PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION

Screening for Cardiovascular Disease

PERIODIC HEALTH EXAMINATION TASK FORCE 2021

DISCLAIMER

This guideline is intended mainly for use by clinicians, particularly primary care physicians, who take care of individuals at the outpatient setting. Primary care physicians refer to practitioners of general pediatrics, general internal medicine, family medicine, or other subspecialties who provide either first-contact guidance for undiagnosed health conditions or continuing care for existing medical conditions. Although adherence to this guideline is encouraged, it should not supplant but rather supplement the healthcare provider's sound clinical judgment.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but this document should not be the sole basis for evaluating insurance claims. Recommendations from this guideline should not also be treated as strict rules on which to base legal action.

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ABBREVIATIONS AND ACRONYMS

Acronyms	Acronyms full name
AAA	Abdominal aortic aneurysm
ABI	Ankle brachial index
ACAS	Asymptomatic carotid artery stenosis
ACC	American College of Cardiology
ACE-I	Angiotensin converting enzyme inhibitor
ACTS-2	Second Asymptomatic Carotid Surgery Trial
AF	Atrial fibrillation
AHA	American Heart Association
ALI	Acute limb ischemia
ALT	Alanine transaminase
APO-B	Apolipoprotein-B
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
CAD	Coronary artery disease
CASCADE-FH	Cardiovascular Disease Burden and Treatment Patterns Among Patients with Familial Hypercholesterolemia
CEA	Carotid endarterectomy
CLI	Critical Limb Ischemia
CVD	Cardiovascular/Cerebrovascular disease
CTA	Computer tomography angiography
DOH	Department of Health
DUS	Doppler ultrasound
DLCN	Dutch Lipide Clinic Network
ESC	European Society of Cardiology
ECG	Electrocardiography
ESVS	European Society for Vascular Surgery
FH	Familial hypercholesterolemia
FNRI	Food and Nutritional Research Institute
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
HR	Hazards Ratio
ICER	Incremental cost-effectiveness ratio
IHD	Ischemic Heart Disease
JBS	Joint British Societies
LDL-C	Low density lipoprotein-cholesterol
LDL-R	Low density lipoprotein receptor
MI	Myocardial ischemia
MRA	Magnetic resonance angiography
NIH	National Institutes of Health
OR	Odds ratio
PAD	Peripheral arterial disease
PALY	Productivity adjusted life year
PCSK-9	Proprotein convertase subtilisin/kexin-9
PAFP	Philippine Academy of Family Physicians
PCP	Philippine College of Physician
PHA	Philippine Heart Association
PLAS	Philippine Lipid and Atherosclerosis Society
PMA	Philippine Medical Association
PNA	Philippine Neurological Association

PNA	Philippine Nurses Association
PSGIM	Philippine Society of General Internal Medicine
PSH	Philippine Society of Hypertension
PSVM	Philippine Society of Vascular Medicine
QALY	Quality adjusted life year
RCT	Randomized controlled trial
RF	Risk factor
USPSTF	United States Preventive Services Task Force
VAC	Veterans Affairs Cooperative Study

ACKNOWLEDGMENT

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This project would not have been possible without the initiative and financial support from the DOH. The DOH neither imposed any condition nor exerted any influence on the operations and the final output formulation.

The NIH-ICE undertook extensive technical work in (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel discussion, and documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups, and committees, and facilitating the *en banc* meeting. The CPG Central Steering Committee and the Task Forces Steering Committee were responsible for overall organization and management and is accountable for the quality of the CPG.

Lastly, this guideline is invaluable because of the contribution and participation of panelists from different sectors of healthcare who committed their time and effort to share their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences in formulating the recommendations with consideration of patients and the current healthcare system in the country.

Queries, suggestions, and other concerns regarding this CPG may be directed to the DOH National Practice Guidelines Program office by email (egmd@doh.gov.ph) or to DOH-HPDPB and UP-NIH.

EXECUTIVE SUMMARY

This Clinical Practice Guideline for the Periodic Health Examination (Cardiovascular disease) is an output from the joint undertaking of the Department of Health and National Institutes of Health- Institute of Clinical Epidemiology.

This clinical practice guideline is a systematic synthesis of evidence to address screening for familial hypercholesterolemia, coronary artery disease, asymptomatic carotid artery stenosis, peripheral arterial disease, abdominal aortic aneurysm and atrial fibrillation among asymptomatic, apparently healthy adult Filipinos . The CPG provided **twelve (12)** recommendations on prioritized questions in the screening for certain disease conditions.

Recommendations are based on the appraisal of the best available evidence on each of the six identified clinical questions. The CPG is intended to be used by general practitioners and specialists in the primary care setting, policy makers, employers and administrators, allied health practitioners and even patients. The guideline development process followed the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation or the GRADE approach including GRADE Adolopment1 , a systematic process of adapting evidence summaries and the GRADE Evidence to Decision or EtD2 framework. It included 1) identification of critical questions and critical outcomes, 2) retrieval of current evidence, 3) assessment and synthesis of the evidence base for these critical questions, 4) formulation of draft recommendations, 5) convening of a multi-sectoral stakeholder panel to discuss values and preferences and assess the strength of the recommendations, and 6) planning for dissemination, implementation, impact evaluation and updating.

The recommendations in this CPG shall hold and will be updated after 3 years or when new evidence arise.

1 Schunemann H, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa R, Manja V. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-10.

2 Schunemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76:89-98.

SUMMARY OF RECOMMENDATIONS

Recommendation	Certainty of Evidence	Strength of Panel Recommendation
Question 1. Should screening for familial hypercholesterolemia be done using family history of premature cardiovascular disease and physical examination for stigmata be done among apparently healthy, asymptomatic adults?		
1.1 Among asymptomatic apparently healthy adults, we recommend screening for family history of premature cardiovascular disease to diagnose familial hypercholesterolemia	Low	STRONG
1.2 Among asymptomatic apparently healthy adults, we recommend screening for stigmata through physical examination to diagnose familial hypercholesterolemia	Low	STRONG
Question 2. Should screening for coronary artery disease be done using resting or stress echocardiography among apparently healthy, asymptomatic adults?		
2.2 Among asymptomatic apparently healthy adults, we recommend against screening for coronary artery disease using resting echocardiography	Moderate	STRONG
2.2 Among asymptomatic apparently healthy adults, we recommend against screening for coronary artery disease using stress echocardiography	Moderate	STRONG
Question 3. Should screening for carotid artery stenosis be done using carotid bruit auscultation or carotid artery ultrasound among apparently healthy, asymptomatic adults?		
3.1 Among asymptomatic apparently healthy adults, we recommend against screening for asymptomatic carotid artery stenosis using carotid bruit auscultation.	Low	STRONG

3.2 Among asymptomatic healthy adults, we recommend against screening for asymptomatic carotid artery stenosis using carotid ultrasound.	Low	STRONG
Question 4. Should screening for peripheral arterial disease be done using pulse palpation or ankle-brachial index measurement among asymptomatic apparently healthy adults?		
4.1 Among asymptomatic apparently healthy adults, we recommend against routine screening for peripheral arterial disease using pulse palpation	Low	STRONG
4.2 Among asymptomatic apparently healthy adults, we recommend against routine screening for peripheral arterial disease using a Doppler ABI	Low	STRONG
Question 5. Should screening for abdominal aortic aneurysm (AAA) be done using abdominal ultrasonography among asymptomatic apparently healthy, asymptomatic adults?		
5.1 Among asymptomatic men aged 60 to 80 years old, we recommend one-time screening for abdominal aortic aneurysm using ultrasonography	Moderate	STRONG
5.2 Among asymptomatic women, we recommend against screening for abdominal aortic aneurysm using ultrasonography.	Low	STRONG
Question 6. Should screening for atrial fibrillation be done using pulse palpation or 12-lead electrocardiography (ECG) among asymptomatic, apparently healthy adults?		
6.1 Among asymptomatic, apparently healthy adults, we recommend against screening for atrial fibrillation using pulse palpation	Moderate	STRONG

6.2 Among asymptomatic, apparently healthy adults, we recommend against screening for atrial fibrillation using single determination 12-lead electrocardiography (12L ECG)	Low	STRONG

1. INTRODUCTION

The Philippine Guidelines on Periodic Health Examination (PHEX) was first published in 2004.(1) It was a comprehensive appraisal and synthesis of evidence on screening interventions committed to providing early prevention services among apparently healthy Filipinos. It was a long-awaited publication and the first to offer evidence-based recommendations for screening tests made possible through the concerted effort of various medical and paramedical organizations composed of more than a hundred experts, researchers, and stakeholders.(1) It was inspired by the Canadian and the US Preventive Services Task Forces, but it was tailored to the Philippine setting.

Due to the evolving technology, scientific evidence, and health policies, there is a pressing need to update this guideline. This 2021 Philippine Guidelines will support the objectives stated in the Universal Health Care Act(2) that all Filipinos are given access to quality and affordable medical services, including primary care benefits.

In the guideline development, evidence-based recommendations for the prioritized health screening were formulated using the GRADE Evidence-to-Decision (EtD) framework.(4, 5) The EtD framework aims to facilitate the adaptation of recommendations and decisions of experts and stakeholders based on specific contexts, essential health outcomes, benefits, and harms while looking through the equity, applicability, and feasibility lenses.

The evidence collated to answer the research questions on screening tests are used in formulating the recommendations. They can be classified into two: (1) screening for a risk factor and (2) screening for early disease. Screening for the former is directed towards determining the effective management of the condition as a risk factor, and screening for the latter is focused on the performance of the tests that will be used to detect and subsequently treat that early disease and prevent it from progressing.

Health screening also carries potential harm, for example, mislabeling the person as being ill. It can pose a threat to the psychological, social, or physical well-being and even to the individual's financial stability. Because of these probable adverse effects of screening, criteria are set to determine if screening for a particular condition can be beneficial and pragmatic. The voting panel members used these criteria (5) aligned with the EtD framework: (1) burden of illness must be high, (2) screening tests must be accurate enough, (3) early treatment must be more effective than late treatment, (4) confirmatory tests and early management must be safe and available, and (5) costs of screening must be proportional with the potential benefit.

Aside from the regulatory agencies and policymakers in the national government, the target users of this guideline on screening strategies include primary care providers, general physicians, specialists, training institutions, payors, patients, the general public, and industry partners

References

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2. SCOPE & PURPOSE

Cardiovascular disease is the number cause of death in the country today. Several factors come into play when dealing with cardiovascular disease and factors related to the environment and change in lifestyle are the biggest culprit. Cigarette smoking, diabetes mellitus, elevated cholesterol, obesity, and physical inactivity are some of the identified factors that can lead to CV death. Early identification of these factors and addressing them may lessen the burden of cardiovascular diseases in the country.

Thus, the need to see the importance of screening in individuals for cardiovascular diseases. This consensus statement covers screening for cardiovascular diseases among apparently healthy, asymptomatic adult Filipino individuals. Such individuals are generally regarded to have no overt symptoms of cardiovascular disease, such as chest pain, difficulty of breathing, or claudication, among others. The consensus panel also defined this individual as devoid of modifiable risk factors such as cigarette smoking, hypertension, and diabetes. The critical cardiovascular outcomes include cardiovascular mortality, all-cause mortality, fatal and non-fatal myocardial infarction, and cerebrovascular disease.

3. GUIDELINE DEVELOPMENT METHODOLOGY

3.1 Organization of the Process

Following the international standards, the DOH (1) outlined the guideline development process into four phases: 1) preparation and prioritization, 2) CPG generation, 3) CPG appraisal, and 4) implementation in the Manual for CPG Development [1].

In the preparation and prioritization phase, the Steering Committee set the CPG objectives, scope, target audience, and clinical questions. They consulted different stakeholders in prioritizing and developing the guideline questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included.

The evidence review experts (ERE) or the technical working group were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the consensus panel members to finalize the recommendations.

The consensus panel comprised of multisectoral representatives tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, they prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations and voted on each

recommendation and its strength. They participated in a modified Delphi activity to decide on recommendations that were not resolved during the *en banc* meeting.

3.2 Creation of the Evidence Summaries

The clinical questions were developed using the PICO (population, intervention, comparator and outcome) format. The ERE searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, National Institute for Health and Care Excellence. If the CPG were of good quality and done within 5 years (2016-2021), the evidence summaries of the CPG were adopted.

Initially, the following cardiovascular risk factors and diseases identified to be part of the PHEX include hypertension, dyslipidemia, atrial fibrillation, carotid artery stenosis (CAS), coronary heart disease, peripheral artery disease (PAD), and abdominal aortic aneurysm (AAA). An initial set of questions were drafted by the reviewers based on the selected topics of interest. During the deliberation, the reviewers and central committee noted there are some gaps in the management of dyslipidemia, particularly in Familial Hypercholesterolemia management. For the second phase of the PHEX CV, the diseases were addressed: Familial Hypercholesterolemia, Atrial Fibrillation, Coronary Artery Disease, Carotid Artery Stenosis, Peripheral Artery Disease, and Abdominal Aortic Aneurysm.

The results of the appraisal of existing CPGs and their evidence summaries determined the need for a systematic search in electronic databases (MEDLINE via PubMed, CENTRAL, Google Scholar) for the need to do de-novo systematic reviews and meta-analysis for each question. All searches were done from May to Nov. of 2021. Details on the time periods were discussed under the specific questions. Please see evidence summaries in Appendices. Relevant local databases and websites of medical societies were also utilized in the search. Keywords were based on PICO (MeSH and free text) set for each question. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. The search strategy and inclusion criteria were based on the PICO question and are included in their respective evidence summaries. Evidence reviewers appraised the directness, methodological validity, results, and applicability of each relevant article included. RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE generated evidence summaries for each of the sixteen (16) questions. Each evidence summary included evidence on the burden of the problem, and diagnostic performance, benefits, harm, and social and economic impact of the screening test/intervention. Evidence/information that will facilitate in the decision (i.e. cost of screening test, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The Quality of Evidence was assessed using the GRADE approach. (2)

The important step in the creation of this clinical practice guidelines (CPGs) is determining the strengths of the recommendation. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used in assessing the recommendations. The SC and the ERE identified the outcomes that were used in deciding the recommendations for the clinical questions (Table 1).

Table 1. Cardiovascular Outcomes GRADE Score

Outcomes	Score Priority	Rank
Cardiovascular Mortality	9	Critical
All cause Mortality	9	Critical
Fatal and non-fatal MI	9	Critical
Stroke or Cerebrovascular disease	9	Critical
Lower limb amputation	8	Critical
MACE	7	Important
Coronary Revascularization	7	Important
Unstable Angina	7	Important
Chronic stable angina	7	Important
Peripheral arterial revascularization	6	Important
Carotid/cerebrovascular revascularization	6	Important
Heart failure	6	Important
Repair of aneurysm	6	Important
Lower limb revascularization	6	Important
Acute limb ischemia	6	Important
Reduction of laboratory parameters (eg: LDL, troponin, BNP reduction)	5	Important
Symptom reduction	4	Important

Table 2. Basis for Assessing the Quality of the Evidence using GRADE Approach

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Factors that lower quality of the evidence are:

- Risk of bias
- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

3.3 Composition of the CPG Panel

The Steering Committee convened the Consensus Panel (CP), considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual (1). Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different settings (e.g., public primary care settings, private practice, occupational health settings). The physicians were members of the different medical societies namely; Philippine College of Physicians, Philippine Heart Association, Philippine Lipid and Atherosclerosis Society, Philippine Society of Hypertension, Philippine Neurological Association and Philippine Society of Vascular Medicine. In the choice of CP, the task force made sure that all stakeholders were part of the target population for the CPGs (See PERIODIC HEALTH EXAMINATION TASK FORCE ON CARDIOVASCULAR DISORDERS).

3.4 Formulation of the Recommendations

Draft recommendations were formulated based on the quality of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps. Prior to the series of online consensus panel meetings, the consensus panel received the draft recommendations together with evidence summaries based on the EtD framework shown in Table 3. These recommendations, together with the evidence summaries, were presented during the *en banc* meeting.

Table 3.Detailed considerations based on the EtD framework (3)

1. Is the problem a priority?
2. How accurate is the test?
3. How substantial are the desirable anticipated effects?
4. How substantial are the undesirable anticipated effects?
5. What is the certainty of the evidence of test accuracy?
6. Is there important uncertainty about or variability in how much people value the main outcomes, including adverse effects and burden of the test and downstream outcomes of clinical management guided by the test results?
7. Does the balance between desirable and undesirable effects favor the test or the comparison?
8. How large are the resource requirements (costs)?
9. What is the certainty of the evidence of resource requirements (costs)?
10. Does the cost-effectiveness of the test favor the test or the comparison?
11. What would be the impact on health equity?
12. Is the test acceptable to key stakeholders?
13. Is the test feasible to implement?

The strength of each recommendation (i.e. strong or weak) was determined by the panel considering all the factors mentioned above. Strong recommendation means that the panel is “confident that the desirable effects of adherence to a recommendation outweigh

the undesirable effects" while weak recommendation means that the "desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident." (4)

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed. (2) If consensus was not reached in the first voting, questions, and discussions were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based draft recommendations were also revised based on input arrived at by consensus in the *en banc* discussions.

3.5 Managing Conflicts of Interest

The Central Executive Committee convened an Oversight Committee (OC) whose task was to thoroughly review the declaration of conflict of interest (DCOI) of each of the Task Force members particularly the Consensus Panelists (CP) and make recommendations on how to manage the COI. For TF members with potential significant COIs, the member of OC conducted additional investigations with due diligence to ensure the integrity of the CPG process and the final recommendations.

All task force members submitted a DCOI and their curriculum vitae (CV) prior to the initiation of guideline development process. The disclosure included a 4-year period of personal potential intellectual and/or financial conflicts of interest (COI).

Management of the COI of the Consensus Panel, Technical Coordinators, and Task Force Steering Committees were deliberated and decided by the OC, using the pre-agreed criteria. A full description of the methods can be found in the Final Technical report.

Those with significant potential COI were either not allowed to join or vote depending on the COI. See Conflict of Interest Declaration at the end of the document.

3.6 External Review Process

The CPG was reviewed by independent stakeholders who were not members of the Task Force. The CPG was also presented in meetings and conferences of relevant societies for their comments and suggestions.

3.7 Planning for Dissemination and Implementation

The SC discussed with relevant stakeholders such as DOH and PhilHealth to prepare a dissemination plan that will actively promote the adoption of this guideline with strategies for copyrights. Suggestions ranged from making guidelines available on websites, press conferences, social media sites, professional society conventions, and journal publications.

References

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2. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6. doi: 10.1016/j.jclinepi.2010.07.015. Epub 2011 Jan 5. PMID: 21208779.
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4.RECOMMENDATIONS AND PANEL DISCUSSION

4.1 Screening for Familial Hypercholesterolemia

RECOMMENDATIONS

1. **Among asymptomatic apparently healthy adults, we recommend screening for family history of premature cardiovascular disease* to diagnose familial hypercholesterolemia *(STRONG recommendation, low level of evidence)***

2. **Among asymptomatic apparently healthy adults, we recommend screening for stigmata** through physical examination to diagnose familial hypercholesterolemia *(STRONG recommendation, low level of evidence)***

**premature cardiovascular disease is defined as occurrence of cardiovascular events (myocardial infarction, ischemic stroke, peripheral arterial disease or sudden cardiac death) before the age of 55 years in males and 65 in females*

***stigmata are pathognomonic findings of familial hypercholesterolemia such as corneal arcus in those aged 45 years or younger, tendon xanthoma, xanthelasma*

Considerations

The consensus panel considered the following when formulating this recommendation:

- Lipid disorder is a priority in a periodic health examination.
- There is a need to have another pathway in identifying the stigmata of FH in the primary care setting

4.1.1 Burden of disease

Epidemiology

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder caused by mutations of the low density lipoprotein receptor (LDLR), apolipoprotein B (APOB) and the proprotein convertase subtilisin/kexin 9 (PCSK9) genes, encoding for the receptors and ligands necessary in lipoprotein synthesis. These genetic mutations lead to very high levels of LDL-C at ≥ 190 mg/dl, above the 95th percentile for age and sex. They also exhibit phenotypic manifestations which are pathognomonic of FH, such tendon xanthomas which are white or yellow lumps of cholesterol deposits seen in the knuckles or Achilles tendon; xanthelasmas described as yellowish deposit of lipid material at the eyelid or medial canthus area and/ or; corneal arcus which is a circular white-grey deposit of lipid material in the edge of the cornea seen among patients ≤45 years old.

In a meta-analysis involving 11 million individuals, the global prevalence of FH is 1 : 313 in the general population, which is 20-fold higher among those with premature ischemic heart disease (IHD) and 23-fold higher among those with severe

hypercholesterolemia. In the Asian population, the prevalence is at 1 : 520 which is lower compared to other ethnic origins, but showed the similar trends in comparison with premature IHD and severe hypercholesterolemia as the general population.(1). Physical stigmata of FH were noted in Asian and Southeast Asian populations. Tendon xanthomas were seen in 9.8% to 87%, xanthelasmas in 9% to 25.3% while corneal arcus was seen in 16% to 72% of the populations (3). These stigmata often lead to manifestations of cardiovascular events as early as in their 20s to 30s. If left untreated, there is a 13.2-fold increase in coronary heart disease (4), 3.6-fold increase in peripheral arterial disease and 1.42-fold increase in ischemic stroke (5) and almost 400-fold increase risk in cardiovascular mortality. (6).

A local study done in a clinic setting noted that 20% of patients with features of FH based on the Dutch Lipid Clinic Network criteria have mutations in the LDL-R gene (2). The odds of having LDL-R gene mutation was twice for those with family history of coronary artery disease while thrice for those with arcus cornealis and tendon xanthomas. (2) There are no local prevalence studies available.

Natural Course of the Disease
FH is an inherited autosomal disorder resulting in very high levels of LDL-C. It is further subdivided into two phenotypes; namely heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH). HeFH is the more common type which is usually inherited from 1 parent. Plasma LDL-C levels range between 5 to 13 mmol/L (190 to 500 mg/dL). (7) It is generally a silent disease and therefore underdiagnosed.(8) In the CASCADE-FH registry from 11 US lipid clinics, the mean age of diagnosis was at 47 years old wherein one third of them had already developed their first cardiovascular event. (9) If left untreated, HeFH patients tend to experience their first coronary event 20 years earlier than the general population. Cumulative risk of coronary artery disease at age 60 increases to 52% in males and 33% in females. (10) HoFH on the other hand is rare and is characterized by extremely high LDL-C levels of ≥13 mmol/L (≥500 mg/dL). It usually arises from mutation causing alleles which are within the same gene. Due to their prolonged exposure from very high LDL-C levels from birth, cutaneous/tendon xanthomas and CV events occur earlier during adolescence. Cholesterol can also deposit in the aortic root and valve cusps resulting to supravalvular aortic stenosis in their first to second decade of life. They rarely survive beyond their second decade. (11)

Management
Life expectancy of patients with FH is decreased and necessitates early treatment. The primary target of treatment is lowering of LDL-C levels. Untreated high cumulative LDL-C levels such as that seen in FH is strongly associated with premature atherosclerosis leading cardiovascular events. (12).

In the Philippine 2020 Clinical Practice Guidelines on the Management of Dyslipidemia, a strong recommendation is given to start a high intensity statin therapy which can lower down LDL-C levels to 50% to achieve a target LDL-C to < 70 mg/dL or lower to prevent cardiovascular events. (13). In the other guidelines, such as that from the European Society of Cardiology (ESC) and American College of Cardiology/ American Heart Association (ACC/AHA), if the goal LDL-C is not reached or for those who are statin-intolerant, ezetimibe and/ or PCSK9 inhibitors can be given in

combination or as an alternative treatment, with a recommendation of I-C and IIb B-R, respectively. (14,15)

Economic impact of the disease
Cardiovascular disease in FH individuals happen early in their life during their productive years. In a study from Australia, it was estimated that there is a 2% decrease in years of life lived. Due to its increased risk for morbidity and mortality there is an average 0.6 productivity-adjusted life years (PALYs) lost per full-time worker. Identifying and treating these patients early on would lead to a prevention of loss of PALYs. (16) There are no cost effective studies done in the Philippines.

Social impact of the disease
Since it is an inheritable disease, a diagnosis of FH may create a stigma to the patient and to their families. It creates a fear of losing a loved one early. Major life choices may also be affected. In a survey done in France, some patients excluded having a child into their lives because of all the risks and uncertainties that the illness brings with it. (17)

4.1.2 Benefits and Harms of Screening Tests

There were no studies looking into screening versus no screening for FH. The dictum is once a proband is identified, cascade screening to their first degree relatives must be done in order to start early treatment on those relatives with the genetic mutation. However, there were cohort studies of FH patients associating family history of premature CVD and presence of stigmata to cardiovascular events since these are component parts of the various criteria used to diagnose FH. In a cohort study from lipid clinics in Netherlands, 1st degree relatives of the 113 identified FH patients were screened. Mortality risk of all relatives from families with premature coronary artery disease (CAD) was higher compared to those without premature CAD, (HR 1.46, 95% CI 1.09-1.94, p= 0.01) (18). In a meta-analysis of seven observational studies that included genetically confirmed FH patients, the frequency of CVD in the those with xanthomas was higher compared to those without xanthomas (OR 3.2, 95% CI 2.12 – 4.82, p<0.01). (19) There were no studies looking into harms related in probing for premature CVD and looking for physical stigmata of FH. Genetic counseling prior to testing is important to address sensitive family and ethical issues. Education of health professionals and the general public will be helpful to avoid discrimination among those people who were tested positive. (20,21)

We also looked into the efficacy and safety of treatment of FH patients. There are no randomized placebo-controlled statin trials looking into its effect on CVD reduction among FH patients probably because for ethical reasons since disease manifestations occur in the early decades of life. Statins are the primary treatment for FH. There were two good quality cohort studies from the Netherlands (22) and South Africa (23) that looked into the effect of statins versus no statins on mortality and major adverse cardiovascular events (MACE). The study from the Netherlands used age- and sex-matched participants from the Rotterdam study while that from South Africa used homozygous FH patients pre-1990s when no lipid lowering therapy was available yet to act as the placebo arm for both of these studies. In the study of Versmissen from the Netherlands, coronary heart disease mortality was decreased by 76% with statin therapy (HR 0.24, 95% CI 0.18-0.24, p<0.001). In the report of Raal from South Africa

mortality was decreased by 66% (HR 0.34, 95% CI 0.14-0.86, p=0.02) and MACE was decreased by 51% (HR 0.49, 95% CI 0.22-1.07, p=0.07) in those taking statins.

Since treatment should be started early in life, there is a meta-analysis of 9 randomized placebo-controlled trials (RCTs) looking into the efficacy and safety of statin treatment as a lipid lowering agent among FH children and adolescents. (24) These RCTs included patients between 6 to 17 years old using mostly moderate-intensity statin therapy. With regards to effectiveness, statins were able to reduce mean LDL-C, total cholesterol and triglyceride levels and increased HDL-C. There were no safety issues seen in the use of statins in these age groups. The summary of evidence on the benefits and harms of statins among children and adolescent is shown in the table below.

As in the Phase 1 of PHEX, screening for lipid disorder with a lipid profile test was recommended among those asymptomatic, apparently healthy adults aged 40 to 75 years old. This was given a conditional recommendation even with a low certainty of evidence since statin treatment led to a significant reduction of cardiovascular events among these individuals based on a meta-analysis from 19 randomized controlled trials. This treatment effect was also seen regardless of sex, race, lipid level and other factors.

Table 4. Critical Cardiovascular Outcomes in Familial Hypercholesterolemia

Outcomes	No. of studies	RR (95%CI)	Absolute MD (95%CI)	Certainty of Evidence
All cause Mortality	1 cohort study	66% (HR 0.34, 95% CI 0.14-0.86, p=0.02)		Low
CV mortality	1 cohort study	76% (HR 0.24, 95% CI 0.18-0.24, p<0.001		Low
MACE	1 cohort study	51% (HR 0.49, 95% CI 0.22-1.07, p=0.07)		Low
Reduction in LDL-C among pediatric patients	6 RCTs		-32.15 (-29.4 to -34.9)	Moderate
Elevation of ALT (> 3x ULN) among pediatric patients	4 RCTs	2.4 (0.29 – 19.85)		Very Low
Elevation of AST (>3x ULN) among pediatric patients	4 RCTs	2.03 (0.24 – 16.95)		Very Low

Myopathy: Change in creatine kinase levels (> 10x ULN) among pediatric patients	2 RCTs	0.67 (0.04 – 10.57)	Very Low

4.1.3 Diagnostic Performance of Screening Tests

There were no direct studies looking into diagnostic accuracy on screening for family history of premature cardiovascular disease and physical examination for stigmata alone to diagnose familial hypercholesterolemia. These aforementioned findings are component parts in different criteria used for FH which is usually coupled with low density lipoprotein cholesterol (LDL-C) levels. The commonly used criteria are the following: Dutch Lipid Clinic Network (DLCN) (25), Simon Broome(26), US Med Ped(27), and the Japanese FH management guideline criteria(28). In the widely used DLCN, presence of tendon xanthoma will give a score of 6 which is a probable FH. Genetic screening for LDL-R mutation, although confirmatory for the presence of FH, is not part of most diagnostic criteria except for the DLCN since it is not easily available and is expensive. However, the FH Foundation convened an international expert panel to assess utility of genetic testing and it recommends that it is a standard of care among definite or probable FH patients to facilitate definitive diagnosis. Pathogenic variants indicate higher cardiovascular risk, which indicates the potential need for more aggressive lipid lowering, increase in initiation of and adherence to therapy and, cascade testing of at-risk relatives.(29) Very high LDL-C levels of ≥190 mg/dL is the sine qua non for the diagnosis of FH. Lifetime exposure to these very high LDL-C levels is independently associated with worse prognosis. (30)

4.1.4 Cost Implication

Screening requires only a visit to a physician to look for these findings. Once these findings are confirmed, a lipid profile maybe recommended and the annual screening cost will amount to six hundred pesos (Php 600) per patient.

4.1.5 Equity, Acceptability, and Feasibility

Being a genetically inherited disease with the propensity to develop cardiovascular disease in their early lives, cascade screening in the family of these FH patients is done. Cascade screening is dependent on identifying a sufficient number of independent index cases, otherwise, detection will only be limited to a small number of families. (31) Once these patient are identified as FH, this may create some worry that they may suffer cardiovascular events in the future especially when they approach the age of their parent or relative who suffered or died from it. Although from a study in Sweden, these worries were brief and did not cause any psychological inconvenience in daily life. Being identified as FH made these patients more health conscious and often experienced guilt if they happen to eat something with a high fat content. Some women were worried that their medications might have an effect in them conceiving or in their pregnancy. Another challenge of these probands is informing and discussing the need for FH screening with their relatives and this depended on how close they were. This should be also guided by their physicians in

trying to encourage and persuade them to share information with their family.(32) It is therefore imperative to increase community awareness of this disease in order to lessen the psychological effects and stigmatization that this may bring.

Screening for FH was found to be cost-effective in Poland and in the UK. (33, 34) These benefits were owed to a reduced burden on the health system and prevention of hospitalization. It was also perceived that screening during childhood was the more efficient approach wherein it is still easy to treat and manage the condition. However, this will require education of the health professionals and provision of counselling services. This may also entail high cost in establishing, running and monitoring a screening program for FH. (35)

4.1.6 Recommendations from Other Groups

FH remains to be underdiagnosed and this is related to lack of awareness for this disease. Due to its genetic predisposition, most countries who recognize FH in their guidelines recommend case finding through cascade screening once an index patient is identified. In the FH guidelines of Taiwan, Japan, China and Hongkong, screening is recommended among the 1st degree relatives, including the children, of these FH patients by doing lipid profile determination only. This is also accompanied by genetic counseling. (36, 37, 38, 39)

FH screening is also done in children in some countries. Universal screening for hypercholesterolemia is being done in Slovenia on pre-school children between 5 to 6 years old. (40) Expert panel from the US National, Lung, Heart and Blood Institute recommends universal screening for dyslipidemia in children aged 9 to 11 years old. (41)

In Singapore, screening can be carried out as early as two years of age if they have a 1st degree relative with FH. Statin therapy should only be considered only in children aged 8 years or older if LDL-C target cannot be achieved by diet and exercise. Cascade screening likewise is recommended in all 1st degree relatives of those patient diagnosed to have FH. (42)

Identification in the primary care setting is being done in the United Kingdom and Australia using electronic research tools. The Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT) of the UK and TARB-Ex of Australia were developed to identify those with high probability of having FH in order to refer these patients to a specialist for further evaluation and management. (43,44)

In the 2016 U.S. Preventive Services Task Force, it was found that there was no direct evidence on screening for FH in the young. However, there was good evidence of the effectiveness of statins in reducing LDL-C concentrations but with limited evidence on its effect on atherosclerosis. These evidences are currently being updated as newer evidences have been seen. (45)

In both ESC and ACC-AHA guidelines, FH is considered in patients with premature CVD or those with severely elevated LDL-C of >190 mg/dL in adults or >150 mg/dL in children with relatives who have a premature CVD or physical signs of FH. Once

diagnosis is confirmed, if possible by DNA analysis, family cascade screening is recommended. (11,12)

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4.2 Screening for Coronary Artery Disease

Use of Resting Echocardiography for Coronary Artery Disease

RECOMMENDATION

Among asymptomatic apparently healthy adults, we recommend against screening for coronary artery disease using resting echocardiography *(STRONG recommendation, moderate level of evidence)*

Use of Stress Echocardiography for Coronary Artery Disease

RECOMMENDATION

Among asymptomatic apparently healthy adults, we recommend against screening for coronary artery disease using stress echocardiography *(STRONG recommendation, moderate level of evidence)*

The consensus panel considered the following when formulating this recommendation:

- Give importance that the recommendations are meant for the asymptomatic, healthy adults
- Modifiable risk factors such as smoking and elevated blood sugars should be identified

4.2.1 Burden of disease

A. Prevalence of Disease

The global and local burden of coronary artery disease is significant. In the Philippines, cardiovascular diseases have consistently ranked among the top 10 leading causes of morbidity for the past 4 decades(1). In 2019 and 2020, ischemic heart disease was the leading cause of mortality in the Philippines, and the numbers appear to be increasing yearly. In 2020, fatalities to ischemic heart disease increased by 7.8 percent from the previous year, and constituted 17.1 percent of all deaths in the country. Furthermore, deaths due to ischemic heart disease in 2020 exceeded the 5 year average (2015-2019) by almost 30 percent.(2)

In 2008, Sy et al conducted a national survey on the prevalence of atherosclerosis-related risk factors and diseases in the Philippines. The authors noted that the prevalence of hypertension, diabetes and dyslipidemia increased compared to 2003 data, but the prevalence of coronary artery disease (1.1%) did not. The data on the prevalence of CAD, however, was based on whether the survey respondents have been previously diagnosed by other physicians, and could therefore underestimate the true prevalence of CAD.(3)

CAD most commonly presents as angina. In 2003, a Food and Nutrition Research Institute (FNRI) study revealed that the prevalence of angina pectoris among Filipinos is 11%, while the prevalence of CAD was 1.1%.(4) In 2012, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial found that women reported less angina-free days in the past month than men (27% vs 37%), as well as more severe chest pain and other symptoms, even if they were found to have less extensive CAD (72.1% with multivessel disease > 50% stenosis vs. 80.7% in men) on further testing.(5)

B. Natural Course of the Disease

CAD may present as one or more of three clinical presentations: stable ischemic heart disease, non-ST elevation acute coronary syndrome, and ST-elevation myocardial infarction. We did not find any local data on the prognosis of patients with asymptomatic CAD. Western data has shown that the average annual incidence of first major cardiovascular event are influenced by age, sex, and race (7 per 1,000 in men ages 35-44 years to 68 per 1,000 in men ages 85-94 years). (6)

In a local cohort of patients undergoing PCI, 44% of cases had stable CAD, while 24% underwent PCI after STEMI.(7) Meanwhile, the PHA ACS registry (November2011-Novemer 2013) revealed that ACS is commonly noted in males (67%). The mean age was 66 years old and the mortality rate was was 7.8%. (8)

In the ISCHEMIA trial, the five-year cumulative event rate (death from cardiovascular causes, MI, or hospitalization) was 18.2% in the medically managed group and 16.4% in those patients managed with percutaneous coronary intervention.(9) **T**he event rates are low even in this population with known or suspected CAD.

Other researchers have observed that, in some groups, particularly women and patients with diabetes, the presence of typical angina, as well as traditional cardiovascular risk assessment tools, may underestimate actual risk of morbidity and mortality from ischemic heart disease.(10,11) In the United States, a prospective cohort of 121 701 women aged 30 to 55 year revealed that 69% women who suffered a SCD had no history of cardiac disease before their death, but 94% had reported at least one coronary heart disease risk factor.(11)

C. Management of the Disease

The management of patients with ischemic heart disease is multifactorial, and involves aggressive **lifestyle modification, risk factor management, medications (aspirin, statins), patient education and revascularization if warranted (12)**

Identifying patients with coronary artery disease allows physicians to initiate medical therapy and discuss invasive diagnostics and interventions for patients at high risk for adverse cardiovascular outcomes. The 2014 Philippine Heart Association guidelines for Ischemic Heart Disease strongly recommends the following medications for all patients with ischemic heart disease, as they reduce the risk for myocardial infarction and death:

1. Aspirin low-dose (80 to 160 mg/day)

2. Clopidogrel in case of aspirin intolerance (75 mg/day)
3. Statins irrespective of LDL-cholesterol levels
4. Beta blockers post-MI
5. ACEIs or ARBs (especially in patients with concomitant HF, hypertension or diabetes)

Meanwhile, revascularization with PCI or CABG surgery is recommended for patients with high risk of mortality based on an analysis of clinical, non-invasive and angiographic variables. Revascularization with CABG may improve survival due to the following mechanisms: improvement in left ventricular function; reduction in LV remodeling; prevention of serious arrhythmias, and a possible reduction in fatal ischemic events.(12)

D. Economic and Social Impact of the Disease

A 2009 study looked at the economic burden of nonfatal acute uncomplicated myocardial infarction, from hospitalization up to 1 month after discharge. Data was gathered from two private hospitals and one government hospital in Manila and nearby suburban area. The cost of hospitalization and follow up ranged from 71,969-143,307, depending on whether the patient was admitted in ward accommodations or in a suite room.(13)

Philhealth case rates for Ischemic heart disease without myocardial infarction, myocardial infarction and angioplasty are at 12000 Php, 18900 Php and 30,300 Php, respectively.(14) While Philhealth provides a Z-benefit package for Coronary Artery Bypass Graft, this can only be availed of in specific centers by patients who pass the selection criteria. This means that the bulk of the expenditure for acute and chronic medical care will be out of pocket for most patients.
In 2018, the Philippine Government spent 253 Billion Philippine Pesos on health care. Among the noncommunicable diseases, cardiovascular diseases accounted for the greatest percentage (45%) of health care costs. Apart from these direct costs, cardiovascular diseases also produce indirect economic losses through reduced labor participation and premature death. Among the noncommunicable diseases, cardiovascular diseases produce the most economic losses resulting from mortality.(15)

4.2.2 Benefits and Harms of Screening Tests

There were no direct studies found on the impact of screening asymptomatic individuals with either resting or stress echocardiography. However, a 2016 meta-analysis done by Bauters and Lemesle investigated the impact of **screening asymptomatic patients with diabetes for coronary artery disease**. One of the modalities used for screening was stress echocardiography. The final analysis included 3314 patients and found no significant differences between screened and unscreened groups in terms of all-cause mortality (OR 1.00, 95% CI 0.67–1.50), cardiovascular mortality (OR 0.72, 95% CI 0.33–1.57) and non-fatal myocardial infarction (OR 0.71, 95% CI 0.40–1.2) at the end of the 5- year follow up period.(10)

Event rates were low even in this relatively higher risk population. Furthermore, only 8% (130 out of 1662) of patients with a positive screening test eventually underwent

coronary angiography. In total, only 2.5% (Percutaneous Coronary Intervention) and 1.5 % (Coronary Artery Bypass Graft) of the total number of screened patients underwent revascularization. There were no significant differences between screened and unscreened groups in terms of Aspirin, ACE/ARB or statin use.(10)

A randomized controlled trial performed by Erne et al in 2007 investigated the impact of anti-ischemic medical therapy (MED) vs risk factor control (RFC) among asymptomatic individuals with positive results on stress imaging. The primary outcome was a composite of cardiac death, non-fatal MI (symptomatic or silent), or unstable angina pectoris leading to hospitalization or revascularization. While limited by the small sample size, the primary outcome occurred significantly less frequently in the MED group than in the RFC group (Hazard ratio 0.12, 95% CI 0.03–0.43, P= 0.001). The event rate per year was likewise significantly lower in the MED group (1.1%) than in RFC patients (8.0%). Most of the events noted were myocardial infarctions, again occurring significantly less frequently in the MED group (HR 0.03, 95% CI 0.01 to 0.23). (16)

In 2012, the ISCHEMIA trial enrolled and randomized patients with known or suspected stable ischemic heart disease in order to determine whether coronary revascularization, in addition to optimal medical therapy, improved prognosis. There were likewise no significant differences between the early invasive strategy and medical therapy groups in terms of the occurrence of the primary outcome, a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest (HR 0.93 95% CI 0.80 to 1.08). (9)

Varga et al pooled data from 71 centers in 17 countries from February 1998 to January 2004 in order to evaluate the safety of various stress echocardiographic modalities. All patients were stable at the time of testing, and 46% of patients had no previous documentation of ischemic heart disease. Out of 85,997 patient examinations, there were 86 life- threatening events, translating to an overall safety of 1 in 1000. The event rates for exercise, dobutamine and dipyridamole stress testing were 1 in 6,574,1 in 557 and 1 in 1,294, respectively. There were 5 fatalities during dobutamine stress testing (ventricular fibrillation, n=2; cardiac rupture, n=3) and 1 after dipyridamole testing (cardiogenic shock), translating to an event rate of 1 in 14332. All patients with fatal stress test outcomes had either recent or previous myocardial infarctions.(17)

4.2.3 Diagnostic Performance of Screening Tests

A. Rest Echocardiography

Studies on the diagnostic accuracy of resting echocardiography for coronary artery disease are limited, mostly focusing on patients with an acute coronary syndrome. Some findings on resting echocardiography that would indicate myocardial ischemia include a depressed ejection fraction, reduction in left ventricular wall motion, or mitral regurgitation. One prospective cohort by Lutfi, et al(18) investigated the diagnostic accuracy of resting left ventricular akinesia/hypokinesia in predicting an abnormal coronary angiography. They found that among diagnostic coronary catheterization candidates, findings on routine echocardiography such as akinesia/hypokinesia and

an ejection fraction less than 55% poorly predicted an abnormal coronary angiography (sensitivity of 87% and 89% respectively, and specificity of 42% and 42% respectively). This was probably due to significant influences of macro- and microvascular ischemia on left ventricular function. Since the predictive value of such echocardiographic findings are influenced by disease prevalence, applying these results in asymptomatic apparently healthy individuals would probably affect the accuracy negatively.

B. Stress Echocardiography

There were no direct studies on screening of asymptomatic individuals without comorbidities. However, a 2021 meta-analysis by Haberkorn et al compared the diagnostic accuracies of dobutamine stress echocardiography and vasodilator myocardial perfusion cardiovascular magnetic resonance imaging (pCMR) in mostly asymptomatic patients deemed at intermediate risk for coronary artery disease.(19)

This meta-analysis included 9 studies (7 prospective, 2 case-control) on dobutamine stress echocardiography, and utilized either coronary angiography (n=436) or fractional flow reserve assessment (n=216) as the reference standard. The pooled analysis revealed that dobutamine stress echocardiography had a sensitivity of 72% (95% CI 0.61–0.81) and a specificity of 89% (95% CI 0.83–0.93) for the detection of relevant CAD (defined as occlusion of 70% or higher). (19)

At low pre-test probability (< 25%) for CAD, a positive DSE yielded a post-test probability of 68% (62-74%), thereby failing to rule in relevant CAD (defined here as a post-test probability > 85%). Meanwhile, at high pre-test probability for CAD (> 75%), a negative DSE yielded a post- test probability of 39-58%, again failing to rule out relevant CAD (defined here as a post test probability < 15%).(19)

For intermediate risk patients (Pretest probability of 50%), a positive dobutamine stress test yielded a post-test probability of 86%, while a negative test yielded a post test probability of 24%.(19)

4.2.4 Cost Implication

In Metro Manila, the cost of a resting echocardiography ranges from 2,000 to 8,000 pesos, while stress echocardiography ranges from 5000 to 20,000 Philippine pesos, depending on the type of institution where the test will be done.

There are no direct studies on the cost-effectiveness of a stress echocardiogram in the approach to asymptomatic, apparently healthy patients. A meta-analysis on the comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected obstructive CAD was done in 2016. It included 70 studies which economically evaluated non-invasive cardiac imaging strategies. The quality of the studies were assessed by independent reviewers, which was deemed generally moderate to good; however, most studies did not provide details on price adjustments for inflation or currency conversion. A major issue of this meta-analysis is heterogeneity of the studies, as most originated from different countries, used a short-term time horizon, nor reported the willingness-to-pay threshold. None of these studies were conducted in the Philippines; and only a few studies considered a “no-testing” strategy. This meta-analysis found that the

diagnostic strategies were strongly influenced by the prior probability of CAD. For those who present with typical or atypical angina, performing a non-invasive diagnostic test is a reasonable use of resources. In this meta-analysis, stress echocardiography or cardiac magnetic was preferred over stress ECG as the initial test; and stress echocardiography was cost-effective in patients with a low-to-intermediate probability.(20)

4.2.5 Equity, Acceptability, and Feasibility

In the ISCHEMIA trial, the authors noted that women were more likely to undergo stress imaging than men (79.1% vs 74.4%). They were, however less likely to undergo exercise stress testing and more likely to have pharmacologic stress testing. As previously mentioned, women reported more frequent and severe angina, despite having a lesser burden of obstructive CAD. The authors postulated that mental stress was more likely to elicit ischemia among women than in men, but mental-stress induced ischemia was not related to the severity of CAD.(5)

In the PROMISE trial, women were found to be less likely to be referred for coronary angiography, less likely to have obstructive CAD, and more likely to have better outcomes (for death, myocardial infarction and hospitalization) than men, despite being less likely to report statin use even if warranted.(21)

4.2.6 Recommendations from Other Groups

The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults states that resting echocardiography is not recommended for cardiovascular risk assessment of CHD in asymptomatic adults without hypertension due to lack of benefit. Stress echocardiography is likewise not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults. (22)

The European Society of Cardiology (2019 guidelines) gave a class III recommendation for screening for asymptomatic patients: In low-risk non-diabetic asymptomatic adults, coronary CTA or functional imaging for ischaemia are not indicated for further diagnostic assessment. (23)

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4.3 Screening for Carotid Artery Stenosis

Use of Carotid Bruit Auscultation for Carotid Artery Stenosis

RECOMMENDATION

Among asymptomatic apparently healthy adults, we recommend against screening for asymptomatic carotid artery stenosis using carotid bruit auscultation *(STRONG recommendation, low level of evidence)*

Use of Carotid Artery Ultrasound for Carotid Artery Stenosis

RECOMMENDATION

Among asymptomatic apparently healthy adults, we recommend against screening for asymptomatic carotid artery stenosis using carotid ultrasound *(STRONG recommendation, low level of evidence)*

Considerations:

- The consensus panel considered that the recommendations for both diagnostic tests not be done in healthy adults due the low level of evidence.

4.3.1 Burden of disease

Asymptomatic carotid artery stenosis is defined as a 50% or greater reduction in the diameter of the carotid artery without a previous stroke or TIA in the territory of the asymptomatic carotid artery. It is associated with stroke outcomes, with the ipsilateral stroke risk being highly dependent on the degree of stenosis. (1)

The prevalence of asymptomatic carotid artery stenosis (ACAS) in the general population is quite low. A meta-analysis by de Weerd et al (2) of 4 population studies from Norway, Sweden and Germany included 23,706 participants without a history of coronary or cerebrovascular disease but with vascular risk factors such as. smoking, dyslipidemia, hypertension and diabetes. Results showed a slightly higher prevalence among men at 0.2% to 7.5% and 0% to 5.0% for women, aged < 50 and ≥ 80 years respectively, for moderate stenosis. The prevalence rates decreased for both sexes at a greater degree of stenosis, 0.1% to 3.1% for men, 0% to 0.9% for women. In another meta-analysis of 40 studies that used the information on the prevalence of asymptomatic carotid stenosis in the control groups of clinical trial resembling the general population, the prevalence of moderate stenosis also increased with age (2.2% to 4.8% for < 70 years old and 6.9% to 12.5% for ≥70 years old) and was higher among men (4.8% to 12.5%) compared to women (2.2% to 6.9%) (3). To date, there is no local data on the prevalence of asymptomatic carotid artery stenosis among Filipinos.

Prediction models for ACAS (4) show that age, sex, history of vascular disease, systolic and diastolic blood pressure, total cholesterol/high-density lipoprotein ratio, diabetes mellitus, and current smoking are predictors of the degree of carotid artery stenosis (>50% as moderate and >70% as severe). This prediction model also underscores that the greater the number of risk factors, the higher the prevalence and the lower the number needed to screen. Conversely, the lesser the number, the lower the prevalence and the higher the number needed to screen. Consequently, to be able to determine whether one should be screened for ACAS, there is a need to determine the above-mentioned variables, and not only base it on history and physical examination.
Screening methods for asymptomatic carotid artery stenosis include carotid bruit auscultation and carotid doppler ultrasound. Other discriminative imaging modalities are usually used as second line confirmatory tests. Carotid angiography remains to be the reference standard for diagnosis. However, issues of cost, availability, safety and lack of validated risk stratification tools make it a non-ideal screening procedure for this condition.
Carotid artery stenosis causes approximately 10% of ischemic strokes. But in the past 20 years, the annual rate of ipsilateral stroke decreased from 2-4% to <1% due to advances in medical, surgical and interventional treatment strategies. (5)

Approaches to management of asymptomatic carotid artery stenosis include medical management with aspirin, antihypertensive therapy, and lipid-lowering therapy; and carotid revascularization procedures, namely, carotid endarterectomy and carotid angioplasty with stenting.

4.3.2 Benefits and Harms of Screening Tests

There are no studies which directly showed evidence that screening for ACAS reduces the risk of stroke and other outcomes. (6.7)

There are also no direct studies on the *harm* of screening. However other potential outcomes of interest include harms associated with false-positive results, of which there are no studies, and harms associated with confirmatory tests such as angiography.

A low prevalence of severe carotid artery stenosis in the general adult population means that large scale community screening may result in high false positive rates. A second line test such as angiography, may be needed to confirm the presence of stenosis but this is not without harm. The Asymptomatic Carotid Artery Sclerosis Study (ACAS) (8)] reported that 5 out of 414 patients (1.2%) who underwent angiography after carotid doppler ultrasonography had postprocedural stroke, with 1 resulting in death. The Veterans Affairs Cooperative Study (VACS) (9) reported 3 out of 714 patients (0.4%) had nonfatal stroke after the confirmatory procedure.

BENEFIT AND HARM OF TREATMENT FOR ASYMPTOMATIC CAROTID ARTERY STENOSIS

A. MEDICAL TREATMENT

Medical intervention associated with treatment of ACAS includes lifestyle modification (e.g., smoking cessation, exercise, and dietary changes) and use of the following,

either alone or in combination - antiplatelets, anticoagulants, antihypertensives, lipid-lowering drugs, and control of diabetes.

In a systematic review (10) of 41 studies with 16,178 subjects with ACAS, the incidence rates of the following outcomes with medical intervention alone were evaluated - ipsilateral carotid territory events (stroke, transient ischemic attack, or both), death, myocardial infarction, other cardiovascular events, and composite cardiovascular outcomes. The average participant age was 68 years, and the participants had the following co-morbidities, namely, hypertension (12 to 90%), coronary artery disease (14 to 81%) and dyslipidemia (5 to 79%). ACAS was defined as 50-99% atherosclerotic narrowing of the carotid bifurcation lumen or extracranial part of the internal artery without ipsilateral carotid territory symptoms in the previous 6 months. Results showed that the incidence rates of ipsilateral stroke (0.61; 95% CI 0.45-0.82, p = 0.001) and ipsilateral stroke or TIA (0.60; 95% 0.47-0.77), p =<0.001) decreased over time with medical intervention. Subgroup analysis on the degree of stenosis showed that the incidence rate of ipsilateral stroke did not differ significantly between populations with ≥70% carotid stenosis from those with 50-70% stenosis (2.1 vs 1.9 events per 100 persons years, respectively; p = 0.427). However, the severity of stenosis in medically treated patients showed a significant higher summary incidence rate for all other cerebrovascular outcomes (ipsilateral stroke or TIA [7.3 vs 4.9; p = 0.001], any stroke [4.2 vs 1.9; p= 0.001], and any stroke or TIA [8.92 vs 5.6; p = 0.001]).

In another systematic and meta-analysis, 2,354 individuals (mean age 77.5 years) [1] with asymptomatic carotid stenosis (defined as ≥50% to 99% without previous stroke or TIA in the territory of the asymptomatic carotid artery detected by carotid duplex ultrasound or MRA) were followed-up for a maximum of 10 years (median 5.9 years). The population included those with hypertension (77-80%), diabetes (19-25%), dyslipidemia (49-54%), and CAD (32%) among others, and on medical therapy (44% on statin therapy, 56% on antiplatelet or anticoagulant). After recruitment, the usage of medical therapy increased (95% for anti-thrombotic treatment, 89% on a statin and 89% on at least one blood pressure-lowering drug). Results showed that the stroke risk is 2.4 (1.7-3.4) and 3.0 f(2.0-4.5) for patients with 70-79% and 80-99% stenoses compared to patients with 50-69% stenoses. The odds decreased to 0.8 (0.5-1.4), for both stenoses of 70-79% and 80-99% for the medically treated group.

Use of Statins

Patients with a higher proportion of using statins (≥25%) resulted in statistically significant lower incidence rates of ipsilateral events (1.2 vs 2.3 events /100 person-year; p = 0.009) and ipsilateral stroke or TIA (3.4 vs 5.8 events /100 person-year; p = 0.001), but did not show statistical difference for any stroke (2.3 vs 3.0 events /100 person-year; p = 0.124) and any stroke or TIA (3.4 vs 6.6 events /100 person-year; p = 0.124). (100

Use of Antiplatelet

Between the proportion of patients receiving antithrombotic (antiplatelet and anticoagulant drugs) , >50% vs <50%, results showed no significant difference in the incidence rate of any stroke (2.9 vs 1.9 events/100 person-year; p = 0.484) and any

stroke or TIA (5.3 vs 5.4 events/100 person-year; p = 964). [10]. One RCT (9) of 444 men (mean age 64.5 years) with asymptomatic carotid stenosis (≥50% luminal narrowing) compared optimal medical treatment (OMT) plus carotid endarterectomy versus OMT only. OMT included the use of aspirin (650 mg twice daily). Among the included patients, 16% discontinued aspirin therapy, due to intolerance, 57% took the full dose, and 27% took 325 mg of aspirin daily.

A systematic review on the optimal antiplatelet therapy in moderate to severe asymptomatic and symptomatic carotid stenosis was done by Murphy et al (11). It included data on prescribed antiplatelet regimens and outcome events in patients with moderate to severe carotid stenosis. Twenty five studies with 24,272 patients were included. One of these studies is the Asymptomatic Cervical Bruit Study-ACB which randomized asymptomatic carotid stenosis patients with ≥ 50% asymptomatic carotid stenosis of at least one artery to either 325 mg of enteric coated aspirin daily (n = 188) versus placebo (n = 184). There were no significant differences in the annual incidence of all ischemic events (TIA, ischemic stroke, unstable angina, MI and death from any cause) between the two comparisons (11.0% vs 12.3%, p = 0.61) after a median follow-up of 2.3 years. In the pooled results of best medical treatment (BMT) involving four RCTs, events occurred in 0-20.6% of patients with asymptomatic >50% stenosis treated with 81-1300 mg of aspirin daily for a period of one month to 10 years. For carotid endarterectomy, majority of patients in the 9 included trials received aspirin monotherapy (81-325 mg daily). Other antiplatelet included clopidogrel monotherapy and aspirin-clopidogrel combination therapy. Overall, primary trial outcomes were seen in 1.5-20.1% of asymptomatic > 50% stenosis patients treated by endarterectomy. For endovascular treatment (EVT), there were six trials that used aspirin-clopidogrel combination therapy (325 mg aspirin once or twice daily for 30 days plus either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily for ≥ 4 weeks). Primary outcome was observed in 1.5-12% over one month to 10 years. Data from interventional trials in asymptomatic patients support the use of 81-325 mg of aspirin daily peri-procedurally. If intolerant to aspirin, it is reasonable to empirically use clopidogrel monotherapy. The use of low to medium dose aspirin (81-325 mg daily) is superior to higher doses (>650 mg daily) in reducing recurrent vascular events in patients undergoing endarterectomy.

In terms of “extra-cerebral” bleeding events and risk of hemorrhagic stroke, one RCT(11) randomized patients with asymptomatic severe (70 to 99%) carotid artery disease to either carotid endarterectomy or carotid stenting. All patients received aspirin (325 mg) daily, 3 days before the procedure and indefinitely after the procedure while patients who underwent stenting received an additional clopidogrel daily, 3 days before the procedure and for 30 days after the procedure. Measured complications included noncerebral bleeding and endarterectomy incision or puncture site bleeding. Results showed a non-significant difference in noncerebral bleeding (1.9% for CAS and 1.6% for CEA, p = 0.83) and endarterectomy incision or puncture site bleeding (0.3% for CAS and 1.1% for CEA; p = 0.07).

Despite modifying risk factors and utilizing medical therapy, there is a residual 1% risk of disabling stroke or death from asymptomatic carotid artery stenosis. Hence for patients with severe stenosis (≥ 70-99%), carotid procedures on top of medical therapy are considered if deemed suitable despite being asymptomatic.

B. MEDICAL MANAGEMENT VERSUS CAROTID ENDARTERECTOMY

No direct evidence on the benefit of medical management versus carotid endarterectomy (CEA) for carotid artery stenosis in asymptomatic apparently healthy adults was found.

However, there was a Bayesian cross-design and network meta-analysis (11) on asymptomatic carotid artery stenosis comparing medical treatment (use of antiplatelet, antihypertensive, lipid-lowering therapy and lifestyle modification) versus CEA. The study included four randomized controlled trials involving patients with no symptoms or ipsilateral symptoms (>6 months) or contralateral symptoms (>1.5 months) or recent symptoms in a different territory, with mean age of 64.1 to 68.5 years and followed-up for 2.7 to 10.0 years. Diabetes mellitus was present in 19.6-30% of included patients. The stenosis was mostly diagnosed using duplex ultrasonography and the degrees were from ≥50 to 70%. Pooled results showed an increase in the risk for any periprocedural stroke plus non-periprocedural ipsilateral stroke in the medical treatment (MT) compared to CEA (OR 1.73, 95% CI 1.06-3.02), but the confidence interval was wide. A nonsignificant increase was noted in MT compared to CEA for the composite of death, stroke, or myocardial infarction during periprocedural period and ipsilateral stroke during long-term follow-up (OR 1.49, 95% CI 0.97-2.49).

However, the trials included were during a period when medical treatment was limited and did not include recent pharmacologic advances. Definitions of asymptomatic conditions were also variable.

C. MEDICAL MANAGEMENT VERSUS CAROTID ARTERY STENTING

No direct evidence on benefit was found comparing medical management versus carotid artery stenting (CAS) in asymptomatic apparently healthy adults. But in the same network meta-analysis above (11), an *indirect analysis* was done and results showed a non-significant difference between the two treatment approaches on the following outcomes: 1) composite of death, stroke, myocardial infarction during periprocedural period and ipsilateral stroke during long term follow-up (OR 1.30, 95% CI 0.74-2.73) and 2) any periprocedural stroke plus non-periprocedural ipsilateral stroke (OR 1.50, 95% CI 0.78-3.54).

D. CAROTID ENDARTERECTOMY VERSUS CAROTID ARTERY STENTING

No direct evidence on benefit comparing carotid endarterectomy (CEA) versus carotid artery stenting (CAS) in asymptomatic apparently healthy adults was found.

However, there was a Cochrane meta-analysis comparing CEA versus CAS for asymptomatic atherosclerotic carotid stenosis (ACAS) done in 2020 (12), involving seven trials (five trials including participants with asymptomatic carotid stenosis only and two trials with subgroups of participants with asymptomatic stenosis). The population had a mean age of 64.9-77.2 years and with stenoses of ≥70 to 99% diagnosed by DUS or arteriography. Some patients had hypertension, dyslipidemia, diabetes and coronary artery disease. The primary treatment safety outcome was

death or any stroke between randomization and 30 days after treatment. Treatment safety analysis showed a non-significant increase in periprocedural death or stroke with stenting compared with endarterectomy (OR 1.72, 95% CI 1.00 - 2.97; P = 0.05, I2 = 0%; 7 trials, 3378 participants, moderate-certainty evidence). There was no statistical difference between treatments with regards to periprocedural death or stroke or ipsilateral stroke during follow-up (OR 1.27, 95% CI 0.87 - 1.84; P = 0.22). For myocardial infarction between randomization and 30 days after treatment, the result did not reach statistical significance (OR 0.53, 95% CI 0.24 - 1.15; P = 0.11). Other outcomes also did not show statistical difference (death or any stroke or myocardial infarction, death or any stroke or ipsilateral stroke until end of follow-up and death or any stroke or myocardial infarction or ipsilateral stroke until end of follow-up). The restenosis rates between the two treatment groups were combined for both symptomatic and asymptomatic participants and no subgroup analysis for asymptomatic subjects could be obtained.

Other safety outcomes (12) evaluated were access complications, namely, incidence of cranial nerve palsies, combined outcomes of death or neurological complications (including stroke and cranial nerve palsy) and access site hematoma (including cervical hematoma arising from skin puncture in endovascular treatment) requiring surgery, blood transfusion, or prolonging hospital stay.

There was an increased risk of cranial nerve palsy within 30 days of procedure among asymptomatic carotid stenosis in the stenting group compared to endarterectomy (OR 0.09, 95% CI 0.03 to 0.27; P = < 0.0001) For death or neurological complication up to 30 days after treatment, there was data from one study (Kentucky 2004) which showed a non-significant difference between the two carotid interventions (OR 0.13; 95% CI 0.01 to 2.59). The wide confidence interval was due to few events and small sample size (0/43 for CAS and 3/42 for CEA). For access site hematoma, there was an 86% reduction in the CAS group compared to CEA group (OR 0.14, 95% CI 0.02 to 0.90; P = 0.04).

In August 2021, a new large trial came out entitled Second Asymptomatic Carotid Surgery Trial (ACST-2) which compared carotid artery stenting versus carotid endarterectomy. (13) It randomized 3625 patients without neurological symptoms in the preceding 6 months and with carotid stenosis of ≥60% on ultrasound The population enrolled had co-morbidities (30% DM, 35% CAD) and 84 to 91% were on antiplatelet, antihypertensive, and lipid-lowering agents. It compared the 30-day hazards of the two procedures and subsequent stroke rates over the following 5 to 10 years. This new study was added to the abovementioned Cochrane meta-analysis. The pooled results showed that the outcome of death or any stroke between randomization and 30 days after treatment carried an increased risk with CAS compared to CEA (RR of 1.45, 95% CI 1.07, 1.98; P =0.02). The increased risk was mostly attributed to an increase in minor, non-disabling strokes occurring in people older than 70 years. However, carotid stenting showed a reduction of myocardial infarction by 51% compared to endarterectomy (RR 0.49, 95% CI 0.26, 0.91. P= 0.02). There were no differences between the two carotid interventions in all other outcomes The test for heterogeneity was not significant for all the six pooled analyses.

It is noteworthy to mention that the ACST-2 trial, being the largest thus far and carries the highest weight in the pooled meta-analysis, did not show significant differences in

treatment effect with respect to age (< 70 vs ≥70 years), sex, degree of ipsilateral stenosis (<70%, 70-79%, 80-89 and 90-99%), and plaque echolucency (<25% vs ≥25% of soft material).

In summary, treatment options for asymptomatic carotid artery disease include medical management, CEA, or CAS. But there is no direct evidence that treating apparently healthy patients with asymptomatic carotid artery stenosis reduces the critical and important outcomes identified for this review. Most trial included patients with concomitant risk factors or co-morbidities. Some variations were found regarding study protocols, patients characteristics, definitions of asymptomatic and clinical endpoints, stent types used and variation in the use of embolic protection devices.
With the low annual rate of stroke and the low certainty of evidence due to indirect issues (the population involved may be asymptomatic but they were not apparently healthy adults they had co-morbidities based on the patient characteristics) and imprecision (some trials had small sample size, low event rate and wide confidence interval), medical management can be maximized.

4.3.3 Diagnostic Performance of Screening Tests

Accuracy of Carotid Bruits in Detecting Carotid Artery Stenosis

There are no direct studies on the diagnostic accuracy of carotid bruit auscultation among exclusively asymptomatic apparently healthy subjects. Most of the studies evaluating the association of carotid bruit and carotid stenosis involved participants with a history of cardiovascular or cerebrovascular diseases or symptoms referable to a carotid artery stenosis. In a meta-analysis by McColgan et al in 2012 (14), all patient populations of the 26 studies included those presenting to neurology or vascular outpatients, patients with coronary artery disease, peripheral vascular disease and patients scheduled to undergo CABG. Carotid bruit was ascertained using an acoustic auscultation for clinically significant stenoses determined by various imaging techniques, including Doppler ultrasonography. Results showed that for clinically relevant stenosis (defined as >70, 75 and 80% stenosis), the pooled sensitivity of carotid bruit auscultation is low at 0.53 (95% CI 0.5, 0.55) and the pooled specificity is high at 0.83 (95% CI 0.82, 0.84). This suggests that the absence of a bruit is useful in ruling out stenosis but its presence does not necessarily imply that a stenosis is present.

Two community-based studies evaluated the use of carotid bruit auscultation as a screening test for asymptomatic subjects, but it can be noted that the subjects had vascular risk factors as well. One of this is the Northern Manhattan Study (NOMAS) which is a prospective cohort study (15) designed to document the incidence of stroke and other vascular events. In this study, carotid bruit was examined by auscultation followed by carotid duplex scanning in 686 participants who were asymptomatic and stroke-free but had the following risk factors hypertension (71.4%), diabetes (21.4%), hypercholesterolemia (50%), smoking (67.9%) and coronary artery disease (17.9%). Results showed a low sensitivity at 0.56 and a high specificity at 0.98. This has been attributed to the low prevalence of a hemodynamically significant carotid stenosis detected by ultrasonography at 2.2% and carotid bruit at 4.1% in this asymptomatic study population with vascular risk factors.

In another community-based prospective observational study (16), the Fremantle Diabetes Study Phase II (FDS2), subjects assessed to have a carotid bruit by auscultation followed by ultrasonography were age- and gender-matched with FDS2 subjects with no carotid bruit. The 50 cases and 50 controls had similar proportions of type 1 and type 2 diabetes and were on antihypertensive therapy (88 to 90%), lipid modifying therapy (76%) and aspirin therapy (44%). Results showed that carotid bruit has a high sensitivity (0.83, 0.88) and a low specificity (0.58, 0.52) for both moderate-(≥50%) and high-grade (≥70%) stenoses detected subsequently by ultrasonography. This has been attributed to the better acoustic quality obtained using electronic auscultation as compared to standard auscultation used in other studies.
All 3 studies evaluated carotid bruits by auscultation followed by detection of stenoses mainly by using carotid ultrasonography. There are no studies which investigated a stepwise approach or algorithm in the evaluation of a carotid stenosis.

Accuracy of Doppler Ultrasonography in Diagnosing Carotid Artery Stenosis

There are no studies on the accuracy of carotid doppler ultrasonography which focused on exclusively asymptomatic subjects as most studies included those with symptomatic carotid stenosis and/or cerebrovascular and cardiovascular risk factors. Furthermore, some studies used symptomatic and asymptomatic to refer to the ipsilateral and contralateral arteries being evaluated, respectively, as shown in the meta-analysis by Chappell et al. (17) This meta-analysis included 12 studies or data sets of 1,456 patients, where 86 to 100% of patients had symptomatic carotid artery stenosis. Nine studies compared noninvasive testing, which included doppler ultrasonography, with intraarterial angiography which is the reference standard for diagnosis.

Results showed that DUS has a sensitivity of 0.31 to 0.83 for symptomatic carotid artery stenosis and 0.48 to 0.67 for asymptomatic carotid stenosis. Specificity ranged from 0.54 to 0.84 for symptomatic carotid stenosis and 0.90 to 0.93 for asymptomatic. The sensitivity of DUS for diagnosing carotid artery stenosis was higher in symptomatic arteries with a greater degree of stenosis. Specificity was higher in the asymptomatic carotid artery in both degrees of stenosis. (15)

In a meta-analysis by Jahromi et al in 2005 (47 studies, n=1,716) using digital subtraction angiography as the reference standard, results showed that DUS has a 98% sensitivity (95% CI 97 to 100%) for detecting stenosis of 50% or greater and a 94% specificity (95% CI 88 to 97%) for detecting stenosis of 70% or greater. (18)

Although with a few studies showing variable results, carotid bruit auscultation and carotid doppler ultrasound, in general, exhibited low sensitivity and high specificity in evaluating for asymptomatic carotid stenosis. With the low prevalence of asymptomatic carotid artery stenosis, these screening tests may yield high false positive test results which may lead to unnecessary therapeutic interventions or further diagnostic testing for confirmation.

4.3.4 Cost Implication

Dongpin (19) studied the cost-effectiveness of ultrasound screening for asymptomatic carotid stenosis with or without arteriography in the US. Using the Markov model and data from studies such as Asymptomatic Carotid Atherosclerosis Study (ACAS), the

results showed that “for a 60-year-old patient with a 5% prevalence of 60% to 99% asymptomatic stenosis, duplex ultrasound screening increased average quality-adjusted life years (QALY; 11.485 vs 11.473) and lifetime cost of care ($5500 vs $5012) under base-case assumptions. The incremental cost per QALY gained (cost-effectiveness ratio) was $39,495”. Moreover, the results showed that screening was cost-effective with the following conditions: “disease prevalence was 4.5% or more, the specificity of the screening test (ultrasound) was 91% or more, the stroke rate of patients who were medically treated was 3.3% or more, the relative risk reduction of surgery was 37% or more, the stroke rate associated with surgery was 160% or less than that of the North American Symptomatic Carotid Endarterectomy Trial or ACAS perioperative complication rates, and the cost of ultrasound screening was $300 or less.” They also found that ‘a one-time screening, compared with a screening every 5 years, had more QALY (11.485 vs 11.482) and lower cost ($5500 vs $5790)”. The authors concluded that the screening test and the interventions must be done in reputable facilities to have a better QALY and achieve cost-effectiveness.

To date, no local data on the cost effectiveness of screening among ACAS patients is found.

In terms of cost, carotid doppler ultrasound in a private hospital range from Php6,615 to Php 3,000 for non-senior and Ph5,292 to Php 2,400 for senior citizens. In a government hospital in Manila, the cost is Php 3,940 for non-senior and Php 3,168 for senior citizens.

4.3.5 Equity, Acceptability, and Feasibility

Carotid bruit auscultation is ideal at the primary care setting as it is a standard examination that can be done by any physician. It is free and does not require any equipments other than the standard stethoscope. However there may be variability in technique and physician experience and acoustic discrimination.

Carotid doppler ultrasound is cheaper compared to other imaging modalities used to assess carotid artery disease. However, it is not readily available in most rural areas and has inter-operator variability. A reputable facility with a skilled operator may be needed if this is to be used as a screening procedure.

Identification of a disease especially if asymptomatic may provide an equipoise for the health provider and the patient. Deciding involves explaining the management options, risk/benefits ratio, and securing an informed patient choice. One study on patient’s preference done in London by Jayasooriya et al (20) using a validated patient information booklet and questionnaire, showed that, with regards to treatment approaches for asymptomatic carotid artery stenosis, 48% of patients preferred pharmacotherapy and 52% opted for non-pharmacologic approaches (30% and 22% for carotid endarterectomy and stenting, respectivel

4.3.6 Recommendations from Other Groups

Based on the recommendations of the different task forces and groups, namely: USPSTF, ESC, AHA, among others, the over-all recommendation is not to screen for asymptomatic carotid artery stenosis, unless there is associated high-risk features (e.g., presence of carotid bruit, existence of co-morbidities or presence of risk factors for the development of atherosclerosis) that will necessitate testing.

The Philippines Society of Vascular Medicine has yet to issue a recommendation in this regard.

Table 5. Summary of Society Recommendations for Asymptomatic Carotid Artery Stenosis

Group	Recommendation	Strength of recommendation and certainty of evidence
Screening for Asymptomatic Carotid Artery Stenosis US Preventive Services Task Force Recommendation (USPSTF) Statement (21)	**Definition of Asymptomatic carotid artery stenosis (ACAS):** persons without a history of ischemic stroke, transient ischemic attack, or other neurologic symptoms referable to the carotid arteries. The prevalence of ACAS in the general population is low (0.5%-1%) but increases with age. Of patients who had angiography (MRA or CTA) as a confirmatory tests , 0.4&-1.2% had strokes.	The USPSTF recommends **with moderate certainty** against screening for ACAS in the general adult population (Class of recommendation D). The task force claims that harms of screening for ACAS outweigh the benefits. The recommendation is consistent with the 2014 USPSTF recommendation.
The Joint British Societies 2nd (JBS2) 2005 guideline (22)	This guideline included all adults from 40 years onwards, who have no history of CVD or diabetes, and who are not already on treatment for blood pressure or lipids, should be considered for an opportunistic comprehensive CVD	No dedicated recommendation on ACAS.

	risk assessment in primary care once every five years. In asymptomatic people without a history of CVD priority should be given to lifestyle. Pharmacologic treatment commences for those apparently healthy individuals at high risk (CVD risk of > 20% over 10 years) of developing symptomatic atherosclerotic disease The cardiovascular risk prediction charts have not been validated in ethnic groups other than white caucasian and therefore they should be used with caution	
Management of carotid stenosis for primary and secondary prevention of stroke: state-of-the-art 2020: a critical review (23)	Current ESC guidelines put a threshold of 60% for symptomatic carotid stenosis. The indications for carotid endarterectomy (CEA) and carotid artery stenting (CAS) are "for asymptomatic patients with tight stenosis (>60%) and a perceived high long-term risk of stroke (determined mainly by imaging criteria)" The authors concluded that "the place of	Recommendation: "The best therapeutic option for asymptomatic plaque is now medical except for selected cases. The benefit of CEA and CAS for asymptomatic plaque is now low, and should be limited to patients selected on the basis of long-life expectancy, low surgical risk, and plaque considered vulnerable (or at 'high risk of stroke') according to the imaging criteria."

	carotid revascularization must necessarily be limited to the plaques at highest risk, leaving a large place for optimized medical treatment as first line management.	
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS) (24)	In the guideline, asymptomatic is defined as no prior symptoms can be identified or when symptoms occurred >6months ago. Features associated with increased risk of stroke in patients with asymptomatic carotid stenosis treated medically:	Recommendations for imaging of extracranial carotid arteries: DUS (as first-line imaging), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses (Class I-B) When CAS is being considered, it is recommended that any DUS study be followed by either MRA or CTA to evaluate the aortic arch as well as the extra- and intracranial circulation (Class I-B) When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated by either MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory) (Class I-B) Recommendations for management of asymptomatic carotid artery disease: In 'average surgical risk' patients with an asymptomatic 60–99% stenosis, CEA should be considered in the presence of clinical and/or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years (Class IIa-B) In asymptomatic patients who have been deemed 'high risk for CEA and who have

		an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years (Class IIa-B) In average surgical risk' patients with an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is > 5 years (Class IIb-B)
2011 ASA/ACCF/AHA/AANN/ AANS/ACR/ASNR/ CNS/ SAIP/SCAI/SIR/SNIS/SVM/ Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease (25)	"Although there is evidence from randomized trials that referred patients with asymptomatic hemodynamically significant carotid stenosis benefit from therapeutic intervention, no screening program aimed at identifying people with asymptomatic carotid stenosis has been shown to reduce their risk of stroke. Hence, there is no consensus on which patients should undergo screening tests for detection of carotid disease."	**Recommendations for Duplex Ultrasonography to Evaluate Asymptomatic Patients With Known or Suspected Carotid Stenosis** Class I 1. In asymptomatic patients with known or suspected carotid stenosis, duplex ultrasonography, performed by a qualified technologist in a certified laboratory, is recommended as the initial diagnostic test to detect hemodynamically significant carotid stenosis. (Level of Evidence: C) Class IIa 1. It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. (Level of Evidence: C) 2. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with

"…The benefit is limited by the low overall prevalence of disease amenable to specific therapy in asymptomatic patients, and that revascularization procedures are associated with tangible risks."	atherosclerosis who have had stenosis greater than 50% detected previously. Once stability has been established over an extended period or the patient's candidacy for further intervention has changed, longer intervals or termination of surveillance may be appropriate. (Level of Evidence: C) Class IIb 1. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic PAD, coronary artery disease (CAD), or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of ECVD in those without carotid bruit would justify actions that affect clinical outcomes. (Level of Evidence: C) 2. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first degree relative of atherosclerosis manifested before age 60 years, or a family history of ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (Level of Evidence: C) Class III: No Benefit 1. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. (Level of Evidence: C) 2. Carotid duplex ultrasonography is not recommended for routine evaluation of patients with neurological or psychiatric disorders unrelated to focal cerebral ischemia, such as brain tumors, familial or

degenerative cerebral or motor neuron disorders, infectious and inflammatory conditions affecting the brain, psychiatric disorders, or epilepsy. (Level of Evidence: C) 3. Routine serial imaging of the extracranial carotid arteries is not recommended for patients who have no risk factors for development of atherosclerotic carotid disease and no disease evident on initial vascular testing. (Level of Evidence: C)

RECOMMENDATIONS FOR SELECTION OF PATIENTS FOR CAROTID REVASCULARIZATION

Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. *(Class I-C)*

It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low. (Class IIa-A)

Class IIb

Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established. *(Class IIb-B)*

In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus

	medical therapy alone is not well established. *(Class IIb- B)*
Canadian Task Force on Preventive Health Care (26)	No recommendation for asymptomatic carotid artery stenosis
UK National Screening Committee (27)	No recommendation for asymptomatic carotid artery stenosis
Philippine Society of Vascular Medicine (28)	No recommendation for asymptomatic carotid artery stenosis

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4.4 Screening for Peripheral Arterial Disease

Use of Pulse Palpation for Peripheral Arterial Disease

RECOMMENDATION
Among asymptomatic apparently healthy adults, we recommend against routine screening for peripheral arterial disease using pulse palpation *(STRONG recommendation, low level of evidence)*

Use of Doppler Ankle Brachial Index for Peripheral Arterial Disease

RECOMMENDATION
Among asymptomatic apparently healthy adults, we recommend against screening for peripheral arterial disease using Doppler ABI *(STRONG recommendation, low level of evidence)*

The consensus panel considered the following when formulating this recommendation:

- *Educate primary health workers in correct physical examination of peripheral pulses, particularly in the posterior tibial and dorsalis pedis.*
- *Age is an important risk factor for PAD, a statement should be made for symptomatic elderly individual*

4.4.1 Burden of disease

In the 2003 National Nutrition and Health Survey, the prevalence of Peripheral Arterial Disease (PAD) in the general Philippine population was determined using the Edinburgh claudication questionnaire and Ankle-Brachial Index (ABI). Of the 4,753 adults included, the overall prevalence of PAD was 4.2% and 5.0% using the claudication questionnaire and ABI respectively, with a steady rise noted with age(1). Based on previous diagnoses of PAD by medical personnel, as indicated on interview questionnaires, age-adjusted prevalence estimates were 0.6% in 2003 and 1.1% in 2008(2).

PAD prevalence increases in populations at high risk for the disease. The 2003 PHILPAD study (mean age 61 years, 64% hypertensive, 56% smokers), showed a PAD prevalence of 31.67% and 26% based on the ABI and Edinburgh Claudication questionnaire, respectively(3). A study of 70 asymptomatic diabetic patients seen at the outpatient clinic using the ABI showed a frequency of PAD of 33% at rest and 37% after a 6-minute walk test(4). In a 2012 study at the Philippine Heart Center among 125 patients with cardiovascular risk factors or atherosclerotic disease (hypertension, diabetes, smoking, chronic kidney disease, cardiovascular and cerebrovascular disease), the prevalence of PAD was 33.2% based on ABI by Doppler method and 39.2% based on ABI by palpation method(5).

In a community-based screening in Korea of 2,044 asymptomatic individuals, PAD was detected in 4.6% using the ABI. Severe PAD was noted in 0.1%. Significant risk factors for PAD were old age (odd ratio, 1.952; P = 0.045), hypertension (odd ratio, 1.645; P = 0.050), and cardiovascular disease (odd ratio, 2.047; P = 0.039)(6).

In the REACH Registry of 68,236 patients who were at least 45 years old with established coronary artery disease (CAD), cerebrovascular disease (CVD) or PAD, or with ≥3 atherothrombotic RFs, 8322 (14.9%) patients had documented symptomatic PAD. PAD patients had a high prevalence of concomitant vascular disease (61.5% having either CAD or CVD, or both) and had fewer risk factors controlled than patients without PAD. Patients with PAD were older, more frequently male, more frequently retired, less frequently in full-time employment and lower level of formal education(7).

In a prospective cohort of 6880 German patients at least 65 years old monitored for 5 years, 836 (12.15%) had asymptomatic PAD while 593 (8.62%) had symptomatic PAD. Of patients without PAD, with asymptomatic PAD, and with symptomatic PAD, 19.5, 41.7, and 53.0 patients per 1000 patient-years had died. Compared with patients without PAD, those with asymptomatic PAD (HR 1.66) or symptomatic PAD (HR, 1.89) had a significantly increased risk of premature death. There were no significant differences between asymptomatic and symptomatic PAD in terms of mortality, but were significantly higher compared to those without PAD. Symptomatic compared with asymptomatic PAD patients was at significantly increased risk for the composite of all-cause death or severe vascular event (myocardial infarction, coronary revascularization, stroke, carotid revascularization, or lower-extremity peripheral vascular events; hazard ratio, 1.48). Lower ankle brachial index categories were associated with increased risk(8).

A systematic review of 124 randomized controlled trials and observational studies showed a significant association between a low ABI with mortality and cardiovascular disease. The results of the review also implied that the risk of stroke and MI in a PAD population is at least equivalent to the risk of these events in patients with coronary artery disease. Furthermore, compared with an ABI < 0.9, the presence of critical limb ischemia was associated with an increased risk of all-cause and CV mortality (RR, 2.26, 95% CI, 1.77–2.89 and 1.42, 1.01–2.01, respectively), MI (RR, 2.63, 95% CI, 1.49–4.64), MACE (RR, 1.73, 95% CI, 1.25–2.38) and major amputations (RR, 3.85, 95% CI, 2.52–5.87). The event rates for stroke were similar in patients with an ABI < 0.9 or CLI(9).

4.4.2 Benefits and Harms of Screening Tests

There are no randomized controlled trials nor cohort studies on the benefits nor harms of using pulse palpation among patients who are apparently healthy or asymptomatic for PAD. A critical appraisal of fourteen international guidelines on the screening and treatment of asymptomatic PAD showed varying recommendations on pulse palpation and the ankle-brachial index. Although the American Heart Association, Belgian Working Group, Central European Venous Forum, European Society of Vascular Surgery, German Society of Angiology and Society of Vascular Surgery had either moderate or strong recommendations on the use of ABI for screening patients who are asymptomatic, these patients must have significant risk factors for atherosclerosis, including increased age, presence of diabetes, hypertension, smoking or family history

of lower extremity arterial disease. Only the US preventive task force stated that there is insufficient evidence to do ABI screening in the asymptomatic population(10).

A meta-analysis of 16 cohorts using the ABI in addition to the Framingham Risk Score improved the accuracy of risk prediction. An abnormal ABI (≤0.90 and >1.4), was associated with increased HRs for total mortality, CV mortality and major coronary events. However, this general population-based study did not classify patients as whether healthy, asymptomatic, or symptomatic for PAD. It also only included those who had ABI screening and not compared to those who were not screened(11).

A systematic review and meta-analysis of 19 studies (randomized and non-randomized) on asymptomatic PAD patients evaluated the association between PAD identified by screening and CV mortality and death but did not directly compare those who were screened and not screened with the ABI. The pooled adjusted HR was 2.99 for all-cause mortality ((95% CI, 2.16-4.12; I2 1⁄4 60%) and 2.35 for CV mortality (95% CI, 1.91-2.89; I2 1⁄4 76%). However, the risk in populations studied were significantly heterogenous. The asymptomatic screen-detected PAD was associated with a heightened risk of CV and all-cause mortality to infer that screening for PAD is of benefit to patients(12).

The Viborg Vascular (VIVA) trial in Denmark, randomized 50,156 men aged 65-74 years, to screening for abdominal aortic aneurysm, peripheral arterial disease, and hypertension, or to no screening. Handheld Dopplers were used to check the ABI and a value of of <0.9 or ≥1.4 was considered to have PAD. There was a significant relative reduction in overall mortality for the screening group after a median follow up of 4·4 years (IQR 3·9–4·8) and 209693 person-years of observation time and 2566 (10·2%) deaths in the screening group and 2715 (10·8%) deaths in the non screening group. The effect of screening and intervention on overall mortality was a HR of 0·93 (95% CI 0·88–0·98; p=0·01), an absolute risk reduction of 0·006 (0·001–0·011), and a number needed to invite of 169 (89–1811). It must be emphasized however, that the baseline characteristics of the population were as follows: mean age of 69 years, 45% were on medical therapy (30% on antithrombotic, 35% on antihyperlipidemic, 22% on antihypertensives, 10% on medications for diabetes) and 21% were current smokers, representing a population already at increased cardiovascular risk(13). Hence, the population included in this large trial does not reflect the apparently healthy, asymptomatic patients we are applying the recommendation to. Furthermore, since the study included screening for abdominal aortic aneurysm and high blood pressure, it is difficult to evaluate the benefit of screening with the ABI alone.

There are several randomized trials on the benefits of treatment using antithrombotic and statin therapy in patients with high cardiovascular risk and patients with symptomatic PAD. However, there are few on apparently healthy or asymptomatic individuals. The POPADAD trial of 1276 patients with diabetes and asymptomatic PAD showed no reduction in the primary end points of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischaemia; and death from coronary heart disease or stroke with aspirin(14).

The Aspirin for Asymptomatic Atherosclerosis Trial randomized 3350 patients with no prior history of vascular disease screened using the ABI to either Aspirin 100mg OD

or placebo. Mean age was 62 years, mean systolic BP 148mmHg, >30% were previous smokers and >30% current smokers. There was no significant reduction in the primary endpoint of a composite of fatal or nonfatal MI, stroke or revascularization and secondary endpoint of all-cause mortality with aspirin. Although not significant, there were numerically more patients in the aspirin group who had major bleeding(15).

A meta-analysis of 9 randomized controlled trials on antiplatelet compared to placebo or control in PAD patients at least 18 years old, some of whom included diabetic patients, with a range of follow-up of 1 month to 6.7 years, showed no significant reduction of the composite of cardiovascular endpoints with aspirin (dose range of 75 to 990mg/day), with moderate heterogeneity in the studies. There was no significant reduction in CV death and mortality with aspirin compared to placebo. Although not statistically significant, there was a numerical increase in the number of major bleeding among those randomized to aspirin(16).

In a systematic review of 28 meta-analysis of 72,181 patients, it was found that there is no secondary prevention benefit for patients with asymptomatic PAD taking antiplatelet monotherapy, but there is a significant increase in the risk of major bleeding. There was high-quality evidence that antiplatelet monotherapy reduced non-fatal strokes (3 fewer per 1000 patients; $P = 0{\cdot}019$), but at a cost of a significantly increased risk of major bleeding (4 more per 1000; $P = 0{\cdot}009$). In asymptomatic patients, there was moderate-quality evidence of a small absolute reduction for non-fatal stroke, which did not reach statistical significance. (5 fewer per 1000 patients; $P = 0{\cdot}055$). Dual antiplatelet therapy resulted in significantly more major bleeding then monotherapy(17). The trials included in the meta-analysis however included those with evidence of coronary artery disease undergoing percutaneous coronary intervention and with several cardiovascular risk factors.

A prospective cohort of 5480 patients, aged 35-85 years with an ABI of $\leq$ 0.95, no PAD symptoms and without clinically recognized CVD were included in a study to look at the effect of statin treatment of MACE and all-cause mortality. Although the study included a low risk population with a median 10-year risk at 6.9%, these were not apparently healthy individuals since diabetes was present in nearly 72%, hypertension in 75%, smoking in 29%, and dyslipidemia in 56%. Statin therapy was significantly associated with a reduction in both MACE and total mortality in those without clinical CVD but with asymptomatic PAD. The absolute reduction was comparable to that achieved in secondary prevention(18). Although results may be applicable to the asymptomatic PAD population, translating it to apparently healthy individuals may be difficult due to directness issues.

4.4.3 Diagnostic Performance of Screening Tests

A. PULSE PALPATION AS A SCREENING TEST

The predictability of absent pulses when compared to the ABI for the diagnosis of PAD in primary clinics in Houston, Texas was studied in 403 patients, among which 67 (16.6%) had PAD. A significant number of patients had hypertension, diabetes and elevated cholesterol. The mean ABI was .72 ± .02 for patients with PAD and 1.13 ±

.01 for patients without PAD (*P*<.0001). Among those with PAD, 25 (37.3%) had no leg symptoms, 37 (55.2%) had atypical leg symptoms, and five (7.5%) had symptoms of classic intermittent claudication. The odds ratio (OR) of a palpable pulse was lower for ABI of 0.51 to 0.69 (OR=.07, 95% confidence interval=.01, .85) when compared to a higher ABI in the range of 0.7 to 0.89.

Sensitivity and specificity was reported at 18-32% and 98-99% respectively, with a positive predictive value of 67%. The study concluded that pulse palpation is an inappropriate screening tool for PAD. A more appropriate tool is the ABI(19).

In another study of 1236 patients, the sensitivity, specificity, NPV, PPV and accuracy of pulse palpation for PAD screening compared with Doppler ABI were 58.2%, 98.3%, 94.9%, 81.1% and 93.8%, respectively(19).

In a mainly asymptomatic primary care population (but at least 1 cardiovascular risk factor), 158 patients (315 legs) underwent pulse palpation and Doppler ABI screening for PAD. The sensitivity if 1 or 2 pulses were missing was 68.4% and 31.6% if both pulses were missing while specificity was 87.4% and 98.6%, respectively. The PPV and NPV if 1 or 2 pulses or 2 pulses were missing were 42.6% or 75% and 95.3 or 91.3%. The study concluded that those without normal or bounding DP and PT pulses should be referred for further evaluation of PAD. The sensitivity of the test was reduced in calcified legs(20).

In the Viborg Vascular Screening Trial, reliability of pedal pulse palpation as initial screening for PAD in a population-based screening program and whether smoking, body mass index (BMI), hypertension, or diabetes affect the reliability of pedal pulse palpation was studied. Analysis of 18,378 showed 12.1% had PAD, 42.3% had hypertension, 10.9% had diabetes and 21.1% were current smokers. Mean BMI was 26.86 kg/m2, and 3246 (18.0%) had a BMI >30 kg/m2 and 3.7% had intermittent claudication. Pedal pulse palpation was misinterpreted in 5022 participants (27.8%): 4420 (24.5%) had a false-positive result, and 602 (3.3%) had a false-negative result. For those with three or fewer pulses, 25.9% were true positive for PAD. Participants with false-positive test results were significantly more obese than participants with a true-positive pulse test. The dorsalis pedis pulse was significantly more often absent compared with the posterior tibialis pulse in participants with three palpable pulses (67.3% vs 32.7%, P < .001), but no difference was found between participants with PAD or without PAD. Four palpable pedal pulses were equal to not having PAD in 11,505 (95.0%). The study found pedal pulse palpation as a reliable initial screening tool for PAD only when four pedal pulses are present. If fewer than four palpable pedal pulses are present, ABI measurements are needed to verify PAD(21).

A study in 24 diabetic patients also observed that the palpation of distal pulses is operator dependent among clinicians with different levels of experience(22).

B. PALPATORY ABI AS A SCREENING TEST

Migliacci compared the ABI measured by palpation against the Doppler method in 196 patients at intermediate cardiovascular risk, of which 4.08% had PAD. Sensitivity of the palpation method was 88%, specificity 82%, positive predictive value 18%,

negative predictive value 99%, positive likelihood ratio = 4.98 and negative likelihood ratio = 0.15. Based on this study, ABI by palpation may be considered as a screening test to exclude PAD(23).

A study of 125 patients with high cardiovascular risk at the Philippine Heart Center tested the diagnostic accuracy of the ABI by palpation compared with Doppler method. PAD prevalence was 33.2% based on ABI by Doppler method and 39.2% based on ABI by palpation method. The sensitivity, specificity, positive predictive value and negative predictive value were 90.4%, 86.1%, 76.5% and 94.7%, respectively, with a high kappa value of 0.732 ± 0.045 and p-value of 0.000. The study concluded that due to high sensitivity and negative predictive value, ABI by palpation can be considered as a good screening tool for patients with PAD(24).

In another study of 79 diabetics (158 ABI readings) at the Makati Medical Center, the accuracy of ABI in predicting PAD with palpation method yielded the following: sensitivity 63.16 % - 73.68%, specificity 94.06% - 98.02%, PPV 85.37% - 95.45%, and NPV within 80.73% - 86.84%. The raters' usage demonstrated a substantial agreement with ABI by Doppler Method performed by the angiologist (Cohen Kappa >0.60). The study concluded that ABI by palpation is a good screening tool for PAD but the person performing it must be adequately trained(25).

All studies above however, were done on patients at increased risk due to presence of cardiovascular risk factors or evidence of atherosclerotic vascular disease, hence, may not be applicable to the apparently healthy individuals we are studying(26).

C. AUSCULTATORY ABI AS A SCREENING TEST

Using a dual- ear piece standard teaching stethoscope and the first Korotkoff sound to determine the systolic pressure for pressure determination for the 4 extremities, the interrater and intrarater reliability of systolic BP measures using a Doppler and stethoscope and correlation between the 2 methods were studied. Use of Doppler to determine systolic pressures to calculate the ABI is most accurate. Interrater and intra-rater ABI measurements with a Doppler were strong to very strong. Interrater and intrarater reliability with a stethoscope was moderate to strong. Correlation between the Doppler and stethoscope was weak to very weak, especially in the lower extremities. Hence, Doppler measurement of ABI is recommended(27).

D. AUTOMATED ABI AS A SCREENING TEST

A study of 54 subjects comparing ABI determined by palpatory, automated BP and Doppler method was done by Aboyans et al. The intra-observer R-coefficient was at 0.89 for dABI vs. 0.60 for pABI ($p < 0.05$). The inter-observer R-coefficients were 0.79 for dABI vs. 0.40 for pABI ($p < 0.05$) and 0.44 for autoABI ($p < 0.05$). There was excessive variability of results obtained by the oscillometric method. The study concluded that neither pulse palpation nor automatic oscillometric devices can be recommended as reliable methods for ABI measurement(28).

E. DOPPLER ABI AS A SCREENING TEST

A systematic review of 8 studies comprising 2043 patients looked at the sensitivity and specificity of ABI ≤ 0.90 for ≥ 50% stenosis compared with a standard reference such as arteriography, Digital Subtraction Angiography (DSA), Computed Tomographic Angiography (CTA), Whole Body Magnetic Resonance Angiography (WBMRA), Doppler Waveform Analysis (DWA), Color Duplex Imaging (CDI) or Color Duplex Ultrasound (CDU). High specificity (83.3–99.0%) and accuracy (72.1–89.2%) were noted, but with different levels of sensitivity (15–79%). Sensitivity was low in elderly individuals and patients with diabetes. The study concluded that the ABI can be a simple and useful tool to identify PAD with significant stenosis, and may be substituted for other non-invasive tests in clinical practice (29).

A Cochrane review on the diagnostic accuracy of ABI in patients with intermittent claudication yielded one study that met the eligibility criteria. The study compared the manual doppler method of obtaining an ABI with the automated oscillometric method. Accuracy of the ABI in detecting significant arterial disease on angiography is superior when stenosis is present in the femoropopliteal vessels, with sensitivity of 97% (95% confidence interval (CI) 93% to 99%) and specificity of 89% (95% CI 67% to 95%) for oscillometric ABI, and sensitivity of 95% (95% CI 89% to 97%) and specificity of 56% (95% CI 33% to 70%) for doppler ABI(30).

A systematic review of 15 studies involving 916 patients looked into the reliability of ABI measurements in different populations. Inter-rater reliability was highly variable, with intraclass correlation coefficients (ICC's) ranging from poor to excellent (ICC 0.42–1.00), while intra-rater also demonstrated considerable variation, with ICCs from 0.42–0.98(31).

4.4.4 Cost Implication

Itoga et al. analyzed the cost effectiveness of ABI screening for asymptomatic peripheral arterial disease. The analysis found benefit from a one-time ABI screening to detect asymptomatic PAD and initiate early medical therapy, reducing CV events and mitigate progression of asymptomatic to symptomatic PAD. With favorable assumptions about the effect of screening on the use of CV risk reducing medications, the ICER was $88,758 per QALY with ABI screening compared to no screening over a 35 year period, which is between the previously reported societal willingness to pay threshold of $50,000 and $100,000. These are similar to previous studies showing benefit from initiation of medication therapy in asymptomatic PAD. Cost effectiveness of screening for asymptomatic PAD with the ABI test depends on the prevalence of disease in the initial population being screened, monthly medication costs, and adherence to medical therapies for CV risk reduction Screening in higher-risk populations under favorable assumptions about medication adherence results in the most favorable cost effectiveness(32).

The VIVA trial of population-based screening and intervention for abdominal aortic anuerysm, peripheral arterial disease or hypertension indicated that vascular screening is cost effective (71% probability for cost effectiveness)(33).

In the Philippines, the cost of Doppler ABI ranges from PHP 500-2,500, depending on the center where it is performed. The Doppler ABI is only available in specialized centers and in clinics of vascular specialists and provision of this test in the primary

clinics may not be feasible since each unit costs PHP 40,000.00. Furthermore, an abnormal ABI test even in an asymptomatic patient might trigger a physician to proceed with more expensive tests to document PAD, such as computed tomographic angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). . Treatment would average 3,650-9125 pesos a year for aspirin and 7,300-20,200 pesos a year for statins, with added potential bleeding risks with antithrombotic therapy in patients with asymptomatic PAD.

4.4.5 Equity, Acceptability, and Feasibility

A systematic review on the quality of life of patients with claudication and critical limb ischemia was done by Abner et al. Seven studies described the impact of PAD on social life and revealed that many patients reported a compromised social life described as not being able to maintain personal role, lack of support from social circle, isolation and the inability to perform hobbies. Problems with isolation and lack of social support were worse among those who had amputations and many felt that a social support group may improve their quality of life. Patients felt their symptoms prevented them from keeping their hobbies, visiting family and friends, and taking part in many activities that they enjoyed.[1]

4.4.6 Recommendations from Other Groups

The 2018 US Preventive Services Task Force stated that there is insufficient evidence to assess screening for PAD using the ABI in asymptomatic adults(35). The 2015 SVS(36), 2016 ACC/AHA(37) and 2020 APSAVD(38-39) guidelines do not recommend screening PAD in the absence of risk factors, history and physical examination findings and symptoms of PAD. The 2017 ESC(40) guidelines however, recommended ABI screening in specific patients at risk for LEAD even if asymptomatic.

Table 6. Summary of Society Recommendations for Peripheral Arterial Disease

Group	Recommendation	Strength of Recommendation and Certainty of Evidence
US Preventive Services Task Force (2018)	Current evidence is insufficient to assess balance of benefits and harms of screening for PAD and CVD risk with the ABI in asymptomatic adults	I statement Low
Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication (2015)	We suggest against routine screening for lower extremity PAD in the absence of risk factors, history, signs, or symptoms of PAD.	Grade 2 LOE C

AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary (2016)	In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD, the ABI is not recommended.	III: No Benefit B-NR
Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease (2020)	In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD, the ABI is not recommended.	Moderate (Class III No Benefit) Moderate (Level B-NR)

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4.5 Screening for Abdominal Aortic Aneurysm

RECOMMENDATIONS

1. **Among asymptomatic men aged 60 to 80 years old, we recommend one-time screening for abdominal aortic aneurysm using ultrasonography *(STRONG recommendation, moderate level of evidence)***

2. **Among asymptomatic women, we recommend against screening for abdominal aortic aneurysm using ultrasonography. *(STRONG recommendation, low level of evidence)***

The consensus panel considered the following when formulating this recommendation:

- Age is a factor in abdominal aortic aneurysm, create recommendations for younger men (age less than 60) who are asymptomatic

4.5.1 Burden of disease

Defined as aortic enlargement with a diameter of 3.0 cm or larger, an abdominal aortic aneurysm (AAA) results from weakening in a section of the abdominal aortic wall which dilates from the pressure exerted by blood flow. (1,2) Based on population-based screening studies done in the United Kingdom, New Zealand, Sweden and Denmark, the prevalence of AAA ranged from 1.2 to 3.3%. (3-13) A similar screening program has not been done in the Philippines. A systematic review involving 17 fair-quality studies and 115, 697 patients showed an AAA prevalence rate of 1.3% (95% CI 1.0% to 1.6%) in the Asian population. (14)

Risk factors associated with AAA include age, sex, smoking status and family history of AAA. The prevalence of AAA is generally 4 to 6 times greater in men than in women. (3) AAA prevalence increases with age. The adjusted odds ratio (OR) for patients aged 55 to 59 years compared to to patients aged <55 years was 2.76 (95% CI 2.6 to 3.0) and 20.4 (95% CI 19.0 to 22.0) for 75 to 79 years. (15) The risk is likewise higher for smokers compared to nonsmokers. The adjusted OR for individuals smoking more than 0.5 packs a day for ≤10 years was 2.6 (95% CI 2.5 to 2.7) compared to 9.0 (95% CI 8.6 to 9.4) for individuals smoking more than 0.5 packs a day >35 years. Family history of AAA in a first-degree relative doubles the risk of developing AAA. (16)

AAA management generally depends on aneurysm size since marked rates of expansion and rupture are often seen in larger aneurysms. (17) The annual risk for rupture is nearly 0% for patients with AAA diameter ranging 3.0 to 3.9 cm, 1% for 4.0 to 4.9 cm and 11% for 5.0 to 5.9 cm. (1) A study which looked at the in-hospital outcomes of patients of 31 patients with small AAAs (diameter of 4.0 to 5.5 cm) at the Philippine Heart Center showed mortality rate of 0%. (18) Because repairing small aneurysms has been found to be more harmful than beneficial, patients with aneurysms measuring 3.0 to 5.5 cm in diameter are advised to maintain ultrasound surveillance at regular intervals as part of current standard of care. (3) In contrast,

patients with aneurysms larger than 5.5 cm or those larger than 4.0 cm that have rapid growth (signified by increase in 1.0 cm diameter in the previous 12 months) are customarily managed by surgical repair. Surgical treatment of large AAAs is currently done via open repair or endovascular aneurysm repair (EVAR). (17)

4.5.2 Benefits and Harms of Screening Tests

One-time screening for AAA using ultrasound among asymptomatic, apparently healthy 65 to 80-year old men was found to be associated with statistically significant reduction in AAA-related mortality, aneurysm rupture, emergency aneurysm operations and 30-day post-operative mortality but has shown no significant effect on all-cause mortality. Screening resulted in increase in the number of AAA-related operations driven largely by the increase in the number of elective operations.

Benefits of Screening

Four population-based randomized controlled trials (n= 134 271) assessing the effect of one-time screening for AAA screening using ultrasound on health outcomes were included in this systematic review: the Multicentre Aneurysm Screening Study (MASS) (10, 19-21), Chichester (11, 22-24), Viborg (12, 25-27), and Western Australia (28) studies. All studies included asymptomatic men aged 64 years and older and initially reported a follow-up of 3 to 5 years. Randomization was done in such a way that the intervention group received one-time screening with ultrasound while the control group received no screening. Analysis was completed by length of follow-up with longest period of 13 to 15 years. The characteristics of these trials are summarized in Table 7.

Table 7. Population-based trials evaluating screening for abdominal aortic aneurysms using ultrasound

RCT	Country	Population (n)	Age of Participants	Sex of Participants	Analysis by Length of Follow-up (years)			
					3 to 5	6 to 7	10 to 11	13 to 15
MASS	United Kingdom	67, 800	65 to 74	Males	Yes	Yes	Yes	Yes
Chichester	United Kingdom	15, 382	65 to 80	Males and Females	Yes	No	Yes	Yes
Viborg	Denmark	12, 639	64 to 73	Males	Yes	Yes	Yes	Yes
Western Australia	Australia	38, 480	65 to 83	Males	Yes	No	No	No

Reported mean ages ranged from 67.7 to 72.6 years with the oldest participants having the age of 83 years. (10-12, 28) Only one trial (Chichester) included women comprising 59% of all participants. Three studies had no trial exclusions; only the MASS trial excluded patients who (1) were identified by their primary care clinicians as too high risk to be screened, (2) were terminally ill, or (3) had other serious health problems or prior AAA repair. All four trials reported AAA-related mortality as primary

outcome. This is defined as all AAA-related deaths plus all deaths within 30 days of AAA surgical repair. All trials also reported all-cause mortality and aneurysm rupture rate as benefit outcomes.

The prevalence of AAA in male participants ranged from 4.0% to 7.6% across the studies. (10-12, 28) Majority of AAAs (87% to 93%) detected were small (measuring <5.5 cm). The overall prevalence of large AAAs (≥5 cm or ≥5.5 cm) in the screened population was 0.3 to 0.6 percent

AAA-related Mortality
Pooled estimate showed 43% reduction in AAA-related mortality (4 trials; RR = 0.57, 95% CI 0.44 to 0.72) for patients who underwent ultrasound screening at follow-up of 3 to 5 years compared to the control group. This effect persisted up to 13 to 15 years of follow-up with 42% reduction (3 trials; RR = 0.58, 95% CI 0.39 to 0.88). Summary evidence is presented in Table 2. The overall quality of evidence was rated moderate and downgraded for serious concerns regarding risk of bias.

All-cause Mortality
To answer the question on benefits of AAA-screening using ultrasound on all-cause mortality, the same 4 RCTs were analyzed. Analysis was completed by length of follow-up (Table 2). AAA screening showed no significant effect on all-cause mortality at 3 to 5 years follow-up (4 trials; RR= 0.94, 95% CI 0.88 to 1.02, p=0.14) but the effect became marginally significant at longer follow-up times and persisted up to 13 to 15 years of follow-up (3 trials; RR = 0.98, 95% CI 0.97 to 1.0; p=0.04). The overall quality of evidence was rated low to moderate and downgraded for serious concerns regarding risk of bias and imprecision.

AAA Rupture
Looking at AAA rupture rate at 3 to 5 years follow-up, pooled estimate from the same RCTs showed 48% reduction (4 trials; RR = 0.52, 95% CI 0.35 to 0.79) in the group which underwent screening compared to the control group. This effect was maintained over a follow-up of 13 to 15 years with 38% reduction (3 trials; RR = 0.62, 95% CI 0.45 to 0.86). The overall quality of evidence was rated moderate to high and downgraded due to serious concerns regarding risk of bias.

Harms of Screening

Data on harms, specifically the frequency of aneurysm operations and 30-day postoperative mortality, were provided by the four trials presented in the benefits section. (10-12, 19-28)

The Viborg Vascular (VIVA) trial is a population-based RCT (n = 50, 156), which evaluated the effect of screening for AAA (using ultrasound), peripheral arterial disease (PAD) (using ankle brachial index) and hypertension on mortality (primary outcome) among men with ages 65 to 74 years. (29) This study, conducted in Central Denmark region from 2008 to 2011, was not included in the review on benefits of screening due to unfeasibility of capturing the independent contribution of AAA screening within the multicomponent screening program. It did, however, provide information on the number of AAA operations (including elective and emergency

procedures) in the study population. Hence, it was included in the current review on the harms of AAA screening.

AAA Operations

One-time AAA screening with ultrasound at follow-up of 3 to 5 years was associated with doubling in the total number of all AAA-related operations (5 trials; RR=2.07 95% CI 1.80 to 2.38). Increase in the number of all AAA operations was maintained over a follow-up of 13 to 15 years (3 trials; RR=1.48 95% CI 1.33 to 1.65). Summary evidence is presented in Table 3. The overall quality of this evidence was rated as moderate to high and downgraded due to serious concerns regarding risk of bias.

The rise in all AAA-related operations appeared to be driven largely by the rise in the number of elective operations (5 trials; RR=2.94 95 % CI 2.16 to 3.99) observed over a follow-up of 3 to 5 years (Table 3). The same effect was seen after 13 to 15-year follow-up (3 trials; RR=2.15 95% CI 1.89 to 2.44). Overall evidence quality was rated as moderate to high and downgraded due to serious concerns regarding risk of bias.

In contrast to the increased rate in elective operations, AAA screening was associated with significant reduction in the frequency of emergency operations performed at 3 to 5-years (5 trials; RR=0.58 95% CI 0.37 to 0.91) This observation persisted up to 13 to 15 years with 50% reduction (3 trials; RR = 0.50 95% CI 0.40 to 0.63). The overall quality of this evidence was rated as moderate to high and downgraded due to serious concerns regarding risk of bias.

30-day Postoperative Mortality

A statistically significant decrease in 30-day post-operative mortality was associated with one-time AAA screening at 3 to 5 years follow-up (3 trials; RR=0.31 95% CI 0.20 to 0.48). This effect persisted over a follow-up of 13 to 15 years (2 trials; RR=0.46 95% CI 0.34 to 0.63). Summary evidence of harms is presented in Table 3. The overall quality of this evidence was rated as moderate to high and downgraded due to serious concerns regarding risk of bias.

Subgroup analysis of elective and emergency AAA operations, however, showed no significant differences between AAA screening and control arms for 30-day post-operative mortality.. For elective operations, the effect of AAA screening on 30-day post-operative mortality was not significant at 3 to 5 years (4 trials; RR=0.51, 95% CI 0.26 to 1.00) and remained so until 13 to 15 years of follow-up (2 trials; RR=0.78 95% CI 0.42 to 1.46). AAA screening had no significant effects also to 30-day post-operative mortality compared to controls at all follow-up time points when data from emergency AAA operations were analyzed. Relative risk was 0.67 (95% CI 0.37 to 1.21) during the 3 to 5-year follow-up period and 0.95 (95% CI 0.69 to 1.31) at 13 to 15-year follow-up period. For both elective and emergency AAA operations subgroups, the overall quality of evidence was rated as low to moderate and downgraded due to serious concerns regarding risk of bias and imprecision

Screening in Women

Among the population-based screening RCTs presented above, only the Chichester trial included women (n=9,342) comprising 59% of all participants. (11) The study

showed lower AAA prevalence among females (aged 65 to 80 years) compared to their male counterparts (1.3% vs 7.6%). Seventy-five percent of the aneuryms were small (3.0 to 3.9 cm in diameter). Emergency repair rates in both screened and control groups were rare (0.02%) at 5-year follow-up. Rupture rates were likewise similar (0.2%) in both groups at 10 year follow-up. Majority of women (70%) suffered rupture after the age 80 years. The trial, however, was insufficiently powered to detect AAA-related mortality or all-cause mortality differences in women and no formal interaction testing was performed. While more than half of AAA-related deaths in men included in the Chichester trial occurred before 80 years of age, more than two-thirds of deaths from AAA occurred in women 80 years and older. (30)

The evidence certainty for screening is found in the appendix. The quality of evidence was downgraded to low because of insufficient sample size and wide confidence intervals resulting in serious concerns about imprecision.

4.5.3 Diagnostic Performance of Screening Tests

In a meta-analysis of 7 studies (n= 655) which looked into the accuracy of bedside abdominal ultrasonography using computed tomography, magnetic resonance imaging, aortography, official ultrasound performed by a radiologist, exploratory laparotomy or autopsy results as comparator, the pooled opearating characteristics of ultrasound for AAA detection included sensitivity of 99% (95% CI 96% to 100%) and specificity of 98% (95% CI 97% to 99%). (32-39). Overall quality of evidence was deemed low due to issues concerning risk of bias and indirectness.

4.5.4 Cost Implication

Studies done in several western countries conclude that AAA screening implementation is generally cost-effective. A systematic review of 15 studies from 7 countries in Europe and North America reported an incremental cost-effectivess ratio (ICER) estimate of $16,854 (95% CI $4,932 to $28,777) per quality-adjusted life-year (QALY) gained . (40) This fulfilled the cost-effectiveness criteria since it fell below the cost effectiveness threshold (CET) traditionally set at $50,0000/QALY based on previous ICER estimates for renal dialysis in the United States.

No local study delving into cost-effectiveness of AAA screening is currently available. The current cost of abdominal ultrasound in the Philippines ranges from Php1,500 to Php2,500. A rough estimate of hospitalization cost for both EVAR and open surgical repair of AAA would be Php500,000 to Php 1,000,000.

4.5.5 Equity, Acceptability, and Feasibility

To examine patients' perceptions of harms and benefits of AAA screening and treatment, a survey among patients 65 to 80 years was done in Canada (n=19). Participants were informed of potential benefits and risks of screening including overdiagnosis. Most participants would choose to be screened if they feel that the risk factors for an AAA applied to them. (41)

Exploring the ethical issues of the publicly-funded screening program for AAA in men in the UK, Brownstorm and Earnshaw concluded that population screening for AAA offers a clear balance of good over harm and is therefore ethically justified as long as patients are given adequate information at every stage of the process. (42) There is no publicly-funded screening program for AAA screening in the Philippines. As out-of-pocket expenses remain to be Filipinos' major source of financing for medical care (43), low uptake is expected if a screening program for AAA will be implemented locally.

4.5.6 Recommendations from Other Groups

The US Preventive Services Task Force (USPSTF) recommends one-time screening for AAA with ultrasonography in men aged 65 to 75 years who have ever smoked. (1) It further recommends that clinicians selectively offer screening for AAA with ultrasonography in men aged 65 to 75 years who have never smoked rather than routinely screening all men in this group. The Canadian Task Force on Preventive Health Care (CTFPHC), on the other hand, recommends one-time screening with ultrasonography for AAA in men aged 65 to 80 years regardless of their smoking history. (2) For men older than 80 years, the Canadian task force recommends no screening. These recommendations are presented in Table 4.
For women who have never smoked and have no family history of AAA, the USPSTF recommends against routine screening for AAA. It concluded that the current evidence is insufficient to assess the balance of benefits and harms for AAA screening in women aged 65-75 years who have ever smoked or have a family history of AAA. The CTFPHC recommends not screening women for AAA altogether. (2)

Table 8. Recommendations for AAA screening from other groups

Group	Recommendation	Strength of Recommendation and Certainty of Evidence
Canadian Task Force on Preventive Health Care (CTFPHC)	The CTFPHC recommends one-time screening with ultrasonography for AAA for men aged 65 to 80	Weak recommendation; moderate quality of evidence
	The CTFPHC recommends not screening men older than 80 years for AAA	Weak recommendation; low quality of evidence
	The CTFPHC recommends not screening women for AAA	Strong recommendation; very low quality of evidence
US Preventive Services Task Force (USPSTF)	The USPSTF recommends one-time screening for AAA with ultrasonography in men aged 65 to 75 years who have ever smoked	B recommendation
	The USPSTF recommends that clinicians selectively offer screening for AAA with ultrasonography in men aged 65 to 75 years who have never smoked rather than routinely screening all men	C recommendation

in this group. Evidence indicates that the net benefit of screening all men in this group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of evidence relevant to the patient's medical history, family history, other risk factors and personal values.	
The USPSTF recommends against routine screening for AAA with ultrasonography in women who have never smoked and have no family history of AAA.	D recommendation
The USTPSF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for AAA with ultrasonography in women aged 65 to 75 who have ever smoked or have family history of AAA.	I statement

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4.6 Screening for Atrial Fibrillation

Use of Pulse Palpation for Atrial Fibrillation

RECOMMENDATION

Among asymptomatic apparently healthy adults, we recommend against screening for atrial fibrillation using pulse palpation. *(STRONG recommendation, moderate level of evidence)*

Use of 12-Lead Electrocardiography for Atrial Fibrillation

RECOMMENDATION

Among asymptomatic apparently healthy adults, we recommend against screening for atrial fibrillation using 12-Lead Electrocardiography. *(STRONG recommendation, low level of evidence)*

The consensus panel considered the following when formulating this recommendation:

- Educate primary healthcare worker to do a one-minute pulse rate during physical examination

4.6.1 Burden of disease

Globally, in 2019, the prevalence of AF is estimated to be 2 to 4% in all adults (1). In 2010, using the Global Burden of Disease framework, the estimated age-adjusted AF prevalence in the Philippines was 400 to 475/ 100,000 population. (2).

In 2003, among the 3907 adults from the general population, 20 years old and above, who were part of the National Health Survey (NHES-FNRI), the overall prevalence of AF diagnosed via a single point 12-lead ECG was 0.2%. AF was observed to be more prevalent in the elderly population, 70 years old and above at 2%, and among males at 2.2% (3).

AF-associated strokes, mostly thought to be via systemic embolization, are observed to result to more permanent disabilities, have higher rates of recurrences, and can sometimes be fatal (4). They occur in 20 to 30% of AF patients, more often among those with comorbidities (1). In the Global Survey of the Frequency of Atrial Fibrillation–Associated Stroke done in 2016, a site in Manila reported that among 175 hospitalized ischemic strokes, 11% was associated with AF. In the same survey, the 30-day mortality of those with AF-associated stroke was significantly higher at 10%, compared with those of patients without AF (5).

Heart failure (HF) can occur in 20 to 30% of patients with AF via multiple mechanisms including atrioventricular dysscynchrony and tachycardia (1). AF and HF often co-exist and their interplay can trigger or exacerbate each other. In the United Kingdom ACALM Registry, it was observed that patients with HF in AF had longer hospital stays and had an all-cause mortality of 70.8% (6).

Management

In patients with AF, stroke is prevented via anticoagulation after risk assessment, in patients who are identified to be at high risk via $CHADS_2VASc$ scoring (Table 1). The risk of HF can be reduced via rhythm or rate control strategies which may include pharmacologic and non-phacologic forms of therapy including DC cardioversion and catheter ablation. While there are currently no guidelines to adapt a rhythm control strategy in asymptomatic patients, it is recommended to control heart rate to less than 110 beats/minute (7).

Table 9. CHADS2VASc Score.

$CHA_2DS2VASc$ score	Risk Factors	Points awarded
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age 75 years or older	2
D	Diabetes mellitus	1
S	Previous Stroke	2
V	Vascular Disease	1
A	Age 65-74 years	1
Sc	Sex category: Female	1
	Maximum score	9

Reference: Hindricks, G., Potpara, T., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journa.l 2020; 00: 1-125

In a systematic review of 24 AF screening studies which included 141,220 participants from 14 countries, 1,539 new AF cases were reported among those aged 65 and above, and using CHADSVASc score, this population was estimated to have higher stroke risks with more than 70% requiring anticoagulation (8).

4.6.2 Benefits and Harms of Screening Tests

There are currently no studies specifically describing benefits nor harms of screening for AF among asymptomatic, apparently healthy adults. The same observation was also stated in the 2021 Evidence Review of the US Preventive Services Task Force (9) and the 2019 UK National Screening Committee (10).

There were 2 RCTs however, which presented clinical outcomes after screening for AF and subsequent medical therapy including anticoagulation if indicated, among adult patients.

The Assessment of Remote Heart Rhythm Sampling using AliveCor heart monitor to screen for Atrial Fibrillation (REHEARSE-AF) enrolled 1001 participants aged 65 and above with other stroke risks (a $CHADS_2VASc$ score of 2 and above), and compared screening for AF using AliveCor Kardia, a handheld device able to record a single lead ECG similar to lead I for 30 seconds twice weekly (n= 500) , with no screening (n= 501) over 12 months. This study only analyzed clinical outcomes as a secondary

endpoint and reported 6 composite events of stroke, transient ischemic attack and systemic embolism in the screening group versus 10 in the no screening group (hazard ratio [HR], 0.6 [95% CI, 0.2 to 1.7]; p=0.34) (11).

The STROKESTOP trial enrolled 75-76 year olds including those with comorbidities, with no prior AF from 2 regions in Sweden and compared screening for AF using intermittent ECG recorced twice daily for 2 weeks, via a handheld single lead ECG, Zenicor (n= 13,979), with no screening (n= 13,996) over a minimum of 5 years. There were less composite endpoints of ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and all-cause death in the screening group (31.9%) versus the no screening group (33%) (hazard ratio 0·96 [95% CI 0·92–1·00]; p=0·045) (12).

While these two trials enrolled patients with no ongoing treatment for AF, both did not exclude patients with comorbidities which are considered individual risk factors for stroke. The primary outcome measured in REHEARSE-AF was time to detection of AF among patients with CHADS2VASc scores of at least 2. Hence, all patients analyzed had pre-existing comorbidities. The STROKESTOP trial aimed to assess systematic screening for AF specifically among the elderly population without excluding pre-existing comorbidities. These two trials show only little to no effect of screening for AF among adults- a significant proportion with comorbidities, in reduction of stroke, systemic embolism, and death.

No trials reported outcomes of patients screened for AF using pulse palpation alone. The D2AF Trial used a composite screening of combined pulse palpation, sphygmomanometer with automated AF detection and handheld single-lead electrocardiogram (ECG) (* D2AF)

Two trials specifically described harm directly related to screening for AF. The SAFE study, a randomized controlled trial and cost-effectiveness study of systematic screening versus routine practice for the detection of atrial fibrillation in people aged 65 and over, employed pulse palpation and single- and 12-lead ECG as screening tools. In a subgroup analysis, it assessed anxiety using the Spielberg Six-Item Anxiety Questionnaire (S6AQ) at 3 different time points: before randomization (n= 750), immediately after screening (n= 1940), and 17 months after baseline (n= 535). The screen-positive patients had higher mean anxiety scores (38.12 [95% CI, 35.89 to 40.35]) compared to the screen-negative patients (34.61 [95% CI, 32.41 to 36.81]) (unadjusted p=0.028). These scores, however, are not considered clinically meaningful and represented only a small proportion of the total study population (13).

The mSToPs trial enrolled a total of 2659 individuals who were randomized to active home-based monitoring using the iRhythm ZioXT, a single-use, water resistant, 14-day, ambulatory ECG monitoring skin adhesive patch for up to 2 weeks. While this particular patch is not currently available in the country, the adhesive used may be similar to the ones used in Holter monitoring. Skin irritation was reported in 40 participants (1.5%), leading to early discontinuation in 32, and the need of topical therapy in 2 (14). It was not reported how early this finding was noted; thus it is uncertain whether a single point ECG tracing will result to the same harm.

There are currently no trials specifically reporting benefits and harms of anticoagulation among patients with screen-detected AF.

From the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) Registry, a cohort of 26,668 newly diagnosed AF patients from 1000 centers from 35 countries over 2 years showed that treatment with anticoagulation reduced stroke and systemic embolism (adjusted HR 0.73, 0.62 to 0.86) but caused more major bleeding (adjusted HR 1.73, 1.33 to 2.25) (15).

The 2 RCTs earlier mentioned which evaluated clinical outcomes of screening for AF also reported bleeding as an adverse event.

REHEARSE-AF trial reported 2 cases of gastrointestinal bleeding among the 500 participants who were screened and 1 case of ocular bleeding among the 501 participants who were not screened. This was not statistically significant (p = 0.56) and all of the 3 patients were not given anticoagulation (11).

STOPSTROKE also reported no significant difference in hospitalization for major bleeding (1431 out of the 13979 who were screened versus 1448 out of the 13996 who were not screened; p= 0.56) (12). (Table 3).

4.6.3 Diagnostic Performance of Screening Tests

The most common screening tests cited in literature which are widely available in the Philippines are pulse palpation and 12-lead ECG. While the diagnosis of AF via recording a single lead ECG for at least 30 seconds or tracing a 12-L ECG documenting the rhythm in patients who may have persistent AF is straightforward, screening can be challenging since AF can be paroxysmal defined as less than 7 days. The risk of stroke and other complications, though assumed to be smaller in paroxsymal AF, is still considered significant, and warrants the same forms of treatment. Hence systematic screening- at times employing different diagnostic modalities performed in different time intervals may be required (1).

A systematic review was conducted by Cooke et al (2006) on the value of doing pulse palpation in ruling out atrial fibrillation. The patient population was in the elderly population, age 65 and above, and utilized radial pulse measured by an experienced healthcare professional. The length of measurement was 20 seconds in one study. The comparator was using a 12 L ECG, which was read by a cardiologist. Results showed a pooled sensitivity of 94% (95% CI 84-97%) and a pooled specificity of 72% (95% CI 69-75%). The use of pulse palpation for ruling out AF may be a useful screening tool for previously undetected AF in patients older than 65 years. However, there is a need to do further testing with an ECG (16) (Table 4).

Using ECG- either single lead or 12-lead confirmed by a doctor as reference, a summary of 4 studies which screened for AF among patients 65 years and above yielded a sensitivity of 87 to 97% and a specificity of 70 to 81% for pulse palpation done by a nurse (17)

A systematic review of 15 diagnostic test accuracy studies which included systematic opportunistic, targeted and population screening for AF reported a 93% sensitivity and

97% specificity for 12-lead ECG using interpretation by a cardiologist as reference (18).

A two-stage screening strategy yielded a mean sensitivity of 94% and a mean specificity of 96%, the best sensitivity was observed when a 12-lead ECG was performed as the second-stage test (18).

4.6.4 Cost Implication

There are no studies reporting cost effectiveness of AF screening in the country.

Pulse palpation can be done by a medical physician during a clinic visit . The cost of a 12-lead ECG with an official interpretation by a doctor, commonly a Cardiologist ranges from P200 to P1200.

The cost effectiveness of the national annual AF screening program in Ireland involving pulse palpation of adults aged 65 and above, followed by a 12 lead ECG interpreted by a general practitioner, done only if initial screening is positive, was calculated using a probabilistic Markov model to stimulate costs and clinical outcomes in a hypothetical cohort over 25 years. The incremental cost-effectiveness ratio (ICER) is 23,004 Euros/QALY and is likely to be cost-effective using conventional willingness to pay thresholds. Considering perceived lower clinical events in this population, a subanalysis of screening using the same methods among those aged 75 and older was shown to be more cost-effective with an ICER of 8,000 Euros/QALY (19).

4.6.5 Equity, Acceptability, and Feasibility

REHEARSE-AF participants were given experience questionnaire answered via scoring a visual analog scale form 1 to 10. There was a slightly higher reported awareness of the risk (mean score, 6.8 ver- sus 6.1; P=0.001) but slightly less anxiety about the risks of outcomes (mean score, 2.2 versus 2.5; P=0.003) and slightly lower reported likelihood of intending to visit their physician (mean score, 7.1 versus 7.5; P=0.04).

There were significantly greater preference among those who were not screened to be switched to the other arm (mean score, 1.9 versus 6.2; P<0.0001) (11).

4.6.6 Recommendations from Other Groups

The 2020 European Society of Cardiology guidelines recommend (Class IB) to do opportunistic screening for AF using pulse palpation or single lead ECG among patients 65 and above, and to consider (a Class IIB) systematic screening for AF among patients 75 and above (1). The 2019 UK National Screening Committee mentioned that while population screening for AF is cost effective, the benefit is not clear, hence it is not recommended (9). The 2021 US Preventive Services Task Force, also concluded that there is insufficient evidence to assess the balance of benefits and harms of screening for AF among asymptomatic adults aged 50 and above (8).

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5. RESEARCH IMPLICATIONS

Many research questions from the identified clinical questions in this CPG were unanswered in terms of benefits and harms of screening, equity, applicability, and feasibility. Direct evidence is still lacking to aid in providing definite recommendations for screening certain conditions using the tests. As recommended by the consensus panel, most of the screening tools in this guideline deal with taking the appropriate history and physical examination such as family history and stigmata in FH, carotid bruit identification in ACAS, pulse palpation in PAD and AF. There are limited data on these tests.

Generating direct evidence (screening *vs.* no screening) may be difficult, particularly in cardiovascular diseases. Because of this challenge, in some instances, establishing the diagnostic performance of tests as indirect evidence can be adequate. However, specific tests' accuracy in detecting early diseases and preventing them from developing into a chronic or more severe state is still not investigated. For example, there are still no studies showing diagnostic performance of a resting 12-LECG in apparently healthy individuals for CAD, or abdominal ultrasound in the younger population.

There have been cost-effectiveness studies available for screening the diseases included in this CPG, but most of them are conducted in Western countries. Cardiovascular disease is increasing in prevalence in the Philippines, and there is lack of local cost effectiveness studies included in this consensus statement. There is a need to look at health economic data for CVD.

Social science research also plays a vital role in examining the impact of the diseases. However, few qualitative studies were found to provide a holistic view of the impact of screening for some conditions. Qualitative studies can also provide information on motivators or determinants among the general population in participating in a screening program despite the probable harm of stigma and mislabeling afterward.

Examining needs and monitoring implementation of screening programs were also found to be not well-established even if, in some conditions, guidelines and programs are already in place. Perspectives and experiences of clinical practitioners and other stakeholders directly involved in screening programs are rarely reported in studies.

Many research questions emerged from collating the evidence for this CPG and can be explored further. Filling in these gaps can provide a clearer picture of the impact of screening programs using previously mentioned tests and may influence the recommendations for updating this guideline.

6. DISSEMINATION AND IMPLEMENTATION

A full copy of this document will be sent to the Department of Health for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC) and health maintenance organizations (HMOs) and NGOs involved in a periodic health examination. The recommendations and the evidence summaries will be posted in the PHEX web based application. They will be also be posted in the different medical societies involved in the consensus panel, such as PCP, PHA, PLAS, PSH, PSVM and PSN.

All strong recommendations in this guideline can be used for monitoring and auditing practices in institutions. These can be converted to key performance indicators and it can also be used in creating clinical pathways.

The DOH planned to develop a simplified version of this CPG and made it available in the format that will be ready for reproduction and dissemination to the patients in different health care settings. It will also be available for interested parties who might visit the DOH website. The different medical societies may also include the guidelines in their own websites.

7. APPLICABILITY ISSUES

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. Comprehensive history taking, physical examination, and monitoring are essential parts of evaluating risk factors and the probability of developing diseases. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those part of the workforce.

8. UPDATING OF THE GUIDELINES

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. The CPGs will be updated every 3-5 years or earlier if new significant evidence becomes available.

9. APPENDICES

1. Familial Hypercholesterolemia

Appendix 1. Quality Assessment of Cohort Study in FH

	Selection				Comparability		Outcome			Total
Study	Representative of Exposed Cohort	Selection of non-exposed cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at the start of the study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of Outcome	Follow-up length	Lost to follow-up rate	Quality Score
Vermissen 2008	1	0	1	1	1	1	1	1	1	7
Raal 2011	1	1	1	1	1	0	1	1	1	7

Vermissen 2008

1) Somewhat representative of exposed cohort – Recruited 2,400 FH patients from 27 lipid clinics in Netherlands with aged ≥ 55 years old
2) Selection of non-exposed cohort – patients were drawn from the Rotterdam study, a large population based prospective cohort
3) Ascertainment of exposure – medical records
4) Demonstration that outcome of interest was not present at the start of the study – excluded patients who had coronary heart disease
5) Comparability – adjusted for age and sex, plus other risk factors such DM, HPN, smoking status, HDL-C and LDL-C levels (different models – table 2)
6) Assessment of outcome - medical records
7) Follow-up of 12 years
8) Lost to follow-up = 8 patients

Raal 2011

1) Exposed cohort – homozygous FH patients post Jan 1, 1990 in South Africa (post-statin)
2) Non-exposed cohort – homozygous FH patients pre-Jan 1, 1990 in SA (pre-statin)
3) Ascertainment of exposure – medical records
4) Demonstration that outcome of interest was not present at the start of the study - For the end point of death, patients still alive at the end of the study period, March 31, 2009, were censored on this date. For the end point of MACE, patients who had not had a MACE at the end of the study period were also censored on this date.
5) Comparability – adjusted for age
6) Assessment of outcome – medical records
7) Follow-up – 40 years
8) Lost to follow-up 16 patients

Appendix 2. GRADE PRO Evidence Table for the Different Parameters in FH

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Change in serum LDL cholesterol level (%) - At end of follow-up												
6	randomised trials	not serious	not serious	serious [a]	not serious	none	451	218	-	MD **32.15 lower** (34.9 lower to 29.4 lower)	⨁⨁⨁◯ MODERATE	5
Change in serum total cholesterol levels (%) - At the end of follow-up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	control	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	not serious	not serious	serious [a]	not serious	none	451	218	-	MD **26.53 lower** (28.54 lower to 24.51 lower)	⨁⨁◯◯ MODERATE	5

Change in serum triglyceride levels (%) - At the end of follow-up

5	randomised trials	not serious	not serious	serious [a]	not serious	none	365	160	-	MD **3.27 lower** (12.03 lower to 5.5 higher)	⨁⨁◯◯ MODERATE	5

Change in serum HDL cholesterol levels (%) - At the end of follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	control	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	not serious	not serious	serious [a]	not serious	none	451	218	-	MD **3.11 higher** (0.55 higher to 5.67 higher)	⨁⨁⨁◯ MODERATE	5

Change in aspartate aminotransferase levels (> 3x ULN) - At 6 months

4	randomised trials	serious [b]	not serious	serious [a]	serious [c]	none	4/344 (1.2%)	0/194 (0.0%)	**RR 2.40** (0.29 to 19.85)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	5

Change in aspartate aminotransferase levels (> 3x ULN) - At 2 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	serious [a]	serious [c]	none	0/104 (0.0 %)	2/107 (1.9 %)	**RR 0.21** (0.01 to 4.23)	**15 fewer per 1,000** (from 19 fewer to 60 more)	⨁◯◯◯ VERY LOW	5

Change in alanine aminotransferase levels (> 3x ULN) - At 6 months

4	randomised trials	serious [b]	not serious	serious [a]	serious [c]	none	3/344 (0.9 %)	0/194 (0.0 %)	**RR 2.03** (0.24 to 16.95)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	5

Change in alanine aminotransferase levels (> 3x ULN) - At 2 years

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	serious [a]	serious [c]	none	0/104 (0.0 %)	0/107 (0.0 %)	not estimable		⨁◯◯◯ VERY LOW	5
Myopathy: Change in creatine kinase levels (> 10x ULN) - At 1 year												
2	randomised trials	serious [b]	not serious	serious [a]	serious [c]	none	1/147 (0.7 %)	1/107 (0.9 %)	**RR 0.67** (0.04 to 10.57)	**3 fewer per 1,000** (from 9 fewer to 89 more)	⨁◯◯◯ VERY LOW	5

Appendix 3. GRADE Pro Evidence for Stress Echocardiography in Coronary Artery Disease

Question:Stress Echocardiography compared to No Screening for asymptomatic, apparently healthy individuals
Bibliography: Bauters C, Lemesle G. Screening for asymptomatic coronary artery disease in pateints with diabetes mellitus: A systematic review and meta-analysis of randomized trials. *BMC Cardiovascular disorders (2016). 16:90*

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stress Echocardiography	No Screening	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All Cause Mortality (follow-up: range 3 years to 5 years)												
5	randomised trials	not serious	not serious	serious[a]	serious[b]	none	49/1400 (3.5%)	50/1394 (3.6%)	**OR 1.00** (0.67 to 1.50)	**0 fewer per 1,000** (from 12 fewer to 17 more)	⨁⨁◯◯ Low	CRITICAL
Cardiovascular Mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stress Echocardiography	No Screening	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	not serious	not serious	serious[a]	serious[b]	none	16/1346 (1.2%)	23/1337 (1.7%)	**OR 0.72** (0.33 to 1.57)	**5 fewer per 1,000** (from 11 fewer to 10 more)	⨁⨁◯◯ Low	CRITICAL
Fatal and Non fatal Myocardial Infarction (follow-up: range 3 years to 5 years)												
5	randomised trials	not serious	not serious	serious[a]	serious[b]	none	26/1346 (1.9%)	38/1337 (2.8%)	**OR 0.71** (0.40 to 1.27)	**8 fewer per 1,000** (from 17 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio

Explanations

a.Study population consisted of asymptomatic diabetics, screening methods included modalities other than stress echocardiography

b.Event rate was too low in either group

Appendix 4. GRADE PRO for Anti-ischemic Therapy in Coronary Artery Disease

Question:Anti-ischemic therapy compared to Risk factor control for asymptomatic individuals with positive results on stress echocardiography

Bibliography: Erne P, Schoenenberger AW, Zuber M, Burckhardt D, Kiowski W, Dubach P, et al. Effects of anti-ischaemic drug therapy in silent myocardial ischemia type I: the Swiss Interventional Study on Silent Ischaemia type I: a randomized, controlled pilot study, Eur. Heart. J 2007; 28: 2110-2117 .

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-ischemic therapy	Risk factor control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All cause mortality												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect	0/26 (0.0%)	4/28 (14.3%)	outcomen ot_estimable		⨁⨁⨁◯ Moderate	CRITICAL
Cardiovascular Mortality (follow-up: mean 11.2 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect	0/26 (0.0%)	3/28 (10.7%)	outcomen ot_estimable		⨁⨁⨁◯ Moderate	CRITICAL
Fatal and Nonfatal MI (follow-up: mean 11.2 years)												

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-ischemic therapy	Risk factor control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious[a]	not serious	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect	1/28 (3.6 %)	16/28 (57.1 %)	**HR 0.03** (0.01 to 0.23)	**546 fewer per 1,000** (from 563 fewer to 394 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio

Explanations

a.Allocation concealment was not feasible

b.Small sample size, few events

Appendix 5. GRADE Pro Evidence Tables in the Use of Angiography in Coronary Artery Disease

Question:Angiography with revascularization compared to medical therapy for asymptomatic coronary artery disease

Bibliography: Maron DJ, Hochman JS, Reynolds HR, Bangalor S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease.N Engl J Med. 2020; 382: 1395-407.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angiography with revascularization	medical therapy	Relative (95% CI)	Absolute (95% CI)		
All cause Mortality (follow-up: median 3.2 years)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	145/2588 (5.6%)	144/2591 (5.6%)	**HR 1.05** (0.83 to 1.32)	**3 more per 1,000** (from 9 fewer to 17 more)	⊕◯◯◯ Very low	CRITICAL
Cardiovascular mortality (follow-up: median 3.2 years)												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	276/2588 (10.7%)	314/2591 (12.1%)	outcome not_estimable		⊕◯◯◯ Very low	CRITICAL
Myocardial Infarction (follow-up: median 3.2 years)												
1	randomised trials	not serious	not serious	very serious[a]	very serious[b]	none	210/2588 (8.1%)	233/2591 (9.0%)	outcome not_estimable		⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; **HR:** hazard Ratio

Explanations

a.Most of participants have had at least a history of angina, and comorbidities like hypertension and diabetes

b.Inadequate sample size

Appendix 6. GRADE Pro Evidence Tables of Resting Echocardiography in Coronary Artery Disease

Question: Should resting echocardiography be used to screen for coronary artery disease in asymptomatic, apparently healthy individuals?

Sensitivity	0.87 (95% CI: 0.75 to 0.94)
Specificity	0.41 (95% CI: 0.29 to 0.55)

Prevalences	25%	50%	75%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
True positives (patients with coronary artery disease)	1 studies 100 patients	cross-sectional (cohort type accuracy study)	not serious	serious[a]	not serious	serious[b]	none	218 (187 to 235)	436 (374 to 470)	654 (561 to 705)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having								32 (15 to 63)	64 (30 to 126)	96 (45 to 189)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
coronary artery disease)											
True negatives (patients without coronary artery disease)	1 studies 100 patients	cross-sectional (cohort type accuracy study)	not serious	serious[a]	not serious	very serious[c]	none	311 (219 to 412)	208 (146 to 275)	104 (73 to 137)	⨁◯◯◯ Very low
False positives (patients incorrectly classified as having coronary artery								439 (338 to 531)	292 (225 to 354)	146 (113 to 177)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
disease)											

Explanations

a. Study included an unspecified number of patients with diabetes. Presence/absence of symptoms and other comorbidities were not stated.

b. Small sample size

c. small sample size, wide confidence intervals

Question: Should resting echocardiography be used to screen for coronary artery disease in asymptomatic, apparently healthy individuals?

Sensitivity	0.89 (95% CI: 0.77 to 0.95)
Specificity	0.42 (95% CI: 0.30 to 0.55)

Prevalences	25%	50%	75%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
True positives (patients with coronary artery disease)	1 studies 100 patients	cross-sectional (cohort type accuracy study)	not serious	serious[a]	not serious	serious[b]	none	222 (191 to 238)	445 (383 to 476)	667 (574 to 714)	⊕⊕◯◯ Low

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
False negatives (patients incorrectly classified as not having coronary artery disease)								28 (12 to 59)	55 (24 to 117)	83 (36 to 176)	
True negatives (patients without coronary artery disease)	1 studies 100 patients	cross-sectional (cohort type accuracy study)	not serious	serious[a]	not serious	very serious[c]	none	314 (223 to 413)	209 (149 to 275)	105 (74 to 138)	⨁◯◯◯ Very low
False positives								436 (337 to 527)	291 (225 to 351)	145 (112 to 176)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
(patients incorrectly classified as having coronary artery disease)											

Explanations

a. Study included an unspecified number of patients with diabetes. Presence/absence of symptoms and other comorbidities were not stated.

b. Small sample size

c. small sample size, wide confidence intervals

Appendix 7. GRADE Pro Evidence Tables in the Use of Stress Echocardiography in Coronary Artery Disease

Question: Should Stress Echocardiography be used to screen for Coronary Heart Disease in Asymptomatic, apparently healthy individuals ?

Sensitivity	0.72 (95% CI: 0.61 to 0.81)
Specificity	0.89 (95% CI: 0.83 to 0.93)

Prevalences	25%	50%	75%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
True positives (patients with Coronary Heart Disease)	9 studies 652 patients	cohort & case-control type studies	not serious	serious[a]	not serious	not serious	none	180 (153 to 203)	360 (305 to 405)	540 (458 to 608)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having Coronary Heart Disease)								70 (47 to 97)	140 (95 to 195)	210 (142 to 292)	
True negatives (patients without Coro	9 studies 652 patients	cohort & case-control typ	not serious	serious[a]	not serious	not serious	none	668 (622 to 698)	445 (415 to 465)	223 (208 to 233)	⨁⨁⨁◯ Moderate

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of25 %	pre-test probability of50 %	pre-test probability of75 %	
nary Heart Disease)		e studies									
False positives (patients incorrectly classified as having Coronary Heart Disease)								82 (52 to 128)	55 (35 to 85)	27 (17 to 42)	

Explanations

a. Studies included patients with atypical chest pain and comorbidities

3. Asymptomatic Carotid Artery Stenosis

Appendix 8: GRADE Pro Evidence Tables Comparing Carotid Artery Stenting compared with Carotid Endarterectomy

Author(s):
Question: Carotid artery stenting compared to Endarterectomy for People with Asymptomatic Carotid stenosis
Setting: Hospital
Bibliography: Müller MD, Lyrer P, Brown MM, Bonati LH. Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis [Data only. When citing

this record quote "Cochrane Database of Systematic Reviews 2020, Issue 2".]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carotid arterystenting	Endarterectomy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Death or any stroke between randomisation and 30 days after treatment												
8	randomised trials	not serious	not serious	serious [a]	serious [b]	none	116/3869 (3.0%)	66/3134 (2.1%)	**RR 1.46** (1.07 to 1.98)	**10 more per 1,000** (from 1 more to 21 more)	⨁⨁◯◯ LOW	CRITICAL
Death or major or disabling stroke between randomisation and 30 days after treatment												
3	randomised trials	not serious	not serious	serious	serious [b]	none	23/3477 (0.7%)	21/2749 (0.8%)	**RR 0.94** (0.51 to 1.74)	**0 fewer per 1,000** (from 4 fewer to 6 more)	⨁⨁◯◯ LOW	CRITICAL
Myocardial infarction between randomisation and 30 days after treatment												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carotid arterystenting	Endarterectomy	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	not serious	not serious	serious [a]	serious [b]	none	17/3655 (0.5%)	28/2915 (1.0%)	**RR 0.49** (0.26 to 0.91)	**5 fewer per 1,000** (from 7 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL

Death or any stroke or myocardial infarction between randomisation and 30 days after treatment

7	randomised trials	not serious	not serious	serious [a]	serious [b]	none	126/3672 (3.4%)	86/2931 (2.9%)	**RR 1.20** (0.91 to 1.58)	**6 more per 1,000** (from 3 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL

Death or any stroke between randomisation and 30 days after treatment or ipsilateral stroke until end of follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carotid arterystenting	Endarterectomy	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	not serious	not serious	serious [a]	serious [b]	none	86/2020 (4.3%)	46/1295 (3.6%)	**RR 1.25** (0.88 to 1.79)	**9 more per 1,000** (from 4 fewer to 28 more)	⨁⨁◯◯ LOW	CRITICAL
Death or any stroke or myocardial infarction between randomisation and 30 days after treatment or ipsilateral stroke until end of follow-up												
5	randomised trials	not serious	not serious	serious [a]	serious [b]	none	82/1806 (4.5%)	52/1076 (4.8%)	**RR 1.09** (0.77 to 1.54)	**4 more per 1,000** (from 11 fewer to 26 more)	⨁⨁◯◯ LOW	CRITICAL

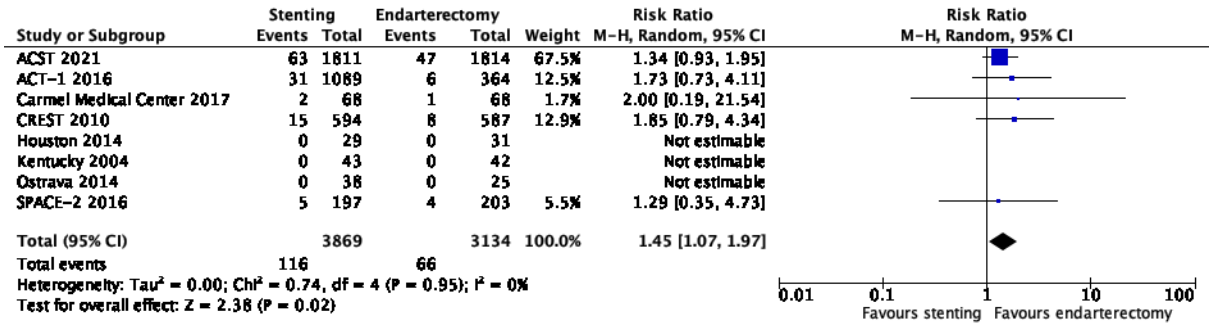
CI: confidence interval; **RR:** risk ratio

Explanations

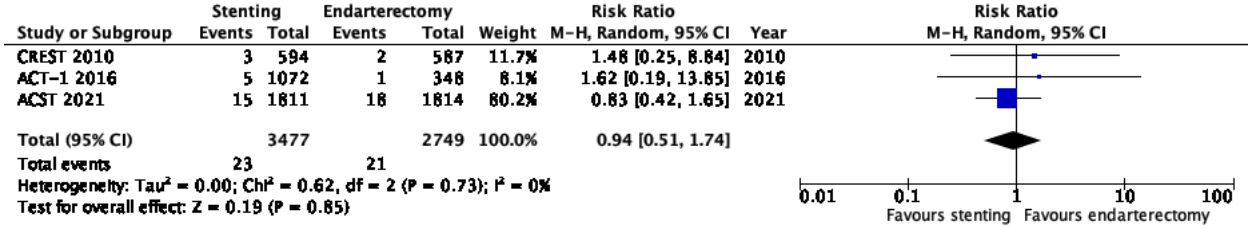
a. The population involved Asymptomatic Carotid artery stenosis but the population are not apparently healthy Filipino adults
b. Six out of the eight studies included had small sample size, low number of events and with wide confidence intervals.
Author(s):

APPENDIX 9: CAROTID ARTERY VERSUS ENDARTERECTOMY FOR TREATMENT OF CAROTID ARTERY STENOSIS (Forrest Plots)

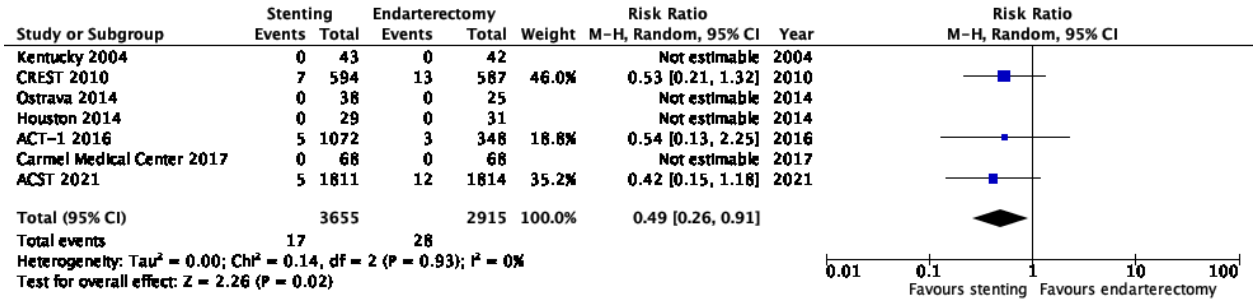
OUTCOME 1: STENTING OR ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS.
DEATH OR ANY STROKE BETWEEN RANDOMISATION AND 30 DAYS AFTER TREATMENT



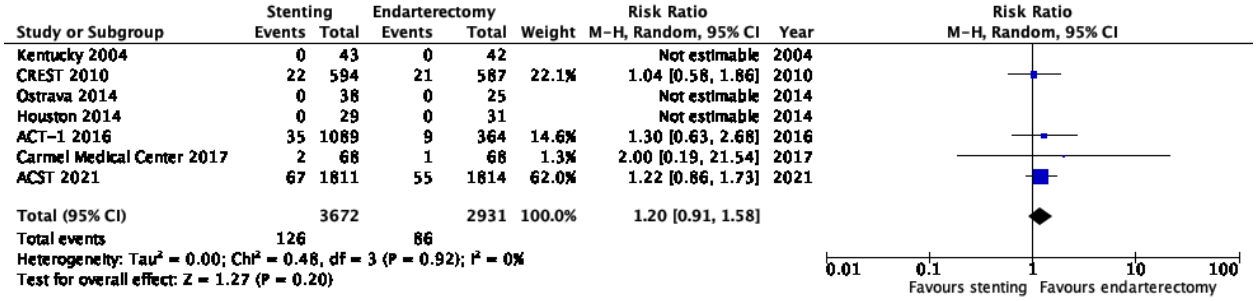
OUTCOME 2: STENTING OR ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS.
DEATH OR MAJOR OR DISABLING STROKE OR MYOCARDIAL INFARCTION BETWEEN RANDOMISATION AND 30 DAYS AFTER TREATMENT



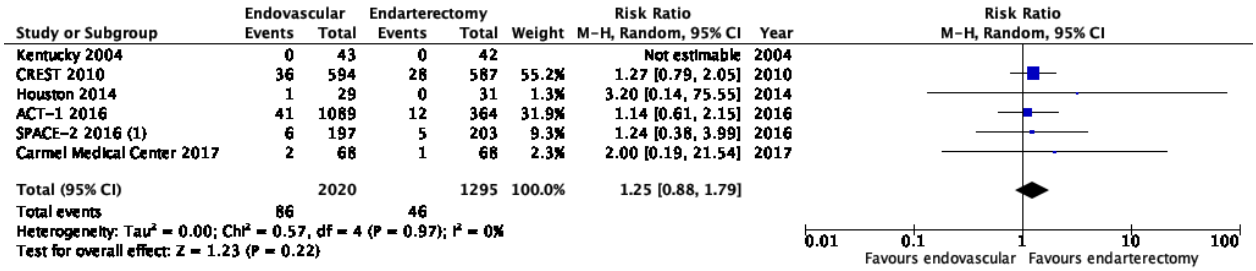
OUTCOME 3: STENTING OR ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS.
MYOCARDIAL INFARCTION BETWEEN RANDOMISATION AND 30 DAYS AFTER TREATMENT



OUTCOME 4: STENTING OR ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS.
DEATH OR ANY STROKE OR MYOCARDIAL INFARCTION BETWEEN RANDOMISATION AND 30 DAYS AFTER TREATMENT

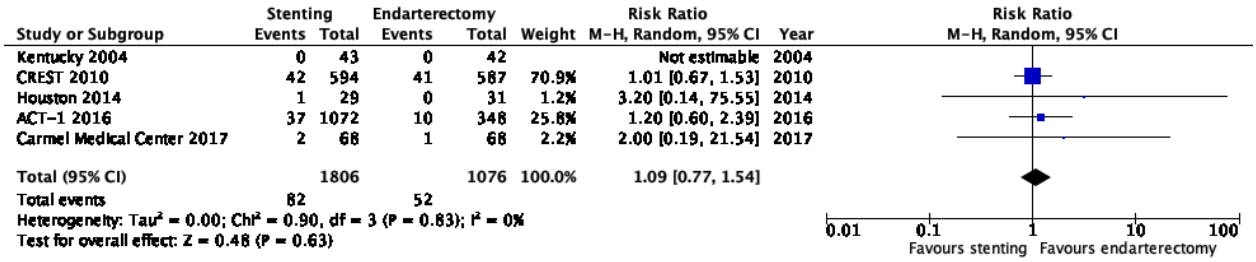


OUTCOME 5: STENTING OR ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS.
DEATH OR ANY STROKE BETWEEN RANDOMISATION AND 30 DAYS AFTER TREATMENT OR IPSILATERAL STROKE UNTIL END OF FOLLOW-UP



Footnotes
(1) number of events derived from percentages published in conference abstract

OUTCOME 6: STENTING OR ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS.
DEATH OR ANY STROKE OR MYOCARDIAL INFARCTION BETWEEN RANDOMISATION AND 30 DAYS AFTER TREATMENT OR IPSILATERAL STROKE UNTIL END OF FOLLOW-UP



APPENDIX 10. GRADE Pro Evidence Tables for Carotid Bruit Auscultation in ASYMPTOMATIC CAROTID ARTERY STENOSIS

A. McColgan, P., et al. Evaluation of the clinical utility of a carotid bruit. Q J Med 2012; 105: 1171-1177

Question: Should carotid bruit auscultation be used to screen for ACAS in [asymptomatic apparently healthy adults?

Sensitivity	0.53 (95% CI: 0.50 to 0.55)
Specificity	0.83 (95% CI: 0.82 to 0.84)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with ACAS)	26 studies 15117 patients	cross-sectional (cohort type accuracy study)	not serious	very serious[a]	not serious	not serious	none	0 (0 to 0)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having ACAS)								0 (0 to 0)	
True negatives (patients without ACAS)	0 studies patients							830 (820 to 840)	-
False positives (patients incorrectly classified as having ACAS)								170 (160 to 180)	

Explanations

a. Patient populations included were not exclusively asymptomatic and included those presenting to neurology or vascular outpatients.

B. Ratchford, E., et al. Carotid bruit for detection of hemodynamically significant carotid stenosis: the Northern Manhattan Study. Neurological Research 2009; 31: 748-752

Question: Should carotid bruit auscultation be used to screen for asymptomatic carotid artery stenosis in asymptomatic apparently healthy adults?

Sensitivity	0.56 (95% CI: 0.30 to 0.82)
Specificity	0.98 (95% CI: 0.97 to 0.99)

Prevalences	4.1%	0%	0%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of4.1%	pre-test probability of0%	pre-test probability of0%	
True positives (patients with asymptomatic carotid artery stenosis)	1 studies 686 patients	cohort & case-control type studies	not serious	serious[a]	not serious	not serious	none	23 (12 to 34)	0 (0 to 0)	0 (0 to 0)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having asymptomatic carotid artery stenosis)								18 (7 to 29)	0 (0 to 0)	0 (0 to 0)	
True negatives (patients without asymptomatic carotid artery stenosis)	0 studies 0 patients							940 (930 to 949)	980 (970 to 990)	980 (970 to 990)	-
False positives (patients incorrectly classified as having asymptomatic carotid artery stenosis)								19 (10 to 29)	20 (10 to 30)	20 (10 to 30)	

Explanations

a. The population in the study is not exclusively asymptomatic

c. Knapp, A., et al. Carotid artery ultrasonographic assessment in patients from the Fremantle Diabetes Study Phase II with carotid bruits detected by electronic auscultation. Diabetes Technology & Therapeutics 2014; 16(9): 604-610

Question: Should carotid bruit auscultation be used to screen for carotid artery stenosis in asymptomatic apparently healthy adults?

Sensitivity	0.88 (95% CI: 0.62 to 0.98)
Specificity	0.58 (95% CI: 0.47 to 0.68)

Prevalences	50%	0%	0%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of50%	pre-test probability of0%	pre-test probability of0%	
True positives (patients with carotid artery stenosis)	1 studies 100 patients	case-control type accuracy study	serious	serious[a]	not serious	not serious	none	440 (310 to 490)	0 (0 to 0)	0 (0 to 0)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having carotid artery stenosis)								60 (10 to 190)	0 (0 to 0)	0 (0 to 0)	
True negatives (patients without carotid artery stenosis)	0 studies 0 patients							290 (235 to 340)	580 (470 to 680)	580 (470 to 680)	-
False positives (patients incorrectly classified as having carotid artery stenosis)								210 (160 to 265)	420 (320 to 530)	420 (320 to 530)	

Explanations

a. The population in the study is not exclusively asymptomatic

APPENDIX 11: GRADE Pro Evidence Tables for CAROTID DOPPLER ULTRASOUND TO SCREEN FOR ASYMPTOMATIC CAROTID ARTERY STENOSIS

Chappell, F., Wardlaw, J., et al. Carotid Artery Stenosis: Accuracy of Noninvasive tests – individual patients data meta-analysis. Radiology 2009; 251 (2): 493-502

Question: Should carotid Doppler ultrasound be used to screen for ACAS in asymptomatic apparently healthy adults?

Sensitivity	0.67 (95% CI: 0.56 to 0.77)
Specificity	0.93 (95% CI: 0.90 to 0.95)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of0%	
True positives (patients with ACAS)	12 studies 1456 patients	cross-sectional (cohort type accuracy study)	not serious	very serious[a]	not serious	not serious	none	0 (0 to 0)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having ACAS)								0 (0 to 0)	
True negatives (patients without ACAS)	0 studies patients							930 (900 to 950)	-
False positives (patients incorrectly classified as having ACAS)								70 (50 to 100)	

Explanations

a. 89 to 100% of patients were symptomatic. In the study the contralateral artery was evaluated and operationally defined as asymptomatic.

4. Peripheral Arterial Disease

Appendix 12. GRADE Pro Evidence Table of Doppler Ankle-Brachial Index in Peripheral Arterial Disease

Question: Doppler Ankle-brachial index compared to No Doppler Ankle-Brachial index for screening for peripheral arterial disease in apparently healthy individuals
Setting: out-patient
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doppler Ankle-brachial index	No Doppler Ankle-Brachial index	Relative (95% CI)	Absolute (95% CI)		
All cause mortality (follow-up: median 4.4 years; assessed with: Time to event or censoring, assessed 5 years after randomisation.)												
1	randomised trial	not serious	not serious	serious[a]	serious[a]	strong association all plausible residual confounding would reduce the demonstrated effect	2566/25074 (10.2%)	2715/25078 (10.8%)	**HR 0.93** (0.88 to 0.98)	**7 fewer per 1,000** (from 12 fewer to 2 fewer)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **HR:** hazard Ratio

Explanations

a. 60-75 years (relatively older); 21% smokers, 22% had early disease signs, 46% were already being treated with medications

Appendix 13. GRADE Pro Evidence Tables of Antiplatelet Treatment in Peripheral Arterial Disease

Question: Antiplatelet compared to No antiplatelet for Peripheral Arterial Disease in Apparently Healthy individuals
Setting: outpatient setting
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No antiplatelet	Relative (95% CI)	Absolute (95% CI)		
Fatal or Non-fatal MI, Stroke or Revascularization (follow-up: mean 8.2 years; assessed with: Clinical Events)												
1	randomised trials	not serious	not serious	serious	not serious	none	181/1675 (10.8%)	176/1675 (10.5%)	**RR 1.03** (0.85 to 1.25)	**3 fewer per 1,000** (from 433 fewer to 478 more)	⨁⨁⨁◯ Moderate	IMPORTANT

All Cause Mortality (follow-up: mean 8.2 years; assessed with: Clinical Events)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No antiplatelet	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious	not serious	none	176/1675 (10.5%)	186/1675 (11.1%)	**RR 0.95** (0.78 to 1.15)	**23 fewer per 1,000** (from 26 fewer to 20 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Major bleeding (follow-up: mean 8.2 years; assessed with: Clinical events)

1	randomised trials	not serious	not serious	serious	not serious	none	34/1675 (2.0%)	20/1675 (1.2%)	**RR 1.70** (0.99 to 2.94)	**2 more per 1,000** (from 1 more to 3 more)	⨁⨁⨁◯ Moderate	IMPORTANT

Composite of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or above ankle amputation for critical limb ischaemia (follow-up: median 6.7 years; assessed with: Clinical Events)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No antiplatelet	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious	not serious	none	116/638 (18.2%)	117/638 (18.3%)	**RR 0.98** (0.78 to 1.23)	**4 fewer per 1,000** (from 40 fewer to 42 more)	⨁⨁⨁◯ Moderate	CRITICAL
Death from CHD or stroke (follow-up: median 6.7 years; assessed with: Clinical events)												
1	randomised trials	not serious	not serious	serious	not serious	none	43/638 (6.7%)	35/638 (5.5%)	**RR 1.22** (0.79 to 1.88)	**12 fewer per 1,000** (from 11 fewer to 48 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Question: Antiplatelet compared to No antiplatelet for Peripheral Arterial Disease in Apparently Healthy individuals
Setting: outpatient setting
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No antiplatelet	Relative (95% CI)	Absolute (95% CI)		
Fatal or Non-fatal MI, Stroke or Revascularization (follow-up: mean 8.2 years; assessed with: Clinical Events)												
1	randomised trials	not serious	not serious	Serious	not serious	none	181/1675 (10.8%)	176/1675 (10.5%)	**RR 1.03** (0.85 to 1.25)	**3 fewer per 1,000** (from 433 fewer to 478 more)	⨁⨁⨁◯ Moderate	IMPORTANT
All Cause Mortality (follow-up: mean 8.2 years; assessed with: Clinical Events)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	Noantiplatelet	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	Serious	not serious	none	176/1675 (10.5%)	186/1675 (11.1%)	**RR 0.95** (0.78 to 1.15)	**23 fewer per 1,000** (from 26 fewer to 20 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Major bleeding (follow-up: mean 8.2 years; assessed with: Clinical events)

1	randomised trials	not serious	not serious	Serious	not serious	none	34/1675 (2.0%)	20/1675 (1.2%)	**RR 1.70** (0.99 to 2.94)	**2 more per 1,000** (from 1 more to 3 more)	⨁⨁⨁◯ Moderate	IMPORTANT

Composite of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or above ankle amputation for critical limb ischaemia (follow-up: median 6.7 years; assessed with: Clinical Events)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	No antiplatelet	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	Serious	not serious	none	116/638 (18.2%)	117/638 (18.3%)	**RR 0.98** (0.78 to 1.23)	**4 fewer per 1,000** (from 40 fewer to 42 more)	⨁⨁⨁◯ Moderate	CRITICAL
Death from CHD or stroke (follow-up: median 6.7 years; assessed with: Clinical events)												
1	randomised trials	not serious	not serious	Serious	not serious	none	43/638 (6.7%)	35/638 (5.5%)	**RR 1.22** (0.79 to 1.88)	**12 fewer per 1,000** (from 11 fewer to 48 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Appendix 14. Benefits of one-time AAA screening with ultrasound in asymptomatic, apparently healthy adults

Outcomes	Length of Follow-up (years)	No. of RCTs	Trials Included	Population (n)	RR (95% CI)	Level of Certainty
AAA-related Mortality	3 to 5	4	MASS, Chichester, Viborg, Western Australia	125, 576	0.57 (0.44 to 0.72)	Moderate
	6 to 7	2	MASS, Viborg	80, 409	0.38 (0.17 to 0.86)	Moderate
	10 to 11	3	MASS, Chichester, Viborg	86, 467	0.50 (0.31 to 0.79)	Moderate
	13 to 15	3	MASS, Chichester, Viborg	86, 449	0.58 (0.39 to 0.88)	Moderate
All-cause Mortality	3 to 5	4	MASS, Chichester, Viborg, Western Australia	125, 576	0.94 (0.88 to 1.02)	Low
	6 to 7	2	MASS, Viborg	80, 409	0.96 (0.94 to 1.00)	Moderate
	10 to 11	2	MASS, Viborg	80, 409	0.97 (0.95 to 1.00)	Moderate
	13 to 15	3	MASS, Chichester, Viborg	86, 449	0.98 (0.97 to 1.00)	Moderate
AAA Rupture	3 to 5	4	MASS, Chichester, Viborg, Western Australia	125, 576	0.52 (0.35 to 0.79)	Moderate
	6 to 7	1	MASS	67, 770	0.53 (0.43 to 0.65)	High

	10 to 11	2	MASS, Viborg	80, 409	0.47 (0.31 to 0.71)	Moderate
	13 to 15	3	MASS, Chichester, Viborg	86, 449	0.62 (0.45 to 0.86)	Moderate

Appendix 15. Harms of one-time AAA screening with ultrasound in asymptomatic, apparently healthy adults

Outcomes	Length of Follow-up (years)	No. of RCTs	Trials Included	Population (n)	RR (95% CI)	Level of Certainty
All AAA Operations	3 to 5	5	MASS, Chichester, Viborg, W. Australia VIVA	175, 732	2.07 (1.80 to 2.38)	Moderate
	6 to 7	1	MASS	67,770	1.85 (1.60 to 2.15)	High
	10 to 11	3	MASS, Chichester, Viborg	86, 467	1.57 (1.35 to 1.83)	Moderate
	13 to 15	3	MASS, Chichester, Viborg	86, 449	1.48 (1.33 to 1.65)	Moderate
Elective Operations	3 to 5	5	MASS, Chichester, Viborg, W. Australia VIVA	175, 732	2.94 (2.16 to 3.99)	Moderate
	6 to 7	1	MASS	67,770	2.90 (2.41 to 3.46)	High
	10 to 11	3	MASS, Chichester, Viborg	86, 467	2.44 (2.12 to 2.81)	Moderate
	13 to 15	3	MASS, Chichester, Viborg	86, 449	2.15 (1.89 to 2.44)	Moderate
Emergency Operations	3 to 5	5	MASS, Chichester, Viborg, W. Australia VIVA	175, 732	0.58 (0.37 to 0.91)	Moderate

	6 to 7	1	MASS	67,770	0.41 (0.29 to 0.57)	High
	10 to 11	3	MASS, Chichester, Viborg	86, 467	0.41 (0.32 to 0.54)	Moderate
	13 to 15	3	MASS, Chichester, Viborg	86, 449	0.50 (0.40 to 0.63)	Moderate
30-day Post-operative Mortality	3 to 5	3	MASS, W. Australian, Chichester	722	0.31 (0.20 to 0.48)	Moderate
	6 to 7	1	MASS	762	0.32 (0.21 to 0.48)	High
	10 to 11	2	MASS, Viborg	1,139	0.35 (0.25 to 0.49)	Moderate
	13 to 15	2	Chichester, MASS	1,220	0.46 (0.34 to 0.63)	Moderate
30-day Post-operative Mortality, Elective AAA Operations	3 to 5	4	MASS, Chichester, Viborg, W. Australia	667	0.51 (0.26 to 1.00)	Moderate
	6 to 7	1	MASS	606	0.52 (0.26 to 1.05)	Moderate
	10 to 11	3	MASS, Chichester, Viborg	936	0.69 (0.36 to 1.32)	Low
	13 to 15	2	MASS, Chichester	982	0.78 (0.42 to 1.46)	Low
30-day Post-operative Mortality, Emergency AAA Operations	3 to 5	3	MASS, W. Australia, Chichester	109	0.67 (0.37 to 1.21)	Low
	6 to 7	1	MASS	156	0.78 (0.47 to 1.31)	Moderate
	10 to 11	2	MASS, Viborg	256	0.83 (0.57 to 1.19)	Low
	13 to 15	2	MASS, Chichester	283	0.95 (0.69 to 1.31)	Low

Appendix 16. GRADE Pro Evidence Table of Benefits of one-time AAA screening in asymptomatic apparently healthy adults

Question: One-time screening for AAA with ultrasound compared to no screening in asymptomatic apparently, healthy adults

Setting: Outpatient or community
Intervention: Ultrasound screening
Comparison: No screening

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
AAA Mortality (3 to 5 years of follow-up) (follow-up: range 3.6 years to 5.0 years)												
4	randomised trials	serious [a]	not serious	not serious	not serious	none	102/62729 (0.2%)	182/62847 (0.3%)	**RR 0.5661** (0.4439 to 0.7221)	**1,257 fewer per 1,000,000** (from 1,610 fewer to 805 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
AAA Mortality (6 to 7 years of follow-up) (follow-up: range 5.9 years to 7 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	114/40216 (0.3%)	235/40193 (0.6%)	**RR 0.3769** (0.1660 to 0.8556)	**3,643 fewer per 1,000,000** (from 4,876 fewer to 844 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

AAA Mortality (10 to 11 years of follow-up) (follow-up: mean 10)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [a]	not serious	not serious	not serious	none	193/43216 (0.4%)	378/43251 (0.9%)	**RR 0.4960** (0.3121 to 0.7883)	**4,405 fewer per 1,000,000** (from 6,012 fewer to 1,850 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

AAA Mortality (13 to 15 years of follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [a]	not serious	not serious	not serious	none	290/43211 (0.7%)	490/43238 (1.1%)	**RR 0.5831** (0.3882 to 0.8759)	**4,725 fewer per 1,000,000** (from 6,933 fewer to 1,406 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

All-cause Mortality (3 to 5 years of follow-up) (follow-up: range 3.6 years to 5 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious [a]	not serious	not serious	serious [b]	none	7453/62729 (11.9%)	7953/62847 (12.7%)	**RR 0.9449** (0.8758 to 1.0195)	**6,973 fewer per 1,000,000** (from 15,717 fewer to 2,468 more)	⨁⨁◯◯ Low	CRITICAL

All-cause Mortality (6 to 7 years of follow-up) (follow-up: range 5.9 years to 7 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	8258/40193 (20.5%)	8571/40193 (21.3%)	**RR 0.9628** (0.9373 to 0.9890)	**7,933 fewer per 1,000,000** (from 13,371 fewer to 2,346 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

All-cause Mortality (10 to 11 years of follow-up) (follow-up: mean 10 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	12458/40216 (31.0%)	12715/40193 (31.6%)	**RR 0.9791** (0.9593 to 0.9993)	**6,612 fewer per 1,000,000** (from 12,875 fewer to 221 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

All-cause Mortality (13 to 15 years of follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [a]	not serious	not serious	not serious	none	18825/43211 (43.6%)	19165/43238 (44.3%)	**RR 0.9849** (0.9706 to 0.9995)	**6,693 fewer per 1,000,000** (from 13,031 fewer to 222 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

AAA Rupture (3 to 5 years of follow-up) (follow-up: range 3.6 years to 5 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious [a]	not serious	not serious	not serious	none	117/62729 (0.2%)	218/62847 (0.3%)	**RR 0.5247** (0.3475 to 0.7922)	**1,649 fewer per 1,000,000** (from 2,263 fewer to 721 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

AAA Rupture (6 to 7 years of follow-up) (follow-up: mean 7 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	135/3383 (0.4%)	257/3887 (0.8%)	**RR 0.5254** (0.4268 to 0.6467)	**3,599 fewer per 1,000,000** (from 4,347 fewer to 2,679 fewer)	⨁⨁⨁⨁ High	CRITICAL

AAA Rupture (10 to 11 years of follow-up) (follow-up: mean 10 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	207/40216 (0.5%)	405/40193 (1.0%)	**RR 0.4663** (0.3070 to 0.7083)	**5,378 fewer per 1,000,000** (from 6,983 fewer to 2,939 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

AAA Rupture (13 to 15 years of follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening for AAA with ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [a]	not serious	not serious	not serious	none	343/43238 (0.8%)	575/43238 (1.3%)	**RR 0.6243** (0.4516 to 0.8631)	**4,996 fewer per 1,000,000** (from 7,293 fewer to 1,821 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Lack of certainty regarding sequence generation, allocation concealment and blinding

b. Sample size is adequate i.e. > 300 (62,729 screening arm, 62,847 control arm) but the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.9449 (0.8758, 1.0195)]. This body of evidence was downgraded for serious concerns regarding imprecision.

Appendix 17. GRADE Pro Evidence Tables of Harms of one-time AAA screening in asymptomatic apparently healthy adults

Question: One-time screening for AAA with ultrasound compared to no screening for asymptomatic, apparently healthy adults
Setting: Outpatient or community
Intervention: Ultrasound screening
Comparison: No screening

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
AAA Operations (3 to 5 years of follow-up) (follow-up: range 3.6 years to 5 years)												
5	randomised trials	serious[a]	not serious	not serious	not serious	none	831/87807 (0.9%)	398/87925 (0.5%)	**RR 2.07** (1.80 to 2.38)	**4,843 more per 1,000,000** (from 3,621 more to 6,247 more)	⨁⨁⨁◯ Moderate	CRITICAL
AAA Operations (6 to 7 years of follow-up) (follow-up: mean 7 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	495/33883 (1.5%)	267/33887 (0.8%)	**RR 1.8542** (1.5990 to 2.1500)	**6,730 more per 1,000,000** (from 4,720 more to 9,061 more)	⨁⨁⨁⨁ High	CRITICAL
AAA Operations (10 to 11 years of follow-up) (follow-up: mean 10 years)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	752/43216 (1.7%)	469/43251 (1.1%)	**RR 1.5700** (1.3502 to 1.8225)	**6,181 more per 1,000,000** (from 3,797 more to 8,919 more)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
AAA Operations (13 to 15 years of follow-up) (follow-up: range 13 years to 15 years)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	846/43211 (2.0%)	571/43238 (1.3%)	**RR 1.4805** (1.3300 to 1.6480)	**6,345 more per 1,000,000** (from 4,358 more to 8,557 more)	⨁⨁⨁◯ Moderate	CRITICAL
Elective AAA Operations (3 to 5 years follow-up) (follow-up: range 3.6 years to 5 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious[a]	not serious	not serious	not serious	none	745/87807 (0.8%)	263/87925 (0.3%)	**RR 2.94** (2.16 to 3.99)	**5,803 more per 1,000,000** (from 3,470 more to 8,944 more)	⨁⨁⨁◯ Moderate	CRITICAL
Elective AAA Operations (6 to 7 years follow-up) (follow-up: mean 7 years)												
1	randomised trials	not serious	not serious	not serious	not serious	none	495/33883 (1.5%)	267/33887 (0.8%)	**RR 1.8542** (1.5990 to 2.1500)	**6,730 more per 1,000,000** (from 4,720 more to 9,061 more)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
Elective AAA Operations (10 to 11 years follow-up) (follow-up: mean 10 years)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	664/43216 (1.5%)	272/43251 (0.6%)	**RR 2.4420** (2.1220 to 2.8106)	**9,069 more per 1,000,000** (from 7,056 more to 11,387 more)	⨁⨁⨁◯ Moderate	CRITICAL
Elective AAA Operations (13 to 15 years follow-up) (follow-up: range 13 years to 15 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	not serious	none	730/43211 (1.7%)	340/43238 (0.8%)	**RR 2.1479** (1.8899 to 2.4412)	**9,026 more per 1,000,000** (from 6,998 more to 11,333 more)	⨁⨁⨁◯ Moderate	CRITICAL

Emergency AAA Operations (3 to 5 years follow-up) (follow-up: range 3.6 years to 5 years)

4	randomised trials	serious[a]	not serious	not serious	not serious	none	81/87807 (0.1%)	135/87925 (0.2%)	**RR 0.58** (0.37 to 0.91)	**645 fewer per 1,000,000** (from 967 fewer to 138 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
Emergency AAA Operations (6 to 7 years follow-up) (follow-up: mean 7 years)												
1	randomised trials	not serious	not serious	not serious	not serious	none	45/33883 (0.1%)	111/33887 (0.3%)	**RR 0.4055** (0.2869 to 0.5731)	**1,947 fewer per 1,000,000** (from 2,336 fewer to 1,398 fewer)	⊕⊕⊕⊕ High	CRITICAL
Emergency AAA Operations (10 to 11 years follow-up) (follow-up: mean 10 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	not serious	none	81/43216 (0.2%)	194/43251 (0.4%)	**RR 0.4192** (0.3234 to 0.5433)	**2,605 fewer per 1,000,000** (from 3,035 fewer to 2,049 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Emergency AAA Operations (13 to 15 years follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	not serious	none	116/43211 (0.3%)	231/43238 (0.5%)	**RR 0.5041** (0.4033 to 0.6302)	**2,649 fewer per 1,000,000** (from 3,188 fewer to 1,976 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Postoperative Mortality (3 to 5 years of follow-up) (follow-up: range 3.6 years to 5 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	not serious	none	29/501 (5.8%)	41/221 (18.6%)	**RR 0.3086** (0.1967 to 0.4841)	**128,269 fewer per 1,000,000** (from 149,029 fewer to 95,710 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Post-operative Mortality (6 to 7 years of follow-up) (follow-up: mean 7 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	31/495 (6.3%)	53/267 (19.9%)	**RR 0.3155** (0.2078 to 0.4789)	**135,875 fewer per 1,000,000** (from 157,253 fewer to 103,439 fewer)	⨁⨁⨁⨁ High	CRITICAL

30-day Post-operative Mortality (10 to 11 years of follow-up) (follow-up: mean 10 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	not serious	none	48/703 (6.8%)	86/436 (19.7%)	**RR 0.3539** (0.2537 to 0.4937)	**127,442 fewer per 1,000,000** (from 147,206 fewer to 99,867 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Post-operative Mortality (13 to 15 years of follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	not serious	none	58/737 (7.9%)	83/483 (17.2%)	**RR 0.4602** (0.3362 to 0.6299)	**92,761 fewer per 1,000,000** (from 114,069 fewer to 63,599 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Postoperative Mortality, Elective AAA Operations (3 to 5 years follow-up) (follow-up: range 3.6 years to 5 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious[a]	not serious	not serious	not serious	none	21/505 (4.2%)	13/162 (8.0%)	**RR 0.5102** (0.2618 to 0.9944)	**39,305 fewer per 1,000,000** (from 59,238 fewer to 449 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Postoperative Mortality, Elective AAA Operations (6 to 7 years follow-up) (follow-up: mean 7 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[b]	none	18/450 (4.0%)	12/156 (7.7%)	**RR 0.5200** (0.2563 to 1.0549)	**36,923 fewer per 1,000,000** (from 57,208 fewer to 4,223 more)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Postoperative Mortality, Elective AAA Operations (10 to 11 years follow-up) (follow-up: mean 10 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	serious[c]	none	24/664 (3.6%)	14/272 (5.1%)	**RR 0.6927** (0.3634 to 1.3204)	**15,817 fewer per 1,000,000** (from 32,766 fewer to 16,491 more)	⨁⨁◯◯ Low	CRITICAL

30-day Postoperative Mortality, Elective AAA Operations (13 to 15 years follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	not serious	none	26/676 (3.8%)	15/306 (4.9%)	**RR 0.7834** (0.4202 to 1.4605)	**10,618 fewer per 1,000,000** (from 28,422 fewer to 22,574 more)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Postoperative Mortality, Emergency AAA Operations (3 to 5 years follow-up) (follow-up: range 3.6 years to 5 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a]	not serious	not serious	serious[d]	none	10/39 (25.6%)	29/70 (41.4%)	**RR 0.6678** (0.3686 to 1.2098)	**137,626 fewer per 1,000,000** (from 261,580 fewer to 86,917 more)	⨁⨁◯◯ Low	CRITICAL

30-day Postoperative Mortality, Emergency AAA Operations (6 to 7 years follow-up) (follow-up: mean 7 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[e]	none	13/45 (28.9%)	41/111 (36.9%)	**RR 0.7821** (0.4655 to 1.3140)	**80,486 fewer per 1,000,000** (from 197,428 fewer to 115,982 more)	⨁⨁⨁◯ Moderate	CRITICAL

30-day Postoperative Mortality, Emergency AAA Operations (10 to 11 years follow-up) (follow-up: mean 10 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	serious[f]	none	24/75 (32.0%)	72/181 (39.8%)	**RR 0.8252** (0.5705 to 1.1938)	**69,534 fewer per 1,000,000** (from 170,851 fewer to 77,092 more)	⨁⨁◯◯ Low	CRITICAL

30-day Postoperative Mortality, Emergency AAA Operations (13 to 15 years follow-up) (follow-up: range 13 years to 15 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening with ultrasound	No screening	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	serious[g]	none	35/96 (36.5%)	69/187 (36.9%)	**RR 0.9527** (0.6930 to 1.3097)	**17,453 fewer per 1,000,000** (from 113,278 fewer to 114,274 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Lack of certainty regarding sequence generation, allocation concealment and blinding

b. Sample size is adequate in screening arm but not adequate in control arm i.e. < 300 (450 screening arm, 156 control arm) and the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.5200 (0.2563, 1.0549)].

c. Sample size is adequate in screening arm but not adequate in control arm i.e. < 300 (664 screening arm, 272 control arm) and the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.6927 (0.3634, 1.3204)].

d. Sample size is not adequate in screening arm and control arms i.e. < 300 (39 screening arm, 70 control arm) and the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.6678 (0.3686, 1.2098)].

e. Sample size is not adequate in screening arm and control arms i.e. < 300 (45 screening arm, 111 control arm) and the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.7821 (0.4655, 1.3140)].

f. Sample size is not adequate in screening arm and control arms i.e. < 300 (75 screening arm, 181 control arm) and the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.8252 (0.5705, 1.1938)].
g. Sample size is not adequate in screening arm and control arms i.e. < 300 (96 screening arm, 187 control arm) and the pooled effect estimate is not precise and confidence interval include the null value "1" [RR= 0.9527 (0.6930, 1.3097)].

Appendix 18. GRADE Pro Evidence Tables of Outcomes of one-time AAA screening in women
Question: AAA screening using ultrasound compared to no screening for asymptomatic, apparently healthy women
Setting: Outpatient

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**AAA screening using ultrasound**	**no screening**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
AAA Mortality (follow-up: 5 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/3052 (0.1%)	2/4660 (0.0%)	**RR 1.49** (0.25 to 8.93)	**210 more per 1,000,000** (from 322 fewer to 3,403 more)	⨁◯◯ Low	CRITICAL
AAA Mortality (follow-up: 10 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AAA screening using ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Not reported	Not reported	**RR 1.00** (0.37 to 2.65)	**1 fewer per 1,000** (from 3 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL

All-cause Mortality

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	236/3052 (7.7%)	508/4660 (10.9%)	**RR 1.05** (0.93 to 1.18)	**5 more per 1,000** (from 8 fewer to 20 more)	⨁⨁◯◯ Low	CRITICAL

AAA Rupture (follow-up: 5 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AAA screening using ultrasound	no screening	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/3052 (0.1%)	2/4660 (0.0%)	**RR 1.49** (0.25 to 8.93)	**0 fewer per 1,000** (from 0 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL

AAA Rupture (follow-up: 10 years)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	10/3052 (0.3%)	9/4660 (0.2%)	**RR 1.11** (0.45 to 2.72)	**0 fewer per 1,000** (from 1 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Lack of certainty regarding sequence generation and allocation concealment

b. Inadequate sample size and wide confidence intervals

Appendix 19. GRADE Pro Evidence Tables of Ultrasound as screening test for abdominal aortic aneurysm

Question: Should ultrasound be used to screen for abdominal aortic aneurysm in asymptomatic, apparently healthy adults?

Sensitivity	0.99 (95% CI: 0.96 to 1.00)
Specificity	0.98 (95% CI: 0.96 to 1.00)

Prevalences	3.3%	0%	0%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of3.3%	pre-test probability of0%	pre-test probability of0%	
True positives (patients with AAA)	7 studies 655 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	not serious	not serious	none	3 (3 to 3)	0 (0 to 0)	0 (0 to 0)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having AAA)								0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
True negatives (patients witho	7 studies 655 patients	cross-sectional (cohort	serious [a]	serious [b]	not serious	not serious	none	95 (93 to 97)	98 (96 to 100)	98 (96 to 100)	⨁⨁◯◯ Low

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of3.3%	pre-test probability of0%	pre-test probability of0%	
ut AAA)		type accuracy study)									
False positives (patients incorrectly classified as having AAA)								2 (0 to 4)	2 (0 to 4)	2 (0 to 4)	

Explanations

a. Blinding not stated in some studies

b. Population include adult patients (18 years and above) suspected of having abdominal aortic aneurysm and not asymptomatic, apparently healthy adults

6. Atrial Fibrillation

Appendix 20. Evidence Table for Benefit of Screening.

Screening for atrial fibrillation compared to no screening for asymptomatic, apparently healthy adults
Patient or population: asymptomatic, apparently healthy adults Setting: outpatient Intervention: Screening for atrial fibrillation Comparison: no screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no screening	Risk with Screening for atrial fibrillation				
ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation, and all-cause death (STROKESTOP) follow-up: range 6 years to 9 years	330 per 1,000	319 per 1,000 (308 to 330)	HR 0.96 (0.92 to 1.00)	27975 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	Screening for atrial fibrillation results in a slight reduction in ischaemic or haemorrhagic stroke, systemic embolism, bleeding leading to hospitalisation, and all-cause death.
stroke/transient ischemic attack/systemic embolic events (REHEARSE-AF) follow-up: range 12 weeks to 52 weeks	20 per 1,000	12 per 1,000 (4 to 33)	HR 0.61 (0.22 to 1.69)	1001 (1 RCT)	⨁⨁⨁◯ Moderate[b,c,d]	Screening for atrial fibrillation results in little to no difference in stroke/transient ischemic attack/systemic embolic events.

Explanations

a. The control group included previously known AF patients not on anticoagulation at the time of enrollment.

b. This trial included patients with comorbidites previously associated with higher stroke risk. It also employed the use of a portable single lead rhythm strip which is not currently widely available in the country.
c. This trial was not specifically powered to evaluate the said outcomes
d. wide confidence interval

References:
1. Halcox, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. Circulation. 2017; 136: 1784- 1794.
2. Svennberg, et al. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. Lancet. 2021; 398: 1498-1506.

Appendix 21. Summary of Findings Table for Atrial Fibrillation

Summary of findings:

Screening for atrial fibrillation compared to no screening for asymptomatic, apparently healthy adults (harms)

Patient or population: asymptomatic, apparently healthy adults (harms)
Setting: outpatient
Intervention: Screening for atrial fibrillation
Comparison: no screening

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no screening	**Risk with Screening for atrial fibrillation**				
hospitalization for major bleeding (STOPSTROKE) follow-up: range 6 years to 9 years	103 per 1,000	**101 per 1,000** (95 to 109)	**HR 0.98** (0.91 to 1.06)	27975 (1 RCT)	⨁◯◯ Low	

Clinically significant bleeds (REHEARSE-AF) follow-up: range 12 weeks to 52 weeks	2 per 1,000	**4 per 1,000** (0 to 0)	**p value 0.56** (-- to --)	1001 (1 RCT)	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard Ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

References:
1. Halcox, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. Circulation. 2017; 136: 1784- 1794.
2. Svennberg, et al. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. Lancet. 2021; 398: 1498-1506.

Appendix 22. GRADE Pro Evidence Table for Pulse Palpation for Atrial Fibrillation
Question: Should pulse palpation be used to diagnose atrial fibrillation in healthy adults age more than 65 years old?

Sensitivity	0.94 (95% CI: 0.84 to 0.97)
Specificity	0.72 (95% CI: 0.69 to 0.75)

Prevalences	3.1%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of3.1%	
True positives (patients with [target condition])	3 studies 2241 patients	cohort & case-control type studies	serious[a]	not serious	not serious	serious[b]	none	29 (26 to 30)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having [target condition])								2 (1 to 5)	
True negatives (patients without [target condition])	3 studies 1712 patients	cohort & case-control type studies	serious[a]	not serious	not serious	serious[b]	none	698 (669 to 727)	⊕⊕◯◯ Low
False positives								271 (242 to 300)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of3.1%	
(patients incorrectly classified as having [target condition])									

Explanations

a. Sampling bias

b. No Filipino patients included

Reference: Cooke, G. et al. Is pulse palpation helpful in detecting atrial fibrillation: A systematic review. *The Journal of Family Practice.* 2006; 55 (2): pp 130-134

PERIODIC HEALTH EXAMINATION TASK FORCE ON CARDIOVASCULAR DISEASES 2021

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Dr. Alejandro Pineda	Philippine Medical Association
Dr. Lourdes Gonzales-Santos	Philippine Heart Association
Dr. Alberto Atilano	Philippine Society of Hypertension
Dr. Danilo Baldemor	Philippine College of Physicians
Dr. Rex Vener Palma	Philippine Society of Vascular Medicine
Dr. Maria Carissa Pineda-Franks	Philippine Neurological Association
Ms. Grace Vender Buot	Patient Advocate
Mr. Melvin Miranda	Philippine Nurses Association
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CONFLICT OF INTEREST DECLARATION

Table 10. Conflict of Interest of Consensus Panelists

Panelist	COI based on Oversight Committee	Remarks
1. Maria Alba Concha (PAFP)	Acceptable	No
2. Alberto Atilano (PSH)	Manageable A	Board member PLAS & PSH
3. Lourdes Ella Santos (PHA)	Manageable A	Board member PLAS & PSH
4. Danilo Baldemor (PCP)	Manageable A	DM directions, board member PCP & pharma company, w/ stocks, w/ Diabetes clinic
5. Alejandro Pineda (PMA)	Manageable A	Board member DFCM
6. Maria Cristina Pineda Franks (PNA)	Manageable A	With stocks at Capitol Medical Center
7. Carmela Remotigue (PSGIM)	Manageable A	Member - PCP, PSGIM
8. Rex Vener Palma (PSVM)	Manageable A	With stocks at Ridgeview Hosp., PHA
9. Grace Buot (Pt. Rep)	Manageable A	Kitchen supervisor – Streetlife
10. Melvin Miranda (PNA)	Manageable A	Board member PNA, member Association of Deans
11. Maria Rosario Sylvia-Uy (DOH)	Manageable B	Medical Officer IV – NCD Division DOH, Lifestyle Program