

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Variation in worthwhile longevity benefit from statin and antihypertensive medications: a cross-sectional study of patients and physicians

| | |
|-------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2017-021309 |
| Article Type: | Research |
| Date Submitted by the Author: | 22-Dec-2017 |
| Complete List of Authors: | Jaspers, Nicole; University Medical Centre Utrecht, Department of Vascular Medicine Visseren, Frank; University Medical Centre Utrecht, Department of Vascular Medicine Numans, Mattijs; Leiden University Medical Centre, Department of Public Health and Primary Care Smulders, Yvo; VU University Medical Center, van Loenen Martinet, Fere; Primary Care Medical Center Randwijck van der Graaf, Yolanda; Julius Center for Health Sciences and Primary Care Dorresteijn, Jannick; University Medical Centre Utrecht, Department of Vascular Medicine |
| Keywords: | PRIMARY CARE, PREVENTIVE MEDICINE, VASCULAR MEDICINE, Doctor-Patient Communication, Shared Decision Making, Individualized Prevention |
| | |

SCHOLARONE™
Manuscripts

Only

1
2
3 1 **Variation in worthwhile longevity benefit from statin and antihypertensive medications: a cross-**
4 **sectional study of patients and physicians**
5 2
6
7 3
8

9 4 **Authors:** Nicole E.M. Jaspers, MD^a; Frank L.J. Visseren, MD PhD^a, Mattijs E Numans MD PhD^b, Yvo M
10 5 Smulders, MD PhD^c; F. van Loenen Martinet MD^d; Yolanda van der Graaf, MD PhD^e; Jannick A.N.
11 6 Dorresteijn, MD PhD^a.
12
13
14 7
15

16 8 ^a Department of Vascular Medicine, University Medical Center Utrecht, the Netherlands;

17
18 9 ^b Department of Public Health and Primary Care, Leiden University Medical Center, the Netherlands

19
20
21 10 ^c Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands

22
23 11 ^d Primary Care Medical Center Randwijck, Amstelveen, the Netherlands

24
25 12 ^e Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
26
27
28 13

29
30 14 *Correspondence: Professor Frank Visseren, MD PhD; Department of Vascular Medicine, University
31 15 Medical Centre Utrecht; PO Box 85500, 3508 GA Utrecht, the Netherlands; Phone: +31(0)887555161;
32 16 Fax: +31(0)887555488; Email: F.L.J.Visseren@umcutrecht.nl
33

34 17
35
36 18 Word count: 4880
37
38 19
39
40 20
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **21 ABSTRACT**
4

5 **22 Objective:** Expressing therapy-benefit from a lifetime perspective, instead of only a 10-year perspective,
6
7 **23** is both more intuitive and of growing importance in doctor-patient communication. In cardiovascular
8
9 **24** disease (CVD) prevention, lifetime estimates are increasingly accessible via online decision-tools.
10
11 **25** However, it is unclear what gain in life-expectancy is considered meaningful by those who would use the
12
13 **26** estimates in clinical practice. We therefore quantified lifetime and 10-year benefit thresholds at which
14
15 **27** physicians and patients perceive statin and antihypertensive therapy as worthwhile, and compared the
16
17 **28** thresholds to clinically attainable benefit.
18

19
20 **29 Design:** Cross-sectional study
21

22
23 **30 Settings:** 1) continuing medical education conference in December 2016 for physicians 2) CVD
24
25 **31** information session in April 2017 for patients.
26

27
28 **32 Participants:** 400 primary care physicians and 523 patients
29

30
31 **33 Outcome:** Months gain of CVD-free life-expectancy at which lifelong statin therapy is perceived as
32
33 **34** worthwhile, and months gain at which 10-years of statin and antihypertensive therapy is perceived as
34
35 **35** worthwhile. Physicians were framed as users for lifelong and prescribers for 10-year therapy.
36

37
38 **36 Results:** A wide range meaningful benefit was reported within each group. Meaningful lifetime statin
39
40 **37** benefit was 24 months (interquartile range, IQR 23–36) in physicians (as users) and 42 months (IQR 12–
41
42 **38** 42) in patients willing to consider therapy. Meaningful ten-year statin benefit was 12 months (IQR 10-12)
43
44 **39** for prescribing (physicians) and 14 months (IQR 10-14) for using (patients). Meaningful ten-year
45
46 **40** antihypertensive benefit was 12 months (IQR 8-12) for prescribing (physicians) and 14 months (IQR 10-
47
48 **41** 14) for using (patients). Females desired greater benefit than males. Age, CVD-status, and co-medication
49
50 **42** had minimal effect on outcomes.
51

52 **43 Conclusion:** Both physicians and patients report a large variation in meaningful longevity-benefit.
53
54 **44** Moreover, desired benefit differs between physicians and patients and exceeds what is clinically
55

1
2
3 45 attainable. Clinicians should recognize these discrepancies when prescribing CVD-prevention and
4
5 46 implement individualized medicine and shared decision-making to avoid one-size fits all standards.
6
7

8 47

9
10 48 **Strengths and Limitations of the Study:**

- 11
12
13 49 • We examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating
14
15 50 pre-conceived notions about the costs, side-effects, and inconveniences of medication which are
16
17 51 a daily part of clinical practice.
18
19 52 • In contrast to previous studies, we surveyed a large sample of both physicians and actual
20
21 53 patients in comparable settings.
22
23 54 • The use of a multiple-choice voting system may have limited response variation.
24
25 55 • Further research would be necessary to analyze how these perspectives would relate to actual
26
27 56 use of medication by patients and prescription of medication by physicians.
28
29

30 57

31 58

32 59

33 60

34 61

35 62

36 63

37 64

38 65

39 66

40 67

41 68

42 69

43

44

45

46

47

70 INTRODUCTION

71 Risk assessment integral to the prevention of cardiovascular disease (CVD). Accordingly, there is an
72 increasing number of risk-scores available to aid in the identification of individuals with a high CVD-risk
73 (e.g. Framingham, Systemic Coronary Risk Evaluation [SCORE], QRISK). (1, 2) Some scores estimate
74 individualized prognosis not only in terms of absolute risk but in also in terms of life-expectancy free of
75 CVD. The use of these lifetime estimations has been endorsed by prevention guidelines to facilitate
76 doctor-patient communication and cultivate patient motivation.(3, 4)

77
78 In addition to prognosis, some algorithms also estimate individual therapy-benefit from common
79 preventive therapies such as lipid- and blood-pressure lowering medications. However, measures such
80 as absolute risk reduction or number needed to treat are often difficult for patients to understand.(5) In
81 contrast, gain in life-expectancy may facilitate patient understanding of preventive therapy.(6, 7) Tools to
82 estimate lifetime therapy benefit are increasingly accessible to both doctors and patients via online
83 calculators. One such decision-aid, the Joint British Societies for prevention of cardiovascular disease
84 (JBS3) risk calculator, (8) has also been endorsed by international guidelines.(3) These decision-aids
85 may further facilitate shared decision-making and doctor-patient communication, both of growing
86 importance in clinical practice and policy,(9) despite evidence that physicians may be insensitive to
87 patient preferences when recommending statin therapy.(10)

88
89 Despite the guideline endorsed importance of lifetime estimates and an increased emphasis on doctor-
90 patient communication and shared decision-making, little research has investigated what lifetime therapy-
91 benefit is deemed by both patients and prescribers as sufficient to offset the inconveniences of specific
92 CVD-pharmacotherapies. As lifetime estimates and decision-tools gain accessibility in clinical practice, it
93 becomes more essential examine perceptions of meaningful therapy, and potential discrepancies
94 between doctor- and patient perceptions. Previous studies have either focused on non-lifetime metrics in
95 hypothetical risk scenarios(11, 12) or on idealized medications, (10, 13-16) which do not exist in clinical
96 practice. Therefore, the study objective was to quantify perceptions on meaningful lifetime and 10-year
97 benefit, defined as the gain in CVD-free life-expectancy above which physicians (as users and

1
2
3 98 prescribers) and patients consider statin and antihypertensive medication worthwhile. We also aimed to
4
5 99 compare these thresholds to what is a clinically achievable benefit in the primary prevention.
6

7 100

8 101 **METHODS**

9 102 **Setting and Participants**

10
11
12
13 103 Two separate settings, in which a large number of patients and physicians could be recruited and
14
15 104 surveyed were chosen for this cross-sectional study. Primary care physicians were recruited and
16
17 105 surveyed on the same day among attendees of the national Continuing Medical Education conference
18
19 106 (Boerhaave “Progress and Practice”), in Leiden, The Netherlands (December 8th, 2016) targeted to
20
21 107 primary prevention health-care providers. Of the survey respondents, only participants reporting
22
23 108 themselves as primary care physicians were included in the analyses. Patients were recruited and
24
25 109 surveyed during three separate plenary sessions at a one-day information conference targeted to primary
26
27 110 and secondary CVD prevention patients at the University Medical Center Utrecht in the Netherlands (April
28
29 111 8th, 2017). All surveyed patients were included in the analyses.
30

31 112 **Survey Preparation and Administration**

32
33
34 113 Both patient organizations and primary care physicians were involved in preparation of the study. The
35
36 114 research question and study design evolved from a discussion session with a patient panel at
37
38 115 PGOSupport conference, an independent nation-wide network for patient-organizations, held in
39
40 116 Amstelveen, the Netherlands in April 2016. A pretest session involving fifty primary care physicians was
41
42 117 conducted in October 2016 to review the research questions and proposed survey, and guide multiple-
43
44 118 choice answer options of the electronic (physician) or paper (patient) questionnaires ultimately used for
45
46 119 data collection (Supplement A&B). The finalized surveys were subsequently administered at the
47
48 120 respective sessions (Boerhaave and Utrecht). To ensure informed and comparable responses, an
49
50 121 audience-appropriate 10-minute introduction on individual therapy-benefit was given prior to each
51
52 122 session. At the start of each session, all participants were informed that a voluntary survey would be
53
54 123 conducted and data collected and treated anonymously. The study was conducted in accordance with the
55
56
57
58
59
60

1
2
3 124 principles of the Declaration of Helsinki and prospectively granted exempt status by the Medical Ethics
4
5 125 Committee of the University Medical Center Utrecht.
6
7

8 126 **Outcome Definition**

9
10 127 Lifetime benefit thresholds for physicians and patients were quantified as the gain in CVD-free life-
11
12 128 expectancy desired prior to considering or continuing personal statin therapy. Ten-year benefit thresholds
13
14 129 were quantified as the gain in CVD-free life-expectancy desired for 10-years of both statin and
15
16 130 antihypertensive medication use prior to considering or continuing prescription (physicians) or personal
17
18 131 use (patients). Physicians were thus framed as users for lifetime thresholds and prescribers for 10-year
19
20 132 thresholds.
21
22

23 133 **Comparison of Clinically Attainable and Meaningful Benefit Thresholds**

24
25 134 Meaningful benefit was compared to clinically attainable benefit using a variant of the European Society
26
27 135 of Cardiology recommended Systematic Coronary Risk Evaluation (SCORE)-chart used in national
28
29 136 primary prevention guidelines.(3, 17) For each of the 600 risk-factor combinations [age, systolic blood
30
31 137 pressure (SBP), smoking status, sex, and total cholesterol] the JBS risk-calculator(18) was used to
32
33 138 estimate the gain in CVD-free life-expectancy for statin and antihypertensive medications. Clinically
34
35 139 attainable lipid-lowering was estimated with simvastatin 40 mg, a mid-potency statin commonly prescribed
36
37 140 as initial therapy(19) which reduces LDL-c levels by 37% irrespective of baseline level.(20) Clinically
38
39 141 attainable blood-pressure lowering was estimated with a single, initial antihypertensive medication, using
40
41 142 the formula $9.1 \text{ mmHg} + 0.10 \text{ mmHg} * (\text{current SBP} - 154 \text{ mmHg})$.(21) To estimate clinically attainable
42
43 143 benefit for 10-years of medication use, gain in life-expectancy estimated by the calculator was divided by
44
45 144 the life-expectancy estimated by the calculator. This estimated gain per 10-years of use was
46
47 145 subsequently graphically juxtaposed against reported 10-year thresholds, expressed as months gain in
48
49 146 CVD-free life-expectancy desired for 10 years of use prior to considering or continuing prescription
50
51 147 (physicians) or personal use (patients). For clarity, values used for the calculations are provided in
52
53 148 supplemental Table 1, and a calculation example is provided in supplement D(22-24).
54

55 149
56
57
58
59
60

150 **Data Analysis**

151 Age was converted to numeric values. Thresholds in terms of minimal desired months gain were
152 described using medians and interquartile ranges (IQR). Wilcoxon rank-sum and spearman correlations
153 were used to analyze lifetime thresholds according to certain characteristics pre-defined to be potentially
154 of influence on response: age, sex, use of either statin or antihypertensive medication (yes/no), and
155 presence of CVD (yes/no). (25, 26) Paired-samples Wilcoxon signed-rank tests were used to assess
156 response differences between 10-year statin and antihypertensive medication thresholds. Missing values
157 were not imputed, and the number of participants in each analysis reported. Analyses were performed
158 using R-Statistical Software, version 3.1.1.

159 **RESULTS**

160 **Participants and Response**

161 Of the 455 physician survey respondents, the 400 participants reporting themselves as primary care
162 physicians were included in the analyses. The participant characteristics of the included 400 primary care
163 physicians and 523 patients are depicted in table 1. Physician sex and age distribution reflected the
164 Dutch primary care physician population: 54% male and 46% female. Median age was 55 years (IQR 40-
165 60) in physicians and 69 years (IQR 63-74) in patients. Approximately half (54%, n=283) of patients
166 reported clinical manifestations of CVD, defined as coronary heart disease (n=131, 25%),
167 cerebrovascular disease (n=60, 11.5%), peripheral artery disease (n=24, 4.6%), or multiple CVD
168 manifestations (n=65, 12.5%).

169 **Personal meaningful lifetime benefit**

170 Meaningful lifetime benefit is presented in figure 1. In total, 12.9% (n=51) of physicians considered the
171 maximum gain (42 months) insufficient for personal use. The remaining physicians desired 24 months
172 (IQR 23-36) gain. Age was not associated with physician thresholds (spearman rho -0.07, p=0.20).
173 Physician responses differed by sex (rank-sum, p=0.003): males, 24 months (IQR 12-36); females 30
174 months (IQR 24-36). In comparison, 20.0% (n=100) of patients considered the maximum gain (also 42
175 months) insufficient. The remaining patients desired 42 months (IQR 12-42) gain. Older patients desired

1
2
3 176 marginally higher gain than younger patients (per year, spearman rho 0.10, $p=0.04$). Patient responses
4
5 177 differed by sex (rank-sum, $p=0.04$): males, 36 months (IQR 6-42); females 42 months (IQR 24-42)
6
7 178 (supplemental figures 1&2). Median threshold did not differ between patients on and off-therapy (rank-
8
9 179 sum, $p=0.47$), although more patients off-therapy (42.1%) than on-therapy (8.1%) considered the
10
11 180 maximum gain of 42 months insufficient. Similarly, median threshold did not differ between patients with
12
13 181 and without clinically manifest CVD (rank-sum, $p=0.49$), although more patients without CVD (24.5%)
14
15 182 than with CVD (16.3%) considered the maximum gain insufficient (supplemental figures 3&4).

17 183 **Meaningful ten-year statin and antihypertensive thresholds**

18
19
20 184 Meaningful ten-year thresholds for statins are depicted in figure 2a. In total, 4.4% ($n=17$) of physicians
21
22 185 considered the maximum gain (14 months for every 10 years of use) insufficient to prescribe statins. The
23
24 186 median worthwhile gain for every 10 years of use was 12 months (IQR 10-12) for the remaining
25
26 187 physicians. In comparison, 16.1% ($n=80$) of patients considered the maximum gain insufficient and the
27
28 188 median ten-year threshold was 14 months (IQR 10-14). Meaningful ten-year thresholds for
29
30 189 antihypertensive medication are depicted in figure 2b. Physician responses for statin and antihypertensive
31
32 190 medication differed (paired signed-rank test, $Z=3736$, $p<0.001$). In total, 2.3% ($n=9$) of physicians
33
34 191 considered the maximum gain (14 months for every 10 years of use) insufficient to prescribe
35
36 192 antihypertensives, and the median worthwhile gain for every 10 years of use was 12 months (IQR 8-12).
37
38 193 Patient responses did not differ for statin and antihypertensive medications ($Z=1795$, $p=0.36$).

40 194 **Comparison of Clinically Attainable and Meaningful Benefit Thresholds**

41
42
43 195 In figure 3, median reported thresholds for prescribing (physicians, 12 months for every 10 years of use)
44
45 196 and using (patients, 14 months for every 10 years of use) statins are juxtaposed against what gain in life-
46
47 197 expectancy is clinically attainable with simvastatin 40mg for each risk-factor combination. Figure 4
48
49 198 provides the same information for a single, daily, antihypertensive medication (physicians, 12 months for
50
51 199 every 10 years of use) and patients (14 months for every 10 years of use).

52
53 200

54
55
56 201

202 DISCUSSION

203 In this study, we quantified lifetime and 10-year benefit thresholds above which 400 physicians and 523
204 patients perceive statin and antihypertensive medications as worthwhile. A high degree of variation in
205 what was perceived as meaningful therapy was reported within both groups. Patients consistently desired
206 a higher lifetime benefit for medication use than physicians. Physicians, but not patients, desired a slightly
207 higher benefit for statin than for antihypertensive medication. In participants willing to use therapy,
208 females desired a higher benefit from statins than their male counterparts. However, other characteristics
209 such as age, use of either statin or antihypertensive medications, and presence of CVD had minimal or
210 no influence on median reported thresholds. The majority of respondents reported desiring a gain in CVD-
211 free life expectancy above what is generally achievable with lifelong use of a single tablet in the primary
212 prevention setting.

213 To our knowledge, this is the first study examining medication-specific thresholds in both physicians and
214 patients in terms of gain in life-expectancy. Previous studies have either focused on non-lifetime metrics
215 in hypothetical risk scenarios,(11, 12)or idealized medications with negligible costs, side-effects, or follow-
216 up requirements.(10, 13-16) Even in these idealized situations, the benefit desired by patients is large,
217 and often greater than the benefit desired by physicians. (11, 12, 25) For an idealized pill, the general
218 public desires 6 months (IQR 1 – 36 months) gain in life-expectancy(15). Health care employees are
219 willing to sacrifice 12.3 (±30) weeks of life to avoid taking a pill.(27) Isolated disutility of pill-taking is
220 applicable in cost-effectiveness studies. However, it does not assess the real-life perceived costs, side-
221 effects, and other inconveniences of specific medications which are encountered in clinical practice. The
222 considerably higher thresholds found in our study can be explained by the use of specific medications
223 and not an idealized tablet.

224 Patients view hypertension treatment as more necessary and effective than hyperlipidemia treatment.(28)
225 However, patients in our study did not distinguish between statin and antihypertensive medications
226 indicating that this discrepancy does not apply if therapy imparts identical benefit. Physicians however did
227 desire greater benefit from statins than antihypertensive medications. Statin side-effects, but not
228 necessarily antihypertensive side-effects, have received wide-spread attention over the previous

1
2
3 229 decades. Negative portrayal of statins in the media and academic press influences healthcare related
4
5 230 behavior and coincides with a decrease in statin use in both primary and secondary prevention.(29) Many
6
7 231 patients may attribute health issues to the use of statins. Myalgia frequency is approximately twice as
8
9 232 high in patients on statins as on placebo in clinical trials. (30) However, this frequency is considerably
10
11 233 higher in observational studies.(31) In clinical practice, physicians are confronted with observational
12
13 234 frequencies.

14
15 235 Compared to a risk-based treatment strategy, treatment based on meaningful therapy thresholds would
16
17 236 produce a shift from mostly older individuals with a high 10-year risk, to a group of younger individuals
18
19 237 with a low 10-year risk, but high lipid levels and high SBP. A previous study investigating eligibility based
20
21 238 on an individualized benefit-based approach described a similar shift in eligibility seen in the present
22
23 239 study. The earlier study based eligibility cut-offs a 10-year absolute risk reduction of $\geq 2.3\%$. (32) The cut-
24
25 240 off was not based on patient perceptions, but on the minimum statin benefit seen in primary prevention
26
27 241 guidelines and resulted in a greater number of eligible patients (34%) compared to current practice (21%).
28
29 242 Other studies have demonstrated that young individuals with high risk-factor levels (i.e. lipid and SBP)
30
31 243 have the greatest net-positive lifetime benefit from CVD-prevention strategies, such as aspirin use(1) and
32
33 244 renin-angiotensin system inhibition.(33) As older patients had a minimal but significantly higher benefit
34
35 245 threshold than younger patients, such a shift is congruent with user views. This shift is also congruent
36
37 246 with changing insights into the benefits of deprescription of the elderly population.(34)

38
39 247 Lifetime based decision-tools have become more accessible in clinical practice to both doctors and
40
41 248 physicians. It is therefore essential to address the high degree of variation in what is considered
42
43 249 meaningful therapy in clinical practice. Choosing a single, uniform, benefit threshold for all patients to
44
45 250 determine therapy eligibility may be too simplistic. Moreover, the discrepancy between perceived
46
47 251 meaningful benefit and clinically attainable benefit should be addressed. Guidelines need not adapt
48
49 252 eligibility thresholds based on views of meaningful therapy. However, the number of prevented CVD-
50
51 253 events is ultimately determined by physicians and patients making guideline-based decisions.
52
53 254 Misperceptions about perceived CVD-risk are commonplace.(35) Likewise, it is conceivable that both
54
55 255 physicians and patients overestimate realistic therapy-benefit and may require guidance as to what

1
2
3 256 longevity benefit may be realistically achieved. Such guidance could be easily incorporated into the same
4
5 257 online decision-aids which are currently available.
6
7

8 258 Certain strengths of this study should be highlighted. First, both parties of the shared decision-making
9
10 259 process were informed and surveyed in comparable settings. Physicians were representative of the
11
12 260 general practitioner population and both primary and secondary prevention patients were surveyed. As
13
14 261 there was no evidence of difference in medians between patients with and without CVD, no stratification
15
16 262 based on primary or secondary prevention was necessary. Secondly, the number of incomplete
17
18 263 responses was low for both physicians (1.0-2.3%) and patients (4.4-5.1%), indicating that both groups
19
20 264 were sufficiently informed to provide valid and reliable responses. Lastly, we examined benefit thresholds
21
22 265 of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-
23
24 266 effects, and inconveniences of medication which are a daily part of clinical practice. Certain study
25
26 267 limitations must also be acknowledged. First, we were restricted to a multiple-choice voting system, which
27
28 268 may have limited response variation. However, the observed variation in our study remained large and
29
30 269 multiple-choice options were based on responses from a pre-test session. Secondly, benefit-threshold
31
32 270 associated with a single medication was surveyed. In practice, if LDL-c or SBP targets are not achieved,
33
34 271 additional medication can be prescribed without necessarily increasing the number of tablets used daily.
35
36 272 However, the value of the opinion-based benefit-thresholds are not altered by this limitation. Thirdly,
37
38 273 patients were recruited at a one-day information conference on CVD-prevention, and may thus represent
39
40 274 a population more interested in CVD-prevention than average. Lastly, further research would be
41
42 275 necessary to analyze how these perspectives would relate to actual use of medication by patients and
43
44 276 prescription of medication by physicians.

45 277

48 278 In conclusion, both physicians and patients report a large variation in meaningful longevity-benefit.
49
50 279 Moreover, desired benefit differed between patients and physicians and exceeded clinically attainable
51
52 280 benefit. Clinicians should recognize these discrepancies when prescribing CVD-prevention and
53
54 281 implement individualized medicine and shared decision-making, thereby avoiding one-size fits all
55
56 282 standards.

1
2
3 283 **Contributors:** NEMJ, FLJV, FLM, YS, YG, and JAND contributed to the conception and/or design of the
4
5 284 work. All authors contributed to the acquisition, analysis or interpretation of the data. NEMJ drafted the
6
7 285 manuscript, and , FLJV, MN, FLM, YS, YG, and JAND critically revised the manuscript. All authors gave
8
9 286 final approval and agree to be accountable for all aspects of work.

10
11 287 **Acknowledgements:** The organizers and participants of the following meetings, conferences, and
12
13 288 sessions: the April 2016 PGOSupport conference in Amstelveen, the November 2016 pilot session in
14
15 289 Roermond, the December 2016 Boerhaave Symposium, the April 2017 University Medical Center Utrecht.

16
17
18 290 **Disclosures:** None

19
20
21 291 **Funding:** This research received no specific grant from any funding agency in the public, commercial or
22
23 292 not-for-profit sectors.

24
25 293 **Data sharing statement:** Data sharing requirements are not applicable as we did not receive informed
26
27 294 consent for data sharing from the participants. However, reasonable inquiries concerning the data may be
28
29 295 made via the corresponding author.

30
31
32 296

33
34
35 297

36
37
38 298

39
40
41 299

42
43 300

44
45
46 301

47
48
49 302

50
51
52 303

53
54 304

305 **REFERENCES:**

- 306 1. Dorresteijn JA, Kaasenbrood L, Cook NR, van Kruijsdijk RC, van der Graaf Y, Visseren FL, et al.
307 How to translate clinical trial results into gain in healthy life expectancy for individual patients. *BMJ*.
308 2016;352:i1548.
- 309 2. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new
310 QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database.
311 *BMJ*. 2010;341:c6624.
- 312 3. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European
313 Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the
314 European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical
315 Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special
316 contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur*
317 *Heart J*. 2016;37(29):2315-81.
- 318 4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, et al. 2013
319 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of
320 Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*.
321 2014;63(25 Pt B):2935-59.
- 322 5. Dickinson R, Raynor DK, Knapp P, MacDonald J. Providing additional information about the
323 benefits of statins in a leaflet for patients with coronary heart disease: a qualitative study of the impact on
324 attitudes and beliefs. *BMJ Open*. 2016;6(12):e012000.
- 325 6. Manuel DG, Abdulaziz KE, Perez R, Beach S, Bennett C. Personalized risk communication for
326 personalized risk assessment: Real world assessment of knowledge and motivation for six mortality risk
327 measures from an online life expectancy calculator. *Inform Health Soc Care*. 2017:1-14.
- 328 7. Galesic M, Garcia-Retamero R. Communicating consequences of risky behaviors: Life
329 expectancy versus risk of disease. *Patient Educ Couns*. 2011;82(1):30-5.
- 330 8. Board JBS. Joint British Societies' consensus recommendations for the prevention of
331 cardiovascular disease (JBS3). *Heart*. 2014;100 Suppl 2:ii1-ii67.
- 332 9. Martin SS, Sperling LS, Blaha MJ, Wilson PW, Gluckman TJ, Blumenthal RS, et al. Clinician-
333 patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to
334 implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol*. 2015;65(13):1361-8.
- 335 10. Halvorsen PA, Aasland OG, Kristiansen IS. Decisions on statin therapy by patients' opinions
336 about survival gains: cross sectional survey of general practitioners. *BMC Fam Pract*. 2015;16:79.
- 337 11. McAlister FA, O'Connor AM, Wells G, Grover SA, Laupacis A. When should hypertension be
338 treated? The different perspectives of Canadian family physicians and patients. *CMAJ*. 2000;163(4):403-
339 8.
- 340 12. Steel N. Thresholds for taking antihypertensive drugs in different professional and lay groups:
341 questionnaire survey. *BMJ*. 2000;320(7247):1446-7.

- 1
2
3 342 13. Stovring H, Gyrd-Hansen D, Kristiansen IS, Nexoe J, Nielsen JB. Communicating effectiveness of
4 343 intervention for chronic diseases: what single format can replace comprehensive information? BMC Med
5 344 Inform Decis Mak. 2008;8:25.
- 7 345 14. Trewby PN, Reddy AV, Trewby CS, Ashton VJ, Brennan G, Inglis J. Are preventive drugs
8 346 preventive enough? A study of patients' expectation of benefit from preventive drugs. Clin Med (Lond).
9 347 2002;2(6):527-33.
- 11 348 15. Fontana M, Asaria P, Moraldo M, Finegold J, Hassanally K, Manisty CH, et al. Patient-accessible
12 349 tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against
13 350 medication disutility. Circulation. 2014;129(24):2539-46.
- 16 351 16. Dahl R, Gyrd-Hansen D, Kristiansen IS, Nexoe J, Bo Nielsen J. Can postponement of an adverse
17 352 outcome be used to present risk reductions to a lay audience? A population survey. BMC Med Inform
18 353 Decis Mak. 2007;7:8.
- 20 354 17. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM. Evaluation of cardiovascular risk
21 355 predicted by different SCORE equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil.
22 356 2010;17(2):244-9.
- 24 357 18. Board JBS. Joint British Societies' consensus recommendations for the prevention of
25 358 cardiovascular disease; JBS3 risk calculator. Available from: <http://www.jbs3risk.com/>.
- 27 359 19. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in
28 360 adults aged 40 and over: United States, 2003-2012. NCHS Data Brief. 2014(177):1-8.
- 30 361 20. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al.
31 362 Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000
32 363 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.
- 34 364 21. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of
35 365 cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from
36 366 prospective epidemiological studies. BMJ. 2009;338:b1665.
- 39 367 22. Recommendations for treatment of hyperlipidemia in adults. A joint statement of the Nutrition
40 368 Committee and the Council on Arteriosclerosis. Circulation. 1984;69(5):1067A-90A.
- 42 369 23. JoJoGenetics. DNA Diagnostics
- 43 370 24. Average Body Mass Index (kg/m²) according to age and gender Netherlands National Institute for
44 371 Public Health and the Environment (RIVM) 2012.
- 46 372 25. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication:
47 373 a systematic review. Heart. 2017.
- 49 374 26. Wegwarth O, Schwartz LM, Woloshin S, Gaissmaier W, Gigerenzer G. Do physicians understand
50 375 cancer screening statistics? A national survey of primary care physicians in the United States. Ann Intern
51 376 Med. 2012;156(5):340-9.
- 53 377 27. Hutchins R, Viera AJ, Sheridan SL, Pignone MP. Quantifying the utility of taking pills for
54 378 cardiovascular prevention. Circ Cardiovasc Qual Outcomes. 2015;8(2):155-63.

- 1
2
3 379 28. Stack RJ, Bundy C, Elliott RA, New JP, Gibson JM, Noyce PR. Patient perceptions of treatment
4 380 and illness when prescribed multiple medicines for co-morbid type 2 diabetes. *Diabetes Metab Syndr*
5 381 *Obes.* 2011;4:127-35.
- 7 382 29. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, et al. Impact of statin
8 383 related media coverage on use of statins: interrupted time series analysis with UK primary care data.
9 384 *BMJ.* 2016;353:i3283.
- 11 385 30. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the
12 386 evidence for the efficacy and safety of statin therapy. *Lancet.* 2016;388(10059):2532-61.
- 14 387 31. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-Associated Side Effects. *J Am Coll Cardiol.*
15 388 2016;67(20):2395-410.
- 17 389 32. Thanassoulis G, Williams K, Altobelli KK, Pencina MJ, Cannon CP, Sniderman AD. Individualized
18 390 Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease.
19 391 *Circulation.* 2016;133(16):1574-81.
- 21 392 33. Schievink B, Kropelin T, Mulder S, Parving HH, Remuzzi G, Dwyer J, et al. Early renin-
22 393 angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal
23 394 disease in patients with type 2 diabetes. *Diabetes Obes Metab.* 2016;18(1):64-71.
- 25 395 34. Jansen J, Naganathan V, Carter SM, McLachlan AJ, Nickel B, Irwig L, et al. Too much medicine
26 396 in older people? Deprescribing through shared decision making. *BMJ.* 2016;353:i2893.
- 28 397 35. Katz M, Laurinavicius AG, Franco FG, Conceicao RD, Carvalho JA, Pesaro AE, et al. Calculated
29 398 and perceived cardiovascular risk in asymptomatic subjects submitted to a routine medical evaluation:
30 399 The perception gap. *Eur J Prev Cardiol.* 2015;22(8):1076-82.

34 400

37 401

39 402

42 403

45 404

48 405

50 406

53 407

56 408

409 **Table 1 Baseline Characteristics**

| | Primary Care Physicians | Patients |
|--------------------------------|-------------------------|----------------|
| | n=400 | n = 523 |
| Gender | | |
| Male | 195 (54%) [†] | 263 (50%) |
| Female | 164 (46%) | 260 (50%) |
| Age | | |
| ≤ 34 | 31 (8%) [†] | 12 (2%) |
| 35-45 | 67 (18%) | 15 (3%) |
| 46-52 | 63 (17%) | 19 (4%) |
| 53-57 | 67 (18%) | 21 (4%) |
| 58-62 | 89 (24%) | 57 (11%) |
| 63-67 | 41 (11%) | 110 (21%) |
| 68-72 | 6 (2%) | 130 (25%) |
| ≥ 73 | 3 (1%) | 159 (30%) |
| Statin Use | | |
| Yes | - | 298 (57%)* |
| No | - | 166 (32%) |
| Previously used | - | 55 (11%) |
| Unknown | - | 4 (1%) |
| Antihypertensive Use | | |
| Yes | - | 301 (58%)* |
| No | - | 187 (36%) |
| Previously used | - | 30 (6%) |
| Unknown | - | 4 (1%) |
| Clinically Manifest CVD | | |
| Yes | - | 283 (54%)* |
| No | - | 238 (46%) |

423 Missing data for baseline characteristics is denoted as * (<1%) or † (between 8% and 10%); Clinically
424 manifest cardiovascular disease (CVD) is defined as presence of one or more of the following: coronary
425 heart disease, cerebrovascular disease, and peripheral artery disease.

426

427

428

429

430

431 Figures Legends**432 Figure 1 Legend:**

433 Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin
434 therapy as worthwhile. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

435 Figure 2 a. and b. Legend:

436 Months gain in CVD-free life-expectancy above which physicians (as prescribers) and patients (as users)
437 consider a) statin and b) antihypertensive therapy worthwhile. Missing responses was seen in 5
438 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients
439 (5.1%) for antihypertensive medication.

440 Figure 3 Legend:

441 Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong
442 therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and
443 smoking status calculated with the JBS3 risk score. Orange blocks represent the CVD-free life-expectancy
444 for which physicians considered prescribing (12 months gain for 10 years of use) and patients considered
445 using a statin medication (14 months gain to 10 years of use).

446 Figure 4 Legend:

447 Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong
448 therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-
449 profile, blood-pressure and smoking status calculated with the JBS3 risk score. Orange blocks represent

1
2
3 450 the CVD-free life-expectancy for which physicians considered prescribing (12 months gain for 10 years of
4
5 451 use) and patients considered using a statin medication (14 months gain to 10 years of use).
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

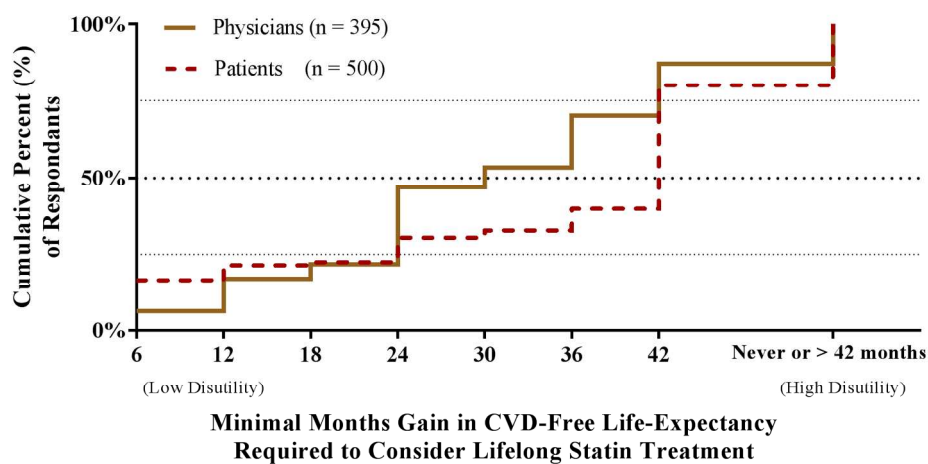


Figure 1. Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin therapy as worthwhile. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

173x87mm (300 x 300 DPI)

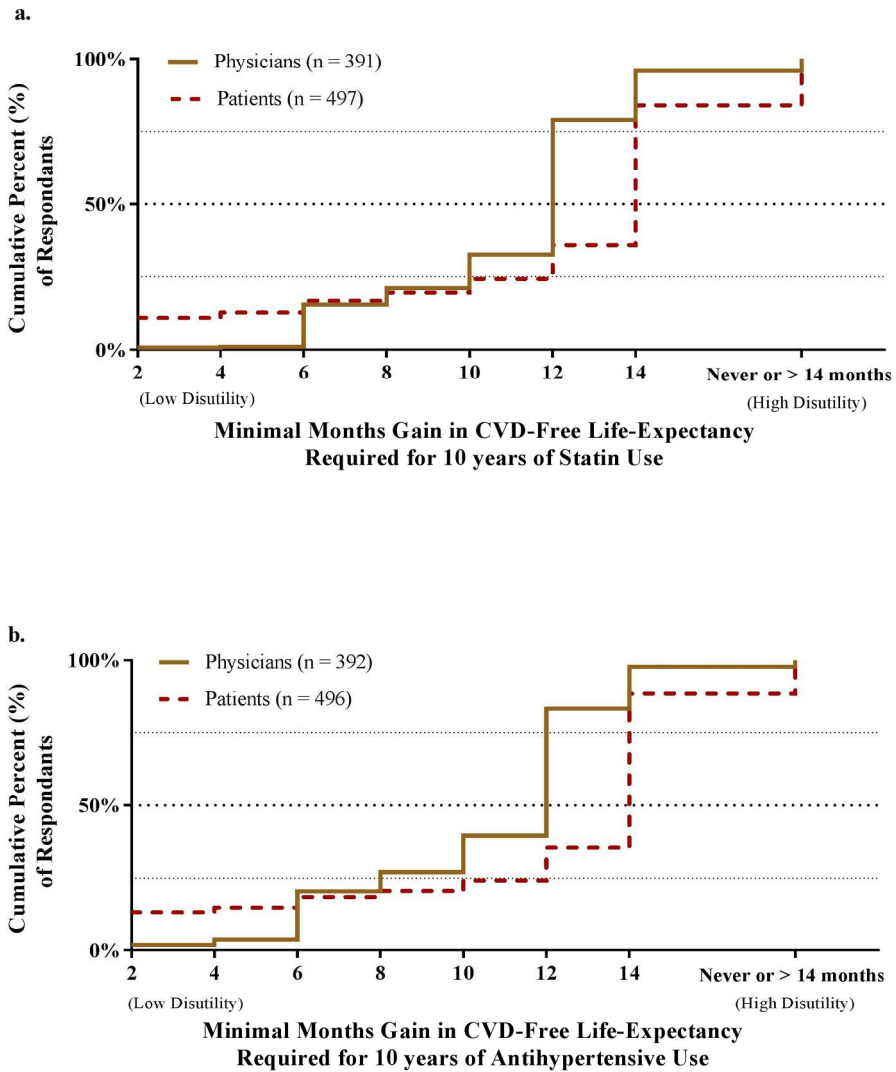


Figure 2. Minimal gain in CVD-free life-expectancy to perceive a) statin and b) antihypertensive therapy as worthwhile. Missing responses was seen in 5 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients (5.1%) for antihypertensive medication.!! †

205x235mm (300 x 300 DPI)

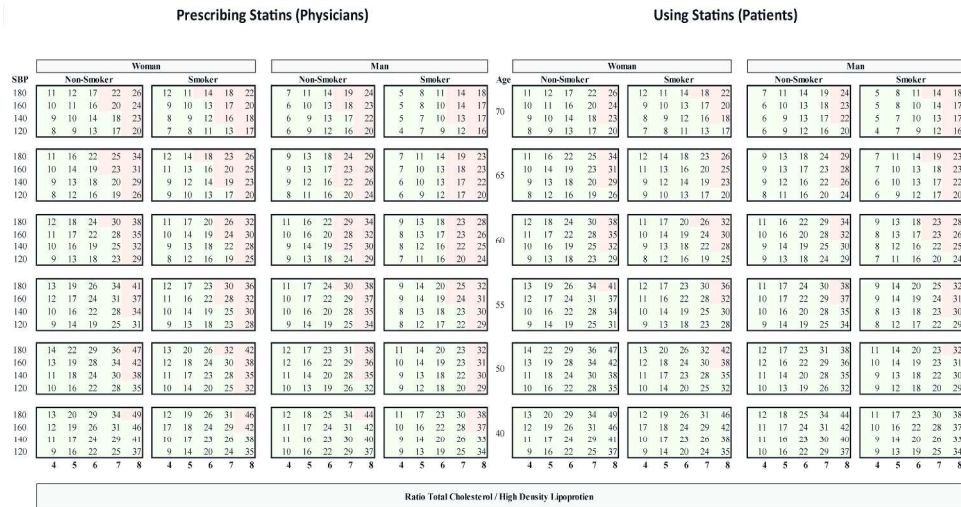


Figure 3. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Orange blocks represent the CVD-free life-expectancy for which physicians considered prescribing (12 months gain for 10 years of use) and patients considered using a statin medication (14 months gain for 10 years of use).

300x176mm (300 x 300 DPI)

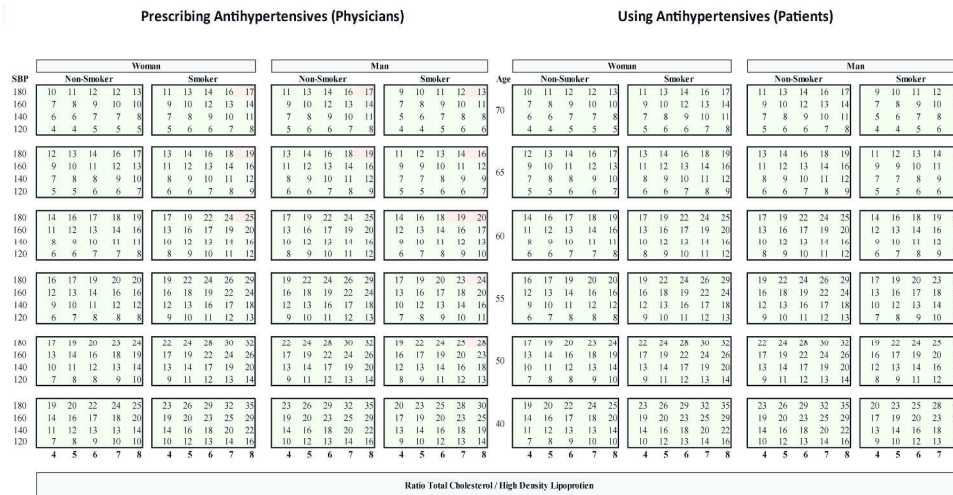


Figure 4. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Orange blocks represent the CVD-free life-expectancy for which physicians considered prescribing (12 months gain for 10 years of use) and patients considered using a statin medication (14 months gain to 10 years of use).

300x175mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SUPPLEMENTAL MATERIAL

- A) Physician Survey:2
- B) Patient Survey:5
- C) Values Used for Calculations :8
- D) Example Calculation:9
- E) Supplemental Figures:10

For peer review only

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 in the Netherlands.*

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

- 1
2
3 4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is
4
5 the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*"
6
7 the medication must provide before you considered use worthwhile?
8
9 a. ½ year (low threshold)
10
11 b. 1 year
12
13 c. 1 ½ year
14
15 d. 2 year
16
17 e. 2 ½ year
18
19 f. 3 year
20
21 g. 3 ½ year (high threshold)
22
23 h. I would never want to use a statin *Or only above these thresholds*
24
25
26
27
28 5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease
29
30 "*healthy life years.*" What is the **maximum** number of years you would personally consider using
31
32 this statin to achieve this benefit?
33
34 a. I would never want to use a statin; *Or only above these thresholds*
35
36 b. 5 year (high threshold)
37
38 c. 10 year
39
40 d. 15 year
41
42 e. 20 year
43
44 f. 30 year
45
46 g. 40 year
47
48 h. 50 year (low threshold)
49
50
51
52
53 6. What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, "*healthy life*
54
55 *years*", necessary before you consider **10 years of statin therapy** for a **patient** worthwhile?
56
57
58
59
60

- 1
2
3 a. 2 months (low threshold)
4
5 b. 4 months
6
7 c. 6 months
8
9 d. 8 months
10
11 e. 10 months
12
13 f. 12 months
14
15 g. 14 months (high threshold)
16
17 h. I would never consider statin prescription worthwhile. *Or only above these thresholds*
18
19
20
21
22 7. And what we aren't talking about statins, but about blood-pressure therapy?
23
24 What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, "*healthy life*
25
26 *years*", necessary before you consider **10 years of blood-pressure therapy** for a **patient**
27
28 worthwhile?
29
30 a. 2 months (low threshold)
31
32 b. 4 months
33
34 c. 6 months
35
36 d. 8 months
37
38 e. 10 months
39
40 f. 12 months
41
42 g. 14 months (high threshold)
43
44 h. I would never consider blood-pressure medication prescription worthwhile; *Or only above*
45
46 *these thresholds*
47
48
49
50
51
52
53
54
55
56
57
58
59
60

B) Patient Survey:

The following patient survey was conducted on April 7th, 2017 at the University Medical Center 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

- 1
2
3 a stent, angioplasty, or other operation of the hart
4
5 an operation of the carotid artery (*major artery of the neck*)
6
7 I have never had *ANY* of the above
8
9
- 10 5. Imagine **you** were considering starting (or continuing) a statin medication. What in the minimum
11 gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication
12 must provide before you considered use worthwhile?
13
14
15
- 16 a. ½ year (low threshold)
17
18 b. 1 year
19
20 c. 1 ½ year
21
22 d. 2 year
23
24 e. 2 ½ year
25
26 f. 3 year
27
28 g. 3 ½ year (high threshold)
29
30 h. I would never want to use a statin ; *Or only above these thresholds*
31
32
- 33 6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease
34 "*healthy life years.*" What is the **maximum** number of years you would consider using the statin
35 to achieve this benefit?
36
37
38
- 39 a. I would never consider a statin worthwhile; *Or only above these thresholds*
40
41 b. 5 years (high threshold)
42
43 c. 10 years
44
45 d. 15 years
46
47 e. 20 years
48
49 f. 30 years
50
51 g. 40 years
52
53 h. 50 years (low threshold)
54
55
56
57
58
59
60

1
2
3 7. What is the minimum gain in life-expectancy without (new) cardiovascular disease,
4 "healthy life years", necessary before you consider 10 years of statin therapy
5 worthwhile?
6

- 7
8
9
10 a. 2 months (low threshold)
11
12 b. 4 months
13
14 c. 6 months
15
16 d. 8 months
17
18 e. 10 months
19
20 f. 12 months
21
22 g. 14 months (high threshold)
23
24 h. I would never consider a statin worthwhile; *Or only above these thresholds*
25
26
27

28 8. And what we aren't talking about statins, but about blood-pressure therapy?
29

30 What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, "healthy life
31
32 years", necessary before you consider **10 years of blood-pressure therapy** worthwhile?
33

- 34
35 a. 2 months (low threshold)
36
37 b. 4 months
38
39 c. 6 months
40
41 d. 8 months
42
43 e. 10 months
44
45 f. 12 months
46
47 g. 14 months (high threshold)
48
49 h. I would never consider blood-pressure medication worthwhile ; *Or only above these*
50
51 *thresholds*
52
53
54
55
56
57
58
59
60

C) 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) (22-24). 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/m²) was used with Joint British Societies for prevention of cardiovascular disease (JBS3) risk calculator (18). 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 | LDL-c, mmol/l | HDL-c, mmol/l | TG, mmol/l | BMI, kg/m ² |
|----------------|-------|---------------|---------------|------------|------------------------|
| Males | 40-49 | 3.51 | 1.12 | 1.35 | 26.2 |
| | 50-54 | 3.72 | 1.14 | 1.41 | 26.5 |
| | 55-59 | 3.77 | 1.20 | 1.29 | 26.5 |
| | 60-64 | 3.72 | 1.27 | 1.22 | 26.8 |
| | 65-69 | 3.80 | 1.27 | 1.19 | 26.8 |
| | > 70 | 3.69 | 1.25 | 5.56 | 26.2 |
| Females | 40-49 | 3.17 | 1.46 | 0.75 | 24.7 |
| | 50-54 | 3.50 | 1.61 | 1.13 | 25.7 |
| | 55-59 | 3.77 | 1.56 | 1.22 | 25.7 |
| | 60-64 | 3.84 | 1.59 | 1.16 | 26.4 |
| | 65-69 | 3.93 | 1.61 | 1.30 | 26.4 |
| | > 70 | 3.82 | 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

D) Example Calculation:

A male patient, medical history negative for diabetes, 40 years of age, BMI of 26.2 kg/m², 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

$$= \text{Total cholesterol} - \text{median HDL} - \text{median triglyceride} / 2.17$$

$$= \text{Ratio} \times \text{median HDL} - \text{median HDL} - \text{median triglyceride} / 2.17$$

$$= 7 \times 1.12 - 1.12 - 1.35/2.17$$

$$= 6.098 \text{ mmol/L}$$

The effects of simvastatin 40 mg was calculated as follows:

LDL-C_{new}

$$= \text{LDL-c}_{\text{old}} * (1 - \text{percent reduction})$$

$$= 6.098 \text{ mmol/L} * 0.63$$

$$= 3.842 \text{ mmol/L}$$

Estimated attainable therapy-benefit in terms of gain in CVD-free life-years according to the JBS3

Online calculator (18):

Calculated life-expectancy off-treatment = 76 years

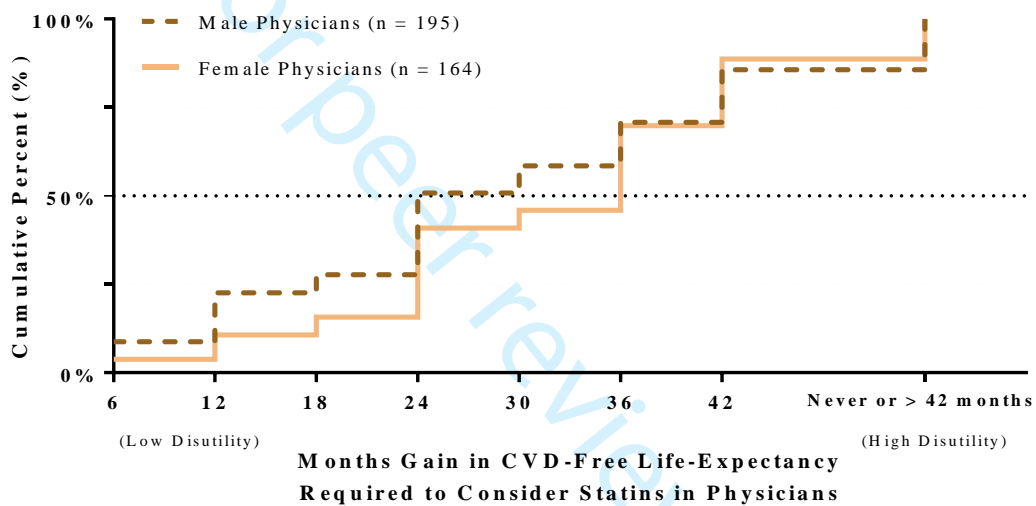
Calculated gain in CVD-free life-expectancy = 2.5 years

Remaining CVD-free life years on-treatment = (76 years + 2.5 years) - 40 years = 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

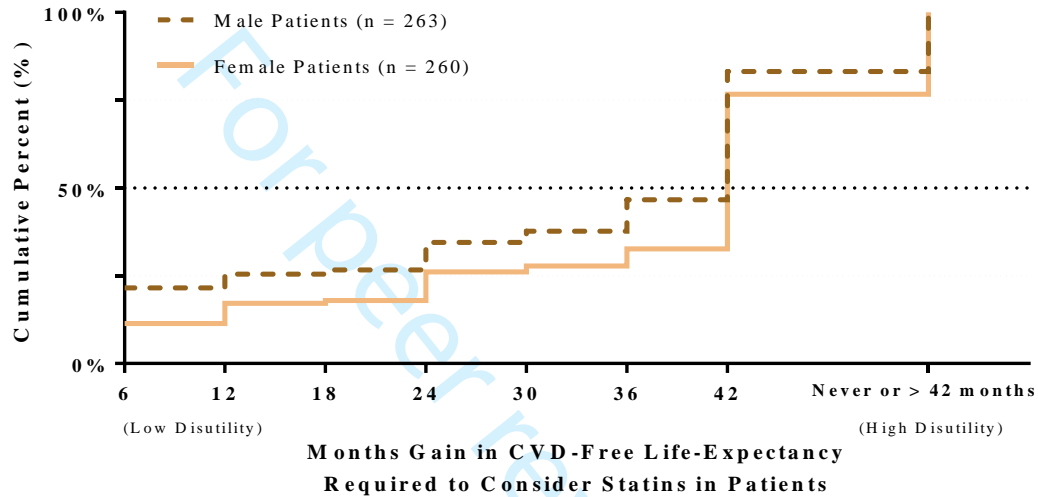
E) Supplemental Figures:

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



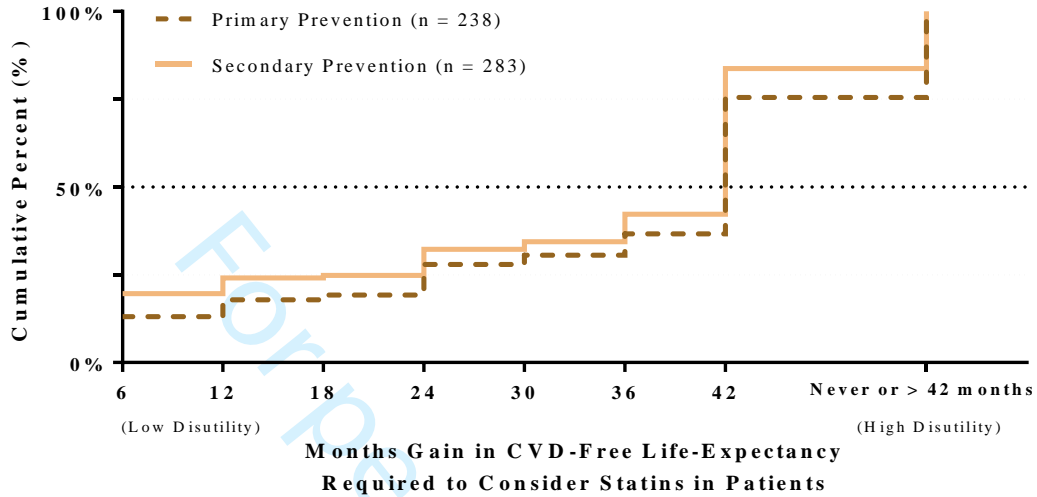
Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin therapy as worthwhile, stratified by gender.

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



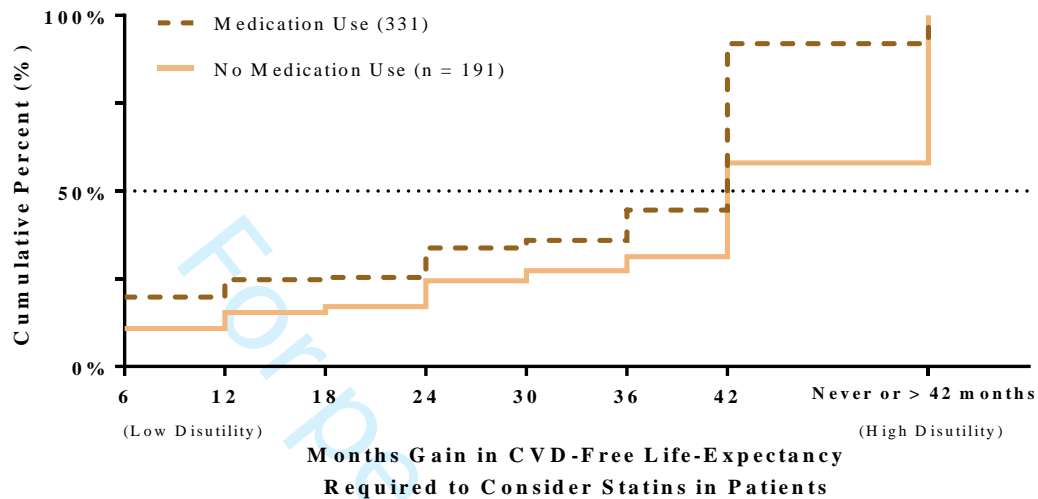
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as worthwhile, stratified by gender.

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 worthwhile, 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 worthwhile, stratified by use of either statin or antihypertensive medication.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

| | Item No | Recommendation | Where? |
|------------------------------|---------|---|--|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | <i>Both in title/abstract Page 1 & 2</i> |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | <i>Structured abstract Page 2</i> |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | <i>Introduction, page 4-5</i> |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | <i>End of introduction, page 4- 5</i> |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | <i>Settings & participants Page 5</i> |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | <i>Settings & participants & Survey preparation and administration pages 5-6</i> |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants | <i>Settings & participants Page 5</i> |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | <i>Settings & participants (5-6), Outcomes (page 6) and data analysis (page 7)</i> |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | <i>Survey preparation and administration Supplemental data a & C for surveys (pages 2- 7)</i> <i>Survey preparation and administration (page 5)</i> |
| Bias | 9 | Describe any efforts to address potential sources of bias | <i>Survey preparation and administration (page 5)</i> |
| Study size | 10 | Explain how the study size was arrived at | <i>Choice of setting (page 5) and after inclusion (page 7)</i> |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | <i>Data analysis (page 7)</i> |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | <i>Data analysis (page 7)</i> |
| | | (b) Describe any methods used to examine subgroups and interactions | <i>Data analysis (page 7)</i> |
| | | (c) Explain how missing data were addressed | <i>Data analysis (page 7)</i> |
| | | (d) If applicable, describe analytical methods taking | <i>n/a/</i> |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| | | | |
|-------------------|-----|--|---|
| | | account of sampling strategy | |
| | | (e) Describe any sensitivity analyses | n/a/ |
| Results | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | <i>Participants and response (page 7)</i> |
| | | (b) Give reasons for non-participation at each stage | <i>Participants and response gives overview of number of individuals at each stage (page 7)</i> |
| | | (c) Consider use of a flow diagram | <i>Information adequately summarized in text</i> |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | <i>Participants and response (page 7) and (baseline table, page 18)</i> |
| | | (b) Indicate number of participants with missing data for each variable of interest | <i>Baseline table (page 16) and per analysis in results (figures 1, & 2a.b., figure legends, page 17)</i> |
| Outcome data | 15* | Report numbers of outcome events or summary measures | <i>Number of participants reported per analysis, see above for page numbers</i> |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | <i>Medians and interquartiles, results, page 7-8</i> |
| | | (b) Report category boundaries when continuous variables were categorized | <i>Survey in supplement, page 2</i> |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | <i>n/a/</i> |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | <i>Analysis per characteristic reported, Personal meaningful lifetime benefit, page 7-8</i> |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | <i>Principal findings, discussion page 9</i> |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | <i>Strengths and limitations, discussion (page 11) and strengths and limitations section on page 3</i> |

| | | | | |
|----------------------------|--------------------------|----|--|--|
| 1 2 3 4 5 6 | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | <i>Discussion(page 9-11)</i> |
| 7 8 9 10 | Generalisability | 21 | Discuss the generalisability (external validity) of the study results | <i>Discussion. Limitations unlikely to alter conclusion. Page 12</i> |
| 11 | Other information | | | |
| 12 13 14 15 16 | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | <i>Reported, page 13</i> |

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Variation in minimal desired longevity benefit from statin and antihypertensive medications: a cross-sectional study of patient and primary care physician perspectives

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2017-021309.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 13-Mar-2018 |
| Complete List of Authors: | Jaspers, Nicole; University Medical Centre Utrecht, Department of Vascular Medicine Visseren, Frank; University Medical Centre Utrecht, Department of Vascular Medicine Numans, Mattijs; Leiden University Medical Centre, Department of Public Health and Primary Care Smulders, Yvo; VU University Medical Center, van Loenen Martinet, Fere; Primary Care Medical Center Randwijck van der Graaf, Yolanda; Julius Center for Health Sciences and Primary Care Dorresteijn, Jannick; University Medical Centre Utrecht, Department of Vascular Medicine |
| Primary Subject Heading: | Patient-centred medicine |
| Secondary Subject Heading: | Communication, Cardiovascular medicine, Patient-centred medicine |
| Keywords: | PRIMARY CARE, PREVENTIVE MEDICINE, VASCULAR MEDICINE, Doctor-Patient Communication, Shared Decision Making, Individualized Prevention |
| | |

SCHOLARONE™
Manuscripts

1
2
3 1
4 2 **Variation in minimal desired longevity benefit from statin and antihypertensive medications: a**
5 3 **cross-sectional study of patient and primary care physician perspectives**
6
7 4
8

9 5 **Authors:** Nicole E.M. Jaspers, MD^a; Frank L.J. Visseren, MD PhD^a, Mattijs E Numans MD PhD^b, Yvo M
10 6 Smulders, MD PhD^c; Fere van Loenen Martinet MD^d; Yolanda van der Graaf, MD PhD^e; Jannick A.N.
11 7 Dorresteijn, MD PhD^a.
12
13

14 8
15
16
17 9 ^a Department of Vascular Medicine, University Medical Center Utrecht, the Netherlands;
18

19 10 ^b Department of Public Health and Primary Care, Leiden University Medical Center, the Netherlands
20

21 11 ^c Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands
22

23 12 ^d Primary Care Medical Center Randwijck, Amstelveen, the Netherlands
24

25 13 ^e Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
26
27

28 14
29
30 15 *Correspondence: Professor Frank Visseren, MD PhD; Department of Vascular Medicine, University
31 16 Medical Centre Utrecht; PO Box 85500, 3508 GA Utrecht, the Netherlands; Phone: +31(0)887555161;
32 17 Fax: +31(0)887555488; Email: F.L.J.Visseren@umcutrecht.nl
33
34

35 18
36 19 Word count main body: 3,297
37
38 20
39
40 21
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22 ABSTRACT

23 **Objective:** Expressing therapy-benefit from a lifetime perspective, instead of only a 10-year perspective,
24 is both more intuitive and of growing importance in doctor-patient communication. In cardiovascular
25 disease (CVD) prevention, lifetime estimates are increasingly accessible via online decision-tools.
26 However, it is unclear what gain in life-expectancy is considered meaningful by those who would use the
27 estimates in clinical practice. We therefore quantified lifetime and 10-year benefit thresholds at which
28 physicians and patients perceive statin and antihypertensive therapy as meaningful, and compared the
29 thresholds to clinically attainable benefit.

30 **Design:** Cross-sectional study

31 **Settings:** 1) continuing medical education conference in December 2016 for primary care physicians 2)
32 information session in April 2017 for patients

33 **Participants:** 400 primary care physicians and 523 patients in the Netherlands

34 **Outcome:** Months gain of CVD-free life-expectancy at which lifelong statin therapy is perceived as
35 meaningful, and months gain at which 10-years of statin and antihypertensive therapy is perceived as
36 meaningful. Physicians were framed as users for lifelong and prescribers for 10-year therapy.

37 **Results:** Meaningful benefit was reported as median (interquartile range, IQR). Meaningful lifetime statin
38 benefit was 24 months (IQR 23–36) in physicians (as users) and 42 months (IQR 12–42) in patients
39 willing to consider therapy. Meaningful ten-year statin benefit was 12 months (IQR 10-12) for prescribing
40 (physicians) and 14 months (IQR 10-14) for using (patients). Meaningful ten-year antihypertensive benefit
41 was 12 months (IQR 8-12) for prescribing (physicians) and 14 months (IQR 10-14) for using (patients).
42 Females desired greater benefit than males. Age, CVD-status, and co-medication had minimal effect on
43 outcomes.

44 **Conclusion:** Both physicians and patients report a large variation in meaningful longevity-benefit.
45 Desired benefit differs between physicians and patients and exceeds what is clinically attainable.
46 Clinicians should recognize these discrepancies when prescribing therapy and implement individualized

1
2
3 47 medicine and shared decision-making. Decision-tools could provide information on realistic therapy
4
5 48 benefit.
6
7

8 49
9

10 50
11
12

13 51 **Strengths and Limitations of the Study:**
14
15

- 16 52 • We examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating
17
18 53 pre-conceived notions about the costs, side-effects, and inconveniences of medication which are
19
20 54 a daily part of clinical practice.
21
22 55 • In contrast to previous studies, we surveyed a large sample of both physicians and actual
23
24 56 patients in comparable settings.
25
26 57 • The use of a multiple-choice voting system may have limited response variation.
27
28 58 • Further research would be necessary to analyze how these perspectives would relate to actual
29
30 59 use of medication by patients and prescription of medication by physicians.
31

32 60
33

34 61
35

36 62
37

38 63
39

40 64
41

42 65
43

44 66
45

46 67
47

48 68
49

50 69
51

52 70
53

54 71
55
56
57
58
59
60

72 INTRODUCTION

73 Risk assessment integral to the prevention of cardiovascular disease (CVD). Accordingly, there is an
74 increasing number of risk-scores available to aid in the identification of individuals with a high CVD-risk
75 (e.g. Framingham, Systemic Coronary Risk Evaluation [SCORE], QRISK).^{1 2} Some scores estimate
76 individualized prognosis not only in terms of absolute risk but in also in terms of life-expectancy free of
77 CVD. The use of these lifetime estimations has been endorsed by prevention guidelines to facilitate
78 doctor-patient communication and cultivate patient motivation.^{3 4}

79
80 In addition to prognosis, some algorithms also estimate individual therapy-benefit from common therapies
81 such as lipid- and blood-pressure lowering medications. However, measures such as absolute risk
82 reduction or number needed to treat are often difficult for patients to understand.⁵ In contrast, gain in life-
83 expectancy may facilitate patient understanding of preventive therapy.^{6 7} Tools to estimate lifetime
84 therapy benefit are increasingly accessible to both physicians and patients via online calculators. One
85 such decision-aid, the Joint British Societies for prevention of cardiovascular disease (JBS3) risk
86 calculator,⁸ has been endorsed by international guidelines.³ These decision-aids may facilitate shared
87 decision-making and doctor-patient communication, both of growing importance in clinical practice and
88 policy,⁹ even though evidence suggests physicians may be insensitive to patient preferences when
89 recommending therapy.¹⁰

90
91 Despite the guideline endorsed importance of lifetime estimates and an increased emphasis on doctor-
92 patient communication and shared decision-making, little research has investigated what lifetime therapy-
93 benefit is deemed by both patients and prescribers as sufficient to offset the inconveniences of specific
94 CVD-pharmacotherapies. The framing (e.g. positive or negative) and format (e.g. absolute risk reduction
95 or gain in life-expectancy) of communication metrics influence both patient and physician opinions on
96 therapy.¹¹ As both lifetime estimates and decision-tools gain accessibility in clinical practice, it becomes
97 more essential examine perceptions of meaningful therapy and potential discrepancies between doctor-
98 and patient perceptions. Previous studies either did not survey both patients and physicians in similar
99 settings, or focused on situations which do not exist in clinical practice, such as non-lifetime metrics in

1
2
3 100 hypothetical risk scenarios^{12 13} on idealized medications.^{10 14-17} We therefore aimed to quantify
4
5 101 perceptions on meaningful lifetime and 10-year benefit, defined as the gain in CVD-free life-expectancy
6
7 102 above which physicians (as users and prescribers) and patients consider statin and antihypertensive
8
9 103 medication meaningful. We also aimed to compare these thresholds to what is a clinically achievable
10
11 104 benefit in the primary prevention.
12
13 105

14 106 **METHODS**

15 107 **Setting and Participants**

16
17
18
19 108 Two separate settings, in which a large number of patients and physicians could be recruited and
20
21 109 surveyed were chosen. Primary care physicians were recruited and surveyed on the same day among
22
23 110 attendees of a national Continuing Medical Education conference (Boerhaave “Progress and Practice”), in
24
25 111 Leiden, The Netherlands (December 8th, 2016) targeted to primary prevention health-care providers. Of
26
27 112 the survey respondents, only participants reporting themselves as primary care physicians were included
28
29 113 in the analyses. Patients were recruited and surveyed during three separate plenary sessions at a one-
30
31 114 day information conference targeted to primary and secondary CVD prevention patients at the University
32
33 115 Medical Center Utrecht in the Netherlands (April 8th, 2017). All surveyed patients were included in the
34
35 116 analyses.
36

37 117 **Survey Preparation and Administration**

38
39
40 118 A pretest session involving fifty primary care physicians was conducted in November 2016 to review the
41
42 119 research questions and proposed survey, and guide multiple-choice answer options of the electronic
43
44 120 (physician) or paper (patient) questionnaires ultimately used for data collection (Supplement A&B). The
45
46 121 finalized surveys were subsequently administered at the respective sessions (Boerhaave and Utrecht). To
47
48 122 ensure informed and comparable responses, an audience-appropriate 10-minute introduction on
49
50 123 individual therapy-benefit was given prior to each session (Supplement C). In this introduction, an
51
52 124 example of lifetime benefit from smoking cessation and aspirin-therapy was provided.^{1 18} The structure of
53
54 125 the introduction and survey was the same in both physician and patient questionnaires. The survey
55
56 126 questions were presented centrally and sequentially by the researcher, thus preventing participants from
57

1
2
3 127 viewing either previous or future questions or benefitting from time-saving heuristics. The questions were
4
5 128 verbally explained before participants were given the opportunity to respond. At the start of each session,
6
7 129 all participants were informed that a voluntary survey would be conducted and data collected and treated
8
9 130 anonymously. The study was conducted in accordance with the principles of the Declaration of Helsinki
10
11 131 and prospectively granted exempt status by the Medical Ethics Committee of the University Medical
12
13 132 Center Utrecht.

15 133 **Outcome Definition**

18 134 Lifetime benefit thresholds for physicians and patients were quantified as the gain in CVD-free life-
19
20 135 expectancy desired prior to considering or continuing personal statin therapy (i.e. the benefit was
21
22 136 considered meaningful). Ten-year benefit thresholds were quantified as the gain in CVD-free life-
23
24 137 expectancy desired for 10-years of both statin and antihypertensive medication use prior to considering or
25
26 138 continuing prescription (physicians) or personal use (patients). Physicians were thus framed as users for
27
28 139 lifetime thresholds and prescribers for 10-year thresholds. For an exploratory analysis, the outcome was
29
30 140 framed differently and participants were asked to report the number of years willing to take statin
31
32 141 medication provided the therapy would give a one-year gain in CVD-free expectancy.

34 142 **Guideline recommendations and participant views of meaningful therapy**

37 143 European Society of Cardiology (ESC) guideline recommendations on lipid¹⁹ and blood-pressure
38
39 144 therapy²⁰ were compared to what participants viewed as meaningful therapy. The ESC-SCORE algorithm
40
41 145 for low-risk countries was used to establish which risk-factor combinations had sufficient 10-year risk of
42
43 146 CVD-mortality to be eligible for lipid-lowering therapy.¹⁹⁻²¹ In order to establish which risk-factor
44
45 147 combinations would be treated based on participant views of meaningful therapy, clinically attainable
46
47 148 benefit from statin and antihypertensive medication was estimated and compared to views of meaningful
48
49 149 benefit. The JBS risk-calculator²² was used to estimate clinically attainable benefit in terms of gain in
50
51 150 CVD-free life-expectancy for each of the 600 risk-factor combinations [age, systolic blood pressure (SBP),
52
53 151 smoking status, sex, and total cholesterol] of a national ESC-SCORE chart variant.^{3 23} Clinically attainable
54
55 152 gain from statin medication was estimated with simvastatin 40 mg, a mid-potency statin commonly

1
2
3 153 prescribed as initial therapy²⁴ which reduces LDL-c levels by 37% irrespective of baseline level.²⁵
4
5 154 Clinically attainable gain from an antihypertensive was estimated with a single, initial antihypertensive
6
7 155 medication, using the formula $9.1 \text{ mmHg} + 0.10 \text{ mmHg} * (\text{current SBP} - 154 \text{ mmHg})$.²⁶ To express the
8
9 156 clinically attainable benefit per year of medication use, the gain in CVD-free life-expectancy estimated by
10
11 157 the calculator (i.e. the lifetime benefit) was divided by the total remaining on-therapy CVD-free life-years
12
13 158 estimated by the calculator (i.e. the duration of medication use required to achieve this lifetime benefit).
14
15 159 The estimated clinically attainable gain per 10-years of medication use was graphically juxtaposed
16
17 160 against participant views of meaningful benefit, expressed as months gain in CVD-free life-expectancy
18
19 161 desired for 10 years of use prior to considering or continuing prescription (physicians) or personal use
20
21 162 (patients). For clarity, all values used for the calculations, and a calculation example are provided in
22
23 163 supplements D&E.²⁷⁻²⁹
24

25 164 **Data Analysis**

26
27
28 165 Age was converted to numeric values. Thresholds in terms of minimal desired months gain were reported
29
30 166 as median (interquartile range, IQR) within each group. Wilcoxon rank-sum and spearman correlations
31
32 167 were used to analyze lifetime thresholds according to certain characteristics pre-defined to be potentially
33
34 168 of influence on response: age, sex, use of either statin or antihypertensive medication (yes/no), and
35
36 169 presence of CVD (yes/no).^{30 31} Paired-samples Wilcoxon signed-rank tests were used to assess
37
38 170 response differences between 10-year statin and antihypertensive medication thresholds. Missing values
39
40 171 were not imputed, and the number of participants in each analysis reported. Analyses were performed
41
42 172 using R-Statistical Software, version 3.1.1.
43

44 173 **Patient and Public Involvement**

45
46
47 174
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 175 The study has been designed to survey the opinion of a large group of both patient and physicians to
4
5 176 better understand their priorities and preferences. Both patient organizations and primary care
6
7 177 physicians were involved during study preparation. The research question and study design evolved from
8
9 178 a discussion session with a patient panel at PGOSupport conference, an independent nation-wide
10
11 179 network for patient-organizations, held in Amstelveen, the Netherlands in April 2016. Physicians were
12
13 180 involved in the pre-test sessions in Roermond, the Netherlands in November 2016. Participants were not
14
15 181 involved in finding the optimal study recruitment procedures. The findings from this study will be
16
17 182 disseminated to physicians and patients via conferences and newsletters.
18
19 183

22 184 **RESULTS**

25 185 **Participants and Response**

27 186 Of the 455 physician survey respondents, the 400 participants reporting themselves as primary care
28
29 187 physicians were included in the analyses. The participant characteristics of the included 400 primary care
30
31 188 physicians and 523 patients are depicted in table 1. Physician sex and age distribution reflected the
32
33 189 national primary care physician population: 54% male and 46% female. Median age was 55 years (IQR
34
35 190 40-60) in physicians and 69 years (IQR 63-74) in patients. Approximately half (54%, n=283) of patients
36
37 191 reported clinical manifestations of CVD, defined as coronary heart disease (n=131, 25%),
38
39 192 cerebrovascular disease (n=60, 11.5%), peripheral artery disease (n=24, 4.6%), or multiple CVD
40
41 193 manifestations (n=65, 12.5%).

44 194 **Personal meaningful lifetime benefit**

46 195 Meaningful lifetime benefit is presented in figure 1. In total, 12.9% (n=51) of physicians considered the
47
48 196 maximum gain (42 months) insufficient for personal use. The remaining physicians desired 24 months
49
50 197 (IQR 23-36) gain. Age was not associated with physician thresholds (spearman rho -0.07, p=0.20).
51
52 198 Physician responses differed by sex (rank-sum, p=0.003): males, 24 months (IQR 12-36); females 30
53
54 199 months (IQR 24-36). In comparison, 20.0% (n=100) of patients considered the maximum gain (also 42
55
56 200 months) insufficient. The remaining patients desired 42 months (IQR 12-42) gain. Older patients desired

marginally higher gain than younger patients (per year, spearman rho 0.10, $p=0.04$). Patient responses differed by sex (rank-sum, $p=0.04$): males, 36 months (IQR 6-42); females 42 months (IQR 24-42) (supplemental figures 1&2). Median threshold did not differ between patients on and off-therapy (rank-sum, $p=0.47$), although more patients off-therapy (42.1%) than on-therapy (8.1%) considered the maximum gain of 42 months insufficient. Similarly, median threshold did not differ between patients with and without clinically manifest CVD (rank-sum, $p=0.49$), although more patients without CVD (24.5%) than with CVD (16.3%) considered the maximum gain insufficient (supplemental figures 3&4). Similar results were obtained in the exploratory analysis when participants were asked to report the number of years willing to take a statin for one year gain of CVD-free life-expectancy. In total, 14.2% of physicians and 21.5% of patients were not willing to use a statin provided the thresholds. For those willing to use therapy, the time trade-off was similar to the main analysis median physicians 10 years (IQR 10-20), median patient 10 years (IQR 5-20). Results are depicted in supplemental figure 5.

213 **Meaningful ten-year statin and antihypertensive thresholds**

214 Meaningful ten-year thresholds for statins are depicted in figure 2a. In total, 4.4% ($n=17$) of physicians
215 considered the maximum gain (14 months for every 10 years of use) insufficient to prescribe statins. The
216 median meaningful gain for every 10 years of use was 12 months (IQR 10-12) for the remaining
217 physicians. In comparison, 16.1% ($n=80$) of patients considered the maximum gain insufficient and the
218 median ten-year threshold was 14 months (IQR 10-14). Meaningful ten-year thresholds for
219 antihypertensive medication are depicted in figure 2b. Physician responses for statin and antihypertensive
220 medication differed (paired signed-rank test, $Z = 3736$, $p < 0.001$). In total, 2.3% ($n=9$) of physicians
221 considered the maximum gain (14 months for every 10 years of use) insufficient to prescribe
222 antihypertensive therapy, and the median meaningful gain for every 10 years of use was 12 months (IQR
223 8-12). Patient responses did not differ for statin and antihypertensive medications ($Z=1795$, $p=0.36$).

224 **Guideline recommendations and participant views of meaningful therapy**

225 ESC-guideline recommendations and participant views of meaningful therapy for statin medications are
226 juxtaposed against clinically attainable lifetime benefit in figure 3. Colors depict (non)-concordance

1
2
3 227 between guideline recommended therapy and participant views of meaningful benefit. The clinically
4
5 228 attainable gain in CVD-free life-expectancy from lifelong simvastatin 40mg ranged from 4 - 49 months.
6
7 229 Larger gains were seen in younger individuals with high SBP and lipid-levels and smaller gains were seen
8
9 230 in older individuals with low risk-factor levels. Treatment is concordant with participant views if the
10
11 231 clinically attainable gain in CVD-free life-expectancy per 10-years of medication is was equal to or greater
12
13 232 than the reported meaningful benefit thresholds for prescribing and using (i.e. physician median 12
14
15 233 months for every 10 years of use and patient median 14 months for every 10 years of use). Figure 4.
16
17 234 provides the same information for a single, daily, antihypertensive medication; clinically attainable lifetime
18
19 235 gain in CVD-free life-expectancy ranged from 4-35 months and followed a similar distribution pattern to
20
21 236 statin therapy.

23 237 **DISCUSSION**

24
25
26 238 Meaningful statin and antihypertensive therapy for lifetime and 10-years of use was quantified in 400
27
28 239 primary care physicians and 523 patients. A high degree of variation in what was perceived as meaningful
29
30 240 therapy was reported within both patients and physicians. Patients consistently desired a higher lifetime
31
32 241 benefit for medication use than physicians. Females desired a higher benefit from statins than males in
33
34 242 both participant groups. Physicians desired a slightly higher benefit for statin than for antihypertensive
35
36 243 medication. Age had minimal influence on thresholds in patients. Compared to those with CVD, a greater
37
38 244 percentage of healthy respondents were not willing to consider statin therapy. However, the median
39
40 245 thresholds for respondents who were willing to consider therapy did not differ between these two patient
41
42 246 groups. Similar results were found when patients on- and off- preventative therapy were compared. The
43
44 247 majority of respondents reported desiring a gain in CVD-free life expectancy above what is generally
45
46 248 achievable with lifelong use of a single tablet in the primary prevention setting.

47
48 249 To our knowledge, this is the first study examining medication-specific thresholds in both physicians and
49
50 250 patients in terms of gain in life-expectancy. The considerably high thresholds found in our study can be
51
52 251 explained by the use of specific medications and not an idealized tablet. Previous studies have either
53
54 252 focused on non-lifetime metrics in hypothetical risk scenarios,^{12 13} or on idealized medications with
55
56 253 negligible costs, side-effects, or follow-up requirements.^{10 14-17} Even in these idealized situations, the

1
2
3 254 benefit desired by patients is large, and often greater than the benefit desired by physicians.^{12 13 30} For an
4
5 255 idealized pill, the general public desires 6 months gain in life-expectancy.¹⁶ Health care employees are
6
7 256 willing to sacrifice 12.3 weeks of life to avoid taking a pill.³² Such isolated disutility of pill-taking is
8
9 257 applicable in cost-effectiveness studies. However, it does not assess the real-life perceived costs, side-
10
11 258 effects, and other inconveniences of specific medications which are encountered in clinical practice.

12
13 259 In this study, patients without CVD and not using preventive therapy were more often not willing to
14
15 260 consider therapy. However, for those who were willing to consider statin therapy, no group differences
16
17 261 were found in median CVD-free life-expectancy desired. The similar numeric thresholds align with exiting
18
19 262 literature in which socio-economic factors effected willingness to use medication whereas traditional risk-
20
21 263 factors such as the presence of CVD and use of antihypertensive or statin therapy did not.³³ Patients view
22
23 264 hypertension treatment as more necessary and effective than hyperlipidemia treatment.³⁴ However,
24
25 265 patients in our study did not distinguish between statin and antihypertensive medications indicating that
26
27 266 this discrepancy does not apply if therapy imparts identical benefit. Physicians however did desire greater
28
29 267 benefit from statins than antihypertensive medications. Statin side-effects, but not necessarily
30
31 268 antihypertensive side-effects, have received wide-spread attention over the previous decades. Negative
32
33 269 portrayal of statins in the media and academic press influences healthcare related behavior and coincides
34
35 270 with a decrease in statin use.³⁵ Myalgia frequency is approximately twice as high in patients on statins as
36
37 271 on placebo in clinical trials.³⁶ However, this frequency is considerably higher in observational studies,³⁷
38
39 272 and clinicians are confronted with observational frequencies in in clinical practice.

40
41 273 Compared to a risk-based treatment strategy in prevention guidelines, treatment based on meaningful
42
43 274 therapy thresholds would treat fewer risk-factor combinations, and would produce a shift in eligibility to
44
45 275 exclude mostly older individuals with a high 10-year risk and include younger individuals with a low 10-
46
47 276 year risk but high lipid levels and high SBP who would not be treated according the risk-based guidelines.
48
49 277 A previous study investigating eligibility based on an individualized benefit-based approach described a
50
51 278 similar shift in eligibility seen in the present study. The earlier study based eligibility cut-offs on a 10-year
52
53 279 absolute risk reduction of $\geq 2.3\%$.³⁸ However, the cut-off was not based on patient perceptions, but on the
54
55 280 minimum statin benefit seen in primary prevention guidelines, and resulted in a greater number of eligible
56
57
58
59
60

1
2
3 281 patients (34%) compared to current practice (21%). Other studies have demonstrated that young
4
5 282 individuals with high risk-factor levels (i.e. lipid and SBP) have the greatest net-positive lifetime benefit
6
7 283 from CVD-prevention strategies, such as aspirin use¹ and renin-angiotensin system inhibition.³⁹ As older
8
9 284 patients had a minimal but significantly higher benefit threshold than younger patients, such a shift is
10
11 285 congruent with user views. This shift is also congruent with changing insights into the benefits of
12
13 286 deprescription of the elderly population.⁴⁰

14
15 287 Lifetime based decision-tools have become more accessible in clinical practice to both patient and
16
17 288 physicians. It is therefore essential to address the high degree of variation in what is considered
18
19 289 meaningful therapy in clinical practice. The discrepancy between perceived meaningful benefit and
20
21 290 clinically attainable benefit should be addressed and a patient's satisfaction with the expected benefit of
22
23 291 agreed upon therapy could be viewed as an additional indicator of quality of care. However, guidelines
24
25 292 need not adapt eligibility thresholds or target values based on perceptions of meaningful therapy. The
26
27 293 number of prevented CVD-events is ultimately determined by physicians and patients making guideline-
28
29 294 based decisions. Misperceptions about perceived CVD-risk are commonplace, and ⁴¹ it is conceivable
30
31 295 that both physicians and patients overestimate realistic therapy-benefit and may require guidance as to
32
33 296 what longevity benefit may be realistically achieved. Such guidance could be easily incorporated into the
34
35 297 same online decision-aids which are currently available.

36
37
38 298 Certain strengths of this study should be highlighted. First, both parties of the shared decision-making
39
40 299 process were informed and surveyed in comparable settings. Physicians were representative of the
41
42 300 general practitioner population and both primary and secondary prevention patients were surveyed. As
43
44 301 there was no evidence of difference in medians between patients with and without CVD, no stratification
45
46 302 based on primary or secondary prevention was necessary. Secondly, the number of incomplete
47
48 303 responses was low for both physicians (1.0-2.3%) and patients (4.4-5.1%), indicating that both groups
49
50 304 were sufficiently informed to provide valid and reliable responses. Lastly, we examined benefit thresholds
51
52 305 of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-
53
54 306 effects, and inconveniences of medication which are a daily part of clinical practice. Certain study
55
56 307 limitations must also be acknowledged. First, we were restricted to a multiple-choice voting system, which

1
2
3 308 may have limited response variation. However, the observed variation in our study remained large and
4
5 309 multiple-choice options were based on responses from a pre-test session. Second, benefit-threshold
6
7 310 associated with a single medication was surveyed. In practice, if LDL-c or SBP targets are not achieved,
8
9 311 additional medication can be prescribed without necessarily increasing the number of tablets used daily.
10
11 312 However, the magnitude of the opinion-based benefit-thresholds are not altered by this limitation. Third,
12
13 313 patients were recruited at a large, information conference on CVD-prevention, and may represent a
14
15 314 population more interested in CVD-prevention than average. Fourth, the survey was pre-tested in
16
17 315 physicians and subsequently adapted for patients. However, the survey and the preceding introduction
18
19 316 were designed to maximize understandability and comparability. Fifth, clinically attainable benefit was
20
21 317 estimated using the JBS3 risk score and best available evidence from meta-analyses. However, the
22
23 318 estimated benefit differs in populations with different event-rates, such as those with clinically manifest
24
25 319 CVD. Lastly, further research would be necessary to analyze how these perspectives would relate to
26
27 320 actual use of medication by patients and prescription of medication by physicians.

28
29 321 In conclusion, both physicians and patients report a large variation in meaningful longevity-benefit.
30
31 322 Moreover, desired benefit differed between patients and physicians and exceeded clinically attainable
32
33 323 benefit. Clinicians should recognize these discrepancies when prescribing CVD-prevention and
34
35 324 implement individualized medicine and shared decision-making. In the future, guidance as to what
36
37 325 realistic benefit entails may be incorporated into online decision-aids to help physicians and patients
38
39 326 reach a consensus.

40
41 327

42
43
44 328 **Contributors:** NEMJ, FLJV, YG, JAND, contributed to the conception/design of the work. All authors
45
46 329 (NEMJ, FLJV, YG, YS, FLM, MN, JAND) contributed to the acquisition, analysis or interpretation of the
47
48 330 data. NEMJ drafted the work. All authors (NEMJ, FLJV, YG, YS, FLM, MN, JAND) critically revised the
49
50 331 manuscript, and gave final approval and agree to be accountable for all aspects of work.

51
52 332 **Acknowledgements:** We would like to acknowledge the organizers and participants of the following
53
54 333 meetings, conferences, and sessions: the April 2016 PGOSupport conference in Amstelveen, the
55
56
57
58
59
60

1
2
3 334 November 2016 pilot session in Roermond, the December 2016 Boerhaave Symposium in Leiden, and
4
5 335 the April 2017 University Medical Center Utrecht session for patients.
6
7

8 336 **Disclosures:** None
9

10 337 **Funding:** This research received no specific grant from any funding agency in the public, commercial or
11
12 338 not-for-profit sectors.
13
14

15 339 **Data Sharing:** No additional data is available for this study in repositories. However, inquiries concerning
16
17 340 the data may be made to the corresponding author.
18
19

20 341

21
22 342 **REFERENCES:**
23
24

25 343 1. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in
26
27 344 healthy life expectancy for individual patients. *BMJ* 2016;**352**:i1548.
28

29 345 2. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK
30
31 346 model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database.
32
33 347 *BMJ* 2010;**341**:c6624.
34
35

36 348 3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease
37
38 349 prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology
39
40 350 and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by
41
42 351 representatives of 10 societies and by invited experts)Developed with the special contribution of
43
44 352 the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*
45
46 353 2016;**37**(29):2315-81.
47

48 354 4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of
49
50 355 cardiovascular risk: a report of the American College of Cardiology/American Heart Association
51
52 356 Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**(25 Pt B):2935-59.
53
54
55
56
57
58
59
60

- 1
2
3 357 5. Dickinson R, Raynor DK, Knapp P, et al. Providing additional information about the benefits of statins
4
5 358 in a leaflet for patients with coronary heart disease: a qualitative study of the impact on attitudes
6
7 359 and beliefs. *BMJ Open* 2016;**6**(12):e012000.
- 8
9 360 6. Manuel DG, Abdulaziz KE, Perez R, et al. Personalized risk communication for personalized risk
10
11 361 assessment: Real world assessment of knowledge and motivation for six mortality risk measures
12
13 362 from an online life expectancy calculator. *Inform Health Soc Care* 2017:1-14.
- 14
15 363 7. Galesic M, Garcia-Retamero R. Communicating consequences of risky behaviors: Life expectancy
16
17 364 versus risk of disease. *Patient Educ Couns* 2011;**82**(1):30-5.
- 18
19 365 8. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular
20
21 366 disease (JBS3). *Heart* 2014;**100** Suppl 2:ii1-ii67.
- 22
23 367 9. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic
24
25 368 cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA
26
27 369 Guidelines. *J Am Coll Cardiol* 2015;**65**(13):1361-8.
- 28
29 370 10. Halvorsen PA, Aasland OG, Kristiansen IS. Decisions on statin therapy by patients' opinions about
30
31 371 survival gains: cross sectional survey of general practitioners. *BMC Fam Pract* 2015;**16**:79.
- 32
33 372 11. Misselbrook D, Armstrong D. Patients' responses to risk information about the benefits of treating
34
35 373 hypertension. *Br J Gen Pract* 2001;**51**(465):276-9.
- 36
37 374 12. McAlister FA, O'Connor AM, Wells G, et al. When should hypertension be treated? The different
38
39 375 perspectives of Canadian family physicians and patients. *CMAJ* 2000;**163**(4):403-8.
- 40
41 376 13. Steel N. Thresholds for taking antihypertensive drugs in different professional and lay groups:
42
43 377 questionnaire survey. *BMJ* 2000;**320**(7247):1446-7.
- 44
45 378 14. Stovring H, Gyrd-Hansen D, Kristiansen IS, et al. Communicating effectiveness of intervention for
46
47 379 chronic diseases: what single format can replace comprehensive information? *BMC Med Inform*
48
49 380 *Decis Mak* 2008;**8**:25.
- 50
51 381 15. Trewby PN, Reddy AV, Trewby CS, et al. Are preventive drugs preventive enough? A study of
52
53 382 patients' expectation of benefit from preventive drugs. *Clin Med (Lond)* 2002;**2**(6):527-33.

- 1
2
3 383 16. Fontana M, Asaria P, Moraldo M, et al. Patient-accessible tool for shared decision making in
4
5 384 cardiovascular primary prevention: balancing longevity benefits against medication disutility.
6
7 385 *Circulation* 2014;**129**(24):2539-46.
8
9 386 17. Dahl R, Gyrd-Hansen D, Kristiansen IS, et al. Can postponement of an adverse outcome be used to
10
11 387 present risk reductions to a lay audience? A population survey. *BMC Med Inform Decis Mak*
12
13 388 2007;**7**:8.
14
15 389 18. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male
16
17 390 British doctors. *BMJ* 2004;**328**(7455):1519.
18
19 391 19. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of
20
21 392 Dyslipidaemias. *Eur Heart J* 2016;**37**(39):2999-3058.
22
23 393 20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial
24
25 394 hypertension: the Task Force for the Management of Arterial Hypertension of the European
26
27 395 Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*
28
29 396 2013;**34**(28):2159-219.
30
31 397 21. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular
32
33 398 disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**(11):987-1003.
34
35 399 22. JBS Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular
36
37 400 disease; JBS3 risk calculator. Secondary Joint British Societies' consensus recommendations for
38
39 401 the prevention of cardiovascular disease; JBS3 risk calculator. <http://www.jbs3risk.com/>.
40
41 402 23. van Dis I, Kromhout D, Geleijnse JM, et al. Evaluation of cardiovascular risk predicted by different
42
43 403 SCORE equations: the Netherlands as an example. *Eur J Cardiovasc Prev Rehabil*
44
45 404 2010;**17**(2):244-9.
46
47 405 24. Gu Q, Paulose-Ram R, Burt VL, et al. Prescription cholesterol-lowering medication use in adults aged
48
49 406 40 and over: United States, 2003-2012. *NCHS Data Brief* 2014(177):1-8.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 407 25. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive
4
5 408 lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised
6
7 409 trials. *Lancet* 2010;**376**(9753):1670-81.
- 8
9 410 26. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of
10
11 411 cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from
12
13 412 prospective epidemiological studies. *BMJ* 2009;**338**:b1665.
- 14
15 413 27. Recommendations for treatment of hyperlipidemia in adults. A joint statement of the Nutrition
16
17 414 Committee and the Council on Arteriosclerosis. *Circulation* 1984;**69**(5):1067A-90A.
- 18
19 415 28. JoJoGenetics. Sectie Moleculaire Diagnostiek van het Laboratorium Experimentele Vasculaire
20
21 416 Geneeskunde, Academisch Medisch Centrum. <http://www.jojogenetics.nl/>.
- 22
23 417 29. Netherlands National Institute for Public Health and the Environment (RIVM). Average Body Mass
24
25 418 Index (kg/m²) according to age and gender. The Netherlands. 2012.
- 26
27 419 30. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a
28
29 420 systematic review. *Heart* 2017.
- 30
31 421 31. Wegwarth O, Schwartz LM, Woloshin S, et al. Do physicians understand cancer screening statistics?
32
33 422 A national survey of primary care physicians in the United States. *Ann Intern Med*
34
35 423 2012;**156**(5):340-9.
- 36
37 424 32. Hutchins R, Viera AJ, Sheridan SL, et al. Quantifying the utility of taking pills for cardiovascular
38
39 425 prevention. *Circ Cardiovasc Qual Outcomes* 2015;**8**(2):155-63.
- 40
41 426 33. Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing
42
43 427 treatments: a randomized trial. *Ann Intern Med* 2007;**146**(12):848-56.
- 44
45 428 34. Stack RJ, Bundy C, Elliott RA, et al. Patient perceptions of treatment and illness when prescribed
46
47 429 multiple medicines for co-morbid type 2 diabetes. *Diabetes Metab Syndr Obes* 2011;**4**:127-35.
- 48
49 430 35. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins:
50
51 431 interrupted time series analysis with UK primary care data. *BMJ* 2016;**353**:i3283.
- 52
53
54
55
56
57
58
59
60

- 1
2
3 432 36. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of
4
5 433 statin therapy. *Lancet* 2016;**388**(10059):2532-61.
6
7 434 37. Thompson PD, Panza G, Zaleski A, et al. Statin-Associated Side Effects. *J Am Coll Cardiol*
8
9 435 2016;**67**(20):2395-410.
10
11 436 38. Thanassoulis G, Williams K, Altobelli KK, et al. Individualized Statin Benefit for Determining Statin
12
13 437 Eligibility in the Primary Prevention of Cardiovascular Disease. *Circulation* 2016;**133**(16):1574-
14
15 438 81.
16
17 439 39. Schievink B, Kropelin T, Mulder S, et al. Early renin-angiotensin system intervention is more
18
19 440 beneficial than late intervention in delaying end-stage renal disease in patients with type 2
20
21 441 diabetes. *Diabetes Obes Metab* 2016;**18**(1):64-71.
22
23 442 40. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through
24
25 443 shared decision making. *BMJ* 2016;**353**:i2893.
26
27 444 41. Katz M, Laurinavicius AG, Franco FG, et al. Calculated and perceived cardiovascular risk in
28
29 445 asymptomatic subjects submitted to a routine medical evaluation: The perception gap. *Eur J Prev*
30
31 446 *Cardiol* 2015;**22**(8):1076-82.
32
33
34
35
36 447
37
38
39 448
40
41 449
42
43
44 450
45
46
47 451
48
49 452
50
51
52
53
54
55
56
57
58
59
60

453 **Table 1 Baseline Characteristics**

| | Primary Care Physicians | Patients |
|--------------------------------|-------------------------|----------------|
| | n=400 | n = 523 |
| Gender | | |
| Male | 195 (54%) [†] | 263 (50%) |
| Female | 164 (46%) | 260 (50%) |
| Age | | |
| ≤ 34 | 31 (8%) [†] | 12 (2%) |
| 35-45 | 67 (18%) | 15 (3%) |
| 46-52 | 63 (17%) | 19 (4%) |
| 53-57 | 67 (18%) | 21 (4%) |
| 58-62 | 89 (24%) | 57 (11%) |
| 63-67 | 41 (11%) | 110 (21%) |
| 68-72 | 6 (2%) | 130 (25%) |
| ≥ 73 | 3 (1%) | 159 (30%) |
| Statin Use | | |
| Yes | - | 298 (57%)* |
| No | - | 166 (32%) |
| Previously used | - | 55 (11%) |
| Unknown | - | 4 (1%) |
| Antihypertensive Use | | |
| Yes | - | 301 (58%)* |
| No | - | 187 (36%) |
| Previously used | - | 30 (6%) |
| Unknown | - | 4 (1%) |
| Clinically Manifest CVD | | |
| Yes | - | 283 (54%)* |
| No | - | 238 (46%) |

467 Missing data for baseline characteristics is denoted as * (<1%) or † (between 8% and 10%); Clinically
 468 manifest cardiovascular disease (CVD) is defined as presence of one or more of the following: coronary
 469 heart disease, cerebrovascular disease, and peripheral artery disease.

470

471

472

473

1
2
3 474 **Figures Legends**
4

5
6 475 **Figure 1 Legend:**
7

8 476 Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin
9
10 477 therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).
11
12

13
14 478 **Figure 2 a. and b. Legend:**
15

16
17 479 Months gain in CVD-free life-expectancy above which physicians (as prescribers) and patients (as users)
18
19 480 consider a) statin and b) antihypertensive therapy meaningful. Missing responses was seen in 5
20
21 481 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients
22
23 482 (5.1%) for antihypertensive medication.
24
25

26
27 483 **Figure 3 Legend:**
28

29
30 484 Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong
31
32 485 therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and
33
34 486 smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance between
35
36 487 ESC-guideline recommendations and participant views of meaningful therapy.
37
38

39
40 488 **Figure 4 Legend:**
41

42
43 489 Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong
44
45 490 therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-
46
47 491 profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the
48
49 492 (non)-concordance between ESC-guideline recommendations and participant views of meaningful
50
51 493 therapy.
52
53
54
55
56
57
58
59
60

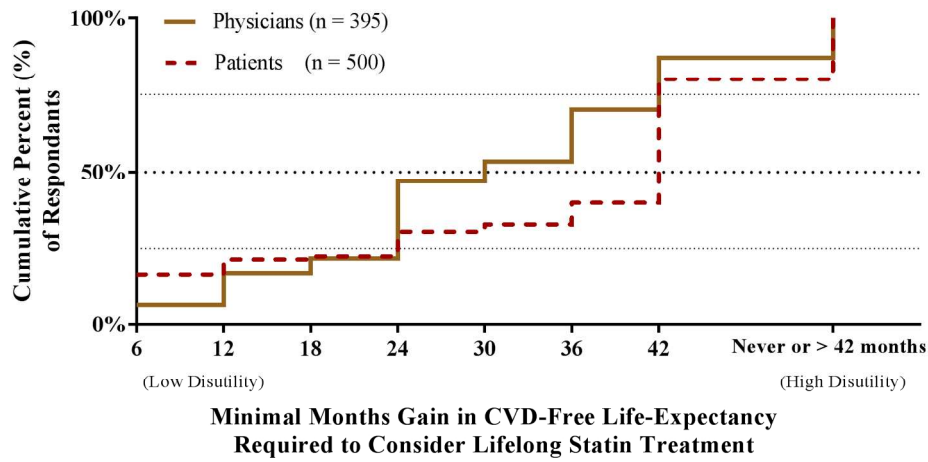


Figure 1. Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

173x87mm (300 x 300 DPI)

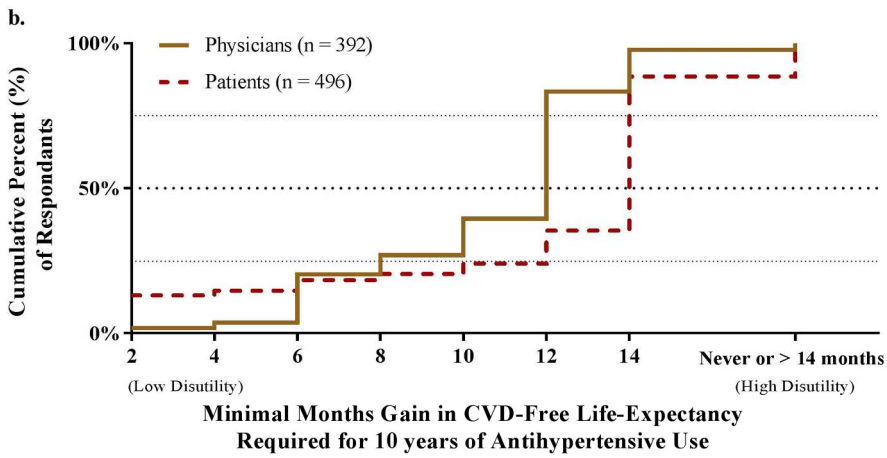
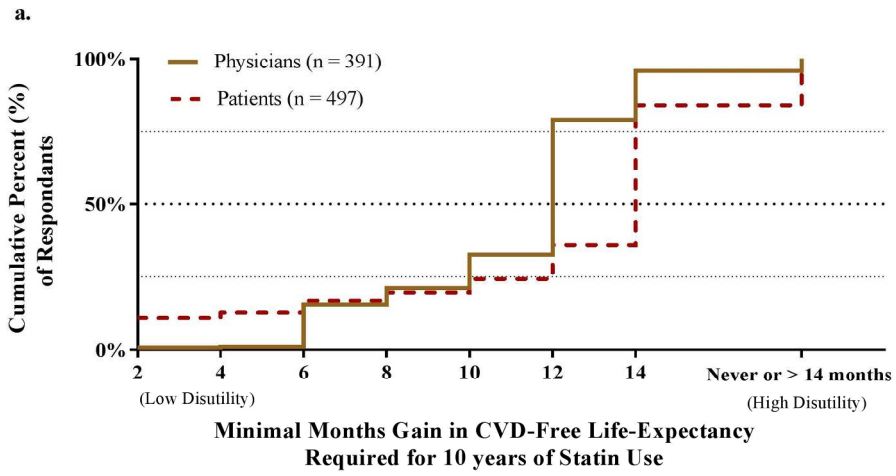


Figure 2. Minimal gain in CVD-free life-expectancy to perceive a) statin and b) antihypertensive therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients (5.1%) for antihypertensive medication.† †

205x235mm (300 x 300 DPI)

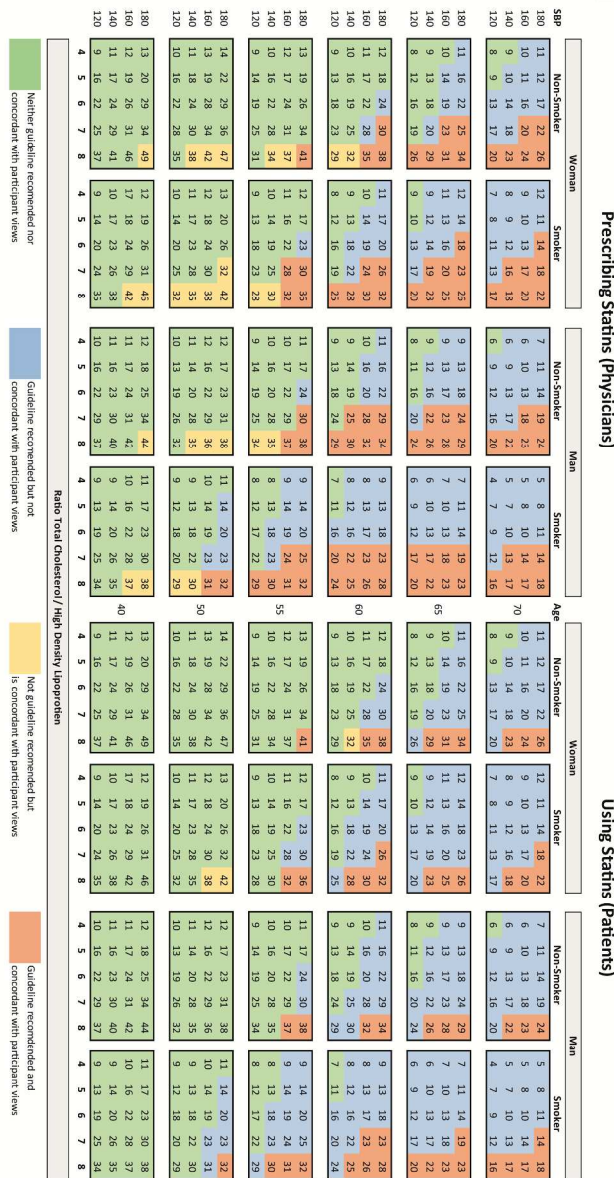


Figure 3. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance between ESC-guideline recommendations and participant views of meaningful therapy.

192x368mm (300 x 300 DPI)

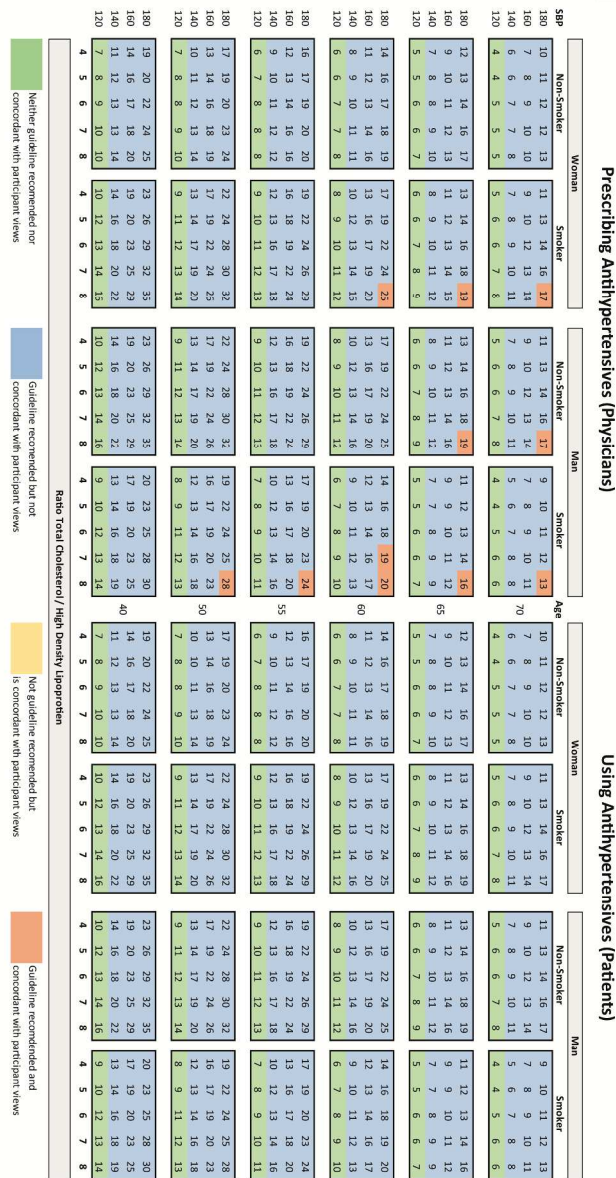


Figure 4 : Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance between ESC-guideline recommendations and participant views of meaningful therapy.

192x368mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **SUPPLEMENTAL MATERIAL**

2

3 A) Physician Survey2

4 B) Patient Survey5

5 C) Short Summary of Introduction Sessions.....8

6 D) Values Used for Calculations11

7 E) Example Calculation.....12

8 F) Supplemental Figures13

For peer review only

1
2
3 21 **A) Physician Survey**
4

5 22 *The following survey was conducted on December 8th, 2016 at the Boerhaave Continuing Medical*
6
7 23 *Education Conference.*
8
9

10 24 1. What is your current position?
11

12
13 25 a. Family Physician
14

15 26 b. Nursing home physician
16

17 27 c. Physician for mentally impaired
18

19 28 d. Resident Family Medicine
20

21 29 e. Nurse practitioner/ Nursing assistant
22

23 30 f. Other
24
25

26
27 31 **Note: Answers a, b, and c, are considered specialties in primary prevention*
28
29

30 32 2. What is your gender?
31

32 33 a. Male
33

34 34 b. Female
35

36 35 3. What is your age?
37

38 36 a. ≤ 34
39

40 37 b. 35-45
41

42 38 c. 46-52
43

44 39 d. 53-57
45

46 40 e. 58-62
47

48 41 f. 63-67
49

50 42 g. 68-72
51

52 43 h. ≥ 72
53
54
55
56
57
58
59
60

- 1
2
3 44 4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is
4
5 45 the minimum gain in life-expectancy without (new) cardiovascular disease “*healthy life years*”
6
7 46 the medication must provide before you considered use worthwhile?
8
9
10 47 a. ½ year (low threshold)
11
12 48 b. 1 year
13
14 49 c. 1 ½ year
15
16 50 d. 2 year
17
18 51 e. 2 ½ year
19
20
21 52 f. 3 year
22
23 53 g. 3 ½ year (high threshold)
24
25 54 h. I would never want to use a statin *Or only above these thresholds*
26
27
28 55
29
30 56 5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease
31
32 57 “*healthy life years.*” What is the **maximum** number of years you would personally consider using
33
34 58 this statin to achieve this benefit?
35
36 59 a. I would never want to use a statin; *Or only above these thresholds*
37
38 60 b. 5 year (high threshold)
39
40 61 c. 10 year
41
42 62 d. 15 year
43
44 63 e. 20 year
45
46 64 f. 30 year
47
48 65 g. 40 year
49
50 66 h. 50 year (low threshold)
51
52
53
54
55
56
57 68
58
59
60

- 1
2
3 69 6. What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, “*healthy life*
4
5 70 *years*”, necessary before you consider **10 years of statin therapy** for a **patient** worthwhile?
6
7 71 a. 2 months (low threshold)
8
9 72 b. 4 months
10
11 73 c. 6 months
12
13 74 d. 8 months
14
15 75 e. 10 months
16
17 76 f. 12 months
18
19 77 g. 14 months (high threshold)
20
21 78 h. I would never consider statin prescription worthwhile. *Or only above these thresholds*
22
23 79
24
25
26
27 80 7. And what we aren’t talking about statins, but about blood-pressure therapy?
28
29 81 What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, “*healthy life*
30
31 82 *years*”, necessary before you consider **10 years of blood-pressure therapy** for a **patient**
32
33 83 worthwhile?
34
35 84 a. 2 months (low threshold)
36
37 85 b. 4 months
38
39 86 c. 6 months
40
41 87 d. 8 months
42
43 88 e. 10 months
44
45 89 f. 12 months
46
47 90 g. 14 months (high threshold)
48
49 91 h. I would never consider blood-pressure medication prescription worthwhile; *Or only above*
50
51 92 *these thresholds*
52
53
54
55
56
57 93
58
59
60

1
2
3 94 **B) Patient Survey**
4

5 95 *The following patient survey was conducted on April 7th, 2017 at the University Medical Centre*

6
7 96 *Utrecht, the Netherlands.*
8
9

10
11 97 1. Do you use a statin?

12
13 98 a. Yes

14
15 99 b. No

16
17 100 c. I have used statins, but stopped taking them

18
19 101 d. I don't know

20
21 102 2. Do you use an antihypertensive medication?

22
23 103 a. Yes

24
25 104 b. No

26
27 105 c. I have used antihypertensive medications, but stopped taking them

28
29 106 d. I don't know

30
31 107 3. What is your gender?

32
33 108 a. Male

34
35 109 b. Female

36
37 110 4. What is your age?

38
39 111years
40
41
42

43
44
45 112 5. Please mark all the complications or medication procedures which you have had. You can also
46
47 113 indicate if you have never had any one of these procedures.
48
49

50
51 114 Heart attack

52
53 115 Stroke

54
55 116 *Intermittent claudication* (Peripheral artery disease)

56
57 117 TIA
58
59
60

- 1
2
3 118 a stent, angioplasty, or other operation of the hart
4
5
6 119 an operation of the carotid artery (*major artery of the neck*)
7
8 120 I have never had *ANY* of the above
9

10 121 5. Imagine **you** were considering starting (or continuing) a statin medication. What in the minimum
11
12 gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication
13 122
14 must provide before you considered use worthwhile?
15 123

- 16
17 124 a. ½ year (low threshold)
18
19 125 b. 1 year
20
21 126 c. 1 ½ year
22
23 127 d. 2 year
24
25 128 e. 2 ½ year
26
27 129 f. 3 year
28
29 130 g. 3 ½ year (high threshold)
30
31 131 h. I would never want to use a statin ; *Or only above these thresholds*
32
33
34

35 132
36
37 133 6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease
38
39 "*healthy life years.*" What is the **maximum** number of years you would consider using the statin
40 134
41 to achieve this benefit?
42 135
43

- 44 136 a. I would never consider a statin worthwhile; *Or only above these thresholds*
45
46 137 b. 5 years (high threshold)
47
48 138 c. 10 years
49
50 139 d. 15 years
51
52 140 e. 20 years
53
54 141 f. 30 years
55
56 142 g. 40 years
57
58 143 h. 50 years (low threshold)
59
60

- 1
2
3 144 7. What is the minimum gain in life-expectancy without (new) cardiovascular disease,
4 145 “*healthy life years*”, necessary before you consider 10 years of statin therapy
5 146 worthwhile?
6
7
8 147
9
10 148 a. 2 months (low threshold)
11
12 149 b. 4 months
13
14 150 c. 6 months
15
16 151 d. 8 months
17
18 152 e. 10 months
19
20 153 f. 12 months
21
22 154 g. 14 months (high threshold)
23
24 155 h. I would never consider a statin worthwhile; *Or only above these thresholds*
25
26 156
27
28 157 8. And what we aren’t talking about statins, but about blood-pressure therapy?
29
30 158 What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, “*healthy life*
31 159 *years*”, necessary before you consider **10 years of blood-pressure therapy** worthwhile?
32
33 160 a. 2 months (low threshold)
34
35 161 b. 4 months
36
37 162 c. 6 months
38
39 163 d. 8 months
40
41 164 e. 10 months
42
43 165 f. 12 months
44
45 166 g. 14 months (high threshold)
46
47 167 h. I would never consider blood-pressure medication worthwhile ; *Or only above these*
48
49 168 *thresholds*
50
51 169
52
53
54
55
56
57
58
59
60

170 C) Short Summary of Introduction Sessions

171

172 Physician Session

173

174 • The session started with a short reiteration that prevention of cardiovascular disease (CVD)

175 incorporates both life-style aspects (such as not smoking or drinking too much alcohol,

176 exercising regularly, eating healthy) and medication aspects (such as cholesterol, blood-

177 pressure and aspirin treatment).

178 • Decision-making cardiovascular disease prevention was described as finding the balance

179 between the benefits (living a longer, healthier, life) and negative effects (side-effects, costs,

180 and taking a pill daily) of therapy. For each individual person, the balance between the

181 benefits and negative effects can be different.

182 • The SCORE-chart as used in national primary prevention guidelines was reviewed.

183 Drawbacks of using the SCORE-chart, and the associated ten-year absolute risk was

184 discussed, namely that it often emphasizes treatment of the elderly, and that interpretation

185 of 10-year risk or risk reduction may be difficult for the patient. Positive aspects of the

186 SCORE-chart were also discussed, namely that it is easy to use, and allows for a variety of

187 different individual risk-factors to be combined.

188 • Prediction algorithms and calculators which can estimate CVD-free life-expectancy for those

189 in the primary prevention were introduced (i.e. the JBS-3 risk score).²² Life-time estimates

190 were described as being more biologically and clinically intuitive, as atherosclerosis is a

191 phenomenon which starts early in life, and manifests itself only after a few decades.

192 • It was illustrated with two examples from peer-reviewed literature that the one “treats” a

193 risk-factor, the greater the potential benefit. The first example provided was meant to show

194 a large life-time benefit from a life-style intervention. It was shown that stopping with

195 smoking between 25-34 years of age extends survival by 10 years, whereas stopping

196 between 55-64 years of age extends survival by 3 years.¹⁸ The second example was meant to

1
2
3 197 show a small benefit, and to provide a reference for preventative medication.¹ It was shown
4
5 198 that the individual effect of aspirin therapy, is not expressed in years, but rather in months
6
7
8 199 gain. These months range between 0-8 according to peer reviewed literature. It was
9
10 200 emphasized that the potential gain in stopping with smoking is of a greater magnitude than
11
12 201 the potential gain of medication, which is better represented by the aspirin example. It was
13
14 202 also emphasized that the longer one “treats” a risk-factor, the longer one must also take the
15
16 203 medication.
17
18
19 204 • Long-term validation results of these prediction models were shown.¹
20
21 205 • In conclusion, it was iterated that starting medication at a young age provides the greatest
22
23 206 net effect of therapy, but that this greater net-effect also goes hand in hand with a longer
24
25 207 period of time in which the therapy would have to be used.
26
27
28 208

29 30 31 209 **Patient Session**

- 32
33 210 • The session started with a short reiteration that prevention of cardiovascular disease (CVD)
34
35 211 incorporates both life-style aspects (such as not smoking or drinking too much alcohol,
36
37 212 exercising regularly, eating healthy) and medication aspects (such as cholesterol, blood-
38
39 213 pressure and aspirin treatment).
40
41
42 214 • Lipid-lowering and blood-pressure lowering were described as two important pillars of CVD-
43
44 215 prevention guidelines. Statin medication were described as some on the most common
45
46 216 cholesterol-lowering drugs, and a number of statin medications (with both generic and
47
48 217 brand-names) were given: simvastatin, rosuvastatin, pravastatin, atorvastatin, fluvastatin. A
49
50 218 few common examples of blood-pressure lowering medications were also given:
51
52 219 hydrochlorothiazide, enalapril, perindopril, losartan, olmesartan, amlodipine, and
53
54 220 metoprolol.
55
56 221 • Decision-making cardiovascular disease prevention was described as finding the balance
57
58 222 between the benefits (living a longer, healthier, life) and negative effects (side-effects, costs,
59
60

1
2
3 223 and taking a pill daily) of therapy. For each individual person, the balance between the
4
5 224 benefits and negative effects can be different.
6
7
8 225 • What exactly “CVD-free life expectancy?” entails was discussed. It was described as the
9
10 226 amount of time you can expect to live *healthily*, without cardiovascular disease. If you
11
12 227 already have had cardiovascular disease, then it was described as the amount of time you
13
14 228 can expect to live without having another major cardiovascular event, such as a heart-
15
16 229 attack. It was discussed that doctors are getting better at predicting what someone’s CVD-
17
18 230 free life-expectancy is, and also what the gain in CVD-free life expectancy is from
19
20 231 medications such as statin and blood-pressure lowering medications.
21
22
23 232 • It was introduced that the longer one “treats” a risk-factor, the greater the benefit (gain in
24
25 233 CVD-free life-expectancy can be). This was illustrated with the same two-examples from
26
27 234 peer-reviewed literature as with the physicians. Likewise, it was emphasized that the
28
29 235 potential gain in stopping with smoking is of a greater magnitude than the potential gain of
30
31 236 medication, which is better represented by the aspirin example. It was also emphasized that
32
33 237 the longer one “treats” a risk-factor, the longer one must also take the medication.
34
35
36 238 • In conclusion, it was iterated that starting medication at a young age provides the greatest
37
38 239 net effect of therapy, but that this greater net-effect also goes hand in hand with a longer
39
40 240 period of time in which the therapy would have to be used. The definition of CVD-free life-
41
42 241 expectancy was given again.
43
44
45
46 242
47
48
49 243
50
51
52 244
53
54
55
56
57
58
59
60

1
2
3 **245 D) Values Used for Calculations**

4 **246** Age and gender-specific medians (50th percentile) of high-density lipoprotein concentration (HDL-c,
5
6 **247** mmol/l) and triglyceride concentration (TG, mmol/l), were used to calculate low-density lipoprotein
7
8 **248** concentration (LDL-c, mmol/l).²⁷⁻²⁹ For each lipid-value depicted on the SCORE-based chart,
9
10 **249** corresponding low-density lipoprotein concentration (LDL-c) was calculated using the Friedewald
11
12 **250** formula and age and sex-specific medians of high density lipoprotein (HDL-c) and triglyceride
13
14 **251** concentrations. Age and gender-specific body-mass index (BMI, kg/m²) was used with Joint British
15
16 **252** Societies for prevention of cardiovascular disease (JBS3) risk calculator²². Patients were assumed to
17
18 **253** have average socio-economic status and have no other comorbidities such as diabetes. Smokers
19
20 **254** used between 10 and 20 cigarettes per day.
21
22
23
24

25 **255 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 |

26 **256** Legend: Abbreviations LDL-c = low-density lipoprotein cholesterol; HDL-c = High density lipoprotein
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54 **257** cholesterol; TC= Total cholesterol; TG = Triglycerides; BMI = Body-Mass Index
55
56
57
58
59
60

1
2
3 **258 E) Example Calculation**

4 259 A male patient, medical history negative for diabetes, 40 years of age, BMI of 26.2 kg/m², systolic
5
6 260 blood-pressure 140 mmHg, and a total cholesterol / HDL ratio of 7. The 50th percentile values for
7
8
9 261 HDL-c is 1.12 mmol/L and TG is 1.35 mmol/L.(1)

10
11
12 262 Calculation LDL-c:

13
14
15 263 Baseline LDL-c = Total cholesterol – median HDL – median triglyceride / 2.17

16
17
18 264 = Ratio x median HDL – median HDL – median triglyceride / 2.17

19
20
21 265 = 7 x 1.12 – 1.12 – 1.35/2.17

22
23
24 266 = 6.098 mmol/L

25
26
27 267 The effects of simvastatin 40 mg was calculated as follows:

28
29
30 268 LDL-c_{new} = LDL-c_{old} * (1 - percent reduction)

31
32
33 269 = 6.098 mmol/L * 0.63

34
35
36 270 = 3.842 mmol/L

37
38
39 271 Estimated attainable therapy-benefit in terms of gain in CVD-free life-years according to the JBS3

40
41
42 272 Online calculator:²²

43
44 273 Calculated CVD-free life-expectancy off-treatment (i.e. current prognosis) = 76 years

45
46 274 Calculated gain in CVD-free life-expectancy = 2.5 years

47
48 275 Remaining CVD-free life years on-treatment (i.e. potential treatment duration) = (76 years +

49
50 276 2.5 years)-40 years(i.e. current age) = 38.5 years

51
52 277 Gain per 10 years of use = (2.5 years gain / 38.5 years of use)*10 = 0.649 years = 7.8 months

53
54
55 278

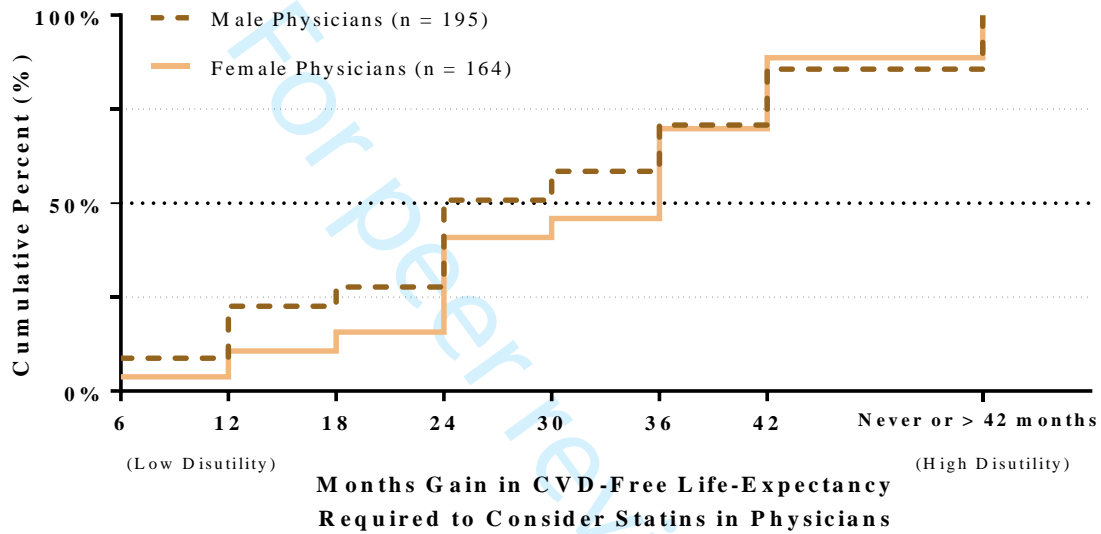
279 **F) Supplemental Figures**

280

281 **Supplemental Figure 1.** Months gain in CVD-free life-expectancy required to consider personal use

282 of statin therapy, stratified by sex in physicians

283



284

285 Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin

286 therapy as meaningful, stratified by gender.

287

288

289

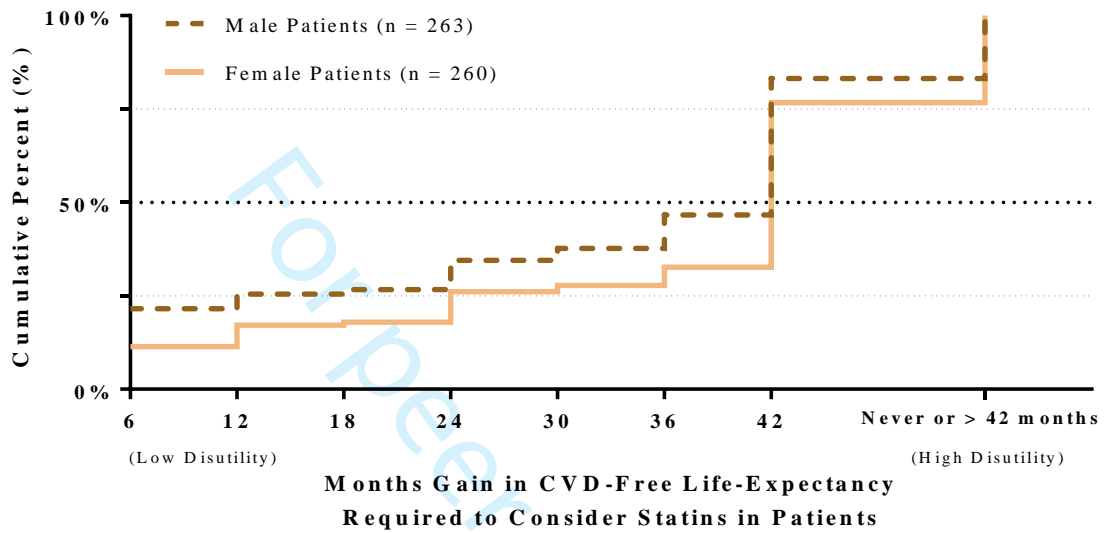
290

291

292

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

295



296

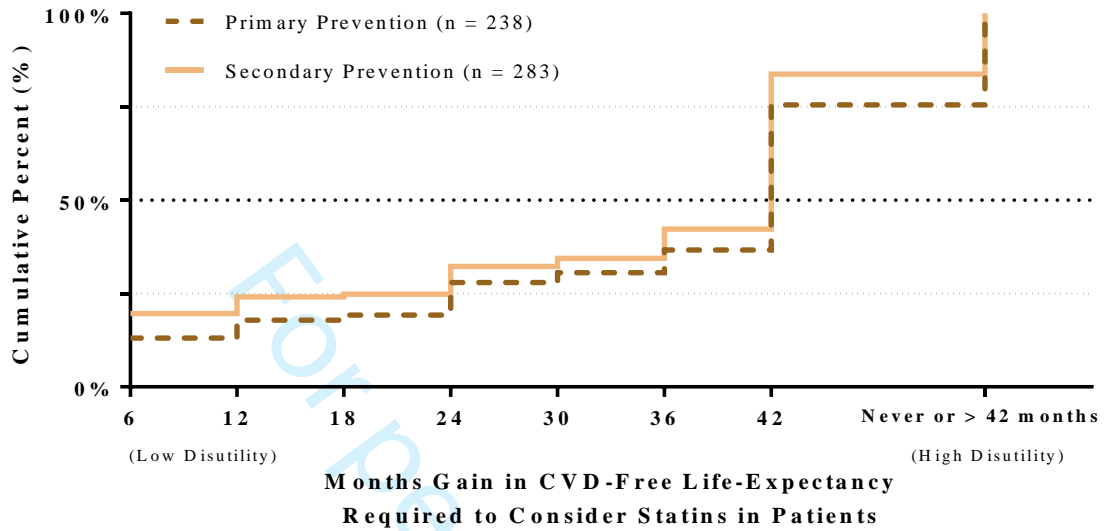
297 Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin
 298 therapy as meaningful, stratified by gender.

299

300

301

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



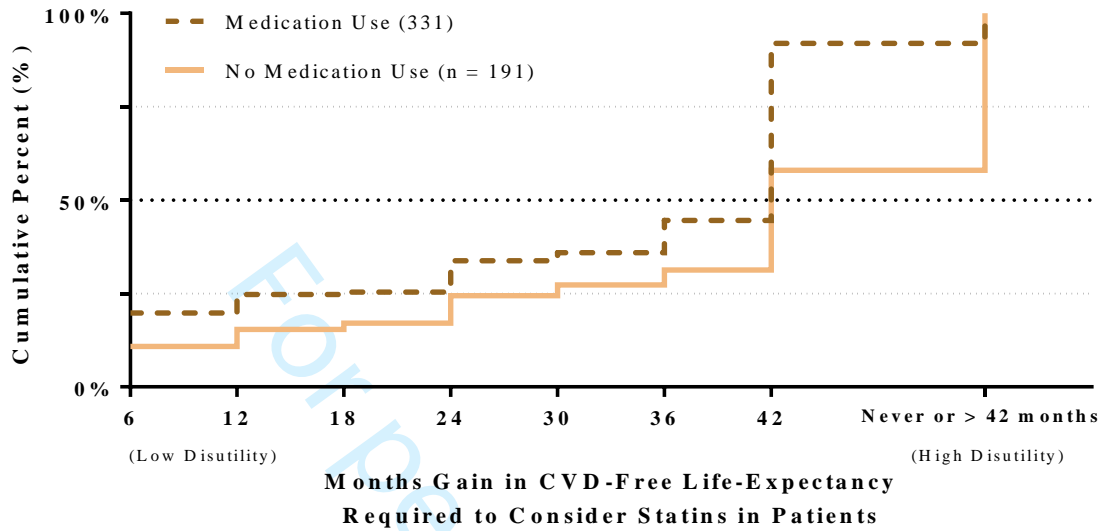
304

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

307

308

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



311

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

314

315

316

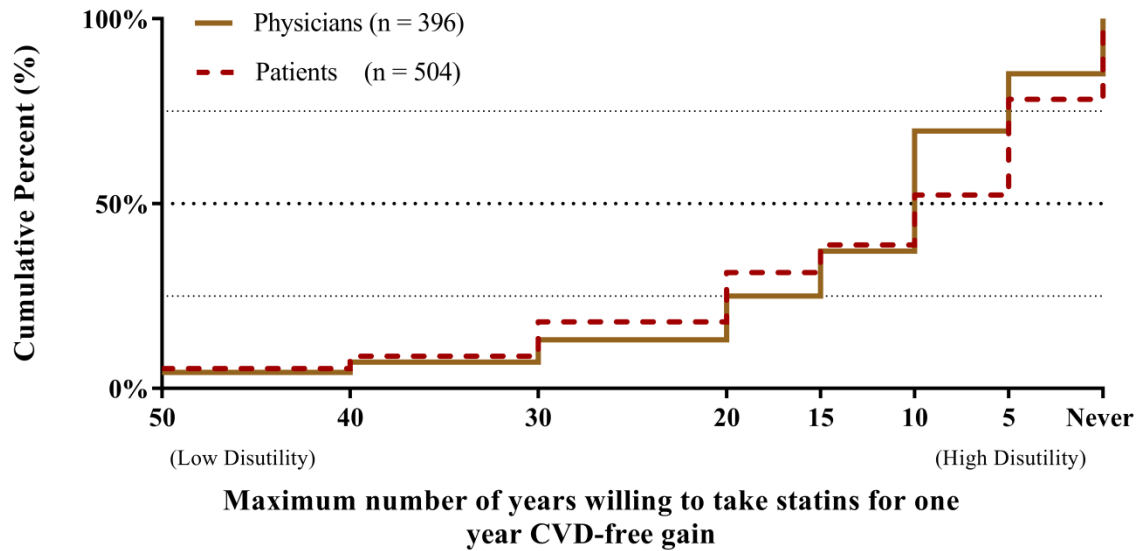
317

318

319

320

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



323

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

STROBE Statement—Checklist of items that should be included in reports of **cross-sectional studies**

| | Item No | Recommendation | Where? |
|------------------------------|----------------|---|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | <i>Both in title/abstract page 1 and 2</i> |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | <i>Structured abstract Page 2</i> |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | <i>Introduction page 4</i> |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | <i>End of introduction page 4-5</i> |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | <i>Settings & participants Survey preparation and administration Page 5-6</i> |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | <i>Settings & participants Survey preparation and administration Page 5-6</i> |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants | <i>Settings & participants Page 5</i> |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | <i>Settings & participants Survey preparation and administration Page 5-6</i> |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | <i>Methods + Supplemental data Page 5</i> |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | <i>Setting and participant Page 5</i> |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | <i>Data analysis Page 7</i> |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | <i>Data analysis Page 7</i> |
| | | (b) Describe any methods used to examine subgroups and interactions | <i>Data analysis Page 7</i> |
| | | (c) Explain how missing data were addressed | <i>Data analysis Page 7</i> |
| | | (d) If applicable, describe analytical methods taking account of sampling strategy | <i>n/a/</i> |
| | | (e) Describe any sensitivity analyses | <i>Exploratory analysis Methods: Page 6 Results: page 8</i> |
| Results | | | |

| | | | |
|-------------------|-----|--|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | <i>Participants and response</i> <i>Page 7-8</i> |
| | | (b) Give reasons for non-participation at each stage | <i>Participants and response</i> <i>gives overview of number of individuals at each stage (page 7)</i> |
| | | (c) Consider use of a flow diagram | <i>Information adequately summarized in text</i> |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | <i>Participants and response (page 7) and (baseline table, page 18)</i> |
| | | (b) Indicate number of participants with missing data for each variable of interest | <i>Baseline table (page 16) and per analysis in results (figures 1, &2a.b., figure legends, page 17)</i> |
| Outcome data | 15* | Report numbers of outcome events or summary measures | <i>Number of participants reported per analysis, see above for page numbers</i> |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | <i>Medians and interquartiles, results, page 8-9</i> |
| | | (b) Report category boundaries when continuous variables were categorized | <i>Survey in supplement,</i> |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | <i>n/a/</i> |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | <i>Analysis per characteristic reported, Personal meaningful lifetime benefit, and exploratory analysis page 7- 8</i> |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | <i>Principal findings, discussion page 9</i> |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | <i>Strengths and limitations, discussion</i> |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | <i>Discussion(page 9-11)</i> |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | <i>Discussion. Limitations unlikely to alter conclusion. Use of risk score for other</i> |

Other information

| | | | |
|---------|----|---|--------------------------|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | <i>Reported. Page 13</i> |
|---------|----|---|--------------------------|

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Variation in minimum desired cardiovascular disease-free longevity benefit from statin and antihypertensive medications: a cross-sectional study of patient and primary care physician perspectives

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2017-021309.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 27-Mar-2018 |
| Complete List of Authors: | Jaspers, Nicole; University Medical Centre Utrecht, Department of Vascular Medicine Visseren, Frank; University Medical Centre Utrecht, Department of Vascular Medicine Numans, Mattijs; Leiden University Medical Centre, Department of Public Health and Primary Care Smulders, Yvo; VU University Medical Center, van Loenen Martinet, Fere; Primary Care Medical Center Randwijck van der Graaf, Yolanda; Julius Center for Health Sciences and Primary Care Dorresteijn, Jannick; University Medical Centre Utrecht, Department of Vascular Medicine |
| Primary Subject Heading: | Patient-centred medicine |
| Secondary Subject Heading: | Communication, Cardiovascular medicine, Patient-centred medicine |
| Keywords: | PRIMARY CARE, PREVENTIVE MEDICINE, VASCULAR MEDICINE, Doctor-Patient Communication, Shared Decision Making, Individualized Prevention |
| | |

SCHOLARONE™
Manuscripts

1
2
3 1
4 2 **Variation in minimum desired cardiovascular disease-free longevity benefit from statin and**
5 3 **antihypertensive medications: a cross-sectional study of patient and primary care physician**
6 4 **perspectives**
7

8 5
9
10 6 **Authors:** Nicole E.M. Jaspers, MD^a; Frank L.J. Visseren, MD PhD^a, Mattijs E Numans MD PhD^b, Yvo M
11 7 Smulders, MD PhD^c; Fere van Loenen Martinet MD^d; Yolanda van der Graaf, MD PhD^e; Jannick A.N.
12 8 Dorresteijn, MD PhD^a.
13
14

15 9
16
17 10 ^a Department of Vascular Medicine, University Medical Center Utrecht, the Netherlands;
18

19
20 11 ^b Department of Public Health and Primary Care, Leiden University Medical Center, the Netherlands
21

22 12 ^c Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands
23

24 13 ^d Primary Care Medical Center Randwijck, Amstelveen, the Netherlands
25

26 14 ^e Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
27
28

29 15
30
31 16 *Correspondence: Professor Frank Visseren, MD PhD; Department of Vascular Medicine, University
32 17 Medical Centre Utrecht; PO Box 85500, 3508 GA Utrecht, the Netherlands; Phone: +31(0)887555161;
33 18 Fax: +31(0)887555488; Email: F.L.J.Visseren@umcutrecht.nl
34

35 19
36
37 20 Word count main body: 3,297
38
39 21
40
41 22
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

23 **ABSTRACT**

24 **Objective:** Expressing therapy-benefit from a lifetime perspective, instead of only a 10-year perspective,
25 is both more intuitive and of growing importance in doctor-patient communication. In cardiovascular
26 disease (CVD) prevention, lifetime estimates are increasingly accessible via online decision-tools.
27 However, it is unclear what gain in life-expectancy is considered meaningful by those who would use the
28 estimates in clinical practice. We therefore quantified lifetime and 10-year benefit thresholds at which
29 physicians and patients perceive statin and antihypertensive therapy as meaningful, and compared the
30 thresholds to clinically attainable benefit.

31 **Design:** Cross-sectional study

32 **Settings:** 1) continuing medical education conference in December 2016 for primary care physicians 2)
33 information session in April 2017 for patients

34 **Participants:** 400 primary care physicians and 523 patients in the Netherlands

35 **Outcome:** Months gain of CVD-free life-expectancy at which lifelong statin therapy is perceived as
36 meaningful, and months gain at which 10-years of statin and antihypertensive therapy is perceived as
37 meaningful. Physicians were framed as users for lifelong and prescribers for 10-year therapy.

38 **Results:** Meaningful benefit was reported as median (interquartile range, IQR). Meaningful lifetime statin
39 benefit was 24 months (IQR 23–36) in physicians (as users) and 42 months (IQR 12–42) in patients
40 willing to consider therapy. Meaningful ten-year statin benefit was 12 months (IQR 10-12) for prescribing
41 (physicians) and 14 months (IQR 10-14) for using (patients). Meaningful ten-year antihypertensive benefit
42 was 12 months (IQR 8-12) for prescribing (physicians) and 14 months (IQR 10-14) for using (patients).
43 Females desired greater benefit than males. Age, CVD-status, and co-medication had minimal effect on
44 outcomes.

45 **Conclusion:** Both physicians and patients report a large variation in meaningful longevity-benefit.
46 Desired benefit differs between physicians and patients and exceeds what is clinically attainable.
47 Clinicians should recognize these discrepancies when prescribing therapy and implement individualized

1
2
3 48 medicine and shared decision-making. Decision-tools could provide information on realistic therapy
4
5 49 benefit.
6
7
8 50
9
10 51
11
12

13 52 **Strengths and Limitations of the Study:**
14
15

- 16 53 • We examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating
17 54 pre-conceived notions about the costs, side-effects, and inconveniences of medication which are
18 55 a daily part of clinical practice.
19
20 56 • In contrast to previous studies, we surveyed a large sample of both physicians and actual
21 57 patients in comparable settings.
22
23 58 • The use of a multiple-choice voting system may have limited response variation.
24
25 59 • Further research would be necessary to analyze how these perspectives would relate to actual
26 60 use of medication by patients and prescription of medication by physicians.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

61

62

63

64

65

66

67

68

69

70

71

72

73 INTRODUCTION

74 Risk assessment integral to the prevention of cardiovascular disease (CVD). Accordingly, there is an
75 increasing number of risk-scores available to aid in the identification of individuals with a high CVD-risk
76 (e.g. Framingham, Systemic Coronary Risk Evaluation [SCORE], QRISK).^{1 2} Some scores estimate
77 individualized prognosis not only in terms of absolute risk but in also in terms of life-expectancy free of
78 CVD. The use of these lifetime estimations has been endorsed by prevention guidelines to facilitate
79 doctor-patient communication and cultivate patient motivation.^{3 4}

80
81 In addition to prognosis, some algorithms also estimate individual therapy-benefit from common therapies
82 such as lipid- and blood-pressure lowering medications. However, measures such as absolute risk
83 reduction or number needed to treat are often difficult for patients to understand.⁵ In contrast, gain in life-
84 expectancy may facilitate patient understanding of preventive therapy.^{6 7} Tools to estimate lifetime
85 therapy benefit are increasingly accessible to both physicians and patients via online calculators. One
86 such decision-aid, the Joint British Societies for prevention of cardiovascular disease (JBS3) risk
87 calculator,⁸ has been endorsed by international guidelines.³ These decision-aids may facilitate shared
88 decision-making and doctor-patient communication, both of growing importance in clinical practice and
89 policy,⁹ even though evidence suggests physicians may be insensitive to patient preferences when
90 recommending therapy.¹⁰

91
92 Despite the guideline endorsed importance of lifetime estimates and an increased emphasis on doctor-
93 patient communication and shared decision-making, little research has investigated what lifetime therapy-
94 benefit is deemed by both patients and prescribers as sufficient to offset the inconveniences of specific
95 CVD-pharmacotherapies. The framing (e.g. positive or negative) and format (e.g. absolute risk reduction
96 or gain in life-expectancy) of communication metrics influence both patient and physician opinions on
97 therapy.¹¹ As both lifetime estimates and decision-tools gain accessibility in clinical practice, it becomes
98 more essential examine perceptions of meaningful therapy and potential discrepancies between doctor-
99 and patient perceptions. Previous studies either did not survey both patients and physicians in similar
100 settings, or focused on situations which do not exist in clinical practice, such as non-lifetime metrics in

1
2
3 101 hypothetical risk scenarios^{12 13} on idealized medications.^{10 14-17} We therefore aimed to quantify
4
5 102 perceptions on meaningful lifetime and 10-year benefit, defined as the gain in CVD-free life-expectancy
6
7 103 above which physicians (as users and prescribers) and patients consider statin and antihypertensive
8
9 104 medication meaningful. We also aimed to compare these thresholds to what is a clinically achievable
10
11 105 benefit in the primary prevention.

12 106

14 107 **METHODS**

16 108 **Setting and Participants**

19 109 Two separate settings, in which a large number of patients and physicians could be recruited and
20
21 110 surveyed were chosen. Primary care physicians were recruited and surveyed on the same day among
22
23 111 attendees of a national Continuing Medical Education conference (Boerhaave “Progress and Practice”), in
24
25 112 Leiden, The Netherlands (December 8th, 2016) targeted to primary prevention health-care providers. Of
26
27 113 the survey respondents, only participants reporting themselves as primary care physicians were included
28
29 114 in the analyses. Patients were recruited and surveyed during three separate plenary sessions at a one-
30
31 115 day information conference targeted to primary and secondary CVD prevention patients at the University
32
33 116 Medical Center Utrecht in the Netherlands (April 8th, 2017). All surveyed patients were included in the
34
35 117 analyses.

37 118 **Survey Preparation and Administration**

40 119 A pretest session involving fifty primary care physicians was conducted in November 2016 to review the
41
42 120 research questions and proposed survey, and guide multiple-choice answer options of the electronic
43
44 121 (physician) or paper (patient) questionnaires ultimately used for data collection (Supplement A&B). The
45
46 122 finalized surveys were subsequently administered at the respective sessions (Boerhaave and Utrecht). To
47
48 123 ensure informed and comparable responses, an audience-appropriate 10-minute introduction on
49
50 124 individual therapy-benefit was given prior to each session (Supplement C). In this introduction, an
51
52 125 example of lifetime benefit from smoking cessation and aspirin-therapy was provided.^{1 18} The structure of
53
54 126 the introduction and survey was the same in both physician and patient questionnaires. The survey
55
56 127 questions were presented centrally and sequentially by the researcher, thus preventing participants from

1
2
3 128 viewing either previous or future questions or benefitting from time-saving heuristics. The questions were
4
5 129 verbally explained before participants were given the opportunity to respond. At the start of each session,
6
7 130 all participants were informed that a voluntary survey would be conducted and data collected and treated
8
9 131 anonymously. The study was conducted in accordance with the principles of the Declaration of Helsinki
10
11 132 and prospectively granted exempt status by the Medical Ethics Committee of the University Medical
12
13 133 Center Utrecht.

15 134 **Outcome Definition**

18 135 Lifetime benefit thresholds for physicians and patients were quantified as the gain in CVD-free life-
19
20 136 expectancy desired prior to considering or continuing personal statin therapy (i.e. the benefit was
21
22 137 considered meaningful). Ten-year benefit thresholds were quantified as the gain in CVD-free life-
23
24 138 expectancy desired for 10-years of both statin and antihypertensive medication use prior to considering or
25
26 139 continuing prescription (physicians) or personal use (patients). Physicians were thus framed as users for
27
28 140 lifetime thresholds and prescribers for 10-year thresholds. For an exploratory analysis, the outcome was
29
30 141 framed differently and participants were asked to report the number of years willing to take statin
31
32 142 medication provided the therapy would give a one-year gain in CVD-free expectancy.

34 143 **Guideline recommendations and participant views of meaningful therapy**

37 144 European Society of Cardiology (ESC) guideline recommendations on lipid¹⁹ and blood-pressure
38
39 145 therapy²⁰ were compared to what participants viewed as meaningful therapy. The ESC-SCORE algorithm
40
41 146 for low-risk countries was used to establish which risk-factor combinations had sufficient 10-year risk of
42
43 147 CVD-mortality to be eligible for lipid-lowering therapy.¹⁹⁻²¹ In order to establish which risk-factor
44
45 148 combinations would be treated based on participant views of meaningful therapy, clinically attainable
46
47 149 benefit from statin and antihypertensive medication was estimated and compared to views of meaningful
48
49 150 benefit. The JBS risk-calculator²² was used to estimate clinically attainable benefit in terms of gain in
50
51 151 CVD-free life-expectancy for each of the 600 risk-factor combinations [age, systolic blood pressure (SBP),
52
53 152 smoking status, sex, and total cholesterol] of a national ESC-SCORE chart variant.^{3 23} Clinically attainable
54
55 153 gain from statin medication was estimated with simvastatin 40 mg, a mid-potency statin commonly

1
2
3 154 prescribed as initial therapy²⁴ which reduces LDL-c levels by 37% irrespective of baseline level.²⁵
4
5 155 Clinically attainable gain from an antihypertensive was estimated with a single, initial antihypertensive
6
7 156 medication, using the formula $9.1 \text{ mmHg} + 0.10 \text{ mmHg} * (\text{current SBP} - 154 \text{ mmHg})$.²⁶ To express the
8
9 157 clinically attainable benefit per year of medication use, the gain in CVD-free life-expectancy estimated by
10
11 158 the calculator (i.e. the lifetime benefit) was divided by the total remaining on-therapy CVD-free life-years
12
13 159 estimated by the calculator (i.e. the duration of medication use required to achieve this lifetime benefit).
14
15 160 The estimated clinically attainable gain per 10-years of medication use was graphically juxtaposed
16
17 161 against participant views of meaningful benefit, expressed as months gain in CVD-free life-expectancy
18
19 162 desired for 10 years of use prior to considering or continuing prescription (physicians) or personal use
20
21 163 (patients). For clarity, all values used for the calculations, and a calculation example are provided in
22
23 164 supplements D&E.²⁷⁻²⁹
24

25 165 **Data Analysis**

26
27
28 166 Age was converted to numeric values. Thresholds in terms of minimal desired months gain were reported
29
30 167 as median (interquartile range, IQR) within each group. Wilcoxon rank-sum and spearman correlations
31
32 168 were used to analyze lifetime thresholds according to certain characteristics pre-defined to be potentially
33
34 169 of influence on response: age, sex, use of either statin or antihypertensive medication (yes/no), and
35
36 170 presence of CVD (yes/no).^{30 31} Paired-samples Wilcoxon signed-rank tests were used to assess
37
38 171 response differences between 10-year statin and antihypertensive medication thresholds. Missing values
39
40 172 were not imputed, and the number of participants in each analysis reported. Analyses were performed
41
42 173 using R-Statistical Software, version 3.1.1.
43

44 174 **Patient and Public Involvement**

45
46
47 175
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 176 The study has been designed to survey the opinion of a large group of both patient and physicians to
4
5 177 better understand their priorities and preferences. Both patient organizations and primary care
6
7 178 physicians were involved during study preparation. The research question and study design evolved from
8
9 179 a discussion session with a patient panel at PGOSupport conference, an independent nation-wide
10
11 180 network for patient-organizations, held in Amstelveen, the Netherlands in April 2016. Physicians were
12
13 181 involved in the pre-test sessions in Roermond, the Netherlands in November 2016. Participants were not
14
15 182 involved in finding the optimal study recruitment procedures. The findings from this study will be
16
17 183 disseminated to physicians and patients via conferences and newsletters.
18
19 184

22 185 **RESULTS**

25 186 **Participants and Response**

27 187 Of the 455 physician survey respondents, the 400 participants reporting themselves as primary care
28
29 188 physicians were included in the analyses. The participant characteristics of the included 400 primary care
30
31 189 physicians and 523 patients are depicted in table 1. Physician sex and age distribution reflected the
32
33 190 national primary care physician population: 54% male and 46% female. Median age was 55 years (IQR
34
35 191 40-60) in physicians and 69 years (IQR 63-74) in patients. Approximately half (54%, n=283) of patients
36
37 192 reported clinical manifestations of CVD, defined as coronary heart disease (n=131, 25%),
38
39 193 cerebrovascular disease (n=60, 11.5%), peripheral artery disease (n=24, 4.6%), or multiple CVD
40
41 194 manifestations (n=65, 12.5%).

44 195 **Personal meaningful lifetime benefit**

46 196 Meaningful lifetime benefit is presented in figure 1. In total, 12.9% (n=51) of physicians considered the
47
48 197 maximum gain (42 months) insufficient for personal use. The remaining physicians desired 24 months
49
50 198 (IQR 23-36) gain. Age was not associated with physician thresholds (spearman rho -0.07, p=0.20).
51
52 199 Physician responses differed by sex (rank-sum, p=0.003): males, 24 months (IQR 12-36); females 30
53
54 200 months (IQR 24-36). In comparison, 20.0% (n=100) of patients considered the maximum gain (also 42
55
56 201 months) insufficient. The remaining patients desired 42 months (IQR 12-42) gain. Older patients desired

marginally higher gain than younger patients (per year, spearman rho 0.10, $p=0.04$). Patient responses differed by sex (rank-sum, $p=0.04$): males, 36 months (IQR 6-42); females 42 months (IQR 24-42) (supplemental figures 1&2). Median threshold did not differ between patients on and off-therapy (rank-sum, $p=0.47$), although more patients off-therapy (42.1%) than on-therapy (8.1%) considered the maximum gain of 42 months insufficient. Similarly, median threshold did not differ between patients with and without clinically manifest CVD (rank-sum, $p=0.49$), although more patients without CVD (24.5%) than with CVD (16.3%) considered the maximum gain insufficient (supplemental figures 3&4). Similar results were obtained in the exploratory analysis when participants were asked to report the number of years willing to take a statin for one year gain of CVD-free life-expectancy. In total, 14.2% of physicians and 21.5% of patients were not willing to use a statin provided the thresholds. For those willing to use therapy, the time trade-off was similar to the main analysis median physicians 10 years (IQR 10-20), median patient 10 years (IQR 5-20). Results are depicted in supplemental figure 5.

Meaningful ten-year statin and antihypertensive thresholds

Meaningful ten-year thresholds for statins are depicted in figure 2a. In total, 4.4% ($n=17$) of physicians considered the maximum gain (14 months for every 10 years of use) insufficient to prescribe statins. The median meaningful gain for every 10 years of use was 12 months (IQR 10-12) for the remaining physicians. In comparison, 16.1% ($n=80$) of patients considered the maximum gain insufficient and the median ten-year threshold was 14 months (IQR 10-14). Meaningful ten-year thresholds for antihypertensive medication are depicted in figure 2b. Physician responses for statin and antihypertensive medication differed (paired signed-rank test, $Z=3736$, $p<0.001$). In total, 2.3% ($n=9$) of physicians considered the maximum gain (14 months for every 10 years of use) insufficient to prescribe antihypertensive therapy, and the median meaningful gain for every 10 years of use was 12 months (IQR 8-12). Patient responses did not differ for statin and antihypertensive medications ($Z=1795$, $p=0.36$).

Guideline recommendations and participant views of meaningful therapy

ESC-guideline recommendations and participant views of meaningful therapy for statin medications are juxtaposed against clinically attainable lifetime benefit in figure 3. Colors depict (non)-concordance

1
2
3 228 between guideline recommended therapy and participant views of meaningful benefit. The clinically
4
5 229 attainable gain in CVD-free life-expectancy from lifelong simvastatin 40mg ranged from 4 - 49 months.
6
7 230 Larger gains were seen in younger individuals with high SBP and lipid-levels and smaller gains were seen
8
9 231 in older individuals with low risk-factor levels. Treatment is concordant with participant views if the
10
11 232 clinically attainable gain in CVD-free life-expectancy per 10-years of medication is was equal to or greater
12
13 233 than the reported meaningful benefit thresholds for prescribing and using (i.e. physician median 12
14
15 234 months for every 10 years of use and patient median 14 months for every 10 years of use). Figure 4.
16
17 235 provides the same information for a single, daily, antihypertensive medication; clinically attainable lifetime
18
19 236 gain in CVD-free life-expectancy ranged from 4-35 months and followed a similar distribution pattern to
20
21 237 statin therapy.

23 238 **DISCUSSION**

24
25
26 239 Meaningful statin and antihypertensive therapy for lifetime and 10-years of use was quantified in 400
27
28 240 primary care physicians and 523 patients. A high degree of variation in what was perceived as meaningful
29
30 241 therapy was reported within both patients and physicians. Patients consistently desired a higher lifetime
31
32 242 benefit for medication use than physicians. Females desired a higher benefit from statins than males in
33
34 243 both participant groups. Physicians desired a slightly higher benefit for statin than for antihypertensive
35
36 244 medication. Age had minimal influence on thresholds in patients. Compared to those with CVD, a greater
37
38 245 percentage of healthy respondents were not willing to consider statin therapy. However, the median
39
40 246 thresholds for respondents who were willing to consider therapy did not differ between these two patient
41
42 247 groups. Similar results were found when patients on- and off- preventative therapy were compared. The
43
44 248 majority of respondents reported desiring a gain in CVD-free life expectancy above what is generally
45
46 249 achievable with lifelong use of a single tablet in the primary prevention setting.

47
48 250 To our knowledge, this is the first study examining medication-specific thresholds in both physicians and
49
50 251 patients in terms of gain in life-expectancy. The considerably high thresholds found in our study can be
51
52 252 explained by the use of specific medications and not an idealized tablet. Previous studies have either
53
54 253 focused on non-lifetime metrics in hypothetical risk scenarios,^{12 13} or on idealized medications with
55
56 254 negligible costs, side-effects, or follow-up requirements.^{10 14-17} Even in these idealized situations, the

1
2
3 255 benefit desired by patients is large, and often greater than the benefit desired by physicians.^{12 13 30} For an
4
5 256 idealized pill, the general public desires 6 months gain in life-expectancy.¹⁶ Health care employees are
6
7 257 willing to sacrifice 12.3 weeks of life to avoid taking a pill.³² Such isolated disutility of pill-taking is
8
9 258 applicable in cost-effectiveness studies. However, it does not assess the real-life perceived costs, side-
10
11 259 effects, and other inconveniences of specific medications which are encountered in clinical practice.

12
13 260 In this study, patients without CVD and not using preventive therapy were more often not willing to
14
15 261 consider therapy. However, for those who were willing to consider statin therapy, no group differences
16
17 262 were found in median CVD-free life-expectancy desired. The similar numeric thresholds align with exiting
18
19 263 literature in which socio-economic factors effected willingness to use medication whereas traditional risk-
20
21 264 factors such as the presence of CVD and use of antihypertensive or statin therapy did not.³³ Patients view
22
23 265 hypertension treatment as more necessary and effective than hyperlipidemia treatment.³⁴ However,
24
25 266 patients in our study did not distinguish between statin and antihypertensive medications indicating that
26
27 267 this discrepancy does not apply if therapy imparts identical benefit. Physicians however did desire greater
28
29 268 benefit from statins than antihypertensive medications. Statin side-effects, but not necessarily
30
31 269 antihypertensive side-effects, have received wide-spread attention over the previous decades. Negative
32
33 270 portrayal of statins in the media and academic press influences healthcare related behavior and coincides
34
35 271 with a decrease in statin use.³⁵ Myalgia frequency is approximately twice as high in patients on statins as
36
37 272 on placebo in clinical trials.³⁶ However, this frequency is considerably higher in observational studies,³⁷
38
39 273 and clinicians are confronted with observational frequencies in in clinical practice.

40
41 274 Compared to a risk-based treatment strategy in prevention guidelines, treatment based on meaningful
42
43 275 therapy thresholds would treat fewer risk-factor combinations, and would produce a shift in eligibility to
44
45 276 exclude mostly older individuals with a high 10-year risk and include younger individuals with a low 10-
46
47 277 year risk but high lipid levels and high SBP who would not be treated according the risk-based guidelines.
48
49 278 A previous study investigating eligibility based on an individualized benefit-based approach described a
50
51 279 similar shift in eligibility seen in the present study. The earlier study based eligibility cut-offs on a 10-year
52
53 280 absolute risk reduction of $\geq 2.3\%$.³⁸ However, the cut-off was not based on patient perceptions, but on the
54
55 281 minimum statin benefit seen in primary prevention guidelines, and resulted in a greater number of eligible
56
57
58
59
60

1
2
3 282 patients (34%) compared to current practice (21%). Other studies have demonstrated that young
4
5 283 individuals with high risk-factor levels (i.e. lipid and SBP) have the greatest net-positive lifetime benefit
6
7 284 from CVD-prevention strategies, such as aspirin use¹ and renin-angiotensin system inhibition.³⁹ As older
8
9 285 patients had a minimal but significantly higher benefit threshold than younger patients, such a shift is
10
11 286 congruent with user views. This shift is also congruent with changing insights into the benefits of
12
13 287 deprescription of the elderly population.⁴⁰

14
15 288 Lifetime based decision-tools have become more accessible in clinical practice to both patient and
16
17 289 physicians. It is therefore essential to address the high degree of variation in what is considered
18
19 290 meaningful therapy in clinical practice. The discrepancy between perceived meaningful benefit and
20
21 291 clinically attainable benefit should be addressed and a patient's satisfaction with the expected benefit of
22
23 292 agreed upon therapy could be viewed as an additional indicator of quality of care. However, guidelines
24
25 293 need not adapt eligibility thresholds or target values based on perceptions of meaningful therapy. The
26
27 294 number of prevented CVD-events is ultimately determined by physicians and patients making guideline-
28
29 295 based decisions. Misperceptions about perceived CVD-risk are commonplace, and ⁴¹ it is conceivable
30
31 296 that both physicians and patients overestimate realistic therapy-benefit and may require guidance as to
32
33 297 what longevity benefit may be realistically achieved. Such guidance could be easily incorporated into the
34
35 298 same online decision-aids which are currently available.

36
37
38 299 Certain strengths of this study should be highlighted. First, both parties of the shared decision-making
39
40 300 process were informed and surveyed in comparable settings. Physicians were representative of the
41
42 301 general practitioner population and both primary and secondary prevention patients were surveyed. As
43
44 302 there was no evidence of difference in medians between patients with and without CVD, no stratification
45
46 303 based on primary or secondary prevention was necessary. Secondly, the number of incomplete
47
48 304 responses was low for both physicians (1.0-2.3%) and patients (4.4-5.1%), indicating that both groups
49
50 305 were sufficiently informed to provide valid and reliable responses. Lastly, we examined benefit thresholds
51
52 306 of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-
53
54 307 effects, and inconveniences of medication which are a daily part of clinical practice. Certain study
55
56 308 limitations must also be acknowledged. First, we were restricted to a multiple-choice voting system, which

1
2
3 309 may have limited response variation. However, the observed variation in our study remained large and
4
5 310 multiple-choice options were based on responses from a pre-test session. Second, benefit-threshold
6
7 311 associated with a single medication was surveyed. In practice, if LDL-c or SBP targets are not achieved,
8
9 312 additional medication can be prescribed without necessarily increasing the number of tablets used daily.
10
11 313 However, the magnitude of the opinion-based benefit-thresholds are not altered by this limitation. Third,
12
13 314 patients were recruited at a large, information conference on CVD-prevention, and may represent a
14
15 315 population more interested in CVD-prevention than average. Fourth, the survey was pre-tested in
16
17 316 physicians and subsequently adapted for patients. However, the survey and the preceding introduction
18
19 317 were designed to maximize understandability and comparability. Fifth, clinically attainable benefit was
20
21 318 estimated using the JBS3 risk score and best available evidence from meta-analyses. However, the
22
23 319 estimated benefit differs in populations with different event-rates, such as those with clinically manifest
24
25 320 CVD. Lastly, further research would be necessary to analyze how these perspectives would relate to
26
27 321 actual use of medication by patients and prescription of medication by physicians.

28
29 322 In conclusion, both physicians and patients report a large variation in meaningful longevity-benefit.
30
31 323 Moreover, desired benefit differed between patients and physicians and exceeded clinically attainable
32
33 324 benefit. Clinicians should recognize these discrepancies when prescribing CVD-prevention and
34
35 325 implement individualized medicine and shared decision-making. In the future, guidance as to what
36
37 326 realistic benefit entails may be incorporated into online decision-aids to help physicians and patients
38
39 327 reach a consensus.

40
41 328

42
43
44 329 **Contributors:** NEMJ, FLJV, YG, JAND, contributed to the conception/design of the work. All authors
45
46 330 (NEMJ, FLJV, YG, YS, FLM, MN, JAND) contributed to the acquisition, analysis or interpretation of the
47
48 331 data. NEMJ drafted the work. All authors (NEMJ, FLJV, YG, YS, FLM, MN, JAND) critically revised the
49
50 332 manuscript, and gave final approval and agree to be accountable for all aspects of work.

51
52 333 **Acknowledgements:** We would like to acknowledge the organizers and participants of the following
53
54 334 meetings, conferences, and sessions: the April 2016 PGOSupport conference in Amstelveen, the

1
2
3 335 November 2016 pilot session in Roermond, the December 2016 Boerhaave Symposium in Leiden, and
4
5 336 the April 2017 University Medical Center Utrecht session for patients.
6
7

8 337 **Disclosures:** None
9

10 338 **Funding:** This research received no specific grant from any funding agency in the public, commercial or
11
12 339 not-for-profit sectors.
13
14

15 340 **Data Sharing:** No additional data is available for this study in repositories. However, inquiries concerning
16
17 341 the data may be made to the corresponding author.
18
19

20 342

21
22 343 **REFERENCES:**
23
24

25 344 1. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in
26
27 345 healthy life expectancy for individual patients. *BMJ* 2016;**352**:i1548.
28

29 346 2. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK
30
31 347 model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database.
32
33 348 *BMJ* 2010;**341**:c6624.
34
35

36 349 3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease
37
38 350 prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology
39
40 351 and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by
41
42 352 representatives of 10 societies and by invited experts)Developed with the special contribution of
43
44 353 the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*
45
46 354 2016;**37**(29):2315-81.
47

48 355 4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of
49
50 356 cardiovascular risk: a report of the American College of Cardiology/American Heart Association
51
52 357 Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**(25 Pt B):2935-59.
53
54
55
56
57
58
59
60

- 1
2
3 358 5. Dickinson R, Raynor DK, Knapp P, et al. Providing additional information about the benefits of statins
4
5 359 in a leaflet for patients with coronary heart disease: a qualitative study of the impact on attitudes
6
7 360 and beliefs. *BMJ Open* 2016;**6**(12):e012000.
- 9 361 6. Manuel DG, Abdulaziz KE, Perez R, et al. Personalized risk communication for personalized risk
10
11 362 assessment: Real world assessment of knowledge and motivation for six mortality risk measures
12
13 363 from an online life expectancy calculator. *Inform Health Soc Care* 2017:1-14.
- 15 364 7. Galesic M, Garcia-Retamero R. Communicating consequences of risky behaviors: Life expectancy
16
17 365 versus risk of disease. *Patient Educ Couns* 2011;**82**(1):30-5.
- 19 366 8. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular
20
21 367 disease (JBS3). *Heart* 2014;**100** Suppl 2:ii1-ii67.
- 23 368 9. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic
24
25 369 cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA
26
27 370 Guidelines. *J Am Coll Cardiol* 2015;**65**(13):1361-8.
- 29 371 10. Halvorsen PA, Aasland OG, Kristiansen IS. Decisions on statin therapy by patients' opinions about
30
31 372 survival gains: cross sectional survey of general practitioners. *BMC Fam Pract* 2015;**16**:79.
- 33 373 11. Misselbrook D, Armstrong D. Patients' responses to risk information about the benefits of treating
34
35 374 hypertension. *Br J Gen Pract* 2001;**51**(465):276-9.
- 37 375 12. McAlister FA, O'Connor AM, Wells G, et al. When should hypertension be treated? The different
38
39 376 perspectives of Canadian family physicians and patients. *CMAJ* 2000;**163**(4):403-8.
- 41 377 13. Steel N. Thresholds for taking antihypertensive drugs in different professional and lay groups:
42
43 378 questionnaire survey. *BMJ* 2000;**320**(7247):1446-7.
- 45 379 14. Stovring H, Gyrd-Hansen D, Kristiansen IS, et al. Communicating effectiveness of intervention for
46
47 380 chronic diseases: what single format can replace comprehensive information? *BMC Med Inform*
48
49 381 *Decis Mak* 2008;**8**:25.
- 51 382 15. Trewby PN, Reddy AV, Trewby CS, et al. Are preventive drugs preventive enough? A study of
52
53 383 patients' expectation of benefit from preventive drugs. *Clin Med (Lond)* 2002;**2**(6):527-33.

- 1
2
3 384 16. Fontana M, Asaria P, Moraldo M, et al. Patient-accessible tool for shared decision making in
4
5 385 cardiovascular primary prevention: balancing longevity benefits against medication disutility.
6
7 386 *Circulation* 2014;**129**(24):2539-46.
8
9 387 17. Dahl R, Gyrd-Hansen D, Kristiansen IS, et al. Can postponement of an adverse outcome be used to
10
11 388 present risk reductions to a lay audience? A population survey. *BMC Med Inform Decis Mak*
12
13 389 2007;**7**:8.
14
15 390 18. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male
16
17 391 British doctors. *BMJ* 2004;**328**(7455):1519.
18
19 392 19. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of
20
21 393 Dyslipidaemias. *Eur Heart J* 2016;**37**(39):2999-3058.
22
23 394 20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial
24
25 395 hypertension: the Task Force for the Management of Arterial Hypertension of the European
26
27 396 Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*
28
29 397 2013;**34**(28):2159-219.
30
31 398 21. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular
32
33 399 disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**(11):987-1003.
34
35 400 22. JBS Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular
36
37 401 disease; JBS3 risk calculator. Secondary Joint British Societies' consensus recommendations for
38
39 402 the prevention of cardiovascular disease; JBS3 risk calculator. <http://www.jbs3risk.com/>.
40
41 403 23. van Dis I, Kromhout D, Geleijnse JM, et al. Evaluation of cardiovascular risk predicted by different
42
43 404 SCORE equations: the Netherlands as an example. *Eur J Cardiovasc Prev Rehabil*
44
45 405 2010;**17**(2):244-9.
46
47 406 24. Gu Q, Paulose-Ram R, Burt VL, et al. Prescription cholesterol-lowering medication use in adults aged
48
49 407 40 and over: United States, 2003-2012. *NCHS Data Brief* 2014(177):1-8.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 408 25. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive
4
5 409 lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised
6
7 410 trials. *Lancet* 2010;**376**(9753):1670-81.
8
9 411 26. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of
10
11 412 cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from
12
13 413 prospective epidemiological studies. *BMJ* 2009;**338**:b1665.
14
15 414 27. Recommendations for treatment of hyperlipidemia in adults. A joint statement of the Nutrition
16
17 415 Committee and the Council on Arteriosclerosis. *Circulation* 1984;**69**(5):1067A-90A.
18
19 416 28. JoJoGenetics. Sectie Moleculaire Diagnostiek van het Laboratorium Experimentele Vasculaire
20
21 417 Geneeskunde, Academisch Medisch Centrum. <http://www.jojogenetics.nl/>.
22
23 418 29. Netherlands National Institute for Public Health and the Environment (RIVM). Average Body Mass
24
25 419 Index (kg/m²) according to age and gender. The Netherlands. 2012.
26
27 420 30. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a
28
29 421 systematic review. *Heart* 2017.
30
31 422 31. Wegwarth O, Schwartz LM, Woloshin S, et al. Do physicians understand cancer screening statistics?
32
33 423 A national survey of primary care physicians in the United States. *Ann Intern Med*
34
35 424 2012;**156**(5):340-9.
36
37 425 32. Hutchins R, Viera AJ, Sheridan SL, et al. Quantifying the utility of taking pills for cardiovascular
38
39 426 prevention. *Circ Cardiovasc Qual Outcomes* 2015;**8**(2):155-63.
40
41 427 33. Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing
42
43 428 treatments: a randomized trial. *Ann Intern Med* 2007;**146**(12):848-56.
44
45 429 34. Stack RJ, Bundy C, Elliott RA, et al. Patient perceptions of treatment and illness when prescribed
46
47 430 multiple medicines for co-morbid type 2 diabetes. *Diabetes Metab Syndr Obes* 2011;**4**:127-35.
48
49 431 35. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins:
50
51 432 interrupted time series analysis with UK primary care data. *BMJ* 2016;**353**:i3283.
52
53
54
55
56
57
58
59
60

- 1
2
3 433 36. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of
4
5 434 statin therapy. *Lancet* 2016;**388**(10059):2532-61.
6
7 435 37. Thompson PD, Panza G, Zaleski A, et al. Statin-Associated Side Effects. *J Am Coll Cardiol*
8
9 436 2016;**67**(20):2395-410.
10
11 437 38. Thanassoulis G, Williams K, Altobelli KK, et al. Individualized Statin Benefit for Determining Statin
12
13 438 Eligibility in the Primary Prevention of Cardiovascular Disease. *Circulation* 2016;**133**(16):1574-
14
15 439 81.
16
17 440 39. Schievink B, Kropelin T, Mulder S, et al. Early renin-angiotensin system intervention is more
18
19 441 beneficial than late intervention in delaying end-stage renal disease in patients with type 2
20
21 442 diabetes. *Diabetes Obes Metab* 2016;**18**(1):64-71.
22
23 443 40. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through
24
25 444 shared decision making. *BMJ* 2016;**353**:i2893.
26
27 445 41. Katz M, Laurinavicius AG, Franco FG, et al. Calculated and perceived cardiovascular risk in
28
29 446 asymptomatic subjects submitted to a routine medical evaluation: The perception gap. *Eur J Prev*
30
31 447 *Cardiol* 2015;**22**(8):1076-82.
32
33
34
35
36 448
37
38
39 449
40
41 450
42
43
44 451
45
46 452
47
48
49 453
50
51
52
53
54
55
56
57
58
59
60

454 **Table 1 Baseline Characteristics**

| | Primary Care Physicians | Patients |
|--------------------------------|-------------------------|----------------|
| | n=400 | n = 523 |
| Gender | | |
| Male | 195 (54%) [†] | 263 (50%) |
| Female | 164 (46%) | 260 (50%) |
| Age | | |
| ≤ 34 | 31 (8%) [†] | 12 (2%) |
| 35-45 | 67 (18%) | 15 (3%) |
| 46-52 | 63 (17%) | 19 (4%) |
| 53-57 | 67 (18%) | 21 (4%) |
| 58-62 | 89 (24%) | 57 (11%) |
| 63-67 | 41 (11%) | 110 (21%) |
| 68-72 | 6 (2%) | 130 (25%) |
| ≥ 73 | 3 (1%) | 159 (30%) |
| Statin Use | | |
| Yes | - | 298 (57%)* |
| No | - | 166 (32%) |
| Previously used | - | 55 (11%) |
| Unknown | - | 4 (1%) |
| Antihypertensive Use | | |
| Yes | - | 301 (58%)* |
| No | - | 187 (36%) |
| Previously used | - | 30 (6%) |
| Unknown | - | 4 (1%) |
| Clinically Manifest CVD | | |
| Yes | - | 283 (54%)* |
| No | - | 238 (46%) |

468 Missing data for baseline characteristics is denoted as * (<1%) or † (between 8% and 10%); Clinically
469 manifest cardiovascular disease (CVD) is defined as presence of one or more of the following: coronary
470 heart disease, cerebrovascular disease, and peripheral artery disease.

471

472

473

474

1
2
3 475 **Figures Legends**
4

5
6 476 **Figure 1 Legend:**
7

8
9 477 Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin
10
11 478 therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).
12

13
14 479 **Figure 2 a. and b. Legend:**
15

16
17 480 Months gain in CVD-free life-expectancy above which physicians (as prescribers) and patients (as users)
18
19 481 consider a) statin and b) antihypertensive therapy meaningful. Missing responses was seen in 5
20
21 482 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients
22
23 483 (5.1%) for antihypertensive medication.
24
25

26
27 484 **Figure 3 Legend:**
28

29
30 485 Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong
31
32 486 therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and
33
34 487 smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance between
35
36 488 ESC-guideline recommendations and participant views of meaningful therapy.
37
38

39
40 489 **Figure 4 Legend:**
41

42
43 490 Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong
44
45 491 therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-
46
47 492 profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the
48
49 493 (non)-concordance between ESC-guideline recommendations and participant views of meaningful
50
51 494 therapy.
52
53
54
55
56
57
58
59
60

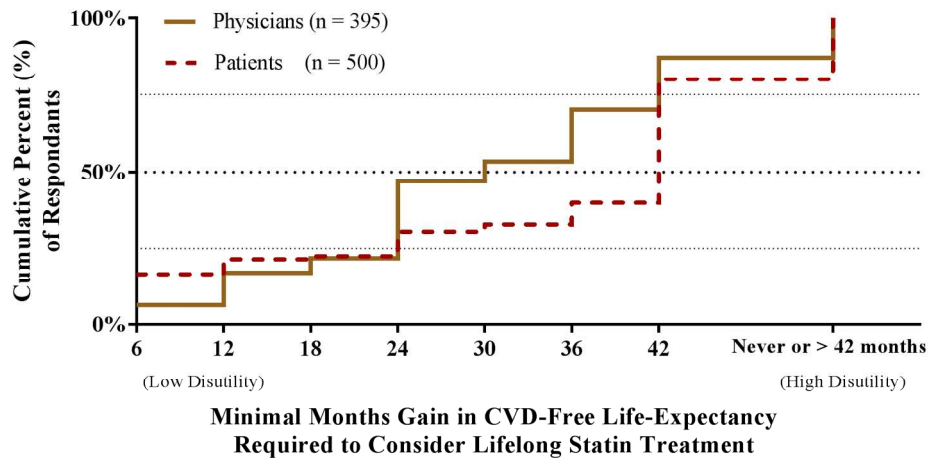


Figure 1. Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

173x87mm (300 x 300 DPI)

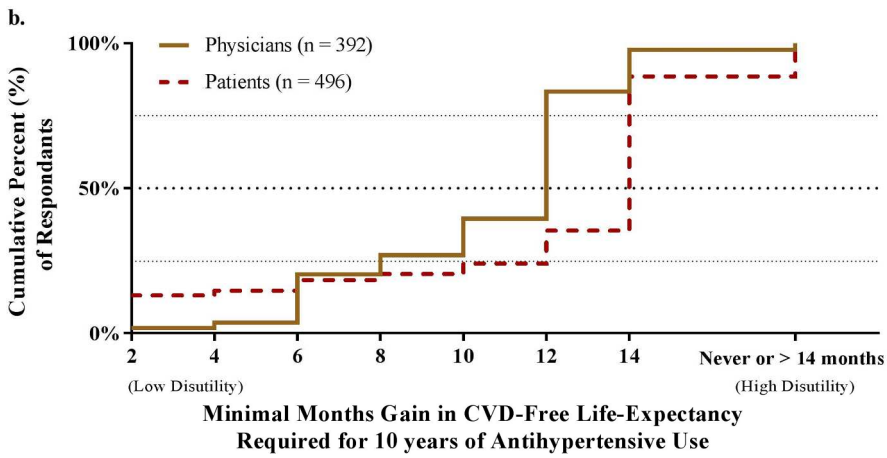
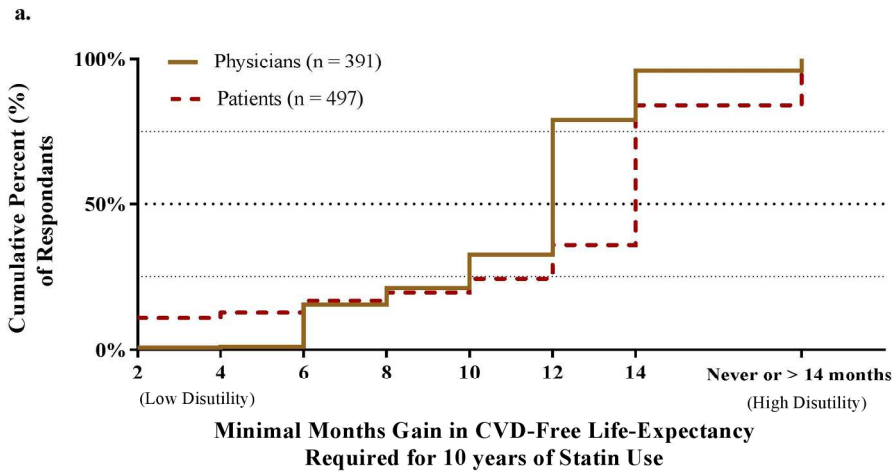


Figure 2. Minimal gain in CVD-free life-expectancy to perceive a) statin and b) antihypertensive therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients (5.1%) for antihypertensive medication.† †

205x235mm (300 x 300 DPI)

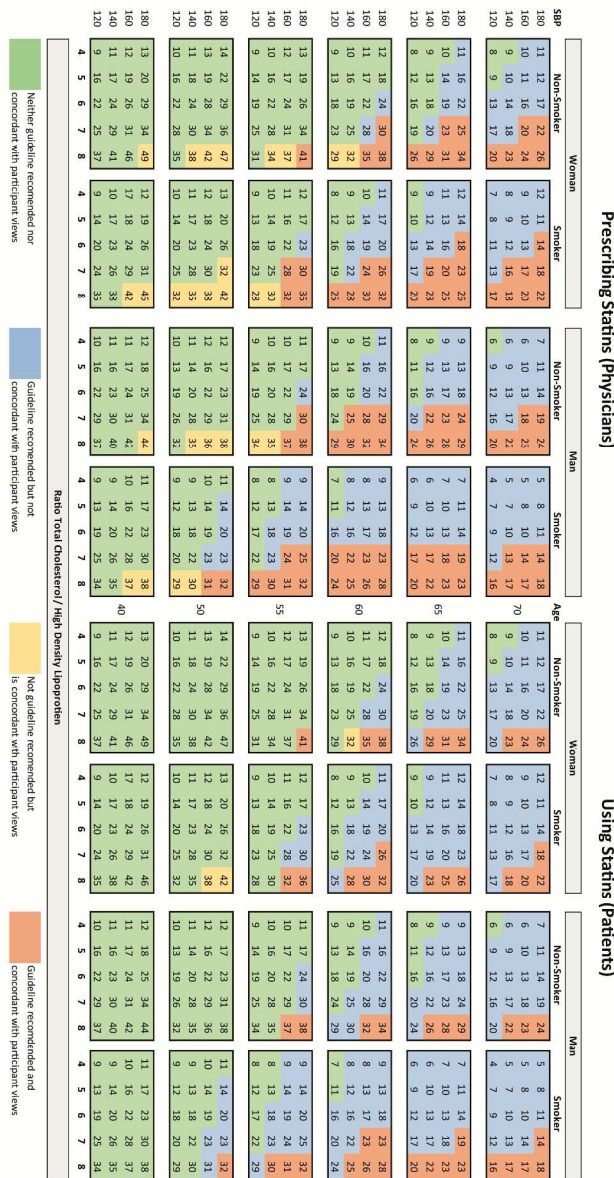


Figure 3. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance between ESC-guideline recommendations and participant views of meaningful therapy.

192x368mm (300 x 300 DPI)

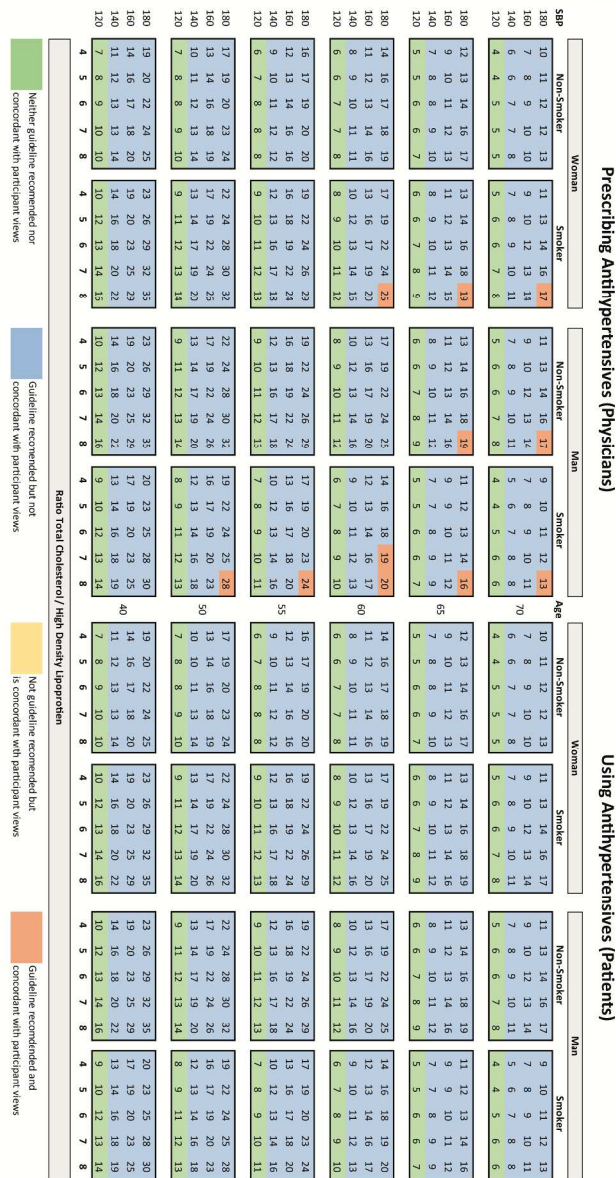


Figure 4 : Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance between ESC-guideline recommendations and participant views of meaningful therapy.

192x368mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **SUPPLEMENTAL MATERIAL**

2

3 A) Physician Survey2

4 B) Patient Survey5

5 C) Short Summary of Introduction Sessions.....8

6 D) Values Used for Calculations11

7 E) Example Calculation.....12

8 F) Supplemental Figures13

For peer review only

1
2
3 21 **A) Physician Survey**
4

5 22 *The following survey was conducted on December 8th, 2016 at the Boerhaave Continuing Medical*
6
7 23 *Education Conference.*
8
9

10 24 1. What is your current position?
11

12
13 25 a. Family Physician

14
15 26 b. Nursing home physician

16
17 27 c. Physician for mentally impaired

18
19 28 d. Resident Family Medicine

20
21 29 e. Nurse practitioner/ Nursing assistant

22
23 30 f. Other
24
25

26
27 31 **Note: Answers a, b, and c, are considered specialties in primary prevention*
28
29

30 32 2. What is your gender?
31

32 33 a. Male

34 34 b. Female

35 35 3. What is your age?
36

37 36 a. ≤ 34

38 37 b. 35-45

39 38 c. 46-52

40 39 d. 53-57

41 40 e. 58-62

42 41 f. 63-67

43 42 g. 68-72

44 43 h. ≥ 72
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 44 4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is
4
5 45 the minimum gain in life-expectancy without (new) cardiovascular disease “*healthy life years*”
6
7 46 the medication must provide before you considered use worthwhile?
8
9
10 47 a. ½ year (low threshold)
11
12 48 b. 1 year
13
14 49 c. 1 ½ year
15
16 50 d. 2 year
17
18 51 e. 2 ½ year
19
20 52 f. 3 year
21
22 53 g. 3 ½ year (high threshold)
23
24 54 h. I would never want to use a statin *Or only above these thresholds*
25
26
27
28 55
29
30 56 5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease
31
32 57 “*healthy life years.*” What is the **maximum** number of years you would personally consider using
33
34 58 this statin to achieve this benefit?
35
36 59 a. I would never want to use a statin; *Or only above these thresholds*
37
38 60 b. 5 year (high threshold)
39
40 61 c. 10 year
41
42 62 d. 15 year
43
44 63 e. 20 year
45
46 64 f. 30 year
47
48 65 g. 40 year
49
50 66 h. 50 year (low threshold)
51
52
53
54
55
56
57 68
58
59
60

- 1
2
3 69 6. What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, “*healthy life*
4
5 70 *years*”, necessary before you consider **10 years of statin therapy** for a **patient** worthwhile?
6
7 71 a. 2 months (low threshold)
8
9 72 b. 4 months
10
11 73 c. 6 months
12
13 74 d. 8 months
14
15 75 e. 10 months
16
17 76 f. 12 months
18
19 77 g. 14 months (high threshold)
20
21 78 h. I would never consider statin prescription worthwhile. *Or only above these thresholds*
22
23 79
24
25
26
27 80 7. And what we aren’t talking about statins, but about blood-pressure therapy?
28
29 81 What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, “*healthy life*
30
31 82 *years*”, necessary before you consider **10 years of blood-pressure therapy** for a **patient**
32
33 83 worthwhile?
34
35 84 a. 2 months (low threshold)
36
37 85 b. 4 months
38
39 86 c. 6 months
40
41 87 d. 8 months
42
43 88 e. 10 months
44
45 89 f. 12 months
46
47 90 g. 14 months (high threshold)
48
49 91 h. I would never consider blood-pressure medication prescription worthwhile; *Or only above*
50
51 92 *these thresholds*
52
53
54
55
56
57 93
58
59
60

1
2
3 94 **B) Patient Survey**
4

5 95 *The following patient survey was conducted on April 7th, 2017 at the University Medical Centre*

6
7 96 *Utrecht, the Netherlands.*
8
9

10
11 97 1. Do you use a statin?

12
13 98 a. Yes

14
15 99 b. No

16
17 100 c. I have used statins, but stopped taking them

18
19 101 d. I don't know

20
21 102 2. Do you use an antihypertensive medication?

22
23 103 a. Yes

24
25 104 b. No

26
27 105 c. I have used antihypertensive medications, but stopped taking them

28
29 106 d. I don't know

30
31 107 3. What is your gender?

32
33 108 a. Male

34
35 109 b. Female

36
37 110 4. What is your age?

38
39 111years
40
41
42

43
44
45
46 112 5. Please mark all the complications or medication procedures which you have had. You can also
47
48 113 indicate if you have never had any one of these procedures.
49

50
51 114 Heart attack

52
53 115 Stroke

54
55 116 *Intermittent claudication* (Peripheral artery disease)

56
57 117 TIA
58
59
60

- 1
2
3 118 a stent, angioplasty, or other operation of the hart
4
5
6 119 an operation of the carotid artery (*major artery of the neck*)
7
8 120 I have never had *ANY* of the above
9
10
11 121 5. Imagine **you** were considering starting (or continuing) a statin medication. What in the minimum
12
13 122 gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication
14
15 123 must provide before you considered use worthwhile?
16
17 124 a. ½ year (low threshold)
18
19 125 b. 1 year
20
21 126 c. 1 ½ year
22
23 127 d. 2 year
24
25 128 e. 2 ½ year
26
27 129 f. 3 year
28
29 130 g. 3 ½ year (high threshold)
30
31 131 h. I would never want to use a statin ; *Or only above these thresholds*
32
33 132
34
35
36
37 133 6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease
38
39 134 "*healthy life years.*" What is the **maximum** number of years you would consider using the statin
40
41 135 to achieve this benefit?
42
43 136 a. I would never consider a statin worthwhile; *Or only above these thresholds*
44
45 137 b. 5 years (high threshold)
46
47 138 c. 10 years
48
49 139 d. 15 years
50
51 140 e. 20 years
52
53 141 f. 30 years
54
55 142 g. 40 years
56
57 143 h. 50 years (low threshold)
58
59
60

- 1
2
3 144 7. What is the minimum gain in life-expectancy without (new) cardiovascular disease,
4 145 “*healthy life years*”, necessary before you consider 10 years of statin therapy
5 146 worthwhile?
6
7
8 147
9
10 148 a. 2 months (low threshold)
11
12 149 b. 4 months
13
14 150 c. 6 months
15
16 151 d. 8 months
17
18 152 e. 10 months
19
20 153 f. 12 months
21
22 154 g. 14 months (high threshold)
23
24 155 h. I would never consider a statin worthwhile; *Or only above these thresholds*
25
26 156
27
28 157 8. And what we aren’t talking about statins, but about blood-pressure therapy?
29
30 158 What is the **minimum** gain in life-expectancy without (new) cardiovascular disease, “*healthy life*
31 159 *years*”, necessary before you consider **10 years of blood-pressure therapy** worthwhile?
32
33 160 a. 2 months (low threshold)
34
35 161 b. 4 months
36
37 162 c. 6 months
38
39 163 d. 8 months
40
41 164 e. 10 months
42
43 165 f. 12 months
44
45 166 g. 14 months (high threshold)
46
47 167 h. I would never consider blood-pressure medication worthwhile ; *Or only above these*
48
49 168 *thresholds*
50
51 169
52
53
54
55
56
57
58
59
60

170 C) Short Summary of Introduction Sessions

171

172 Physician Session

173

174 • The session started with a short reiteration that prevention of cardiovascular disease (CVD)

175 incorporates both life-style aspects (such as not smoking or drinking too much alcohol,

176 exercising regularly, eating healthy) and medication aspects (such as cholesterol, blood-

177 pressure and aspirin treatment).

178 • Decision-making cardiovascular disease prevention was described as finding the balance

179 between the benefits (living a longer, healthier, life) and negative effects (side-effects, costs,

180 and taking a pill daily) of therapy. For each individual person, the balance between the

181 benefits and negative effects can be different.

182 • The SCORE-chart as used in national primary prevention guidelines was reviewed.

183 Drawbacks of using the SCORE-chart, and the associated ten-year absolute risk was

184 discussed, namely that it often emphasizes treatment of the elderly, and that interpretation

185 of 10-year risk or risk reduction may be difficult for the patient. Positive aspects of the

186 SCORE-chart were also discussed, namely that it is easy to use, and allows for a variety of

187 different individual risk-factors to be combined.

188 • Prediction algorithms and calculators which can estimate CVD-free life-expectancy for those

189 in the primary prevention were introduced (i.e. the JBS-3 risk score).²² Life-time estimates

190 were described as being more biologically and clinically intuitive, as atherosclerosis is a

191 phenomenon which starts early in life, and manifests itself only after a few decades.

192 • It was illustrated with two examples from peer-reviewed literature that the one “treats” a

193 risk-factor, the greater the potential benefit. The first example provided was meant to show

194 a large life-time benefit from a life-style intervention. It was shown that stopping with

195 smoking between 25-34 years of age extends survival by 10 years, whereas stopping

196 between 55-64 years of age extends survival by 3 years.¹⁸ The second example was meant to

1
2
3 197 show a small benefit, and to provide a reference for preventative medication.¹ It was shown
4
5 198 that the individual effect of aspirin therapy, is not expressed in years, but rather in months
6
7
8 199 gain. These months range between 0-8 according to peer reviewed literature. It was
9
10 200 emphasized that the potential gain in stopping with smoking is of a greater magnitude than
11
12 201 the potential gain of medication, which is better represented by the aspirin example. It was
13
14 202 also emphasized that the longer one “treats” a risk-factor, the longer one must also take the
15
16 203 medication.
17
18
19 204 • Long-term validation results of these prediction models were shown.¹
20
21 205 • In conclusion, it was iterated that starting medication at a young age provides the greatest
22
23 206 net effect of therapy, but that this greater net-effect also goes hand in hand with a longer
24
25 207 period of time in which the therapy would have to be used.
26
27
28 208

29 30 31 209 **Patient Session**

- 32
33 210 • The session started with a short reiteration that prevention of cardiovascular disease (CVD)
34
35 211 incorporates both life-style aspects (such as not smoking or drinking too much alcohol,
36
37 212 exercising regularly, eating healthy) and medication aspects (such as cholesterol, blood-
38
39 213 pressure and aspirin treatment).
40
41
42 214 • Lipid-lowering and blood-pressure lowering were described as two important pillars of CVD-
43
44 215 prevention guidelines. Statin medication were described as some on the most common
45
46 216 cholesterol-lowering drugs, and a number of statin medications (with both generic and
47
48 217 brand-names) were given: simvastatin, rosuvastatin, pravastatin, atorvastatin, fluvastatin. A
49
50 218 few common examples of blood-pressure lowering medications were also given:
51
52 219 hydrochlorothiazide, enalapril, perindopril, losartan, olmesartan, amlodipine, and
53
54 220 metoprolol.
55
56 221 • Decision-making cardiovascular disease prevention was described as finding the balance
57
58 222 between the benefits (living a longer, healthier, life) and negative effects (side-effects, costs,
59
60

1
2
3 223 and taking a pill daily) of therapy. For each individual person, the balance between the
4
5 224 benefits and negative effects can be different.
6
7
8 225 • What exactly “CVD-free life expectancy?” entails was discussed. It was described as the
9
10 226 amount of time you can expect to live *healthily*, without cardiovascular disease. If you
11
12 227 already have had cardiovascular disease, then it was described as the amount of time you
13
14 228 can expect to live without having another major cardiovascular event, such as a heart-
15
16 229 attack. It was discussed that doctors are getting better at predicting what someone’s CVD-
17
18 230 free life-expectancy is, and also what the gain in CVD-free life expectancy is from
19
20 231 medications such as statin and blood-pressure lowering medications.
21
22
23 232 • It was introduced that the longer one “treats” a risk-factor, the greater the benefit (gain in
24
25 233 CVD-free life-expectancy can be). This was illustrated with the same two-examples from
26
27 234 peer-reviewed literature as with the physicians. Likewise, it was emphasized that the
28
29 235 potential gain in stopping with smoking is of a greater magnitude than the potential gain of
30
31 236 medication, which is better represented by the aspirin example. It was also emphasized that
32
33 237 the longer one “treats” a risk-factor, the longer one must also take the medication.
34
35
36 238 • In conclusion, it was iterated that starting medication at a young age provides the greatest
37
38 239 net effect of therapy, but that this greater net-effect also goes hand in hand with a longer
39
40 240 period of time in which the therapy would have to be used. The definition of CVD-free life-
41
42 241 expectancy was given again.
43
44
45
46 242
47
48
49 243
50
51
52 244
53
54
55
56
57
58
59
60

1
2
3 **245 D) Values Used for Calculations**

4 **246** Age and gender-specific medians (50th percentile) of high-density lipoprotein concentration (HDL-c,
5
6 **247** mmol/l) and triglyceride concentration (TG, mmol/l), were used to calculate low-density lipoprotein
7
8 **248** concentration (LDL-c, mmol/l).²⁷⁻²⁹ For each lipid-value depicted on the SCORE-based chart,
9
10 **249** corresponding low-density lipoprotein concentration (LDL-c) was calculated using the Friedewald
11
12 **250** formula and age and sex-specific medians of high density lipoprotein (HDL-c) and triglyceride
13
14 **251** concentrations. Age and gender-specific body-mass index (BMI, kg/m²) was used with Joint British
15
16 **252** Societies for prevention of cardiovascular disease (JBS3) risk calculator²². Patients were assumed to
17
18 **253** have average socio-economic status and have no other comorbidities such as diabetes. Smokers
19
20 **254** used between 10 and 20 cigarettes per day.
21
22
23
24

25 **255 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 |

26 **256** Legend: Abbreviations LDL-c = low-density lipoprotein cholesterol; HDL-c = High density lipoprotein
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56 **257** cholesterol; TC= Total cholesterol; TG = Triglycerides; BMI = Body-Mass Index
57
58
59
60

1
2
3 **258 E) Example Calculation**

4 259 A male patient, medical history negative for diabetes, 40 years of age, BMI of 26.2 kg/m², systolic
5
6 260 blood-pressure 140 mmHg, and a total cholesterol / HDL ratio of 7. The 50th percentile values for
7
8
9 261 HDL-c is 1.12 mmol/L and TG is 1.35 mmol/L.(1)

10
11
12 262 Calculation LDL-c:

13
14
15 263 Baseline LDL-c = Total cholesterol – median HDL – median triglyceride / 2.17

16
17
18 264 = Ratio x median HDL – median HDL – median triglyceride / 2.17

19
20
21 265 = 7 x 1.12 – 1.12 – 1.35/2.17

22
23
24 266 = 6.098 mmol/L

25
26
27 267 The effects of simvastatin 40 mg was calculated as follows:

28
29
30 268 LDL-c_{new} = LDL-c_{old} * (1 - percent reduction)

31
32
33 269 = 6.098 mmol/L * 0.63

34
35
36 270 = 3.842 mmol/L

37
38
39 271 Estimated attainable therapy-benefit in terms of gain in CVD-free life-years according to the JBS3

40
41
42 272 Online calculator:²²

43
44 273 Calculated CVD-free life-expectancy off-treatment (i.e. current prognosis) = 76 years

45
46 274 Calculated gain in CVD-free life-expectancy = 2.5 years

47
48 275 Remaining CVD-free life years on-treatment (i.e. potential treatment duration) = (76 years +

49
50 276 2.5 years)-40 years(i.e. current age) = 38.5 years

51
52 277 Gain per 10 years of use = (2.5 years gain / 38.5 years of use)*10 = 0.649 years = 7.8 months

53
54
55 278

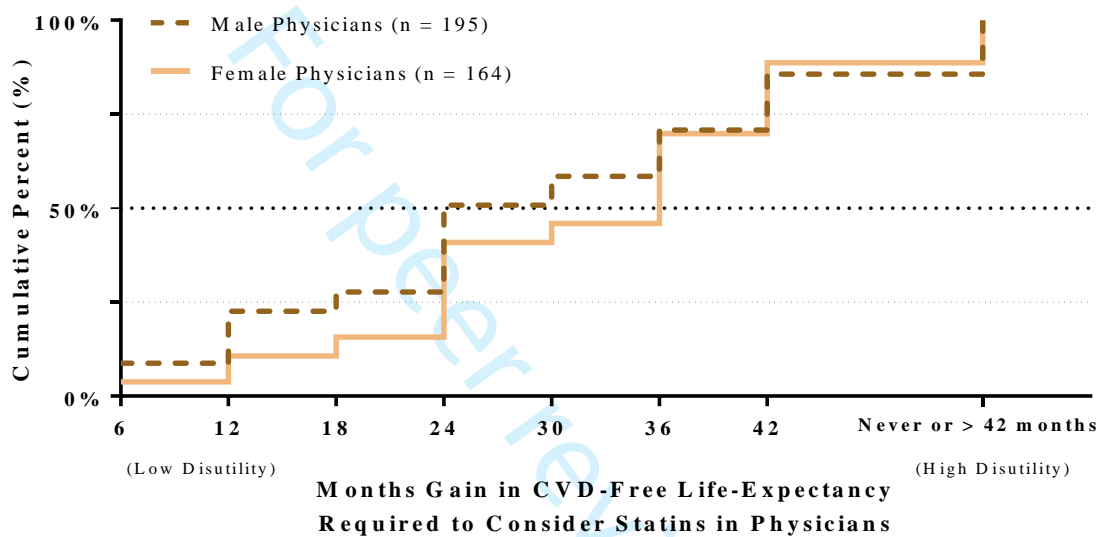
279 **F) Supplemental Figures**

280

281 **Supplemental Figure 1.** Months gain in CVD-free life-expectancy required to consider personal use

282 of statin therapy, stratified by sex in physicians

283



284 Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin
 285 therapy as meaningful, stratified by gender.
 286

287

288

289

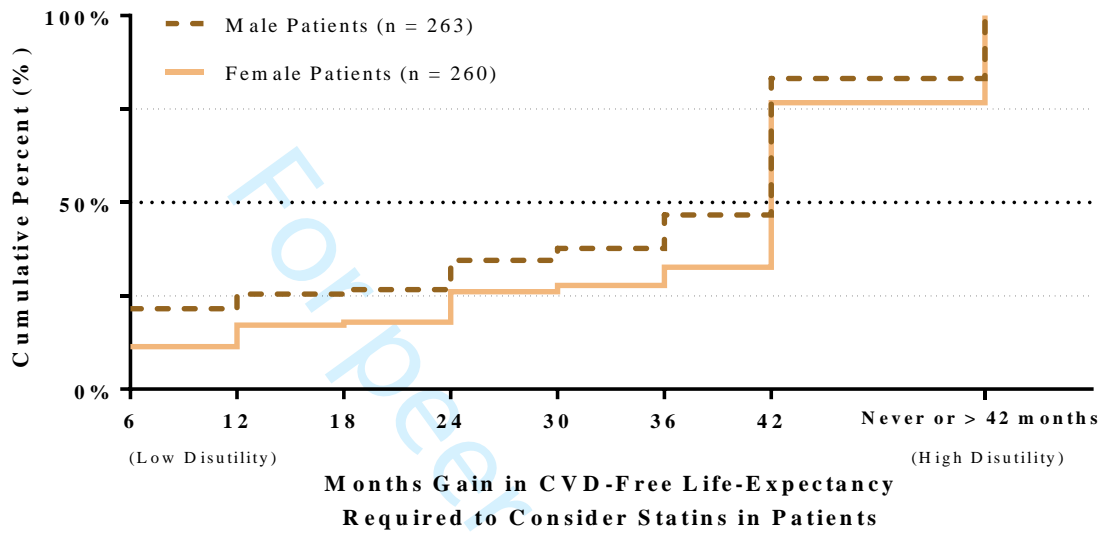
290

291

292

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

295



296

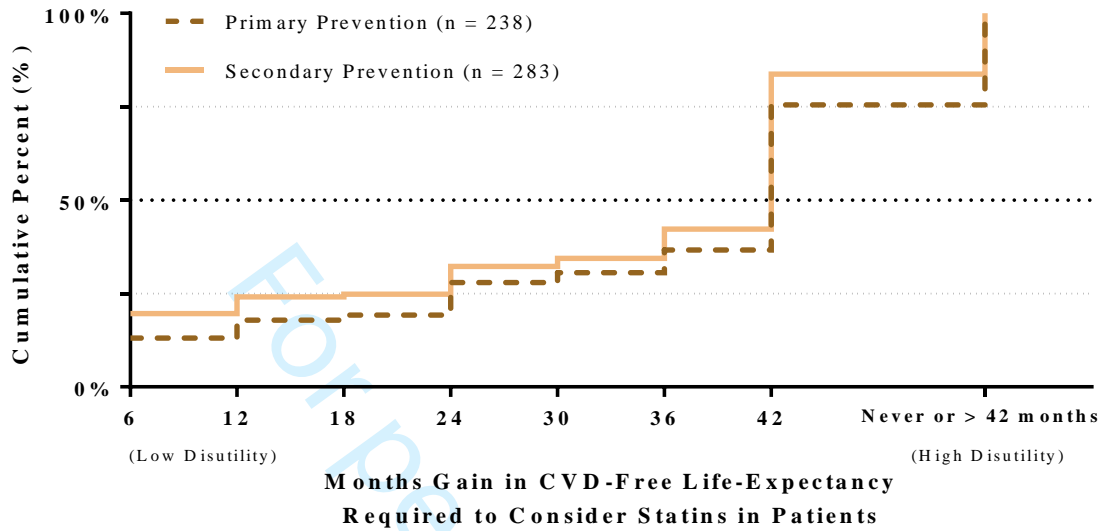
297 Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin
 298 therapy as meaningful, stratified by gender.

299

300

301

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



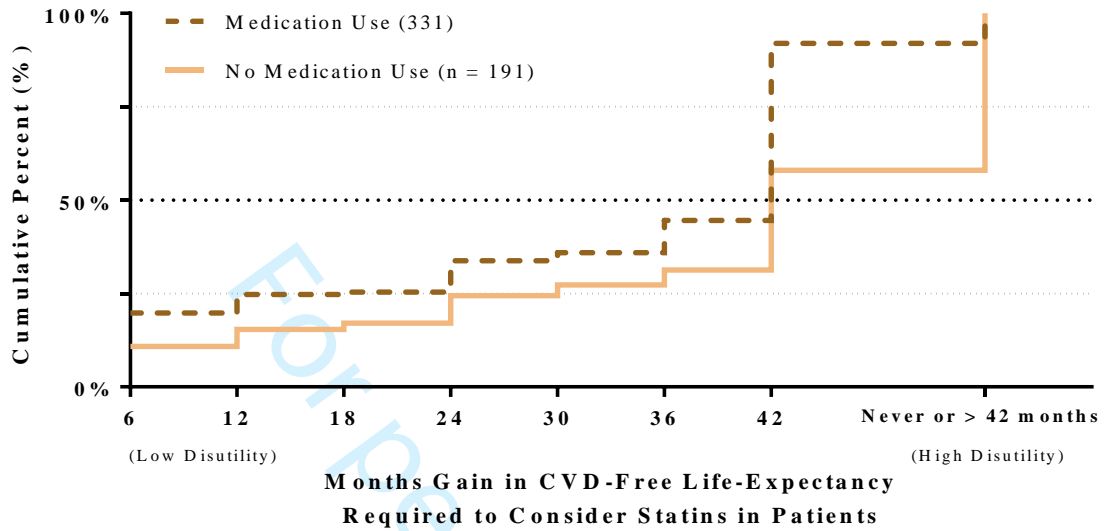
304

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

307

308

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



311

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

314

315

316

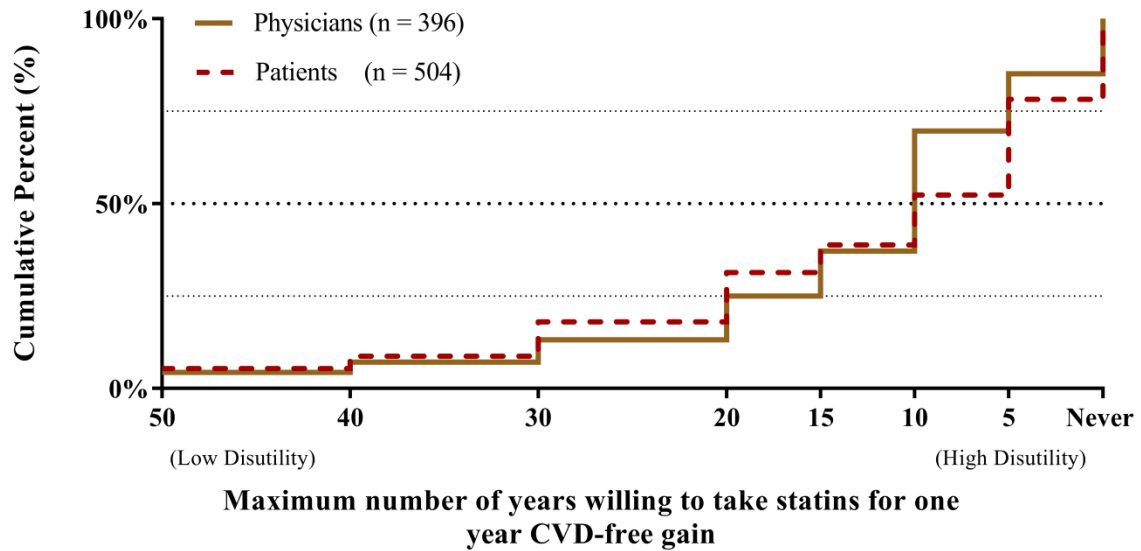
317

318

319

320

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



323

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

STROBE Statement—Checklist of items that should be included in reports of **cross-sectional studies**

| | Item No | Recommendation | Where? |
|------------------------------|----------------|---|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | <i>Both in title/abstract page 1 and 2</i> |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | <i>Structured abstract Page 2</i> |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | <i>Introduction page 4</i> |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | <i>End of introduction page 4-5</i> |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | <i>Settings & participants Survey preparation and administration Page 5-6</i> |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | <i>Settings & participants Survey preparation and administration Page 5-6</i> |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants | <i>Settings & participants Page 5</i> |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | <i>Settings & participants Survey preparation and administration Page 5-6</i> |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | <i>Methods + Supplemental data Page 5</i> |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | <i>Setting and participant Page 5</i> |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | <i>Data analysis Page 7</i> |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | <i>Data analysis Page 7</i> |
| | | (b) Describe any methods used to examine subgroups and interactions | <i>Data analysis Page 7</i> |
| | | (c) Explain how missing data were addressed | <i>Data analysis Page 7</i> |
| | | (d) If applicable, describe analytical methods taking account of sampling strategy | <i>n/a/</i> |
| | | (e) Describe any sensitivity analyses | <i>Exploratory analysis Methods: Page 6 Results: page 8</i> |
| Results | | | |

| | | | |
|-------------------|-----|--|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | <i>Participants and response</i> <i>Page 7-8</i> |
| | | (b) Give reasons for non-participation at each stage | <i>Participants and response</i> <i>gives overview of number of individuals at each stage (page 7)</i> |
| | | (c) Consider use of a flow diagram | <i>Information adequately summarized in text</i> |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | <i>Participants and response (page 7) and (baseline table, page 18)</i> |
| | | (b) Indicate number of participants with missing data for each variable of interest | <i>Baseline table (page 16) and per analysis in results (figures 1, & 2a.b., figure legends, page 17)</i> |
| Outcome data | 15* | Report numbers of outcome events or summary measures | <i>Number of participants reported per analysis, see above for page numbers</i> |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | <i>Medians and interquartiles, results, page 8-9</i> |
| | | (b) Report category boundaries when continuous variables were categorized | <i>Survey in supplement,</i> |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | <i>n/a/</i> |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | <i>Analysis per characteristic reported, Personal meaningful lifetime benefit, and exploratory analysis page 7- 8</i> |
| Discussion | | | |
| Key results | 18 | Summarise key results with reference to study objectives | <i>Principal findings, discussion page 9</i> |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | <i>Strengths and limitations, discussion</i> |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | <i>Discussion (page 9-11)</i> |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | <i>Discussion. Limitations unlikely to alter conclusion. Use of risk score for other</i> |

Other information

| | | | |
|---------|----|---|--------------------------|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | <i>Reported. Page 13</i> |
|---------|----|---|--------------------------|

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.