# Frequency and clinical characteristics of renal artery stenosis in patients with coronary artery disease undergoing cardiac catheterization

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**Diploma thesis**

**Academic year:**

**2021/2022**

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# LIST OF ABBREVIATIONS

**CAD –** Coronary artery disease

**HDL** – High-density lipoproteins

**LDL** – Low-density lipoproteins

**DALIs** – Disability adjusted Life Years

**MI** – Myocardial infarction

**ACS** – Acute coronary syndrome

**NSTEMI** – Non-ST-segment elevation myocardial infarction

**STEMI** – ST-segment elevation myocardial infarction

**CCS** – Canadian Cardiovascular Society

**SIHD** – Stable ischemic heart disease

**CHF** – Congestive heart failure

**PCI** – Percutaneous coronary intervention

**CABG** – Coronary artery bypass graft

**ESC** – European Society of Cardiology

**ICA** – Invasive coronary angiography

**ARAS** – Atherosclerotic renal artery stenosis

**RAS** – Renal artery stenosis

**CKD** – Chronic kidney disease

**ESRD** – End-stage renal disease

**RAAS** – Renin-angiotensin-aldosterone system

**GFR** – Glomerular filtration rate

**MRA** – Magnetic resonance angiography

**CTA** – Computed tomography angiography

**ACE** – Angiotensin-converting enzyme

# 1. INTRODUCTION

## 1.1 Coronary artery disease

Atherosclerotic plaque development in the arterial lumen is a typical feature of coronary artery disease (CAD). As a result, the myocardium receives less oxygen, and the blood flow is impaired (1). The phenomenon has multiple causes where the causative elements broadly can be categorized into; changeable and immutable factors. Gender, age, family history, and genetics are characteristics of changeable factors. Obesity, smoking, lipid levels, hypertension, and psychosocial variables are all immutable factors. The leading factor in cardiovascular illnesses is still smoking. But individuals, especially in the Western world, eat more fast food and unhealthy meals which is a factor that increases the prevalence of ischemic heart disease. In addition to smoking, dyslipidemia plays a significant role in CAD development. Decreased levels of high-density lipoproteins (HDL) and elevated low-density lipoproteins (LDL) rise the risk and occurrence of CAD (2). Due to a improved primary care in the middle and upper socioeconomic classes, the incidences are shifting towards later age (1).

### 1.1.1 Epidemiology

CAD is the major cause of death, and reduction in Disability adjusted Life Years (DALYs) worldwide. Nearly 7 million fatalities and 129 million DALYs per year are accounted for by middle- and low-income nations. 8.9 million fatalities and 164 million DALYs were attributed to CAD in 2015. In comparison to people who do not have CAD, survivors of myocardial infarction (MI) have a mortality rate that is at least five to six times greater annually and are at great risk for recurrent infarction (3). Even though the mortality rate from CAD has declined over the past forty years, it still accounts for over one third of fatalities in people over the age of 35. Therefore, the likelihood of dying from CAD increases markedly with aging while systolic blood pressure is the most significant modifiable risk factor explaining certain additional CAD risks that increase with age (3).

### 1.1.2 Pathophysiology and clinical aspects

Manifestations of CAD might be asymptomatic or symptomatic, but the main mechanism behind it is the presence of atherosclerosis in the coronary arteries (4). The development of a “fatty streak” is the initial stage of this process. By depositing lipid-rich macrophages beneath the endothelium, commonly known as foam cells, “fatty streaks” are created. The intima layer ruptures as a result of a vascular injury, and monocytes aggregate in the subendothelial layer where they develop into macrophages. After ingesting oxidized low-density lipoprotein particles, these macrophages produce foam cells. T-cells become activated,

which mediates the pathological process by cytokine release. Growth factors are generated, which activate vascular smooth muscle cells. Along with oxidized LDL particles and collagen, these growth factors also increase the quantity of foam cells by depositing them with activated macrophages. Subendothelial plaque is created as a result of this process (5).

After a while, the plaque may increase in size, or if no more injury to the endothelium occurs, stabilize. If it stabilizes, a fibrous cap will develop, as well as the lesion eventually turn calcific. As time goes on, the lesion may become hemodynamically significant enough for angina symptoms such as substernal chest pain to develop in case that not enough blood reaches the cardiac tissue during times of elevated energy demand. However, as the oxygen requirements decreases, symptoms might disappear. A lesion must be at least 90 percent stenosed in order to elicit angina while at rest. Moreover, some atherosclerotic plaques have the potential to break, exposing tissue factor to denuded endothelium thus propagating thrombosis. Depending on the severity of the vascular insult, this intraarterial thrombosis may result in a partial or complete blockage of the coronary vessel lumen and transform "stable" coronary disease into an acute coronary syndrome (ACS), manifesting in three distinguished clinical entities: unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI) (5).

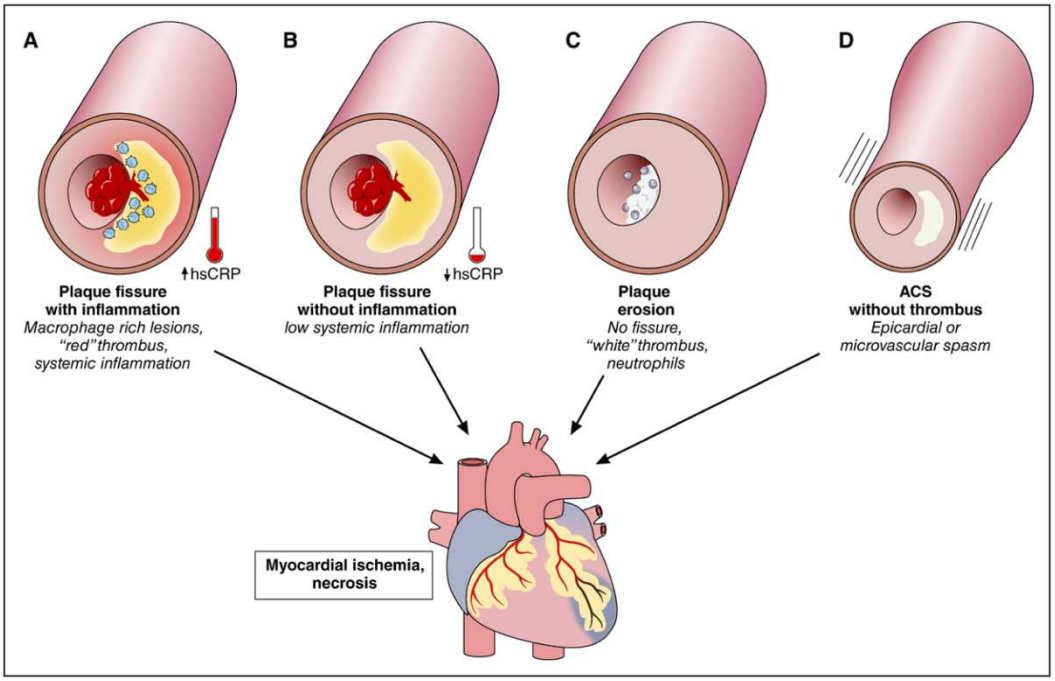


**Figure 1:** Pathophysiology of acute coronary syndrome (ACS).
Source: Crea F, Libby P. Acute coronary syndromes: The way forward from mechanisms to precision treatment. Circulation. 2017;136:1155-66.

Plaque rupture, also known as fissure, is generally thought to be the principal cause of ACS. As shown in figure 1A, it is typically associated with both local and low-grade systemic inflammation. This is seen as the gauge showing how an increase in blood C-reactive protein (CRP) and the blue monocytes that represent local inflammation. Plaque rupture can sometimes exacerbate atheroma that are not characterized by optical coherence tomography (OCT) criteria for the presence of significant intimal macrophage collections or by circulating high-sensitivity CRP elevations. This is shown as B in figure 1. Red thrombi that have a high fibrin content are frequently caused by plaque rupture. A rising fraction of ACS cases seems to be caused by plaque erosion as shown in figure 1C. This frequently results in NSTEMI. The thrombi that lie on top or adjacent to areas of intimal erosion often show signs of white platelet-rich formations. Vasospasm, which has long been known to damage the coronary microcirculation as well as the epicardial arteries can also result in ACS, as shown in figure 1D (6). In this case, ACS can occur without visible coronary obstruction in the epicardial coronary vessel still causing MI – this has been recently recognized as MI with non-obstructive coronary arteries (MINOCA).

According to the Canadian Cardiovascular Society (CCS), *angina pectoris* can be classified into four grades. Grade I is when normal activity, such as walking or ascending stairs do not cause angina while this might occur with strenuous or prolonged exertion. When angina slightly limits ordinary activities and if it happens during activities such as walking or stair climbing after meals then is classified as grade II. Marked limitation of ordinary physical activity is classified as CCS grade III angina. Finally, class IV angina occurs when a person cannot engage in any physical activity without discomfort while anginal symptoms may be present at rest (7).

### 1.1.3 Diagnosis

It might be challenging to make a diagnosis of CAD. 12-lead electrocardiograms can be caused by pre-existing abnormalities, patients may arrive with unusual or absent chest pain, while cardiac biomarkers might be chronically elevated in patients with chronic or acute heart failure, independently of ACS. ECG changes and chest pain symptoms usually always accompany ACS (4). Therefore, before moving further with escalated diagnostic work-up, it is crucial to conduct a thorough medical history taking and physical examination. Acute coronary syndrome (ACS) or stable ischemic heart disease (SIHD), nowadays known as chronic coronary syndrome (CCS) are two possible manifestations of CAD and they differ in epidemiology, management, and prognosis. If inflicted myocardial injury due to MI is

substantial and accompanied with large myocyte loss and necrosis it may result in left ventricular dysfunction and turn into congestive heart failure (CHF). It is, therefore, of cardinal importance that the patient with suspected CAD is thoroughly investigated with respect to symptoms of chest pain – their quality (sharp or dull), their duration (lasting seconds, minutes or hours); if the chest pain varies according to rest or exercise, and whether it radiates to other body structures such as jaw, neck, arms, or back. Both at rest and during physical activity, dyspnea must be evaluated. The foundational elements of diagnostic work-up should therefore be based on symptoms, careful history taking and physical examination, 12-lead electrocardiogram recording, biochemical work-up measuring cardioselective enzymes such as cardiac troponins and/or natriuretic peptides. Another adjunct tests to determine the probability of CAD are transthoracic ultrasound, stress testing while the gold standard of assessment is diagnostic cardiac catheterization (coronary angiography). Depending on the patients' presentation some of these or all of these modalities might be employed.

### 1.1.4 Treatment

Acute coronary syndrome or stable ischemic heart disease (chronic coronary syndrome – CCS) are two possible manifestations of coronary artery disease. The former is more acutely present, whilst the latter are more chronically prevalent.
The treatment varies on the specific type of condition.

Chronic coronary syndrome is a hallmark of "stable" ischemic heart disease, and it often manifests as substernal chest discomfort or pressure that lasts for two months. It grows worse with activity or mental stress and is eased by rest or nitroglycerin. It is crucial to be aware that in some groups, such as women, the elderly, and those with diabetes, the conventional anginal symptoms may not exist and may instead manifest differently with atypical symptoms and exertional dyspnea. Both non-pharmacologic and pharmaceutical therapies are used to treat CCS. Lifestyle changes like regular exercise, smoking cessation, a healthy diet, and good control of diabetes mellitus and arterial hypertension are some of the measures that can be undertaken. Cardioprotective and antianginal medications are examples of pharmacologic treatment. Every patient needs to receive medical care that follows recommended guidelines and include as-needed nitroglycerin, low-dose aspirin, beta-blockers, and medium to high-intensity statins. Beta blocker therapy should be increased to target heart rates of 55 to 60 if symptoms are not controlled by these drugs. The addition of calcium channel blockers and long-acting nitrates should also be taken into account (8). To treat persistent anginal symptoms, drugs affecting cardiac metabolism and energetics such as ranolazine or trimetazidine may also

be administered. Cardiovascular catheterization shall properly be performed in order to see the coronary anatomy if maximal guideline-directed medical therapy has failed to relieve angina. Based on the patient profile, comorbidities, and severity of coronary lesions, a treatment decision might favor percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery (9).

ACS is characterized by abrupt onset of pressure or pain in the substernal chest that frequently radiates to the left arm and neck. It also includes other symptoms such as dyspnea, disorientation, palpitation, syncope, cardiac arrest, or newly developed heart failure. All patients with ACS require an immediate 12-lead electrocardiogram to evaluate if it is STEMI presentation. This is routinely performed prehospital by an emergency medical service crew. A 1 mm ST elevation in contiguous limb leads or precordial leads, identifies a STEMI. For a STEMI diagnosis in V2 and V3, men must have elevations of 2 mm, whereas women must have elevation of 1.5 mm. Left bundle branch block (LBBB) with new onset is regarded as the STEMI analogue. In STEMI is diagnosed, immediate primary PCI is required. If the distance between the patient and the closest PCI facility is greater than 120 minutes, intravenous thrombolytic treatment is suggested per guidelines.

It is critical to distinguish between a STEMI and other myocardial abnormalities such as pericarditis, early benign repolarization abnormalities and left ventricular hypertrophy changes that sometimes might mimic STEMI on the EKG. At the time of presentation, sublingual aspirin (300 to 324 mg loading) should be given to all patients in its entirety. For pain management, morphine is usually administered. Nitrates might be administered for angina relief and coronary vasodilatation if there are no contraindications and blood pressure allows it. Beta-blockers and high-dose high-potency statins should be instituted as soon as possible. Second antiplatelet agent in the form of $P_2Y_{12}$ inhibitor should be added – in case of NSTEMI, at the time of coronary angiography and once the coronary anatomy is known and in STEMI as soon as possible – patients diagnosed for STEMI should immediately be preloaded with agents such as clopidogrel, prasugrel or ticagrelor (in the absence of specific contraindications). After administering dual antiplatelet treatment for STEMI, an immediate coronary angiography to determine culprit lesion and primary PCI should follow. Anticoagulation therapy, like use of unfractionated heparin or low-molecular weight heparin, are beneficial for patients with non-ST-elevation ACS. And for patients with NSTEMI, invasive coronary work-up might differ with respect to patient risk profile (10, 11).

The foundation of effective long-term care of CAD is being regular with check-ups with the cardiologist and family doctors (primary care doctors). Both lifestyle changes (acquittal of smoking, exercising, losing weight) and adherence to prescribed medications are crucial.

## 1.2 History of coronary angiography

The most reliable and precise method for assessing CAD is cardiac catheterization and is among the most widely used surgical techniques in the world. Coronary angiography, to this date, remains a gold standard for diagnosis of CAD. Sones invented selective coronary angiography in 1958 (12). A few years later, Judkins and Amplatz created specifically prepared catheters, greatly enhancing the simplicity of selective coronary artery engagement. In 1977, in Zurich, Switzerland, Dr. Andreas Gruentzig performed the first coronary angioplasty on an awake human patient and started revolution in invasive treatment of coronary disease. Since then, invasive coronary angiography and methods that were later derived from its core techniques have fundamentally changed how we understand and treat heart disease (13, 14).

### 1.2.1 Procedure and complications

Every time information on the existence and/or severity of CAD is needed to enhance patient symptoms or prognosis, the invasive coronary angiography is preferred method of choice. The management of chronic coronary syndrome, acute coronary syndromes without ST-segment elevation, and acute myocardial infarction with ST-segment elevation is covered in detail in the European Society of Cardiology (ESC) guidelines. The basic principle seems to be straight forward; the higher the clinical risk and the severity of the symptoms, the more strongly the invasive coronary angiography is indicated (15).

The actual procedure is performed in the specially equipped catheterization laboratory under local anesthesia, and usually takes ten to fifteen minutes, if the case is straight-forward. The majority of treatments are done without conscious sedation even though it is optional, and the threshold is low for worried patients. Sedation in the senior population is not risk free, and in this case, local anesthesia is recommended. The Seldinger method is used to establish artery access, and both coronary ostia are cannulated using the over-the-wire approach once the vascular sheath has been introduced. It is important to maneuver with extreme care. If resistance is encountered, the operator should only move forward while viewing the object through an x-ray. Small diameter catheters are increasingly being used, and the majority of operators employ 5 french (Fr) or 6 Fr catheter equipment. Utilizing pre-warmed contrast agents lowers their viscosity and enhances coronary artery filling (16).

There are always potential health hazards involved since it is an invasive procedure, and the procedure is therefore not appropriate for everyone. The risk of vascular access site related morbidity, mostly bleeding, follows femoral access diagnostic invasive coronary angiography in 0,5-1 percent of patients. In patients with more intensive anticoagulation and antiplatelet therapy it occurs 2-3 more frequently following percutaneous coronary intervention. Significantly less local bleeding and other complications result from using radial/transradial artery access (17).

The composite rate of myocardial infarction, stroke, or death is 0.1-0.2 percent in elective procedures, and for patients with acute coronary syndromes it is approximately 1%. These are major hazards with serious long-term effects. The significance of proper patient hydration due to contrast use cannot be overstated because contrast nephropathy is known to have a negative impact on long-term prognosis (18, 19).

A comprehensive list of reported problems includes risks that are uncommon and/or have a low likelihood of having long-term effects. Allergic responses to contrast substances, vasovagal reaction, supraventricular or ventricular arrhythmias, and major artery dissections are just some of the examples of potential serious complications.

The ideal candidates for coronary angiography in non-ACS conditions are often those with an intermediate pretest likelihood. All the STEMI patients in ACS scenario and a subset of NSTEMI/UA patients get an urgent cardiac catheterization.

### 1.2.2 Advantages and disadvantages of invasive coronary angiography

There are numerous newly developed diagnostic procedures that could be helpful in assessing coronary artery disease, and still coronary angiography is the best procedure in assessing CAD. Despite that, it has its advantages and disadvantages.

Patients have been enrolled in the vast majority of revascularization studies based on the findings of invasive coronary angiography (ICA). This has allowed numerous studies to demonstrate the prognostic value of ICA findings such as the location of the lesion, the degree of luminal blockage and number of diseased arteries. Currently, ICA is the only technique that assess the distal portion of coronary veins and around 100 mm provides excellent resolution of coronary arteries that are selectively filled with non-diluted contrast agent. For this reason, it is regarded as the industry gold standard for coronary artery imaging as a result of the exceptional image quality (20). Also, angiography can be combined with left ventriculography. Even though this is no longer a normal procedure, it can occasionally be helpful in an emergency situation or when non-invasive results are uncertain. Some other advantages of

coronary angiography are a right-hearted catheterization combined with a hemodynamic investigation, which can yield very useful data. There is also a minimal waiting line in developed countries, it is easily accessible, and in some circumstances ad hoc PCI can be effective, economical, and patient-friendly.

Despite its advantages, invasive coronary angiography also has its disadvantages. The risk of exposure to ionizing radiation is one complication that is related to ICA. It is a two-dimensional luminogram, which complicates the interpretation of asymmetries and widespread diseases that lack a "normal" part because it is based on the summation of pictures that will never view the vessel wall.

There is a lot of interobserver variation in ICA interpretation. Due to this, quantitative coronary angiography with computer-assisted boundary identification was developed. Visual evaluation frequently causes the severity of the lesion to be overestimated (15, 21).

Putting all of this together, the patient can benefit from the utilization of all available scientific evidence by receiving safe treatment and having an accurate diagnosis established as the basis for successful therapy. In the vast majority of patients, high-quality invasive coronary angiography permits scientifically accurate and effective treatment in addition to providing a clear diagnosis.

### 1.3 Atherosclerotic renal artery stenosis (ARAS)

A major contributor to systemic arterial hypertension is renal artery disease. Takayasu arteritis, fibromuscular dysplasia, and atherosclerosis are only a few of its etiologies. These conditions could progress to cause renal artery stenosis (RAS), blockage, or aneurysms (22). Atherosclerotic renal stenosis (ARAS) is a type of peripheral artery disease that typically affects older people with other coexisting vascular insufficiencies like a history of smoking or hyperlipidemia. When compared to peripheral procedures used elsewhere, this form of peripheral artery disease is uncommon in that stenting and angioplasty do not appear to change the disease´s clinical course. It can be diagnosed by a variety of indicators, such as an abdominal bruit, peripheral artery disease, flash pulmonary oedema, a history of cigarette smoking, and the emergence of acute kidney injury in response to renin-angiotensin system inhibitors (23).

As people get older and more conventional cardiovascular risk factors are present, ARAS prevalence rises. Only 1 to 6 percent of individuals with hypertension show signs of ARAS, but more than 30 percent of cardiac catheterization patients and more that 50 percent of older patients with documented atherosclerotic disease experience ARAS (24).

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are frequently complicated by atherosclerotic renal artery stenosis. Up to 5 to 15 percent of patients who develop ESRD and 5 to 22 percent of CKD patients over the age of 50 could have ARAS. The absolute risk of cardiovascular outcomes is higher in those with non-ESRD chronic kidney disease than it is in people who will develop ESRD. In three years, there is a 50% death rate in the ERSD group (25).

Stenosis severity has an unfavorable relationship with survival. Up to 10 years following diagnosis, patients with incidentally discovered mild ARAS by angiography frequently have stable renal function and may not be at any higher risk of ESRD than the general population. Patients who later develop ESRD typically have worse renal function at the time of diagnosis and experience a faster rate of deterioration in their remaining renal function (23, 26).

### 1.3.1 Pathogenesis and clinical presentation

The main cause of ARAS is the presence of atherosclerotic plaque in the left and right renal arteries which is the kidneys major blood vessel. It progresses gradually and has the same underlying pathophysiology as coronary artery disease, peripheral arterial disease, carotid stenosis, and other atherosclerotic vascular disorders. Compared to fibromuscular dysplasia which usually affects the middle section of the renal artery, ARAS more frequently affect the proximal renal artery or the ostium. Fibromuscular dysplasia also appears more often in younger female individuals (27). Gradually over time, the kidney´s blood flow is hampered by the atherosclerotic plaques which leads to severe ischemia of the renal cortex where the glomerulus is located. As an early compensatory process, autoregulation, the blood flow is maintained to some extent. When the stenosis reaches about 60 percent, it starts to fail. At this time, decreased renal blood flow and tissue hypoxia cause renin to be released and the renin-angiotensin-aldosterone system (RAAS) to be activated, which results in salt and water retention as well as peripheral vasoconstriction. Together, all of this causes hypertension linked to ARAS and eventually local release of cytokines, localized inflammation, fibrosis and a decline renal function (23).

ARAS frequently manifest as a persistent, silent condition. The renal function will become affected as the ARAS crosses the critical threshold from moderate to severe. As expected with aging, the glomerular filtration rate (GFR) declines out of proportion. Traditional symptoms of ARAS include hypertensive crisis and related sudden pulmonary oedema. Diagnosis indicators include worsening renal function after initial RAAS blockade, ischemic

nephropathy, or renal function that is overly sensitive to intravascular volume. When using such drugs, many suggest stopping RAAS blockage if the serum creatinine increases by more than 30%. Atherosclerotic illnesses of other types are virtually invariably linked to ARAS. Age over 50, hyperlipidemia, and smoking are typical risk factors. During a physical examination, a bruit in the abdomen caused by turbulent blood flow in the artery may be audible. Imaging the kidneys can identify asymmetrical or smaller-than-normal kidneys, which makes it very important (25, 28).

### 1.3.2 Diagnosis and method for the assessment of RAS

An increased serum aldosterone concentration and plasma renin assay indicates ARAS. And further diagnostic aids include duplex ultrasound, magnetic resonance angiography (MRA), and computed tomography angiography (CTA) (25). Ultrasonography is frequently the initial imaging examination utilized to find ARAS since it is widely accessible, secure, and reasonable priced (29). But despite this, it is the least sensitive and specific modality. It requires a lot of work, takes a long time, depends on the operator, and has limited use for some patients, especially obese people. RAS may be easier to diagnose when the resistive index is combined with duplex doppler ultrasonography. A greater resistive index suggests an atherosclerotic burden distal to the primary renal arteries that is more significant (30).

MRA demonstrates great sensitivity and specificity for the detection of stenosis of the main renal artery, meanwhile in accessory renal arteries are less useful. But it increases the risk of gadolinium-induced nephrogenic systemic fibrosis, a phenomenon associated with people who have a GFR below 30 mL/min (31).

CTA is becoming a crucial technique in the diagnosis of ARAS due to the potential for 3-dimensional reconstructions. A substantial amount of contrast is needed for CTA, which makes it potential dangerous for people with advanced CKD. Multidetector spiral CTA offers a great sensitivity and specificity but still likely only marginally less accurate than MRA. The diagnosis can also be confirmed with conventional intraarterial angiography, although this procedure entails the risk of contrast nephropathy and atheroemboli (23, 24). When comparing CTA with MRA, it has a higher spatial resolution and can therefore identify small auxiliary renal arteries. Additionally, it is favored for patients with implanted devices, those who have a limited capacity for breath holding, and those who are claustrophobic (32).

Although imaging techniques have advanced technologically, renal angiography is thought to be important for diagnosing renal artery disorders. With the right procedure, can offer anatomical view of the renal arteries. It can identify intrarenal vascular anomalies as well

as anatomical issues with the renal arteries, kidneys, and aorta, and determining the severity of ARAS. Additionally, therapeutic choices are based on the physical characteristics of the lesion at arteriography and it can deliver images for fast diagnostic and endovascular treatment while the process is being done. Digital subtraction angiography enhances contrast resolution and can use as little as 15 mL of contrast material. However, since renal angiography is invasive, there are hazards involved with penetrating the artery wall and manipulating the catheter or wire. This can lead to arterial damage, thromboembolic event, or spasms. As an advantage, carbon dioxide can be administered as a non-nephrotoxic contrast agent in persons with renal kidney disease or a sensitivity to contrast materials (22, 33).

### 1.3.3 Management

The prognosis of patients has improved thanks to technical advancements in imaging diagnosis and therapy during the past few decades. There is general consensus that all symptomatic ARAS patients need medical treatment. For the purpose of managing hypertension and lowering clinical events in people with known cardiovascular disease, it is advised to use angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors to suppress the sympathetic- and renin-angiotensin system. Although it is neither a sensitive nor specific finding, a deterioration in renal function following the start of ACE inhibitor or angiotensin receptor blocker is frequently linked to bilateral RAS (24). For patients with severe bilateral RAS, high-grade unilateral stenosis with a single kidney, or advanced chronic disease, these drugs can cause acute renal failure. Renal failure in these patients is associated with a reduction in renal perfusion pressure brought on by the RAAS inhibitor or by the intrarenal effects of these drugs on chronically ill kidneys. But for patients with ARAS, chronic renal failure, renal atrophy and intrarenal vascular disease, medical therapy is preferable over revascularization (34).

According to the American Heart Association (AHA) and American College of Cardiology (ACC), there are directions to patients that most likely profit from revascularization. The patients who will mostly profit from renal artery stenting should have hemodynamically significant ARAS and either recurrent chronic heart failure, progressive chronic kidney disease caused by bilateral or unilateral ARAS, those who are unable to tolerate guided-directed medical therapy or have refractory hypertension (35).

It is critical to evaluate whether renal hypoperfusion is the origin of the patients' symptoms or if ARAS is merely a bystander. When assessing the patient for other symptoms, normal abdominal imaging may reveal ARAS. Revascularization has no indication,

nevertheless, if ARAS is not the cause of any clinical issues. For patients with uncontrolled blood pressure who are not taking a total of three antihypertensive medications, including diuretics, as a part of a maximally tolerated guided-directed medical therapy, are unlikely to benefit from renal artery stenting. Chronic renal disease patients and those who are on hemodialysis for more than three months are among those with ischemic nephropathy who are also unlikely to benefit from revascularization (36).

When patients undergo coronary angiography, finding out that they have renal artery stenosis is not unusual. Among those who have coronary artery disease, we planned this thesis to determine the prevalence and clinical factors associated with renal artery stenosis.

# 2. OBJECTIVES

## 2.1. Aims of the study

The present thesis aimed to investigate which proportion of patients undergoing diagnostic coronary angiography due to stable coronary artery disease (CAD) or suspicion for CAD will have concomitant renal artery stenosis (RAS) and to examine which of the established risk factors and clinical characteristics may be associated with the occurrence of RAS. Therefore, this thesis aimed to determine the following:

**a)** Proportion of patients with stable CAD undergoing diagnostic catheterization having significant RAS (≥ 50% stenosis in at least one of the renal arteries), severe RAS (≥ 70% stenosis in at least one of the renal arteries), and bilateral RAS (both renal arteries having significant stenosis of at least 50%)

**b)** Proportion of patients with stable CAD undergoing diagnostic catheterization having severe CAD defined as a three-vessel disease (3VD) and left-main (LM) coronary disease

**c)** Whether anthropometric variables such as female sex and chronological age will be associated with RAS occurrence during diagnostic cardiac catheterization

**d)** Whether the presence of comorbidities and standard modifiable risk factors such as diabetes mellitus (DM), arterial hypertension, dyslipidemia, current smoking, chronic kidney disease (CKD), and peripheral artery disease (PAD) will be associated with RAS occurrence during diagnostic cardiac catheterization

**e)** Whether the presence of angiographically severe CAD such as 3VD and/or LM disease will be associated with RAS occurrence during diagnostic cardiac catheterization

## 2.2. Hypotheses

Regarding the prespecified aims of the thesis, the following hypotheses were proposed:

**a)** Proportion of patients with stable CAD undergoing diagnostic catheterization having significant RAS will be greater than 1 in 10 while the proportions of patients having severe and bilateral RAS will be clinically relevant

**b)** Proportion of patients having severe CAD will be greater than 15% for 3VD and greater than 5% for LM disease

**c)** Female sex and older age will be significantly associated with a higher risk of RAS

**d)** All of the prespecified comorbidities and standard modifiable risk factors will be significantly associated with a higher risk of RAS occurrence

**e)** Presence of angiographically severe CAD features will be significantly associated with a higher risk of RAS occurrence during diagnostic cardiac catheterization

# 3. PATIENTS AND METHODS

### 3.1. Study design

This diploma thesis was envisioned as a systematic review of the literature and quantitative meta-analysis of observational cohort studies (retrospective and prospective) that examined the occurrence of RAS with varying degrees of severity among patients with stable CAD or suspected CAD undergoing diagnostic coronary catheterization. The main objectives of the present thesis were to investigate which proportion of these patients will have concomitant significant RAS, severe RAS, and bilateral RAS and which clinical characteristics and risk factors will be associated with an increased risk of having RAS. Prior to the start of this analysis, no predetermined protocol was registered, and this type of study did not require Ethics Committee permission from the University of Split School of Medicine. The study was conducted under the sponsorship of the Department of Pathophysiology, University of Split School of Medicine (USSM).

### 3.2. Search strategy

The search strategy was devised by the student mentor (JAB) while the search of electronic databases was independently carried out by the student (ISB) and student mentor (JAB). Electronic databases included in the search were the National Library of Medicine (NLM) – PubMed, Ovid MEDLINE, Ovid Journals (full text), and SCOPUS. Search was conducted by using search terms: „renal artery stenosis“ AND „coronary artery disease“ AND „diagnostic angiography“ AND/OR „cardiac catheterization“. These databases were manually searched to obtain full records of original articles (observational cohort studies) that were specifically designed to investigate and to report on occurrence of renal artery stenosis in the setting of cardiac catheterization for stable CAD or suspected CAD. The search was limited to records published in relevant peer-reviewed journals in the English language in the last 20 years (from 2002 until 2022). Similarly, only observational cohort studies involving adult human subjects were considered. The date of the last database search was performed on June 13th, 2022. No grey literature search was performed and no external authors were contacted to provide additional data or to obtain additional studies. Both the student (ISB) and mentor (JAB) manually performed the literature search, deleted duplicate records, screened available titles and abstracts for relevance, and classified obtained studies as *„excluded“* or requiring further assessment or additional clarification. Such studies were labeled as *„potential for inclusion“*. Finally, prespecified eligibility and exclusion criteria were applied consistently among

potentially inclusive studies. If there was a discrepancy between the two investigators concerning the search strategy, this was resolved by the joint discussion involving the opinion of the third expert (member of the Department of Pathophysiology, University of Split School of Medicine).

### 3.3. Selection and inclusion of studies based on predefined PICOS critieria

To be included in the systematic review and meta-analysis, screened studies had to fulfill a number of inclusion criteria according to PICOS principles (**P**atient, problem, or population/**I**ntervention/**C**omparison/**O**utcomes/**S**tudy design) questions, as follows:

1. **Patient population:** Patients with stable CAD/chronic coronary syndrome (CCS) or suspected CAD undergoing elective diagnostic cardiac catheterization (coronary angiography) with the prespecified intent of undergoing peripheral angiography of renal arteries
2. **Intervention:** No specific intervention was investigated; all patients were managed according to best clinical practices for elective invasive cardiology work-up and all patients received renal artery angiography along with standard cardiac catheterization
3. **Comparison:** patients in the control group were those that did not have significant renal artery stenosis as assessed by renal diagnostic angiography while the group of interest were patients that had significant RAS, as assessed by renal angiography
4. **Outcome:** the outcomes of interest were weighted mean proportions of significant, severe, and bilateral RAS among patients with established or suspected CAD that underwent cardiac catheterization. Secondarily, we wanted to investigate whether the variables such as age, female sex, diabetes mellitus, arterial hypertension, dyslipidemia, smoking, chronic kidney disease, peripheral artery disease, three-vessel coronary disease, and left-main disease will have significant impact on the risk of RAS in this population.
5. **Study design:** studies had to be designed as observational cohort studies in order to be considered for the potential inclusion in the statistical analysis.

### 3.4. Exclusion criteria

In short, studies were considered for potential inclusion only if they explicitly reported on the proportion of significant RAS among enrolled patients and if they were specifically designed to capture RAS cases. Studies that did not satisfy these criteria were exlcuded.

**We excluded studies in the following circumstances:**

1. If the study had an RCT design or if it was not an original article (*e.g.* a review, etc.)
2. If the study did not report on any of the principal outcomes of interest or if the study did not provide basic data on study length, study setting and location, and baseline characteristics that are relevant for the studied population such as age, sex, comorbidity burden, risk factor information, etc.
3. If study was older than 20 years (earlier than year of 2002)
4. If the study involved patients with acute coronary syndromes (ACS) such as non-ST segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), or unstable angina (UA) – these studies were excluded from potential analysis
5. If the study involved minors (<18 years of age) or pediatric patients
6. If the study was a duplicate report without additional or updated outcome data

### 3.5. Data extraction

Data were manually extracted by both the mentor (JAB) and the student (ISB) and were inserted in prespecified tables in MS Word format. Study quality assessment was performed bu using the Ottawa-Newcastle Scale (insert reference link here Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Loso M, Tugwell P. The Newcastle-Ottawa Scale (NOS) For assessing the quality of nonrandomised studies in meta-analyses. Available at: https://www.ohri.ca//programs/clinical_epidemiology/oxford.Asp. Last accessed 6 July 2022.)

### 3.6. Statistical analysis (data synthesis)

Data analysis was performed by proposed Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (37).

As the primary summary metric for effect estimates on predetermined dichotomous outcomes, risk ratio (RR) with 95% confidence intervals (95% CI) was used. Mean difference analysis was performed to ascertain differences in prespecified continuous outcome (age). For the meta-analysis, a random-effects model with Mantel-Haenszel statistical method was used. Meta-analysis was performed by using Review Manager software (RevMan, version 5.4, The Cochrane Collaboration, 2020) and MedCalc Statistical software (version 20.112, Medcalc Software Ltd, Ostend, Belgium).

Chi-square ($\chi^2$) test of heterogeneity and Higgins $I^2$ statistic of non-consistency were used to assess heterogeneity across included studies. Studies with an $I^2$ statistic of 15% to <35% were considered to have low heterogeneity; >35% to 75% - moderate heterogeneity, and those with $I^2$ statistic >75% were considered to have a high heterogeneity.

Publication bias was assessed by visual inspection of obtained funnel plots and formal Egger's test calculation - P-values <0,05 indicated significant publication bias across included studies. All P-values reported were two-tailed and results were considered statistically significant if P <0,05 at all instances.

# 4. RESULTS

A total of 28 studies enrolling 18,274 patients with CAD undergoing cardiac coronary catheterization and the concomitant assessment for renal artery stenosis were included in the statistical analysis.

Basic information about the studies including number of patients, study period, study location, and study type are shown in **Table 1**.

The mean age of patients with diagnosed RAS was 65,3 ± 9,3 years while those without RAS at angiography had the mean age of 60,9 ± 10,4 years.

Across whole patient sample, women were represented with a weighted average of 37% (N=6761) while the weighted mean proportion of standard modifiable cardiovascular risk factors such as diabetes mellitus, arterial hypertension, dyslipidemia, and smoking were 26,2%, 73%, 66,3%, and 40%, respectively. The baseline characteristics of included patients with respect to comorbidities and clinical characteristics are shown in **Table 2**.

We included 28 observational studies in the quantitative analysis. Two studies, by Rihal et al. 2002 and by Aqel et al. 2003, were conducted in the USA (38,39). Weber et al. conducted their study in Austria (40). Following studies were conducted at specific countries, as follows: Park et al. 2004 from South Korea (41), Cohen et al. 2005 from Argentina (42), Tumelero et al. 2006 from Brazil (43), El-Mawardy et al. 2008 from Egypt (44), Przewlocki et al. 2008 from Poland (45), Omeish et al. 2009 from Jordan (46), Kobo et al. 2010 from Israel (47), Rimoldi et al. 2010 from Switzerland (48), Bageacu et al. 2011 from France (49), Marcantoni et al. 2011 from Italy (50), Yorgun et al. 2012 from Turkey (51), and Buller et al. 2014 from Canada (52). A total of four studies were conducted in Asia - Yamashita et al. 2002 and Imori et al. 2014 were conducted in Japan (53,54), while Wang et al. 2003 and Liu et al. 2004 counducted their studies in China (55,56). Most of the studies were conducted in Iran, encompassing a total of 9 studies, as follows: Sani et al. 2008 (57), Ghaffari et al. 2009 (58), Salehi et al. 2011 (59), Vahedparast et al. 2011 (60), Rokni et al. 2012 (61), Zandparsa et al. 2012 (62), Khatami et al. 2014 (63), Payami et al. 2016 (64), and Mirbolouk et al. 2019 (65).

**Table 1.** Basic information on study design and setting in which selected studies were performed

| First author of the study and year | Total number of patients | Study period | Study location | Multicentric or single-centre study | Study type |
|---|---|---|---|---|---|
| **Rihal et al. 2002** | N=300 | July 1998 to March 1999 | Mayo Clinic, Rochester, USA | Single-center | Prospective cohort study |
| **Weber et al. 2002** | N=177 | - | University Graz, Austria | Single-center | Cohort study |
| **Yamashita et al. 2002** | N=289 | April 2000 to October 2000 | Kitami Red Cross Hospital, Japan | Single-center | Cohort study |
| **Aqel et al. 2003** | N=542 | February 2001 to November 2001 | Veterans´ Administration (VA) Medical Center, USA | Single-center | Prospective study |
| **Wang et al. 2003** | N=230 | - | Queen Mary Hospital, Hong Kong | Single-center | Prospective study |
| **Liu et al. 2004** | N=141 | January 2000 to March 2004 | Zhong Da Hospital, Nanjing, PR China | Single-center | Cohort study |
| **Park et al. 2004** | N=1,459 | March 1998 to July 1999 | Yonsei University Cardiovascular Center, Seoul | Single-center | Multivariate analysis |
| **Cohen et al. 2005** | N=843 | September 2000 to May 2002 | Hospital Italiano de Buenos Aires | Single-center | Prospective study |
| **Tumelero et al. 2006** | N=1,656 | January 2002 to February 2004 | Hospital Sao Vicente de Paulo, Passo Fondo, Brazil | Single-center | Prospective cross-sectional study |
| **El-Mawardy et al. 2008** | N=525 | November 2000 to June 2002 | Ain Shams University Hospital, Cairo, Egypt | Single-center | Cohort study |
| **Przewlocki et al. 2008** | N=1,036 | Period of 12 months | University Hospital, Krakow, Poland | Single-center | Cohort study |
| **Sani et al. 2008** | N=260 | April 2005 to 2006 | Two educational hospitals in Mashhad (Emam Reza & Qaem) | Multicentric | Cross-sectional study |
| **Ghaffari et al. 2009** | N=732 | April 2007 to May 2008 | 3 hospitals in Tabriz, Iran | Multicenter | Cross-sectional descriptive-analytical study |

| | | | | | |
|---|---|---|---|---|---|
| **Omeish et al. 2009** | N=870 | Januar 2006 to April 2006 | Queen Alia Heart Institute, Amman, Jordan | Single-center | Prosprective observational cross-sectional study |
| **Kobo et al. 2010** | N=7,500 | 2001 to 2007 | Bnai-Zion Medical Center, Haifa, Izrael | Single-center | Cohort study |
| **Rimoldi et al. 2010** | N=1,504 | 1st of January 2004 to 31st of August 2007 | Swiss Cardiovascular Center Bern, University Hospital Bern, Bern, Switzerland | Single-center | Retrospective study |
| **Bageacu et al. 2011** | N=492 | 4 months period | University Hospital of Saint-Erienne, France | Single-center | Prospective study |
| **Marcantoni et al. 2011** | N=1,298 | April 2007 to March 2008 | The Division of Cardiology, University of Catania, Italy | Single-center | Prospective study |
| **Salehi et al. 2011** | N=500 | Period of 12 months from November 2008 | Shaheed Rajeie Cardiovascular Medical, and Research Center, Iran | Single-center | Prospective cohort study |
| **Vahedparast et al. 2011** | N=835 | August 2008 to August 2009 | Bent Al-Hoda Hospital od Bushehr University of Medical Science, Iran | Single-center | Prospective cross-sectional study |
| **Rokni et al. 2012** | N=18,419 | October 2009 to July 2011 | Tehran Heart Center, Iran | Single-center | Retrospective cross-sectional study |
| **Yorgun et al. 2012** | N=832 | - | Hacettepe University, Ankara, Turkey | Single-center | Observational study |
| **Zandparsa et al. 2012** | N=165 | September 2010 to May 2011 | Tehran University of Medical Sciences, Tehran, IR Iran | Single-center | Cohort study |
| **Buller et al. 2014** | N=851 | June 2001 to May 2002 | Vancouver Hospital, Canada | Single-center | Prospective cohort study |
| **Imori et al. 2014** | N=2,571 | September 2010 to July 2011 | Shonan Kamakura General Hospital, Kanagawa, Japan | Single-center | Cross-sectional study |
| **Khatami et al. 2014** | N=173 | - | Tehran Unviversity of Medical Sciences, Tehran, Iran | Single-center | Cross-sectional study |
| **Payami et al. 2016** | N=312 | March 2009 to October 2010 | Emam Hospital, Ahvaz, Iran | Single-center | Cross-sectional study |
| **Mirbolouk et al. 2019** | N=247 | May 2015 to June 2016 | Heshmat heart hospital, Rasht, Iran | Single-center | Cross-sectional study |

**Table 2.** Age, sex, and comorbidities of patients from included studies (data extracted where available)

| **First author of the study and year** | **Average age** (y) | **Female sex** N/N total (%) | **Diabetes mellitus** N/N total (%) | **Arterial Hypertension** N/N total (%) | **Dyslipidemia** N/N total (%) | **Smoking** N/N total (%) | **Renal failure** N/N total (%) | **Peripheral artery disease** N/N total (%) | **Carotid artery stenosis** N/N total (%) | **Previous myocardial infarction** N/N total |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rihal et al. 2002** | 64,9 ± 10,2 | 123/297 (41,4%) | 67/297 (22,6%) | 297/297 (100%) | 124/297 (47,1%) | 172/297 (57,9%) | - | - | - | 80/297 (26,9%) |
| **Weber et al. 2002** | 61±10 | 62/177 (35,0%) | 30/177 (16,9%) | 159/177 (89,8%) | - | 33/177 (18,6%) | - | - | - | 46/177 (26,0%) |
| **Yamashita et al. 2002** | 65,8±10,6 | 125/289 (43,3%) | 81/289 (28,0%) | 138/289 (47,8%) | 91/289 (31,5%) | 90/289 (31,1%) | - | - | - | - |
| **Aqel et al. 2003** | 65,3±9,4 | 2/90 (2,2%) | 42/90 (46,7%) | 85/90 (94,4%) | 68/90 (75,6%) | 34/90 (37,8) | - | - | - | 15/90 (16,7%) |
| **Wang et al. 2003** | 65,1±10,2 | 82/230 (35,7%) | 81/230 (35,2%) | 153/230 (66,5%) | - | 119/230 (51,8%) | - | 27/230 (11,7%) | 44/230 (19,1%) | 52/230 (22,7%) |
| **Liu et al. 2004** | 59±10 | 82/141 (58,2%) | 21/141 (14,9%) | 69/141 (48,9%) | 17/141 (12,1%) | - | 14/141 (9,9%) | - | - | - |
| **Park et al. 2004** | 59,2±9,9 | Male:female 2.05:1 N=1301 | 287/1301 (22,1%) | 575/1301 (44,2%) | - | 676/1299 (52,0%) | 53/785 (6,8%) | 103/1301 (7,9%) | 46/1186 (3,9%) | - |
| **Cohen et al. 2005** | 64 (55-73) | 252/843 (29,9%) | 133/843 (15,8%) | 549/843 (65,1%) | - | 181/843 (21,1%) | 40/843 (4,7%) | - | - | 141/843 (16,7%) |
| **Tumelero et al. 2006** | 61,6±11,8 | 765/1656 (46,2%) | 169/1656 (10,2%) | 1199/1656 (72,4%) | - | - | - | - | - | - |
| **El-Mawardy et al. 2008** | 52,6±8,5 | 122/525 (23,2%) | 197/525 (37,5%) | 525/525 (100%) | - | 272/525 (51,8%) | - | - | - | 127/525 (24,0%) |
| **Przewlocki et al. 2008** | 62,1±9,7 | 336/1036 (32,4%) | 189/1036 (18,2%) | 832/1036 (80,3%) | 899/1036 (86,8%) | 566/1036 (54,6%) | - | - | 80/1036 (7,7%) | 312/1036 (30,1%) |
| **Sani et al. 2008** | 57,2±10,1 | 125/260 (48,1%) | 88/260 (33,8%) | 175/260 (67,3%) | 165/260 (63,5%) | 39/260 (15,0%) | - | - | - | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Ghaffari et al. 2009** | 59,01±9,7 | 416/732 (56,8%) | 208/732 (28,4%) | 732/732 (100%) | 374/732 (51,1%) | 145/732 (19,8%) | | 21/732 (2,9%) | | 114/732 (15,6%) |
| **Omeish et al. 2009** | 64,5±9,5 | 284/870 (32,6%) | 318/870 (36,6%) | 228/870 (26,2%) | - | 286/870 (32,9%) | - | - | - | - |
| **Kobo et al. 2010** | 65,7±9,8 | 130/450 (28,9%) | 122/450 (27,1%) | 300/450 (66,7%) | 160/450 (35,6%) | - | 43/450 (9,6%) | - | - | - |
| **Rimoldi et al. 2010** | 67±9,5 | 642/1403 (45,8%) | 263/1403 (16,8%) | 1403/1403 (100%) | 1143/1403 (81,5%) | 259/1403 (18,5%) | 251/1403 (17,9%) | 129/1403 (9,2%) | - | - |
| **Bageacu et al. 2011** | 62,1±10,8 | 127/450 (28,2%) | 82/450 (18,2%) | 196/450 (43,6%) | - | 187/450 (41,6%) | - | - | - | - |
| **Marcantoni et al. 2011** | 64±10 | 371/1298 (28,6%) | 467/1298 (36,0%) | 1129/1298 (87,0%) | 974/1298 (75,0%) | 831/1298 (64,0%) | - | 247/1298 (19,0%) | - | 351/1298 (27,0%) |
| **Salehi et al. 2011** | 60,1±9,4 | 236/500 (47,2%) | 219/500 (43,8%) | 373/500 (74,6%) | 445/500 (89,0%) | 108/500 (21,6%) | - | - | - | - |
| **Vahedparast et al. 2011** | 59,25±10,81 | 239/481 (49,7%) | 146/481 (30,4%) | 481/481 (100%) | 207/481 (43,0%) | 201/481 (41,8%) | - | - | - | - |
| **Rokni et al. 2012** | 63,06±10,32 | 372/866 (43,0%) | 328/866 (37,9%) | 687/866 (79,3%) | 635/866 (73,3%) | 178/866 (20,6%) | 137/866 (15,8%) | 57/866 (6,6%) | - | 309/866 (35,7%) |
| **Yorgun et al. 2012** | 61,2±8,2 | 178/832 (21,4%) | 164/832 (12,7%) | 832/832 (100%) | 534/832 (64,2%) | 442/832 (53,1%) | - | 32/832 (3,8%) | - | - |
| **Zandparsa et al. 2012** | 59,9±8,9 | 78/165 (47,3%) | 71/165 (43,0%) | 119/165 (72,1%) | 129/165 (78,2%) | 63/165 (38,2%) | - | - | - | - |
| **Buller et al. 2014** | 67,0±9,9 | 211/837 (25,2%) | 264/837 (31,5%) | 264/837 (31,5%) | - | 476/837 (56,9%) | - | - | - | - |
| **Imori et al. 2014** | 71±9 | 527/1734 (30,4%) | 524/1734 (30,2%) | 1179/1734 (68,0%) | 1104/1734 (63,6%) | 819/1734 (47,2%) | - | - | - | 234/1734 (18,7%) |
| **Khatami et al. 2014** | 61,2±9,47 | 51/146 (34,9%) | 54/146 (37,0%) | 100/146 (68,5%) | 81/146 (55,5%) | 43/146 (29,5%) | - | - | - | - |
| **Payami et al. 2016** | 60,75±10,92 | 166/274 (60,6%) | 98/274 (35,8%) | 274/274 (100%) | 126/274 (46,0%) | 37/274 (13,5%) | 23/274 (8,4%) | - | - | - |
| **Mirbolouk et al. 2019** | 64±10 | 130/233 (55,8%) | 110/233 (47,2%) | 179/233 (76,8%) | - | - | - | - | - | 46/233 (19,7%) |

Angiographic characteristics of renal artery stenosis (RAS) across included studies are provided in the **Table 3.**

**Table 3.** Angiographic characteristics of detected RAS based on disease severity in terms of percent stenosis and if the disease was bilateral (data extracted where available)

| First author of the study and year | RAS ≥50% (or significant) N/N total (%) | RAS ≥70% (or severe) N/N total (%) | Bilateral RAS N/N total (%) |
|---|---|---|---|
| **Rihal et al. 2002** | 57/297 (19,2%) | 21/297 (7,0%) | 11/297 (3,7%) |
| **Weber et al. 2002** | 19/177 (10,7%) | 12/177 (6,8%) | 8/177 (4,5%) |
| **Yamashita et al. 2002** | 21/289 (7,0%) | - | 3/289 (3,0%) |
| **Aqel et al. 2003** | 25/90 (28,0%) | 14/90 (16,0%) | 14/90 (16,0%) |
| **Wang et al. 2003** | 34/230 (14,8%) | - | 6/230 (2,6%) |
| **Liu et al. 2004** | 26/141 (18,4%) | - | 5/141 (3,5%) |
| **Park et al. 2004** | 109/1459 (7,5%) | 73/1459 (5,0%) | 24/1459 (1,6%) |
| **Cohen et al. 2005** | 154/843 (18,3%) | 99/843 (11,7%) | 15/843 (1,8%) |
| **Tumelero et al. 2006** | 228/1656 (13,8%) | 58/1656 (3,5%) | 25/1656 (1,5%) |
| **El-Mawardy et al. 2008** | 19/525 (3,6%) | - | - |
| **Przewlocki et al. 2008** | 38/1036 (3,7%) | 26/1036 (2,5%) | 124/1036 (12,0%) |
| **Sani et al. 2008** | 37/260 (14,2%) | 30/260 (11,5%) | 14/260 (5,4%) |
| **Ghaffari et al. 2009** | 87/732 (11,9%) | 35/732 (4,8%) | 37/732 (5,1%) |
| **Omeish et al. 2009** | 21/870 (2,4%) | 10/870 (1,2%) | 5/870 (0,6%) |
| **Kobo et al. 2010** | 41/450 (9,1%) | - | - |
| **Rimoldi et al. 2010** | 112/1403 (8,0%) | - | - |
| **Bageacu et al. 2011** | 35/450 (7,8%) | 15/450 (3,3%) | 5/450 (1,1%) |
| **Marcantoni et al. 2011** | 70/1298 (5,4%) | 7/1298 (0,5%) | 11/1298 (0,9%) |
| **Salehi et al. 2011** | 70/500 (14,0%) | 45/500 (9,0%) | 24/500 (4,8%) |
| **Vahedparast et al. 2011** | 136/481 (28,3%) | - | - |
| **Rokni et al. 2012** | 345/866 (39,8%) | - | 77/866 (8,9%) |
| **Yorgun et al. 2012** | 136/832 (16,4%) | 62/832 (7,5%) | - |
| **Zandparsa et al. 2012** | 64/165 (38,8%) | - | - |
| **Buller et al. 2014** | 120/837 (14,3%) | 61/837 (7,3%) | 12/837 (1,4%) |
| **Imori et al. 2014** | 128/1734 (7,4%) | - | - |
| **Khatami et al. 2014** | 25/146 (17,0%) | - | 9/146 (6,2%) |
| **Payami et al. 2016** | 50/274 (18,2%) | - | 9/274 (3,3%) |
| **Mirbolouk et al. 2019** | 53/233 (22,7%) | 23/233 (9,9%) | 38/233 (16,3%) |

The distribution of coronary artery disease (CAD) severity (single-, two-, three- vessel disease and left main - LM disease) across included studies is presented in **Table 4**.

**Table 4.** Angiographic CAD burden among enrolled patients (data extracted where available)

| First author of the study and year | 1-vessel CAD N/N total (%) | 2-vessel CAD N/N total (%) | 3-vessel CAD N/N total (%) | LM disease N/N total (%) |
|---|---|---|---|---|
| **Rihal et al. 2002** | 42/297 (14,1%) | 64/297 (21,5%) | 74/297 (24,9%) | - |
| **Weber et al. 2002** | - | - | - | - |
| **Yamashita et al. 2002** | 30/289 (10,0%) | 26/289 (9,0%) | 55/289 (19,0%) | - |
| **Aqel et al. 2003** | - | - | - | - |
| **Wang et al. 2003** | 7/230 (3,0%) | 15/230 (6,5%) | 14/230 (6,1%) | - |
| **Liu et al. 2004** | 21/141 (14,9%) | 10/141 (7,1%) | 21/141 (14,9%) | - |
| **Park et al. 2004** | 385/1459 (26,4%) | 271/1459 (18,6%) | 322/1459 (22,1%) | 128/1459 (8,8%) |
| **Cohen et al. 2005** | 125/843 (14,8%) | 159/843(18,9%) | 201/843 (23,8%) | 22/843 (2,6%) |
| **Tumelero et al. 2006** | - | - | - | - |
| **El-Mawardy et al. 2008** | 118/525 (22,5%) | 78/525 (14,9%) | 68/525 (13,0%) | 6/525 (1,1%) |
| **Przewlocki et al. 2008** | 291/1036 (28,1%) | 169/1036 (16,3%) | 173/1036 (16,7%) | - |
| **Sani et al. 2008** | - | - | - | 5/260 (1,9%) |
| **Ghaffari et al. 2009** | 100/732 (13,7%) | 114/732 (15,6%) | 220/732 (30,1%) | - |
| **Omeish et al. 2009** | 206/870 (23,7%) | 145/870 (16,7%) | 45/870 (5,2%) | 10/870 (0,2%) |
| **Kobo et al. 2010** | - | - | - | - |
| **Rimoldi et al. 2010** | - | - | - | - |
| **Bageacu et al. 2011** | - | - | - | - |
| **Marcantoni et al. 2011** | 278/1298 (21,4%) | 241/1298 (18,6%) | 158/1298 (12,2%) | 69/1298 (5,3%) |
| **Salehi et al. 2011** | 77/500 (15,4%) | 102/500 (20,4%) | 167/500 (33,4%) | 26/500 (5,2%) |
| **Vahedparast et al. 2011** | 88/481 (18,3%) | 94/481 (19,5%) | 170/481 (35,3%) | 20/481 (4,2%) |
| **Rokni et al. 2012** | 153/866 (17,7%) | 165/866 (19,1%) | 367/866 (42,4%) | 38/866 (4,4%) |
| **Yorgun et al. 2012** | 215/832 (25,8%) | 122/832 (14,6%) | 85/832 (10,2%) | 8/832 (0,96%) |
| **Zandparsa et al. 2012** | 50/165 (30,3%) | 33/165 (20,0%) | 82/165 (49,7%) | 7/165 (4,2%) |
| **Buller et al. 2014** | 74/837 (8,8%) | 133/837 (15,9%) | 386/837 (46,1%) | 89/837 (10,6%) |
| **Imori et al. 2014** | 506/1734 (29,2%) | 386/1734 (22,3%) | 206/1734 (11,9%) | 155/1734 (8,9%) |
| **Khatami et al. 2014** | 26/146 (18,0%) | 44/146 (30,0%) | 57/146 (39,0%) | - |
| **Payami et al. 2016** | 38/274 (18,3%) | 56/274 (20,4%) | 123/274 (44,9%) | - |
| **Mirbolouk et al. 2019** | 44/233 (18,9%) | 58/233 (24,9%) | 131/233 (56,2%) | - |

It was found that pooled proportion of RAS (weight-adjusted for the size of the studies and defined as at least ≥ 50% stenosis in at least one of the renal arteries) in analyzed sample was 13,82% with 95% CI 10,69 to 17,27% (**Figure 2**). This finding was based on 18,274 patients pooled from 28 individual studies. The data were marked by high degree of heterogeneity ($I^2$=97,6%, P<0,001) while no significant publication bias was detected (Egger's test P=0,065; **Figure 3**).

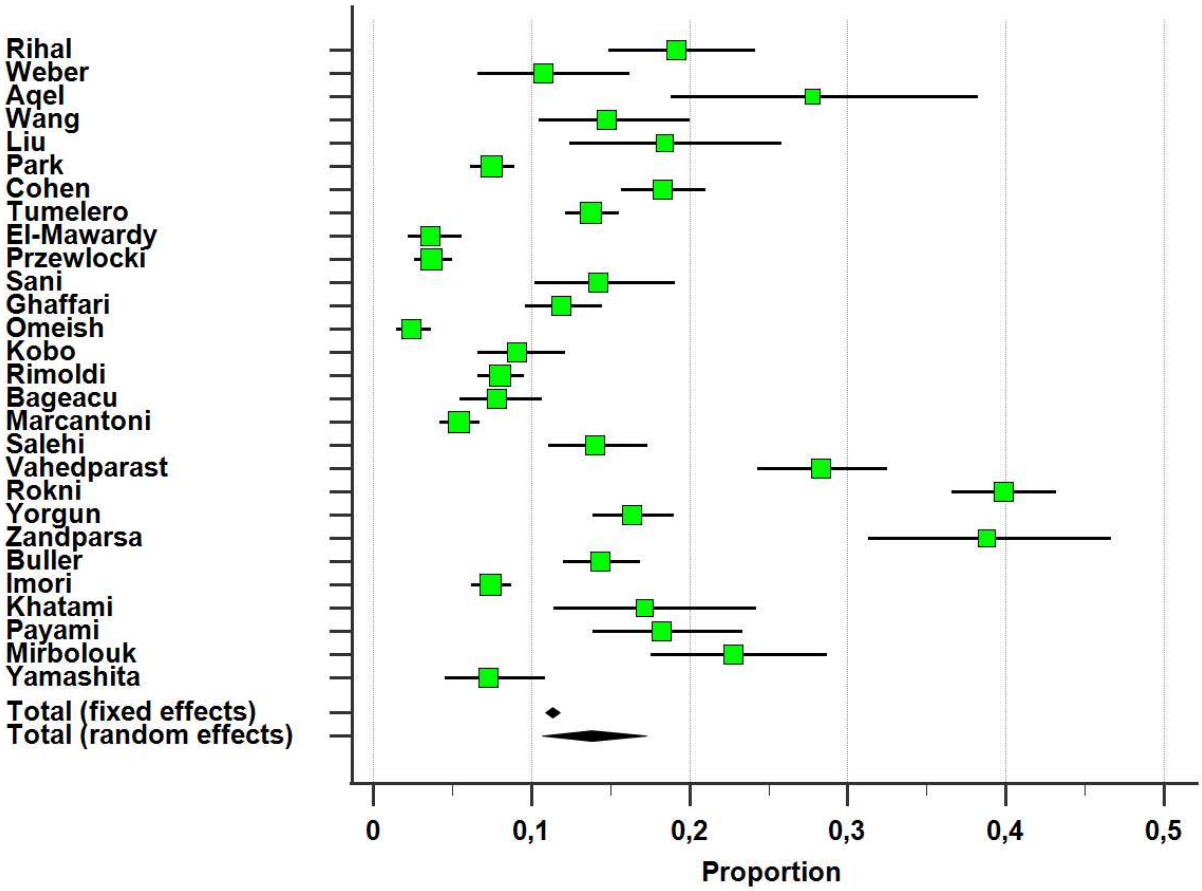


**Figure 2.** The pooled proportion of significant RAS in 18,274 patients with CAD undergoing cardiac catheterization

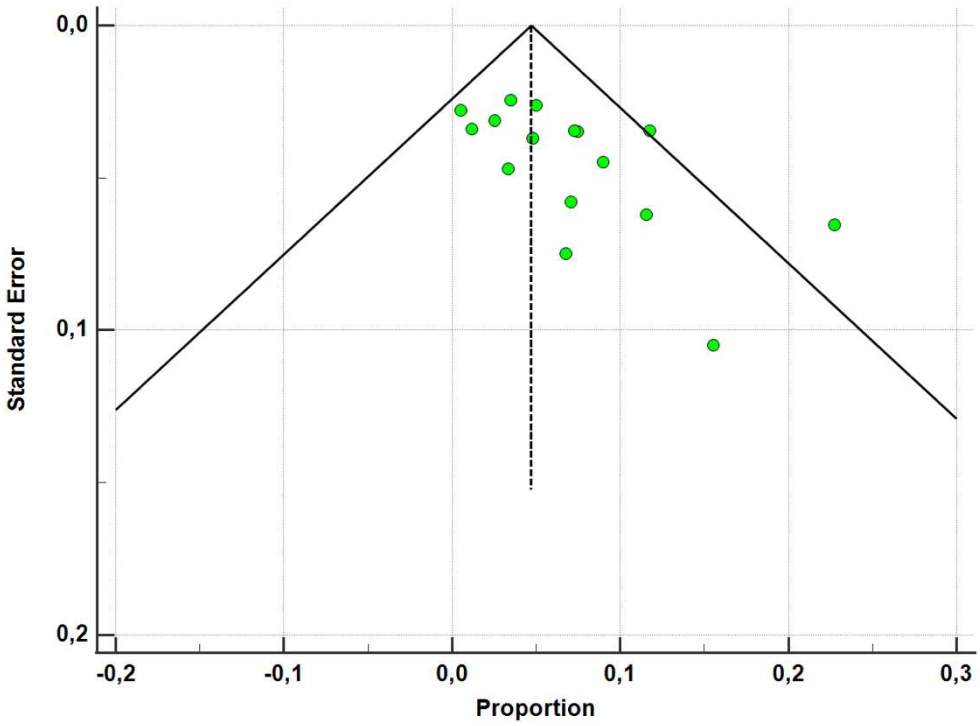


**Figure 3.** The publication bias plot for the pooled proportion of RAS

Furthermore, pooled proportion of severe RAS (weight-adjusted for the size of studies and defined as at least ≥70% stenosis in at least one of the renal arteries) in analyzed sample was 6,46% (95% CI 4,36-8,95%, **Figure 4**). This finding was based on 11,570 patients pooled from 16 individual studies. The data were marked by high degree of heterogeneity ($I^2$=96%, P<0,001) while significant publication bias was also detected for this endpoint (Egger's test P=0,0278; **Figure 5**).

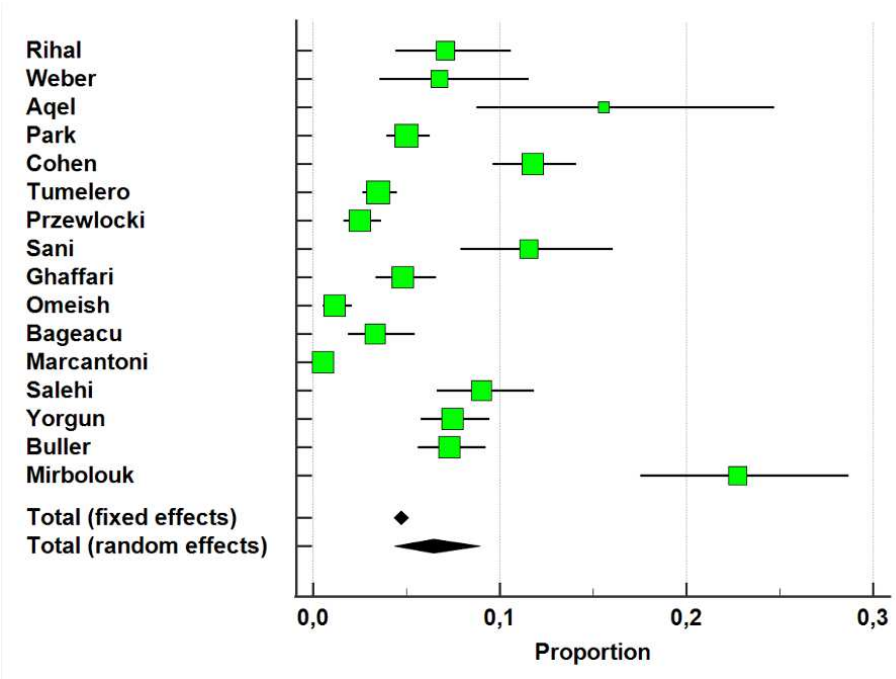


**Figure 4.** The pooled proportion of severe RAS in 11,570 patients with CAD undergoing cardiac catheterization

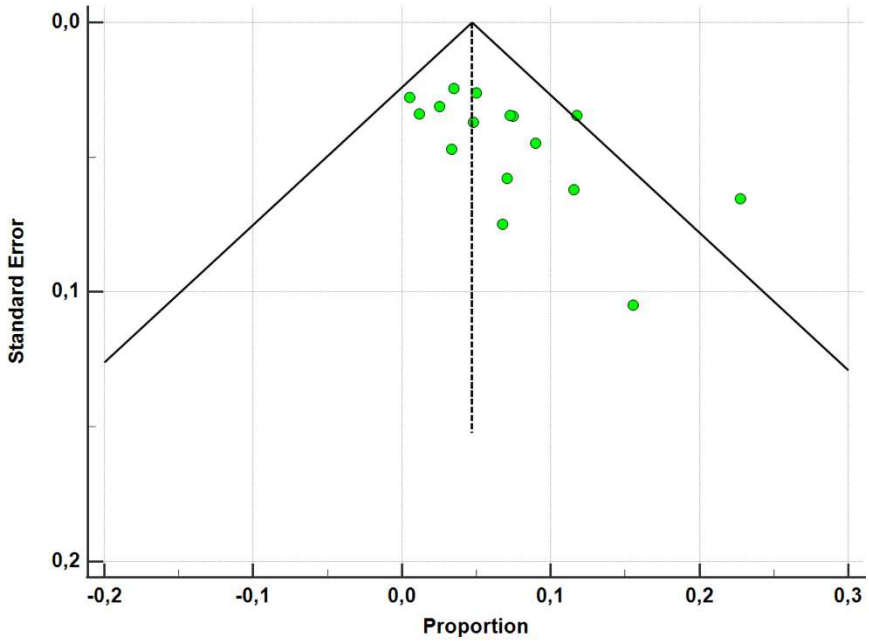


**Figure 5.** The publication bias plot for the pooled proportion of severe RAS

Bilateral RAS was marked by the pooled weight-adjusted proportion of 4,03% (95% CI 2,58-5,78%) as shown in **Figure 6** while this finding was based on 12,684 patients pooled from 21 study. A high degree of heterogeneity was established ($I^2$=95%, P<0,001) while no significant publication bias was detected (Egger's test P=0,1338; **Figure 7**).

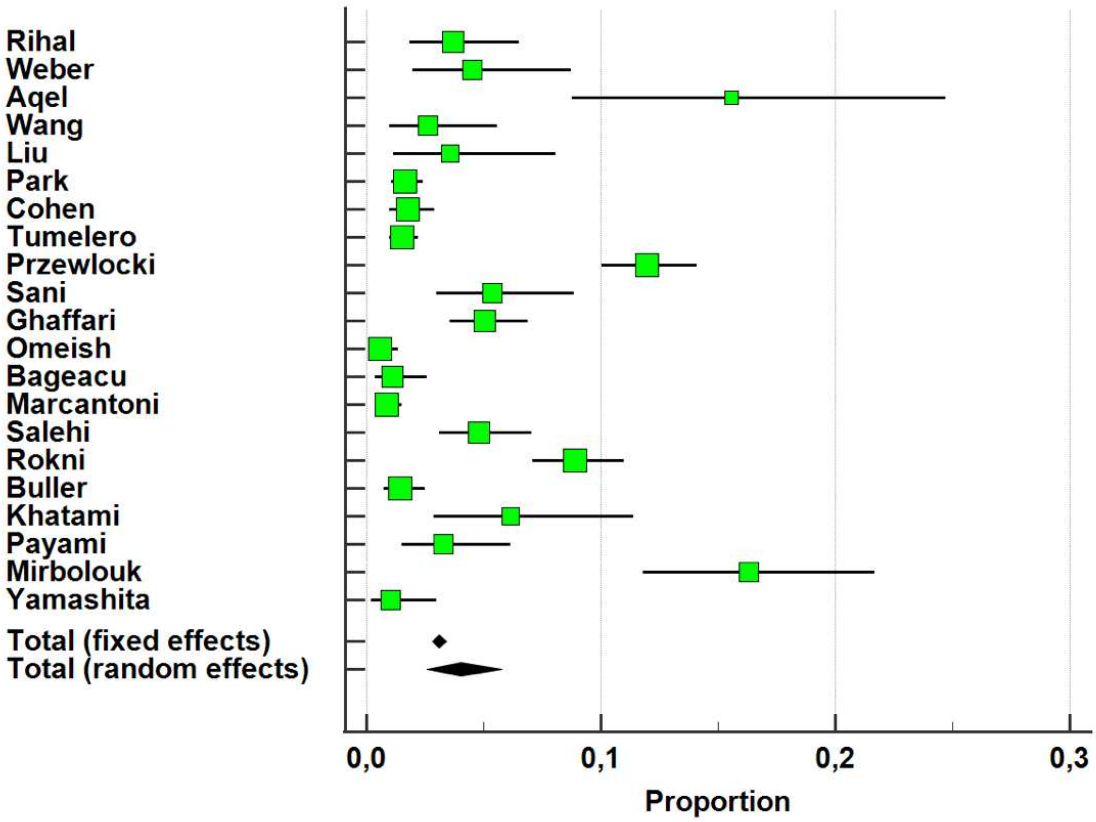


**Figure 6.** The pooled proportion of bilateral RAS in 12,684 patients with CAD undergoing cardiac catheterization

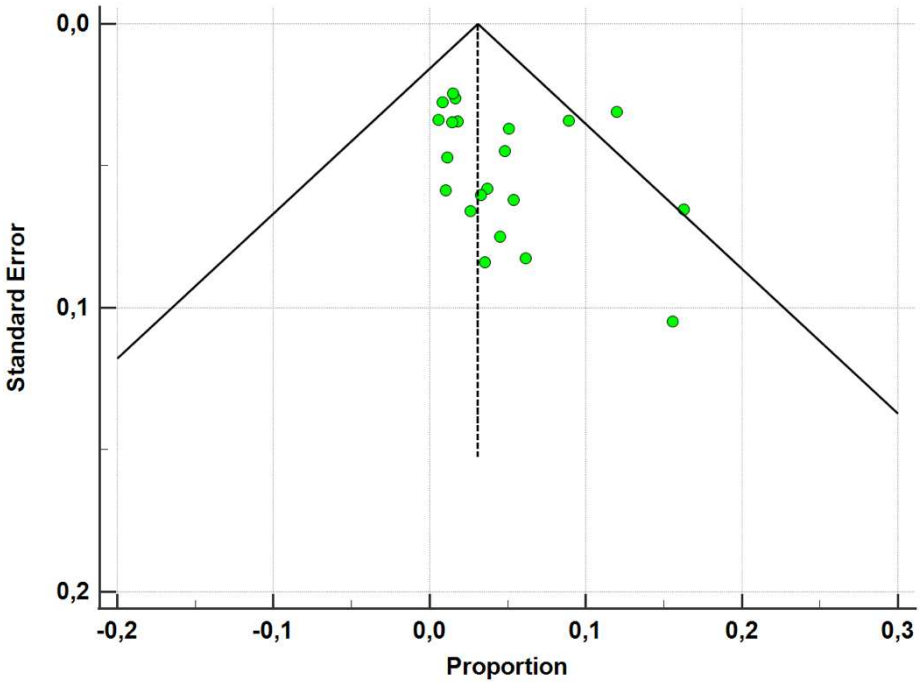


**Figure 7.** The publication bias plot for the pooled proportion of bilateral RAS

In terms of angiographic coronary artery disease (CAD) burden, the pooled weight-adjusted proportion of three-vessel disease (3VD) was 25,0% (95% CI 19,13 to 31,38%, **Figure 8**) and this finding was based on data from 13,788 patients pooled from 21 study. Data were marked by the high degree of heterogeneity ($I^2$=98%, P<0,001) while no significant publication bias was detected (Egger's test P=0,1047; **Figure 9**).

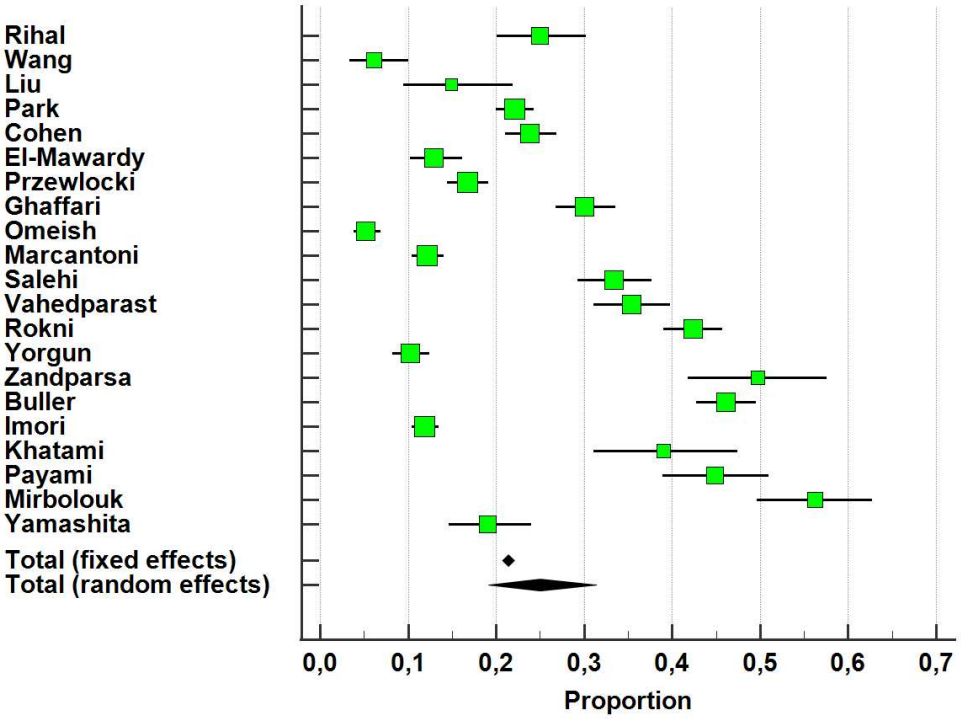


**Figure 8.** The pooled proportion of 3VD in 13,788 patients with CAD undergoing cardiac catheterization

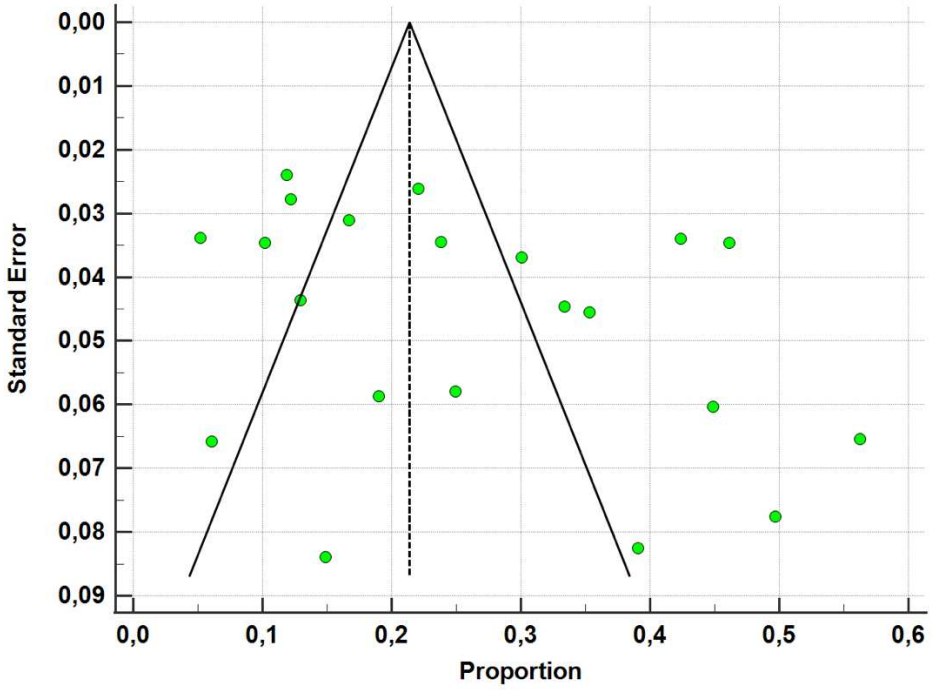


**Figure 9.** The publication bias plot for the pooled proportion of 3VD

The pooled weight-adjusted proportion of left-main (LM) disease was 4,2% (95% CI 2,57-6,19%) as shown in **Figure 10** while this finding was based on dana from 10,670 patients pooled from 13 studies. Data were marked by the high degree of heterogeneity ($I^2$=95%, P<0,001) while no signifiant publication bias was detected (Egger's test P=0,1241; **Figure 11**).

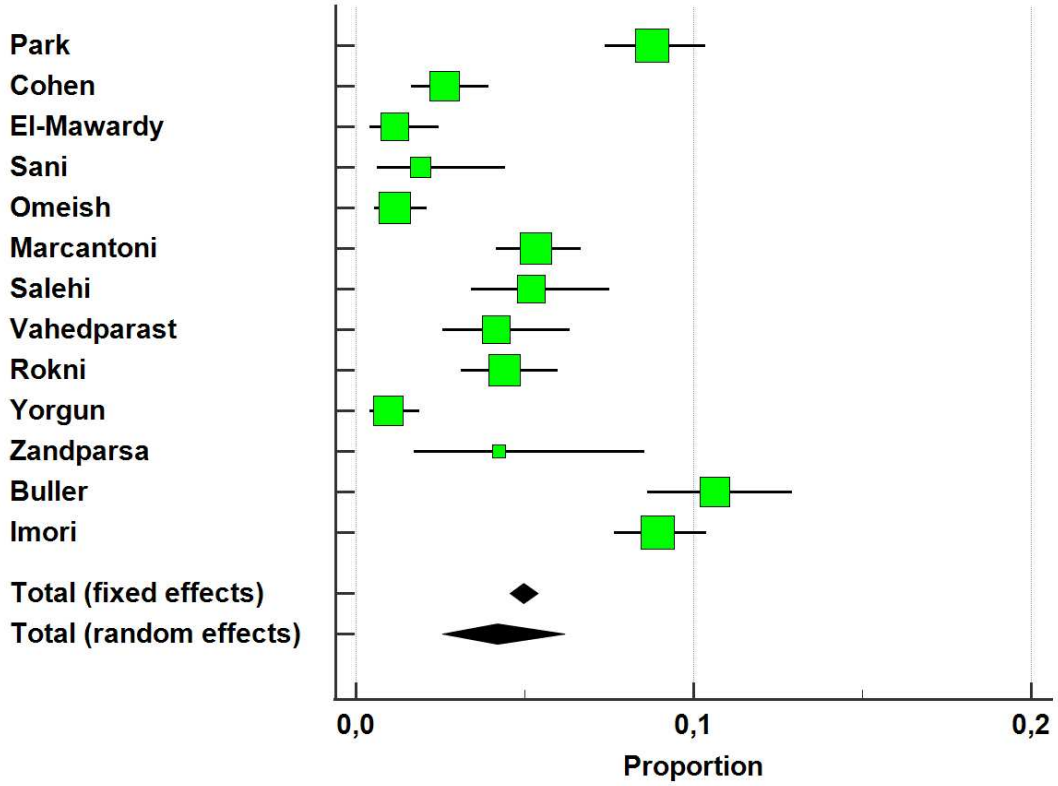


**Figure 10.** The pooled proportion of left main disease in 13,788 patients with CAD undergoing cardiac catheterization

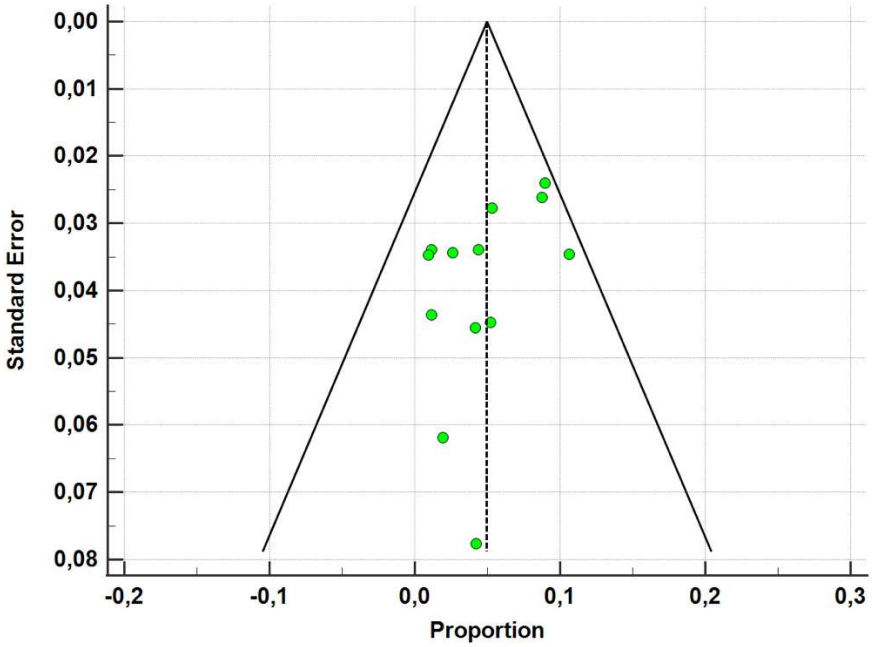


**Figure 11.** The publication bias plot for the pooled proportion of LM disease

The impact of anthropometric factors such as age and female sex, and cardiovascular risk factors/clinical characteristics including diabetes mellitus (DM), arterial hypertension, dyslipidemia, smoking, chronic kidney disease (CKD), three-vessel coronary disease (3VD), left-main (LM) disease and peripheral artery disease (PAD) were evaluated as predictors of RAS occurence in the meta-analysis.

As shown in **Table 5.** and in the order of decreasing magnitude, CKD was found to be the most robust predictor of RAS as it was associated with nearly 3-fold increase in the relative risk of RAS compared to patients without CKD (RR 2,80). This was followed by PAD and LM disease that were associated with a 2,5-fold and 1,9-fold increases in the relative risk of RAS occurence (RR 2,46 and RR 1,86; respectively).

Female sex and arterial hypertension were both associated with a 33% increase in a relative risk of RAS (RR 1,33 for both variables) while smoking was not identified as a significant variable impacting on RAS occurence.

Similarly, diabetes mellitus and dyslipidemia were associated with a 22% and 12% increases in the relative risk of RAS occurence (RR 1,22 and RR 1,12; respectively).

In terms of age, meta-analysis showed that patients with RAS were significantly older than patients without RAS. In fact, there was a mean age difference of 4,26 years (95% CI 3,50-5,02 years, P<0,001) between patients with RAS *versus* those without RAS.

**Table 5.** Anthropometric, comorbidity and clinical risk factors impacting on RAS occurrence during coronary angiography in patients with CAD, based on the results obtained from individual meta-analyses

| Variable | Risk ratio (RR) | 95% confidence interval | P-value | Heterogeneity |
|---|---|---|---|---|
| **Female sex** | 1,33 | 1,07-1,66 | 0,010 | **HIGH** |
| **Diabetes mellitus** | 1,22 | 1,09-1,37 | <0,001 | **MODERATE** |
| **Arterial hypertension** | 1,33 | 1,22-1,45 | <0,001 | **HIGH** |
| **Dyslipidemia** | 1,12 | 1,06-1,19 | <0,001 | **MODERATE** |
| **Current smoking** | 1,02 | 0,94-1,12 | 0,590 | **LOW** |
| **Chronic kidney disease** | 2,80 | 2,03-3,88 | <0,001 | **MODERATE** |
| **Three-vessel disease** | 1,56 | 1,28-1,90 | <0,001 | **HIGH** |
| **Left-main disease** | 1,86 | 1,30-2,67 | <0,001 | **MODERATE** |
| **Peripheral artery disease** | 2,46 | 1,85-3,27 | <0,001 | **MODERATE** |

As reported earlier, meta-analysis showed that older age was significantly associated with an increased relative risk for RAS occurrence among patients with CAD undergoing coronary catheterization. This observation was based on pooled data from 15,153 individuals derived from 25 studies. This analysis was based on data marked by the moderate level of heterogeneity ($I^2$=62%; **Figure 12**).

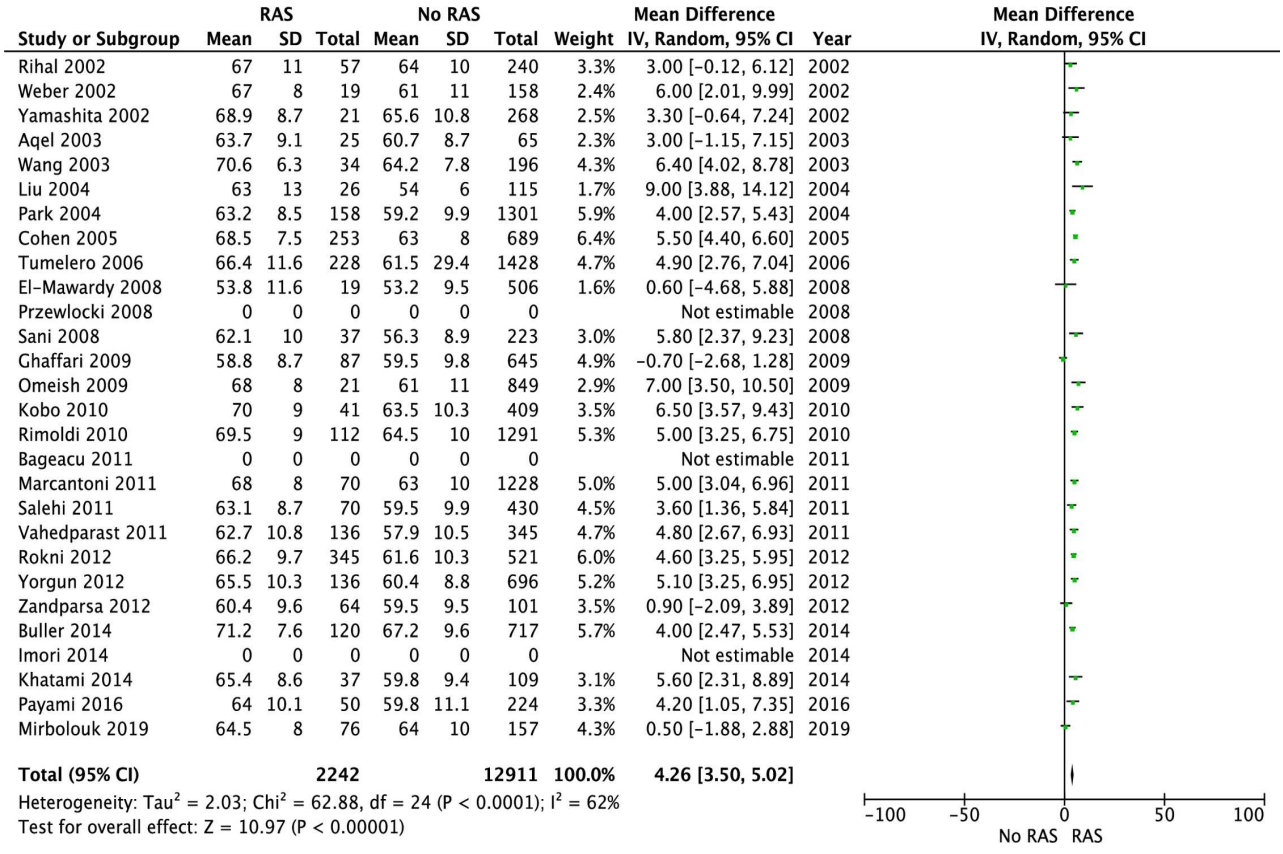


**Figure 12.** Increased age as a variable impacting on the occurrence of RAS

A female sex was associated with a significant 33% relative risk increase of renal artery stenosis finding during diagnostic coronary angiography. This result was obtained after analysis of 24 studies pooling 13,847 individuals. Additionally, there was a high degree of heterogeneity across studies for this variable ($I^2$= 93%; **Figure 13**).

Likewise, presence of diabetes mellitus was associated with a 22% increase in the relative risk of renal artery stenosis occurrence and this finding was statistically significant. This finding was based on data derived from 15,306 patients from 25 studies. Furthermore, these results were marked by the moderate degree of heterogeneity ($I^2$= 62%; **Figure 14**).

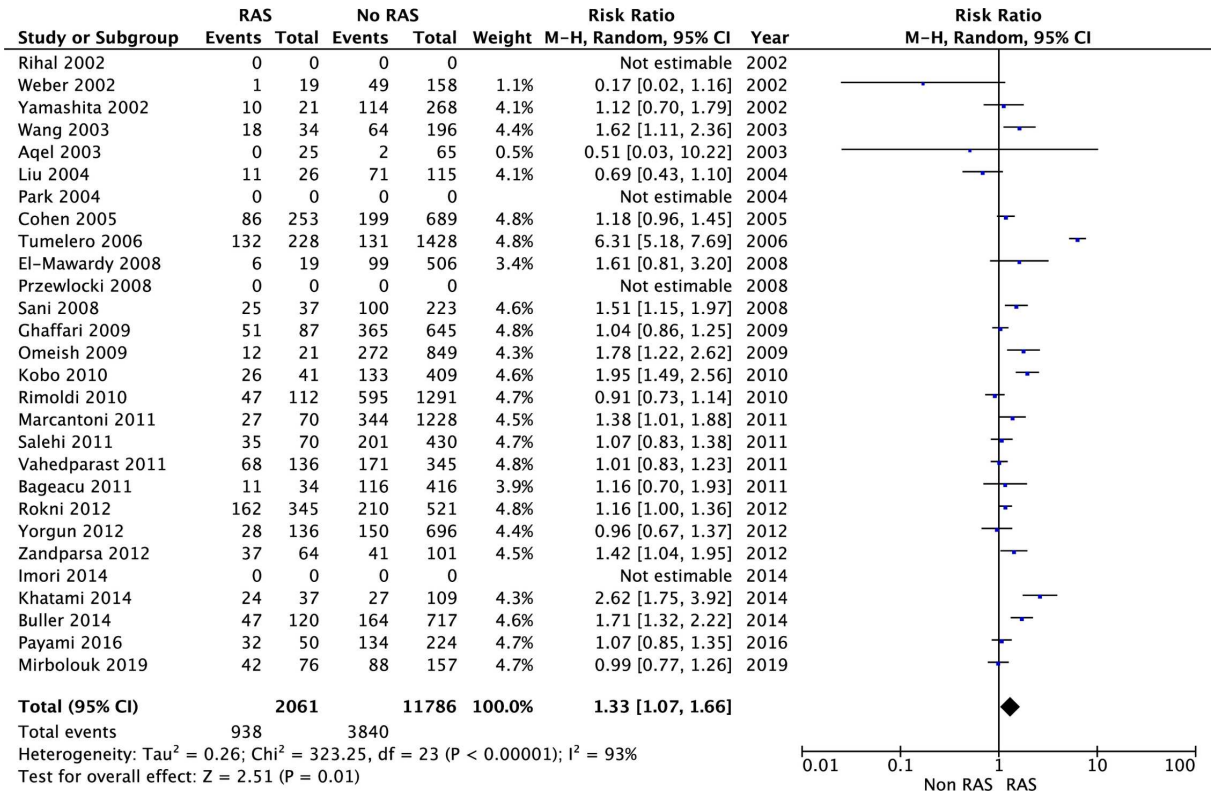


**Figure 13.** Female sex as a variable impacting on the occurrence of RAS

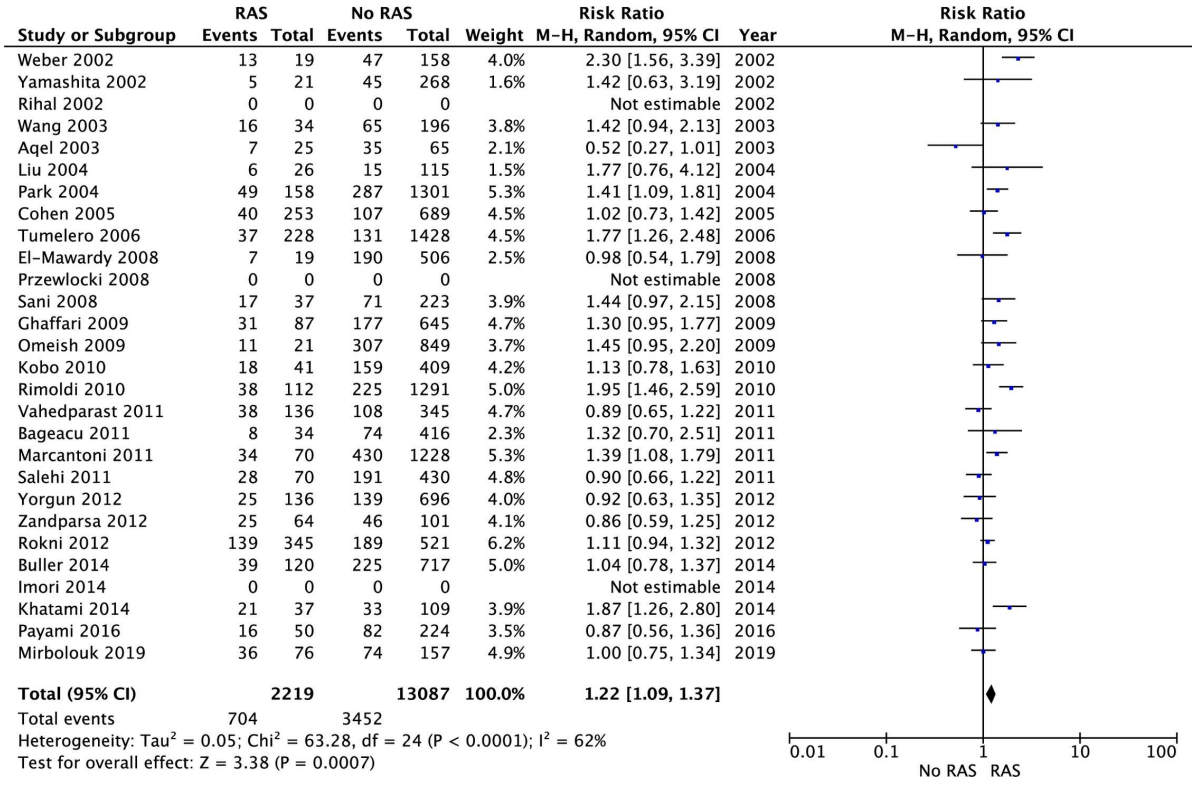


**Figure 14.** Diabetes mellitus as a variable impacting on the occurrence of RAS

Presence of systemic arterial hypertension was significantly associated with a 33% relative risk increase of renal artery stenosis. This finding was based on the analysis of 21 study enrolling 8,116 patients. Included studies were marked by the high degree of heterogeneity ($I^2$=88%; **Figure 15**).

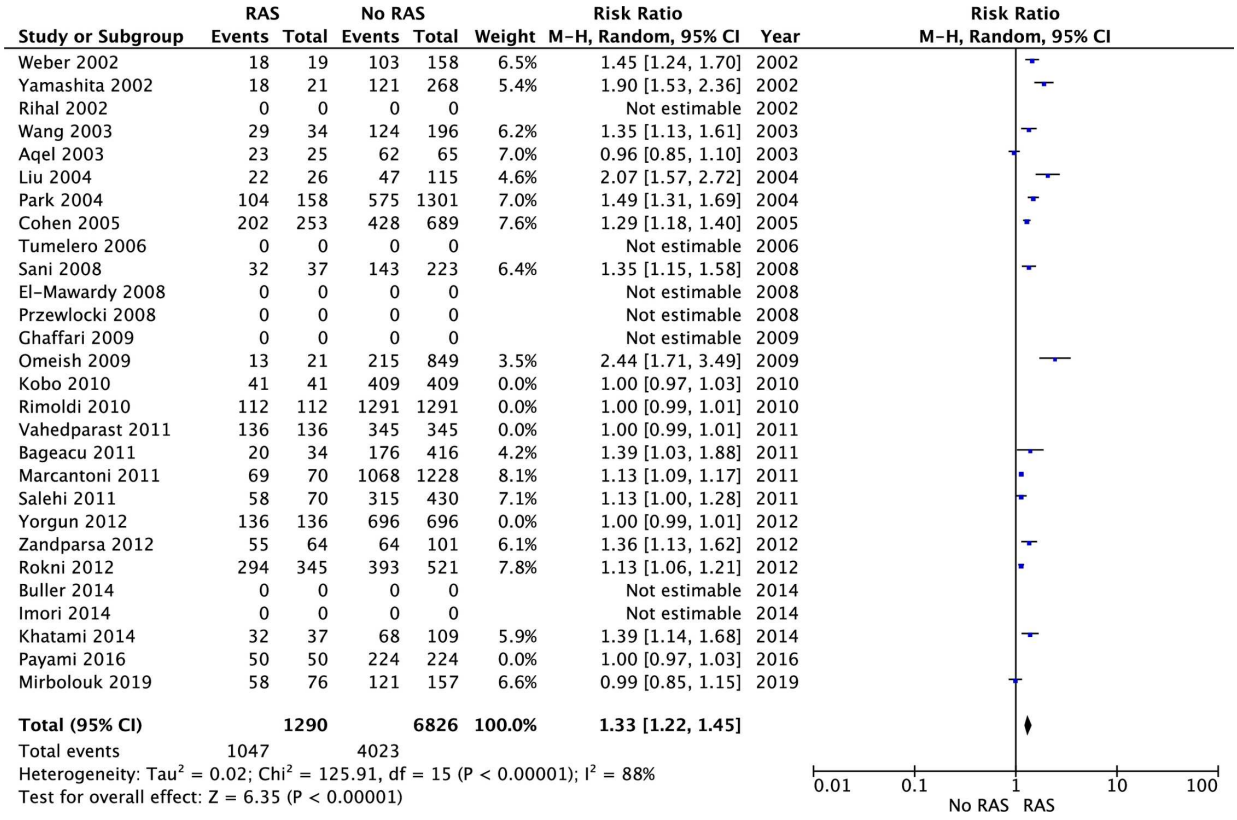


**Figure 15.** Arterial hypertension as a variable impacting on the occurrence of RAS

Dyslipidemia was significantly related with a 12% increase in the relative risk of having renal artery stenosis and this result was based on the analysis of 11,338 patients derived from 21 study. The moderate degree of heterogeneity ($I^2$=59%) was observed for this analysis (**Figure 16**).

Out of all standard modifiable cardiovascular risk factors that were analyzed, current smoking was not found as a significant variable impacting on the occurrence of renal artery stenosis (RR 1,02, 95% CI 0,94-1,12, P=0,590). This finding was based on the analysis of 12,826 patients from 21 study.

A low degree of heterogeneity was established for this analysis ($I^2$=32%; **Figure 17**).

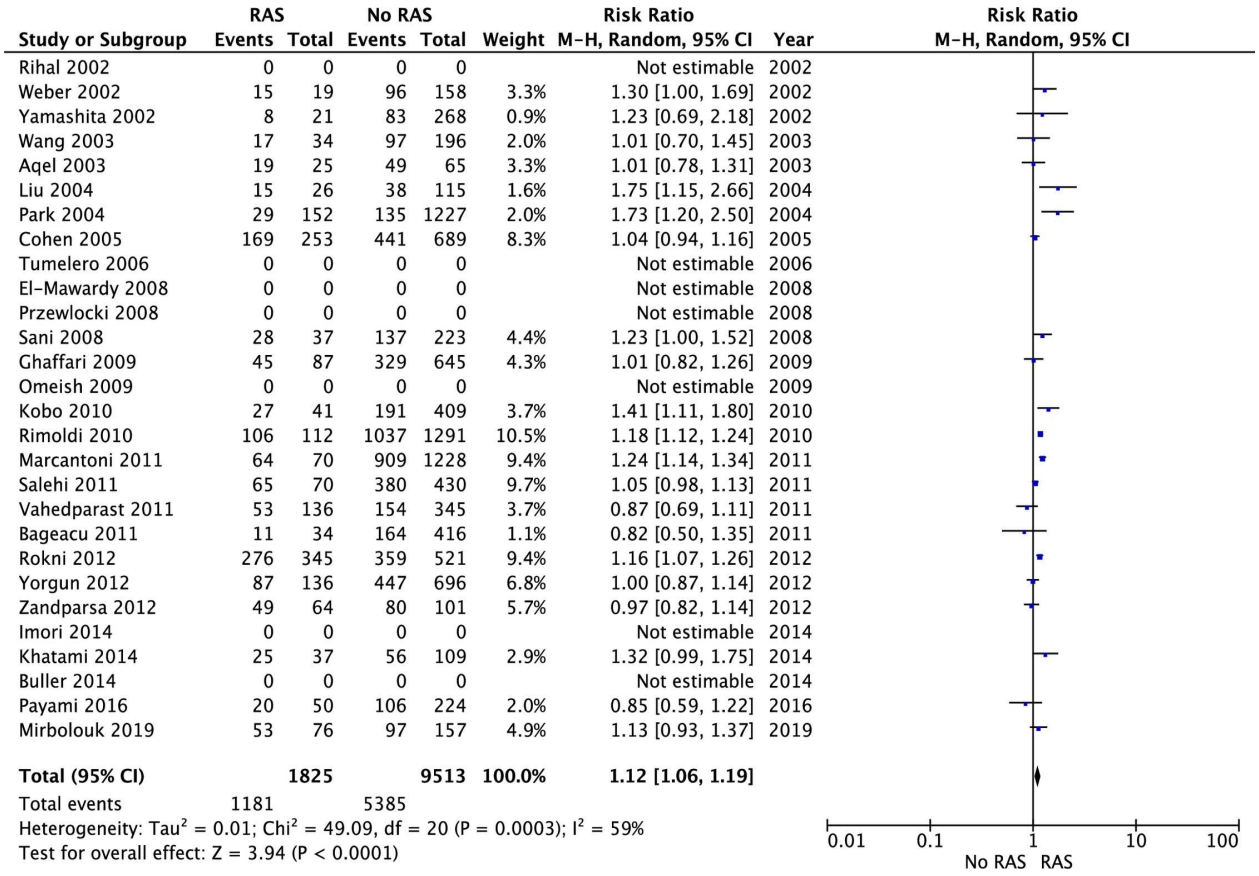


**Figure 16**. Dyslipidemia as a variable impacting on the occurrence of RAS

As shown in **Figure 18**, chronic kidney disease (CKD) was the strongest predictor for renal artery stenosis out of all examined variables. Having CKD was associated with a significant and nearly a 3-fold higher relative risk of RAS occurrence. These findings were based on data obtained from 6,727 patients from 10 studies and were corroborated by the moderate level of heterogeneity ($I^2$=72%).

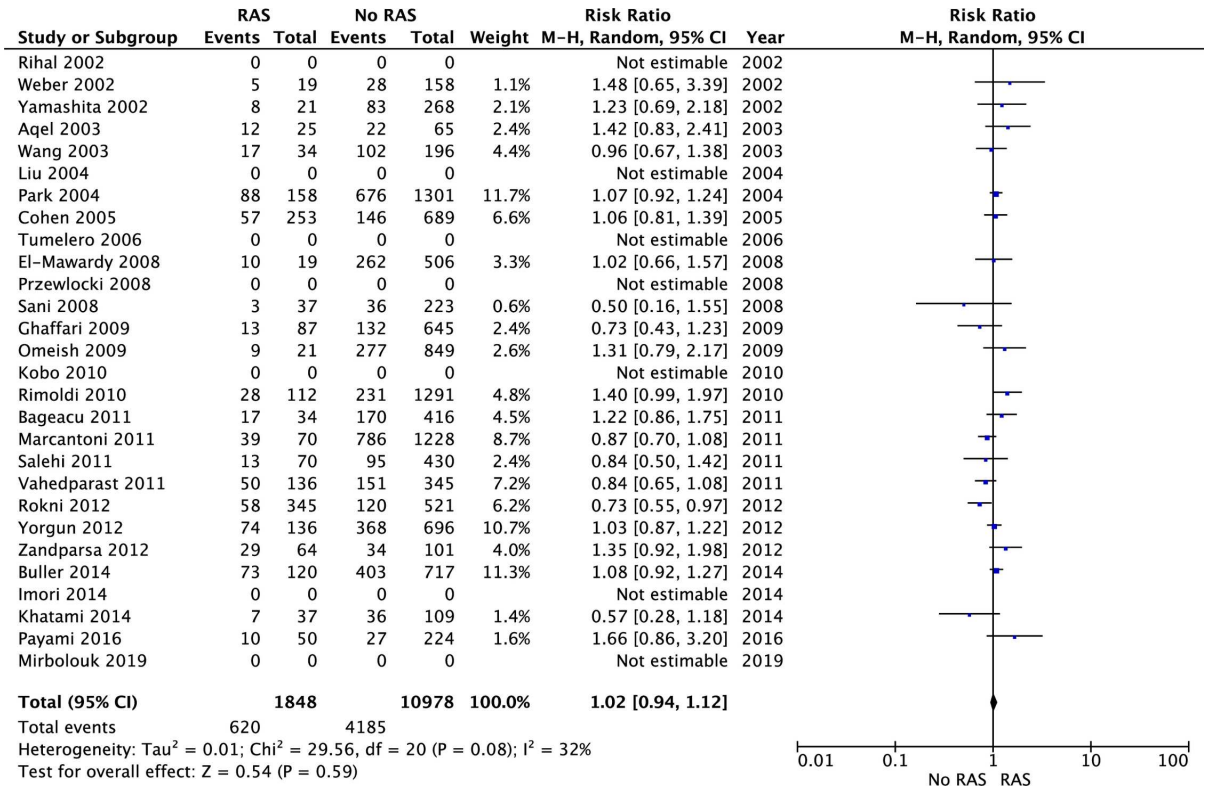


**Figure 17.** Current smoking as a variable with no impact on the occurrence of RAS

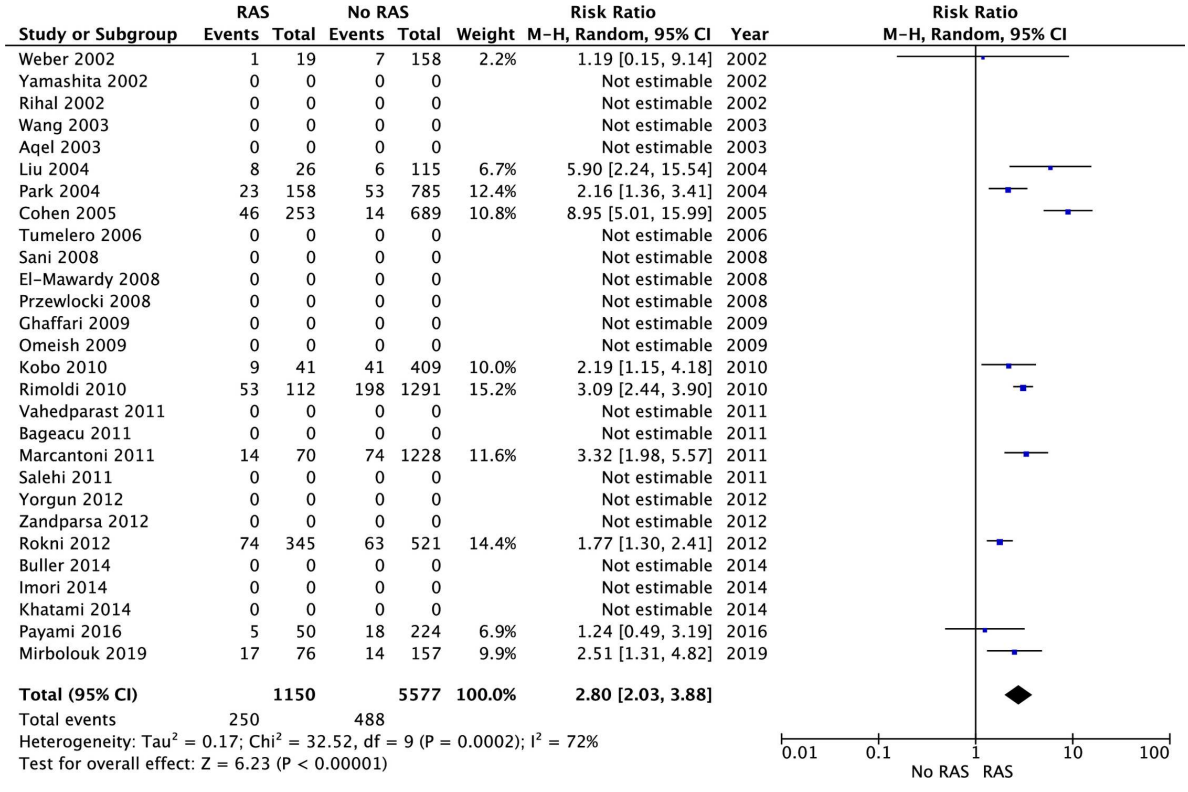


**Figure 18.** CKD as a variable impacting on the occurrence of RAS

A severe coronary artery disease affecting three coronary vessels (3VD), as established by diagnostic angiography, was significantly associated with a 56% relative risk increase of finding concomitant renal artery stenosis (**Figure 19**). This result was based on findings from 15 studies pooling 10,425 patients. This analysis was also marked by the high degree of heterogeneity across available studies ($I^2$=83%).

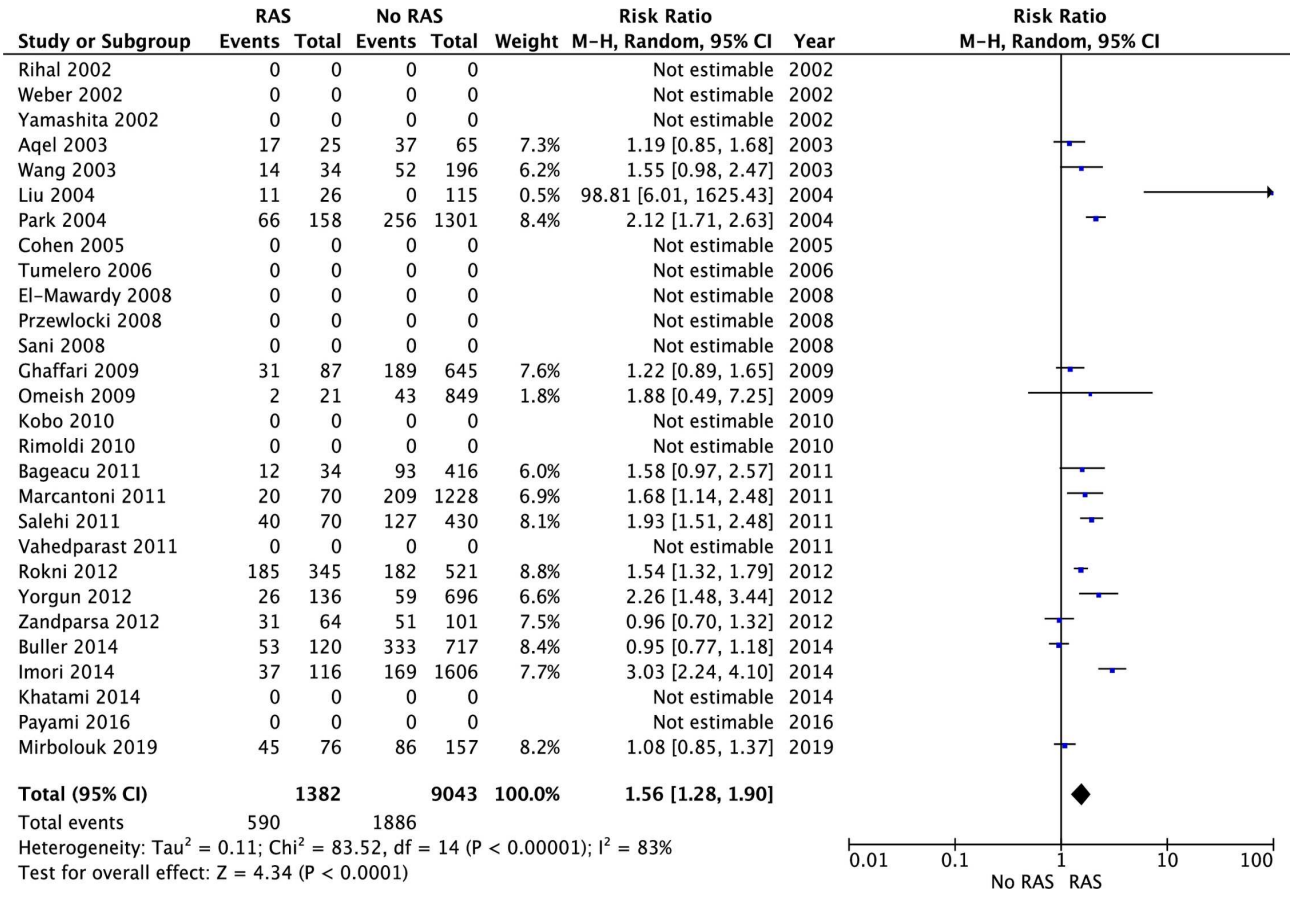


**Figure 19.** The 3VD as a variable impacting on the occurrence of RAS

Similarly, a significant stenosis involving left main coronary artery was associated with a significant 86% higher relative risk of renal artery stenosis occurrence during diagnostic cardiac catheterization (**Figure 20**). This result was based on data from 8,644 patients enrolled in 9 studies.

A moderate degree of heterogeneity across studies was detected for this endpoint ($I^2$=56%).

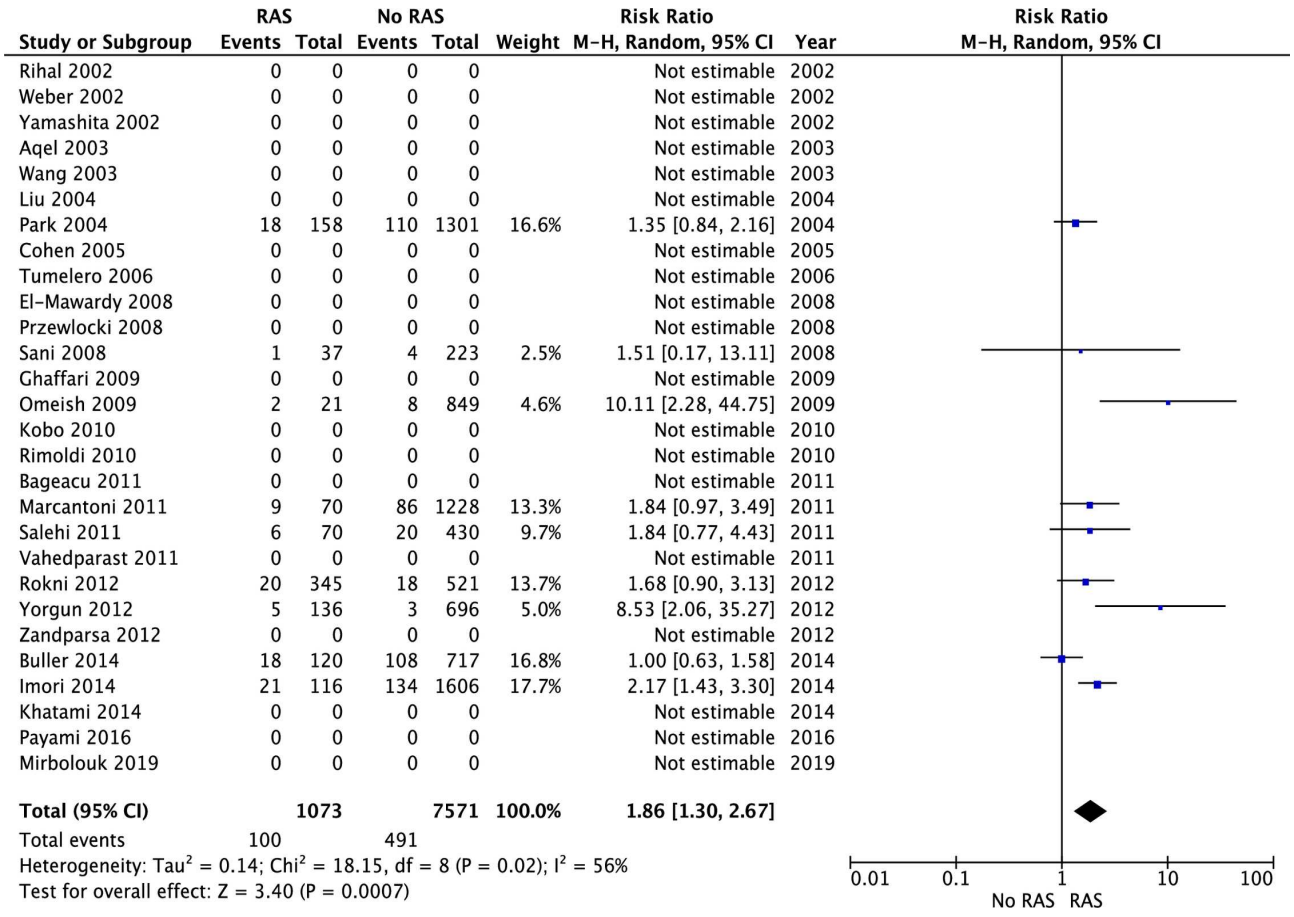


**Figure 20.** Left-main coronary stenosis as a variable impacting on the occurrence of concomitant RAS

Finally, having peripheral artery disease (PAD) was associated with a significant and nearly a 2,5-fold higher risk of renal artery stenosis occurrence during diagnostic coronary angiography (**Figure 21**). This finding was based on the data accruing 8,149 patients from 10 studies and was supported by the moderate degree of heterogeneity across studies ($I^2$=74%).

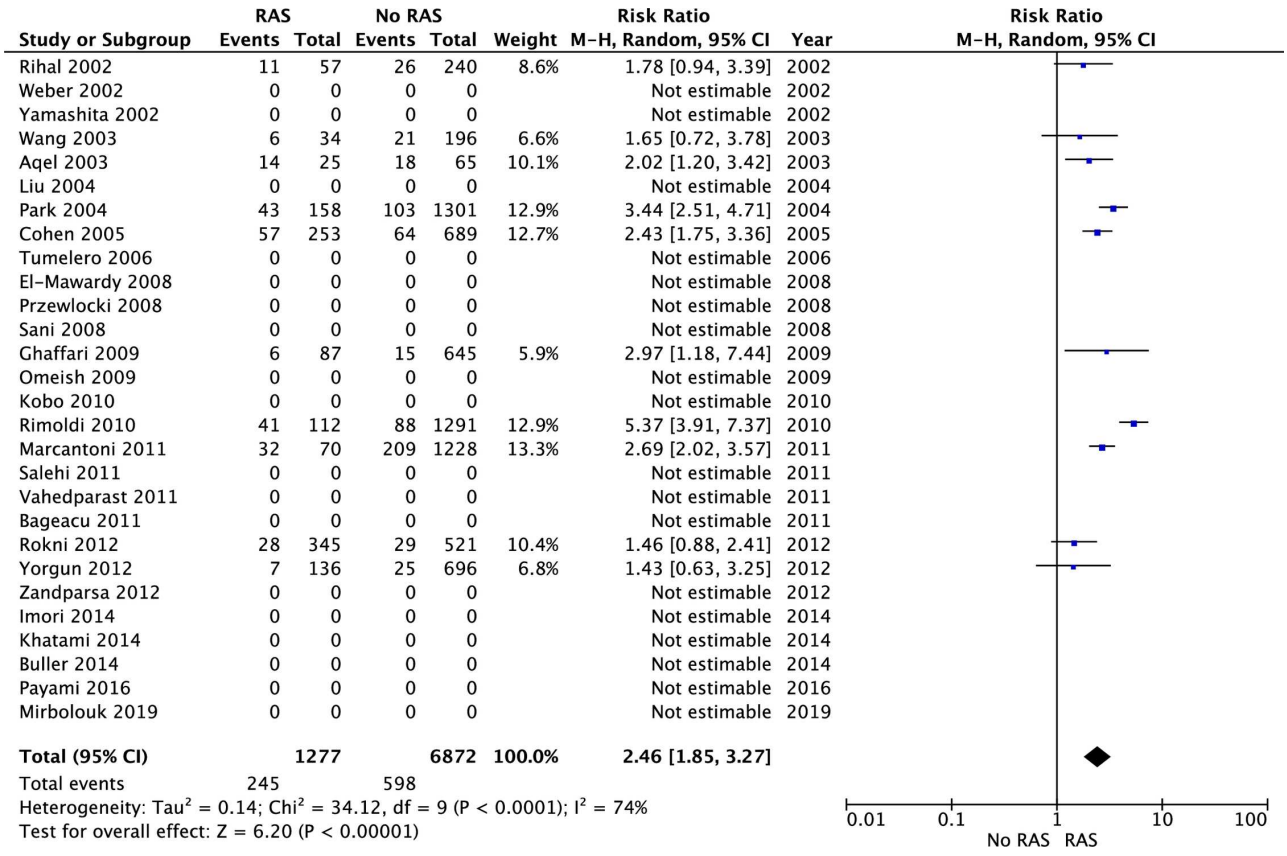


**Figure 21.** Peripheral artery disease as a variable impacting on the occurrence of concomitant RAS

# 5. DISCUSSION

The results of this systematic review and meta-analysis of observational studies demonstrate that approximately 14 out of every 100 patients with stable or suspected CAD undergoing diagnostic catheterization will also have significant RAS. Furthermore, nearly 7 out of every 100 patients will have severe RAS while 4 out of 100 will have significant stenosis in both renal arteries. This study also shows that patients with significant RAS during diagnostic coronary angiography for established or suspected CAD are more likely to be older, women, and are more likely to have diabetes mellitus, chronic renal disease, arterial hypertension, peripheral artery disease and dyslipidemia as all these variables were notably linked to an increased risk of RAS finding during diagnostic cardiac catheterization. Of importance, severe CAD in the form of three-vessel disease and/or left-main disease was associated with a substantially higher likelihood of discovering significant RAS during diagnostic cardiac catheterization. On the other hand, current smoking, as an important standard modifiable risk factor, was not associated with RAS occurrence.

We hold that these findings illustrate that the significant RAS among patients with established or suspected CAD undergoing routine cardiac catheterization might be more present than what is conventionally thought. In examined studies, proportion of significant RAS finding during angiography varied greatly and was in range from 2,4% up to even 39,8%, however, vast majority of studies reported values over 10%. Risk factors and clinical characteristics that we identified as significantly associated with RAS seem to be concordant with other reports available in the literature. For example, Elmorshidy and colleagues showed that patients with arterial hypertension and those who had a positive family history of CAD had a considerably greater prevalence of severe RAS (66). Moreover, Bageacu et al. revealed that significant RAS predictors included female sex, advanced age, and the prevalence of two- and three-vessel coronary artery disease (49).

While the present study was focused on stable CAD (nowadays referred as chronic coronary syndrome – CCS) it is worth noting that similar predictors of RAS are at play in the setting of myocardial infarction (MI). In that sense, Uzu and colleagued demonstrated that arterial hypertension, proteinuria, and renal insufficiency were associated with 3,4-, 13,5-, and 4,8- fold increased risk of RAS in population with MI, respectively. Furthermore, the number of diseased coronary vessels and especially multivessel CAD were significantly linked to an increased incidence of RAS (67). Similarly, a large Chinese study that evaluated diverse population of 1,200 patients undergoing coronary angiography for suspected CAD, CCS, and acute MI found that older age, hypercholesterolemia, >10 years of having arterial hypertension, proteinuria and serum creatinine >133 μmol/L were significant predictors of clinically relevant

RAS (68). Among patients with ST-elevation myocardial infarction (STEMI) it was shown that scores that are routinely used for the estimation of CAD burden such as clinical SYNTAX score were able to yield 85% specificity, 60% sensitivity and 92% negative predictive value for significant RAS (defined as RAS >50%) thus confirming that coronary disease burden might indeed serve as a reliable proxy for renal atherosclerotic disease (69). Arterial hypertension, renal insufficiency and multivessel CAD were the main predictors of RAS in the study of 650 consecutive CAD patients undergoing angiography (70). In a study of 333 consecutive hypertensive patients with CAD undergoing coronary and renal angiography it was also found that besides number of coronary arteries stenosed, carotid intima-media thickness, increased serum creatinine concentrations, decreased body mass index and number of antihypertensive drugs taken were variables independently associated with RAS in the regression model (71).

It is biologically plausible that older age and higher comorbidity burden in general will be associated with more advanced cardiovascular disease and coronary disease burden, and this, in turn, is often associated with higher atherosclerotic burden in other arterial vascular territories, outside coronary arterial bed. It is well substantiated that the severity of atherosclerotic disease in one major arterial bed positively correlates with disease in additional arterial beds. This observation likely holds true for the atherosclerotic RAS as well, as standard modifiable risk factors (SMuRFs) such as cigarette smoking, arterial hypertension, diabetes mellitus, and dyslipidemia are in tight association with polyvascular disease thus sharing the same pathophysiological backbone (72–74). A large systematic review on the prevalence of atherosclerotic RAS in risk groups revealed that RAS has a high prevalence especially in groups with extrarenal atherosclerosis, end-stage renal disease and heart failure (75). Same study showed that the prevalence of RAS among consecutive patients undergoing coronary angiography was 10,5% (95% CI 9,8-11,2%). Taken together, it can be concluded that cardiovascular and clinical characteristics associated with RAS occurrence in our study seem to be in agreement with several reports obtained from the literature.

Our study findings also demonstrated that female sex was found to be connected with a higher risk of significant RAS at the time of diagnostic angiography which is consistent with the previous investigations of Buller et al. and Cohen et al (42, 76). Khatami and colleagues concluded, according to the outcomes of their study, that older females with deteriorating renal function and long-standing hypertension should be carefully evaluated for early detection of the RAS as female sex was, among others, was a strong predictor of RAS presence in their study (63). However, there were also studies showing that there was no clear correlation

between the patient´s gender, or that men were more likely than women to have significant RAS. These findings were reported in Alhaddad et al., and Olliver et al., respectively (70, 77). Many other studies agreed to our findings that age of the patients and the frequency of renal artery stenosis have a strong association, among them the study from Buller et al (76). As a rule of a thumb, as patients' age increases, RAS incidence increases substantially. Majority of the studies that were included in our analysis confirm the notion that older age is a significant risk enhancer for RAS and this has been also validated in many other real-world cohort studies (78,79). On the other hand, a few studies have reported the opposite, showing that the prevalence of RAS was not significantly correlated with the age of the patients (66).

In addition, our findings corroborate that there was a significant link between the risk of RAS and variables such as chronic kidney disease and peripheral artery disease. Respectively, we observed almost a 3-fold and a 2,5-fold increase in risk of having a significant RAS in the presence of CKD and PAD, respectively. Similar findings were reported in the study by Endo et al. in which CKD and PAD complications were significantly more prevalent in patients with RAS (80). Vice-versa, RAS is a common entity in patients with PAD, and its prevalence seems to increase with the increasing severity of PAD (81, 82). Leertouwer and colleagues reported that significant RAS was present in even up to 33% of patients that underwent angiography for PAD thus clearly demonstrating the bi-directional relationship of these entities is strongly present as they largely share common risk factors and atherosclerotic pathophysiology (83).

Another notable finding of our study was that presence of diabetes mellitus and arterial hypertension was connected to a considerably increased risk of RAS in patients undergoing cardiac catheterization. The study from Carmelita et al. provided similar findings for both of these relevant comorbidities (84). Furthermore, Sawicki et al. showed several decades ago that the presence of non-insulin-dependent diabetes mellitus increases the risk of RAS while the risk of bilateral RAS is greater in diabetic *vs.* non-diabetic patients (85). Diabetic patients have a high prevalence of RAS and some studies showed that this proportion might be around 33% (86). The relationship of diabetes mellitus and RAS was recognized by Shapiro and colleagues in 1965, stating that high incidence of renal artery stenosis should be perceived as a phenomenon secondary to systemic arterial hypertension and an increased tendency to atherosclerosis in diabetes mellitus, rather than a primary phenomenon in the development of hypertension (87).

This meta-analysis could have some potential limitations that no grey data was searched and studies in languages other than English were not evaluated meaning that there is a

possibility that some relevant studies might not have been captured and were omitted from the analysis. Secondly, due to studies being conducted over a long-time span and in different regions of the world, there was a certain degree of heterogeneity to be expected. Our formal analysis showed that moderate heterogeneity of included studies was present for most of the examined outcomes while associations of some variables with risk of RAS were based on the data that was highly heterogeneous. On the other hand, all of the included studies reflect real-world practice and data were derived from many international centers thus increasing generalizability and clinical value of our findings. Furthermore, in order to decrease the chance of false findings, we applied more rigorous random-effects statistical model and this algorithm was used for all effect estimates. Finally, our study did not account for renal artery stenosis among individuals with acute coronary syndromes as we only focused on patients undergoing diagnostic cardiac catheterization due to established (stable) CAD or suspected CAD occurring outside of the acute setting.

In conclusion, findings of this thesis show that the proportion of significant RAS is substantial among patients with established or suspected CAD undergoing diagnostic cardiac catheterization. Clinicians should be aware about greater possibility of RAS presence in specific groups of patients such as females of older age, and patients having diabetes mellitus, long-standing arterial hypertension, chronic kidney disease, peripheral artery disease, and dyslipidemia. Finally, patients having these characteristics in addition to severe coronary disease burden detected by angiography might be particularly susceptible to significant atherosclerotic RAS. We also found that smoking did not have significant impact on RAS occurrence. Taken together, these findings might facilitate identification of patients in clinical practice that are likely to have significant RAS and are undergoing diagnostic cardiac catheterization for suspected or established CAD.

# 6. CONCLUSIONS

Based on the systematic review followed by the quantitative and meta-analytic synthesis of obtained data derived from 28 observational cohort studies examining the occurrence of renal artery stenosis (RAS) among patients with stable or suspected CAD undergoing diagnostic coronary catheterization, we can conclude the following:

1. The weighted mean proportion of angiographically significant RAS in analyzed studies was 13,82% meaning that nearly 14 out of 100 patients with stable CAD undergoing diagnostic catheterization will have significant RAS.
2. Weighted mean proportions of angiographically severe and bilateral RAS were 6,5% and 4%, meaning that nearly 7 out of 100 and 4 out of 100 patients with stable CAD undergoing diagnostic catheterization will have severe and bilateral RAS, respectively.
3. Weighted mean proportions of three-vessel disease and left-main disease in analyzed patient sample were 25% and 4,2%, respectively.
4. Patients with RAS were significantly older (+ 4,3 years) than patients without RAS while female sex was significantly associated with a 33% relative risk increase in the RAS occurrence.
5. The presence of chronic kidney disease, peripheral artery disease, arterial hypertension, diabetes mellitus, and dyslipidemia were all significantly associated with an increased relative risk of RAS finding during a diagnostic catheterization.
6. Current smoking was not found as a variable with a significant impact concerning the risk of significant RAS.
7. Angiographic presence of three-vessel coronary disease was associated with a 56% higher relative risk of RAS and this was even more pronounced for the left-main coronary disease which was associated with an 86% higher risk of RAS finding during diagnostic catheterization.

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# 8. SUMMARY

**Objectives:** The aims of this study were to determine the incidence of renal artery stenosis (RAS) in patients undergoing diagnostic coronary angiography for stable coronary artery disease (CAD) or suspected coronary artery disease. Additionally, to investigate the influence of risk factors and certain clinical characteristics on the risk of finding significant RAS during diagnostic coronary angiography.

**Patients and methods:** Systematic review and quantitative meta-analysis included a total of 28 observational cohort studies that were primarily designed to determine the prevalence and risk factors for RAS in patients with coronary artery disease. The main outcomes of interest were the mean incidence of significant, severe, and bilateral RAS in the previously described population, statistically adjusted for individual study size. The second objective was to investigate the potential association of established cardiovascular risk factors, comorbidities, and angiographic parameters of the severity of coronary disease with the frequency of RAS. Relative risk (RR) with 95% confidence interval (95% CI) was used as the main outcome measure, and a random effect model and the Mantel-Haenszel statistical algorithm were used for meta-analysis.

**Results:** The average frequency of RAS in the mentioned population was 13,82% (95% CI 10,69-17,27%), 6,46% (95% CI 4,36-8,95%) and 4,03% (95% CI 2,58-5,78%) for significant, severe and bilateral RAS. Chronic kidney disease was associated with almost 3-fold higher relative risk for RAS (RR 2,80, 95% CI 2,03-3,38), followed by peripheral artery disease (RR 2,46, 95% CI 1,85-3,27), left-main artery disease (RR 1,86, 95% CI 1,30-2,67) and three-vessel disease (RR 1,56, 95% CI 1,28-1,90). Of the classic risk factors for cardiovascular disease, arterial hypertension (RR 1,33, 95% CI 1,22-1,45), diabetes (RR 1,22, 95% CI 1,09-1,37) and dyslipidemia (RR 1,12, 95% CI 1,06-1,19) were significant associated with a higher relative risk for significant RAS. Smoking was not significantly associated with a higher risk of RAS (RR 1,02, 95% CI 0,94-1,12). Female gender was associated with a 33% higher relative risk for RAS compared to the male gender (RR 1,33, 95% CI 1,07-1,66). Finally, patients with RAS were significantly older that those without RAS (+4,6 years of age, 95% CI 3,50-5,02).

**Conclusion:** This study showed that significant RAS is present in nearly 14 out of 100 patients undergoing routine cardiac catheterization for coronary artery disease. Variables that were significantly associated with a higher risk of finding RAS were older age, female sex, chronic kidney disease, peripheral artery disease, diabetes mellitus, arterial hypertension, and dyslipidemia. Of the angiographic variables, RAS was found to be significantly more frequent in patients with left-main disease and three-vessel disease.

# 9. CROATIAN SUMMARY

**Naslov rada: Učestalost i kliničke karakteristike stenoze bubrežnih arterija u bolesnika sa koronarnom bolesti koji se podvrgavaju kateterizaciji srca**

**Ciljevi:** Glavni ciljevi ove studije su bili utvrditi učestalost stenoze bubrežnih arterija (SBA) u bolesnika koji se podvrgavaju dijagnostičkoj koronarnoj angiografiji zbog stabilne koronarne bolesti (kroničnog koronarnog sindroma) ili sumnje na koronarnu bolest. Također je cilj bio istražiti utjecaj čimbenika rizika i određenih kliničkih karakteristika na rizik pronalaska značajne SBA za vrijeme dijagnostičke koronarografije.

**Pacijenti i metode:** Sustavni pregled i kvantitativna meta-analiza su uključile ukupno 28 opservacijskih presječnih istraživanja koja su bila primarno osmišljena s ciljem utvrđivanja prevalencije i rizičnih faktora za nastanak SBA u bolesnika s koronarnom bolesti. Glavni ishodi od interesa su bili srednja učestalost značajne, teške i bilateralne SBA u prethodno opisanoj populaciji, statistički prilagođeno za veličinu pojedinačnih studija. Drugi cilj je bio istražiti potencijalnu povezanost etabliranih kardiovaskularnih čimbenika rizika, komorbiditeta te angiografskih parametara težine koronarne bolesti sa učestalosti SBA. Relativni rizik (RR) sa 95%-tnim intervalima pouzdanosti (95% CI) je korišten kao glavna mjera ishoda, a model s nasumičnim učinicima i Mantel-Haenszel statističkim algoritmom je korišten za meta-analizu.

**Rezultati:** Prosječna učestalost SBA u navedenoj populaciji iznosila je 13,82% (95% CI 10,69-17,27%), 6,46% (95% CI 4,36-8,95%) te 4,03% (95% CI 2,58-5,78%) za značajnu, tešku i bilateralnu SBA. Kronična bubrežna bolest je bila povezana sa gotovo 3-puta većim relativnim rizikom za SBA (RR 2,80, 95% CI 2,03-3,38), nakon čega je slijedila periferna arterijska bolest (RR 2,46, 95% CI 1,85-3,27), stenoza debla lijeve koronarne arterije (RR 1,86, 95% CI 1,30-2,67) te trožilna koronarna bolest (RR 1,56, 95% CI 1,28-1,90). Od klasičnih čimbenika rizika za kardiovaskularnu bolest, arterijska hipertenzija (RR 1,33, 95% CI 1,22-1,45), šećerna bolest (RR 1,22, 95% CI 1,09-1,37) i dislipidemija (RR 1,12, 95% CI 1,06-1,19) bili su značajno povezani sa većim relativnim rizikom za značajnu SBA. Pušenje nije bilo značajno povezano sa većim rizikom za SBA (RR 1,02, 95% CI 0,94-1,12). Ženski spol je bio povezan sa 33% višim relativnim rizikom za SBA u odnosu na muški spol (RR 1,33, 95% CI 1,07-1,66). Konačno, bolesnici sa SBA su bili značajno stariji od onih kojima nije pronađena SBA (+4,6 godina starosti, 95% CI 3,50-5,02).

**Zaključci:** Ovo istraživanje je pokazalo da je značajna SBA prisutna u gotovo 14 od 100 bolesnika koji se podvrgavaju rutinskoj kateterizaciji srca zbog koronarne bolesti. Varijable koje su bile značajno povezane sa većim rizikom za pronalazak SBA bile su starija životna dob, ženski spol, kronična bubrežna bolest, periferna arterijska bolest, šećerna bolest, arterijska

hipertenzija te dislipidemija. Od angiografskih varijabli pronađeno je da je SBA značajno učestalija u bolesnika sa stenozom debla i trožilnom koronarnom bolesti.

# 10. CURRICULUM VITAE

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