BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021309
Article Type:	Research
Date Submitted by the Author:	22-Dec-2017
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Keywords:	PRIMARY CARE, PREVENTIVE MEDICINE, VASCULAR MEDICINE, Doctor-Patient Communication, Shared Decision Making, Individualized Prevention

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

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Word count: 4880

ABSTRACT

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

Design: Cross-sectional study

Settings: 1) continuing medical education conference in December 2016 for physicians 2) CVD information session in April 2017 for patients.

Participants: 400 primary care physicians and 523 patients

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

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

Conclusion: Both physicians and patients report a large variation in meaningful longevity-benefit. Moreover, desired benefit differs between physicians and patients and exceeds what is clinically

attainable. Clinicians should recognize these discrepancies when prescribing CVD-prevention and implement individualized medicine and shared decision-making to avoid one-size fits all standards.

Strengths and Limitations of the Study:

- We examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-effects, and inconveniences of medication which are a daily part of clinical practice.
- In contrast to previous studies, we surveyed a large sample of both physicians and actual patients in comparable settings.
- The use of a multiple-choice voting system may have limited response variation.
- Further research would be necessary to analyze how these perspectives would relate to actual use of medication by patients and prescription of medication by physicians.

INTRODUCTION

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

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

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

prescribers) and patients consider statin and antihypertensive medication worthwhile. We also aimed to compare these thresholds to what is a clinically achievable benefit in the primary prevention.

METHODS

Setting and Participants

Two separate settings, in which a large number of patients and physicians could be recruited and surveyed were chosen for this cross-sectional study. Primary care physicians were recruited and surveyed on the same day among attendees of the national Continuing Medical Education conference (Boerhaave "Progress and Practice"), in Leiden, The Netherlands (December 8th, 2016) targeted to primary prevention health-care providers. Of the survey respondents, only participants reporting themselves as primary care physicians were included in the analyses. Patients were recruited and surveyed during three separate plenary sessions at a one-day information conference targeted to primary and secondary CVD prevention patients at the University Medical Center Utrecht in the Netherlands (April 8th, 2017). All surveyed patients were included in the analyses.

Survey Preparation and Administration

Both patient organizations and primary care physicians were involved in preparation of the study. The research question and study design evolved from a discussion session with a patient panel at PGOSupport conference, an independent nation-wide network for patient-organizations, held in Amstelveen, the Netherlands in April 2016. A pretest session involving fifty primary care physicians was conducted in October 2016 to review the research questions and proposed survey, and guide multiple-choice answer options of the electronic (physician) or paper (patient) questionnaires ultimately used for data collection (Supplement A&B). The finalized surveys were subsequently administered at the respective sessions (Boerhaave and Utrecht). To ensure informed and comparable responses, an audience-appropriate 10-minute introduction on individual therapy-benefit was given prior to each session. At the start of each session, all participants were informed that a voluntary survey would be conducted and data collected and treated anonymously. The study was conducted in accordance with the

principles of the Declaration of Helsinki and prospectively granted exempt status by the Medical Ethics Committee of the University Medical Center Utrecht.

Outcome Definition

Lifetime benefit thresholds for physicians and patients were quantified as the gain in CVD-free life-expectancy desired prior to considering or continuing personal statin therapy. Ten-year benefit thresholds were quantified as the gain in CVD-free life-expectancy desired for 10-years of both statin and antihypertensive medication use prior to considering or continuing prescription (physicians) or personal use (patients). Physicians were thus framed as users for lifetime thresholds and prescribers for 10-year thresholds.

Comparison of Clinically Attainable and Meaningful Benefit Thresholds

Meaningful benefit was compared to clinically attainable benefit using a variant of the European Society of Cardiology recommended Systematic Coronary Risk Evaluation (SCORE)-chart used in national primary prevention guidelines.(3, 17) For each of the 600 risk-factor combinations [age, systolic blood pressure (SBP), smoking status, sex, and total cholesterol] the JBS risk-calculator(18) was used to estimate the gain in CVD-free life-expectancy for statin and antihypertensive medications. Clinically attainable lipid-lowering was estimated with simvastatin 40 mg, a mid-potency statin commonly prescribed as initial therapy(19) which reduces LDL-c levels by 37% irrespective of baseline level.(20) Clinically attainable blood-pressure lowering was estimated with a single, initial antihypertensive medication, using the formula 9.1 mmHg + 0.10 mmHg * (current SBP-154 mmHg).(21) To estimate clinically attainable benefit for 10-years of medication use, gain in life-expectancy estimated by the calculator was divided by the life-expectancy estimated by the calculator. This estimated gain per 10-years of use was subsequently graphically juxtaposed against reported 10-year thresholds, expressed as months gain in CVD-free life-expectancy desired for 10 years of use prior to considering or continuing prescription (physicians) or personal use (patients). For clarity, values used for the calculations are provided in supplemental Table 1, and a calculation example is provided in supplement D(22-24).

Data Analysis

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

RESULTS

Participants and Response

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

Personal meaningful lifetime benefit

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

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 worthwhile 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 antihypertensives, and the median worthwhile 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).

Comparison of Clinically Attainable and Meaningful Benefit Thresholds

In figure 3, median reported thresholds for prescribing (physicians, 12 months for every 10 years of use) and using (patients, 14 months for every 10 years of use) statins are juxtaposed against what gain in life-expectancy is clinically attainable with simvastatin 40mg for each risk-factor combination. Figure 4 provides the same information for a single, daily, antihypertensive medication (physicians, 12 months for every 10 years of use) and patients (14 months for every 10 years of use).

DISCUSSION

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

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

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

decades. Negative portrayal of statins in the media and academic press influences healthcare related behavior and coincides with a decrease in statin use in both primary and secondary prevention.(29) Many patients may attribute health issues to the use of statins. Myalgia frequency is approximately twice as high in patients on statins as on placebo in clinical trials. (30) However, this frequency is considerably higher in observational studies.(31) In clinical practice, physicians are confronted with observational frequencies.

Compared to a risk-based treatment strategy, treatment based on meaningful therapy thresholds would produce a shift from mostly older individuals with a high 10-year risk, to a group of younger individuals with a low 10-year risk, but high lipid levels and high SBP. A previous study investigating eligibility based on an individualized benefit-based approach described a similar shift in eligibility seen in the present study. The earlier study based eligibility cut-offs a 10-year absolute risk reduction of ≥2.3%. (32) The cut-off was not based on patient perceptions, but on the minimum statin benefit seen in primary prevention guidelines and resulted in a greater number of eligible patients (34%) compared to current practice (21%). Other studies have demonstrated that young individuals with high risk-factor levels (i.e. lipid and SBP) have the greatest net-positive lifetime benefit from CVD-prevention strategies, such as aspirin use(1) and renin-angiotensin system inhibition.(33) As older patients had a minimal but significantly higher benefit threshold than younger patients, such a shift is congruent with user views. This shift is also congruent with changing insights into the benefits of deprescription of the elderly population.(34)

Lifetime based decision-tools have become more accessible in clinical practice to both doctors and physicians. It is therefore essential to address the high degree of variation in what is considered meaningful therapy in clinical practice. Choosing a single, uniform, benefit threshold for all patients to determine therapy eligibility may be too simplistic. Moreover, the discrepancy between perceived meaningful benefit and clinically attainable benefit should be addressed. Guidelines need not adapt eligibility thresholds based on views of meaningful therapy. However, the number of prevented CVD-events is ultimately determined by physicians and patients making guideline-based decisions. Misperceptions about perceived CVD-risk are commonplace.(35) Likewise, it is conceivable that both physicians and patients overestimate realistic therapy-benefit and may require guidance as to what

longevity benefit may be realistically achieved. Such guidance could be easily incorporated into the same online decision-aids which are currently available.

Certain strengths of this study should be highlighted. First, both parties of the shared decision-making process were informed and surveyed in comparable settings. Physicians were representative of the general practitioner population and both primary and secondary prevention patients were surveyed. As there was no evidence of difference in medians between patients with and without CVD, no stratification based on primary or secondary prevention was necessary. Secondly, the number of incomplete responses was low for both physicians (1.0-2.3%) and patients (4.4-5.1%), indicating that both groups were sufficiently informed to provide valid and reliable responses. Lastly, we examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-effects, and inconveniences of medication which are a daily part of clinical practice. Certain study limitations must also be acknowledged. First, we were restricted to a multiple-choice voting system, which may have limited response variation. However, the observed variation in our study remained large and multiple-choice options were based on responses from a pre-test session. Secondly, benefit-threshold associated with a single medication was surveyed. In practice, if LDL-c or SBP targets are not achieved, additional medication can be prescribed without necessarily increasing the number of tablets used daily. However, the value of the opinion-based benefit-thresholds are not altered by this limitation. Thirdly, patients were recruited at a one-day information conference on CVD-prevention, and may thus represent a population more interested in CVD-prevention than average. Lastly, further research would be necessary to analyze how these perspectives would relate to actual use of medication by patients and prescription of medication by physicians.

In conclusion, both physicians and patients report a large variation in meaningful longevity-benefit. Moreover, desired benefit differed between patients and physicians and exceeded clinically attainable benefit. Clinicians should recognize these discrepancies when prescribing CVD-prevention and implement individualized medicine and shared decision-making, thereby avoiding one-size fits all standards.

Contributors: NEMJ, FLJV, FLM, YS, YG, and JAND contributed to the conception and/or design of the work. All authors contributed to the acquisition, analysis or interpretation of the data. NEMJ drafted the manuscript, and , FLJV, MN, FLM, YS, YG, and JAND critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work.

Acknowledgements: The organizers and participants of the following meetings, conferences, and sessions: the April 2016 PGOSupport conference in Amstelveen, the November 2016 pilot session in Roermond, the December 2016 Boerhaave Symposium, the April 2017 University Medical Center Utrecht.

Disclosures: None

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement: Data sharing requirements are not applicable as we did not receive informed consent for data sharing from the participants. However, reasonable inquiries concerning the data may be made via the corresponding author.

REFERENCES:

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

13. Stovring H, Gyrd-Hansen D, Kristiansen IS, Nexoe J, Nielsen JB. Communicating effectiveness of intervention for chronic diseases: what single format can replace comprehensive information? BMC Med Inform Decis Mak. 2008;8:25.

14. Trewby PN, Reddy AV, Trewby CS, Ashton VJ, Brennan G, Inglis J. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. Clin Med (Lond). 2002;2(6):527-33.

15. Fontana M, Asaria P, Moraldo M, Finegold J, Hassanally K, Manisty CH, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. Circulation. 2014;129(24):2539-46.

16. Dahl R, Gyrd-Hansen D, Kristiansen IS, Nexoe J, Bo Nielsen J. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey. BMC Med Inform Decis Mak. 2007;7:8.

17. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM. Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil. 2010;17(2):244-9.

18. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease; JBS3 risk calculator. Available from: http://www.jbs3risk.com/.

19. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. NCHS Data Brief. 2014(177):1-8.

20. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.

21. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.

22. Recommendations for treatment of hyperlipidemia in adults. A joint statement of the Nutrition Committee and the Council on Arteriosclerosis. Circulation. 1984;69(5):1067A-90A.

23. JoJoGenetics. DNA Diagnostics

24. Average Body Mass Index (kg/m2) according to age and gender Netherlands National Institute for Public Health and the Environment (RIVM) 2012.

25. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a systematic review. Heart. 2017.

26. Wegwarth O, Schwartz LM, Woloshin S, Gaissmaier W, Gigerenzer G. Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. Ann Intern Med. 2012;156(5):340-9.

27. Hutchins R, Viera AJ, Sheridan SL, Pignone MP. Quantifying the utility of taking pills for cardiovascular prevention. Circ Cardiovasc Qual Outcomes. 2015;8(2):155-63.

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

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%)

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

Figures Legends

Figure 1 Legend:

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%).

Figure 2 a. and b. Legend:

Months gain in CVD-free life-expectancy above which physicians (as prescribers) and patients (as users) consider a) statin and b) antihypertensive therapy 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.

Figure 3 Legend:

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. 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).

Figure 4 Legend:

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).

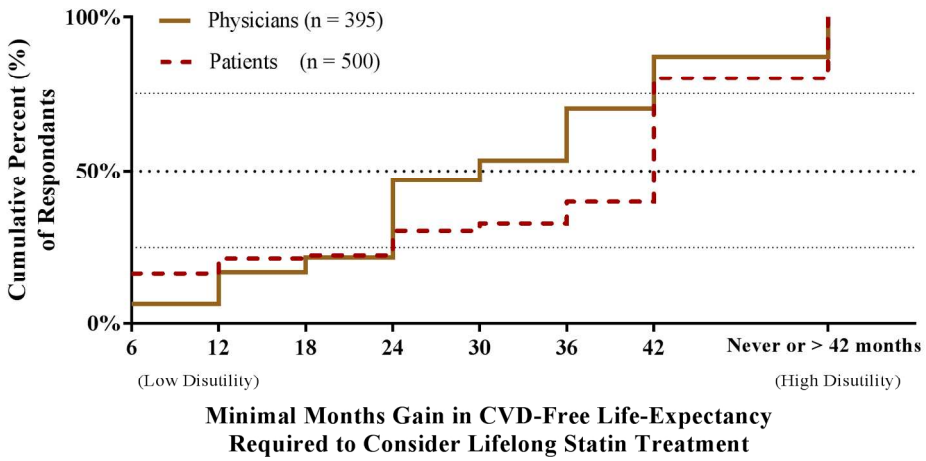


Figure 1. Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin therapy as worthwhile. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

173x87mm (300 x 300 DPI)

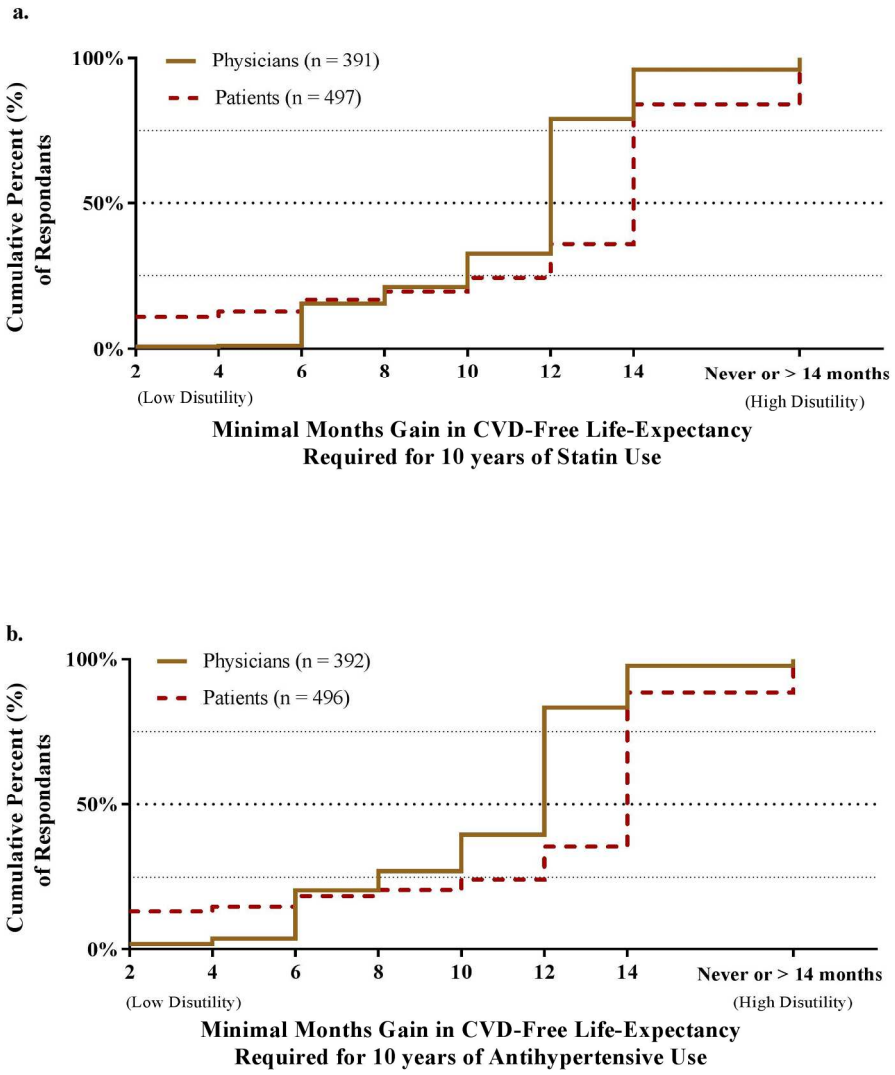


Figure 2. Minimal gain in CVD-free life-expectancy to perceive a) statin and b) antihypertensive therapy as worthwhile. Missing responses was seen in 5 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients (5.1%) for antihypertensive medication.‼ ┼

205x235mm (300 x 300 DPI)

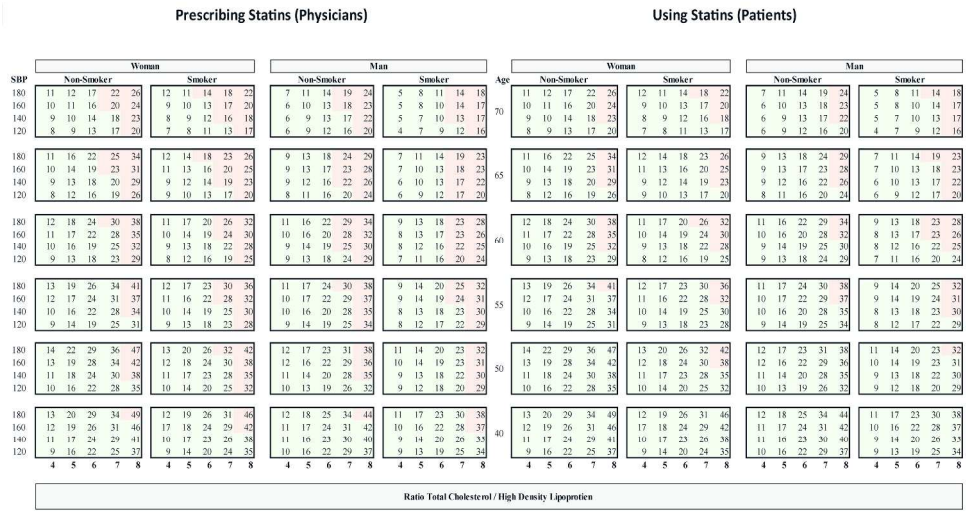


Figure 3. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Orange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

300x176mm (300 x 300 DPI)

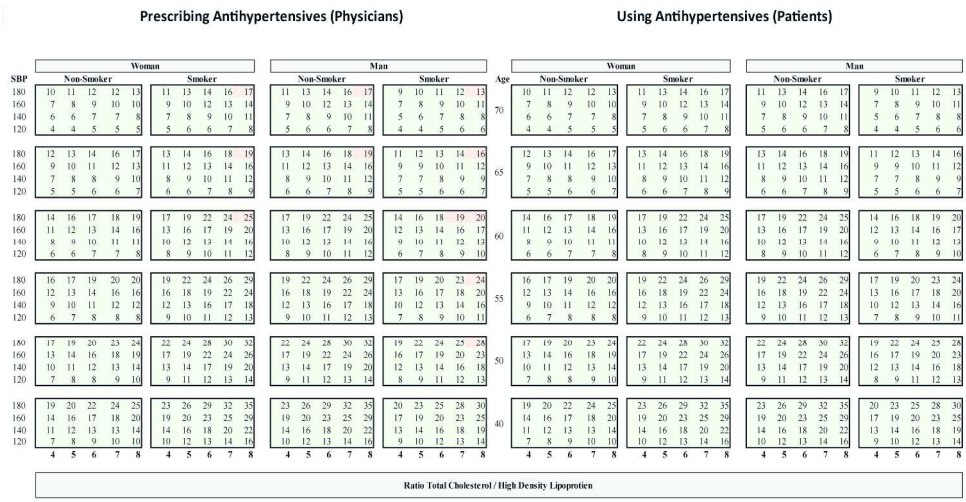


Figure 4. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Orange 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)

SUPPLEMENTAL MATERIAL

A) Physician Survey:

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

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

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

4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication must provide before you considered use worthwhile?

   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin *Or only above these thresholds*

5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would personally consider using this statin to achieve this benefit?

   a. I would never want to use a statin; *Or only above these thresholds*
   b. 5 year (high threshold)
   c. 10 year
   d. 15 year
   e. 20 year
   f. 30 year
   g. 40 year
   h. 50 year (low threshold)

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

a. 2 months (low threshold)

b. 4 months

c. 6 months

d. 8 months

e. 10 months

f. 12 months

g. 14 months (high threshold)

h. I would never consider statin prescription worthwhile. *Or only above these thresholds*

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

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

a. 2 months (low threshold)

b. 4 months

c. 6 months

d. 8 months

e. 10 months

f. 12 months

g. 14 months (high threshold)

h. I would never consider blood-pressure medication prescription worthwhile; *Or only above these thresholds*

B) Patient Survey:

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

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

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

□ I have never had *ANY* of the above

5. Imagine **you** were considering starting (or continuing) a statin medication. What in the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication must provide before you considered use worthwhile?
   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin ; *Or only above these thresholds*
6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would consider using the statin to achieve this benefit?
   a. I would never consider a statin worthwhile; *Or only above these thresholds*
   b. 5 years (high threshold)
   c. 10 years
   d. 15 years
   e. 20 years
   f. 30 years
   g. 40 years
   h. 50 years (low threshold)

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

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

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

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

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

C) 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/m^2) 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/m^2, systolic blood-pressure 140 mmHg, and a total cholesterol / HDL ratio of 7. The 50th percentile values for HDL-c is 1.12 mmol/L and TG is 1.35 mmol/L.(1)

Calculation LDL-c:

Baseline LDL-c

= Total cholesterol – median HDL – median triglyceride / 2.17

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

= 7 x 1.12 – 1.12 – 1.35/2.17

= 6.098 mmol/L

The effects of simvastatin 40 mg was calculated as follows:

LDL-c $_{new}$

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

= 6.098 mmol/L * 0.63

= 3.842 mmol/L

Estimated attainable therapy-benefit in terms of gain in CVD-free life-years according to the JBS3 Online calculator (18):

Calculated life-expectancy off-treatment = 76 years

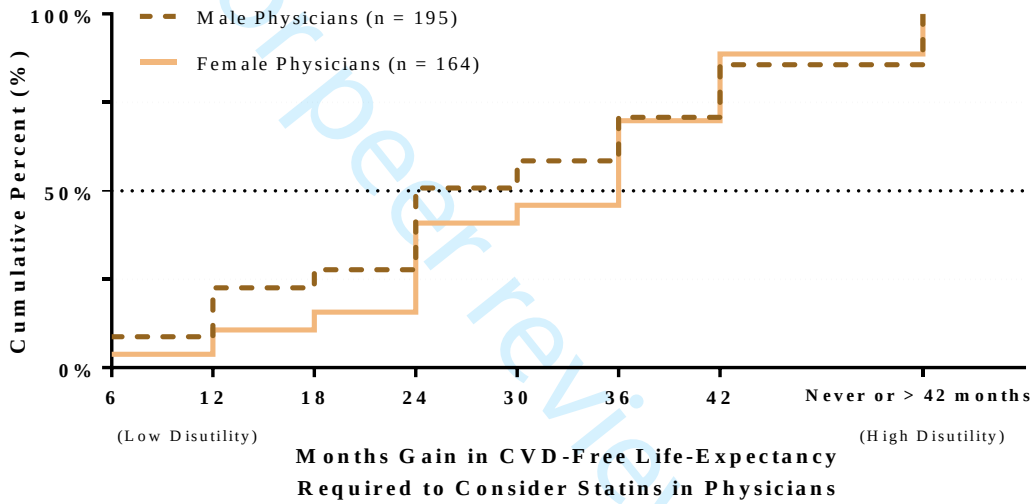
Calculated gain in CVD-free life-expectancy = 2.5 years

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

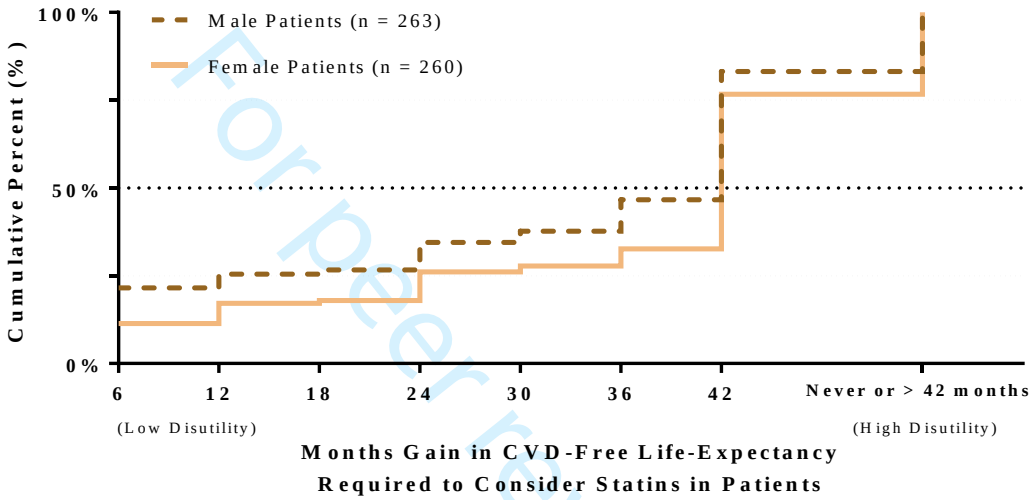
E) Supplemental Figures:

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



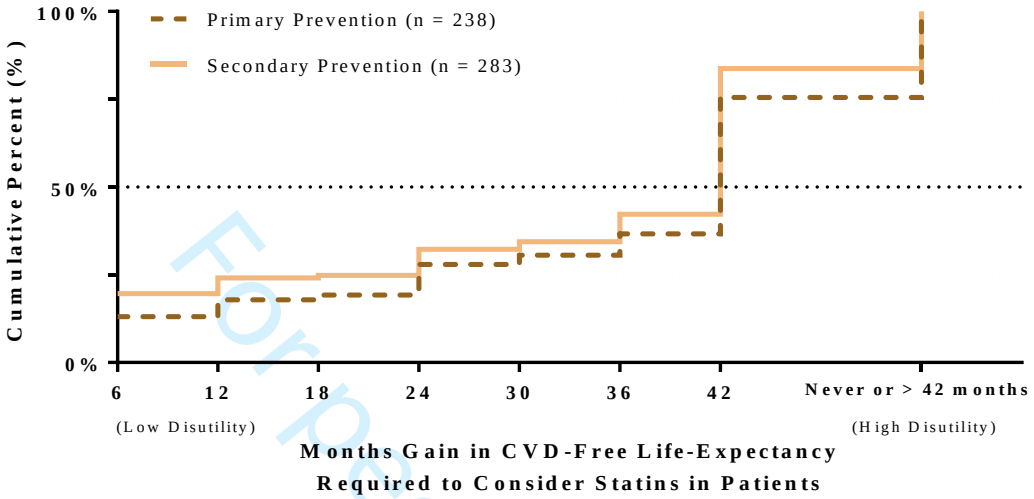
Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin therapy as worthwhile, stratified by gender.

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



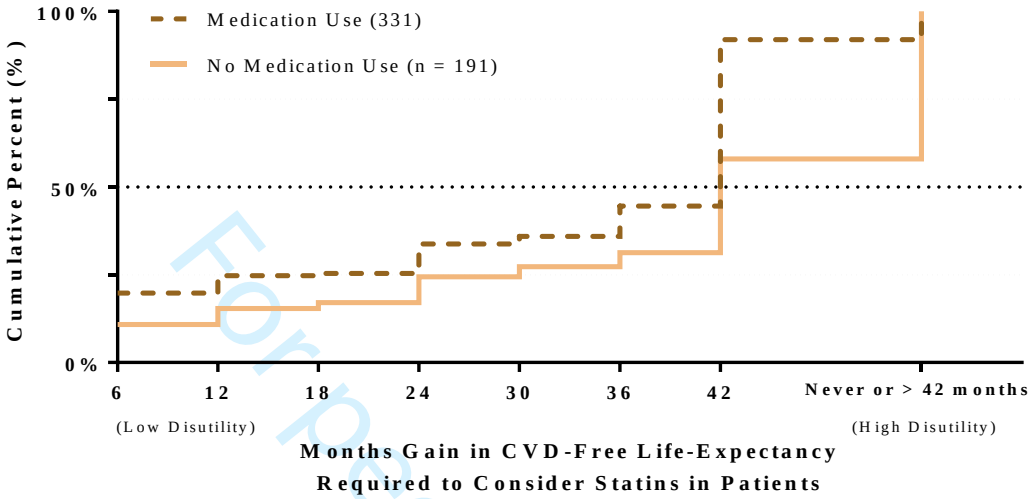
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as worthwhile, stratified by gender.

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	*Both in title/abstract Page 1 & 2*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	*Structured abstract Page 2*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Introduction, page 4-5*
Objectives	3	State specific objectives, including any prespecified hypotheses	*End of introduction, page 4- 5*
Methods			
Study design	4	Present key elements of study design early in the paper	*Settings & participants Page 5*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Settings & participants & Survey preparation and administration pages 5-6*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	*Settings & participants Page 5*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Settings & participants (5-6), Outcomes (page 6) and data analysis (page 7)*
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	*Survey preparation and administration Supplemental data a & C for surveys (pages 2-7)* *Survey preparation and administration (page 5)*
Bias	9	Describe any efforts to address potential sources of bias	*Survey preparation and administration (page 5)*
Study size	10	Explain how the study size was arrived at	*Choice of setting (page 5) and after inclusion (page 7)*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Data analysis (page 7)*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	*Data analysis (page 7)*
		(*b*) Describe any methods used to examine subgroups and interactions	*Data analysis (page 7)*
		(*c*) Explain how missing data were addressed	*Data analysis (page 7)*
		(*d*) If applicable, describe analytical methods taking	n/a/

		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	*Participants and response (page 7)*
		(b) Give reasons for non-participation at each stage	*Participants and response gives overview of number of individuals at each stage (page 7)*
		(c) Consider use of a flow diagram	*Information adequately summarized in text*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Participants and response (page 7) and (baseline table, page 18)*
		(b) Indicate number of participants with missing data for each variable of interest	*Baseline table (page 16) and per analysis in results (figures 1,&2a.b., figure legends, page 17)*
Outcome data	15*	Report numbers of outcome events or summary measures	*Number of participants reported per analysis, see above for page numbers*
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	*Medians and interquartiles, results, page 7-8*
		(*b*) Report category boundaries when continuous variables were categorized	*Survey in supplement, page 2*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*n/a/*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Analysis per characteristic reported, Personal meaningful lifetime benefit, page 7-8*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Principal findings, discussion page 9*
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	*Strengths and limitations, discussion (page 11) and strengths and limitations section on page 3*

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Discussion(page 9-11)*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Discussion. Limitations unlikely to alter conclusion. Page 12*
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	*Reported, page 13*

*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:	*BMJ Open*
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

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

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Word count main body: 3,297

ABSTRACT

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

Design: Cross-sectional study

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

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

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

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

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

medicine and shared decision-making. Decision-tools could provide information on realistic therapy benefit.

Strengths and Limitations of the Study:

- We examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-effects, and inconveniences of medication which are a daily part of clinical practice.
- In contrast to previous studies, we surveyed a large sample of both physicians and actual patients in comparable settings.
- The use of a multiple-choice voting system may have limited response variation.
- Further research would be necessary to analyze how these perspectives would relate to actual use of medication by patients and prescription of medication by physicians.

INTRODUCTION

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

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

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

hypothetical risk scenarios[12 13] on idealized medications. [10 14-17] We therefore aimed to quantify perceptions on meaningful lifetime and 10-year benefit, defined as the gain in CVD-free life-expectancy above which physicians (as users and prescribers) and patients consider statin and antihypertensive medication meaningful. We also aimed to compare these thresholds to what is a clinically achievable benefit in the primary prevention.

METHODS

Setting and Participants

Two separate settings, in which a large number of patients and physicians could be recruited and surveyed were chosen. Primary care physicians were recruited and surveyed on the same day among attendees of a national Continuing Medical Education conference (Boerhaave "Progress and Practice"), in Leiden, The Netherlands (December 8th, 2016) targeted to primary prevention health-care providers. Of the survey respondents, only participants reporting themselves as primary care physicians were included in the analyses. Patients were recruited and surveyed during three separate plenary sessions at a one-day information conference targeted to primary and secondary CVD prevention patients at the University Medical Center Utrecht in the Netherlands (April 8th, 2017). All surveyed patients were included in the analyses.

Survey Preparation and Administration

A pretest session involving fifty primary care physicians was conducted in November 2016 to review the research questions and proposed survey, and guide multiple-choice answer options of the electronic (physician) or paper (patient) questionnaires ultimately used for data collection (Supplement A&B). The finalized surveys were subsequently administered at the respective sessions (Boerhaave and Utrecht). To ensure informed and comparable responses, an audience-appropriate 10-minute introduction on individual therapy-benefit was given prior to each session (Supplement C). In this introduction, an example of lifetime benefit from smoking cessation and aspirin-therapy was provided.[1 18] The structure of the introduction and survey was the same in both physician and patient questionnaires. The survey questions were presented centrally and sequentially by the researcher, thus preventing participants from

viewing either previous or future questions or benefitting from time-saving heuristics. The questions were verbally explained before participants were given the opportunity to respond. At the start of each session, all participants were informed that a voluntary survey would be conducted and data collected and treated anonymously. The study was conducted in accordance with the principles of the Declaration of Helsinki and prospectively granted exempt status by the Medical Ethics Committee of the University Medical Center Utrecht.

Outcome Definition

Lifetime benefit thresholds for physicians and patients were quantified as the gain in CVD-free life-expectancy desired prior to considering or continuing personal statin therapy (i.e. the benefit was considered meaningful). Ten-year benefit thresholds were quantified as the gain in CVD-free life-expectancy desired for 10-years of both statin and antihypertensive medication use prior to considering or continuing prescription (physicians) or personal use (patients). Physicians were thus framed as users for lifetime thresholds and prescribers for 10-year thresholds. For an exploratory analysis, the outcome was framed differently and participants were asked to report the number of years willing to take statin medication provided the therapy would give a one-year gain in CVD-free expectancy.

Guideline recommendations and participant views of meaningful therapy

European Society of Cardiology (ESC) guideline recommendations on lipid[19] and blood-pressure therapy[20] were compared to what participants viewed as meaningful therapy. The ESC-SCORE algorithm for low-risk countries was used to establish which risk-factor combinations had sufficient 10-year risk of CVD-mortality to be eligible for lipid-lowering therapy.[19-21] In order to establish which risk-factor combinations would be treated based on participant views of meaningful therapy, clinically attainable benefit from statin and antihypertensive medication was estimated and compared to views of meaningful benefit. The JBS risk-calculator[22] was used to estimate clinically attainable benefit in terms of gain in CVD-free life-expectancy for each of the 600 risk-factor combinations [age, systolic blood pressure (SBP), smoking status, sex, and total cholesterol] of a national ESC-SCORE chart variant.[3 23] Clinically attainable gain from statin medication was estimated with simvastatin 40 mg, a mid-potency statin commonly

prescribed as initial therapy[24] which reduces LDL-c levels by 37% irrespective of baseline level.[25] Clinically attainable gain from an antihypertensive was estimated with a single, initial antihypertensive medication, using the formula 9.1 mmHg + 0.10 mmHg * (current SBP-154 mmHg).[26] To express the clinically attainable benefit per year of medication use, the gain in CVD-free life-expectancy estimated by the calculator (i.e. the lifetime benefit) was divided by the total remaining on-therapy CVD-free life-years estimated by the calculator (i.e. the duration of medication use required to achieve this lifetime benefit). The estimated clinically attainable gain per 10-years of medication use was graphically juxtaposed against participant views of meaningful benefit, expressed as months gain in CVD-free life-expectancy desired for 10 years of use prior to considering or continuing prescription (physicians) or personal use (patients). For clarity, all values used for the calculations, and a calculation example are provided in supplements D&E.[27-29]

Data Analysis

Age was converted to numeric values. Thresholds in terms of minimal desired months gain were reported as median (interquartile range, IQR) within each group. Wilcoxon rank-sum and spearman correlations were used to analyze lifetime thresholds according to certain characteristics pre-defined to be potentially of influence on response: age, sex, use of either statin or antihypertensive medication (yes/no), and presence of CVD (yes/no). [30 31] Paired-samples Wilcoxon signed-rank tests were used to assess response differences between 10-year statin and antihypertensive medication thresholds. Missing values were not imputed, and the number of participants in each analysis reported. Analyses were performed using R-Statistical Software, version 3.1.1.

Patient and Public Involvement

The study has been designed to survey the opinion of a large group of both patient and physicians to better understand their priorities and preferences. Both patient organizations and primary care physicians were involved during study preparation. The research question and study design evolved from a discussion session with a patient panel at PGOSupport conference, an independent nation-wide network for patient-organizations, held in Amstelveen, the Netherlands in April 2016. Physicians were involved in the pre-test sessions in Roermond, the Netherlands in November 2016. Participants were not involved in finding the optimal study recruitment procedures. The findings from this study will be disseminated to physicians and patients via conferences and newsletters.

RESULTS

Participants and Response

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

Personal meaningful lifetime benefit

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

between guideline recommended therapy and participant views of meaningful benefit. The clinically attainable gain in CVD-fee life-expectancy from lifelong simvastatin 40mg ranged from 4 - 49 months. Larger gains were seen in younger individuals with high SBP and lipid-levels and smaller gains were seen in older individuals with low risk-factor levels. Treatment is concordant with participant views if the clinically attainable gain in CVD-free life-expectancy per 10-years of medication is was equal to or greater than the reported meaningful benefit thresholds for prescribing and using (i.e. physician median 12 months for every 10 years of use and patient median 14 months for every 10 years of use). Figure 4. provides the same information for a single, daily, antihypertensive medication; clinically attainable lifetime gain in CVD-fee life-expectancy ranged from 4-35 months and followed a similar distribution pattern to statin therapy.

DISCUSSION

Meaningful statin and antihypertensive therapy for lifetime and 10-years of use was quantified in 400 primary care physicians and 523 patients. A high degree of variation in what was perceived as meaningful therapy was reported within both patients and physicians. Patients consistently desired a higher lifetime benefit for medication use than physicians. Females desired a higher benefit from statins than males in both participant groups. Physicians desired a slightly higher benefit for statin than for antihypertensive medication. Age had minimal influence on thresholds in patients. Compared to those with CVD, a greater percentage of healthy respondents were not willing to consider statin therapy. However, the median thresholds for respondents who were willing to consider therapy did not differ between these two patient groups. Similar results were found when patients on- and off- preventative therapy were compared. The majority of respondents reported desiring a gain in CVD-free life expectancy above what is generally achievable with lifelong use of a single tablet in the primary prevention setting.

To our knowledge, this is the first study examining medication-specific thresholds in both physicians and patients in terms of gain in life-expectancy. The considerably high thresholds found in our study can be explained by the use of specific medications and not an idealized tablet. Previous studies have either focused on non-lifetime metrics in hypothetical risk scenarios,[12 13] or on idealized medications with negligible costs, side-effects, or follow-up requirements.[10 14-17] Even in these idealized situations, the

benefit desired by patients is large, and often greater than the benefit desired by physicians. [12 13 30] For an idealized pill, the general public desires 6 months gain in life-expectancy.[16] Health care employees are willing to sacrifice 12.3 weeks of life to avoid taking a pill.[32] Such isolated disutility of pill-taking is applicable in cost-effectiveness studies. However, it does not assess the real-life perceived costs, side-effects, and other inconveniences of specific medications which are encountered in clinical practice.

In this study, patients without CVD and not using preventive therapy were more often not willing to consider therapy. However, for those who were willing to consider statin therapy, no group differences were found in median CVD-free life-expectancy desired. The similar numeric thresholds align with exiting literature in which socio-economic factors effected willingness to use medication whereas traditional risk-factors such as the presence of CVD and use of antihypertensive or statin therapy did not.[33] Patients view hypertension treatment as more necessary and effective than hyperlipidemia treatment.[34] However, patients in our study did not distinguish between statin and antihypertensive medications indicating that this discrepancy does not apply if therapy imparts identical benefit. Physicians however did desire greater benefit from statins than antihypertensive medications. Statin side-effects, but not necessarily antihypertensive side-effects, have received wide-spread attention over the previous decades. Negative portrayal of statins in the media and academic press influences healthcare related behavior and coincides with a decrease in statin use.[35] Myalgia frequency is approximately twice as high in patients on statins as on placebo in clinical trials. [36] However, this frequency is considerably higher in observational studies, [37] and clinicians are confronted with observational frequencies in in clinical practice.

Compared to a risk-based treatment strategy in prevention guidelines, treatment based on meaningful therapy thresholds would treat fewer risk-factor combinations, and would produce a shift in eligibility to exclude mostly older individuals with a high 10-year risk and include younger individuals with a low 10-year risk but high lipid levels and high SBP who would not be treated according the risk-based guidelines. A previous study investigating eligibility based on an individualized benefit-based approach described a similar shift in eligibility seen in the present study. The earlier study based eligibility cut-offs on a 10-year absolute risk reduction of ≥2.3%. [38] However, the cut-off was not based on patient perceptions, but on the minimum statin benefit seen in primary prevention guidelines, and resulted in a greater number of eligible

patients (34%) compared to current practice (21%). Other studies have demonstrated that young individuals with high risk-factor levels (i.e. lipid and SBP) have the greatest net-positive lifetime benefit from CVD-prevention strategies, such as aspirin use[1] and renin-angiotensin system inhibition.[39] As older patients had a minimal but significantly higher benefit threshold than younger patients, such a shift is congruent with user views. This shift is also congruent with changing insights into the benefits of deprescription of the elderly population.[40]

Lifetime based decision-tools have become more accessible in clinical practice to both patient and physicians. It is therefore essential to address the high degree of variation in what is considered meaningful therapy in clinical practice. The discrepancy between perceived meaningful benefit and clinically attainable benefit should be addressed and a patient's satisfaction with the expected benefit of agreed upon therapy could be viewed as an additional indicator of quality of care. However, guidelines need not adapt eligibility thresholds or target values based on perceptions of meaningful therapy. The number of prevented CVD-events is ultimately determined by physicians and patients making guideline-based decisions. Misperceptions about perceived CVD-risk are commonplace, and [41] it is conceivable that both physicians and patients overestimate realistic therapy-benefit and may require guidance as to what longevity benefit may be realistically achieved. Such guidance could be easily incorporated into the same online decision-aids which are currently available.

Certain strengths of this study should be highlighted. First, both parties of the shared decision-making process were informed and surveyed in comparable settings. Physicians were representative of the general practitioner population and both primary and secondary prevention patients were surveyed. As there was no evidence of difference in medians between patients with and without CVD, no stratification based on primary or secondary prevention was necessary. Secondly, the number of incomplete responses was low for both physicians (1.0-2.3%) and patients (4.4-5.1%), indicating that both groups were sufficiently informed to provide valid and reliable responses. Lastly, we examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-effects, and inconveniences of medication which are a daily part of clinical practice. Certain study limitations must also be acknowledged. First, we were restricted to a multiple-choice voting system, which

may have limited response variation. However, the observed variation in our study remained large and multiple-choice options were based on responses from a pre-test session. Second, benefit-threshold associated with a single medication was surveyed. In practice, if LDL-c or SBP targets are not achieved, additional medication can be prescribed without necessarily increasing the number of tablets used daily. However, the magnitude of the opinion-based benefit-thresholds are not altered by this limitation. Third, patients were recruited at a large, information conference on CVD-prevention, and may represent a population more interested in CVD-prevention than average. Fourth, the survey was pre-tested in physicians and subsequently adapted for patients. However, the survey and the preceding introduction were designed to maximize understandability and comparability. Fifth, clinically attainable benefit was estimated using the JBS3 risk score and best available evidence from meta-analyses. However, the estimated benefit differs in populations with different event-rates, such as those with clinically manifest CVD. Lastly, further research would be necessary to analyze how these perspectives would relate to actual use of medication by patients and prescription of medication by physicians.

In conclusion, both physicians and patients report a large variation in meaningful longevity-benefit. Moreover, desired benefit differed between patients and physicians and exceeded clinically attainable benefit. Clinicians should recognize these discrepancies when prescribing CVD-prevention and implement individualized medicine and shared decision-making. In the future, guidance as to what realistic benefit entails may be incorporated into online decision-aids to help physicians and patients reach a consensus.

Contributors: NEMJ, FLJV, YG, JAND, contributed to the conception/design of the work. All authors (NEMJ, FLJV, YG, YS, FLM, MN, JAND) contributed to the acquisition, analysis or interpretation of the data. NEMJ drafted the work. All authors (NEMJ, FLJV, YG, YS, FLM, MN, JAND) critically revised the manuscript, and gave final approval and agree to be accountable for all aspects of work.

Acknowledgements: We would like to acknowledge the organizers and participants of the following meetings, conferences, and sessions: the April 2016 PGOSupport conference in Amstelveen, the

November 2016 pilot session in Roermond, the December 2016 Boerhaave Symposium in Leiden, and the April 2017 University Medical Center Utrecht session for patients.

Disclosures: None

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data Sharing: No additional data is available for this study in repositories. However, inquiries concerning the data may be made to the corresponding author.

REFERENCES:

1. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ 2016;**352**:i1548.
2. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;**341**:c6624.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;**37**(29):2315-81.
4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;**63**(25 Pt B):2935-59.

5. Dickinson R, Raynor DK, Knapp P, et al. Providing additional information about the benefits of statins in a leaflet for patients with coronary heart disease: a qualitative study of the impact on attitudes and beliefs. BMJ Open 2016;**6**(12):e012000.

6. Manuel DG, Abdulaziz KE, Perez R, et al. Personalized risk communication for personalized risk assessment: Real world assessment of knowledge and motivation for six mortality risk measures from an online life expectancy calculator. Inform Health Soc Care 2017:1-14.

7. Galesic M, Garcia-Retamero R. Communicating consequences of risky behaviors: Life expectancy versus risk of disease. Patient Educ Couns 2011;**82**(1):30-5.

8. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;**100 Suppl 2**:ii1-ii67.

9. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. J Am Coll Cardiol 2015;**65**(13):1361-8.

10. Halvorsen PA, Aasland OG, Kristiansen IS. Decisions on statin therapy by patients' opinions about survival gains: cross sectional survey of general practitioners. BMC Fam Pract 2015;**16**:79.

11. Misselbrook D, Armstrong D. Patients' responses to risk information about the benefits of treating hypertension. Br J Gen Pract 2001;**51**(465):276-9.

12. McAlister FA, O'Connor AM, Wells G, et al. When should hypertension be treated? The different perspectives of Canadian family physicians and patients. CMAJ 2000;**163**(4):403-8.

13. Steel N. Thresholds for taking antihypertensive drugs in different professional and lay groups: questionnaire survey. BMJ 2000;**320**(7247):1446-7.

14. Stovring H, Gyrd-Hansen D, Kristiansen IS, et al. Communicating effectiveness of intervention for chronic diseases: what single format can replace comprehensive information? BMC Med Inform Decis Mak 2008;**8**:25.

15. Trewby PN, Reddy AV, Trewby CS, et al. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. Clin Med (Lond) 2002;**2**(6):527-33.

16. Fontana M, Asaria P, Moraldo M, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. Circulation 2014;**129**(24):2539-46.

17. Dahl R, Gyrd-Hansen D, Kristiansen IS, et al. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey. BMC Med Inform Decis Mak 2007;**7**:8.

18. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;**328**(7455):1519.

19. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;**37**(39):2999-3058.

20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;**34**(28):2159-219.

21. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;**24**(11):987-1003.

22. JBS Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease; JBS3 risk calculator. Secondary Joint British Societies' consensus recommendations for the prevention of cardiovascular disease; JBS3 risk calculator. http://www.jbs3risk.com/.

23. van Dis I, Kromhout D, Geleijnse JM, et al. Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil 2010;**17**(2):244-9.

24. Gu Q, Paulose-Ram R, Burt VL, et al. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. NCHS Data Brief 2014(177):1-8.

25. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;**376**(9753):1670-81.

26. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;**338**:b1665.

27. Recommendations for treatment of hyperlipidemia in adults. A joint statement of the Nutrition Committee and the Council on Arteriosclerosis. Circulation 1984;**69**(5):1067A-90A.

28. JoJoGenetics. Sectie Moleculaire Diagnostiek van het Laboratorium Experimentele Vasculaire Geneeskunde, Academisch Medisch Centrum. http://www.jojogenetics.nl/.

29. Netherlands National Institute for Public Health and the Environment (RIVM). Average Body Mass Index (kg/m2) according to age and gender. The Netherlands. 2012.

30. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a systematic review. Heart 2017.

31. Wegwarth O, Schwartz LM, Woloshin S, et al. Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. Ann Intern Med 2012;**156**(5):340-9.

32. Hutchins R, Viera AJ, Sheridan SL, et al. Quantifying the utility of taking pills for cardiovascular prevention. Circ Cardiovasc Qual Outcomes 2015;**8**(2):155-63.

33. Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. Ann Intern Med 2007;**146**(12):848-56.

34. Stack RJ, Bundy C, Elliott RA, et al. Patient perceptions of treatment and illness when prescribed multiple medicines for co-morbid type 2 diabetes. Diabetes Metab Syndr Obes 2011;**4**:127-35.

35. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ 2016;**353**:i3283.

36. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;**388**(10059):2532-61.

37. Thompson PD, Panza G, Zaleski A, et al. Statin-Associated Side Effects. J Am Coll Cardiol 2016;**67**(20):2395-410.

38. Thanassoulis G, Williams K, Altobelli KK, et al. Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease. Circulation 2016;**133**(16):1574-81.

39. Schievink B, Kropelin T, Mulder S, et al. Early renin-angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. Diabetes Obes Metab 2016;**18**(1):64-71.

40. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. BMJ 2016;**353**:i2893.

41. Katz M, Laurinavicius AG, Franco FG, et al. Calculated and perceived cardiovascular risk in asymptomatic subjects submitted to a routine medical evaluation: The perception gap. Eur J Prev Cardiol 2015;**22**(8):1076-82.

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%)

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

Figures Legends

Figure 1 Legend:

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%).

Figure 2 a. and b. Legend:

Months gain in CVD-free life-expectancy above which physicians (as prescribers) and patients (as users) consider a) statin and b) antihypertensive therapy 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.

Figure 3 Legend:

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.

Figure 4 Legend:

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.

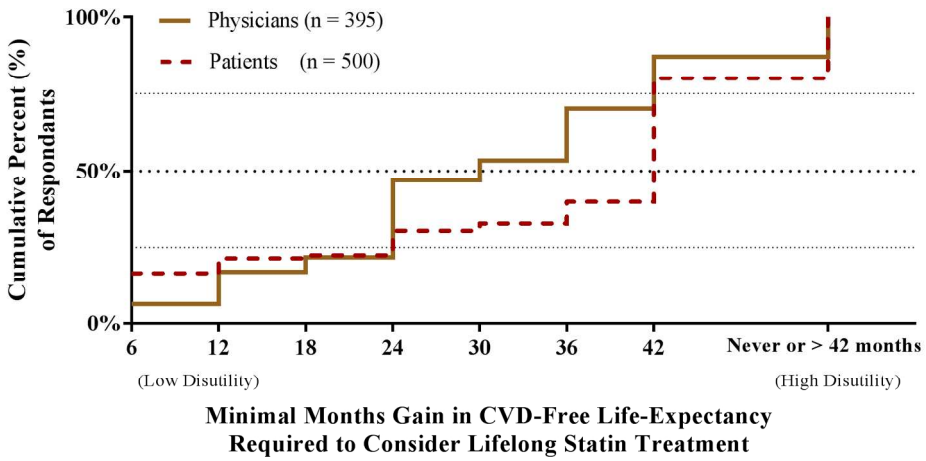

Figure 1. Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

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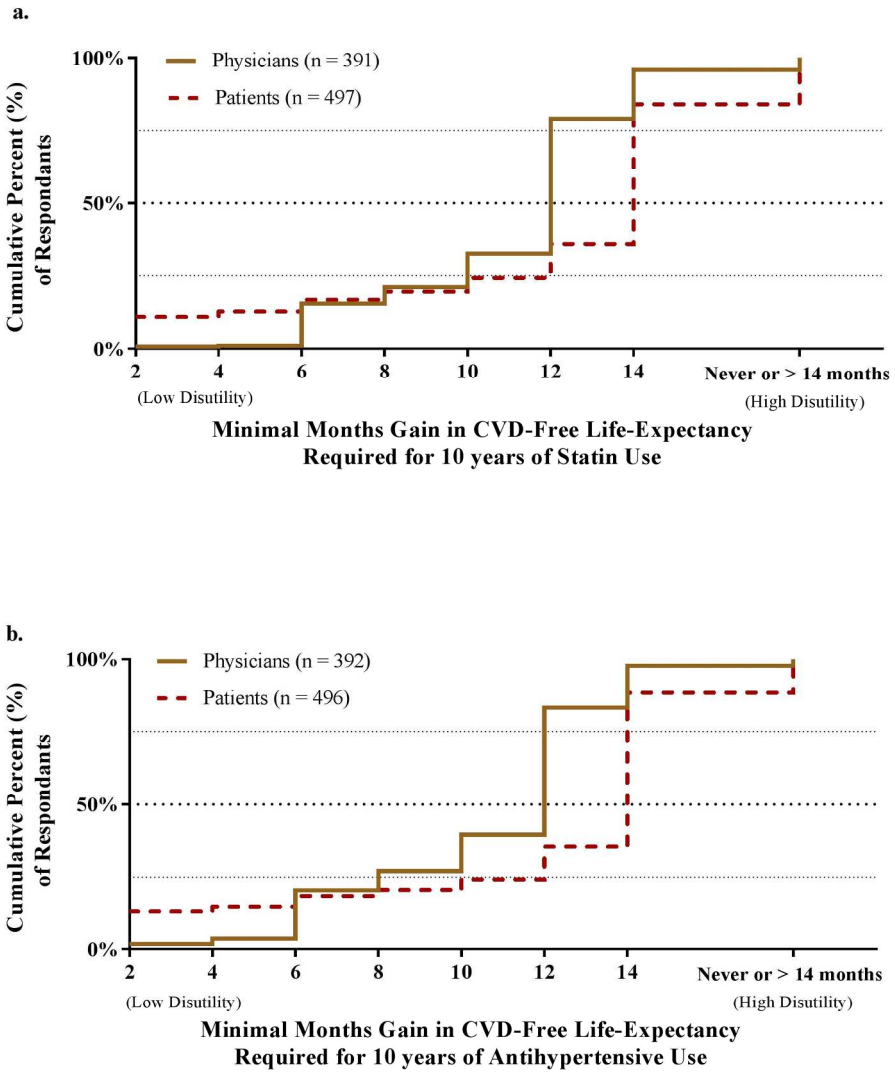

Figure 2. Minimal gain in CVD-free life-expectancy to perceive a) statin and b) antihypertensive therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients (5.1%) for antihypertensive medication.

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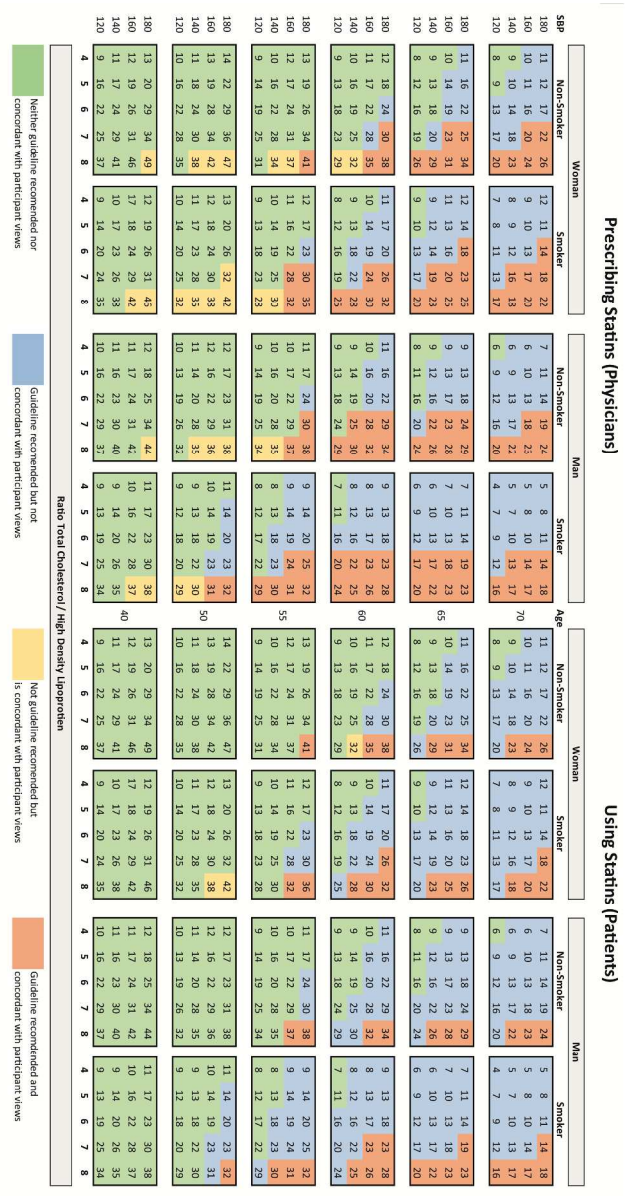

Figure 3. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance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

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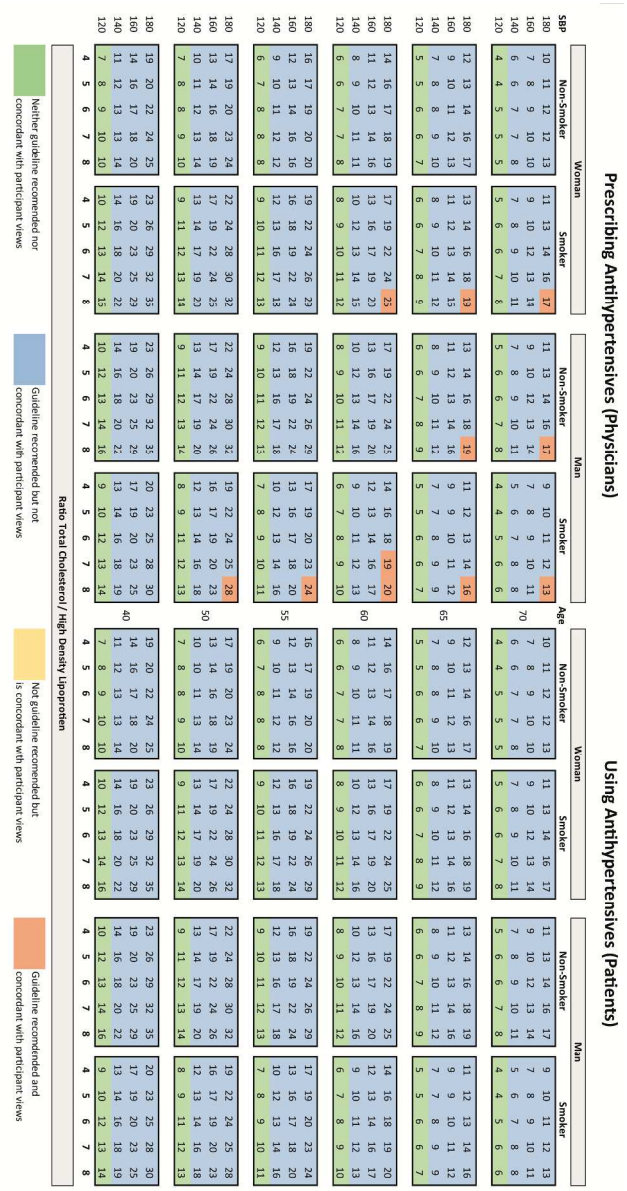


Figure 4 : Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors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

192x368mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

A) Physician Survey

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

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

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

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

4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication must provide before you considered use worthwhile?

   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin *Or only above these thresholds*

5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would personally consider using this statin to achieve this benefit?

   a. I would never want to use a statin; *Or only above these thresholds*
   b. 5 year (high threshold)
   c. 10 year
   d. 15 year
   e. 20 year
   f. 30 year
   g. 40 year
   h. 50 year (low threshold)

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

   a. 2 months (low threshold)

   b. 4 months

   c. 6 months

   d. 8 months

   e. 10 months

   f. 12 months

   g. 14 months (high threshold)

   h. I would never consider statin prescription worthwhile. *Or only above these thresholds*

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

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

   a. 2 months (low threshold)

   b. 4 months

   c. 6 months

   d. 8 months

   e. 10 months

   f. 12 months

   g. 14 months (high threshold)

   h. I would never consider blood-pressure medication prescription worthwhile; *Or only above these thresholds*

B) Patient Survey

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

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

   …….years

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

   □ Heart attack
   □ Stroke
   □ *Intermittent claudication (*Peripheral artery disease)
   □ TIA

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

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

□ I have never had *ANY* of the above

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

   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin ; *Or only above these thresholds*

6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would consider using the statin to achieve this benefit?

   a. I would never consider a statin worthwhile; *Or only above these thresholds*
   b. 5 years (high threshold)
   c. 10 years
   d. 15 years
   e. 20 years
   f. 30 years
   g. 40 years
   h. 50 years (low threshold)

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

a. 2 months (low threshold)

b. 4 months

c. 6 months

d. 8 months

e. 10 months

f. 12 months

g. 14 months (high threshold)

h. I would never consider a statin worthwhile; *Or only above these thresholds*

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

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

a. 2 months (low threshold)

b. 4 months

c. 6 months

d. 8 months

e. 10 months

f. 12 months

g. 14 months (high threshold)

h. I would never consider blood-pressure medication worthwhile ; *Or only above these thresholds*

C) Short Summary of Introduction Sessions

Physician Session

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

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

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

Patient Session

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

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

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

D) Values Used for Calculations

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

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

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

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

E) Example Calculation

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

Calculation LDL-c:

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

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

= 7 x 1.12 – 1.12 – 1.35/2.17

= 6.098 mmol/L

The effects of simvastatin 40 mg was calculated as follows:

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

= 6.098 mmol/L * 0.63

= 3.842 mmol/L

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

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

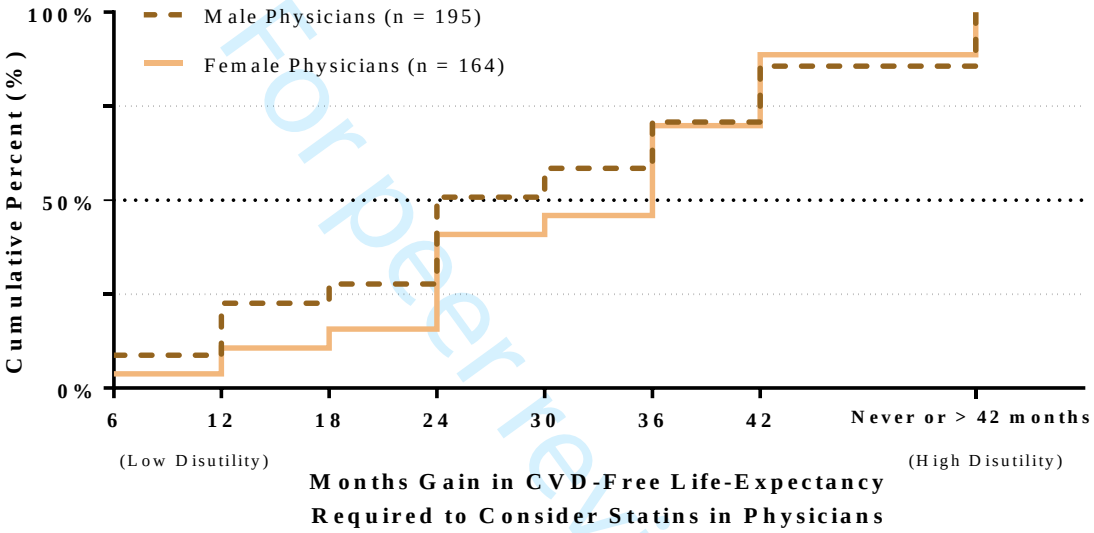
Calculated gain in CVD-free life-expectancy = 2.5 years

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

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

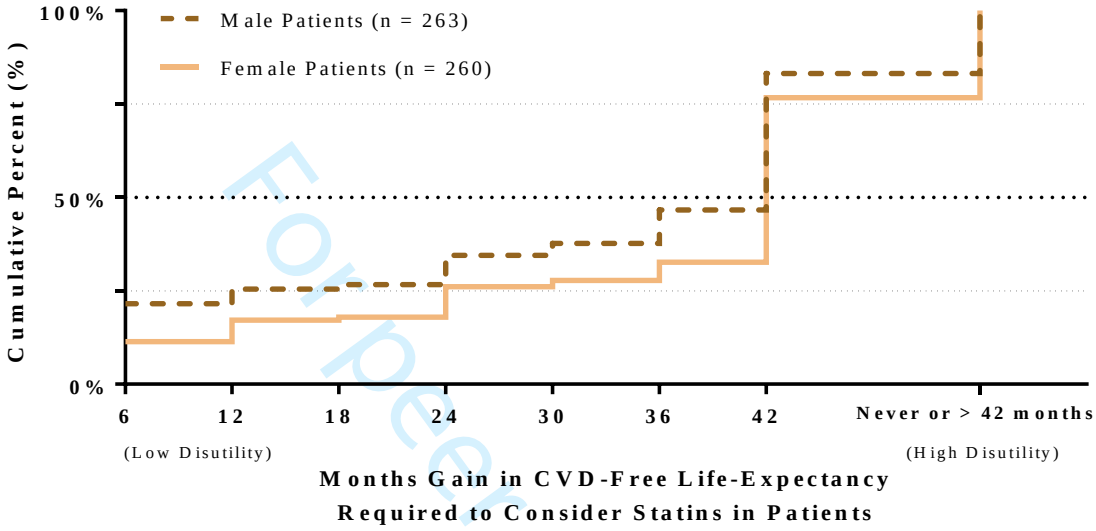
F) Supplemental Figures

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



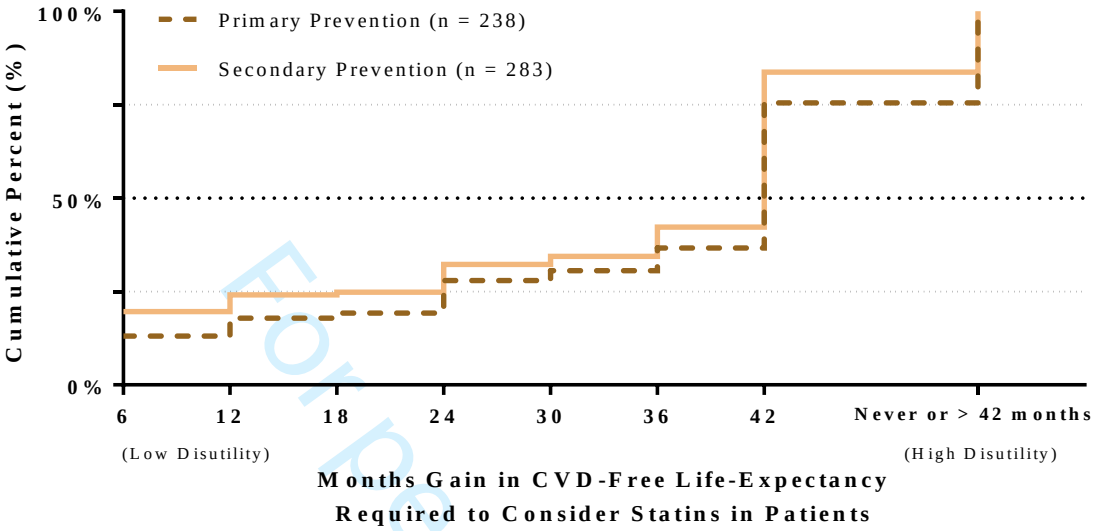
Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin therapy as meaningful, stratified by gender.

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



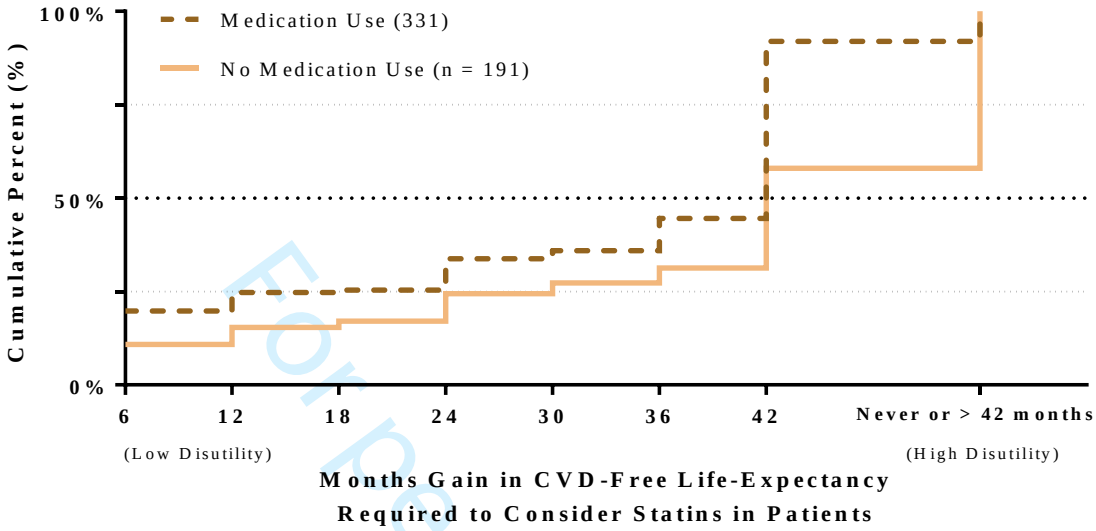
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by gender.

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



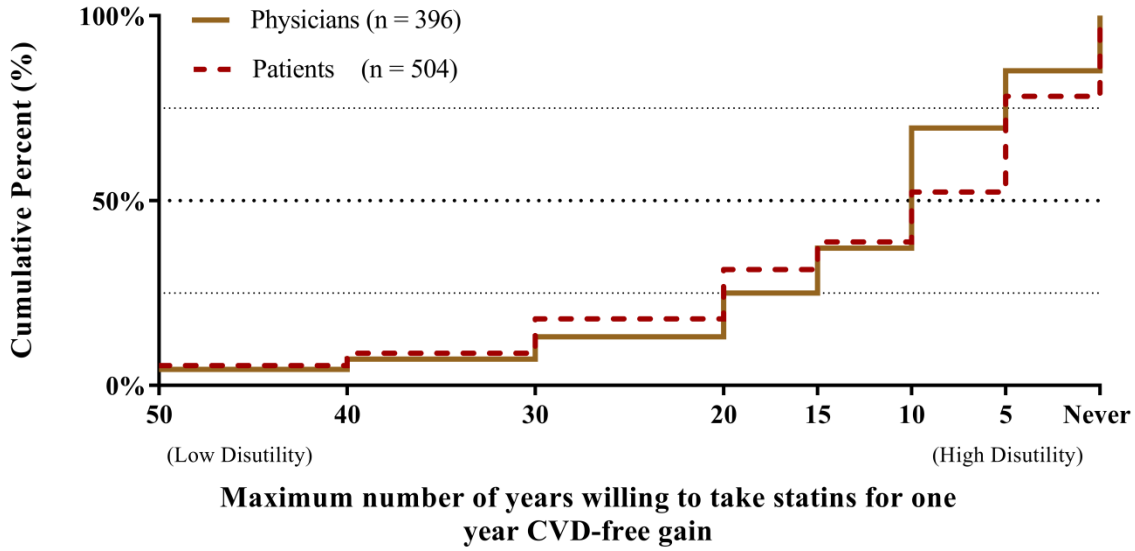
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by presence of CVD.

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



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

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



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

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	*Both in title/abstract page 1 and 2*
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	*Structured abstract Page 2*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Introduction page 4*
Objectives	3	State specific objectives, including any prespecified hypotheses	*End of introduction page 4-5*
Methods			
Study design	4	Present key elements of study design early in the paper	*Settings & participants Survey preparation and administration Page 5-6*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Settings & participants Survey preparation and administration Page 5-6*
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	*Settings & participants Page 5*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Settings & participants Survey preparation and administration Page 5-6*
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	*Methods + Supplemental data Page 5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	*Setting and participant Page 5*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Data analysis Page 7*
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	*Data analysis Page 7*
		(b) Describe any methods used to examine subgroups and interactions	*Data analysis Page 7*
		(c) Explain how missing data were addressed	*Data analysis Page 7*
		(d) If applicable, describe analytical methods taking account of sampling strategy	*n/a/*
		(e) Describe any sensitivity analyses	*Exploratory analysis Methods: Page 6 Results: page 8*
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	*Participants and response Page 7-8*
		(b) Give reasons for non-participation at each stage	*Participants and response gives overview of number of individuals at each stage (page 7)*
		(c) Consider use of a flow diagram	*Information adequately summarized in text*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Participants and response (page 7) and (baseline table, page 18)*
		(b) Indicate number of participants with missing data for each variable of interest	*Baseline table (page 16) and per analysis in results (figures 1,&2a.b., figure legends, page 17)*
Outcome data	15*	Report numbers of outcome events or summary measures	*Number of participants reported per analysis, see above for page numbers*
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	*Medians and interquartiles, results, page 8-9*
		(b) Report category boundaries when continuous variables were categorized	*Survey in supplement,*
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*n/a/*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Analysis per characteristic reported, Personal meaningful lifetime benefit, and exploratory analysis page 7- 8*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Principal findings, discussion page 9*
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	*Strengths and limitations, discussion*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Discussion(page 9-11)*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Discussion. Limitations unlikely to alter conclusion. Use of risk score for other*

			populations. Page 12
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	*Reported. Page 13*

*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:	*BMJ Open*
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

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

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Word count main body: 3,297

ABSTRACT

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

Design: Cross-sectional study

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

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

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

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

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

medicine and shared decision-making. Decision-tools could provide information on realistic therapy benefit.

Strengths and Limitations of the Study:

- We examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-effects, and inconveniences of medication which are a daily part of clinical practice.
- In contrast to previous studies, we surveyed a large sample of both physicians and actual patients in comparable settings.
- The use of a multiple-choice voting system may have limited response variation.
- Further research would be necessary to analyze how these perspectives would relate to actual use of medication by patients and prescription of medication by physicians.

INTRODUCTION

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

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

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

hypothetical risk scenarios[12 13] on idealized medications. [10 14-17] We therefore aimed to quantify perceptions on meaningful lifetime and 10-year benefit, defined as the gain in CVD-free life-expectancy above which physicians (as users and prescribers) and patients consider statin and antihypertensive medication meaningful. We also aimed to compare these thresholds to what is a clinically achievable benefit in the primary prevention.

METHODS

Setting and Participants

Two separate settings, in which a large number of patients and physicians could be recruited and surveyed were chosen. Primary care physicians were recruited and surveyed on the same day among attendees of a national Continuing Medical Education conference (Boerhaave "Progress and Practice"), in Leiden, The Netherlands (December 8th, 2016) targeted to primary prevention health-care providers. Of the survey respondents, only participants reporting themselves as primary care physicians were included in the analyses. Patients were recruited and surveyed during three separate plenary sessions at a one-day information conference targeted to primary and secondary CVD prevention patients at the University Medical Center Utrecht in the Netherlands (April 8th, 2017). All surveyed patients were included in the analyses.

Survey Preparation and Administration

A pretest session involving fifty primary care physicians was conducted in November 2016 to review the research questions and proposed survey, and guide multiple-choice answer options of the electronic (physician) or paper (patient) questionnaires ultimately used for data collection (Supplement A&B). The finalized surveys were subsequently administered at the respective sessions (Boerhaave and Utrecht). To ensure informed and comparable responses, an audience-appropriate 10-minute introduction on individual therapy-benefit was given prior to each session (Supplement C). In this introduction, an example of lifetime benefit from smoking cessation and aspirin-therapy was provided.[1 18] The structure of the introduction and survey was the same in both physician and patient questionnaires. The survey questions were presented centrally and sequentially by the researcher, thus preventing participants from

viewing either previous or future questions or benefitting from time-saving heuristics. The questions were verbally explained before participants were given the opportunity to respond. At the start of each session, all participants were informed that a voluntary survey would be conducted and data collected and treated anonymously. The study was conducted in accordance with the principles of the Declaration of Helsinki and prospectively granted exempt status by the Medical Ethics Committee of the University Medical Center Utrecht.

Outcome Definition

Lifetime benefit thresholds for physicians and patients were quantified as the gain in CVD-free life-expectancy desired prior to considering or continuing personal statin therapy (i.e. the benefit was considered meaningful). Ten-year benefit thresholds were quantified as the gain in CVD-free life-expectancy desired for 10-years of both statin and antihypertensive medication use prior to considering or continuing prescription (physicians) or personal use (patients). Physicians were thus framed as users for lifetime thresholds and prescribers for 10-year thresholds. For an exploratory analysis, the outcome was framed differently and participants were asked to report the number of years willing to take statin medication provided the therapy would give a one-year gain in CVD-free expectancy.

Guideline recommendations and participant views of meaningful therapy

European Society of Cardiology (ESC) guideline recommendations on lipid[19] and blood-pressure therapy[20] were compared to what participants viewed as meaningful therapy. The ESC-SCORE algorithm for low-risk countries was used to establish which risk-factor combinations had sufficient 10-year risk of CVD-mortality to be eligible for lipid-lowering therapy.[19-21] In order to establish which risk-factor combinations would be treated based on participant views of meaningful therapy, clinically attainable benefit from statin and antihypertensive medication was estimated and compared to views of meaningful benefit. The JBS risk-calculator[22] was used to estimate clinically attainable benefit in terms of gain in CVD-free life-expectancy for each of the 600 risk-factor combinations [age, systolic blood pressure (SBP), smoking status, sex, and total cholesterol] of a national ESC-SCORE chart variant.[3 23] Clinically attainable gain from statin medication was estimated with simvastatin 40 mg, a mid-potency statin commonly

prescribed as initial therapy[24] which reduces LDL-c levels by 37% irrespective of baseline level.[25] Clinically attainable gain from an antihypertensive was estimated with a single, initial antihypertensive medication, using the formula 9.1 mmHg + 0.10 mmHg * (current SBP-154 mmHg).[26] To express the clinically attainable benefit per year of medication use, the gain in CVD-free life-expectancy estimated by the calculator (i.e. the lifetime benefit) was divided by the total remaining on-therapy CVD-free life-years estimated by the calculator (i.e. the duration of medication use required to achieve this lifetime benefit). The estimated clinically attainable gain per 10-years of medication use was graphically juxtaposed against participant views of meaningful benefit, expressed as months gain in CVD-free life-expectancy desired for 10 years of use prior to considering or continuing prescription (physicians) or personal use (patients). For clarity, all values used for the calculations, and a calculation example are provided in supplements D&E.[27-29]

Data Analysis

Age was converted to numeric values. Thresholds in terms of minimal desired months gain were reported as median (interquartile range, IQR) within each group. Wilcoxon rank-sum and spearman correlations were used to analyze lifetime thresholds according to certain characteristics pre-defined to be potentially of influence on response: age, sex, use of either statin or antihypertensive medication (yes/no), and presence of CVD (yes/no). [30 31] Paired-samples Wilcoxon signed-rank tests were used to assess response differences between 10-year statin and antihypertensive medication thresholds. Missing values were not imputed, and the number of participants in each analysis reported. Analyses were performed using R-Statistical Software, version 3.1.1.

Patient and Public Involvement

The study has been designed to survey the opinion of a large group of both patient and physicians to better understand their priorities and preferences. Both patient organizations and primary care physicians were involved during study preparation. The research question and study design evolved from a discussion session with a patient panel at PGOSupport conference, an independent nation-wide network for patient-organizations, held in Amstelveen, the Netherlands in April 2016. Physicians were involved in the pre-test sessions in Roermond, the Netherlands in November 2016. Participants were not involved in finding the optimal study recruitment procedures. The findings from this study will be disseminated to physicians and patients via conferences and newsletters.

RESULTS

Participants and Response

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

Personal meaningful lifetime benefit

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

between guideline recommended therapy and participant views of meaningful benefit. The clinically attainable gain in CVD-fee life-expectancy from lifelong simvastatin 40mg ranged from 4 - 49 months. Larger gains were seen in younger individuals with high SBP and lipid-levels and smaller gains were seen in older individuals with low risk-factor levels. Treatment is concordant with participant views if the clinically attainable gain in CVD-free life-expectancy per 10-years of medication is was equal to or greater than the reported meaningful benefit thresholds for prescribing and using (i.e. physician median 12 months for every 10 years of use and patient median 14 months for every 10 years of use). Figure 4. provides the same information for a single, daily, antihypertensive medication; clinically attainable lifetime gain in CVD-fee life-expectancy ranged from 4-35 months and followed a similar distribution pattern to statin therapy.

DISCUSSION

Meaningful statin and antihypertensive therapy for lifetime and 10-years of use was quantified in 400 primary care physicians and 523 patients. A high degree of variation in what was perceived as meaningful therapy was reported within both patients and physicians. Patients consistently desired a higher lifetime benefit for medication use than physicians. Females desired a higher benefit from statins than males in both participant groups. Physicians desired a slightly higher benefit for statin than for antihypertensive medication. Age had minimal influence on thresholds in patients. Compared to those with CVD, a greater percentage of healthy respondents were not willing to consider statin therapy. However, the median thresholds for respondents who were willing to consider therapy did not differ between these two patient groups. Similar results were found when patients on- and off- preventative therapy were compared. The majority of respondents reported desiring a gain in CVD-free life expectancy above what is generally achievable with lifelong use of a single tablet in the primary prevention setting.

To our knowledge, this is the first study examining medication-specific thresholds in both physicians and patients in terms of gain in life-expectancy. The considerably high thresholds found in our study can be explained by the use of specific medications and not an idealized tablet. Previous studies have either focused on non-lifetime metrics in hypothetical risk scenarios,[12 13] or on idealized medications with negligible costs, side-effects, or follow-up requirements.[10 14-17] Even in these idealized situations, the

benefit desired by patients is large, and often greater than the benefit desired by physicians. [12 13 30] For an idealized pill, the general public desires 6 months gain in life-expectancy.[16] Health care employees are willing to sacrifice 12.3 weeks of life to avoid taking a pill.[32] Such isolated disutility of pill-taking is applicable in cost-effectiveness studies. However, it does not assess the real-life perceived costs, side-effects, and other inconveniences of specific medications which are encountered in clinical practice.

In this study, patients without CVD and not using preventive therapy were more often not willing to consider therapy. However, for those who were willing to consider statin therapy, no group differences were found in median CVD-free life-expectancy desired. The similar numeric thresholds align with exiting literature in which socio-economic factors effected willingness to use medication whereas traditional risk-factors such as the presence of CVD and use of antihypertensive or statin therapy did not.[33] Patients view hypertension treatment as more necessary and effective than hyperlipidemia treatment.[34] However, patients in our study did not distinguish between statin and antihypertensive medications indicating that this discrepancy does not apply if therapy imparts identical benefit. Physicians however did desire greater benefit from statins than antihypertensive medications. Statin side-effects, but not necessarily antihypertensive side-effects, have received wide-spread attention over the previous decades. Negative portrayal of statins in the media and academic press influences healthcare related behavior and coincides with a decrease in statin use.[35] Myalgia frequency is approximately twice as high in patients on statins as on placebo in clinical trials. [36] However, this frequency is considerably higher in observational studies, [37] and clinicians are confronted with observational frequencies in in clinical practice.

Compared to a risk-based treatment strategy in prevention guidelines, treatment based on meaningful therapy thresholds would treat fewer risk-factor combinations, and would produce a shift in eligibility to exclude mostly older individuals with a high 10-year risk and include younger individuals with a low 10-year risk but high lipid levels and high SBP who would not be treated according the risk-based guidelines. A previous study investigating eligibility based on an individualized benefit-based approach described a similar shift in eligibility seen in the present study. The earlier study based eligibility cut-offs on a 10-year absolute risk reduction of ≥2.3%. [38] However, the cut-off was not based on patient perceptions, but on the minimum statin benefit seen in primary prevention guidelines, and resulted in a greater number of eligible

patients (34%) compared to current practice (21%). Other studies have demonstrated that young individuals with high risk-factor levels (i.e. lipid and SBP) have the greatest net-positive lifetime benefit from CVD-prevention strategies, such as aspirin use[1] and renin-angiotensin system inhibition.[39] As older patients had a minimal but significantly higher benefit threshold than younger patients, such a shift is congruent with user views. This shift is also congruent with changing insights into the benefits of deprescription of the elderly population.[40]

Lifetime based decision-tools have become more accessible in clinical practice to both patient and physicians. It is therefore essential to address the high degree of variation in what is considered meaningful therapy in clinical practice. The discrepancy between perceived meaningful benefit and clinically attainable benefit should be addressed and a patient's satisfaction with the expected benefit of agreed upon therapy could be viewed as an additional indicator of quality of care. However, guidelines need not adapt eligibility thresholds or target values based on perceptions of meaningful therapy. The number of prevented CVD-events is ultimately determined by physicians and patients making guideline-based decisions. Misperceptions about perceived CVD-risk are commonplace, and [41] it is conceivable that both physicians and patients overestimate realistic therapy-benefit and may require guidance as to what longevity benefit may be realistically achieved. Such guidance could be easily incorporated into the same online decision-aids which are currently available.

Certain strengths of this study should be highlighted. First, both parties of the shared decision-making process were informed and surveyed in comparable settings. Physicians were representative of the general practitioner population and both primary and secondary prevention patients were surveyed. As there was no evidence of difference in medians between patients with and without CVD, no stratification based on primary or secondary prevention was necessary. Secondly, the number of incomplete responses was low for both physicians (1.0-2.3%) and patients (4.4-5.1%), indicating that both groups were sufficiently informed to provide valid and reliable responses. Lastly, we examined benefit thresholds of specific real-life (non-idealized) agents, thus incorporating pre-conceived notions about the costs, side-effects, and inconveniences of medication which are a daily part of clinical practice. Certain study limitations must also be acknowledged. First, we were restricted to a multiple-choice voting system, which

may have limited response variation. However, the observed variation in our study remained large and multiple-choice options were based on responses from a pre-test session. Second, benefit-threshold associated with a single medication was surveyed. In practice, if LDL-c or SBP targets are not achieved, additional medication can be prescribed without necessarily increasing the number of tablets used daily. However, the magnitude of the opinion-based benefit-thresholds are not altered by this limitation. Third, patients were recruited at a large, information conference on CVD-prevention, and may represent a population more interested in CVD-prevention than average. Fourth, the survey was pre-tested in physicians and subsequently adapted for patients. However, the survey and the preceding introduction were designed to maximize understandability and comparability. Fifth, clinically attainable benefit was estimated using the JBS3 risk score and best available evidence from meta-analyses. However, the estimated benefit differs in populations with different event-rates, such as those with clinically manifest CVD. Lastly, further research would be necessary to analyze how these perspectives would relate to actual use of medication by patients and prescription of medication by physicians.

In conclusion, both physicians and patients report a large variation in meaningful longevity-benefit. Moreover, desired benefit differed between patients and physicians and exceeded clinically attainable benefit. Clinicians should recognize these discrepancies when prescribing CVD-prevention and implement individualized medicine and shared decision-making. In the future, guidance as to what realistic benefit entails may be incorporated into online decision-aids to help physicians and patients reach a consensus.

Contributors: NEMJ, FLJV, YG, JAND, contributed to the conception/design of the work. All authors (NEMJ, FLJV, YG, YS, FLM, MN, JAND) contributed to the acquisition, analysis or interpretation of the data. NEMJ drafted the work. All authors (NEMJ, FLJV, YG, YS, FLM, MN, JAND) critically revised the manuscript, and gave final approval and agree to be accountable for all aspects of work.

Acknowledgements: We would like to acknowledge the organizers and participants of the following meetings, conferences, and sessions: the April 2016 PGOSupport conference in Amstelveen, the

November 2016 pilot session in Roermond, the December 2016 Boerhaave Symposium in Leiden, and the April 2017 University Medical Center Utrecht session for patients.

Disclosures: None

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data Sharing: No additional data is available for this study in repositories. However, inquiries concerning the data may be made to the corresponding author.

REFERENCES:

1. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. BMJ 2016;**352**:i1548.
2. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;**341**:c6624.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;**37**(29):2315-81.
4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;**63**(25 Pt B):2935-59.

5. Dickinson R, Raynor DK, Knapp P, et al. Providing additional information about the benefits of statins in a leaflet for patients with coronary heart disease: a qualitative study of the impact on attitudes and beliefs. BMJ Open 2016;**6**(12):e012000.

6. Manuel DG, Abdulaziz KE, Perez R, et al. Personalized risk communication for personalized risk assessment: Real world assessment of knowledge and motivation for six mortality risk measures from an online life expectancy calculator. Inform Health Soc Care 2017:1-14.

7. Galesic M, Garcia-Retamero R. Communicating consequences of risky behaviors: Life expectancy versus risk of disease. Patient Educ Couns 2011;**82**(1):30-5.

8. Board JBS. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;**100 Suppl 2**:ii1-ii67.

9. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. J Am Coll Cardiol 2015;**65**(13):1361-8.

10. Halvorsen PA, Aasland OG, Kristiansen IS. Decisions on statin therapy by patients' opinions about survival gains: cross sectional survey of general practitioners. BMC Fam Pract 2015;**16**:79.

11. Misselbrook D, Armstrong D. Patients' responses to risk information about the benefits of treating hypertension. Br J Gen Pract 2001;**51**(465):276-9.

12. McAlister FA, O'Connor AM, Wells G, et al. When should hypertension be treated? The different perspectives of Canadian family physicians and patients. CMAJ 2000;**163**(4):403-8.

13. Steel N. Thresholds for taking antihypertensive drugs in different professional and lay groups: questionnaire survey. BMJ 2000;**320**(7247):1446-7.

14. Stovring H, Gyrd-Hansen D, Kristiansen IS, et al. Communicating effectiveness of intervention for chronic diseases: what single format can replace comprehensive information? BMC Med Inform Decis Mak 2008;**8**:25.

15. Trewby PN, Reddy AV, Trewby CS, et al. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. Clin Med (Lond) 2002;**2**(6):527-33.

16. Fontana M, Asaria P, Moraldo M, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. Circulation 2014;**129**(24):2539-46.

17. Dahl R, Gyrd-Hansen D, Kristiansen IS, et al. Can postponement of an adverse outcome be used to present risk reductions to a lay audience? A population survey. BMC Med Inform Decis Mak 2007;**7**:8.

18. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;**328**(7455):1519.

19. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;**37**(39):2999-3058.

20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;**34**(28):2159-219.

21. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;**24**(11):987-1003.

22. JBS Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease; JBS3 risk calculator. Secondary Joint British Societies' consensus recommendations for the prevention of cardiovascular disease; JBS3 risk calculator. http://www.jbs3risk.com/.

23. van Dis I, Kromhout D, Geleijnse JM, et al. Evaluation of cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil 2010;**17**(2):244-9.

24. Gu Q, Paulose-Ram R, Burt VL, et al. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. NCHS Data Brief 2014(177):1-8.

25. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;**376**(9753):1670-81.

26. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;**338**:b1665.

27. Recommendations for treatment of hyperlipidemia in adults. A joint statement of the Nutrition Committee and the Council on Arteriosclerosis. Circulation 1984;**69**(5):1067A-90A.

28. JoJoGenetics. Sectie Moleculaire Diagnostiek van het Laboratorium Experimentele Vasculaire Geneeskunde, Academisch Medisch Centrum. http://www.jojogenetics.nl/.

29. Netherlands National Institute for Public Health and the Environment (RIVM). Average Body Mass Index (kg/m2) according to age and gender. The Netherlands. 2012.

30. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a systematic review. Heart 2017.

31. Wegwarth O, Schwartz LM, Woloshin S, et al. Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. Ann Intern Med 2012;**156**(5):340-9.

32. Hutchins R, Viera AJ, Sheridan SL, et al. Quantifying the utility of taking pills for cardiovascular prevention. Circ Cardiovasc Qual Outcomes 2015;**8**(2):155-63.

33. Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. Ann Intern Med 2007;**146**(12):848-56.

34. Stack RJ, Bundy C, Elliott RA, et al. Patient perceptions of treatment and illness when prescribed multiple medicines for co-morbid type 2 diabetes. Diabetes Metab Syndr Obes 2011;**4**:127-35.

35. Matthews A, Herrett E, Gasparrini A, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ 2016;**353**:i3283.

36. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;**388**(10059):2532-61.

37. Thompson PD, Panza G, Zaleski A, et al. Statin-Associated Side Effects. J Am Coll Cardiol 2016;**67**(20):2395-410.

38. Thanassoulis G, Williams K, Altobelli KK, et al. Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease. Circulation 2016;**133**(16):1574-81.

39. Schievink B, Kropelin T, Mulder S, et al. Early renin-angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. Diabetes Obes Metab 2016;**18**(1):64-71.

40. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. BMJ 2016;**353**:i2893.

41. Katz M, Laurinavicius AG, Franco FG, et al. Calculated and perceived cardiovascular risk in asymptomatic subjects submitted to a routine medical evaluation: The perception gap. Eur J Prev Cardiol 2015;**22**(8):1076-82.

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%)

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

Figures Legends

Figure 1 Legend:

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%).

Figure 2 a. and b. Legend:

Months gain in CVD-free life-expectancy above which physicians (as prescribers) and patients (as users) consider a) statin and b) antihypertensive therapy 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.

Figure 3 Legend:

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.

Figure 4 Legend:

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.

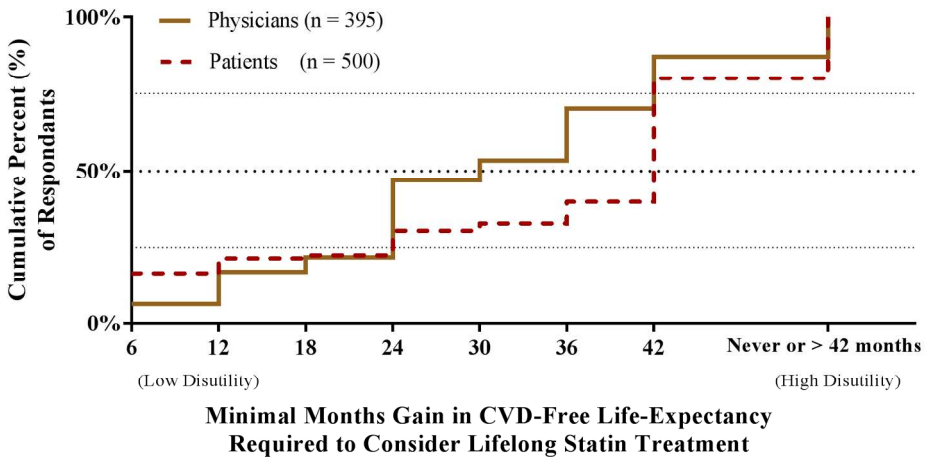

Figure 1. Months gain in CVD-free life-expectancy above which physicians and patients perceive lifelong statin therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 23 patients (4.4%).

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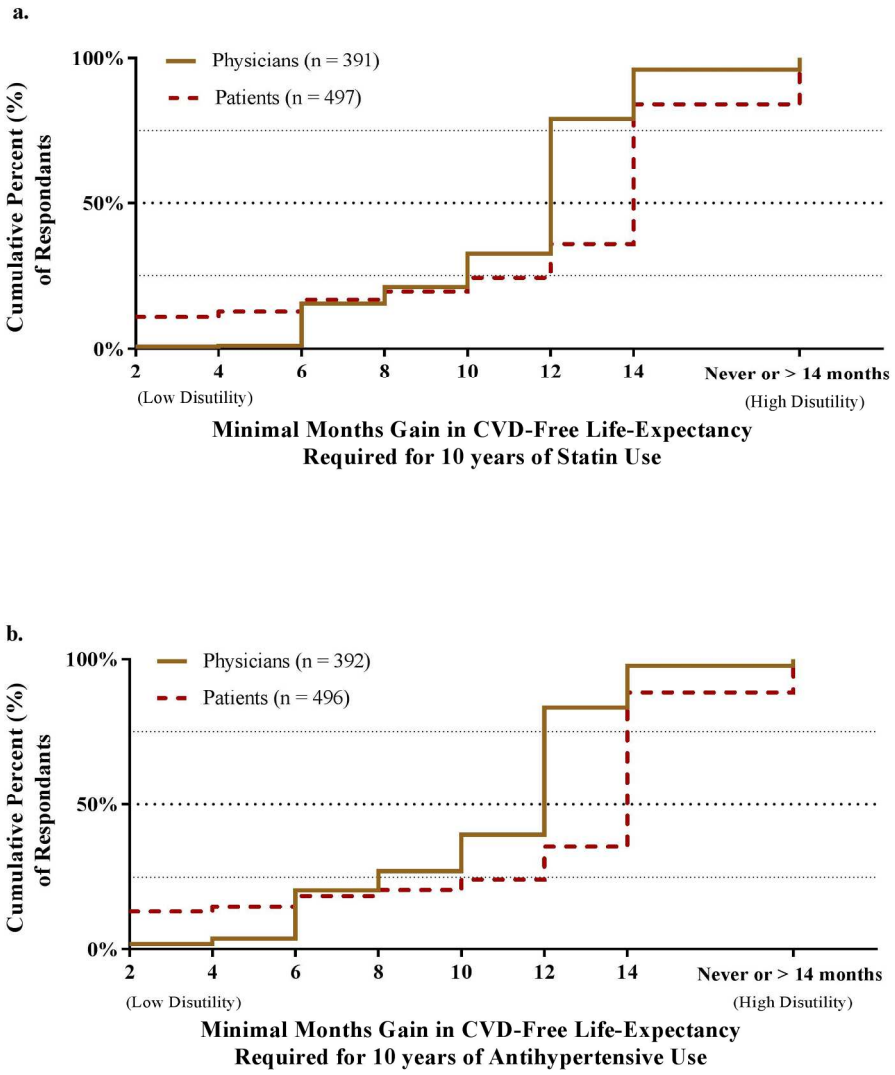

Figure 2. Minimal gain in CVD-free life-expectancy to perceive a) statin and b) antihypertensive therapy as meaningful. Missing responses was seen in 5 physicians (1%) and 26 patients (5.0%) for statin medication and 8 physicians (2%) and 27 patients (5.1%) for antihypertensive medication.

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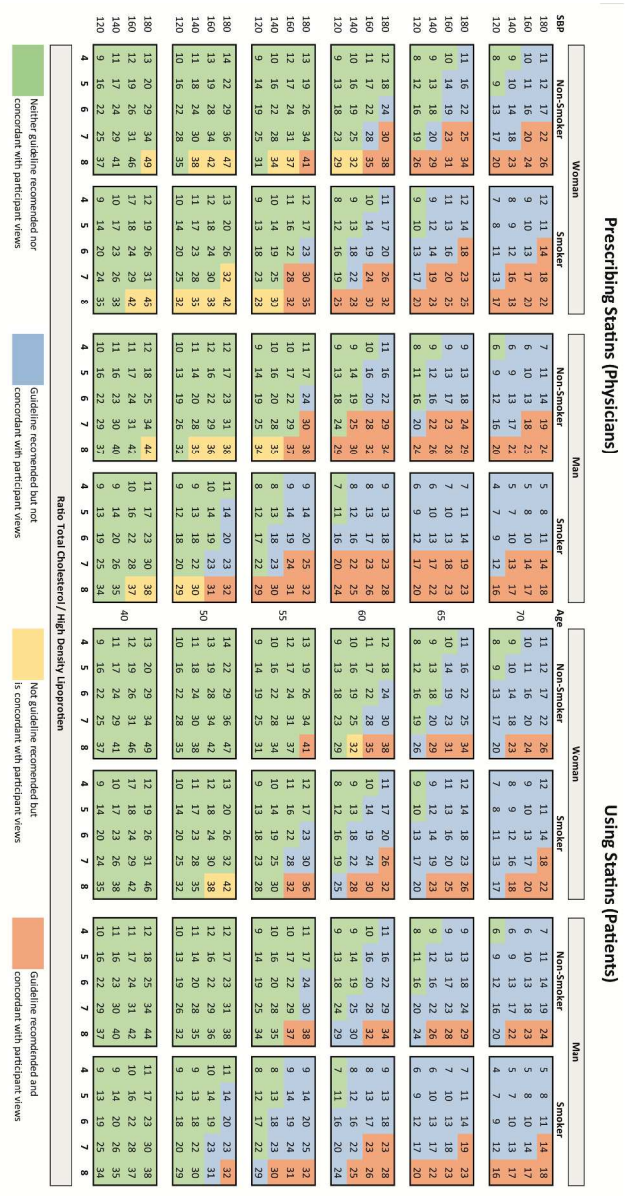

Figure 3. Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with simvastatin 40mg for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors represent the (non)-concordance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

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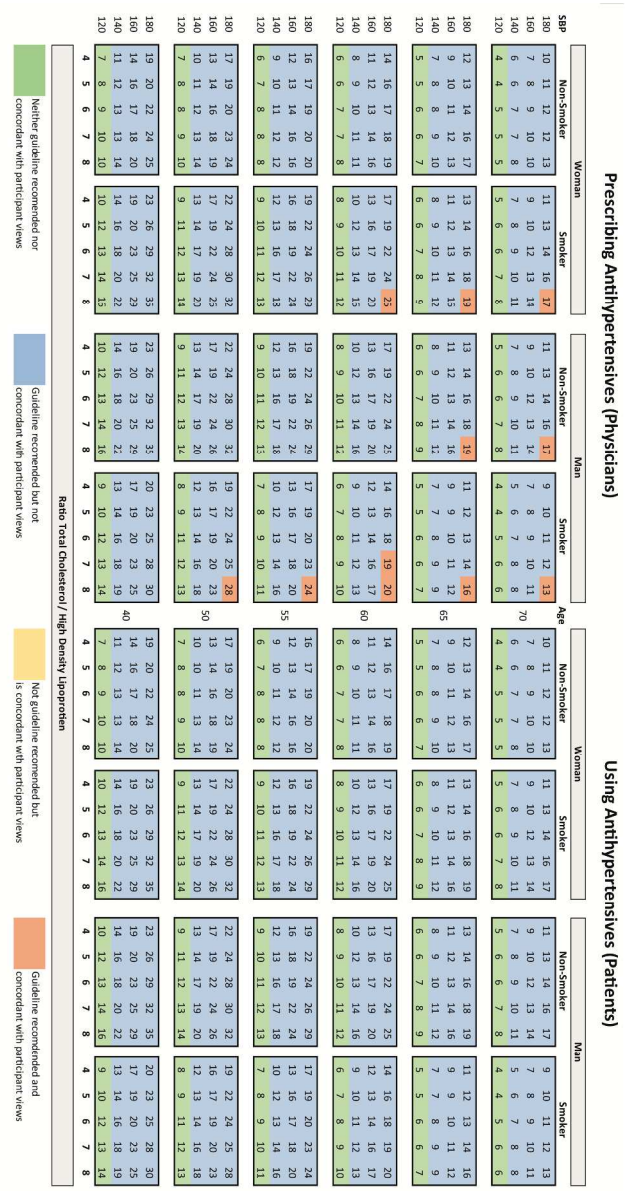


Figure 4 : Numbers represent total gain (in months) of CVD-free life-expectancy to be attained from lifelong therapy with a single, blood-pressure lowering medication for the specific combination of age, sex, lipid-profile, blood-pressure and smoking status calculated with the JBS3 risk score. Colors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

192x368mm (300 x 300 DPI)

SUPPLEMENTAL MATERIAL

A) Physician Survey

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

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

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

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

4. Imagine **you** were considering starting (or continuing) a statin medication **for yourself**. What is the minimum gain in life-expectancy without (new) cardiovascular disease "*healthy life years*" the medication must provide before you considered use worthwhile?

   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin *Or only above these thresholds*

5. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would personally consider using this statin to achieve this benefit?

   a. I would never want to use a statin; *Or only above these thresholds*
   b. 5 year (high threshold)
   c. 10 year
   d. 15 year
   e. 20 year
   f. 30 year
   g. 40 year
   h. 50 year (low threshold)

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

   a. 2 months (low threshold)

   b. 4 months

   c. 6 months

   d. 8 months

   e. 10 months

   f. 12 months

   g. 14 months (high threshold)

   h. I would never consider statin prescription worthwhile. *Or only above these thresholds*

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

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

   a. 2 months (low threshold)

   b. 4 months

   c. 6 months

   d. 8 months

   e. 10 months

   f. 12 months

   g. 14 months (high threshold)

   h. I would never consider blood-pressure medication prescription worthwhile; *Or only above these thresholds*

B) Patient Survey

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

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

   …….years

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

   □ Heart attack
   □ Stroke
   □ *Intermittent claudication (*Peripheral artery disease)
   □ TIA

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

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

□ I have never had *ANY* of the above

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

   a. ½ year (low threshold)
   b. 1 year
   c. 1 ½ year
   d. 2 year
   e. 2 ½ year
   f. 3 year
   g. 3 ½ year (high threshold)
   h. I would never want to use a statin ; *Or only above these thresholds*

6. Imagine you were to gain **1 year** of life-expectancy without (new) cardiovascular disease "*healthy life years.*" What is the **maximum** number of years you would consider using the statin to achieve this benefit?

   a. I would never consider a statin worthwhile; *Or only above these thresholds*
   b. 5 years (high threshold)
   c. 10 years
   d. 15 years
   e. 20 years
   f. 30 years
   g. 40 years
   h. 50 years (low threshold)

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

a. 2 months (low threshold)

b. 4 months

c. 6 months

d. 8 months

e. 10 months

f. 12 months

g. 14 months (high threshold)

h. I would never consider a statin worthwhile; *Or only above these thresholds*

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

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

a. 2 months (low threshold)

b. 4 months

c. 6 months

d. 8 months

e. 10 months

f. 12 months

g. 14 months (high threshold)

h. I would never consider blood-pressure medication worthwhile ; *Or only above these thresholds*

C) Short Summary of Introduction Sessions

Physician Session

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

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

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

Patient Session

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

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

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

D) Values Used for Calculations

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

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

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

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

E) Example Calculation

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

Calculation LDL-c:

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

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

= 7 x 1.12 – 1.12 – 1.35/2.17

= 6.098 mmol/L

The effects of simvastatin 40 mg was calculated as follows:

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

= 6.098 mmol/L * 0.63

= 3.842 mmol/L

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

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

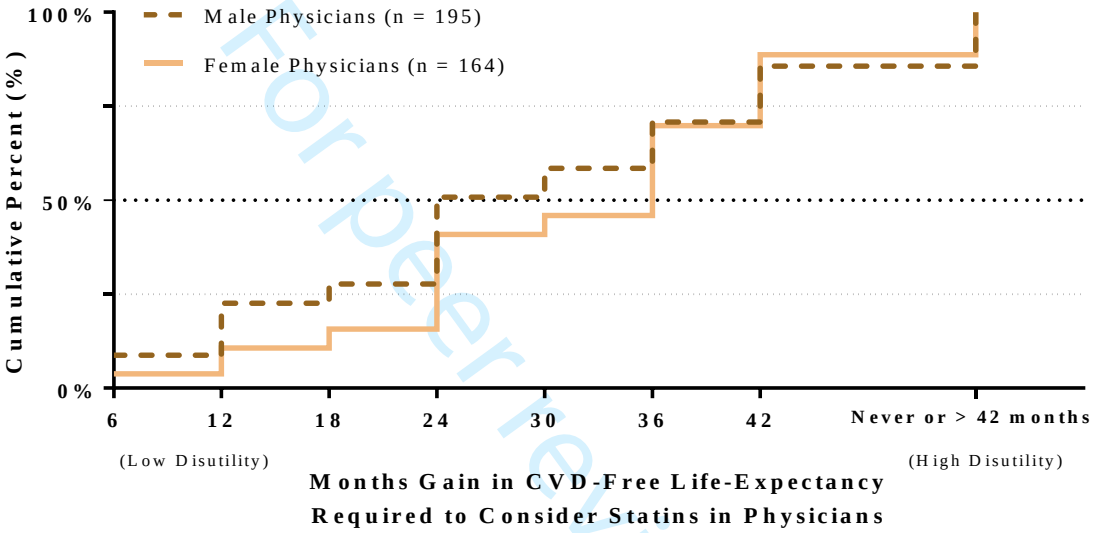
Calculated gain in CVD-free life-expectancy = 2.5 years

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

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

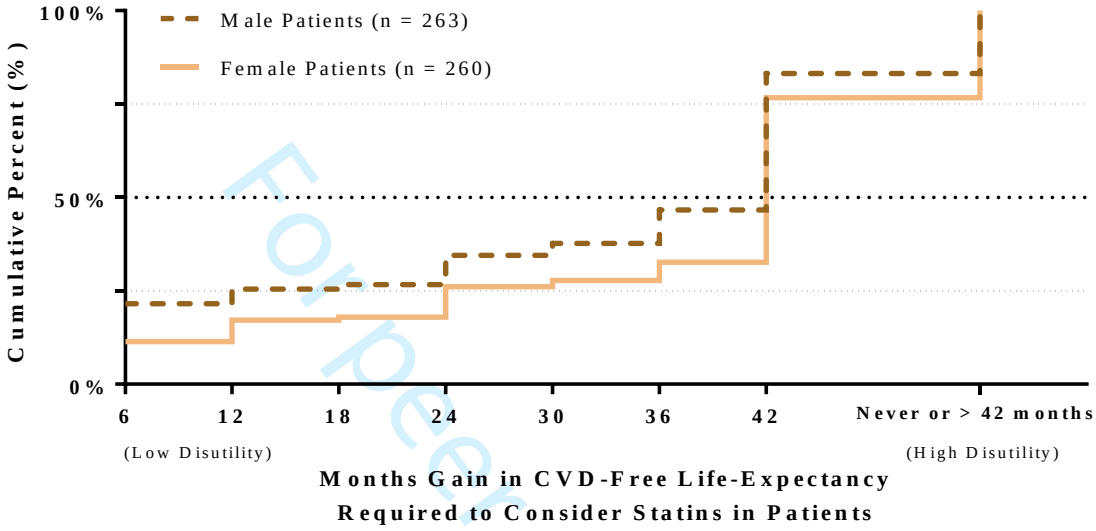
F) Supplemental Figures

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



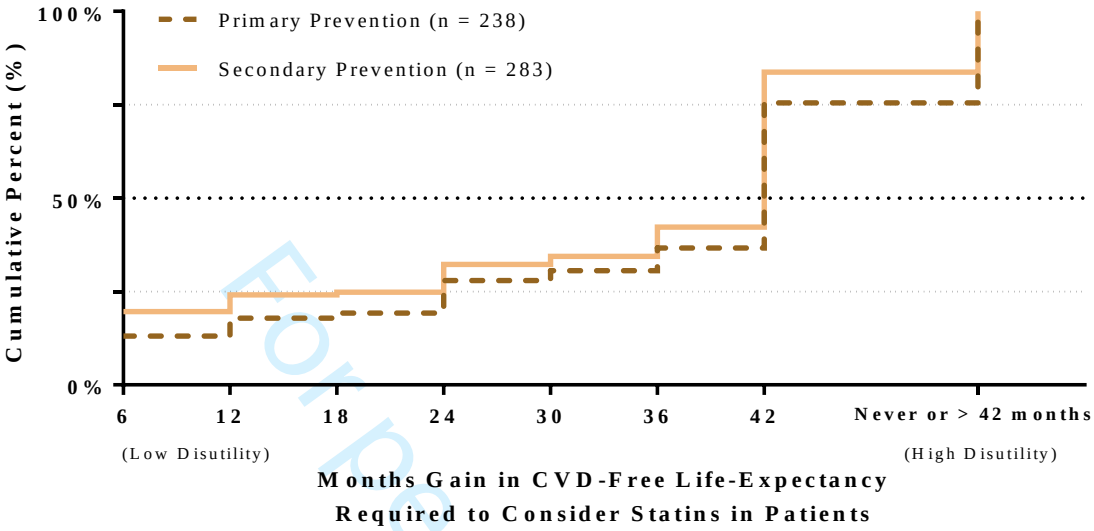
Legend: Months gain in CVD-free life-expectancy above which physicians perceive lifelong statin therapy as meaningful, stratified by gender.

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



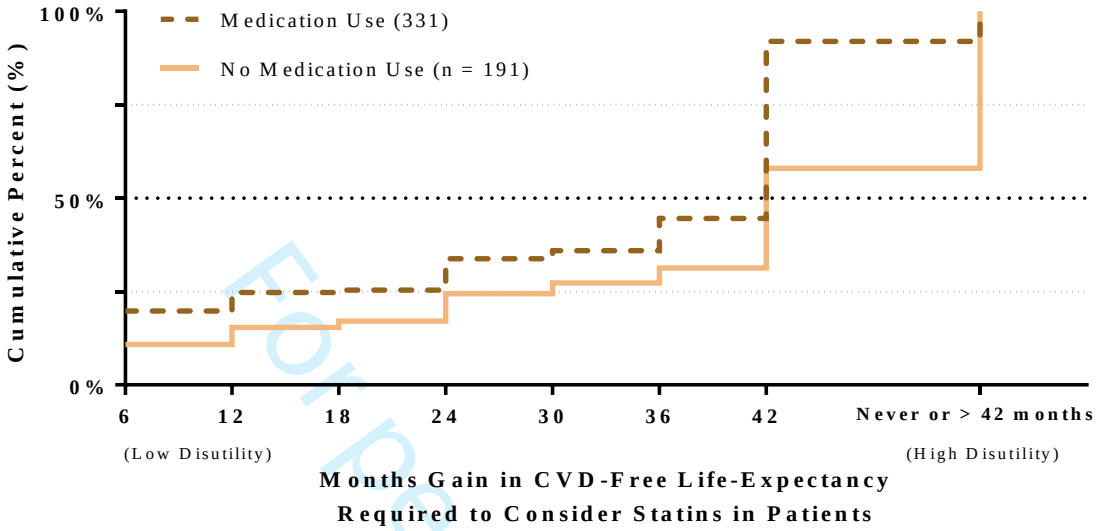
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by gender.

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



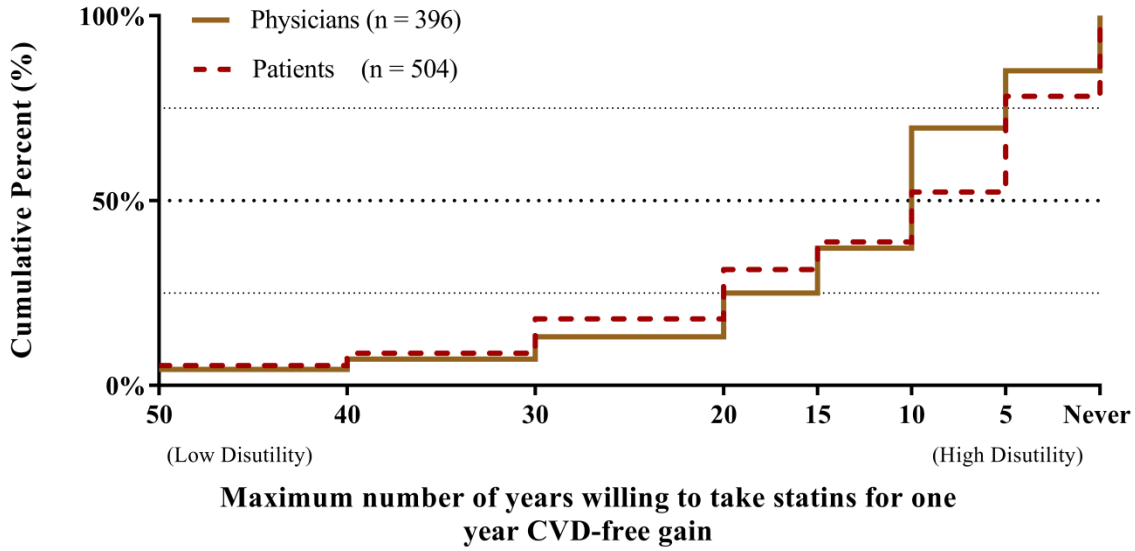
Legend: Months gain in CVD-free life-expectancy above which patients perceive lifelong statin therapy as meaningful, stratified by presence of CVD.

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



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

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



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

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	*Both in title/abstract page 1 and 2*
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	*Structured abstract Page 2*
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	*Introduction page 4*
Objectives	3	State specific objectives, including any prespecified hypotheses	*End of introduction page 4-5*
Methods			
Study design	4	Present key elements of study design early in the paper	*Settings & participants Survey preparation and administration Page 5-6*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Settings & participants Survey preparation and administration Page 5-6*
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	*Settings & participants Page 5*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	*Settings & participants Survey preparation and administration Page 5-6*
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	*Methods + Supplemental data Page 5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	*Setting and participant Page 5*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	*Data analysis Page 7*
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	*Data analysis Page 7*
		(b) Describe any methods used to examine subgroups and interactions	*Data analysis Page 7*
		(c) Explain how missing data were addressed	*Data analysis Page 7*
		(d) If applicable, describe analytical methods taking account of sampling strategy	*n/a/*
		(e) Describe any sensitivity analyses	*Exploratory analysis Methods: Page 6 Results: page 8*
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	*Participants and response Page 7-8*
		(b) Give reasons for non-participation at each stage	*Participants and response gives overview of number of individuals at each stage (page 7)*
		(c) Consider use of a flow diagram	*Information adequately summarized in text*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	*Participants and response (page 7) and (baseline table, page 18)*
		(b) Indicate number of participants with missing data for each variable of interest	*Baseline table (page 16) and per analysis in results (figures 1,&2a.b., figure legends, page 17)*
Outcome data	15*	Report numbers of outcome events or summary measures	*Number of participants reported per analysis, see above for page numbers*
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	*Medians and interquartiles, results, page 8-9*
		(b) Report category boundaries when continuous variables were categorized	*Survey in supplement,*
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	*n/a/*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	*Analysis per characteristic reported, Personal meaningful lifetime benefit, and exploratory analysis page 7- 8*
Discussion			
Key results	18	Summarise key results with reference to study objectives	*Principal findings, discussion page 9*
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	*Strengths and limitations, discussion*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	*Discussion(page 9-11)*
Generalisability	21	Discuss the generalisability (external validity) of the study results	*Discussion. Limitations unlikely to alter conclusion. Use of risk score for other*

			populations. Page 12
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	*Reported. Page 13*

*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.