardiovascular events in patients with acute coronary syndromes receiving percutaneous coronary intervention by suppressing miR-155/SHIP-1 signaling pathway, Cardiovasc. Ther. 32 (2014) 276–282.
[124] K.K. Koh, J.W. Son, J.Y. Ahn, D.K. Jin, H.S. Kim, Y.M. Choi, et al., Comparative effects of diet and statin on NO bioactivity and matrix metalloproteinases in hypercholesterolemic patients with coronary artery disease, Arterioscler. Thromb. Vasc. Biol. 22 (2002) e19–e23.
[125] S. Zhao, Q. Li, L. Liu, Z. Xu, J. Xiao, Simvastatin reduces interleukin-1β secretion by peripheral blood mononuclear cells in patients with essential hypertension, Clin. Chim. Acta 344 (2004) 195–200.
[126] S. Huptas, H.C. Geiss, C. Otto, K.G. Parhofer, Effect of atorvastatin (10 mg/day) on glucose metabolism in patients with the metabolic syndrome, Am. J. Cardiol. 1 (July (98)) (2006) 66–69.
[127] B. Banaszewska, L. Pawelczyk, R.Z. Spaczynski, J. Dziura, A.J. Duleba, Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover tria, J. Clin. Endocrinol. Metab. 14 (November (92)) (2006) 456–461.
[128] A.M. Cueto-Manzano, J.R. Ángel-Zúñiga, G. Ornelas-Carrillo, E. Rojas-Campos, H.R. Martínez-Ramírez, Cortés-Sanabria, Anti-inflammatory interventions in end-stage kidney disease: a randomized, double-blinded, controlled and crossover clinical trial on the use of pravastatin in continuous ambulatory peritoneal dialysis, Arch. Med. Res. 44 (2013) 633–637.
[129] A.M. Wägner, J.L. Sánchez-Quesada, S. Benítez, C. Bancells, J. Ordóñez-Llanos, A. Pérez, Effect of statin and fibrate treatment on inflammation in type 2 diabetes. A randomized, cross-over study, Diabetes Res. Clin. Pract. 1 (July (93)) (2011) 25–28.
[130] G.K. Dogra, G.F. Watts, D.C. Chan, K. Stanton, Statin therapy improves brachial artery vasodilator function in patients with Type 1 diabetes and microalbuminuria, Diabet. Med. 1 (March (22)) (2005) 239–242.
[131] M.B.S. Moohebati, M.R. Azarpazhooh, M.H. Daloee, M. Ghayour-Mobarhan, S. Tavallaie, M. Amini, A. Momenzadeh, A. Sahebkar, R. Paydar, A.A. Rahsepar, Simvastatin treatment reduces heat shock protein 60, 65, and 70 antibody titers in dyslipidemic patients: a randomized, double-blind, placebo-controlled, cross-over trial, Clin. Biochem. 1 (February (44)) (2011) 192–197.
[132] H.E.S.E. Bays, A.K. Shah, D.L. Maccubbin, Y.B. Mitchel, M. Mercuri, Effects of simvastatin on C-reactive protein in mixed hyperlipidemic and hypertriglyceridemic patients, Am. J. Cardiol. 1 (November (90)) (2002) 942–946.
[133] H.E.O.L. Bays, N. Fraser, D.L. Tribble, K. Quinto, R. Reyes, A.O. Johnson-Levonas, A. Sapre, S.R. Donahue, A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia, Clin. Ther. 1 (November (26)) (2004) 1758–1773.
[134] M.R.E. Farnier, B. Gil-Extremera, G.F. Mendez, G. Macdonell, C. Hamlin, I. Perevozskaya, M.J. Davies, D. Kush, Y.B. Mitchel, Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia, Am. Heart J. 1 (February (153)) (2007) 335-e1.
[135] A.C.S.A. Goldberg, J. Liu, R. Capece, Y.B. Mitchel, Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial, In Mayo Clin. Proc. 1 (May (79)) (2004) 620–629.
[136] T.M.D.Y. Lu, H.B. Leu, W.H. Yin, W.H. Sheu, K.M. Chu, Effect of rosuvastatin on plasma levels of asymmetric dimethylarginine in patients with hypercholesterolemia, Am. J. Cardiol. 15 (July (94)) (2004) 157–161.
[137] K.C.C.W. Tan, S.C. Tam, V.H. Ai, C.H. Lam, K.S. Lam, Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus, J. Clin. Endocrinol. Metab. 1 (February (87)) (2002) 563–568.
[138] A.K.H. Strom, S. Martin, C. Herder, M.C. Simon, W. Koenig, T. Heise, L. Heinemann, M. Roden, N.C. Schloot, DIATOR Study Group.IMproved preservation of residual beta cell function by atorvastatin in patients with recent onset type 1 diabetes and high CRP levels (DIATOR trial), PLoS One 20 (March (7)) (2012) e33108.
[139] G.R.P. Rudofsky, J.B. Groener, Z. Djuric, T. Fleming, C. Metzner, I.A. Grafe, A. Bierhaus, P.P. Nawroth, Identical LDL-cholesterol lowering but non-identical effects on NF-κB activity: high dose simvastatin vs combination therapy with ezetimibe, Atherosclerosis 1 (July (223)) (2012) 190–196.
[140] L.C.C. Vernaglione, P. Muscogiuri, S. Chimienti, Does atorvastatin influence serum C-reactive protein levels in patients on long-term hemodialysis? Am. J. Kidney Dis. 1 (March (43)) (2004) 471–478.
[141] T.J.S. Almquist, F. Mobarrez, P. Näsman, P. Hjemdahl, Lipid-lowering treatment and inflammatory mediators in diabetes and chronic kidney disease, Eur. J. Clin. Invest. 1 (March(44)) (2014) 276–284.
[142] Folkeringa R.J. dVC, Y.M. Pinto, J. Habets, P.W. De Leeuw, R.G. Tieleman, M.H. Prins, M. Van Dieijen-Visser, H.J. Crijns, No effect of rosuvastatin on left ventricular hypertrophy in patients with hypertension: a prospective randomised open-label study with blinded endpoint assessment, Int. J. Cardiol. 5 (November145) (2010) 156–158.