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Impact of the 2021 European Society for Cardiology prevention guideline's stepwise approach for cardiovascular risk factor treatment in patients with established atherosclerotic cardiovascular disease

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Aims	This study aimed to evaluate the stepwise approach for cardiovascular (CV) risk factor treatment as outlined by the European Society for Cardiology 2021 guidelines on CV disease (CVD) prevention in patients with established atherosclerotic CVD (ASCVD).
Methods and results	In patients with ASCVD, included in UCC-SMART ($n = 8730$) and European parts of the REACH registry ($n = 18\,364$), the 10-year CV risk was estimated using SMART2. Treatment effects were derived from meta-analyses and trials. Step 1 recommendations were LDL cholesterol (LDLc) < 1.8 mmol/L, systolic blood pressure (SBP) < 140 mmHg, using any antithrombotic medication, sodium–glucose co-transporter 2 (SGLT2) inhibition, and smoking cessation. Step 2 recommendations were LDLc < 1.4 mmol/L, SBP < 130 mmHg, dual-pathway inhibition (DPI, aspirin plus low-dose rivaroxaban), colchicine, glucagon-like peptide (GLP)-1 receptor agonists, and eicosapentaenoic acid. Step 2 was modelled accounting for Step 1 non-attainment. With current treatment, residual CV risk was 22%, 32%, and 60% in the low, moderate, and pooled (very) high European risk regions, respectively. Step 2 could prevent up to 198, 223 and 245 events per 1000 patients treated, respectively. Intensified LDLc reduction, colchicine, and DPI could be applied to most patients, preventing up to 57, 74, and 59 events per 1000 patients treated, respectively. Following Step 2, the number of patients with a CV risk of <10% could increase from 20%, 6.4%, and 0.5%, following Step 1, to 63%, 48%, and 12%, in the respective risk regions.
Conclusion	With current treatment, residual CV risk in patients with ASCVD remains high across all European risk regions. The intensified Step 2 treatment options result in marked further reduction of residual CV risk in patients with established ASCVD.
Lay summary	Patients with established cardiovascular disease are at high risk for new cardiovascular events. The European Society of Cardiology guideline for the prevention of cardiovascular disease introduced a stepwise treatment approach. Step 1 in this approach are treatments that apply to all patients, and Step 2 are intensive treatments that can be prescribed to patients who are still at high risk of new events even with Step 1 treatments. The current study investigates the effect of Steps 1 and 2 on the risk of cardiovascular disease in 27 094 patients all across Europe. With the conventional treatments of Step 1 the risk

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of cardiovascular disease remains high, with a 10-year risk of new events higher than 10% in 80–99% of patients. The intensive treatment options from Step 2 could prevent additional 198–245 new cardiovascular events for every 1000 patients that are treated. With intensive treatment, up to 63% of patients could achieve a 10-year risk of new cardiovascular disease below 10%.

Key findings Guideline-recommended intensive treatment of patients with cardiovascular disease could prevent additional 198–245 new cardiovascular events for every 1000 patients treated.

Graphical Abstract
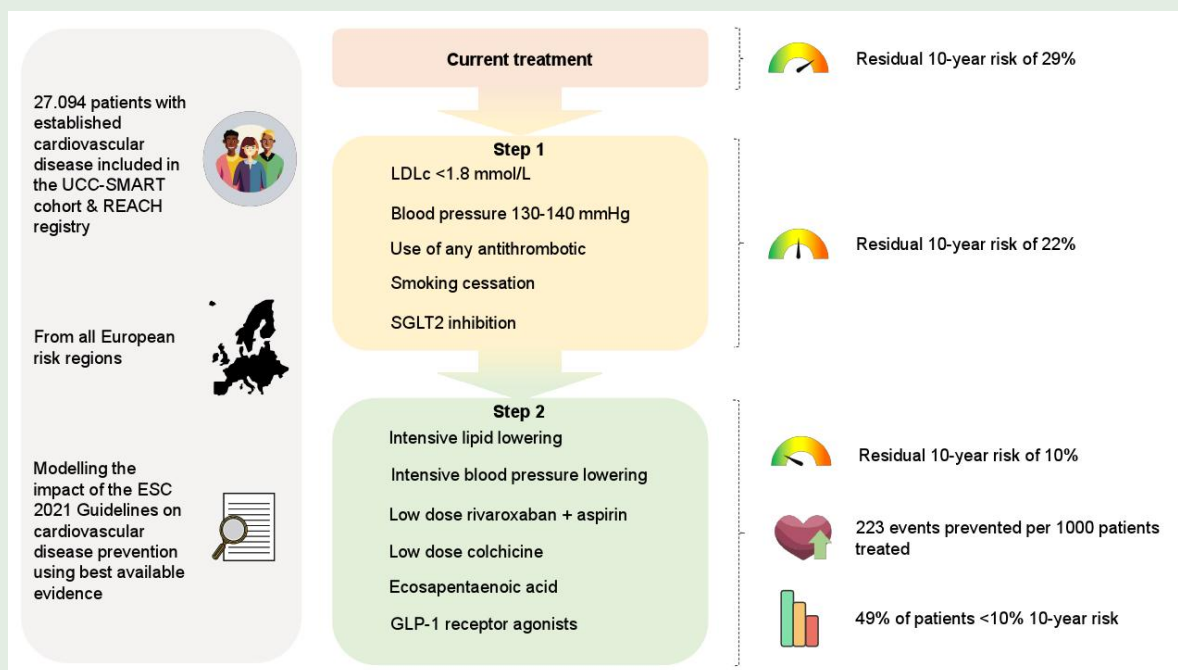
Keywords Secondary prevention • Residual risk • Guideline adherence • Risk factors • Recurrent risk

Introduction

Patients with established atherosclerotic cardiovascular (CV) disease (ASCVD) are at high risk for CV events.[1] This residual risk is highly variable among patients with ASCVD and is dependent on the degree of attainment of treatment goals.[1] While this risk of recurrence can be reduced by treatment of modifiable risk factors, a substantial number of patients remain at high residual risk of CV events, even with perfect attainment of guideline-recommended treatment goals.[1–3] In the European Society for Cardiology (ESC) guideline on cardiovascular disease (CVD) prevention in clinical practice, the well-established strategies and recently explored novel treatments aimed at reducing this residual risk have been combined into a two-step approach for risk factor treatment.[4] In this approach, the Step 1 treatments are the general preventive measures that apply to all patients with ASCVD, including lifestyle recommendations and target values such as a LDL cholesterol (LDLc) < 1.8 mmol/L and systolic blood pressure (SBP) between 130 and 140 mmHg. Additionally, the guideline recommends considering Step 2 treatments, also referred to as intensified treatment options, on an individual basis using predicted residual 10-year or lifetime CV risk, and taking into account comorbidities, frailty, and patient preferences. Step 2 includes stricter control of certain targets such as LDLc reduction to <1.4 mmol/L and lowering of SBP to 120–<130 mmHg, as well as novel interventions such as dual-pathway inhibition (DPI).[4]

While the Step 2 interventions have been proven to reduce the risk of CV events in clinical trials, the real-world impact of their combined implementation according to guideline recommendations has not yet been investigated.

The aim of the current study is to provide insight into the impact of the 2021 ESC guideline's stepwise approach to CVD prevention in clinical practice on residual 10-year risk of CV events in patients with ASCVD in each of the European risk regions.

Methods

Participants from the Utrecht Cardiovascular Cohort-Secondary Manifestations of Arterial Disease (UCC-SMART), included between September 1996 and January 2020, and from the European countries within the Reduction of Atherothrombosis for Continued Health (REACH) registry, included between December 2003 and June 2004, with established ASCVD at baseline were eligible for analyses. Descriptions of both are published elsewhere.[5,6] Briefly, all measurements are standardized (e.g. fasting lipid measurements) and assessed at baseline. Atherosclerotic CVD at baseline was defined as coronary artery disease (CAD), cerebrovascular disease (CeVD), abdominal aortic aneurysm (AAA), and/or peripheral artery disease (PAD) as per study definition (see Supplementary material online, Table S1).

Risk estimation

In accordance with guideline recommendations, the SMART2 risk score with region-specific recalibration factors was used to predict 10-year risk

of CV events.[4,7] In line with the intended use of SMART2, the analyses were restricted to patients aged between 40 and 80 years old. Risk regions are defined as per SMART2-definitions.[7] Due to their limited population sizes individually, the high- and very high-risk regions were pooled. Since LDLc, HDL cholesterol (HDLc), C-reactive protein, and years since first CV event were unavailable in the REACH registry, these data were imputed using multilevel single imputation with predictive mean matching based on pooled REACH and SMART data. Convergence of the imputation model was assessed visually.

Treatment effects

Treatment targets were derived from the 2021 ESC guideline on CVD prevention in clinical practice.[4] Supplementary material online, *Table S2* lists an overview of the assumptions made in modelling treatment effects.[8–14] For analyses purposes, treatment targets for SBP were translated to reaching the midpoint of the target range, i.e. 135 mmHg in Step 1 and 125 mmHg in Step 2, unless the SBP was already lower. Step 1 LDLc target was translated to reduction to 1.7 mmol/L, unless the LDLc was already lower. Since information on intensity of lipid-lowering therapy was unavailable, Step 2 LDLc reduction was modelled as an additional 30% decrease in LDLc, for those patients with an LDLc of ≥1.4 mmol/L. This reduction might be achievable through (a combination of) higher intensity statins, addition of ezetimibe and bempedoic acid, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition, which could feasibly result in a 59% additional LDLc reduction.[15–18] For patients with diabetes mellitus type 2 (DM) with ASCVD, Step 1 was modelled as initiation of sodium–glucose co-transporter-2 inhibitors (SGLT2i). Step 1 lifestyle effects other than smoking cessation were not included in analyses since unambiguous targets and efficacy measures are lacking, and effects are likely to be mediated by changes in other risk factors (e.g. blood pressure).[19,20] An exploratory analysis was performed to investigate the potential impact of increasing physical activity and adhering to the Mediterranean diet as part of extended lifestyle interventions in Step 1 (see Supplementary methods). No explicit preference is expressed in the guideline with regard to intensive antithrombotic treatment in Step 2. For analyses purposes, this was modelled as DPI (i.e. adding low-dose rivaroxaban to aspirin) which has been evaluated in patients with CAD and PAD and therefore applies to more patients than dual antiplatelet therapy (DAPT). Correspondingly, the effect of colchicine was only modelled for patients with a history of CAD and the effect of eicosapentaenoic acid (EPA) was only modelled for patients with fasting triglycerides levels ≥150 and <500 mg/dL (1.52–5.63 mmol/L). For patients with DM and ASCVD, Step 2 was modelled as initiation of glucagon-like peptide 1 receptor agonists (GLP1-RA).

Scenarios

Two scenarios for Step 2 implementation were investigated. The first assumed imperfect attainment of Step 1 targets, illustrating the possible real-world impact of Step 2. The second scenario assumed perfect attainment of all Step 1 targets which, while unrealistic in the real-world, demonstrates the most cautious estimate for the effect of Step 2.[21] The attainment of Step 1 targets within the cohorts is unlikely to reflect achievable attainment rates in a contemporary population since risk factor control and use of medication have improved since conception of these cohorts.[22] Therefore, estimates for non-attainment rates were derived from the more contemporary EUROASPIRE-IV survey. This survey, conducted ≥6 months after the index event, assessed attainment of all Step 1 targets simultaneously within a single population. To avoid underestimation of the effect of Step 1, the average attainment rates for the low-risk region were used as estimates for attainment rates that would be achievable in all risk regions (see Supplementary material online, *Table S4* and *Figure S1*). In cases where Step 1 attainment rates within the cohorts were lower, a number of patients equal to that difference were modelled as having achieved that Step 1 target. A more thorough description of the incorporation of non-attainment is available in the supplementary material (see Supplementary methods). Intensification of SBP control and DPI from Step 1 targets to Step 2 targets (e.g. from <140–<130 mmHg) was limited to those patients who met their initial Step 1 treatment goal for these respective treatments. Consequently, in the scenario with non-attainment of Step 1, the Step 2 treatments could be applied to fewer patients. No information on Europe-wide SLGT2i initiation is available within EUROASPIRE surveys. Therefore, it was assumed that 25% of patients with DM and ASCVD would receive SGLT2i in the scenario assuming non-attainment of Step 1. Assumptions for the exploratory analysis into additional lifestyle effects are available in the Supplementary methods. Due to limited data on dietary and activity habits, this exploratory analysis is restricted to the scenario assuming non-attainment only.

Impact of treatment on population level

The eligibility for each respective Step 2 treatment was calculated as percentage relative to the entire population. For each Step 2 treatment, the absolute risk reduction (ARR) was calculated (Supplementary material online, *Table S3*). The ARR was rescaled to account for simultaneous initiation of other treatments (see Supplementary methods). For those patients receiving a particular treatment, the ARR was translated into number needed to treat (NNT; 1/ARR) and the number of events saved per 1000 patients treated (1000/NNT) with that treatment. The impact of the stepwise approach was visualized using histograms and alluvial plots using the following risk categories: <10%, 10–20%, 20–30%, and ≥30%. Effects were analysed for the population as a whole and in mutually exclusive subgroups of patients. Mutually exclusive subgroups were made per CVD type. Patients with DM and ASCVD were considered a separate subgroup. In patients without DM, subgroups of patients with polyvascular disease [involving ≥2 of the following types of CVD: only CAD, only CeVD, or only PAD (including AAA; PAD/AAA), all without concomitant DM] were made.

Since Step 2 treatments are to be considered based on residual risk following Step 1, clinicians might maintain different threshold levels of residual risk at which to consider Step 2 treatments (e.g. a clinician might consider implementing Step 2 treatments only in patients with a residual risk of >15%). To demonstrate the impact of such a threshold, a dynamic web application was constructed. This application allows users to choose a threshold value of residual risk following Step 1 between 0% (treat all) and 30% (treat those with ≥30% CV event risk). Additionally, it allows for specifying which Step 2 treatments to include (e.g. leaving out low-dose colchicine from Step 2). Users can investigate the effect these choices on the main analyses displayed in this article. All treatment effects and risks in the main analyses are 10-year risk without a threshold for implementation (treat all) unless otherwise specified. Estimates for risk are median with 25–75th percentile ranges, unless otherwise specified.

All analyses were performed using R Statistical Software Version 4.2.2. (Vienna, Austria).

Results

Study population and risk at current treatment

In total, 27 094 patients were included, 8730 of whom were part of the UCC-SMART cohort and 18 364 were part of the REACH registry. Baseline blood pressure, use of blood pressure–lowering drugs, LDLc, and prevalence of polyvascular disease increased with higher levels of regional risk. Among those enrolled, CAD was the most common type of CVD, followed by CeVD and PAD/AAA. Peripheral artery disease was present in 20%, 24%, and 13% of patients, in the low-, moderate-, and (very) high-risk regions, respectively. Compared with patients without DM, patients with DM had on average higher SBP, triglyceride levels, longer duration of CVD, and higher body mass index (BMI) (see Supplementary material online, *Tables S5* and *S6*). In the total study population, the overall 10-year risk of CV events with current treatment was 28% (18–47) and was 22% (15–32), 32% (22–46), and 60% (44–76) in the low-, moderate-, and (very) high-risk regions, respectively (*Table 1*). With current treatment, respectively, 7%, 1%, and 0.04% of patients in the low-, moderate-, and (very) high-risk regions were <10% risk of CV events (*Figure 3*).

Step 2 in the presence of non-attainment in Step 1

In the scenario assuming non-attainment of Step 1 targets, the overall residual risk after Step 1 was 22% (14–36) and 17% (11–26), 24% (16–36), and 46% (32–63) for the low-, moderate-, and (very) high-risk

Table 1 Baseline characteristics across the European risk regions

	Low risk (n = 15 610)	Moderate risk (n = 6266)	(Very) high risk (n = 5218)
Age (years)	64.5 (57–72)	68 (62–73)	63 (56–70)
Male, % (n)	75% (11739)	71% (4475)	67% (3499)
Systolic blood pressure (mmHg)	139 (20)	141 (19)	143 (20)
Systolic blood pressure at target, % (n)	61% (9543)	58% (3631)	54% (2809)
Use of antihypertensives, % (n)	82% (12830)	93% (5823)	95% (4958)
LDLc (mmol/L)	2.9 (1.0)	3.1 (1.1)	3.5 (1.1)
LDLc at target, % (n)	13% (2016)	8.6% (542)	5.2% (273)
Use of lipid-lowering therapy, % (n)	71% (11098)	74% (4629)	58% (3034)
Total cholesterol (mmol/L)	4.9 (1.1)	5.2 (1.1)	5.6 (1.2)
Triglycerides (mmol/L)	1.4 (1.0–2.0)	1.7 (1.2–2.3)	1.7 (1.2–2.4)
HDL cholesterol (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)
C-reactive protein (mg/dL)	2.2 (1.0–4.6)	2.4 (1.2–5.0)	2.4 (1.2–4.9)
eGFR (mL/min/1.73m^2)	75 (18)	72 (19)	73 (20)
Years since first diagnosis	0.0 (0.0–6.0)	1.0 (0.0–10)	1.0 (0.0–9.0)
BMI (kg/m^2)	27.3 (4.3)	28.0 (4.5)	28.1 (4.3)
Using antithrombotics, % (n)	76% (11930)	69% (4347)	76% (3959)
DM with ASCVD, % (n)	23% (3618)	38% (2389)	26% (1360)
Polyvascular disease no DM, % (n)	12% (1818)	13% (841)	18% (937)
CAD	10% (1597)	12% (760)	16% (845)
CeVD	6.1% (955)	8.0% (504)	10% (524)
PAD/AAA	7.9% (845)	12% (753)	7.0% (363)
Only CAD no DM, % (n)	39% (6082)	31% (1949)	39% (2008)
Only CeVD no DM, % (n)	16% (2466)	11% (701)	15% (790)
Only PAD/AAA no DM, % (n)	10% (1626)	6.2% (386)	2.4% (123)
Current smoking, % (n)	24% (3725)	18% (1118)	21% (1078)
10-year SMART2 risk	22% (15–32)	32% (22–46)	59 (44–76)

Summary statistics are mean and standard deviation (SD) or median (interquartile range) unless otherwise indicated. Targets are Step 1 targets. SMART2 risk is 10-year risk of recurrent cardiovascular disease. n, count; LDLc, low-density lipoprotein cholesterol; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration; BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; PAD, peripheral artery disease; AAA, abdominal aortic aneurysm; DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease.

regions, respectively. Following Step 2, residual risk decreased to 10% (6–18) overall and 8% (5–13), 10% (7–17), and 22% (14–34), for the respective risk regions. Of all Step 2 treatments, Step 2 LDLc reduction could be applied to the most patients regardless of residual risk threshold, followed by low-dose colchicine and DPI (*Figure 1A*). Apart from CVD subtype-specific therapies, applicability patterns for Step 2 treatments remained relatively comparable within CVD subtypes (see Supplementary material online, *Figure S5*). Depending on the threshold that was maintained, Step 2 could prevent up to 198, 223, and 245 additional events per 1000 patients treated, for the respective risk regions (*Figure 1B*). On a population level, the number of events prevented per 1000 patients for individual treatments was the highest for low-dose colchicine, followed by EPA, DPI, SBP < 130 mmHg, Step 2 LDLc reduction, and GLP-1 RA initiation (*Figure 1B*). Within CVD subtypes, the treatments with the highest number of events prevented per 1000 patients treated were colchicine when applicable or DPI or EPA in those where colchicine could not be considered (see Supplementary material online, *Figure S5*). Within CVD subtypes, the average residual risk following Step 1, as well as Step 2, was the highest for patients with polyvascular disease. Following Step 2, the residual risk was lowest for patients with CAD (*Figure 2*). The number of patients with a residual CV event risk <10% increased to 20%, 6.4%, and 0.5%, for the respective risk regions, following Step 1, and increased

to 63%, 48%, and 12%, respectively, following Step 2 (*Figure 3*). The effect of a threshold in residual risk after Step 1 for the implementation of Step 2 on all the analyses can be accessed at here.

Exploratory analysis with extended lifestyle effects

In the scenario assuming non-attainment of Step 1 targets and extended lifestyle effects (increased physical activity and adherence to Mediterranean diet), the overall residual risk after Step 1 was 18% (11–31) and 14% (9–22), 20% (13–31), and 39% (26–56) for the low-, moderate-, and (very) high-risk regions, respectively. Following Step 2, residual risk decreased to 8.3% (5–15) overall and 6.6% (4–11), 8.5% (5–14), and 18% (11–29), for the respective risk regions. Other than the number of events prevented per 1000 patients treated being lower for each Step 2 treatment, compared to the main analysis, the pattern applicability and prevented events remained unchanged (see Supplementary material online, *Figure S7*). Within CVD subtypes, the effect of Step 1 was more pronounced, but Step 2 patterns remained unaffected (see Supplementary material online, *Figure S8*). The number of patients with a residual CV event risk <10% increased to 31%, 14%, and 1.8%, for the respective risk regions, following Step 1,
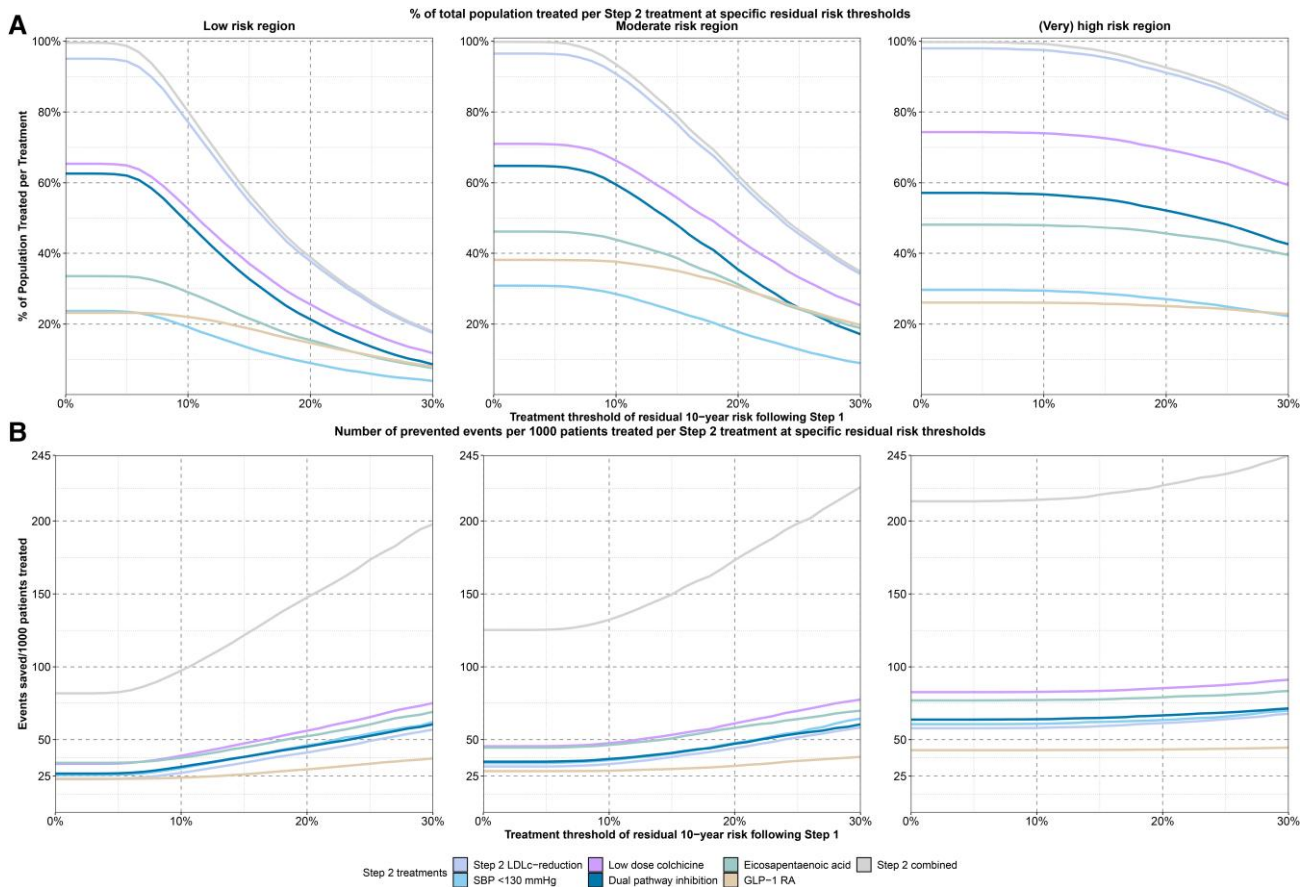
Figure 1 Percentage treated (*A*) and events saved per 1000 patients treated (*B*) across residual risk thresholds across the European risk regions with non-attainment in Step 1. The three columns are for the three separate risk regions, with, on the first row, (*A*) the percentage of the total population in that region that receives a particular treatment and, on the second row, (*B*) the number of events saved per 1000 patients receiving the particular treatment. The x-axis represents the threshold in residual risk following Step 1, with, for example, an x-axis value at 10% in the low-risk region; all patients with a residual risk of 10% or higher are treated, meaning that 80% of the population would receive all Step 2 treatments for which they are eligible (*A*). Correspondingly when treating 1000 of these patients, 97 events might be prevented per 1000 patients treated (*B*). LDLc, low-density lipoprotein cholesterol; SBP, systolic blood pressure; GLP-1 RA, glucagon-like peptide 1 receptor agonists.

and increased to 71%, 56%, and 20%, respectively, following Step 2 (see Supplementary material online, *Figure S9*).

Step 2 in the presence of perfect attainment of step 1

In the scenario assuming perfect attainment of Step 1 targets, the overall residual risk following Step 1 was 15% (9–24) and 11% (8–17), 16% (11–23), and 30% (21–43) for the low-, moderate-, and (very) high-risk regions, respectively. Following Step 2, overall residual risk decreased to 7% (4–12) and 5% (4–9), 7% (5–11), and 14% (9–22), for the respective risk regions. Compared with the scenario with non-attainment of Step 1, the Step 2 SBP reduction and DPI could be applied to more patients (see Supplementary material online, *Figure S2A*). Apart from CVD subtype-specific therapies, applicability patterns for Step 2 treatments remained relatively comparable within CVD subtypes (see Supplementary material online, *Figure S6*). Compared with the scenario with non-attainment of Step 1, the number of events prevented per 1000 patients treated was lower for Step 2 as a whole and each

individual treatment when assuming perfect attainment of Step 1 (see Supplementary material online, *Figure S2B*). At a population level, Step 2 could prevent up to 181, 202, and 217 additional events per 1000 patients treated, for the low-, moderate-, and (very) high-risk regions, respectively, depending on the threshold that was maintained (see Supplementary material online, *Figure S2B*). The pattern with regard to the highest number of events prevented per 1000 patients treated within CVD subtypes was similar in both scenarios; however, compared with the scenario with non-attainment of Step 1, Step 2 treatments yielded fewer prevented events in the scenario with perfect attainment (see Supplementary material online, *Figure S6*). The pattern in reductions in residual risk within the CVD subtypes in the scenario assuming perfect attainment of Step 1 followed a similar pattern as to that in the scenario assuming imperfect attainment of Step 1 (see Supplementary material online, *Figure S3*). The number of patients in the low-, moderate-, and (very) high-risk regions <10% risk of CV events increased to 41%, 21%, and 3%, respectively, following Step 1, which further increased to 82%, 70%, and 30%, respectively, following Step 2 (see Supplementary material online, *Figure S4*).
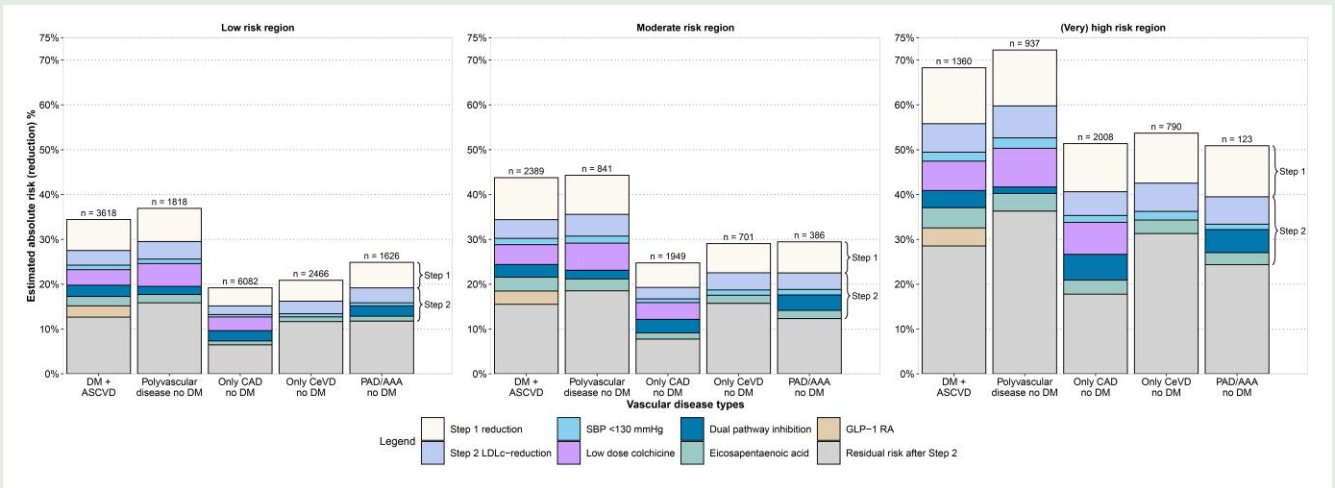
Figure 2 Average residual risk and risk reduction per treatment and CVD subtype across European risk regions with non-attainment in Step 1. The brackets refer to the combined effect of Steps 1 and 2, respectively. DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CeVD, cerebrovascular disease; PAD, peripheral artery disease; AAA, abdominal aortic aneurysm; LDLc, low-density lipoprotein cholesterol; SBP, systolic blood pressure; GLP-1 RA, glucagon-like peptide 1 receptor agonists.
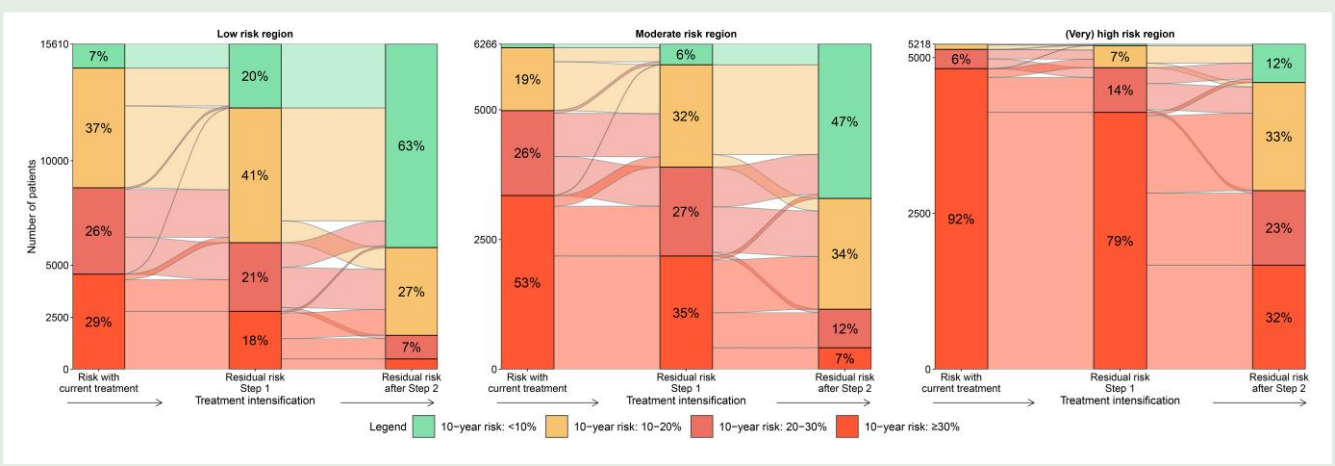
Figure 3 Changes in residual risk categories per treatment Step across the European risk regions with non-attainment in Step 1. The three separate plots are for the three separate risk regions. On the y-axis of each alluvial plot, the number of patients per risk region is seen. The stacked bars display the percentage of the total population with a risk smaller than the upper limit of each category (i.e. for 10–20%, all patients have a risk <20%). On the x-axis, the subsequent treatment steps can be seen (left to right): current treatment, Step 1, and Step 2. The stacked bar chart at each step on the x-axis refers to the residual risk following that Step (i.e. Step 2 is the distribution of risk following Step 2). Flows between bars illustrate movements of patients between categories following each treatment step.

Discussion

The 10-year risk of recurrent CVD in patients with ASCVD varies across European risk regions and CVD subtypes. In the presence of non-attainment of Step 1, treatment targets up to 20% of patients are <10% risk for CV events; with Step 2, this could increase to 63%, and up to 245 CV events per 1000 patients treated could be prevented.

In recent decades, residual risk in patients with established ASCVD has captured significant attention, leading to concerted efforts aimed at its reduction. These efforts include investigations into stricter risk factor control, such as intensive SBP lowering, as in the SPRINT trial,

and intensive lipid-lowering, with, for example, PCSK9mabs, both of which were proven to be beneficial.[23,24] These two risk factors have long since been the cornerstones of CV risk reduction. Other paths to address residual risk have been investigated. For example, apart from CV risk reduction due to LDLc lowering, the effects of statins can also partly be ascribed to anti-inflammatory effects. This has prompted investigations into 'residual inflammatory risk', a concept that has subsequently been shown to provide useful treatment approaches in the LODOCO and CANTOS trials.[25,26] Furthermore, the COMPASS and PEGASUS trials demonstrated the effectiveness of intensive antithrombotic therapy and illustrated the concept of

'residual thrombotic risk'.[27,28] Additionally, the REDUCE-IT trial demonstrated the efficacy of EPA in patients with optimal statin therapy and it was hypothesized to be the result of both anti-inflammatory effects and lowering of residual triglyceride risk.[29] Novel drugs like GLP-1 RA possibly affect multiple of the aforementioned pathways by addressing obesity, which is part of the common soil for these risk factors.[30] The degree to which these multiple pathways contribute to the overall risk of a patient varies. While Step 1 sets targets for the population as a whole, Step 2 is aimed at personalization addressing these individual pathways. The new ESC guideline shaped this need for individualization into the stepwise approach and proposes considering the use of these novel treatments in selected individuals based on (predicted) residual risk.[4] The current study demonstrates the effects of this individualized approach at a population level, in real-world cohorts in patients with multiple CVD subtypes, and across multiple European risk regions. Additionally, the current study models the effect of Step 2 interventions in a combined and integrated approach, corresponding to clinical practice.

The high residual risk and the variability therein observed in the current study are in line with the few studies that estimate this risk in a secondary prevention population.[1,31–34] This high residual risk is partly due to delay in initiation of preventative treatments until the underlying disease has progressed to the point where clinical symptoms occur. Prior to the availability of novel treatments, guideline recommendations often only consisted of Step 1 targets and their intensification. The current analysis shows that even with perfect attainment of these targets, many patients remained at >10% risk of recurrent CV events. By implementation of Step 2 treatments, this residual CV event risk could be substantially reduced, both for patients already at Step 1 targets and those for whom these targets prove difficult to attain (e.g. smoking cessation). However, it is important to note that Step 1 interventions remain crucial in the management of ASCVD and should not be replaced by Step 2 treatment. The cohorts used in the analysis consist of patients receiving usual care; similar to Step 1, the effect of Step 1 here is smaller than in treatment-naïve patients. Notably, the reductions in risk from Step 2 treatment in patients with DM in combination with ASCVD are on average larger for the CVD specific treatments, like colchicine for CAD, then for DM-specific treatments like GLP-1 RA, indicating that these treatments should not be neglected in patients with DM and ASCVD.[30] Importantly, in patients eligible for DAPT, the risk reduction due to DPI would be comparable had they been prescribed DAPT, given the similar relative risk reductions.[35] However, Step 2 treatments should not be compared individually based on the current study since estimated effects could differ from real-world effects, for example, due to discontinuation due to side effects. Nonetheless, as illustrated in the current analysis, the combined initiation of Step 2 treatments is a potent strategy to reduce residual risk. Due to the advanced nature of atherosclerosis in these patients, CV event risk should be estimate on a regular basis to assess the need for treatment intensification.

The burden of CVD in Europe remains high, with a prevalence of 22 million, 25 million, and 7.8 million for, respectively, CAD, PAD, and CeVD in those countries included in this analysis alone.[36] Even with perfect attainment of Step 1 goals, ~4.3 million additional events might be prevented by treating all with Step 2 treatments for 10 years, assuming that these patients resemble those studied in this analysis. The effects of the stepwise approach on a population level have to be placed into the context of the providing healthcare system.[37] This is especially important given the differences in risk of recurrent CVD per geographical region which can partly be explained by differences in lifestyle, access to healthcare, and wealth.[38–40] In situations where resources limit the implementation of Step 2 interventions, policymakers might consider promoting access to relatively low-cost interventions such as colchicine or they might consider access to costly interventions to be restricted to special populations. Choices such as these are acknowledged in the guideline, which states that as treatment decisions

have an impact on healthcare costs and resources, countries or regions may decide on using higher or lower treatment thresholds.[4] The online application in the current study can help visualize the effect of limiting prescription of certain treatments to certain risk thresholds as well as omitting certain treatments from Step 2. In this way, insights from studies such as these might help guide decision-making. Regionally tailored treatment strategies may be necessary in different regions to optimize CV outcomes.

Strengths of the current study include the large cohorts with regional variation, the complementary scenarios, and the web application conforming to the individualized nature of Step 2. Limitations of this study should be considered. Among these are, firstly, the inability to incorporate lifestyle and weight loss explicitly, thus possibly mistakenly underrepresenting their importance. However, since no assumption was made on how LDLc and SBP reduction were achieved, their effects should reflect the effect of equivalent reductions attained by lifestyle intervention. Additionally, even in the exploratory analysis with the effect of highly optimistic estimates for lifestyle changes, the implementation of Step 2 results in substantial benefits. Secondly, due to the nature of evidence available, the effects of all Step 2 interventions had to be assumed to be independent from each other, possibly overestimating the effect of their combined implementation. Thirdly, the cohorts used for analyses could be considered somewhat historical, possibly resulting in differences in risk factor level control compared with patients today. However, since high-intensity statin therapy was available at the time, this is unlikely to be a substantial issue. Additionally, the scenario with perfect Step 1 attainment would be unaffected by such historical bias if it were present. While assumptions made on attainment might be seen as a limitation, the general principles, like the enhanced effectiveness of Step 2 treatments amidst Step 1 non-attainment, remain valid irrespective of true attainment. Not incorporating non-attainment would yield unrealistic estimates for the real-world efficacy of Step 2. Additionally, since non-attainment is likely to vary between populations and healthcare settings and systems, these assumptions have to be made regardless. Other limitations are the missingness in some predictor variables.

In conclusion, despite the current standards of care, residual CV risk in patients with ASCVD remains high across all European risk regions. Intensified Step 2 treatment as indicated in the 2021 ESC prevention guidelines results in marked further reduction of residual CV risk.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology.*

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Author contribution

J.A.N.D., F.L.J.V., and J.H. contributed to the design and data-analysis. J.H., F.L.J.V., J.A.N.D., and D.L.B. provided data for analysis. J.H., F.L.J.V., and J.A.N.D. drafted the manuscript. All authors critically revised the manuscript and contributed to design of analyses. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

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

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