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PREVALENCE OF ASYMPTOMATIC CAROTID ARTERY STENOSIS IN PATIENTS WITH ISCHEMIC HEART DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

BY

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ABSTRACT

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Title: Prevalence of Asymptomatic Carotid Artery Stenosis in Patients with Ischemic Heart Disease: A Systematic Review and Meta-analysis

Supervisor of Thesis: Dr. Mujahed Shraim.

Background: The coexistence of carotid artery disease in patients undergoing Coronary artery bypass graft (CABG) is a risk factor for stroke and death. Moreover, significant carotid artery disease in ischemic heart disease (IHD) patients increases the risk of developing peri-operative neurological events. For determining the value of screening in these high risk patients, reliable prevalence estimates are crucial. The aim of this systematic review and meta-analysis was to summarize the prevalence of asymptomatic carotid artery stenosis in patients with IHD at global, regional, and among low, middle and high income countries.

Objectives: The specific objectives of this study were to estimate the pooled prevalence of ACAS in IHD patients globally, regionally and country income group levels.

Methods: In this systematic review and meta-analysis, EMBASE, Medline and CINAHL databases were searched from inception to June 2020. We included observational studies published in English reporting the prevalence of ACAS in IHD patients. Two reviewers independently assessed articles for inclusion, extracted data, and appraised the methodological quality of included studies. Statistical heterogeneity was assessed by using the I^2 statistic and random effects models were employed in meta-analysis to pool effect estimates.

Results: Of 5486 articles identified, 51 were included in the systematic review and

meta-analysis, with a total sample of 31,001 patients from five different regions. The pooled prevalence of ≥ 50% ACAS is 11% (95% CI 8-15%). The prevalence of ≥ 50% ACAS is 10% in American (AMR) region, 13% in both European (EUR) and Western pacific region (WPR), 9% in Eastern Mediterranean and 10% in South East Asian (SEAR) region. The pooled prevalence of ≥ 60% ACAS is 12% (95% CI 8-15%). The prevalence of ≥ 60% ACAS is 14%, 13% and 4% in AMR, EUR and EMR regions respectively. The pooled prevalence of ≥ 70% ACAS is 7% (95% CI 5-9%). According to the region, the prevalence of ≥ 70% ACAS is 7% in both AMR and EUR region, 4% in EMR and 6% in SEAR region. The pooled prevalence of ≥ 80% ACAS is 2% (95% CI 1-4%). Furthermore, the prevalence of ≥ 50% ACAS is 12% and 10% in high income (HIC) and low and middle income countries (LMIC). The prevalence is 13% and 8% in HIC and LMICs for ≥ 60% ACAS and 7% for both HIC and LMICs for ≥ 70% ACAS.

Conclusion: This study suggested that the burden of ACAS in IHD patients remains substantial. The pooled prevalence of ACAS is variable among regions but overall the prevalence is higher in HICs compared to LMICs. Further longitudinal studies may provide information about the potential impact of screening for ACAS on morbidities and mortality in IHD patients.

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TABLE OF CONTENTS

ACKNOWLEDGMENTS v

LIST OF TABLES ix

LIST OF FIGURES x

Chapter 1: INTRODUCTION 12

Chapter 2: LITERATURE REVIEW 14

2.1. Global burden of Cerebrovascular disease 14

2.2. Ischemic Heart Disease 15

2.3. Risk factors for IHD and CeVD 16

2.4. Asymptomatic carotid artery stenosis 17

2.5. Risk factors for CAS 17

2.6. Relationship between ACAS, IHD and stroke 18

2.7. Diagnosis of ACAS 20

2.8. Treatment of concomitant ACAS and IHD 21

2.9. Screening recommendations for ACAS in IHD population 23

2.10. Screening for ACAS in IHD patients 25

Chapter 3: METHODS 28

3.1. Search strategy 28

3.2. Study selection and eligibility criteria 30

..... 30

3.3. Exclusion criteria 30

3.4. Data extraction 30

3.5. Methodological quality assessment 31

3.6. Data analysis 31

3.7. Ethical considerations 33

Chapter 4: RESULTS 34

4.1. Study Selection 34

4.2. Study characteristics 36

4.3. Diagnostic method for ACAS 37

4.4. Grading of ACAS 38

4.5. Methodological quality assessment of included studies 53

4.6. Meta-analysis 58

4.6.1. Prevalence of ≥ 50% ACAS 58

4.6.2. Prevalence of ≥ 60% ACAS 61

4.6.3. Prevalence of ≥ 70% ACAS 64

4.6.4 Prevalence of > 80% ACAS 67

4.7. Meta-regression results 69

4.8. Risk of bias due to missing results in meta-analysis 69

Chapter 5: DISCUSSION 75

5.1. Summary of evidence 75

5.2. Strengths and limitations 77

5.3. Implications 78

5.4. Conclusion 78

Source of funding 78

Conflict of interest 79

References 80

APPENDIX A: HOY'S RISK OF BIAS TOOL (THE 10 CRITERIA USED TO ASSESS THE RISK OF BIAS IN EACH INCLUDED STUDIES) 101

APPENDIX B: SEARCH STRATEGY 102

APPENDIX C: TABLE FOR PREVALENCE OF ≥ 50% ACAS IN INDIVIDUAL STUDIES 104

APPENDIX D: TABLE FOR PREVALENCE OF ≥ 60% ACAS IN INDIVIDUAL STUDIES 106

APPENDIX E: TABLE FOR PREVALENCE OF ≥ 70% ACAS IN INDIVIDUAL STUDIES 107

LIST OF TABLES

Table 1: Characteristics of included studies (n=51) 39

Table 2: Risk of bias summary 54

Table 3: Summary of Meta-analysis results 68

LIST OF FIGURES

Figure 1: PRISMA flow diagram of articles through the review 35

Figure 2: Prevalence of ≥ 50% asymptomatic carotid artery stenosis plot (Random effects) 59

Figure 3: Prevalence of ≥ 50% asymptomatic carotid artery stenosis plot by region (Random effects) 60

Figure 4: Prevalence of ≥ 50% asymptomatic carotid artery stenosis by income group (Random effects) 61

Figure 5: Prevalence of ≥ 60% asymptomatic carotid artery stenosis plot (Random effects)Figure 6: Prevalence of ≥ 60% asymptomatic carotid artery stenosis plot by region (Random effects) 62

Figure 7: Prevalence of ≥ 60% asymptomatic carotid artery stenosis by income group (Random effects) 64

Figure 8: Prevalence of ≥ 70% asymptomatic carotid artery stenosis plot (Random effects)Figure 9: Prevalence of ≥ 70% asymptomatic carotid artery stenosis plot by region (Random effects) 65

Figure 10: Prevalence of ≥ 70% asymptomatic carotid artery stenosis by income group (Random effects) 67

Figure 11: Prevalence of ≥ 80% asymptomatic carotid artery stenosis (Random effects) 67

Figure 12: Funnel plot of REM of ≥ 50% asymptomatic carotid artery stenosis 70

Figure 13: Trim and fill method showing no significance publication bias for ≥ 50% ACAS 71

Figure 14: Doi plot of REM of ≥ 50% asymptomatic carotid artery stenosis 71

Figure 15: Funnel plot of REM of ≥ 60% asymptomatic carotid artery stenosis 72

Figure 16: Trim and fill method showing no significance publication bias for ≥ 60% ACAS 72

Figure 17: Doi plot of REM of ≥ 60% asymptomatic carotid artery stenosis 73

Figure 18: Funnel plot of REM of ≥ 70% asymptomatic carotid artery stenosis 73

Figure 19: Trim and fill method showing no significance publication bias for ≥ 70% ACAS 74

Figure 20: Doi plot of REM of ≥ 70% asymptomatic carotid artery stenosis 74

CHAPTER 1: INTRODUCTION

Cardiovascular disease has become a leading cause of disability and premature mortality globally. Approximately 30% of all cases of global mortality are due to cardiovascular diseases and 10% due to cerebrovascular disease (4). Atherosclerotic disease affecting the extracranial portion of carotid artery accounts for 15-20% of all events of stroke, the third leading cause of death in industrialized nations and a major cause of long-term disability (5).

ACAS in patients with coronary artery disease (CAD) is a significant clinical and economic issue, detrimentally affecting the outcomes on cardiac revascularisation procedures that are costly to healthcare system. Joint ACAS and CAD is of special interest for cardiologists and cardiac surgeons given the fact that CABG is one of the frequent procedures and that carotid artery stenosis (CAS) cause 30% of all post-CABG strokes (6). IHD patients who are undergoing myocardial revascularization have significant CAS (7). The coexistence of carotid artery stenosis (CAS) increases the risk of postoperative stroke in patients undergoing coronary artery bypass graft (CABG) (8). The incidence of cerebrovascular events (CVE) in patients undergoing elective CABG surgery is reported to be as high as 15.6% (9). Several studies have shown that the existence of CAS in subjects undergoing CABG procedures increases the risk of significant neurological deficits (8, 10-12). So, early detection of ACAS in IHD patients is of paramount importance to reduce associated morbidity and mortality.

Preoperative screening and management of ACAS in patients undergoing cardiac surgery is an important public health issue (13). To date, there is no consensus on which patients should undergo carotid screening for the detection of carotid stenosis. Studies on pre-operative carotid ultrasonography have previously shown the prevalence of

significant CAS in candidates of CABG is from 2-18% (14). This highlights the need for routine ultrasonic carotid assessment in candidates of CABG. As carotid stenosis may be an avoidable cause of stroke, the strategy of routine screening prior to surgery should be evaluated (15). If a group could be identified with a higher prevalence of CAS and therefore a higher risk of stroke, this could translate into a larger potential benefit of screening and treatment (16). A contemporary understanding of the worldwide burden of ACAS in IHD patients is indispensable to develop effective policy schemes on screening strategies for management of ACAS and notify stakeholders. Currently, there are no systematic reviews that has summarized the prevalence of ACAS in IHD patients at global and regional levels. Therefore, the aim of this thesis was to fill this gap in knowledge by conducting a systematic review and meta-analysis. This systematic review reviewed published peer-reviewed article assessing the prevalence of ACAS in IHD patients. This thesis will include the following sections and chapters: aims and objectives, literature review, methods, results and discussion.

1.1. Aim and objectives

The aim of this thesis is to estimate the prevalence of ACAS amongst IHD patients by conducting a systematic literature review and meta-analysis.

Objectives

The specific objectives of the systematic review are:

A. To estimate the pooled global prevalence of ACAS in IHD patients
B. To estimate the prevalence of ACAS in IHD patients according to regions and among low, middle and high-income countries.

CHAPTER 2: LITERATURE REVIEW

The literature review chapter presents a summary of disease burden of ACAS, risk factors, usefulness of screening for ACAS in patients with CAD and their management. Atherosclerosis is a systemic disorder that includes a group of major diseases- CAD, CAS and peripheral artery disease (PAD), which share common risk factors and results in various CVE (17). According to the WHO, the world's first and second highest causes of mortality in 2016 were CAD and stroke (18). Both of these diseases result from pre-existing atherosclerosis (18). Atherosclerosis related cardiovascular and CVE are the cause of death in almost 50% of cases in developed countries (19).

2.1. Global burden of Cerebrovascular disease

Stroke is the leading cause of morbidity and mortality worldwide. Approximately 30% of all cases of global mortality are due to cardiovascular diseases and 10% due to cerebrovascular diseases (CeVD) (4).

Among 240 causes of death, stroke is globally the second cause of death after IHD (20) and it is projected to remain so by 2030 (21). From 1990 to 2010, overall there was no significant changes in age standardized incidence of stroke, the direction of changes was different between countries by income level; a 12% (95% CI 6-17%) statistically significant decrease in HIC and a 12% (95% CI -3 to 22%) non- significant increase in LMICs (22).

Stroke is the leading cause of death and hospitalization in both men and women in nearly all European countries and the third major cause of death in the United States (23). Globally, 70% of strokes and 87% of both stroke-related deaths and disability-adjusted life years (DALYs) occur in LMICs (24, 25). Over the last four decades, the stroke incidence in LMICs has increased by more than two folds (24). However, during

the same period, stroke incidence has declined by 42% in HICs (24). On average, stroke occurs 15 years earlier in and causes more deaths of people living in LMICs when compared to HICs (26).

Based on the Global burden of diseases (GBD) data 2017, the global crude number of new stroke events has increased by 76% from 6.8 million new events in 1990 to 11.9 million in 2017 (21). However, compared to 1990, the age standardized global stroke mortality rate has decreased by 25% in low income countries (27), 23% in low middle income countries (L-MICs), 36% and 56% in upper middle income (UMIC) and HICs (21). In 2017, stroke was associated with about 132.1 million DALYs globally, in particular, 6.8 million DALYs in LICs, 47.1 million DALYSs in L-MICs, 63.1 million DALYs in UMICs and 14.2 million DALYs in HICs (21).

2.2. Ischemic Heart Disease

IHD, also called CAD or coronary heart disease (CHD) is the term given to heart problems caused by narrowed coronary arteries that supply blood to the heart muscle. Although the narrowing can be caused by a blood clot or constriction of the blood vessel, most often it is caused by build-up of plaque, called atherosclerosis (28). It is well known that atherosclerosis, which is a progressive systemic inflammatory disorder, is the underlying cause of cardiovascular diseases (3), and multiple risk factors augment the atherosclerotic process (29).

CHD is the single largest cause of death in the developed countries and is one of the leading causes of disease burden in developing countries as well (30). In 2001, there were 7.3 million deaths and 58 million DALYs lost due to CHD worldwide (31). Three-fourths of global deaths and 82% of the total DALYs are attributed to CHD occurring in the LMICs (30). Even though CAD mortality rates have declined since 1980s, it still

accounts for approximately one-third of all deaths of individuals aged over 35 years (32). Among cardiovascular illnesses, IHD ranks as the most prevalent cause of death worldwide (33). Indeed, IHD is acknowledged as an important threat to sustainable development in the 21st century (34). From the WHO mortality data in 2015, IHD remains the leading cause of death in countries of all income groups (35). However, while IHD mortality is falling globally, mortality rates in many countries, particularly those in LMICs remain very high (35). The increasing incidence of IHD is expected to continue, due to increased prevalence of obesity, diabetes and metabolic syndrome, and aging populations (36). According to the World Heart Federation (WHF), the global cost of CVD in 2010 was approximately US $863 billion, which is expected to rise to more than US$1 trillion by 2030 (37). Notably, the median total cost of IHD care in LMICs country-specific health expenditure per capita was 10% (37).

2.3. Risk factors for IHD and CeVD

The prevalence of cardiovascular risk factors also continues to rise. Globalization seems to have contributed to a higher prevalence of risk factors in developing countries (35). Rapid urbanization and globalization in the LMICs have led to a shift in disease-related deaths and disabilities from infectious disease to non-communicable disease such as IHD (38).The risk factors for stroke are similar to those for CAD and other vascular diseases. Risk factors for stroke have been extensively examined and are well known; these include hypertension (39), diabetes mellitus (DM), cardiac disease and smoking (40). The risk factors for CVD include non-modifiable ones such as age and sex and modifiable risk factors such as HTN, dyslipidemia, obesity, DM and smoking (41, 42). In the GBD study, 72%, 66%, and 28% of stroke DALYs were attributed to metabolic factors- high blood pressure (BP), BMI, fasting plasma glucose (FBG), and total

cholesterol and low glomerular filtration rate ,behavioral factors (smoking, poor diet and physical inactivity), and environmental risks (air pollution and lead exposure), respectively (43).

2.4. Asymptomatic carotid artery stenosis

CAS is a manifestation of atherosclerotic diseases. CAS is the narrowing of internal carotid arteries, which limits blood flow to the brain and is caused by atherosclerosis (16). Asymptomatic carotid atherosclerotic disease refers to the presence of atherosclerotic narrowing of the extracranial internal carotid artery in individuals without a history of ipsilateral carotid territory ischemic stroke or transient ischemic attack (TIA) (44-46). The prevalence of ACAS in general population is considered to be low and increases with age. In a recent systematic review of population-based studies, moderate stenosis (≥ 50%) of carotid artery was found in 4.8% of men and 2.2% of women younger than 70 years, but this increases to 12.5% in men and 6.9% in women older than 70 years (47). A recent systematic review and meta-analysis reported a prevalence of CAS of 1.5% equivalent to 57.79 million affected people in general population aged 30-79 years (48).

2.5. Risk factors for CAS

There is much literature on the risk factors for developing CAS. Important risk factors or combinations thereof for clinically significant CAS are age >65 years, male sex, smoking, heart disease, HTN and poor glycemic control in diabetic patients (49-51). The presence of the strongest reported risk factors, smoking or heart disease, approximately doubles the risk of CAS (51). However, no single risk factor and no clinically useful risk model incorporating multiple factors, clearly discriminates people who have clinically important CAS from people who do not (52). For example, a

Chinese study found significant associations between the presence of CAS and older age, current drinking, systolic blood pressure (SBP), and low density lipoprotein cholesterol (LDL-C) (53). Each 1 mmHg increase in SBP was associated with increased risk of CAS by 1.01 times (OR= 1.01, 95% CI 1.004 to 1.019), each 1 mmol/L increase in LDL-C increased the risk of CAS by 19.2% (OR= 1.19, 95% CI 1.056 to 1.346), and each 1mmol/L increased in FBG increased the risk of CAS by 6.7% (OR= 1.06, 95% CI 1.004 to 1.019) (53).

2.6. Relationship between ACAS, IHD and stroke

It is known that a relationship exists between coronary and carotid arterial disease as atherosclerosis is a systemic condition (54). ACAS is not only a well-recognized risk factor for ischemic stroke and TIA but is also a marker of elevated cardiovascular morbidity and mortality (7, 55, 56). Stroke associated with CAS could occur via several mechanisms, such as atheroembolism of cholesterol crystals, artery to artery embolism of thrombus, structural disintegration of wall, acute thrombotic occlusion and reduced cerebral perfusion with plaque growth (57). IHD patients who are undergoing myocardial revascularization have significant CAS (7). Similar atherosclerotic plaque morphology at both vascular sites suggest that development of atherosclerotic changes at both sites share similar systemic factors (58, 59). The prevalence of carotid artery atherosclerosis in patients with known CAD differs depending on study population and is highly dependent on the extent of CAD (60). A study found that 50% of men with ACAS has signs and symptoms of IHD(61, 1). The vascular mortality rate in men with carotid artery disease and concomitant IHD was more than twice as high in man with carotid stenosis without IHD (61) . Several studies suggested that stroke risk during CABG is related to the degree of carotid stenosis. In a meta-analysis, patients with no

significant carotid disease had a 1.9% risk of stroke, increasing to 3% in predominantly asymptomatic patients with unilateral 50-99% stenosis, 5% in those with bilateral 50-99% stenosis and 7-11% in patients with carotid occlusion (49).

Risk factors most commonly associated with CAS in patients with CAD are extension of CAD, older age and a history of CeVD and concomitant PAD (10, 62-64). Conversely, few studies have been performed to estimate the prevalence of CAD in patients with CAS. The prevalence of CAD (defined as ≥ 50% stenosis of coronary artery or previous percutaneous coronary intervention (PCI) /CABG) in patients who are admitted for elective carotid artery stenting (CS) as being as high as 77.1% (65). The concomitant presence of CAS and CAD is a frequently encountered clinical problem, given the ageing population and is expected to continue to increase in the future which is a major challenge in clinical management to reduce associated morbidity and mortality (65).

CABG is the major surgical procedure performed the most commonly, with more than 650,000 operations every year in the United States (66). The incidence of CVE in patients undergoing elective CABG surgery is reported to be as high as 15.6% (9, 67, 68). Stroke is a devastating complication of CABG (69). Despite advances in cardiac surgery techniques and anesthesia, stroke remains the most common iatrogenic neurologic complication of myocardial revascularization (70). The presence of carotid artery disease is considered to be a risk factor for adverse neurological outcomes following CABG (16). Several studies have shown that the existence of CAS in subjects undergoing CABG procedures increases the risk of significant neurological deficits (8, 10-12). Among other complications of CABG surgery, surgical site infections (SSI) are also a cause of substantial morbidity and mortality. In a population based cohort study,

the SSI incidence rate is found to be 7% (95% CI 5.7 to 8.4%) in patients undergoing CABG surgery (71) .

IHD patients undergoing surgical myocardial revascularization were found to have significant CAS (7). In a meta-analysis of CAS and stroke after CABG, the probability of perioperative stroke ranged from 2% to 7% (72). In previous studies of CABG of the patients who suffered from 50% to 80% CAS, the incidence for ischemic stroke varied from 3-10% and the incidence was higher, around 22%, among patients having ≥ 80% carotid stenosis (73). The prevalence of perioperative stroke after CABG is 2% in patients without CAS and increases to 6.5% in patients with 50-99% CAS and 11.5% for those with carotid occlusion (74). There are various mechanisms that can cause perioperative strokes in patients undergoing CABG other than carotid artery disease. The most common cause is embolism (75-77). This can originate from various sources, such as arrhythmias, left ventricular thrombus, aortic dissection, particulate micro-emboli, emboli arising from aortic arch disease, aortic "crunch" occurring with cross-clamping or cannulation, and air and fat emboli (75-78). Nevertheless, concomitant CAS plays a significant role in the etiology of perioperative stroke in patients undergoing CABG (79). Patients with pre-existing CVD and risk factors for further developing vascular disease are perceived as having a greater likelihood of developing carotid artery atherosclerosis and subsequently stroke by gradual progression of stenosis and embolization (79).

2.7. Diagnosis of ACAS

The diagnosis of CAS maybe accomplished by non-invasive studies of the carotid artery such as carotid duplex ultrasonography (DUS), magnetic resonance angiography (MRA), or computed tomography angiography (80) and by auscultation for carotid

bruits during the physical examination (81). These imaging modalities have high sensitivities and specificities for diagnosing 70-99% internal CAS in patients with ipsilateral carotid territory ischemic symptoms (82). Digital subtraction angiography (DSA) has been considered the gold standard for the evaluation of 70-90% CAS which provides a sensitivity and specificity of 95% and 99% (83, 84). However, angiography is associated with a small but real risk of stroke. The most feared complication is embolization with consequent stroke; with the incidence of permanent stroke of <1% all of which makes it unsuitable for use as screening test (84, 85).

Accurate measurement of stenosis is critical in identifying patients requiring surgery. Although DSA is considered as gold standard in the assessment of stenosis, the preferred method for diagnosis and grading of CAS is most often specific to institutions and usually depends on available equipment and personnel competencies. The use of different imaging modalities introduces disagreement in the assessment of the degree of carotid stenosis and leads to a difference of opinion as to which method is more accurate(86). Based on the results of the North American Symptomatic Endarterectomy trial (NASCET), only discrimination between 50-60% and 70-99% stenosis was considered to be important. However, recent studies used different cut-off values for patient selection for carotid surgery, using stenosis degree of 50%, 60%, 70% and 80%, depending on the symptoms present and comorbidities (87).

2.8. Treatment of concomitant ACAS and IHD

The management strategy for concomitant CAD and CAS is very controversial. Treatment options for ACAS consist of medical therapy and in some cases, revascularization (88). Medical therapy for CAS comprises management of associated risk factors such as HTN, dyslipidemia, DM, tobacco use and the use of antiplatelet

therapy (5).There is no consensus on the surgical management of ACAS in patients undergoing CABG (89). The efficacy of carotid endarterectomy (CEA) before or combined with CABG remains controversial (89).

Several international vascular guidelines like the American standard association (ASA), American Heart association (AHA), American college of cardiology foundation (ACCF) recommends that carotid revascularization by CEA or CS with embolic protection before or concurrent with myocardial revascularization surgery is reasonable in patients with greater than 80% stenosis who have experienced ipsilateral retinal or hemispheric cerebral ischemic symptoms within 6 months (5). They also state that in patients with ACAS, even if severe, the safety and efficacy of carotid revascularization before or concurrent with myocardial revascularization are not well-established (5). The American College of Cardiology (ACC) and AHA CABG guidelines state that it is reasonable to revascularize extracranial carotid artery stenosis (90) of 50-99% in patients with previous history of stroke or TIA and in those who do not have a prior history of stroke or TIA, they consider it reasonable to revascularize especially in the setting of bilateral ECAS of 70-99% or unilateral ECAS of 70-99% with contralateral occlusion (88).

The results of trials assessing CEA in patients with ACAS is conflicting. Several randomised trials have compared the efficacy and safety of CEA with best medical treatment with antithrombotic therapy in patients with ACAS (91). A meta-analysis consisting of five trials (2440 patients with carotid stenosis >50%), showed a significant reduction in the odds (OR 0.62; 95% CI 0.44 to 0.86) of ipsilateral stroke plus perioperative stroke or death, corresponding to a 2% absolute risk reduction over about 3.1 years in patients undergoing CEA (91). During the immediate postoperative period

an increased prevalence of stroke and death among such patients was observed (91). The Asymptomatic Carotid Surgery Trial (ACST) showed that in asymptomatic patients those who aged 75 years with >70% stenosis, immediate CEA halved the 5-year stroke risk from 12% to 6% (92).

The AHA has published guidelines regarding the appropriateness of synchronous CABG+CEA versus staged CABG and CEA procedure in CABG patients with asymptomatic occlusive carotid disease (93). The consensus view is that synchronous CEA+CABG is recommended although there is lack of sufficient evidence or trials (78)in patients with unilateral >60% asymptomatic stenosis where there is a proven operative stroke and death risk of <3%. In those units with an operative stroke and death risk of >3%, the guidelines qualified the appropriateness of synchronous procedures as "uncertain" (93). Despite the above mentioned AHA recommendations, the most favourable surgical management of patients with >60% ACAS planning to undergo CABG remains unclear (89). Regarding the new endovascular approaches, the SAPPHIRE trial showed that in high risk patients with severe ACAS (>80%), carotid stenting with the use of embolic protection device was not inferior to CEA (94). In summary, carotid revascularization by CEA or CAS with embolic protection before or concurrent with myocardial revascularization surgery is reasonable in patients with >80% CAS who have experienced ipsilateral retinal or hemispheric cerebral ischemic symptoms within 6 months In patients with ACAS, even if severe, the safety and efficacy of carotid revascularization before or concurrent with myocardial revascularization are not well established (class 11a level C evidence) (93)

2.9. Screening recommendations for ACAS in IHD population

Screening for ACAS maybe accomplished by non-invasive studies of the carotid artery

(e.g. carotid DUS, MRA, or CTA) and by auscultation for carotid bruits during the physical examination (81). The choice among the non-invasive carotid artery imaging methods depends mainly upon the clinical indications for imaging and the availability and expertise at individual centers (81). DUS is a widely available, non-invasive screening test with estimated sensitivity and specificity of 94% and 92%, respectively, for detecting CAS at 60-99%. The reliability of ultrasound is questionable, as accuracy can vary considerably between laboratories (95). Conventional cerebral angiography has been considered the gold standard for the evaluation of ICAS (83). However, confirmatory testing using digital subtraction angiography can have complications such as stroke, and therefore, it is rarely used in clinical practice (95). The use of DUS in a low prevalence population would result in many false positive tests (95). If no confirmatory tests are done and all persons with positive tests are referred for intervention, many unnecessary interventions and harms would occur (95).

To date, there is no consensus on which patients should undergo carotid screening for the detection of carotid stenosis. In 2011, the ACC foundation and the AHA, in collaboration with several other organizations, including the American Stroke association, American association of Neurological surgeons, American college of radiology, American society of neuroradiology, society for vascular surgery and Society for vascular medicine have recommended against the use of carotid DUS for routine screening of asymptomatic patients with no clinical manifestations or risk factors for atherosclerosis (5). As per the National stroke association, Canadian stroke consortium and the U.S Preventive services taskforce (USPSTF), screening of the general population is not indicated (96-98). Despite evidence on important risk factors, there are no externally validated, reliable risk-stratification tools to distinguish persons

who are more likely to have CAS (95).

The ACC/AHA guidelines note that the carotid screening before CABG is probably indicated in the following subset of patients: age >65 years, left main coronary stenosis, history of smoking, history of TIA/stroke or carotid bruit and PAD (99). The 2011 European PAD strategies have extended their recommendations for preoperative duplex scan for CAS in CABG patients to include patients more than 70 years of age or those with evidence of carotid bruit, multi-vessel CAD, CeVD or evidence of PAD class 1 (4).

2.10. Screening for ACAS in IHD patients

The risk of perioperative stroke in patients with normal carotid artery undergoing CABG is between 0.2% and 5.3% which increases to 15% in patient with critical CAS (>70% lesion) (100-102). Studies on pre-operative carotid ultrasonography have previously shown the prevalence of significant CAS in candidates of CABG from 2-18% (14). This highlights the need for routine ultrasonic carotid assessment in candidates of CABG. Early detection and prompt management of carotid disease irrespective of degree of stenosis may prevent CVEs pre and post CABG (14). If a group could be identified with a higher prevalence of CAS and therefore a higher risk of stroke, this could translate into a larger potential benefit of screening and treatment (16). However, there is currently no externally validated risk stratification tool to reliably identify those patients who are at greater risk of CAS (16) as no studies reported risk stratification tools to predict who is at decreased or increased risk for ipsilateral stroke or death caused by CAS (16). As carotid stenosis may be an avoidable cause of stroke, the strategy of routine screening prior to surgery should be evaluated (15). Routine carotid screening has a class IIa recommendation for patients with multivessel

CAD, PVD or >70 years of age (103). The detection of carotid lesions in patients with CAD maybe useful for two reasons: (a) identification of severe carotid stenosis makes it possible to manage it appropriately; and (b) carotid lesions maybe helpful for stratifying the risk of CAD patients and thus assessing prognosis more accurately (104). In conclusion, ultrasonic screening for ACAS maybe of paramount importance mainly as a tool to identify high-risk individuals for CVD and manage them early rather than waiting for them high grade ACAS requiring intervention. Preoperative screening and management of ACAS in patients undergoing cardiac surgery is an important public health issue for reducing morbidity and has been studied extensively with some conflicting results (13).

Prevalence of ACAS in general population is very low to justify routine screening. The American Stroke Association/AHA Stroke Council concluded that highly selected patient populations may benefit, but screening of the general population for asymptomatic carotid stenosis was unlikely to be cost-effective and might have the potential adverse effect of false-negative or false positive results (13) . Data published by the Society for Vascular Surgery Outcomes Committee demonstrated that real-world CAS was associated with a significantly higher rate of major complications than CEA in asymptomatic patients (13). The 30-day outcome analysis of CAS and CEA in 2818 patients revealed the combined death, stroke, or MI rate for 1450 CAS patients was 4.6% vs 1.97% for 1368 CEA patients. Other studies of larger databases have yielded similar results (13). Many studies reporting the prevalence of ACAS in IHD patients is quite heterogenous ranging from 2% to 30% for $\geq$ 50% ACAS (105-107). Such high-risk patients might still benefit from such preventive measure if studied separately.

A contemporary understanding of the worldwide burden of ACAS in IHD patients is

indispensable for management of ACAS. Nevertheless, no current estimates of the prevalence of ACAS in IHD patients are available at global level. Because precise and valid prevalence estimates are important for recommendations regarding population based screening and management of the disease, we aimed to fill this gap in knowledge by determining the prevalence of ACAS amongst patients who have IHD through systematic review and meta-analysis.

CHAPTER 3: METHODS

This chapter presents a brief about the methods used in this systematic review and meta-analysis including search strategy, selection of studies along with eligibility and study exclusion criteria, and data extraction methods. Additionally, the quality assessment method and data analysis of the included studies are discussed in this chapter.

We included population based observational studies that reported on ACAS in IHD population irrespective of geographic location. We considered only observational studies because our research question is more likely to be addressed by diagnostic studies rather than clinical trials. Asymptomatic carotid atherosclerotic disease was operationally defined as the presence of atherosclerotic narrowing of the extracranial internal carotid artery in individuals without a history of ipsilateral carotid territory ischemic stroke or TIA (45). IHD is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand (108). Study participants with history of CAD, left main disease or who has been admitted into hospital for acute coronary syndrome (ACS) and patients undergoing CABG or PCI were operationally defined as patients with IHD. Left main disease is one of the highest risk lesion subset of IHD (109). N

3.1. Search strategy

The review was guided by the recommendations from the Preferred Reporting items for Systematic Reviews and Meta-Analysis (PRISMA), the specific guidelines for reporting meta-analysis of observational studies and guidelines for undertaking systematic reviews of incidence and prevalence studies (110). The following

bibliographic databases were searched from their inception to June 2020: EMBASE, Medline and CINAHL. The inception years of EMBASE, CINAHL and MEDLINE are 1974, 1981 and 1946, respectively. These databases were selected and searched because they are the key databases covering biomedical sciences and allied health professions. Additionally, index of included papers were screened to find relevant papers. The databases were searched using controlled vocabularies (Medical Subject Heading or Emtree terms) and free-text terms on the following concepts in the title and abstract were used to identify relevant papers: CAS (carotid stenosis, carotid artery disease, carotid artery stenosis, carotid artery thrombosis, carotid artery atherosclerosis, carotid artery plaque, carotid artery obstruction, carotid artery occlusion, carotid artery arteriosclerosis, carotid artery ulcer, carotid artery disorder, carotid artery narrowing) and terms related to CAD (myocardial ischemia, coronary artery bypass graft, coronary artery syndrome, coronary artery atherosclerosis). The Medical subject heading (MeSH) or Emtree terms of each keyword and combinations by using Boolean operators such as 'AND' and 'OR' were explored in each database. The full search strategy is presented in details in Appendix B.

Reference lists of relevant papers on the topic were hand searched to identify any relevant papers for potential inclusion in the current systematic review. Citations of relevant papers were traced to identify any relevant papers. Only papers published in English were considered for inclusion in the review because English is the language spoken by the reviewers and this MPH thesis had no funding for professional translation service for papers that are published in other languages. Any disagreements for inclusion of relevant papers were resolved by discussion or recourse to a third reviewer (the supervisor of this thesis). Duplicate studies were identified and removed using

EndNote software.

3.2. Study selection and eligibility criteria

Assessment of study eligibility for inclusion in the review was conducted by two reviewers- Sadia Mahmood (SM) and Nazmul Islam (NI) independently. The titles and abstracts of all identified papers were screened and irrelevant papers were excluded. Then the full-text of potentially relevant studies, or when a final decision could not be made based on screening titles and abstracts; were retrieved and reviewed. No restrictions were placed on patient's severity of either coronary or carotid artery disease or degree of stenosis or on the method of determining the degree of stenosis. We considered studies to be eligible for inclusion if the full text articles were available and if they were observational studies reporting on ACAS.

3.3. Exclusion criteria

To avoid selection bias, we excluded studies that have evaluated the prevalence of ACAS in patients with clinical manifestations of CAS and studies that included participants with any history of CEA or CS, stroke, TIA, amaurosis fugax or any cerebrovascular attacks. Selection bias can be induced as the history of these conditions can influence the detection and assessment method by the assessor, which could influence the outcome. In addition, studies that diagnosed ACAS by subjective assessment (auscultation) such as the presence of carotid bruit only were excluded.

3.4. Data extraction

Data extraction was performed by two reviewers. Discrepancies between the two reviewers were resolved by discussion or by the involvement of a third reviewer. Data were extracted manually. A standardized data extraction form was piloted and then used to extract the following data from included studies: first author and publication year,

country, study design, number of participants, mean age, proportion of participants according to gender, methods used to diagnose/define CAS and IHD, prevalence of ACAS in IHD patients, including numerator (number of patients with ACAS) and denominator (number of IHD patients), timeframe of prevalence estimate and any prevalence estimates reported stratified by age or sex. Also, data about participant's history of CAD, HTN, DM, smoking, hyperlipidemia, peripheral vascular disease (PVD) and obesity was extracted. We stratified data according to percentage of ACAS reported in the primary studies (50%, 60%, 70% and ≥80%). All the included studies were available as full text article, so there wasn't any need to contact authors of included studies for further details.

3.5. Methodological quality assessment

Two reviewers independently conducted quality assessment and discrepancies between them were resolved through discussion, until consensus is reached. The methodological quality of studies was appraised using the Hoy's risk of bias tool, which is designed to assess bias in prevalence studies (111). This tool comprises 10 items plus a summary assessment. Item 1 to 4 assess the external validity of the study (domains represent selection and nonresponse bias). And items 5 to 10 assess the internal validity of the study (domains represent measurement bias and analysis bias). Each item is assigned a score of 1 (yes) or 0 (no). Scores are summed across items to generate an overall quality score range from 0 to 10. Then the overall score is used to classify the study into three different risk of bias categories including low (8-10), moderate (5-7) or high (≤ 4) risk of bias (112). The details and description of the tool is presented in Appendix A.

3.6. Data analysis

Summary tables of extracted data were created to summarize the characteristics and

findings of included studies. Meta-analysis of prevalence of ACAS in IHD patients was conducted. Unadjusted estimates were calculated, and 95% confidence intervals (CI) were determined based on the crude numerators and denominators provided in individual studies. Forest plots were used to show the pooled prevalence as diamonds, with their lateral points indicating 95% confidence intervals. A forest plot displays effect estimates and confidence intervals for both individual studies and meta-analysis. Each study is represented by a block at the point effect estimate of with a horizontal line extending either side of block (113).We also stratified data into five geographic regions (AMR, EUR, WPR, EMR and SEAR) according to the WHO classification or regions and according to country income group (UIC, LMIC) as designated by World Bank for 2019-2020 (114).

Heterogeneity across studies was assessed by using the I-squared statistic (I^2), which describes the percentage of total variation in ACAS prevalence across studies that is due to heterogeneity rather than chance (115). Significant heterogeneity is indicated by a significant P-value (<0.05) of the Cochrane-Q test or the I^2 statistic value of $\geq$50% (115). If moderate or high heterogeneity was identified among studies, random effect model (REM) (Dersimonian and Laird method) was employed to obtain a crude summary estimate for prevalence using the standard error scale (116). A REM assumes the observed estimates can vary across studies because of real differences in each study as well as due to sampling variability (chance) (117). Sensitivity analysis was undertaken to assess the impact of low methodological quality studies on the pooled prevalence estimate (118). Meta-regression was used to explore potential sources of variance across included studies.

Publication and/or reporting bias was assessed using funnel plot (119), Egger's test

(121) and Doi plot along with Luis Furuya-Kanamori index (LFK) (120). Doi plot is used for graphical examination and LFK index provides quantitative examination for potentially small study effects (120). A LFK index value greater than 1 or less than -1 indicates minor asymmetry, and a value greater than 2 or less than -2 indicates major asymmetry (120). Egger's test is a test that uses linear regression to assess the relation between the standardized effect estimates and the standardized error (121). Moreover, funnel plot asymmetry was examined by trim and fill method to assess the significance of publication bias and provide the bias-adjusted results (173). Meta-analyses were conducted using MetaXL version 5.3 (122).

3.7. Ethical considerations

IRB was not needed for this systematic review.

CHAPTER 4: RESULTS

4.1. Study Selection

The initial systematic search identified 5486 articles (Figure 1). An additional 5 studies were identified from the list of references in published articles. After removal of duplicates, 5066 articles were recorded. A total of 4729 articles were excluded after screening of the titles and abstracts. A total of 337 full-text articles were reviewed for eligibility, and 286 of them were excluded due to various reasons. Articles were excluded due to inclusion of patients with history of neurovascular events, TIA or stroke (n=109); no usable prevalence data (n=12); studies with measurements of CIMT or plaques only (n=17); not IHD based patients or all heart procedures included (n=50); not available in English (n=23); editorials/letters/review articles and conference abstracts (n=34); combined extracranial carotid artery disease (ECAD) & intracranial carotid artery disease (ICAD) reported (n=4); intracranial artery stenosis (ICAS) reported (n=2); not an observational study design (n=5); supplementary material (n=16); studies that were not available (n=13) and one study was excluded because of diagnosis of CAS was made by carotid bruit only. The remaining 51 articles were included in the review. The prevalence of ≥ 50% ACAS was reported in 34 studies, ≥ 60% ACAS in 13 studies, ≥ 70% ACAS in 17 studies and ≥ 80% in 3 studies.

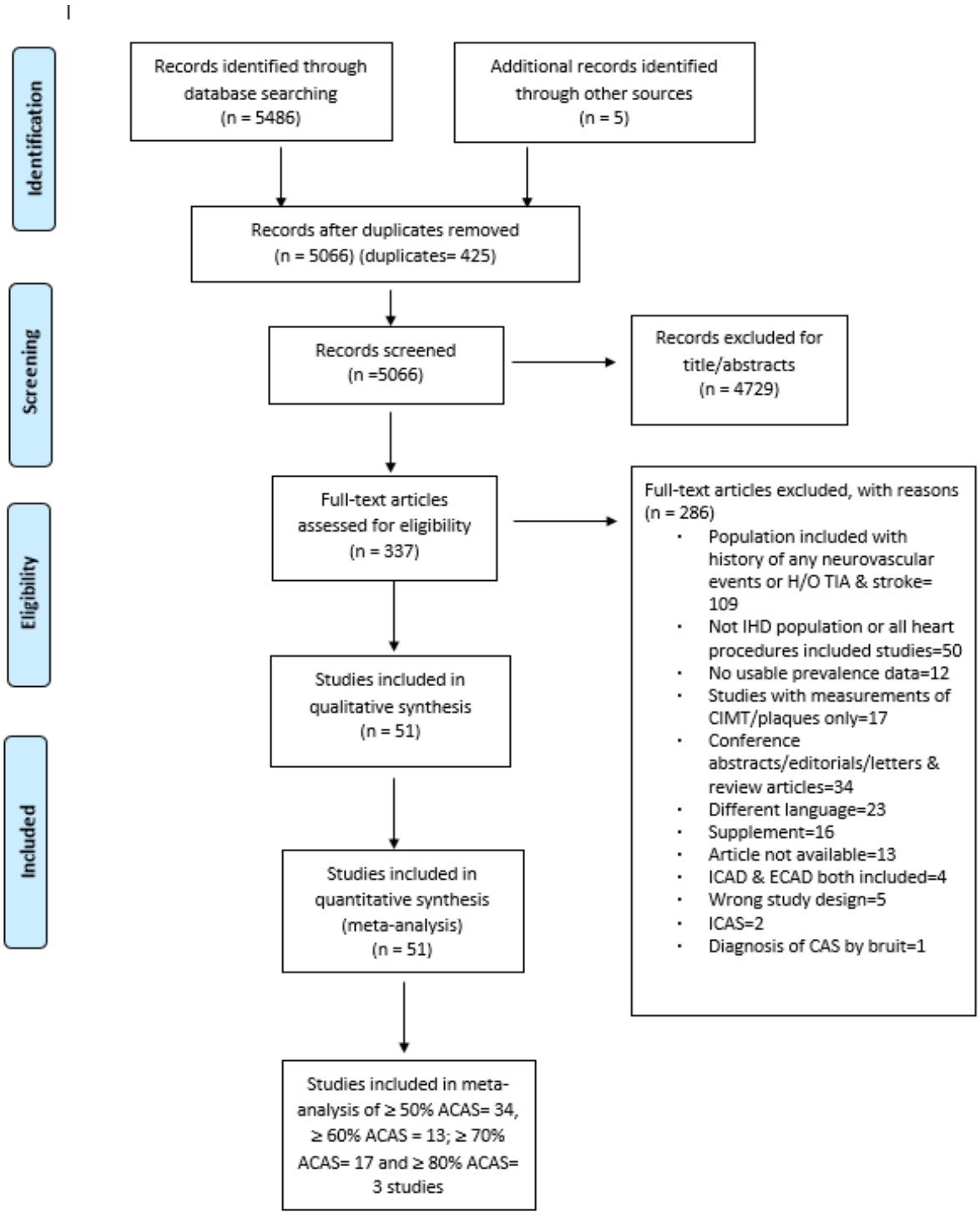

Figure 1: PRISMA flow diagram of articles through the review

4.2. Study characteristics

The characteristics of the 51 included studies are described in Table 1. ACAS prevalence in IHD patients was collected from 20 different countries among five regions globally as designated by WHO. Most of the included studies came from the EUR region (n=24, 47%) and AMR (n=12, 23%). The rest were from the EMR (n=7, 14%), SEAR (n=5, 10%) and the WPR (n=3, 6%).

Total 51 studies included 31,001. participants The highest number of population was from one study (67) with the sample size of 4047 (13%). Two studies included population of around 3000 participants (123, 124) that comprised 21% of total population and the lowest number of study participants recorded were 45 (125).

Study publication year ranged from 1981 to 2019. A total of 12 studies (24%) were published between the year of 1981 and 2000 and rest of the 39 studies (76%) were published from 2001 to 2019. Among the 51 included studies, 40 were cross-sectional, 10 were cohort studies and 1 was case –control study. One study duration was of 10 years (79); one for 7 years (67); two for 4 years (126, 127); 7 studies for 3 years (105, 107, 123, 124, 128-130); 5 studies for 2 years (131-135) and 22 of the studies were below of 2 years duration. A total of 11 of the observational studies didn't report on the study duration (2, 106, 136-144). Out of the 11 studies; 6 (2, 106, 139, 142-144) were cohort; 4 (136-138, 140) were cross sectional study design and 1 (141) was case-control study.

The mean age of participants ranged from 57 to 73 years old. Four studies did not report on the age of the study participants (67, 126, 132, 145). A total of 12 (24%) studies did not report on the number of male and female participants. All the studies that reported on number of male and female participants had higher proportions of males than

females ranging from 51% (138) to 94% (139).

Most study populations were undergoing CABG or were scheduled for CABG or PCI. Two studies included patients who were addressed for coronary angiography due to suspected CAD (137, 146); 8 studies participants included patients with diagnosed CAD (105, 107, 128, 134, 136, 140, 141, 147, 148), 1 with MI (138); 1 study included patients who were admitted to ICU for ACS (149) and 1 study with patients of Left main disease (132). Two studies included IHD patients specifically with DM only (79, 140).

Out of the 51 included studies, the selection criteria for participants inclusion were: ACAS patients in 7 studies (105, 128, 129, 150-153); 1 study with no TIA/ stroke in last 12 months (154); 3 studies with no TIA/ stroke in last 6 months (106, 141, 155); 1 study excluded patients who had recent neurological symptoms (67); 12 studies did not specify about any inclusion or exclusion criteria of study participants but had mentioned about evaluation for CAS was either for screening purpose or as part of preoperative evaluation in IHD or patients undergoing CABG (4, 14, 126, 127, 132, 133, 140, 143, 148, 156-158). The remaining 27 studies included individuals with no history of any TIA, stroke, CVD, known CAS and history of any carotid intervention (CEA or CS).

4.3. Diagnostic method for ACAS

Diagnosis of ACAS was made by DUS in majority of studies with both methods DUS and angiography were used in 9 studies (67, 105, 107, 124, 126, 134, 146, 148, 155). The source of information of the included studies was based on medical records. DUS were performed mostly by ultra-sonographer, vascular technologist, radiologist, physicians including neurologists and interventional cardiologists for the assessment and grading of CAS.

4.4. Grading of ACAS

There was a considerable variation among studies with respect to methods of stenosis grading and the stenosis cut-off point used. Five studies (4, 14, 131, 144, 146) reported on prevalence of CAS using the criteria defined by the Society of Radiologists in the Ultrasound consensus (SUR) (159). Thirty four out of 51 studies reported on ≥50% stenosis (2, 4, 14, 67, 105-107, 123, 125, 126, 129-131, 133-139, 141, 143-146, 152-155, 158, 160-163). Twelve studies mentioned reported on ≥ 60% stenosis (79, 124, 127, 132, 140, 147, 149, 156, 157, 164-166); 18 studies reported on ≥70% stenosis (2, 4, 14, 125, 128, 131, 133, 135, 138, 142, 143, 148, 150-152, 158, 161, 162) and only 2 studies reported on ≥ 80% stenosis (135, 137). Nine studies reported on prevalence according to gender (2, 107, 131, 133, 134, 152, 158, 165, 166), 1 study reported according to age (157) and 2 studies reported according to both age and gender (4, 138).

Table 1: Characteristics of included studies (n=51)

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Barnes 1981(123)	1 year	USA	AMR	HIC	198	CAD	Periorbital & direct carotid Doppler	NR	NR	NR	≥ 50%	History of TIA/stroke/CEA excluded	21 (10.6%)	NR	NR
Breslau 1981(145)	6 months	USA	AMR	HIC	78	CABG	DUS	NR	NR	NR	10-49%; 50-99%	No sign and symptoms of ACAS	10-49%=17 (21.7%); 50-99%=5 (6.4%)	NR	NR
Brener 1987(67)	7 years	USA	AMR	HIC	4047	Cardiac surgery	DUS and Angiogram	NR	NR	NR	> 50%	Recent neurologic symptoms patients excluded; but remote history of neurological symptoms patients included	153 (3.7%)	NR	NR

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Minami 1988(105)	3 years	Germany	EUR	HIC	1471	CAD	DUS and Angiogram	NR	NR	51-78 (64)	≥ 50%	ACAS patients included	≥50%= 35 (2.37%)	NR	NR
Faggioli 1990(154)	9 months	USA	AMR	HIC	539	CABG	DUS	Medical data	377 (70%)	63.45	≥ 50%	No history of TIA/stroke in last 6 months included	107 (19.8%)	NR	HTN=46.8%; DM=19.7%; Smoking=58.6%; Hypercholesterolemia=66.4%
Sanguigni 1993(136)	NR	Italy	EUR	HIC	184	CAD	DUS	NR	NR	45-70 (62.3)	> 50%	Symptomatic CAS patients excluded	>50%=30 (16.3%)	NR	NR
Uehara 1996(146)	5 months	Japan	WPR	HIC	67	Coronary angiography (MI/Angina)	MRA	NR	49 (73.3%)	40-78 (60.1)	25-49%= Mild; 50-74%= Moderate; >70%= Severe	No history of stroke included	25-49%= 11(16.4%); 50-74%= 3(4.5%); 75-99%= 1(1.5%)	NR	HTN=28.3%; DM=29.8%; Smoking=50.7%; Hyperlipidaemia= 35.8%
Takach 1997(150)	21 years	USA	AMR	HIC	512	Coronary revascularisation	NR	Hospital records and clinical charts	358 (70%)	29-83 (64.9)	≥ 70%	NR	≥ 70%= 316 (61.7%)	NR	HTN= 66.6%; DM= 22.9%; Hyperlipidaemia= 20.5%; Smoking= 35.7% ; PVD= 31.3%; Obesity=5.1%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Kallikazaros 1999(137)	NR	Greece	EUR	HIC	225	Patients addressed for angiography	DUS	NR	225(88%)	58	≥ 50%; > 80%	History of CVD patients excluded	≥ 50%= 28 (13%); 80% stenosis= 10 (5%)	NR	HTN-35.5%; DM-24.8%; Smoking-60.4%;
Cheng 1999(128)	3 years	China	WPR	UMIC	207	CAD	DUS	NR	128 (61.83%)	65.9	30-69%; ≥ 70%	Asymptomatic patients included	30-69%= 42 (20.3%); ≥70%= 23 (11.1%)	NR	NR
Tunio 1999(156)	3 years	USA	AMR	HIC	3344	CABG	DUS	Medical records	1973 (59%)	NR	≥ 60 %	No mention about symptoms; nor in baseline table	≥ 60 % = 243 (7.2%)	NR	HTN= 74%; DM= 35%; Smoking= 53.5%
Cirilo 2000(151)	11 months	Italy	EUR	HIC	302	CABG	DUS	NR	253 (83.8%)	33-81 (63)	≥ 70%	ACAS patients included	≥ 70%= 23 (7.6%)	NR	Smoking=79.1%; Dyslipidaemia=54%; T2DM= 28.1%; Obesity= 20.2%
Ascher 2001(124)	3 years	USA	AMR	HIC	3081	CABG	DUS and MRA	NR	NR	40-98 (68)	≥ 60%	History of TIA/stroke/CEA excluded	≥60%= 249.5 (8.1%)	NR	HTN=74%; Smoking=54%; DM=35%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Lombardo 2004(106)	NR	Italy	EUR	HIC	365	stable/unstable angina with CABG	DUS	Database	273(77%)	66	≥ 50%	No TIA/stroke in < 6months included	128 (35%)	NR	HTN- 63%; DM=31% ; Smoking- 20%; Overweight/obesity= 37%
Aboyans 2004(147)	2 months	France	EUR	HIC	99	History of CAD	DUS	NR	NR	35-94 (64)	≥ 60%	History of TIA/stroke/CEA excluded	7 (7.1%)	NR	NR
Kablak 2004(148)	8 months	Poland	EUR	HIC	463	CAD	DUS and Angiography	NR	NR	40-81 (58.8)	≥ 70%	No mention about asymptomatic; also not in baseline table	≥70%= 10.1%	NR	HTN=61.9%, Smoking=64.4%; Hyperlipidaemia= 84.2% ; NIDDM=19.7%; Obesity= 20.3%
Ambrosetti 2004(131)	2 years	Italy	EUR	HIC	168	CAD, CABG, PCI	DUS	NR	127 (75.5%)	47-84 (65)	Mild= < 50% ; Moderate = 50-69%; Severe= > 70%	Known CVD patients excluded	< 50%= 68%; 50-70%= 24 (14%); > 70%= 11 (6%)	Males (n=127) = with 50-70% CAS is 14 (13%) and >70% CAS is 7(6%)	HTN= 63%; DM= 30%; Smoking=43%; Hypercholesterolemia=60%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Farhoudi 2004 (125)	16 months	Iran	EMR	UMIC	45 (Available DUS results)	CABG	DUS	NR	105 (81.4%)	57	50-70%; > 70%	No history of TIA in patients included	50-70%= 5(11%); > 70%= 1(2%)	NR	HTN= 38%; DM= 18.6%; Hypercholesterolemia= 29%; Smoking= 44.8%
Arai 2006(129)	3 years	Japan	WPR	HIC	221	CABG	DUS	Computer database	161 (73%)	40-84 (67)	> 50%	ACAS patients included	>50%= 19%		HTN=68%; DM=40%; Hyperlipidaemia= 59%; Smoking=53%; PVD=14%
Shirani 2006(129)	1 year	Iran	EMR	UMIC	1045	CABG	DUS	NR	728(70%)	27-88 (60)	> 60%; > 80%	No mention about symptoms ; nor in baseline table	>60% stenosis= 72(6.9%) ; >80% stenosis= 10 (1.0%)	50-65 years= 21 (4.3%) had >60% CAS; >65 years= 49 (12.5%) had > 60% CAS ; >65 years= 12 (3%) had CAS > 80%	DM= 23.3%; Smoking=31.7%
Rajamani 2006(138)	NR	USA	AMR	HIC	101	MI	DUS	Hospital records	52 (51%)	59.6	> 30% ; > 50%; >70%	Known CVA/Stroke patients excluded	> 30%= 21(20.8%); >50%= 11(10.9%); >70%= 5(5%)	Male with >30%= 13.7%; >50%= 6%; >70%= 4%; and for age >60yrs= 71.4%;	HTN=86.1%; DM= 35.6%; Smoking= 59.4%; Hyperlipidaemia= 65.3%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
														<60yrs= 12%	
Sonecha 2006(139)	NR	UK	EUR	HIC	153	CABG	DUS	NR	144 (94%)	48-76 (167)	≥ 50%	Patients with no history of cerebrovascular events included	7 (4.6%)	NR	NR
Bosevski 2007(140)	NR	Macedonia	EUR	UMIC	145 (patients with CAD & DM)	CAD	DUS	NR	92 (62.8%)	59.85	≥ 60%	No mention about symptoms; nor in baseline table	28 (25.2%) for unilateral CAS & 15 (13.5%) for bilateral CAS (only in DM population)	NR	HTN= 81.4%;

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Doonan 2007(132)	2 years	USA	AMR	HIC	186	Left main disease	DUS	Database	NR	NR	≥ 60%	No mention about symptoms; nor in baseline table	≥ 60% = 58 (31.2%)	NR	NR
Fichet 2008(149)	9 months	France	EUR	HIC	152	Admitted for ICU for ACS	DUS	Registry	103 (68%)	28-88 (66)	30-60%; > 60%	History of symptomatic CAS patients excluded	30-60% stenosis= 9 (6%); >60%= 3.9(2.6%)	NR	HTN=60%; DM=27%; Smoking=27%; PAD=5.3%
Shirani 2008(160)	16 months	Iran	EMR	UMIC	2044	CABG	DUS	Hospital records	1429 (70%)	31-84 (61)	50-99%	Previous CS patients excluded	50-99%= 136 (6.6%)	NR	HTN= 32.2%; Smoking= 29.2%; DM= 28.9%; Dyslipidaemia= 63%
Brevetti 2009(141)	NR	Italy	EUR	HIC	90	Stable CAD	DUS	Hospital records	76 (84.4%)	62	≥ 50%	No TIA/stroke in <6months	≥ 50%= 16.7%	NR	DM=31.1%; HTN=87.8%; Hypercholesterolemia=76.7%; smoking=15.6%
Akhtar 2009(130)	3 years	Pakistan	EMR	L-MIC	176	CABG	DUS	Medical record	150 (85.2%)	65	≥ 50%	Known CAS patients excluded	≥50-75%= 24 (13.6%); >75%= 11 (6.2%)	NR	NR

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Ghanaati 2009(133)	2 years	Iran	EMR	UMIC	301	CABG	DUS	Medical records and datasheet	215 (71.4%)	41-88 (60.3)	50-69%; ≥ 70%	No mention about symptoms; nor in baseline table	50-69%= 29(9.6%); ≥ 70%= 13(4.3%)	≥ 70% stenosis= Male is 10 (5.1%); Female= 3 (3.8%)	HTN= 42.2%; DM=28.9%; Smoking= 37.5%; Hyperlipidaemia= 81.7%
Salehiomran 2009(164)	1 year	Iran	EMR	UMIC	1604	CABG	DUS	NR	1187 (74%)	20-84 (58.3)	> 60%	No history of CVA included	> 60%= 21 (1.3%)	NR	HTN= 66%; DM= 36.9%; Hypercholesterolemia= 76.1%; PVD= 4.1%; Smoking= 37.5%
Komorovsky 2009(161)	1 year	Italy	EUR	HIC	337	ACS	DUS	Hospital charts	259 (77%)	64	> 50%; > 70%	No CAS symptoms patients included	> 50%= 19 (5.63%); > 70%= 9 (2.67%)	NR	HTN= 77.7%; DM= 18%; Smoking= 70%
Pereira 2010(158)	1 year	Brazil	AMR	UMIC	393	CABG	DUS	Data review	257 (65.3%)	38-85 (62.4)	50-69%; ≥ 70%	No mention about symptoms; nor in baseline table	50-69%= 47 (12%); ≥ 70%= 29 (7.4%)	NR	HTN= 83.7%; DM= 28.4%; Obesity= 32.1% Smoking=17.8%; Dyslipidaemia=27 %

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Abbaszadeh 2011(126)	4 years	Iran	EMR	UMIC	1978	CABG	DUS and MRA	Medical records	NR	NR	Severe= 50-69% ; critical/occluded stenosis	No mention about symptoms ; nor in baseline table	Severe = 30 (1.5%); critical/occluded= 10 (0.5%)	NR	HTN= 43.8%; DM= 19.9%; Smoking= 2.2%
Adeoye 2012(14)	6 months	India	SEAR	L-MIC	73	CABG	DUS	NR	NR	65	< 50%; 50-69%; ≥ 70%	No mention about symptoms ; nor in baseline table	No stenosis= 21(28.8 %); <50%= 45(61.6 %); 50-69% = 4(5.5%); ≥70% =3(4.1%)	NR	NR
Rosa 2013(152)	1 year	Brazil	AMR	UMIC	450	CABG	DUS	NR	295 (65.6 %)	38-85 (62 .2)	50-69%; ≥ 70%	Only asymptomatic patients included; patients with indications of CEA was excluded	50-69%= 52 (11.6%); ≥ 70%= 32 (7.1%)	NR	HTN= 83.9%; DM= 29.81%; Dyslipidaemia= 26.2%; Smoking= 82.4%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Podolecka 2013 (165)	1 year	Poland	EUR	HIC	123	CABG	DUS	Medical records	91 (74%)	65.31	60-99%	Significant CAS patients excluded	60-99%= 35 (28.45%)	Male with 60-99% CAS= 25 (71.4%)	HTN= 78%; DM= 46.3%; PAD= 10.5%; Smoking= 27.6%
Benetos 2015 (142)	NR	Greece	EUR	HIC	200	CAD, CABG, PCI	DUS	NR	164 (82%)	64.15	≥70%= 22(11%)	History of TIA/stroke/CEA excluded	≥70%= 22 (11%)	NR	HTN= 71%; DM= 38%; Smoking=45.5%; Dyslipidaemia=78 %
Costanzo 2015 (166)	18 months	Italy	EUR	HIC	244	CAD ,PCI, CABG	DUS	NR	205 (84%)	65.37	≥ 60%	No previous history of carotid atherosclerosis included	≥ 60% = 44 (18%)	Male= 33 (16.1%)	HTN= 85.2%; DM=43%; Dyslipidaemia=77 .5%; smoking=69.7%
Luchowski 2015 (143)	NR	Poland	EUR	HIC	175	CABG	DUS	Medical records	124 (71%)	44-85 (66.1)	50-69%; ≥ 70%	No mention about symptoms ; nor in baseline table	50-69%= 13 (7.42%); ≥ 70%= 19 (10.8%)	NR	HTN= 82.8%; DM= 29.7%; Hyperlipidaemia= 21%; smoking=26.8%
Taneja 2015 (144)	NR	India	SEAR	L-MIC	100	CABG	DUS	Medical records	76 (76%)	59.27	< 50% ; > 50%	History of TIA/stroke/CEA excluded	< 50%= 28(28%); >50%= 10 (10%)	NR	Smoking=31%; Dyslipidaemia=20 %; HTN=52%; DM=40%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Wiberg 2015 (155)	7 months	Denmark	EUR	HIC	46	CABG	MRA	NR	42 (91.3 %)	67	> 50%= Significant stenosis	No TIA/stroke in <6 months included	> 50%= 6(13%)	NR	Dyslipidaemia= 73.9%; HTN= 82.2%; Smoker= 60.9%; DM= 22.2%;
Bosevski 2015 (127)	4 years	Greece	EUR	HIC	340	CAD & T2DM	DUS	NR	NR	60.28	≥ 60%	No mention about symptoms; nor in baseline table	Unlilateral CS= 68 (20%); Bilateral CS= 32 (9.4%)	NR	HTN= 78.8%; Hyperlipidaemia= 85.9%; Smoking= 42.1%; Obesity= 35%; PAD= 82.35%
Torbey 2015 (79)	10 years	USA	AMR	HIC	192	History of CAD (PCI & CABG) & DM	DUS	Charts and reports	100 (52%)	73	≥ 60%	Patients with no prior history of stroke/TIA included	≥ 60% = 35 (18%)	NR	HTN= 83%; DM2= 98%; Smoking= 70%; IDDM= 2%;
Avci 2016 (2)	NR	Turkey	EUR	UMIC	225	CABG	DUS	Retrospective chart review	168 (74.7 %)	66.16	50-69%; ≥70%	Acute symptomatic CAS patients excluded; patients with history of CEA, CS & history of stroke	50-69%= 40 (17.8%); ≥70%= 19 (8.4%)	Male with ≥ 50% CAS= 51 (86%)	HTN=84%; DM= 43.1%; Hyperlipidaemia= 28.4%; Smoking= 32%; PAD=4.4%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
												were excluded			
Hamid 2016 (107)	3 years	India	SEAR	L-MIC	50	CAD	Carotid angiogram	Medical records	33 (66%)	40-71 (59)	≥ 50%	History of TIA/stroke/CEA excluded	≥ 50% = 10 (20%)	Male ≥ 50% stenosis= 10 (80%); female with ≥ 50% stenosis= 2 (20%)	HTN= 82%; DM=48%; Dyslipidaemia=28%; Smoking=50%
Kazum 2016 (134)	2 years	Israel	EUR	HIC	325	CAD	DUS	Medical records	237 (73%)	33-87 (69)	30-49%; ≥ 50%	Known CAS/previous stroke patients excluded	≥ 50%= 83 (25.5%)	Male ≥ 50% CAS= 57 (68.7%)	Smoking= 31.6%; HTN= 62.4%; DM= 37%; Hyperlipidaemia= 77%
Obrenovic 2016 (153)	12 months	Serbia	EUR	UMIC	272	CABG	DUS	NR	217 (79.8%)	31-81 (58)	≥ 50%	ACAS patients included	≥ 50% = 18 (7.1%)	NR	HTN= 79.4%; DM= 20%; Smoking= 61%; BMI >30= 19.4%
Santarpino 2018 (135)	2 years	Finland	EUR	HIC	2813	CABG	DUS	Registry	2336 (83%)	68	50-59%; 60-69%; 70-79%; >90%	History of TIA/stroke/CEA excluded	50-59%= 311(11.1%); 60-69%= 170(6%); 70-79%= 86(3.1%)	NR	HTN= 87.6%; DM= 35.7%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
													; >80%= 82(2.9%)		
Adhikary 2019 (4)	1 year	Bangladesh	SEAR	LIC	200	History of IHD; CABG	DUS	NR	136 (68%)	57.7	Mild= < 50% ; Moderate = 50-69%; Severe= > 70%	No mention about symptoms ; nor in baseline table	<50%= 82%; 50-69%= 24(12%); >70%= 12 (6%)	50-59 years= mild 73.2%; moderate 62.5%; severe 66.7%; >60 yrs= mild 26.8%; moderate 37.5; > severe 33.3%; Male= mild 67.1%; moderate 66.7%; severe 83.3%; Female= mild 32.9%; moderate 33.3%; severe=16.7 %	HTN=81.4%; DM=35.7%; Hyperlipidaemia= 17.4%; Obese= 34.5%

Author name	Study duration	Country	Region	WB Income group	Sample size (31,001)	CABG / CAD	Diagnostic method used for ACAS	Source of information	Male	Age	% of stenosis reported	Inclusion/ Exclusion criteria	Prevalence of ACAS in IHD patients	Prevalence of ACAS in IHD patients according to age and gender	Sociodemographic and medical characteristics (comorbidities)
Akansel 2019 (162)	1 year	Turkey	EUR	UMIC	291	CABG	DUS	Database	225 (77.3 %)	34-81 (61)	≥ 50% ; ≥ 70%	Previous CEA/stenting/stroke patients excluded	<50%= 8(2.7); ≥ 50%= 47 (16.2%); ≥70%= 21(7.2%)	NR	HTN=73.5%; DM=39.9%; Hyperlipidaemia= 38.1%; Smoking= 14.4%; PAD= 4.8%
Chakravarthy 2019 (163)	6 months	India	SEAR	L-MIC	561	CABG	DUS	Medical records;	421 (75%)	58.9	≥ 50%	No symptoms of CAS included	> 50%= 28 (5%)	NR	HTN= 43.1%; DM= 37.2%; Smoking-= 28.1%

ACAS= Asymptomatic carotid artery stenosis, ACS=Acute coronary syndrome, AMR= American region, CABG= Coronary artery bypass graft, CAD= Coronary artery disease, CAS= Carotid artery stenosis, CEA= Carotid endarterectomy, CeVD= Cerebrovascular disease, CS= Carotid stenting, CVA=Cerebrovascular accident, DM= Diabetes mellitus, DUS= Duplex ultrasonography, EMR= Eastern Mediterranean region, EUR= European region, HIC= High income country, HTN= Hypertension, LIC= Low income country, L-MIC= Low middle income country, MI= Myocardial infarction, MRA= Magnetic resonance angiography, NIDDM= Non-insulin dependent diabetes mellitus, NR= Not reported, PCI= Percutaneous coronary intervention, PVD= Peripheral vascular disease, SEAR= South East Asian region, TIA= Transient ischemic attack, T2DM= Type 2 Diabetes mellitus, UMIC= Upper middle income coun

4.5. Methodological quality assessment of included studies

The overall methodological quality of the 51 included studies was high in 4 studies (8%), moderate in 42 (82%) studies and low in 5 studies (9%). Figure 2 and 3 present details of the risk of bias results and analysis of all included studies.

High risk of bias was seen mostly in 3 criteria of external validity (Item 1, 2 and 3) and 4 criteria of internal validity (Item 6, 7, 8 and 9). High risk of bias was likely because 2 studies (67, 105) did not use the same method for diagnosing CAS for all the included participants (not all patients underwent angiography for carotid lesions); a predefined CAS or an validated method of stenosis grading was not used in 4 studies (105, 127, 154, 163) and length of the study period was low in 3 studies (127, 154, 163).

Low risk of bias was seen in 4 studies (4, 134, 135, 158). It was due to random selection method used to select the sample (Item 3) for 3 studies (4, 134, 158) compared to other studies that either didn't mention about the participants selection process or was non-random selection process. And the remaining one study (135), study participants were selected from a multicentre E-CABG registry that enrolled patients from 16 European centres of cardiac surgery, which indicates that the sampling frame was likely to be representative of target population (Item 2).

Moderate risk of bias seen in 42 studies was most frequently seen in 3 criteria of external validity (Item 1, 2 and 3) that focus on selection bias and non-response bias. Selection bias was likely because most studies were conducted in a single site, and no evidence was provided that the study's target population was representative of the general population. In addition, the sampling frame was not clearly reported in about half of the studies. In addition, the majority of the studies rarely reported on the selection method that was used to select the sample.

Table 2: Risk of bias summary

Each element: Low risk=1; High risk=0	**External Validity**					**Internal validity**					**Summary on the overall risk of study bias**
Study name	**1. Was the target population a close representation of national population in relation to relevant variables eg: age, sex, occupation**	**2. Was the sampling frame a true/close representation of target population**	**3. Was some form of random selection used to select the sample, OR, was a census undertaken?**	**4. Was the likelihood of non-response bias minimal?**	**5. Were data collected directly from the subjects (as opposed to a proxy)?**	**6. Was an acceptable case definition used in the study?**	**7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?**	**8. Was the same mode of data collection used for all subjects?**	**9. Was the length of the shortest prevalence period for the parameter of interest appropriate?**	**10. Were the numerator(s) and denominator(s) for the calculation of the prevalence appropriate?**	**11. Overall score Low risk (>7) Moderate risk (6-7) High risk (<6)**
Barnes 1981	0	0	0	1	1	1	1	1	1	1	7
Breslau 1981	0	0	0	1	1	1	1	1	1	1	7
Brener 1987,	0	0	0	1	1	1	0	0	1	1	5
Minami 1988,	0	0	0	1	1	0	1	0	1	1	5
Sanguigni 1993	0	0	0	1	1	1	1	1	1	1	7
Uehara 1996	0	0	0	1	1	1	1	1	1	1	7
Takach 1997	0	0	0	1	1	0	1	1	1	1	6

Each element: Low risk=1; High risk=0		**External Validity**					**Internal validity**				**Summary on the overall risk of study bias**
Kallikazaros 1999	0	0	0	1	1	1	1	1	1	1	7
Faggioli 1999	0	0	0	1	1	0	1	1	0	1	5
Cheng 1999	0	0	0	1	1	1	1	1	1	1	7
Tunio 1999	0	0	0	1	1	0	1	1	1	1	6
Cirilo 2000	0	0	0	1	1	1	1	1	0	1	6
Ascher 2001	0	0	0	1	1	1	1	1	1	1	7
Lombardo 2004	0	0	0	1	1	1	1	1	1	1	7
Aboyans 2004	0	0	1	1	1	1	1	0	0	1	6
Kablak-Ziembicka 2004	0	0	0	1	1	1	1	1	1	1	7
Ambrosetti 2004	0	0	0	1	1	1	1	1	1	1	7
Farhoudi 2004	0	0	0	0	1	1	1	1	1	1	6
Arai 2006	0	0	0	1	1	1	1	0	1	1	6
Shirani 2006	0	0	0	1	1	1	1	1	1	1	7
Rajamani 2006	0	0	0	1	1	1	1	1	1	1	7
Sonecha 2006	0	0	0	1	1	1	1	1	0	1	6
Bosevski 2007	0	0	0	1	1	1	1	1	0	1	6
Doonan 2007	0	0	0	0	1	1	1	1	1	1	6

Each element: Low risk=1; High risk=0		**External Validity**					**Internal validity**				**Summary on the overall risk of study bias**
Fichet 2008	0	0	0	1	1	1	1	1	1	1	7
SHIRANI 2008	0	0	0	1	1	1	1	1	1	1	7
Brevetti 2009	0	0	0	1	1	1	1	1	0	1	6
Akhtar 2009	0	0	0	1	1	1	1	1	1	1	7
Ghanaati 2009	0	0	0	1	1	1	1	1	1	1	7
Salehiomran 2009	0	0	0	1	1	1	1	0	1	1	6
Komorovsky 2009	0	0	0	1	1	1	1	1	1	1	7
PEREIRA 2010	0	0	1	1	1	1	1	1	1	1	8
Abbaszadeh	0	0	0	1	1	0	1	1	1	1	6
Adeoye 2012	0	0	1	0	1	1	1	1	1	1	7
Rosa 2013	0	0	0	1	1	1	1	1	1	1	7
Podolecka 2013	0	0	0	1	1	1	1	1	1	1	7
Benetos 2015	0	0	1	1	1	1	1	1	0	1	7
Costanzo 2015	0	0	0	1	1	1	1	1	1	1	7
Luchowski 2015	0	0	0	1	1	1	1	1	1	1	7
Taneja 2015	0	0	0	1	1	1	1	1	0	1	6
Wiberg	0	0	0	1	1	1	1	1	0	1	6

Each element: Low risk=1; High risk=0		**External Validity**					**Internal validity**				**Summary on the overall risk of study bias**
2015											
Bosevski 2015	0	0	0	1	1	0	1	1	0	1	5
Torbey 2015	0	0	0	1	1	0	1	1	1	1	6
Avci 2016	0	0	0	1	1	1	1	1	0	1	6
Hamid 2016	0	0	0	1	1	1	1	1	1	1	7
Kazum 2016	0	0	1	1	1	1	1	1	1	1	8
Obrenovic 2016	0	0	0	1	1	1	1	1	1	1	7
Santarpino 2018	1	1	1	1	1	0	1	1	0	1	8
Adhikary 2019	0	0	1	1	1	1	1	1	1	1	8
Akansel 2019	0	0	0	1	1	1	1	1	1	1	7
Chakravarthy 2019	0	0	0	1	1	0	1	1	0	1	5

4.6. Meta-analysis

4.6.1. Prevalence of ≥ 50% ACAS

Thirty four out of 51 studies provided data reporting the prevalence of ≥ 50% ACAS in patients with IHD (2, 4, 14, 67, 105-107, 123, 125, 126, 129-131, 133-139, 141, 143-146, 152-155, 158, 160-163). The fixed effect model (FEM) showed a pooled prevalence of 7% (95% CI 7-8%). Significant statistical heterogeneity was observed which was evident by I^2 value of 96% with a p-value of <0.001. As a result, REM was used to pool the prevalence. The REM revealed a prevalence of 11% (95% CI 9-14%) (Fig 4). Sensitivity analysis was carried out by excluding 4 studies (67, 105, 154, 163) with low qualitywhich revealed a pooled prevalence of 12% (95% CI 9-15%).Plotting the studies according to 5 region on the forest plot revealed a lowest prevalence of 9% (95% CI 4-14%) in EMR region and a similar prevalence of 13% in both EUR (95% CI 8-18%) and WPR region (95% CI 2-27%) and 10% both in AMR (95% CI 5-17%) and SEAR region (95% CI 5-15%) (Fig 5).

According to the country income group, the prevalence of ≥ 50% ACAS was 12% (95% CI 8-16%) and 10% (95% CI 7-14%) in HIC and LMICs, respectively (Fig 6).

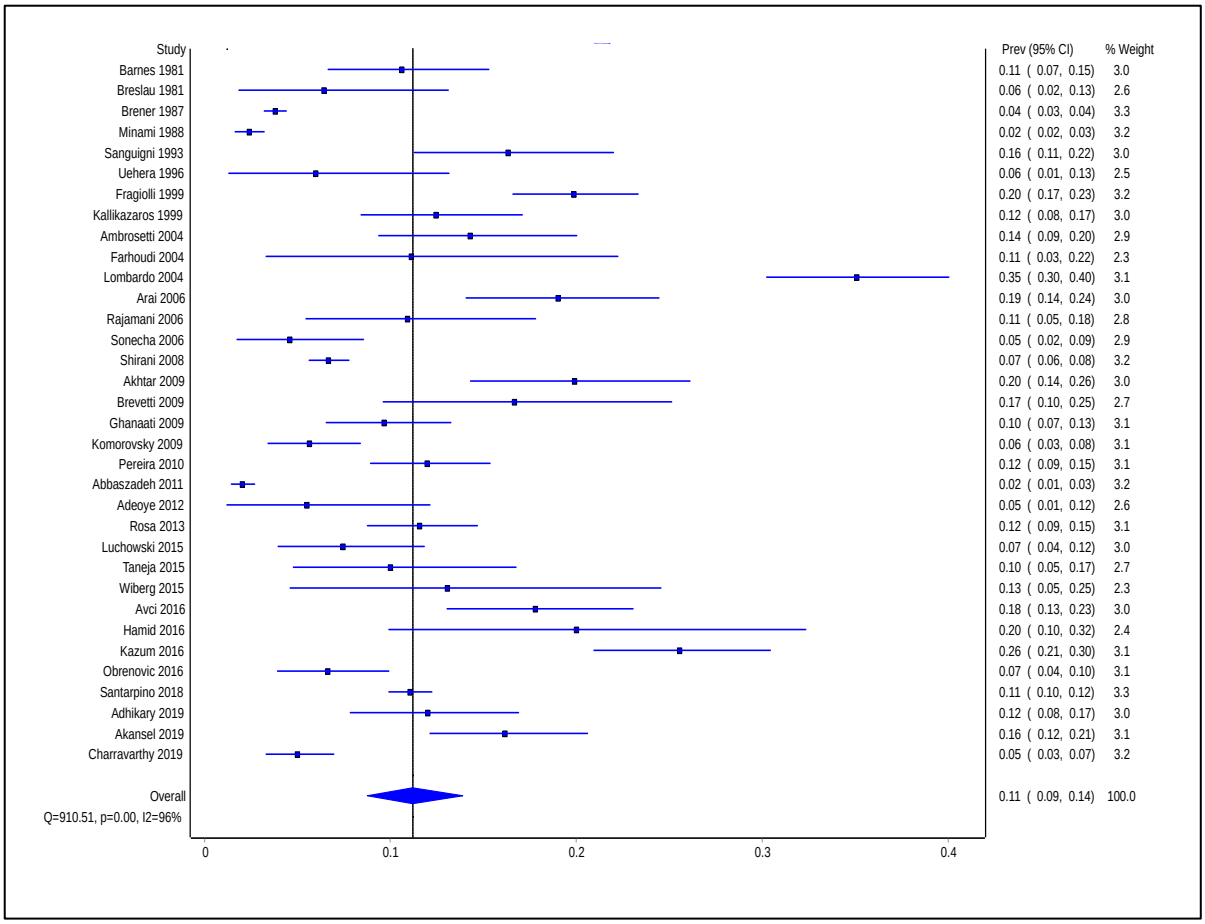

Figure 2: Prevalence of ≥ 50% asymptomatic carotid artery stenosis plot (Random effects)

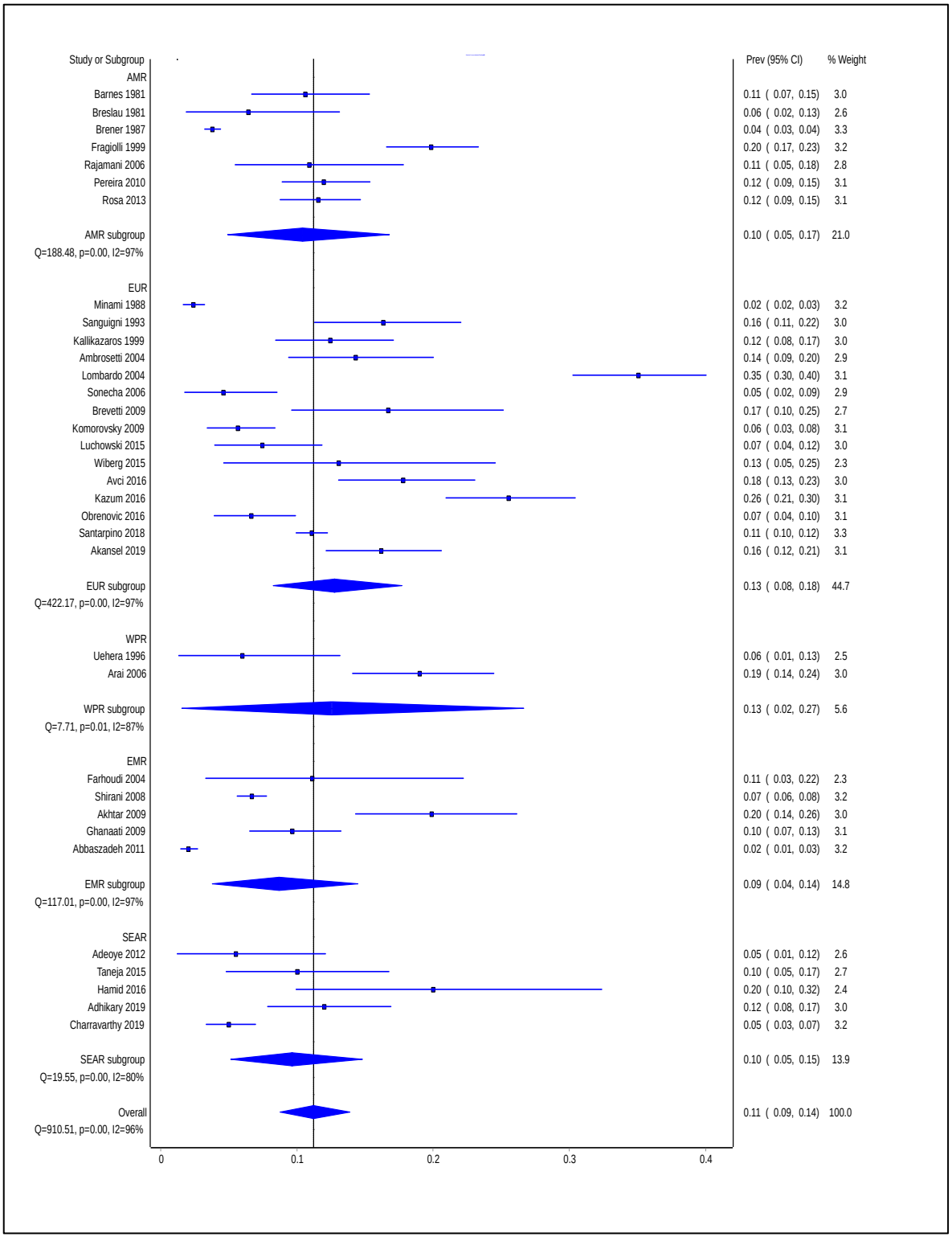

Figure 3: Prevalence of ≥ 50% asymptomatic carotid artery stenosis plot by region (Random effects)

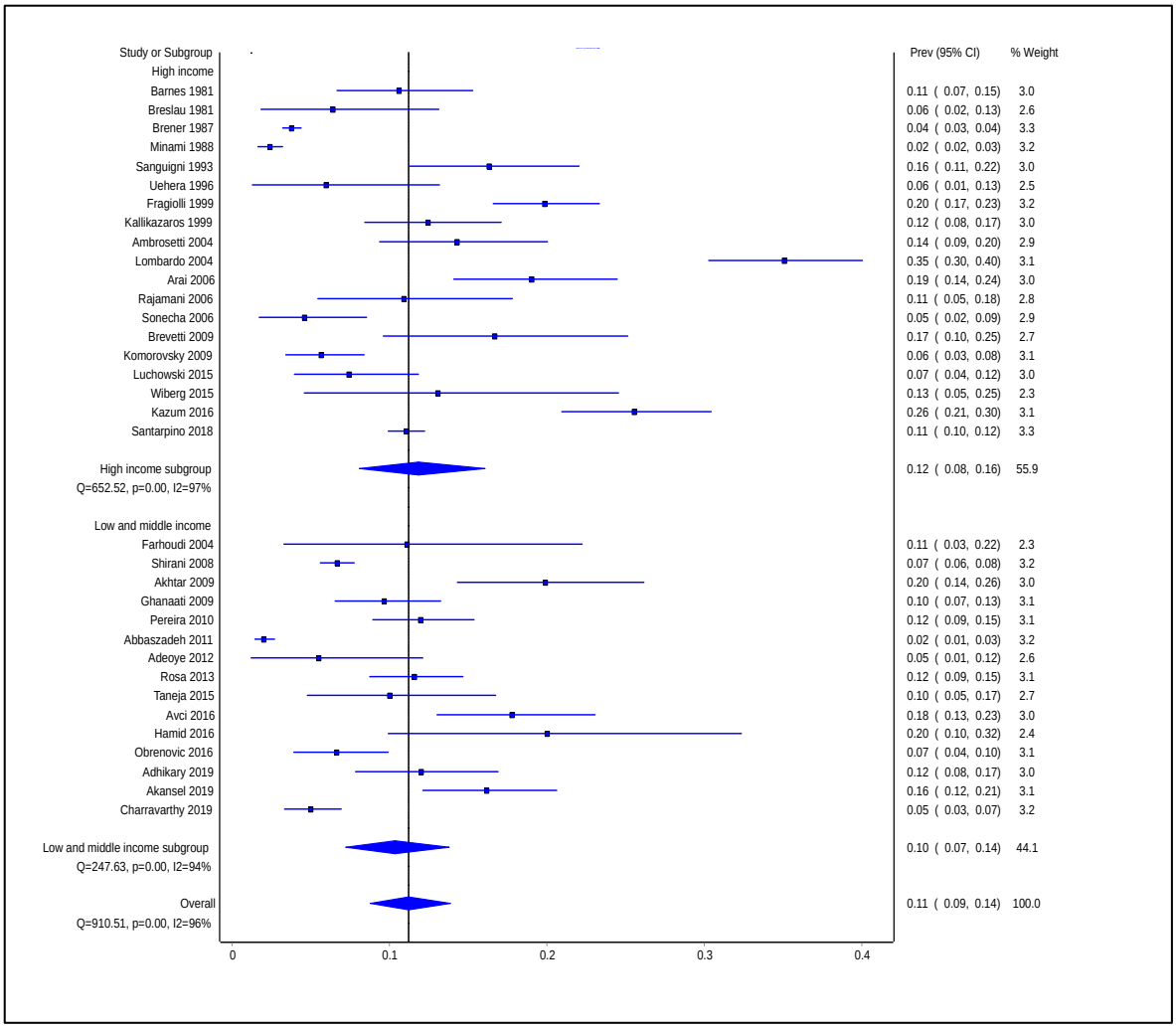

Figure 4: Prevalence of ≥ 50% asymptomatic carotid artery stenosis by income group (Random effects)

4.6.2. Prevalence of ≥ 60% ACAS

Thirteen out of the 51 studies provided data for prevalence of ≥ 60% ACAS. The FEM revealed a pooled prevalence of 7% (95% CI 7-8%). Significant heterogeneity was also observed here which was evident by I^2 value of 97% with a p-value of <0.001. The REM revealed a prevalence of 12% (95% CI 8-15%) (Fig 7). According to the subgroup analysis by region, the lowest prevalence of 4% (95% CI 0-12%) was seen in EMR

region. The prevalence of ≥ 60% ACAS in AMR and the EUR regions was 14% (95% CI 9-20%) and 13% (95% CI 7-21%), respectively (Fig 8). No studies reported on ≥ 60% ACAS prevalence in WPR and SEAR regions. The prevalence of ≥ 60% ACAS was 12% (95% CI 8-15%) in LMICs and 13% (95% CI 10-17%) in HICs (Fig 9). Sensitivity analysis was performed by excluding one low quality study which revealed similar pooled prevalence.

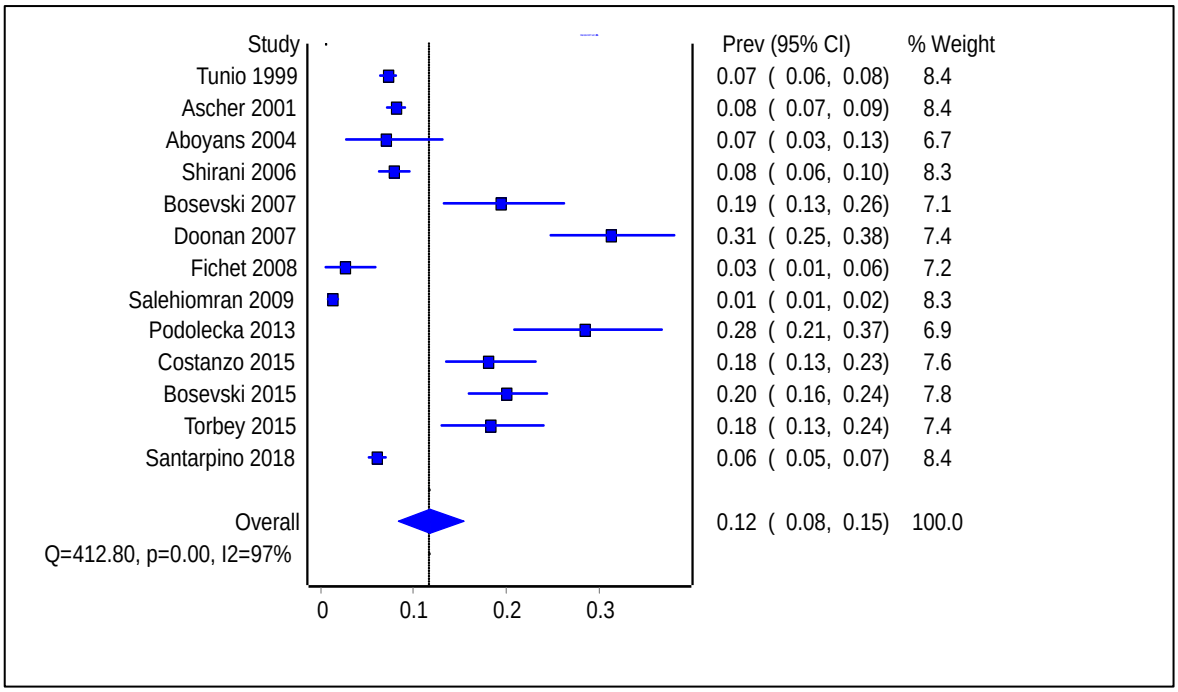

Figure 5: Prevalence of ≥ 60% asymptomatic carotid artery stenosis plot (Random effects)

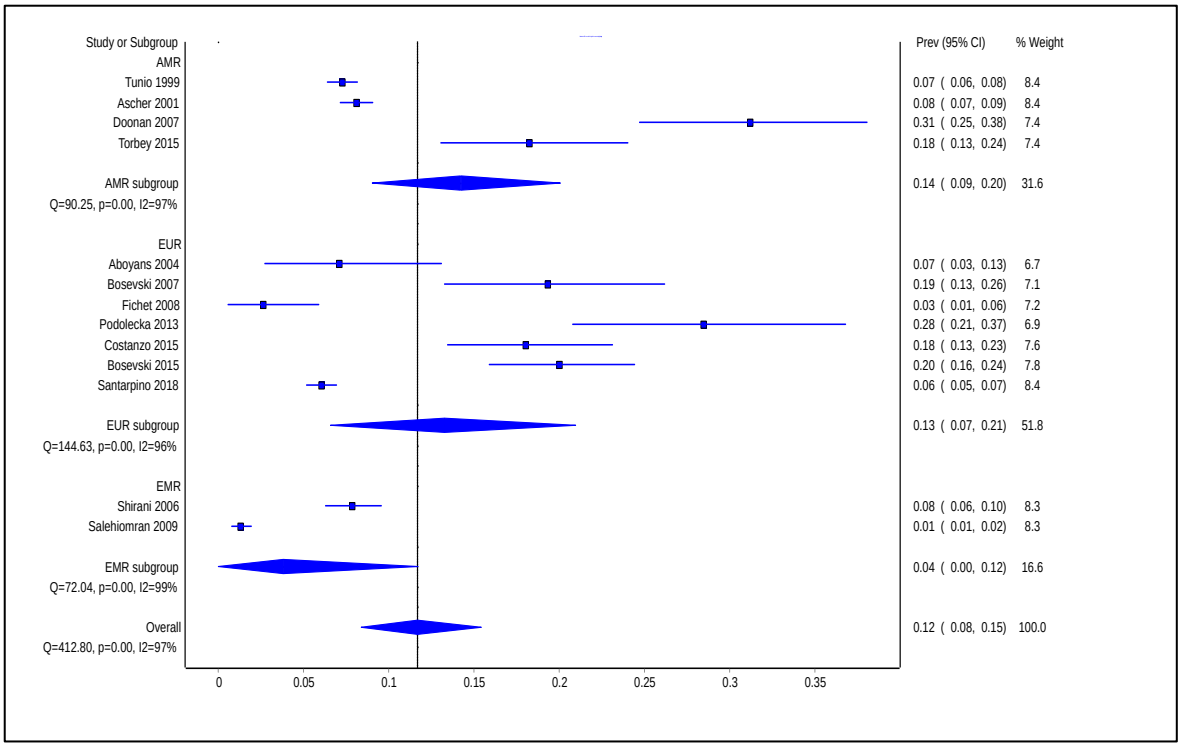

Figure 6: Prevalence of ≥ 60% asymptomatic carotid artery stenosis plot by region (Random effects)

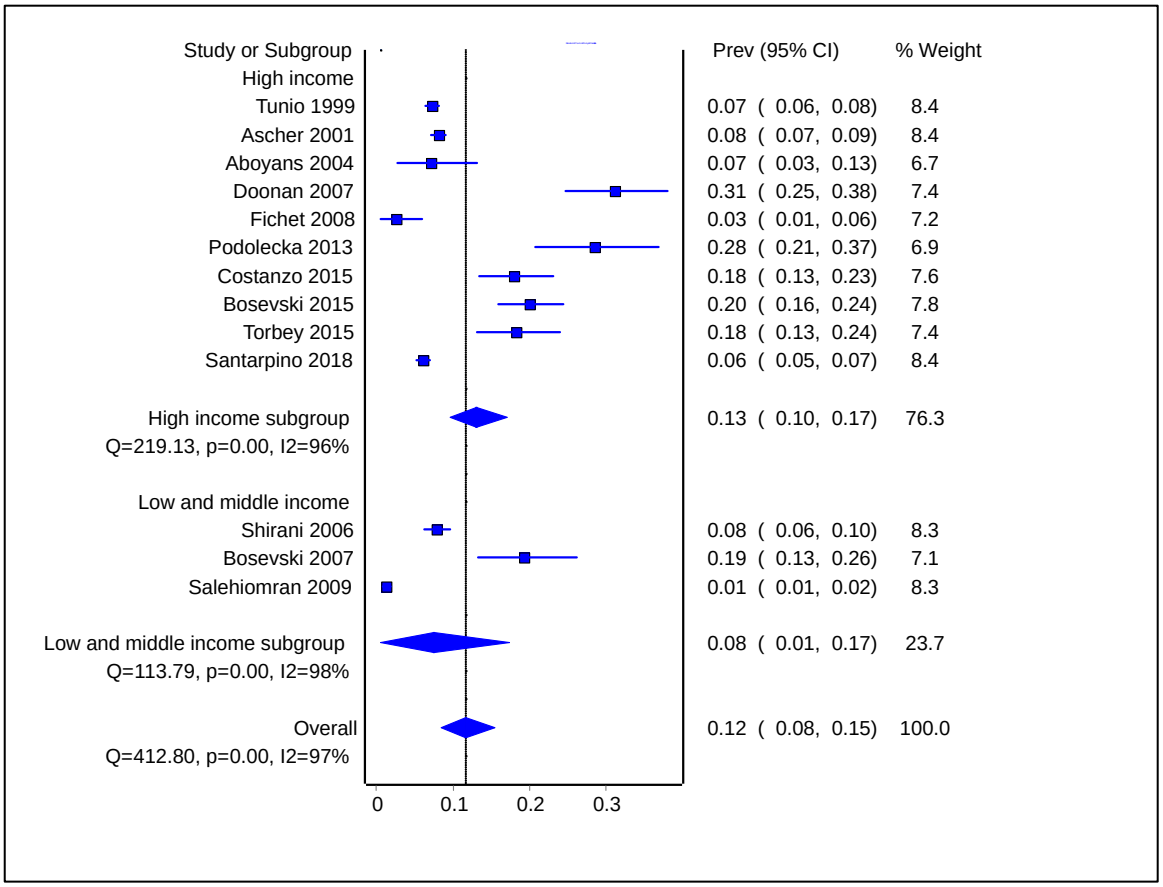

Figure 7: Prevalence of ≥ 60% asymptomatic carotid artery stenosis by income group (Random effects)

4.6.3. Prevalence of ≥ 70% ACAS

Out of 51 studies, 18 studies reported on the prevalence of ≥ 70% ACAS. The FEM revealed a pooled prevalence of 5% (95% CI 5-6%). Significant heterogeneity was observed which was evident by I^2 value of 84% with a p-value of <0.001 and the REM revealed a prevalence of 7% (95% CI 5-9%) (Fig 10). One study (150) was excluded from the meta-analysis due to reported large prevalence of 67% that differs significantly from the other studies. In addition, the aforementioned did not specify the grading criteria for CAS.

Subgroup analysis by region revealed a prevalence of 7% both in AMR (95% CI 6-9%)

and EUR regions (95% CI 5-10%). The prevalence of ACAS ≥ 70% was 11% (95% CI 7-16%) in WPR region and 5% (95% CI 3-7%) in EMR and SEAR region(Fig 11). The prevalence of ≥ 70% ACAS was similar (7%) in both HIC (95% CI 4-10%) and LMICs (95% CI 5-9%) (Fig 12).

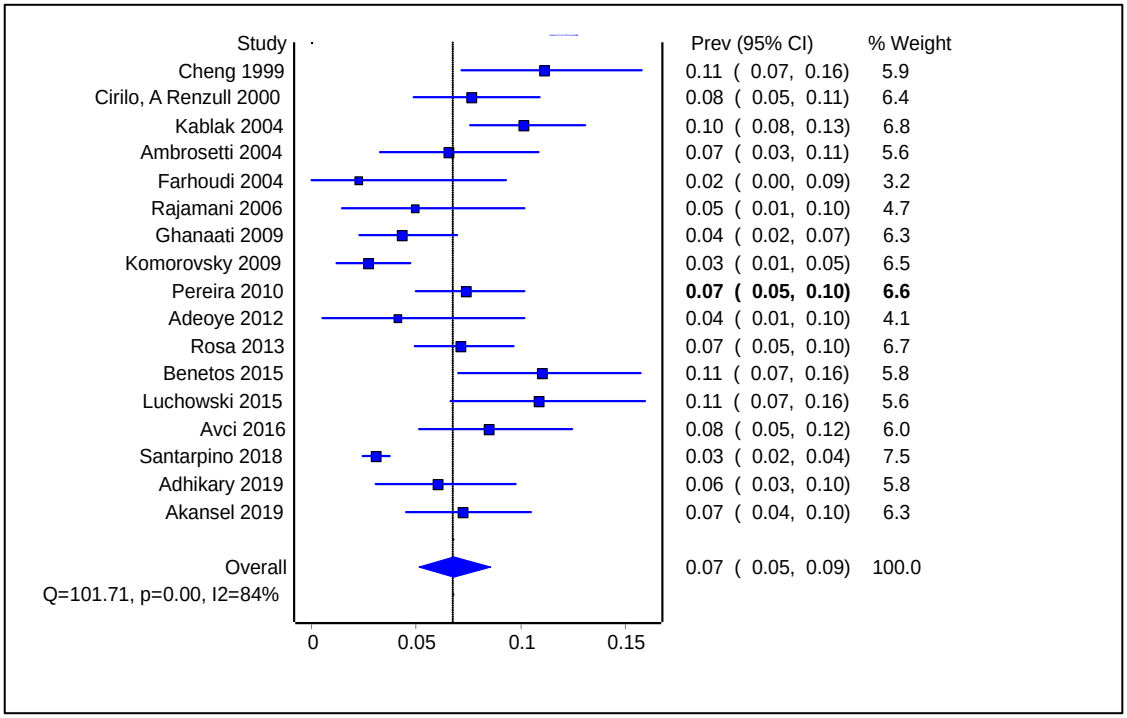

Figure 8: Prevalence of ≥ 70% asymptomatic carotid artery stenosis plot (Random effects)

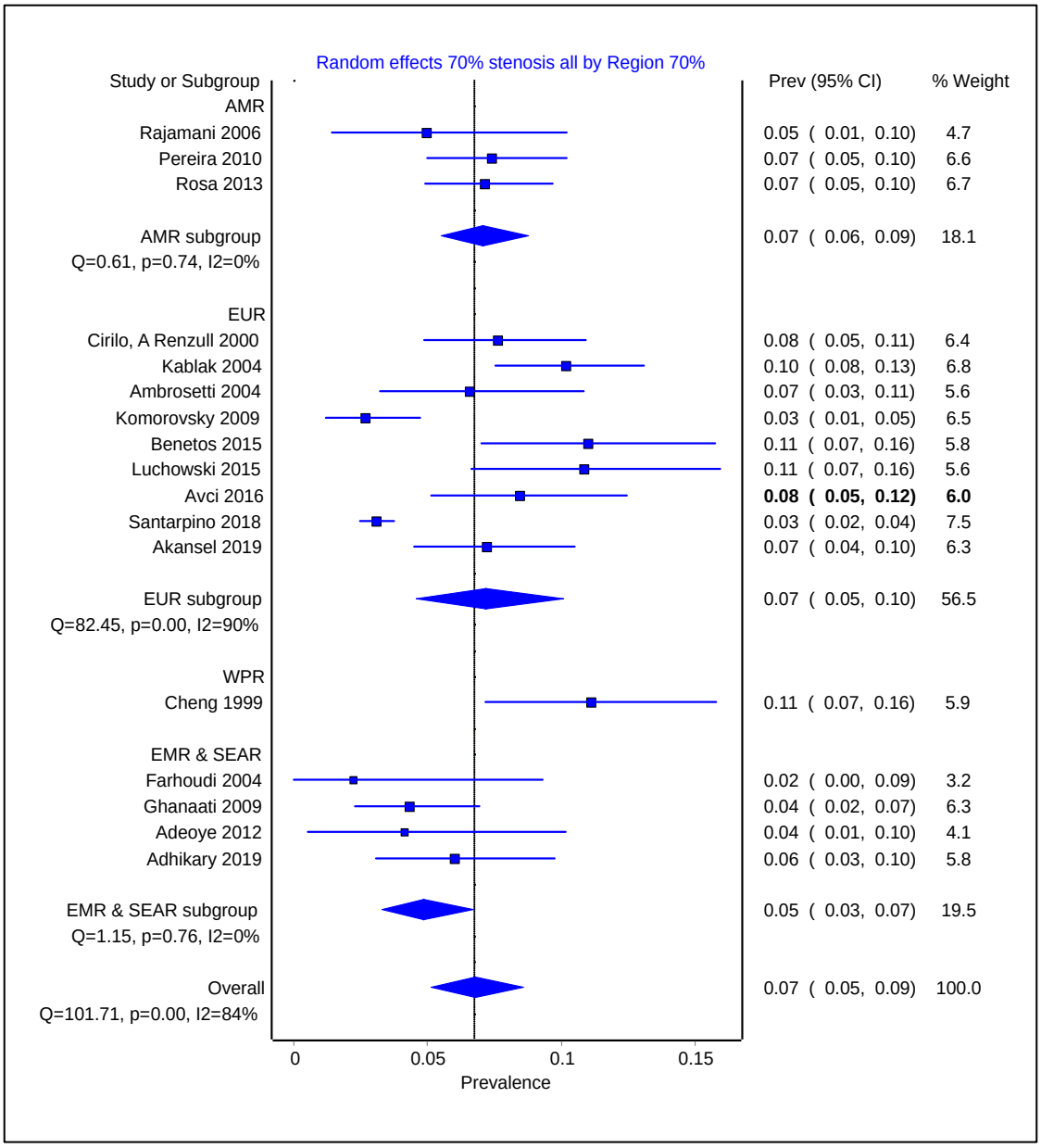

Figure 9: Prevalence of ≥ 70% asymptomatic carotid artery stenosis plot by region (Random effects)

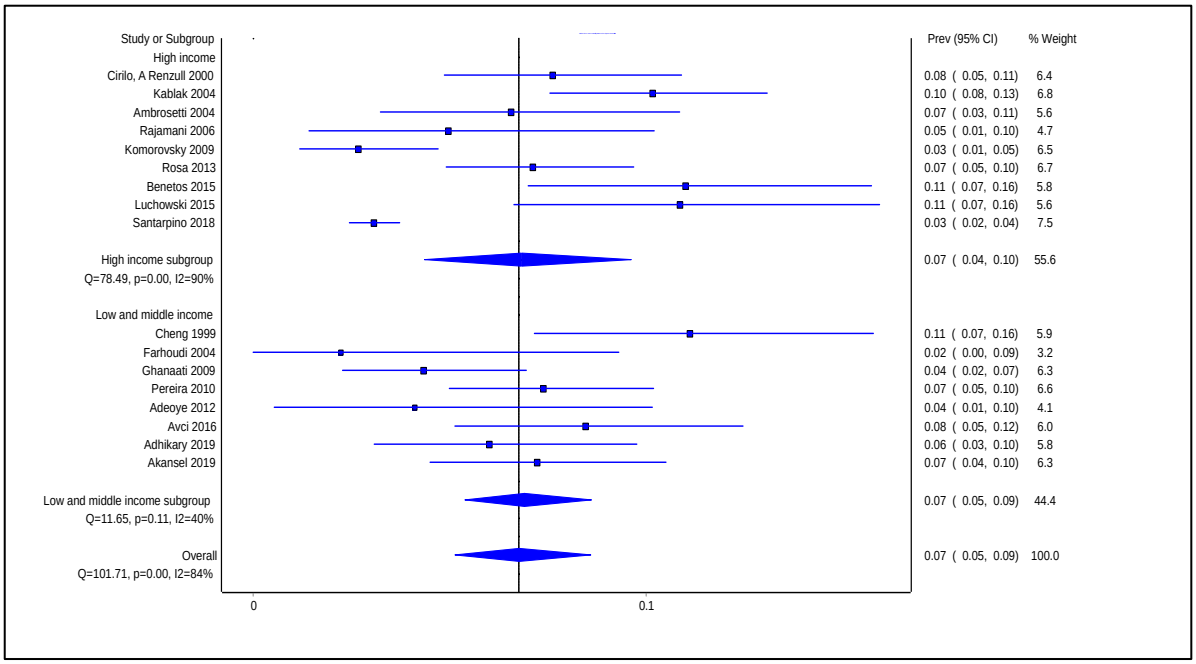

Figure 10: Prevalence of ≥ 70% asymptomatic carotid artery stenosis by income group (Random effects)

4.6.4 Prevalence of > 80% ACAS

Three studies (135, 137, 157) provided data regarding the prevalence of >80% ACAS. The pooled prevalence of > 80% ACAS is 2% (95% CI 1-4%).

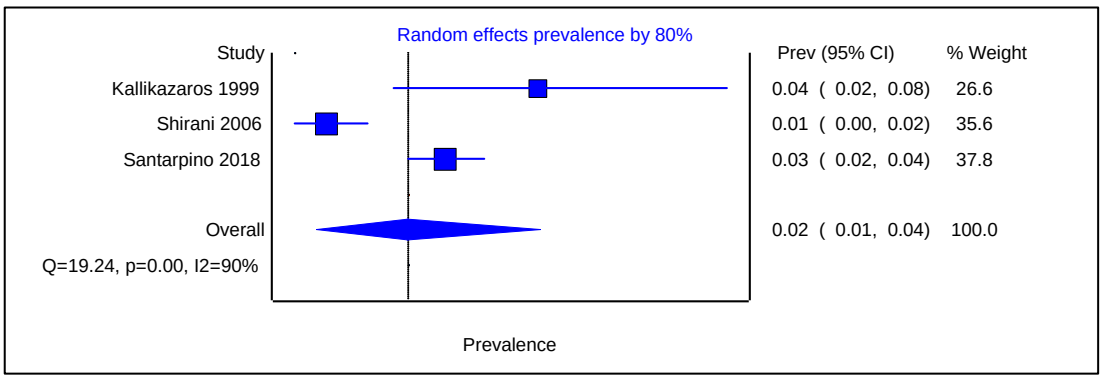

Figure 11: Prevalence of ≥ 80% asymptomatic carotid artery stenosis (Random effects)

Table 3 presents a summary of the meta-analyses findings.

Table 3: Summary of Meta-analysis results

Items	Study (n)	Patients (n)	Pooled estimates (Random effects)	*95% CI*	*I^2 (%)*	*P value*
Prevalence of ≥ 50% ACAS						
Overall	34	18762	11%	9-14%	96	<0.01
Excluding high risk of bias studies	30	12144	12%	9-15%	95	<0.01
Region subgroups						
AMR	7	5806	10%	5-17%	97	<0.01
EUR	15	7140	13%	8-18%	97	<0.01
WPR	2	288	13%	2-27%	87	<0.01
EMR	5	4544	9%	4-14%	97	<0.01
SEAR	5	984	10%	5-15%	80	<0.01
Income subgroups						
High income	19	11603	12%	8-16%	97	<0.01
Low and middle income	15	7159	10%	7-14%	94	<0.01
Prevalence of ≥ 60% ACAS						
Overall	13	13368	12%	8-15%	97	<0.01
Region subgroups						
AMR	4	6803	14%	9-20%	97	<0.01
EUR	7	3916	13%	7-21%	96	<0.01
EMR	2	2649	4%	0-12%	99	<0.01
Income groups						
High income	10	10574	13%	10-17%	96	<0.01
Low and middle income	3	2794	8%	1-17%	98	<0.01
Prevalence of ≥ 70% ACAS						
Overall	18	6744	7%	5-9%	84	<0.01
Region subgroups						
AMR	3	944	7%	6-9%	0	0.74
EUR	9	4974	7%	5-10%	90	<0.01
WPR	1	207	11%	7-16%		
EMR	2	346	4%	2-7%	0	0.67
SEAR	2	273	6%	3-9%	0	0.63
Income groups						
High income	11	5009	7%	4-10%	90	<0.01
Low and middle income	8	1735	7%	5-9%	84	0.11

ACAS= Asymptomatic carotid artery stenosis, AMR=America, EUR= Europe, WPR=Western Pacific region, EMR=Eastern Mediterranean region, SEAR=South East Asia region

4.7. Meta-regression results

The variability of prevalence of ACAS between studies were assessed by study characteristics including region, income group, study design, study quality, publication year, gender and mean age by univariate and multivariate meta-regression analysis.

Only the variables mean age and study quality in the multivariable model were associated with statistically significant variability (Tau^2 =0.34,Q= 434.24; p<0.001) in prevalence ≥ 50% ACAS between studies. This model explained 13% of between study variability in ≥ 50% ACAS prevalence. For the prevalence of ≥ 60% ACAS and ≥ 70% ACAS, none of the study characteristics were associated with significant between study variability in meta-regression analysis.

4.8. Risk of bias due to missing results in meta-analysis

As shown in figures 12 to 20, both funnel plots and LFK index of Doi plots were asymmetrical for studies reporting on the prevalence of all ≥ 50%, ≥ 60% and ≥ 70% stenosis. The funnel plot for ≥ 50% ACAS studies (Figure 12) showed that studies with small sample size and low prevalence were more likely to be missing. LFK index (3.23; major asymmetry) and Doi plot (Figure 14) showed asymmetry indicating missing results. Further assessment for publication bias by trim and fill method revealed no evidence for publication bias (Figure 13) and Egger's test also showed non-significant result (Intercept 0.10, SE 1.75, p value 0.95)

The Funnel plot of ≥ 60% ACAS (Figure 15) showed that studies with small sample size with low prevalence are less likely to be present. Trim and fill method (Figure 16) and Egger's test (Intercept 3.54, SE 3.13, p-value 0.28) further showed no evidence for publication bias. The LFK index (3.42) and Doi plot also indicates missing studies (Figure 17).

The funnel plot of ≥ 70% ACAS (Figure 18) indicates that the small studies with both low and high prevalence are less likely to be present and LFK index (4.01) and Doi plot (Figure 20) also showed missing results. Moreover, trim and fill method (Figure 19) showed no evidence for publication bias which is further confirmed by Egger's test (Intercept 1.01, SE 1.49, p value 0.50).

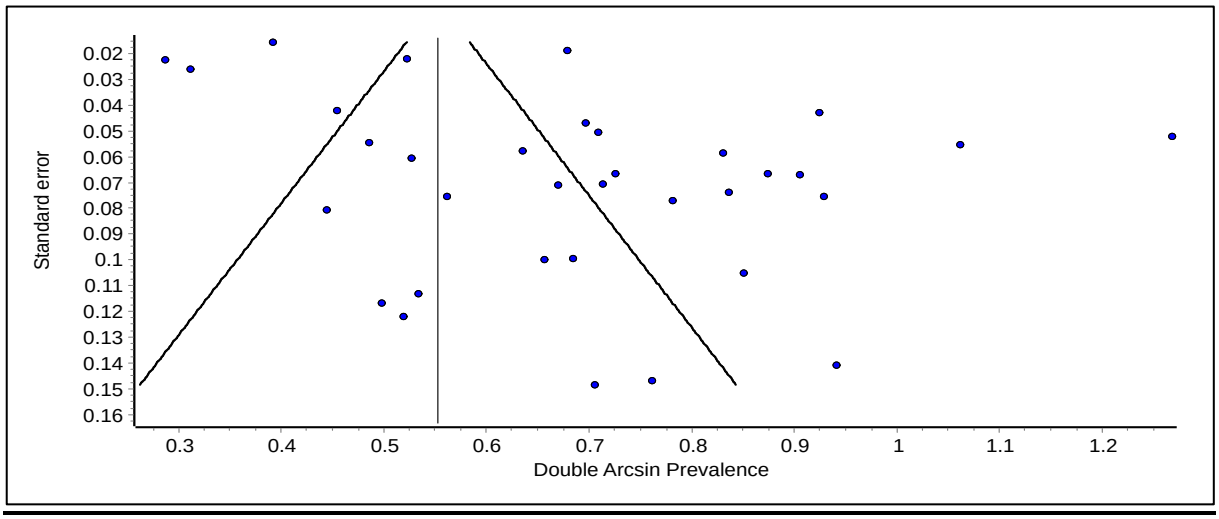

Figure 12: Funnel plot of REM of ≥ 50% asymptomatic carotid artery stenosis

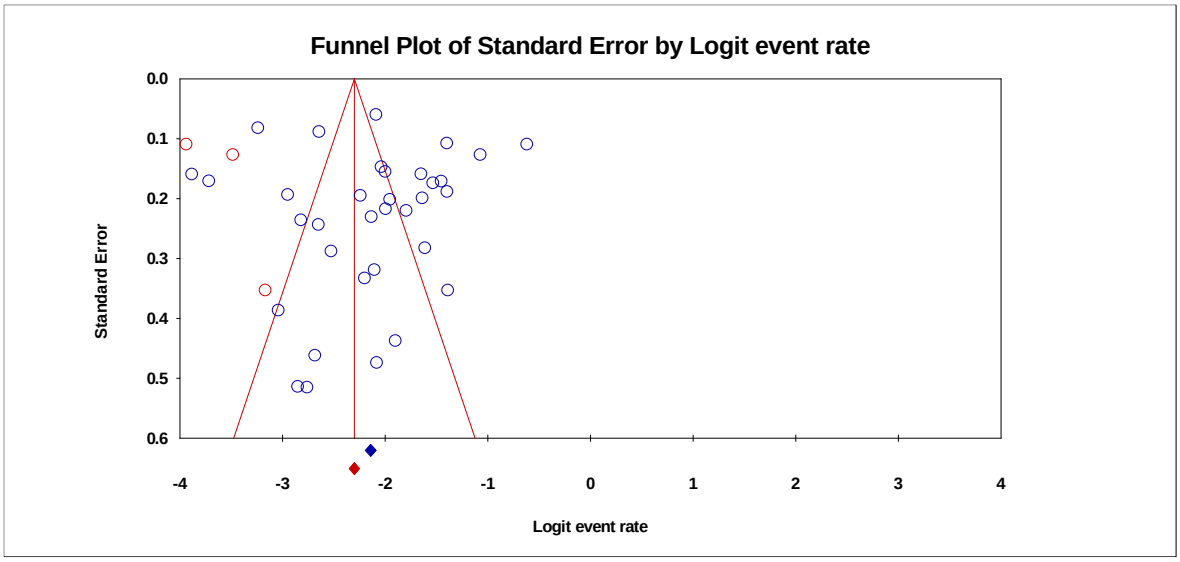

Figure 13: Trim and fill method showing no significance publication bias for ≥ 50% ACAS

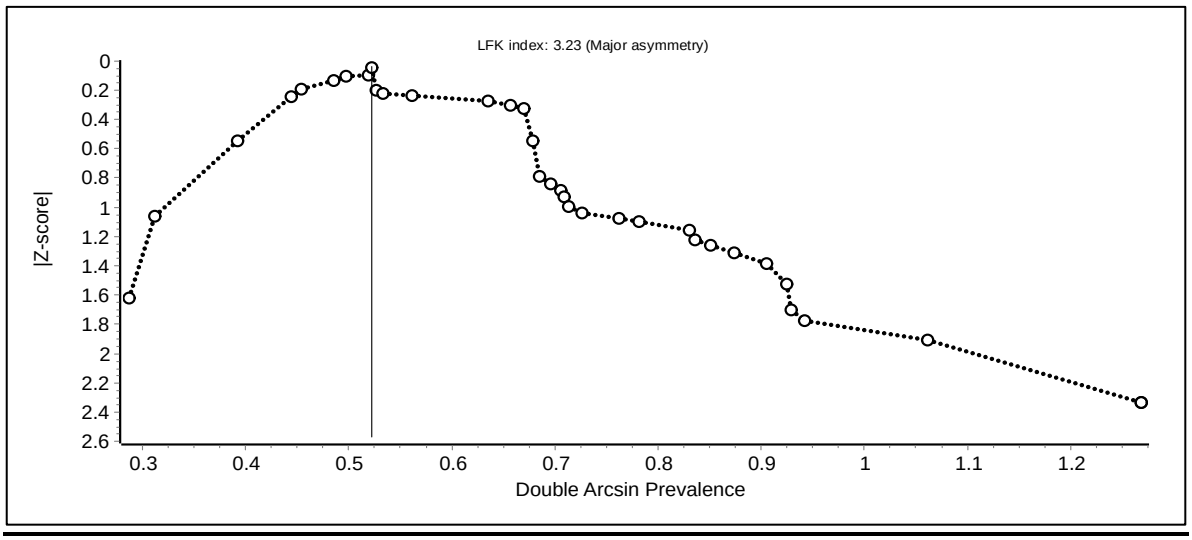

Figure 14: Doi plot of REM of ≥ 50% asymptomatic carotid artery stenosis

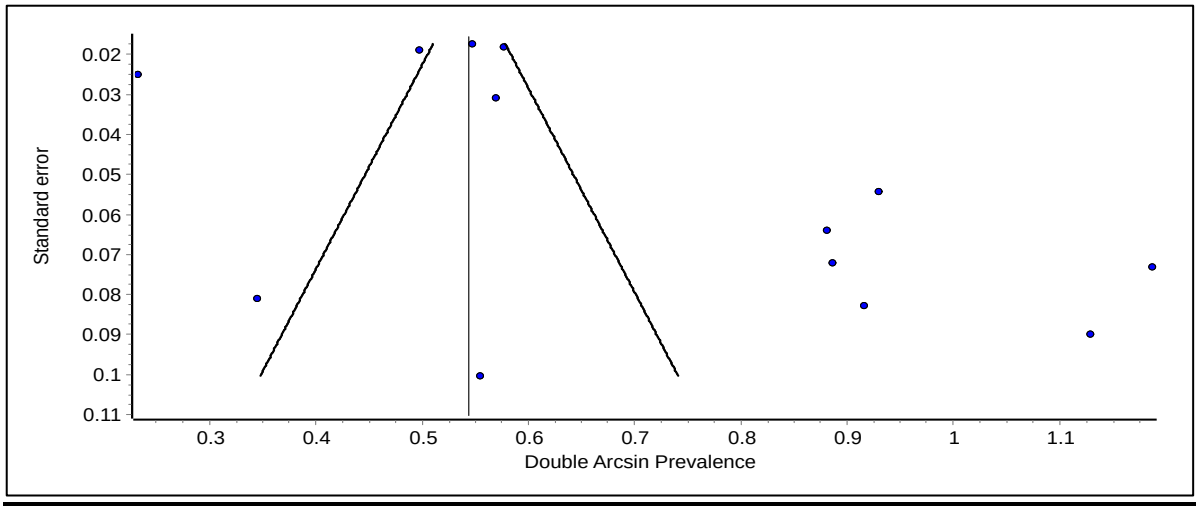

Figure 15: Funnel plot of REM of ≥ 60% asymptomatic carotid artery stenosis

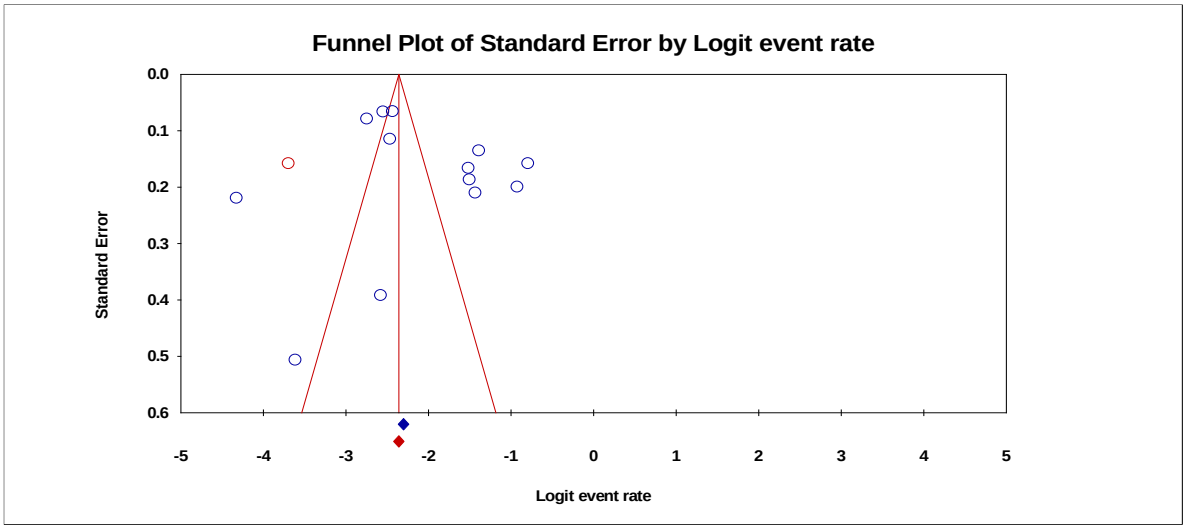

Figure 16: Trim and fill method showing no significance publication bias for ≥ 60% ACAS

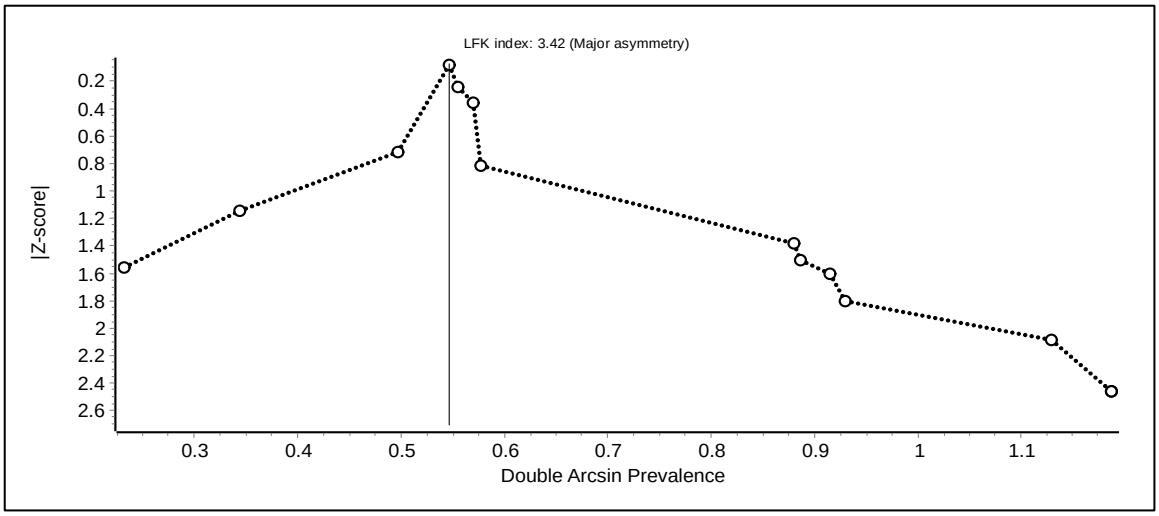

Figure 17: Doi plot of REM of ≥ 60% asymptomatic carotid artery stenosis

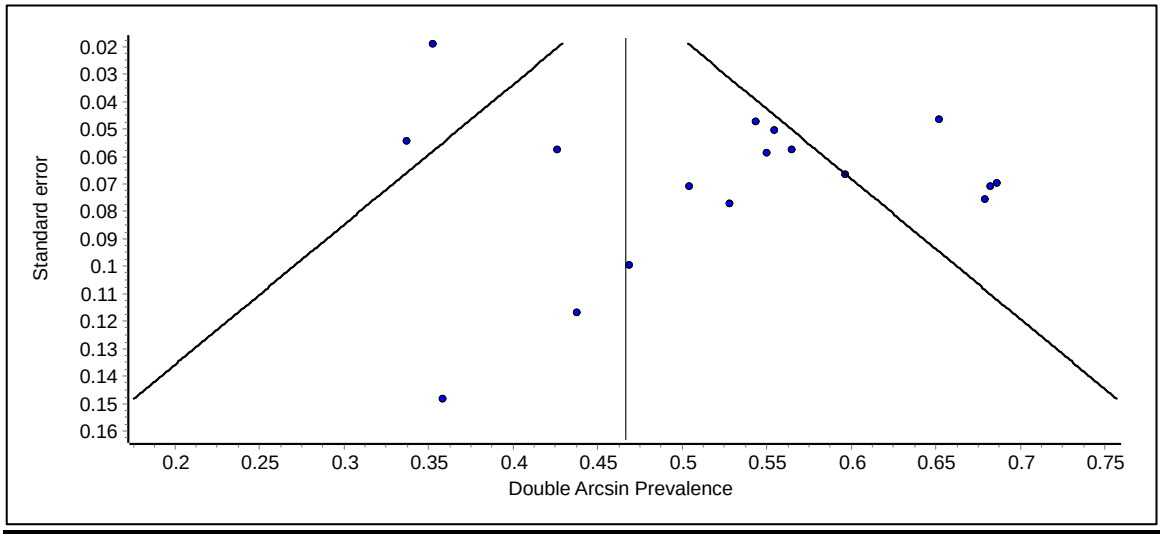

Figure 18: Funnel plot of REM of ≥ 70% asymptomatic carotid artery stenosis

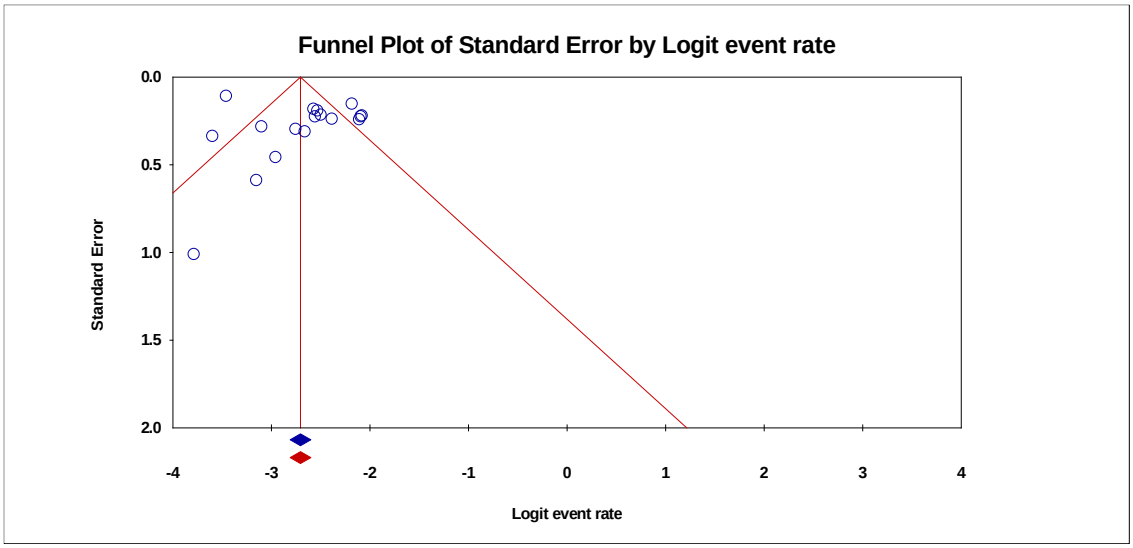

Figure 19: Trim and fill method showing no significance publication bias for ≥ 70% ACAS

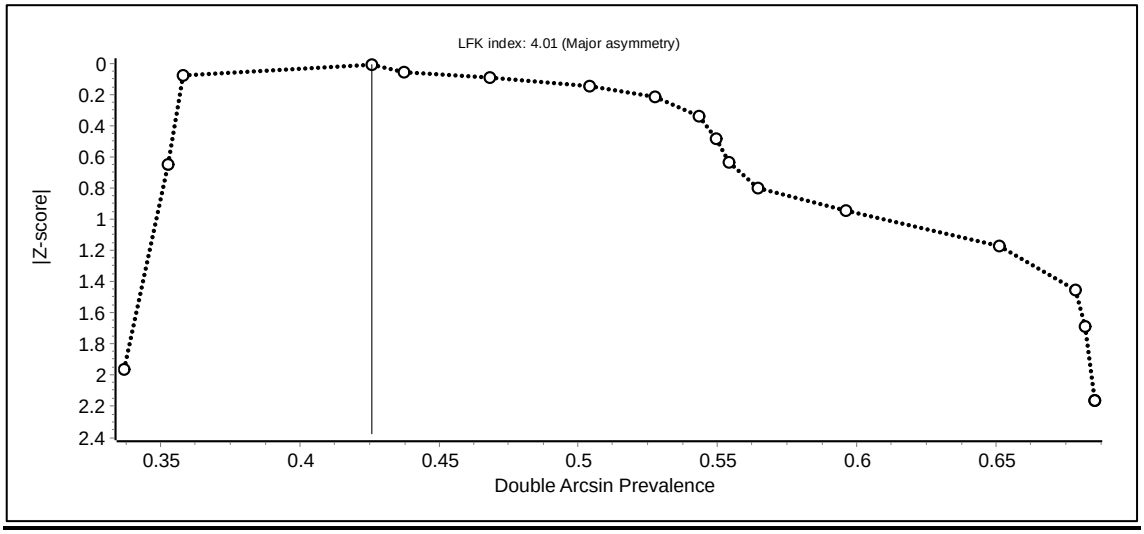

Figure 20: Doi plot of REM of ≥ 70% asymptomatic carotid artery stenosis

CHAPTER 5: DISCUSSION

5.1. Summary of evidence

We conducted a systematic review and meta-analysis to estimate the ACAS prevalence in IHD patients. We included 51 studies with 31,001 participants from the year 1981 to 2019 from 20 different countries from five regions. The mean age of the participants ranged from 57 to 73 years. The majority of participants were males. The REM pooled prevalence of ≥ 50% ACAS was 11% (95% CI 9-14%) in IHD patients. In addition, the REM pooled prevalence of ≥ 60% and ≥ 70% ACAS was 12% (95% CI 8-15%) and 7% (95% CI 5-9%), respectively.. The pooled prevalence of ≥ 50% ACAS in HIC and LMICs is quite similar, 12% (95% CI 8-16%) and 10% (95% CI 7-14%), respectively. Prevalence of ≥ 60% ACAS was lower 8% in LMICs compared to 13% in HICs and the prevalence for ≥ 70% ACAS was similar (7%) in both HIC and LIMCs. No studies were published from the African region. The EUR region had the highest prevalence of ≥ 50% ACAS in IHD patients, whereas AMR region had the highest prevalence of ≥ 60% ACAS among IHD patients. The lower pooled prevalence of ACAS in other regions maybe due to fewer studies conducted in those regions. Overall, we found the pooled prevalence of ACAS (≥ 50%, ≥ 60%, and ≥ 70%) in IHD patients to be higher in HICs compared to LMICs.

The largest prevalence of 35% for ≥ 50% ACAS has been reported in one study (106). This could be due to larger proportion of included patients (68%) presented with unstable angina compared to stable angina (32%) which is in line with previous study that concluded that severity of coronary artery disease (Gensini score) is associated with severity of carotid stenosis in patients undergoing CABG (2). The highest reported prevalence of ≥ 60% ACAS among our included studies is 31% (132) but this study duration period was for 2 years and of moderate risk of bias as it neither specified about

participant's inclusion and exclusion criteria nor it mentioned it in the baseline characteristics of the study population. However, the pooled prevalence didn't change much after excluding that study. One of the studies (150) included in our review reported a relatively high prevalence of 62% ACAS in IHD patients compared to other studies which is inconsistent with other included study findings. Three of the studies (135, 137, 157) that reported on the prevalence of > 80% ACAS reported a relatively low prevalence (3-5%) compared to other studies, respectively. In addition, two of these studies (137, 157) did not mention about specific participant's inclusion or exclusion criteria.

DM, HTN, PVD, hyperlipidaemia, smoking and obesity are the common comorbidities in patients presenting with ACAS along with IHD. Up to 98% and 88% included patients had DM and HTN. These findings are alike the previous findings that diabetes is recognized as a major risk factor for CAD, PVD and CeVD (168) and HTN strongly influence carotid atherosclerosis (169). Carotid atherosclerosis prevalence among patients with HTN is found to be 78% in > 60 years of age and 86.3% in > 70 years old individuals (169) and the strong association between carotid artery disease and PAD is well known (170).

In a meta-analysis study published in 2010, the prevalence of moderate (≥50%) ACAS ranged from 0.2% to 7.5% and 0.1% to 3.1% for severe ACAS (≥70%) in general population (171). The prevalence of ACAS in general population is found to be quite low to justify routine screening. In another meta-analysis, the pooled prevalence of moderate and severe ACAS was 4.2% (95% CI 3.1 to 5.7%) and 1.7% (95% CI 0.7 to 3.9%), respectively (47). But the prevalence of ACAS is found to be higher in subgroup of patients who have other atherosclerotic diseases. A similar prevalence of ACAS has been reported in patients with PVD, which found that the pooled prevalence of >50%

ACAS is 25% and 14% for >70% ACAS in PVD patients (172).

5.2. Strengths and limitations

To the best of our knowledge, this study is the first systematic review to report on the prevalence estimates of ACAS in patients with IHD at global, regional and country income group levels. This can inform policy makers of the epidemiological magnitude of this public health issue. Following a comprehensive search strategy and dual review process, we included 51 studies that enabled us to provide the broadest research scope to date of the epidemiological burden of ACAS in IHD patients. The methodologies of included studies were comprehensive. Also the mean age of the participants and higher proportion of males compared to females with common comorbidities, all of which enhances the generalizability of findings. In addition, we have searched key bibliographic databases, searched the grey literature, and followed a systematic approach for study selection, data extraction, and appraisal of the methodological quality of included studies. Further assessment of publication bias by trim and fill method and Egger's test revealed no evidence for publication bias.

Our study has several limitations. The pooled prevalence might be affected by the sample size of the included studies. There is considerable variation among studies with respect to the cut-off point used for grading ACAS. Additionally, the studies included in this review used different methods to determine the degree of stenosis i.e. duplex, doppler or angiography which may have an effect on determining degree and accuracy of stenosis. Furthermore, the method of measuring stenosis (NASCET or ECST), was not reported in many studies, which could influence prevalence estimates. For example, NASCET criteria of 50% stenosis is roughly equal to 75% stenosis by ECST criteria (84). It is difficult to assess the magnitude in heterogeneity between studies that could be attributed to selection bias, variability in diagnostic criteria of detecting ACAS by

duplex, or reporting bias. Moreover, only articles published in English were included and some of the identified articles were not available.

5.3. Implications

This study provided a summary of the magnitude of prevalence of ACAS in IHD patients. This information may provide insight into the planning and allocation of funds for future screening to detect patients who may benefit from preventative management. However, this needs to be informed by future research assessing the benefits of screening programs for ACAS in IHD patients using long-term outcomes including stroke, disability, and mortality. Such research may provide valuable information on the feasibility and cost-effectiveness of screening for ACAS among IHD patients.

5.4. Conclusion

This systematic review and meta-analysis show that the prevalence of ACAS in patients with IHD is considerable. There is substantial amount of heterogeneity between studies which was not explained by any of the characteristics of the included studies or their methodological quality.. The pooled prevalence of ACAS is variable between regions that could be due to fewer studies conducted in some regions, but the overall prevalence was higher in HICs compared to LMICs. Further longitudinal studies examining early screening and management of ACAS may provide useful information about the potential impact of screening for ACAS on morbidities and mortality among IHD patients. Such information could be very useful for healthcare systems considering conducting national screening programs for ACAS among IHD patients.

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Conflict of interest

The author has no conflict of interest to declare

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APPENDIX A: HOY'S RISK OF BIAS TOOL (THE 10 CRITERIA USED TO ASSESS THE RISK OF BIAS IN EACH INCLUDED STUDIES)

Name of author(s):

Year of publication:

Study title:

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK)**: The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK)**: The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK)**: A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK)**: The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK)**: All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	**Yes (LOW RISK)**: An acceptable case definition was used. **No (HIGH RISK)**: An acceptable case definition was NOT used	0 1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK)**: The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes (LOW RISK)**: The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominato r(s) for the parameter of interest appropriate	**Yes (LOW RISK)**: The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

APPENDIX B: SEARCH STRATEGY

	CAS	IHD
MEDLINE	carotid stenosis/	myocardial ischemia/
	carotid artery diseases/	coronary artery disease/
	carotid artery thrombosis/	coronary artery bypass/
	“carotid artery stenosis”	“coronary artery bypass graft”
	“carotid artery disease”	myocardi## adj3 hypoxia
	“carotid artery thrombosis”	myocardi## adj3 isch*4
	“carotid artery” adj3 narrow*5	myocardi## adj3 anoxia
	“carotid artery” adj3 plaque#	isch*4 adj2 time
	“carotid artery” adj3 ulcer*5	cardiac adj3 isch*4
	“carotid artery” adj3 disorder#	heart adj3 isch*4
	“carotid artery” adj3 atheroscler*11	heart adj3 anoxia
	“carotid artery” adj3 arterioscler*12	heart adj3 hypoxia
	“carotid artery” adj3 thromb*6	“coronary artery disease”
	“carotid artery” adj3 obstruct*7	“coronary artery” adj3 isch*4
	“carotid artery” adj3 occlu*5	“coronary artery” adj3 syndrome#
		“coronary artery” adj3 arterioscler*12
		“coronary artery” adj3 atheroscler*11
		subendocardial adj3 isch*4
EMBASE	carotid artery disease/	heart muscle ischemia/
	carotid artery obstruction/	coronary artery disease/
	carotid artery thrombosis/	coronary artery bypass graft/
	internal carotid artery occlusion/	“coronary artery bypass graft”
	“carotid artery stenosis”	myocardi## adj3 hypoxia
	“carotid artery disease”	myocardi## adj3 isch*4
	“carotid artery thrombosis”	myocardi## adj3 anoxia
	“carotid artery” adj3 narrow*5	isch*4 adj2 time
	“carotid artery” adj3 plaque#	cardiac adj3 isch*4
	“carotid artery” adj3 ulcer*5	heart adj3 isch*4
	“carotid artery” adj3 disorder#	heart adj3 anoxia
	“carotid artery” adj3 atheroscler*11	heart adj3 hypoxia
	“carotid artery” adj3 arterioscler*12	“coronary artery disease”

	“carotid artery” adj3 thromb*6	“coronary artery” adj3 isch*4
	“carotid artery” adj3 obstruct*7	“coronary artery” adj3 syndrome#
	“carotid artery” adj3 occlu*5	“coronary artery” adj3 arterioscler*12
		“coronary artery” adj3 atheroscler*11
		subendocardial adj3 isch*4
CINAHL	carotid stenosis/	myocardial ischemia/
	carotid artery diseases/	Coronary Arteriosclerosis/
	carotid artery thrombosis/	coronary artery bypass/
	“carotid artery stenosis”	“coronary artery bypass graft”
	“carotid artery disease”	myocardi## adj3 hypoxia
	“carotid artery thrombosis”	myocardi## adj3 isch*4
	“carotid artery” adj3 narrow*5	myocardi## adj3 anoxia
	“carotid artery” adj3 plaque#	isch*4 adj2 time
	“carotid artery” adj3 ulcer*5	cardiac adj3 isch*4
	“carotid artery” adj3 disorder#	heart adj3 isch*4
	“carotid artery” adj3 atheroscler*11	heart adj3 anoxia
	“carotid artery” adj3 arterioscler*12	heart adj3 hypoxia
	“carotid artery” adj3 thromb*6	“coronary artery disease”
	“carotid artery” adj3 obstruct*7	“coronary artery” adj3 isch*4
	“carotid artery” adj3 occlu*5	“coronary artery” adj3 syndrome#
		“coronary artery” adj3 arterioscler*12
		“coronary artery” adj3 atheroscler*11
		subendocardial adj3 isch*4

APPENDIX C: TABLE FOR PREVALENCE OF ≥ 50% ACAS IN INDIVIDUAL STUDIES

Serial No	Name of the study	Cases	Sample size	Prevalence of ≥ 50% ACAS	95% CI	Quality score
1	Barnes 1981	21	198	11%	7-15%	7
2	Breslau 1981	5	78	6%	2-13%	7
3	Brener 1987	153	4047	4%	3-4%	5
4	Minami 1988	35	1471	2%	2-35%	5
5	Sanguigni 1993	30	184	16%	11-22%	7
6	Uehera 1996	4	67	6%	1-13%	7
7	Fragiolli 1999	107	539	20%	17-23%	5
8	Kallikazaros 1999	28	225	12%	8-17%	7
9	Ambrosetti 2004	24	168	14%	9-20%	7
10	Farhoudi 2004	5	45	11%	3-22%	6
11	Lombardo 2004	128	365	35%	30-40%	7
12	Arai 2006	42	221	19%	14-24%	6
13	Rajamani 2006	11	101	11%	5-18%	7
14	Sonecha 2006	7	153	5%	2-9%	6
15	Shirani 2008	136	2044	7%	6-8%	7
16	Akhtar 2009	35	176	20%	14-26%	7
17	Brevetti 2009	15	90	17%	10-25%	6
18	Ghanaati 2009	29	301	10%	7-13%	7
19	Komorovsky 2009	19	337	6%	3-8%	7
20	Pereira 2010	47	393	12%	9-15%	8
21	Abbaszadeh 2011	40	1978	2%	1-3%	6
22	Adeoye 2012	4	73	5%	1-12%	7
23	Rosa 2013	52	450	12%	9-15%	7

Serial No	Name of the study	Cases	Sample size	Prevalence of ≥ 50% ACAS	95% CI	Quality score
24	Luchowski 2015	13	175	7%	4-12%	7
25	Taneja 2015	10	100	10%	5-17%	6
26	Wiberg 2015	6	46	13%	5-25%	6
27	Avci 2016	40	225	18%	13-23%	6
28	Hamid 2016	10	50	20%	10-32%	7
29	Kazum 2016	83	325	26%	21-30%	8
30	Obrenovic 2016	18	272	7%	4-10%	7
31	Santarpino 2018	311	2813	11%	10-12%	8
32	Adhikary 2019	24	200	12%	8-17%	8
33	Akansel 2019	47	291	16%	12-21%	7
34	Charravarthy 2019	28	561	5%	3-7%	5

APPENDIX D: TABLE FOR PREVALENCE OF ≥ 60% ACAS IN INDIVIDUAL STUDIES

Serial No	**Name of the study**	**Cases**	**Sample size**	**Prevalence of ≥ 60% ACAS**	**95% CI**	**Quality score**
1	Tunio 1999	243	3344	7%	6-8%	6
2	Ascher 2001	249	3081	8%	7-9%	7
3	Aboyans 2004	7	99	7%	3-13%	6
4	Shirani 2006	82	1045	8%	6-10%	7
5	Bosevski 2007	28	145	19%	13-26%	6
6	Doonan 2007	58	186	31%	25-38%	6
7	Fichet 2008	4	152	3%	1-6%	7
8	Salehiomran 2009	21	1604	1%	1-2%	6
9	Podolecka 2013	35	123	28%	21-37%	7
10	Costanzo 2015	44	244	18%	13-23%	7
11	Bosevski 2015	68	340	20%	16-24%	5
12	Torbey 2015	35	192	18%	13-24%	6
13	Santarpino 2018	170	2813	6%	5-7%	8

APPENDIX E: TABLE FOR PREVALENCE OF ≥ 70% ACAS IN INDIVIDUAL STUDIES

Serial No	Name of the study	Cases	Sample size	Prevalence of ≥ 70% ACAS	95% CI	Quality score
1	Takach 1997	316	512	61%	57-66%	6
2	Cheng 1999	23	207	11%	7-16%	7
3	Cirilo 2000	23	302	8%	5-11%	6
4	Kablak 2004	47	463	10%	8-13%	7
5	Ambrosetti 2004	11	168	7%	3-11%	7
6	Farhoudi 2004	1	45	2%	0-9%	6
7	Rajamani 2006	5	101	5%	1-10%	7
8	Ghanaati 2009	13	301	4%	2-7%	7
9	Komorovsky 2009	9	337	3%	1-5%	7
10	Pereira 2010	29	393	7%	5-10%	8
11	Adeoye 2012	3	73	4%	1-10%	7
12	Rosa 2013	32	450	7%	5-10%	7
13	Benetos 2015	22	200	11%	7-16%	7
14	Luchowski 2015	19	175	11%	7-16%	7
15	Avci 2016	19	225	8%	5-12%	6
16	Santarpino 2018	86	2813	3%	2-4%	8
17	Adhikary 2019	12	200	6%	3-10%	8
18	Akansel 2019	21	291	7%	4-10%	7