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Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial.

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Abstract

Objective: To determine whether communicating personalized statin therapy-effects leads to lower decisional conflict associated with statin use among patients with stable cardiovascular disease (CVD) compared to standard (non-personalized) effects.

Design: Hypothesis-blinded, three-armed randomized controlled trial

Setting and participants: 303 statin-users with stable CVD enrolled in a cohort

I**ntervention:** Participants were randomized in a 1:1:1 ratio to standard (non-personalized) practice (control-group) or one of two intervention arms. Intervention arms received standard practice plus 1) a *personalized health profile*, 2) educational videos, and 3) a structured telephone consultation. Intervention arms received personalized estimates of prognostic changes associated with both discontinuation of current statin and intensification to the most potent statin type and dose (i.e. atorvastatin 80 mg). Intervention arms differed in how these changes were expressed: either change in 10-year absolute CVD risk (iAR-group) or CVD-free life-expectancy (iLE-group) calculated with the SMART-REACH model (http://U-Prevent.com).

Outcome: Primary outcome was patient decisional conflict score (DCS) after one-month. The score varies from 0 (no conflict) to 100 (high conflict). Secondary outcomes were collected at one or six months: DCS, quality of life, illness perception, patient activation, patient perception of statin efficacy and shared decision-making, self-reported statin adherence, understanding of statin-therapy, post-randomization low-density lipoprotein cholesterol (LDL-c) level, and physician opinion of the intervention. Outcomes are reported as median (25^{th} – 75^{th} percentile).

Results: Change in 10-year absolute CVD-risk was -2.4(-1.2 - -3.9%) from intensification and +10.2% (+7.7 - +13.5) from discontinuation. Change in CVD-free life-expectancy was +0.5 years (+0.3 – +0.8) from intensification and -2.0 years (-1.3 - -2.8) from discontinuation.

Decisional conflict differed between the intervention arms: median control 27 (20-43), iAR-group 22 (11-30; p-value versus control 0.002), and iLE-group 25 (10–31; p-value versus control 0.02). No differences in secondary outcomes were observed.

Conclusion: In patients with clinically manifest CVD, providing personalized estimations of treatment-effects lowers decisional conflict associated with statin use. The results support the use of personalized predictions for supporting decision-making.

Registration: Netherlands Trial Registry (Identifier NTR6227)

Strenths and limitations of the study

Strengths:

- In our study, patients were provided with estimations of their actual causal therapy-effects, unlike many previous studies which tested the preferences of patients using hypothetical therapy-effects.
- Performance bias was limited by hypothesis blinding.

Limitations:

- In the control group of this clinically stable cohort population, decisional-conflict was low and the belief in the effectivity of statin medications was high.
- The personalized effects were not used directly during a clinical consultation, but provided prior to any potential consultation with a physician.
- A number of questionnaires were created specific for this study, and were thus not externally validated.

Introduction

Several online tools have recently become available which can calculate the personalized therapy effects for various cardiovascular disease (CVD) prevention strategies. Such calculators often express the therapy-benefit in terms absolute 10-year CVD risk reduction, and most recently, in terms of gain in healthy life-expectancy.(1)

In general, using decision tools is associated with increased knowledge and less decisional conflict, and providing patients with information regarding therapy increases patient participation in medical decision-making.(1-5) However, most investigated patient decision-aids use hypothetical or non-personal effects of CVD-prevention, and not the actual, personalized causal effects an individual can expect from CVD-prevention. However, patients often desire a far greater therapy-benefit than can be expected from preventive therapy.(6-8) One survey showed that patients desire around 42 months increase in life-expectancy from life-long statin-use(6) whereas the actual benefit is often less than half this amount.(7) Being presented with an actual predicted benefit of a therapy far smaller than the benefit desired beforehand might discourage patients from using medication. Moreover, metrics to used communicate therapy-effects illicit different opinions on the value of preventive therapy, motivation to use therapy, and possibly therapy-adherence.(9-12)

We conducted a hypothesis blinded, three-armed, randomized controlled trial (RCT) to determine whether communication strategies involving personalized therapy-effects of statin therapy, expressed as change in CVD-free life-expectancy or absolute 10-year CVD-risk reduction, lead to improved decisional certainty about the use of statins compared to standard communication strategies and compared to one another.

Methods

Population

The SMART-Inform study was nested within the previously described Secondary Manifestations of ARTerial disease (SMART) study, an ongoing, single-center, prospective cohort of patients referred to the University Medical Center Utrecht (UMCU) in the Netherlands for CVD screening. (13) All patients invited to participate in a SMART-examination were screened, telephonically informed of the SMART-Inform sub-study, and sent further information about the sub-study by mail. Additional inclusion criteria for the SMART-Inform study were current statin used, being between 45-80 years old, having CVD (i.e. coronary artery disease, cerebrovascular disease, and peripheral artery disease and abdominal aortic aneurysm). Additional exclusion criteria for the SMART-Inform was terminal malignancy, and not returning the baseline questionnaires.

Design, randomization, and follow-up

The SMART-Inform study was a three-armed, hypothesis-blinded, randomized controlled trial (RCT). RCT participants were informed that study goal was to investigate if information about cholesterol-lowering medications would impact motivation for use, and that everyone would receive at least standard SMART-protocol practice. Patients were blinded to treatment arm differences and allocation. The statistical algorithm R randomly designated assignment with a 1:1:1 ratio in block-sizes of 12. An independent investigator performed randomization and allocation via an anonymous patient number. The study was registered in the Netherlands Trial Registry (Identifier NTR6227). The Medical Ethics Review Committee of the UMCU approved the study. All participants provided written informed consent. Follow-up questionnaires were sent by mail one and six months post-intervention, with telephone reminders ensuing after two weeks if the questionnaires were not returned.

Patient and public involvement

The study design and goal was discussed at an open conference of patient-organizations held in Amstelveen, the Netherlands in April 2016 to gain and incorporate input from patients at an early stage.

Description of standard practice

All participants received cardiovascular care as usually delivered by their own referring general practitioner or medical specialist. In addition, all participants received written information on their baseline examinations as part of the SMART-study consisting of general lifestyle advice based on which treatment targets recommended by the European Society of Cardiology (14) had not yet been met. (supplement 1A).

Intervention arms

In addition to standard practice, patients in the two intervention arms additionally received 1) a *personalized health profile* (supplement 1B and 1C show examples for two hypothetical, fictional patients), 2) educational videos via a USB device, and 3) a structured telephone consultation (supplement 2). The *'personal health profile'* outlined three treatment options: continue with the type and dose of statin-therapy ('current prognosis'); discontinue statin therapy ('stop statins'); and intensify to maximum statin-therapy, defined as once-daily atorvastatin 80 mg ('increase statins'). Intervention arms differed only in measures used to communicate the prognostic change associated with the therapy-effects: 10-year risk (iAR-group) or CVD-free life-expectancy (iLE-group). The USB-device contained intervention-group specific educational videos on how to read and interpret the *'personal health profile'* and the effect of statin-medications on CVD. The structured telephone consultation for the intervention arms ensured the information regarding personal therapy effects was well-received and understood by the patients. No face-to-face contact after receiving the intervention was incorporated into the study; however as the information was not designed to

replace a physician's advice, all patients were encouraged to visit their general practitioner within two weeks after to discuss the SMART-Inform study information.

Predicted therapy-effects

The therapy-effects of statin-medication was modelled as this is a preventive medication which is often used, and which the effect can easily be modelled. The personalized estimations in the *'personal health profile'* were obtained with the SMART-REACH score, an internationally validated model which predicts the personalized effects of CVD-prevention including statin-therapy for patients aged 45-80 years with prior CVD (http://U-Prevent.com).(2) The score estimates the personalized effects of preventative therapy in patients aged 45-80 years with prior CVD. A 1 mmol/L reduction in LDL-c was modelled to correspond to the CVD-specific hazard ratio of 0.80 (15) and the expected LDL-c -reduction from baseline for each statin was derived from a previous meta-analysis.(16) Supplemental figure 1 shows the distribution of the predicted therapy-effects for the trial patients.

Primary outcome

The study's primary outcome was the intergroup difference in experienced decisional conflict at 1 month regarding the decision to continue, discontinue, or intensify statin therapy. Decisional conflict was measured using the Decisional Conflict Scale (DCS), a validated, translated, measure of patient perception of uncertainty in choosing between options.(17, 18) The DCS consists of 16 statements pertaining to the decision to use statins as prescribed (e.g., "I am clear about which benefits matter most to me"). Summary scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). Scores >37.5 are associated with feeling unsure about implementation of the decision (i.e. statin use), and those <25 are associated with following through with a decision.

Patient reported secondary outcomes

Secondary outcomes at 6 months included the DCS, and quality of life measured using the eight subscales of the RAND Medical Outcomes Study Short Form Survey (SF-36).(19) Other patient-reported secondary outcomes were reported at both 1 and 6 months. The Brief Illness Perception Questionnaire (brief IPQ)(20) was used to measure the degree to which CVD was considered threatening by patients. A Visual Analog Scale (VAS) was used to measure how effective patients perceived statin therapy (supplement 3). The thirteen question Patient Activation Measure (PAM-13) (21) was used to assess patient knowledge, skills, and confidence for self-management of health. Patient's perception of shared decision-making was measured with the Shared Decision Making Questionnaire (SDMQ-9). Self-reported statin adherence was determined with the 2003 Brief Medication Questionnaire (BMQ).(22) Patient understanding of statin-therapy was measured with a questionnaire developed for the trial (supplement 4). The possible numeric ranges and interpretation of the secondary outcomes are shown in supplement 5.

Physician reported secondary outcomes

General practitioners (GPs) received a copy of the personalized health profile received by their patients. Upon enrollment of the first patient from their practice, GPs were provided a short telephonic explanation of the study and asked to fill in a questionnaire (supplement 6). Questionnaire results and the last known post-intervention LDL-value at 6 months were secondary outcomes.

Statistical analyses

An intention-to treat-analysis was performed. A minimum sample size of 258 (86 patients per arm) was calculated to detect a difference of 8.5 on the DCS (alpha 0.05; power 0.80) using a two-sided student t-test.(23) Differences among the three arms were detected with ANOVA. If ANOVA $p<0.05$, direct consecutive comparisons between arms were determined using t-testing or with the Wilcoxon-rank sum test for not normally distributed data. Assumptions of

normal (residual) distribution and homoscedasticity were visually inspected. A Kruskal-Wallis one-way analysis of variance was performed to deal with heteroscedasticity. Analyses were performed using R-Statistical Software, V 1.0.14.

Subgroups

Pre-specified subgroup analyses via a two-way ANOVA investigated whether the effect of the intervention on DCS at one month differed according to the following: gender; age (<65 versus >65); years since first CVD event (<1 versus >1 years); educational level (low, medium or high (24)); low versus high patient activation (low a PAM-13 level of 1-2 and high a PAM-13 level of 3-4 based on a conversion of the 100-point PAM-13 score to a 4-point scale (21, 25); health literacy categories based on the Dutch version of the Newest Vital Sign (NVS)(26); and disutility defined as the minimum gain in life-expectancy desired to offset the inconvenience of taking a lifelong, hypothetical, idealised daily tablet.(7)

Results

Participant flow

Between March 2017 and August 2018, 303 participants were enrolled. Baseline characteristics are shown in table 1 and the flow of participants throughout the trial in figure 1. The primary outcome was collected in 260 participants (86%) (control=83, iAR group=87, iLE group=90). Supplemental table 1 displays characteristics for those with and without the primary endpoint. At one-month, 12% (n=10) of control, 8% (n=7) of iAR, and 11% (n=9) of iLE patients reported increasing their statin dose after the intervention. Respective numbers for decreased statin dose were 2% (n=2) in the control arm, 1% (n=1) in the iAR arm, and 3% (n=3) in the iLE arm.

DCS at one month

There was a significant difference between the groups (ANOVA χ^2, p=0.002) with a median (25^{th}-75^{th} percentile) DCS of 27 (20–43) for control arm, 22 (11–30) for the iAR arm, and 25 (10–31) for iLE arm. Subsequent Wilcoxon-rank sum tests showed the difference between the control and iAR arm (W=2707, p=0.002) and the control and iLE arm (W=4219, p=0.02) to be significant. The difference between iAR and iLE arms was not significant (W=3317, p=0.21, Figure 2)

Patient reported secondary outcomes

After 6 months, there was no longer a significant difference between the groups in de DCS score (ANOVA χ^2, p=0.10) with a median DCS of 25 (16–38) for control arm, 22 (9–29) for the iAR arm, and 25 (7–29) for iLE arm. All other secondary outcomes likewise showed now intergroup differences. There was no difference in how threatening patients perceived their CVD (Brief-IPQ) or how effective patients perceived statin medications (VAS 8) at either 1 or 6 months. There was no difference in PAM, understanding of statin effects, self-reported adherence (BMQ Adherence Scale), or patients' perceptions of shared-decision making between arms (SDMQ9). At six months, quality of life did not differ on any RAND SF-36 subscale (table 2).

Physician reported secondary outcomes

Physician reported secondary outcomes are shown in supplemental table 2. Between randomization and 6 months, 119 patients had their LDL-c values determined (control n=51, iAR n=48, iLE=39), with no difference in median serum LDL-c levels found (median 1.9 mmol/L in all groups) between study-arms. In total, 267 physicians were approached after the inclusion of their first patient of which 141 (53%) participated in the questionnaire. Physicians believed statins-medication to be equally worthwhile for patients in all study-arms. There was no difference of opinion between how iAR and iLE formats could positively influence doctor-patient communication, consultation efficiency, and therapy-adherence.

Subgroup analysis

No evidence of subgroup effects was found for sex (p-values for interaction =0.32), age (p=0.90), years since first CVD-event (p=0.24), number of months gain in CVD-free life-expectancy desired prior to taking an idealized medication daily (i.e. disutility, p=0.54), and educational level (p=0.09). An interaction was found for health literacy (p = 0.02). The median (25^{th}-75^{th} percentile) DCS scores for all subgroups are shown in supplemental table 3, and T-testing for differences in each health literacy group is shown in supplemental figure 2. Across health literacy categories, decisional conflict was lowest in the in intervention arms than in the control arms, with the largest difference between control and intervention arms found in people with a low health literacy.

Discussion

Providing personalized estimates of the prognostic changes associated with statin use in terms of 10-year CVD risk and CVD-free life-years (compared to a control group) resulted in lower decisional conflict associated with statin use measures after one month. After six months no differences were found. Likewise, no group differences were found in secondary outcomes, which included the degree to which people perceived their CVD to be threatening, how effective patients viewed their statin-medications, or LDL-c levels after six months. This indicates that although the actual benefit from CVD-prevention may be smaller than people initially desire, providing the estimated effects of CVD prevention still positively impacts patient's opinions on taking these medications for a short period of time.

Many tools designed for decision-support report DCS differences of 8-10 points immediately post intervention in favour of the decision-aid.(23) We measured the outcomes after one month to measure provide enough time for patients to visit their physician. The already low decisional conflict in the control arm, may explain the relatively small absolute differences in

median scores found in this study (2-5 points). The gradual loss of statistical significance, seen at six months, is in line with previous studies investigating the long-term effects of decision-support tools of for statin medications indicating that positive results of such interventions fade over time.(27)

The use of patient communication-aids is known to make people feel better informed and to help them form accurate opinions of therapy benefit-harm ratios.(23, 28) A number of studies have examined the effect of providing estimations of hypothetical or generalised therapy-benefit to patients with clinically manifest CVD.(10, 29-31) One study examined the effect of providing primary care patients without any prior statin-exposure, with the approximated personalized effect of statin medications.(11, 32) Absolute risk reduction estimates resulted in a greater likelihood to redeem statin-medications compared to patients who had received the predictions in terms of prolongation of life. However, there were no differences in patient satisfaction and confidence in decision. Patients already using medication may respond differently to personalized estimations than patients initiating a new medication. Willingness to take a new therapy may be more sensitive to the perceived side-effects than to the perceived benefits.(33) Similarly, worry about side-effects is a stronger determinant of intentional non-adherence than belief in the effectiveness of statin-medications(34). As opposed to first-time statin-users, all patients in our study had already been using statins, and may therefore already know if they have experienced statin-related side-effects.

Similar to our study, previous literature shows that patients often overestimate the relative effects of medication and desire a greater absolute therapy-benefit than clinically feasible.(6, 7) Although the majority of patients in our study indeed desired more benefit than clinically feasible (median disutility score 61 months), statin discontinuation was minimal and there was no evidence of subgroup effects based on baseline disutility. Although physicians may

also over-estimate the effects of preventive therapy,(6) there were no inter-groups differences in how physicians perceived the necessity of statin-medications.

Strengths of this study involve providing patients with estimations of their actual causal therapy-effects. As we assessed current statin users, we were able to provide information on multiple treatment-options. Systematically approaching cohort patients who were due to receive physical examinations during a certain time-frame minimized the risk of preferentially selecting patients likely to respond to personalized predictions. Use of the cohort's standard procedures also allowed for a structured and well-defined control group, and via the use of structured telephonic consultations it was ensured patients had each interventional format explained in a similar fashion. Furthermore, the SMART-REACH algorithm was published on http://U-Prevent.com after the randomization of the last patient, reducing the risk of cross-contamination between intervention arms. Performance bias was limited by hypothesis blinding. A number of study limitations should be highlighted. First, in the control group of this clinically stable cohort population, decisional-conflict was low and the belief in the effectivity of statin medications was high. The effects described here may thus be different in a population with very recent CVD-events, or who are statin-naïve. Moreover, the personalized effects were not used directly during a clinical consultation, but provided prior to any potential consultation with a physician, and the effects may be different compared to a population of patients who are involved in a clinical consultation in which statin therapy is discussed. Second, the loss to follow-up was 14% for the primary outcome. This is however lower than other communication-trials involving follow-up questionnaires.(11) and baseline characteristics of missing and non-missing individuals were relatively similar. Correction for baseline health literacy, a characteristic which may have differed between missing and non-missing individuals did not level-off the effects. Third, in particular for questions relating to drug-adherence, self-reported measures may be subject to

recall and reporting biases. Fourth, a number of questionnaires were created specific for this study, and were thus not externally validated.

A number of risk-prediction tools capable of estimating treatment-effects for lipid-lowering, blood pressure-lowering, and anti-thrombotic medications are now readily available in clinical practice for patients with and without cardiovascular disease.(1) Future (cluster) RCTs of general practitioners could investigate the use of such tools in populations with or without prior medication use during actual consultations.

In conclusion, in patients with clinically manifest CVD advised to use statin medications, providing personalized estimations of treatment-effects, both in terms of 10-year absolute risk and CVD-free life-expectancy resulted in small but significantly lower decisional conflict associated with statin use. The results support the use of personalized predictions of absolute therapy benefit in clinical practice.

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Conflict of interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests."

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author Contributor statement

NEMJ, FLJV, YdG, OCD, CB, JAND contributed to the conception, design of the work and interpretation of the data, YMS & GEHMR contributed to the interpretation. NEMJ drafted the work, FLJV, YdG, OCD, CB, JAND, YMS & GEHMR critically revised the work, all authors gave final approval and agree to be accountable for the work.

Data sharing statement

Some individual deidentified participant data (including data dictionaries) may be shared upon reasonable request pending approval by the department and institution on a case-by-case basis. Approval will be based the scientific question to be answered with the data, ability of the authors of this manuscript to co-operate on the project, and compliance with contracts acquired for the questionnaires in this study and hospital and SMART-cohort policy.

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Figure Legends:

Figure 1: Participant flow during the trial

Figure 2: DCS at 1 month and Kruskal-Wallace analysis of variance and pos-hoc Wilcoxon-rank sum t-test. Boxes denote the median (25^{th}–75^{th} percentiles). Whiskers denote the 25^{th} percentile-1.5*(Inter-Quartile Range) and the 75^{th} percentile + 1.5(Inter Quartile Range).

Tables:

Table 1: Baseline characteristics

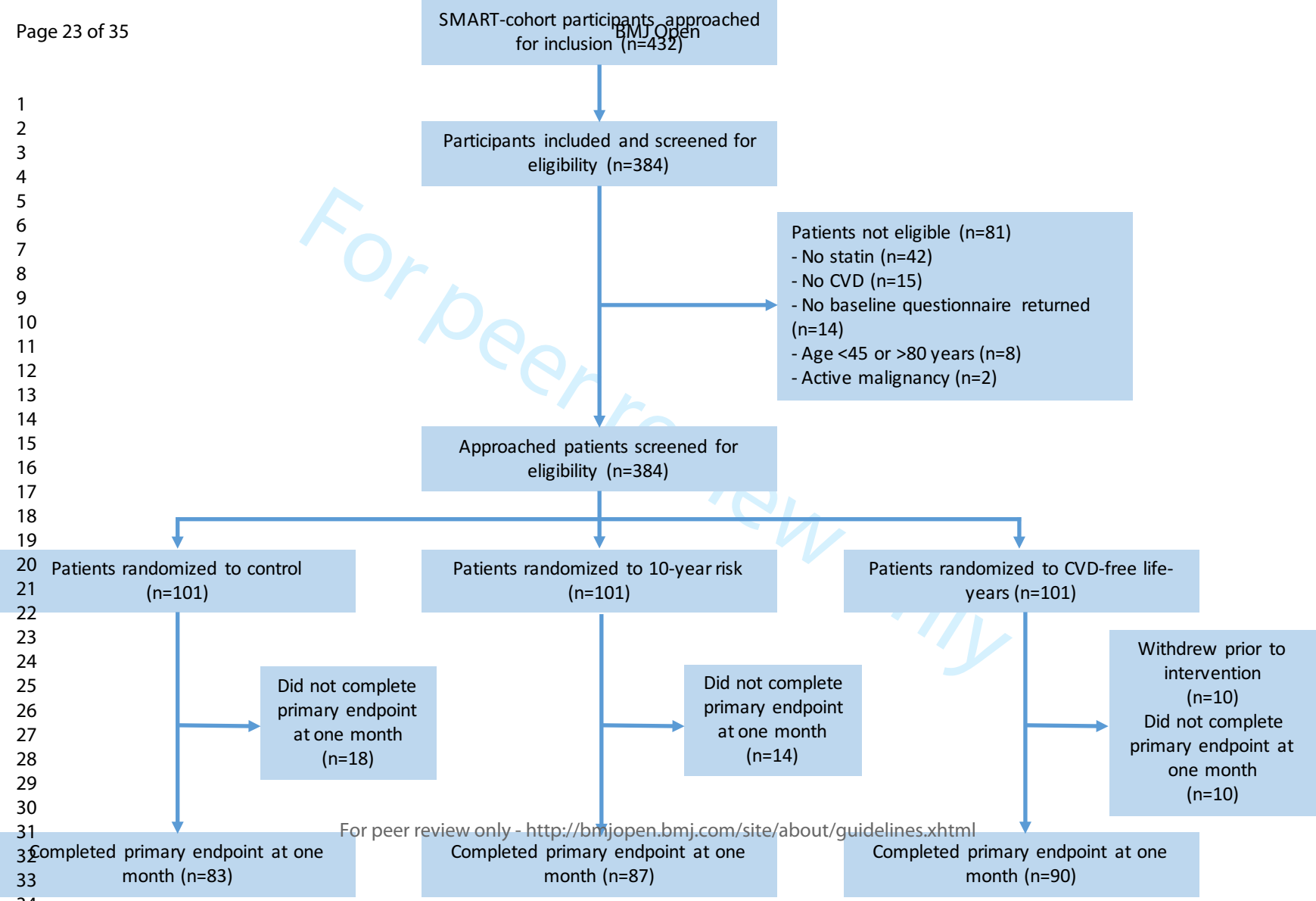
	Control-group	iAR-group	iLE-group
	n=101	n=101	n=101
Age	66(59-70)	66(58-71)	64(59-71)
Gender (male)	86%	82%	85%
More than one CVD location	11%	10%	10%
Current Smoker	17%	16%	9%
Years clinically manifest CVD	0(0-10)	0(0-10)	3(0-10)
Diabetes Mellitus	14%	27%	23%
LDL-cholesterol (mmol/L)	2.0(1.7-2.4)	2.0(1.6-2.4)	2.0(1.6-2.5)
Already on maximum statin therapy	1.3%	1.0%	1.0%
Creatinin (umol/L)	84(78-93)	83(75-96)	85(75-94)
Systolic blood pressure (mmHg)	13(121-142)	13(121-143)	129(122-142)
Number of medications per day	5(4-6)	6(4-9)	6(4-8)
Disutility score	61(9-97)	61(5-97)	61(9-97)
Adequate health literacy	83%	83%	81%

Legend: Data are reported as mean ± SD, median (interquartile range) or (%). CVD locations defined as coronary artery disease, peripheral artery disease, or abdominal aortic aneurysm in addition to cerebrovascular disease. Health literacy was based on the Newest Vital Sign score in the baseline questionnaire(35). Disutility is months required to offset inconvenience of daily pill-taking of an idealized medication.(7) Number of

Table 2: Patient Reported Secondary Outcomes

	Median (25th-75th percentile)			ANOVA	
	Control-group	iAR-group	iLE-group	Test-statistic	p-value
DCS (6)	25(16-38)	22(9-29)	25(7-31)	$\chi2$=15.0	p=0.10
Brief-IPQ (1)	36(26-42)	34(28-44)	37(30-42)	F=4.6	p=0.68
Brief-IPQ (6)	34(26-43)	35(30-41)	37(29-44)	F=1.7	p=0.19
PAM (1)	60(51-70)	58(53-68)	63(56-75)	F=1.9	p=0.20
PAM (6)	64(54-77)	63(56-77)	63(56-78)	F=0.8	p=0.48
Perceived Statin Efficacy (1)	8(7-9)	8(7-9)	8(7-9)	$\chi2$=0.15	p=0.92
Perceived Statin Efficacy (6)	8(7-9)	8(7-9)	8(7-9)	$\chi2$=0.50	p=0.98
Understanding of therapy-effects (1)	88(75-88)	88(75-100)	88(75-100)	$\chi2$=5.9	p=0.07
Understanding of therapy-effects (6)	88(75-100)	88(75-100)	88(63-100)	$\chi2$=1.4	p=0.60
BMQ Adherence Risk Scale (1)	1(0-1)	1(0-1)	1(0-1)	$\chi2$=1.4	p=0.60
BMQ Adherence Risk Scale (6)	1(0-1)	1(0-1)	1(0-1)	$\chi2$=1.7	p=0.41
SDMQ9 (1); Reported visiting GP (n)	44(9-69); (46)	42(18-62); (58)	58(22-76); (55)	$\chi2$=1.8	p=0.40
SDMQ9 (6); reported visiting GP (n)	44(24-73); (60)	48(32-63); (49)	62(22-84); (47)	$\chi2$=2.6	p=0.28
RAND-36 Quality of life (6)					
Physical functioning	80(70-85)	75(60-85)	80(65-85)	$\chi2$=4.3	p=0.11
Role limitations due to physical health	80(70-85)	75(60-85)	80(65-85)	$\chi2$=1.13	p=0.57
Role limitations due to emotional problems	100(100-100)	100(100-100)	100(100-100)	$\chi2$=0.45	p=0.80
Energy/fatigue	75(65-80)	70(60-80)	73(55-80)	$\chi2$=3.2	p=0.20
Emotional well-being	84(73-92)	84(72-92)	80(72-88)	$\chi2$=4.4	p=0.11
Social Functioning	88(75-88)	88(63-88)	88(75-88)	$\chi2$=1.4	p=0.49
Pain	90(78-100)	90(68-100)	100(78-100)	$\chi2$=0.14	p=0.93
General health	70(55-75)	60(49-75)	65(50-74)	$\chi2$=0.47	p=0.10

Legend: Data are for one (1) or six (6) months.



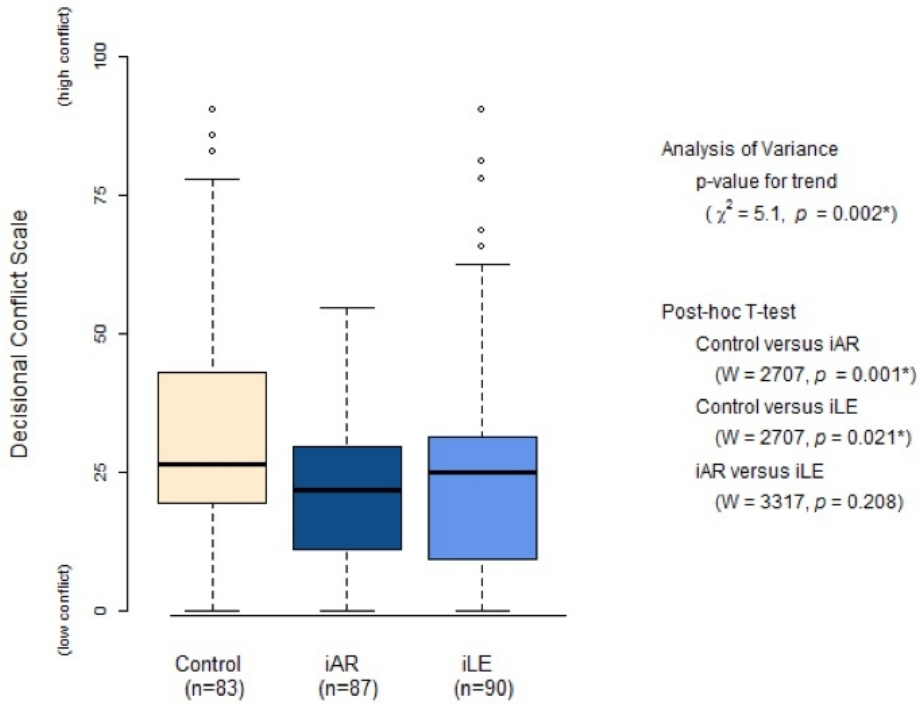


Figure2: DCS at 1 month and Kruskal-Wallace analysis of variance and pos-hoc Wilcoxon-rank sum t-test. Boxes denote the median (25th–75th percentiles). Whiskers denote the 25th percentile-1.5*(Inter-Quartile Range) and the 75th percentile + 1.5(Inter Quartile Range).

125x89mm (150 x 150 DPI)

Supplement

Supplement 1 (A, B, and C):

The following examples are for a 55-year-old non-smoking non-diabetic Dutch male, with a history of coronary heart disease systolic blood pressure of 140 mmHg, a total cholesterol of 6.0 mmol/L, a creatinine of 93 umol/L, and LDL-cholesterol of 3.4 mmol/L. The patient currently uses atorvastatin 40 mg. *Disclaimer: These examples are for a fictionalized, hypothetical patient and not based on any actual individual.*

Supplement 1A: Anonymous example of standard-care.

Cholesterol:

Prevention program findings

The concentration of cholesterol in your blood is elevated. An elevated cholesterol level can increase the atherosclerotic process, or the accumulation of cholesterol and other deposits in the walls of your blood vessels.

Advice from the vascular team:

You are already being treated with a cholesterol lowering medication. Yet, your cholesterol level is still elevated. We therefore recommend adjusting the dose of your cholesterol lowering medication or switching to different cholesterol lowering medication. Talk to your doctor about considering this switch.

You can find more information about cholesterol and other risk factors on the internet: www.cholesterol.nl, www.hartstichting.nl, www.voedingscentrum.nl and www.vaatcentrum.nl.

Supplement 1B: Example of a 'personal health profile' for a hypothetical patient in the individualized absolute risk arm. ***Disclaimer: This is a fictionalized, hypothetical patient***

My Personal Heath Profile

Part of the SMART-INFORM study

In this folder you will find your personal heath profile, which we have made as part of your participation in the SMART-INFORM study. Elements of your medical status were used to complete the profile.

VIDEOS MADE FOR YOU

In this envelope, you will find six short videos designed to give you a bit of background information about this health profile and cardiovascular disease in general. The six videos are:

1. What is cardiovascular disease?
2. What is cholesterol?
3. What does a statin do?
4. Do statins have side-effects?
5. How do I read my personal health profile
6. What now?

The videos have been loaded onto the USB-card you are receiving with this Health Profile. You can watch the videos by plugging the USB card into a computer.

PERSONAL HEALTH PROFILE

- Mr. J. Smith, 73 years old
- Type of cardiovascular disease: Heart
- You are a non-smoker
- Creatinine-level (Kidney function): 100 umol/L
- Blood pressure: 140 / 90 mmHg
- Prescribed statin: Simvastatin 40 mg
- Total cholesterol: 4.7 mmol/L
- You do not have diabetes
- You do not report having atrial fibrillation (a type of abnormal heart rhythm)
- You do not report having heart-failure

In order to calculate how statin medication effects your prognosis, we used the aspects of your profile listed above. We have based these aspects on the medical records on-file at the hospital.

2

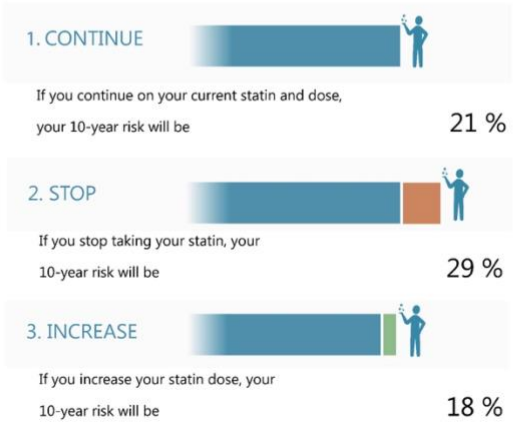
10-YEAR RISK

A 10-year risk estimates the chance that you will suffer a heart attack, stroke, or sudden death withi the next 10 years. We have estimated your 10-year risk in three different situations from which you can choose.

THREE SITUATIONS FROM WHICH TO CHOOSE

You can choose from the following three situations:

1. Continue with your current statin and dose, this is your current prognosis.
2. Stop taking your statin.
3. Increase your statin effectiveness by taking the highest dose of the strongest statin (atorvastatin 80mg).



3

QUESTIONS?

If you have any questions about the SMART-INFORM study you can contact the investigators. They can be reached on weekdays on 000 00 000 00.

WE WILL CONTACT YOU

Within a few weeks, a researcher will be in contact with you to answer any additional questions or provide additional explanation regarding the personal health profile.

UMC Utrecht

4

Supplement 1C: Example of a 'personal health profile' for a hypothetical patient in the individualized life-expectancy arm. ***Disclaimer: This is a fictionalized, hypothetical patient***

My Personal Heath Profile

Part of the SMART-INFORM study

In this folder you will find your personal heath profile, which we have made as part of your participation in the SMART-INFORM study. Elements of your medical status were used to complete the profile.

VIDEOS MADE FOR YOU

In this envelope, you will find six short videos designed to give you a bit of background information about this health profile and cardiovascular disease in general. The six videos are:

1. What is cardiovascular disease?
2. What is cholesterol?
3. What does a statin do?
4. Do statins have side-effects?
5. How do I read my personal health profile
6. What now?

The videos have been loaded onto the USB-card you are receiving with this Health Profile. You can watch the videos by plugging the USB card into a computer.

PERSONAL HEALTH PROFILE

- Mr. J. Smith, 73 years old
- Type of cardiovascular disease: Heart
- You are a non-smoker
- Creatinine-level (Kidney function) 100 umol/L
- Blood pressure 140 / 90 mmHg
- Prescribed statin Simvastatin 40 mg
- Total cholesterol 4.7 mmol/L
- You do not have diabetes
- You do not report having atrial fibrillation (a type of abnormal heart rhythm)
- You do not report having heart-failure

In order to calculate how statin medication effects your prognosis, we used the aspects of your profile listed above. We have based these aspects on the medical records on-file at the hospital.

2

DISEASE-FREE LIFE EXPECTANCY

The disease-free life-expectancy indicates how long you can expect to live without having a heart attack, stroke, or sudden death. We have estimated your disease-free life expectancy in three different situations from which you can choose.

THREE SITUATIONS FROM WHICH TO CHOOSE

You can choose from the following three situations:

1. Continue with your current statin and dose, this is your current prognosis.
2. Stop taking your statin.
3. Increase your statin effectiveness by taking the highest dose of the strongest statin (atorvastatin 80mg).

3

QUESTIONS?

If you have any questions about the SMART-INFORM study you can contact the investigators. They can be reached on weekdays on 000 00 000 00.

WE WILL CONTACT YOU

Within a few weeks, a researcher will be in contact with you to answer any additional questions or provide additional explanation regarding the personal health profile.

UMC Utrecht

4

Supplement 2: Telephone consultation

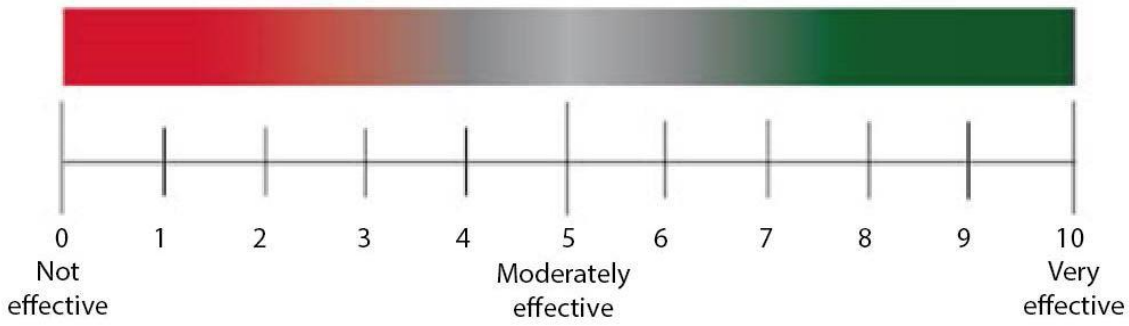
Short motivational telephone consultation following a structured interview asking the following questions:

- Did you receive the information?
- Have you been able to watch the videos?
- Did you understand all the information?
- Which questions did you have after studying the information?
- Did you already decide which statin treatment option you prefer?
- If yes, did you discuss this with your physician?

Supplement 3: Visual analogue scale

Estimation of therapy-effects

How great do you think the beneficial effects of your cholesterol lowering statin therapy are for you? Circle one number on the scale Below. A zero "0" means you believe that this medication is NOT effective for you and a ten "10" means you believe that is medication is VERY effective for you.



Supplement 4: Patient questionnaire to assess statin knowledge

What do you know about medication?

Below are a number of statements with answer choices. Please circle the answer choice which you believe is correct. If you do not know the correct answer, you can mark 'I don't know'

Where in the body can you get cardiovascular disease?

❒ heart ❒ legs ❒ both ❒ I don't know

Possible side-effects of statins is/are

❒ muscle pain ❒ breathing problems ❒ neither one ❒ I don't know

A high cholesterol gives a greater risk of

❒ stomach bleeds ❒ muscle or joint pain ❒ stroke/heart-attack ❒ I don't know

By using statins, I reduce my risk of

❒ stomach bleeds ❒ pneumonias ❒ heart-attacks ❒ I don't know

Due to the use of statins, the cholesterol levels in my blood will

❒ increase ❒ decrease ❒ stay the same ❒ I don't know

Through the use I statins, I reduce

❒ the fatty plaques in my arteries ❒ my blood pressure ❒ both ❒ I don't know

How long are people usually advised to use statins?

❒ for life ❒ 0-1 years ❒ 1-10 years ❒ I don't know

How does cholesterol get into to blood?

❒ My body produces cholesterol ❒ I get it from my food ❒ Both answers are correct ❒ I don't know

Supplement 5: Secondary outcomes score ranges

Scores on the IPQ range from 0 (non-threatening) to 80 (very threatening). Patient Activation Measure (PAM-13) scores range from 0 (low activation) to 100 (high activation). Perceived statin efficacy ranged from 0 (statins perceived as ineffective) to 10 (high level of statin effectiveness). The 9-item shared decision-making questionnaire ranged from 0 (poor shared decision-making) to 100 (optimal shared decision-making. BMQ Adherence Risk Scale ranged from 0 (no-self-reported non-adherence) to 4 (self-reported non-adherence). Understanding of statin-therapy ranges from 0 (no answer correct) to 100 (all answers correct). RAND Medical Outcomes Study Short Form Survey (SF-36) questionnaire ranges from 0 (low quality of life) to 100 (high quality of life).

Supplement 6: General practitioner questionnaire

	Definitely not (1)	Probably not (2)	Uncertain (3)	Probably yes (4)	Definitely yes (5)
1. How convinced are you that a statin is worthwhile for this patient?	□	□	□	□	□
2. Do you think the patient could benefit from a greater statin dose?	□	□	□	□	□
3. Would you consider statin discontinuation in this patient if the guidelines allowed?	□	□	□	□	□
The following three questions are only applicable if the patient was part of an intervention arm.					
4. How probable is it that you would use this information to aid in doctor-patient communication?	□	□	□	□	□
5. Do you think the consultation would be more efficient if you had this information beforehand?	□	□	□	□	□
6. Do you think this information would encourage therapy-adherence?	□	□	□	□	□

Legend: Questions 1-3 were asked of every GP. Questions 4-6 were additionally asked for physicians with patients randomized to the individualized absolute risk or the individualized life-expectancy groups.

Supplement table 1: Baseline characteristics per missing and non-missing for primary outcome

	Non-missing	Missing
Population	n=260	n=43
Age	66 (59 - 71)	63 (60 - 69)
Gender (male)	85%	84%
One CVD location	89%	91%
More than one CVD locations	9%	9%
Current smokers	13%	19%
Years clinically manifest CVD	1 (0 - 10)	0 (0 - 10)
Diabetes Mellitus	22%	19%
LDL-c (mmol/L)	2.0 (1.6 - 2.4)	1.9 (1.6 – 2.4)
LDL-c >1.8mmol/L	67%	52%
Creatinine (umol/L)	83 (75 - 94)	85 (79 - 97)
Systolic blood pressure (mmHg)	130 (121 - 142)	132 (119 - 146)
Number of medications per day	5 (4 - 8)	6 (4 - 8)
Months required to offset disutility of daily pill-taking	61 (6 - 97)	61 (11 - 97)
High likelihood limited literacy	7%	19%
Possibility of limited literacy	9%	12%
Adequate literacy	85%	70%
Bachelor or equivalent education	39%	37%

Legend: Data are reported as mean ± SD, median (interquartile range) or n (%). CVD locations defined as coronary artery disease, peripheral artery disease, or abdominal aortic aneurysm in addition to cerebrovascular disease. Health literacy based on the Newest Vital Sign baseline questionnaire.(32) Disutility derived from questionnaire based on an idealized medication(22) Number of medications excludes over the counter medications, (nasal) sprays, and topical medications.

Supplemental table 2: Physician reported secondary outcomes

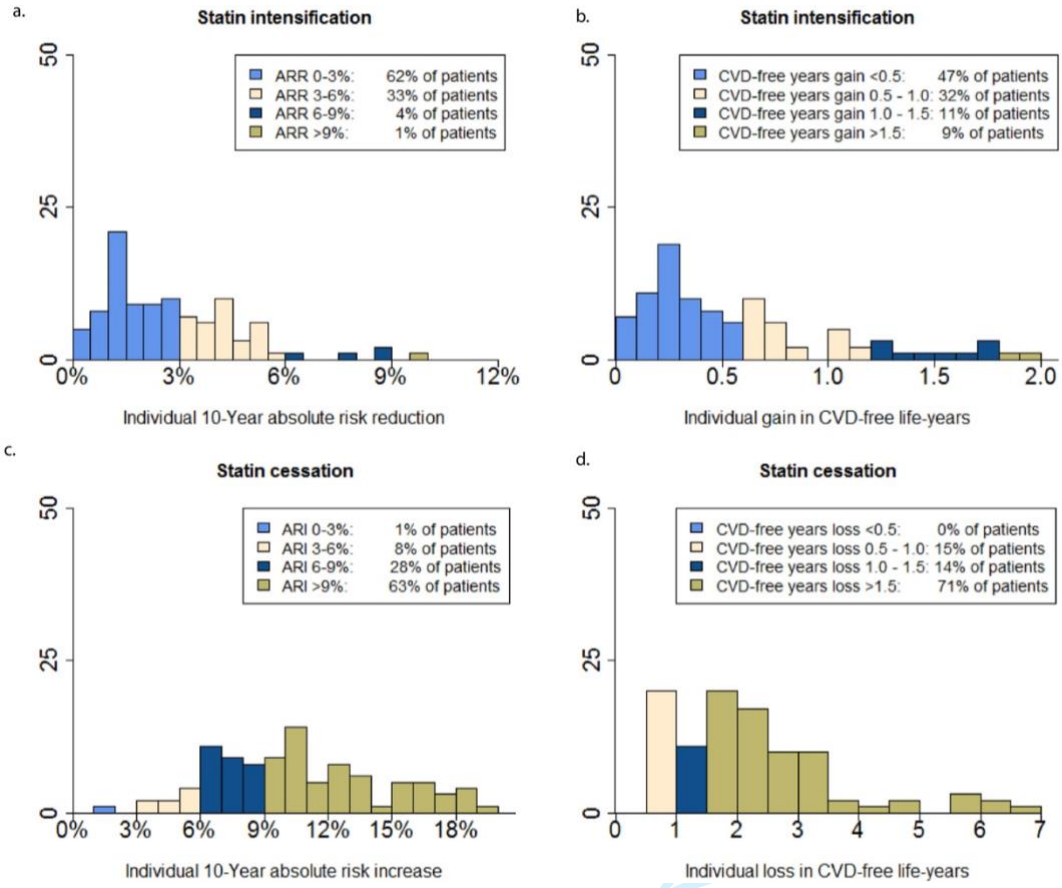
	Median (IQR)			Analysis of Variance	
	Control-group	iAR-group	iLE-group	Test-statistic	Two-sided p-value
Post-interventional LDL-c					
LDL-c values determined	n=55	n=43	n=43		
No LDL-c values determined	n=27	n=42	n=42		
Post-interventional LDL-c at 6 months	1.9 (1.6 - 2.3)	1.9 (1.4 - 2.3)	1.9 (1.5 - 2.4)	F=0.50	p=0.60
Physician opinion of intervention					
Approached	n=93	n=88	n=87		
Participated	n=51	n=48	n=42		
Convinced that a statin is worthwhile for the patient	5 (4-5)	5 (5-5)	5 (5-5)	$\chi2$=1.4	p=0.50
Believes patient could use a higher dose	3 (2-4)	3 (2-4)	3 (2-4)	$\chi2$=0.4	p=0.11
Would consider statin discontinuation if guidelines allowed	2 (1-3)	2 (1-4)	2 (1-4)	$\chi2$=0.3	p=0.84
How probable to use information†	N/A	4 (4-5)	4 (3-5)	w=978	p=0.84
Believes that consultation would be more efficient†	N/A	4 (3-5)	4 (3-5)	w=114	p=0.4
Believes that information would encourage therapy adherence†	N/A	4 (3-5)	4 (3-4)	w=1083	p=0.50

Legend: Data are reported as median (interquartile range) or n (%). †Only applicable for the intervention groups LDL-c=low-density lipoprotein cholesterol. Precise questions and answer choices are shown in supplement 6 "General Practitioner Questionnaire."

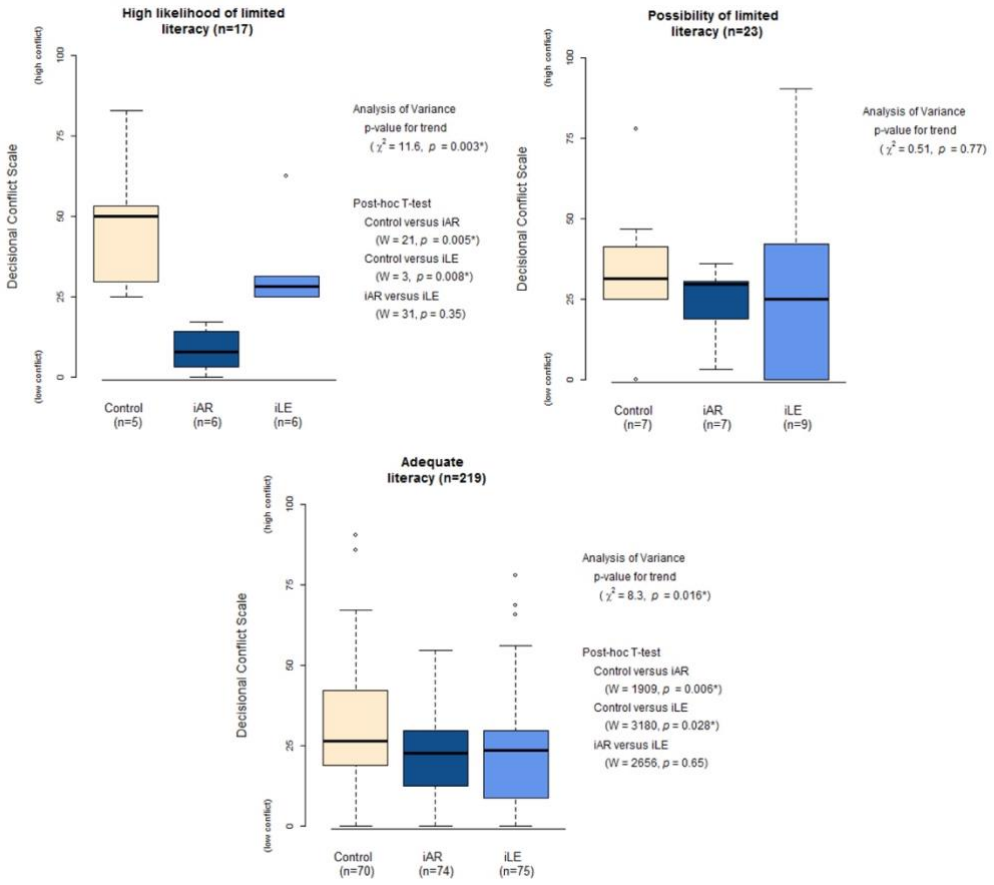
Supplemental table 3: Median DCS score per subgroup strata

	Control –group		iAR –group		iLE –group	
Gender (F=7.02, p-value for interaction=0.32)						
Men	29.7 (19.5 - 42.2)	n=71	23.4 (11.7 - 29.7)	n=72	25.0 (10.9 - 32.8)	n=77
Women	25.8 (21.0 - 47.7)	n=12	14.1 (10.2 - 25)	n=15	26.6 (9.4– 29.7)	n=13
Age (F=0.17, p-value for interaction=0.90)						
>65	19.0 (20.3 - 42.2)	n=45	18.8 (9.0 - 28.6)	n=44	25.0 (8.6 - 31.3)	n=42
≤65	30.0 (19.5 - 42.6)	n=38	23.5 (13.3 - 30.7)	n=43	25.0 (12.9 - 31.6)	n=48
Patient activation (F=1.4, p-value for interaction=0.40)						
Low	26.7 (14.8 - 39.1)	n=21	21.9 (3.1 - 25.0)	n=13	26.6 (24.2 - 49.2)	n=15
High	26.7 (25.2 - 42.2)	n=43	23.4 (12.5 - 30.7)	n=43	22.4 (4.7 - 29.7)	n=49
Years since first CVD-event (F=1.4, p-value for interaction=0.24)						
>1 year	29.7 (20.3 - 45.3)	n=33	23.4 (4.7 - 29.7)	n=43	25.0 (14.9 - 33.2)	n=52
≤1 year	26.7 (19.9 - 39.8)	n=50	21.0 (14.1 - 30.0)	n=44	23.5 (5.5 - 33.2)	n=38
Educational level (F=2.8, p-value for interaction=0.09)						
Low	28.1 (25.0 - 37.5)	n=14	6.3 (3.1 - 18.8)	n=17	14.1 (1.6 - 25.0)	n=15
Middle	29.7 (13.3 - 46.1)	n=35	25.0 (16.4 - 30.7)	n=40	25.0 (22.3 - 30.5)	n=38
High	26.6 (20.7 - 41.0)	n=34	21.9 (17.2 - 30.9)	n=30	25.0 (7.8 - 34.4)	n=37
Health literacy* (F=4.0, p-value for interaction=0.02)						
High likelihood limited literacy	50.0 (29.7 - 53.1)	n=5	7.8 (3.1 - 13.7)	n=6	28.1 (25.0 - 31.3)	n=6
Possibility limited literacy	31.2 (25.0 - 41.4)	n=7	29.7 (18.7 - 30.5)	n=7	25.0 (0.0 - 42.1)	n=9
Adequate literacy	26.6 (18.8 - 41.8)	n=70	22.7 (12.9 - 29.7)	n=74	23.4 (8.6 - 29.7)	n=75
Disutility (F=0.6, p-value for interaction=0.54)						
Low (<9 months)	26.6 (14.1 - 45.3)	n=23	18.8 (3.1 - 25.0)	n=25	22.7 (9.0 - 25.4)	n=24
Middle (9-97 months)	32.0 (23.4 - 44.5)	n=18	23.4 (20.7 - 28.5)	n=14	27.3 (14.8 - 41.8)	n=26
High (>97 months)	32.0 (25.0 - 43.0)	n=24	17.2 (3.1 - 29.7)	n=31	23.4 (0.39 - 35.0)	n=22

Legend: Data are reported as median (25^{th} – 75^{th} percentile. *Further analyses for health-literacy are shown in supplemental figure 2. Patient activation level based on summary scores of the Patient Activation Measure.(16) Health literacy based on the Newest Vital Sign.(32) Due to limitations free for academic use licenses, patient activation (PAM) was only used for the last 213 participants in the study.



Supplemental Figure 1: Therapy-benefit from statin intensification to atorvastatin 80mg for a) iAR arm and b) iLE arm. Loss of benefit from statin discontinuation in c) iAR arm and d) iLE arm. In the iAR group, the median baseline 10-year absolute CVD risk was 37.6% (28.1-49.0). The estimated absolute 10-year risk change was -2.4% (-1.2 to -3.9) after intensification and 10.2% (7.7- 13.5) after discontinuation. In the iLE group, the median CVD-free life-expectancy was 75.4 years (73.0-82.7). The median change in CVD-free life-years was 0.5 years (0.3 – 0.8) after intensification and -2.0 years (- 1.3 - - 2.8) after discontinuation.



Supplemental figure 2: Subgroup analysis. Box-and-whisker plot depict the decisional conflict score at one month stratified by baseline health literacy. The colored boxes denote the median (25th – 75th percentiles). Whiskers denote the 25th percentile-1.5*(Inter-Quartile Range) and the 75th percentile + 1.5(Inter Quartile Range) in whiskers.

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	Page 1, line 6
Authors *	Contact details for the corresponding author	Page 1 line 38
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	Page 6, line 27
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	Page 5, line 60
Interventions	Interventions intended for each group	Page 7, line 13 and 26
Objective	Specific objective or hypothesis	Page 5, line 46
Outcome	Clearly defined primary outcome for this report	Page 8, line 36
Randomization	How participants were allocated to interventions	Page 6, line 38
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	Page 6, line 29
Results		
Numbers randomized	Number of participants randomized to each group	Page 10, line 39 & fig. 1
Recruitment	Trial status	Page 10, line 39
Numbers analysed	Number of participants analysed in each group	Fig 1
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	Page 11, line 3 & Fig 2
Harms	Important adverse events or side effects	None
Conclusions	General interpretation of the results	Page 15, line 19
Trial registration	Registration number and name of trial register	Page 3, line 17
Funding	Source of funding	Page 15, line 51

**this item is specific to conference abstracts*

BMJ Open

Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial.

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Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial.

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Abstract

Objective: To determine whether communicating personalized statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use among patients with stable cardiovascular disease (CVD) compared to standard (non-personalized) effects.

Design: Hypothesis-blinded, three-armed randomized controlled trial

Setting and participants: 303 statin-users with stable CVD enrolled in a cohort

Intervention: Participants were randomized in a 1:1:1 ratio to standard (non-personalized) practice (control-group) or one of two intervention arms. Intervention arms received standard practice plus 1) a *personalized health profile*, 2) educational videos, and 3) a structured telephone consultation. Intervention arms received personalized estimates of prognostic changes associated with both discontinuation of current statin and intensification to the most potent statin type and dose (i.e. atorvastatin 80 mg). Intervention arms differed in how these changes were expressed: either change in 10-year absolute CVD risk (iAR-group) or CVD-free life-expectancy (iLE-group) calculated with the SMART-REACH model (http://U-Prevent.com).

Outcome: Primary outcome was patient decisional conflict score (DCS) after one-month. The score varies from 0 (no conflict) to 100 (high conflict). Secondary outcomes were collected at one or six months: DCS, quality of life, illness perception, patient activation, patient perception of statin efficacy and shared decision-making, self-reported statin adherence, understanding of statin-therapy, post-randomization low-density lipoprotein cholesterol (LDL-c) level, and physician opinion of the intervention. Outcomes are reported as median (25^{th} – 75^{th} percentile).

Results: Decisional conflict differed between the intervention arms: median control 27 (20-43), iAR-group 22 (11-30; p-value versus control 0.002), and iLE-group 25 (10–31; p-value versus control 0.02). No differences in secondary outcomes were observed.

Conclusion: In patients with clinically manifest CVD, providing personalized estimations of treatment-effects resulted in a small but significantly lower decisional conflict after one month. The results support the use of personalized predictions for supporting decision-making.

Registration: Netherlands Trial Registry (Identifier NTR6227/NL6080)

Strengths and limitations of the study

- Patients were provided with estimations of their personalized causal therapy-effects, unlike many previous studies which used hypothetical therapy-effects.
- Performance bias was limited by hypothesis blinding.
- The decisional-conflict was low and the belief in the effectivity of statin medications was high in the control group, possibly underestimating the effect compared to the general population.
- The personalized effects were not used directly during a clinical consultation, but provided prior to any potential consultation with a physician.
- Some questionnaires were created for this study and were not externally validated.

Introduction

Several online tools have recently become available which can calculate the personalized therapy effects for various cardiovascular disease (CVD) prevention strategies. Such calculators often express the therapy-benefit in terms absolute 10-year CVD risk reduction, and most recently, in terms of gain in healthy life-expectancy.(1)

The use of decision tools is associated with increased knowledge and less decisional conflict, and providing patients with information regarding therapy increases patient participation in medical decision-making.(1-5) In general, decision aids do not provide personalized benefits and harms. (6) Most investigated patient decision-aids use hypothetical or non-personal, population-based effects of CVD-prevention, and not the actual, personalized causal effects an individual can expect from CVD-prevention. However, patients often desire a far greater therapy-benefit than can be expected from preventive therapy.(7-9) One survey showed that patients desire increase in life-expectancy of around 42 months from life-long statin-use(7) whereas the actual benefit is often less than half this amount.(8) Being presented with an actual predicted benefit of a therapy far smaller than the benefit desired beforehand might discourage patients from using medication. Moreover, metrics to used communicate therapy-effects elicit different opinions on the value of preventive therapy, motivation to use therapy, and possibly therapy-adherence.(10-13)

We conducted a hypothesis blinded, three-armed, randomized controlled trial (RCT) to determine whether communication strategies involving personalized therapy-effects of statin therapy obtained by algorithm, expressed as change in CVD-free life-expectancy or absolute 10-year CVD-risk reduction, lead to improved decisional certainty about the use of statins compared to standard communication strategies and compared to one another.

Methods

Population

The SMART-Inform study was nested within the previously described Secondary Manifestations of ARTerial disease (SMART) study, an ongoing, single-center, prospective cohort of patients referred to the University Medical Center Utrecht in the Netherlands for CVD screening. (14) All patients invited to participate in a SMART-examination were telephonically informed of the SMART-Inform sub-study and sent further information about the sub-study by mail. Additional inclusion criteria for the SMART-Inform study were current statin use, being between 45-80 years old, having CVD (i.e. coronary artery disease, cerebrovascular disease, and peripheral artery disease and abdominal aortic aneurysm). Additional exclusion criteria for the SMART-Inform was terminal malignancy and not returning the baseline questionnaires.

Design, blinding, and randomization

The SMART-Inform study was a three-armed, hypothesis-blinded, RCT. Hypothesis blinding means patients and their general practitioners were informed that everyone would receive at least standard SMART-protocol practice and that the study goal was to investigate if information about cholesterol-lowering medications would impact motivation for use, but were unaware whether the content they received was part of the active or control arms and were unaware what the primary and secondary outcomes were. Researchers and outcome assessors were not blinded. A computer generated random allocation sequence was used to assign each patient after inclusion, by order of inclusion. The investigator generating the random sequence was not involved in other aspects of the study. All other investigators had no access to the sequence.

Ethics Statement and Registration

The Medical Ethics Review Committee of the UMCU approved the study (16-665/D). All participants provided written informed consent. The study was registered in the Netherlands Trial Registry (Identifier NTR6227 and NL6080).

Patient and public involvement

The study design and goal was discussed at an open conference of patient-organizations held in Amstelveen, the Netherlands in April 2016 to gain and incorporate input from patients at an early stage.

Description of standard practice

All participants received cardiovascular care as usually delivered by their own referring general practitioner or medical specialist plus written information consisting of general lifestyle advice based on which treatment targets recommended by the European Society of Cardiology (15). (supplement 1A).

Description of intervention arms

There were three intervention arms: the control group, the 10-year risk (iAR-group) and CVD-free life-expectancy (iLE-group). The control group received only standard practice. Both intervention arms received standard practice plus: 1) a leaflet entitled *personalized health profile* (supplement 1B and 1C for two fictional patients); 2) a USB device containing educational videos; 3) a structured telephone consultation enforcing uptake of the information (supplement 2). The *'personal health profile'* outlined the individual effect of the following treatment options: 1) continue with the type and dose of statin-therapy ('current prognosis'); 2) discontinue statin therapy ('stop statins'); 3) intensify to maximum statin-therapy, defined as once-daily atorvastatin 80 mg ('increase statins'). The only difference between the

intervention arms was the measure used to communicate the prognostic change associated with the therapy-effects, individual treatment effects were estimated in terms of change in 10-year risk (iAR-group) or CVD-free life-expectancy (iLE-group). The USB-device contained intervention-group specific educational videos on how to read and interpret the *'personal health profile'* and the effect of statin-medications on CVD. The structured telephone consultation for the intervention arms ensured the information was well-received and understood by the patients. Within the SMART-study, patients are encouraged to visit a treating physician to discuss the results and decide whether or not to change their statin prescription. Participants are free to decide whether they want to follow-up on this advice. No extra face-to-face contact after receiving the intervention was incorporated into the SMART-Inform sub-study; however as the information was not designed to replace a physician's advice, all patients were additionally encouraged to visit their general practitioner within two weeks to discuss the SMART-Inform study information. Follow-up questionnaires were sent by mail one and six months post-intervention, with telephone reminders ensuing after two weeks if the questionnaires were not returned.

Predicted therapy-effects

The estimations in the *'personal health profile'* were obtained with the SMART-REACH score, an internationally validated model predicting the personalized effects of secondary CVD-prevention for patients aged 45-80 years (http://U-Prevent.com).(2) The model combines hazard ratio's derived from meta-analyses with a prediction algorithm incorporating individual patient characteristics to derive the personalized therapy effects. A 1 mmol/L reduction in LDL-c was modelled to correspond to the CVD-specific hazard ratio of 0.80 (16) and the expected LDL-c -reduction for each statin was derived from a previous meta-analysis.(17) As far as statins concerned, subgroup analyses in literature provide no

evidence for relevant differences on a relative effect scale. Therefore, personalized treatment effect estimates based on the SMART-REACH score are only different on an absolute effect scale. Supplemental figure 1 shows the distribution of the predicted therapy-effects for the trial patients.

Primary outcome

The study's primary outcome was the intergroup difference in experienced decisional conflict at 1 month regarding the decision to continue, discontinue, or intensify statin therapy. Decisional conflict was measured using the Decisional Conflict Scale (DCS), a validated, translated, measure of patient perception of uncertainty in choosing between options.(18, 19) The DCS consists of 16 statements pertaining to the decision to use statins as prescribed (e.g., "I am clear about which benefits matter most to me"). The DCS scale measures the amount of internal conflict a patient feels regarding a medical decision. Summary scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). Scores >37.5 are associated with feeling unsure about implementation of the decision, possibly leading to discontinuation of the chosen option or fretting about the chosen option (i.e. using statins as prescribed by the physician), and <25 are associated with following through with a decision. To limit loss to follow-up, patients who did not initially respond to the follow-up questionnaire were approached telephonically and a reminder sent by mail if the patient could not be contacted.

Patient reported secondary outcomes

Secondary outcomes at 6 months included the DCS, and quality of life measured using the eight subscales of the RAND Medical Outcomes Study Short Form Survey (SF-36).(20) Other patient-reported secondary outcomes were reported at both 1 and 6 months. The Brief

Illness Perception Questionnaire (brief IPQ)(21) was used to measure the degree to which CVD was considered threatening by patients. A Visual Analog Scale (VAS) was used to measure how effective patients perceived statin therapy (supplement 3). The thirteen question Patient Activation Measure (PAM-13) (22) was used to assess patient knowledge, skills, and confidence for self-management of health. Due to limitations on maximum population size of academic use licenses, PAM-13 was only used for the last 213 study participants. Patient's perception of shared decision-making was measured with the Shared Decision Making Questionnaire (SDMQ-9). Self-reported statin adherence was determined with the 2003 Brief Medication Questionnaire (BMQ).(23) Patient understanding of statin-therapy was measured with a questionnaire developed for the trial (supplement 4). The possible numeric ranges and interpretation of the secondary outcomes are shown in supplement 5.

Physician reported secondary outcomes

General practitioners (GPs) received a copy of the personalized health profile received by their patients. Upon enrolment of the first patient from their practice, GPs were provided a short telephonic explanation of the study and asked to fill in a questionnaire (supplement 6). Questionnaire results and the last known post-intervention LDL-value at 6 months were secondary outcomes. Interviewed GP's were blinded to study outcomes and treatment arm differences. GPs were interviewed and questioned after being sent the intervention material of their first included patient. GP's were not approached if they had subsequent patients included in the study, as receiving material from multiple patients would have unblinded them to treatment arm differences.

Statistical analyses

We used a T-test for the sample size as the primary analysis of this trial compared the two intervention with the control group. Calculations were conducted using G*Power version 3.1. Sample size was based on an effect size (Cohen's d = mean difference / standard deviation) of 0.43, a standard deviation of 0.80 to detect a mean difference of 0.34 on the 5-point scale (ranging from 0-4) corresponding to 8.6 on the 100-point scale.(24, 25) A power of 80% and a two-tailed alpha of 0.05 was used. A minimum of 86 patients per arm was needed.

An intention-to treat-analysis was performed. Differences among the three arms were detected with ANOVA, or a Kruskal-Wallis one-way ANOVA to deal with heteroscedasticity. Assumptions of normal (residual) distribution and homoscedasticity were visually inspected. If ANOVA $p<0.05$, pairwise comparisons between arms were determined using a t-test or with the Wilcoxon-rank sum test for the difference in ranked means if ANOVA assumptions were not met after transformation attempts. Analyses were performed using R-Statistical Software, V 1.0.14.

Subgroups

Pre-specified subgroup analyses were performed using an ANCOVA test to investigate whether the effect of the intervention on DCS at one month differed according to the following: gender; age (<65 versus >65); years since first CVD event (<1 versus >1 years); educational level (low, medium or high (26)); low versus high patient activation (low a PAM-13 level of 1-2 and high a PAM-13 level of 3-4 based on a conversion of the 100-point PAM-13 score to a 4-point scale (22, 27); health literacy categories based on the Dutch version of the Newest Vital Sign (NVS) (28); and disutility defined as the minimum gain in life-expectancy desired to offset the inconvenience of taking a lifelong, hypothetical, idealised daily tablet.(8) The study was not powered to detect any subgroup differences. A Bonferroni

correction corresponding to the 22 secondary outcomes was applied. The new p-value for statistical significance was 0.002.

Sensitivity analyses

Sensitivity analyses were performed to account for baseline characteristics possibly differing in missing outcomes between trial arms by conducting an ANCOVA with gender, age, smoking status, diabetes status, LDL-cholesterol (mmol/L), creatinine (umol/L), disutility score, NVS health literacy, and number of medications used daily.

Results

Participant flow

Between March 2017 and August 2018, 303 participants were enrolled. Baseline characteristics are shown in table 1 and the flow of participants throughout the trial in figure 1. The primary outcome was collected in 260 participants (86%) (control=83, iAR group=87, iLE group=90). Supplemental table 1 displays characteristics for those with and without the primary endpoint. At one-month, 12% (n=10) of control, 8% (n=7) of iAR, and 11% (n=9) of iLE patients reported increasing their statin dose after the intervention. Respective numbers for decreased statin dose were 2% (n=2) in the control arm, 1% (n=1) in the iAR arm, and 3% (n=3) in the iLE arm.

DCS at one month

There was a significant difference between the groups (ANOVA χ^2, p=0.002) with a median (25^{th}-75^{th} percentile) DCS of 27 (20–43) for control arm, 22 (11–30) for the iAR arm, and 25 (10–31) for iLE arm. Subsequent Wilcoxon-rank sum tests showed the difference between

the control and iAR arm (W=2707, p=0.001) and the control and iLE arm (W=4219, p=0.02) to be significant. The difference between iAR and iLE arms was not significant (W=3317, p=0.21, Figure 2). All groups showed a DCS of around 25, the value associated with following through with a decision.

Patient reported secondary outcomes

After 6 months, there was no longer a significant difference between the groups in de DCS score (ANOVA χ^2, p=0.10) with a median (25^{th}-75^{th} percentile) DCS of 25 (16–38) for control arm, 22 (9–29) for the iAR arm, and 25 (7–29) for iLE arm. All other secondary outcomes also showed no intergroup differences. There was no difference in how threatening patients perceived their CVD (Brief-IPQ) or how effective patients perceived statin medications (VAS 8) at either 1 or 6 months. There was no difference in PAM, understanding of statin effects, self-reported adherence (BMQ Adherence Scale), or patients' perceptions of shared-decision making between arms (SDMQ9). At six months, quality of life did not differ on any RAND SF-36 subscale (table 2).

Physician reported secondary outcomes

Physician reported secondary outcomes are shown in supplemental table 2. Between randomization and 6 months, 119 patients had their LDL-c values determined (control n=51, iAR n=48, iLE=39), with no difference in median serum LDL-c levels found (median 1.9 mmol/L in all groups) between study-arms. In total, 267 physicians were approached after the inclusion of their first patient of which 141 (53%) participated in the questionnaire. Physicians viewed statin-medication as equally worthwhile for patients in all study-arms. There was no difference of opinion between how iAR and iLE formats could positively influence doctor-patient communication, consultation efficiency, and therapy-adherence.

Subgroup analysis

No evidence of subgroup effects was found for sex (p-values for interaction =0.32), age (p=0.90), years since first CVD-event (p=0.24), number of months gain in CVD-free life-expectancy desired prior to taking an idealized medication daily (i.e. disutility, p=0.54), and educational level (p=0.09). An interaction was found for health literacy (p = 0.02). The median (25^{th}-75^{th} percentile) DCS scores for all subgroups are shown in supplemental table 3, and a t-test for differences in each health literacy group is shown in supplemental figure 2. Across health literacy categories, decisional conflict was lowest in the in intervention arms than in the control arms, with the largest difference between control and intervention arms found in people with a low health literacy.

Sensitivity analyses

Supplemental table 4 shows the sensitivity analyses which corrected for baseline characteristics. After correction none of the outcomes were significant.

Discussion

Providing personalized estimates of the prognostic changes associated with statin use in terms of 10-year CVD risk and CVD-free life-years (compared to a control group) resulted in lower decisional conflict associated with statin use measures after one month. After six months no differences were found. Likewise, no group differences were found in secondary outcomes, which included the degree to which people perceived their CVD to be threatening, how effective patients viewed their statin-medications, or LDL-c levels after six months. The actual benefit from CVD-prevention is smaller than people initially report acceptable. Still, openly communicating the individual estimated of statin use on the prevention of CVD resulted in lower decisional conflict, without may people discontinuing their treatments. However, the effect was small in a population with a low baseline DCS.

Many tools designed for decision-support report DCS differences of 8-10 points immediately post intervention in favour of the decision-aid.(6) We measured the outcomes after one month to provide time for patients to visit their physician. The already low decisional conflict in the control arm, may explain the relatively small absolute differences in median scores found in this study (2-5 points). The gradual loss of statistical significance, seen at six months, is in line with previous studies investigating the long-term effects of decision-support tools of for statin medications indicating that positive results of such interventions fade over time. (29)

The use of patient communication-aids is known to make people feel better informed and to help them form accurate opinions of therapy benefit-harm ratios.(6, 30) A number of studies have examined the effect of providing estimations of hypothetical or generalised therapy-benefit to patients with clinically manifest CVD.(11, 31-33) One study examined the effect of providing primary care patients without any prior statin-exposure, with the approximated personalized effect of statin medications.(12) Absolute risk reduction estimates resulted in a greater likelihood to redeem statin-medications compared to patients who had received the predictions in terms of prolongation of life. However, there were no differences in patient satisfaction and confidence in decision. Patients already using medication may respond differently to personalized estimations than patients initiating a new medication. Willingness to take a new therapy may be more sensitive to the perceived side-effects than to the perceived benefits.(34) Similarly, worry about side-effects is a stronger determinant of intentional non-adherence than belief in the effectiveness of statin-medications(35). As opposed to first-time statin-users, all patients in our study had already been using statins, and may therefore already know if they have experienced statin-related side-effects.

Similar to our study, previous literature shows that patients often overestimate the relative effects of medication and desire a greater absolute therapy-benefit than clinically feasible.(7,

8) Although the majority of patients in our study indeed desired more benefit than clinically feasible (median disutility score 61 months), statin discontinuation was minimal and there was no evidence of subgroup effects based on baseline disutility. Although physicians may also over-estimate the effects of preventive therapy,(7) there were no inter-groups differences in how physicians perceived the necessity of statin-medications.

Strengths of this study include providing patients with estimations of their actual causal therapy-effects, in contrast to pre-existing decision aids which presented participants with either hypothetical or population-based therapy-effects. As we assessed current statin users, we were able to provide information on multiple treatment-options. Systematically approaching cohort patients who were due to receive physical examinations during a certain time-frame minimized the risk of preferentially selecting patients likely to respond to personalized predictions. Use of the cohort's standard procedures also allowed for a structured and well-defined control group, and via the use of structured telephonic consultations it was ensured patients had each interventional format explained in a similar fashion. Performance bias was limited by hypothesis blinding. A number of study limitations should be highlighted. First, in the control group of this clinically stable cohort population, decisional-conflict was low and the belief in the effectivity of statin medications was high. The effects described here may thus be different in patients who experience adverse effects during statin therapy or consider starting more intensive preventive treatment options on top of standard statin treatment, e.g. intensive blood pressure reduction or antithrombotic treatment. Moreover, the personalized effects were not used directly during a clinical consultation, but provided prior to any potential consultation with a physician, and the effects may be different compared to a population of patients who are involved in a clinical consultation in which statin therapy is discussed. Second, the loss to follow-up was 14% for the primary outcome. This is however lower than other communication-trials involving

follow-up questionnaires(12) and baseline characteristics of missing and non-missing individuals were relatively similar. Correction for baseline health literacy, a characteristic which may have differed between missing and non-missing individuals did not level-off the effects. Third, in particular for questions relating to drug-adherence, self-reported measures may be subject to recall and reporting biases. Fourth, a number of questionnaires were created specific for this study, and were thus not externally validated.

A number of risk-prediction tools capable of estimating treatment-effects for lipid-lowering, blood pressure-lowering, and anti-thrombotic medications are now readily available in clinical practice for patients with and without CVD.(1) Statins are usually prescribed to patients with CVD during hospital admission for the first CVD event. Outpatient decision-making regarding statins in this population usually pertain to continuing or altering the current statin dose. In the present study, we aimed to examine a setting closely resembling the outpatient practice. The present study showed only a small effect in patients with a low baseline DCS. Therefore future studies could focus on populations with higher baseline decisional conflict such as patients experiencing adverse effects or considering more intensive preventive treatment options on top of standard treatment such as intensive blood pressure reduction or combination antithrombotic treatment.

In conclusion, in patients with clinically manifest CVD advised to use statin medications, providing personalized estimations of treatment-effects, both in terms of 10-year absolute risk and CVD-free life-expectancy resulted in small but significantly lower decisional conflict associated with statin use after one month follow-up. This effect of the intervention had disappeared after 6 months follow-up. The results support the use of personalized predictions of absolute therapy benefit in clinical practice. Future studies may focus on decisions associated with higher decisional conflict such as the addition of more intensive preventive treatment options on top of standard treatment.

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Conflict of interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests."

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author Contributor statement

NEMJ, FLJV, YdG, OCD, CB, JAND contributed to the conception, design of the work and interpretation of the data, YMS & GEHMR contributed to the interpretation. NEMJ drafted the work and performed the analyses, FLJV, YdG, OCD, CB, JAND, YMS & GEHMR

critically revised the work, all authors gave final approval and agree to be accountable for the work.

Data sharing statement

Some individual deidentified participant data (including data dictionaries) may be shared upon reasonable request pending approval by the department and institution on a case-by-case basis. Approval will be based the scientific question to be answered with the data, ability of the authors of this manuscript to co-operate on the project, and compliance with contracts acquired for the questionnaires in this study and hospital and SMART-cohort policy.

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Figure Legends:

Figure 1: Participant flow during the trial

Figure 2: DCS at 1 month and Kruskal-Wallis analysis of variance and pos-hoc Wilcoxon-rank sum t-test. Boxes denote the median (25^{th}–75^{th} percentiles). Whiskers denote the 25^{th} percentile-1.5*(Inter-Quartile Range) and the 75^{th} percentile + 1.5(Inter Quartile Range).

Tables:

Table 1: Baseline characteristics

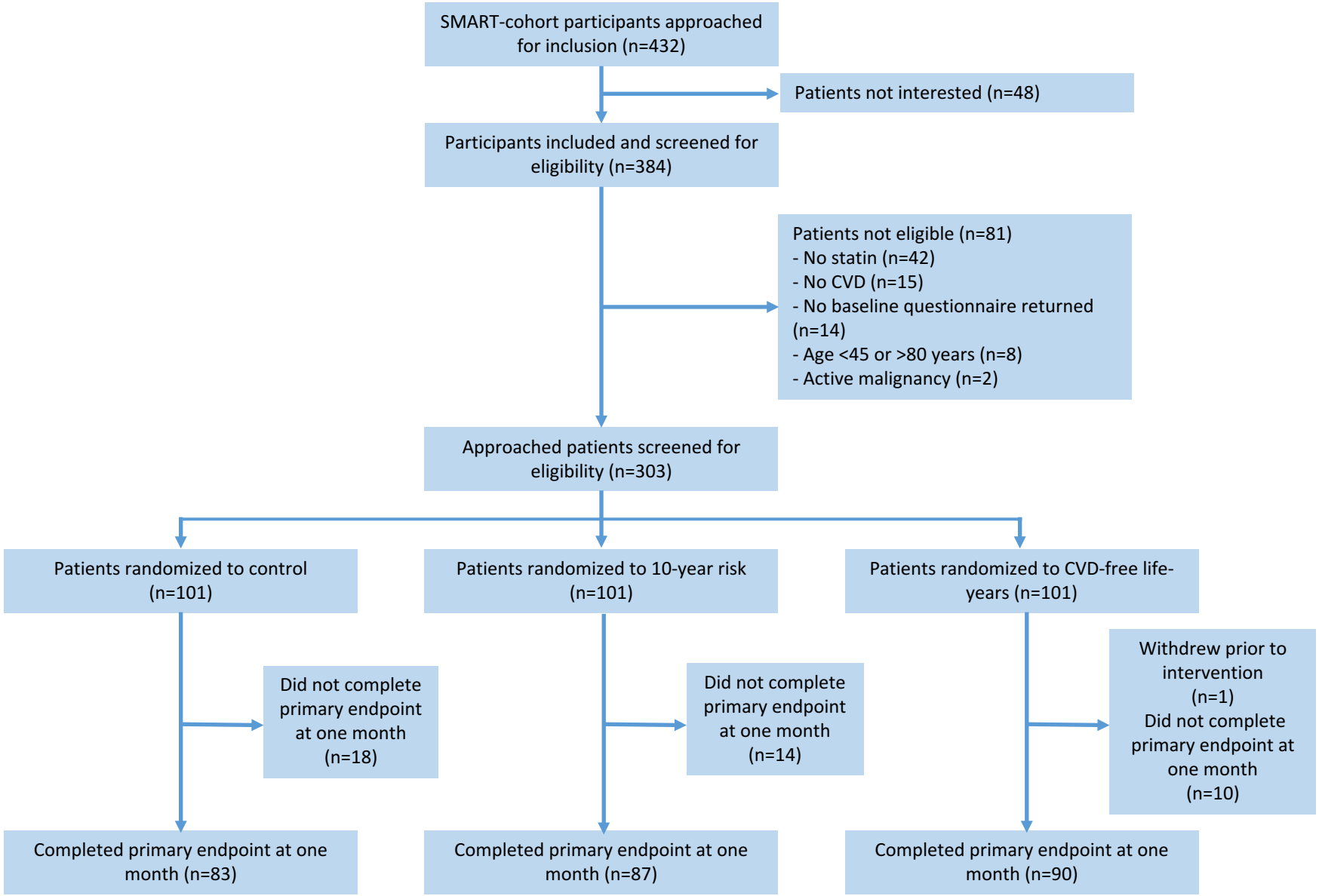
	Control-group	iAR-group	iLE-group
	n=101	n=101	n=101
Age	66(59-70)	66(58-71)	64(59-71)
Gender (male)	86%	82%	85%
More than one CVD location	11%	10%	10%
Current Smoker	17%	16%	9%
Years clinically manifest CVD	0(0-10)	0(0-10)	3(0-10)
Diabetes Mellitus	14%	27%	23%
LDL-cholesterol (mmol/L)	2.0(1.7-2.4)	2.0(1.6-2.4)	2.0(1.6-2.5)
LDL-cholesterol > 1.8 mmol/L	65%	67%	60%
Already on maximum statin therapy	1.3%	1.0%	1.0%
Creatinin (umol/L)	84(78-93)	83(75-96)	85(75-94)
Systolic blood pressure (mmHg)	131(121-142)	131(121-143)	129(122-142)
Number of medications per day	5(4-6)	6(4-9)	6(4-8)
Disutility score	61(9-97)	61(5-97)	61(9-97)
Adequate health literacy	83%	83%	81%

Legend: Data are reported as mean ± SD, median (interquartile range) or (%). CVD locations defined as coronary artery disease, peripheral artery disease, or abdominal aortic aneurysm in addition to cerebrovascular disease. Health literacy was based on the Newest Vital Sign score in the baseline questionnaire(28). Disutility is months required to offset inconvenience of daily pill-taking of an idealized medication.(8) Number of medications excludes over the counter medications, (nasal) sprays, and topical medications. Maximum therapy was atorvastatin 80 mg.

Table 2: Patient Reported Secondary Outcomes

	Median (25th-75th percentile)			
	Control-group	iAR-group	iLE-group	p-value
DCS (6)	25(16-38)	22(9-29)	25(7-31)	p=0.10*
Brief-IPQ (1)	36(26-42)	34(28-44)	37(30-42)	p=0.68
Brief-IPQ (6)	34(26-43)	35(30-41)	37(29-44)	p=0.19
PAM (1)	60(51-70)	58(53-68)	63(56-75)	p=0.20
PAM (6)	64(54-77)	63(56-77)	63(56-78)	p=0.48
Perceived Statin Efficacy (1)	8(7-9)	8(7-9)	8(7-9)	p=0.92*
Perceived Statin Efficacy (6)	8(7-9)	8(7-9)	8(7-9)	p=0.98*
Understanding of therapy-effects (1)	88(75-88)	88(75-100)	88(75-100)	p=0.07*
Understanding of therapy-effects (6)	88(75-100)	88(75-100)	88(63-100)	p=0.60*
BMQ Adherence Risk Scale (1)	1(0-1)	1(0-1)	1(0-1)	p=0.60*
BMQ Adherence Risk Scale (6)	1(0-1)	1(0-1)	1(0-1)	p=0.41*
SDMQ9 (1); Reported visiting GP (n)	44(9-69); (46)	42(18-62);	58(22-76); (55)	p=0.40*
SDMQ9 (6); reported visiting GP (n)	44(24-73); (60)	48(32-63);	62(22-84); (47)	p=0.28*
RAND-36 Quality of life (6)				
Physical functioning	80(70-85)	75(60-85)	80(65-85)	p=0.11*
Role limitations due to physical health	80(70-85)	75(60-85)	80(65-85)	p=0.57*
Role limitations due to emotional problems	100(100-100)	100(100-100)	100(100-100)	p=0.80*
Energy/fatigue	75(65-80)	70(60-80)	73(55-80)	p=0.20*
Emotional well-being	84(73-92)	84(72-92)	80(72-88)	p=0.11*
Social Functioning	88(75-88)	88(63-88)	88(75-88)	p=0.49*
Pain	90(78-100)	90(68-100)	100(78-100)	p=0.93*
General health	70(55-75)	60(49-75)	65(50-74)	p=0.10*

Legend: Data are for one (1) or six (6) months. Bonferroni p-value for significance was 0.002. * Denotes a non-parametric test was applied.


SMART-cohort participants approached for inclusion (n=432)
Patients not interested (n=48)
Participants included and screened for eligibility (n=384)
Patients not eligible (n=81)
- No statin (n=42)
- No CVD (n=15)
- No baseline questionnaire returned (n=14)
- Age <45 or >80 years (n=8)
- Active malignancy (n=2)
Approached patients screened for eligibility (n=303)
Patients randomized to control (n=101)
Patients randomized to 10-year risk (n=101)
Patients randomized to CVD-free life-years (n=101)
Did not complete primary endpoint at one month (n=18)
Did not complete primary endpoint at one month (n=14)
Withdrew prior to intervention (n=1)
Did not complete primary endpoint at one month (n=10)
Completed primary endpoint at one month (n=83)
Completed primary endpoint at one month (n=87)
Completed primary endpoint at one month (n=90)

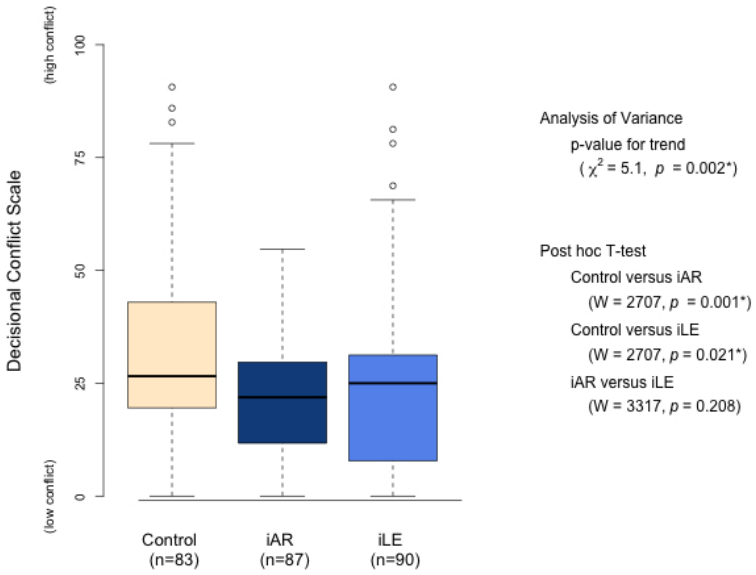


Figure 2

268x169mm (72 x 72 DPI)

Supplement

Supplement 1 (A, B, and C):

The following examples are for a 55-year-old non-smoking non-diabetic Dutch male, with a history of coronary heart disease systolic blood pressure of 140 mmHg, a total cholesterol of 6.0 mmol/L, a creatinine of 93 umol/L, and LDL-cholesterol of 3.4 mmol/L. The patient currently uses atorvastatin 40 mg. *Disclaimer: These examples are for a fictionalized, hypothetical patient and not based on any actual individual.*

Supplement 1A: Anonymous example of standard-care.

Cholesterol:

Prevention program findings

The concentration of cholesterol in your blood is elevated. An elevated cholesterol level can increase the atherosclerotic process, or the accumulation of cholesterol and other deposits in the walls of your blood vessels.

Advice from the vascular team:

You are already being treated with a cholesterol lowering medication. Yet, your cholesterol level is still elevated. We therefore recommend adjusting the dose of your cholesterol lowering medication or switching to different cholesterol lowering medication. Talk to your doctor about considering this switch.

You can find more information about cholesterol and other risk factors on the internet: www.cholesterol.nl, www.hartstichting.nl, www.voedingscentrum.nl and www.vaatcentrum.nl.

Supplement 1B: Example of a 'personal health profile' for a hypothetical patient in the individualized absolute risk arm. ***Disclaimer: This is a fictionalized, hypothetical patient***

My Personal Heath Profile

Part of the SMART-INFORM study

In this folder you will find your personal heath profile, which we have made as part of your participation in the SMART-INFORM study. Elements of your medical status were used to complete the profile.

VIDEOS MADE FOR YOU

In this envelope, you will find six short videos designed to give you a bit of background information about this health profile and cardiovascular disease in general. The six videos are:

1. What is cardiovascular disease?
2. What is cholesterol?
3. What does a statin do?
4. Do statins have side-effects?
5. How do I read my personal health profile
6. What now?

The videos have been loaded onto the USB-card you are receiving with this Health Profile. You can watch the videos by plugging the USB card into a computer.

PERSONAL HEALTH PROFILE

- Mr. J. Smith, 73 years old
- Type of cardiovascular disease: Heart
- You are a non-smoker
- Creatinine-level (Kidney function): 100 umol/L
- Blood pressure: 140 / 90 mmHg
- Prescribed statin: Simvastatin 40 mg
- Total cholesterol: 4.7 mmol/L
- You do not have diabetes
- You do not report having atrial fibrillation (a type of abnormal heart rhythm)
- You do not report having heart-failure

In order to calculate how statin medication effects your prognosis, we used the aspects of your profile listed above. We have based these aspects on the medical records on-file at the hospital.

2

10-YEAR RISK

A 10-year risk estimates the chance that you will suffer a heart attack, stroke, or sudden death withi the next 10 years. We have estimated your 10-year risk in three different situations from which you can choose.

THREE SITUATIONS FROM WHICH TO CHOOSE

You can choose from the following three situations:

1. Continue with your current statin and dose, this is your current prognosis.
2. Stop taking your statin.
3. Increase your statin effectiveness by taking the highest dose of the strongest statin (atorvastatin 80mg).

1. CONTINUE

If you continue on your current statin and dose, your 10-year risk will be **21 %**

2. STOP

If you stop taking your statin, your 10-year risk will be **29 %**

3. INCREASE

If you increase your statin dose, your 10-year risk will be **18 %**

3

QUESTIONS?

If you have any questions about the SMART-INFORM study you can contact the investigators. They can be reached on weekdays on 000 00 000 00.

WE WILL CONTACT YOU

Within a few weeks, a researcher will be in contact with you to answer any additional questions or provide additional explanation regarding the personal health profile.

UMC Utrecht

4

Supplement 1C: Example of a 'personal health profile' for a hypothetical patient in the individualized life-expectancy arm. ***Disclaimer: This is a fictionalized, hypothetical patient***

My Personal Heath Profile

Part of the SMART-INFORM study

In this folder you will find your personal heath profile, which we have made as part of your participation in the SMART-INFORM study. Elements of your medical status were used to complete the profile.

VIDEOS MADE FOR YOU

In this envelope, you will find six short videos designed to give you a bit of background information about this health profile and cardiovascular disease in general. The six videos are:

1. What is cardiovascular disease?
2. What is cholesterol?
3. What does a statin do?
4. Do statins have side-effects?
5. How do I read my personal health profile
6. What now?

The videos have been loaded onto the USB-card you are receiving with this Health Profile. You can watch the videos by plugging the USB card into a computer.

PERSONAL HEALTH PROFILE

- Mr. J. Smith, 73 years old
- Type of cardiovascular disease: Heart
- You are a non-smoker
- Creatinine-level (Kidney function) 100 umol/L
- Blood pressure 140 / 90 mmHg
- Prescribed statin Simvastatin 40 mg
- Total cholesterol 4.7 mmol/L
- You do not have diabetes
- You do not report having atrial fibrillation (a type of abnormal heart rhythm)
- You do not report having heart-failure

In order to calculate how statin medication effects your prognosis, we used the aspects of your profile listed above. We have based these aspects on the medical records on-file at the hospital.

2

DISEASE-FREE LIFE EXPECTANCY

The disease-free life-expectancy indicates how long you can expect to live without having a heart attack, stroke, or sudden death. We have estimated your disease-free life expectancy in three different situations from which you can choose.

THREE SITUATIONS FROM WHICH TO CHOOSE

You can choose from the following three situations:

1. Continue with your current statin and dose, this is your current prognosis.
2. Stop taking your statin.
3. Increase your statin effectiveness by taking the highest dose of the strongest statin (atorvastatin 80mg).

3

QUESTIONS?

If you have any questions about the SMART-INFORM study you can contact the investigators. They can be reached on weekdays on 000 00 000 00.

WE WILL CONTACT YOU

Within a few weeks, a researcher will be in contact with you to answer any additional questions or provide additional explanation regarding the personal health profile.

UMC Utrecht

4

Supplement 2: Telephone consultation

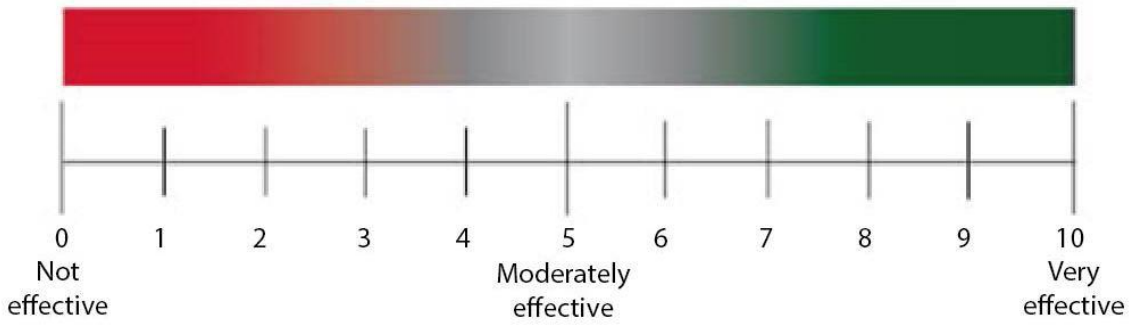
Short motivational telephone consultation following a structured interview asking the following questions:

- Did you receive the information?
- Have you been able to watch the videos?
- Did you understand all the information?
- Which questions did you have after studying the information?
- Did you already decide which statin treatment option you prefer?
- If yes, did you discuss this with your physician?

Supplement 3: Visual analogue scale

Estimation of therapy-effects

How great do you think the beneficial effects of your cholesterol lowering statin therapy are for you? Circle one number on the scale Below. A zero "0" means you believe that this medication is NOT effective for you and a ten "10" means you believe that is medication is VERY effective for you.



Supplement 4: Patient questionnaire to assess statin knowledge

What do you know about medication?

Below are a number of statements with answer choices. Please circle the answer choice which you believe is correct. If you do not know the correct answer, you can mark 'I don't know'

Where in the body can you get cardiovascular disease?

❒ heart ❒ legs ❒ both ❒ I don't know

Possible side-effects of statins is/are

❒ muscle pain ❒ breathing problems ❒ neither one ❒ I don't know

A high cholesterol gives a greater risk of

❒ stomach bleeds ❒ muscle or joint pain ❒ stroke/heart-attack ❒ I don't know

By using statins, I reduce my risk of

❒ stomach bleeds ❒ pneumonias ❒ heart-attacks ❒ I don't know

Due to the use of statins, the cholesterol levels in my blood will

❒ increase ❒ decrease ❒ stay the same ❒ I don't know

Through the use I statins, I reduce

❒ the fatty plaques in my arteries ❒ my blood pressure ❒ both ❒ I don't know

How long are people usually advised to use statins?

❒ for life ❒ 0-1 years ❒ 1-10 years ❒ I don't know

How does cholesterol get into to blood?

❒ My body produces cholesterol ❒ I get it from my food ❒ Both answers are correct ❒ I don't know

Supplement 5: Secondary outcomes score ranges

Scores on the IPQ range from 0 (non-threatening) to 80 (very threatening). Patient Activation Measure (PAM-13) scores range from 0 (low activation) to 100 (high activation). Perceived statin efficacy ranged from 0 (statins perceived as ineffective) to 10 (high level of statin effectiveness). The 9-item shared decision-making questionnaire ranged from 0 (poor shared decision-making) to 100 (optimal shared decision-making. BMQ Adherence Risk Scale ranged from 0 (no-self-reported non-adherence) to 4 (self-reported non-adherence). Understanding of statin-therapy ranges from 0 (no answer correct) to 100 (all answers correct). RAND Medical Outcomes Study Short Form Survey (SF-36) questionnaire ranges from 0 (low quality of life) to 100 (high quality of life).

Supplement 6: General practitioner questionnaire

	Definitely not (1)	Probably not (2)	Uncertain (3)	Probably yes (4)	Definitely yes (5)
1. How convinced are you that a statin is worthwhile for this patient?	□	□	□	□	□
2. Do you think the patient could benefit from a greater statin dose?	□	□	□	□	□
3. Would you consider statin discontinuation in this patient if the guidelines allowed?	□	□	□	□	□
The following three questions are only applicable if the patient was part of an intervention arm.					
4. How probable is it that you would use this information to aid in doctor-patient communication?	□	□	□	□	□
5. Do you think the consultation would be more efficient if you had this information beforehand?	□	□	□	□	□
6. Do you think this information would encourage therapy-adherence?	□	□	□	□	□

Legend: Questions 1-3 were asked of every GP. Questions 4-6 were additionally asked for physicians with patients randomized to the individualized absolute risk or the individualized life-expectancy groups.

Supplement table 1: Baseline characteristics per missing and non-missing for primary outcome

	Control		**iPOL**		**iARR**	
	Non-missing	Missing	Non-missing	Missing	Non-missing	Missing
Population	n=90	n=11	N=87	N=14	N=83	N = 18
Age	64 (59 - 72)	62 (60 - 67)	66 (59-71)	68 (59-73)	66 (59-72)	63 (59 – 68)
Gender (male)	77 (85%)	9 (82%)	72 (83%)	11 (79%)	71 (86%)	16 (89%)
One CVD location	79 (88%)	10 (91%)	77 (89%)	14 (100%)	75 (90%)	15 (83%)
Current smokers	13 (16%)	4 (22%)	9 (10%)	1 (9%)	9 (10%)	1 (9%)
Years clinically manifest CVD	5 (0 - 11)	0 (0 - 12)	5 (0-10)	0 (0-2)	0 (0-10)	6 (0-12)
Diabetes Mellitus	19 (21%)	4 (36%)	24 (28%)	3 (21%)	13 (16%)	1 (6%)
LDL-c (mmol/L)	2.0 (1.6 - 2.5)	1.8 (1.6 - 2.4)	2.1 (1.7 - 2.4)	1.7 (1.6 - 2.1)	2.0 (1.6 - 2.4)	2.0 (1.7 - 2.3)
LDL-c >1.8mmol/L	56 (62%)	5 (50%)	62 (71%)	6 (43%)	55 (66%)	11 (61%)
Creatinine (umol/L)	85 (75 - 92)	85 (74 - 97)	82 (74 – 96)	91 (80 – 106)	83 (78 – 95)	85 (80 – 90)
Systolic blood pressure (mmHg)	129 (122 - 142)	132 (116 - 150)	132 (121-145)	129 (120-132)	130 (121 - 140)	140 (124-148)
Number of medications per day	5 (4 - 7)	7 (5 - 10)	6 (4-9)	7 (6-8)	5 (4 - 7)	5 (4 - 6)
Months required to offset disutility of daily pill-taking	42 (9 - 97)	97 (35 - 97)	61 (3 – 97)	97 (70 – 97)	61 (9-97)	12 (9-61)
High likelihood limited literacy	6 (7%)	2 (18%)	6 (7%)	2 (14%)	5 (4%)	4 (22%)
Possibility of limited literacy	9 (10%)	2 (18%)	7 (8%)	2 (14%)	7 (9%)	1 (56%)
Adequate literacy	75 (83%)	7 (63%)	74 (85%)	10 (71%)	70 (85%)	13 (72%)

Legend: Data are reported as median (interquartile range) or n (%). CVD locations defined as coronary artery disease, peripheral artery disease, or abdominal aortic aneurysm in addition to cerebrovascular disease. Health literacy based on the Newest Vital Sign baseline questionnaire.(32) Number of medications excludes over the counter medications, (nasal) sprays, and topical medications.

Supplemental table 2: Physician reported secondary outcomes

	Median (IQR)			
	Control-group	iAR-group	iLE-group	Two-sided p-value
Post-interventional LDL-c				
LDL-c values determined	n=55	n=43	n=43	
No LDL-c values determined	n=27	n=42	n=42	
Unknown**	n=19	n=21	n=16	
Post-interventional LDL-c at 6 months (mmol/L)	1.9 (1.6 - 2.3)	1.9 (1.4 - 2.3)	1.9 (1.5 - 2.4)	p=0.60
Physician opinion of intervention				
Approached	n=93	n=88	n=87	
Participated	n=51	n=48	n=42	
Convinced that a statin is worthwhile for the patient*	5 (4-5)	5 (5-5)	5 (5-5)	p=0.50
Believes patient could use a higher dose*	3 (2-4)	3 (2-4)	3 (2-4)	† p=0.11
Would consider statin discontinuation if guidelines allowed*	2 (1-3)	2 (1-4)	2 (1-4)	† p=0.84
How probable to use information†*	N/A	4 (4-5)	4 (3-5)	† p=0.84
Believes that consultation would be more efficient†*	N/A	4 (3-5)	4 (3-5)	p=0.4
Believes that information would encourage therapy adherence†*	N/A	4 (3-5)	4 (3-4)	p=0.50

Legend: Data are reported as median (interquartile range) or n (%). †Only applicable for the intervention groups LDL-c=low-density lipoprotein cholesterol. Precise questions and answer choices are shown in supplement 6 "General Practitioner Questionnaire." *Median numbers of five-point scale where 1 = definitely not, 2= probably not, 3= uncertain, 4= probably yes, 5 = definitely yes. ** No link with dossier from general practioner possible after six months. † Denotes a non-parametric test was applied.

Supplemental table 3: Median DCS score per subgroup strata

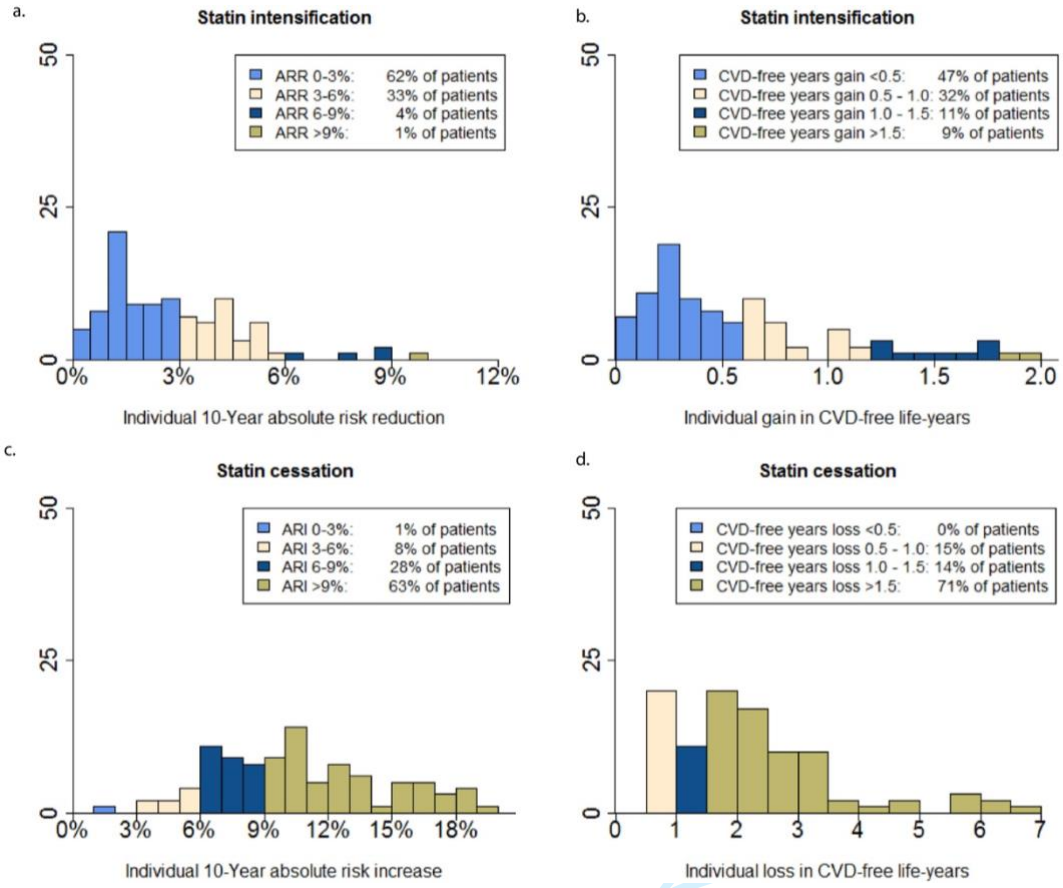
	Control –group		iAR –group		iLE –group	
Gender (F=7.02, p-value for interaction=0.32)						
Men	29.7 (19.5 - 42.2)	n=71	23.4 (11.7 - 29.7)	n=72	25.0 (10.9 - 32.8)	n=77
Women	25.8 (21.0 - 47.7)	n=12	14.1 (10.2 - 25)	n=15	26.6 (9.4– 29.7)	n=13
Age (F=0.17, p-value for interaction=0.90)						
>65	19.0 (20.3 - 42.2)	n=45	18.8 (9.0 - 28.6)	n=44	25.0 (8.6 - 31.3)	n=42
≤65	30.0 (19.5 - 42.6)	n=38	23.5 (13.3 - 30.7)	n=43	25.0 (12.9 - 31.6)	n=48
Patient activation measure (F=1.4, p-value for interaction=0.40)						
Low	26.7 (14.8 - 39.1)	n=21	21.9 (3.1 - 25.0)	n=13	26.6 (24.2 - 49.2)	n=15
High	26.7 (25.2 - 42.2)	n=43	23.4 (12.5 - 30.7)	n=43	22.4 (4.7 - 29.7)	n=49
Years since first CVD-event (F=1.4, p-value for interaction=0.24)						
>1 year	29.7 (20.3 - 45.3)	n=33	23.4 (4.7 - 29.7)	n=43	25.0 (14.9 - 33.2)	n=52
≤1 year	26.7 (19.9 - 39.8)	n=50	21.0 (14.1 - 30.0)	n=44	23.5 (5.5 - 33.2)	n=38
Educational level (F=2.8, p-value for interaction=0.09)						
Low	28.1 (25.0 - 37.5)	n=14	6.3 (3.1 - 18.8)	n=17	14.1 (1.6 - 25.0)	n=15
Middle	29.7 (13.3 - 46.1)	n=35	25.0 (16.4 - 30.7)	n=40	25.0 (22.3 - 30.5)	n=38
High	26.6 (20.7 - 41.0)	n=34	21.9 (17.2 - 30.9)	n=30	25.0 (7.8 - 34.4)	n=37
Health literacy* (F=4.0, p-value for interaction=0.02)						
High likelihood limited literacy	50.0 (29.7 - 53.1)	n=5	7.8 (3.1 - 13.7)	n=6	28.1 (25.0 - 31.3)	n=6
Possibility limited literacy	31.2 (25.0 - 41.4)	n=7	29.7 (18.7 - 30.5)	n=7	25.0 (0.0 - 42.1)	n=9
Adequate literacy	26.6 (18.8 - 41.8)	n=70	22.7 (12.9 - 29.7)	n=74	23.4 (8.6 - 29.7)	n=75
Disutility (F=0.6, p-value for interaction=0.54)						
Low (<9 months)	26.6 (14.1 - 45.3)	n=23	18.8 (3.1 - 25.0)	n=25	22.7 (9.0 - 25.4)	n=24
Middle (9-97 months)	32.0 (23.4 - 44.5)	n=18	23.4 (20.7 - 28.5)	n=14	27.3 (14.8 - 41.8)	n=26
High (>97 months)	32.0 (25.0 - 43.0)	n=24	17.2 (3.1 - 29.7)	n=31	23.4 (0.39 - 35.0)	n=22

Legend: Data are reported as median (25^{th} – 75^{th} percentile). *Further analyses for health-literacy are shown in supplemental figure 2. Health literacy based on the Newest Vital Sign.(32).

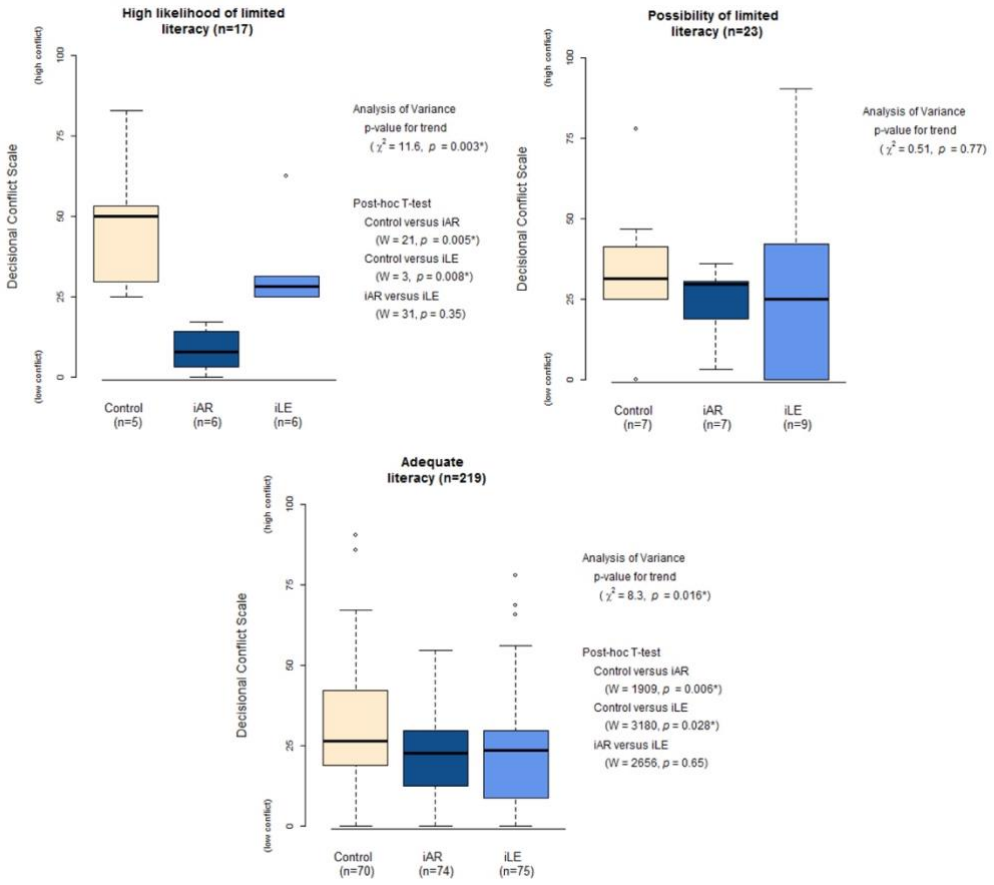
Supplemental table 4: Sensitivity analyses: Patient Reported Secondary Outcomes corrected for baseline characteristics.

	ANCOVA
	p-value
DCS (1)	p=0.49
DCS (6)	p=0.50
Brief-IPQ (1)	p=0.21
Brief-IPQ (6)	p=0.63
PAM (1)	p=0.39
PAM (6)	p=0.29
Perceived Statin Efficacy (1)	p=0.67
Perceived Statin Efficacy (6)	p=0.44
Understanding of therapy-effects (1)	p=0.16
Understanding of therapy-effects (6)	p=0.60
BMQ Adherence Risk Scale (1)	p=0.382
BMQ Adherence Risk Scale (6)	p=0.32
SDMQ9 (1); Reported visiting GP (n)	p=0.21
SDMQ9 (6); reported visiting GP (n)	p=0.35
RAND-36 Quality of life (6)	
Physical functioning	p=0.12
Role limitations due to physical health	p=0.48
Role limitations due to emotional problems	p=0.69
Energy/fatigue	p=0.86
Emotional well-being	p=0.25
Social Functioning	P = 0.71
Pain	p = 0.53
General health	P = 0.86

Sensitivity analyses for all outcomes at one (1) and six (6) months post intervention corrected for baseline characteristics: gender, age, smoking status, diabetes status, LDL-cholesterol (mmol.L), creatinine (umol/L), disutility score, NVS health literacy, and number of medications used per day



Supplemental Figure 1: Therapy-benefit from statin intensification to atorvastatin 80mg for a) iAR arm and b) iLE arm. Loss of benefit from statin discontinuation in c) iAR arm and d) iLE arm. In the iAR group, the median baseline 10-year absolute CVD risk was 37.6% (28.1-49.0). The estimated absolute 10-year risk change was -2.4% (-1.2 to -3.9) after intensification and 10.2% (7.7- 13.5) after discontinuation. In the iLE group, the median CVD-free life-expectancy was 75.4 years (73.0-82.7). The median change in CVD-free life-years was 0.5 years (0.3 – 0.8) after intensification and -2.0 years (- 1.3 - - 2.8) after discontinuation.



Supplemental figure 2: Subgroup analysis. Box-and-whisker plot depict the decisional conflict score at one month stratified by baseline health literacy. The colored boxes denote the median (25th – 75th percentiles). Whiskers denote the 25th percentile-1.5*(Inter-Quartile Range) and the 75th percentile + 1.5(Inter Quartile Range) in whiskers.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2/3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6/7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7/8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10 manuscript and in supplemental material
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10/11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6, more details in 10
	11b	If relevant, description of the similarity of interventions	7/8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 and figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 12, figures 1 and supplemental table 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1, supplemental table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 12. Figure 1.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Figure 2, table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Pg 14, supplemental table 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Pg 16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Pg 16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pg 14-17

Other information			
Registration	23	Registration number and name of trial registry	Pg 6
Protocol	24	Where the full trial protocol can be accessed, if available	Pg 18
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Pg 18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial.

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Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: does it improve decisional conflict? Three-armed, blinded, randomised controlled trial.

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Abstract

Objective: To determine whether communicating personalized statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use among patients with stable cardiovascular disease (CVD) compared to standard (non-personalized) effects.

Design: Hypothesis-blinded, three-armed randomized controlled trial

Setting and participants: 303 statin-users with stable CVD enrolled in a cohort

Intervention: Participants were randomized in a 1:1:1 ratio to standard (non-personalized) practice (control-group) or one of two intervention arms. Intervention arms received standard practice plus 1) a *personalized health profile*, 2) educational videos, and 3) a structured telephone consultation. Intervention arms received personalized estimates of prognostic changes associated with both discontinuation of current statin and intensification to the most potent statin type and dose (i.e. atorvastatin 80 mg). Intervention arms differed in how these changes were expressed: either change in 10-year absolute CVD risk (iAR-group) or CVD-free life-expectancy (iLE-group) calculated with the SMART-REACH model (http://U-Prevent.com).

Outcome: Primary outcome was patient decisional conflict score (DCS) after one-month. The score varies from 0 (no conflict) to 100 (high conflict). Secondary outcomes were collected at one or six months: DCS, quality of life, illness perception, patient activation, patient perception of statin efficacy and shared decision-making, self-reported statin adherence, understanding of statin-therapy, post-randomization low-density lipoprotein cholesterol (LDL-c) level, and physician opinion of the intervention. Outcomes are reported as median (25^{th} – 75^{th} percentile).

Results: Decisional conflict differed between the intervention arms: median control 27 (20-43), iAR-group 22 (11-30; p-value versus control 0.002), and iLE-group 25 (10–31; p-value versus control 0.02). No differences in secondary outcomes were observed.

Conclusion: In patients with clinically manifest CVD, providing personalized estimations of treatment-effects resulted in a small but significantly lower decisional conflict after one month. The results support the use of personalized predictions for supporting decision-making.

Registration: Netherlands Trial Registry (Identifier NTR6227/NL6080)

Strengths and limitations of the study

- Patients were provided with estimations of their personalized causal therapy-effects, unlike many previous studies which used hypothetical therapy-effects.
- Performance bias was limited by hypothesis blinding.
- Because the control group reported a low decisional conflict and a high confidence in stating medication, the effect seen in the study is possibly underestimated compared to the general population,
- The personalized effects were not used directly during a clinical consultation, but provided prior to any potential consultation with a physician.
- Some questionnaires were created for this study and were not externally validated.

Introduction

Several online tools have recently become available which can calculate the personalized therapy effects for various cardiovascular disease (CVD) prevention strategies. Such calculators can express the therapy-benefit in terms absolute 10-year CVD risk reduction, or in recent years, gain in healthy life-expectancy.[1]

The use of decision tools is associated with increased knowledge and less decisional conflict, and providing therapy-related information increases patient participation in medical decision-making.[1-5] However, most decision aids do not provide personalized benefits and harms.[6] Rather, most investigated patient decision-aids use hypothetical or population-based effects of CVD-prevention and not the actual, personalized causal effects an individual can expect. One obstacle in providing these causal effects however, is that patients often desire a far greater therapy-benefit than can be expected from preventive therapy.[7-9] One survey showed that patients desire an increase in life-expectancy of around 42 months from life-long statin-use whereas the actual benefit is often less than half this amount.[7 8] Being presented with an actual predicted therapy-benefit far smaller than the benefit desired might discourage patients from using medication. Moreover, metrics to used communicate therapy-effects elicit different opinions on the value of preventive therapy, motivation to use therapy, and possibly therapy-adherence.[10-13]

We conducted a hypothesis blinded, three-armed, randomized controlled trial (RCT) to determine whether communication strategies involving personalized therapy-effects of statin therapy obtained by algorithm, expressed as change in CVD-free life-expectancy or absolute 10-year CVD-risk reduction, lead to improved decisional certainty about the use of statins compared to standard communication strategies and compared to one another.

Methods

Population

The SMART-Inform study was nested within the previously described Secondary Manifestations of ARTerial disease (SMART) study, an ongoing, single-center, prospective cohort of patients referred to the University Medical Center Utrecht in the Netherlands for CVD screening.[14] All patients invited to participate in a SMART-examination were telephonically informed of the SMART-Inform sub-study and sent further information about by mail. Additional inclusion criteria for SMART-Inform were current statin use, being between 45-80 years old, and having CVD (i.e. coronary artery disease, cerebrovascular disease, and peripheral artery disease and abdominal aortic aneurysm). Additional exclusion criteria for SMART-Inform were terminal malignancy and not returning the baseline questionnaires.

Design, blinding, and randomization

The SMART-Inform study was a three-armed, hypothesis-blinded, RCT. Hypothesis blinding entailed informing patients and their general practitioners (GPs) that all patients would receive at least standard SMART-protocol practice and that the study goal was to investigate if information about cholesterol-lowering medications would impact motivation for use. Patients were unaware what aspect of the received content was additional to standard practice, and what the primary and secondary outcomes were. Researchers and outcome assessors were not blinded. A computer generated random allocation sequence was used to assign each patient after inclusion by order of inclusion. The investigator generating the random sequence was not involved in other aspects of the study. All other investigators had no access to the sequence.

Ethics Statement and Registration

The Medical Ethics Review Committee of the UMCU approved the study (16-665/D). All participants provided written informed consent. The study was registered in the Netherlands Trial Registry (Identifier NTR6227 and NL6080).

Patient and public involvement

The study design and goal was discussed at an open conference of patient-organizations held in Amstelveen, the Netherlands in April 2016 to gain and incorporate input from patients at an early stage.

Description of standard practice

All participants received cardiovascular care as usual from their own referring GP or medical specialist and written information consisting of general lifestyle advice based on the treatment targets recommended by the European Society of Cardiology (SMART-study standard practice supplement 1A).[15]

Description of intervention arms

There were three intervention arms: the control group, the 10-year risk (iAR-group) and CVD-free life-expectancy (iLE-group). The control group received only standard practice. Both intervention arms received standard practice plus: 1) a leaflet entitled *personalized health profile* (supplement 1B and 1C for two fictional patients); 2) a USB device containing educational videos; 3) a structured telephone consultation enforcing uptake of the information (supplement 2). The *'personal health profile'* outlined the individual effect of the following treatment options: 1) continue with the type and dose of statin-therapy ('current prognosis'); 2) discontinue statin therapy ('stop statins'); 3) intensify to maximum statin-therapy, defined as once-daily atorvastatin 80 mg ('increase statins'). The only difference between the

intervention arms was the measure used to communicate the prognostic change associated with the therapy-effects; individual treatment effects were estimated in terms of change in 10-year risk (iAR-group) or CVD-free life-expectancy (iLE-group). The USB-device contained intervention-group specific educational videos on how to read and interpret the *'personal health profile'* and the effect of statin-medications on CVD. The structured telephone consultation for the intervention arms ensured the information was well-received and understood by the patients. In the SMART-study, patients are encouraged to discuss the results with their own doctor and decide whether or not to change their statin prescription. Participants were free to decide whether to follow this advice or not. In the SMART-Inform study, the received information was not designed to replace a doctor's advice and there was no extra face-to-face contact; however, all patients were strongly encouraged to visit their GP within two weeks to discuss the received information. Follow-up questionnaires were sent by mail one and six months post-intervention, with telephone reminders ensuing after two weeks if the questionnaires were not returned.

Predicted therapy-effects

The estimations in the *'personal health profile'* were obtained with the SMART-REACH score, an internationally validated model predicting the personalized effects of secondary CVD-prevention for patients aged 45-80 years (http://U-Prevent.com).[2] The model combines hazard ratio's derived from meta-analyses with a prediction algorithm incorporating individual patient characteristics to derive the personalized therapy effects. A 1 mmol/L reduction in LDL-c was modelled to correspond to the CVD-specific hazard ratio of 0.80 and the expected LDL-c -reduction for each statin was derived from a previous meta-analysis.[16 17] Subgroup analyses in literature provide no evidence for differences of treatment effects on a relative effect scale for statins. Therefore, the treatment effect estimates based on the

SMART-REACH score differ only on an absolute effect scale. Supplemental figure 1 shows the distribution of the predicted therapy-effects for the trial patients.

Primary outcome

The study's primary outcome was the intergroup difference in experienced decisional conflict at 1 month regarding the decision to continue, discontinue, or intensify statin therapy. Decisional conflict was measured using the Decisional Conflict Scale (DCS), a validated, translated, measure of patient perception of uncertainty in choosing between options.[18 19] The DCS consists of 16 statements pertaining to the decision to use statins as prescribed (e.g., "I am clear about which benefits matter most to me"). The DCS scale measures the amount of internal conflict a patient feels regarding a medical decision. Summary scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). Scores >37.5 are associated with feeling unsure about implementation of the decision, possibly leading to discontinuation of the chosen option or fretting about the chosen option (i.e. using statins as prescribed by the physician), and <25 are associated with following through with a decision.

Patient reported secondary outcomes

Secondary outcomes reported only at 6 months were the DCS and quality of life measured using the eight subscales of the RAND Medical Outcomes Study Short Form Survey (SF-36).[20] Other patient-reported secondary outcomes were reported at both 1 and 6 months. The Brief Illness Perception Questionnaire (brief IPQ) was used to measure the degree to which CVD was considered threatening by patients.[21] A Visual Analog Scale (VAS) was used to measure how effective patients perceived statin therapy (supplement 3). The thirteen question Patient Activation Measure (PAM-13) was used to assess patient knowledge, skills, and confidence for self-management of health.[22] Due to limitations on maximum population size

of academic use licenses, PAM-13 was only used for the last 213 study participants. Patient's perception of shared decision-making was measured with the Shared Decision Making Questionnaire (SDMQ-9).[23] Self-reported statin adherence was determined with the 2003 Brief Medication Questionnaire (BMQ).[24] Patient understanding of statin-therapy was measured with a questionnaire developed for the trial (supplement 4). The possible numeric ranges and interpretation of the secondary outcomes are shown in supplement 5.

Physician reported secondary outcomes

Patients' GPs' received a copy of the personalized health profile. Upon enrolment of the first patient from their practice, GPs were provided a short telephonic explanation of the study and asked to fill in a questionnaire (supplement 6). Questionnaire results and the last known post-intervention LDL-value at 6 months were secondary outcomes. Interviewed GPs were blinded to study outcomes and treatment arm differences. GPs were not approached if they had subsequent patients included in the study, as receiving material from multiple patients would have unblinded them to treatment arm differences.

Sample size

The aim of this study was a pairwise comparison between study arms. To limit the overall probability of type 1 errors to 0.05, first an ANOVA was used to detect the presence of any differences between the three groups. If the ANOVA detected a difference, subsequent T-test were performed. Therefore, the sample-size was calculated to detect a difference in two groups using the T-test. Sample-size calculations were conducted using G*Power version 3.1. Sample size was based on an effect size (Cohen's d = mean difference / standard deviation) of 0.43, a standard deviation of 0.80 to detect a mean difference of 0.34 on the 5-

point scale (ranging from 0-4) corresponding to 8.6 on the 100-point scale.[25 26] A power of 80% and a two-tailed alpha of 0.05 was used. A minimum of 86 patients per arm was needed.

Statistical analyses

An intention-to treat-analysis was performed. Differences among the three arms were detected with ANOVA, or a Kruskal-Wallis one-way ANOVA to deal with heteroscedasticity. Assumptions of normal (residual) distribution and homoscedasticity were visually inspected. If ANOVA $p<0.05$, pairwise comparisons between arms were determined using a t-test or with the Wilcoxon-rank sum test for the difference in ranked means if ANOVA assumptions were not met after transformation attempts. Analyses were performed using R-Statistical Software, version 1.0.14.

Subgroups

Pre-specified subgroup analyses were performed using an ANCOVA test to investigate whether the effect of the intervention on DCS at one month differed according to the following: gender; age (<65 versus >65); years since first CVD event (<1 versus >1 years); educational level (low, medium or high);[27] low versus high patient activation (low a PAM-13 level of 1-2 and high a PAM-13 level of 3-4 based on a conversion of the 100-point PAM-13 score to a 4-point scale;[22 28] health literacy categories based on the Dutch version of the Newest Vital Sign (NVS);[29] and disutility defined as the minimum gain in life-expectancy desired to offset the inconvenience of taking a lifelong, hypothetical, idealised daily tablet.[8] The study was not powered to detect any subgroup differences. A Bonferroni correction corresponding to the 22 secondary outcomes was applied; the new p-value for statistical significance was 0.002.

Sensitivity analyses

Sensitivity analyses were performed to account for possible differences in baseline characteristics for missing outcomes between trial arms by conducting an ANCOVA with gender, age, smoking status, diabetes status, LDL-cholesterol (mmol/L), creatinine (umol/L), disutility score, NVS health literacy, and number of medications used daily.

Results

Participant flow

Between March 2017 and August 2018, 303 participants were enrolled. Baseline characteristics are shown in table 1 and the flow of participants throughout the trial in figure 1. The primary outcome was collected in 260 participants (86%) (control=83, iAR group=87, iLE group=90). Supplemental table 1 displays characteristics for those with and without the primary endpoint. At one-month, 12% (n=10) of control, 8% (n=7) of iAR, and 11% (n=9) of iLE patients reported increasing their statin dose after the intervention. Respective numbers for decreased statin dose were 2% (n=2) in the control arm, 1% (n=1) in the iAR arm, and 3% (n=3) in the iLE arm.

DCS at one month

There was a significant difference between the groups (ANOVA χ^2, p=0.002) with a median (25^{th}-75^{th} percentile) DCS of 27 (20–43) for control arm, 22 (11–30) for the iAR arm, and 25 (10–31) for iLE arm. Subsequent Wilcoxon-rank sum tests showed the difference between the control and iAR arm (W=2707, p=0.001) and the control and iLE arm (W=4219, p=0.02) to be significant. The difference between iAR and iLE arms was not significant (W=3317, p=0.21, Figure 2). All groups showed a DCS of around 25, the value associated with following through with a decision.

Patient reported secondary outcomes

After 6 months, there was no longer a significant difference between the groups in DCS score (ANOVA χ^2, p=0.10) with a median (25^{th}-75^{th} percentile) DCS of 25 (16–38) for control arm, 22 (9–29) for the iAR arm, and 25 (7–29) for iLE arm. All other secondary outcomes also showed no intergroup differences. There was no difference in how threatening patients perceived their CVD (Brief-IPQ) or how effective patients perceived statin medications (VAS 8) at either 1 or 6 months. There was no difference in PAM, understanding of statin effects, self-reported adherence (BMQ Adherence Scale), or patients' perceptions of shared-decision making between arms (SDMQ9). At six months, quality of life did not differ on any RAND SF-36 subscale (table 2).

Physician reported secondary outcomes

Physician reported secondary outcomes are shown in supplemental table 2. Between randomization and 6 months, 119 patients had their LDL-c values determined (control n=51, iAR n=48, iLE=39), with no difference in median serum LDL-c levels found (median 1.9 mmol/L in all groups) between study-arms. In total, 267 physicians were approached after the inclusion of their first patient of which 141 (53%) participated in the questionnaire. Physicians viewed statin-medication as equally worthwhile for patients in all study-arms. There was no difference of opinion between how iAR and iLE formats could positively influence doctor-patient communication, consultation efficiency, and therapy-adherence.

Subgroup analysis

No evidence of subgroup effects was found for sex (p-value for interaction = 0.32), age (p=0.90), years since first CVD-event (p=0.24), months gain in CVD-free life-expectancy desired prior to taking an idealized medication daily (i.e. disutility, p=0.54), and educational level (p=0.09). An interaction was found for health literacy (p = 0.02). The median (25^{th}-75^{th}

percentile) DCS scores for all subgroups are shown in supplemental table 3, and a t-test for differences in each health literacy group is shown in supplemental figure 2. Across health literacy categories, decisional conflict was lower in the in intervention arms than in the control arm, with the largest differences found in people with a low health literacy.

Sensitivity analyses

Supplemental table 4 shows the sensitivity analyses which corrected for baseline characteristics. After correction none of the outcomes were significant.

Discussion

Providing personalized estimates of the prognostic changes associated with statin use in terms of 10-year CVD risk and CVD-free life-years (compared to a control group) resulted in lower decisional conflict after one month. After six months no differences were found. Likewise, no differences were found in secondary outcomes, which included the degree to which people perceived their CVD to be threatening, how effective patients viewed their statin-medications, and LDL-c levels after six months. Although the actual benefit from CVD-prevention is smaller than people initially report acceptable, communicating the individual benefit resulted in lower decisional conflict, without may people discontinuing their treatments. However, the effect was small in a population with a low baseline DCS. Many tools designed for decision-support report DCS differences of 8-10 points immediately post intervention in favour of the decision-aid.[6] We measured the outcomes after one month to provide time for patients to visit their physician. The already low decisional conflict in the control arm, possibly explaining the relatively small absolute differences in median scores found in this study (2-5 points). The loss of statistical significance at six months, is in line with previous studies investigating the long-term effects of decision-support tools of for statin medications indicating that positive results of such interventions fade over time.[30]

The use of patient communication-aids is known to make people feel better informed and help them form accurate opinions of therapy benefit-harm ratios.[6 31] A number of studies have examined the effect of providing estimations of hypothetical or generalised therapy-benefit to patients with clinically manifest CVD.[11 32-34] One study examined the effect of providing primary care patients without any prior statin-exposure with the approximated personalized effect of statin medications.[12] Receiving the predictions in the form of absolute risk reduction estimates resulted in a greater likelihood to redeem statin-medications compared to prolongation of life. However, no differences were found in patient satisfaction and decision confidence. A possible explanation for this discrepancy between literature and our study could be that patients already using medication may respond differently to personalized estimations than patients initiating a new medication. As opposed to first-time statin-users, all patients in our study had already been using statins, and may therefore already know if they have experienced statin-related side-effects. Willingness to take a new therapy may be more sensitive to the perceived side-effects than the perceived benefits.[35] Similarly, worry about side-effects is a stronger determinant of intentional non-adherence than belief in the effectiveness of statin-medications.[36]

Similar to our study, previous literature shows that patients often overestimate the relative effects of medication and desire a greater absolute therapy-benefit than clinically feasible.[7 8] Although the majority of patients in our study desired more benefit than clinically feasible (median disutility score 61 months), statin discontinuation was minimal and there was no evidence of subgroup effects based on baseline disutility. Although physicians may also over-estimate the effects of preventive therapy,[7] there were no inter-groups differences in how physicians perceived the necessity of statin-medications.

Strengths of this study include providing patients with estimations of their actual causal therapy-effects, in contrast to pre-existing decision aids which present participants with either

hypothetical or population-based therapy-effects. As we assessed current statin users, we were able to provide information on multiple treatment-options. Use of the cohort's standard procedures allowed for several strengths. Systematically approaching cohort patients who were already due to receive physical examinations minimized the risk of preferentially selecting patients likely to respond to personalized predictions. Moreover, it was possible to select a structured and well-defined control group. The structured telephonic consultations ensured patients had each interventional format explained in a similar fashion. Performance bias was limited by hypothesis blinding. A number of study limitations must also be highlighted. First, the control group of this clinically stable cohort population has low decisional-conflict and high belief in the effectivity of statin medications. The effects described here may thus be different in patients who have pre-existing negative associations with statins due to adverse effects, or who are considering a new, more intensive strategy with additional medication such as blood pressure reduction or antithrombotic treatment. Second, the personalized effects were not used directly during a clinical consultation, but provided prior to any potential consultation with a physician. The effects may therefore be different compared to a population of patients who are involved in a clinical consultation in which statin therapy is discussed. Third, the loss to follow-up was 14% for the primary outcome. This is however lower than other communication-trials involving follow-up questionnaires[12] and baseline characteristics of missing and non-missing individuals were relatively similar. Correction for baseline health literacy, a characteristic which may have differed between missing and non-missing individuals did not level-off the effects. Fourth, self-reported measures may be subject to recall and reporting biases, in particular for questions relating to adherence. Fifth, a number of questionnaires were created specific for this study, and were thus not externally validated.

A number of risk-prediction tools capable of estimating treatment-effects for lipid-lowering, blood pressure-lowering, and anti-thrombotic medications are now readily available in clinical practice for patients with and without CVD.[1] Statins are usually prescribed to patients with CVD during hospital admission for the first CVD event. Outpatient decision-making regarding statins in this population usually pertain to continuing or altering the current statin dose. In the present study, we aimed to examine a setting closely resembling the outpatient practice. However, only a small effect was found. Therefore, future studies could focus on populations with higher baseline decisional conflict such as patients experiencing adverse effects or considering intensifying preventive treatment with additional medication such as blood-pressure lowering or antithrombotic treatment.

In conclusion, providing statin users with clinically manifest CVD personalized estimations of treatment-effects, both in terms of 10-year absolute risk and CVD-free life-expectancy, resulted in small but significantly lower decisional conflict associated with statin use after one month of follow-up. This effect of the intervention disappeared after 6 months of follow-up. The results support the use of personalized predictions of absolute therapy benefit in clinical practice. Future studies may focus on decisions associated with higher decisional conflict such as the addition of more intensive preventive treatment options on top of standard treatment.

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Conflict of interest

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests."

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author Contributor statement

NEMJ, FLJV, YdG, OCD, CB, JAND contributed to the conception, design of the work and interpretation of the data, YMS & GEHMR contributed to the interpretation. NEMJ drafted the work and performed the analyses, FLJV, YdG, OCD, CB, JAND, YMS & GEHMR critically revised the work, all authors gave final approval and agree to be accountable for the work.

Data sharing statement

Some individual deidentified participant data (including data dictionaries) may be shared upon reasonable request pending approval by the department and institution on a case-by-

case basis. Approval will be based the scientific question to be answered with the data, ability of the authors of this manuscript to co-operate on the project, and compliance with contracts acquired for the questionnaires in this study and hospital and SMART-cohort policy.

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Figure Legends:

Figure 1: Participant flow during the trial

Figure 2: DCS at 1 month and Kruskal-Wallis analysis of variance and pos-hoc Wilcoxon-rank sum t-test. Boxes denote the median (25^{th}–75^{th} percentiles). Whiskers denote the 25^{th} percentile-1.5*(Inter-Quartile Range) and the 75^{th} percentile + 1.5(Inter Quartile Range).

Tables:

Table 1: Baseline characteristics

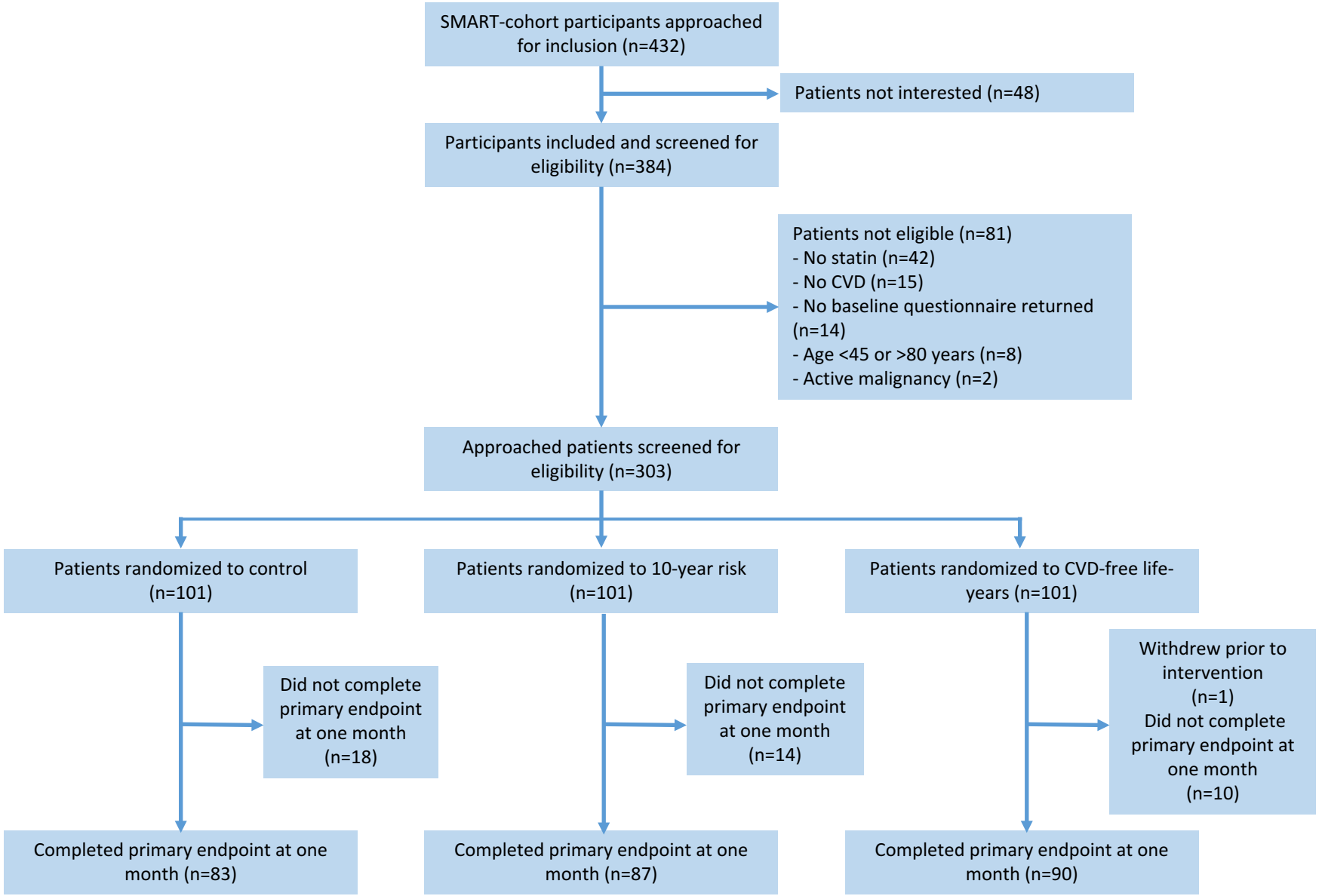
	Control-group	iAR-group	iLE-group
	n=101	n=101	n=101
Age	66(59-70)	66(58-71)	64(59-71)
Gender (male)	86%	82%	85%
More than one CVD location	11%	10%	10%
Current Smoker	17%	16%	9%
Years clinically manifest CVD	0(0-10)	0(0-10)	3(0-10)
Diabetes Mellitus	14%	27%	23%
LDL-cholesterol (mmol/L)	2.0(1.7-2.4)	2.0(1.6-2.4)	2.0(1.6-2.5)
LDL-cholesterol > 1.8 mmol/L	65%	67%	60%
Already on maximum statin therapy	1.3%	1.0%	1.0%
Creatinin (umol/L)	84(78-93)	83(75-96)	85(75-94)
Systolic blood pressure (mmHg)	131(121-142)	131(121-143)	129(122-142)
Number of medications per day	5(4-6)	6(4-9)	6(4-8)
Disutility score	61(9-97)	61(5-97)	61(9-97)
Adequate health literacy	83%	83%	81%

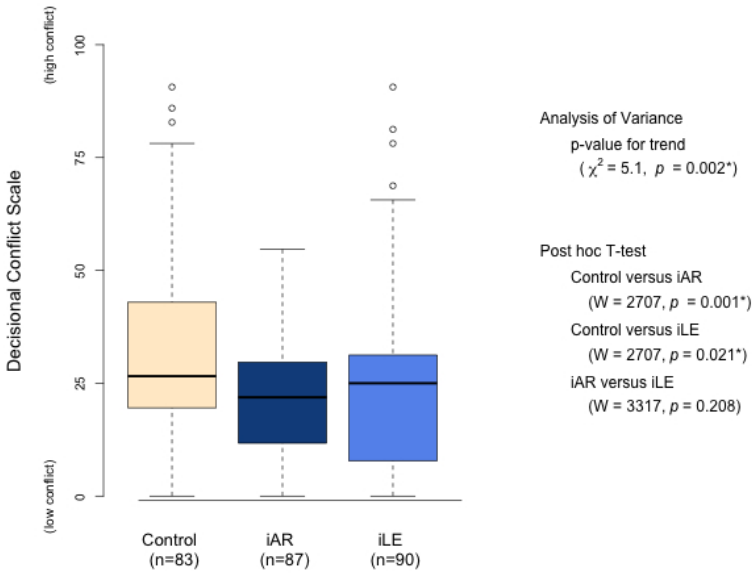
Legend: Data are reported as mean ± SD, median (interquartile range) or (%). CVD locations defined as coronary artery disease, peripheral artery disease, or abdominal aortic aneurysm in addition to cerebrovascular disease. Health literacy was based on the Newest Vital Sign score in the baseline questionnaire.[29] Disutility is months required to offset inconvenience of daily pill-taking of an idealized medication.[8] Number of medications excludes over the counter medications, (nasal) sprays, and topical medications. Maximum therapy was atorvastatin 80 mg.

Table 2: Patient Reported Secondary Outcomes

	Median (25th-75th percentile)			
	Control-group	iAR-group	iLE-group	p-value
DCS (6)	25(16-38)	22(9-29)	25(7-31)	p=0.10*
Brief-IPQ (1)	36(26-42)	34(28-44)	37(30-42)	p=0.68
Brief-IPQ (6)	34(26-43)	35(30-41)	37(29-44)	p=0.19
PAM (1)	60(51-70)	58(53-68)	63(56-75)	p=0.20
PAM (6)	64(54-77)	63(56-77)	63(56-78)	p=0.48
Perceived Statin Efficacy (1)	8(7-9)	8(7-9)	8(7-9)	p=0.92*
Perceived Statin Efficacy (6)	8(7-9)	8(7-9)	8(7-9)	p=0.98*
Understanding of therapy-effects (1)	88(75-88)	88(75-100)	88(75-100)	p=0.07*
Understanding of therapy-effects (6)	88(75-100)	88(75-100)	88(63-100)	p=0.60*
BMQ Adherence Risk Scale (1)	1(0-1)	1(0-1)	1(0-1)	p=0.60*
BMQ Adherence Risk Scale (6)	1(0-1)	1(0-1)	1(0-1)	p=0.41*
SDMQ9 (1); Reported visiting GP (n)	44(9-69); (46)	42(18-62);	58(22-76); (55)	p=0.40*
SDMQ9 (6); reported visiting GP (n)	44(24-73); (60)	48(32-63);	62(22-84); (47)	p=0.28*
RAND-36 Quality of life (6)				
Physical functioning	80(70-85)	75(60-85)	80(65-85)	p=0.11*
Role limitations due to physical health	80(70-85)	75(60-85)	80(65-85)	p=0.57*
Role limitations due to emotional problems	100(100-100)	100(100-100)	100(100-100)	p=0.80*
Energy/fatigue	75(65-80)	70(60-80)	73(55-80)	p=0.20*
Emotional well-being	84(73-92)	84(72-92)	80(72-88)	p=0.11*
Social Functioning	88(75-88)	88(63-88)	88(75-88)	p=0.49*
Pain	90(78-100)	90(68-100)	100(78-100)	p=0.93*
General health	70(55-75)	60(49-75)	65(50-74)	p=0.10*

Legend: Data are for one (1) or six (6) months. Bonferroni p-value for significance was 0.002. * Denotes a non-parametric test was applied.


SMART-cohort participants approached for inclusion (n=432)
Patients not interested (n=48)
Participants included and screened for eligibility (n=384)
Patients not eligible (n=81)
- No statin (n=42)
- No CVD (n=15)
- No baseline questionnaire returned (n=14)
- Age <45 or >80 years (n=8)
- Active malignancy (n=2)
Approached patients screened for eligibility (n=303)
Patients randomized to control (n=101)
Patients randomized to 10-year risk (n=101)
Patients randomized to CVD-free life-years (n=101)
Did not complete primary endpoint at one month (n=18)
Did not complete primary endpoint at one month (n=14)
Withdrew prior to intervention (n=1)
Did not complete primary endpoint at one month (n=10)
Completed primary endpoint at one month (n=83)
Completed primary endpoint at one month (n=87)
Completed primary endpoint at one month (n=90)



DCS at 1 month and Kruskal-Wallis analysis of variance and pos-hoc Wilcoxon-rank sum t-test. Boxes denote the median (25th–75th percentiles). Whiskers denote the 25th percentile-1.5*(Inter-Quartile Range) and the 75th percentile + 1.5(Inter Quartile Range).

268x169mm (72 x 72 DPI)

Supplement

Supplement 1 (A, B, and C):

The following examples are for a 55-year-old non-smoking non-diabetic Dutch male, with a history of coronary heart disease systolic blood pressure of 140 mmHg, a total cholesterol of 6.0 mmol/L, a creatinine of 93 umol/L, and LDL-cholesterol of 3.4 mmol/L. The patient currently uses atorvastatin 40 mg. *Disclaimer: These examples are for a fictionalized, hypothetical patient and not based on any actual individual.*

Supplement 1A: Anonymous example of standard-care.

Cholesterol:

Prevention program findings

The concentration of cholesterol in your blood is elevated. An elevated cholesterol level can increase the atherosclerotic process, or the accumulation of cholesterol and other deposits in the walls of your blood vessels.

Advice from the vascular team:

You are already being treated with a cholesterol lowering medication. Yet, your cholesterol level is still elevated. We therefore recommend adjusting the dose of your cholesterol lowering medication or switching to different cholesterol lowering medication. Talk to your doctor about considering this switch.

You can find more information about cholesterol and other risk factors on the internet: www.cholesterol.nl, www.hartstichting.nl, www.voedingscentrum.nl and www.vaatcentrum.nl.

Supplement 1B: Example of a 'personal health profile' for a hypothetical patient in the individualized absolute risk arm. ***Disclaimer: This is a fictionalized, hypothetical patient***

My Personal Heath Profile

Part of the SMART-INFORM study

In this folder you will find your personal heath profile, which we have made as part of your participation in the SMART-INFORM study. Elements of your medical status were used to complete the profile.

VIDEOS MADE FOR YOU

In this envelope, you will find six short videos designed to give you a bit of background information about this health profile and cardiovascular disease in general. The six videos are:

1. What is cardiovascular disease?
2. What is cholesterol?
3. What does a statin do?
4. Do statins have side-effects?
5. How do I read my personal health profile
6. What now?

The videos have been loaded onto the USB-card you are receiving with this Health Profile. You can watch the videos by plugging the USB card into a computer.

PERSONAL HEALTH PROFILE

- Mr. J. Smith, 73 years old
- Type of cardiovascular disease: Heart
- You are a non-smoker
- Creatinine-level (Kidney function): 100 umol/L
- Blood pressure: 140 / 90 mmHg
- Prescribed statin: Simvastatin 40 mg
- Total cholesterol: 4.7 mmol/L
- You do not have diabetes
- You do not report having atrial fibrillation (a type of abnormal heart rhythm)
- You do not report having heart-failure

In order to calculate how statin medication effects your prognosis, we used the aspects of your profile listed above. We have based these aspects on the medical records on-file at the hospital.

2

10-YEAR RISK

A 10-year risk estimates the chance that you will suffer a heart attack, stroke, or sudden death withi the next 10 years. We have estimated your 10-year risk in three different situations from which you can choose.

THREE SITUATIONS FROM WHICH TO CHOOSE

You can choose from the following three situations:

1. Continue with your current statin and dose, this is your current prognosis.
2. Stop taking your statin.
3. Increase your statin effectiveness by taking the highest dose of the strongest statin (atorvastatin 80mg).

1. CONTINUE

If you continue on your current statin and dose, your 10-year risk will be **21 %**

2. STOP

If you stop taking your statin, your 10-year risk will be **29 %**

3. INCREASE

If you increase your statin dose, your 10-year risk will be **18 %**

3

QUESTIONS?

If you have any questions about the SMART-INFORM study you can contact the investigators. They can be reached on weekdays on 000 00 000 00.

WE WILL CONTACT YOU

Within a few weeks, a researcher will be in contact with you to answer any additional questions or provide additional explanation regarding the personal health profile.

UMC Utrecht

4

Supplement 1C: Example of a 'personal health profile' for a hypothetical patient in the individualized life-expectancy arm. ***Disclaimer: This is a fictionalized, hypothetical patient***

My Personal Heath Profile

Part of the SMART-INFORM study

In this folder you will find your personal heath profile, which we have made as part of your participation in the SMART-INFORM study. Elements of your medical status were used to complete the profile.

VIDEOS MADE FOR YOU

In this envelope, you will find six short videos designed to give you a bit of background information about this health profile and cardiovascular disease in general. The six videos are:

1. What is cardiovascular disease?
2. What is cholesterol?
3. What does a statin do?
4. Do statins have side-effects?
5. How do I read my personal health profile
6. What now?

The videos have been loaded onto the USB-card you are receiving with this Health Profile. You can watch the videos by plugging the USB card into a computer.

PERSONAL HEALTH PROFILE

- Mr. J. Smith, 73 years old
- Type of cardiovascular disease: Heart
- You are a non-smoker
- Creatinine-level (Kidney function) 100 umol/L
- Blood pressure 140 / 90 mmHg
- Prescribed statin Simvastatin 40 mg
- Total cholesterol 4.7 mmol/L
- You do not have diabetes
- You do not report having atrial fibrillation (a type of abnormal heart rhythm)
- You do not report having heart-failure

In order to calculate how statin medication effects your prognosis, we used the aspects of your profile listed above. We have based these aspects on the medical records on-file at the hospital.

2

DISEASE-FREE LIFE EXPECTANCY

The disease-free life-expectancy indicates how long you can expect to live without having a heart attack, stroke, or sudden death. We have estimated your disease-free life expectancy in three different situations from which you can choose.

THREE SITUATIONS FROM WHICH TO CHOOSE

You can choose from the following three situations:

1. Continue with your current statin and dose, this is your current prognosis.
2. Stop taking your statin.
3. Increase your statin effectiveness by taking the highest dose of the strongest statin (atorvastatin 80mg).

3

QUESTIONS?

If you have any questions about the SMART-INFORM study you can contact the investigators. They can be reached on weekdays on 000 00 000 00.

WE WILL CONTACT YOU

Within a few weeks, a researcher will be in contact with you to answer any additional questions or provide additional explanation regarding the personal health profile.

UMC Utrecht

4

Supplement 2: Telephone consultation

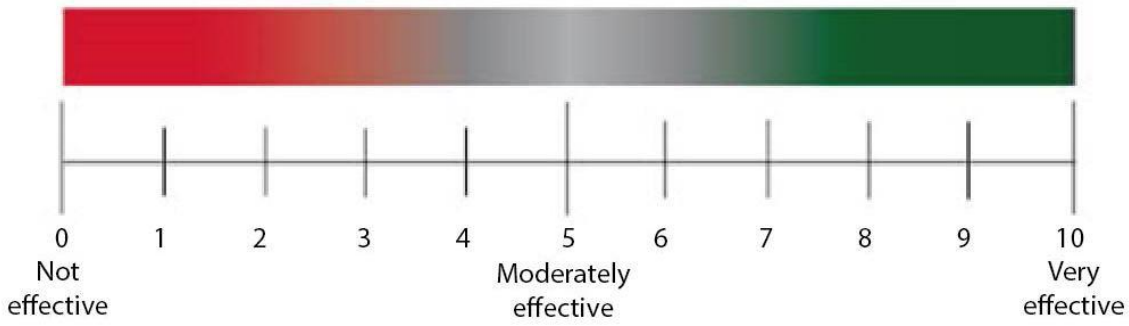
Short motivational telephone consultation following a structured interview asking the following questions:

- Did you receive the information?
- Have you been able to watch the videos?
- Did you understand all the information?
- Which questions did you have after studying the information?
- Did you already decide which statin treatment option you prefer?
- If yes, did you discuss this with your physician?

Supplement 3: Visual analogue scale

Estimation of therapy-effects

How great do you think the beneficial effects of your cholesterol lowering statin therapy are for you? Circle one number on the scale Below. A zero "0" means you believe that this medication is NOT effective for you and a ten "10" means you believe that is medication is VERY effective for you.



Supplement 4: Patient questionnaire to assess statin knowledge

What do you know about medication?

Below are a number of statements with answer choices. Please circle the answer choice which you believe is correct. If you do not know the correct answer, you can mark 'I don't know'

Where in the body can you get cardiovascular disease?

❒ heart ❒ legs ❒ both ❒ I don't know

Possible side-effects of statins is/are

❒ muscle pain ❒ breathing problems ❒ neither one ❒ I don't know

A high cholesterol gives a greater risk of

❒ stomach bleeds ❒ muscle or joint pain ❒ stroke/heart-attack ❒ I don't know

By using statins, I reduce my risk of

❒ stomach bleeds ❒ pneumonias ❒ heart-attacks ❒ I don't know

Due to the use of statins, the cholesterol levels in my blood will

❒ increase ❒ decrease ❒ stay the same ❒ I don't know

Through the use I statins, I reduce

❒ the fatty plaques in my arteries ❒ my blood pressure ❒ both ❒ I don't know

How long are people usually advised to use statins?

❒ for life ❒ 0-1 years ❒ 1-10 years ❒ I don't know

How does cholesterol get into to blood?

❒ My body produces cholesterol ❒ I get it from my food ❒ Both answers are correct ❒ I don't know

Supplement 5: Secondary outcomes score ranges

Scores on the IPQ range from 0 (non-threatening) to 80 (very threatening).[21] Patient Activation Measure (PAM-13) scores range from 0 (low activation) to 100 (high activation).[22] Perceived statin efficacy ranged from 0 (statins perceived as ineffective) to 10 (high level of statin effectiveness). The 9-item shared decision-making questionnaire ranged from 0 (poor shared decision-making) to 100 (optimal shared decision-making.[29] BMQ Adherence Risk Scale ranged from 0 (no-self-reported non-adherence) to 4 (self-reported non-adherence). Understanding of statin-therapy ranges from 0 (no answer correct) to 100 (all answers correct). RAND Medical Outcomes Study Short Form Survey (SF-36) questionnaire ranges from 0 (low quality of life) to 100 (high quality of life).[20]

Supplement 6: General practitioner questionnaire

	Definitely not (1)	Probably not (2)	Uncertain (3)	Probably yes (4)	Definitely yes (5)
1. How convinced are you that a statin is worthwhile for this patient?	□	□	□	□	□
2. Do you think the patient could benefit from a greater statin dose?	□	□	□	□	□
3. Would you consider statin discontinuation in this patient if the guidelines allowed?	□	□	□	□	□
The following three questions are only applicable if the patient was part of an intervention arm.					
4. How probable is it that you would use this information to aid in doctor-patient communication?	□	□	□	□	□
5. Do you think the consultation would be more efficient if you had this information beforehand?	□	□	□	□	□
6. Do you think this information would encourage therapy-adherence?	□	□	□	□	□

Legend: Questions 1-3 were asked of every GP. Questions 4-6 were additionally asked for physicians with patients randomized to the individualized absolute risk or the individualized life-expectancy groups.

Supplement table 1: Baseline characteristics per missing and non-missing for primary outcome

	Control		**iPOL**		**iARR**	
	Non-missing	Missing	Non-missing	Missing	Non-missing	Missing
Population	n=90	n=11	N=87	N=14	N=83	N = 18
Age	64 (59 - 72)	62 (60 - 67)	66 (59-71)	68 (59-73)	66 (59-72)	63 (59 – 68)
Gender (male)	77 (85%)	9 (82%)	72 (83%)	11 (79%)	71 (86%)	16 (89%)
One CVD location	79 (88%)	10 (91%)	77 (89%)	14 (100%)	75 (90%)	15 (83%)
Current smokers	13 (16%)	4 (22%)	9 (10%)	1 (9%)	9 (10%)	1 (9%)
Years clinically manifest CVD	5 (0 - 11)	0 (0 - 12)	5 (0-10)	0 (0-2)	0 (0-10)	6 (0-12)
Diabetes Mellitus	19 (21%)	4 (36%)	24 (28%)	3 (21%)	13 (16%)	1 (6%)
LDL-c (mmol/L)	2.0 (1.6 - 2.5)	1.8 (1.6 - 2.4)	2.1 (1.7 - 2.4)	1.7 (1.6 - 2.1)	2.0 (1.6 - 2.4)	2.0 (1.7 - 2.3)
LDL-c >1.8mmol/L	56 (62%)	5 (50%)	62 (71%)	6 (43%)	55 (66%)	11 (61%)
Creatinine (umol/L)	85 (75 - 92)	85 (74 - 97)	82 (74 – 96)	91 (80 – 106)	83 (78 – 95)	85 (80 – 90)
Systolic blood pressure (mmHg)	129 (122 - 142)	132 (116 - 150)	132 (121-145)	129 (120-132)	130 (121 - 140)	140 (124-148)
Number of medications per day	5 (4 - 7)	7 (5 - 10)	6 (4-9)	7 (6-8)	5 (4 - 7)	5 (4 - 6)
Months required to offset disutility of daily pill-taking	42 (9 - 97)	97 (35 - 97)	61 (3 – 97)	97 (70 – 97)	61 (9-97)	12 (9-61)
High likelihood limited literacy	6 (7%)	2 (18%)	6 (7%)	2 (14%)	5 (4%)	4 (22%)
Possibility of limited literacy	9 (10%)	2 (18%)	7 (8%)	2 (14%)	7 (9%)	1 (56%)
Adequate literacy	75 (83%)	7 (63%)	74 (85%)	10 (71%)	70 (85%)	13 (72%)

Legend: Data are reported as median (interquartile range) or n (%). CVD locations defined as coronary artery disease, peripheral artery disease, or abdominal aortic aneurysm in addition to cerebrovascular disease. Health literacy based on the Newest Vital Sign baseline questionnaire.[29] Number of medications excludes over the counter medications, (nasal) sprays, and topical medications.

Supplemental table 2: Physician reported secondary outcomes

	Median (IQR)			
	Control-group	iAR-group	iLE-group	Two-sided p-value
Post-interventional LDL-c				
LDL-c values determined	n=55	n=43	n=43	
No LDL-c values determined	n=27	n=42	n=42	
Unknown**	n=19	n=21	n=16	
Post-interventional LDL-c at 6 months (mmol/L)	1.9 (1.6 - 2.3)	1.9 (1.4 - 2.3)	1.9 (1.5 - 2.4)	p=0.60
Physician opinion of intervention				
Approached	n=93	n=88	n=87	
Participated	n=51	n=48	n=42	
Convinced that a statin is worthwhile for the patient*	5 (4-5)	5 (5-5)	5 (5-5)	p=0.50
Believes patient could use a higher dose*	3 (2-4)	3 (2-4)	3 (2-4)	† p=0.11
Would consider statin discontinuation if guidelines allowed*	2 (1-3)	2 (1-4)	2 (1-4)	† p=0.84
How probable to use information†*	N/A	4 (4-5)	4 (3-5)	† p=0.84
Believes that consultation would be more efficient†*	N/A	4 (3-5)	4 (3-5)	p=0.4
Believes that information would encourage therapy adherence†*	N/A	4 (3-5)	4 (3-4)	p=0.50

Legend: Data are reported as median (interquartile range) or n (%). †Only applicable for the intervention groups LDL-c=low-density lipoprotein cholesterol. Precise questions and answer choices are shown in supplement 6 "General Practitioner Questionnaire." *Median numbers of five-point scale where 1 = definitely not, 2= probably not, 3= uncertain, 4= probably yes, 5 = definitely yes. ** No link with dossier from general practioner possible after six months. † Denotes a non-parametric test was applied.

Supplemental table 3: Median DCS score per subgroup strata

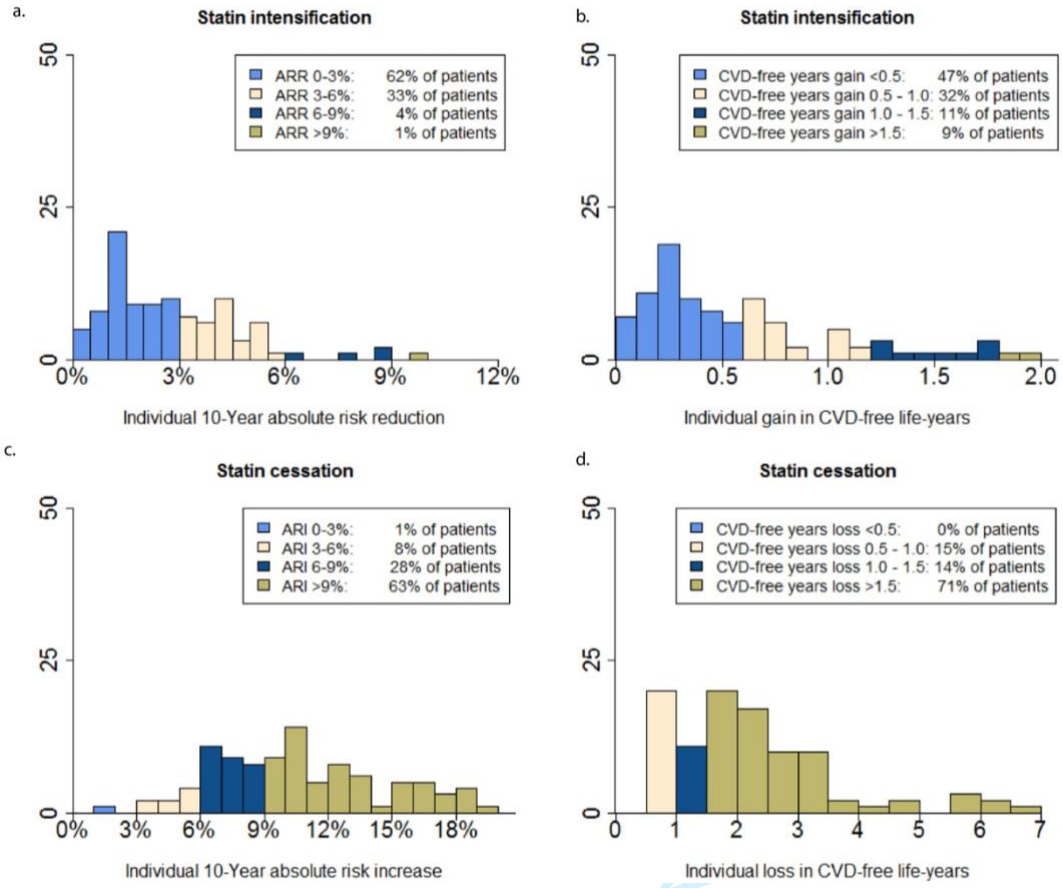
	Control –group		iAR –group		iLE –group	
Gender (F=7.02, p-value for interaction=0.32)						
Men	29.7 (19.5 - 42.2)	n=71	23.4 (11.7 - 29.7)	n=72	25.0 (10.9 - 32.8)	n=77
Women	25.8 (21.0 - 47.7)	n=12	14.1 (10.2 - 25)	n=15	26.6 (9.4– 29.7)	n=13
Age (F=0.17, p-value for interaction=0.90)						
>65	19.0 (20.3 - 42.2)	n=45	18.8 (9.0 - 28.6)	n=44	25.0 (8.6 - 31.3)	n=42
≤65	30.0 (19.5 - 42.6)	n=38	23.5 (13.3 - 30.7)	n=43	25.0 (12.9 - 31.6)	n=48
Patient activation measure (F=1.4, p-value for interaction=0.40)						
Low	26.7 (14.8 - 39.1)	n=21	21.9 (3.1 - 25.0)	n=13	26.6 (24.2 - 49.2)	n=15
High	26.7 (25.2 - 42.2)	n=43	23.4 (12.5 - 30.7)	n=43	22.4 (4.7 - 29.7)	n=49
Years since first CVD-event (F=1.4, p-value for interaction=0.24)						
>1 year	29.7 (20.3 - 45.3)	n=33	23.4 (4.7 - 29.7)	n=43	25.0 (14.9 - 33.2)	n=52
≤1 year	26.7 (19.9 - 39.8)	n=50	21.0 (14.1 - 30.0)	n=44	23.5 (5.5 - 33.2)	n=38
Educational level (F=2.8, p-value for interaction=0.09)						
Low	28.1 (25.0 - 37.5)	n=14	6.3 (3.1 - 18.8)	n=17	14.1 (1.6 - 25.0)	n=15
Middle	29.7 (13.3 - 46.1)	n=35	25.0 (16.4 - 30.7)	n=40	25.0 (22.3 - 30.5)	n=38
High	26.6 (20.7 - 41.0)	n=34	21.9 (17.2 - 30.9)	n=30	25.0 (7.8 - 34.4)	n=37
Health literacy* (F=4.0, p-value for interaction=0.02)						
High likelihood limited literacy	50.0 (29.7 - 53.1)	n=5	7.8 (3.1 - 13.7)	n=6	28.1 (25.0 - 31.3)	n=6
Possibility limited literacy	31.2 (25.0 - 41.4)	n=7	29.7 (18.7 - 30.5)	n=7	25.0 (0.0 - 42.1)	n=9
Adequate literacy	26.6 (18.8 - 41.8)	n=70	22.7 (12.9 - 29.7)	n=74	23.4 (8.6 - 29.7)	n=75
Disutility (F=0.6, p-value for interaction=0.54)						
Low (<9 months)	26.6 (14.1 - 45.3)	n=23	18.8 (3.1 - 25.0)	n=25	22.7 (9.0 - 25.4)	n=24
Middle (9-97 months)	32.0 (23.4 - 44.5)	n=18	23.4 (20.7 - 28.5)	n=14	27.3 (14.8 - 41.8)	n=26
High (>97 months)	32.0 (25.0 - 43.0)	n=24	17.2 (3.1 - 29.7)	n=31	23.4 (0.39 - 35.0)	n=22

Legend: Data are reported as median (25^{th} – 75^{th} percentile). *Further analyses for health-literacy are shown in supplemental figure 2. Health literacy based on the Newest Vital Sign.[29]

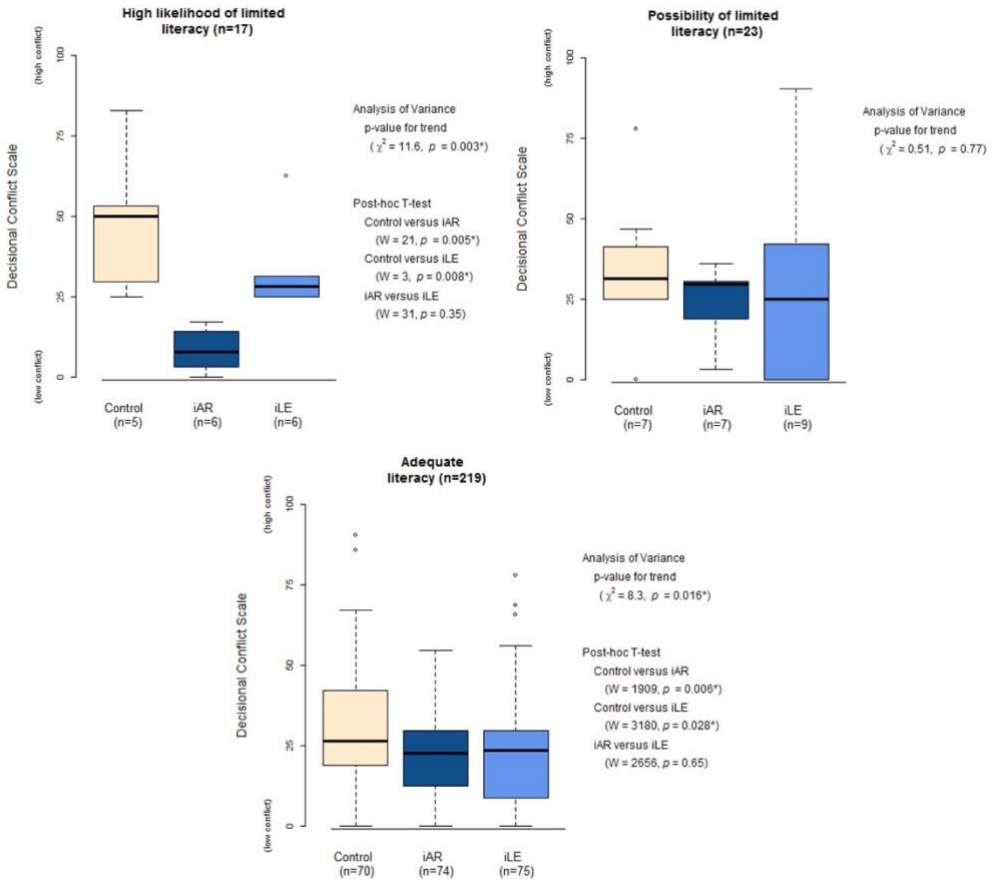
Supplemental table 4: Sensitivity analyses: Patient Reported Secondary Outcomes corrected for baseline characteristics.

	ANCOVA
	p-value
DCS (1)	p=0.49
DCS (6)	p=0.50
Brief-IPQ (1)	p=0.21
Brief-IPQ (6)	p=0.63
PAM (1)	p=0.39
PAM (6)	p=0.29
Perceived Statin Efficacy (1)	p=0.67
Perceived Statin Efficacy (6)	p=0.44
Understanding of therapy-effects (1)	p=0.16
Understanding of therapy-effects (6)	p=0.60
BMQ Adherence Risk Scale (1)	p=0.382
BMQ Adherence Risk Scale (6)	p=0.32
SDMQ9 (1); Reported visiting GP (n)	p=0.21
SDMQ9 (6); reported visiting GP (n)	p=0.35
RAND-36 Quality of life (6)	
Physical functioning	p=0.12
Role limitations due to physical health	p=0.48
Role limitations due to emotional problems	p=0.69
Energy/fatigue	p=0.86
Emotional well-being	p=0.25
Social Functioning	P = 0.71
Pain	p = 0.53
General health	P = 0.86

Sensitivity analyses for all outcomes at one (1) and six (6) months post intervention corrected for baseline characteristics: gender, age, smoking status, diabetes status, LDL-cholesterol (mmol.L), creatinine (umol/L), disutility score, NVS health literacy, and number of medications used per day



Supplemental Figure 1: Therapy-benefit from statin intensification to atorvastatin 80mg for a) iAR arm and b) iLE arm. Loss of benefit from statin discontinuation in c) iAR arm and d) iLE arm. In the iAR group, the median baseline 10-year absolute CVD risk was 37.6% (28.1-49.0). The estimated absolute 10-year risk change was -2.4% (-1.2 to -3.9) after intensification and 10.2% (7.7- 13.5) after discontinuation. In the iLE group, the median CVD-free life-expectancy was 75.4 years (73.0-82.7). The median change in CVD-free life-years was 0.5 years (0.3 – 0.8) after intensification and -2.0 years (- 1.3 - - 2.8) after discontinuation.



Supplemental figure 2: Subgroup analysis. Box-and-whisker plot depict the decisional conflict score at one month stratified by baseline health literacy. The colored boxes denote the median (25th – 75th percentiles). Whiskers denote the 25th percentile-1.5*(Inter-Quartile Range) and the 75th percentile + 1.5(Inter Quartile Range) in whiskers.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2/3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6/7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7/8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10 manuscript and in supplemental material
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	10/11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6, more details in 10
	11b	If relevant, description of the similarity of interventions	7/8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 and figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 12, figures 1 and supplemental table 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1, supplemental table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 12. Figure 1.
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Figure 2, table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Pg 14, supplemental table 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Pg 16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Pg 16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pg 14-17

Other information			
Registration	23	Registration number and name of trial registry	Pg 6
Protocol	24	Where the full trial protocol can be accessed, if available	Pg 18
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Pg 18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.