Individual lifetime benefit from low-dose colchicine in patients with chronic coronary artery disease

Pascal M. Burger, MD[1]; Jannick A.N. Dorresteijn, MD, PhD[1,*]; Aernoud T.L. Fiolet, MD, PhD[1,2,*]; Stefan Koudstaal, MD, PhD[2,3]; John W. Eikelboom, MD[4]; Stefan M. Nidorf, MD[5,6]; Peter L. Thompson, MD[5,6]; Jan H. Cornel, MD, PhD[2,7]; Charley A. Budgeon, PhD[8]; Iris C.D. Westendorp, MD, PhD[9]; Driek P.W. Beelen, MD[10]; Fabrice M.A.C. Martens, MD, PhD[2,11]; P. Gabriel Steg, MD[12]; Folkert W. Asselbergs, MD, PhD[1]; Maarten J. Cramer, MD, PhD[1]; Martin Teraa, MD, PhD[1]; Deepak L. Bhatt, MD, MPH[13,†]; Frank L.J. Visseren, MD, PhD[1,†]; Arend Mosterd, MD, PhD[2,14,†,‡]; for the LoDoCo2 Trial Investigators^, UCC-SMART Study Group^, and REACH Registry Investigators^

* Contributed equally.

† Contributed equally.

^ Listed in the Supplemental Material.

‡ Corresponding author: Arend Mosterd, MD, PhD, Meander Medical Centre, Maatweg 3, 3813 TZ Amersfoort, the Netherlands, A.Mosterd@meandermc.nl, + 31 33 8501101

[1] University Medical Centre Utrecht, Utrecht, the Netherlands

[2] Dutch Cardiovascular Research Network (WCN), Utrecht, the Netherlands

[3] Green Heart Hospital, Gouda, the Netherlands

[4] Department of Medicine, McMaster University, Hamilton, Canada

[5] GenesisCare Western Australia, Perth, Australia

[6] Heart Research Institute of Western Australia, Perth, Australia

[7] Radboud University Medical Centre, Nijmegen, the Netherlands

[8] School of Population and Global Health, University of Western Australia, Perth, Australia

[9] Red Cross Hospital, Beverwijk, the Netherlands

[10] IJsselland Hospital, Capelle aan den IJssel, the Netherlands

[11] Deventer Hospital, Deventer, the Netherlands

[12] Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Université de Paris, Paris, France

[13] Brigham and Women's Hospital Heart & Vascular Centre and Harvard Medical School, Boston, USA

[14] Meander Medical Centre, Amersfoort, the Netherlands

Keywords

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Abstract

Background and Aims

Low-dose colchicine reduces cardiovascular risk in patients with coronary artery disease (CAD), but absolute benefits may vary between individuals. This study aimed to assess the range of absolute benefit from low-dose colchicine according to individual patient risk profile.

Methods

The ESC guideline-recommended SMART-REACH model was combined with the relative treatment effect of low-dose colchicine, and applied to CAD patients from the LoDoCo2 trial and UCC-SMART cohort (n = 10,830). Individual treatment benefit was expressed as 10-year absolute risk reductions (ARRs) for myocardial infarction, stroke, or cardiovascular death (MACE), and MACE-free life-years gained. Predictions were also performed for MACE plus coronary revascularization (MACE+), using a new lifetime model derived in the REACH registry. Colchicine was compared to other ESC guideline-recommended intensified (step 2) prevention strategies, i.e. low density lipoprotein-cholesterol (LDL-c) reduction to 1.4 mmol/L, and systolic blood pressure (SBP) reduction to 130 mmHg. Generalizability to other populations was assessed in CAD patients from REACH North America and Western Europe (n = 25,812).

Results

Median 10-year ARR from low-dose colchicine was 4.6% (interquartile range [IQR] 3.6–6.0%) for MACE, and 8.6% (IQR 7.6–9.8%) for MACE+. Lifetime benefit was 2.0 (IQR 1.6–2.5) MACE-free years, and 3.4 (IQR 2.6–4.2) MACE+-free life-years gained. For LDL-c and SBP reduction respectively, median 10-year ARR for MACE was 3.0% (IQR 1.5-5.1%) and 1.7% (IQR 0.0-5.7%), and lifetime benefit was 1.2 (IQR 0.6-2.1) and 0.7 (IQR 0.0-2.3) MACE-free life-years gained. Similar results were obtained for MACE+, and in American and European patients from REACH.

Conclusions

The absolute benefits of low-dose colchicine vary between individual patients with chronic CAD. They may be expected to be of at least similar magnitude to those of intensified LDL-c and SBP reduction in a majority of patients already on conventional lipid-lowering and blood pressure-lowering therapy.

Lay summary

The long-term benefits of treatment with low-dose colchicine were estimated for 36,642 individuals with coronary heart disease, and compared to those of lipid- and blood pressure-lowering therapy.

- On average, low-dose colchicine was estimated to lower the risk of cardiovascular disease in the next 10 years from 17.8% to 13.2% (a reduction of 4.6 percentage points), and to afford 2.0 additional years of life without cardiovascular disease.

- Low-dose colchicine was estimated to be the most effective treatment in 49%, intensive blood pressure-lowering therapy in 28%, and intensive lipid-lowering therapy in 23% of patients.

Introduction

Patients with coronary artery disease (CAD) remain at high risk of cardiovascular events, despite the routine use of lipid-lowering, blood pressure-lowering, and antithrombotic therapies.[1,2] In recent years, anti-inflammatory therapy has emerged as another effective prevention strategy for patients with CAD.[3–5] In the 2021 European Society of Cardiology (ESC) Cardiovascular Disease (CVD) Prevention Guidelines, the anti-inflammatory drug colchicine (in a low dose; 0.5 mg once daily) has a class IIb recommendation (level A evidence).[1] Together with intensified lipid-lowering (i.e. low density lipoprotein-cholesterol [LDL-c] <1.4 mmol/L) and blood pressure-lowering (i.e. systolic blood pressure [SBP] <130 mmHg) therapy, dual antiplatelet therapy, low-dose rivaroxaban, and eicosapentaenoic acid (EPA), low-dose colchicine is among the intensified (step 2) prevention strategies that may be considered in patients with established CVD in addition to conventional (step 1) preventive therapy (i.e. smoking cessation, LDL-c <1.8 mmol/L, SBP <140 mmHg, and antithrombotic therapy).

The absolute benefits of preventive therapies are expected to vary between patients, depending on baseline CVD risk, remaining life expectancy, and current levels of treatment targets.[6] Patients with a high CVD risk and long potential treatment duration will likely gain the most from intensified treatment, whereas patients with a very low risk or limited life expectancy will receive a smaller benefit that may not outweigh the costs and risk of side effects. Moreover, patients with high levels of LDL-c and SBP may benefit most from intensified lipid-lowering and blood pressure-lowering therapy, whereas patients already on these therapies and with LDL-c and SBP

levels close to treatment targets may benefit more from other therapies to further reduce their residual risk of CVD. Therefore, the ESC Guidelines recommend that decisions on intensification of preventive therapy are based on a patient's 10-year CVD risk, lifetime risk, and individual treatment benefit, as estimated by the SMART-REACH model.[1,7] Applying this model to a group of patients with chronic CAD and otherwise varying characteristics could provide insight into the distribution of the individual absolute benefit from low-dose colchicine, and how this relates to other prevention strategies in this population.

The primary objective of this study was to assess the range of individual absolute benefit from low-dose colchicine in patients with chronic CAD according to patient risk profile. The secondary objective was to compare low-dose colchicine to other ESC guideline-recommended step 2 prevention strategies, i.e. LDL-c reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg, in addition to conventional therapy.

Methods

Study populations

Data were used from all participants enrolled in the LoDoCo2 trial (n = 5,522), a randomized, placebo-controlled clinical trial comparing low-dose colchicine (0.5 mg once daily) to placebo for the prevention of major cardiovascular events in patients with chronic CAD from the Netherlands and Australia.[5] In addition, data from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study were used, an ongoing prospective cohort study of patients with established CVD at the University Medical Centre Utrecht, the Netherlands.[8] Patients with chronic CAD (defined as a history of myocardial infarction [MI], percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]) included

between September 1996 and January 2019 were selected (n = 5,308). Finally, we used data from the REACH registry, a prospective cohort study of patients with established CVD recruited from general practitioners and medical specialist outpatient clinics worldwide.[9] Western European patients with established CVD, i.e. CAD, cerebrovascular disease, or peripheral artery disease (n = 14,522), and North American patients with chronic CAD (n = 15,764) were selected. Detailed descriptions of the original studies have been published elsewhere.[5,8,9] All studies were approved by an institutional review board, and written informed consent was obtained from all participants. Eligibility criteria are described in Table S1. Missing data (Table S2) were handled by multiple imputation (Methods S1).

Outcomes

Outcomes of interest were (i) MI, ischemic stroke, or cardiovascular death (MACE), and (ii) coronary revascularization (i.e. PCI or CABG), MI, ischemic stroke, or cardiovascular death (MACE+). The competing outcome was non-cardiovascular mortality. Detailed endpoint definitions are provided in Table S3.

External validation of the SMART-REACH model

The SMART-REACH model is the ESC guideline-recommended tool for prediction of 10-year risk of MACE, and MACE-free life expectancy in patients with established CVD.[1,7] In this study, the model was externally validated in LoDoCo2, and temporal validation was performed in UCC-SMART (validation had previously been performed on a smaller dataset).[7] If necessary, the model was recalibrated for differences in baseline risk. Model performance was assessed using measures of discrimination and calibration, i.e. plots of predicted vs. observed risk.

Development and validation of a lifetime prediction model for MACE+

As the primary endpoint of the LoDoCo2 trial included coronary revascularizations, we developed a new model (i.e. the SMART-REACH+ model) based on the same methodology used for the original SMART-REACH model.[7,10] Cox proportional hazards functions were derived in REACH Western Europe (n = 14,522) for: (i) MACE+, and (ii) non-cardiovascular mortality. Predictors, pre-specified based on the original SMART-REACH model, were: sex, current smoking, diabetes mellitus, SBP, total cholesterol, creatinine, CAD, cerebrovascular disease, peripheral artery disease, atrial fibrillation, and heart failure. Age was used as the time scale of the model (i.e. left truncation), so that participants contributed data to the model from their age at study entry to their age at time of an event or censoring. This allows for the estimation of age-specific baseline survivals, used to make predictions beyond the follow-up duration of the original cohort (Methods S2 & Figure S1). Model assumptions are described in Table S4.

Consistent with the original SMART-REACH model, the SMART-REACH+ model was externally validated in LoDoCo2 and UCC-SMART.

Estimating CVD risk and CVD-free life expectancy for individual patients

For all patients in LoDoCo2 and UCC-SMART (n = 10,830), survival free of MACE, and MACE+ (i.e. the CVD events of interest) were estimated using the SMART-REACH and SMART-REACH+ models, by making use of life-tables.[10] Starting from the age of each patient at baseline, the risk of the CVD event of interest (a_t) and the risk of non-cardiovascular mortality (b_t) were estimated for each consecutive life-year, up to the maximum age of 100 years. A CVD-free survival probability (p_t) was obtained for each life-year, by subtracting CVD risk and non-cardiovascular mortality risk from 1 ($p_t = 1 - a_t - b_t$). The probability of being alive and free of

the CVD event of interest at the start of each life-year (e_t), was calculated by multiplying the CVD-free survival probabilities of all the previous life-years (e.g. for a 60-year old: $e_{t=63} = p_{t=60} * p_{t=61} * p_{t=62}$). Altogether, these predictions form an individual life-table for each patient. Predictions of 10-year risk of MACE and MACE+ were derived from the life-tables by calculating the cumulative cause-specific event risk truncated at 10 years after the starting age. MACE-free and MACE+-free life expectancy were defined as the age where the cumulative MACE-free and MACE+-free survival probabilities (e_t) in the life-table equalled 0.50 (= 50%).

Prediction of individual benefit from low-dose colchicine

The prognostic models were combined with hazard ratios (HRs) from the LoDoCo2 trial, in line with previously described methods.[7,10] HRs were 0.72 for MACE, and 0.69 for MACE+.[5] Subsequently, ten-year risks of MACE and MACE+, and MACE-free and MACE+-free life expectancies on low-dose colchicine were estimated for each patient in LoDoCo2 and UCC-SMART. Individual 10-year absolute risk reduction (ARR) was defined as the difference between the predicted 10-year risk with and without low-dose colchicine. Likewise, lifetime benefit was defined as the difference between on- and off-colchicine life expectancies, expressed as MACE-free and MACE+-free life-years gained. Low-dose colchicine was assumed to have no effect on non-cardiovascular mortality, among other assumptions (Table S4). Additionally, analyses were performed stratified by smoking status, baseline risk and age, cohort, and country.

Comparison with other step 2 prevention strategies

Low-dose colchicine was compared to the following ESC guideline-recommended intensified (step 2) prevention goals: LDL-c reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg.[1] Benefits from achieving these targets were estimated for all patients with available baseline

measurements of LDL-c and SBP by combining the models with an HR of 0.78 for every 1 mmol/L reduction from baseline to target LDL-c (i.e. $HR_{LDL\text{-}c\ reduction} = 0.78^{\wedge(baseline\ LDL\text{-}c\ -\ 1.4)}$), and a hazard ratio of 0.80 for every 10 mmHg reduction from baseline to target SBP (i.e. $HR_{SBP\ reduction} = 0.80^{\wedge(baseline\ SBP\ -\ 130)/10}$), in line with large-scale meta-analyses.[11,12] Estimates should be interpreted as the predicted benefits of achieving these targets, regardless of the lipid-lowering and blood pressure-lowering therapies currently used by a patient and the therapies prescribed to reach the targets. As some patients meeting treatment targets reflects clinical practice, patients with baseline LDL-c ≤1.4 mmol/L or SBP ≤130 mmHg were not excluded from the analyses, but were considered to have no benefit from reaching targets they already met at baseline. A sensitivity analysis was performed in patients not meeting treatment targets at baseline.

Generalizability to other populations

As LoDoCo2 and UCC-SMART only include patients from the Netherlands and Australia, a sensitivity analysis was performed in which the models were applied to patients with chronic CAD from REACH North America (n = 15,764) and REACH Western Europe (n = 10,048).

All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

To facilitate use of the models in clinical practice, low-dose colchicine was added to the existing online SMART-REACH calculator (available at www.U-Prevent.com), and a new calculator was developed for the SMART-REACH+ model (Supplemental Material; Calculator).

Results

Patient characteristics

Patients from UCC-SMART and REACH Western Europe more often had extracardiac vascular disease, and had higher cholesterol and creatinine levels than patients from LoDoCo2 (Table 1). Despite differences in cardiovascular risk profiles, the distribution in medical treatment strategies was similar between LoDoCo2 and UCC-SMART. In the combined LoDoCo2 and UCC-SMART study population, mean baseline LDL-c was 2.4±0.9 mmol/L (n = 8,595) and SBP was 137±19 mmHg (n = 8,801). Respectively, 26.6% and 10.0% of patients met the LDL-c step 1 (≤1.8 mmol/L) and step 2 (≤1.4 mmol/L) targets, and 63.5% and 41.7% met the SBP step 1 (≤140 mmHg) and step 2 (≤130 mmHg) targets at baseline (Figure S2).

Outcomes

In LoDoCo2, 272 MACE, 451 MACE+, and 88 non-cardiovascular deaths occurred during a median follow-up of 2.5 years (interquartile range [IQR] 1.8-4.0). In UCC-SMART, 1,026 MACE, 1,885 MACE+, and 616 non-cardiovascular deaths occurred during a median follow-up of 9.0 years (IQR 4.7-13.0). Kaplan-Meier curves are presented in Figure S3.

Development of the SMART-REACH+ model

Multivariable hazard ratios are presented in Table S5. Age-specific baseline survivals and the completed risk algorithms are provided in Table S6 & S7. The interactive calculator is provided in the Supplemental Material.

External validation in LoDoCo2 and UCC-SMART

External validation of the SMART-REACH and SMART-REACH+ models showed good agreement between the predicted and observed 3-year (LoDoCo2) and 10-year (UCC-SMART) risk of MACE and MACE+ (Figure S4).

Absolute benefit from low-dose colchicine

The estimation of (lifetime) benefit from low-dose colchicine for an individual patient is illustrated in Figure 1A (outcome is MACE), and Figure S5A (outcome is MACE+).

In the combined LoDoCo2 and UCC-SMART study population, median 10-year baseline risk (without low-dose colchicine) of MACE was 17.8% (IQR 13.4-23.9%), MACE+ was 32.0% (IQR 27.6-37.7%), and non-cardiovascular mortality was 6.3% (IQR 3.2-11.1%) (distributions in Figure S6 & S7). Median predicted baseline survival free of MACE was 18.0 years (IQR 13.7-23.0), and free of MACE+ was 13.6 years (IQR 10.9-16.8). The distribution of the estimated 10-year and lifetime benefit from low-dose colchicine is shown in Figure 2. The median 10-year benefit from low-dose colchicine, in terms of the estimated absolute reduction in the 10-year risk of MACE, was 4.6% (IQR 3.6–6.0%) (Table 2). This translates to an individual number needed to treat (iNNT) of 21.6 (IQR 16.7–28.2) to avoid one MACE event over 10 years of treatment (Figure S8). The median estimated lifetime benefit, in terms of years gained in life expectancy free of MACE, was 2.0 years (IQR 1.6–2.5 years). Median predicted 10-year ARR for MACE+ was 8.6% (IQR 7.6–9.8%), 10-year iNNT was 11.6 (IQR 10.2–13.2), and gain in MACE+-free life expectancy was 3.4 years (IQR 2.6–4.2 years) (Table 2).

Stratified analyses

Estimated CVD risk reductions from low-dose colchicine were larger for current smokers compared to non-smokers (median 10-year ARR: 5.2% vs. 4.5% for MACE, and 8.9% vs. 8.5% for MACE+), but as smoking increases the risk of non-cardiovascular mortality, gains in CVD-free life expectancy were similar or smaller (median 2.1 vs. 2.0 MACE-free years gained, and 3.1 vs. 3.4 MACE+-free years gained; Figure S9). Estimated 10-year CVD risk reductions increased with increasing baseline risk, while gains in CVD-free life expectancy decreased with increasing age and remained relatively stable over risk strata (Figure 3 & Figure S10). Due to the increased (i.e. real-world) incidence of non-cardiovascular mortality in UCC-SMART, the estimated gain in MACE-free (median 1.7 vs. 2.3 years) and MACE+-free life expectancy (median 3.1 vs. 3.6 years) was lower in this cohort compared to the LoDoCo2 trial population, while 10-year risk reductions were similar (Figure S11). Likewise, within LoDoCo2, the slightly higher risk of non-cardiovascular mortality in participants from Australia led to slightly smaller estimated gains in MACE-free (median 2.2 vs. 2.5 years) and MACE+-free life expectancy (median 3.5 vs. 3.8 years) as compared to participants from the Netherlands (Figure S12).

Comparison with intensified LDL-c and SBP reduction

Comparison of low-dose colchicine with intensified LDL-c and SBP reduction is demonstrated for three individual patients in Figure 1B and Figure S5B.

The median estimated 10-year CVD risk reductions and gains in CVD-free life expectancy were smaller with intensified LDL-c and SBP reduction than with low-dose colchicine (Table 2 & Figure S13). For each individual patient, differences in the estimated lifetime benefits of low-dose colchicine as compared to intensified LDL-c and SBP reduction are shown in Figure 4

(MACE) and Figure S14 (MACE+). These differences are also presented in histograms in Figure S15. Based on the estimated gain in MACE-free life expectancy, low-dose colchicine was expected to be the most, second most, and least effective strategy in 48.7%, 40.9%, and 10.4% of patients respectively (Figure 5).

In patients not meeting the LDL-c target at baseline (n = 7,729), median estimated CVD risk reductions and gains in CVD-free life expectancy were still smaller with intensified LDL-c reduction than with low-dose colchicine (Table 2). In patients not meeting the SBP target at baseline (n = 5,055), the median estimated benefits of intensified SBP reduction and low-dose colchicine were similar. For all patients individually, comparisons are presented in Figure S16. Low-dose colchicine was expected to be the most, second most, and least effective strategy in respectively 31.0%, 49.7%, and 19.3% of patients not meeting any of the two targets at baseline (n = 4,567; Figure S16E).

Benefits of combined therapy

Median estimated 10-year ARRs from combined therapy with low-dose colchicine, LDL-c reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg, were 8.7% (IQR 6.2–12.5%) for MACE, and 15.9% (IQR 12.2–21.1%) for MACE+ (Table 2; distributions in Figure S17). Median estimated gains in MACE- and MACE+-free life expectancy were 4.0 years (IQR 2.9–5.5 years), and 6.6 years (IQR 4.6–9.5 years) respectively.

Generalizability to North America and Western Europe

CAD patients from REACH North America and Western Europe were older and more often had extracardiac vascular disease and diabetes mellitus than patients from LoDoCo2 and UCC-

SMART (Table S8). Patients from REACH Western Europe also had higher cholesterol levels. Performance of the models was adequate in these populations as well (Figure S18). Baseline CVD risk was higher in REACH North America (e.g. median predicted 10-year risk of MACE; 29.1%) and Western Europe (29.8%), than in LoDoCo2 and UCC-SMART (17.8%). As a result, estimated 10-year CVD risk reductions from low-dose colchicine and other therapies were larger (Table S9 & Figure S19). But due to the older age and increased risk of non-cardiovascular mortality (median 10-year risk; 9.8% and 8.4% vs. 6.3%), estimated gains in CVD-free life expectancy were similar. In REACH North America, like in LoDoCo2 and UCC-SMART, the estimated benefits of low-dose colchicine exceeded those of intensified LDL-c and SBP reduction in the majority of patients (Figure S20). In REACH Western Europe, the estimated benefits of low-dose colchicine exceeded those of intensified SBP reduction, but due to the higher baseline cholesterol levels, were smaller than those of intensified LDL-c reduction in the majority of patients.

Discussion

Using data of 36,642 patients with chronic CAD from various populations, we demonstrated the range of individual absolute 10-year and lifetime benefit from anti-inflammatory treatment with low-dose colchicine. When added to conventional lipid-lowering and blood pressure-lowering therapy, the estimated absolute benefits of low-dose colchicine regularly exceeded those of intensified LDL-c and SBP reduction. The SMART-REACH and SMART-REACH+ models enable identification of patients with a relevant benefit from low-dose colchicine in clinical practice.

An important challenge for physicians in everyday clinical practice is translating trial results and guideline recommendations to individual patients. The lifetime models presented in this study provide personalized estimates of the absolute 10-year and lifetime benefit from low-dose colchicine, and other preventive therapies, expressed as absolute risk reductions and CVD-free life-years gained. A physician could use these estimates to discuss with a patient whether the estimated benefit from low-dose colchicine is worthwhile by comparing colchicine to other preventive therapies, and by weighing benefit against the potential burden of taking an extra pill, costs, and risk of side effects. This could support clinical and shared decision-making with respect to the initiation of ESC guideline-recommended step 2 prevention strategies in clinical practice.

The 2021 ESC CVD Prevention Guidelines recommend that low-dose colchicine may be considered as a step 2 secondary prevention strategy, particularly in high-risk patients with other insufficiently controlled risk factors or recurrent CVD events under optimal therapy.[1] This study showed that 10-year absolute risk reductions from low-dose colchicine are largest for patients with a high baseline risk of CVD. However, as with other preventive therapies, lifetime benefit in terms of CVD-free life-years gained was shown to be largest for younger individuals, irrespective of baseline CVD risk. So, the benefits of low-dose colchicine exist for low-risk individuals as well, and as also shown in this study, may be expected to be of at least similar magnitude to those of intensified LDL-c and SBP reduction. This is a supported by a recent analysis of three contemporary cardiovascular trials, showing that among patients receiving contemporary statins, inflammation (assessed by C-reactive protein [CRP]) is a stronger predictor of cardiovascular events and death than LDL-c.[2] This suggests that lowering inflammation may be a more effective approach to reducing the residual risk of CVD than intensification of lipid-lowering therapy.

These findings may support a broader use of low-dose colchicine in the secondary prevention of CVD.

In this study of patients with chronic CAD, the majority of whom were already using lipid-lowering (88%) and blood pressure-lowering (90%) medication, the expected benefits of low-dose colchicine regularly exceeded those of intensified LDL-c reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg. This observation can be partially attributed to the fact that some patients already met the LDL-c and SBP targets at baseline. But a majority of patients using lipid-lowering and blood pressure-lowering medication, and a proportion of patients already (closely) meeting treatment targets reflects clinical practice.[13,14] Also, low-dose colchicine was still estimated to be the most or second most effective preventive therapy in large proportions of patients not meeting LDL-c and SBP targets. Patients with high levels of LDL-c (>3.0 mmol/L) or SBP (>145 mmHg) were generally estimated to have a larger benefit from LDL-c or SBP reduction. But this is assuming that treatment targets are reached, and maintained for the patients' remaining lifetimes. In practice, reaching and maintaining LDL-c and SBP targets is not always possible due to side-effects of, and non-adherence to lipid-lowering and blood pressure-lowering medication.[14,15] Low-dose colchicine is relatively cheap, with low-priced generics available worldwide (though not in the US), and may therefore be a reasonable alternative to expensive therapies such as proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, especially in low- and middle-income countries.[16] Lastly, colchicine treatment does not preclude intensified lipid-lowering or blood pressure-lowering therapy. In fact, all could be used simultaneously, resulting in the combined benefits also presented in this study.

On the other hand, intensive lipid-lowering (e.g. PCSK9 inhibition) or blood pressure-lowering therapy might lead to LDL-c or SBP reductions beyond treatment targets, associated with greater benefits than presented in this study.[17] Also, the relative treatment effects of LDL-c and SBP reduction are well established, while those of low-dose colchicine were based on the results of a single trial. Ongoing trials should help to further establish the efficacy of low-dose colchicine.[18,19] Side-effects and non-adherence might occur with low-dose colchicine as well. In LoDoCo2, 15.4% of patients who entered the one-month open-label colchicine run-in period did not undergo randomization (9.4% due to perceived side effects, predominantly gastrointestinal upset).[5] Early intolerance due to gastrointestinal effects has been estimated to affect ~10% of patients receiving low-dose colchicine.[20] After randomization, 10.5% of participants in the colchicine arm prematurely discontinued study medication (3.4% due to perceived side effects). The discontinuation rate was exactly the same (10.5%) in the placebo arm, with the same proportion of participants (3.4%) discontinuing study treatment due to perceived side effects. The discontinuation rate of low-dose colchicine in LoDoCo2 was lower than that observed with statins (average 13.9%) and PCSK9 inhibitors (average 13.0%) in previous trials.[21–23] By using hazard ratios from the per-protocol analysis, the estimates presented in this study take into account the discontinuation rate of colchicine observed during the trial. Myalgia was reported by 21.2% in the colchicine group vs 18.5% in the placebo group (cumulative incidence ratio, 1.15; 95% CI 1.01-1.31). But the rates of cancer, hospitalization for infection, pneumonia, or a gastrointestinal reason, and all other adverse events were similar in the colchicine and placebo groups.[5] This is in line with evidence collected over decades of use of low-dose colchicine in a range of diseases (e.g. gout and Familial Mediterranean Fever), and several meta-analyses including one of all trials in CAD (>11,000 patients), which together have indicated that long-term tolerance is excellent, and low-dose colchicine is safe, i.e. does not increase the risk of

infection, cancer, cytopenia, or myotoxicity.[20,24–27] As the analyses in the current study rely on effect estimates derived from LoDoCo2 and other previous trials, and these effect estimates were neutral with respect to infections and other adverse events, new analyses of these outcomes using the methodology applied in this study would yield neutral results as well, and would not provide new evidence. Therefore, calculations were not performed for non-cardiovascular outcomes.

An assumption made in this study is that the relative treatment effects of low-dose colchicine, derived from the LoDoCo2 trial conducted in the Netherlands and Australia, are generalizable to other countries. The COLCOT and CANTOS trials demonstrated the efficacy of anti-inflammatory therapy in patients with CAD from various countries and several continents, but region-specific results have not been reported.[3,4] Although it is possible that the relative treatment effects of low-dose colchicine differ between regions, this is not expected based on the results of geographic subgroup analyses of other recent cardiovascular trials.[23,28,29] Assuming consistent relative treatment effects, it was shown in this study that the absolute long-term treatment benefits of low-dose colchicine, and how these relate to benefits of intensified LDL-c and SBP reduction, are largely generalizable to North America and Western Europe. This said, the estimated absolute risk reductions were larger in REACH North America and Western Europe. This was due to the higher baseline CVD risk in these cohorts, which might be explained by older age, increased prevalence of comorbidities, and higher cholesterol levels that might be related to the study period (2003-2009) and the inclusion of patients from primary care. The higher cholesterol levels in REACH Western Europe led to increased predicted benefits for intensified LDL-c reduction, which exceeded the benefits of low-dose colchicine in the majority of patients. When determining whether the results from LoDoCo2/UCC-SMART, REACH North America, or REACH Western Europe are most representative, one should therefore keep the population of

interest in mind. The model also assumes that low-dose colchicine has no effect on non-cardiovascular mortality. In LoDoCo2, there were numerically more non-cardiovascular deaths in the colchicine (53 [1.9%]) compared to the placebo group (35 [1.3%]), but this difference was not significant.[5] Colchicine was not associated with any specific cause of death, in particular, deaths due to cancer and infection were equivalent.[30] This is in line with previous trials. In COLCOT (low-dose colchicine after MI), the rates of non-cardiovascular (23 [1.0%] vs 20 [0.8%] deaths) and all-cause mortality (43 [1.8%] vs 44 [1.8%] deaths) were similar between the colchicine and placebo groups.[4] In a meta-analysis of all trials with colchicine in CAD, low-dose colchicine was not associated with an increased risk of non-cardiovascular or all-cause mortality.[24] For all-cause mortality, this is supported by meta-analyses of trials with colchicine for any cardiovascular indication, and across a range of diseases (non-cardiovascular mortality was not reported in these studies).[25,31] So, as there is no evidence that low-dose colchicine affects the risk of non-cardiovascular or all-cause mortality, separate calculations were not performed for these outcomes. But by including functions that predict non-cardiovascular mortality in the models, the calculations for MACE(+) presented in this study were adjusted for the competing risk of non-cardiovascular death.

Strengths of this study are the large sample size, inclusion of both trial and real-world patients from various regions, and the translation of short-term relative treatment effects of colchicine on a group-level to long-term absolute treatment benefits for individual patients. Study limitations should be considered. The models predict lifetime risk but could only be validated for a 3-year period in LoDoCo2 and REACH, due to the limited follow-up time in these studies. The models assume that risk factors follow a natural course over age and that the relative treatment effects of low-dose colchicine remain constant over time, so that the CVD-free survival curve stays on the

expected trajectory and the benefits of low-dose colchicine continue to accrue over a patient's remaining lifetime (which mostly goes far beyond three years). This study therefore shows a projection of the lifetime benefits of low-dose colchicine, which might deviate from the actual benefits. However, it is reassuring that the models performed well over a 10-year period in UCC-SMART, one of the cohorts with the longest follow-up of CAD patients worldwide, and that the validation in UCC-SMART was consistent with the shorter-term validations in LoDoCo2 and REACH. In addition, in a previous study, lifetime estimates based on the methodology applied in this study were shown to be reliable for up to at least 17 years.[10] Discriminative ability of the models was moderate, which is in line with other commonly used risk scores in patients with established CVD, e.g. the ESC guideline-recommended SMART and EUROASPIRE models.[1,32,33] As treatment decisions are usually based on predicted risk, the goodness of fit of these risk estimates, i.e. calibration, is especially important in this setting.[34–36] Calibration of the models used in this study was adequate in both trial, and real-world data from various regions. There were missing data for some of the model predictors. However, even the predictor variable with the largest number of missing values, i.e. total cholesterol, was still available for 32,999 (80%) patients across all populations. Multiple imputation was used to minimize the effect of missing data on the study results. If all data had been available, this likely would have yielded slightly different risk estimates for individual patients with missing predictor information. But on a population-level it is unlikely that missing data has substantially affected the results presented in this study, as validation of the models showed that despite of predictor information being partially imputed for some patients, CVD risks were still accurately predicted. As treatment benefits directly depend on the predicted risk, the adequate calibration of the model across all populations indicates that these were reliably predicted as well. Finally, the effects of low-dose colchicine may vary according to baseline levels of, and on-treatment reductions in inflammatory

markers. In CANTOS, cardiovascular risk reduction with canakinumab was shown to be greater among patients with a more pronounced on-treatment reduction in CRP, and patients reaching a CRP level <2 mg/L.[37] A similar effect is conceivable for patients on colchicine. As CRP and other inflammatory markers were not routinely measured in LoDoCo2, this could not be evaluated or included in the model.

The absolute benefit from low-dose colchicine varies between individual patients with chronic CAD. This study showed that in an era where lipid-lowering and blood pressure-lowering therapies are already routinely used, the benefits of low-dose colchicine may be expected to be of at least similar magnitude to those of intensified LDL-c and SBP reduction in a majority of patients with chronic CAD. Using the ESC guideline-recommended SMART-REACH model and newly developed SMART-REACH+ model, lifetime benefit from low-dose colchicine (and other therapies) can be estimated for individual patients, supporting decision-making with respect to the initiation of ESC guideline-recommended step 2 prevention strategies in clinical practice.

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Conflict of interest

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

PMB, JAND, ATLF, SK, DLB, FLJV, and AM conceptualized the study. ATLF, CAB, DLB, FLJV, and AM contributed to the acquisition of the data. PMB conducted the analysis. PMB, JAND, ATLF, CAB, DLB, FLJV, and AM have responsibility for the data integrity and accuracy of the data analyses. PMB, JAND, ATLF, SK, DLB, FLJV, and AM interpreted the data. PMB

drafted the manuscript. All authors critically reviewed the manuscript, and gave their final approval to submit the manuscript for publication.

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Figure legends

Figure 1. Estimation of 10-year ARR for MACE and MACE-free life-years gained from low-dose colchicine in an individual patient (A), and a comparison of low-dose colchicine with LDL-c reduction to 1.4 mmol/L and SBP reduction to 130 mmHg in three individual patients (B). For

viewing purposes, not all predictors were presented in the figure. These were as follows: total cholesterol = 4.0 (1), 4.5 (2), and 6.0 (3) mmol/L; creatinine = 100 (1), 90 (2), and 80 (3) µmol/L; AF = No for all; HF = No for all. If a condition is not mentioned in the description of the patient, it means the condition was absent (e.g. for patients 2 and 3 diabetes mellitus is not mentioned in the description, which means these patients did not have diabetes mellitus). All patients were real-world patients (recalibration factors from UCC-SMART were applied).

Abbreviations: AF = atrial fibrillation, AHT = antihypertensive, APT = antiplatelet therapy, ARR = absolute risk reduction, DM = diabetes mellitus, HF = heart failure, LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular event, SBP = systolic blood pressure, TC = total cholesterol.

Figure 2. Distribution of the individual absolute benefit from low-dose colchicine in the combined LoDoCo2 and UCC-SMART study population (n = 10,830), expressed as 10-year ARR for MACE (A), MACE-free life-years gained (B), 10-year ARR for MACE+ (C), and MACE+-free life-years gained (D).

Abbreviations: ARR = absolute risk reduction, MACE(+) = major adverse cardiovascular event (+ coronary revascularization).

Figure 3. Mean 10-year ARR for MACE (A), and years gained in MACE-free life expectancy (B) from low-dose colchicine, stratified by baseline 10-year risk and age. As there were no patients aged 66 years or older with a baseline risk <10%, these cells were left blank.

Abbreviations: ARR = absolute risk reduction, MACE = major adverse cardiovascular event.

Figure 4. Difference in MACE-free life-years gained from low-dose colchicine, as compared to intensified LDL-c (A) and SBP (B) reduction for all individuals with available baseline LDL-c (n = 8,595) and SBP (n = 8,801). Differences are calculated as individual MACE-free life-years gained from low-dose colchicine minus individual MACE-free life-years gained from LDL-c reduction to 1.4 mmol/L, or SBP reduction to 130 mmHg. From left to right, individuals are ranked from largest benefit in favour of colchicine to largest benefit in favour of LDL-c or SBP reduction.

Abbreviations: LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular event, SBP = systolic blood pressure.

Figure 5. Low-dose colchicine, LDL-c reduction to 1.4 mmol/L, and SBP reduction to 130 mmHg ranked from most to least effective based on the number of MACE-free life-years gained in patients with available baseline LDL-c and SBP (n = 8,576). If patients already met both LDL-c and SBP targets, this was reported under 'Least effective', and low-dose colchicine was considered the most effective strategy. If one of LDL-c or SBP targets was already met, this was considered the least effective strategy, and the two remaining strategies were divided into most and second most effective.

Abbreviations: LDL-c = low density lipoprotein cholesterol, MACE = major adverse cardiovascular event, SBP = systolic blood pressure.

Table 1. Baseline characteristics

Characteristic	LoDoCo2 (n = 5,522)	UCC-SMART (n = 5,308)	REACH Western Europe (n = 14,522)
Age	65.8±8.6	60.9±9.6	68.4±9.6
Female sex	846 (15%)	1,007 (19%)	4,073 (28%)
Current smoker	651 (12%)	1,272 (24%)	2,300 (16%)
Systolic blood pressure (mmHg)	137±19	137±20	140±19
≤140 mmHg	2,299 (64%)	3,287 (62%)	8,827 (61%)
≤130 mmHg	1,516 (42%)	2,151 (41%)	5,459 (38%)
Total cholesterol (mmol/L)	4.1±1.0	4.6±1.1	5.1±1.2
LDL-cholesterol (mmol/L)	2.1±0.8	2.6±0.9	3.2±1.0[c]
≤1.8 mmol/L	1,360 (40%)	924 (17%)	669 (7%)
≤1.4 mmol/L	518 (15%)	338 (6%)	234 (2%)
Creatinine (µmol/L)	84±14	93±31	96±25
Medical History			
Prior acute coronary syndrome	4,658 (84%)	2,919 (55%)	6,680 (46%)
Prior coronary revascularization[a]	4,621 (84%)	3,875 (73%)	6,390 (44%)
Coronary artery disease	5,522 (100%)	5,308 (100%)	10,048 (69%)
Cerebrovascular disease	398 (11%)	495 (9%)	4,551 (31%)
Peripheral artery disease	72 (2%)	414 (8%)	3,426 (24%)
Diabetes mellitus	1,007 (18%)	1,008 (19%)	4,893 (34%)
Atrial fibrillation	649 (12%)	275 (5%)[b]	1,670 (12%)
Heart failure	NA	NA	2,275 (16%)
Left ventricular ejection fraction <50%	1,805 (33%)	NA	NA
Medication			
Antiplatelet therapy	5,031 (91%)	4,610 (87%)	9,674 (67%)
Anticoagulant	672 (12%)	665 (13%)	1,904 (13%)
Statin	5,188 (94%)	4,297 (81%)	10,340 (71%)
Antihypertensive medication	4,980 (90%)	4,782 (90%)	13,138 (90%)

Baseline characteristics are based on non-imputed data. Continuous variables are presented as mean±SD, categorical variables as N (%). Percentages refer to complete cases.

Abbreviations: LDL = low density lipoprotein, NA = not available.

[a] Prior percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG).

[b] Only atrial fibrillation at baseline (based on an electrocardiogram). History of atrial fibrillation was not available.

[c] Calculated using a modified Friedewald formula including total cholesterol and triglycerides, as LDL-cholesterol (and HDL-cholesterol) measurements were not available in REACH.[38]

Table 2. Median benefit from low-dose colchicine and intensive LDL-c and SBP reduction

		MACE		MACE+	
	n	**10-year ARR, median (IQR)**	**Life-years gained, median (IQR)**	**10-year ARR, median (IQR)**	**Life-years gained, median (IQR)**
Total population					
Low-dose colchicine	10,830	4.6% (3.6–6.0%)	2.0 (1.6–2.5)	8.6% (7.6–9.8%)	3.4 (2.6–4.2)
LDL-c reduction to 1.4 mmol/L	8,595[a]	3.0% (1.5–5.1%)	1.2 (0.6–2.1)	5.2% (2.5–8.7%)	1.8 (0.8–3.3)
SBP reduction to 130 mmHg	8,801[b]	1.7% (0.0–5.7%)	0.7 (0.0–2.3)	2.9% (0.0–9.5%)	0.9 (0.0–3.4)
All three strategies combined	8,576[c]	8.7% (6.2–12.5%)	4.0 (2.9–5.5)	15.9% (12.2–21.1%)	6.6 (4.6–9.5)
Patients not on targets					
LDL-c reduction to 1.4 mmol/L	7,729[d]	3.3% (1.9–5.4%)	1.4 (0.8–2.3)	5.8% (3.3–9.1%)	2.0 (1.1–3.6)
SBP reduction to 130 mmHg	5,055[e]	4.7% (2.4–8.4%)	2.0 (1.0–3.4)	8.2% (4.3–13.6%)	2.9 (1.4–5.1)

Median estimated benefit from low-dose colchicine, LDL-c reduction to 1.4 mmol/L, SBP reduction to 130 mmHg, and combined therapy with all three strategies, in the combined LoDoCo2 and UCC-SMART study population (n = 10,830). Additionally, median benefit from LDL-c and SBP reduction are presented for patients not yet meeting LDL-c and SBP targets at baseline.

Abbreviations: ARR = absolute risk reduction, IQR = interquartile range, LDL-c = low density lipoprotein cholesterol, MACE(+) = major adverse cardiovascular event (+ coronary revascularization), SBP = systolic blood pressure.

[a] Patients with available baseline LDL-c.
[b] Patients with available baseline SBP.
[c] Patients with available baseline LDL-c and SBP.
[d] Patients with baseline LDL-c >1.4 mmol/L.
[e] Patients with baseline SBP >130 mmHg.

1

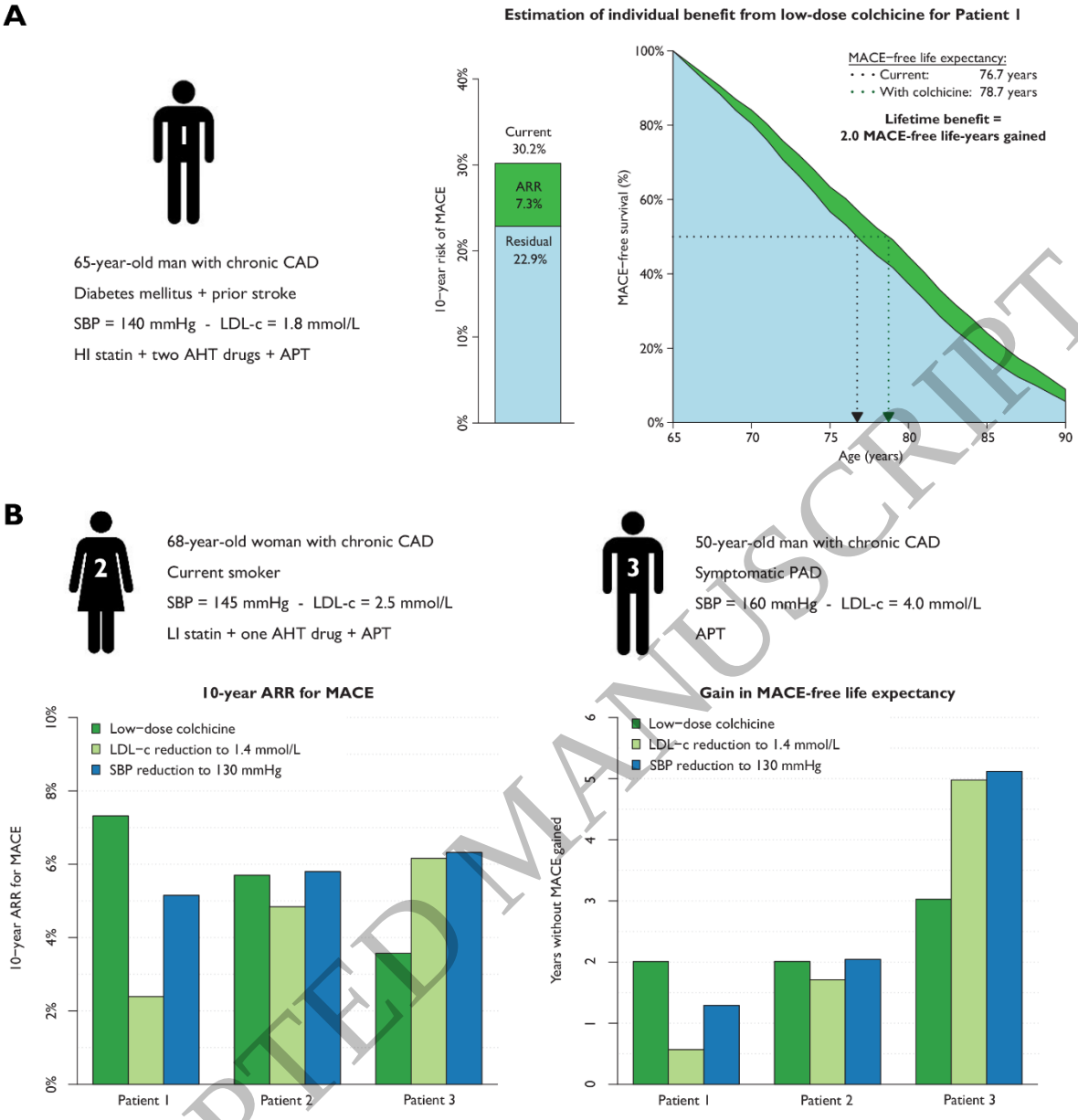


Figure 1
206x216 mm (x DPI)

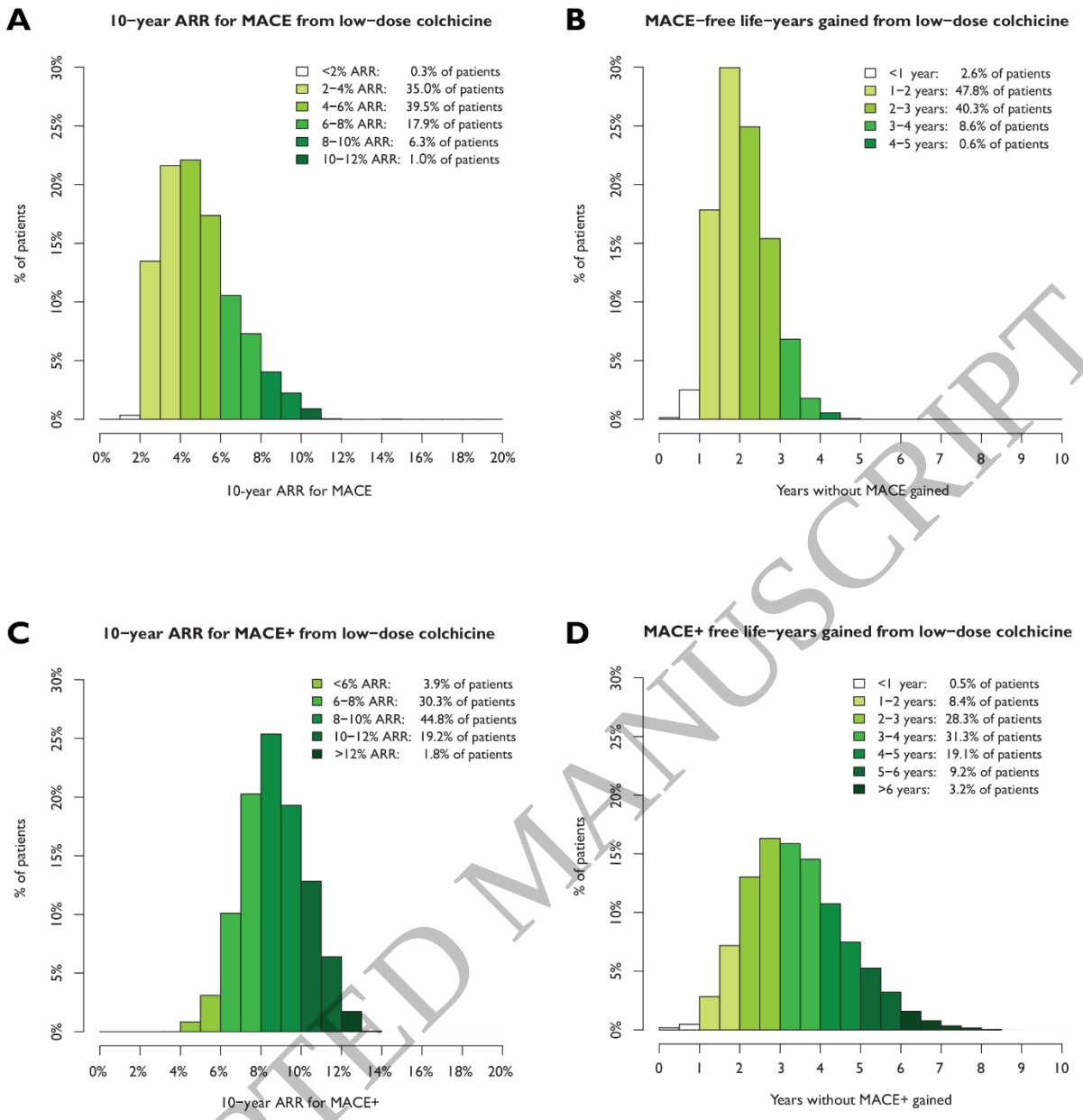


Figure 2
196x202 mm (x DPI)

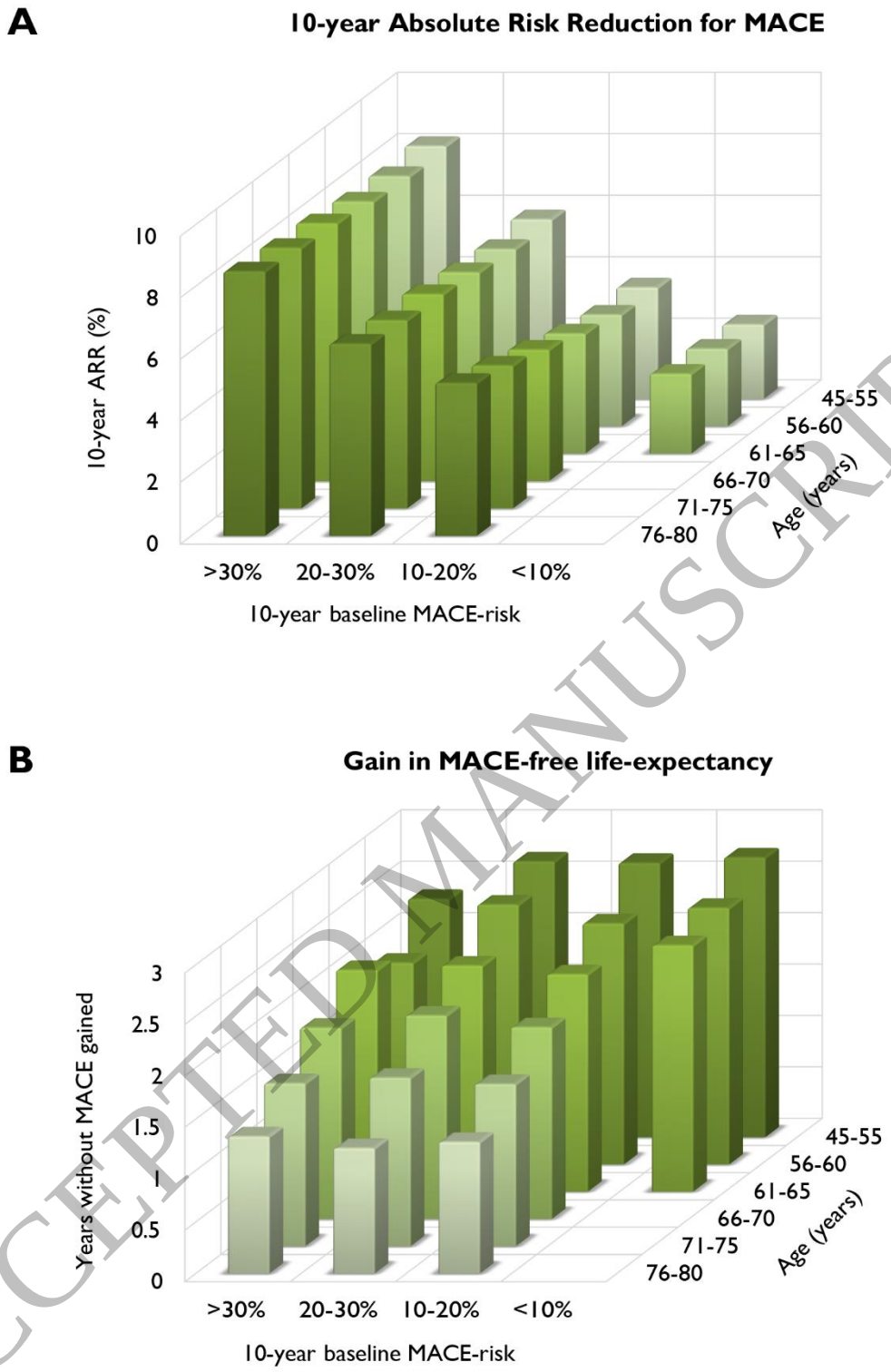


Figure 3
132x201 mm (x DPI)

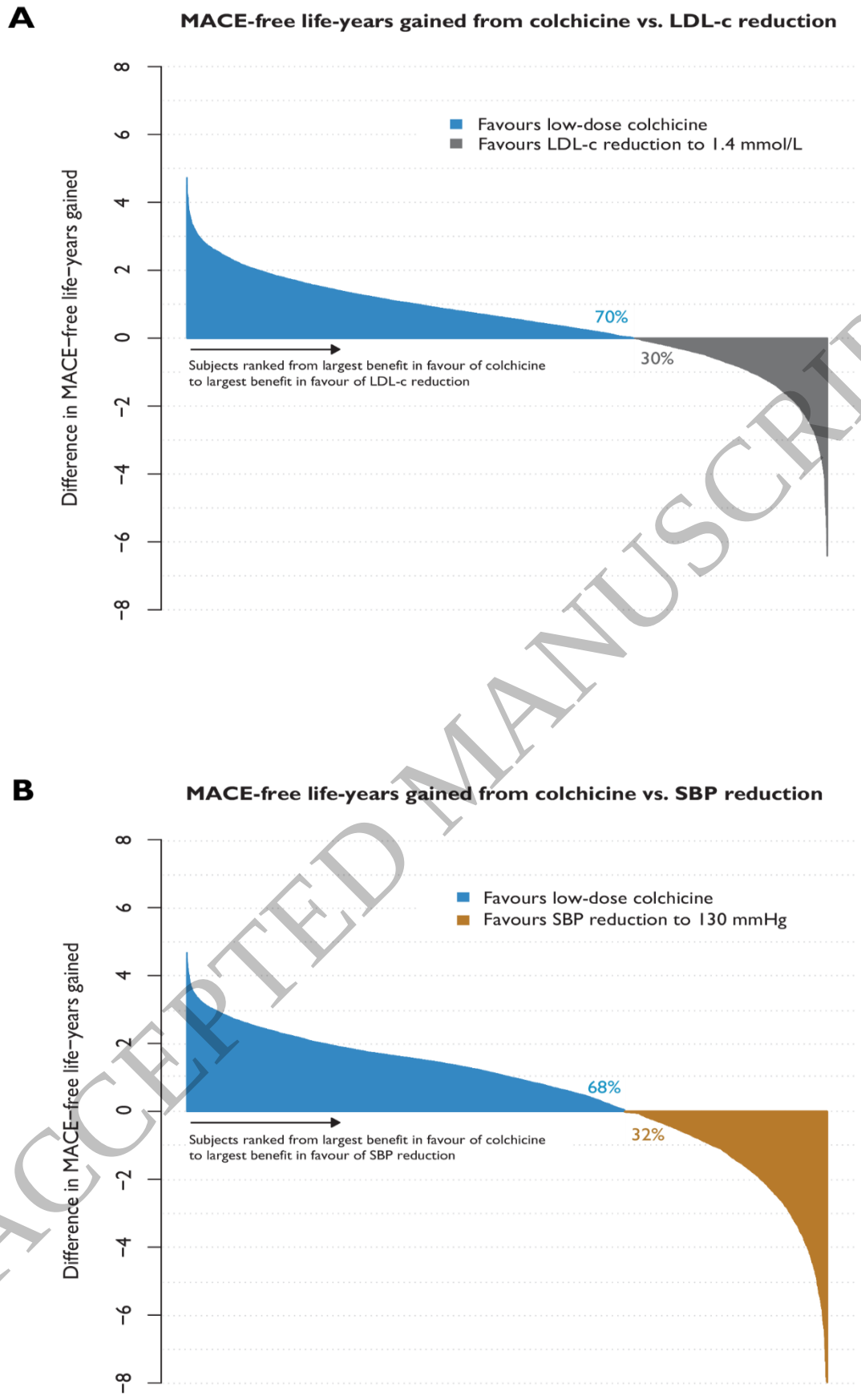


Figure 4
156x264 mm (x DPI)

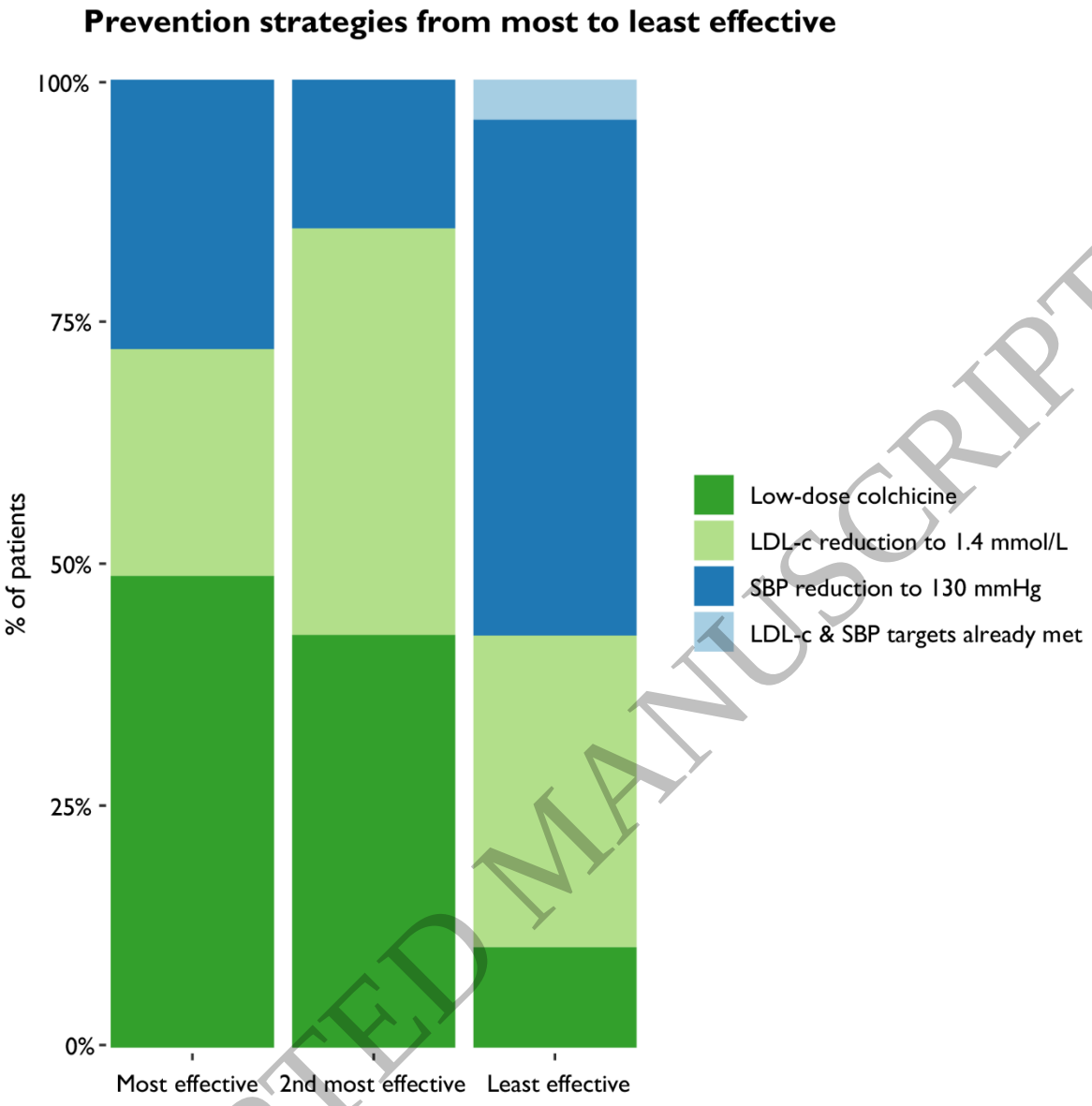
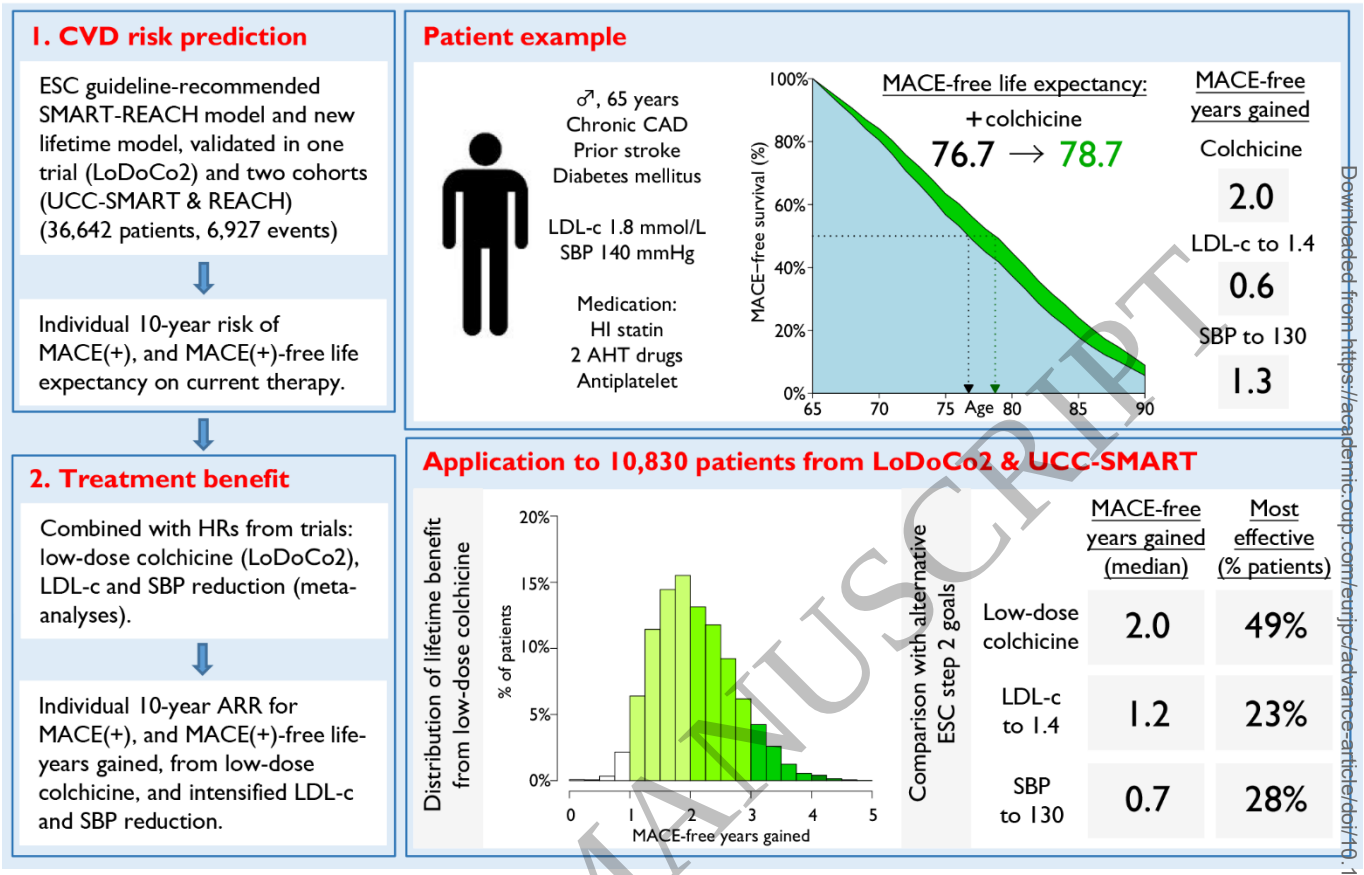


Figure 5
161x156 mm (x DPI)

Individual lifetime benefit from low-dose colchicine in chronic CAD



Graphical Abstract
180x125 mm (x DPI)