Supplementary Material for ‘Statins and Cardiovascular Primary Prevention in CKD: A Meta-Analysis’

Medline Literature Search Criteria

Database: Ovid MEDLINE(R) <2009 to September Week 2 2013>

Search Strategy:

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1 ckd.tw. (5810)

2 exp Renal Insufficiency, Chronic/ (15734)

3 'chronic kidney disease'.tw. (9308)

4 renal.tw. (65869)

5 nephro$.tw. (19522)

6 kidney*.tw. (55152)

7 1 or 2 or 3 or 4 or 5 or 6 (106014)

8 exp Lipids/ (135671)

9 hyperlipid?emi*.tw. (3852)

10 lipid*.tw. (66958)

11 dyslipid?emi*.tw. (6235)

12 hypercholesterol?emia.tw. (3467)

13 (triglyceride$ or cholesterol* or lipoportein$ or chylomicron$ or apoprotein$ or apolipoprotein$).tw. (41299)

14 (ldl or vdl or hdl).tw. (15247)

15 (ldl or vdl or hdl).tw. (15247)

16 8 or 9 or 11 or 12 or 13 or 14 or 15 (157387)

17 'HMG CoA reductase inhibitor$'.tw. (505)

18 'hydroxymethylglutaryl-CoA reductase inhibitor$'.tw. (20)

19 expHydroxymethylglutaryl-CoA Reductase Inhibitors/ (7986)

20 (cholesterol* adj2 lower*).tw. (2047)

21 (lipid* adj2 lowering*).tw. (2373)

22 17 or 18 or 19 or 20 or 21 (10929)

23 statin$.tw. (8466)

24 atorvastatin.tw.or 110862-48-1.rn. (1782)

25 cerivastatin.tw.or 145599-86-6.rn. (33)

26 fluvastatin.tw.or 93957-54-1.rn. (307)

27 lovastatin.tw.or 75330-75-5.rn. (565)

28 mevastatin.tw.or 73573-88-3.rn. (49)

29 pitavastatin.tw.or 147511-69-1.rn. (221)

30 pravastatin.tw.or 81093-37-0.rn. (671)

31 rosuvastatin.tw.or 287714-41-4.rn. (985)

32 simvastatin.tw.or 79902-63-9.rn. (2097)

33 (Lipitor or Torvast or Lipobay or Batcol or Lescol or Mevacor or Altocor or Altoprev or Compactin or Livalo or Pitava).tw. (87)

34 Pravachol.tw. (2)

35 Selektine.tw. (0)

36 Lipostat.tw. (1)

37 Crestor.tw. (12)

38 Zocor.tw. (13)

39 Lipex.tw. (1)

40 Vytorin.tw. (7)

41 Advicor.tw. (0)

42 Caduet.tw. (11)

43 Simcor.tw. (3)

44 Inegy.tw. (3)

45 23 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (11146)

46 fenofibrate.tw.or 49562-28-9.rn. (752)

47 gemfibrozil.tw.or 25812-30-0.rn. (265)

48 clofibrate.tw.or 637-07-0.rn. (112)

49 ciprofibrate.tw.or 52214-84-3.rn. (14)

50 bezafibrate.tw.or 41859-67-0.rn. (211)

51 cholestyramine.tw.or 11041-12-6.rn. (122)

52 colesevelam.tw.or 182815-44-7.rn. (97)

53 colestipol.tw.or 50925-79-6.rn. (6)

54 ezetimibe.tw.or 163222-33-1.rn. (721)

55 lopid.tw. (1)

56 jezil.tw. (0)

57 'gen-fibro'.tw. (0)

58 atromid*.tw. (1)

59 'atromid-s'.tw. (0)

60 modalim.tw. (0)

61 questran.tw. (3)

62 bezalip.tw. (0)

63 cholybar.tw. (0)

64 welchor.tw. (0)

65 cholestagel.tw. (1)

66 lodalis.tw. (0)

67 cholestabyl.tw. (0)

68 colestid.tw. (0)

69 zatia.tw. (0)

70 ezetrol.tw. (5)

71 niacin.tw.or 59-67-6.rn. (962)

72 exp Niacin/ (642)

73 'nicotinic acid'.tw. (457)

74 vitamin b3.tw. (47)

75 vitamin pp.tw. (2)

76 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 (3245)

77 45 or 76 (13480)

78 exp Clinical Trials as Topic/ or exp Randomized Controlled Trials as Topic/ (54930)

79 exp Controlled Clinical Trial/ (7630)

80 placebo$.tw. (29193)

81 random$.tw. (168305)

82 trial$.tw. (154660)

83 ('single blind*' or 'single-blind*').tw. (2500)

84 (double blind* or double-blind*).tw. (18207)

85 'comparative stud*'.tw. (10251)

86 exp Evaluation Studies/ (66930)

87 'evaluation stud*'.tw. (809)

88 'prospective stud*'.tw. (25368)

89 'cross-over stud*'.tw. (809)

90 'follow-up stud*'.tw. (5983)

91 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 (378602)

92 16 or 22 or 77 (164760)

93 7 and 91 and 92 (1741)

94 limit 93 to yr="2012 -Current" (509)

Event Definitions

AFCAPS - ‘fatal and nonfatal cardiovascular events‘

CARDS - ‘major cardiovascular disease’

JUPITER - ‘cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization’

MEGA - ‘all cardiovascular events‘

1. Definite fatal and nonfatal myocardial infarction (1 or more of the following criteria must be met):
   (a) Diagnostic ECG at the time of the event.
   (b) Ischemic cardiac pain (and/or unexplained acute left ventricular failure) and diagnostic enzymes.
   (c) Ischemic cardiac pain and/or unexplained acute left ventricular failure with both equivocal enzymes and equivocal ECG.
   (d) Diagnostic enzymes and equivocal ECG.
   (e) Angiographic evidence of occlusion of a major artery with appropriate ventriculographic wall motion abnormality where previous angiogram since randomization showed no such abnormality.
   (f) Postmortem examination.
2. Angina pectoris (stable or unstable, both of the following criteria must be met):
   (a) Ischemic cardiac pain, relieved by nitrates.
   (b) Equivocal ECG.
3. Ischemic stroke (1 of the following conditions must be met):
   (a) Rapid onset of focal neurologic deficit lasting at least 24 h or leading to death plus evidence from neuroimaging (computed tomography or magnetic resonance imaging) showing cerebral/cerebellar infarction or no abnormality, or postmortem examination showing cerebral and/or cerebellar infarction).
   (b) Rapid onset of global neurologic deficit (eg, coma) lasting at least 24 h or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.
   (c) Focal neurologic deficit (mode of onset uncertain) lasting at least 24 h or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.
4. Primary intracerebral hemorrhage (1 of the following conditions must be met):
   (a) Rapid onset of focal neurologic deficit lasting at least 24 h or leading to death, plus neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.
   (b) Rapid onset of global neurologic deficit (eg, coma) lasting at least 24 h or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and cerebellar hemorrhage.
   (c) Focal neurologic deficit (mode of onset uncertain) lasting at least 24h or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.

5. Transient ischemic attack:
    (a) Rapid onset of focal neurologic deficit or loss of monocular function lasting less than 24 h.
    (b) Negative neuroimaging.
6. ASO (atherosclerosis obliterans):
    (a) At least Fontaine Classification II.
    (b) Less than 0.9 (ankle brachial presssure index).
    (c) Positive vascular imaging.

PREVEND-IT - 'Hospitalization for: Nonfatal myocardial infarction and/or myocardial ischemia, Heart failure, Peripheral vascular disease, Cerebrovascular accident'

- Nonfatal myocardial infarction was defined as all nonfatal events accompanied by at least 2 of 4 of the following, which should include either new Q waves or enzyme elevation: (1) presence or history of typical or atypical chest pain of at least 15 minutes' duration; (2) ECG detection of ST-segment changes of at least 0.1 mV and/or T-wave inversion in at least 2 of 12 leads; (3) ECG detection of new significant Q waves in at least 2 of 12 leads; and (4) elevation of measurements of total creatine kinase (CK) and/or its isoenzyme CK-MB in at least 2 samples drawn within 48 hours of development of chest pain'
- Myocardial ischemia was defined as all ischemic events accompanied by the appearance of an ST-segment change of 0.1 mV or T-wave inversion in at least 2 of 12 leads, objective evidence by means other than ECG, or a need for revascularization (PTCA/CABG) that was severe enough to justify immediate hospital admission.
- Heart failure was regarded as heart failure for which hospital admission (hospitalization or documented outpatient clinic visit) was necessary and for which there was objective evidence of left ventricular dysfunction or for which specific medication (diuretics and ACE inhibitors) was needed.
- Peripheral vascular disease was diagnosed when PTA or bypass operation was necessary.
- Cerebrovascular accident was diagnosed when 1 of the following symptoms was present: recent onset of severe headache, loss of consciousness, or unequivocal objective findings of a localizing neurological deficit, duration 24 hours, and absence of other disease process– causing neurological deficit, such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder in combination with an abnormal CT scan or MRI scan.

WOSCOPS - 'cardiovascular mortality, nonfatal MI, coronary revasculization, or stroke'

- expanded outcome of trial
    - see below for further details

Coronary Heart Disease Events Definitions

AFCAPS - 'fatal and nonfatal coronary events'

- Fatal myocardial infarction or sudden cardiac death: The definition requires that there be no noncardiac cause of death and 1 of the following: fatal myocardial infarction-death within 28 days from the onset of symptoms of a definite acute myocardial infarction; witnessed unexpected sudden cardiac death-within 1 hour of symptoms; death occurring 1hour but ¡24 hours after collapse; and unwitnessed unexpected death, presumed sudden-must have confirming autopsy data or, if autopsy not performed, preceding history of CHD events or symptoms.
- Nonfatal myocardial infarction: Acute Q-Wave Myocardial Infarction - requires definitive electrocardiogram (ECG): Acute Non–Q-wave myocardial infarction—definitive ECG or, if equivocal, enzymes must be diagnostic. Non–Q-wave myocardial infarction includes myocardial infarctions reperfused by either mechanical or pharmacologic means providing there is supporting ECGs and enzyme data; Silent subclinical (remote) myocardial infarction—definitive ECG, or, if ECG is equivocal, focal wall motion abnormality consistent with myocardial infarction on rest echo or stress thallium (fixed defect) and on catheterization, a ¢50% stenosis in a major corresponding epicardial vessel. Participants who have had a cardiac catheterization as the first diagnostic test for presumed silent (or remote)

myocardial infarction are considered to have met criteria for an end point event if the catheterization findings indicate focal wall abnormalities consistent with myocardial infarction and ¢50% stenosis in a corresponding artery.

- Unstable angina:* New-onset exertional and/or accelerated or rest angina and requires at least 1 of the following: stress perfusion study- ¢1 mm ST-segment changes and reversible defect; 90% epicardial vessel stenosis or ¢50% stenosis in the left main artery; ¢1 mm ST-segment changes with pain on stress testing and/or resting ECG and evidence of ¢50% stenosis in a major epicardial vessel.

CARDS

'Hospital-verified non-fatal acute myocardial infarction'

(a) Non-fatal definite acute myocardial infarction

(i) Definite ECG or

(ii) Typical symptoms AND highly abnormal enzymes, irrespective of ECG or

(iii) Typical or atypical or inadequately described symptoms AND probable ECG AND highly abnormal enzymes or

(iv) Troponin I or T above the 99th centile for the reference population of the local (testing) lab in the presence of typical or atypical ischaemic symptoms, irrespective of ECG.

(b) Non-fatal probable acute myocardial infarction

(i) Typical symptoms AND probable ECG or abnormal enzymes or

(ii) Atypical or inadequately described symptoms AND probable ECG AND abnormal enzymes.

'Silent myocardial infarction'

This category includes definite myocardial infarctions diagnosed on the basis of serial readings of annual ECGs for which no corresponding hospital-verified myocardial infarction exists.

'Coronary heart disease (CHD) deaths'

(a) Fatal definite acute myocardial infarction

This means death within 28 days from the onset of symptoms of a hospital-verified definite acute myocardial infarction, or in cases of death occurring outside the hospital, autopsy findings showing a recent myocardial infarction or a recent occluding coronary thrombus.

(b) Fatal probable acute myocardial infarction

This means death within 28 days from the onset of symptoms of a hospital-verified probable acute myocardial infarction in the absence of autopsy confirmation. This category also includes cases where an available autopsy report indicates a probable acute myocardial infarction.

(c) CHD death - new acute myocardial infarction not confirmed

This includes the following subcategories:

(i) Witnessed instantaneous unexpected death occurring without any preceding symptoms.

(ii) Cardiac death occurring within 1 h after the onset of typical chest pain, syncope, acute pulmonary oedema, or cardiogenic shock.

(iii) Cardiac death occurring > 1 h but < 24 h after the onset of typical chest pain, syncope, acute pulmonary oedema, or cardiogenic shock.

(iv) Cardiac death occurring >24 h but <72 h after the onset of typical chest pain, syncope, acute pulmonary oedema or cardiogenic shock.

(v) Non-witnessed unexpected death, if other causes of death can be excluded with reasonable certainty (excluded are those patients who were known to have signs or symptoms of other fatal disease when last observed).

'Coronary artery bypass graft surgery (CABG)'

Other coronary artery revascularization procedures

This includes angioplasty, atherectomy, laser ablation or stenting or any newly introduced invasive method for the management of coronary artery disease.

'Unstable angina'

Chest pain event or symptoms consistent with angina of sufficient severity to cause the patient to have a hospital-verified episode within 28 days of symptom onset, accompanied by:

(i) New resting ECG changes, defined as any new Minnesota code change consistent with ischaemia or
(ii) A troponin rise not sufficient to meet the definition of an MI, i.e. above the 50th centile but below the 99th centile of the reference population, in association with ischaemic symptoms.

'Resuscitated cardiac arrest'

Ischaemic cardiac arrest with successful resuscitation which involved DC shock, in which a non-fatal definite or probable

JUPITER - 'myocardial infarction'

MEGA - fatal or nonfatal myocardial infarction, sudden cardiac death, development of unstable angina and coronary revascularization procedures, either coronary artery bypass grafting or percutaneous coronary intervention.

- primary outcome of study - composite of major CHD events

PREVEND-IT - hospitalisation for 'Nonfatal myocardial infarction and/or myocardial ischemia' or 'Heart failure'

- See above for precise definitions

WOSCOPS - 'coronary mortality, nonfatal MI, and coronary revascularization'

- primary outcome of trial
  - All deaths will be recorded, and details sought from death certificates, autopsy reports, hospital case records, general practitioner's records and interview of family and/or witness. The principal endpoints of the trial have been specified as follows:

    (1) CHD death plus non-fatal myocardial infarction.
    (2) CHD death (whether preceded by a non-fatal myocardial infarction or not).
    (3) Non-fatal myocardial infarction.
- In the categories of CHD death and myocardial infarction, there will be sub-categories of "definite" and "suspect". These conditions will be defined as follows:

  (1) Definite atherosclerotic CHD death-ither or both of the following categories:
  (A) Death certificate with consistent underlying or immediate cause plus one or more of the following:

  Preterminal hospitalization with definite or

suspect myocardial infarction (see below).
Previous definite angina or suspect or definite myocardial infarction when no cause other than atherosclerotic CHD could be ascribed as the cause of death.
Autopsy evidence of acute coronary arterial thrombosis and/or acute myocardial infarction.

(B) Sudden and unexpected death (requires all 3 characteristics):

Deaths occurring within 1 hr after the onset of severe symptoms or having last been seen without them.
No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal.
An “unexpected” death occurs only in a person who is not confined to his home, hospital, or other institution because of illness within 24 hr before death.

(2) Criteria for definite non-fatal myocardial infarctionany one or more of the following categories using the stated definitions:

(i) Diagnostic ECG at the time of the event.
(ii) Ischaemic cardiac pain and diagnostic enzymes.
(iii) Ischaemic cardiac pain with both equivocal enzymes and equivocal ECG.
(iv) An ECG at the annual visit or at an unscheduled visit is diagnostic for myocardial infarction while the previous one was not.

(3) Suspect atherosclerotic CHD death-one or both of the following categories:

(i) Death certificate with consistent underlying or immediate cause but neither adequate preterminal documentation of the event nor previous atherosclerotic CHD diagnosis.
(ii) Rapid and unexpected death (requires all 3 characteristics):

(a) Death occurring between one and 24 hr after the onset of severe symptoms or having last been seen without them.
(b) No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal.
(c) An “unexpected death” occurs only in a person who is not confined to his home, hospital or other institution because of illness within 24 hr before death.

(4) Suspect myocardial infarction-any one or more of the following categories using the stated definitions:

(i) Ischaemic cardiac pain, except when infarction is excluded by ECG or enzymes.
(ii) Diagnostic enzymes.
(iii) Equivocal ECG and equivocal enzymes.

(iv) Equivocal ECG alone, provided that it is not based on ST or T-wave changes only.

Other endpoints

As well as the main endpoints, statistics will also be reported on the frequency of:

(1) All cause mortality.

(2) Coronary artery bypass surgery/angioplasty: subjects will be deemed to have reached the secondary endpoint on the day on which the procedure is undertaken.

(3) Coronary arteriography.

(4) Angina: positive response to chest pain questionnaire when previously negative.

(5) Intermittent claudication: positive response to claudication questionnaire when previously negative.

(6) Cerebrovascular disease: a single episode of motor paralysis, sensory or speech dysfunction, diplopia or visual disturbance lasting more than 1 hr, or repetitive episodes of a similar nature lasting for 5 min or more.

Risk of Bias Assessment

Study	Pre-published Methods	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias			Overall Bias Assessment
		Random Sequence Generation	Allocation Concealment					Proteinuira Measurement	eGFR Measurement	Subgroup	
AFCAPS (16)	Yes	Unclear	Low	Low	Low	Low	Low	Unclear	Medium	Downgrade by 1	Medium
CARDS (17)	Yes	Low	Low	Low	Low	Low	Low	Medium	Medium	Downgrade by 1	Medium
JUPITER (18)	Yes	Low	Low	Low	Low	Unclear	Low	Unclear	Medium	Downgrade by 1	Medium
MEGA (19)	Yes	Low	Low	High	Low	Low	Low	Unclear	Medium	Downgrade by 2	High
PREVEND-IT (20)	Yes	Low	Low	Low	Low	Unclear	Low	Low	Medium	No downgrade	Low
WOSCOPS (21)	Yes	Low	Low	Low	Low	Unclear	Low	Unclear	Medium	Downgrade by 2	High

Summary of Adverse events

Study	Information in Relation to Adverse Events
AFCAPS (16)	No significant increase in creatinine kinase levels or any cases of rhabdomyolysis in participants with CKD in the lovastatin group. Abnormal liver function tests were 'rare' and 'the incidence was similar in both treatment groups'.
CARDS (17)	None published for CKD sub-analysis.
JUPITER (18)	Similar rates of 'serious adverse events', 9.16 per 100 person-years (PYs) for rosuvastatin group and 9.40 per 100 PYs for placebo (p=0.73). 1 case of rhabdomyolysis in rosuvastatin group versus none in the placebo group. For full details see table 4, reference 15
MEGA (19)	Rates of 'serious adverse events or subjective complaints of side effects' similar (diet group 11.3%; diet plus pravastatin group 10.5%; P = 0.088). Rates of abnormal laboratory finding were similar. ALT >100 IU/L 2.7% and 2.5% (P = 0.73); creatine kinase > 500 IU/L was 2.6% and 2.6% (P = 0.96). No significant difference was found in total cancer incidence.
PREVEND-IT (20)	‘Intolerability' of medication 5.1% in the placebo group versus 3.0% in pravastatin group. No specific other statin related side effects reported.
WOSCOPS (21)	None published for CKD sub-analysis.

Basis for Calculations of Reduction in Events

	Mortality	Excess MIs	Stroke
CKD Stage 3-5 England prevalence or excess events calculated (26)	1810000	12100	6500
x			
Proportion of CKD 3-5 who are CKD 3 (26)	0.92537	0.92537	0.92537
x			
Proportion eligible for primary prevent (1, Hallan *et el*, Stadler *et al*)	0.8	0.8	0.8
x			
proportion not on statin already (40)	0.5337	0.5337	0.5337
x			
rate per PY of total mortality in CKD population ((2) and current study control group rate)	0.011	N/A	N/A
x			
for number over 5 years	5	5	5
x			
This study's RR reduction (CKD3)	0.38	0.45	0.57
Reduction in total mortality over 5 years	**14,946**	**10,756**	**7,319**
Upper CI RR	0.18	0.27	0.25
Upper CI Events	**7080**	**6454**	**3210**
Lower CI RR	0.53	0.58	0.75
Lower CI Events	**20846**	**13864**	**9630**

All numerical references are as numbered in the main text of the manuscript.

Additional References for Supplementary Material:

Hallan S, Astor B, Romundstad S, Aasarød K, Kvenild K, Coresh J. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. *Arch Intern Med* 167: 2490-2496, 2007

Stadler SL, Bhardwaja B, Olson KL, Powers JD, Lanese D. An assessment of cholesterol goal attainment in patients with chronic kidney disease. *J Clin Lipidol* 4: 298-304, 2010