"Hausärztliche Risikoberatung zur kardiovaskulären Prävention"

DEGAM S3-Leitlinie Version 2

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Evidenzbericht 1: Recommendations for the primary prevention of atherosclerotic cardiovascular disease in primary care: A systematic guideline review

Stand: Juni 2023

Das dieser Veröffentlichung zugrundeliegende Projekt wurde mit Mitteln des Innovationsausschusses beim Gemeinsamen Bundesausschuss unter dem Förderkennzeichen 01VSF22012 gefördert.

Mitarbeitende: Ana Gonzalez Gonzalez[1], Maren Bredehorst[2], Dennis Firmansyah[2,] Lara Schürmann[1], Veronika van der Wardt[2], Svetlana Puzhko[1], Jörg Haasenritter[2]

1: Medizinische Fakultät OWL; Allgemein- und Familienmedizin; Universität Bielefeld

2: Institut für Allgemeinmedizin, Philipps Universität Marburg

Content

INTRODUCTION

In Germany, like other developed countries, cardiovascular disease (CVD) remains the leading cause of death, accounting for 33% of all fatalities in 2021 (1). Atherosclerotic cardiovascular disease (ASCVD) involves the accumulation of cholesterol plaque in various arteries, such as the coronary, cerebral, iliac, femoral, and aorta, and encompasses conditions like coronary heart disease, stroke, transient ischemic attacks, peripheral artery disease, and aortic disease (2).

The key modifiable risk factors for ASCVD include hypertension, diabetes, dyslipidemia, obesity, and certain lifestyles like smoking, physical inactivity, and an unhealthy diet (3,4). Roughly, one-third of adults in Germany, with 31% of women and 33% of men, have been diagnosed with high blood pressure (BP) (5). Diabetes affects 8% of adults, excluding gestational diabetes (6), and dyslipidemia is present in 65% of men and 66% of women (7). Additionally, 47% of women and 61% of men in Germany are overweight, and obesity affects 19% of both genders (8,9). Only 45% of the German population adheres to the recommended 2.5 hours of moderate-intensity aerobic physical activity per week, as outlined by the World Health Organization (10,11), and 29% of adults in Germany are occasional smokers (12). These risk factors are also prevalent in other industrialized societies (13–16), highlighting the importance of cardiovascular prevention not only in Germany but also in other European countries.

The modification of these risk factors through lifestyle changes or pharmacological treatment can significantly reduce the likelihood of cardiovascular events (17–22). In Germany, primary prevention interventions within the medical system primarily involve general practitioners (GPs) (23). GPs, due to the continuity of care, are well positioned to assess individual risks and benefits for their patients, provide informed decision-making support, and follow up with patients to ensure the maintenance of behavioral and pharmacological changes (24–26).

Clinical practice guidelines (CPGs) are meant to provide evidence-based recommendations aimed at optimizing patient care. The German College of General Practitioners and Family Physicians (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e. V., DEGAM) is currently updating its CPG on the primary prevention of ASCVD. This guideline will focus on counselling adult patients without clinically manifested or established ASCVD diagnoses on preventing cardiovascular events. It will provide recommendations on identifying patients eligible for counselling, calculating the (untreated or mostly untreated) global cardiovascular risk, and

available options to mitigate this risk, such as lifestyle modifications and medical treatments. The guideline will also cover the desirable and undesirable effects of these options and strategies to effectively communicate recommendations to patients. This includes explaining risks, offering preventive choices, discussing uncertainties, and supporting patients in implementing their health-related decisions.

Our systematic guideline review aims to inform the German guideline update but may also benefit other guideline developers and clinicians. The review question was "What do national and international guidelines recommend regarding the primary prevention of ASCVD in adults receiving primary care?" We payed special attention to tailoring recommendations for different age groups, ethnicities, sexes, and genders, as well as for individuals living with diabetes, multimorbidity (including frailty), and polypharmacy.

METHODOLOGY

A systematic review of CPGs on the primary prevention of cardiovascular events was conducted. The review followed the systematic guideline review methodology outlined by Muth et al. (27,28). The protocol was registered with PROSPERO (ID CRD42023394605), with provisions for updates in the event of future changes.

Inclusion and exclusion criteria

Type of records

CPGs that provided recommendations for primary prevention of cardiovascular events in adults without ASCVD were included. These guidelines needed to be informed by a systematic review of evidence and provide references for the underlying evidence, as well as an assessment of the benefits and harms of alternative care options (29). To focus on recent evidence since the last update of the German guideline in 2016, guidelines published or updated in English, Spanish, German, or Dutch languages after 2016 were eligible. Expired guidelines, those not published on behalf of a professional organization, and guidelines not employing a global/overall ASCVD risk assessment approach were excluded (30).

Target population

The target population for the guidelines included in the review were individuals 18 years of age or older without a diagnosis of manifested ASCVD. The guidelines provided a holistic approach to managing the overall ASCVD risk of individuals and usually covered various risk factors, including but not limited to type 2 diabetes, hypertension, smoking, dyslipidemia, obesity, physical inactivity, and unhealthy diet. Guidelines focused on specific populations (e.g., pregnant women) or specific healthcare processes (e.g., surgery preparation) were excluded, unless primary prevention of ASCVD was within their scope.

Type of intervention

The review encompassed guidelines on various types of primary care interventions for the primary prevention of cardiovascular events, including risk assessment, risk communication, counselling, decision-making, and non-pharmacological and pharmacological prevention.

Scope of the included guidelines

Our review included guidelines that addressed the primary prevention of ASCVD as their main scope and adopted a global risk-based approach. The detailed algorithm outlining the criteria for inclusion and exclusion can be found in Annex 1.

Information sources and literature search

The literature search was conducted using multiple information sources. MEDLINE via PubMed and the 'Turning Research Into Practice' (TRIP) database were searched using Medical Subject Headings (MeSH) terms and keywords related to cardiovascular diseases, primary prevention, and clinical practice guidelines. The search was limited to publications from 2016 onwards. Annex 2 shows the full search strategies for the two electronic databases. In addition, guideline-specific databases and websites of societies in the fields of cardiology, hypertension, diabetes, and primary care were searched (Annex 3).

Selection process

Data management

We downloaded the bibliographic details of all the records we identified in MEDLINE and TRIP as RIS files. These files were then uploaded into the reference manager, Zotero (31). To ensure a systematic and efficient review process, we imported the RIS files into Covidence (32), a dedicated systematic review platform. Covidence allowed us to eliminate duplicate records and conduct the title and abstract screening process.

For the retrieval of full-text articles, we utilized Zotero, which facilitated the collection of complete research papers and relevant documents. We then used Covidence to screen these full texts, assessing their eligibility for inclusion in our review and evaluating the quality of the guidelines. Throughout this process, all screening decisions and guideline assessments were documented using Covidence, ensuring transparency and consistency in our review methodology.

Selection of records

Two researchers independently screened the titles and abstracts of identified records for eligibility. Prior to screening, a calibration test was performed on a subset of records to ensure agreement between reviewers (33). If the desired level of agreement (80%) was not achieved, the inclusion and exclusion criteria were refined, and the calibration test was repeated. Two reviewers,

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with any discrepancies resolved through discussion and consensus, conducted full-text assessment of potentially relevant guidelines. A third reviewer was available if needed.

Guideline repositories and societies' websites were hand-searched by two reviewers, and references of included guidelines were checked for additional CPGs to be included in the review.

Dealing with duplicate and associated records

After completing the search, we saved the identified CPGs in the reference manager, along with their full-text versions and any relevant documents, such as methodological and evidence reports, journal publications, and executive summaries. To ensure a comprehensive analysis, all documents associated with a specific guideline were grouped together and considered as a single "guideline document set."

To further refine our dataset, we integrated the records obtained from the manual search of guideline repositories and societies' websites with those obtained from PubMed and TRIP. By merging these sources, we aimed to create a consolidated and non-redundant collection of CPGs. Through this process, we effectively eliminated any duplicate entries, ensuring the integrity and accuracy of our dataset.

Data collection and data items

Two reviewers undertook the data extraction process from the included guidelines in two consecutive stages (27,28).

In the first stage, the reviewers carefully assessed the characteristics of the complete guideline document set and recorded various items, including the guideline's identification details (such as name, publication year, and country of origin), target audience (e.g., primary care professionals), target population, and outcomes addressed.

Next, in the second stage, the reviewers extracted individual recommendations from each guideline for further qualitative data analysis using the ATLAS.ti software (34). Recommendations that fell outside the scope of primary ASCVD prevention were excluded from the analysis. During the extraction process, the following data items were collected: the clinically relevant question underlying a recommendation (translated into codes); the content (scope and

directionality) of the recommendation; the grade of recommendation assigned; the level of evidence supporting the recommendation; the guideline authors' evaluation of the evidence; and the cited literature that formed the basis of the recommendation.

To facilitate the extraction and analysis, a code system was employed in ATLAS.ti, which helped identify text segments relevant to the specific interventions considered in the review, based on a predefined framework (Annex 4). The main categories in the code system included risk assessment, patient-provider interaction (i.e., risk communication and decision-making), and non-pharmacological and pharmacological interventions. The code system also accounted for sub-groups within the population covered in the review, such as individuals with diabetes, multimorbidity, polypharmacy, different age groups, and those from diverse ethnic, gender, and sex backgrounds. Information pertaining to interventions targeted at specific populations was double-coded accordingly to facilitate retrieval for any further analysis.

Once one researcher per guideline completed the coding with the original code system, the code system was refined in a consensual manner by the research team. In a second round of coding, the four main categories of interventions were divided among several researchers. Reviewing all coding belonging to a specific category across all included guidelines also served to identify any errors or inconsistencies for correction. The development process of the code system and the analytical framework (epidemiological model) were thus interlaced (Annex 4).

Overall, this meticulous process allowed for the targeted retrieval and synthesis of text segments belonging to specific (sub-)categories or aspects of preventive interventions, providing for a comprehensive analysis of the extracted recommendations (35).

Assessment of quality

Two researchers appraised the quality of the CPGs using the MiChe list (36,37). This list comprised eight specific questions and two holistic items designed to evaluate the guidelines' quality. The overall assessment was rated on a Likert scale ranging from '1' (very good) to '7' (very poor), providing a comprehensive evaluation (Annex 5).

The results of the quality assessment were compiled and presented in a tabular format, offering a concise overview of the findings. In case of any discrepancies during the assessment process, the

two reviewers engaged in discussion and reached a consensus. If necessary, a third reviewer was involved to facilitate the resolution of any disagreements.

By employing the MiChe list and conducting a rigorous quality appraisal, the researchers ensured a thorough evaluation of the included CPGs, enhancing the reliability and validity of the review.

Consistency analysis and validation

The recommendations presented in the included CPGs underwent an assessment through consistency analysis (27). Two reviewers compared the content, including the scope and directionality, as well as the cited literature, encompassing the level of evidence and grading, for recommendations on similar interventions provided by different guidelines included in the review.

Based on the comparison, the findings were classified into seven distinct categories, taking into account their external consistency and evidence base. These categories encompassed four types of consistency and three types of inconsistency, namely major and minors. In the event of any discrepancies, a third reviewer was involved to facilitate resolution (Annex 6).

To critically evaluate the validity of the recommendations, the most pertinent evidence from the cited guidelines was selected. We utilized the highest levels of evidence recommended by the Oxford Centre for Evidence-Based Medicine (38). We restricted the validation to groups with concordant strong recommendations and consistency type 1-4. Our evaluation primarily focused on systematic reviews, with or without meta-analyses, and relevant clinical studies. In cases where secondary publications lacked the desired evidence, we considered studies of appropriate design. Based on the content of the evidence selected, recommendations were classified into three categories: completely justified, partially justified and unjustified. Any discrepancies that arose during the validation process were addressed through discussion and consensus, with the involvement of a third reviewer if required.

By employing consistency analysis and the validity criteria, the researchers ensured a comprehensive evaluation of the recommendations within the included CPGs, fostering appropriateness and reliability in the assessment of evidence and reinforcing the validity of the review.

Data synthesis

The key findings, including the recommendations extracted from the guidelines, were presented in tables to facilitate their comprehension. To provide a comprehensive overview, a narrative synthesis of the findings was structured based on the clinically relevant questions derived from the qualitative text analysis of the data (39).

Moreover, all the data extracted concerning population sub-groups, such as individuals living with multimorbidity, were categorized according to the specific sub-groups and their corresponding interventions, whether risk assessment, patient-provider interaction, non-pharmacological or pharmacological in nature.

As a conclusion, the review highlighted the knowledge gaps identified during the analysis, emphasizing areas that require further research to enhance the optimization of guidelines for the primary prevention of ASCVD in Germany. By identifying these gaps, the review aimed to contribute to the advancement of knowledge in the field and promote evidence-based decision-making in cardiovascular care.

RESULTS

Literature search and selection

Following a rigorous screening process of 5,123 distinct references, 26 CPGs were deemed eligible for inclusion in the systematic guideline review (Annex 7). The 26 guidelines were produced by 15 different organizations.

In Annex 8 and 9, we present essential characteristics of the CPGs that were included in our analysis. It is worth noting that out of the 26 guidelines included, 17 were developed in North America, while seven originated from Europe. All included guidelines were published in English, although guidelines in other languages (German, Dutch, and Spanish) were principally eligible. Evidence-based German guidelines, i.e., those meeting the S3-criteria of the AWMF, had to be excluded because either they did not focus on the primary prevention of ASCVD or they concentrated on the management of selected risk factors.

The 2021 guidelines from the European Society of Cardiology (ESC) (40) on CVD prevention in clinical practice are consensus-based guidelines, which were confirmed by the first author upon our request. They therefore did not meet the inclusion criteria of our systematic guideline review and their recommendations are not part of our findings presented in the following sections.

Appraisal of the methodological quality

Out of the total 26 guidelines assessed for quality, the majority, specifically 21 guidelines (22,41–62), demonstrated a high level of quality, being rated as "very good." However, five guidelines (63–65) did exhibit minor shortcomings, primarily related to limit reporting of the systematic search for evidence and selection criteria. For a comprehensive breakdown of the quality appraisal, please refer to Annex 10, where you can find detailed information regarding the assessment of each guideline's quality.

Framework development and data extraction

We followed a systematic process to formulate 223 clinical questions that align with the structure of our developed framework (Annex 11): Twenty for risk assessment, two for patient-provider

interaction, 86 for non-pharmacological interventions, 115 for pharmacological interventions. To compile the necessary data, we meticulously recorded all pertinent details in tables using the specified format mentioned earlier.

In total, we extracted 581 recommendations (median: Seven recommendations per guideline; IQR: 38; range: 1 to 88). The most common recommendations assessed pharmacological interventions (n = 248), followed by non-pharmacological interventions (n = 225), risk assessment (n = 147) and patient-provider interaction (n = 18). There were recommendations that evaluated multiple types of interventions according to our predefined framework in order to provide comprehensive guidance (n =57).

Consistency analysis and validation

In order to assess the consistency for the recommendations on similar interventions provided by the included CPGs, there was a need to compare the different classifications of level of evidence and grading that the CPGs used (Annex 12).

Among the recommendations, 17 were classified as concordant strong recommendations with consistency type 1-4: Eleven for non-pharmacological interventions and six for pharmacological interventions. These recommendations underwent further scrutiny during the validation process. From this pool, we selected 17 studies for reassessment, comprising an umbrella review of systematic reviews (SRs), eight SR with or without meta-analyses, one cohort study and one evidence report for a CPG.

Summary of recommendations from international primary prevention of cardiovascular disease guidelines

We present below a summary of the recommendations derived from the clinical practice guidelines examined in this review, taking into account the extent of consensus, dissent, and areas that require further research (For details see Annex 13).

Recommendations for risk assessment, risk calculation, risk communication and decision-making

We found 165 recommendations across 19 distinct guidelines regarding risk assessment, risk calculation, risk communication and decision making for the primary prevention of ASCVD.

Risk assessment and calculation

Who should have ASCVD risk assessment?

Population defined by age: We identified five recommendations with varying levels of strength of recommendations and evidence stating that people older than 40 years should have ASCVD risk assessment (consistency type 4). In addition, one guideline recommended assessing ASCVD risk in people 20-39 years of age every four to six years and one guideline recommended to assess risk in people > 30 years of age (inconsistency type C).

Named different conditions: People at risk of stroke, people who have had a stroke, patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), erectile dysfunction, before prescribing Contraceptives (COCs) and patients infected with the HIV. One guideline recommended prioritizing people based on an estimate of their ASCVD risk before a full formal risk assessment.

What are the benefits and harms of screening for a single risk factor or condition?

Screening for atherosclerotic plaques/ stenosis in carotid arteries by use of carotid ultrasound: We identified three highly inconsistent recommendations (inconsistency type A) for this clinical question, two against and one in favor of screening.

Screening for diabetes: Three guidelines gave weak recommendations in favor of screening, however they referred to different populations (adults aged 35 to 70 years who have overweight or obesity, individuals with metabolic risk and individuals aged ≥ 40 and high risk for diabetes) (inconsistency type B).

Screening for hyper-/ dyslipidemia: One guideline gave a strong recommendation in favor of lipid and lipoprotein screening while another guideline voted against a routine monitoring (inconsistency type A).

Screening for hypertension: One guideline gave a strong recommendation in favor of screening.

Screening for obesity: Five / five recommendations were in favor of screening, but they referred to different modalities and measures and varied by strengths of recommendation and level of evidence (inconsistency type A).

Screening for smoking/ tobacco use: Two guidelines gave recommendations in favor of screening but for different populations (all adults and patients with psychosis) and with varying strengths of recommendations and level of evidence (inconsistency type A).

Screening for arterial stiffness: One guideline gave a recommendation against screening for arterial stiffness.

Screening for presence of coronary artery disease by use of non-invasive Tests (ECG (Resting or Exercise), stress tests, coronary computed tomography angiography (CCTA)): We identified seven recommendations referring to this question, five recommendations against, one weak recommendation for and one guideline stated that the evidence was inclusive. However, the recommendations referred to different test modalities (inconsistency type A).

What are the benefits and harms of using a systematic versus an opportunistic ASCVD risk screening strategy?

We identified four highly inconsistent recommendations (inconsistency type A). One guideline recommended using a systematic and avoiding an opportunistic strategy, while one guideline recommended using an opportunistic approach and another guideline recommended against a systematic strategy.

When should CVD risk be assessed?

We identified two recommendations with varying levels of strength and evidence (inconsistency type C). One guideline recommended an annual risk assessment to discuss lifestyle modification, medicines adherence and to address CVD risk factors. The other guideline recommended

reassessing a patient's risk in the future, if their CVD risk is at a level where intervention is recommended but they decline the offer of treatment.

Should specific groups generally be considered at high risk?

We identified 12 inconsistent recommendations with varying levels of strength and evidence stating that patients with:

- an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2,
- albuminuria,
- pre-existing CVD,
- familial hypercholesterolemia,
- LDL-C 70 to 189 mg/dL (1.8 to 4.9 mmol/L) (in aged 40 to 75),
- type 1 or type 2 diabetes,
- stage 3 or higher chronic kidney disease,
- target organ damage,
- significantly elevated cardiovascular risk factors,
- rheumatoid arthritis,
- ankylosing spondylitis,
- psoriatic arthritis,
- metabolic risk or
- patients aged 85 or older should be considered at high risk for ASCVD, whereby the guidelines often named different risk factors (inconsistency type C).

What are the benefits and harms of using a standardized risk assessment tool assess ASCVD risk?

We identified eight recommendations referring to this clinical question. Among these, eight were in favor of using a risk assessment tool and four different tools were explicitly mentioned. Seven recommendations referred to additional aspects of risk assessment (e.g., age group) (inconsistency type C).

What are the benefits and harms of using additional, non-traditional risk factors to determine global cardiovascular risk?

Coronary artery calcium (CAC): We identified five recommendations referring to this clinical question. Among these, two recommendations were in favor of using CAC Score, two recommended against and one guideline stated that the evidence was inconclusive (inconsistency type A).

Ankle-brachial index (ABI): We identified two recommendations referring to this clinical question. Among these, one recommended against and the guideline stated that the evidence was inconclusive (consistency type 3). The validity was completely justified.

High-sensitivity C-reactive protein (hsCRP): We identified two recommendations referring to this clinical question. Among these, one recommended against and the guideline stated that the evidence was inconclusive (consistency type 3). The validity was completely justified.

Psychosocial factors: We identified three recommendations in favor of considering psychosocial factors and socioeconomic status, but with varying strengths of recommendations and conflicting levels of evidence (inconsistency type B).

Body mass index (BMI): One guideline recommended considering severe obesity (BMI > 40).

Existing medical conditions and treatments: Two guidelines recommended considering different conditions and existing treatment (people with HIV, serious mental health problems, people taking medicines that can cause dyslipidemia, such as antipsychotic medication, corticosteroids or immunosuppressant drugs, people with autoimmune disorders, such as systemic lupus erythematosus, and other systemic inflammatory disorders and, atrial fibrillation).

Which cholesterol measures should be used?

We identified nine recommendations with varying levels of strength and evidence (inconsistency type C). The guidelines recommended measuring both total and high-density lipoprotein (HDL) cholesterol, two guidelines also recommended to measure triglyceride concentrations and one guideline recommended to measure non-HDL cholesterol.

Should lifetime or 30-year ASCVD risk be considered to guide decisions about preventive strategies?

We identified one recommendation stating that for patients aged 20 to 39 years or aged 40 to 59 years with <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk could be considered.

What are the benefits and harms of considering additional, non-traditional risk factors to reclassify persons with intermediate or borderline risk to guide decisions about preventive strategies?

We identified 13 recommendations referring to this clinical question. Non-traditional risk factors which assessment was recommended were Ankle Brachial Index (ABI index) (one recommendation), Carotid Intima-Media Thickness Test (CIMT) (one recommendation), high-sensitivity C-reactive protein (hsCRP) (one recommendation) and coronary artery calcium score (CAC score) (four recommendations). Two guidelines recommended considering risk-enhancing factors naming a specific risk factor. The recommendations in favor of CAC Score were somewhat consistent (consistency type 2).

What risk thresholds are stated to recommend i) pharmacological or non-pharmacological treatments; ii) lipid management interventions or BP management interventions or antithrombotic therapy?

We identified 40 recommendations referring to thresholds of ASCVD risk. Even after categorizing these recommendations in terms of different dimensions of treatment (pharmacological *versus* non-pharmacological treatments and lipid management interventions *versus* BP management interventions *versus* antithrombotic therapy), the recommendations were highly inconsistent (inconsistency type C) according to risk thresholds, patient populations, but also strengths of recommendations and levels of evidence.

In summary, we found a tendency that ASCVD risk assessment should be offered to patients older than 30-40 years, that the intensity of prevention efforts should match the absolute CVD risk and that a standardized risk assessment tool should be used. Besides that, the recommendations on

risk assessment and risk calculation are often inconsistent (e.g., which risk tool to be used, if and which additional non-traditional risk factors should be considered, concrete thresholds for treatment) and sometimes contradictory (e.g., populations in which risk calculation should be performed).

Risk communication and decision making

Should a shared decision-making approach be used?

We identified eight recommendations across five distinct guidelines referring very general to a shared decision process. One guideline explicitly and general recommended shared decision-making to guide discussions about best strategies to reduce ASCVD risk, while other guidelines referred to specific treatment decisions (e.g., decision about statins) or specific situations (e.g., intermediate or borderline risk).

Should absolute risk be used as basis of decision-making?

We identified four recommendations across two guidelines stating that the patients should be offered information about their CVD risk and that the treatment decisions should be individualized.

How to communicate risk?

We identified seven recommendations across two distinct guidelines referring to how communicating risk. However, all recommendations referred to different aspects (e.g., using every day, jargon free language, presenting individualized risk, using appropriate diagrams and text).

In summary, the recommendations are very inconsistent and relate to different aspects of risk communication and decision-making. However, there is general agreement that the decision on pharmacological and non-pharmacological treatment measures should be a shared one, taking into account the individual characteristics of the patient.

Recommendations for non-pharmacological interventions

We found 225 recommendations across 16 distinct guidelines dealing with non-pharmacological interventions for the primary prevention of ASCVD.

Behavioral counselling

Who should be the recipients of lifestyle advice and behavioral counseling?

Adults at increased ASCVD risk: We identified two recommendations from one guideline stating that adults 18 years or older at increased risk of ASCVD should be referred to behavioral counseling.

What is the recommended approach for delivering lifestyle advice and behavioral counseling effectively?

Accounting for personal circumstances: We identified two strong recommendations from two guidelines stating that individual circumstances should be taken into account. While one was addressing related health issues, the other was related to social determinants of health (inconsistency type C).

Emphasize benefits and show opportunities: We identified two recommendations from two guidelines suggesting positive approaches for motivation. One additionally recommended to provide the person with written information about the benefits of activity and local opportunities to be active (inconsistency type C).

Content and mode of behavioral counselling: We identified five recommendations from three guidelines dealing with various aspects of how to provide counseling. One guideline outlined different steps to follow in the process of risk communication and counseling. Additionally, it referred to other guidelines on behavior change, healthy eating and physical activity. Another guideline listed what kind of advice was commonly given on nutrition and physical activity. A third guideline referred to the optimal duration of complex lifestyle interventions, stating that there is no clear evidence on this (inconsistency type C).

Competencies for counselling: We identified two recommendations from the same guideline, one referring to the need for appropriate training when applying psychological techniques, the other emphasizing the requirement of educational competencies in the field of dietary advice.

Team-based care: We identified two recommendations from different guidelines. One was generally suggesting a team-based approach to risk factor control; the other recommended the referral to a dietitian for nutritional advice.

Regarding behavioral counseling, recommendations often address different aspects. In summary, the guidelines suggest that lifestyle and behavioral counseling should be targeted adults who are at increased risk for ASCVD. Behavioral counseling should take into account patients' personal circumstances and emphasize the benefits of changing habits. Regarding the form of lifestyle counseling, recommendations are very inconsistent and address different aspects of counseling, including recommending a team-based approach or referral to specialists (e.g., dietitians).

Physical activity

What key principles should be considered when providing advice on physical activity?

Reduction of sedentary behavior: We identified two recommendations with varying levels of strength and evidence stating that sedentary behavior in adults should be decreased to reduce the risk of ASCVD (consistency type 4).

Encouragement of activity: We identified two recommendations with varying levels of strength and evidence stating that all patients should be encouraged to increase physical activity. One guideline recommended to routinely counseling adults in healthcare visits to optimize a physically active lifestyle (consistency type 4).

Exercise at maximum safe capacity: We identified four strong recommendations stating that physical activity of at least moderate intensity is recommended for the whole population, unless contraindicated by an individual’s condition. Those individuals should be encouraged to exercise at their maximum safe capacity. Individuals who are moderately active and are able to increase their activity should be encouraged to do so (inconsistency type C).

What modes of physical activity are beneficial to cardiovascular health?

Any physical activity: We identified two recommendations with varying levels of strength and evidence stating that any amount of physical activity is recommended for the primary prevention of ASCVD (consistency type 3).

Incorporation of walking: We identified three recommendations with varying levels of evidence stating that (brisk) walking should be encouraged to increase physical activity and reduce the risk of ASCVD (consistency type 3). The validity was completely justified.

Muscle strengthening: We identified one strong recommendation stating that patients should be advised to do muscle-strengthening activities on two or more days a week.

What levels of physical activity are beneficial to cardiovascular health?

Time of moderate or vigorous activity per week: We identified four strong recommendations stating that patients should be encouraged to do moderate physical activity for 150 minutes/week or vigorous activity for 75 minutes/week to reduce the risk of ASCVD (consistency type 3). The validity was partly justified.

Supportive tools: We identified one recommendation stating that the initiation of physical activity in previously inactive or highly sedentary populations should preferably take place within a comprehensive health behavioral change program.

Recommendations on physical activity are mostly consistent. In general, it is recommended to reduce sedentary periods and increase activity levels. Overall, engagement in at least 150 minutes of moderate physical activity per week or 75 minutes of vigorous activity per week and muscle-strengthening activities on two or more days per week appear as broadly accepted recommendations, unless contraindicated by the patient's condition.

Nutrition

What dietary patterns are considered beneficial for promoting health and well-being?

Reference to national guidelines: We identified four recommendations with varying levels of strength and evidence, which refer to other guidelines on the topic of healthy nutrition (inconsistency type C).

Components of a healthy diet: We identified four strong recommendations with varying levels of evidence on the topic of components of a healthy diet (consistency type 4). The validity was partly justified. Two guidelines recommended the Mediterranean diet to reduce the risk of ASCVD. Two guidelines recommended the increased intake of fruit and vegetables, which are part of the Mediterranean diet.

Plant *versus* animal-based foods: We identified two recommendations from one guideline stating that healthy dietary patterns, mainly based on large amounts of plant foods, were recommended.

What general rules or guidelines are applicable for maintaining a healthy and balanced nutrition?

Reduce consumption of processed foods (sodium, refined carbohydrates, and saturated fats): We identified five recommendations with varying levels of strength and evidence (inconsistency type C). The recommendations stated to reduce the intake of sodium, sugars, cholesterol or saturated fats by avoiding processed foods like processed meats and sweetened beverages.

Limited sugar intake: We identified one strong recommendation based on high quality evidence stating that for adults, <10% of total energy intake should be from added sugar. An intake of sugar contributing to <5% of total energy intake has additional health benefits.

Reduce saturated fats, replaced by unsaturated fats: We identified eight recommendations with varying levels of strength and evidence (inconsistency type C). The recommendations stated that the intake of saturated fats should be reduced and that the intake of monounsaturated and polyunsaturated fats should be decreased to reduce the risk of ASCVD.

What are the recommended serving sizes or amounts of specific types of food that should be consumed for a balanced diet?

Whole grain: We identified two recommendations with varying levels of strength and evidence stating that the dietary intake of whole grain reduces the risk of ASCVD and should be encouraged (consistency type 4).

Fruits and vegetables: We identified three strong recommendations with varying levels of evidence stating that patients should be advised to eat at least five portions of fruit and vegetables per day (consistency type 4). The validity was completely justified.

Fish: We identified three recommendations with varying levels of strength and evidence (inconsistency type C) stating that the consumption of fish was recommended to reduce the risk of ASCVD. Two guidelines recommended eating fish twice a week.

Olive oil and nuts: We identified four recommendations with varying levels of strength and evidence (inconsistency type C). Three guidelines recommended a daily consumption of 20-30 g of (unsalted) nuts for the prevention of ASCVD. Moreover, two guidelines recommended extra virgin olive oil to reduce the risk of ASCVD.

Legumes: We identified one recommendation stating that the dietary intake of legumes had beneficial effects for the prevention of ASCVD and is therefore recommended.

Meat: We identified one strong recommendation stating that the dietary intake of meat should be limited to 1-2 times a week and that the consumption of processed meat should be only occasional.

Dairy products: We identified one strong recommendation stating that the regular consumption of low-fat milk and dairy products is recommended.

Coffee: We identified one strong recommendation stating that the moderate consumption of coffee was recommended.

Tea: We identified one strong recommendation stating that the moderate consumption of tea, and especially green tea, was recommended.

Dark chocolate: We identified one strong recommendation stating that the moderate consumption of dark chocolate was recommended.

Unsweetened Beverages: We identified two strong recommendations stating that the consumption of sweetened beverages should be discouraged and the consumption of water instead should be encouraged (consistency type 4). The validity was completely justified.

What are the recommended proportions or percentages of different fatty acids that are considered relevant for a healthy diet?

Limits of fat intake: We identified five recommendations with varying levels of strength and evidence (inconsistency type C). Two guidelines recommended that the total fats should contribute to about 20-25% with an upper safe limit of 30% of the total calorie intake. One guideline recommended that the average male should aim to consume no more than 30 g of saturated fat and that the average female should aim to consume no more than 20 g of saturated fat per day. Moreover, another guideline recommended that the intake of saturated fatty acid should be <10% of the total calorie intake and that trans fatty acid should contribute <1% of the total calorie intake.

Which modes of intake for unsaturated fatty acids (dietary, supplements, preparations) are advisable?

Fat supplementation: We identified five recommendations with varying levels of strength and evidence stating that the use of fat supplementation should be avoided and was not recommended for the primary prevention of ASCVD (consistency type 4).

Icosapent ethyl in persons with elevated triglycerides: We identified four recommendations with varying levels of strength and evidence stating that icosapent ethyl could be recommended if used as described in NICE's technology appraisal guidance on icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (consistency type 4). One guideline stated that there is insufficient evidence to recommend for or against icosapent ethyl in patients on statin therapy with persistently elevated fasting triglycerides.

What level of dietary sodium intake is considered harmful or potentially detrimental to health?

Limits of sodium intake: We identified three recommendations with varying levels of strength and evidence (consistency type 4) stating that the Sodium (salt) intake should be reduced to or below 2g / day (5g of salt). One guideline recommended a salt intake below 6g / day.

Reduction of sodium: We identified two recommendations from one guideline. The guideline recommended a reduction in sodium intake by approximately 1,000 mg/day to reduce the ASCVD risk by about 30 percent. They did not recommend a low sodium diet in populations with a low salt intake.

Which other plant-based components and modes of intake are considered relevant or important for maintaining a healthy diet?

Fiber: We identified two strong recommendations with varying levels of evidence stating that the dietary fiber intake should be increased to 20 - 30 g/day by consumption of adequate amounts of plant foods (consistency type 4). The validity was completely justified.

Plant extracts: We identified two recommendations with varying levels of strength and evidence (inconsistency type C). One guideline stated that there was insufficient evidence to recommend for or against the use of fiber, garlic, ginger, green tea, and red yeast rice supplements to reduce ASCVD risks. Another guideline recommended against the use of plant stanols or sterols for the prevention of ASCVD.

Which vitamins or provitamins are considered relevant for maintaining good health, and what are the recommended modes of intake for these nutrients?

Niacin / vitamin B3: We identified three strong recommendations stating that nicotinic acid was not recommended for ASCVD risk reduction (consistency type 1). The validity was completely justified.

Folate (B9) - or B-vitamin: We identified three recommendations with varying levels of strength and evidence (inconsistency type B). Two guidelines recommended against Vitamin B6/Vitamin B12/folate supplements for the prevention of ASCVD. One guideline recommended the regular consumption of high folate-containing foods.

Vitamin C: We identified one recommendation stating that an adequate dietary intake of vitamin C is recommended.

Antioxidant vitamins (B2, C, E): We identified two strong recommendations against the use of antioxidant vitamin supplements for the prevention of ASCVD (consistency type 4). The validity was completely justified.

Vitamin E or beta-carotene (provitamin A): We identified two recommendations from one guideline stating that beta-carotene or vitamin E supplements should not be used for the primary prevention of ASCVD.

Vitamin D: We identified one recommendation stating Vitamin D deficiency (indicated by a plasma concentration of 25- hydroxycholecalciferol below 50 nmoL/L (20 ng/ mL)) should be corrected appropriately.

Multivitamin supplements: We identified one recommendation stating that there was insufficient evidence to assess the balance of benefits and harms of the use of multivitamin supplements for the prevention of ASCVD.

Which minerals are considered relevant for maintaining good health, and what are the recommended modes of intake for these minerals?

Calcium: We identified two recommendations from one guideline. The guideline recommended an adequate dietary calcium intake according to age. Moreover, they recommended extreme caution in the prescription of calcium supplements, unless needed to correct proven deficits.

Magnesium: We identified one recommendation recommending an adequate dietary magnesium intake according to age.

Potassium: We identified one recommendation stating that the dietary potassium intake should be increased possibly to 100 mmol (3.9 g)/day.

What are the potential advantages and disadvantages or risks associated with the use of nutrient supplementation?

Single- or paired-nutrient supplements: We identified one recommendation stating that there was insufficient evidence to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (other than beta-carotene and vitamin E) for the prevention of ASCVD.

The dietary recommendations are both consistent and inconsistent, though many inconsistencies are due to the fact that different aspects or levels of detail within the field of nutritional advice are addressed.
The guidelines consistently recommend a Mediterranean diet, the consumption of whole grains and at least five servings of fruits and vegetables per day, a reduction in the consumption of sweetened beverages, a lower salt intake (<6 g salt per day), and an increased intake of dietary fiber (20-30 g per day) to reduce ASCVD risk.

In addition, the guidelines consistently discourage the use of nicotinic acid and antioxidant vitamin supplements for reducing ASCVD risk.

Substance use and miscellaneous aspects

How is nicotine use addressed or managed in the primary prevention of ASCVD?

Advice to stop smoking: We identified eight mostly strong recommendations from six guidelines with varying levels of evidence. They called on health care providers to clearly advise patients to stop smoking (consistency type 4).

Referral to smoking cessation services: We identified five recommendations from different guidelines with varying strength and levels of evidence. Two guidelines recommended the combination of pharmacotherapy and behavioral counselling; two suggested referring patients to

specific smoking cessation services and one guideline recommended dedicating specifically trained staff to this task (consistency type 4).

Smoking cessation in persons with mental illness: We identified two recommendations from the same guideline related to substance use, including nicotine, in psychotic patients. An optimized antipsychotic treatment and tailored smoking cessation programs were recommended.

Pharmacotherapy for smoking cessation: We identified three recommendations from two guidelines concerning the provision of pharmacotherapy to support smoking cessation, ideally in combination with a comprehensive behavioral program. While one guideline recommended varenicline, the other additionally suggested a combination nicotine replacement therapy or – under certain conditions - Bupropion and single nicotine replacement therapy (inconsistency type B).

E-cigarettes and shisha: We identified one recommendation discouraging the use of e-cigarettes and shisha.

Prioritization of smoking cessation interventions: We identified two recommendations from the same guideline suggesting to focus smoking cessation efforts on young people and on persons with low income.

What is the rating or assessment of tobacco smoke in terms of its association with the risk of ASCVD?

Avoid passive smoking: We identified four mostly strong recommendations from different guidelines with varying levels of evidence dealing with exposure to passive smoke. They emphasized that tobacco smoke increases CVD risk and should be avoided or minimized (consistency type 4).

How is alcohol consumption addressed or managed as part of the primary prevention strategy for ASCVD?

Screening for excess alcohol use: We identified one recommendation against universal screening as a case-finding exercise in primary care.

Interventions regarding alcohol: We identified four recommendations from two guidelines. One guideline was referring to a national guideline for advice on alcohol consumption. The second guideline suggested that examples of what constitutes a 'drink' or unit of alcohol should be given to the patient and that any patient should be confronted with the cardiovascular risk stemming from even moderate alcohol consumption. In case of hazardous drinking levels, brief multicontact interventions should be used (inconsistency type C).

Limits of alcohol intake: We identified four recommendations from different guidelines specifying potentially hazardous drinking levels. However, one recommendation was setting the limit at >30 g per day, while the other three are setting it at > 10g for women and >20g for men (inconsistency type B).

Assessment in people with schizophrenia: We identified one recommendation on this particular sub-population highlighting the negative impact of any harmful substance use, meaning that it should be carefully assessed and that treatment should be appropriately focused.

What specific measures or interventions are implemented in relation to mental health?

Avoid chronic stress: We identified one statement recommending the avoidance of chronic exposure to personal, family, and work-related stress.

Mind-body-practices: We identified one recommendation stating that mind body practices have a positive impact on cardiovascular health.

Therapy in case of anxiety or depression: We identified two recommendations from different guidelines. One stated that individual CBT is recommended as a treatment option for patients with depression or anxiety disorders. The other one suggested offering patients with clinically significant depression or anxiety treatment with psychotherapy and antidepressant/ anxiolytic medication (inconsistency type B).

Referral in case of complex psychological problems: We identified two recommendations from different guidelines. One suggested that patients who present with more complex psychological problems should be considered for referral to mental health services for assessment and delivery, where appropriate, of high-intensity or specialist treatments. The second one stated that programs might work best if designed specifically for those with psychosis and if they combine elements of group and individual patient approaches (inconsistency type B).

What are some alternative or additional treatment measures that are commonly considered or suggested?

Traditional or alternative medicine: We identified recommendations against different treatments, but all coming from the same guideline. The use of herbal medicine, chelation therapy, ozone therapy and stem cells for ASCVD prevention was discouraged, as is acupuncture as a form of BP lowering therapy (inconsistency type C).

In summary, it can be said that the recommendations on tobacco smoking are mostly consistent. Both active and passive smoking should be avoided because of the increased risk of CVD, and smokers should be referred to smoking cessation services. When it comes to alcohol consumption, the recommendations are inconsistent with regard to various alcohol consumption interventions and daily limits for low-risk alcohol consumption (> 30g/day, > 10g/day for women and > 20g/day for men). Also, the recommended measures and interventions related to mental health (avoid chronic stress, mind-body-practices, different forms of therapy in case of anxiety or depression, referral to programs or mental health services in case of complex psychological problems) and more traditional and alternative medicine (herbal medicine, chelation therapy, ozone therapy and stem cells) are inconsistent.

Risk factor management

What are the effective approaches or strategies for managing ASCVD risk?

Components of lifestyle change: We identified one recommendation generally stating that lifestyle modification by exercise, improved nutrition, smoking cessation and weight control, has been shown to reduce ASCVD risk and improve sexual function.

Lifestyle changes alone in persons at moderate risk: We identified two recommendations with varying strength and levels of evidence from different guidelines. One states that most individuals who are at moderate risk can be managed by lifestyle changes alone, while those at high risk may require pharmacotherapy. The second one suggests lifestyle management to lower blood pressure to < 130/80 mm Hg in individuals with a 10- year cardiovascular risk ≤ 10% (consistency type 4).

Assessment and management in special populations: We identified three recommendations from different guidelines addressing the treatment of people at particular risk of stroke, patients with HIV infection, and patients with psychosis (inconsistency type C).

What are the effective approaches or strategies for managing ASCVD risk in individuals with (pre-) diabetes?

Lifestyle modification in relation to medication: We identified seven recommendations from three guidelines specifically aimed at persons with manifest diabetes. They put varying emphasis on glycated hemoglobin (HbA1c) and BP treatment targets, weight control by diet and physical activity, smoking cessation, and they suggest various types of medication (inconsistency type C).

Lifestyle changes for persons at high risk of diabetes: We identified four recommendations from three guidelines dealing with preventive measures in persons at metabolic risk, i.e., risk of developing diabetes. Lifestyle modification was recommended as the first-line of therapy, before considering blood-glucose lowering medication (inconsistency type C).

What are the effective approaches or strategies for managing ASCVD risk in individuals with hypertension?

Lifestyle modification components: We identified one recommendation stating that in adults with elevated BP or hypertension, including those requiring antihypertensive medications no pharmacological interventions to reduce BP were recommended.

Reduced salt intake: We identified two recommendations suggesting the reduction of sodium consumption to reduce hypertension (consistency type 4). The validity was partly justified.

Relation of lifestyle changes and medication: We identified two recommendations from different guidelines with varying levels of strength and evidence. One stated that individuals with hypertension whose ten-year risk of a first ASCVD event was below the threshold for consideration of pharmacological therapy should continue with lifestyle strategies and have their BP and total ASCVD risk reassessed every one to five years, depending on clinical circumstances. The other one suggested that in adults without a history of ASCVD with metabolic risk who have a 10-year cardiovascular risk of >10% and BP of >130/80 mm Hg, BP-lowering medication should only be used in addition to lifestyle modifications for primary prevention of ASCVD only when lifestyle modification alone has failed (inconsistency type B).

Persons with persistent high BP: We identified one statement recommending that all individuals with a persistent clinic BP ≥140/90 mm Hg or a family history of hypertension should receive lifestyle advice to help reduce their BP and ASCVD risk, even after initiation of drug treatment.

BP target: We identified four recommendations from two guidelines (inconsistency type B). One guideline stated that individuals with uncomplicated hypertension should be supported to achieve a BP target of <140/90 mm Hg, but lowering BP below 130/80 mm Hg was not routinely recommended. It highlighted that these treatment targets should only be seen as a general guide. The second guideline suggested that in adults with confirmed hypertension without additional markers of increased ASCVD risk, a BP target of less than 130/80 mm Hg might be reasonable.

BP target in case of chronic kidney disease (CKD): We identified one guideline recommending treatment to a BP goal of less than 130/80 mm Hg.

What are the effective approaches or strategies for managing ASCVD risk in individuals with dyslipidemia?

Lifestyle modification in relation to medication: We identified four recommendations from two guidelines. One guideline stated that in individuals without established ASCVD, particularly in those with combined dyslipidemia, lifestyle measures to reduce cholesterol levels should be encouraged, irrespective of the need for pharmacological treatment. The second guideline gave specific advice on treatment targets and medication in persons with diabetes and a very high ASCVD risk or hypertriglyceridemia (inconsistency type C).

Target setting and monitoring: We identified two recommendations from different guidelines. One stated that in intermediate risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk, levels should be reduced by 50% or more. The other one suggested against the routine monitoring of lipid levels in patients taking statins (inconsistency type A).

Counselling for adherence to medication: We identified one recommendation suggesting to offer intensified patient care to improve adherence to lipid-lowering medications.

What are the effective approaches or strategies for managing ASCVD risk in individuals with excess body weight?

Weight control to improve risk profile: We identified three statements from different guidelines strongly recommending weight control or weight loss respectively to reduce ASCVD risk (consistency type 3). The validity was partly justified.

Weight reduction targets: We identified two recommendations from different guidelines stating specific but diverging targets. One suggested to reduce weight by at least 3 kg, and to maintain this reduction, while the other recommended to achieve 5 to 10% weight loss and to maintain this over a period of 1-2 years before attempting further weight loss (inconsistency type B).

Weight control strategies: We identified four recommendations from two guidelines (inconsistency type C). One suggested dietary intervention combined with multiple behavioral strategies, while acknowledging that in primary care, behavioral interventions yielded very small reductions in body weight. The second one focused on psychotic patients and suggested behavioral interventions to attenuate weight gain in first-episode initiations of antipsychotics, plus additional metformin to be considered in the context of the individual.

Physical activity dosage for weight loss: We identified four recommendations from two guidelines. The first one stated that aerobic physical activity (30–60 min of moderate to vigorous intensity most days of the week) could already be considered beneficial for adults who want to achieve weight reduction and fat loss. The second one stated that for weight loss, increased

physical of approximately 250 to 450 minutes of moderate-intensity physical activity per week, including strength training 2 to 3 times per week is required (inconsistency type C).

Comprehensive interventions: We identified four recommendations from different guidelines suggesting comprehensive behavioral interventions particularly for obese persons (consistency type 4). The validity was partly justified.

What additional therapeutic measures can be considered in managing cardiovascular risk in individuals with excess body weight?

Pharmacotherapy: We identified two statements from one guideline recommending pharmacotherapy for persons with enhanced obesity and complications.

Bariatric surgery: We identified four recommendations from two guidelines, which suggested bariatric surgery as a measure in persons with enhanced obesity and complications, as an alternative or complementary to pharmacological intervention (inconsistency type B).

To sum up, the recommendations regarding the (non-pharmacological) management of risk factors are mostly inconsistent, with occasional consistencies (i.e., most moderate risks can be managed by lifestyle changes alone; sodium consumption should be reduced to lower hypertension; weight control or weight loss through dietary interventions combined with multiple behavioral strategies are recommended to reduce ASCVD risk). The inconsistent recommendations regarding management of diabetes, hypertension, dyslipidemia, and excess bodyweight highlight the need for further research that is clearly oriented at the effects of interventions on the overall cardiovascular risk and the primary prevention of ASCVD.

Recommendations for pharmacological interventions

We found 248 recommendations across 15 distinct guidelines regarding pharmacological interventions for the primary prevention of ASCVD. The most relevant findings related to recommendations on pharmacological interventions found in the selected guidelines are summarized below.

Statins

What are the benefits and harms of using statins as blood cholesterol-lowering medication when used for the primary prevention of ASCVD?

We found 93 recommendations in total derived from 11 distinct guidelines specifically focused on the utilization of statins as blood cholesterol-lowering medication for the primary prevention of ASCVD. Included guidelines that referred to the management of blood cholesterol focused on statin therapy as the preferred pharmacological treatment for ASCVD prevention.

Statins general indication: There were five strong recommendations from two different guidelines regarding the use of statin therapy for the primary prevention of ASCVD (inconsistency type C). One guideline emphasized the importance of discussing the benefits of lifestyle modifications and optimizing the management of other modifiable ASCVD risk factors before considering statin treatment. It suggested that statin therapy should be offered only after these measures have been addressed. Additionally, the decision to initiate statin therapy should be made through an informed discussion between the clinician and the patient, taking into account factors such as the risks and benefits of statin treatment, potential benefits from lifestyle modifications, patient preference, comorbidities, polypharmacy, general frailty, and life expectancy. Another guideline strongly recommended that the decision to start statin therapy should be based solely on estimated ASCVD risk and should not be influenced by the patient's sex. This highlights the importance of considering the overall risk profile of the patient rather than gender-specific factors when determining the appropriateness of statin treatment.

Elderly: We found two recommendations of different strength and evidence levels (inconsistency type A). One guideline stated that there was insufficient evidence to assess the benefits and harms of starting statin use in adults aged 76 and older. The other guideline suggested discussing the benefits of statin therapy with patients aged over 75 without diabetes and a 10-year risk of 7.5% or more, considering potential benefits versus risks/side effects.

Borderline ASCVD risk: One recommendation suggested that in patients with borderline risk (5% to <7.5% 10-year ASCVD risk), the presence of risk-enhancing factors may justify starting moderate-intensity statin therapy during risk discussions.

Intermediate ASCVD risk: For patients at intermediate risk (≥ 7.5% to < 20% 10-year ASCVD risk), three guidelines provided five recommendations (inconsistency type C). One guideline recommended statin therapy to reduce ASCVD risk and suggested using a moderate-intensity statin if the decision was made to pursue treatment. Another guideline recommended statin therapy for individuals at intermediate risk (modified Framingham Risk Score 10%–19%) with LDL-C levels ≥ 3.5 mmol/L to decrease the risk of ASCVD events. It also suggested considering statin therapy for intermediate-risk individuals with LDL-C levels < 3.5 mmol/L but with ApoB ≥ 1.2 g/L or non-HDL-C ≥ 4.3 mmol/L. Additionally, it suggested considering statin therapy for men aged 50 years and older and women aged 60 years and older with at least one ASCVD risk factor.

High and very high ASCVD risk: Regarding high-risk individuals, there were four recommendations from two guidelines with different strengths and levels of evidence (inconsistency type C). One guideline strongly advised seeking specialist advice to explore treatment options for those at high risk of ASCVD, including individuals with CKD, type 1 diabetes, type 2 diabetes, genetic dyslipidemias, or those intolerant to three different statins. Another guideline suggested considering adding a second lipid lowering drug to the treatment regimen of patients already taking a statin and at high or very high risk of ASCVD.

CKD: For patients with CKD and micro- or macroalbuminuria who were not on dialysis, one guideline strongly recommended offering statin therapy. However, patients with diabetes and CKF who are on dialysis and do not have chronic liver disease should not be offered statins according to another guideline. For patients with CKD who were already on statin therapy before initiating dialysis, it was advised not to discontinue the statins.

Diabetes: From one guideline, we found two recommendations regarding statin treatment for primary prevention of ASCVD in patients with diabetes. It suggested considering statins for patients with type 1 diabetes and offering statins to patients with type 2 diabetes who were older than 40 years, have had diabetes for over 10 years, have established nephropathy, or have other ASCVD risk factors. Another recommendation stated that moderate-intensity statin therapy was indicated for adults aged 40 to 75 years with diabetes, regardless of estimated 10-year ASCVD risk. Additionally, we found a recommendation stating that patients with diabetes at very high ASCVD risk should start statins at the highest tolerable dose as soon as possible to meet cholesterol targets. Regular lipid profile reviews every 1-3 months were advised, and treatment

should be intensified if targets were not met, which may involve switching to a more potent statin, increasing the statin dose, adding ezetimibe, and/or improving lifestyle modifications. For patients with diabetes at high ASCVD risk and stratifying factors or confirmed subclinical atherosclerosis, another recommendation suggested initiating statin therapy to meet cholesterol targets. Furthermore, we identified four recommendations with varying levels of strength and evidence (inconsistency type C). One recommendation advised against combining statins and fibrates for reducing ASCVD risk in patients with diabetes and mild to moderate hypertriglyceridemia. However, in specific cases with high triglycerides and low HDL-C levels, the combination of Fenofibrate and a statin could be considered after failed lifestyle modifications. Another guideline strongly recommended statins for managing diabetes patients with mixed dyslipidemia and elevated LDL-C, and suggested considering combination therapy with a statin and Fibrate for combined dyslipidemia. Additionally, it recommended considering Fenofibrate as adjunct therapy for patients at metabolic risk who were taking statins with adequate LDL-C reduction, elevated triglyceride levels (>200 mg/dL), and reduced HDL levels (<50 mg/dL in females or <40 mg/dL in males).

Dosage: We found three recommendations from two different guidelines with different strengths (inconsistency type A). One guideline suggested using a high-intensity statin of low cost, or if not tolerated, using the maximum tolerated dose. Another guideline recommended moderate-dose statins for primary prevention of ASCVD. A strong recommendation with moderate quality evidence suggested using high-intensity statin therapy to achieve an LDL-C reduction of ≥ 50% in patients aged 40 to 75 years with LDL-C ≥190 mg/dL (≥5.9 mmol/L). In addition, we identified two recommendations based on moderate quality evidence (inconsistency type A). One recommended high-intensity statin therapy for patients aged 40 to 75 years without diabetes and a 10-year risk ≥7.5% to achieve an LDL-C goal of <100 mg/dL (<2.6 mmol/L) or an LDL-C reduction of ≥50%. Another recommendation suggested initiating low- to moderate-dose statins for adults aged 40 to 75 years without a history of ASCVD but with one or more ASCVD risk factors and a calculated 10-year CVD event risk of 10% or greater. Moreover, we found a strong recommendation stating that patients with a >12% 10-year cardiovascular risk, LDL-C >190 mg/dL, or diabetes should be offered moderate-dose statin therapy. A weak recommendation suggested offering moderate-dose statin therapy to patients with a 10-year cardiovascular risk between 6% and 12% after discussing risks, limited benefit, and considering the patient's values and preferences. Regarding patients aged 40 to 75 years without a history of ASCVD and a calculated 10-year ASCVD event risk, we identified two recommendations with varying strengths

based on moderate quality evidence (inconsistency type C). One suggested selectively offering low- to moderate-dose statins for a 10-year risk of 7.5% to 10%. The other recommended offering moderate statin therapy as an option for a 10-year risk of 5% to 7.5%, considering risk reduction, adverse events, drug interactions, and patient preferences, to achieve an LDL-C goal of <130 mg/dL (<3.4 mmol/L) or an LDL-C reduction of 30% to 50%. In addition, we found two recommendations with different strengths and levels of evidence (inconsistency type C). One recommended prescribing high-intensity statin therapy to patients with diabetes and multiple ASCVD risk factors to achieve an LDL-C reduction of 50% or more. The other recommended initiating statins at the highest tolerable dose for patients with diabetes and very high ASCVD risk. Lastly, for patients with CKD, one recommendation suggested offering Atorvastatin 20 mg for primary prevention of ASCVD.

Drug of choice: We found two strong recommendations suggesting that patients at high risk of ASCVD should be offered 20 mg Atorvastatin for primary prevention of ASCVD after assessing their risk and having an informed discussion with their clinician (consistency type 1). The validity was partially justified. Additionally, there was a strong recommendation that patients with diabetes should be offered 20 mg Atorvastatin. Furthermore, we identified two recommendations from one guideline. It advised against offering Simvastatin 80 mg for primary prevention of ASCVD due to the risk of myopathy. However, patients currently stable on this regimen might continue with it for at least one year. Additionally, patients using medications that affect cytochrome P450 metabolism should avoid concurrent use of Atorvastatin or Simvastatin, and instead consider pravastatin or Rosuvastatin as alternative lipid-lowering therapies. Lastly, a strong recommendation suggested that considering atorvastatin 20 mg for primary prevention of ASCVD could be an option for patients aged 85 years or older.

Cholesterol levels target: We found three strong recommendations based on high to moderate quality evidence (inconsistency type C). One guideline emphasized LDL-C as the primary target of therapy, with the target level depending on the individual's overall risk. Another guideline suggested discussing add-on therapy if LDL-C, ApoB, or non-HDL-C levels consistently exceeded certain thresholds. Additionally, for patients with diabetes and very high ASCVD risk, the recommended lipid targets were LDL-C below 50 mg/dL or non-HDL-C below 80 mg/dL. Intensifying treatment was advised if targets were not achieved after three months. Furthermore, we identified two recommendations (inconsistency type C). One recommended maintaining LDL-C below 70 mg/dL and/or non-HDL-C below 100 mg/dL in high ASCVD risk diabetic patients.

Alternatively, if not on statins, an initial reduction of >50% in LDL-C or non-HDL-C was recommended, with treatment intensification if targets were not met after three months. Another guideline suggested prescribing high-intensity statin therapy to adults with diabetes and multiple ASCVD risk factors to achieve an LDL-C reduction of 50% or more. Lastly, a strong recommendation with moderate quality evidence advised offering high-intensity statin therapy to patients aged 40 to 75 years with LDL-C ≥190 mg/dL (≥5.9 mmol/L) to achieve an LDL-C reduction of ≥ 50%.

Lipid profile review: We found four recommendations with different strengths and levels of evidence (inconsistency type B). One guideline suggested reviewing the lipid profile every 1-3 months for patients with diabetes and very high ASCVD risk. Another guideline advised against routine monitoring of lipid levels in patients on statin therapy. Additionally, one recommendation recommended annual lipid level reviews for individuals taking statins, while another suggested measuring total cholesterol, HDL cholesterol, and non-HDL cholesterol in people who have started high-intensity statin treatment at 3 months of therapy.

Other blood tests follow-up: We found two strong recommendations from one guideline. They recommended against measuring creatine kinase levels in asymptomatic individuals on statin therapy and suggested measuring baseline liver transaminase enzymes before initiating statin treatment. Another recommendation suggested that creatine kinase levels should be measured, and if they were more than five times the upper limit of normal, re-measurement after seven days was advised. If levels remained elevated, statin treatment should not be initiated. If levels were raised but less than five times the upper limit of normal, starting statin treatment at a lower dose was recommended. Additionally, liver transaminase levels should be measured within 3 months of starting treatment and at 12 months, with further testing only if clinically indicated. In relation to statin therapy and glycaemia, we identified three recommendations with varying levels of strength and evidence (inconsistency type C). One guideline advised monitoring glycaemia at least annually in patients without diabetes but with metabolic risk who are on statin therapy to detect new-onset diabetes mellitus. Another guideline suggested not discontinuing statins solely based on an increase in blood glucose levels or HbA1c.

Adherence: We found two recommendations with different strengths and levels of evidence (inconsistency type B). One guideline suggested offering intensified patient care, such as phone calls, emails, patient education, and drug regimen simplification, to enhance adherence to lipid-

lowering medications. Another recommendation advised conducting annual medication reviews for individuals taking statins, utilizing these reviews to discuss medication adherence, lifestyle modifications, and address ASCVD risk factors. Additionally, we identified a strong recommendation stating that coenzyme Q10 or vitamin D should not be offered as a means to improve adherence to statin treatment

Change of doses: We found one strong recommendation stating that the benefits and potential risks of changing from a low- or middle-intensity statin to a high-intensity statin should be discussed with the patient during a medication review.

Drug interactions: We identified three strong recommendations from one guideline. They suggested advising patients on statin therapy about potential drug interactions with other medications, certain foods (e.g., grapefruit juice), and supplements. Patients were encouraged to consult the patient information leaflet, a pharmacist, or prescriber for advice when starting new medications or considering supplements. Furthermore, patients should be reminded to restart statin therapy if they had stopped due to drug interactions or to treat intercurrent illnesses.

Adverse events: We found one strong recommendation stating that patients should be asked about persistent generalized unexplained muscle pain, particularly associated with previous lipid-lowering therapy, before offering statin treatment. Lastly, we identified seven recommendations with varying levels of strength and evidence (inconsistency type C). Three guidelines suggested advising individuals on statin therapy to promptly report any unexplained muscle pains, tenderness, weakness, or other adverse effects. If adverse effects occurred with high-intensity statins, possible strategies to discuss with the patient include stopping the statin temporarily and trying again, once symptoms have resolved, reducing the dose within the same intensity group, or switching to a lower intensity statin. If statin intolerance persisted, an alternative statin should be offered to the patient.

These recommendations emphasized the need for a comprehensive and individualized approach to statin therapy, considering various factors such as lifestyle modifications, informed patient preference, and cardiovascular risk estimation. Shared decision-making between healthcare professionals and patients is essential in determining the most appropriate course of action for primary prevention of ASCVD with statin therapy.

The evidence for recommending statins for the prevention of ASCVD is robust and widely supported. Statins have consistently shown efficacy in reducing cardiovascular events and mortality in various populations, including high-risk individuals and certain primary prevention populations with specific risk factors. Literature describes a relationship between greater LDL cholesterol reduction and a proportional reduction in major vascular events, suggesting that lower LDL cholesterol targets may yield additional benefits. The choice of specific statin dose and LDL cholesterol target depends on various factors, including the individual's baseline risk, comorbidities, and tolerability. It is important to discuss these factors with healthcare professionals to determine the most appropriate dose and target for each individual.

Non-Statins

What are the benefits and harms of using other blood lipid-lowering medication when used for the primary prevention of ASCVD?

We identified 99 recommendations pertaining to the pharmacological treatment for the primary prevention of ASCVD across 11 distinct clinical practice guidelines.

Fibrates: Fibrates were the subject of five guidelines, which collectively offered nine recommendations. Two guidelines strongly advised against the routine use of Fibrates alone for primary prevention of ASCVD. This recommendation was based on extensive research and clinical trials that have failed to demonstrate consistent cardiovascular benefits in individuals without pre-existing cardiovascular disease (consistency type 1). The validity was partly justified. Three recommendations with varying levels of strength and level of evidence stated that Fibrates should not be co-administered with statins for the primary prevention of ASCVD: Two weak recommendations against and one strong recommendation against (consistency type 4). Four recommendations with varying levels of strength and evidence stated that patients with combined dyslipidemia (e.g., hypertriglyceridemia plus low LDL cholesterol) should be considered for treatment for treatment with a Fibrate in combination with a statin (inconsistency type C).

Nicotinic Acid (Niacin): Three recommendations concerning Nicotinic Acid were found across two guidelines. Two guidelines provided a strong recommendation against the use of Niacin for ASCVD risk reduction in any group (consistency type 4). The validity was completely justified. This recommendation was based on substantial evidence from clinical trials that have failed to

show consistent cardiovascular benefits with this medication. One guideline provided a strong recommendation against the use of Niacin in combination with statins.

Ezetimibe: Five guidelines discussed ezetimibe and provided nine recommendations. Two guidelines provided weak recommendation for considering Ezetimibe in patients with familial hypercholesterolemia (consistency type 4). Four guidelines indicated that adding ezetimibe to statin therapy might provide additional cardiovascular benefits, especially in high-risk patients (weak recommendation for, inconsistency type C) or those who require further LDL cholesterol reduction. However, for primary prevention, there is insufficient evidence to recommend for or against using ezetimibe with or without statins.

PCSK9 inhibitors: PCSK9 inhibitors were the focus of four guidelines, yielding a cumulative of seven recommendations. Three guidelines provided weak/strong recommendations for using PCSK9 inhibitors in patients at high or very high CVD risk with cholesterol levels remaining above target levels despite other tolerated lipid-lowering therapy (inconsistency type C). However, one guideline strongly recommended against offering PCSK9 inhibitors due to unknown long-term safety, inconclusive evidence for benefit, and high cost.

Bile acid sequestrants: Two recommendations from one guideline dealt about bile acid sequestrants. Bile acid sequestrants had strong recommendations against as a primary therapy or in combination with statins for ASCVD prevention. The evidence for not recommending bile acid sequestrants, specifically anion exchange resins, for the prevention of ASCVD is primarily based on the lack of robust clinical trial data demonstrating their effectiveness in reducing ASCVD events.

Overall, the recommendations on non-statins are rather consistent in that fibrates, nicotinic acid, and bile acid sequestrants are not routinely recommended for primary prevention of ASCVD. Regarding the use of ezetimibe and PCSK9 inhibitors, patients' individual ASCVD risk and characteristics (such as cholesterol levels) must be considered before a shared-decision is made.

Blood pressure lowering medication

What are the benefits and harms of using BP-lowering medication when used for the primary prevention of ASCVD?

We identified 41 recommendations from six different guidelines specifically addressing the use of BP lowering medications for the primary prevention of ASCVD.

General BP lowering medication indication: Recommendations regarding prescribing BP lowering medication depended on an individual's risk profile and BP values. Five guidelines suggested, with varying strength and evidence levels, initiating BP-lowering medication in individuals with a systolic BP (SBP) of 130 mm Hg/140 mm Hg or higher and an ASCVD risk of 10% or greater (inconsistency type C).

Drug of choice - monotherapy: We identified two recommendations with varying levels of strength stating that initial drug therapy on hypertension should be with either monotherapy or single pill combination based on efficacy, tolerability, cost, and presence of comorbidities (inconsistency type C). One guideline recommended for initial monotherapy diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or calcium channel blockers (CCB). Another guideline recommended a thiazide or thiazide-like diuretic, with longer-acting diuretics preferred, a β-blocker (in patients younger than 60), an ACE inhibitor (in patients who are not black), an ARB or a long-acting CCB.

Drug of choice - combinations: Two guidelines provided six recommendations with varying strengths and evidence levels about combination of different BP lowering medication when target levels of BP have not been achieved with monotherapy (inconsistency type C). One guideline recommended combining either an ACE inhibitor or an ARB with a dihydropyridine CCB. It recommended not combining an ACE inhibitor and an ARB. Another guideline stated that single pill combination choices are those in which an ACE inhibitor is combined with a CCB, ARB with a CCB, or ACE inhibitor or ARB with a diuretic. Moreover, it also recommended not combining an ACE inhibitor and an ARB. One recommendation stated that add-on drugs should be chosen from first-line choices. Choices should include a thiazide or thiazide-like diuretic or CCB with an ACE inhibitor, ARB or β-blocker. Other recommended individualizing choices for combination therapy for patients with high-risk hypertension. It stated that the combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a thiazide or thiazide-like diuretic.

BP targets: Regarding targets, we identified two recommendations with varying strengths and evidence levels stating that in patients with uncomplicated hypertension and low ASCVD risk, BP targets should be 130/80 mm or <140/90 mm Hg (inconsistency type C). Three recommendations from two guidelines provided recommendations with varying strengths and evidence levels for BP targets in patients with hypertension and high ASCVD risk (inconsistency type C). One guideline recommended that in patients with confirmed hypertension and at high CVD risk BP target should be <130/80 mm Hg. Another guideline stated that for high-risk patients, aged 50 years or older, with systolic BP ≥ 130mm Hg, the target SBP should be ≤ 120 mm Hg. Moreover, four recommendations from three guidelines with varying strength and evidence levels stated that for patients with diabetes BP target should be less than 130/80 mm Hg (consistency type 4).

Therefore, the decision to prescribe BP-lowering medication for primary prevention of ASCVD, the choice of specific BP-lowering medication and dosage should be based on a comprehensive assessment of individual risk factors, including age, comorbidities, overall cardiovascular risk, and BP levels.

Antiplatelet and anticoagulant medication

What are the benefits and harms of antiplatelet treatment (including aspirin) when used for the primary prevention of ASCVD?

Thirty-five recommendations concerning aspirin were found across six guidelines.

We identified three guidelines providing strong recommendations against the use of aspirin for the primary prevention of ASCVD (consistency type 1. The validity was partly justified.

In general, included guidelines recommended individualized assessment of benefits and risks, considering age, bleeding risk, and overall ASCVD risk. Identifying specific subgroups that may benefit most from aspirin therapy and determining the optimal dose and duration are areas that require further research.

Antiplatelet treatment (including not only aspirin) was the subject of one guideline, which offered one recommendation about not offering antiplatelet treatment to patients with diabetes for the primary prevention of ASCVD.

Diabetes medication

What are the benefits and harms of pharmacotherapy for the treatment of diabetes when used for the primary prevention of ASCVD?

Pharmacotherapy for the treatment of diabetes was discussed in six guidelines, which collectively presented 31 recommendations.

We identified three recommendations from three guidelines with varying strength and evidence levels related to the use of metformin as monotherapy (inconsistency type C). Two guidelines recommended initiating metformin as first-line therapy along with lifestyle measures at the time of diagnosis to improve glycemic control and reduce ASCVD risk. One guideline recommended considering the prescription of metformin for those patients not responding to intensive lifestyle measures.

Eight guidelines provided recommendations regarding the use of a second drug alongside metformin for the treatment of diabetes in order to prevent ASCVD (inconsistency type C). The recommendations varied in strength and level of evidence. One guideline suggested considering the initiation of a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist for patients with type 2 diabetes and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin. The aim was to improve glycemic control and reduce the risk of ASCVD. Another guideline recommended combining metformin with a second antihyperglycemic agent as the first-line therapy for asymptomatic patients recently diagnosed with type 2 diabetes and HbA1c levels above 8.5%. If target HbA1c levels were not achieved with monotherapy, any antidiabetic drug could be considered as an add-on option to metformin for glycemic control. The guidelines stated that there was no significant difference between classes of antidiabetic agents when used as a second therapy alongside metformin. The guideline suggested considering pioglitazone, DPP4 inhibitors, or GLP-1 analogues to achieve glycemic control. Furthermore, another guideline proposed considering incretin agents (DPP4 inhibitors or GLP1-RA), SGLT2 inhibitors, acarbose,

or pioglitazone as add-on medications to improve glycemic control with a lower risk of hypoglycemia compared to other agents if reducing the risk of hypoglycemia is a priority. If weight loss is a priority, the guideline recommended considering a GLP1-RA or SGLT2 inhibitor as an add-on medication. For patients aged 60 years or older with type 2 diabetes and at least two ASCVD risk factors, the guideline recommended a GLP1-RA with proven ASCVD outcome benefit or an SGLT2 inhibitor with proven cardiorenal outcome benefit if eGFR is above 30-mL/min/1.73 m2. Finally, one guideline emphasized the individualization of pharmacological therapy for lowering blood glucose based on factors such as efficacy, mechanism of action, presence of comorbidities, risk of hypoglycemia, weight gain, adverse effects, and costs.

We found four recommendations regarding the use of insulin for the treatment of diabetes in the primary prevention of ASCVD, with varying levels of strength and level of evidence (inconsistency type C). One guideline suggested that insulin can be a safe option for glycemic control in patients with type 2 diabetes who are already receiving one or more antidiabetic agents but are unable to achieve their target HbA1c levels or experience typical symptoms of hyperglycemia, especially if they have a high ASCVD risk. Insulin therapy, either alone or in combination with other agents, should be considered for these patients. Another guideline recommended considering the addition of a basal insulin regimen for patients who are not able to reach their glycemic targets with existing non-insulin antihyperglycemic medications. This approach aims to improve glycemic control in those individuals.

There were four recommendations regarding the target for glycemic control in patients with diabetes for the primary prevention of ASCVD. For adult patients with type 1 or type 2 diabetes mellitus, one guideline suggested aiming for a HbA1c level below 7.0%. This target was recommended unless there were other factors such as severe cognitive impairment or reduced life expectancy that may influence individualized treatment decisions. Another guideline also recommended targeting an HbA1c level of ≤ 7.0% in most individuals with type 1 or type 2 diabetes to reduce the risk of microvascular complications. Regarding patients with diabetes and CKD, one recommendation suggested targeting an HbA1c level of ≤ 6.5% in individuals with type 2 diabetes. This lower target was aimed at reducing the risk of developing or worsening CKD.

Prescribing medication for diabetes for the primary prevention of ASCVD involves considering various factors, including the individual's risk profile and specific diabetes management goals.

Guidelines recommend an individualized approach considering multiple factors such as glycemic control, comorbidities, cardiovascular risk, and patient preferences.

Other pharmacological measures

What are the benefits and harms of pharmacotherapy for weight loss control when used for the primary prevention of ASCVD?

We encountered 17 recommendations related to the pharmacological treatment for weight loss / obesity in the context of primary prevention of ASCVD across three different CPGs.

We identified one recommendation stating that pharmacotherapy for weight loss can be used for people with BMI ≥ 30 kg/m2 or BMI ≥ 27 kg/m2 with adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and psychological interventions.

When non-pharmacological methods alone are ineffective and the option to switch to relatively weight-neutral antipsychotics is not feasible, one guideline strongly recommended using metformin concomitantly as the preferred pharmacological intervention to counteract weight gain and other metabolic complications caused by antipsychotic medication in individuals with psychosis. Other options strongly recommended by the same guideline were Orlistat and Glucagon-like peptide-1 (GLP-1) for their efficacy for weight loss.

What are the benefits and harms of pharmacotherapy for smoking cessation when used for the primary prevention of ASCVD?

In relation to pharmacotherapy for smoking cessation, five guidelines put forth eight recommendations.

These recommendations supporting the use of pharmacological interventions, such as varenicline, bupropion, and nicotine replacement therapy, for smoking cessation in the primary prevention of ASCVD. However, it is important to note that medication use should be tailored to each individual and may benefit of being part of a comprehensive smoking cessation program that includes

behavioral support and counseling (consistency type 4). The validity of this recommendation based on the evidence source provided was not justified.

What are the benefits and harms of menopausal hormone replacement therapy (HRT) when used for the primary prevention of ASCVD?

We found 16 recommendations concerning HRT for the primary prevention of ASCVD belonging to three distinct guidelines. HRT has been a subject of interest for the primary prevention of ASCVD, particularly in postmenopausal women. However, the included guidelines do not support the use of HRT for primary prevention of ASCVD (consistency type 4).

While covering a wide therapeutic spectrum, recommendations on other specific pharmacological interventions are rather consistent. This includes pharmacotherapy for smoking cessation (pharmacological interventions for smoking cessation are recommended but should be tailored to the needs and characteristics of the individual), and recommendations on HRT (not recommended for the primary prevention of CVD). The consistency of recommendations on pharmacotherapy for weight loss control cannot be assessed because the majority of recommendations was stated by only one guideline.

Recommendations addressing specific population subgroups or health conditions

Aligning to our predefined framework, specific sub-populations with regard to demography (age groups, sexes/gender and ethnic groups) and with regard to health conditions (diabetes mellitus, other diseases, multimorbidity, polypharmacy) formed part of the coding system. While demographic sub-populations were addressed in n=131 quotations (text segments, including background text) from the included guideline documents, this was only the case for n=45 consented recommendation statements. Particular health conditions in the sense of existing (co-)morbidity or potential modifiers of ASCVD risk, including diabetes as a major risk factor, were addressed in n=227 quotations, out of which n=45 were consented recommendation statements. (Annex 14). The following paragraphs summarize the coded recommendations statements.

Age: Our analysis yielded 17 recommendations related to patient age. These recommendations primarily focused on elderly patients (60 years or older), with some also applicable to middle-

aged or elderly patients (40 years or older). Eight recommendations pertained to risk assessments and thresholds, eleven addressed medication intake and dosages, and one recommendation emphasized non-pharmacological measures such as smoking cessation.

Sex: We identified 24 recommendations related to patient sex. The majority of these recommendations (n=21) focused on pharmacological measures, particularly HRT in menopausal women or testosterone replacement therapy in men. One recommendation addressed non-pharmacological measures, specifying alcohol intake limits for women and men. Additionally, one recommendation emphasized that the decision to initiate statin therapy should be based on estimated cardiovascular risk, regardless of the patient's sex.

Gender: No guidelines provided recommendations specifically related to patient gender.

Ethnicity: We found four recommendations regarding patient ethnicity. Three of these recommendations focused on assessing ASCVD risk, while one addressed pharmacological measures. The recommendations included routinely recording patient ethnicity, considering ethnicity as an ASCVD risk factor, avoiding ACE inhibitors as first-line therapy for uncomplicated hypertension in black patients, and taking ethnicity into account when evaluating BMI results.

Diabetes: In our analysis, we found 94 recommendations related to diabetes. Among these recommendations, 68 focused on pharmacological measures for the treatment of diabetes, 17 pertained to non-pharmacological interventions, and 16 were related to risk assessment. These recommendations encompassed various aspects of diabetes management, including both medication and lifestyle interventions, as well as considerations for incorporating diabetes into the calculation of ASCVD risk.

Other diseases: We identified 86 recommendations related to various diseases and conditions. The ones most frequently addressed were psychological conditions (n=38), CKD (n=18), metabolic risk (n=10), and familial hypercholesterolemia (n=8). These recommendations predominantly centered on pharmacological measures (n=48), followed by non-pharmacological measures (n = 22) and risk assessment (n=17).

Multimorbidity: We discovered six recommendations specifically addressing multimorbidity, with two focusing on pharmacological measures, two on non-pharmacological measures, and two on risk assessment. These recommendations emphasized the importance of considering patients' multimorbidities in both pharmacological and non-pharmacological interventions, as well as in the assessment of their overall risk profile. By recognizing and addressing the complexities of multimorbidity, healthcare providers can develop comprehensive and tailored approaches to patient care.

Polypharmacy: Our study revealed 41 recommendations concerning polypharmacy, with 34 focused on pharmacological measures, eight on risk assessment, and three on non-pharmacological approaches. The recommendations primarily addressed the appropriate use of multiple medications, particularly in relation to lipid or BP management, as well as the use of pharmacotherapies for psychological conditions. These guidelines aimed to provide guidance on ensuring safe and effective use of multiple drugs in clinical practice.

The substantial number of recommendations concerning particular sub-populations or health conditions in certain guidelines owes to the fact that the overall guideline in question focuses on ASCVD risk in these groups. For example, mental illness was in the focus of the BAP 2016 guidelines, which dealt with weight gain, metabolic disturbances, and ASCVD risk associated with psychosis and antipsychotic drug treatment. Diabetes was a major topic in the SBD/SBC/SBEM 2017 and the CCH 2022 guidelines. The SOGC 2021 guidelines' focus on menopause and cardiovascular disease explains the high number of recommendations pertaining to women in this document.

The difference between the grand total of codings for these sub-groups in the overall guidelines (including background text) and the number in consented recommendation statements illustrates that usually recommendations are geared towards the broader target population as defined in the scope of the respective guidelines. The background text often provides more detail on these sub-groups, but these text segments were not covered in our detailed analysis.

Another possibility of providing for details regarding specific sub-groups in clinical practice guidelines is through the structure of the documents, as reflected in the table of contents. Guidelines may dedicate complete chapters, sections or paragraphs to these sub-groups. As an example, see the 2021 ESC guidelines on cardiovascular disease prevention in clinical practice

(Annex 15). The example shows that the sub-groups' characteristics may be dealt with as risk factors, as a stratifying variable in ASCVD risk classification, as potential risk modifiers or as clinical conditions that need to be considered in the management of overall ASCVD risk. The latter can also be dealt with by highlighting important sub-groups in the management and treatment of particular risk factors, or e.g., by outlining sex-specific health conditions. The epidemiological model for the primary prevention of ASCVD, which we have developed in parallel to our analytical framework for the systematic guideline review (Annex 4), provides for these options in the update procedure of the clinical practice guideline for the German context of primary care.

DISCUSSION

The recommendations that were assessed within our analytical framework encompassed a variety of interventions. Most recommendations evaluated multiple types or facets of interventions in order to provide comprehensive guidance. It was usually possible to discretely assign a recommendation to one of our three domains, with the majority counting as a pharmacological intervention, followed by non-pharmacological interventions and finally risk assessment and patient-provider interaction. However, there are also significant overlaps between these domains, which is reflected in the coding. This points out that by the nature of a comprehensive risk management approach, all domains need to be considered as intertwined, and an individualized shared decision-making approach is central in the primary prevention of ASCVD.

On the methodological side, it has to be noted that the assessment of consistency among these recommendations was complicated by this great variability. Only 17 clusters of recommendations addressing the same clinical key question and sub-topic were found to show any consistency in their content and directionality (Type 1-4), in combination with a high strength of recommendation.

Our findings, in terms of consistency pertaining to the major categories of interventions, are summarized in the list below, while for the inconsistencies we refer to the respective results section. A moderate level of consistency indicates that there are common tendencies among the recommendations within a cluster, but the Type 4 consistency was predominant (i.e., recommendations are consistent in content, but evidence levels and grading conflict.)

- For risk assessment and calculation, we found a tendency that the assessment should be offered to patients older than 30-40 years, that the intensity of prevention efforts should match the absolute ASCVD risk and that a standardized risk assessment tool should be used.
- For risk communication and decision making, there was general agreement that the decision on pharmacological and non-pharmacological treatment measures should be a shared one, taking into account the individual characteristics of the patients.
- For behavioral counseling, agreement between the guidelines is limited to suggesting that lifestyle and behavioral counseling should be targeted to adults with an increased ASCVD risk and that it should take into account patients' personal circumstances and emphasize the benefits of changing habits.

- For physical activity, there is some consistency regarding the reduction of sedentary periods and a general increase of activity levels. The engagement in at least 150 minutes of moderate physical activity per week or 75 minutes of vigorous activity per week and muscle-strengthening activities on two or more days per week seems to be broadly accepted.
- For nutrition, there is moderate consistency regarding the recommendation of a Mediterranean diet, the consumption of whole grains and at least five servings of fruits and vegetables per day, a reduction of sweetened beverages and salty foods, and an increased intake of dietary fiber. The use of nicotinic acid and antioxidant vitamin supplements for reducing ASCVD risk is discouraged.
- For substance use and miscellaneous aspects, we found broad agreement that both active and passive smoking should be avoided, and that smokers should be referred to smoking cessation services.
- For risk factor management, we found only occasional consistencies, e.g., concerning the recommendation that most moderate risks can be managed by lifestyle changes alone.
- For statins, the recommendations emphasized the need for a comprehensive and individualized approach to statin therapy. Although the evidence supporting statin use for the prevention of ASCVD is robust, the choice of a specific statin dose and LDL cholesterol target depends on various factors.
- For non-statins, there is some consistency in that fibrates, nicotinic acid, and bile acid sequestrants are not routinely recommended for primary prevention of ASCVD.
- For blood pressure lowering medication, the agreement between guidelines consists in grounding the medication in a comprehensive assessment of individual risk factors, including age, comorbidities, overall cardiovascular risk, and BP levels.
- For antiplatelet and anticoagulant medication, the guidelines similarly recommend individualized assessment of benefits and risks, considering age, bleeding risk, and overall ASCVD risk.
- For diabetes medication, an individualized approach is also broadly recommended, considering multiple factors such as glycemic control, comorbidities, ASCVD risk, and patient preferences.
- For other pharmacological measures, some consistencies were found regarding pharmacotherapy for smoking cessation, and the discouragement of prescribing HRT for the primary prevention of ASCVD.

In the light of the limited content-wise comparability of recommendations identified within the scope of our review, and also of the prevailing moderate consistencies or inconsistencies within the clusters of comparable recommendations, it is important to acknowledge that CPGs are context-specific, normative documents. They are usually meant to be applied in a specific national health system. Recommendations may vary among different guideline–producing organizations, also depending on which stakeholders were involved in the consensus process. In addition, individual patient factors should always be considered, and consultation with healthcare professionals is essential for personalized care.

Strengths

In our systematic review, we conducted a comprehensive search across relevant literature databases using a highly sensitive search strategy. Additionally, we complemented this approach by manually searching guideline-specific databases and websites to ensure a thorough exploration of available resources.

To assess the quality of the included guidelines, we adopted a two-step approach developed by Muth et al (27). First, we utilized the mini-checklist (MiChe) to evaluate and rate the quality of the guidelines. This checklist consists of specific criteria that provide a structured assessment framework. Secondly, we performed a consistency analysis to examine the recommendations within these guidelines, ensuring coherence and alignment.

Considering the potential heterogeneity among the CPGs included in our review, we employed qualitative data analysis software (ATLAS.ti) (34). This software aided in managing and analyzing the diverse data sets, enabling us to effectively navigate and interpret the findings.

By employing these rigorous methods, we aimed to provide a comprehensive and reliable synthesis of the available evidence and recommendations regarding the primary prevention of ASCVD.

Limitations

While our review encompassed a wide range of clinically relevant questions and population sub-groups, it is important to note that we did not cover pediatric populations or the topic of secondary

prevention of cardiovascular disease. Our focus primarily evolved around the primary prevention of cardiovascular events in adults.

One of the primary challenges arises from the lack of a universally accepted classification system. Different organizations and guideline development groups often adopt their own grading systems based on factors such as the type of evidence considered, the level of consensus among experts, and the context-specific considerations. For instance, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system and the modified Oxford Centre for Evidence-Based Medicine (OCEBM) system are two commonly used frameworks, each with its unique approach to categorizing evidence and making recommendations (38,66).

We were confronted with a far greater variety of classifications providing the strength of recommendations and the level of evidence across guidelines, however. Clinical practice guidelines serve as essential tools for healthcare professionals, providing evidence-based recommendations to guide decision-making and improve patient care. To ensure consistency and comparability between guidelines, it is crucial to have standardized systems for grading the strength of recommendations and the level of evidence supporting those recommendations. However, various classification systems exist, leading to inconsistency and confusion when synthesizing and implementing guidelines from different sources.

The variations in grading systems can lead to inconsistencies when comparing guidelines and hinder the ability to establish a unified approach to clinical decision-making. This can cause confusion for healthcare professionals who rely on guidelines to inform their practice and may result in inconsistent patient care across different settings. Moreover, it can also pose challenges for policymakers and healthcare administrators in developing policies and allocating resources based on varying guideline recommendations.

Another challenge arises from the interpretation and translation of the strength of recommendations and levels of evidence across different grading systems. Even when guidelines use similar terminology (e.g., strong, weak, high, moderate), the criteria for assigning these labels may differ. For example, a recommendation labeled as "strong" in one system may correspond to a "moderate" recommendation in another system, leading to potential misinterpretation and misapplication of guidelines.

The complexity of clinical evidence further compounds the challenge. Evidence for clinical practice guidelines is often derived from a combination of randomized controlled trials, observational studies, expert opinion, and patient values and preferences. Integrating and synthesizing such diverse evidence sources requires careful consideration and can be influenced by the subjective judgments of guideline developers. Different grading systems may prioritize certain types of evidence over others or have varying thresholds for assigning levels of evidence, resulting in inconsistencies in the strength of recommendations.

In addition, the style of writing, the mode of citation and the layout of published guidelines (including any available methodological or evidence reports) often do not allow for retrospectively tracking the actual evidence that individual recommendations are based on. This finding emerged only during the process of consistency analysis and validation, and it even applies to guidelines that rated high in our quality assessment with the MiChe checklist.

Conclusions

The findings of the present systematic guideline review provide a comprehensive overview of the current state of clinical guidance on the primary prevention of ASCVD internationally. This review demonstrates which topic areas are commonly dealt with and which approaches are taken to structuring and presenting the guidance. Notably, the degree of heterogeneity in the content and scope of recommendations was found to be higher than expected in advance. With regard to the development of an updated CPG in the German context, this means that there are very few topics that would lend themselves to a formal adoption or adaptation of recommendations at all.

The strength of recommendation in particular has not proven to be a reliable indicator for identifying the most relevant topics. Limited consistency among comparable recommendations was mostly due to conflicting strength of recommendations or levels of evidence. As outlined above, this partly relates to the different classifications used across the CPGs included in our review. In addition, there is usually no clear or formalized linkage between the level of evidence and the strength of recommendation.

This variance in classifications has not only been a challenge for our analysis, but also presents significant challenges in healthcare. The lack of a universally accepted grading system, variations in interpretation and translation of recommendations, and the complexity of clinical evidence all

contribute to the inconsistency and confusion surrounding guideline implementation. Harmonization and standardization efforts are crucial to promote consistency and improve the comparability and usability of guidelines, ultimately enhancing the quality of patient care.

To address the above-mentioned challenges, efforts have been made to establish harmonization and standardization of guideline development processes and grading systems. Organizations such as the Guidelines International Network (G-I-N) and the Institute of Medicine (IOM) have provided recommendations and frameworks to promote consistency and transparency in guideline development (67,68). Additionally, initiatives such as the GRADE approach have been developed to create a common language for grading evidence and recommendations, facilitating more standardized guideline development and implementation (66). For the subsequent stages of guideline development, we will consequently orient our work at the GRADE criteria.

The data gathered, analyzed and synthesized in the scope of our systematic guideline review provides a broad and differentiated basis for this approach. Taking the findings as a starting point, the guideline development team will identify the clinically relevant key questions that shall be further elaborated. However, since in existing guidelines it is often difficult to reconstruct the link between the level of evidence formally assigned to a recommendation and the studies or systematic reviews cited to support it, we will use the extracted references relating to the selected key questions to then perform our own assessment. The most recent and most robust studies or systematic reviews identified will then be independently assessed for their risk of bias, as will be any evidence found by means of systematic complementary or update literature searches. This approach is coherent with the GRADE approach and will allow for the transparent development of sound recommendations on the primary prevention of ASCVD.

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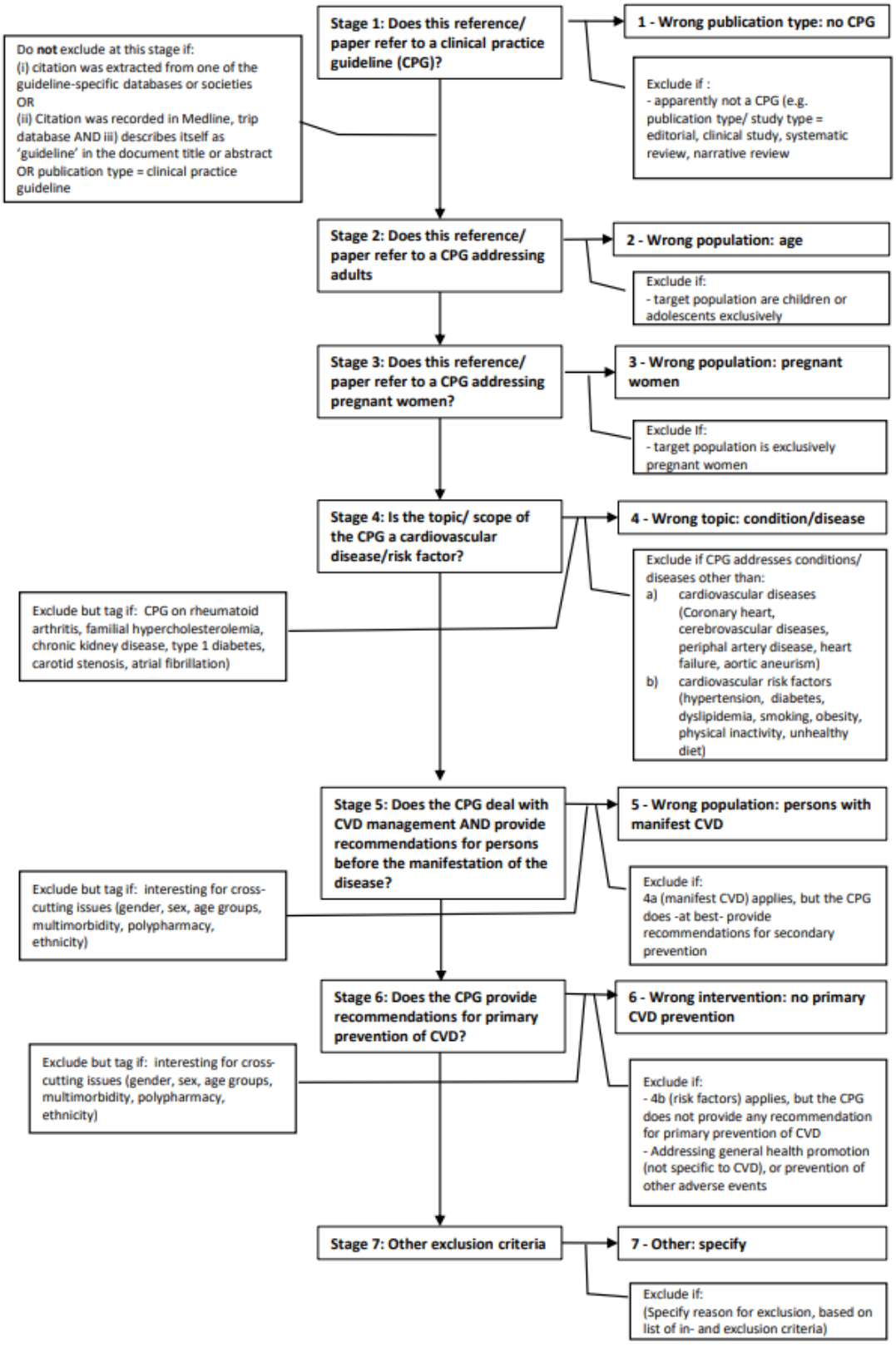
ANNEXES

ANNEX 1. ALGORITHM for eligibility of guidelines



ANNEX 2. SEARCH STRATEGY for clinical practice guidelines on the primary prevention of cardiovascular disease in primary care

Annex 2a: Search strategy in Medline via PubMed (date: 2023-01-30)

#	Searches	Annotation
1	((cardiovascular diseases[MeSH Terms]) OR (cardiovascular[Title/Abstract])) OR (CVD[Title/Abstract]) OR (cardiac[Title/Abstract])	3209765
2	((((((((((((((abdominal aortic aneurysm[MeSH Terms]) OR (aortic aneurysm[MeSH Terms])) OR (arterial occlusive disease[MeSH Terms])) OR (arteriosclerosis[MeSH Terms])) OR (atheroscleroses[MeSH Terms])) OR (brain infarction[MeSH Terms])) OR (brain ischemia[MeSH Terms])) OR (cerebrovascular disorder[MeSH Terms])) OR (coronary disease[MeSH Terms])) OR (coronary heart disease[MeSH Terms]))) OR (heart failure[MeSH Terms])) OR (myocardial ischemia[MeSH Terms])) OR (peripheral vascular disease[MeSH Terms])) OR (cerebral stroke[MeSH Terms])) OR (aneurysm, thoracoabdominal aortic[MeSH Terms])) OR (metabolic syndrome x[MeSH Terms]) OR ((((((((((((((((aneurysm[Title/Abstract]) OR (“arterial occlusion”[Title/Abstract])) OR (“arterial stenosis”[Title/Abstract])) OR (Arteriosclerosis[Title/Abstract])) OR (atherosclerosis[Title/Abstract])) OR (“Brain infarction”[Title/Abstract])) OR (“Brain Ischemia”[Title/Abstract])) OR (“cerebrovascular disease”[Title/Abstract])) OR (“cerebrovascular disorder”[Title/Abstract])) OR (“coronary disease”[Title/Abstract])) OR(“coronary heart disease”[Title/Abstract])) OR (“heart attack”[Title/Abstract])) OR (“heart failure”[Title/Abstract])) OR (“myocardialischemia”[Title/Abstract])) OR (“Occlusive peripheral arterial disease”[Title/Abstract])) OR (“peripheral vascular disease”[Title/Abstract])) OR (Stroke[Title/Abstract])) OR (“thoracoabdominal aneurysm”[Title/Abstract])) OR (“metabolic syndrome” [Title/Abstract]) OR (ischaemi*[Title/Abstract]) OR (cerebral[Title/Abstract])	1862653
3	((diabetes mellitus[MeSH Terms]) OR (type 2 diabetes mellitus[MeSH Terms]) OR (diabetes[Title/Abstract])) OR (diabetic[Title/Abstract]) OR(diabetics[Title/Abstract])	817341
4	((dyslipidemia[MeSH Terms]) OR (dyslipidemias[MeSH Terms]) OR (hyperlipidemia[MeSH Terms]) OR (dyslipidemia[Title/Abstract]) OR (hyperlipidemia[Title/Abstract])) OR (cholesterol[Title/Abstract]) OR (hypercholesterolemia[Title/Abstract])	358094
5	(((((hypertension[MeSH Terms]) OR (high blood pressure[MeSH Terms]) OR (hypertensi*[Title/Abstract]) OR (“high blood pressure”[Title/Abstract]))) OR (“anti hypertensive”[Title/Abstract])) OR (antihypertensive[Title/Abstract])) OR (“anti-	584381

#	Searches	Annotation
	hypertensive”[Title/Abstract])	
6	(((((body weight[MeSH Terms]) OR (overweight[MeSH Terms])) OR (weight[Title/Abstract])) OR (overweight[Title/Abstract])) OR (obes*[Title/Abstract]))	1371608
7	((((((diets[MeSH Terms]) OR (saturated fatty acids[MeSH Terms])) OR (diet[Title/Abstract])) OR (“dietary pattern”[Title/Abstract])) OR (“saturated fat”[Title/Abstract])) OR (salt[Title/Abstract])) OR (alcohol[Title/Abstract]) OR (sodium[Title/Abstract])	1766096
8	(((((activity, physical[MeSH Terms]) OR (physical activities[MeSH Terms])) OR (exercise[MeSH Terms])) OR (exercise[Title/Abstract])) OR (activity[Title/Abstract])) OR (inactivity[Title/Abstract]) OR (sedentary[Title/Abstract])	3370188
9	(((cessation, smoking[MeSH Terms]) OR (cigarette smoking[MeSH Terms])) OR (tobacco[Title/Abstract]) OR (smok*[Title/Abstract]))	388110
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9	9396128
11	((((primary prevention[MeSH Terms]) OR (prevent*[Title/Abstract]) OR (risk assessment[MeSH Terms]) OR (assessment[Title/Abstract]) OR (risk management[MeSH Terms]) OR (“risk management”[Title/Abstract]) OR (“early intervention”[Title/Abstract]) OR (“health screening”[Title/Abstract]) OR (“periodic check-up”[Title/Abstract]) OR (“periodic evaluation” [Title/Abstract]) OR (“periodic examination”[Title/Abstract]) OR (“risk intervention”[Title/Abstract]) OR (“risk reduction”[Title/Abstract]) OR (“risk communication”[Title/Abstract]) OR (counsel*[Title/Abstract]) OR (“decision making”[Title/Abstract]) OR (screening[Title/Abstract])) OR (decision making[MeSH Terms])) OR (counseling[MeSH Terms]))	4162985
12	10 AND 11	1408601
13	(Guideline[Title/Abstract]) OR (clinical practice guideline[MeSH]) OR (clinical practice guideline[Publication Type])	133457
14	12 AND 13	19278
15	2016-2023 Abstracts Guideline English, German, Dutch, Spanish	1050

Annex 2b: Search strategy in TRIP database (date: 2023-01-30)

#	Searches	Annotations	Search Field / Search Term
1	cardiovascular CVDcardiac	769.526	ANY of these words
2	diabetes diabetic diabetics	321.808	ANY of these words
3	dyslipidemia hyperlipidemia cholesterol hypercholesterolemia	96.068	ANY of these words
4	high blood pressure	179.004	THIS exact phrase
5	hypertension hypertensive	223.786	ANY of these words
6	aneurysm arteriosclerosis atherosclerosis cerebrovascular cerebral coronary infarction ischemia ischaemia ischaemic myocardial occlusion occlusive stenosis stroke	1.087.505	ANY of these words
7	peripheral arterial disease	9.289	THIS exact phrase
8	peripheral artery disease	9.289	THIS exact phrase
9	heart attack	142.833	THIS exact phrase
10	heart failure	32.832	THIS exact phrase
11	metabolic syndrome	61.262	THIS exact phrase
12	smoke smoking cigarette tobacco	146.150	ANY of these words
13	smoke cessation	16.419	THIS exact phrase
14	diet dietary salt sodium alcohol	371.471	ANY of these words
15	saturated fat	3.538	THIS exact phrase
16	activity physical exercise inactivity sedentary	1.392.134	ANY of these words

#	Searches	Annotations	Search Field / Search Term
17	overweight obese obesity	154.726	ANY of these words
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	2.571.775	(overweight OR obese OR obesity) OR (activity OR physical OR exercise OR inactivity OR sedentary) OR ("saturated fat") OR (diet OR dietary OR salt OR sodium OR alcohol) OR ("smoke cessation") OR (smoke OR smoking OR cigarette OR tobacco) OR ("metabolic syndrome") OR ("heart failure") OR ("heart attack") OR ("peripheral artery disease") OR ("peripheral arterial disease") OR (aneurysm OR arteriosclerosis OR atherosclerosis OR cerebrovascular OR cerebral OR coronary OR infarction OR ischemia OR ischaemia OR ischaemic OR myocardial OR occlusion OR occlusive OR stenosis OR stroke) OR (hypertension OR hypertensive) OR ("high blood pressure") OR (dyslipidemia OR hyperlipidemia OR cholesterol OR hypercholesterolemia) OR (diabetes OR diabetic OR diabetics) OR (cardiovascular OR cvd OR cardiac)
19	prevention preventrisk screening counseling counselling	1.659.079	ANY of these words
20	periodic assessment	1.037	THIS exact phrase
21	periodic evaluation	675	THIS exact phrase
22	risk assessment	26.281	THIS exact phrase
23	risk communication	1.732	THIS exact phrase
24	#19 OR #20 OR #21 OR #22 OR #23	3.447.353	("risk communication") OR ("risk assessment") OR ("periodic evaluation") OR ("periodic assessment") OR (prevention OR prevent OR risk OR screening OR counseling OR counselling)
25	Title:guideline	24.128	ALL of these words - Title
26	#18 AND #24 AND #25	6.339	((overweight OR obese OR obesity) OR (activity OR physical OR exercise OR inactivity OR sedentary) OR ("saturated fat") OR (diet OR dietary OR salt OR sodium OR alcohol) OR ("smoke cessation") OR (smoke OR smoking OR cigarette OR tobacco) OR ("metabolic syndrome") OR ("heart failure")

#	Searches	Annotations	Search Field / Search Term
			OR ("heart attack") OR ("peripheral artery disease") OR ("peripheral arterial disease") OR (aneurysm OR arteriosclerosis OR atherosclerosis OR cerebrovascular OR cerebral OR coronary OR infarction OR ischemia OR ischaemia OR ischaemic OR myocardial OR occlusion OR occlusive OR stenosis OR stroke) OR (hypertension OR hypertensive) OR ("high blood pressure") OR (dyslipidemia OR hyperlipidemia OR cholesterol OR hypercholesterolemia) OR (diabetes OR diabetic OR diabetics) OR (cardiovascular OR cvd OR cardiac)) AND (title:guideline) AND (("risk communication") OR ("risk assessment") OR ("periodic evaluation") OR ("periodic assessment") OR (prevention OR prevent OR risk OR screening OR counseling OR counselling))
27	Guidelinessince 2016	1.360	Filter

ANNEX 3. LIST OF DATABASES AND DATE OF SEARCH

Annex 3a: List of databases and date of search

Abbreviation	Name, country and internet address	Date
Medline	Medline https://pubmed.ncbi.nlm.nih.gov/	2023-01-30
TRIP	Trip Database www.tripdatabase.com	2023-01-30

Annex 3b: List of websites of CPG repositories and date of search

Abbreviation	Name, country and internet address	Date
AWMF	AWMF Guideline register Germany https://register.awmf.org/de/start	2023-01-24
G-I-N	Guideline International Network https://g-i-n.net	2023-02-07
guisalud	Catálogo de Guías de Práctica Clínica en el Sistema Nacionalde Salud (Spain) https://portal.guiasalud.es	2023-01-10
NICE	National Institute of Clinical Excellence https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines	2023-01-29
SIGN	Scottish Intercollegiate Guidelines Network (UK) https://www.sign.ac.uk/our-guidelines/	2023-01-30

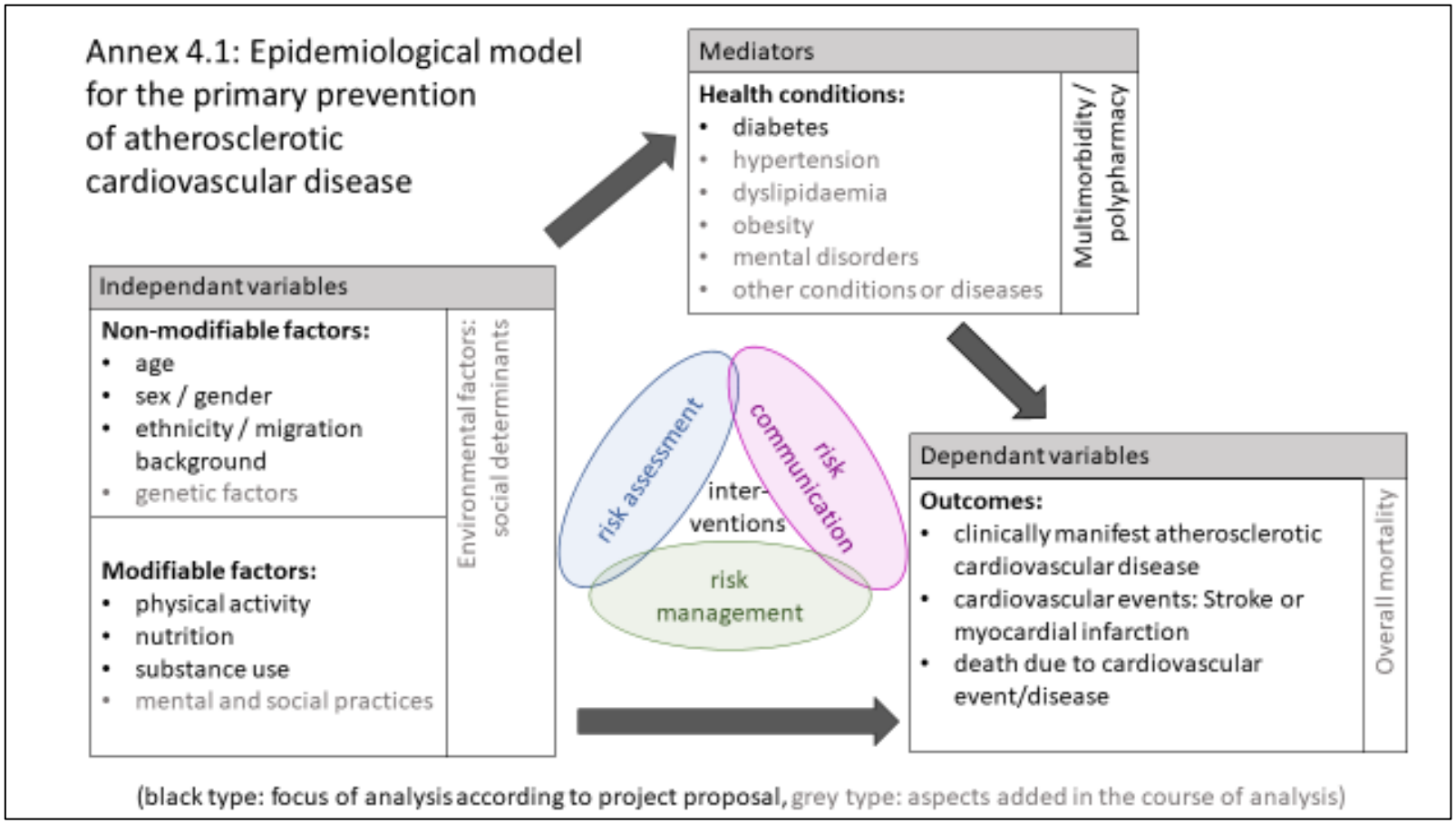
Annex 3c: List of websites and organizations and date of search

Abbreviation	Name (country) and internet address	Date
ACC	American College of Cardiology (USA) https://www.acc.org/guidelines /	2023-01-24
AGS	American Geriatrics Society https://www.americangeriatrics.org/publications-tools	2023-01-24
AHA	American Heart Association (USA) https://professional.heart.org/en/guidelines-and-statements	2023-01-24

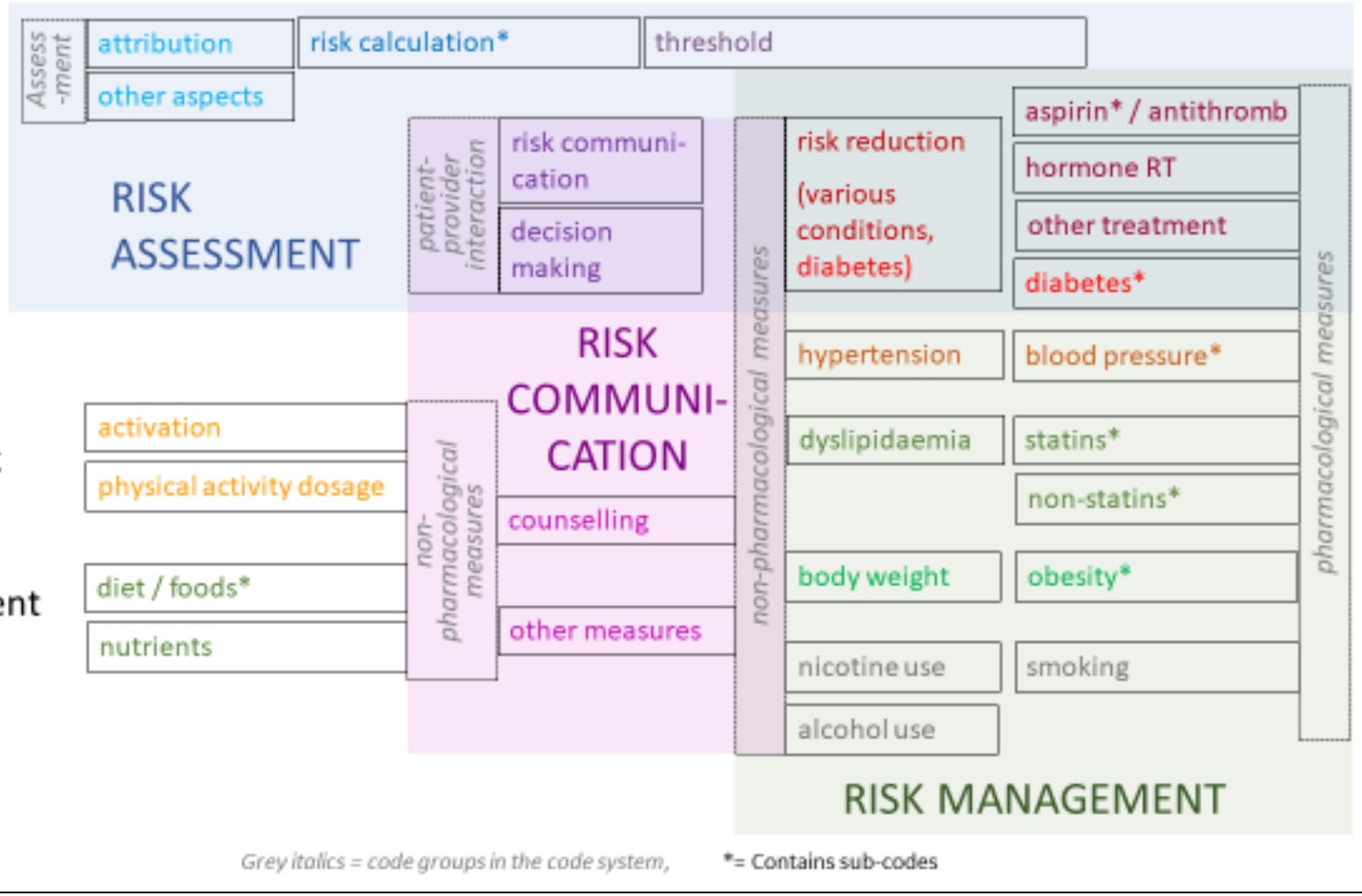
Abbreviation	Name (country) and internet address	Date
AMA	Alberta Medical Association (Canada) http://www.albertadoctors.org/	2023-01-24
BCS	British Cardiovascular Society https://www.britishcardiovascularsociety.org/resources/publi cations-reports	2023-01-24
BIHS	British and Irish Hypertension Society https://bihsoc.org/guidelines/	2023-01-24
CCS	Canadian Cardiovascular Society https://ccs.ca/guidelines-and-position-statement-library/	2023-01-24
CDHSH	Commonwealth Department of Human Services and Health(Australia) www.health.gov.au	2023-01-26
CHS	Hypertension Canada https://guidelines.hypertension.ca/chep-resources/	2023-01-04
CTFPHC	Canadian Task Force on Preventive Health Care (Canada) https://canadiantaskforce.ca	2023-01-30
EASD	European Association for the Study of Diabetes (Europe) https://www.easd.org/guidelines.html	2023-01-24
ESC	European Society of Cardiology (Europe) https://www.escardio.org/Guidelines/Clinical-Practice- Guidelines	2023-01-24
ESH	European Society of Hypertension (Europe) https://www.eshonline.org	2023-01-24
GR	Gezondheidsraad (The Netherlands) https://www.gezondheidsraad.nl	2023-02-08
HHS	Unites States Department of Health and Human Services (USA) http://www.hhs.gov	2023-01-30
HIS	Healthcare Improvement Scotland https://www.healthcareimprovementscotland.org	2023-01-30
IDF	International Diabetes Foundation https://www.idf.org/e-library/guidelines.html	2023-01-24
ICSI	Institute for Clinical Systems Improvement (USA) https://www.icsi.org/guideline/	2023-01-30
ISH	International Society of Hypertension https://ish-world.com/ish-global-hypertension-practice-guidelines/	2023-01-24
MSAC	Medical Services Advisory Committee (Australia) http://www.msac.gov.au/	2023-01-30

Abbreviation	Name (country) and internet address	Date
NHG	Nederlands Huisartsen Genootschap (The Netherlands) https://www.nhg.org	2023-02-08
NHS	National Health Services (UK) http://www.nhsdirect.nhs.uk	2023-01-30
SEA	Sociedad Española de Arteriosclerosis https://www.se-arteriosclerosis.org	2023-01-25
SEC	Sociedad Española de Cardiología https://secardiologia.es	2023-01-26
SEHLELHA	Sociedad Española de Hipertensión – Liga Española para laLucha contra la Hipertensión Arterial http://seh-lelha.org	2023-01-26
semFyC	Sociedad Española de Medicina de Familia y Comunitaria https://www.semfyc.es	2023-01-26
SEMG	Sociedad Española de Médicos Generales y de Familia https://www.semg.es	2023-01-26
USPSTF	United States Preventive Services Task Force (USA) https://www.uspreventiveservicestaskforce.org/uspstf/	2023-01-30
WHO	World Health Organization https://www.who.int	2023-01-30
ZonMW	Netherlands Organization for Health Research and Development (The Netherlands) https://www.zonmw.nl/nl/	2023-02-08

ANNEX 4. DEVELOPMENT OF ANALYTICAL FRAMEWORK AND CODE SYSTEM



Annex 4.2: Analytical framework and code system development



Grey italics = code groups in the code system, *= Contains sub-codes

Annex 4.3. Codes referring to preventive interventions

(Part of final code system, including code identifiers to structure further analysis and results presentation)

Code identifier	full name (code group and code name)	short code name	code definition
A.1.1	intervention: assessment: attribution	assess: attribution	Refers to whom, when and how often counselling on primary cardiovascular prevention should be offered in the first place. Includes recommendations referring to - systematic screening for specific risk factors or the presence of cardiovascular disease. - using an opportunistic versus a systematic approach for screening
A.1.2	intervention: assessment: calculate definite risk	assess: calculate definite risk	The recommendation states if persons with specific conditions (e.g., patients with diabetes, known CAD ...) should or should not be considered to be at high risk without further risk calculation. Recommendation could also state that in specified group (e.g. persons with diabetes) a formal risk assessment should be conducted.
A.1.3	intervention: assessment: basic risk calculation	assess: basic risk calculation	The recommendation states how to calculate/ to determine the cardiovascular risk, including which risk factor to consider in the basic calculation of cardiovascular risk.

Code identifier	full name (code group and code name)	short code name	code definition
A.1.4	intervention: assessment: advanced risk calculation	assess: advanced risk calculation	The recommendation states a risk range (mostly intermediate range) at which further tests (e.g. computer tomography, ECG) or consideration of further risk factors (e.g. BMI, socioeconomic status) are recommended for decision making.
A.1.5	intervention: assessment: threshold	assess: threshold	The recommendation states a threshold above which a treatment should be started/ be intensified. Could also be a range of cardiovascular risk instead of a single threshold. Could refer to a pharmacological and a non-pharmacological treatment.
A.1.6	intervention: assessment: other	assess: other	Refers to recommendations that do not fit to any other assessment codes.
B.1.1	intervention: PP interaction: risk communication	interact: risk communication	Refers to how to communicate about perceived and/or systematically assessed risk for CVD. Sometimes labeled as risk counselling, but can be distinguished from lifestyle counselling (which aims at motivating and supporting patients to change behavioral risk factors such as smoking, unhealthy diet, sedentary behavior).
B.1.2	intervention: PP interaction: decision making	interact: decision making	Refers to the decision about preventive measures, which constitutes a communicative process between patient and provider (ideally: shared decision-making).

Code identifier	full name (code group and code name)	short code name	code definition
C.1.1	intervention: non-pharmacological: counselling	non-pharma: counselling	Refers to the provision of professional assistance and guidance in resolving personal or psychological problems related with CVD risk. Aiming at motivating and supporting patients to change risky lifestyles (such as unhealthy diet, sedentary behavior etc.) and providing specifications on how to counsel (e.g., using special techniques, emphasizing or observing particular aspects). If the recommendation focuses on particular risk groups or the control of certain risk factors, use the code "non-pharma: risk reduction" or the specific non-pharma codes, and double-code with "Pharma: other" (or the specific pharma-codes) if it includes pharmacological besides non-pharmacological measures. For substance use with addictive potential, use separate codes ("non-pharma: nicotine use", "non-pharma: alcohol use", "non-pharma: other"). If the recommendation refers to communicating about perceived and/or systematically assessed risk for CVD (sometimes labelled "risk counselling"), use risk communication as a code.
D.1.1	intervention: non-pharmacological: activation	non-pharma: activation	Refers to advice to increase the level of physical activity or reduce sedentary behavior in order to reduce overall CVD risk, but without providing further instructions on the mode or dosage of activity.
D.1.2	intervention: non-pharmacological: PA dosage	non-pharma: PA dosage	Refers to promoting a healthy level of physical activity (PA), giving details on the recommended mode (cardiovascular strain, muscle strengthening, flexibility, and coordination), the intensity (moderate/vigorous) and/or the amount (duration, frequency per week).

Code identifier	full name (code group and code name)	short code name	code definition
E.1.1	intervention: non-pharmacological: diet	non-pharma: diet	Refers to general advice on nutrition, healthy-eating patterns (e.g., Mediterranean diet), or cross-reference to other guidelines, e.g. national recommendations for the general population. (Pharmacological support to lose weight should be coded "pharmacological: other treatment". Surgical procedures should be coded "non-pharma: other measures")
E.1.2	intervention: non-pharmacological: foods	non-pharma: foods	Refers to quantified recommendations for eating certain types of food per day or week, e.g., vegetables, meat, wholegrain cereals, nuts etc., but also processed or sweetened foods (Pharmacological support to lose weight should be coded "pharmacological: other treatment". Surgical procedures should be coded "non-pharma: other measures")
E.1.3	intervention: non-pharmacological: fat intake	non-pharma: fat intake	Refers to recommended daily intake of different types of fat or fatty acids (in grams or as percentage of daily energy intake). The intake may be through natural food items, processed or supplemented foods, or supplementary preparations such as pills. (Pharmacological support to lose weight should be coded "pharmacological: other treatment". Surgical procedures should be coded "non-pharma: other measures")

Code identifier	full name (code group and code name)	short code name	code definition
E.1.4	intervention: non-pharmacological: salt intake	non-pharma: salt intake	Refers to advice on eating salty foods or recommended daily intake of salt (sodium), related to overall CVD risk. The intake may be through natural food items or processed foods. For advice on salt intake in people with hypertension, use "non-pharma: hypertension".
E.1.5	intervention: non-pharmacological: nutrients	non-pharma: nutrients	Refers to recommended daily intake of vitamins, minerals etc. (in milligrams or grams). The intake may be through natural food items, supplemented foods, or supplementary preparations such as pills or powders. (Pharmacological support to lose weight should be coded "pharmacological: other treatment". Surgical procedures should be coded "non-pharma: other measures")
F.1.1	intervention: non-pharmacological: nicotine use	non-pharma: nicotine use	Refers exclusively to the risk factor tobacco smoking (including passive smoking) and the general advice to stop or avoid it. May include specific programs, techniques or therapies to support smoking cessation. (Pharmacological support to stop smoking should be coded "pharma: other treatment")
F.1.2	intervention: non-pharmacological: alcohol use	non-pharma: alcohol use	Refers exclusively to the risk factor of drinking alcohol and the advice to stop or limit it. May include specific programs, techniques or therapies to modify drinking behavior.

Code identifier	full name (code group and code name)	short code name	code definition
F.1.3	intervention: non-pharmacological: other measures	non-pharma: other measures	May include preventive or therapeutic measures or any behavior change other than: nicotine or alcohol use, nutrition, physical activity.
G.1.1	intervention: non-pharmacological: risk reduction	non-pharma: risk reduction	Refers to advice that is aimed at the control or reduction of overall CVD risk, in particular for the risk group of persons with diabetes or other conditions of interest (combine with "condit: diabetes" or "condit: other"). May comprise various lifestyle changes or provide instructions with different levels of detail. Double-code with "Pharma: diabetes" or "Pharma: other" if it includes pharmacological besides non-pharmacological measures. For exclusive recommendations on substance use with addictive potential, use separate codes ("non-pharma: nicotine use", "non-pharma: alcohol use", "non-pharma: other"). If the recommendation refers to communicating about perceived and/or systematically assessed risk for CVD (sometimes labelled "risk counselling"), use risk communication as a code.
G.1.2	intervention: non-pharmacological: hypertension	non-pharma: hypertension	Refers to advice that is aimed at the control and reduction of overall CVD risk, in particular for the risk group or the control of the specific risk factor hypertension. May comprise various lifestyle changes or provide instructions with different levels of detail. Double-code with "Pharma: hypertension" if it includes pharmacological besides non-pharmacological measures. For exclusive recommendations on substance use with addictive potential, use separate codes ("non-pharma: nicotine use", "non-pharma: alcohol use", "non-pharma: other"). If the recommendation refers to communicating about perceived and/or systematically assessed risk for CVD (sometimes labelled "risk counselling"), use risk communication as a code.

Code identifier	full name (code group and code name)	short code name	code definition
G.1.3	intervention: non-pharmacological: dyslipidemia	non-pharma: dyslipidemia	Refers to advice that is aimed at the control and reduction of overall CVD risk, in particular for the risk group or the control of the specific risk factor dyslipidemia. May comprise various lifestyle changes or provide instructions with different levels of detail. Double-code with "Pharma: statins" or pharma: non-statins" if it includes pharmacological besides non-pharmacological measures. For exclusive recommendations on substance use with addictive potential, use separate codes ("non-pharma: nicotine use", "non-pharma: alcohol use", "non-pharma: other"). If the recommendation refers to communicating about perceived and/or systematically assessed risk for CVD (sometimes labelled "risk counselling"), use risk communication as a code.
G.1.4	intervention: non-pharmacological: body weight	non-pharma: body weight	Refers to advice that focuses on a particular risk group or the control of the specific risk factor overweight/obesity. May comprise various lifestyle changes or provide instructions with different levels of detail. May also include Bariatric surgery. Double-code with "Pharma: obesity" if it includes pharmacological besides non-pharmacological measures. For exclusive recommendations on substance use with addictive potential, use separate codes ("non-pharma: nicotine use", "non-pharma: alcohol use", "non-pharma: other"). If the recommendation refers to communicating about perceived and/or systematically assessed risk for CVD (sometimes labelled "risk counselling"), use risk communication as a code.
H.1.1	intervention: pharmacological: statins	pharma: statins	Any recommendation on the use of statins as a form of cholesterol-lowering medication that does not fall under the more specific statin-codes below.
H.1.2	intervention: pharmacological: statin indication	pharma: statin indication	Refers to the who-and-when of statin as a form of cholesterol-lowering medication.

Code identifier	full name (code group and code name)	short code name	code definition
H.1.3	intervention: pharmacological: statin dosage	pharma: statin dosage	Refers to the drug choice and dose of statins as a form of cholesterol-lowering medication.
H.1.4	intervention: pharmacological: statin target	pharma: statin target	Refers to the treat-to-target of statins as a form of cholesterol-lowering medication.
H.1.5	intervention: pharmacological: statin follow-up	pharma: statin follow-up	Refers to the follow-up of patients being prescribed statins as a form of cholesterol-lowering medication.
I.1.1	intervention: pharmacological: non-statins	pharma: non-statins	Any recommendation on the use of non-statins aimed at lowering cholesterol level that does not fall under the more specific non-statin-codes below.
I.1.2	intervention: pharmacological: fibrate	pharma: fibrate	Refers to the who-and-when of fibrates as a non-statin medication, aimed at lowering cholesterol levels.
I.1.3	intervention: pharmacological: nicotinic acids	pharma: nicotinic acids	Refers to the who-and-when of nicotinic acids as a non-statin medication, aimed at lowering cholesterol levels.
I.1.4	intervention: pharmacological: ezetimibe	pharma: ezetimibe	Refers to the who-and-when of ezetimibe as a non-statin medication, aimed at lowering cholesterol levels.
I.1.5	intervention: pharmacological: PCSK9 inhibitors	pharma: PCSK9 inhibitors	Refers to the who-and-when of PCSK9 inhibitors as a non-statin medication, aimed at lowering cholesterol levels.

Code identifier	full name (code group and code name)	short code name	code definition
I.1.6	intervention: pharmacological: bile acid sequestrants	pharma: bile acid sequestrants	Refers to the who-and-when of bile acid sequestrants as a non-statin medication, aimed at lowering cholesterol levels.
J.1.1	intervention: pharmacological: blood pressure	pharma: blood pressure	Any recommendation on medication aimed at lowering blood pressure that does not fall under the more specific BP-codes below.
J.1.2	intervention: pharmacological: BP indication	pharma: BP indication	Refers to the who-and-when of any medication aimed at lowering blood pressure.
J.1.3	intervention: pharmacological: BP dosage	pharma: BP dosage	Refers to the drug choice and dose of any medication aimed at lowering blood pressure.
J.1.4	intervention: pharmacological: BP target	pharma: BP target	Refers to the treat-to-target for any medication aimed at lowering blood pressure.
K.1.1	intervention: pharmacological: aspirin	pharma: aspirin	Any recommendation on the use of aspirin as an anticoagulant/ antiplatelet medication that does not fall under the more specific ASA-codes below.
K.1.2	intervention: pharmacological: ASA indication	pharma: ASA indication	Refers to the who-and-when of Aspirin (acetylsalicylic acid) as a form of antithrombotic medication. (All other antithrombotic/antiplatelet medication should be coded "pharma: antithromb various")

Code identifier	full name (code group and code name)	short code name	code definition
K.1.3	intervention: pharmacological: ASA dosage	pharma: ASA dosage	Refers to the drug choice and dose of aspirin (acetylsalicylic acid) as a form of antithrombotic medication. (All other antithrombotic/antiplatelet medication should be coded "pharma: antithromb various")
K.1.4	intervention: pharmacological: atithromb various	pharma: antithromb various	Refers to non-Aspirin anticoagulant/ antiplatelet medication.
L.1.1	intervention: pharmacological: diabetes indication	pharma: diabetes indication	Refers to the who-and-when of any medication aimed at controlling or preventing diabetes.
L.1.2	intervention: pharmacological: diabetes dosage	pharma: diabetes dosage	Refers to the drug choice and dose of any medication aimed at controlling or preventing diabetes.
L.1.3	intervention: pharmacological: diabetes target	pharma: diabetes target	Refers to the treat-to-target for any medication aimed at controlling or preventing diabetes.
M.1.1	intervention: pharmacological: obesity	pharma: obesity	Refers to medication to control overweight/obesity as a risk factor.
M.1.2	intervention: pharmacological: smoking	pharma: smoking	Refers to medication to control the risk factor "nicotine use", usually to support smoking cessation.

Code identifier	full name (code group and code name)	short code name	code definition
M.1.3	intervention: pharmacological: hormone RT	pharma: hormone RT	Refers to hormone replacement therapy (HRT) in relation to CVD risk, usually in post-menopausal women.
M.1.4	intervention: pharmacological: other treatment	pharma: other treatment	Any recommendation on medication related to managing CVD risk that does not fall under the codes for specific risk factors above.

Annex 4.4: Codes referring to population, outcome, or formal aspects

(Part of original code system, unchanged)

Code group	short code name	code definition
population: sub-population	sub-pop: age group	Different age groups constitute sub-populations that we are giving special attention to, according to the project proposal. This also includes elderly people with frailty.
population: sub-population	sub-pop: ethnicity	Different ethnic groups constitute sub-populations that we are giving special attention to, according to the project proposal. In the German context, this is often referring to "having a migration background".
population: sub-population	sub-pop: gender	Gender refers to a socially constructed notion and (self-)ascribed identity. Use this code if guideline authors explicitly distinguish gender from the biological sex.
population: sub-population	sub-pop: sex	Refers to the biological sex, as opposed to gender as a socially constructed notion and (self-)ascribed identity. Use this code if guideline authors do NOT distinguish gender from the biological sex.
population: condition	condit: diabetes	Diabetes (Type 1 and 2) is the only risk factor mentioned explicitly in the project proposal.
population: condition	condit: multimorbidity	Multimorbidity is a condition that we are giving special attention to, according to the project proposal.
population: condition	condit: other disease	Covers conditions or particular comorbidities other than the major risk factors for ASCVD (i.e., diabetes, dyslipidemia, smoking, hypertension, excess weight/obesity). Such diseases could be e.g. chronic kidney disease, rheumatic arthritis, atrial fibrillation, carotid stenosis, familial hypercholesterolemia.
population: condition	condit: polypharmacy	Polypharmacy is a condition that we are giving special attention to, according to the project proposal. It refers to persons taking several drugs, or to drug interaction with other drugs/ other diseases.

Code group	short code name	code definition
outcome: cv event	card vasc event: coronary	Coronary events or myocardial infarction (lethal or non-lethal) is one of the outcomes of interest according to the project proposal, besides stroke.
outcome: cv event	card vasc event: other endpoints	Any additional endpoint in combination with stroke or coronary event (as per diagnosis), which is relevant to the patient, e.g. quality of life, physical/mental functioning, or social participation.
outcome: cv event	card vasc event: stroke	Stroke (lethal or non-lethal) is one of the outcomes of interest according to the project proposal, besides coronary events/myocardial infarction. It comprises hemorrhagic and ischemic stroke including Transitory Ischemic Attack (TIA).
normative: recommendation	recommend: evidence level	Meant to serve for the retrieval and extraction of the level of evidence underlying consented recommendation statements. This formal code should be used in addition to any thematic codes (colored, referring to the PICO scheme) that might also apply to the text segment. In these cases, use double coding. If the guideline authors apply a scheme (letters, numbers, symbols) to indicate particular evidence levels, please insert a translation/explanation in the comment space of the quotation. Also, track the full references of the evidence (systematic reviews or primary studies) from the reference list or evidence report and insert them as comments to this quotation.
normative: recommendation	recommend: statement	Meant to serve for the retrieval and extraction of the core consented recommendation statements. This formal code should be used in addition to any thematic codes (colored, referring to the PICO scheme) that might also apply to the text segment. In these cases, use double coding.

Code group	short code name	code definition
normative: recommendation	recommend: strength	Meant to serve for the retrieval and extraction of the consented strength of core recommendations. This formal code should be used in addition to any thematic codes (colored, referring to the PICO scheme) that might also apply to the text segment. In these cases, use double coding. If the guideline authors apply a scheme (letters, numbers, symbols) to indicate particular a particular emphasis (strength of recommendation), please insert a translation/explanation in the comment space of the quotation.
normative: recommendation	recommend: question	Meant to serve for the retrieval of clinical key questions underlying the recommendations
normative: recommendation	recommend: exclude	Meant to distinguish recommendations that do not fall into the defined scope of analysis (primary privation of ASCVD) and are thus to be excluded

ANNEX 5. MINI-CHECKLIST (MiChe)

MiChe items	Description	Assessment options
1. Identification of key recommendations and comprehensibleness	The guideline is organized in such a way that it is generally easy to understand, and the key recommendations are easy to identify.	Yes To some extent No
2. Specification of the guideline's target audiences and scope	The target users are clearly defined, as are the target situations in which the guideline is to be applied.	Yes To some extent No
3. Specification of the objectives and the target population	The background and purpose of the guideline and the patients for whom it is to be applied are clearly defined.	Yes To some extent No
4. Independence and potential conflicts of interests	The developers of the guideline are all identified by name. Their conflicts of interest are declared, and the financial independence of the guideline is suing body is documented	Yes To some extent No
5. Systematic search for evidence and selection criteria	The search for evidence was performed systematically, and the criteria for the selection of evidence are described.	Yes To some extent No
6. Unambiguity of recommendation	The recommendations are clear, and their derivation from the evidence is explicit	Yes To some extent No
7. Different treatment options according to potential benefits, side effects and risks	Multiple management options are presented with a discussion of their utility, side effects, and risks	Yes To some extent No

MiChe items	Description	Assessment options
8. Information on update procedures	The date of issuance of the guideline and its expiration date are clearly indicated	Yes To some extent No
Overall assessment	Likert scale	From 1 (very good) to 7 (very poor)
Recommendation for further use		Yes Yes, with certain reservation no

Translated and adapted from Semlitsch T, Jeitler K, Kopp IB, Siebenhofer A. Entwicklung einer praktikablen Mini-Checkliste zur Bewertung der methodischen Leitlinienqualität. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen. 2014;108(5–6):299–312.

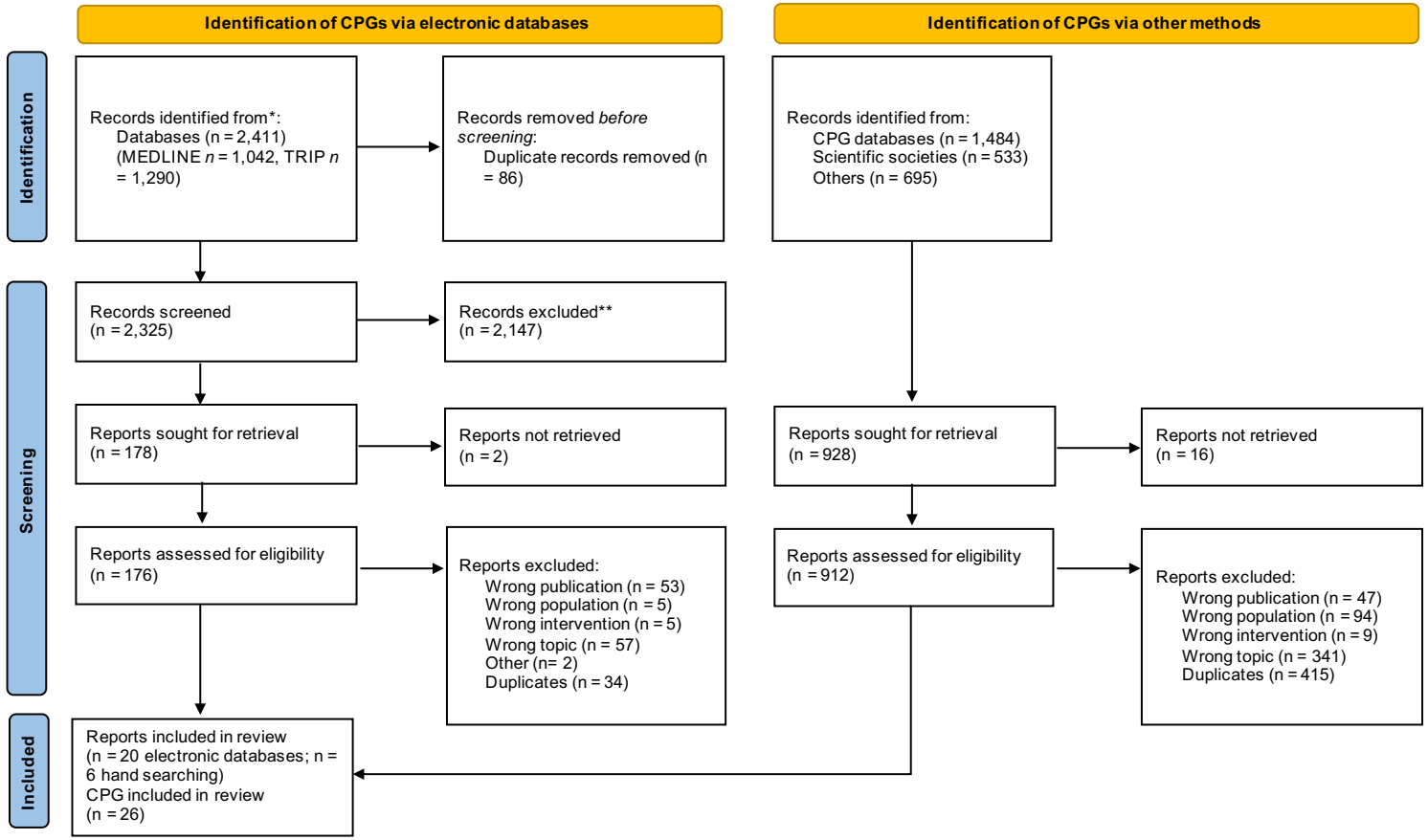
ANNEX 6. CATEGORIES OF CONSISTENCY AND INCONSISTENCY

Type	Definition	Further Action Plan for Guidance Development
Consistency		
(1)	**Recommendations are consistent** in content, evidence level and grading, and **based on a large body of high-level evidence** (e.g., multiple primary or secondary studies of high internal and external validity)	Verification of cited sources with highest evidence level, and update searches, if necessary
(2)	**Recommendations are consistent** in content, evidence level and grading, and **based on a small body of high-level evidence** (e.g. a single or a few primary studies of high internal and external validity)	Verification of cited sources, further research on safety aspects in particular, and update searches
(3)	**Recommendations are consistent** in content, evidence level and grading, and **based on** evidence from studies of **low-level evidence** (e.g. studies with design-related biases or where methodological flaws reduce internal or external validity) **or based on expert opinion** (where evidence is lacking)	Further research on evidence
(4)	**Recommendations are consistent** in content, but evidence levels and grading conflict	Verification of cited sources, and update searches
Inconsistency		
(A)	**Recommendations are completely inconsistent**, neither a mainstream trend nor even a common denominator can be identified	Further research on evidence

Type	Definition	Further Action Plan for Guidance Development
(B)	**Recommendations are** consistent in the majority of guidelines, but **differing** or even conflicting **recommendations are to be found in a minority**	Verification of cited sources to decide whether further research is necessary, and update-searches
(C)	**Recommendations** cover a **common topic or even have a common trend,** but put forward **different specific aspects or a combination of those**	Verification of cited sources to decide whether further research is necessary, and update-searches

Modified from source: Muth C, Gensichen J, Beyer M, Hutchinson A, Gerlach FM. The Systematic Guideline Review: Method, rationale, and test on chronic heart failure. BMC Health Serv Res. 2009 Dec;9(1):74.

ANNEX 7. PRISMA FLOW DIAGRAM



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

ANNEX 8. KEY CHARACTERISTICS of the included guidelines

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
PPCVD 1 (22)	ACC/AHA	2019	ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease	USA	Primary prevention of ASCVD in adults, focused on outcomes of ASCVD	Mostly medical practice in the United States	Adults (≥18 years of age)	Morbidity and mortality from atherosclerotic ASCVD (i.e., acute coronary syndromes, MI, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin), as well as heart failure and atrial fibrillation
PPCVD 2 (41,42)	ADA/ESE	2019	Primary Prevention of ASCVD and T2DM in Patients at Metabolic Risk: An Endocrine Society* Clinical Practice Guideline	USA	Reduce the risks and consequences of dyslipidemia. It provides guidance on screening, risk assessment, and treatment recommendations for a	Endocrinologists, other health care professionals, health-related, organizations, and regulatory bodies	Individuals with components of the metabolic syndrome who do not yet have diagnosed ASCVD or T2DM and the steps that can be taken to prevent these two diseases	Morbidity and mortality from ASCVD and type 2 diabetes mellitus

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
					range of individuals with various lipid disorders.			
PPCVD 3 (64)	BAP	2016	BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment.	UK	Provide recommendations regarding the monitoring and management of risk factors for diabetes and cardiovascular disease, in adults over the age of 18 years with psychosis, taking into account the effects of antipsychotic medications and with particular emphasis on overweight and diabetes.	Psychiatrists, general practitioners, pharmacists, nurses, other mental health practitioners and commissioners of services	Adults over the age of 18 years with psychosis	Morbidity and mortality from cardiovascular and metabolic disorders
PPCVD 4 (63)	SBD/SBC/SBEM	2017	Brazilian guidelines on prevention of cardiovascular disease in patients with diabetes: a position statement from the Brazilian Diabetes Society (SBD), the	Brazil	Risk stratification and prevention of cardiovascular disease in diabetes	Clinicians	Type 1 and type 2 diabetes	Non-clinical, subclinical and clinical ASCVD

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
			Brazilian Cardiology Society (SBC) and the Brazilian Endocrinology and Metabolism Society (SBEM)					
PPCVD 5 (43)	British Medical Journal (BMJ) Rapid Recommendations	2022	PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: a clinical practice guideline with risk-stratified recommendations	UK	Adding another lipid-lowering drug, either a proprotein convertase subtilisin / kexin 9 (PCSK9) inhibitor or ezetimibe	Clinicians	Adults with elevated LDL-C (over 70 mg/dl, 1.8 mmol/L) using high dose statins or intolerant to statins	Major ASCVD events
PPCVD 6 (65)	Canadian Cardiovascular Harmonized (CCH)	2022	Canadian Cardiovascular Harmonized National Guideline Endeavour (C-CHANGE) guideline for the prevention and management of cardiovascular disease	Canada	Assist health care providers in managing patients who often have multiple cardiovascular comorbidities, through the initiation and implementation of individualized ASCVD risk reduction strategies, based on their	Primary care professionals	Patients with multiple comorbidities	Morbidity and mortality from ASCVD

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
			in primary care: 2022 update		expert knowledge of their patient's preferences, goals and values			
PPCVD 7 (44)	European League Against Rheumatism (EULAR) Task Force	2016	EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update.	Europe	Aid in ASCVD risk management in IJD, based on expert opinion and scientific evidence.	Rheumatologist	Patients with rheumatoid arthritis (RA) and other inflammatory joint disorders (IJD), in particular ankylosing spondylitis (AS) and psoriatic arthritis (PsA)	Morbidity and mortality from ASCVD
PPCVD 9 (46)	SINU	2018	Diet and primary prevention of stroke: Systematic review and dietary recommendations by the ad hoc Working Group of the Italian	Italy	Relation between nutrition and primary prevention of stroke	Healthcare professionals and all interested readers	*Primary prevention of stroke*	Morbidity and mortality from total, ischemic and hemorrhagic strokes

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
			Society of Human Nutrition.					
PPCVD 10 (69)	Ministry of Health Malaysia (MoH MY)	2017	Clinical Practice Guidelines on Primary & Secondary Prevention of Cardiovascular Disease 2017	Malaysia	Assess the effectiveness of strategies for the primary and secondary prevention of ASCVD, educate healthcare workers on methods of assessing and stratifying ASCVD risk in our local population and suggest appropriate preventive steps against ASCVD at the individual, community and governmental level.	Health care providers	Individuals with and without established ASCVD	Morbidity and mortality from ASCVD
PPCVD 11 (47)	NICE	2014, revised 2023	Cardiovascular disease: risk assessment and reduction, including lipid modification	UK	Assessment and care of adults who are at risk of or who have ASCVD, such as heart disease and stroke	Healthcare professionals	People who are at risk of ASCVD or who have had ASCVD	Morbidity and mortality from ASCVD

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
PPCVD 12 (48)	SIGN	2017	Risk estimation and the prevention of cardiovascular disease	UK	Estimation of cardiovascular risk and interventions to reduce this risk in people with and without established CVD	Healthcare professionals involved in the management of patients with cardiovascular disease including cardiologists, dietitians, general practitioners, lipidologists, pharmacists, physiotherapists, practice nurses, psychologists and public health staff, as well as patients, careers, voluntary organizations and policy makers.	People with and without established CVD.	Morbidity and mortality from ASCVD

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
PPCVD 13 (70)	SOGC	2021	Guideline No. 422e: Menopause and Cardiovascular Disease.	Canada	Provide strategies for improving the care of perimenopausal and postmenopausal women based on the most recent published evidence.	Physicians, including gynecologists, obstetricians, family physicians, internists, emergency medicine specialists; nurses, including registered nurses and nurse practitioners; pharmacists; medical trainees, including medical students, residents, fellows; and other providers of health care for the target population.	Perimenopausal and postmenopausal women	Morbidity and mortality from ASCVD and venous thromboembolism
PPCVD 14 (71)	SEN	2021	Recommendations of the Spanish Society of Neurology for the prevention of stroke. Interventions on lifestyle and air pollution.	Spain	Address lifestyle habits as smoking, alcohol consumption, stress, diet, obesity, and sedentary lifestyles, and the potential benefits for stroke prevention of	Neurologists, public health authorities	Primary prevention of stroke	Morbidity and mortality from stroke

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
					modifying these habits. Also stroke risk associated with exposure to air pollution			
PPCVD 15 (49,50)	USDVA/USDoD	2020	Management of Dyslipidemia for Cardiovascular Disease Risk Reduction	USA	Managing dyslipidemia to reduce CVD risk	Primary care physicians, cardiologists, dietitians, pharmacists, nurse practitioners, and physician assistants	Adults aged ≥40 years without ASCVD	Morbidity and mortality from ASCVD
PPCVD 16 (51,72)	USPSTF	2018a	Screening for Cardiovascular Disease Risk With Electrocardiography	USA	Assess whether screening with resting or exercise ECG improves health outcomes compared with the use of traditional ASCVD risk assessment alone in asymptomatic adults	Primary care professionals	Adults without symptoms of or a diagnosis of ASCVD	Morbidity and mortality from ASCVD
PPCVD 17 (73,74)	USPSTF	2018b	Behavioral Weight Loss Interventions to Prevent Obesity-	USA	Assess interventions (behavioral and pharmacotherapy) for weight loss or weight loss	Primary care professionals	Adults 18 years or older	Obesity-Related Morbidity and Mortality

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
			Related Morbidity and Mortality in Adults		maintenance that can be provided in or referred from a primary care setting			
PPCVD 18 (62,75)	USPSTF	2018c	Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors	USA	Benefits and harms of using nontraditional risk factors (ankle brachial index, high sensitivity C-reactive protein level, or coronary artery calcium score)	Primary care professionals	Asymptomatic adults without a history of ASCVD	Morbidity and mortality from ASCVD
PPCVD 19 (76,77)	USPSTF	2020	Behavioral Counseling Interventions to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults With Cardiovascular Risk Factors	USA	Behavioral counseling to promote a healthy diet and physical activity for ASCVD prevention in adults with cardiovascular risk factors	Primary care professionals	Adults 18 years or older with known hypertension or elevated blood pressure, those with dyslipidemia, or those who have mixed or multiple risk factors such as metabolic syndrome or an estimated 10-year ASCVD risk of 7.5% or greater.	Morbidity and mortality from ASCVD

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
PPCVD 20 (54,78)	USPSTF	2021a	Screening for Hypertension in Adults	USA	Benefits and harms of screening for hypertension in adults, the accuracy of office blood pressure measurement for initial screening, and the accuracy of various confirmatory blood pressure measurement methods	Primary care professionals	Adults 18 years or older without known hypertension.	Morbidity and mortality from ASCVD
PPCVD 21 (55,79)	USPSTF	2021b	Screening for Asymptomatic Carotid Artery Stenosis	USA	Potential benefits and harms of screening and interventions, including revascularization procedures designed to improve carotid artery blood flow, in persons with asymptomatic carotid artery stenosis	Primary care professionals	Adults without a history of transient ischemic attack, stroke, or other neurologic signs or symptoms referable to the carotid arteries	Morbidity and mortality from ASCVD
PPCVD 22 (80,81)	USPSTF	2021c	Screening for Prediabetes and Type 2 Diabetes	USA	Screening for prediabetes and type 2 diabetes in asymptomatic nonpregnant adults and	Primary care professionals	Nonpregnant adults aged 35 to 70 years seen n primary care settings who have overweight or obesity (defined as a BMI > 25) and no symptoms of diabetes	Morbidity and mortality from ASCVD

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
					preventive interventions for those with prediabetes			
PPCVD 23 (57,82)	USPSTF	2022a	Vitamin, Mineral, and Multivitamin Supplementation to Prevent Cardiovascular Disease and Cancer	USA	Efficacy of supplementation with single nutrients, functionally related nutrient pairs, or multivitamins as well as the harms of supplementation	Primary care professionals	Community-dwelling, nonpregnant adults	ASCVD, cancer, and mortality
PPCVD 24 (20,58)	USPSTF	2022b	Statin Use for the Primary Prevention of Cardiovascular Disease in Adults	USA	Benefits and harms of statins	Primary care professionals	Adults 40 years or older without a history of known ASCVD and who do not have signs and symptoms of ASCVD. Adults with a LDL-C level greater than 190 m/dl (4.92 mmol/L) or known familial hypercholesterolemia are excluded	ASCVD-related morbidity or mortality or all-cause mortality

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
PPCVD 25 (59,83)	USPSTF	2022c	Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons	USA	Benefits and harms of systemic hormone therapy for the prevention of chronic conditions in postmenopausal persons and whether outcomes vary by age or by timing of intervention after menopause.	Primary care professionals	Asymptomatic postmenopausal persons who are considering hormone therapy for the primary prevention of chronic medical conditions	Chronic diseases prevention (i.e., coronary heart disease, stroke, fractures, breast cancer, colorectal cancer, thromboembolic events, dementia, gallbladder disease, urinary incontinence, all-cause mortality)
PPCVD 26 (60,84)	USPSTF	2022d	Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement	USA	Effectiveness of aspirin to reduce the risk of ASCVD events (myocardial infarction and stroke), cardiovascular mortality, and all-cause mortality in persons without a history of ASCVD.	Primary care professionals	Adults 40 years or older without signs or symptoms of ASCVD or known ASCVD (including history of myocardial infarction or stroke) who are not at increased risk for bleeding (eg, no history of gastrointestinal ulcers, recent bleeding, other medical conditions, or use of medications that increase bleeding risk)	ASCVD events (myocardial infarction and stroke), cardiovascular mortality, and all-cause mortality

Id	Developer (Acronym)	Year	Title	Country	Scope	Target audience	Target population	Outcomes
PPCVD 27 (61,76)	USPSTF	2022e	Behavioral Counseling Interventions to Promote a Healthy Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Cardiovascular Disease Risk Factors: US Preventive Services Task Force Recommendation Statement.	USA	Benefits and harms of behavioral counseling interventions to promote healthy behaviors in adults without ASCVD risk factors	Primary care professionals	Adults 18 years or older without known ASCVD risk factors, which include hypertension or elevated blood pressure, dyslipidemia, impaired fasting glucose or glucose tolerance, or mixed or multiple risk factors such as metabolic syndrome or an estimated 10-year ASCVD risk of 7.5%or greater.	Morbidity and mortality from ASCVD

ANNEX 9. DESCRIPTIVE SUMMARY OF INCLUDED GUIDELINES

Variable	Total – n (%)
Guidelines characteristics	
Geographical location	
North America	17 (65.39)
Europe	7 (26.92)
South America	1 (3.85)
Asia	1 (3.85)
Scope	
Management of ASCVD risk factors in general	5 (19.23)
Management of ASCVD risk factors in rheumatic disease	1 (3.85)
Management of prediabetes / diabetes	3 (11.54)
Management of dyslipidemia	4 (15.38)
Management of weight loss	1 (3.85)
Promote healthy behaviors	4 (15.38)
Benefits and harms of using non-traditional risk factors	3 (11.54)
Benefits and harms of hormone replacement therapy	2 (7.69)
Benefits and harms of aspirin	1 (3.85)
Benefits and harms of vitamin, mineral, and multivitamin supplementation	1 (3.85)
Target audience	
Primary care professionals only	13 (50.00)
Healthcare professionals in general	12 (46.15)
Target population	
Adults 18 or older without ASCVD	5 (19.23)
Adults 18 or older without ASCVD with psychosis	1 (3.85)
Adults 18 or older without ASCVD with ASCVD risk factors	1 (3.85)
Adults without ASCVD with hypertension	1 (3.85)
Adults without ASCVD with type 1 or type 2 diabetes	1 (3.85)

Variable	Total – n (%)
Adults without ASCVD with metabolic syndrome	1 (3.85)
Adults 40 or older without ASCVD	2 (7.69)
Adults 40 or older without ASCVD with dyslipidemia	1 (3.85)
Adults 40 or older without ASCVD with dyslipidemia with high dose statins or intolerant	1 (3.85)
Adults 35- 70 without ASCVD with obesity	1 (3.85)
Perimenopausal and postmenopausal women	2 (7.69)
Adults with and without ASCVD	3 (11.54)
Adults without stroke	2 (7.69)
Adults with multimorbidity	1 (3.85)
Adults with rheumatic disease	1 (3.85)
Outcomes	
ASCVD	25 (96.15)
Stroke	1 (3.85)

ASCVD = Atherosclerotic Cardiovascular Disease

ANNEX 10. QUALITY APPRAISAL OF INCLUDED GUIDELINES

MiChe items / ***Guidelines***	1. Identification of key recommendations and comprehensibleness	2. Specification of the guideline's target audiences and scope	3. Specification of the objectives and the target population	4. Independence and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguity of recommendations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommendation for further use
PPCVD 1 - ACC/AHA 2019 (22)	Yes	Yes	Yes	Yes	To some extent	Yes	Yes	To some extent	2	Yes
PPCVD 2 - ADA/ESE 2019 (41,42)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	To some extent	1	Yes
PPCVD 3 - BAP 2016 (64)	Yes	Yes	Yes	Yes	No	Yes	Yes	To some extent	3	Yes, with certain reservations
PPCVD 4 - SBD/SBC/SBEM 2017 (63)	Yes	To some extent	Yes	Yes	To some extent	Yes	Yes	To some extent	3	Yes, with certain reservations
PPCVD 5 - BMJ Rapid Reviews 2022 (43)	Yes	To some extent	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes

MiChe items / ***Guidelines***	1. Identification of key recommendations and comprehensibleness	2. Specification of the guideline's target audiences and scope	3. Specification of the objectives and the target population	4. Independence and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguity of recommendations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommendation for further use
PPCVD 6 - CCH 2022 (65)	Yes	Yes	Yes	Yes	No	To some extent	Yes	Yes	3	Yes, with certain reservations
PPCVD 7 - EULAR 2016 (44)	Yes	To some extent	Yes	Yes	Yes	Yes	Yes	To some extent	1	Yes
PPCVD 9 - SINU 2018 (46)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	To some extent	1	Yes
PPCVD 10 - Ministry of Health Malaysia (MoH MY) 2017 (69)	Yes	Yes	Yes	Yes	To some extent	Yes	Yes	Yes	1	Yes
PPCVD 11 - NICE 2014, revised 2023 (47)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 12 - SIGN 2017 (48)	Yes	Yes	Yes	Yes	To some extent	Yes	Yes	Yes	1	Yes

MiChe items / ***Guidelines***	1. Identification of key recommendations and comprehensibleness	2. Specification of the guideline's target audiences and scope	3. Specification of the objectives and the target population	4. Independence and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguity of recommendations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommendation for further use
PPCVD 13 - SOGC 2021 (70)	Yes	Yes	Yes	To some extent	No	Yes	Yes	To some extent	4	Yes, with certain reservations
PPCVD 14 - SEN 2021 (71)	Yes	To some extent	Yes	To some extent	To some extent	Yes	Yes	To some extent	4	Yes, with certain reservations
PPCVD 15 - USDVA/USDoD 2020 (49,50)	Yes	Yes	Yes	To some extent	Yes	Yes	Yes	To some extent	2	Yes
PPCVD 16 - USPTF 2018a (51,72)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 17 - USPTF 2018b (73,74)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes

MiChe items / ***Guidelines***	1. Identification of key recommendations and comprehensibleness	2. Specification of the guideline's target audiences and scope	3. Specification of the objectives and the target population	4. Independence and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguity of recommendations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommendation for further use
PPCVD 18 - USPTF 2018c (62,75)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 19 - USPTF 2020 (76,77)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 20 - USPTF 2021a (54,78)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 21 - USPTF 202b1 (55,79)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 22 - USPTF 2021c (80,81)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 23 - USPTF 2022a (57,82)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 24 - USPTF 2022b (20,58)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes

MiChe items / ***Guidelines***	1. Identification of key recommendations and comprehensibleness	2. Specification of the guideline's target audiences and scope	3. Specification of the objectives and the target population	4. Independence and potential conflicts of interests	5. Systematic search for evidence and selection criteria	6. Unambiguity of recommendations	7. Different treatment options according to potential benefits, side effects and risks	8. Information on update procedures	Overall assessment	Recommendation for further use
PPCVD 25 - USPTF 2022c (59,83)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 26 - USPTF 2022d (60,84)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes
PPCVD 27 - USPTF 2022e (61,76)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1	Yes

ANNEX 11. LIST OF CLINICAL QUESTIONS

Annex 11a. Clinical questions for risk assessment, risk calculation, risk communication and decision-making

1. Who should have ASCVD risk assessment?
    a. Population defined by age.
    b. Population defined by condition/ risk factor.
2. What are the benefits and harms of using a systematic versus an opportunistic ASCVD risk screening strategy?
3. What are the benefits and harms of screening for a single risk factor or condition?
    a. Screening for atherosclerotic plaques/ stenosis in carotid arteries by use of carotid ultrasound.
    b. Screening for diabetes.
    c. Screening for hyper-/ dyslipidemia.
    d. Screening for hypertension.
    e. Screening for obesity.
    f. Screening for smoking/ tobacco use.
    g. Screening for arterial stiffness.
    h. Screening for presence of coronary artery disease by use of non-invasive Tests (ECG (Resting or Exercise), stress tests, coronary computed tomography angiography (CCTA)).
4. What are the benefits and harms of using a standardized risk assessment tool assess ASCVD risk?
5. What are the benefits and harms of using additional, non-traditional risk factors to determine global ASCVD risk?
6. What are the benefits and harms of considering additional, non-traditional risk factors to reclassify persons with intermediate or borderline risk to guide decisions about preventive strategies?
7. What risk thresholds are stated to recommend i) pharmacological or non-pharmacological treatments; ii) lipid management interventions or blood pressure management interventions or antithrombotic therapy?

Annex 11b. Clinical questions for non-pharma interventions

1. Who should be the recipients of lifestyle advice and behavioral counseling?
2. What is the recommended approach for delivering lifestyle advice and behavioral counseling effectively?
3. What key principles should be considered when providing advice on physical activity?
4. What modes of physical activity are beneficial to cardiovascular health?
5. What levels of physical activity are beneficial to cardiovascular health?
6. What dietary patterns are considered beneficial for promoting health and well-being?
7. What general rules or guidelines are applicable for maintaining a healthy and balanced nutrition?
8. What are the recommended serving sizes or amounts of specific types of food that should be consumed for a balanced diet?
9. What are the recommended proportions or percentages of different fatty acids that are considered relevant for a healthy diet?
10. What level of dietary sodium intake is considered harmful or potentially detrimental to health?
11. Which macronutrients (such as carbohydrates, proteins, and fats) and modes of intake are considered relevant or important for maintaining a healthy diet?
12. Which other plant-based components and modes of intake are considered relevant or important for maintaining a healthy diet?
13. Which vitamins or provitamins are considered relevant for maintaining good health, and what are the recommended modes of intake for these nutrients?
14. Which minerals are considered relevant for maintaining good health, and what are the recommended modes of intake for these minerals?
15. What are the potential advantages and disadvantages or risks associated with the use of nutrient supplementation?
16. How is nicotine use addressed or managed in the primary prevention of ASCVD?
17. What is the rating or assessment of tobacco smoke in terms of its association with the risk of ASCVD?
18. How is alcohol consumption addressed or managed as part of the primary prevention strategy for ASCVD?

19. What specific measures or interventions are implemented in relation to mental health?
20. What are some alternative or additional treatment measures that are commonly considered or suggested?
21. What are the effective approaches or strategies for managing cardiovascular risk?
22. What are the effective approaches or strategies for managing cardiovascular risk in individuals with (pre-)diabetes?
23. What are the effective approaches or strategies for managing cardiovascular risk in individuals with hypertension?
24. What are the effective approaches or strategies for managing cardiovascular risk in individuals with dyslipidemia?
25. What are the effective approaches or strategies for managing cardiovascular risk in individuals with excess body weight?
26. What additional therapeutic measures can be considered in managing cardiovascular risk in individuals with excess body weight?

Annex 11c. Clinical questions for pharmacological interventions

1. What are the benefits and harms of statin use in reducing ASCVD events and mortality in adults without a history of ASCVD events? Do the benefits of statin use vary by subgroup, clinical characteristics, or dosage?
2. What are the benefits and harms of using other blood lipid-lowering medication when used for the primary prevention of ASCVD?
3. What are the benefits and harms of using medication for lowering blood pressure (BP) when used for the primary prevention of ASCVD?
4. What are the benefits and harms of using antiplatelet treatment (including aspirin) for the primary prevention of ASCVD?
5. What are the benefits and harms of pharmacotherapy for the treatment of diabetes when used for the primary prevention of ASCVD
6. What are the benefits and harms of pharmacotherapy for weight loss control when used for the primary prevention of ASCVD?

7. What are the benefits and harms of pharmacotherapy for smoking cessation when used for the primary prevention of ASCVD?
8. What are the benefits of menopausal hormone therapy when used for the primary prevention of ASCVD? What are the harms of menopausal hormone replacement therapy (HRT) when used for the primary prevention of ASCVD?

ANNEX 12. STRENGTH OF RECOMMENDATIONS AND LEVEL OF EVIDENCE: Comparison across guidelines

Annex 12a. Strength of recommendation: Comparison across guidelines

	PPCVD 1 - ACC/AHA 2019 (22,85)	**PPCVD 2 - ADA/ESE 2019** (41,66,86)	**PPCVD 3 - BAP 2016** (64,87)	**PPCVD 4 - SBD/SBC/ SBEM 2017** (63)	**PPCVD 5 - BMJ Rapid Reviews 2022** (43,88)	**PPCVD 6 - CCH 2022** (65,89–91)		**PPCVD 7 - EULAR 2016** (44,86)	**PPCVD 9 - SINU 2018** (92,93)	**PPCVD 10 - Ministry of Health Malaysia 2017** (69,94)	**PPCVD 11 - NICE 2014, revised 2023** (47,95)	**PPCVD 12 - SIGN 2017** (48)	**PPCVD 13 - SOGC 2021** (70,96)	**PPCVD 14 - SEN 2021** (71)	**PPCVD 15 - USDVA_ USDoD 2020** (49,50)	**PPCVD 16-27 – USPSTF** (20,62,72,74,76,78,79,82–84,97,98)
Strong recommendation for	Class I Benefit >>> Risk	Strong recommendation for	A (based on cat. I evidence)	Class I	Strong recommendation for	1A, 1B. 1C	A	A	Strong recommendation for	I	Offer/ advice or ask about	Strong recommendation for	Strong recommendation for	Class I	Strong recommendation for	A
Weak recommendation for	Class IIa (Moderate) Benefit >> Risk	Conditional recommendation for	B (based on cat. II evidence	Class IIa	Weak recommendation for	2A,2B, 2C	B	B	Weak recommendation for	IIa	consider	conditional recommendation	Weak recommendation for	Class IIa	Weak recommendation for	B
	Class IIb (Moderate) Benefit ≥ Risk		C/D (based on cat. III/ IV evidence)	Class IIb			C/D	C/ D		IIb				Class IIb		C

	PPCVD 1 - ACC/AHA 2019 (22,85)	**PPCVD 2 - ADA/ESE 2019** (41,66,86)	**PPCVD 3 - BAP 2016** (64,87)	**PPCVD 4 - SBD/SBC/ SBEM 2017** (63)	**PPCVD 5 - BMJ Rapid Reviews 2022** (43,88)	**PPCVD 6 - CCH 2022** (65,89–91)		**PPCVD 7 - EULAR 2016** (44,86)	**PPCVD 9 - SINU 2018** (92,93)	**PPCVD 10 - Ministry of Health Malaysia 2017** (69,94)	**PPCVD 11 - NICE 2014, revised 2023** (47,95)	**PPCVD 12 - SIGN 2017** (48)	**PPCVD 13 - SOGC 2021** (70,96)	**PPCVD 14 - SEN 2021** (71)	**PPCVD 15 - USDVA_ USDoD 2020** (49,50)	**PPCVD 16-27 – USPSTF** (20,62,72,74,76,78,79,82–84,97,98)
No recommendation	Class III: No benefit (Moderate) Benefit = Risk															Inconclusive
Weak recommendation against		Conditional recommendation against			Weak recommendation against				Weak recommendation against				Weak recommendation against		Weak recommendation against	
Strong recommendation against	Class III Harm (Strong) Risk > Benefit	Strong recommendation against		Class III	Strong recommendation against				Strong recommendation against	III	'do not offer', 'advise', or 'ask about'	Strong recommendation against	Strong recommendation against	Class III	Strong recommendation against	D

Annex 12b. Evidence levels: Comparison across guidelines

PPCVD 1 - ACC/AHA 2019 (22,85)	**PPCVD 2 - ADA/ESE 2019** (41,66,86)	**PPCVD 3 - BAP 2016** (64,87)	**PPCVD 4 - SBD/SBC/ SBEM 2017** (63)	**PPCVD 5 - BMJ Rapid Reviews 2022** (88,99)	**PPCVD 6 - CCH 2022** (65,89,90)	**PPCVD 7 - EULAR 2016** (44,86)	**PPCVD 9 - SINU 2018** (92)	**PPCVD 10 - Ministry of Health Malaysia 2017** (69,94)	**PPCVD 11 - NICE 2014, revised 2023** (47,95)	**PPCVD 12 - SIGN 2017** (48)	**PPCVD 13 - SOGC 2021** (70,96)	**PPCVD 14 - SEN 2021** (71)	**PPCVD 15 - USDVA_USDoD 2020** (49,50)	**PPCVD 16-27 – USPSTF** (20,62,72,74,76,78,79,81–84,97,98)
A	1|⌖⌖⌖⌖ 2|⌖⌖⌖⌖		A		Strong / 1a / 1A / High		1++	A	High	1++	High	A		High
	1|⌖⌖⌖⌖* 2|⌖⌖⌖⌖*				1B / 1		2++			2++				
B-R	1|⌖⌖⌖0 2|⌖⌖⌖0				2 / 1b / Moderate		1+		Moderate	1+	Moderate			Moderate
	1|⌖⌖⌖0** 2|⌖⌖⌖0**		B		2 / 2a		2+	B		2+		B		
B-NR	1|⌖⌖00*** 2|⌖⌖00***				3 /2a / Low				Low		Low			Low
C-LD	1|⌖⌖00 2|⌖⌖00						1-		Very low	1-	Very low			
C-LD					3		2-			2-		C		
	1|⌖000 2|⌖000				3		3	C		3				
C-RO			C		D / Consensus / 4		4			4				

* Includes very strong evidence from unbiased observational studies.

** Includes strong evidence from unbiased observational studies.

*** Includes some evidence from unbiased observational studies.

ANNEX 13. RECOMMENDATIONS from international primary prevention of cardiovascular disease guidelines

We provide overviews of all recommendations including the sources, strengths of recommendations, levels of evidence and results of the consistency analysis in accompanying excel files.

Topic/ key question	Excel file	Excel sheet
Risk assessment, risk calculation, risk communication and decision making		
Who should have CVD risk assessment?	consistency_analysis_assess_interaction	A.1.1 assess_attribution
What are the benefits and harms of screening for a single risk factor or condition?	consistency_analysis_assess_interaction	A.1.1 assess_attribution
What are the benefits and harms of using a systematic versus an opportunistic CVD risk screening strategy?	consistency_analysis_assess_interaction	A.1.1 assess_attribution
When should CVD risk be reassessed?	consistency_analysis_assess_interaction	A.1.1 assess_attribution
Should specific groups generally be considered at high risk?	consistency_analysis_assess_interaction	A.1.2 assess_calculate_definite_risk
What are the benefits and harms of using a standardized risk assessment tool assess CVD risk?	consistency_analysis_assess_interaction	A.1.3 assess_basic_risk_calculation
What are the benefits and harms of considering additional, non-traditional risk factors to determine global cardiovascular risk?	consistency_analysis_assess_interaction	A.1.3 assess_basic_risk_calculation
Which cholesterol measures should be used?	consistency_analysis_assess_interaction	A.1.3 assess_basic_risk_calculation
Should lifetime or 30-year ASCVD risk be considered to guide decisions about preventive strategies?	consistency_analysis_assess_interaction	A.1.4 assess_adv_risk_calc
What are the benefits and harms of considering additional, non-traditional risk factors to reclassify persons with	consistency_analysis_assess_interaction	A.1.4 assess_adv_risk_calc

Topic/ key question	Excel file	Excel sheet
intermediate or borderline risk to guide decisions about preventive strategies?		
Which risk thresholds are stated to recommend 1) pharmacological or non-pharmacological treatments; 2) lipid management interventions or BP management interventions or antithrombotic therapy?	consistency_analysis_assess_interaction	A.1.5 assess_threshold
Should a shared decision-making approach be used?	consistency_analysis_assess_interaction	B.1.1 interact_decision_making
Should absolute risk be used as basis of decision-making?	consistency_analysis_assess_interaction	B.1.1 interact_decision_making
How to communicate risk?	consistency_analysis_assess_interaction	B.1.2 interact_risk_com
Recommendations for non-pharmacological interventions		
Who should be the recipients of lifestyle advice and behavioural counselling?	consistency_analysis_non_pharma	C.1.1 non_pharma_counselling
What is the recommended approach for delivering lifestyle advice and behavioral counseling effectively?	consistency_analysis_non-pharma	C.1.1 non_pharma_counselling
What key principles should be considered when providing advice on physical activity?	consistency_analysis_non-pharma	D.1.1 non_pharma_activation
What modes of physical activity are beneficial to cardiovascular health?	consistency_analysis_non_pharma	D.1.2 non_pharma_PA_dosage
What levels of physical activity are beneficial to cardiovascular health?	consistency_analysis_non_pharma	D.1.2 non_pharma_PA_dosage
What dietary patterns are considered beneficial for promoting health and well-being?	consistency_analysis_non_pharma	E.1.1 non_pharma_diet
What general rules or guidelines are applicable for maintaining a healthy and balanced nutrition?	consistency_analysis_non_pharma	E.1.1 non_pharma_diet

Topic/ key question	Excel file	Excel sheet
What are the recommended serving sizes or amounts of specific types of food that should be consumed for a balanced diet?	consistency_analysis_non_pharma	E.1.2 non_pharma_foods
What are the recommended proportions or percentages of different fatty acids that are considered relevant for a healthy diet?	consistency_analysis_non_pharma	E.1.3 non_pharma_fat_intake
Which modes of intake for unsaturated fatty acids (dietary, supplements, preparations) are advisable?	consistency_analysis_non_pharma	E.1.3 non_pharma_fat_intake
What level of dietary sodium intake is considered harmful or potentially detrimental to health?	consistency_analysis_non_pharma	E.1.4 non_pharma_salt_intake
Which other plant-based components and modes of intake are considered relevant or important for maintaining a healthy diet?	consistency_analysis_non_pharma	E.1.5 non_pharma_nutrients
Which vitamins or provitamins are considered relevant for maintaining good health, and what are the recommended modes of intake for these nutrients?	consistency_analysis_non_pharma	E.1.5 non_pharma_nutrients
Which minerals are considered relevant for maintaining good health, and what are the recommended modes of intake for these minerals?	consistency_analysis_non_pharma	E.1.5 non_pharma_nutrients
What are the potential advantages and disadvantages or risks associated with the use of nutrient supplementation?	consistency_analysis_non_pharma	E.1.5 non_pharma_nutrients
How is nicotine use addressed or managed in the primary prevention of ASCVD?	consistency_analysis_non_pharma	F.1.1 non_pharma_nicotine_use
What is the rating or assessment of tobacco smoke in terms of its association with the risk of ASCVD?	consistency_analysis_non_pharma	F.1.1 non_pharma_nicotine_use

Topic/ key question	Excel file	Excel sheet
How is alcohol consumption addressed or managed as part of the primary prevention strategy for ASCVD?	consistency_analysis_non_pharma	F.1.2 non_pharma_alcohol_use
What specific measures or interventions are implemented in relation to mental health?	consistency_analysis_non_pharma	F.1.2 non_pharma_alcohol_use
What are some alternative or additional treatment measures that are commonly considered or suggested?	consistency_analysis_non_pharma	F.1.3 non_pharma_other_measures
What are the effective approaches or strategies for managing ASVCD risk?	consistency_analysis_non_pharma	G.1.1 non_pharma_risk_reduction
What are the effective approaches or strategies for managing cardiovascular risk in individuals with (pre-diabetes)?	consistency_analysis_non_pharma	G.1.1 non_pharma_risk_reduction
What are the effective approaches or strategies for managing cardiovascular risk in individuals with hypertension?	consistency_analysis_non_pharma	G.1.2 non_pharma_hypertension
What are the effective approaches or strategies for managing cardiovascular risk in individuals with dyslipidaemia?	consistency_analysis_non_pharma	G.1.3 non_pharma_dyslipidaemia
What are the effective approaches or strategies for managing cardiovascular risk in individuals with excess body weight?	consistency_analysis_non_pharma	G.1.4 non_pharma_body_weight
What additional therapeutic measures can be considered in managing cardiovascular risk in individuals with excess body weight?	consistency_analysis_non_pharma	G.1.4 non_pharma_body_weight
Recommendations for pharmacological interventions		

Topic/ key question	Excel file	Excel sheet
What are the benefits and harms of using statins as blood cholesterol-lowering medication when used for the primary prevention of ASCVD?	consistency_analysis_pharma	H.1.2_statin_indication H.1.3_statin_dosage H.1.4_statin_target H.1.5 statin_follow_up
What are the benefits and harms of using other blood lipid-lowering medication when used for the primary prevention of ASCVD?	consistency_analysis_pharma	I.1.2_fibrate I.1.3_nicotinic acid I.1.4_ezetimibe I.1.5_PCSK9 inhibitors I.1.6_bile acid sequestrants
What are the benefits and harms of using BP-lowering medication when used for the primary prevention of ASCVD?	consistency_analysis_pharma	J.1.2_BP_indication J.1.3_BP_dosage J.1.4_BP_target
Does regular aspirin use in patients without known ASCVD reduce ASCVD and CRC incidence and mortality, or all-cause mortality? Does the effect vary between a priori subgroups defined by age, sex, 10-year cardiovascular risk, diagnosis of diabetes mellitus, or race and ethnicity? Does the effect vary by dose or duration of aspirin use?	consistency_analysis_pharma	K.1.2_ASA indication K.1.3_ASA dosage K.1.4_anthithromb various
What are the benefits and harms of pharmacotherapy for the treatment of diabetes when used for the primary prevention of ASCVD?	consistency_analysis_pharma	L.1.2_diabetes_indication L.1.3_diabetes_dosage L.1.4_diabetes_target
What are the benefits and harms of pharmacotherapy for weight loss control when used for the primary prevention of ASCVD?	consistency_analysis_pharma	M.1.1_obesity
What are the benefits and harms of pharmacotherapy for smoking cessation when used for the primary prevention of ASCVD?	consistency_analysis_pharma	M.1.2_smoking

Topic/ key question	Excel file	Excel sheet
What are the benefits and harms of menopausal hormone replacement therapy (HRT) when used for the primary prevention of ASCVD?	consistency_analysis_pharma	M.1.3_HRT

ANNEX 14. ADDRESSING SUB-POPULATIONS

Demographic characteristics and health conditions addressed across the included guidelines

Guideline document	● sub-pop: age group Gr=49	● sub-pop: sex Gr=54	● sub-pop: gender Gr=1	● sub-pop: ethnicity Gr=27	Totals (sub-pop)	● condit: diabetes Gr=142	○ condit: other Gr=149	● condit: multi-morbidity Gr=9	● condit: poly-pharmacy Gr=46	Totals (codit)
ACC/AHA 2019 (Gr=52)	1	0	0	0	**1**	7	1	0	0	**8**
ADA/ESE 2019 (Gr=30)	1	1	0	0	**2**	6	10	0	0	**16**
BAP 2016 (Gr=46)	0	1	0	1	**2**	1	33	0	15	**49**
SBD/SBC/SBEM 2017 (Gr=51)	2	0	0	0	**2**	30	4	0	4	**38**
BMJ 2022	0	0	0	0	**0**	0	0	0	5	**5**
CCH 2022 (Gr=79)	1	0	0	1	**2**	27	2	0	4	**33**
EULAR 2016 (Gr=17)	0	0	0	0	**0**	0	8	0	3	**11**
SINU 2018 (Gr=37)	0	0	0	0	**0**	0	0	0	0	**0**
MoH MY 2017 (Gr=116)	0	6	0	0	**6**	6	6	0	0	**12**
NICE 2023_update (Gr=93)	3	0	0	1	**4**	11	7	5	5	**28**
SIGN 2017 (Gr=339)	4	2	0	1	**7**	5	14	1	4	**24**
SOGC 2021 (Gr=16)	0	12	0	0	**12**	0	0	0	0	**0**
SEN 2021 (Gr=17)	0	0	0	0	**0**	0	0	0	0	**0**
USDVA/USDoD 2020 (Gr=57)	1	0	0	0	**1**	0	0	0	1	**1**
USPSTF 2018a_Electr (Gr=11)	0	0	0	0	**0**	0	0	0	0	**0**
USPSTF 2018b_Weight (Gr=9)	0	0	0	0	**0**	0	0	0	0	**0**
USPSTF 2018c_Nontrad (Gr=10)	0	0	0	0	**0**	0	0	0	0	**0**

Guideline document	● sub-pop: age group Gr=49	● sub-pop: sex Gr=54	● sub-pop: gender Gr=1	● sub-pop: ethnicity Gr=27	Totals (sub-pop)	● condit: diabetes Gr=142	○ condit: other Gr=149	● condit: multi-morbidity Gr=9	● condit: poly-pharmacy Gr=46	Totals (codit)
USPSTF 2020_Behav (Gr=2)	0	0	0	0	**0**	0	0	0	0	**0**
USPSTF 2021a_Hypert (Gr=2)	0	0	0	0	**0**	0	0	0	0	**0**
USPSTF 2021b_Carot (Gr=2)	0	0	0	0	**0**	0	1	0	0	**1**
USPSTF 2021c_Diabetes (Gr=2)	0	0	0	0	**0**	1	0	0	0	**1**
USPSTF 2022a_Vit Min (Gr=4)	0	0	0	0	**0**	0	0	0	0	**0**
USPSTF 2022b_Statin (Gr=11)	1	0	0	0	**1**	0	0	0	0	**0**
USPSTF 2022c_Hormone (Gr=3)	1	2	0	0	**3**	0	0	0	0	**0**
USPSTF 2022d_Aspirin (Gr=3)	2	0	0	0	**2**	0	0	0	0	**0**
USPSTF 2022e_Behav (Gr=2)	0	0	0	0	**0**	0	0	0	0	**0**
Totals	**17**	**24**	**0**	**4**	**45**	**94**	**86**	**6**	**41**	**227**
	● sub-pop: age group Gr=49	● sub-pop: sex Gr=54	● sub-pop: gender Gr=1	● sub-pop: ethnicity Gr=27	Totals (sub-pop)	● condit: diabetes Gr=142	○ condit: other Gr=149	● condit: multi-morbidity Gr=9	● condit: poly-pharmacy Gr=46	Totals (codit)

* Gr= grand total of quotations marked in this document, or of quotations linked with this code across all documents

total Gr (sub-pop): 131

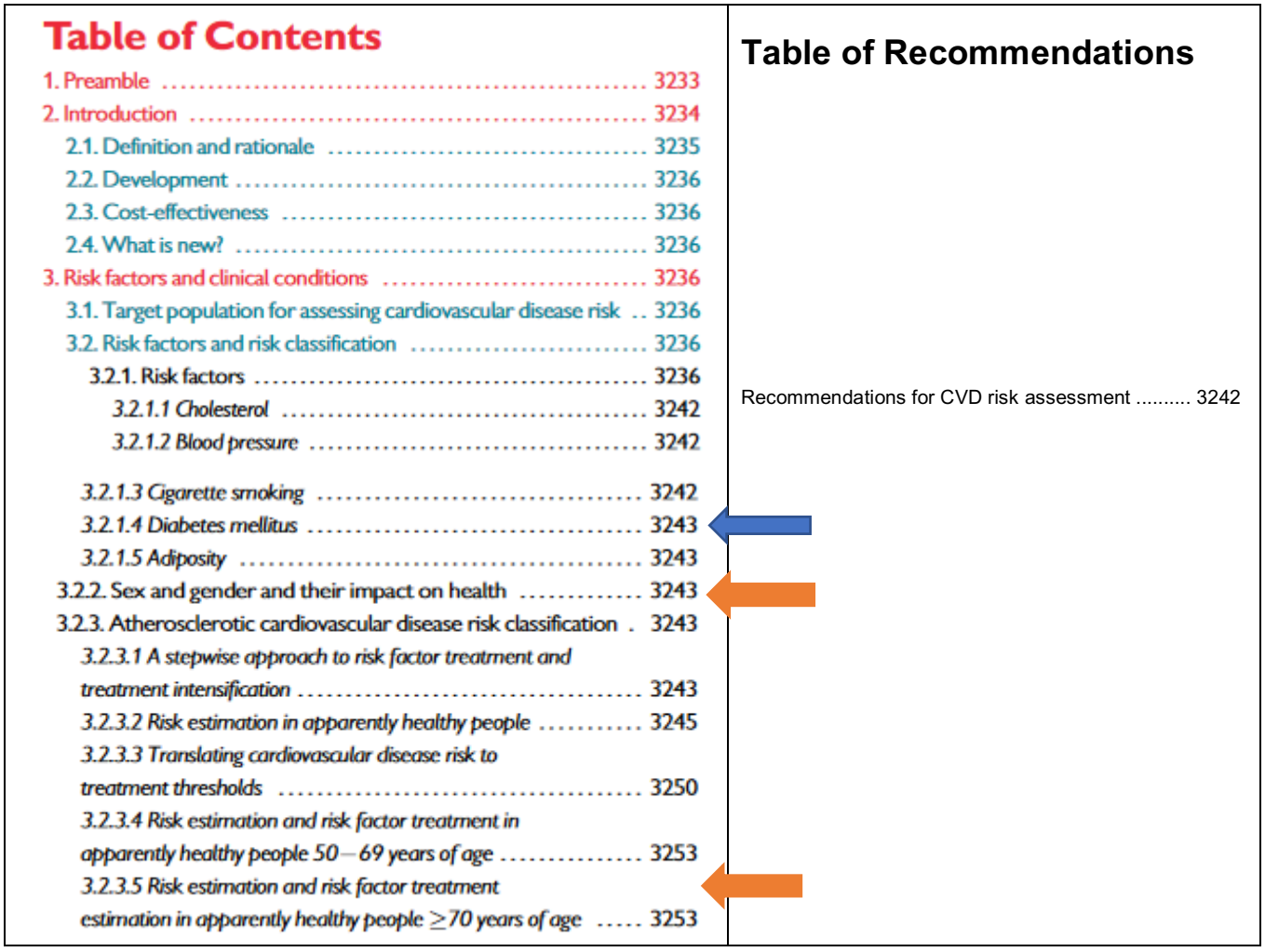
total Gr (condit): 346

ANNEX 15. CURRENT ESC GUIDELINES ON CVD PREVENTION

The 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice (40) have not been not included in the systematic guideline review, since they did not meet the inclusion criteria. However, since they are widely referenced throughout Europe and in Germany, we present an integrated table of contents and recommendations as an option for comparison. We also use it as an example for how the document structure is another option (besides specific recommendations) to provide for details when addressing sub-populations in a clinical practice guideline.

= demographic characteristics addressed

= health conditions addressed



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