A systematic review and meta-analyses on the effects of atorvastatin on blood pressure and heart rate

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Aims	Considering the inconsistencies in the literature on the atorvastatin effect on blood pressure (BP), we performed these meta-analyses.
Methods and results	Through a search of the Excerpta Medica Database (EMBASE), PubMed, and Web of Science databases, 1412 articles were identified, from which 33 randomized clinical trials (RCT) and 44 pre-clinical were selected. Populations from RCT were stratified according to baseline BP and lipid levels. We performed meta-analyses of the effect of atorvastatin on systolic (SBP), diastolic and mean BP; heart rate (HR); HR variability, and baroreflex. Atorvastatin reduced SBP in the overall population ($P = 0.05$ vs. placebo; $P = 0.03$ vs. baseline), in normotensive and hyperlipidaemic ($P = 0.04$ vs. placebo; $P = 0.0001$ vs. baseline) and in hypertensive and hyperlipidaemic ($P = 0.02$ vs. placebo; $P = 0.008$ vs. baseline) individuals in parallel RCT, but it did not affect SBP in normotensive and normolipidaemic individuals ($P = 0.51$ vs. placebo; $P = 0.4$ vs. baseline). Although an effect of atorvastatin was detected in hyperlipidaemic individuals, the meta-regression coefficient for the association of low density lipoprotein (LDL)-cholesterol reduction with SBP reduction in the overall population demonstrated that SBP reduction is not dependent on the changes in LDL-cholesterol. A meta-analysis of preclinical reports demonstrated that SBP was reduced in atorvastatin-treated hypertensive and normolipidaemic rats (control rats: $P = 0.97$). Atorvastatin also reduced the HR in spontaneously hypertensive rat.
Conclusion	Atorvastatin lowers BP independent of LDL-cholesterol levels. Additional studies are needed to estimate the involvement of the autonomic nervous system in the BP-lowering effect of atorvastatin.
Keywords	Atorvastatin • Autonomic modulation • Blood pressure • Cholesterol

Introduction

Hypertension is one of the most common modifiable risk factors for cardiovascular disease, chronic kidney disease, and cognitive impairment, being the leading single contributor to all-cause death and disability worldwide.¹ The maintenance of physiological blood pressure (BP) levels involves a complex interplay of various elements of an integrated neurohumoral system that includes the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system, the natriuretic peptides, the endothelial function, and the immune system.² In addition, there is growing evidence that the involvement of

the renin-angiotensin system can be considered as the common link between hypertension and hypercholesterolaemia. $^{\rm 3}$

Atorvastatin is a drug commonly used to reduce cholesterol in the treatment of hypercholesterolaemia, which acts by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.⁴ Previous studies have shown that statins potentially affect the autonomic nervous system⁵ and also prevent or improve cardiac dysfunction by inhibiting oxidative stress,^{6–8} inflammation,⁹ and endothelial dysfunction.¹⁰ These pleiotropic effects suggest a potential hypotensive effect of atorvastatin. However, some studies show that treatment with statins is associated with significant reductions in

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BP levels,^{11–13} while others do not confirm this effect.^{5,14–17} Studies performed on rodents also produced inconsistent results.^{18–20}

The effects of atorvastatin on heart rate (HR) are also controversial. Several studies demonstrate that atorvastatin does not alter HR, $^{5,13,15-17,21}$ but there is one study showing a slight but significant reduction in the HR of hypertensive patients.¹¹ In hypertensive rats, oral administration of atorvastatin had no effects on HR, $^{22-24}$ but central administration significantly reduced HR.²⁵

There is evidence that atorvastatin also alters the autonomic nervous system, evaluated by heart rate variability (HRV). It has been demonstrated that patients treated with atorvastatin showed an increase in standard deviation between normal intervals (SDNN) and parasympathetic nervous system activity.^{15,26,27} In addition, patients treated with atorvastatin showed a reduction in sympathetic activity.^{14,26} The only rodent study that investigated the effect of central administration of atorvastatin on SBP variability in hypertensive rats also suggests a reduction in SNS activity.²⁵ Studies in humans^{17,27,28} and rodents^{22,25} have shown that atorvastatin increases baroreflex sensitivity.

Considering the evidence and inconsistencies in the effects of atorvastatin on BP and HR in humans and rodents, we performed a systematic review with meta-analyses on these issues. The correlation between the changes in BP and cholesterol levels was also investigated, as well as the effect of atorvastatin on HRV and baroreflex.

Materials and methods

This study followed the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²⁹ Thus, a systematic review was performed by searching the Excerpta Medica Database (EMBASE), PubMed, and Web of Science databases (17, September 2021) using the following search Medical Subject Headings (MeSH) terms: ('atorvastatin' OR 'Lipitor' OR 'Liptonorm' OR 'CI 981') AND ('baroreflex' OR 'autonomic nervous system' OR 'BP ' OR 'pulse pressure' OR 'heart rate' OR 'heart rate variability'). Details of the search strategy are presented in the Supplementary material (Supplementary material online, *Table S1*). Two reviewers conducted independent searches and included all relevant articles published in English, Spanish, and Portuguese, with no restriction on the publication date. If there was a lack of consensus between the reviewers, regardless of the stage of the study, a third reviewer was consulted.

For study selection, we used the PICOS acronym (Population, Intervention, Comparison, Outcome, Study design)³⁰ to determine the general eligibility of studies as follows: *Population*: mammals; *Intervention*: atorvastatin therapy; *Comparison*: values after atorvastatin treatment were compared with baseline or placebo/control; *Outcomes*: BP, HR, baroreflex, HRV; *Study design*: randomized clinical trials (RCT) or preclinical studies. There were no restrictions regarding the sample size. The titles and abstracts of all articles identified in the searches were initially evaluated, and the full texts of those considered relevant by at least one of the researchers were then analysed thoroughly. Papers that were inaccessible even after attempts to contact the corresponding author or purchase them were excluded (Supplementary material online, *Table S2*).

Populations from RCT were stratified according to the baseline values of BP and lipid levels.^{31–33} The population was considered hypertensive if the baseline SBP values were \geq 140 mmHg and/or the baseline diastolic BP (DBP) was \geq 90 mmHg.³² For classification of hyperlipidaemia, the parameters were low-density lipoprotein (LDL)-cholesterol \geq 160 mg/dL and/or triacylglycerol \geq 150 mg/dL.^{31,33} To enable the stratification of populations, the International System Units (mmol/L) were converted to conventional units (milligrams per decilitre) using the conversion factors 38.67 for total, LDL- and high-density lipoprotein (HDL)-cholesterol, and 88.57 for triacylglycerol.³⁴

Populations from preclinical studies were stratified according to the animal model or treatment.

Data related to the number of patients; age; body mass index; dose, time, and route of administration of atorvastatin; SBP, DBP, and mean BP (MBP); HR; spontaneous baroreflex, and HRV in the time and frequency domains were extracted from the included RCT (*Table 1*). Data related to the lineage; age; body weight; experimental model; dose, time, and route of administration of atorvastatin; SBP, DBP and MBP; HR; spontaneous baroreflex, and HRV were extracted from the preclinical studies included (*Table 2*). When necessary,^{35,36} mean and standard deviation were estimated from sample size, median, and interquartile range.³⁷

Quality analysis

The methodological quality of the studies included in this review was evaluated by two authors independently, and divergent opinions were resolved by consensus. The quality of the RCT was evaluated using the Jadad scale.³⁸ The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool, which assesses the risk of bias for animal studies, was also used.³⁹ This tool contains the following evaluation items: selection bias, performance bias, detection bias, friction bias, reporting bias, and other sources of bias. Ten questions were applied to the articles included in the systematic review, with the possible answers 'YES', indicating a low risk of bias; 'NO', indicating a high risk of bias, and 'UNCERTAIN', indicating an uncertain risk of bias. Calculating the sum score of each individual study using this tool is not recommended.

Meta-analyses

For the meta-analyses, we considered the population characteristics and the study design (parallel RCT or cross-over RCT and preclinical studies). For RCT, we performed a meta-analysis considering all individuals (overall effect) and then stratified the studies according to the population features (normotensive and normolipidaemic; normotensive and hyperlipidaemic; hypertensive and hyperlipidaemic; hypertensive). Independent meta-analyses were performed for SBP, DBP and MBP; HR; spontaneous baroreflex, and HRV. For pre-clinical studies, we performed a meta-analysis of SBP considering the stratified studies [standard diet-fed rats; spontaneously hypertensive rats (SHR); spontaneously hypertensive rats stroke-prone (SHR-SP); highsalt diet-fed rats (8 and 4% NaCl); surgically hypertensive rats; diabetic rats; hyperlipidaemic rats; dexamethasone-induced hypertensive rats]. The results of each primary study were described by subtracting the mean after treatment from the mean before treatment or the mean from the placebo/control group. Estimates of individual studies and their variances were combined using random effects models to estimate the pooled mean difference and its confidence intervals. Heterogeneity in primary results was analysed using Cochran's Q statistical test and the I^2 statistic. In all procedures, the significance level was 5%. All analyses were performed using the software Review Manager 5.4. The effect of atorvastatin on the outcome (plotted as a mean difference for the change in SBP [mmHg] upon the y-axis) as a function of a given factor (plotted as a difference in the change in LDL-cholesterol [mg/dl] upon the x-axis) was estimated using meta-regression. Metaregression coefficients (slopes of the meta-regression line) show the estimated change in the SBP mean difference per unit of the covariate change. This statistical analysis was performed with the Comprehensive Meta-Analysis 3.3.070 (Biostat, Englewood, NJ, USA).

Results

A total of 1412 relevant papers were identified on Embase, PubMed, and Web of Science, of which 1335 were excluded for the reasons described in *Figure 1*, and 33 RCT and 44 preclinical studies were included in the final analyses.

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Article ¹	RCT ² 1. Parallel 2. Cross-over	Age ³ ; n (men/women) ⁴ ; BMI ⁵ (atorvastatin and placeboor total population)	Use of antihyper tensive	Dose/weeks ⁶	Group 1. Basal 2. Placebo	Jadad Scale
NORMOTENSIVE AND NO	DRMOLIPIDAEMIC					
BLESKE 2006 ⁵⁵	2	$56.00 \pm 11.00; 9/6; 29.39 \pm 4.53^{b}$	Yes	80/12	1; 2	5
JOYEUX-FAURE 2014 ⁵⁶	~	51.00 ± 12.00 ; $21/4$; 28.58 ± 5.12^{b} ; 56.00 ± 9.00 ; $18/8$; 28.70 ± 3.94^{b}	No	40/12	1; 2	2
MUKHERJEE 2008 ⁵⁷		$47.92 \pm 11.42; 40/31; 22.46 \pm 3.76^{b}$	No	10/24	2	m
ORR 2009 ⁵⁸	~	$53.00 \pm 2.00; 6/10; 31.90 \pm 0.90^{\circ};$ $55.00 \pm 3.00; 5/5; 31.10 \pm 0.90^{\circ}$	No	80/12	1; 2	m
PAULSEN 2008 ³⁵	2	$33.66 \pm 13.56; 13/7; 25.50 \pm 3.19^{b}$	No	80/4	2	4
PAULSEN 2010 ³⁶	2	51.00 ± 5.56 ; 15/6; 28.66 \pm 4.77 ^b	No	80/2 days	2	4
RAJA-KHAN 2011 ⁵⁹	~	38.80	No	40/6	1; 2	m
RIAHI 2006 ⁶⁰	2	$64.30 \pm 8.90; 71/18; 28.40 \pm 4.40^{b}$	Yes	80/6	2	5
SZRAMKA 2007 ²¹	2	63.40 ± 7.17 ; 8/2; 29.39 $\pm 4.53^{b}$	No	80/4	2	5
TERAMOTO 2014 ⁶¹	~	49.00 ± 8.80; 8/19; 24.00 ± 3.30 ^b ; 50.00 ± 9.60, 18/10; 25.00 ± 3.70 ^b	No	10/12	1; 2	5
ZALESKI 2014 ⁶²	-	44.10 ± 0.80 ; 203/216; 26.40 $\pm 0.20^{3}$; 44.0 + 1.50, 104/113, 26.50 + 0.45 ^a	No (n:400); Yes (n:19)	80/74	C • F	ſ
ZOU 2018 ⁶³	, -	59.30 ± 7.28 ; $45/30$; $23.80 \pm 3.15^{\circ}$;	Yes	20/48	1:2	, г о
2	-	61.21 ± 7.59 ; $37/38$; 25.21 ± 4.72^{b}	2	2	1)
NORMOTENSIVE						
RENKE 2010 ⁶⁴	2	34.20 ± 6.94; 7/7; ND	Yes	40/12	2	c
VRTOVEC 2005 ¹⁵	~	67.00 ± 13.00; 41/35; ND 67.00 ± 13.00; 41/35, ND	Yes	10/12	1; 2	2
NORMOTENSIVE AND HYI	PERLIPIDAEMIC					
HAMAAD 2005 ¹⁴	~	67.00 ± 10.00; 19/3; ND ^b ; 66.00 ± 10.00; 7/2; ND ^b	Yes	40/12	1; 2	Μ
HORWICH 20115	~	$47.00 \pm 14.00; 5/9; 31.00 \pm 7.00^{a};$ $49.00 \pm 17.00; 10/2; 31.00 \pm 6.00^{a}$	Yes	3/12	1; 2	N
KADOGLOU1 201065	-	64.76 土 7.31; 30/35; ND ^b	Yes	10 or 20/48	-	£
KADOGLOU2 2010 ⁶⁵	-	63.24 ± 6.76; 30/36; ND ^b	Yes	80/48	-	ĸ
MELENOVSK 2003 ²⁷	2	47.00 ± 8.00; 29/0; 27.80 ± 2.00 ^b	No	10/10	~	c
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Article ¹	RCT ² 1. Parallel 2. Cross-over	Age ³ ; <i>n</i> (men/women) ⁴ ; BMI ⁵ (atorvastatin and placeboor total population)	Use of antihyper tensive	Dose/weeks ⁶	Group 1. Basal 2. Placebo	Jadad Scale
HYPERTENSIVE AND NOR	40LIPIDAEMIC					
MANISTY 2009 ⁶⁷	1	79.00; 127/15; 28.50 ± 4.00 ^b	Yes	10/72	2	ſ
MARTIN-VENTURA 2008 ⁶⁸	~	$70.00 \pm 7.00; 21/5; ND^3$	No	20/4	-	ĸ
HYPERTENSIVE AND HYPE	RLIPIDAEMIC					
FASSET 2010 ⁶⁹	~	60.20 ± 15.10 ; $80/43$; 28.50 ± 6.00^{b} ; 60.30 ± 15.20 ; $44/21$; 28.60 ± 6.10^{b}	Yes	10/144	1; 2	Ŋ
FASSET 2010 ⁷⁰	1	$63.55 \pm 15.60; 16/16; 28.50 \pm 5.55^{b}$	Yes	10/90	1; 2	5
FOGARI 2004 ⁷¹	2	56.30 ± 5.10 ; 22/23; ND ^b	Yes	20/12	. 	ĸ
KANAKI 2013 ⁷²	~	$59.70 \pm 8.80; 12/13; 29.40 \pm 4.30^{b};$ $58.80 \pm 10.80; 12/13; 29.60 \pm 3.80^{b}$	Yes	10/26	1; 2	Μ
KANAKI 2012 ⁷³	~	$59.70 \pm 8.90; 12/13; 29.40 \pm 4.30^{b};$ $58.80 \pm 10.80; 12/13; 29.60 \pm 3.80^{b}$	Yes	10/26	1; 2	Μ
KOH 2011 ¹¹	2		No	20/8	-	ĸ
MAGEN 2004 ⁷⁴	-	54.10 ± 13.50 ; $8/7$; 27.90 ± 1.80^{b} ; 51.40 ± 12.80 ; $7/9$; 27.70 ± 2.10^{b}	Yes	20/8	1; 2	M
RAISON 2002 <mark>75</mark>	4	56.10 ± 9.50; 7/4; 29.30 ± 3.50 ^b	Yes	10/12	-	5
HYPERTENSIVE						
FERRIER 2002 ⁷⁶	2	60.00 ± 14.00; 18/4: ND ^b	No	80/12	2	S
GOMES 2010 ¹⁶	2	$54.00 \pm 16.00; 9/4; 26.70 \pm 1.00^{b}$	Yes	20/3	2	Ŋ

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Article ¹	Lineage	Age ² and/or body weight ³	Dose/weeks ⁴	n ⁵
STANDARD DIET-FED RATS				
CRESPO 2015 ⁷⁷	Male Sprague—Dawley rats	4/120–125	10/4	10
FIORE 2011 ⁷⁸	Male Wistar rats	ND/185	30/6	10
KISHI 2008 ²⁴	Male SHR-SP rats	15/ND	50/4	5
KISHI 2003 ²⁰	Male Wistar Kyoto rats	15/ND	50/4	5
MARUMO 2001 ⁷⁹	Male Sprague—Dawley rats	8/ND	2/4 days	8
MOHAMMADI 2013 ⁸⁰	Male Wistar rats	ND/280-300	20/4	5
MANICKAVASAGAM 2007 ⁸¹	Male Sprague—Dawley rats	ND/250	2/3 days	8
MONDO1 2006 ⁸²	Male Sprague—Dawley rats	ND/180-240	30/2	10
MONDO2 2006 ⁸³	Male Sprague—Dawley rats	ND/180-240	30/2	10
MONDO3 2006 ⁸⁴	Male Sprague—Dawley rats	ND/180-260	30/2	10
OKAMURA 2014 ⁸⁵	Male Sprague—Dawley rats	5/ND	10/8	8
QUIDGLEY 2014 ⁸⁶	Male Sprague—Dawley rats	4/ND	10/4	10
SARATH 2014 ⁸⁷	Male Wistar rats	ND/100-120	10/4	15
SUBRAMANI 2009 ⁸⁸	Male Wistar rats	ND/ND	10/48, 24, and 2 hours	5
TOTOSON 2013 ⁸⁹	Male Wistar rats	ND/275-299	10/2	8
SPONTANEOUSLY HYPERTENSIV	e rats (Shr)			
CHANG-JIANG 2003 ⁹⁰	Male SHR	118 ± 3	-	6
CHEN 2018 ⁹¹	Male SHR	$11/254 \pm 5$	10/6	8
DOYON1 2011 ⁹²	Male SHR	11/ND	50/3	8
DOYON2 2011 ⁹²	Male SHR	11/ND	50/6	12
FANG1 2019 ⁹³	Male SHR	16/ND	10/6	8
FANG2 2019 ⁹³	Male SHR	16/ND	25/6	8
FANG3 2019 ⁹³	Male SHR	16/ND	50/6	8
GENG1 2010 ⁹⁴	Male SHR	16/ND	10/8	6
GENG2 2010 ⁹⁴	Male SHR	16/ND	25/8	6
GENG3 2010 ⁹⁴	Male SHR	16/ND	50/8	6
HUANG 2020 ⁹⁵	Male SHR	ND/210–265	10/8	8
ITO 2010 ⁹⁶	Male SHR	5/ND	20/8	6
KANG1 200797	Male SHR	18/115–130	50/10	6
KANG2 2007 ⁹⁸	Male SHR	8/108–132	50/10	6
LU1 2016 ⁹⁹	Male SHR	36/ND	10/12	10
LU2 2016 ¹⁰⁰	Male SHR	36/ND	10/12	8
WASSMANN 2001	Male SHR	18/ND	50/4	10
YUAN 2020 ¹⁰²	Male SHR	16/ND	50/8	10
ZHAO 2010 ¹⁰³	Male SHR	8/ND	50/12	8
SPONTANEOUSLY HYPERTENSIV	E RAIS STROKE-PRONE (SHR-SP)		a /a	
HAYASHI1 2004 ¹⁰⁴	Male SHR-SP	9/120–125	3/3	33
HAYASHI2 2004 ¹⁰⁴	Male SHR-SP	9/120–125	30/3	33
KISHI 2003 ²⁰	Male SHR-SP	15/ND	50/4	5
	Male SHR-SP	15/ND	50/4	5
KISHI 200922	Male SHR-SP	ND/280-340	20/4	5
KISHI 2012 ¹⁰⁵	Male SHR-SP	12-14/350-425	20/4	5
MASON 2015	Male SHR-SP	7-9/250-270	20/5	29–64
HIGH-SALI DIET-FED RATS (8% N		7/510	20/47	10
AKAHORI 2014	Salt-sensitive male Dani rats	7/ND	20/16	10
		12/ND	10/10	12
HIGH-SALI DIET-FED RATS (4% N	IaCI)		2014	10
FIORE 2011/*	Male VVistar—Hokkaido rats	ND/185	30/6	10
	Mala Samarua - Da		30/10	۲ ک
	Male Sprague—Dawley rats		30/6	6
	Male Sprague—Dawley rats		30/10	ŏ
	Male Semerue Devular met		30/0	ъ г
ZHOU 2014	i™ale sprague—Dawley rats	6/IND	15/6	5

Table 2 Baseline characteristics of the preclinical study population.

Table 2 Continued

Article ¹	Lineage	Age ² and/or body weight ³	Dose/weeks ⁴	n ⁵
SURGICALLY HYPERTENSIV	E RATS			
GUIMARAES 2015 ¹¹²	Male Wistar Rats	ND/250-300	50/8	8
GUIMARÃES 2013113	Male Wistar Rats	ND/180-200	50/8	7
DIABETIC RATS				
CRESPO 201577	Male Sprague—Dawley rats	4/120–125	10/4	10
QUIDGLEY 2014 ⁸⁶	Male Sprague—Dawley rats	4/ND	10/4	10
PATEL1 2010 ¹¹⁴	Male Sprague—Dawley rats	ND/229	20/8	6
PATEL2 2010 ¹¹⁴	Male Sprague—Dawley rats	ND/230	40/8	6
HYPERLIPIDAEMIC RATS				
BEZEK 2017 ¹¹⁵	Male hereditary hypertriglyceridemic rats	12-16/240-260	50/4	8
PARVIN 2019 ¹¹⁶	Male Wistar Rats	ND/180	40/4	8
SOTNIKOVA1 2012 ¹¹⁷	Male Prague hereditary hypertriglyceridemic rats	ND/44	3/8	8
SOTNIKOVA2 2012 ¹¹⁷	Female Prague hereditary hypertriglyceridemic rats	ND/44	3/8	8
KNEZL 2017 ¹¹⁸	Male hereditary hypertriglyceridemic rats	$12-16/373 \pm 18$	50/4	8
DEXAMETHASONE-INDUC	ED HYPERTENSIVE RATS			
MONDO1 2006 ⁸²	Male Sprague—Dawley rats	ND/180-240	30/2	10
MONDO2 2006 ⁸³	Male Sprague—Dawley rats	ND/180-240	30/2	10
MONDO3 2006 ⁸⁴	Male Sprague—Dawley rats	ND/180-260	30/2	10

¹Author, year of publication (Reference); ²age (weeks); ³body weight (g); ⁴mg.day⁻¹/weeks orally; ⁵sample number per group. ND, not determined.

The baseline characteristics of the populations from studies included in the meta-analyses are shown in Table 1 and Table 2.

The quality analysis of the RCT showed that most articles were considered of high quality, and only one was of low quality (*Table 1*). Considering baseline characteristics and other sources of bias from preclinical studies, the quality analysis indicated that this systematic review had a low risk of bias. However, for most of the questions evaluated, the risk of bias in preclinical studies was uncertain, which suggested that it should not be overlooked (Supplementary material online, *Table S3*).

In general, the heterogeneity analysis of the RCT showed greater homogeneity in the results after stratification of the primary studies, as there was a decrease in l^2 and an increase in the *P* value for Cochran's Q statistical test (*Figure 2*). In preclinical studies, despite considerable heterogeneity (>75%) in the meta-analysis, most primary studies demonstrated a decrease in SBP (*Figure 3*).

Considering the whole set of studies (overall effect of atorvastatin), the meta-analysis of parallel RCT showed that atorvastatin induces significant reduction of BP. In fact, atorvastatin reduced the SBP with mean difference (MD) of -1.62 mmHg [95% confidence interval (CI) -3.26 to 0.02] compared with placebo (Figure 2) and with MD of -3.00 mmHg [95% CI -5.71 to -0.29] compared with baseline (Table 3). The atorvastatin effect on SBP compared with placebo was small and on the threshold of statistical significance (P = 0.05). Atorvastatin also reduced the DBP, without changes in the MBP and HR, compared with placebo and baseline (Table 3). The absence of statistical significance in MBP may be related to the small number of trials (n = 4) and, therefore, to the sample size (Table 3). The meta-regression coefficient showed that the correlation between LDL-cholesterol changes vs. SBP changes induced by atorvastatin was not statistically significant compared with baseline and to placebo (Table 4). Similar meta-regression results were found for DBP vs. baseline and vs. placebo (Table 4).

The meta-analysis of the global effect of the crossover RCT showed that atorvastatin did not significantly affect SBP when compared with

placebo (*Table 3*). However, when compared with baseline, atorvastatin indeed reduced the SBP with MD of -4.31 mmHg [95% CI -6.68 to -1.95], but it did not reduce the HR (*Table 3*). In addition, atorvastatin had no effects in low-frequency and high-frequency (LF/HF) band ratio and high-frequency (HF) band when compared with placebo, but there were only two trials for these analyses, and their sample sizes were small (*Table 3*).

In the normotensive and normolipidaemic groups, the metaanalysis of parallel RCT showed that atorvastatin does not affect SBP and MBP, both compared with placebo and baseline (Figure 2; Table 3). However, atorvastatin reduced DBP with MD of -1.36 mmHg [95% Cl -2.44 to -0.28] compared with placebo, but it did not affect DBP compared with baseline (Table 3). The meta-regression coefficient showed that the correlations between LDL-cholesterol changes vs. SBP or DBP changes induced by atorvastatin compared with baseline or to placebo were not statistically significant (Table 4). In addition, the meta-analysis of cross-over RCT showed that, in normotensive and normolipidaemic individuals, atorvastatin did not change the HRV in the time domain in the parameters: SDNN, and root mean square of successive differences between normal heart beats (RMSSD) compared with baseline (Table 3). However, when compared with placebo, atorvastatin increased the RMSSD with MD 4.47 milliseconds [95% CI-0.01 to 8.96], without increasing the SDNN. However, the low number of trials must be pointed (Table 3).

In normotensive and hyperlipidaemic individuals, the meta-analysis of parallel RCT showed that atorvastatin reduced SBP with MD -10.90 mmHg [95% CI -21.44 to -0.35] compared with placebo (*Figure 2*) and with MD -7.41 mmHg [95% CI -11.18 to -3.65] compared with baseline (Table 3), but it did not decrease DBP when compared with placebo or baseline, nor did it decrease baroreflex sensitivity compared with baseline (*Table 3*).

In hypertensive and hyperlipidaemic individuals, the meta-analysis of parallel RCT showed that atorvastatin reduced the SBP with MD -3.05 mmHg [95% Cl -5.62 to -0.49] compared with placebo



(Figure 2) and with MD -2.99 mmHg [95% CI -5.20 to -0.79] compared with baseline (*Table 3*), and the DBP compared with placebo and baseline (*Table 3*). Atorvastatin did not induce a significant difference in MBP, however there was a low number of trials (*Table 3*). In this group of hypertensive and hyperlipidaemic individuals, the meta-analysis of crossover RCT also showed that atorvastatin reduced the SBP with MD -4.42 mmHg [95% CI -6.79 to -2.04] and DBP when compared with baseline (*Table 3*). In hypertensive individuals, atorvastatin did not induce significant differences in SBP when compared with placebo (*Table 3*).

The meta-analysis of preclinical studies showed that atorvastatin reduced the SBP in high-salt (4% NaCl) diet-fed rats with MD -27.70 mmHg [95% Cl -41.60 to -13.80], surgically hypertensive rats with MD -55.11 mmHg [95% Cl -65.64 to -44.58], diabetic rats with MD -26.59 mmHg [95% Cl -37.68to -15.50], dexamethasone-induced hypertensive rats with MD -10.14 mmHg [95% Cl -12.29 to -7.99], hyperlipidaemic rats with MD -22.62 mmHg [95% Cl -36.15 to -9.08], SHR-SP with MD -13.46 mmHg [95% Cl -26.12 to -0.80] and SHR with MD -31.06 mmHg [95% Cl -39.36 to -22.77], without affecting the SBP in standard diet-fed control rats (*Figure 3*). The meta-regression coefficient showed that the reducing effect of atorvastatin on SBP occurred independently of changes in LDL-cholesterol levels in SHR (*Table 4*). In addition, atorvastatin reduced the DBP and MBP in SHR-SP (*Table 3*) and did not induce significant differences in DBP in hyperlipidaemic rats and in MBP in SHR, in very high-salt (8%) diet-fed rats and in standard diet-fed control rats. Atorvastatin also reduced the HR in SHR with MD -13.36 mmHg [95% CI -23.96 to -2.76], but not in SHR-SP and standard diet-fed control rats (*Table 3*).

Discussion

The main finding of this meta-analyses of RCT was that atorvastatin reduces BP in hypertensive individuals, independently of hyperlipidaemia. The meta-regression clarified that the hypotensive effect of atorvastatin occurs independently of LDL-cholesterol level changes. In addition, atorvastatin reduced SBP in hyperlipidaemic individuals when compared with baseline and placebo, with or without hypertension. Concordantly, a meta-analysis of preclinical studies showed

	At	orvastatin			Placebo			Mean Difference	Mean Difference	
A Study or Subgroup	Mean [mmH	g] SD[mmHg	g] Tota	Mean [mmH] SD [mmHg] Tota	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	
Fasset1, 2010 (10mg/day by 36 months)	138	.8 2	4 4	6 137	.4 23.1	43	3 2.4%	1.40 [-8.39, 11.19]		
Fasset2, 2010 (10mg/day by 36 months)	147	.6 20	.2 10	6 148	.3 22.1	1 18	3 1.2%	-0.70 [-14.92, 13.52]	• •	
Hamaad, 2005 (40mg/day by 3 months)	11	18 1	4 1:	2 12	25 21	1 5	9 1.0%	-7.00 [-22.84, 8.84]	• •	
Horwich, 2011 (10mg/day by 3 months)	10	02 1	8 9	9 11	6 12	2 9	9 1.2%	-14.00 [-28.13, 0.13]	•	
Joyeux-Faure, 2014 (40mg/day by 3 months)	121.2	23 9.6	8 2	5 127.4	6 12.77	26	4.8%	-6.23 [-12.43, -0.03]	• • •	
Kanaki, 2012 (10mg/day by 26 weeks)	141	.6 7.	.6 2	5 147	.8 6.8	3 25	5 7.9%	-6.20 [-10.20, -2.20]		
Kanaki.2013 (10mg/day by 26 weeks)	14	17	7 2	5 15	i0 7	25	5 8.2%	-3.00 [-6.88, 0.88]		
Kukliska1, 2010 (80mg/day by 3 months)	12	24	2 3	9 12	8 4	1 17	7 12.3%	-4.00 [-6.00, -2.00]		
Magen, 2004 (20mg/day by 2 months)	150	.9 6.	.8 1	5 151	.1 7.4	1 16	6.3%	-0.20 [-5.20, 4.80]		
Manisty, 2009 (10mg/day by 18 months)	14	11 1	1 7:	3 14	2 12	2 59	8.0%	-1.00 [-4.97, 2.97]		
Mukheriee, 2008 (10mg/day by 6 months)	116.3	32 6.	.4 2	9 114.3	6.32	2 28	9.3%	1.98 [-1.32, 5.28]		
Orr. 2009 (80mg/day by 3 months)	12	24 1	16 10	6 12	4 4	1 10	3.1%	0.00 [-8.22, 8.22]		-
Rhaia Khan, 2011 (40mg/day by 6 weeks)	11	12 13	2 1	9 111	4 8.8	3 11	1 2.3%	0.60 [-9.47, 10.67]		-
Teramoro, 2014 (10mg/day by 3 months)	12	2 1	2 2	7 11	8 10) 28	5.2%	4.00 [-1.85, 9.85]		
Vrtovec 2005 (10mg/day by 3 months)	11	10 1	0 3	9 11	0 14	1 37	7 5.6%	0.00 [-5.50, 5.50]		
Zaleski 2014 (80mg/day by 6 months)	115	3 90	14 203	2 114	7 883	217	7 12.7%	0.60 [-1.21.2.41]		
Zou 2018 (20mg/day by 12 months)	120	6 11	5 7	5 132	7 11 5	2 74	5 8 5%	-3 10 [-6.83 0.63]		
200, 2010 (2011grday by 12 months)	125			102			0.070	-0.10[-0.00, 0.00]		
Total (95% CI)			683	2		653	100.0%	-1.62 [-3.26, 0.02]	•	
Heterogeneity: Tau ² = 4.65; Chi ² = 32.39. df = 1	16 (P = 0.009):	l ² = 51%							1. 1. 1. 1	+
Test for overall effect: Z = 1.93 (P = 0.05)									-10 -5 0 5 Atorvastatin Placebo	10
	A	torvastatin			Placebo			Mean Difference	Mean Difference	
B Study or Subgroup	Mean [mmH	g] SD[mmH	g] Tota	al Mean (mmH	g] SD [mmHo	1 Tota	al Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Joveux-Eaure 2014 (40mg/day by 3 months)	121 :	23 96	68 2	5 127	16 127	7 2	6 9.0%	-6 23 [-12 43 -0 03]	+ +	
Kukliska1 2010 (80mg/day by 3 months)	1	24	2 3	9 1	28	4 1	7 19.7%	-4 00 [-6 00 -2 00]		
Mukheriee 2008 (10mg/day by 6 months)	116	32 6	4 2	9 114	34 63	2 2	8 15.9%	1 98 [-1 32 5 28]		
Orr. 2009 (80mg/day by 3 months)	1	24 4	16 1	6 1	24 0.0	4 1	0 6.2%	0.00 [-8.22, 8.22]		
Rhaia Khan 2011 (40mg/day by 6 weeks)	1	12 13	2	9 111	4 8	8 1	1 4.5%	0.60[-0.22, 0.22]		
Toramore 2014 (10mg/day by 2 months)	1	12 13	12 2	7 4	.4 0.	0 7	0 0.70/	4 00 [4 95 0 95]		
Zaloski, 2014 (20mg/day by 6 months)	115	3 00	04 20	2 114	7 99	3 20	2 20.2%	0.60[1.03, 3.03]		
Zou, 2018 (20mg/day by 12 months)	129	0.6 11	.5 7	5 132	.7 0.0	8 7	5 14.7%	-3.10 [-6.83, 0.63]		
Total (95% CI)			42	2		30	7 100 0%	-0.96 [-3.35 1.44]		
Hataraaasita Tau2 - 6 52 Chi2 - 21 52 df - 3	7 (D = 0.002).	2 - 070/	44	~		55	100.07	-0.50 [-5.55, 1.44]		
Test for overall effect: $Z = 0.78$ (P = 0.43)	7 (P = 0.003); 1	- = 07 %							-10 -5 0 5 Atorvastatin Placebo	10
	Ator	vastatin		P	acebo			Mean Difference	Mean Difference	
C Study or Subaroup	Aean [mmHq]	SD [mmHa]	Total	Mean [mmHq]	SD [mmHa]	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI	
Easset1 2010 (10mg/day by 36 months)	138.8	24	46	137.4	23.1	43	6.6%	1 40 [-8 39 11 19]		
Fasset2 2010 (10mg/day by 36 months)	147.6	20.2	16	148 3	22.1	18	3.2%	-0 70 [-14 92 13 52]	•	
Kanaki 2012 (10mo/day by 26 weeks)	141.6	7.6	25	147.9	6.8	25	32 0%	6 20 [10 20 -2 20]		
Kanaki, 2012 (Tomg/day by 20 weeks)	141.0	7.0	20	147.0	0.0	25	34.5%	2 00 1 6 99 0 991		
Manaki.2013 (Tomg/day by 26 weeks)	147	C 0	20	150	7.4	20	34.5%	-3.00 [-0.00, 0.00]		
Magen, 2004 (20mg/day by 2 months)	150.9	0.8	15	151.1	7.4	16	22.1%	-0.20 [-5.20, 4.80]		
Total (95% CI)			127			127	100.0%	-3.05 [-5.62, -0.49]	-	
Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 4.52$, $df = 4$	$(P = 0.34); I^2$	= 12%							-10 -5 0 5	10
Test for overall effect: Z = 2.33 (P = 0.02)									Atorvastatin Placebo	
	Atorva	astatin		Pla	cebo			Mean Difference	Mean Difference	
D Study or Subgroup Me	ean [mmHg]	SD [mmHg]	Total I	Mean [mmHg]	SD [mmHg]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hamaad, 2005 (40mg/day by 3 months)	118	14	12	125	21	9	44.3%	-7.00 [-22.84, 8.84]		
Horwich, 2011 (10mg/day by 3 months)	102	18	9	116	12	9	55.7%	-14.00 [-28.13, 0.13]	-	
Total (95% CI)			21			18	100.0%	10.90 [-21.44, -0.35]		
Heterogeneity: Tau ² = 0.00: Chi ² = 0.42 df = 1	$(P = 0.52) \cdot 1^2$	= 0%								
		- 10							-20 -10 0 10	20

Figure 2 Meta-analysis of the effect of atorvastatin on systolic blood pressure in parallel and randomized clinical trials compared with placebo: overall effect (A); normotensive and normolipidaemic (B); hypertensive and hyperlipidaemic (C) and normotensive and hyperlipidaemic (D).

that atorvastatin reduced the SBP in hypertensive rats, even without hyperlipidaemia.

The quality analysis of the RCT showed that most studies were considered of high quality, and only one was of low quality. High quality in the Jadad classification was obtained through adequate blinding and the description of the study as double-blind. Regarding the quality of preclinical studies, 50% of the questions on the SYRCLE scale had uncertain answers. Thus, it is not recommended that this tool be used to perform a global assessment of each individual study.

Previous meta-analyses demonstrated, by comparing intervention and control groups, that statin and atorvastatin, including combined therapy with amlodipine, reduced the mean SBP difference between baseline and end-of-treatment.^{40,41} The effect of atorvastatin on the DBP was less clear, because one study showed a decrease,⁴¹ and another showed only a tendency to decrease this parameter.⁴⁰ More recently, an association between the use of atorvastatin and decreases in BP was demonstrated through the reporting odds ratio (ROR) statistics.⁴² It has been previously suggested that the hypotensive effect of statin is greater in individuals with high BP and that it is not related to the decrease in serum cholesterol levels.⁴⁰ By contrast, Takagi et *al.*⁴³ reported that atorvastatin, alone or in combination with amlodipine, had an LDL-cholesterol-dependent effect on BP.⁴³ The present meta-regression shows that atorvastatin has an LDLcholesterol-independent effect on SBP and DBP reduction when compared with either baseline or placebo, in the overall population and in a normotensive-normolipidaemic subgroup. The limited number of studies did not allow us to perform a meta-regression among hyperlipidaemic individuals with and without hypertension.

In preclinical studies, atorvastatin reduced the SBP in high-salt (4%) diet-fed rats, genetically (SHR and SHR-SP), surgically and

Study or Subgroup	Mean [mmHg] SD	[mmHg] T	otal M	Contro an [mmHg] SD	n [mmHg] To	otal V	Veight	IV, Random, 95% CI	IV, Random, 95% CI	
FIORE, 2011 (30mg.kg by 6 weeks)	108	3	13	116	3	9	16.8%	-8.00 [-10.55, -5.45]	•	
JUNCOS, 2012 (50mg.kg by 7 weeks)	122	10.94	11	137	7.29	11	16.1%	-15.00 [-22.77, -7.23]		
ZHOU, 2003 (30mg.kg by 6 weeks)	152	4.89	6	205	17.14	6	14.4% -	53.00 [-67.26, -38.74]		
ZHOU, 2004.1 (30mg.kg by 10 weeks)	174	21.16	7	208	22.62	8	11.8% -	34.00 [-56.17, -11.83]		
ZHOU, 2014 (15mg.kg by 6 weeks) ZHOU 2, 2004 (30mg kg by 6 weeks)	152	4.89	6	205	17.14	6	14.4% -	53.00 [-67.26, -38.74] -11.00 [-24.14.2.14]		
Line of Line (conging by c means)	100	1.00		201	10.01	2 1990 - 19				
Total (95% CI)	8 df = 6 (P < 0.0000	1)- 12 - 0.2%	58			55 1	00.0% -	27.70 [-41.60, -13.80]	-	
Test for overall effect: Z = 3.91 (P < 0.000)1)	1), 1 = 32.70							100 -50 0 50 Atoprestatin Control	100
	Atovas	statin		Cont	rol			Mean Difference	Mean Difference	
Study or Subgroup	Mean [mmHg] S	D [mmHg]	Total	Mean [mmHg] S	D [mmHg]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
GUIMARAES, 2013 (50mg.kg by 8 weeks)	148	18.97	10	200	12.64	10	55.6%	-52.00 [-66.13, -37.87]		
GUIMARAES, 2015 (SUMB.kg by 8 weeks)	140	22.13	10	207	12.04	10	44.4%	-59.00 [-74.80, -43.20]		
Total (95% CI)			20			20	100.0%	-55.11 [-65.64, -44.58]	•	
Test for overall effect: Z = 10.26 (P < 0.00)	= 1 (P = 0.52); P = 0% 001)	6							-100 -50 0 50	100
	Atomas	tatio		Cont	rol			Maan Difforence	Moan Difference	
Study or Subgroup	Mean [mmHg] SI	D [mmHg]	Total I	Mean [mmHg] S	D [mmHg]	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	
CRESPO, 2015 (10mg.kg by 4 weeks)	100.91	16.28	10	116.52	12.04	10	23.1%	-15.61 [-28.16, -3.06]	-	
QUIDGLEY, 2014 (10mg.kg by 4 weeks) TIMIR 1, 2010 (20mg kg by 8 weeks)	100.9	16.28	10	116.53	12.04	10	23.1%	-15.63 [-28.18, -3.08]	-	
TIMIR.2, 2010 (20mg.kg by 8 weeks)	112.74	12.61	6	151.98	6.93	6	24.3%	-39.24 [-50.75, -27.73]		
Total (95% CI)			22			32	100.0%	26 69 1.37 69 45 501	•	
Heterogeneity: Tau ² = 97.59; Chi ² = 13.51	. df = 3 (P = 0.004); l ²	= 78%	34			32	100.0 %	-20.00 [-07.00, -10.00]		
Test for overall effect: Z = 4.70 (P < 0.000	01)								-100 -50 0 50 Atorvastatin Control	100
	Atorvas	tatin	_	Cont	trol			Mean Difference	Mean Difference	
Study or Subgroup	Mean [mmHg] SI	D [mmHg]	Total	Mean [mmHg] S	D [mmHg]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	
MONDO, 2006 (30mg.kg by 2 weeks) MONDO, 2006 (30mg.kg by 2 weeks)	119	4.74	10	133	6.32	10	26.9%	-14.00 [-20.78, -7.22] -11.00 [-14.16, -7.84]	-	
MONDO, 2006-2 (30mg.kg by 2 weeks)	124	4.74	10	135	1.89	10	26.9%	-11.00 [-14.16, -7.84]		
MONDO, 2006-2 (30mg.kg by 2 weeks)	129	1.89	10	137	3.16	10	37.4%	-8.00 [-10.28, -5.72]		
Total (95% CI)			35			40	100.0%	-10.14 [-12.29, -7.99]	•	
Heterogeneity: Tau ² = 1.86; Chi ² = 4.97, e	df = 3 (P = 0.17); l ² = 4	40%							-20 -10 0 10	20
Test for overall effect: Z = 9.24 (P < 0.00)	JU1) Atory:	astatin		Cor	ntrol			Mean Difference	Atorvastatin Control Mean Difference	
Study or Subgroup	Mean [mmHg]	SD [mmHg]	Total	Mean [mmHg]	SD [mmHg]	Tota	Weigh	IV, Random, 95% C	IV, Random, 95% CI	
BEZEK, 2017 (50mg.kg by 4 weeks)	113	19.79	8	124	19.79	8	3 16.6%	-11.00 [-30.39, 8.39	-	
KNEZL, 2017 (50mg.kg by 4 weeks) PARVIN 2019 (40mg kg by 4 weeks)	135.55	12.55	8	151.11	12.55	8	3 20.8% 3 18.1%	-15.56 (-27.86, -3.26 -58.13 (-75.04, -41.22		
SOTNIKOVA.1, 2012 (3mg.kg by 8 weeks	s) 115.7	4.27	8	134.3	18.69	8	3 20.3%	-18.60 [-31.88, -5.32		
SOTNIKOVA.1, 2012 (3mg.kg by 8 weeks SOTNIKOVA.2, 2012 (3mg.kg by 8 weeks	s) 115.7 s) 120.32	4.27 6.56	8 8	134.3 133.82	18.69 4.27	8	3 20.3% 3 24.2%	-18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08	-	
SOTNIKOVA.1, 2012 (3mg.kg by 8 weeks SOTNIKOVA.2, 2012 (3mg.kg by 8 weeks SOTNIKOVA.2, 2012 (3mg.kg by 8 weeks Total (95% CI)	s) 115.7 s) 120.32	4.27 6.56	8 8 40	134.3 133.82	18.69 4.27	8 8 40	3 20.3% 3 24.2% 0 100.0%	-18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08	↓	
SOTNIKOVA.1, 2012 (3mg,kg by 8 weeks SOTNIKOVA.2, 2012 (3mg,kg by 8 weeks SOTNIKOVA.2, 2012 (3mg,kg by 8 weeks Total (95% CI) Heterogeneity: Tau ² = 189,46; Chi ² = 24,7	s) 115.7 5) 120.32 9, df = 4 (P < 0.0001);	4.27 6.56 ; I² = 84%	8 8 40	134.3 133.82	18.69 4.27	8 40	3 20.3% 3 24.2% 0 100.0%	-18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08	-100 -50 0 50	100
SOTNIKOVA.1, 2012 (3mg.kg by 8 weeks SOTNIKOVA.2, 2012 (3mg.kg by 8 weeks SOTNIKOVA.2, 2012 (3mg.kg by 8 weeks Total (95% CI) Heterogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.01)	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);)	4.27 6.56 ; ² = 84%	8 8 40	134.3 133.82	18.69 4.27	40	3 20.3% 3 24.2% 0 100.0%	-18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08] -22.62 [-36.15, -9.08]	-100 -50 0 50 Atorvastatin Control	100
SOTNIKOVA 1, 2012 (3mg.kg by 8 weeks SOTNIKOVA 2, 2012 (3mg.kg by 8 weeks Total (95% CI) Heterogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 Study or Subgroup	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);) Atorvas Mean [mmHg] Si	4.27 6.56 ; I² = 84% statin D [mmHg]	8 8 40 Total	134.3 133.82 Con Mean [mmHg] \$	18.69 4.27 trol SD [mmHg]	40 Total	3 20.3% 3 24.2% 0 100.0%	 -18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 Mean Difference IV, Random, 95% Cl 	-100 -50 0 50 Atorvastatin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 weeks SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks Total (95% CI) Heterogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.01 Study or Subgroup HAYASHL1, 2004 (3mg,kg by 2 weeks)	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] Sl</u> 212	4.27 6.56 ; I ² = 84% statin <u>D [mmHg]</u> 19.79	8 40 <u>Total</u> 8	134.3 133.82 Con <u>Mean [mmHg] \$</u> 214	18.69 4.27 trol <u>SD [mmHg]</u> 16.97	40 40 Total	3 20.3% 3 24.2% 0 100.0% 1 Weight 1 29.3%	 -18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08] -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] 	-100 -50 0 50 Atorvastatin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks) Tota(195% (01) Heterogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001) Studyor Studgroup HAYASHI.1, 2004 (3mg,kg by 2 weeks) HAYASHI.2, 2004 (3mg,kg by 2 weeks)	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] Si</u> 212 203 173	4.27 6.56 ; ² = 84% ; tatin D[mmHg] 19.79 22.62 20 12	8 40 <u>Total</u> 8 8	134.3 133.82 Con <u>Mean (mmHg) \$</u> 214 214 214 214	18.69 4.27 trol 5D [mmHg] 16.97 16.97 13.41	40 Total 8 8	3 20.3% 3 24.2% 100.0% 100.0% 1 Weight 29.3% 26.5% 23.0%	 -18.60 [-31.88, -5.32 -13.50 [-18.92, -8.08] -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] -11.00 [-30.60, 8.60] -26.00 (-21.9, -4.81) 	-100 -50 0 50 Atorvastatin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks) Total (95% CI) Heterogeneity: Tau ² = 189.46; Ch ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1, 2004 (3mg,kg by 2 weeks) HAYASHI.2, 2004 (3mg,kg by 2 weeks) KISHI, 2008 (50mg,kg by 4 weeks)	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg]</u> SJ 212 203 173 173	4.27 6.56 tatin <u>D [mmHg]</u> 19.79 22.62 20.12 42.93	8 40 <u>Total</u> 8 5 5	134.3 133.82 Con Mean [mmHg] 5 214 214 199 211.2	18.69 4.27 trol 5D [mmHg] 16.97 16.97 13.41 21.46	40 40 Total 8 8 5 5	3 20.3% 3 24.2% 100.0% 100.0% 100.0% 29.3% 26.5% 23.9% 8.1%	 -18.60 [-31.88, -5.32] -13.50 [-18.92, -8.08] -22.62 [-36.15, -9.08] Wean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] -11.00 [-30.60, 8.60] -28.00 [-47, 19, -48.1] 12.43 [-29.44, 54.50] 	-100 -50 0 50 Alorvastalin Control Mean Difference IV, Random, 95% Cl	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks) Total (95% CI) Heterogeneity: Tau ² = 189,46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHL1, 2004 (3mg,kg by 2 weeks) HAYASHL2, 2004 (3mg,kg by 2 weeks) KISHI, 2009 (20mg,kg by 4 weeks) KISHI, 2009 (20mg,kg by 4 weeks)	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] 81</u> 212 203 173 223.63 166	4.27 6.56 tatin D[mmHg] 22.62 20.12 42.93 70	8 8 40 Total 8 8 5 5 29	134.3 133.82 Mean [mmHg] \$ 214 214 199 211.2 209	18.69 4.27 trol 5D[mmHg] 16.97 16.97 16.97 13.41 21.46 102.31	40 40 Total 8 8 5 5 29	 20.3% 24.2% 100.0% 100.0% 29.3% 26.5% 23.9% 8.1% 7.1% 	-18.60 [-31.88, -5.32] -13.50 [-18.92, -8.08] -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% CI -20.00 [-20.06, 16.06] -11.00 [-30.60, 8.60] -20.00 [-47.19, -48.1] 12.43 [-29.64, 54.50]	-100 -50 0 50 Alorvastatin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 week; SOTNIKOVA 2, 2012 (3mg,kg by 8 week; SOTNIKOVA 2, 2012 (3mg,kg by 8 week; Total (95% CI) Helerogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 Study or Subgroup HAYASHI 1, 2004 (3mg,kg by 2 weeks) KISHI, 2008 (50mg,kg by 4 weeks) KISHI, 2008 (50mg,kg by 4 weeks) KISHI, 2008 (50mg,kg by 4 weeks) MASON 1, 2015 (20mg,kg by 5 weeks) MASON 2, 2015 (20mg,kg by 5 weeks)	s) 115.7 s) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] Si</u> 212 203 173 223.63 166 178	4.27 6.56 tatin D[mmHg] 19.79 22.62 20.12 42.93 70 102.31	8 8 40 Total 8 8 5 5 5 29 29	134.3 133.82 Mean [mmHg] 4 214 199 211.2 209 211	18.69 4.27 trol 5D[mmHg] 16.97 16.97 13.41 21.46 102.31 107.7	40 40 Total 8 8 5 5 29 29	 20.3% 24.2% 100.0% 100.0% 29.3% 26.5% 23.9% 8.1% 7.1% 5.1% 	- 18.60 [-31.88, -5.32 - 13.50 [-18.92, -8.08] - 22.62 [-36.15, -9.08] Wean Difference IV, Random, 95% CI - 2.00 [-20.06, 16.06] - 26.00 [-47.19, -4.81] 12.43 [-29.84, -54.50] - 43.00 [-88.12, 2.12] - 33.00 [-87.07, 21.07]	-100 50 0 50 Atorvastalin Control Mean Difference IV, Random, 95% Cl	100
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SOTNIKOVA 1, 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneity: Tau ² = 189.46; Ch ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 Study or Subgroup HAYASHI.1, 2004 (3mg, kg by 2 weeks) HAYASHI.2, 2004 (3mg, kg by 2 weeks) KISHI, 2008 (20mg, kg by 4 weeks) MASON.1, 2015 (20mg, kg by 4 weeks) MASON.2, 2015 (20mg, kg by 5 weeks)	 i) 115.7 i) 120.32 g, df = 4 (P < 0.0001); i) Atorvas Mean [mmHa]. Si 212 203 173 223.63 166 178 i, df = 5 (P = 0.26); P = 	4.27 6.56 statin D[mmHg] 19.79 22.62 20.12 42.93 70 102.31	8 40 Total 8 8 5 5 29 29 29 84	134.3 133.82 Mean [mmHG] 5 214 214 214 199 211.2 209 211	18.69 4.27 trol 3D [mmHg] 16.97 16.97 13.41 21.46 102.31 107.7	40 Total 8 8 5 29 29 84	3 20,3% 3 24,2% 100.0% 100.0% 100.0% 29,3% 26,5% 23,9% 5,1% 100.0%	-18.60 [-31.88], -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 Mean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] -10.00 [-30.60, 8.60] -2.00 [-40.46, 45.60] -3.00 [-88.12, 2.12] -3.300 [-87.07, 21.07] -3.46 [-26.12, -0.80]	-100 -50 - 50 Abovastalin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneily: Tau ² = 189,46; Ch ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1, 2004 (3mg, kg by 2 weeks) HAYASHI.2, 2004 (3mg, kg by 2 weeks) KISHI, 2008 (20mg, kg by 4 weeks) MASON 1, 2015 (20mg, kg by 4 weeks) MASON 2, 2015 (20mg, kg by 5 weeks) Total (95% CI) Heterogeneily: Tau ² = 57.49; Ch ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04	b) 115.7 (c) 120.32 (c) 1	4.27 6.56 tatin D [mmHg] 19.79 22.62 20.12 42.93 70 102.31 = 23%	8 8 40 Total 8 8 5 5 29 29 29 84	134.3 133.82 Mean [mmHg] 5 214 214 199 211.2 209 211	18.69 4.27 trol 3D [mmHg] 16.97 13.41 21.46 102.31 107.7	8 40 Total 8 8 8 8 5 5 29 29 29 84	20.3% 24.2% 100.0% 100.0% 29.3% 26.5% 23.9% 8.1% 5.1% 5.1%	- 18.60 [-31.88, -5.32 - 13.50 [-38.92, -8.08 - 22.62 [-36.15, -9.08 Mean Difference IV, Random, 95% CI - 2.00 [-20.66, 16.06 - 11.00 [-30.60, 8.60 - 26.00 [-47.19, -4.81] - 24.3 [-29.44, 54.50 - 43.00 [-88.12, 2.12] - 33.00 [-87.07, 21.07] - 13.46 [-26.12, -0.80]	-100 -50 0 50 Aborvastalin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks) Total (95% CI) Heterogeneity: Tau" = 189,46; Chi ² = 24,7 Test for overall effect: Z = 3.27 (P = 0.001 Study or Subgroup HAYASHI.1, 2004 (3mg,kg by 2 weeks) HAYASHI.2, 2004 (3mg,kg by 2 weeks) KISHI, 2009 (20mg,kg by 4 weeks) KISHI, 2009 (20mg,kg by 4 weeks) MASON.2, 2015 (20mg,kg by 5 weeks) Total (95% CI) Heterogeneity: Tau" = 57.49; Chi ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04) Study or Subgroup	b) 115.7 b) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] Si</u> 203 173 223.63 165 178 df = 5 (P = 0.26); P = 0.26); P = 0.26) Atorvas Mean [mmHg] 1 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 1000 10	4.27 6.56 tatin D[mmHg] 19.79 22.62 20.12 42.93 70 102.31 = 23% astatin SD[mmHa]	8 8 40 <u>Total</u> 8 8 5 5 29 29 29 84 Total	134.3 133.82 Con Mean [mmHg] 5 214 214 214 219 211.2 209 211 211 209 211 211 Cor Mean [mmHg]	18.69 4.27 trol 3D[mmHg] 16.97 13.41 21.46 102.31 107.7 htrol SD[mmHa]	8 8 8 5 5 29 29 84 84	20.3% 24.2% 100.0% 100.0% 29.3% 26.5% 23.9% 26.5% 23.9% 5.1% 5.1% 100.0%	 -18.60 [-31.88] -5.32 -13.50 [-18.92, -8.08] -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% CI -20.00 [-20.06, 16.60] -20.00 [-47.19, -48.1] 12.43 [-29.45, 54.50] -43.00 [-88.12, 2.12] -33.00 [-87.07, 21.07] -13.46 [-26.12, -0.80] Mean Difference IV, Random, 95% CI 	-100 -50 0 50 Mean Difference IV, Random, 95% CI -100 -50 0 50 Atorvastatin Control Mean Difference V, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg,kg by 8 weeks SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks SOTNIKOVA 2, 2012 (3mg,kg by 8 weeks Total (95% CI) Heterogeneily: Tau ² = 189,46; Chi ² = 24,7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1, 2004 (3mg,kg by 2 weeks) KISHI, 2008 (50mg,kg by 4 weeks) KISHI, 2008 (50mg,kg by 4 weeks) KISHI, 2008 (20mg,kg by 4 weeks) MASON.1, 2015 (20mg,kg by 4 weeks) MASON.2, 2015 (20mg,kg by 5 weeks) MASON.2, 2015 (20mg,kg by 5 weeks) MASON.2, 2015 (20mg,kg by 5 weeks) Heterogeneily: Tau ² = 57.49; Chi ² = 6.53 Total (95% CI) Heterogeneily: Tau ² = 57.49; Chi ² = 6.04 <u>Study or Subgroup</u> CHANG-JIANG; 2003	b) 115.7 b) 120.32 9, df = 4 (P < 0.0001);) Mean [mmHg] 212 203 173 223.63 166 178 4.00722 Mean [mmHg] 1 Atorvas Mean [mmHg] 1 134.17	4.27 6.56 tatin D[mmHg] 19.79 22.62 20.12 42.93 70 102.31 * 23% statin SD[mmHg] 3.6	8 8 40 Total 8 8 5 5 5 29 29 29 84 84 70tal 6	134.3 133.82 Con <u>Mean [mmHg] 214</u> 214 214 219 211.2 209 211 211.2 209 211 211.2 209 211 211.2 209 211 211 211 211 211 211 211 211 211 21	18.69 4.27 so [mmHg] 16.97 13.41 21.46 102.31 107.7 so [mmHg] 3.78	8 8 8 29 29 84 84	20.3% 24.2% 100.0% 100.0% 29.3% 29.3% 29.3% 29.3% 29.3% 29.3% 29.3% 29.3% 20.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 1	-18.60 [-31.88] -5.32 -13.50 [-18.92, -8.08 -3.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 Mean Difference IV, Random, 95% CO, 16.06 -2.00 [-20.06, 16.06] -10.00 [-30.60, 8.60] -26.00 [-40.06, 16.06] -11.00 [-30.60, 8.60] -20.00 [-20.00 [-47.19, -4.81] 12.43 [-29.44, 54.50] -33.00 [-87.07, -21.07] -13.46 [-26.12, -0.80] Mean Difference IV, Random, 95% CC -38.83 [-43.01, -34.65	-100 -50 -50 Altorvastatin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.2, 2004 (3mg, kg by 2 weeks) HAYASHI.2, 2004 (3mg, kg by 2 weeks) KISHI, 2008 (50mg, kg by 4 weeks) KISHI, 2008 (20mg, kg by 4 weeks) MASON.1, 2015 (20mg, kg by 4 weeks) MASON.2, 2015 (20mg, kg by 5 weeks) MASON.2, 2015 (20mg, kg by 5 weeks) MASON.2, 2015 (20mg, kg by 5 weeks) Total (95% CI) Heterogeneity: Tau ² = 5.749; Chi ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04) <u>Study or Subgroup</u> CHANG-1, 2019 (10mg, kg by 5 weeks) FANG.1, 2019 (10mg, kg by 5 weeks) FANG.1, 2019 (10mg, kg by 5 weeks)	b) 115.7 b) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] SI</u> 212 203 173 173 166 178 400 400 178 186 178 186 178 186 178 186 178 186 178 186 178 186 178 186 178 186 178 186 186 186 186 186 186 186 18	4.27 6.56 .tatin D[mmHg] 22.62 20.12 42.93 70 102.31 = 23% astatin SD[mmHg] 3.66 19.79 20.62	8 8 40 <u>Total</u> 8 8 5 5 29 29 29 84 <u>Total</u> 6 8 8	134.3 133.82 Con Mean [mmHg] 2 214 214 214 219 211.2 209 211 Cor Mean [mmHg] 173 216	18.69 4.27 trol 5D [mmHg] 16.97 16.97 13.41 102.31 107.7 sD [mmHg] 3.78 16.97 3.78	8 40 Total 8 8 8 5 5 5 29 29 29 84 84 5 5 5 5 29 29 84 84	Weight 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0%	- 18.60 [-31.88, -5.32 - 13.50 [-18.92, -8.08 - 22.62 [-36.15, -9.08 - 22.62 [-36.15, -9.08 - 22.0 [-20.06, 16.06] - 11.00 [-30.60, 16.06] - 11.00 [-30.60, 16.06] - 12.00 [-47.09, -4.81] - 24.0 [-20.64, 15.00] - 43.00 [-88.12, -2.12] - 33.00 [-87.07, -21.07] - 13.46 [-26.12, -0.80] Mean Difference IV, Random, 95% C - 38.83 [-43.01, -34.66 - 29.00 [-47.06, -10.9] - 38.60 [-40.01, -34.66] - 29.00 [-47.06, -10.9] - 38.60 [-40.01, -34.66] - 29.00 [-47.06, -10.9] - 36.00 [-47.	-100 50 50 Alorvastalin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg, kg by 8 week; SOTNIKOVA 2, 2012 (3mg, kg by 8 week; SOTNIKOVA 2, 2012 (3mg, kg by 8 week; Total (95% CI) Heterogeneily: Tau ² = 189.46; Ch ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1, 2004 (3mg, kg by 2 weeks) KISHI, 2008 (20mg, kg by 4 weeks) KISHI, 2008 (20mg, kg by 4 weeks) MASON 2, 2015 (20mg, kg by 4 weeks) MASON 2, 2015 (20mg, kg by 4 weeks) Total (95% CI) Heterogeneily: Tau ² = 57.49; Ch ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04 <u>Study or Subgroup</u> CHANG-JIANG, 2003 CHANG-JIANG, 2003 FANG 3, 2019 (10mg, kg by 5 weeks) FANG 3, 2019 (10mg, kg by 5 weeks) FANG 3, 2019 (10mg, kg by 5 weeks)	b) 115.7 b) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmH6] Si</u> 212 203 173 122.83 166 178 (df = 5 (P = 0.26); I ² =) Atorva <u>Mean [mmH6] 1</u> 134.17 134.17 181 143	4.27 6.56 .tatin D[mmHg] 22.62 20.12 42.93 70 102.31 = 23% statin SD[mmHg] 9.23% statin SD[mmHg] 22.62 2.62 2.62 2.62 2.62 2.62 2.62 2.	8 8 40 7 0 8 8 5 5 29 29 29 84 84 7 0 6 8 8 8 8 8	134.3 133.82 Con <u>Mean [mmHig]</u> 214 214 199 211.2 209 211 209 211 209 211 713 216 216 218	18.69 4.27 50 [mmHg] 16.97 13.41 21.46 102.31 107.7 htrol <u>SD [mmHg]</u> 3.76 8.6.97 16.97 16.97	8 40 Total 8 8 8 5 5 5 29 29 84 84 8 4 8 8 8 8 8 8 8 8 8 8 8 8 8 8	Image: Weight	-18.60 [-31.88], -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 Mean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] -11.00 [-30.60, 8.60] -26.00 [-47.19, -48.1] 12.43 [-29.46, 54.50] -33.00 [-87.07, 21.07] -33.46 [-26.12, -0.80] Mean Difference IV, Random, 95% CI -38.8 [-43.01, -34.6] -38.8 [-43.01, -34.6] -30.00 [-57.63, -10.95, -52.1]	-100 -50 0 50 Aborvastatin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA.1.2012 (3mg,kg by 8 weeks) SOTNIKOVA.2.2012 (3mg,kg by 8 weeks) Total (95% CI) Heterogeneily: Tau" = 189,46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1.2004 (3mg,kg by 2 weeks) HAYASHI.2.004 (3mg,kg by 2 weeks) KISHI.2009 (20mg,kg by 4 weeks) MASON.1.2015 (20mg,kg by 4 weeks) MASON.2.2015 (20mg,kg by 5 weeks) MASON.2.2015 (20mg,kg by 5 weeks) MASON.2.2015 (20mg,kg by 5 weeks) Total (95% CI) Heterogeneily: Tau" = 57.49; Chi ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04) <u>Study or Subgroup</u> CHANG.JIANG.2003 FANG.1.2019 (10mg,kg by 6 weeks) FANG.2.2019 (25mg,kg by 6 weeks) FANG.3.2019 (25mg,kg by 6 weeks)	 i) 115.7 i) 120.32 i) 120.32 i) 120.32 i) 120.32 i) Atorvas Mean [mmHg] Si 212 203 173 223.63 166 178 166 i) Atorvas Mean [mmHg] 1 134.17 181 143 196 	4.27 6.56 tatin 19.79 22.62 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20	8 8 40 Total 8 8 8 5 5 29 29 29 84 84 5 6 8 8 8 8 10	134.3 133.82 Con <u>Mean [mmHg] 5</u> 214 214 199 211.2 209 211 219 211 219 211 213 216 216 216 218 218 218 218	18.69 4.27 50 [mmHg] 16.97 13.41 21.46 102.31 107.7 strol <u>SD [mmHg]</u> 3.78 16.97 16.97 16.97 16.97 26.29	E E E E E E E E E E E E E E E E E E E	Weight Weight 100.0% Weight 29.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 20.3% 21.3% 22.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.3% 23.	-18.60 [-31.88, -5.32] -13.60 [-31.88, -5.32] -13.60 [-18.92, -8.08] -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] -11.00 [-30.60, 8.60] -26.00 [-47.19, -4.81] 12.43 [-29.44, 54.50] -33.00 [-87.07, 21.07] -13.46 [-26.12, -0.80] Mean Difference IV, Random, 95% CI -33.83 [-43.01, -34.6] -38.3 [-43.01, -34.6] -30.00 [-57.63, -10.9] -35.00 [-56.52, 11 -75.00 [-76.55, 52.11 -9.00 [-28.24, 10.22	-100 -50 0 50 Alorvastalin Control Mean Difference IV, Random, 95% CI -100 -50 0 50 Alorvastalin Control Mean Difference IV, Random, 95% CI	100
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SOTNIKOVA 1, 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneily: Tau ² = 189.46; Ch ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1, 2004 (3mg, kg by 2 weeks) HAYASHI.1, 2004 (3mg, kg by 2 weeks) KISHI, 2008 (20mg, kg by 4 weeks) KISHI, 2008 (20mg, kg by 4 weeks) MASON 1, 2015 (20mg, kg by 4 weeks) MASON 2, 2015 (20mg, kg by 4 weeks) MASON 2, 2015 (20mg, kg by 4 weeks) Total (95% CI) Heterogeneily: Tau ² = 57.49; Ch ²² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04) <u>Study or Subgroup</u> CHANG-JANG, 2003 FANG 3, 2019 (20mg, kg by 6 weeks) FANG 3, 2019 (20mg, kg by 6 weeks) FANG 3, 2019 (20mg, kg by 6 weeks) GENG 1, 2010 (10mg, kg by 6 weeks) GENG 1, 2010 (10mg, kg by 6 weeks) GENG 3, 2010 (20mg, kg by 6 weeks) GENG 3, 2010 (20mg, kg by 6 weeks) GENG 3, 2010 (20mg, kg by 8 weeks) GENG 3, 2010 (20mg, kg by 8 weeks) IVANG 3, 2020 (10mg, kg by 8 weeks)	b) 115.7 b) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmH6] Si</u> 212 203 173 166 178 (df = 5 (P = 0.26); I ^a =) Atorva <u>Mean [mmH6] 1</u> 134.17 134.17 181 143 196 180 182 183 185 185 185 185 185 185 185 185	4.27 6.56 tatin D[mmHg] 19,79 22.62 20.12 42.93 70 102.31 * 23% * 23% * 3.6 19.79 22.62 28.28 * 19.79 22.62 28.28 * 19.79 * 23% * 19.79 * 23% * 19.79 * 23% * 23%	8 8 40 Total 8 8 5 5 29 29 29 84 84 Total 6 8 8 8 8 10 10 10 8 6 6 6	134.3 133.82 Con Mean [mmHg] 214 214 219 211.2 209 211 173 216 216 216 218 205 205 205 205 205 205	18.69 4.27 trol 5D [mmHg] 16.97 13.41 21.46 102.31 107.7 8D [mmHg] 3.78 16.97 16.97 16.97 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29	E E E E E E E E E E E E E E E E E E E	3 20.3% 1 Weight 1 29.3% 20.3% 26.5% 20.3% 23.9% 3 24.2% 1 20.3% 20.5% 23.9% 3 5.1% 1 Weight 3 5.6% 4 Weight 3 5.6% 4 Weight 5 9.6% 5 9.6% 5 9.6% 5 9.6% 5 9.6%	-18.60 [-31.88], -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% CI -2.01 [-20.66, 16.06] -10.01 [-30.60, 8.60] -20.01 [-47.19, -48.11] 12.43 [-29.46, 54.50] -33.00 [-87.07, 21.07] -33.00 [-87.07, 21.07] -33.83 [-43.01, -34.66] -38.83 [-43.01, -34.66] -39.00 [-47.06, -10.94] -35.00 [-58.52, 11 -90.00 [-28.24, 10.22] -20.00 [-28.49, -55.52] -31.00 [-48.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.27, -16.77] -30.00 [-28.52, -17.67] -30.00 [-28.52, -17.67] -30.00 [-28.52, -17.67] -30.00 [-28.52, -16.77] -30.00 [-28.52, -16.77] -30.00 [-38.52, -16.77] -30.00 [-38.52, -16.77] -30.00 [-38.52, -16.77] -30.00 [-38.52, -16.77] -30.00 [-38.5	-100 -50 - 50 Abovastalin Control Mean Difference IV, Random, 95% CI	100
SOTNIKOVA 1, 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2, 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneily: Tau" = 189,46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1, 2004 (3mg, kg by 2 weeks) KISHI, 2008 (20mg, kg by 4 weeks) MASON.1, 2015 (20mg, kg by 4 weeks) MASON.2, 2015 (20mg, kg by 4 weeks) MASON.2, 2015 (20mg, kg by 4 weeks) MASON.2, 2015 (20mg, kg by 4 weeks) Total (95% CI) Heterogeneily: Tau" = 57.49; Chi ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04) <u>Study or Subgroup</u> CHANG-JIANG, 2003 FANG, 1, 2019 (10mg, kg by 6 weeks) FANG, 2, 2019 (25mg, kg by 6 weeks) GENG, 2, 2010 (10mg, kg by 6 weeks) GENG, 2, 2010 (25mg, kg by 6 weeks) GENG, 2, 2010 (25mg, kg by 6 weeks) GENG, 2, 2010 (25mg, kg by 6 weeks) GENG, 2, 2010 (10mg, kg by 8 weeks) GENG, 3, 2001 (50mg, kg by 8 weeks) KANG, 1, 2007 (50mg, kg by 6 weeks) KANG, 1, 2007 (50mg, kg by 6 weeks) KANG, 2, 2007 (50mg, kg by 6 weeks) KANG, 2, 2007 (50m, kg by 10 weeks)	 i) 115.7 i) 120.32 i) 120.32 i) 120.32 i) 120.32 i) 120.32 i) Atorvas Mean [mmHg] Si 212 203 173 223.63 166 167 168 168 169 164.17 184 196 180 172 143 181 196 180 172 143 181 159 166.66 	4.27 6.56 tatin D[mmHg] 19.79 22.62 20.12 42.93 70 102.31 * 23% * 23% * 23% * 3.6 19.79 22.62 28.22 8 8 15.81 31.62 18 22.62 28.22 8 8 15.81 13.62 16.27 5.55	8 8 40 Total 8 8 5 5 5 29 29 29 29 84 84 8 8 8 8 8 8 10 10 10 10 8 6 6 6 6	134.3 133.82 Con Mean [mmHg] 5 214 214 199 211.2 209 211 173 216 216 215 205 205 205 205 205 205 205 205 205 20	18.69 4.27 trol 3D [mmHg] 16.97 13.41 21.46 102.31 107.7 5D [mmHg] 3.78 10.97 16.97 16.97 16.97 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29	E E E E E E E E E E E E E E E E E E E	1 20.3% 1 0.00.0% 1 Weight 29.3% 26.5% 20.3% 23.9% 20.5% 23.9% 3 24.2% 1 20.5% 1 25.5% 1 20.0% 1 23.9% 1 23.9% 1 100.0% 1 Weight 3 5.6% 0 6.4% 0 5.6% 0 6.5% 0 6.5% 0 5.9% 0 5.9% 0 5.9% 0 5.9% 0 5.9% 0 5.9%	-18.60 [-31.88], -5.32 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 Mean Difference IV, Random, 95% CI -2.00 [-20.06, 16.06] -11.00 [-30.50, 8.60] -26.00 [-47.19, -48.1] 12.43 [-29.44, 54.50] -3.00 [-87.07, 21.07] -33.00 [-87.07, 21.07] -33.46 [-26.12, -0.80] Mean Difference IV, Random, 95% CI -33.00 [-87.07, 21.07] -33.60 [-54.00, -15.4] -30.00 [-54.00, -15.4] -30.00 [-54.00, -15.4] -30.00 [-58.21, -21.2] -30.00 [-58.21, -7.90] -30.00 [-58.21, -7.90] -30.00 [-58.22, -1.30.0] -30.00 [-58.22, -1.30.0] -30.00 [-58.22, -1.30.0] -30.00 [-58.22, -1.30.7]	-100 50 50 Mean Difference IV, Random, 95% Cl -100 50 0 50 Altorvastatin Control Mean Difference IV, Random, 95% Cl	100
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4000 178 134.17 134.17 134.17 181 143 166 180 172 143 181 156 166 166 166 166 166 166 16	4.27 6.56 tatin D[mmHg] 22.62 20.12 42.93 70 102.31 * 23% astatin SD[mmHg] 3.6 19.79 22.62 20.12 42.93 70 102.31 * 23% astatin 85 (mmHg) 3.6 28.88 19.79 22.62 28.28 19.79 19.79 22.62 28.28 19.79 22.62 28.28 19.79 22.62 28.28 19.79 22.62 28.28 19.79 22.62 28.28 19.79 22.62 28.28 19.79 22.62 28.28 19.79 22.62 20.12 10.23 10.23 10.23 10.23 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 10.25 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SOTNIKOVA 1. 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2. 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneity: Tau ² = 189.46; Chi ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI. 2.004 (3mg, kg by 2 weeks) KISHI. 2008 (30mg, kg by 2 weeks) KISHI. 2008 (30mg, kg by 2 weeks) KISHI. 2008 (30mg, kg by 4 weeks) MASON.1. 2015 (20mg, kg by 4 weeks) MASON.2. 2015 (20mg, kg by 4 weeks) Total (95% CI) Heterogeneity: Tau ² = 57.49; Chi ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04) <u>Study or Subgroup</u> CHANG-JIANG, 2003 FANG.1. 2019 (10mg, kg by 5 weeks) FANG.2. 2019 (20mg, kg by 6 weeks) FANG.3. 2010 (20mg, kg by 6 weeks) TOJADI (2007, kg by 8 weeks) KANG.3. 2001 (50mg, kg by 10 weeks) YUAN, 2020 (50mg, kg by 10 weeks) YUAN, 2020 (50mg, kg by 10 weeks) YUAN, 2020 (50mg, kg by 10 weeks) TAIG.2. 2007 (50mg, kg by 10 weeks) YUAN, 2020 (50mg, kg by 10 weeks) TAIG.2. 2007 (50mg, kg by 12 weeks) TAIG.2. 2007 (50mg, kg by 12 weeks) Teat for overall effect: Z = 7.34 (P < 0.000	 a) 115.7 b) 120.32 c) f = 4 (P < 0.0001); b) Atorvas Mean [mmHg] Si 203 203 273 223.63 166 178 166 180 181 196 204 181 196 204 204 181 196 204 205 204 204 205 204 205 204 205 204 166.66 204 172 166 204 166.60 204 172 166 204 166.60 204 172 166 204 167 204 167 204 167 204 167 204 166 204 166 204 166 204 172 166 204 166 204 172 166 204 167 204 172 166 204 172 166 204 172 166 204 137 145 146 147 147 146 147 147 148 148 148 148 148 1	4.27 6.56 it if = 84% itatin D(mmHg) 22.62 20.12 20.12 42.93 70 102.31 * 23% astatin SD(mmHg) 3.6 19.79 22.62 20.12 42.93 70 102.31 * 23% astatin 5.5 18.97 31.62 18.97 31.62 33 001); I [‡] = 90° astatin	8 8 40 Total 8 8 5 5 29 29 84 84 5 5 29 29 84 84 8 8 8 8 8 8 8 8 10 10 0 10 8 6 6 6 6 8 8 10 10 10 10 10 10 10 10 10 10 10 10 10	134.3 133.82 Con Mean [mmHg] 2 214 214 219 211.2 209 211 211 209 211 211 209 211 211 209 211 211 209 211 211 209 211 211 212 209 211 211 212 209 211 213 214 209 211 214 209 211 214 209 211 214 209 211 214 214 214 209 211 214 209 211 214 214 214 214 214 214 214 214 214	18.69 4.27 trol 3D [mmHg] 16.97 13.41 21.46 102.31 107.7 htrol 3.78 16.97 16.97 10.97 25.29 25.29 25.29 10 4 2.36 5.55 15.81 18.97 25.59 10.87 25.59 10.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 16.97 10.97 10.97 16.97 16.97 10.97 16.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 10.97 1	E E E E E E E E E E E E E E E E E E E	3 20.3% 3 24.2% 0 100.0% 1 Weight 1 29.3% 1 26.5% 1 29.3% 1 26.5% 1 29.3% 1 26.5% 1 23.9% 1 26.5% 1 5.1% 1 00.0% 1 Weight 5 9.6% 3 5.6% 5 9.6% 5 9.4% 5 9.4% 5 9.4% 5 9.4% 5 9.4% 5 9.4% 5 9.3% 7.4% 9.5% 3 100.0%	-18.60 [-31.88], -5.32 -13.50 [-18.92, -8.08 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 -22.62 [-36.15, -9.08 -20.01 [-20.06, 16.06] -11.00 [-30.60, 18.06] -20.01 [-20.06, 16.06] -20.01 [-20.06, 16.06] -20.01 [-20.06, 14.06] -30.01 [-30.70, -10.71] -30.01 [-30.70, -20.07] -30.01 [-30.77, -21.07] -33.00 [-47.06, -10.94] -38.30 [-48.07, -79.07] -38.30 [-48.01, -34.64] -30.00 [-47.06, -10.94] -30.00 [-47.06, -10.94] -30.00 [-47.06, -10.94] -30.00 [-47.06, -10.94] -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41 -30.00 [-47.36], -32.41	-100 -50 - 50 Altorvastatin Control Mean Difference IV, Random, 95% CI -100 -50 - 50 Mean Difference IV, Random, 95% CI -100 -50 - 50 Mean Difference IV, Random, 95% CI -100 -50 - 50 Mean Difference IV, Random, 95% CI -100 - 50 - 50 Mean Difference IV, Random, 95% CI -100 - 50 - 50 Mean Difference	100 10
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-9.00 [-28.52, -21.10] -30.00 [-47.06], -15.34] -30.00 [-47.06], -15.34] -30.00 [-47.85], -22.11! -30.00 [-47.85], -23.11! -30.00 [-47.85], -23.11! -30.00 [-47.85], -23.11! -30.00 [-47.85], -23.11! -30.00 [-47.85], -23.11!	-100 -50 - 50 Alorvastalin Control Mean Difference IV, Random, 95% CI -100 -50 - 50 Alorvastalin Control Mean Difference IV, Random, 95% CI	100 10 10
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203, df = 13 (P < 0.000 Atorva Mean [mmHg] Mean [mmHg] 110 	4.27 6.56 title 4.27 4.27 4.27 19.79 22.62 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.12 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.22 20.23 20.22 20.23 20.22 20.23 20.22 20.23 20.22 20.23 20.22 20.23 20.22 20.33 20.12 20.22 20.33 20.12 20.22 20.33 20.12 20.22 20.33 20.12 20.22 20.33 20.12 20.22 20.33 20.12 20.22 20.22 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Chi ² = 129, Test for overall effect: <i>Z</i> = 7.34 (P < 0.000 <u>Study or Subgroup</u> CRESPO, 2016 (10mg, kg by 4 weeks) FIORE, 2011 (30mg, kg by 7 weeks) FIORE, 2011 (30mg, kg by 7 weeks) FIORE 2011 (30mg, kg by 7 weeks)	 a) 115.7 b) 120.32 c) 120.32 	4.27 6.56 statin D(mmHg) 19.79 22.62 20.12 42.93 70 102.31 * 23% astatin SD(mmHg) 31.62 18.75 18.97 31.62 18.97 31.62 18.93 33.00 19.79 31.62 33.00 19.79 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 19.79 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 18.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 31.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 33.62 33.97 34.62 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55 35.55	8 8 40 Total 8 8 5 5 29 29 29 84 Total 6 6 6 8 8 8 8 10 10 10 8 8 6 6 6 10 10 10 10 10 10 10 10 10 10 10 10 10	134.3 133.82 Con Mean [mmHg] 214 214 214 219 211.2 209 211 211.2 209 211 211 209 211 211 209 211 211 209 211 211 209 211 211 209 211 212 209 211 212 209 211 212 209 211 212 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 211 209 209 211 209 209 211 209 209 211 209 209 211 209 209 211 209 209 211 209 209 209 209 209 209 209 209 209 209	trol 5D [mmHg] 16.97 16.97 13.41 21.46 102.31 107.7 htrol 5D [mmHg] 25.29 25.29 25.29 10 4 2.36 5.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 18.97 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 18.97 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 25.55 15.81 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.97 18.	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166 119 120 119 120 120 121 	4.27 6.56 statin D[mmHg] 19,79 19,79 22,62 20,12 42.93 70 102.31 3.6 3.6 22,62 20,12 42.93 3.6 22,62 28,28 19,79 22,62 28,28 19,79 3.62 3.6 22,62 3.6 19,79 3.62 3.6 28,28 15,81 3.1,62 3.3 3.6 2,62 5,55 18,97 3.62 3.3 3.6 2,62 5,55 18,97 3.6 2,62 5,55 18,97 3.6 2,53 3.6 2,53 3.5 15,85 15,85 15,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 1,5,85 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-53.33 -50.01 [-10.44, -1.51.54<	-100 -50 -50 Altorvastalin Control Mean Difference IV, Random, 95% Cl -100 -50 - 50 Altorvastalin Control Mean Difference	100 10
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[-47.45.27, -16.7] -30.0 [-47.45.27, -16.7] -30.0 [-47.45.27, -16.7] <td>-100 -50 - 50 Altorvastatin Control Mean Difference IV, Random, 95% CI -100 -50 - 50 Mean Difference IV, Random, 95% CI -100 - 50 - 50 Mean Difference</td> <td></td>	-100 -50 - 50 Altorvastatin Control Mean Difference IV, Random, 95% CI -100 -50 - 50 Mean Difference IV, Random, 95% CI -100 - 50 - 50 Mean Difference	
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16.97 16.97 16.97 16.97 25.29 25.29 100 4 2.5.29 25.29 100 4 2.3.68 5.55 15.81 18.97 25.15 1.8,11 18.97 2.5.15 1.8,11 18.97 2.5.15 1.8,11 18.97 2.5.15 1.8,11 1.1,31 1.3,11 2.5.15 1.5,11 1.3,11 2.5.15 1.5,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 1.3,11 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-30.00 [-47.06, -154 -30.00 [-47.06, -33 -31.00 [-45.22, -16.77 -30.00 [-47.40, -35.52, 11 -30.00 [-47.40, -35.52, 11 -30.00 [-47.66, -33.53] -75.00 [-97.45, -52.11</td><td>-100 -50 - 50 Alorvestatin Control Mean Difference IV, Random, 95% CI -100 -50 - 50 Alorvestatin Control Mean Difference</td><td>100 100 100</td></tr<>	-18.60 [-31.88], -5.32 -13.50 [-18.92, -8.08 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08] Mean Difference IV, Random, 95% Cl -2.01 [-20.06, 16.06] -11.00 [-30.68, 16.06] -11.00 [-30.68, 16.06] -30.01 [-47.09, -48.1] 12.43 [-29.64, 54.50] -30.00 [-47.07, 21.07] -33.00 [-47.07, 21.07] -33.00 [-47.07, 21.07] -33.00 [-47.06, -109 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -104 -30.00 [-47.06, -154 -30.00 [-47.06, -154 -30.00 [-47.06, -154 -30.00 [-47.06, -154 -30.00 [-47.06, -33 -31.00 [-45.22, -16.77 -30.00 [-47.40, -35.52, 11 -30.00 [-47.40, -35.52, 11 -30.00 [-47.66, -33.53] -75.00 [-97.45, -52.11	-100 -50 - 50 Alorvestatin Control Mean Difference IV, Random, 95% CI -100 -50 - 50 Alorvestatin Control Mean Difference	100 100 100
SOTNIKOVA 1. 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2. 2012 (3mg, kg by 8 weeks) SOTNIKOVA 2. 2012 (3mg, kg by 8 weeks) Total (95% CI) Heterogeneily: Tau ² = 189.46; Ch ² = 24.7 Test for overall effect: Z = 3.27 (P = 0.001 <u>Study or Subgroup</u> HAYASHI.1. 2004 (3mg, kg by 2 weeks) KISHI. 2008 (20mg, kg by 4 weeks) MASON 1. 2015 (20mg, kg by 4 weeks) MASON 2. 2015 (20mg, kg by 4 weeks) MASON 2. 2015 (20mg, kg by 4 weeks) MASON 2. 2015 (20mg, kg by 4 weeks) Total (95% CI) Heterogeneily: Tau ² = 57.49; Ch ² = 6.53 Test for overall effect: Z = 2.08 (P = 0.04 <u>Study or Subgroup</u> CHANG-JANG, 2003 FANG 3. 2019 (20mg, kg by 5 weeks) FANG 3. 2019 (20mg, kg by 6 weeks) FANG 3. 2019 (20mg, kg by 6 weeks) FANG 3. 2019 (20mg, kg by 6 weeks) GENG 3. 2010 (20mg, kg by 6 weeks) CANG 3. 2007 (50mg, kg by 10 weeks) KANG 3. 2007 (50mg, kg by 10 weeks) KANG 3. 2007 (50mg, kg by 10 weeks) KANG 3. 2007 (50mg, kg by 10 weeks) Total (95% CI) Heterogeneity; Tau ² = 182.11; Ch ² = 129; Test for overall effect: Z = 7.34 (P < 0.000 <u>Study or Subgroup</u> CRESPO, 2016 (10mg, kg by 4 weeks) KISHI, 2008 (50mg, kg by 7 weeks) MONDO, 2006 - 2 (30mg, kg by 7 weeks) KISHI, 2008 (50mg, kg by 7 weeks) MONDO, 2006 - 2 (30mg, kg by 7 weeks) KISHI, 2008 (50mg, kg by 7 weeks) MONDO, 2006 - 2 (30mg, kg by 7 weeks) MONDO, 2006 - 2 (30mg, kg by 7 weeks) MONDO, 2006 - 2 (30mg, kg by 7 weeks) CHORSON 1. 2013 (10mg, kg by 7 weeks) CHORSON 1. 2013 (10mg, kg by 7 weeks) CHORSON 1. 2013 (10mg, kg by 7 weeks) CHORSON 2. 20	b) 115.7 b) 120.32 9, df = 4 (P < 0.0001);) Atorvas <u>Mean [mmHg] Si</u> 212 203 173 166 178 (df = 5 (P = 0.26); I ^a =) Atorva <u>Mean [mmHg] 1</u> 134.17 134.17 134.17 181 182 183 196 00, df = 13 (P < 0.000 01) Atorva 166.66 0) 204 172 166 03, df = 13 (P < 0.000 01) Atorva 166 166 03, df = 13 (P < 0.000 110 120 121 122 122 123 123 124 125 124 125 124 125 124 125 124 125 124 125 124 125 124 125 124 125 124 125 126 126 127 123 125 126 127 125 127 127 127 127 127 127 127 127	4.27 6.56 title 4.27 4.27 4.293 22.62 20.12 42.93 102.31 * 23% * 24% * 25% * 26% * 26% * 26% * 26% * 26% * 26% * 26% * 31.62% * 31	8 8 40 Total 8 8 5 5 5 5 29 29 84 Total 6 6 8 8 8 8 10 10 10 8 8 10 10 10 10 10 10 10 10 12 5 10 10 10 12 5 10 10 10 12 5 10 10 10 10 12 5 10 10 10 10 10 10 10 10 10 10 10 10 10	134.3 133.82 Con Mean [mmHg] 214 214 219 209 211.2 209 211.2 209 211.2 209 211.2 209 211.2 205 205 205 205 205 205 205 205 205 20	18.69 4.27 trol 5D [mmHg] 16.97 13.41 21.46 102.31 107.7 10.37 8D [mmHg] 3.78 16.97 16.97 16.97 16.97 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29 25.29	8 8 5 5 29 29 29 84 Total 8 6 6 6 6 8 113 113 1 13 1 13 1 13 1 13 1 13 1 13 1 14 1	3 20.3% 3 24.2% 3 24.2% 4 29.3% 1 26.5% 1 29.3% 1 29.3% 1 26.5% 1 26.5% 1 26.5% 1 26.5% 3 5.1% 1 00.0% 1 00.0% 1 00.0% 1 00.0% 3 5.6% 0 6.5% 3 7.5% 3 4.5% 3 100.0% 4 Weight 5 9.6% 3 7.5% 3 4.5% 3 100.0% 4 Weight 0 11.5% 0 16.6% 0 17.6% 0 17.6% 0 17.6% 0 17.6% 0	-18.60 [-31.88]5.32 -13.50 [-18.92, -8.08 -13.50 [-18.92, -8.08 -22.62 [-36.15, -9.08 -22.62 [-36.15, -9.08 -2.01 [-20.06, 16.06] -11.00 [-30.60, 16.06] -11.00 [-30.60, 16.06] -33.00 [-47.07, 19, -4.81] -33.00 [-87.07, 21.07] -33.00 [-87.07, 21.07] -33.00 [-87.07, 21.07] -33.46 [-26.12, -0.80] Mean Difference I/V, Random, 95% C -33.00 [-87.07, 21.07] -33.46 [-26.12, -0.80] Mean Difference I/V, Random, 95% C -35.00 [-44.60, -15.44 -35.00 [-44.60, -15.44 -35.00 [-44.60, -15.44 -35.00 [-44.80, -15.44 -30.00 [-46.95.22.11 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -31.00 [-62.95.22.13 -30.00 [-46.95.22.13 -30.00 [-46.95.22.13 -30.0	-100 -50 -50 Altorvastalin Control Mean Difference IV, Random, 95% CI Altorvastatin Control Mean Difference IV, Random, 95% CI Altorvastatin Control Mean Difference IV, Random, 95% CI IV, Random, 95% CI	100 100

Figure 3 Meta-analysis of the effect of atorvastatin on systolic blood pressure in preclinical studies: high-salt (4% NaCl) diet-fed rats (A); surgically hypertensive rats (B); diabetic rats (C); dexamethasone-induced hypertensive rats (D); hyperlipidaemic rats (E); spontaneously hypertensive rats stroke-prone (SHR-SP) (F); spontaneously hypertensive rats (SHR) (G) and standard diet-fed rats (H).

Number of Number participants: Effect size MD **Overall effect**, Heterogeneity Title of trials ATV/CTRL [95% CI] p value I² value Parallel and randomized clinical trials Overall effect Placebo control DBP 17 680/666 -1.39 [-2.14, -0.64] P = 0.0003 $l^2 = 0\%$ MRP $|^2 = 37\%$ 4 268/286 -1.44 [-4.33, 1.46] P = 0.33HR 132/128 0.99 [-1.67, 3.65] P = 0.47 $l^2 = 25\%$ 4 Basal control SBP 18 749/761 -3.00 [-5.71, -0.29] P = 0.03 $|^2 = 84\%$ P = 0.004 $|^2 = 52\%$ DBP 18 747/761 -1.82 [-3.08, -0.57] MBP -0.35 [-2.50, 1.80] P = 0.75 $|^2 = 14\%$ 4 264/264 $l^2 = 0\%$ HR 3 116/116 -0.68 [-2.39, 1.04] P = 0.44Normotensive and Normolipidaemic Placebo control DBP 8 422/412 -1.36 [-2.44, -0.28] P = 0.01 $|^2 = 22\%$ $|^2 = 70\%$ MBP 2 227/243 -1.22 [-6.82, 4.38] P = 0.67Basal control SBP $|^2 = 86\%$ 8 432/432 -1.38 [-5.02, 2.27] P = 0.46DBP 8 432/432 -1.70 [-3.56, 0.17] P = 0.08 $l^2 = 69\%$ MBP 2 $l^2 = 11\%$ 227/227 0.58 [-1.85, 3.01] P = 0.64Normotensive and Hyperlipidaemic Placebo control DBP 2 21/21 -2.37 [-7.80, 3.05] P = 0.39 $l^2 = 0\%$ Basal control SBP 3 143/143 P = 0.0001 $l^2 = 0\%$ -7.41 [-11.18, -3.65] $|^2 = 76\%$ DBP 3 143/143 -1.10 [-5,9, 3.76] P = 0.662 20/20 P = 0.99 $|^2 = 39\%$ Baroreflex 0.02 [-3.16, 3.19] Hypertensive and Hyperlipidaemic Placebo control $l^2 = 0\%$ DBP 5 127/137 -2.56 [-4.48, -0.63] P = 0.009MBP 2 P = 0.15 $l^2 = 0\%$ 41/43 -2.62 [-6.20, 0.96] Basal control SBP 5 $l^2 = 0\%$ -2.99 [-5.20, -0.79] P = 0.008123/135 DBP 5 123/135 -2.19 [-4.20, -0.19] P = 0.03 $|^2 = 0\%$ MBP 2 -2.78 [-6.54, 0.98] P = 0.15 $l^2 = 0\%$ 37/37 Cross-over and randomized clinical trials Overall effect Placebo control SBP 5 90/90 -0.91 [-4.64, 2.82] P = 0.63 $l^2 = 0\%$ LF/HF 2 23/23 -1.03 [-2.67, 0.61] P = 0.22 $l^2 = 0\%$ $l^2 = 0\%$ HF 2 23/23 6.13 [-71.41, 83.67] P = 0.88Basal control $l^2 = 0\%$ SBP 3 97/97 -4.31 [-6.68, -1.95] P = 0.00033 P < 0.00001 $l^2 = 0\%$ DBP 97/97 -3.79[-5.31, -2.27]2 -3.46 [-7.33, 0.42] P = 0.08 $|^2 = 0\%$ HR 56/52 Normotensive and Normolipidaemic Placebo control SDNN 4 75/75 4.39 [-1.20, 9.98] P = 0.12 $l^2 = 0\%$ $l^{2} = 0\%$ RMSSD 4 75/75 4.47 [-0.01, 8.96] P = 0.05Basal control SDNN 2 55/55 2.66 [-9.68, 15.01] P = 0.67 $l^2 = 0\%$ RMSSD 2 -0.80 [-7.49, 5.88] P = 0.81 $|^2 = 0\%$ 55/55

Table 3 Effect sizes of the overall and subgroup analysis from parallel or cross-over randomized clinical trials and preclinical studies.

Table 3 Continued

Title	Number of trials	Number of participants: ATV/CTRL	Effect size MD [95% Cl]	Overall effect, p value	Heterogeneity I ² value
Hypertensive and Hyperli	pidaemic				
Basal control					
SBP	2	87/87	-4.42 [-6.79, -2.04]	P = 0.0003	$l^2 = 0\%$
DBP	2	87/87	-3.86 [-5.39, -2.33]	P < 0.00 001	$l^2 = 0\%$
Hypertensive					
Placebo control					
SBP	2	35/35	-3.29 [-14.37, 7.79]	P = 0.56	$l^2 = 0\%$
Preclinical Studies					
Standard diet-fed rats					
MBP	6	46/46	1.72 [-4.61, 8.04]	P = 0.60	$l^2 = 38\%$
HR	5	34/34	8.15 [—19.47, 35.77]	P = 0.56	$l^2 = 68\%$
Hyperlipidaemic rats					
DBP	2	16/16	-7.04 [-18.20, 4.13]	P = 0.24	$l^2 = 0\%$
SHR-SP rats					
DBP	4	74/74	-14.69 [-26.92, -2.46]	P = 0.02	$l^2 = 0\%$
MBP	6	84/84	-25.92 [-40.96, -10.88]	P = 0.0007	$l^2 = 82\%$
HR	6	36/36	—11.79 [—31.50, 7.93]	P = 0.24	$l^2 = 15\%$
SHR rats					
MBP	4	32/32	-7.22 [-22.68, 8.23]	P = 0.36	$l^2 = 86\%$
HR	9	84/84	-13.36 [-23.96, -2.76]	P = 0.01	$l^2 = 62\%$
Rats fed high salt 8%					
MBP	2	22/22	-21.32 [-79.03, 36.39]	P = 0.47	$l^2 = 85\%$

ATV, atorvastatin; CI, confidence interval; CTRL, control; DBP, diastolic blood pressure; HF, high-frequency band; HR, heart rate; LF, low-frequency band; LF/HF, low-frequency and high-frequency band ratio; MBP, mean blood pressure; MD, mean difference; RMSSD, root mean square of successive differences between normal heart beats; SBP, systolic blood pressure; SDNN, standard deviation between normal intervals; SHR, spontaneously hypertensive rats; SHR-SP, spontaneously hypertensive rats stroke prone.

dexamethasone-induced hypertensive rats, and diabetic rats. In addition, in SHR rats, the meta-regression analysis showed that the reduction in SBP was independent of changes in LDL-cholesterol. Although it was not possible to perform a meta-regression in other animal models, they showed no plasma lipid changes, suggesting that the effect of atorvastatin is indeed independent of serum cholesterol levels.

These analyses did not allow us to clarify whether the BP-reducing effect of atorvastatin is dependent on the autonomic nervous system because the RMSSD, LF/HF, and HF were estimated only in normotensive individuals, and atorvastatin does not modulate SBP in this group. Further experiments are needed to clarify the involvement of the autonomic nervous system in the hypotensive effect of atorvastatin.

It is possible that atorvastatin regulates BP through peripheral vascular mechanisms. To the best of our knowledge, there is only one preclinical study evaluating simultaneously the effect of atorvastatin on BP and on these mechanisms.⁴⁴ Atorvastatin (50 mg.kg⁻¹ by 30 days) decreased SBP and angiotensin II-induced vasoconstriction and improved endothelial dysfunction in normocholesterolaemic SHR. Endothelial dysfunction was assessed by carbachol-induced vasorelaxation in aortic segments.44 These results are likely related to the ability of atorvastatin to increase the expression and activity of endothelial nitric oxide synthase (eNOS) in the aortas of rodents^{44,45} and block the negative regulation exerted by oxidized LDL-cholesterol on the eNOS mRNA and protein levels in vascular endothelial cells.⁴⁶ In patients with peripheral arterial disease (n = 30), a prospective study showed a decrease in plasma nitrite levels after 1 month of atorvastatin treatment, suggesting an increase in the bioavailability of nitric oxide (NO).⁴⁷ Several mechanisms may explain the increase in atorvastatin-induced NO, as follows. (1) Atorvastatin increases eNOS phosphorylation. In mouse aorta and myocardium, atorvastatin increased adenosine monophosphate-activated protein kinase (AMPK), acetyl-CoA carboxylase and eNOS phosphorylation. In cultured human vascular endothelial cells, atorvastatin-induced eNOS phosphorylation was inhibited by AMPK blockade.⁴⁸ (2) Atorvastatin decreased Ras homolog family member A (RhoA)/Ras homology (Rho) kinase signalling and activation of the nitric oxide/protein kinase G (PKG) pathway.45,49,50 In the myocardium of rats with heart failure, atorvastatin decreased mRNA and protein expression of RhoA/Rho kinase and increased the mRNA and protein expression of eNOS.⁴⁹ In the livers of cirrhotic rats, atorvastatin decreased Rho-kinase activity and the membrane association of RhoA and Ras (from Rat sarcoma virus) and increased eNOS mRNA and protein levels, eNOS phosphorylation, nitrite/nitrate, and the activity of PKG. In addition, incubation with atorvastatin dose-dependently relaxed the contraction of hepatic stellate cells, resulting in decreased portal pressure.⁵⁰ In mouse aorta and cultured endothelial cells, atorvastatin decreased isoprenoid-dependent Rho membrane translocation and GTP-binding activity. Atorvastatin increased Rho gene transcription but not Rho mRNA stability and led to the accumulation of non-isoprenylated Rho in the cytosol. Withdrawal of statin treatment restored the availability of isoprenoids and resulted in a massive membrane translocation and activation of Rho, causing downregulation of endothelial NO production.⁴⁵ (3) Atorvastatin promotes NO production by decreasing caveolin-1 expression in endothelial cells. This effect occurs with no changes in eNOS abundance and is reversed by providing mevalonate.⁵¹ (4)

Title	Covariata	Coofficient	Standard orror			Number of trials	P value
The	Covariate	Coemcient	Standard error	75% LOwer	33% Opper	Number of trials	r-value
Parallel and r	andomized clinical tria	als					
Overall Effec	t						
Placebo							
SBP	Intercept	-1.196	1.794	-4.712	2.321	11	0.51
	LDL-cholesterol	0.016	0.043	-0.068	0.100	11	0.70
DBP	Intercept	-1.714	0.637	-2.963	-0.466	11	0.007
	LDL-cholesterol	-0.005	0.018	-0.041	0.030	11	0.77
Basal							
SBP	Intercept	-0.012	5.036	-9.881	9.858	14	0.99
	LDL-cholesterol	0.067	0.087	-0.104	0.237	14	0.44
DBP	Intercept	-3.576	1.964	-7.426	0.274	14	0.07
	LDL-cholesterol	-0.032	0.036	-0.102	0.038	14	0.37
Normotensi	ve and normolipidaem	ic individuals					
Placebo							
SBP	Intercept	-1.376	2.625	-6.521	3.768	6	0.60
	LDL-cholesterol	-0.022	0.069	-0.158	0.114	6	0.75
DBP	Intercept	-1.720	0.583	-2.864	-0.577	6	0.003
	LDL-cholesterol	-0.032	0.027	-0.085	0.021	6	0.24
Basal							
SBP	Intercept	1.465	8.091	-14.393	17.323	7	0.86
	LDL-cholesterol	0.072	0.148	-0.219	0.363	7	0.63
DBP	Intercept	-1.166	2.458	-5.983	3.652	7	0.64
	LDL-cholesterol	0.025	0.051	-0.075	0.125	7	0.63
Preclinical tr	ials						
SHR							
SBP	Intercept	-27.475	11.653	-50.313	-4.636	9	0.02
	LDL-cholesterol	-0.055	0.937	-1.891	1.782	9	0.96

 Table 4
 Meta-regression analyses relating serum LDL-cholesterol differences to blood pressure changes induced by atorvastatin.

DBP, diastolic blood pressure; LDL-cholesterol, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; SHR, spontaneously hypertensive rats.

Atorvastatin decreases the expression of microRNAs 221/222 and increases NO levels and NOS3 mRNA expression.⁵² In human umbilical vein endothelial cells, the magnitude of the reduction of microRNAs 221 and 222 after atorvastatin treatment was correlated with the increment in NOS3 mRNA levels.⁵²

Additional vascular mechanisms may mediate the effects of atorvastatin on BP, as follows. (1) Reduction of endothelin-1.46 Atorvastatin decreased the pre-pro endothelin mRNA expression in a concentration- and time-dependent fashion and decreased immunoreactive endothelin-1 levels in bovine aortic endothelial cells. This inhibitory effect was maintained in the presence of oxidized LDL-cholesterol and blocked by mevalonate administration.⁴⁶ (2) Reduction in angiotensin II-induced vasoconstriction.44 Atorvastatin increased carbachol-induced vasodilation and decreased AT1 receptor mRNA and protein expression in the aortas of SHR.⁴⁴ (3) Reduction in angiotensin II-induced vascular fibrosis.53 In cultured vascular smooth muscle cells, atorvastatin inhibited angiotensin II-induced connective tissue growth factor (CTGF) production, an effect reversed by the mevalonate and geranylgeranylpyrophosphate (GGPP) supply. In cultured vascular smooth muscle cells, atorvastatin inhibited angiotensin II-induced Rho membrane localization and activation. Atorvastatin downregulated angiotensin II/CTGF-induced activation of p38 mitogen-activated protein kinase (MAPK) and c-lun N-terminal kinase (INK), as well as redox processes. In rats infused with angiotensin II, atorvastatin decreased aortic CTGF and Rho activation without modifying BP. Statins also decreased extracellular matrix overexpression caused by angiotensin II *in vivo* and *in vitro*.⁵³ (4) Reduction in serotonin-induced pulmonary artery smooth muscle cell mitogenesis and migration.⁵⁴ Atorvastatin dose dependently inhibited serotonin [5-hydroxytryptamine (5-HT)]-induced mitogenesis and migration of cultured bovine pulmonary artery smooth muscle cells. This inhibition was reversed by mevalonate and GGPP supplementation. Concordantly, atorvastatin inhibited 5-HT-induced cellular RhoA activation, membrane localization, and Rho kinase-mediated phosphorylation of the myosin phosphatase-1 subunit. Atorvastatin also inhibited Rho signalling in human embryonic kidney (HEK)293 cells in a GGPP-dependent manner. While 5-HT-induced Akt kinase activation was unaffected by atorvastatin, 5-HT-induced Extracellular signal-Related Kinase (ERK) nuclear translocation was attenuated in a GGPP-dependent fashion.⁵⁴

This study has some limitations. First, this study-level meta-analysis is not based on individual patient data. Second, stratification on several subgroups reduced considerably the number of studies and, thus, the power of the meta-analysis. In this regard, it was also not possible to group the studies by time and dose, because there was great heterogeneity regarding the treatment protocol. It was also not possible to perform meta-regression on the hypertensive and hyperlipidaemic group, due to the lack of data on serum lipid measurements. Finally, it was not possible to assess whether the antihypertensive effect of atorvastatin was related to changes in the autonomic nervous system, because the number of studies evaluating the effect of atorvastatin on HRV parameters is limited. Since SNS can activate the reninangiotensin-aldosterone system, including it in the searching algorithm could contribute to clarify the action mechanism of atorvastatin. All these limitations indicate the need to increase the number of primary studies with this focus.

In summary, the present meta-analyses of clinical and preclinical studies indicate that atorvastatin lowers BP by vascular mechanisms independent of LDL-cholesterol levels. Additional studies are needed to estimate the involvement of the autonomic nervous system in the BP-lowering effect of atorvastatin.

Supplementary material

Supplementary material is available at *European Heart Journal— Cardiovascular Pharmacotherapy* online.

Author contributions

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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