SUPPLEMENTAL MATERIAL

A) Physician Survey

The following survey was conducted on December 8th, 2016 at the Boerhaave Continuing Medical Education Conference.

1. What is your current position?
    a. Family Physician
    b. Nursing home physician
    c. Physician for mentally impaired
    d. Resident Family Medicine
    e. Nurse practitioner/ Nursing assistant
    f. Other

**Note: Answers a, b, and c, are considered specialties in primary prevention*

2. What is your gender?
    a. Male
    b. Female
3. What is your age?
    a. ≤ 34
    b. 35-45
    c. 46-52
    d. 53-57
    e. 58-62
    f. 63-67
    g. 68-72
    h. ≥72

4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication must provide before you considered use worthwhile?
    a. ½ year (low threshold)
    b. 1 year
    c. 1 ½ year
    d. 2 year
    e. 2 ½ year
    f. 3 year
    g. 3 ½ year (high threshold)
    h. I would never want to use a statin *Or only above these thresholds*

5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would personally consider using this statin to achieve this benefit?
    a. I would never want to use a statin; *Or only above these thresholds*
    b. 5 year (high threshold)
    c. 10 year
    d. 15 year
    e. 20 year
    f. 30 year
    g. 40 year
    h. 50 year (low threshold)

6. What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, "*healthy life years",* necessary before you consider **10 years of statin therapy** for a **patient** worthwhile?
    a. 2 months (low threshold)
    b. 4 months
    c. 6 months
    d. 8 months
    e. 10 months
    f. 12 months
    g. 14 months (high threshold)
    h. I would never consider statin prescription worthwhile. *Or only above these thresholds*

7. And what we aren't talking about statins, but about blood-pressure therapy?
    What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, "*healthy life years",* necessary before you consider **10 years of blood-pressure therapy** for a **patient** worthwhile?
    a. 2 months (low threshold)
    b. 4 months
    c. 6 months
    d. 8 months
    e. 10 months
    f. 12 months
    g. 14 months (high threshold)
    h. I would never consider blood-pressure medication prescription worthwhile; *Or only above these thresholds*

B) Patient Survey

The following patient survey was conducted on April 7th, 2017 at the University Medical Centre Utrecht, the Netherlands.

1. Do you use a statin?
    a. Yes
    b. No
    c. I have used statins, but stopped taking them
    d. I don't know
2. Do you use an antihypertensive medication?
    a. Yes
    b. No
    c. I have used antihypertensive medications, but stopped taking them
    d. I don't know
3. What is your gender?
    a. Male
    b. Female
4. What is your age?

    …….years

5. Please mark all the complications or medication procedures which you have had. You can also indicate if you have never had any one of these procedures.

    □ Heart attack

    □ Stroke

    □ *Intermittent claudication (*Peripheral artery disease)

    □ TIA

□ a stent, angioplasty, or other operation of the hart

□ an operation of the carotid artery (*major artery of the neck)*

□ I have never had *ANY* of the above

5. Imagine **you** were considering starting (or continuing) a statin medication. What in the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication must provide before you considered use worthwhile?
   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin ; *Or only above these thresholds*

6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would consider using the statin to achieve this benefit?
   a. I would never consider a statin worthwhile; *Or only above these thresholds*
   b. 5 years (high threshold)
   c. 10 years
   d. 15 years
   e. 20 years
   f. 30 years
   g. 40 years
   h. 50 years (low threshold)

7. What is the minimum gain in life-expectancy without (new) cardiovascular disease, "*healthy life years",* necessary before you consider 10 years of statin therapy worthwhile?

   a. 2 months (low threshold)
   b. 4 months
   c. 6 months
   d. 8 months
   e. 10 months
   f. 12 months
   g. 14 months (high threshold)
   h. I would never consider a statin worthwhile; *Or only above these thresholds*

8. And what we aren't talking about statins, but about blood-pressure therapy?

   What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, "*healthy life years",* necessary before you consider **10 years of blood-pressure therapy** worthwhile?

   a. 2 months (low threshold)
   b. 4 months
   c. 6 months
   d. 8 months
   e. 10 months
   f. 12 months
   g. 14 months (high threshold)
   h. I would never consider blood-pressure medication worthwhile ; *Or only above these thresholds*

C) Short Summary of Introduction Sessions

Physician Session

- The session started with a short reiteration that prevention of cardiovascular disease (CVD) incorporates both life-style aspects (such as not smoking or drinking too much alcohol, exercising regularly, eating healthy) and medication aspects (such as cholesterol, blood-pressure and aspirin treatment).
- Decision-making cardiovascular disease prevention was described as finding the balance between the benefits (living a longer, healthier, life) and negative effects (side-effects, costs, and taking a pill daily) of therapy. For each individual person, the balance between the benefits and negative effects can be different.
- The SCORE-chart as used in national primary prevention guidelines was reviewed. Drawbacks of using the SCORE-chart, and the associated ten-year absolute risk was discussed, namely that it often emphasizes treatment of the elderly, and that interpretation of 10-year risk or risk reduction may be difficult for the patient. Positive aspects of the SCORE-chart were also discussed, namely that it is easy to use, and allows for a variety of different individual risk-factors to be combined.
- Prediction algorithms and calculators which can estimate CVD-free life-expectancy for those in the primary prevention were introduced (i.e. the JBS-3 risk score).[22] Life-time estimates were described as being more biologically and clinically intuitive, as atherosclerosis is a phenomenon which starts early in life, and manifests itself only after a few decades.
- It was illustrated with two examples from peer-reviewed literature that the one “treats” a risk-factor, the greater the potential benefit. The first example provided was meant to show a large life-time benefit from a life-style intervention. It was shown that stopping with smoking between 25-34 years of age extends survival by 10 years, whereas stopping between 55-64 years of age extends survival by 3 years.[18] The second example was meant to

show a small benefit, and to provide a reference for preventative medication.[1] It was shown that the individual effect of aspirin therapy, is not expressed in years, but rather in months gain. These months range between 0-8 according to peer reviewed literature. It was emphasized that the potential gain in stopping with smoking is of a greater magnitude than the potential gain of medication, which is better represented by the aspirin example. It was also emphasized that the longer one "treats" a risk-factor, the longer one must also take the medication.

- Long-term validation results of these prediction models were shown.[1]
- In conclusion, it was iterated that starting medication at a young age provides the greatest net effect of therapy, but that this greater net-effect also goes hand in hand with a longer period of time in which the therapy would have to be used.

Patient Session

- The session started with a short reiteration that prevention of cardiovascular disease (CVD) incorporates both life-style aspects (such as not smoking or drinking too much alcohol, exercising regularly, eating healthy) and medication aspects (such as cholesterol, blood-pressure and aspirin treatment).
- Lipid-lowering and blood-pressure lowering were described as two important pillars of CVD-prevention guidelines. Statin medication were described as some on the most common cholesterol-lowering drugs, and a number of statin medications (with both generic and brand-names) were given: simvastatin, rosuvastatin, pravastatin, atorvastatin, fluvastatin. A few common examples of blood-pressure lowering medications were also given: hydrochlorothiazide, enalapril, perindopril, losartan, olmesartan, amlodipine, and metoprolol.
- Decision-making cardiovascular disease prevention was described as finding the balance between the benefits (living a longer, healthier, life) and negative effects (side-effects, costs,

and taking a pill daily) of therapy. For each individual person, the balance between the benefits and negative effects can be different.

- What exactly “CVD-free life expectancy?” entails was discussed. It was described as the amount of time you can expect to live *healthily,* without cardiovascular disease. If you already have had cardiovascular disease, then it was described as the amount of time you can expect to live without having another major cardiovascular event, such as a heart-attack. It was discussed that doctors are getting better at predicting what someone’s CVD-free life-expectancy is, and also what the gain in CVD-free life expectancy is from medications such as statin and blood-pressure lowering medications.
- It was introduced that the longer one “treats” a risk-factor, the greater the benefit (gain in CVD-free life-expectancy can be). This was illustrated with the same two-examples from peer-reviewed literature as with the physicians. Likewise, it was emphasized that the potential gain in stopping with smoking is of a greater magnitude than the potential gain of medication, which is better represented by the aspirin example. It was also emphasized that the longer one “treats” a risk-factor, the longer one must also take the medication.
- In conclusion, it was iterated that starting medication at a young age provides the greatest net effect of therapy, but that this greater net-effect also goes hand in hand with a longer period of time in which the therapy would have to be used. The definition of CVD-free life-expectancy was given again.

D) Values Used for Calculations

Age and gender-specific medians (50th percentile) of high-density lipoprotein concentration (HDL-c, mmol/l) and triglyceride concentration (TG, mmol/l), were used to calculate low-density lipoprotein concentration (LDL-c, mmol/l).[27-29] For each lipid-value depicted on the SCORE-based chart, corresponding low-density lipoprotein concentration (LDL-c) was calculated using the Friedewald formula and age and sex-specific medians of high density lipoprotein (HDL-c) and triglyceride concentrations. Age and gender-specific body-mass index (BMI, kg/m^2) was used with Joint British Societies for prevention of cardiovascular disease (JBS3) risk calculator[22]. Patients were assumed to have average socio-economic status and have no other comorbidities such as diabetes. Smokers used between 10 and 20 cigarettes per day.

Supplemental Table 1: Lipid levels used for calculation of therapy effects

	Age	HDL-c, mmol/l	TG, mmol/l	BMI, kg/m^2
Males	40-49	1.12	1.35	26.2
	50-54	1.14	1.41	26.5
	55-59	1.20	1.29	26.5
	60-64	1.27	1.22	26.8
	65-69	1.27	1.19	26.8
	> 70	1.25	5.56	26.2
Females	40-49	1.46	0.75	24.7
	50-54	1.61	1.13	25.7
	55-59	1.56	1.22	25.7
	60-64	1.59	1.16	26.4
	65-69	1.61	1.30	26.4
	> 70	1.56	1.21	26.4

Legend: Abbreviations LDL-c = low-density lipoprotein cholesterol; HDL-c = High density lipoprotein cholesterol; TC= Total cholesterol; TG = Triglycerides; BMI = Body-Mass Index

E) Example Calculation

A male patient, medical history negative for diabetes, 40 years of age, BMI of 26.2 kg/m^2, systolic blood-pressure 140 mmHg, and a total cholesterol / HDL ratio of 7. The 50th percentile values for HDL-c is 1.12 mmol/L and TG is 1.35 mmol/L.(1)

Calculation LDL-c:

Baseline LDL-c = Total cholesterol – median HDL – median triglyceride / 2.17

= Ratio x median HDL – median HDL – median triglyceride / 2.17

= 7 x 1.12 – 1.12 – 1.35/2.17

= 6.098 mmol/L

The effects of simvastatin 40 mg was calculated as follows:

LDL-c_{new} = LDL-c_{old} * (1 - percent reduction)

= 6.098 mmol/L * 0.63

= 3.842 mmol/L

Estimated attainable therapy-benefit in terms of gain in CVD-free life-years according to the JBS3 Online calculator:[22]

Calculated CVD-free life-expectancy off-treatment (i.e. current prognosis) = 76 years

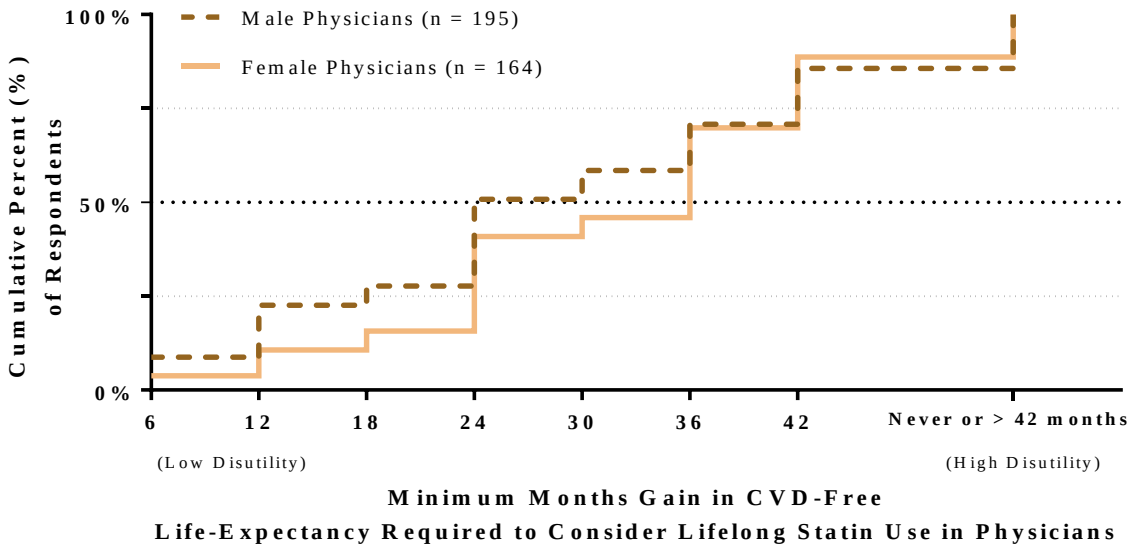
Calculated gain in CVD-free life-expectancy = 2.5 years

Remaining CVD-free life years on-treatment (i.e. potential treatment duration) = (76 years + 2.5 years)-40 years(i.e. current age) = 38.5 years

Gain per 10 years of use = (2.5 years gain / 38.5 years of use)*10 = 0.649 years = 7.8 months

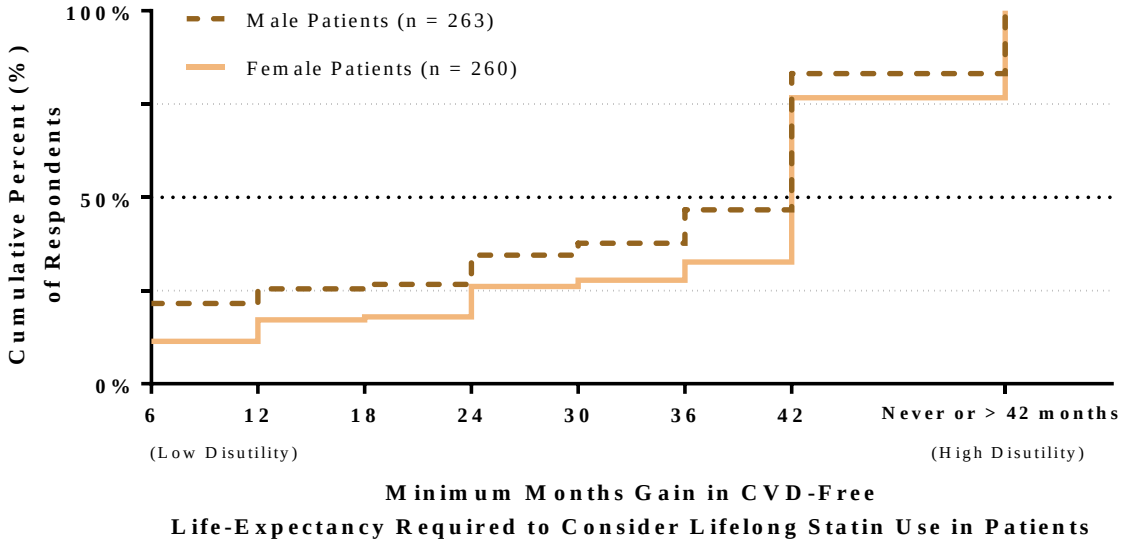
F) Supplemental Figures

Supplemental Figure 1. Months gain in CVD-free life-expectancy required to consider personal use of statin therapy, stratified by sex in physicians



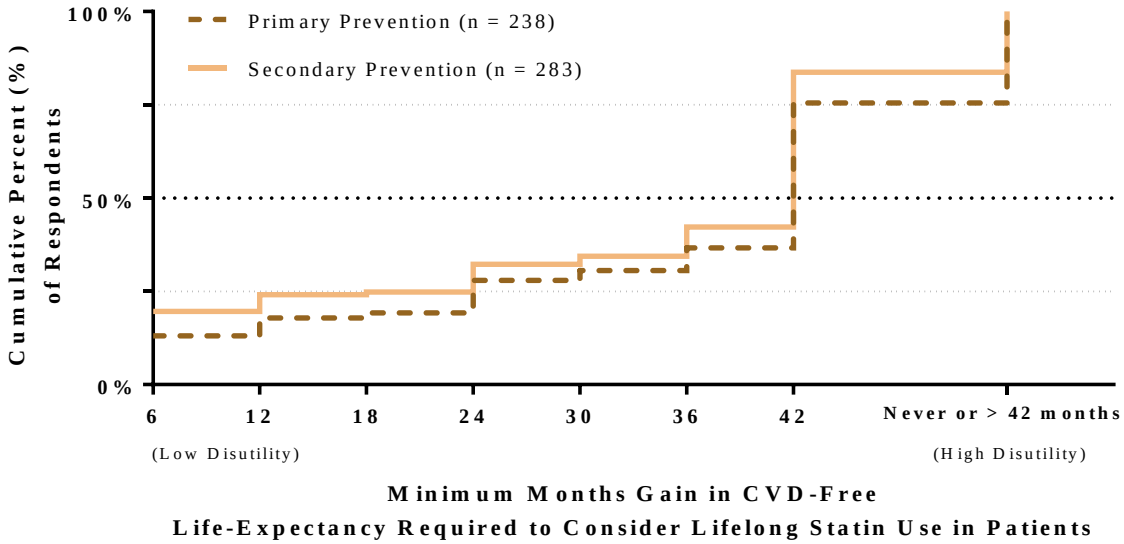
Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin therapy as meaningful, stratified by gender.

Supplemental Figure 2. Months gain in CVD-free life-expectancy required to consider personal use of statin therapy, stratified by sex in patients



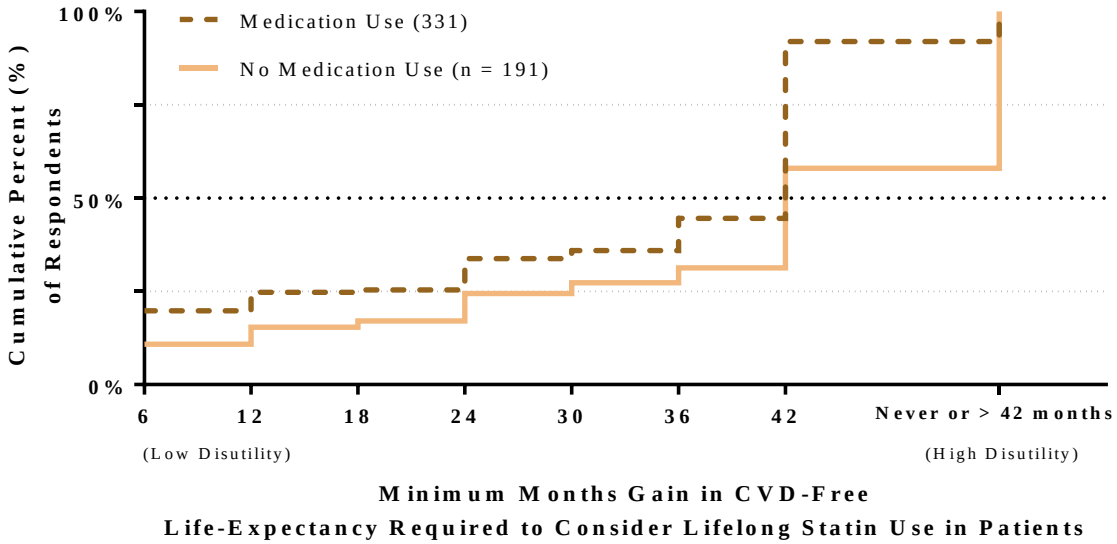
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by gender.

Supplemental Figure 3. Months gain in CVD-free life-expectancy required to consider personal use of statin therapy in patients, stratified by medical history of CVD in patients



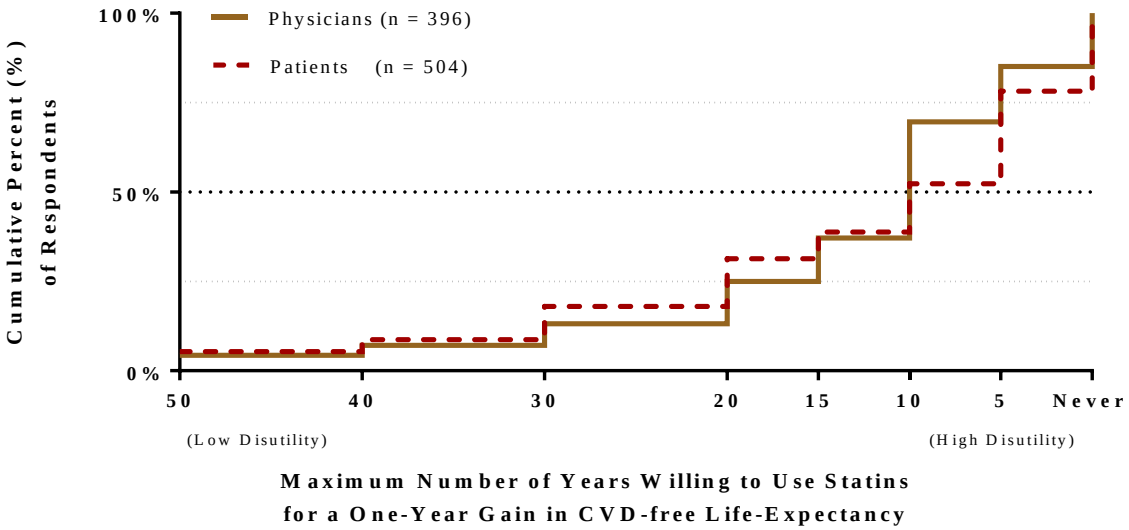
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by presence of CVD.

Supplemental Figure 4. Months gain in CVD-free life-expectancy required to consider personal use of statin therapy in patients, stratified by medication use in patients



Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by use of either statin or antihypertensive medication.

Supplemental Figure 5. Years willing use statin therapy for a one year gain in CVD-free life-expectancy



Legend: Maximum number of years patients and physicians would be willing to take statin medication (for personal use). Results were similar to main analysis. In total, 14.2% of physicians were unwilling to use a statin provided the thresholds. Comparatively, 21.5% of patients were unwilling to use a statin provided the thresholds. For those willing to consider therapy, physicians reported a median of 10 years (IQR 10-20), and patients reported a median of 10 years (IQR 5-20).