Title Page

Cardiovascular Risk Assessment:

A Systematic Review of Guidelines

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Abstract

Background:

A number of guidelines exist for primary prevention cardiovascular screening and risk assessment for the apparently healthy population.

Purpose:

To systematically review current primary prevention guidelines on adult cardiovascular risk assessment and highlight the similarities and differences in order to aid clinician's decision-making.

Data sources:

Publications in MEDLINE and CINAHL between May 3, 2009 and June 30, 2016 were identified. In addition on June 30, 2016 we searched the G-I-N International Guideline Library, National Guidelines Clearing-house, National Library for Health, Canadian Medical Association InfoBase and websites of organizations responsible for guidelines development.

Study selection:

Two reviewers screened titles and abstracts to identify guidelines from Western countries containing recommendations for cardiovascular risk assessment for healthy adults.

Data extraction:

Two reviewers independently assessed rigor of guideline development using AGREE II and one extracted the recommendations.

Data synthesis:

Of the 21 guidelines, 17 showed considerable rigor of guideline development. The rigorously developed recommendations address assessment of total cardiovascular risk (5 guidelines), dysglycemia (7), dyslipidemia (2), and hypertension (3). All recommendations, with the exception of one, advocate screening and the majority include prediction models integrating multiple, relatively simple risk factors either for deciding on further screening or to guide subsequent

management. There is no consensus on the strategy for screening, recommended target population, screening tests or treatment thresholds.

Limitations:

Only guidelines developed by Western national or international medical organizations are included.

Conclusion:

Considerable discrepancies in recommendations still exist in cardiovascular screening guidelines with no consensus on optimum screening strategies or treatment threshold.

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Introduction

Many national and international bodies highlight primary prevention of cardiovascular disease (CVD), through risk factor reduction, as a potential solution to reduce future burden (1). The optimal target group and intervention that maximize benefit, however, remain unclear. Cardiovascular screening through health checks are now widely implemented in many Western countries to systematically detect high-risk individuals who may require aggressive risk reduction through pharmacotherapy and/or lifestyle interventions. Guidelines advocate use of screening with the aim of making the apparently healthy population healthier and reducing risk factors for future CVD. The institute of medicine (IOM) defines clinical practice guidelines as "systematically developed statements to assist practitioners and patient decisions about the appropriate health care for specific clinical circumstances" (2). However, to date an internationally agreed guideline for cardiovascular health checks does not exist.

Primary care physicians maintain a central role in the prevention of CVD but still find implementation of prevention strategies challenging and management of those with increased CVD risk remains suboptimal (3). Time constraints, lack of perceived usefulness, inadequate knowledge, and inconsistency in published recommendations have been cited as common reasons for not using CVD prevention guidelines or global CVD risk assessment tools (4). Concerns exist regarding poor uptake of the program by those invited with only about 50% attending for a National Health Service health check, much lower than the 75% government target (5). Additionally, there are doubts raised concerning the morbidity and mortality benefits from such programs posed by a Cochrane review and a subsequent Danish randomized controlled trial (6,7).

Ferket et al performed a systematic review in 2010, identifying differences amongst guidelines that would lead to variations in allocation of resources for prevention between different Western health care systems (8). Since that time, the reviewed guidelines were revised and replaced and new evidence has also become available on statin and blood pressure lowering therapy in low risk individuals (9,10). This systematic review revisits the CVD risk assessment guidelines and the selection of appropriate screening interventions based on currently available evidence.

Methods

We conducted an updated systematic review, using our previous search strategy (8), of guidelines containing recommendations for CVD risk assessment in the apparently healthy adult population not already receiving treatment for high-risk cardiovascular conditions such as diabetes, hypertension and hypercholesterolemia.

Data source and searches

A systematic literature search was performed to identify appropriate guidelines following the methods of our previous publication(8). We searched for published guidelines using MEDLINE and CINAHL between May 3, 2009 and June 30, 2016 (see Appendix for search strategy). We supplemented this search by using the following 4 guidelines specific databases; The National Guideline Clearinghouse (US), National Library for Health on Guidelines Finder (United Kingdom), Canadian Medical Association InfoBase (Canada), and G-I-N International Guideline Library (www.g-i-n.net). We also carried out a search of a number of websites of guidelines development organizations, including websites affiliated with all the guidelines included in our previous publication, to find additional or updated guidelines that were relevant (see Appendix Table 1). Our search was restricted to national guidelines from the United States, Canada, the United Kingdom, Australia and New Zealand and to international guidelines written in English.

Study selection

References that met the Institute of Medicine definition of a guideline were included. Guidelines were excluded if they (1) did not contain recommendations involving the healthy adult population, (2) were entirely focused on early detection of CVD, (3) were not produced on behalf of a professional organization, or (4) were not applicable to Western countries. In addition, only

guidelines produced or updated as of May 2009 were eligible for inclusion to avoid overlap with our previous systematic review and to ensure that only current guidelines were included.

Data extraction and quality assessment

Titles and abstracts were assessed by 2 independent reviewers (MK and VB). Articles were only excluded if both reviewers agreed they were ineligible. Discrepancies between the reviewers were resolved by consensus following discussion. Both reviewers performed the final selection for full data extraction.

We used the latest 23-item Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument to determine the rigor of development for each guideline (11). The Rigor of development domain considers the reporting of (1) methods to search for evidence, (2) criteria for selection of evidence, (3) strengths and limitations of the body of evidence, (4) methods for formulating the recommendations, (5) health benefits, side effects, and risks, (6) explicit link between recommendations and the evidence, (7) procedures for external expert peer review, and the (8) updating process. Each item is rated on a 7-point Likert scale. Conforming to the instructions of the AGREE II tool, 2 reviewers (MK and CV) independently rated the 8 items. Both reviewers assessed background information on the guideline development process from developers' websites. Average rigor scores were obtained by expressing the sum of the individual scores as a percentage of the maximum possible score and reproducibility of the 2 reviewers scores was good, with an interclass correlation of 0.75. We ranked the guidelines according to their scores. Editorial independence from the funding body, external funding and disclosure of relationships with industry by individual guideline group members were also assessed.

Data synthesis and analysis

One reviewer (MK) extracted all the relevant recommendations from the guidelines that had an AGREE II score above 50%. General lifestyle advice was not included. A recommendation matrix was produced grouped by the conditions being detected by screening. Each matrix was divided into (1) a methods section, (2) target group and delivery of screening, (3) recommended screening test, and (4) thresholds for the follow up. Consistent with our previous format, the strength of recommendation was classified as “for”, “consider”, “not for not against”, “insufficient evidence” and “against”. If feasible cardiovascular risk factors were classified into major, underlying and emerging risk factors according to the World Heart and Stroke Forum scientific statement (12).

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Results

Our search retrieved 3553 titles, of which 180 were identified as potentially eligible. On the basis of the abstracts 133 were excluded and on review of the full reports a further 26 were excluded. Guidelines such as the United States Preventative Service Task Force (USPSTF) guidelines on aspirin use were excluded as they did not include recommendations on the screening of healthy adult population (13). Finally 21 guidelines on cardiovascular risk assessment were included (Appendix Figure 1). Table 1 summarizes the selected guidelines, along with rigor score and conflicts of interest

17 of the 21 guidelines had a rigor score greater than or equal to 50%. Guidelines were categorized according to the main purpose of the screening. These included 5 guidelines on total cardiovascular screening (Table 2), 7 guidelines for dysglycemia screening (Appendix Table 2), 2 guidelines for dyslipidemia screening (Appendix Table 3) and 3 guidelines for hypertension screening (Appendix Table 4).

Areas of agreement

Recommendations from 16 of the 17 guidelines supported CVD risk assessment, either as the primary approach (five guidelines) or as a secondary step (eleven guidelines). In general there was consensus on how screening tests should be administered in the general population. A selective screening system based on knowledge of prior patient characteristics (record based screening) or during non-preventive patient visits (case finding or opportunistic screening) was advocated in 14 of the 17 guidelines. Two guidelines did not explicitly specify a screening method (Centre for Disease Control (CDC)/ American Heart Association (AHA) and USPSTF hypertension).

Most guidelines recommended integrating age, sex, smoking, blood pressure and lipid levels into CVD risk assessment by using prediction models. However there was no consensus on which prediction model to use. All seven dysglycemia guidelines recommended selecting individuals at high-risk of type 2 diabetes mellitus through formal short-term (10- year) or informal diabetes risk algorithms based on antecedent risk factors along with the often used threshold of 40 years. Diabetes risk algorithms were also used to decide on whether further formal diabetes screening with blood testing was required. The most commonly mentioned risk assessment tool for diabetes was the Finland Diabetes Risk Assessment Questionnaire or a modified version tailored to the country implementing it.

The majority of guidelines agreed on the need to consider ethnicity as a risk factor for CVD risk and citing specific high-risk ethnic groups. The United Kingdom (National Institute for Health and Clinical Excellence (NICE)) and the American (American College of Cardiology (ACC)/ AHA) guidelines use ethnicity in global CVD risk scoring algorithms. The United Kingdom-based CVD risk score (QRISK2) calculator advocated by NICE includes multiple ethnic groups. In the dysglycemia guidelines the United Kingdom, Australian and Canadian diabetes risk assessment questionnaires all incorporate ethnicity in the prediction of type 2 diabetes onset.

There is general consensus on the limited role of novel biomarkers (e.g. C reactive protein, Apo lipoprotein and prothrombin markers) and markers of subclinical atherosclerosis (e.g. ankle brachial index (ABI), Coronary artery calcium score and carotid ultrasound). The European Society of Cardiology (ESC) and ACC/AHA are the two main guidelines that consider the use of these markers in limited situations. The ACC/AHA suggests that in selected individuals who are not in one of the four statin benefit groups, and for whom a decision to initiate statin therapy is

otherwise unclear, additional factors may be considered to inform treatment decision-making. These additional factors include high-sensitivity C-reactive protein >2 mg/L, coronary artery calcium score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity and ankle-brachial index <0.9. The ESC states that routine use of novel biomarkers is not recommended for refinement of CVD risk stratification. Carotid atheroma using ultrasound, measurement of coronary artery calcification and the ankle brachial index may be considered as a risk modifier in CVD risk assessment but is only useful in individuals near thresholds for risk categorization.

Thresholds for initiating treatment are predominantly based on 5-or 10-year absolute risk for CVD or based on combining age and additional CVD risk factors. There were often exceptions made for those with extreme levels of a single risk factor or those considered in a high-risk category (kidney disease, diabetes mellitus).

A conservative approach to aspirin use in primary prevention is taken. Of the 8 guidelines that make recommendations on aspirin use, 3 do not recommend routine use in primary prevention, 3 of the dysglycemia guidelines recommend considering aspirin therapy but only in the presence of additional factors putting patients in a high-risk category and only 2 guidelines based the recommendation of aspirin use on age alone. The CDC/AHA guideline, which is the only guideline in this review that is gender specific, makes recommendations for women only, suggests aspirin use in women over 65 years and the Canadian Hypertension Education Program recommends its use in hypertensive patients over 55 years, both with the caveat that aspirin use should be guided by individual factors. The latest USPSTF guideline on aspirin use in primary prevention, in contrast, recommends aspirin for all adults aged 50 to 59 years with a 10-year cardiovascular disease risk of 10% or more, who are not at increased risk of bleeding, have a life expectancy of over 10 years (13).

There was a general consensus on the importance of addressing lifestyle factors in all target groups independent of pharmacotherapy. Recommendations on who should receive intensive lifestyle counseling differed between the guidelines with no consensus based on global risk scores. The dysglycemia guidelines do, however, advocate that all those at high risk for developing diabetes (impaired fasting glucose or impaired glucose tolerance) should receive intensive lifestyle intervention to prevent the onset of diabetes.

There were no firm statements regarding screening intervals. However, the total CVD risk guidelines advocated 5-yearly screening in low risk individuals. Recommended dysglycemia screening intervals in those without evidence of diabetes was 3-5 years. One dyslipidemia guideline recommended 5-yearly intervals for adults less than 45 years and 1-2 yearly for those older. For those identified as having impaired fasting glucose or impaired glucose tolerance, there was a general consensus that subsequent annual monitoring be undertaken.

Areas of disagreement

There was no consensus on the target population for screening between the recommendations. The American guidelines for total cardiovascular risk (ACC/AHA, CDC/AHA), dyslipidemia (American Association of Clinical Endocrinologists) and dysglycemia (American Diabetes Association) combined with the Canadian dysglycemia (Canadian Task Force on Preventive Health Care) and hypertension (Canadian Hypertension Education Program and Canadian Task Force on Preventive Health Care) guidelines advocate screening at a younger age (20 years). The European, United Kingdom and Australian guidelines advocate an older target population of over 40-year olds.

Although guidelines mostly agree on the use of risk prediction models as part of the risk assessment process or in guiding therapy there is no consensus on which model to use particularly with regards to total CVD risk. All 5 total CVD risk guidelines use different risk scores including the QRISK2 (NICE), Systematic Coronary Risk Estimation (SCORE, ESC), 5-year Framingham (National Vascular Disease Prevention Alliance), Pooled Cohort Equation (ACC/AHA), 10-year Framingham or Reynolds (CDC/AHA). These risk models differed in the end points, and the risk factors they consider in their development.

Guidelines on total cardiovascular risk differ regarding when to initiate statin treatment. There was no consensus regarding CVD risk threshold although direct comparison is challenging as all 5 guidelines used different risk prediction models. The more recent American (ACC/AHA) and United Kingdom (NICE) recommendations on total cardiovascular risk have lowered their threshold for initiation of statins. However, these two updated guidelines have also changed the CVD risk equations that they now utilize which makes direct comparison to older thresholds difficult due to different datasets or endpoints that are used in developing the algorithms. The NICE guideline now advocates the use of the QRISK2 algorithm and the ACC/AHA now advocates the Pooled Cohort Equation predicting general CVD whereas previously they both used the Framingham risk score. The 2016 ESC guideline has maintained the same statin thresholds as recommended in the 2012 version. Statin recommendations were made in 3 out of the 7 dysglycemia guidelines with only one using age over 40-years as a sole deciding factor in those diagnosed with diabetes.

The recommendations on initiating antihypertensive medication varied between guidelines with no consensus on what global risk threshold or blood pressure level to use. Most of the guidelines

346 did, however, agree on the importance of considering antihypertensive medications in diabetic
347 patients but again varied on the blood pressure threshold used to guide this.
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349 There was no consensus on the use of lifetime or relative risk in young adults to overcome the
350 problem of using a 5 to 10-year time horizon for predictions. The ACC/AHA advocate the use of
351 lifetime risk to guide intensive lifestyle intervention in the young. The ESC recommends the use of
352 relative risk charts for informing young individuals of risk whereas the NICE guideline generally
353 advises against using lifetime risk tools.
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355 With regard to subclinical atherosclerosis screening tests there was no agreement between the
356 guidelines regarding which tests to use. Only 2 total CVD risk guidelines (ACC/AHA and ESC)
357 suggested utilizing imaging tests (coronary artery calcium scoring and carotid ultrasound for
358 atheroma detection) but this was only in select individuals to guide management decisions. The
359 Australian guideline (National Vascular Disease Prevention Alliance) was the only total CVD
360 guideline to recommend assessing left ventricular hypertrophy in the primary risk assessment.
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Discussion

We identified 21 guidelines, of which 17 were rigorously developed, on cardiovascular screening interventions that could be performed within a cardiovascular health check program. The aim of this systematic review was not to provide a comprehensive integration of the guidelines but rather a summary of rigorously developed national and international guidelines available to physicians in the form of a quick reference, which allows easy comparison. There was a general consensus with regard to undertaking CVD risk screening and use of prediction models for risk stratification and guiding treatment. They also agreed on the use of relatively simple risk markers including age, gender, ethnicity and smoking history. Novel biomarkers or markers of subclinical atherosclerosis are generally not recommended except in very select subgroup of individuals. A conservative approach to aspirin initiation in primary prevention was advocated and there was a general agreement on intervals for repeat screening. Guidelines differ with respect to selection of the ideal target population, which risk prediction model to use and which thresholds to utilize to initiate statin or antihypertensive treatment.

We performed a broad search utilizing major medical publication repositories, guideline library websites and manually searching individual guideline development group websites. In contrast to our previous paper, this review only summarizes recommendations from guidelines. Other reports such as position and scientific statements are not in the remit of the AGREE II instrument, and were excluded. All the guidelines included in this review were published in the last 7 years and represent the most recent recommendations. None of the current 21 guidelines were included in our previous review.

Guidelines generally recommend that decisions on management be based on global cardiovascular risk that considers multiple risk factors. However, they differ regards risk thresholds to utilize. This is partly because the risk models advocated in the guidelines vary over the use of data sets, predictors used and their end points. The SCORE model (ESC) uses only hard end points of CVD mortality whereas the Framingham (CDC/ AHA, National Vascular Disease Prevention Alliance) utilizes the broadest end points consisting of coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure. Furthermore, the risk threshold for initiating a statin used by the ACC/AHA of 7.5% is based on the newer Pooled Cohort Equation which uses the 10-year non-fatal myocardial infarction, coronary heart disease death, or stroke end points (18). This variability can lead to different groups receiving treatment, makes comparison between different health care systems challenging and could also lead to inequality of health care. The AHA/ACC guidelines for example, would recommend statins for nearly all men and two-thirds of women over the age of 55-years, exceeding the proportions that would be eligible based on other guidelines such as the ESC, when tested in a European cohort (38). Standardization of various risk scoring systems, with validation and calibration, may help improve clinical outcomes in individuals at risk of developing CVD (39).Risk scoring systems would need to be developed/updated for different countries due to country/ region specific differences in event rates and mortality.

There are many challenges faced by programs that attempt to provide population-based interventions that determine the overall impact achieved. The diversity in guidelines on CVD may partly reflect the uncertainty on benefit of screening. Although there is evidence to support the effectiveness of particular interventions to appropriate individuals the difficulties in screening programs include the achievement of high enough uptake rates to invitations, the ability to deliver effective interventions and patient adherence to recommendations.

Most guidelines recommended a selective screening strategy with some newer guidelines advocating a lower threshold for initiating treatment such as statin therapy, citing recent meta-analysis and the reduced costs of statins due to patent expiry, as the main reasons for this shift(9). Thresholds utilized for deciding high risk are often arbitrary and at best decided on by mathematical modeling. Studies that show modest benefit have mainly been based on improvements in surrogate markers rather than CVD events, with inherent limitations (40).

A MEDLINE search identified four previous systematic reviews relevant to our study, published between January 1, 2009 and June 30, 2016 (see appendix for search strategy). Two were from our group including the previous (now outdated) version of this review and another focused on guidelines of screening for peripheral vascular disease only (8,41). The remaining two publications were limited to guidelines on primary CVD prevention in the elderly (searches up to December 2013) (42) or the diagnosis, assessment and management of hypertension (searches up to September 2011).

This systematic review represents contemporary guidelines with a broad inclusion of conditions eligible for cardiovascular risk assessment in apparently healthy adults along with an assessment of the guidelines rigor of development. Compared to our previous publication from 6 years ago, the target populations, risk prediction models and its consequences are still areas of disagreement across guidelines (8). Over the last 6 years there has been a trend towards advocating a lower threshold for initiating intensive lifestyle modification and statin therapy. Risk prediction models have been updated with a move away from the Framingham risk score, which previously predominated. There is a more conservative approach to aspirin, with most guidelines generally advocating against its use in primary prevention. The use of tests for assessment of subclinical

atherosclerosis has been further restricted.

The optimal strategy for systematic screening for the apparently healthy remains to be answered. Some advocate continuing with the current strategy of screening with the aim of trying to mold it into a system that eventually shows benefit whereas others are asking for the programs to be halted until such a time that the evidence of benefit justifies the resources invested in screening (43,44). Recent publications addressing some of these gaps and future research in identifying the most effective strategies will help shape future guideline recommendations (45-47).

There are some limitations that could bias our findings and limit generalizability. Only guidelines developed by Western national or international medical organizations were reviewed. We controlled for selection bias by having a comprehensive search strategy, as previously generated with a librarian and the articles were selected and appraised by two independent researchers. However, researchers were not blinded to the organization names or countries of origin. Finally, we considered the guideline development process but did not assess the clinical validity of the recommendation or review recommendations for specific lifestyle interventions as it was beyond the scope of this review.

Conclusion

Considerable discrepancies in recommendations still exist in cardiovascular screening guidelines with no consensus on optimum screening strategies or treatment threshold. Physicians should assess the strength of the recommendations and the level of evidence to decide which of the discrepant recommendations they may implement.

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Table 1. Characteristics of 21 Guidelines

Guideline by Medical Condition, year	Organization Responsible for Guideline Development	Country Applied	AGREE2 Rigor score, %	Conflicts of Interest
	Total Cardiovascular risk			
NICE (14), 2014	National Institute for Health and Clinical Excellence	UK	86	EI,SCI*†
ESC (15), 2012	European Society of Cardiology	Europe	86	SCI*
NVDPA (16), 2012	National Vascular Disease Prevention Alliance	Australia	85	EI,SCI†
ACC/AHA (17-19), 2013	American College of Cardiology	United States	83	SCI*†
CDC (20), 2011	Centres for Disease Control and Prevention	United States	65	EI,SCI*†
BCS (21), 2014	British Cardiovascular Society	UK	45	SCI*
NZGG (22), 2012	New Zealand Guidelines Group	New Zealand	20	EI,SCI‡
	Dyslipidemia			
ESC (23), 2011	European Society of Cardiology	Europe	72	SCI*
ACCE (24), 2012	American Association of Clinical Endocrinologists	United States	64	SCI*
CCS (25), 2013	Canadian Cardiovascular society	Canada	42	EI,SCI*
	Dysglycemia			
ADS/DAGDC (26), 2009	Australian Diabetes Society	Australia	87	SCI‡
CDA (27), 2013	Canadian Diabetes Association	Canada	83	EI,FIP,SCI*†
ADA (28), 2014	American Diabetes Association	United States	68	SCI*
USPSTF (29), 2015	U.S. Preventative Services Task Force	United States	76	EI, SCI
NICE (30), 2012	National Institute for Health and Clinical Excellence	UK	73	
CTFPHC (31), 2012	Canadian Task Force on Preventive Health Care	Canada	68	EI,SCI*
ESC (32), 2013	European Society of Cardiology	Europe	66	SCI*
IDF (33), 2012	International Diabetes Federation	International	47	FIP, SCI§
	Hypertension			
CHS (34,35), 2015	Canadian Hypertension Society	Canada	90	EI,SCI*†
USPSTF (36),2015	U.S. Preventative Services Task Force	United States	79	EI, SCI
CTFPHC (37), 2013	Canadian Task Force on Preventive Health Care	Canada	78	SCI

Abbreviations: AGREE2, Appraisal of Guidelines Research and Evaluation II; EI, editorial; independence declared; FIP, funding by industrial partner reported; SCI, statement about conflicts of interest of group members present; UK, United Kingdom

*Relationship with industry is reported by any group member;

† A group member is reported recused when a relevant area is under discussion;

‡ Conflicts of interest only available on request;

§ Conflicts of interest only reported to the group

Table 2. Recommendations for Screening in Total CVD Risk in 5 Guidelines

	ESC	NICE	NVDPA	ACC/ AHA	CDC/ AHA
Country	Europe	UK	Australia	USA	USA
Year	2016	2014	2012	2013	2011
AGREE 2 Score	86%	86%	85%	83%	65%
Method to evaluate evidence	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review
Methods to formulate recommendations	Formal consensus	Formal consensus	Formal consensus	Formal consensus	Formal consensus and voting
Consideration of costs	Review of CEA studies	Systematic review of published literature/ Performed CEA	Review of CEA studies	Not performed	Review of CEA studies
Target Group	Men > 40 y, Women >50 y or post menopausal	Aged 40-74 (NHS Health Check)	All adults aged >45 y or Aboriginal & Torres Strait Islanders >35y	Aged 21 and above	Women ≥20 y
Strategy	Opportunistic screening/ case finding	Opportunistic screening/ case finding/ record based	Opportunistic screening/ case finding	Opportunistic screening/ case finding	NR
Strength of recommendation	For	For	For	For	Not for and not against
Major risk factors prediction model	SCORE, general ASCVD mortality at 10 y	QRISK2, CHD/stroke/TIA events at 10 y	Framingham, CHD/stroke events at 5 y	Pooled Cohort Equations, CHD/stroke events at 10 y if age 40-79 y or lifetime (30 y) risk for 20-59 y with 10 y risk ≤ 7.5%	Framingham/ Reynolds Risk Score, CHD/stroke at 10 y
Age	✓1	✓1	✓1	✓1	✓1
Sex	✓1	✓1	✓1	✓1	✓1
Blood pressure	✓1	✓1	✓1	✓1	✓1
TC level	✓1	✓1	✓1	✓1	✓1
LDL-C level	✓2	✓2	✓2		
HDL-C level	✓1	✓1	✓1	✓1	✓1
TC:HDL-C ratio	✓1	✓1	✓1	✓1	
Smoking	✓1	✓1	✓1	✓1	✓1
Glucose levels		✓2	✓2		
Underlying risk factors					
Overweight/obesity	✓2	✓1	✓2		✓1
Physical inactivity	✓2		✓2		✓1
Atherogenic diet					
Socioeconomic factors	✓2	✓1	✓2		
Family history of premature CVD	✓2	✓1	✓2	✓3	✓1
Genetic/racial factors	✓2	✓1	✓2	✓1	✓1
Diabetes	✓2	✓1	✓1	✓1	✓1
Antihypertensives	✓2	✓1		✓1	
Emerging risk factors					
TG levels	✓2	✓2	✓2		
Renal function	✓2	✓1	✓2		✓1

Table 2. Recommendations for Screening in Total CVD Risk in 5 Guidelines (continued).

	ESC	NICE	NVDPA	ACC/ AHA	CDC/ AHA
Heart rate	✓2				
Apo/lipoprotein levels	✓4				
Glucose therapy for insulin resistance					
Prothrombotic markers	✓4				
C-reactive protein level	✓4			✓3	
Subclinical atherosclerosis	✓4 (ABI, CAC score, carotid US for plaque)		✓1 (LVH)	✓3 (ABI, CAC score)	
Thresholds					
Aspirin	Not recommended in primary prevention	Not applicable	Not recommended in primary prevention	Not applicable	Useful in women ≥65 depending on risk benefit; reasonable in DM
Statins	10 y CVD mortality ≥10% and LDL-C level ≥70 mg/dL; 10 y risk 5%-10% and LDL-C level ≥100 mg/dL; consider if 10 y risk <5% and LCL-C >115mg/dL; DM2 or DM1 and age >40 y	10 y CHD/stroke/TIA risk ≥10%; DM2 and 10 y CVD risk ≥10% (according to UKPDS tool); DM1; CKD with eGFR <60	5 y CHD/stroke risk ≥15%; persistent BP ≥160/100 mmHg; TC >7.5mmol/L; 5 y CHD/stroke risk 10%-15% and family history of premature CVD	40 -75 y with 10 y CHD/stroke risk ≥7.5% and LDL-C 70-189 mg/dL; 40-75 y with DM and LDL-C 70-189mg/dL; LDL-C level ≥190 mg/dL	10 y risk >20%; DM
Antihypertensives	10 y CVD mortality ≥10% and BP ≥140/90 mmHg; consider if 10 y risk 5-10% and BP ≥140/90 mmHg; DM1 or DM2 and BP ≥140/85 mmHg; over 60 y and systolic BP >150mmHg or more than 80 y and systolic BP >160mmHg; BP ≥180/110 mmHg	NR	5 y FRS ≥ 15%; FRS 10-15% and BP persistently ≥ 160/100/ FHx CVD, high risk ethnicity; consider if FRS <10% but BP persistently ≥160/100 mmHg	NR	BP ≥140/90 mmHg; >130/85 in CKD and DM
Intensive Lifestyle Counseling	10 y CVD mortality >1% or LDL-C >100mg/dL	10 y CHD/stroke/TIA risk ≥10%	5 y CHD/stroke risk ≥10%.	10 y CHD/ stroke risk ≥7.5% and LDL-C 70-189 mg/dL; DM1 or DM2; LDL-C level ≥190 mg/dL	NR

Table 2. Recommendations for Screening in Total CVD Risk in 5 Guidelines (continued).

	ESC	NICE	NVDPA	ACC/ AHA	CDC/ AHA
High-risk Monitoring	NR	NR	Monitor risk profile according to clinical context if 5 y CHD/stroke risk ≥ 15%. Monitor risk profile every 6-12 months if 5 y CHD/stroke risk 10 -15%	NR	NR
Screening Intervals	NR	Further risk assessment on an on going basis. 5 yearly as per NSF	Further risk assessment every 2 y if 5 y CHD/stroke risk <10%	Further risk assessment every 4-6 y if 10 y CHD/stroke risk <7.5%	NR

Abbreviations: ABI, ankle brachial index; ASCVD, atherosclerotic cardiovascular disease; CEA, cost-effectiveness analysis; CAC, coronary artery calcium; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM - diabetes mellitus; FHx, family history; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NHS, National Health Service; NR, not reported; NSF, National Service Framework; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; UK, United Kingdom; US, ultrasound; y, years;
✓1, Formal screening test (included in the prediction model);
✓2, Additional screening test
✓3, In selected individuals who are not in 1 of the 4 main statin benefit groups, and for who a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision-making. These factors include; 1. Primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias, 2. First degree relative with premature ASCVD, 3. High-sensitivity C-reactive protein >2 mg/L, 4. CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity, 5. Ankle-brachial index <0.9, or 6. Elevated lifetime risk of ASCVD.
✓4, Novel biomarkers have only limited additional value when added to CVD risk assessment with the SCORE algorithm in come limited cases.

Appendix Table 1: Website searches of guideline development organizations, including websites affiliated with all the guidelines included in our previous publication

Organization Responsible for Guideline Development	Country	Website Searched
American Academy of Family Physicians (AAFP)	United States	http://www.aafp.org/online/en/home.html
American Association of Clinical Endocrinologists	United States	www.aace.com
American College of Cardiology	United States	http://www.acc.org/
American College of Physicians	United States	http://www.acponline.org/
American College for Preventive Medicine	United States	http://www.acpm.org/
American Diabetes Association (ADA)	United States	http://www.diabetes.org/
American Geriatrics Society (AGS)	United States	http://www.americangeriatrics.org/
American Heart Association (AHA)	United States	http://www.americanheart.org/
American Medical Association (AMA)	United States	http://www.ama-assn.org/
American Stroke Association	United States	http://www.strokeassociation.org/
Australian Diabetes Society (ADS)	Australia	https://www.diabetessociety.com.au/
Australian Medical Association (AMA)	Australia	http://www.ama.com.au/web.nsf/
British Cardiac Society (BCS)	United Kingdom	http://www.bcs.com/pages/default.asp
British Hypertension Society (BHS)	United Kingdom	http://www.bhsoc.org/default.stm
Canadian Diabetes Association	Canada	http://guidelines.diabetes.ca/
Canadian Hypertension Society (CHS)	Canada	http://www.hypertension.ca/
Canadian Task Force on Preventive Health Care (CTFPHC)	Canada	http://canadiantaskforce.ca/
Cardiac Society of Australia and New Zealand (CSANZ)	Australia	http://www.csanz.edu.au/
Centers for Disease Control and Prevention (CDC)/ AHA	United States	http://www.cdc.gov/
Department of Health (DOH)	United Kingdom	http://www.dh.gov.uk/en/index.htm
European Society of Cardiology	Europe	http://www.escardio.org/
International Diabetes Federation (IDF)	International	http://www.idf.org/
International Society of Hypertension	International	http://www.ish-world.com/
National Health and Medical Research Council (NHMRC)	Australia	http://www.nhmrc.gov.au/index.htm
National Heart Foundation	Australia	http://www.heartfoundation.org.au/index.htm
National Heart Lung and Blood Institute	United States	http://www.nhlbi.nih.gov/guidelines/index.htm
National Institute for Health and Clinical Excellence (NICE)	United Kingdom	http://www.nice.org.uk/
New Zealand Guidelines Group	New Zealand	http://www.nzgg.org.nz/index.cfm?
Royal College of General Practitioners (RCGP)	United Kingdom	http://www.rcgp.org.uk/default.aspx

Appendix Table 1: Website searches of guideline development organizations, including websites affiliated with all the guidelines included in our previous publication (continued)

Organization Responsible for Guideline Development	Country	Website Searched
Scottish Intercollegiate Guidelines Network (SIGN)	United Kingdom	http://www.sign.ac.uk/
U.S. Preventive Services Task Force (USPSTF)	United States	http://www.ahrq.gov/clinic/uspstfix.htm
World Heart Federation	International	http://www.world-heart-federation.org/
World Health Organisation (WHO)	International	http://www.who.int/en/
World Hypertension League	International	http://www.worldhypertensionleague.org/Pages/Home.aspx
International Diabetes Federation European Region	International	http://diabetespreventionforum.org/index.php/projects/6-image-project

Appendix Table 2. Recommendations for Screening for Dysglycemia in 6 Guidelines

	DAGDC	CDA	ADA	USPSTF	NICE PH38	CTFPHC	ESC
Country	Australia	Canada	USA	USA	UK	Canada	Europe
Year	2009	2013	2016	2015	2012	2012	2013
AGREE 2 Score	87%	83%	82%	76%	73%	68%	66%
Method to evaluate evidence	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review
Methods to formulate recommendations	Formal consensus	Formal consensus	Formal consensus	Consensus	Consensus	Formal consensus	Formal consensus
Consideration of costs	Review of CEA studies	Review of CEA studies	Review of CEA studies	Review of CEA studies	Review of CEA studies	Systematic review of published literature/ Performed CEA	NR
Target Group	All adults aged ≥40y or Aboriginal & Torres Strait Islanders >=18y	All adults aged ≥40y or high risk groups using risk calculator	All adults over 45 y or all Adults with BMI ≥25 (or ≥23 kg/m2 in Asian Americans) and 1 additional DM risk factor	Adults aged 40-70 y with BMI ≥25	> 40 y; 25-39 y South Asian, Chinese, Black with high risk scores	Asymptomatic adults	FINDRISC ≥ 15/26 (high risk for DM)
Strategy	Opportunistic screening	Opportunistic screening/ case finding	Opportunistic screening/ case finding	Opportunistic screening	Opportunistic screening including during NHS Health Checks; case finding/ record based	Opportunistic screening	Case finding/ Patient completed questionnaire based information
Strength of recommendation	For	For	For	For - moderate overall benefit for screening and implementing intensive lifestyle intervention	For - only in high risk groups	For - only in high risk groups	For - only in high risk group

Appendix Table 2. Recommendations for Screening for Dysglycemia in 6 Guidelines (continued)

	DAGDC	CDA	ADA	USPSTF	NICE PH38	CTFPHC	ESC4
Major risk factors prediction model	Diabetes risk assessment, e.g. AUSDRISK >= 15 high risk	Diabetes risk assessment	Diabetes risk assessment	NR	Diabetes UK score	FINDRISC, 10 y DM risk or other validated risk score (e.g. CANRISK)	FINDRISC, 10 y DM risk
Age	✓1	✓1	✓1	✓1	✓1	✓1	✓1
Sex	✓1			✓1	✓1	✓1	✓1
Blood pressure			✓1				✓1
TC level							
HDL-C level	✓2	✓1	✓1				
TC:HDL-C ratio				✓1			
Smoking	✓1		✓1	✓1			
Glucose levels	✓2	✓1 (or HBA1C)	✓1		✓2 (or HBA1C)	✓2 (or HBA1C)	
Underlying risk factors							
Overweight/obesity	✓1	✓1	✓1	✓1	✓1	✓1	✓1
Physical inactivity	✓1		✓1	✓1		✓1	✓1
Atherogenetic diet						✓1	
Family history of premature CVD		✓1	✓1				
Genetic/racial factors	✓1	✓1	✓1	✓1	✓1	✓1	
Antihypertensive Therapy	✓1	✓1	✓1	✓1		✓1	✓1
Emerging risk factors							
TG levels	✓2	✓1	✓1				
Renal function							
Thresholds							
Aspirin	NR	Not routinely recommended. May be used in presence of other CVD risk factors	Consider if DM with 10 y ASCVD risk ≥10%. Consider aspirin in women ≥50 y. Clinical judgment required for antiplatelet use if <50 y with multiple risk factors and 10 y ASCVD risk 5-10%	Not recommended	NR	NR	Consider in high risk DM patients on an individual basis

Appendix Table 2. Recommendations for Screening for Dysglycemia in 6 Guidelines (continued)

	DAGDC	CDA	ADA	USPSTF	NICE PH38	CTFPHC	ESC4
Statins	NR	If found diabetic in men > 40 y; < 40 y with microvascular complications, diabetes for >15 y and >30 y old	Consider moderate or high intensity statin if DM and 40-75 y, DM and > 75 y or if DM and < 40 y with one or more other ASCVD risk factors (family history of premature ASCVD, hypertension, smoking, overweight or obese, LDL >100mg/dL; High intensity statin if 40-75 y with additional ASCVD risk factor. Moderate to high intensity statin if >75 y and additional ASCVD risk factors	NR	NR	NR	Very high risk; Severe renal disease, 1 other CVD risk factor or target organ damage and LDL-C >70mg/dL; T2DM and LDL-C >100mg/dL
Antihypertensives	NR	If found diabetic and BP>130/80 mmHg	DM and BP >140/90mmHg	NR	NR	NR	DM and BP >140/85mmHg
Intensive Lifestyle Counseling	IFG; IGT	IFG; IGT	IGT or IFG or A1C 5.7-6.4 mmol/L	For those with abnormal blood glucose (IGT, IFG or diabetes); BMI >25 kg/ m2 and additional CVD risk factors; BMI ≥ 30 kg/ m2	High risk and IFG/HBA1C 42 -47	NR	High risk for developing DM
High-risk Monitoring	Yearly if IFG/ IGT	Yearly if IFG/ IGT	Annual screening if IGT or IFG or A1C 5.7-6.4 mmol/L	NR	Every year if high risk and IFG or HBA1C 42 -47 mmol/mol	Annual screening if very high risk (e.g. FIND RISK >20)	Depending on clinical context

Appendix Table 2. Recommendations for Screening for Dysglycemia in 6 Guidelines (continued).

	DAGDC	CDA	ADA	USPSTF	NICE PH38	CTFPHC	ESC4
Screening Intervals	3 y; annual if IFG/IGT	3 y; annual if IFG/IGT	3 y if normal; 6-12 postpartum if GDM then every 3 years if normal	3 y if normal glucose levels	At least 5 y starting with risk assessment tool for low risk; 3 yearly for those at moderate risk of diabetes	3- 5 y	NR

Appendix Table 3. Recommendations for Screening for Dyslipidemia in 2 Guidelines

	ESC	AACE
Country	Europe	USA
Year	2011	2012
AGREE 2 Score	72%	64%
Method to evaluate evidence	Systematic review	Review of published systematic reviews and RCTs; literature identified by panel members
Methods to formulate recommendations	Formal consensus	Formal consensus
Consideration of costs	NR	Review of CEA studies
Target Group	DM, hypertension, smokers, BMI ≥ 30, FHx premature CVD, FHx of familial hypercholesterolemias, CKD, Chronic inflammatory conditions, Men > 40 y, Women >50 y or post menopausal	Aged ≥ 20 y
Strategy	Opportunistic screening/ case finding	Opportunistic screening/ case finding
Strength of recommendation	For	For
Major risk factors prediction model	SCORE, general ASCVD mortality at 10 y	Framingham/ Reynolds Risk Score, CHD/stroke at 10 y
Age	✓1	✓1
Sex	✓1	✓1
Blood pressure	✓1	✓1
TC level	✓1	✓1
LDL-C level	✓1	✓1
HDL-C level	✓1	✓1
TC:HDL-C ratio	✓1	✓1
Smoking	✓1	✓1
Underlying risk factors		
Family history of premature CVD		✓1
Diabetes		✓1
Emerging risk factors		
TG levels	✓1	✓2
Apo lipoprotein/lipoprotein levels	✓2	✓2
Glucose therapy for insulin resistance		✓1
Prothrombotic markers		✓3
C-reactive protein level		✓3
Thresholds		
Aspirin	NR	NR
Statins	10 y CVD mortality risk ≥10% and LDL-C level ≥70 mg/dL; 10 y CVD mortality 5%-9% and LDL-C level ≥100 mg/dL; (Type 1 DM or Type 2 DM) and LDL-C level ≥70 mg/dL; very high CV risk (Type 2 DM, Type 1 DM with target organ damage, CKD)	Treat to target based on personalized risk LDL-C to < 100mg/dL if average or elevated LDL; other parameters based on target levels
Antihypertensives	NR	NR
Intensive Lifestyle Counseling	10 y CVD mortality >1% or LDL-C > 100mg/dL	10 y risk ≥20%
High-risk Monitoring	NR	NR
Screening Intervals	NR	Every 5 y if risk aged ≥ 20 y, every 1-2 y if aged ≥45 male or aged ≥55 y female

Abbreviations: ABI, ankle brachial index; ASCVD, atherosclerotic cardiovascular disease; CEA, cost-effectiveness analysis; CHD, coronary heart disease; CKD, chronic kidney disease; CVD,

cardiovascular disease; DM - diabetes mellitus; FHx, family history; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NR, not reported; RCT, randomized controlled trial; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; y, years;
✓1, Formal screening test (included in the prediction model);
✓2, Additional screening test
✓3, In selected individuals who are not in 1 of the 4 main statin benefit groups, and for who a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision-making. These factors include; 1. Primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias, 2. First degree relative with premature ASCVD, 3. High-sensitivity C-reactive protein >2 mg/L, 4. CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity, 5. Ankle-brachial index <0.9, or 6. Elevated lifetime risk of ASCVD.

Appendix Table 4. Recommendations for Screening for Hypertension in 2 Guidelines

	CHEP	USPSTF	CTFPHC
Country	Canada	USA	Canada
Year	2015	2015	2013
AGREE 2 Score	90%	79%	78%
Method to evaluate evidence	Systematic review	Systematic review	Systematic review
Methods to formulate recommendations	Formal consensus	Consensus	Consensus
Consideration of costs	NR	NR	NR
Target Group	All adults	≥ 18 y with increased risk of high BP: high-normal blood pressure (130–139/85–89 mm Hg), overweight or obese, and African Americans	≥ 18 y
Strategy	Opportunistic screening at 'appropriate visits'	NR	Opportunistic screening at 'appropriate visits'/ case finding
Strength of recommendation	For	For	For
Major risk factors prediction model	SCORE - Canada, general ASCVD mortality at 10 y	NR	NR
Age	✓1	✓1	✓1
Sex	✓1		
Blood pressure	✓1	✓1	✓1
TC level	✓1		
HDL-C level	✓1		
Smoking	✓1		
Underlying risk factors			
Overweight/obesity	✓1	✓1	
Physical inactivity	✓1		
Atherogenetic diet	✓1		
Family history of premature CVD			
Genetic/racial factors		✓1	✓1
Diabetes	✓1		
Emerging risk factors			
Renal function	✓1		
Subclinical atherosclerosis	LVH/ resting ECG		LVH/ resting ECG
Thresholds			
Aspirin	Consider if ≥ 50 y and hypertensive	NR	NR
Statins	If 3 or more of - (male/ ≥55 y/ smoking/ Type 2 DM/ Total-C/HDL-C ration ≥ 6/ FHx CVD/ LVH/ ECG abnormalities/ Microalbuminuria/ PVD	NR	NR
Antihypertensives	If found diabetic and BP>130/80mmHg; High-risk for diabetes and BP >140/90;Low-risk and BP >160/100; ≥ 80 y and systolic >160	NR	NR
Intensive Lifestyle Counseling	In all with hypertension	NR	NR

Appendix Table 4. Recommendations for Screening for Hypertension in 2 Guidelines (continued)

	CHEP	USPSTF	CTFPHC
High-risk Monitoring	Annual if BP high normal (≥ 130/85)	Annually if ≥40 y and at increased risk for high BP	Annual if BP high normal (≥ 130/85)
Screening Intervals	NR	Annually if ≥40 y and at increased risk for high BP. Every 3 to 5 y if 18 to 39 y with normal BP (<130/85 mm Hg) and not other risk factors.	Further risk assessment based on clinical judgment

Abbreviations: ABI, ankle brachial index; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM - diabetes mellitus; FHx, family history; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NR, not reported; PVD, peripheral vascular disease; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; US, ultrasound; y, years;
✓1, Formal screening test (included in the prediction model);

Appendix Figure 1.