The Sweet Truth on Statins
Statins in New Onset-Diabetes

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# Table of Content

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation Slides</td>
<td>3-9</td>
</tr>
<tr>
<td>Appendix A</td>
<td>10</td>
</tr>
<tr>
<td>Appendix B</td>
<td>11</td>
</tr>
<tr>
<td>Appendix C</td>
<td>12</td>
</tr>
<tr>
<td>Appendix D</td>
<td>13</td>
</tr>
<tr>
<td>Appendix E</td>
<td>14</td>
</tr>
<tr>
<td>Appendix F</td>
<td>15</td>
</tr>
</tbody>
</table>
THE SWEET TRUTH ON STATINS

Statins in New Onset Diabetes

ALEX BAO
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Objectives

- Review pharmacotherapy recommendations for primary prevention in 2018 & 2019 American Heart Association/American College of Cardiology and statin associated side effects provided in the guidelines.

- Explain pathophysiology, risk factors, signs and symptoms of hypercholesterolemia.

- Analyze the effects of statins on new onset diabetes mellitus in literature and apply knowledge when making a recommendation in a patient case.

Patient Case

CL is a 55-year-old man of Asian descent here for his physical exam. PMH of HTN and was a former smoker. He has seasonal allergies and experiences insomnia on occasional nights. His blood pressure is 145/95 mm Hg, ASCVD risk of 7.2%, and his last A1C was 6.1%. He weighs in at 83 kg and measures at 5'6" tall. He states that he goes to the park once a week to play with his daughter. Recently his CAC measured a score of 9. There was no significant family history noted.

![Recent lipid panel]

- Recent lipid panel: TC of 220 mg/dl
- LDL-C of 140 mg/dl
- HDL-C of 65 mg/dl
- TG of 75 mg/dl

- 136 96 9 110
- 3.7 24 0.9

Patient Case

Current Medications

- Hydrochlorothiazide 25 mg po qd for HTN
- Lisinopril 10 mg po qd for HTN
- Cetirizine 10 mg po qd for Allergies
- Melatonin 3 mg po qhs for Sleep
- Multivitamin po qd

The medical resident consults you for a recommendation regarding CL's risk factors and whether you would initiate statin therapy in this patient. What recommendation would you tell the resident?

a. Initiate Pravastatin 40 mg PO QD
b. Initiate Atorvastatin 10 mg PO QD
c. Initiate Rosuvastatin 5 mg PO QD
d. No therapy needed at this time.

Atherosclerotic Cardiovascular Disease (ASCVD)

- Globally, approximately 17.8 million deaths per year from heart attacks, stroke, or other CVD event.

- Diabetes
- Hypertension
- Obesity
- Smoking

- Hypercholesterolemia
Pathophysiology and Risk Factors

- Cholesterol
  - LDL, HDL, VLDL
- Diet

Risk Factors:

<table>
<thead>
<tr>
<th>Cigarette Smoking</th>
<th>Hypertension</th>
<th>Dysglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Metabolic syndrome</td>
<td>Family hypercholesterolemia (FH)</td>
</tr>
</tbody>
</table>

Signs and Symptoms

- Signs
  - Abdominal Pain
  - Pancreatitis
  - Eruptive Xanthomas
  - Peripheral Polyneuropathy
  - High BP
  - BMI > 30 kg/m²

- Symptoms
  - Chest pain
  - Palpitations
  - Sweating
  - Anxiety
  - SOB

ASCVD and Risk Stratification

- ASCVD:
  - ACS
  - PAD
  - TIA
  - Stroke
  - Stable or unstable angina
- ASCVD Risk Stratification:

<table>
<thead>
<tr>
<th>ASCVD %</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>Low Risk</td>
</tr>
<tr>
<td>5% - 7.5%</td>
<td>Borderline Risk</td>
</tr>
<tr>
<td>7.5% - 20%</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>≥ 20%</td>
<td>High Risk</td>
</tr>
</tbody>
</table>

2019 AHA/ACC Primary Prevention Recommendations

- Assess ASCVD Risk & Emphasize Adherence to Healthy Lifestyle
- Age 20-79 & LDL ≥ 190 mg/dL
- High Intensity statin
- Age 40-75 & LDL ≥ 190 mg/dL without DM
- Age 40-75 & DM
- Moderate to high Intensity statin
- Age > 75
- Clinical Assessment, Risk Discussion

Primary Prevention Goals

- LDL-C > 190 mg/dL
  - > 50% reduction and LDL < 100 mg/dL
- LDL-C > 70 and < 180 mg/dL
  - ≥ 30% - 50% reduction
- DM or High ASCVD Risk
  - > 50% reduction

Statins Mechanism of Action

- Competitively antagonize HMG-CoA reductase
- Reduces liver production of cholesterol
- Increase in LDL receptors on hepatocytes
- Decrease LDL in blood stream

2019 AHA/ACC Primary Prevention Recommendations

- Assess ASCVD Risk & Emphasize Adherence to Healthy Lifestyle
- Age 20-79 & LDL ≥ 190 mg/dL
- High Intensity statin
- Age 40-75 & LDL ≥ 190 mg/dL without DM
- Age 40-75 & DM
- Moderate to high Intensity statin
- Age > 75
- Clinical Assessment, Risk Discussion

Statin Treatment Intensity Definitions and Options

- High Intensity Daily Dose ↓ LDL ≥ 50%
  - Atorvastatin 40-80 mg
  - Rosuvastatin 20-40 mg
- Moderate Intensity ↓ LDL 30%-40%
  - Atorvastatin 10-20 mg
  - Rosuvastatin 5-10 mg
  - Simvastatin 20-40 mg
  - Pravastatin 40-80 mg
  - Lovastatin 40 mg
  - Fluvastatin 30-80 mg
  - HMG-CoA reductase inhibitors 40 mg 80%
  - Pitavastatin 2-4 mg
- Low Intensity ↓ LDL ≥ 30%
  - Simvastatin 10mg
  - Pravastatin 10-20 mg
  - Lovastatin 20mg
  - Fluvastatin 20-40 mg
  - Pitavastatin 3 mg

REVIEW OF LITERATURE
Statin Controversies

Studies
- Most widely prescribed, cholesterol-lowering drugs in the world.
- Total sales on track to reach an estimated US$1 trillion by 2020.

NCEP
- Panel members agreed to lower threshold for high cholesterol.
- 8 out of 9 panel members had direct ties with statin manufacturers.

Byrne P et al. 2019
- Lowering threshold significantly increased % of people eligible for a statin for primary prevention.
- From 1987% to 61% in 2016.

CTT Meta Analysis
- 20% decrease of CV events for every 38 mg/dl decrease in LDL.
- Reduction of CV events just as good in those at low – risk (<10% in 10 years).
- Argued that everyone over 50 should be on a statin.

- Side effects were not mentioned.
- Statistics and raw data is not made public to independent researchers.
- Many studies used in the analysis had run-in periods.

STUDY I- Carter et al. (2013)
Risk of Incident Diabetes Among Patients Treated with Statins

Objective
- Examine the risk NODM among patients treated with different statins.

Study Design
- Population based, retrospective cohort study.
- Maximum follow-up of 5 years.

Inclusion
- Patients ≥66 years old without DM who started treatment with statins from August 1, 1997 to March 31, 2010.
- At least one year with no prescription for a statin.

STUDY I- Carter et al. (2013)
Incident Diabetes
- Any prescription for a diabetics drug or blood glucose test strips.

Baseline Characteristics
- 47,1250 patients identified.
- Median age was 73 year (69-78).
- Women (54.1%) vs. men (45.9%)
- 22,794 (48.3%) statin for primary prevention.
- 24,326 (51.7%) statin for secondary prevention.

STUDY I- Carter et al. (2013)
Results
- Consistent results for both primary prevention and secondary prevention subgroups.

Atorvastatin 1.20 CI (1.10 to 1.30)
Rosuvastatin 1.12 CI (1.02 to 1.23)
Simvastatin 1.12 CI (1.02 to 1.23)
Lovastatin 0.98 CI (0.79 to 1.22)
Fluvastatin 1.01 CI (0.82 to 1.23)

Statistically Significant
Not Statistically Significant

Adjusted Hazard Ratio

<table>
<thead>
<tr>
<th>Statin</th>
<th>Incidence Rate (Outcomes per 1000 Person Years)</th>
<th>Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>1.22, 99% CI (1.13 to 1.29)</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>1.20, 99% CI (1.10 to 1.49)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1.10, 99% CI (1.04 to 1.17)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>0.99, 95% CI (0.82 to 1.15)</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>1.09, 99% CI (0.84 to 1.44)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio Relative to Risk in Pravastatin.

*Hazard Ratios Relative to Risk in Pravastatin.
STUDY I - Carter et al. (2013)

Strengths
- Large sample size, population-based design.
- Use of Pravastatin as a reference group.

Limitations
- Did not identify potential risk factors for DM.
- Did not have data on lipids, Hemoglobin A1C, Triglycerides.

Implications
- Other patients treated with Atorvastatin, Rosuvastatin, and Simvastatin are at higher risk in developing diabetes.
- Clinicians should consider this risk when treating individuals with statins.

STUDY II – Porath et al. (2018)

Statin Therapy: Diabetes Mellitus Risk and Cardiovascular Benefit in Primary Prevention

Objective
- Assess the risk-benefit of statin therapy, prescribed for the prevention of CVD, in the development of DM.

Study Design
- Retrospective Cohort study, population based real life study.
- Maximum follow up of 5 years.
- The European SCORE formula stratifies its’ patients into 3 categories.

Inclusion
- Patients aged 40-70, no DM or CVD.
- No statin prescription for at least 2 years before the index date.
- At least 1 prescription filled from January 1, 2010 – December 31, 2014.

Endpoints
- Incidence of NODM and CVD.

Baseline Characteristics
- 365,414 eligible individuals
- Male (43%), Female (57%)
- Mean age 50.8 years
- Low risk for CVD (12%)
- Moderate risk for CVD (33.6%)
- High risk CVD (3.4%)

Incidence of DM in subjects with low intensity statin and high adherence was 2x of subjects not taking statins.
Study II – Porath et al. (2018)

Results

- Subjects on low dose statin and was >50% adherent saw reduced incidence rate at moderate to high risk SCORE.

<table>
<thead>
<tr>
<th>SCORE Risk Categories</th>
<th>Risk of DM in High Adherence Taking Low Intensity Statin Vs Non-statin users</th>
<th>Relative Risk</th>
<th>P-value</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Score Risk Category (≤1.9%)</td>
<td>5.2% vs 7.7%</td>
<td>1.9</td>
<td>P &lt; 0.001</td>
<td>NA</td>
<td>40</td>
</tr>
<tr>
<td>Moderate Score Risk Category (1-5%)</td>
<td>8.2% vs 6.2%</td>
<td>1.3</td>
<td>P &lt; 0.001</td>
<td>125</td>
<td>50</td>
</tr>
<tr>
<td>High Score Risk Category (≥5%)</td>
<td>11.1% vs 10.6%</td>
<td>1.04</td>
<td>P &lt; 0.001</td>
<td>29</td>
<td>200</td>
</tr>
</tbody>
</table>

Study II – Porath et al. (2018)

Strengths

- Large sample size, population-based design.
- Uses administrative databases.

Limitations

- Adherence was measured by dispensing information.
- Short length of the study.

Implications

- Low dose statins for primary prevention of CVD is beneficial in patients at high risk and may be harmful in patients at low CV risk.
- In patients with intermediate risk, clinician should individualize treatment.

Study II – Porath et al. (2018)

Critique

- Unable to assess the effects of higher doses and explore a possible dose response effect.
- Unable to assess whether different statins can convey different levels of DM risk.

Study III – Kim et al. (2019)

Statin Use Increased New-Onset Diabetes in Hypercholesterolemic Individuals

Objective

- Investigate the association between statin use and new onset diabetes in Korean adults with hypercholesterolemia.

Study Design

- Cohort study
- Identified high-risk statin users according to MPFR and hypercholesterolemia patients that never used a statin over the entire follow-up period (12.5 years)

Inclusion

- Subjects with total cholesterol ≥ 250 mg/dL
- Subjects taking anti-hyperlipidemic drugs including statins and fibric acid derivatives between 2002 and 2003
- 76,371 participants selected

Study III – Kim et al. (2019)

Statin Use Increased New-Onset Diabetes in hypercholesterolemic individuals

Endpoints

- Incidence of NODM defined as
  2. A fasting blood glucose level ≥ 126 mg/dL.

Baseline Characteristics

- Statin users (10,880) Male (43%), Female (57%)
- Statin non-users (10,580) Male (64%), Female (36%)

Baseline Characteristics
Study III – Kim et al. (2019)

Statin Use Increased New-Onset Diabetes in hypercholesterolemic individuals

Baseline Characteristics

Results

- Compared to non-users vs. statin-users

- 1.43, CI (1.31–1.57)* in men
- 1.86, CI (1.66–2.09)* in women

- Compared to high-users vs. low-statin users

- 1.16, CI (1.01–1.30)* in men
- 1.28, CI (1.16–1.43)* in women

- Compared to non-users vs. higher risk for DM statin users**

- Low-users: 1.45, CI (1.21–1.73)* Men, 2.09, CI (1.62–2.45)* Women
- High-users: 1.25, CI (1.04–1.50)* Men, 1.70, CI (1.38–2.10)* Women

Strengths

- Long duration of follow-up (12.5 years)

Limitations

- Analysis of total statin use in association with NODM instead of specific statins.
- Classification of diabetes diagnosis.

Implications

- Periodic diabetic screening should be considered in patients who are taking statins.

Critique

- Good study design in focusing in a population.
- Study design comparing higher-users vs low-users can be misleading and interpreted as comparing high-intensity vs. low intensity statins.
- Didn’t confound for variables such as unhealthy lifestyle, more tobacco use, and low economic status in low-users, resulted in higher users having lower incidence of diabetes.

Summary of Table of Literature

Study I (Carli et al., 2013)

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Non-users</th>
<th>Low-dose (25)</th>
<th>Moderate (50)</th>
<th>High (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Rosuvastatin, Simvastatin, Fluvastatin, Pravastatin</td>
<td>Atorvastatin (25%)</td>
<td>Rosuvastatin (18%)</td>
<td>Simvastatin (10%)</td>
</tr>
</tbody>
</table>

Study II (Perez et al., 2018)

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Non-users</th>
<th>Low-dose (25)</th>
<th>Moderate (50)</th>
<th>High (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>Rosuvastatin</td>
<td>Pravastatin (25%)</td>
<td>Rosuvastatin (50%)</td>
<td>Pravastatin (100%)</td>
</tr>
</tbody>
</table>

Study III (Kim et al., 2019)

<table>
<thead>
<tr>
<th>Statin Use</th>
<th>Non-users</th>
<th>High-users vs Low-users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin Users vs Non-users</td>
<td>High users vs Low users</td>
<td></td>
</tr>
<tr>
<td>Statin users had a higher risk of developing NODM than non-users</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient Case

CI. is a 55-year-old man of Asian decent here for his physical exam. PMH of HTN and was a former smoker. He has seasonal allergies and experiences insomnia on occasional nights. His blood pressure is 145/95 mm Hg, ASCVD risk of 7.2%, and his last A1C was 6.1%. He weighs in at 83kg and measures at 5'10" tall. He states that he goes to the park once a week to play with his daughter. Recently his CAC measured a score of 9. There was no significant family history noted.

Recent lipid panel:
- TC of 220 mg/dL
- LDL-C of 140 mg/dL
- HDL-C of 65 mg/dL
- TG of 75 mg/dL
Patient Case

Current Medications
- Hydrochlorothiazide 25mg po qd for HTN
- Lisinopril 10 mg po qd for HTN
- Cetirizine 10mg po qd for Allergies
- Melatonin 3mg po qhs for Sleep
- Multivitamin po qd

Patient Case

Based off objective findings from the patient case. What are CLi’s risk factors for diabetes?

a. Age
b. Race
c. Use of thiazide
d. Elevated glucose
e. A1C of 6.3%
f. All the above

Patient Case

The medical resident consults you for a recommendation regarding CLi's risk factors and whether you would initiate statin therapy in this patient. What recommendation would you tell the resident?

a. Initiate Pravastatin 40mg PO QD
b. Initiate Atorvastatin 10mg PO QD
c. Initiate Rosuvastatin 5mg PO QD
d. No therapy needed at this time.

Reference

1. Levenson J A. JAMA, 2013;310(12):1349
4. Levenson J A. JAMA, 2017;310(12):1349
Appendix A: Abbreviations

ACC: American College of Cardiology
ACS: Acute Coronary Syndrome
AHA: American Heart Association
ASCVD: Atherosclerotic Cardiovascular Disease
CAC: Coronary Artery Calcium
CTT: Cholesterol Treatment Trialist
CV: Cardiovascular
CVD: Cardiovascular Disease
DM: Diabetes Mellitus
FPG: Fasting Plasma Glucose
HDL: High Density Lipoprotein
HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA
HTN: Hypertension
LDL: Low Density Lipoprotein
MPR: Medication Possession Ratio
NCEP: National Cholesterol Education Program
NODM: New Onset Diabetes Mellitus
ODD: Ontario Diabetes Database
OGTT: Oral Glucose Tolerance Test
PAD: Peripheral Artery Disease
SCORE: The European Systematic Coronary Risk Evaluation
TIA: Transient Ischemic Attack
TG: Triglycerides
Appendix B: Type 2 Diabetes Risk Factors

**Weight**: Higher body fat makes your cells insulin resistant.

**Inactivity**: The less active you are, the greater your risk.

**Family history**: Increases risk if a parent or sibling has type 2 diabetes.

**Race**: Black, Hispanics, American Indians and Asians are at higher risk.

**Age**: Your risk increases as you get older.

**Gestational diabetes**: If you have gestational diabetes, you have a higher risk of developing type 2 diabetes later on in life.

**Polycystic ovary syndrome**: For women, increases the risk of diabetes.

**High blood pressure**: Having blood pressure over 140/90 millimeters of mercury (mm Hg) can increase your risk of type 2 diabetes.

**Abnormal cholesterol and triglyceride levels**: Having low HDL and high triglycerides levels can increase your risk for type 2 diabetes.

**Prediabetic Ranges:**

FPG: 100-125 mg/dL

2-hour plasma glucose 75-g OGTT: 140-199

A1C: 5.7-6.4
Appendix C: Grundy SM. et al. J Am Coll Cardiol.2018.10.1016

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**Primary Prevention:**
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of familial hypercholesterolemia-9 studies

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dl (4.1 mmol/l)

- **Age 40-75 y and LDL-C ≥70-<190 mg/dl (≥1.8-<4.9 mmol/l)**
  - No risk assessment; High-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Moderate-intensity statin (Class IIa)
  - Risk assessment to consider high-intensity statin (Class IIb)

- **Age >75 y**
  - Clinical assessment, Risk discussion

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dl (≥4.1 mmol/l)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., premenopause, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

**Uplift/Biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dl, ≥2.0 mmol/l)

**In selected individuals if measured:**
- hs-CRP >2.0 mg/l
- Lp(a) levels ≥50 mg/dl or ≥125 nmol/l
- apoB ≥130 mg/dl
- Arterial-brachial index (ABI) <0.9

**Risk discussion:**
- Emphasize lifestyle to reduce risk factors (Class I)
- Risk discussion: if risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class III)

**Risk discussion:**
- if risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30%-49% (Class I)
- Risk discussion: Initiate statin to reduce LDL-C ≥50% (Class I)

**If risk decision is uncertain:**
- Consider measuring CAC in selected adults:
  - CAC = 0: No statin (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
  - CAC = 1.99 favors statin (especially after age 55)
  - CAC = 100+ and/or ≥75th percentile, initiate statin therapy

**Colors correspond to Class of Recommendation in Table I.**
All indicates ankle-brachial index; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a). Reproduced with permission from Grundy et al. (54.3-1). Copyright © 2018, American Heart Association, Inc., and American College of Cardiology Foundation.
Appendix D: Carter et al. BMJ. 2013;346: f2610

Table 1: Baseline characteristics for new statin users. Figures are numbers (percentage) of patients unless stated otherwise

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n=38 470)</th>
<th>Atorvastatin (n=298 254)</th>
<th>Fluvastatin/lovastatin (n=11 923)</th>
<th>Rosuvastatin (n=78 774)</th>
<th>Simvastatin (n=17 829)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years at start of cohort drug)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>73.04 (5.62)</td>
<td>72.57 (5.44)*</td>
<td>72.63 (5.49)</td>
<td>72.24 (5.29)</td>
<td>72.80 (5.06)*</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>72 (68-77)</td>
<td>71 (68-77)</td>
<td>72 (68-77)</td>
<td>72 (68-77)</td>
<td>73 (69-78)*</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 173 (44.6)</td>
<td>123 607 (41.1)</td>
<td>4 826 (41.5)</td>
<td>35 345 (44.6)</td>
<td>35 383 (46.7)</td>
</tr>
<tr>
<td>Female</td>
<td>23 306 (55.4)</td>
<td>174 647 (58.9)</td>
<td>7 154 (58.5)</td>
<td>42 429 (55.4)</td>
<td>42 546 (53.3)</td>
</tr>
<tr>
<td><strong>Median IQR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>20 355 (53.3)</td>
<td>143 025 (51.6)</td>
<td>5 040 (37.1)*</td>
<td>30 915 (39.3)*</td>
<td>42 559 (57.4)</td>
</tr>
<tr>
<td>Previous acute coronary syndrome</td>
<td>12 243 (31.8)</td>
<td>84 586 (31.5)</td>
<td>3 113 (23.1)*</td>
<td>14 671 (18.1)*</td>
<td>26 854 (35.4)</td>
</tr>
<tr>
<td>Chronic coronary artery disease</td>
<td>16 999 (47.8)</td>
<td>121 600 (45.9)</td>
<td>4 991 (41.5)*</td>
<td>24 762 (32.0)*</td>
<td>38 029 (50.2)</td>
</tr>
<tr>
<td>Smoker/transient ischemic attack</td>
<td>5206 (13.5)</td>
<td>43 222 (15.6)</td>
<td>1 423 (10.6)</td>
<td>2472 (12.3)</td>
<td>12 212 (16.1)</td>
</tr>
<tr>
<td><strong>Charlson score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7027 (18.2)</td>
<td>48 327 (16.1)</td>
<td>2 110 (17.7)</td>
<td>16 677 (17.8)*</td>
<td>13 715 (18.1)</td>
</tr>
<tr>
<td>1</td>
<td>4618 (12.0)</td>
<td>32 005 (11.3)</td>
<td>1 111 (9.5)</td>
<td>3 015 (3.9)*</td>
<td>8995 (11.3)</td>
</tr>
<tr>
<td>2</td>
<td>3616 (10.2)</td>
<td>24 787 (8.7)</td>
<td>1 084 (8.9)</td>
<td>3 286 (4.3)*</td>
<td>9658 (11.2)</td>
</tr>
<tr>
<td>No admission to hospital</td>
<td>22 316 (60.0)</td>
<td>160 701 (59.9)</td>
<td>7 022 (53.9)</td>
<td>22 799 (55.9)</td>
<td>44 552 (55.8)</td>
</tr>
<tr>
<td>Daily statin dose (any effect dose)</td>
<td>901 (23.9)</td>
<td>11 851 (4.1)*</td>
<td>1 753 (14.7)</td>
<td>2084 (7.7)</td>
<td>1601 (9.5)*</td>
</tr>
<tr>
<td>Missing</td>
<td>115 (0.3)</td>
<td>500 (0.2)</td>
<td>50 (0.4)</td>
<td>223 (0.3)</td>
<td>250 (0.3)</td>
</tr>
</tbody>
</table>

Fifth of income distribution:

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n=38 470)</th>
<th>Atorvastatin (n=298 254)</th>
<th>Fluvastatin/lovastatin (n=11 923)</th>
<th>Rosuvastatin (n=78 774)</th>
<th>Simvastatin (n=17 829)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>7027 (18.2)</td>
<td>48 327 (16.1)</td>
<td>2 110 (17.7)</td>
<td>16 677 (17.8)*</td>
<td>13 715 (18.1)</td>
</tr>
<tr>
<td><strong>Charlson score</strong></td>
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<tr>
<td>0</td>
<td>7027 (18.2)</td>
<td>48 327 (16.1)</td>
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<td>Missing</td>
<td>115 (0.3)</td>
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<td>50 (0.4)</td>
<td>223 (0.3)</td>
<td>250 (0.3)</td>
</tr>
</tbody>
</table>

Table 2: Previous drug use in year before cohort entry in new users of statins. Figures are numbers (percentage) of patients

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n=38 470)</th>
<th>Atorvastatin (n=298 254)</th>
<th>Fluvastatin/lovastatin (n=11 923)</th>
<th>Rosuvastatin (n=78 774)</th>
<th>Simvastatin (n=17 829)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>10 331 (26.3)</td>
<td>78 496 (25.3)</td>
<td>2715 (22.8)</td>
<td>21 287 (27.9)</td>
<td>22 183 (29.3)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>1526 (4.0)</td>
<td>24 819 (9.2)*</td>
<td>317 (2.7)</td>
<td>13 363 (17.4)*</td>
<td>4621 (6.4)*</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>10 481 (27.2)</td>
<td>69 292 (23.5)</td>
<td>2762 (22.3)</td>
<td>16 706 (21.4)</td>
<td>20 184 (26.6)</td>
</tr>
</tbody>
</table>
## Appendix E: Porath et al. IMAJ. 2018;20

### Table 1. Distribution of demographics and risk factors [A] According to cardiovascular SCORE risk [B] According to statin treatment

#### A

<table>
<thead>
<tr>
<th>SCORE 10 year CV mortality Risk</th>
<th>N (%)</th>
<th>Male gender</th>
<th>Age, mean ± SD</th>
<th>BMI, mean ± SD</th>
<th>Hypertension N (%)</th>
<th>Total cholesterol (mmol/L), mean ± SD</th>
<th>LDL (mmol/L), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1%</td>
<td>167,207 (93.0)</td>
<td>34.4%</td>
<td>48.4 ± 4.4</td>
<td>28.8 ± 5.1</td>
<td>17,416 (10.4)</td>
<td>5.05 ± 0.84</td>
<td>3.09 ± 0.71</td>
</tr>
<tr>
<td>1-5%</td>
<td>89,067 (53.6)</td>
<td>55.2%</td>
<td>57.7 ± 5.4</td>
<td>27.8 ± 4.8</td>
<td>26,333 (13.8)</td>
<td>5.38 ± 0.85</td>
<td>3.25 ± 0.71</td>
</tr>
<tr>
<td>≥ 5%</td>
<td>9,140 (3.4)</td>
<td>65.9%</td>
<td>64.8 ± 4.0</td>
<td>28.1 ± 4.7</td>
<td>5042 (55.2)</td>
<td>5.59 ± 0.93</td>
<td>3.52 ± 0.77</td>
</tr>
<tr>
<td>All</td>
<td>265,414 (100)</td>
<td>42.5%</td>
<td>50.8 ± 7.6</td>
<td>27.2 ± 5.0</td>
<td>50,701 (19.1)</td>
<td>5.10 ± 0.87</td>
<td>3.2 ± 0.73</td>
</tr>
</tbody>
</table>

*P value*  < 0.001  < 0.001  < 0.001  < 0.001  < 0.001  < 0.001

#### B

<table>
<thead>
<tr>
<th>Statin use</th>
<th>N (%)</th>
<th>Male gender</th>
<th>Age, mean ± SD</th>
<th>BMI, mean ± SD</th>
<th>Hypertension, N (%)</th>
<th>Total cholesterol (mmol/L), mean ± SD</th>
<th>LDL (mmol/L), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statin</td>
<td>217,603 (83.4)</td>
<td>41.4%</td>
<td>50.2 ± 7.4</td>
<td>27.2 ± 5.2</td>
<td>36,802 (16.8)</td>
<td>5.05 ± 0.8</td>
<td>3.08 ± 0.86</td>
</tr>
<tr>
<td>Low statin, adherence &lt; 50%</td>
<td>25,986 (10.0)</td>
<td>45.2%</td>
<td>53.0 ± 7.4</td>
<td>28.3 ± 5.0</td>
<td>7079 (27.2)</td>
<td>5.84 ± 0.65</td>
<td>3.77 ± 0.70</td>
</tr>
<tr>
<td>Low statin, adherence &gt; 50%</td>
<td>17,233 (6.6)</td>
<td>47.4%</td>
<td>54.3 ± 7.5</td>
<td>28.0 ± 4.8</td>
<td>5551 (32.2)</td>
<td>5.76 ± 0.78</td>
<td>3.68 ± 0.86</td>
</tr>
<tr>
<td>All</td>
<td>261,022 (100)</td>
<td>42.2%</td>
<td>50.8 ± 7.6</td>
<td>27.4 ± 5.2</td>
<td>40,431 (18.9)</td>
<td>5.17 ± 0.86</td>
<td>3.10 ± 0.72</td>
</tr>
</tbody>
</table>

*P value*  < 0.001  < 0.001  < 0.001  < 0.001  < 0.001  < 0.001

*BMI = body mass index, CV = cardiovascular, LDL = low-density lipoprotein, SCORE = European Systematic COronary Risk Evaluation*
Appendix F: Kim et al. Prim Care Diab. 2019; PCD-822

Fig. 1 – Flowchart of inclusion and exclusion Conditions in exclusion criteria (1) are not mutually exclusive.