# Simulating the impact of targeting lower systolic blood pressure and LDL-cholesterol levels on type 2 diabetes complication rates

**Running title: Estimating benefits of targeting lower systolic blood pressure and LDL-cholesterol**

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Abbreviations:

SBP = systolic blood pressure

TECOS = Trial Evaluating Cardiovascular Outcomes with Sitaglitpin

T2DM = type 2 diabetes mellitus

UK Prospective Diabetes Study Outcomes Model© version 2 = UKPDS_OM2

Abstract

Aims

There are few data available on the incremental benefits of risk factor modification in type 2 diabetes mellitus (T2DM). We simulated the potential benefits of achieving lower systolic blood pressure (SBP) and LDL-cholesterol targets.

Methods

We used the UKPDS Outcomes Model v2.0 to estimate 10-year event rates for complications using baseline data from 5,717 participants with T2DM in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin Study. All risk factor values were held constant over 10 years. In separate analyses, different levels of SBP between 160 and 120mmHg and LDL-cholesterol between 5.0 and 1.0mmol/l were imposed on the cohort. Cumulative relative risk reductions (CRRR) at each 10mmHg and 1.0mmol/l decrements respectively were compared using Kruskal-Wallis tests.

Results

CRRRs for each 10mmHg SBP decrement from 160mmHg were 2.2%, 4.5%, 7.0% and 10.0% for myocardial infarction (MI); 12.5%, 24.8%, 35.6% and 44.9% for stroke; 5.4%, 10.9%, 16.2% and 20.9% for blindness; 7.4%, 14.7%, 21.6% and 27.4% for amputation, respectively.

CRRRs for each 1.0mmol/l LDL-cholesterol decrement from 5.0mmol/l were 16.9%, 30.8%, 41.2% & 51.0% for MI; 9.2%, 19.7%, 29.6% & 38.8% for stroke ($p<0.001$ in all cases).

Conclusions

These simulated outcomes illustrate the potential benefits of targeting progressively lower SBP and LDL-cholesterol values.

## Introduction

Controlling modifiable risk factors in type 2 diabetes mellitus (T2DM) reduces some of the excess risk of complications associated with this disease (1-5). Randomised controlled trials of risk factor lowering for systolic blood pressure (SBP) and LDL-cholesterol have demonstrated the benefits on reducing microvascular and/ or macrovascular complication rates. However, the effect size attributable to either SBP or LDL-cholesterol lowering can be difficult to determine as such trials report effects according to the observed risk factor reduction between intervention and control arms (4-7), rather than by specific decrements. Also, such trials rarely have interventions that last beyond 5 to 7 years (1, 5, 8).

The benefits of SBP and LDL-cholesterol lowering can be simulated. Even though the modelled benefits may not represent actual patient outcomes, such simulation exercises have certain advantages. These include (1) selecting a range of pre-determined monotonic interval reductions of risk factor lowering (e.g. estimating the outcome benefits per 10mmHg SBP or 1.0mmol/l LDL-cholesterol decrements), (2) modelling for estimated outcome benefits for pre-selected time periods (e.g. for 10 years) and not have to account for patient drop-out rates, (3) examining of the impact of targeting multiple levels with the same population and (4) allowing independent examination that SBP or LDL-cholesterol contributes to developing T2DM complications, without interference from many other risk factors. It is feasible to use modelling studies to augment trial data.

Within the SBP management, the optimal target SBP level in people with diabetes compared to those without diabetes has been under recent debate (5-7, 9-13). In people without diabetes, randomised controlled trials of SBP lowering which assessed the advantages of targeting a SBP level less than 140mmHg suggested beneficial effects may occur to a level of 120mmHg (9). The same overall beneficial effects have not been demonstrated to date in trials using participants with T2DM (5). Secondly, within LDL-cholesterol management, recent US recommendations suggest initiating statin therapy in adults aged 40 to 75 years without cardiovascular disease with a LDL-cholesterol greater than 4.9mmol/l and another

adverse risk factor, but no specific level has been suggested for those with established cardiovascular disease and T2DM (14).

In these simulations, we have used a T2DM-specific outcomes model to estimate the impact of a range of SBP and LDL-cholesterol reductions to different targets, and the likely scale of the possible benefits on 10-year outcomes that may be achieved.

## Materials and methods

### *T2DM-specific outcomes model*

The modelling exercise was performed using the UK Prospective Diabetes Study Outcomes Model© version 2 (UKPDS_OM2), a second-generation lifetime simulation model developed to estimate the period and lifetime risk of microvascular and microvascular disease events and mortality in people with diagnosed T2DM (15). The model accounts for first events and in the case of myocardial infarction and stroke for recurrent events. The model equations built into the UKPDS_OM2 are based on patient-level data, featuring a median of 17.6 years follow-up with up to 89,760 patient-years of data (2). The model is internally valid over 25 years, and external validation has shown similar prediction results to version 1.0 and that model performed well when evaluated in contemporaneous cohorts (15-17).

### *T2DM cohort*

To utilise real world risk factor variables from a contemporaneous T2DM cohort with cardiovascular disease, we modelled baseline participant-level data from the Trial Evaluating Cardiovascular Outcomes with Sitaglitpin (TECOS; clinical trials.gov registration number NCT00790205). Recruitment was between 2008 and 2012 and the trial finished by 2015 (18). The trial methods have been described elsewhere (19-20). No TECOS follow-up data were used in this analysis.

### *Model Simulation*

The risk factor variables required by UKPDS_OM2 are age, sex, ethnic group (white European, Asian and African-Caribbean), duration of T2DM, weight, height, HbA1c, SBP, HDL-cholesterol, LDL-cholesterol, smoking status (current smoker vs combined ex- and non-

smoker), heart rate, eGFR, haemoglobin, white blood cell count and a personal history of (a) microvascular events including renal failure (doubling of baseline serum creatinine level, macroalbuminuria or renal replacement therapy), single-eye blindness, amputation (any digit or limb) and ulcer, (b) macrovascular events including ischaemic heart disease (angina, atherosclerosis, acute coronary syndrome), myocardial infarction, stroke, peripheral vascular disease (atherosclerosis of an artery in the extremities, intermittent claudication, ulceration, gangrene or any interventional repair), heart failure and (c) albuminuria or atrial fibrillation.

To investigate the independent contribution of (1) SBP to 10-year micro- and macrovascular disease event risk and (2) LDL-cholesterol to 10-year macrovascular risk, all baseline risk factor variables (shown in Table 1) were held constant in the model for 10 years. During SBP modelling, individual patient baseline LDL-cholesterol values were used (cohort mean LDL-cholesterol 2.28 mmol/l). Similarly, during LDL-cholesterol modelling, individual patient baseline SBP values were used (cohort mean SBP 134.1 mmHg).

Assumptions were made for two baseline variables required for use in the model that were not collected in TECOS: personal history of renal failure and white blood cell count. Because TECOS excluded participants with an eGFR < 30 mL/min/1.73m$^2$, we assumed that no participants possessed a personal history of renal failure. For white blood cell count, participants were allocated a level of 8.0 x $10^9$ cells/L, approximating the mid-normal range. To explore the potential effect of this assumption on the outcomes of interest, sensitivity analyses were performed at white blood cell count levels of 4.0 and 12.0 x $10^9$ cells/L revealed no meaningful differences and only the analysis using white blood cell count of 8.0 x $10^9$ cells is reported here (21). Furthermore, within the model we assumed any personal history of medical events occurred more than 12 months prior to study enrolment.

To simulate the outcomes of 10-year risk estimates and 95% confidence intervals of macro- and micro-vascular events at five different imposed SBP levels, we ran the model

sequentially with SBP levels held constant at 160mmHg, 150mmHg, 140mmHg, 130mmHg and 120mmHg in turn. In the first simulation, all participants were assigned a SBP of 160mmHg, which was held constant for 10 years, as well as all other risk factor variables in the model. This process was repeated using the other imposed SBP levels mentioned above.

To simulate the outcomes of risk estimates and 95% confidence intervals for LDL-cholesterol on macro-vascular events, the simulations were repeated using sequential simulations with imposed LDL-cholesterol levels of 5.0mmol/l, 4.0mmol/l, 3.0mmol/l, 2.0mmol/l and 1.0mmol/l, which were held constant for 10 years, as well as all other risk factor variables in the model.

The outcomes for comparison of SBP targets were risk estimates of myocardial infarction, stroke, amputation, renal failure, blindness in one eye and all-cause mortality. Myocardial infarction and stroke included recurrent events. For LDL-cholesterol, the outcomes compared were risk estimates for myocardial infarction, stroke, heart failure and all-cause mortality. Outcomes were not simulated where the simulation model did not include either SBP or LDL-cholesterol to be a statistically significant independent risk factor for the events, as no clinically meaningful differences would be expected from comparing different levels of these risk factors (15).

All simulations generated risk estimates using 5000 loops and 500 bootstraps in the model for optimal precision of risk estimates and their 95% CI to examine the variability in estimates; these values were derived by testing the model for stability in estimates.

***Statistical analyses***

The distributions of continuous variables and 10-year cumulative risk estimates for all individual outcomes were visually inspected for normality using histograms. Subsequently,

variables were expressed as means (standard deviation) or medians (interquartile range), as appropriate. Risk estimates were compared between within categories of (1) SBP and (2) LDL-cholesterol using ANOVA and Kruskal-Wallis tests for parametric and non-parametric data, respectively. The cumulative risk estimates were used to calculate relative risk changes between SBP levels (expressed as percentages with 95% CI). The median cumulative risk estimate for a modelled constant SBP of 160mmHg over 10 years was compared with the corresponding median risk estimates of a modelled constant SBP of 150, 140, 130 and 120mmHg over 10 years, to investigate if each progressively lower 10mmHg SBP interval change led to larger relative risk reductions. A similar process was conducted for LDL-cholesterol levels between 5.0mmol/l and 1.0mmol/l at decrements of 1.0mmol/l.

Significance was determined by a two-sided statistical test with a p-value of <0.05 adjusted to account for multiple comparisons using a Bonferroni correction. A two-sided statistical test producing a p-value of <0.05 was considered as significant. Multiple comparisons were accounted for using a Bonferroni correction. Analyses were conducted using Minitab 17 statistical Software (State College, PA, USA) and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

## Results

From a total of 14,724 initial TECOS participants, 8690 (59.0%) people had at least one missing variable at baseline and 60 (1.0%) had a risk factor variable value beyond limits of use in the model (15). The remaining 5717 (38.8%) people with a complete set of baseline variables required for the model were used in these analyses. Baseline characteristics of the analysis cohort are shown in Table 1. The risk factor variables for those included and excluded from the analysis are presented in Supplementary Table 1. There were significant differences present for proportions of men (72.0% vs 69.9%, p=0.005), people of white European origin (74.2% vs 75.2%, p=0.001), smoking (53.7% vs 49.5%, p<0.001), history of heart failure (15.4% vs 19.6%, p<0.001) and peripheral vascular disease (17.9% vs 15.7%, p<0.001) respectively (see supplementary appendix 1).

The median absolute risk estimates for (1) 10-year macrovascular and microvascular events and mortality according to targeted SBP levels and (2) 10-year macrovascular events for targeted LDL-cholesterol levels are listed in Tables 2 and 3 respectively, and plotted in line-graphs in Figure 1 respectively.

Considering SBP estimates, for the risk of stroke over 10 years, the absolute median estimate was highest, 14.9% (95% CI 14.6, 15.2), for a modelled constant SBP of 160mmHg and was lower with each modelled 10mmHG SBP decrement (p for trend <0.001). Therefore, compared with the highest SBP level of 160mmHg, the median estimated 10-year cumulative relative risk reduction for stroke increased progressively with decreasing SBP, from a 12.5% reduction (95% CI 12.3, 12.7) for the smallest decrement of SBP from 160 to 150mmHg up to 44.9% (95% CI 44.8, 45.1) for comparison of SBP values held at 160 vs 120mmHg. Similar trends were noted for myocardial infarction, single-eye blindness, amputation, renal failure and all-cause mortality.

For each modelled 1.0 mmol/l LDL-cholesterol decrement there were similar trends were noted for median estimated 10-year cumulative relative risk reductions for myocardial infarction, stroke, heart failure and all-cause mortality (p for trend <0.001).

## Discussion

There are few data available on the possible scale of the incremental benefits that may be achieved by progressively decreasing SBP and LDL-cholesterol targets in T2DM, where the interventions are maintained for 10 years. This modelling study quantified the differential benefits in 10-year risk estimates of macrovascular and microvascular events attributable to lowering SBP alone and macrovascular events for LDL-cholesterol levels, by targeting lower thresholds starting from elevated baseline levels. Simulating monotonic 10mmHg SBP and 1.0 mmol/l LDL-cholesterol decrements and examining the corresponding T2DM outcomes allowed a detailed investigation of relative changes between targeted thresholds, in contrast to randomised controlled trials which report outcomes according to the observed risk factor level reductions. Maintaining all risk factor variables constant, including SBP and LDL-cholesterol, at their baseline values allowed us to examine the independent impact of SBP or LDL-cholesterol to T2DM complications, without the need to account for interference from other risk factors. As a result of using imposed SBP or LDL-cholesterol values and holding them and all other risk factor levels constant in model meant the estimated results were not representative of outcomes observed in the TECOS cohort.

To our knowledge this is the first T2DM study to report on multiple modelled SBP and LDL-cholesterol levels for T2DM complications, as well as all-cause mortality. Previous modelling studies have reported T2DM outcomes on one or two targeted risk factor level reductions for complications or life expectancy (22). Modelling the TECOS baseline cohort provided a large, modern day resource of participant-level risk factor variables of people with T2DM. These people were at high cardiovascular risk ensuring sufficient event rates for modelled outcomes to allow the examination of event rates between different SBP and LDL-cholesterol levels. While we appreciate modelling any high risk T2DM cohort is likely to produce higher absolute event rates compared with a population based T2DM cohort, the aim of this study was to demonstrate principles of SBP and LDL-cholesterol lowering for T2DM outcomes at each level modelled and not the absolute event rates themselves.

Regarding the 10-year risk estimate results, there were continuous reductions of all modelled events on progressively reducing SBP and LDL-cholesterol from constant monotonic decrements starting from 160mmHg and 5.0mmol/l respectively. For SBP, the largest magnitude of 10-year estimated relative risk reductions occurred for stroke events at 12% per 10mmHg SBP decrement. Assessing the scale of potential benefits of targeting a SBP of 120mmHg from 160mmHg led to 10-year estimated relative risk reductions of 44.9%, 10.0%, 20.9% and 27.3% for stroke, myocardial infarction, blindness and amputation respectively. The scale of potential benefits of targeting a LDL-cholesterol of 5.0 mmol/l to 1.0 mmol/l led to 10-year estimated relative risk reductions that were highest in myocardial infarction (51.0%), followed by stroke (38.8%) and heart failure (38.8%).

We consider the UKPDS_OM2 appropriate in these simulations given the high number of patient-years and events used to develop the risk factor projection equations, together with its internal and external validation of the model in modern cohorts. Use of the updated version 2.0 of the UKPDS_OM2 is likely to have improved precision of the risk estimates compared to version 1.0 and allowed us to account for some recurrent events (myocardial infarction and stroke). Other models could have been used for this analysis and may have produced different risk estimates, depending on the nature of the risk equations in the models (23-26). When these various models were evaluated for accuracy of risk predictions for outcomes compared to those observed in modern trials, each model appeared to have its own strengthens and weakness (16). Version 1.0 of the UKPDS_OM2 was also included in these evaluations and generally appeared to perform well at replicating trial outcomes in nearly all circumstances.

There are some limitations in the present study to consider. Firstly, the simulated results from this modelling study may not necessarily translate as robustly into real world findings. For example, risk factor variables were held constant over 10 years which is unlikely to occur. However, our aim was to demonstrate what might be achieved by isolating SBP and

LDL-cholesterol alone between models without taking into account changes in other risk factors, such as possible glucose lowering secondary to lipid profile improvements. Secondly, 5,717 people with T2DM were included from the initial baseline cohort of 14,724 people; they possessed some more adverse baseline risk factor variables compared to the people excluded from the analysis, including personal history of ever smoking and peripheral vascular disease. Overall, this may have contributed to a slight overestimate of simulated complication risks. However another risk factor, prevalence of heart failure, was significantly higher in those people included in the analysis and other risk factor variables were similarly matched between those excluded and included. Thirdly, the median absolute risk estimates for renal outcomes were relatively low as this outcome definition was based on end-stage renal disease and the baseline cohort possessed an eGFR ≥ 30 mL/min/1.73m$^2$. Fourthly, risk estimates could not be simulated for earlier forms of disease progression such microalbuminuria and background retinopathy. Fifthly, the results of the simulations are dependent on the UKPDS Outcomes Model, in which risk factors such as SBP and LDL-Cholesterol were found to have a mainly linear relationship with predicted events. Insofar as that is not the case, there could be some over- or under-estimation of benefits for given changes in these risk factors. Finally, use of the TECOS data limits our findings to people with T2DM and established cardiovascular disease, the majority of whom were White Caucasian, and acknowledging that the UKPDS Outcomes Model is validated only for people of White Caucasian, Asian or Afro-Caribbean ethnicity.

The current analysis does not account for any adverse effects of targeting lower risk factor levels in T2DM, which is important for SBP. The ACCORD-blood pressure trial reported in patients with T2DM and a baseline SBP of 139mmHg, use of intensive and standard therapy regimes decreased SBP to 119mmHg and 133mmHg which led to higher rates (3.3% vs 1.27%) of patients respectively experiencing an adverse event attributed to the therapies (5). From these events, hypotension rates were reported as 0.7% and 0.04% of cases

respectively. Arrhythmias (0.5% vs 0.13%) and hyperkalaemia (0.4 vs 0.04%) were also more common with use of the intensive regime. When LDL-cholesterol lowering is achieved through use of statin medications it can be associated with muscular problems (27-28).

There has been recent debate about whether the optimal target SBP level for T2DM should be lower than 140mmHg. The SPRINT trial of 9,361 high risk people without diabetes demonstrated that a targeted SBP of less than 120mmHg compared to 140mmHg led to lower rates of fatal and non-fatal cardiovascular events and all-cause death over 3 years (9). In contrast, the results of the ACCORD-blood pressure trial of people with T2DM used similar SBP targets over 4.7 years but only demonstrated a non-significant 12% lower risk of its primary cardiovascular composite outcome (hazard ratio 0.88, 95% CI 0.73 to 1.06) through intensive regimes (5). However, there was a significant secondary outcome of reduced annual rate of stroke by 41%. There are some important differences between these trials, which may be accounted for by population sizes, definitions of primary outcomes, expected versus observed event rates and choice of therapeutic agents used (5, 8). When the event outcomes from these two trials were combined, an overall benefit of aiming for SBP of 120mmHg was observed (11).

Modelling studies can be used to produce evidence to augment trial results by simulating scenarios that may not be feasible to re-create in trials or the real world. They can be especially useful when trial results may be under debate. Our simulated study suggests there are benefits of targeting a SBP less than 140 mmHg in people with T2DM, which is contrary to recent ACCORD trial results and suggests future trial evidence may require examining (5).

Further evidence from three recent meta-analyses differs on the benefits of lowering SBP targets beyond 140mmHg. The first meta-analysis of 49 randomised controlled trials consisting of 73,738 patients with diabetes (type 1 and 2) found treatment of baseline SBP to

less than 140 mmHg was associated with a 15% and 5% increased risk of cardiovascular and all-cause mortality respectively (6). A second meta-analysis of 19 trials consisting of 44,989 participants found patients on intensive treatment, mean SBP 133mmHg, had reduced major cardiovascular events and total mortality of 14% and 9% respectively compared to the standard arm who had mean SBP of 140mmHg. Within sub-group analyses, further benefits were observed in people with diabetes (7). A third meta-analysis of 74 trials with more 300,000 patients from the general population, found the effect of treating SBP less than 140mmHg may be associated with possible benefits on non-fatal cardiovascular events in people with existing coronary heart disease, but not for primary prevention (29).

Our study results also help to define the potential benefits of targeting individual decrements of 10mmHg for SBP management (and 1.0mmol/l for LDL-cholesterol), on which there is less evidence, and could be used clinically to define patient-specific targets for SBP management.

In conclusion, in this modelling study, targeting progressively lower SBP and LDL-cholesterol levels leads to a progressive reduction of estimated risk of T2DM macro- and microvascular complications between 160mmHg and 120mmHg and 5.0 mmol/l and 1.0 mmol/l respectively. In the case of SBP, there were benefits of targeting a level less than 140mmHg, which is contrary to recent trial evidence. Future research should focus on benefits and risks of targeting SBP levels lower than 140mmHg in T2DM.

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**Declarations**

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Other authors have no declarations.

**Contributions**

SM – designed the study, wrote the manuscript and performed the data modelling and statistical analysis under close supervision of the research statisticians (RC and OA). SM is guarantor of this paper.

RC – supervised the statistical analysis and data modelling, revised the manuscript

OA – supervised the statistical analysis and data modelling, revised the manuscript

AG - revised the manuscript

RRH – designed the study, revised the manuscript, provided material support

MAB - designed the study, revised the manuscript

**Table 1. Baseline characteristics of risk factor variables used for modelling in UKPDS_OM2 (n=5717)**

| Variable | Response |
|---|---|
| Age (years) | 66.2 (7.9) |
| Men (n, %) | 4119 (72.0) |
| White European (n, %) | 4241 (74.2) |
| Diabetes duration (years) | 9.6 (5.1 – 15.6) |
| Ever smoked (n, %) | 3068 (53.7) |
| Height (m) | 1.68 (0.1) |
| Weight (kg) | 85.2 (19.3) |
| SBP | 134.1 (16.9) |
| LDL-C (mmol/l) | 2.28 (0.9) |
| HDL-C (mmol/l) | 1.13 (0.3) |
| HbA1c (%, mmol/l) | 7.3 (0.6), 56 |
| Heart rate (bpm) | 71.6 (11.1) |
| Haemoglobin (g/dl) | 13.6 (1.5) |
| eGFR (ml/min/1.73m$^2$) | 75.1 (21.1) |
| Albuminuria (n, %) | 1378 (24.1) |
| Myocardial infarction (n, %) | 2428 (40.1) |
| Heart failure (n, %) | 880 (15.4) |
| Stroke (n, %) | 965 (16.9) |
| Atrial fibrillation (n, %) | 478 (8.4) |
| Peripheral vascular disease (n, %) | 1022 (17.9) |
| Renal failure (n, %) | 0 (0) |
| Blindness (n, %) | 97 (1.7) |
| Diabetes-related ulcer (n, %) | 158 (2.8) |
| Amputation (n, %) | 138 (2.4) |

Data is expressed as mean (standard deviation) or median (interquartile range) for continuous variables and n (%) for category variables. Key: bpm = beats per minute, eGFR = estimated glomerular filtration rate

**Table 2. 10-year estimated absolute risks and 95% confidence intervals for macrovascular and microvascular events at different systolic blood pressure (SBP) levels and corresponding relative risk reductions from a SBP of 160mmHg**

| SBP (mmHg) | 160 | 150 | 140 | 130 | 120 |
|---|---|---|---|---|---|
| **Myocardial Infarction (%)*** | 21.1 (20.8-21.4) | 20.7 (20.4-21.0) | 20.4 (20.2-20.6) | 20.1 (19.9-20.3) | 19.8 (19.6-19.9) |
| RRR (%) † | Reference | 2.2 (2.1-2.4) | 2.2 (2.0-2.3) | 2.1 (2.0-2.3) | 2.2 (2.0-2.3) |
| Cumulative RRR (%) * | Reference | 2.2 (2.1-2.4) | 4.5 (4.3-4.7) | 7.0 (6.7-7.4) | 10.0 (9.7-10.4) |
| **Stroke (%)** * | 14.9 (14.6-15.2) | 13.1 (12.8-13.4) | 11.4 (11.1-11.6) | 9.8 (9.6-10.1) | 8.5 (8.3-8.7) |
| RRR (%) § | Reference | 12.5 (12.3-12.7) | 12.4 (12.2-12.6) | 12.7 (12.5-13.0) | 12.7 (12.4-13.0) |
| Cumulative RRR (%) * | Reference | 12.5 (12.3-12.7) | 24.8 (24.6-25.0) | 35.6 (35.4-35.8) | 44.9 (44.8-45.1) |
| **Cardiovascular mortality (%)*** | 21.1 (20.7-21.5) | 20.2 (19.8-20.6) | 19.3 (18.9-19.7) | 18.5 (18.1-18.9) | 17.8 (17.4-18.1) |
| RRR (%) * | Reference | 4.1 (4.0-4.2) | 3.9 (3.8-4.1) | 3.9 (3.7-4.0) | 3.6 (3.5-3.7) |
| Cumulative RRR (%) * | Reference | 4.1 (4.0-4.2) | 8.1 (8.0-8.3) | 11.9 (11.7-12.1) | 15.2 (15.0-15.4) |
| **All-cause mortality (%)** * | 52.6 (51.7-53.4) | 51.7 (50.9-52.5) | 50.8 (50.0-51.8) | 50.1 (49.3-51.0) | 49.3 (48.5-50.3) |
| RRR (%) * | Reference | 1.4 (1.3-1.4) | 1.3 (1.2-1.4) | 1.2 (1.2-1.3) | 1.1 (1.0-1.2) |
| Cumulative RRR (%) * | Reference | 1.4 (1.3-1.4) | 2.8 (2.7-2.8) | 4.1 (4.0-4.2) | 5.2 (5.1-5.3) |
| **Single eye blindness (%)** * | 4.8 (4.8-4.9) | 4.6 (4.5-4.6) | 4.3 (4.2-4.4) | 4.0 (4.0-4.1) | 3.8 (3.8-3.9) |
| RRR (%) † | Reference | 5.4 (5.1-5.7) | 5.7 (5.5-6.0) | 5.7 (5.4-5.9) | 5.7 (5.5-6.0) |

| | | | | | |
|---|---|---|---|---|---|
| Cumulative RRR (%) * | Reference | 5.4 (5.1-5.7) | 10.9 (10.6-11.2) | 16.2 (16.0-16.4) | 20.9 (20.7-21.2) |
| **Amputation (%)** * | 2.4 (2.3-2.4) | 2.2 (2.1-2.2) | 2.0 (1.9-2.1) | 1.8 (1.8-1.9) | 1.7 (1.7-1.8) |
| RRR (%) † | Reference | 7.4 (6.9-8.0) | 7.2 (6.8-7.6) | 7.1 (6.8-7.7) | 6.9 (6.3-7.3) |
| Cumulative RRR (%) * | Reference | 7.4 (6.9-8.0) | 14.7 (14.3-15.1) | 21.6 (21.3-22.1) | 27.4 (27.0-27.8) |
| **Renal failure (%)** * | 0.3 (0.3-0.3) | 0.3 (0.2-0.3) | 0.2 (0.2-0.2) | 0.2 (0.2-0.2) | 0.2 (0.2-0.2) |
| RRR (%) † | Reference | 7.6 (6.7-8.3) | 7.1 (6.3-7.9) | 8.1 (7.1-9.1) | 7.4 (6.3-8.3) |
| Cumulative RRR (%) * | Reference | 7.6 (6.8-8.3) | 14.4 (13.9-15.4) | 21.7 (20.8-22.4) | 28.2 (27.3-28.6) |

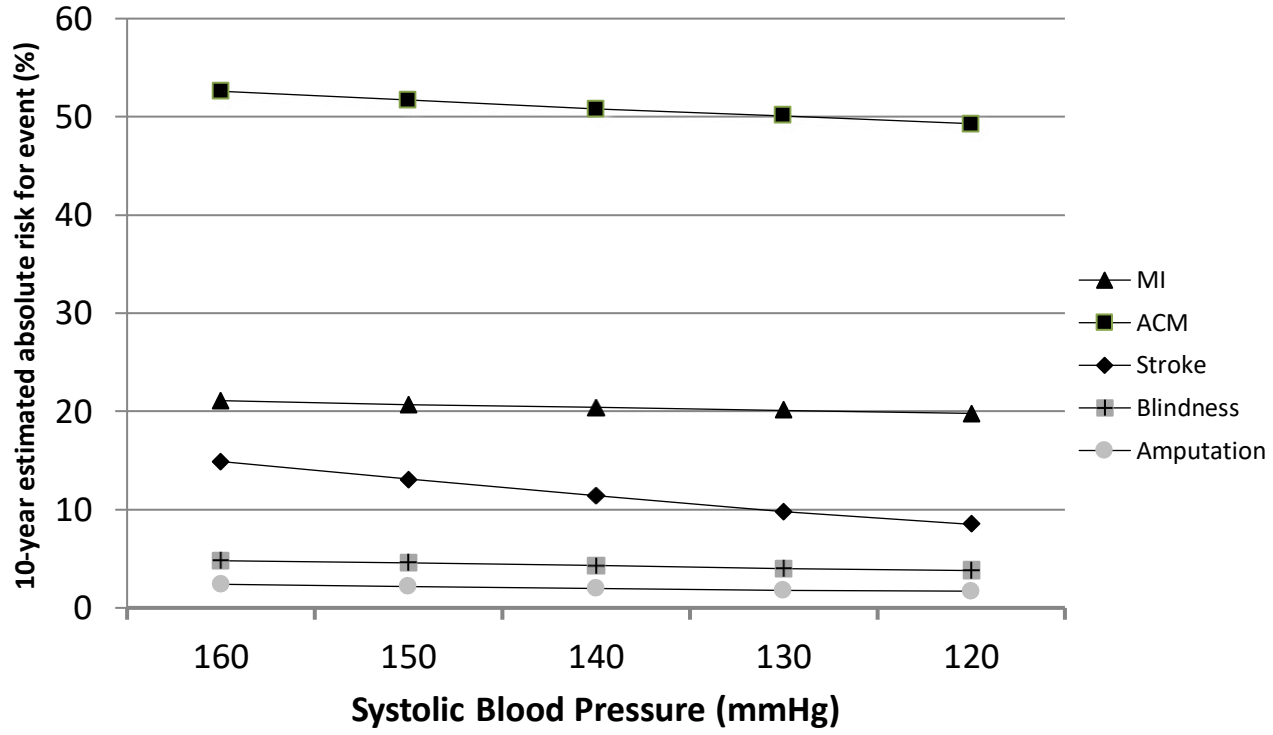
Data is expressed as median absolute point risk estimates for events with 95% confidence intervals with Bonferroni corrections applied to p-values to account for multiple comparisons. Myocardial infarction and stroke include both fatal and non-fatal events. All-cause mortality is included here for comparison, which is a composite of microvascular, macrovascular and non-vascular causes of death. Renal failure is defined as doubling of serum creatinine level, macroalbuminuria or renal replacement therapy). Amputation is defined as any digit or limb. Key: RRR = relative risk reduction, SBP = systolic blood pressure, * = $p<0.001$, § = $p<0.05$, † = $p> 0.05$

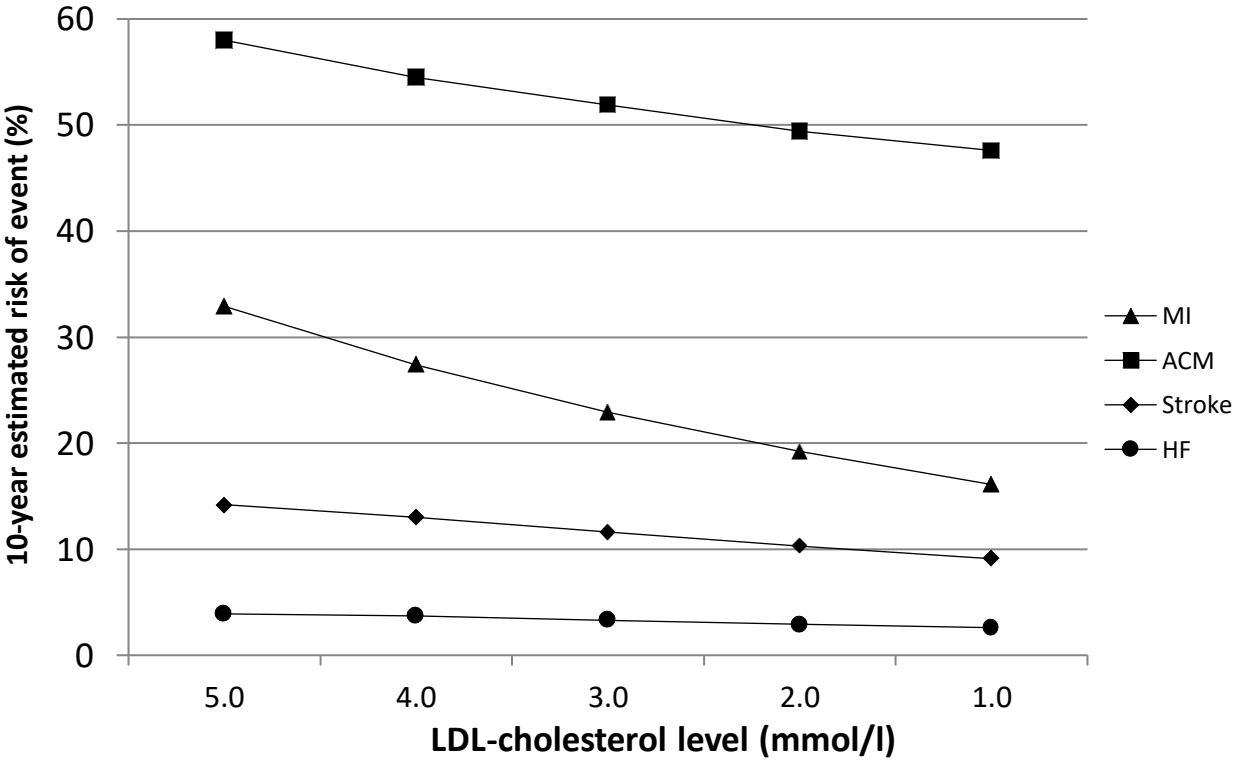
**Table 3. 10-year estimated absolute risks and 95% confidence intervals for macrovascular events at different LDL-cholesterol and corresponding relative risk reductions from a LDL-cholesterol of 5.0mmol/l**

| LDL-C (mmol/l) | 5.0 | 4.0 | 3.0 | 2.0 | 1.0 | p-value for trend |
|---|---|---|---|---|---|---|
| **Myocardial Infarction (%)** | 32.9 (32.7-33.2) | 27.4 (27.2-27.5) | 22.9 (22.7-23.0) | 19.2 (19.0-19.3) | 16.1 (16.0-16.2) | <0.001 |
| RRR (%) | Reference | 16.9 (16.7-17.0) | 16.3 (16.2-16.4) | 16.3 (16.1-16.5) | 16.7 (16.5-16.8) | <0.001 |
| Cumulative RRR (%) | Reference | 16.9 (16.7-17.0) | 30.8 (30.6-30.9) | 41.2 (41.1-41.4) | 51.0 (50.8-51.2) | <0.001 |
| **Stroke (%)** | 14.2 (13.8-14.5) | 13.0 (12.6-13.3) | 11.6 (11.4-11.9) | 10.3 (10.1-10.6) | 9.1 (8.9-9.3) | <0.001 |
| RRR (%) | Reference | 9.2 (8.9-9.4) | 9.8 (9.6-10.1) | 10.3 (10.1-10.6) | 10.7 (10.4-11.0) | <0.001 |
| Cumulative RRR (%) | Reference | 9.2 (8.9-9.4) | 19.7 (19.5-20.0) | 29.6 (29.4-29.9) | 38.8 (38.5-39.1) | <0.001 |
| **Heart failure (%)** | 3.9 (3.8-4.0) | 3.7 (3.5-3.7) | 3.3 (3.1-3.4) | 2.9 (2.9-3.0) | 2.6 (2.5-2.7) | <0.001 |
| RRR (%) | Reference | 7.6 (7.4-7.9) | 8.3 (8.0-8.7) | 9.3 (9.0-9.6) | 9.9 (9.6-10.1) | <0.001 |
| Cumulative RRR (%) | Reference | 7.6 (7.4-7.9) | 15.5 (15.1-15.8) | 23.7 (23.3-24.0) | 31.5 (31.2-31.9) | <0.001 |
| **All-cause mortality (%)** | 58.0 (57.1-58.9) | 54.5 (53.7-55.7) | 51.9 (50.8-52.9) | 49.4 (48.7-50.4) | 47.6 (46.7-48.5) | <0.001 |
| RRR (%) | Reference | 5.4 (5.3-5.5) | 4.6 (4.5-4.7) | 3.7 (3.6-3.9) | 3.6 (3.5-3.7) | <0.001 |
| Cumulative RRR (%) | Reference | 5.4 (5.3-5.5) | 10.2 (10.0-10.3) | 13.8 (13.6-14.1) | 17.3 (16.9-17.5) | <0.001 |

Data is expressed as median absolute point risk estimates for events with 95% confidence intervals with Bonferroni corrections applied to p-values to account for multiple comparisons. Myocardial infarction and stroke include both fatal and non-fatal events. All-cause mortality is included here for comparison, which is a composite of macrovascular and non-macrovascular causes of death. Key: RRR = relative risk reduction.

**Figure 1. Line graphs to represent 10-year estimated risk of (panel a) microvascular and macrovascular events at various targeted systolic blood pressure levels and (panel b) macrovascular events at target LDL-cholesterol levels**




Key for event: ACM = all-cause mortality, CVM = cardiovascular mortality, HF = heart failure, MI = myocardial infarction. Blindness is for a single-eye; amputation is defined as any limb or digit. Estimated risks were calculated as median point estimates (95% confidence intervals not shown as they are too narrow to be represented on the scales).