Statins and Blood Pressure

Prof. Maciej Banach
Head, Department of Hypertension,
Medical University of Lodz, PL
Small HDL subfractions are independent predictors of new onset hypertension? More potent than sdLDL?
The prevalence of hypercholesterolemia (≥ 190 mg/dl) in patients ≥65 years old in Poland

M – men, W – women

POLSENIOR Registry (Sept. 2011)
The changes of hipercholestrolemia prevalence in Poland in years 2002-2011

- 2002: 62%
- 2011: 61%
Hipercholesterolemia control in Poland (Natpol 2011 registry)

- NATPOL 18-79 18 mln
- POLSENIOR 80+ >1 mln

Hipercholesterolemia:
- Not diagnosed
- Diagnosed but not treated
- Ineffective therapy
- Effective therapy
The predicted changes of number of patients with hypercholesterolemia in Poland in years 2011-2035
The ratio of patients receiving statins in Poland

Distribution smoothed using kernel density estimator function; thin lines are local confidence limits.
The prevalence of hypercholesterolemia depending on the hypertension occurrence

<table>
<thead>
<tr>
<th>Age:</th>
<th>Total</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>56%</td>
<td>37%</td>
<td>56%</td>
</tr>
<tr>
<td>60-79</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Non-HA

Age:

18-39: 34% 60-79: 83%

18-39: 39% 60-79: 76%
Hypertension is the most common direct cause of death in the world

Dane wg. WHO 2011
The prevalence of hypertension in Poland

- M: 72%
- W: 78%
- All: 76%
- All over 65
The prevalence of hypertension (≥140/90 mmHg)

NATPOL 18-79  9,5 mln
POLSENIOR 80+  0,95 mln
ALL 18+  10,45 mln

32%
Hypertension control in Poland

Nadciśnienie tętnicze:
- Not diagnosed
- Diagnosed but not treated
- Ineffective therapy
- Effective therapy
The improvement of HT control in Poland in years 2002-2011

- **NATPOL 2002**
  - Effective therapy: 12%
  - Ineffective therapy: 42%
  - Diagnosed but not treated: 34%
  - Not diagnosed: 9%

- **NATPOL 2011**
  - Effective therapy: 26%
  - Ineffective therapy: 36%
  - Diagnosed but not treated: 30%
  - Not diagnosed: 9%
The predicted changes of number of patients with hypertension in Poland in years 2011-2035

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients (Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>9</td>
</tr>
<tr>
<td>2015</td>
<td>14</td>
</tr>
<tr>
<td>2020</td>
<td>19</td>
</tr>
<tr>
<td>2025</td>
<td>14</td>
</tr>
<tr>
<td>2030</td>
<td>19</td>
</tr>
<tr>
<td>2035</td>
<td>14</td>
</tr>
</tbody>
</table>
The factors that influenced the CAD mortality reduction in Poland in years 1991-2005

-4% - BMI
-2% - Diabetes
0% - Population Blood Pressure
39% - Population Cholesterol
11% - Smoking
10% - Physical Activity

Statin Evidence: Expanding Benefits

Acute coronary event

- No history of CAD
  - AFCAPS / TexCAPS / WOSCOPS
  - MIRACL

- Unstable CAD
  - t = 0
  - CARE/LIPID
  - 4S

- Stable CAD
  - 4 mo
  - 3 mo
  - 6 mo
  - HPS
  - HPS

Primary prevention

Secondary prevention

Hypertension
PATIENT POPULATION

CHD
n = 13,379 (65%)

- with MI 8510 (41%)
- no MI 4876 (24%)

CVD
n = 3280 (16%)

- with CHD 1458 (7%)
- no CHD 1822 (9%)

PVD
n = 6748 (33%)

- with CHD 4042 (20%)
- no CHD 2701 (13%)

Diabetes
n = 5963 (29%)

- with CHD 1978 (10%)
- no CHD 3982 (19%)

Hypertension
n = 8457 (41%)

- with CHD 5595 (27%)
- no CHD 2860 (14%)

Vascular event

Major coronary event
- Nonfatal MI
- Coronary death

Stroke

Revascularization

ANY MAJOR VASCULAR EVENT

Simvastatin better

Placebo better

27% risk reduction
$P < .0001$

25% risk reduction
$P < .0001$

24% risk reduction
$P < .0001$

24% risk reduction
$P < .0001$

Risk ratio and 95% CI

Statin Evidence: Heart Protection Study

Baseline level

LDL-C (mg/dL)
- <100 (2.6 mmol/L)
- ≥100 < 130
- ≥130 (3.4 mmol/L)

ALL PATIENTS

Risk Ratio and 95% CI

Simvastatin better

Placebo better

24% risk reduction

P < .0001

ASCOT is a multicenter, international trial that involves 2 treatment comparisons in a factorial design:

- A Prospective, Randomized, Open, Blinded End point (PROBE) design comparing 2 antihypertensive regimens

- A double-blind, placebo-controlled trial of atorvastatin 10 mg in a large prospective cohort of those hypertensive patients studied (lipid-lowering arm [ASCOT-LLA])

ASCOT is composed of almost 20,000 hypertensive patients with multiple risk factors for CHD

Eligibility criteria for ASCOT-LLA

- SBP > 160 mm Hg and/or DBP > 100 mm Hg (untreated) or SBP > 140 mm Hg and/or DBP > 90 mm Hg (treated)
- TC ≤ 250 mg/dL (≤ 6.5 mmol/L) and triglycerides ≤ 400 mg/dL (≤ 4.5 mmol/L)
- 40-79 years of age
- 3+ CVD risk factors
- No history of CHD

Blood Pressure Changes

- **Atorvastatin 10 mg**
- **Placebo**

**Baseline**: 164/95 mm Hg
**Treated**: 138/80 mm Hg

Statin Evidence: ASCOT-LLA

Statin Evidence: ASCOT-LLA

Primary Endpoint:
Nonfatal MI and Fatal CHD

Secondary Endpoint:
Fatal and Nonfatal Stroke

HR = 0.64 (0.50-0.83)
P = .0005
36% reduction

HR = 0.73 (0.56-0.96)
P = .0236
27% reduction

Secondary Endpoint: All CV Events and Procedures

Atorvastatin 10 mg Number of events 389
Placebo Number of events 486

HR = 0.79 (0.69-0.90)
P = .0005

21% reduction

Secondary Endpoint: All Coronary Events

Atorvastatin 10 mg Number of events 178
Placebo Number of events 247

HR = 0.71 (0.59-0.86)
P = .0005

29% reduction

Sept. 2002: The Data Safety Monitoring Board (DSMB) recommended that the double-blind, cholesterol-lowering study treatment arm be terminated since the results were outside of the stopping rules of the trial. The Steering Committee endorsed the recommendation of the DSMB, and the lipid arm was closed after a median follow-up period of 3.3 years.

ESC 2011: 11-year follow-up of ASCOT-LLA Trial

Sever P S et al. Eur Heart J 2011;eurheartj.ehr333
I admit statins may lower BP by some few mmHg – which is fine and different from NSAIDS, glitazones and some other drugs. But for me the most important thing with statins in hypertensive patients is the fact that they prevent the endpoints – the reason why we had to abort the atorvastatin arm of ASCOT prematurely – 36 and 27% reductions in MI and stroke, respectively.

Prof. Sverre E. Kjeldsen
Nov. 17th, 2009
Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study

Claudio Borghi, MD, Ada Dormi, MB, Maddalena Veronesi, MD, Zina Sangiorgi, MS, and Antonio Gaddi, MD, on behalf of the Brisighella Heart Study Working Party* Bologna, Italy

Background  Small studies have suggested that lipid-lowering strategies, and particularly statins, could influence blood pressure (BP) control. The aim of the present study was to evaluate the effect of different lipid-lowering strategies on BP control of subjects with hypercholesterolemia who were enrolled in the prospective, population-based, longitudinal Brisighella Heart Study.

Methods  A total of 1356 subjects with total cholesterol levels \(\geq 239\) mg/dL were randomly treated for 5 years (1988–1993) with 1 of these lipid-lowering regimens: low-fat diet, cholestyramine, gemfibrozil, or simvastatin. Participants were divided at baseline into 4 quartiles according to systolic BP level and examined for the percent change in systolic and diastolic BP during the 5 years of treatment.

Results  A significant decrease in BP was observed in the 2 upper quartiles of systolic BP (\(\geq 140\) mm Hg) and was greater in subjects treated with cholesterol-lowering drugs who also had a greater reduction in plasma levels of low-density lipoprotein cholesterol. The BP decrease was greater in patients treated with statin drugs and, among those treated with antihypertensive drugs, in subjects in the fourth quartile.

Conclusion  The use of lipid-lowering measures could significantly improve BP control in subjects with both hypercholesterolemia and hypertension. The reduction in BP seems to be enhanced in subjects treated with statins. (Am Heart J 2004;148:285–92.)
Percent change in systolic and diastolic blood pressure after 5 years of treatment with statins and non-statin lipid-lowering drugs in quartiles of baseline systolic blood pressure. *P < .001; †P < .005; ‡P < .0001 vs quartile 1; §P < .005 vs non-statin drugs.

Percent change in systolic and diastolic blood pressure after 5 years of treatment with lipid-lowering measures in quartiles of baseline systolic blood pressure and in subjects treated with anti-hypertensive drugs. *P < .001; †P < .005 vs quartile 1; ‡P < .005 vs non-statin drugs; §P < .005 vs lipid-lowering diet.

Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

Journal of Hypertension 2009
Time for new indications for statins?

Maciej Banach¹, Dimitri P. Mikhailidis², Sverre E. Kjeldsen³, Jacek Rysz⁴

¹ Department of Hypertension, Medical University of Łódź, Łódź, Poland
² Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London, London, U.K.
³ Department of Cardiology, Oslo University Hospital, Ullevaal, Oslo, Norway
⁴ Department of Nephrology, Hypertension and Family Medicine, Medical University of Łódź, Łódź, Poland

Source of support: none

Table 1. Recommendations of statin therapy in patients with hypertension [2,10–16,23,24].

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Target</th>
<th>Suggested treatment</th>
</tr>
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<tbody>
<tr>
<td>Patients with arterial hypertension</td>
<td></td>
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</tr>
</tbody>
</table>
| — with coronary artery disease (secondary prevention) | LDL <100 mg/dL    | — Simvastatin 40 mg  
|                                                  |                   | — atorvastatin 20–40 mg or other statins according to Roberts’ rule.                |
| Patients with arterial hypertension                | LDL <115 mg/dL    | Consider hypolipaemic treatment with statins (simvastatin 20 mg/atorvastatin 10 mg or other statins according to Roberts’ rule) |
| — without symptoms of CVD + from the group of high risk (10-year risk according to Framingham Score >20% or with moderate risk — about 15% with the elevated CRP) |                   |                                                                                     |
| Patients with arterial hypertension                | LDL <100 mg/dL    | — Atorvastatin 40 mg  
| — with type 2 diabetes with or without CVD        | optional therapy to achieve: LDL <70 mg/dL | — Simvastatin 40–80 mg                                                                 |
Statins in hypertensive patients
Recommendations

Systolic BP should be lowered to <140 mmHg (and diastolic BP <90 mmHg) in all hypertensive patients.

All hypertensive patients with established cardiovascular disease, or with type 2 diabetes, or with an estimated 10-year risk of cardiovascular death ≥5% (based on the SCORE chart) should be considered for statin therapy.

Antiplaque therapy in particular low dose aspirin, is recommended for hypertensive patients with cardiovascular disease.


The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)²

Authors/Task Force Members: Joep Perk (Chairperson) (Sweden)⁴, Guy De Backer¹ (Belgium), Helmut Gohlke¹ (Germany), Ian Graham¹ (Ireland), Željko Reiner² (Croatia), Monique Verschuren¹ (The Netherlands), Christian Albus¹ (Germany), Pascale Berlian¹ (France), Gudrun Boysen⁴ (Denmark), Renata Cifkova² (Czech Republic), Christi Deaton¹ (UK), Shah Ebrahim¹ (UK), Miers Fisher⁶ (UK), Giuseppe Germano¹ (Italy), Richard Hobbs²³⁷ (UK), Arno Hoes¹ (The Netherlands), Sehnaz Karadeniz⁴ (Turkey), Alessandro Mezzani¹ (Italy), Eva Prescott¹ (Denmark), Lars Ryden¹ (Sweden), Martin Scherder¹ (Germany), Mikko Syvänne⁶ (Finland), Wilma J.M. Scholte Op Reimer¹ (The Netherlands), Christiana Yrints¹ (Belgium), David Wood¹ (UK), José Luis Zamorano¹ (Spain), Faiez Zama¹ (France).
Mohammad Abdollahi (Iran/Canada), Ali Ahmed (USA), Wilbert S. Aronow (USA), Maciej Banach (PL), George Howard (USA), Jolanta Malyszko (PL), Dimitri P. Mikhailidis (UK), Krzysztof Narkiewicz (PL), Stephen Nicholls (USA/Australia), Shekoufeh Nikfar (Iran), Michael J. Pencina (USA), Roja Rahimi (Iran), Manfredi Rizzo (IT), Kausik K. Roy (UK), Jacek Rysz (PL), Peter P. Toth (USA), Nathan D. Wong (USA), Alberto Zanchetti (IT).
The effects of statins on blood pressure in normotensive or hypertensive subjects — A meta-analysis of randomized controlled trials

Maciej Banach a,*, 1, Shekoufeh Nikfar b,c, 1, Roja Rahimi d, Agata Bielecka-Dabrowa a, Michael J. Pencina e, Dimitri P. Mikhailidis f, Krzysztof Narkiewicz g, Jacek Rysz h, Kausik K. Ray i, Mohammad Abdollahi d, **Lipid and Blood Pressure Meta-Analysis Collaboration Group

a Department of Hypertension, Medical University of Lodz, Poland
b Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Iran
c Food and Drug Laboratory Research Center, Ministry of Health and Medical Education, Tehran, Iran
d Department of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
e Department of Biostatistics, Boston University, Harvard Clinical Research Institute, Boston, MA, USA
f Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London (UCL), London, UK
g Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland
h Department of Nephrology, Hypertension and Family Medicine, Medical University of Lodz, Poland
i Cardiovascular Sciences Research Centre, St George’s University of London, UK
Statins and blood pressure

- Scopus, PubMed, Web of Science (WoS), and the Cochrane Central Register of Controlled Trials were searched for studies that investigated the effect of statins on BP either in normotensive or in hypertensive subjects;
- Data were collected for the years 1966 to 2012 (up to January 2012);
- All randomized controlled clinical trials (RCTs) that investigated the effect of statins on BP were considered. Studies and abstracts that were presented at meetings were also considered;
- In some of these studies, BP was not measured as primary outcome and some were not designed to evaluate the effects of statins on BP; but BP was measured as a side or secondary outcome;
- We excluded studies with other factors (drugs other than hypotensives, concomitant diseases), which could have influenced BP;
- Changes in systolic and diastolic BP were the key outcomes of interest.
The effects of statins on blood pressure in normotensive or hypertensive subjects – a meta-analysis

9033 potentially relevant reports identified and screened for retrieval from electronic search
3540 PubMed
197 Cochrane Library
2286 Web of Science
3010 Scopus

7140 excluded because of duplication;
1841 reports excluded on basis of title and abstract

52 reports retrieved

34 reports excluded upon full-text search:
- n=9: crossover
- n=3: renal transplant recipients
- n=1: patients with cirrhosis
- n=1: cohort
- n=6: BP not measured
- n=8: measured BP not reported
- n=2: no placebo group
- n=3: standard deviation not reported
- n=1: BP measured during exercise test

18 eligible clinical trials included in the meta-analysis

5628 subjects (4692 normotensive and 936 hypertensive patients)
<table>
<thead>
<tr>
<th>Study</th>
<th>Sex (M/F)</th>
<th>Mean age (years)</th>
<th>Disease</th>
<th>Type of statin</th>
<th>Dosage per day</th>
<th>ΔSBP after therapy (no. of patients)</th>
<th>ΔDBP after therapy (no. of patients)</th>
<th>Concomitant therapy</th>
<th>Duration of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysandrovski et al., 2010 [21]</td>
<td>Statin 15/0 Placebo 16/0</td>
<td>Statin 39 Placebo 38.3</td>
<td>Hypertensive, hypercholesterolemic normolipemic with well-controlled hypertension</td>
<td>Simvastatin</td>
<td>40 mg</td>
<td>-6.0 ± 15.2 (15)</td>
<td>-5.0 ± 15.6 (16)</td>
<td>Anti-hypertensives</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Kuklinska et al., 2010 [22]</td>
<td>Statin 32/24 Placebo 53</td>
<td>Statin 53 Placebo 53</td>
<td>Hypertensive, normolipemic with well-controlled hypertension</td>
<td>Atorvastatin</td>
<td>80 mg</td>
<td>-5.7 ± 14.1 (39)</td>
<td>-1.0 ± 15.2 (17)</td>
<td>Anti-hypertensives</td>
<td>3 months</td>
</tr>
<tr>
<td>Marciu et al., 2010 [23]</td>
<td>Statin 141/105 Placebo 155/99</td>
<td>Statin 58.5 Placebo 58.3</td>
<td>Hypertensive, hypercholesterolemic</td>
<td>Pravastatin</td>
<td>40 mg</td>
<td>-18.1 ± 15.1 (199)</td>
<td>-19.6 ± 11.5 (198)</td>
<td>Hydrochlorothiazide Fosinopril</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Maility et al., 2009 [24]</td>
<td>Statin 70/8 Placebo 57/5</td>
<td>Statin 64 Placebo 64</td>
<td>Hypertensive, hypercholesterolemic, normolipemic, 25% diabetics</td>
<td>Atorvastatin</td>
<td>10 mg</td>
<td>-17.8 ± 22.1 (78)</td>
<td>-22.0 ± 21.3 (62)</td>
<td>Anti-hypertensives</td>
<td>3.3 years</td>
</tr>
<tr>
<td>Torelli et al., 2006 [25]</td>
<td>Statin 1764/285 Placebo 1769/288</td>
<td>Statin 58.5 Placebo 58.7</td>
<td>Had acute myocardial infarction, some hypertensive hypercholesterolemic with well-controlled hypertension</td>
<td>Pravastatin</td>
<td>40 mg</td>
<td>-2.4 ± 18.2 (2069)</td>
<td>-2.8 ± 18.1 (2057)</td>
<td>Anti-hypertensives</td>
<td>3 months</td>
</tr>
<tr>
<td>Kanbay et al., 2005 [26]</td>
<td>Statin 16/20 Placebo 11/13</td>
<td>Statin 56 Placebo 54.9</td>
<td>Hypertensive hypercholesterolemic with well-controlled hypertension</td>
<td>Atorvastatin</td>
<td>20 mg</td>
<td>-5.1 ± 15.2 (32)</td>
<td>2.0 ± 12.3 (17)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Ballashofer et al., 2005 [27]</td>
<td>Statin 14/6 Placebo 9/9</td>
<td>Statin 60 Placebo 61</td>
<td>Diabetic with or without hypertension</td>
<td>Cefazolin</td>
<td>0.2 mg</td>
<td>-1.6 ± 33.4 (20)</td>
<td>6.0 ± 21.3 (18)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Dresca et al., 2003 [28]</td>
<td>Statin 11/13 Placebo 11/12</td>
<td>Statin 56.6 Placebo 52.4</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Fluvastatin</td>
<td>80 mg</td>
<td>-3.8 ± 50.24</td>
<td>-4.0 ± 64.23</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>6 months</td>
</tr>
<tr>
<td>Mondillo et al., 2003 [29]</td>
<td>Statin 31/12 Placebo 30/13</td>
<td>Statin 67 Placebo 67</td>
<td>Hypertensive hypercholesterolemic with peripheral arterial disease, 57% diabetics, 48% hypertensive</td>
<td>Simvastatin</td>
<td>40 mg</td>
<td>1.5 ± 19.96</td>
<td>-1.0 ± 9.22</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>3 months</td>
</tr>
<tr>
<td>Jenkins et al., 2003 [30]</td>
<td>Statin 7/7 Placebo 11/5</td>
<td>Statin 57 Placebo 60.4</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Lovastatin</td>
<td>20 mg</td>
<td>-2.4 ± 10.5 (14)</td>
<td>-7.6 ± 10.8 (16)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>1 month</td>
</tr>
<tr>
<td>Lee et al., 2003 [31]</td>
<td>Statin 15/10 Placebo 16/9</td>
<td>Statin 52 Placebo 50</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Pravastatin</td>
<td>10 mg</td>
<td>-1.0 ± 14.9 (25)</td>
<td>0.0 ± 12.8 (25)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>6 months</td>
</tr>
<tr>
<td>Raflor et al., 2002 [32]</td>
<td>Statin 8/4 Placebo 7/4</td>
<td>Statin 56.8 Placebo 56.1</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Atorvastatin</td>
<td>10 mg</td>
<td>-2.7 ± 7.8 (12)</td>
<td>-6.9 ± 8.3 (11)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Nakamura et al., 2001 [33]</td>
<td>Statin 18/12 Placebo 20/10</td>
<td>Statin 58 Placebo 55</td>
<td>Hypertensive hypercholesterolemic normolipemic, diabetic with microalbuminuria</td>
<td>Cefazolin</td>
<td>0.15 mg</td>
<td>-4.0 ± 21.2 (30)</td>
<td>2.0 ± 15.9 (30)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>6 months</td>
</tr>
<tr>
<td>Borghi et al., 2003 [34]</td>
<td>Statin 3/0 Placebo 31/13</td>
<td>Statin 61.5 Placebo 59.4</td>
<td>Hypertensive, hypercholesterolemic hypercholesterolemic with microalbuminuria</td>
<td>Pravastatin</td>
<td>10 to 40 mg</td>
<td>-1.8 ± 27.9 (41)</td>
<td>-10.7 ± 25.0 (44)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>3 months</td>
</tr>
<tr>
<td>Bak et al., 1998 (1) [35]</td>
<td>Statin 53 Placebo 54/0</td>
<td>Statin 55 Placebo 54.6</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Pravastatin</td>
<td>20 mg</td>
<td>2.3 ± 16.1 (49)</td>
<td>0.6 ± 13.6 (51)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>6 months</td>
</tr>
<tr>
<td>Bak et al., 1998 (2) [35]</td>
<td>Statin 53 Placebo 55/0</td>
<td>Statin 55 Placebo 54.8</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Pravastatin</td>
<td>20 mg</td>
<td>-5.1 ± 17.6 (46)</td>
<td>-2.3 ± 15.6 (51)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>6 months</td>
</tr>
<tr>
<td>O'Callaghan et al., 1994 [36]</td>
<td>Statin 6/6 Placebo 6/6</td>
<td>Statin 58 Placebo 62</td>
<td>Hypertensive hypercholesterolemic normolipemic</td>
<td>Pravastatin</td>
<td>30 or 40 mg</td>
<td>-3.0 ± 24.9 (12)</td>
<td>-3.0 ± 21.5 (12)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Hommel et al., 1992 [37]</td>
<td>Statin 6/6 Placebo 6/3</td>
<td>Statin 41 Placebo 35</td>
<td>Hypertensive hypercholesterolemic normolipemic, diabetic with diabetic nephropathy</td>
<td>Simvastatin</td>
<td>10 or 20 mg</td>
<td>-5.0 ± 27.7 (12)</td>
<td>3.0 ± 26.2 (9)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>12 weeks</td>
</tr>
<tr>
<td>McDowell et al., 1991 [38]</td>
<td>Statin 15 Placebo 12</td>
<td>Statin NR Placebo NR</td>
<td>Hypercholesterolemic normolipemic</td>
<td>Simvastatin</td>
<td>40 mg</td>
<td>3.0 ± 27.4 (12)</td>
<td>7.0 ± 27.1 (12)</td>
<td>Anti-diabetics Anti-hypertensives</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

* Abbreviations: DBP: diastolic blood pressure; SBP: systolic blood pressure; NR: not reported; CCBs: calcium channel blockers, ACEIs: angiotensin-converting enzyme inhibitors.
* Values are presented as mean difference ± standard deviation.
Materially the effect was consistent with the overall effect when the largest study (n = 2069 in the statin group), single gender study, as well as trials with diabetic and non-diabetic patients were excluded from the analysis (p = 0.22, p = 0.93, p = 0.83 and p = 0.17, respectively).

The effect was maintained when trials with single gender, diabetic and non-diabetic patients were excluded from the analysis (p = 0.27, p = 0.32 and p = 0.41, respectively).
After excluding the largest study (n = 2069 in the statin group), a significant effect of statins on DBP was observed (the difference was \(-2.27\) mm Hg [95% CI: \(-4.1\) to \(-0.44\)] [\(-1.73\) mm Hg vs. \(0.54\) mm Hg — comparing statin and placebo groups, respectively; the weighted mean difference: \(-1.46\); 95% CI: \(-2.88\) to \(-0.04\), \(p = 0.04\)]. However, given that these observations are based on a relatively small number of patients in each of the studies included (e.g. \(n = 53\) normotensive patients in the statin subgroup in the largest study), as well as small difference of final DBP in this group of patients, these findings should be treated with caution.
The effect was maintained in this group when the largest (n = 253 in the statin group), with long-term follow-up (2.5 and 3.3 years), and single gender studies, as well as trials with diabetic and non-diabetic patients were excluded from the analysis (p = 0.13, p = 0.26, p = 0.13, p = 0.52, and p = 0.09, respectively). The lack of efficacy of statins was also observed when analyzing only trials with the duration of therapy longer than 2 years (the weighted mean difference was 1.28 with 95% CI = −1.33 to 3.89; p = 0.34).

The effect was maintained in this group when the largest (n = 253 in the statin group), with long-term follow-up (2.5 and 3.3 years) and single gender studies, as well as trials with diabetic and non-diabetic patients were excluded from the analysis (p = 0.40, p = 0.34, p = 0.39, p = 0.52, and p = 0.75, respectively). The lack of efficacy of statins was also observed when analyzing only trials with the duration of therapy longer than 2 years (the weighted mean difference was −0.11 with 95% CI = −1.27 to 1.05; p = 0.86).
Effect of statins on pulse pressure (PP) in normotensive patients

The weighted mean difference on pulse pressure (ΔPP) in normotensive patients from 11 included trials for statin therapy was 0.51 with 95% CI: −0.28 to 1.31 (p = 0.21).

Effect of statins on pulse pressure (PP) in hypertensive patients

The weighted mean difference on pulse pressure (ΔPP) in hypertensive patients for 8 included trials for statin therapy was 4.46 with 95% CI: −0.76 to 9.69 (p = 0.09).
In conclusion, our meta-analysis provides reliable evidence against any substantial BP-lowering effect of statins in both normotensive and hypertensive patients, suggesting that the established protective effects of these drugs on the CV system do not materially depend on reductions in BP.
Mean SBP in the statin group decreased by **2.62 mm Hg** (95% confidence interval [CI], 3.41 to 1.84; \(P<.001\)) and DBP by **0.94 mm Hg** (95% CI, 1.31 to 0.57; \(P<.001\)).

In studies including hypertensive patients, the decrease in blood pressures with statins was slightly greater (SBP, **3.07 mm Hg**; 95% CI, 4.00 to 2.15 and DBP, **1.04 mm Hg**; 95% CI, 1.47 to 0.61).
Comparison of the meta-analyses

9033 potentially relevant reports identified and screened for retrieval from electronic search
- 3540 PubMed
- 197 Cochrane Library
- 2286 Web of Science
- 3010 Scopus

7140 excluded because of duplication; 1841 reports excluded on basis of title and abstract

52 reports retrieved

34 reports excluded upon full-text search:
- n=9: crossover
- n=3: renal transplant recipients
- n=1: patients with cirrhosis
- n=1: cohort
- n=6: BP not measured
- n=8: measured BP not reported
- n=2: no placebo group
- n=3: standard deviation not reported
- n=1: BP measured during exercise test

18 eligible clinical trials included in the meta-analysis

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. CI indicate 95% confidence interval.