# The prevalence of atherosclerosis in a population of Croatian islands - the use of the ankle-brachial pressure index (ABPI)

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**Ferdinand Schulenburg**

**THE PREVALENCE OF ATHEROSCLEROSIS IN A POPULATION OF CROATIAN ISLANDS – THE USE OF THE ANKLE-BRACHIAL PRESSURE INDEX (ABPI)**

**Diploma Thesis**

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**Abbreviations**

ABPI - Ankle-Brachial Pressure Index
A1C - Hemoglobin A1c
BMI - Body Mass Index
CVD - Cardiovascular Disease
HDL - High-Density Lipoprotein
IDL - Intermediate-Density Lipoprotein
LDL - Low-Density Lipoprotein
OGTT - Oral Glucose Tolerance Test
PAD - Peripheral Artery Disease
PAR - Population-Attributable Risk
VLDL- Very Low-Density Lipoprotein
WHO- World Health Organization

# 1. INTRODUCTION

## 1.1. Cardiovascular Diseases

### 1.1.1  Definition

Cardiovascular disease (CVD) refers to all conditions that affect the heart and vasculature, the organs responsible for the movement and transportation of blood, respectively (1). CVD is primarily caused by the progression of atherosclerosis, leading to numerous problems, for example, coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) and aortic atherosclerosis. As an acute event, these diseases present as myocardial infarctions, strokes and claudication (2). In the European Region, CVD is the leading cause of death (3). According to the American Heart Association, cardiovascular disease is projected to cause a substantial economic burden, with medical expenses and productivity losses estimated to escalate from $555 billion in 2015 to $1.1 trillion by 2035 (4).

### 1.1.2  Atherosclerosis

Atherosclerosis is the underlying mechanism that leads to CVD. Initially, endothelial activation leads to a series of events that in the end lead to the formation of plaques.  These plaques cause CVD by narrowing the lumen and or by rupturing (5).

Endothelial dysfunction serves as a key initiating event in atherosclerosis. Under the influence of risk factors that trigger an inflammatory response, such as hypertension, dyslipidemia, and smoking, the endothelial lining of blood vessels undergoes structural and functional changes. Once the endothelial barrier is damaged, cells and particles can enter and deposit into the matrix of the tunica intima. Due to these changes, low-density lipoprotein (LDL) infiltrates the intima. While in the intima, LDL particles get oxidized, which is enhanced by the lack of protective plasma antioxidants (5). The oxidation of LDL particles has a key influence on the inflammatory process that leads to the formation of atherosclerotic plaques (6). Under the influence of these inflammatory mediators, the vessel undergoes morphological changes, such as changes in vascular tone and permeability. The prolonged influence of certain proinflammatory agents, such as Interleukin 1(IL-1), tissue necrosis factor (TNF), endotoxins, and advanced glycosylation end products (AGEs) can lead to permanent phenotypic changes described as endothelial type II activation (5). Activated endothelial walls trigger the uptake of monocytes, which then differentiate into macrophages (5). Macrophages pick up LDLs by their scavenger receptors which turns them into cholesterol-laden foam cells (7). These cholesterol-loaded macrophages are a characteristic finding of early atherogenesis and are present under

the microscope as fatty streaks (8). Despite CVD being a disease mostly affecting adults and the older population, fatty streaks begin to form from childhood on. Regardless of gender, race, or nationality, the majority of people between the ages of 20 and 29 have some degree of coronary fatty streaking. According to one study, the majority of teenagers between the ages of 10 and 14 have microscopic equivalents of fatty streaks in their left anterior descending coronary arteries (9).

Fatty streaks have the potential to evolve into plaques, which can subsequently become symptomatic and contribute to the development of cardiovascular disease. Plaque formation starts with the release of proliferation factors, such as platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β), which lead to the build-up of extracellular matrix. Migrating vascular smooth muscle cells (VSMC) and the extracellular matrix create a fibrous cap that covers the necrotic, lipid-loaded core. A necrotic core covered by a fibrous cap is an essential sign of advanced atherosclerosis (5). The fibrous cap acts as a barrier keeping the thrombogenic material of the core inside. Therefore, a weak and thin cap combined with a large necrotic core is more susceptible to rupturing. Stable plaques on the other hand are considered to have a thick fibrous layer that covers small lipid collection in the core (5) Once a plaque ruptures, a thrombus is formed by the aggregation of platelets and the activation of the coagulation cascade. In the end, the protein fibrin and platelets create a solid web that sticks to the ruptured area. Clinically, in the example of a coronary vessel, this can further narrow the artery leading to symptoms of angina, or to a complete closure presenting as myocardial infarction (5). Figure 1 describes and summarizes the process of atherogenesis.
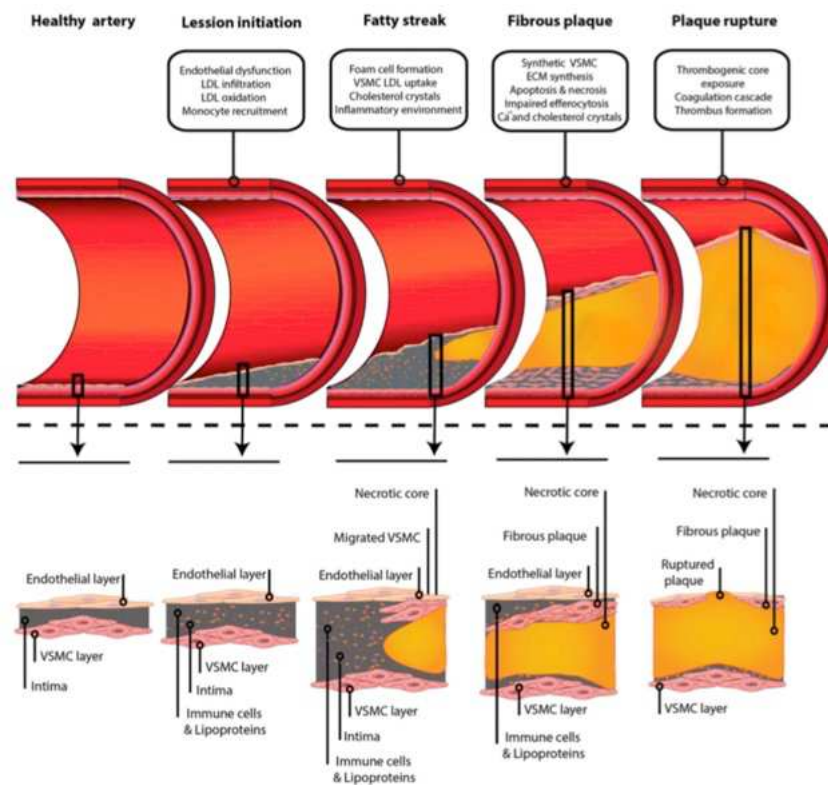
**Figure 1:** Diagram illustrating the development of atheroma plaque from a healthy artery to plaque rupture, highlighting the key events in each stage

**Source:** Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of Atherosclerosis. International Journal of Molecular Sciences 2022, Vol 23, Page 3346. 2022 Mar 20;23(6):3346.

### 1.1.3 Risk Factors

Numerous landmark studies have significantly contributed to our understanding of cardiovascular disease risk factors, including the Framingham Heart Study, the INTERHEART and the INTERSTROKE study. The Framingham Heart Study, initiated in 1948, paved the way for our current understanding of cardiovascular disease risk factors by identifying key factors such as high blood pressure, high cholesterol, smoking, and obesity (10)(11). Subsequent studies like the INTERHEART study and INTERSTROKE further expanded our knowledge by investigating the impact of lifestyle factors, genetic predisposition, and other novel risk markers on cardiovascular health. The INTERHEART study, which involved over 30,000 participants from 52 different countries, discovered several similar risk factors linked to a higher risk of myocardial infarction. In combination, nine risk factors accounted for 90% of all population-attributable risks (PAR) in men and 94% in women for getting a first myocardial infarction: smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits and vegetables, regular alcohol consumption, and physical

inactivity. These findings were consistent across different regions and age groups, highlighting the global impact of these risk factors (12). Figures 2 and 3 show the population-attributable risk and odds ratio according to the INTERHEART and INTERSTROKE study(11).



**Figure 2**: Summarized odds ratios for cardiovascular risk factors from the INTERHEART14 and INTERSTROKE15 studies.

**Source:** Teo KK, Rafiq T. Cardiovascular Risk Factors and Prevention: A Perspective From Developing Countries. Canadian Journal of Cardiology. 2021 May 1;37(5):733–43.
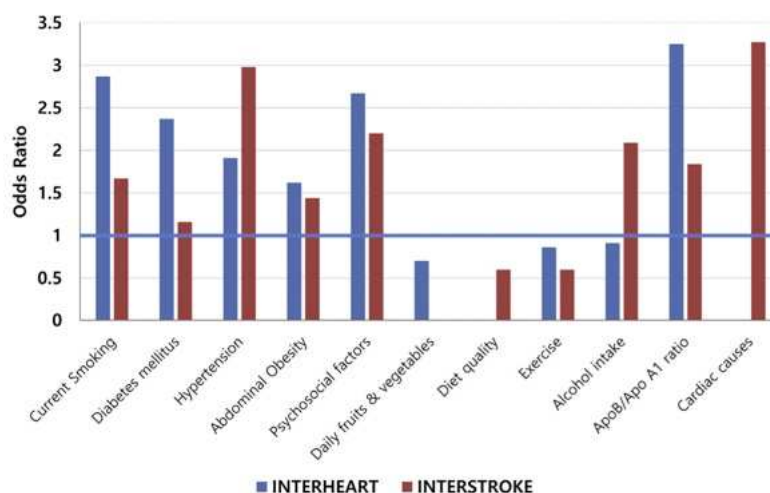


**Figure 3**: Population attributable risk factor for cardiovascular risk factors from the INTERHEART14 and INTERSTROKE15 studies.

**Source:** Teo KK, Rafiq T. Cardiovascular Risk Factors and Prevention: A Perspective From Developing Countries. Canadian Journal of Cardiology. 2021 May 1;37(5):733–43.
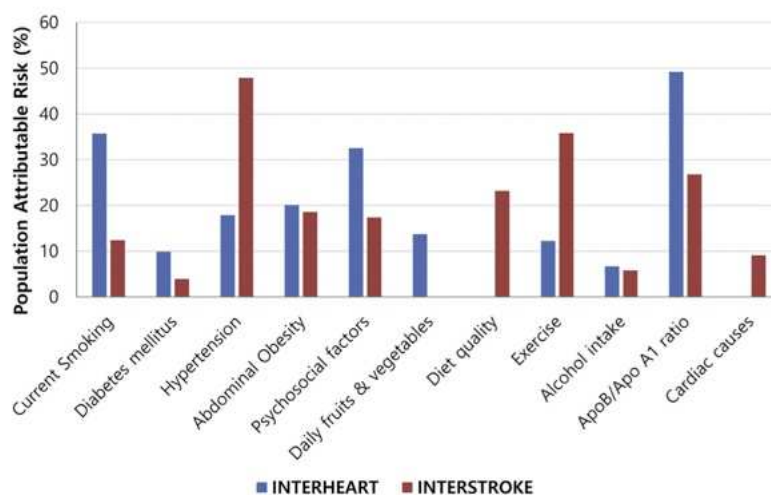
In general, risk factors can be divided into two groups, modifiable risk factors that can be controlled by lifestyle modifications, and non-modifiable risk factors which can not be influenced by the individual but still contribute to the overall risk. The group of non-modifiable risk factors consists of age, gender and hereditary factors. On the other hand smoking, hypertension, elevated cholesterol, reduced high-density lipoprotein cholesterol, and diabetes can be targeted by lifestyle modifications and medication (13).

In 1960, the Framingham Study made a significant milestone by discovering that smoking is a risk factor for cardiovascular disease (14). Today tobacco usage is still one of the main reasons for avoidable deaths worldwide. The use of tobacco products raises the risk of heart disease, cancer, chronic respiratory diseases, diabetes, and early mortality. According to the World Health Organization (WHO) status report of noncommunicable diseases in 2014, 7 % of female deaths worldwide and 12 % of male deaths are related to tobacco usage. By 2030, the deaths are expected to rise to 8 million yearly, leading to 10 % of all estimated deaths that year (15). In the INTERHEART study, mentioned above and in Figure 3, smoking accounts for 35,7 % of the total population attributable risk (PAR) of myocardial infarction (12). In the context of CVD, smoking increases atherogenesis, the underlying mechanism leading to CVD, as described in 1.2.2. It affects multiple steps in the generation of plaque formation, such as the availability of nitric oxide (NO) and free radical-mediated oxidative stress. Further, the consumption of tobacco alters prothrombic and inflammatory mediators, which are fundamental influencing factors of CVD (16).

Merely a year later, in 1961, another crucial revelation emerged from the Framingham Study, identifying hypertension as an additional significant risk factor for cardiovascular disease (14). According to the WHO status report of noncommunicable diseases in 2014, hypertension is anticipated to have contributed 7 % to the burden of disease and accounted for a total of 9.4 million deaths in 2010 (15). Stroke, myocardial infarction, heart failure, dementia, kidney failure, and visual impairment can be caused by elevated blood pressure. In randomized trials, a 10 mmHg drop in systolic blood pressure was linked to a 22% drop in coronary heart disease and a 41% drop in stroke (15,17). In the INTERHEART study hypertension accounts for 17,9 % of the total PAR of myocardial infarction, as shown in Figure 3 (12). Notably, the PAR of hypertension as a risk factor for stroke was found to be 34,6 % in the INTERSTROKE study. Therefore hypertension is one of the leading risk factors for developing stroke (18). According to the American Heart Association, hypertension is present if a patient's systolic

blood pressure is ≥140 Hg or diastolic blood pressure ≥90 Hg (19). The key reason for hypertension causing atherosclerosis is the induced growth of vascular smooth muscle cells and the resulting thickening of the arterial wall. The proliferation of smooth muscle cells causes the lumen to narrow and increases the distance needed for oxygen to diffuse from the lumen into the vessel, resulting in a lack of oxygen that causes further damage (20).

Another important risk factor is diabetes mellitus. The WHO status report stated that diabetes caused 89 million disease-adjusted life years (DALYs) and 1.5 million deaths directly in 2012. In 2014, 9% of people worldwide were expected to have diabetes(15). Diabetes complications can be microvascular or macrovascular in nature. Cardiovascular disease, stroke, and peripheral vascular disease are examples of macrovascular consequences. Damage to the nerve system (neuropathy), the kidneys (nephropathy), and the eyes (retinopathy) are all examples of microvascular consequences (21). Diabetes can be categorized into four groups: type 1 diabetes, type 2 diabetes, specific types of diabetes due to other causes, and gestational diabetes mellitus. Out of the four classification types, type 1 accounts for 5-10% and type 2 for 90-95% of diabetes cases. Type 2 diabetes is primarily brought on by a combination of insulin resistance and exhaustion of insulin production by the pancreas. Type 1 on the other hand is primarily brought on by an autoimmune response in which the immune system attacks and destroys the insulin-producing cells in the pancreas. Due to the autoimmune character, diabetes type 1 tends to present with a complete lack of insulin, often leading to a sudden onset of its clinical picture, including polyuria, polydipsia and diabetic ketoacidosis. Further, type 1 is characterized by a low body mass index (BMI), unintentional weight loss, and glucose >360 mg/dL (20 mmol/L). In contrast, type two usually presents later in life and is strongly associated with lifestyle factors such as poor diet, sedentary behavior, and obesity (22). According to the American Diabetes Association, the diagnosis of Diabetes is clear if one or more of the following criteria are fulfilled: fasting plasma glucose(FPG) ≥126mg/dl (7.0 mmol/L), plasma glucose≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT), hemoglobin A1C ≥6.5% (48 mmol/mol), symptoms of hyperglycemia or hyperglycemic crisis(22). Diabetes causes atherosclerosis through multiple mechanisms. Dyslipidemia, hyperglycemia with advanced glycation end-products (AGE) formation, increased oxidative stress, and inflammation are a few of the known pathophysiological pathways linking diabetes with atherosclerosis (23)

The 2014 status report of the WHO reported that 38 % of adult men and 40 % of adult women in 2014 were overweight. Between 1980 and 2014, the prevalence of obesity roughly doubled globally. Worldwide, 11 % of men and 15 % of women were obese in 2014. Therefore, more than 500 million persons globally are considered obese. The prevalence of a BMI that is considered to be high rises as a country's income level rises. More than twice as many people in high- and upper-middle-income countries are obese compared to low-income countries (15). Class 1 obesity is defined by a BMI of 30 kg/m2 to 34.9 kg/m$^2$, class 2 obesity is defined by a BMI of 35 kg/m to 39.9 kg/m$^2$, and class 3 obesity is defined by a BMI of at least 40 kg/m$^2$. A normal BMI ranges between 18.5 to 24.9 kg/m$^2$ (24). In the INTERHEART study, mentioned above and in Figure 3, abdominal obesity accounts for 20.1% of the total PAR of myocardial infarction (12). Yet for obesity, it is important to mention that it is itself a risk factor for other CVD-causing diseases such as hypertension, insulin resistance and dyslipidemia. Since all these risk factors are of metabolic origin and tend to occur in clusters rather than being independent of each other, they are often described together as metabolic Syndrome. One of the biggest risk factors for developing metabolic syndrome is a sedentary lifestyle and an unhealthy diet. Yet this highlights the importance of lifestyle changes since multiple CVD risk factors can be prevented at once(25). This conclusion can be further supported by looking at Figure 3. It is clear that a lack of physical activity and an unhealthy diet contribute to the population-attributable risk (12).

In conclusion, numerous studies have demonstrated that many risk factors for cardiovascular disease are modifiable and therefore may be prevented. Lifestyle choices, including diet, physical activity, and smoking cessation, play a central role in influencing these risk factors and can significantly impact an individual's cardiovascular health.

### 1.1.4 Diagnosis

The complex topic of calculating cardiovascular risk and evaluating individual risk variables will be covered in the following chapter. Understanding how to evaluate cardiovascular risk is essential for effective prevention and management strategies. We will discuss how the overall cardiovascular risk can be assessed using different scores and prediction models, and how each risk factor can be diagnosed. Assessing cardiovascular disease risk is crucial for early detection and effective management of cardiovascular conditions, ultimately improving patient outcomes and reducing the burden of heart disease

Risk scores and assessment tools can be used to calculate an individual´s risk of developing cardiovascular disease. These tools combine various risk factors, such as age, gender, blood pressure, cholesterol levels, and smoking status, to generate a numerical score or risk category. The 10-year risk of cardiovascular events can be calculated using a number of risk prediction methods, including SCORE, Pooled Cohort Equations, Framingham Risk Score, and others. Furthermore, blood biomarkers, genetics, and imaging markers contribute valuable information for accurate risk prediction. Out of the mentioned scores, the Pooled Cohort Equations Calculator stands out as it is now one of the most up-to-date and widely used risk equation model. It calculates the 10-year risk of a first cardiovascular incident and was initially incorporated in the 2013 American College of Cardiology and American Heart Association guidelines. It has its advantage in incorporating information from different cohorts including both White and African American populations and therefore broadens its relevance to people of different racial and cultural backgrounds. In comparison, other risk calculators such as the QRISK3 Score are designed for the English population or the SCORE model for Europe (26).

For the correct treatment of individual risk factors, a correct diagnosis must be established first. In general, CVD risk factors can be assessed by physical examination, blood values and hemodynamic measurement. Physical examinations for cardiovascular disease include a variety of assessments, including measuring blood pressure, listening to heart sounds, palpating peripheral pulses, measurement of ankle brachial pressure Index (ABPI), an inspection of the jugular venous pulse, examining the lower extremities, evaluating edema, calculating body mass index, and examination of carotid arteries. Blood tests can provide valuable information for assessing cardiovascular disease risk factors by measuring various parameters such as lipid profile, fasting blood glucose, C-reactive protein (CRP) levels, renal function markers and cardiac biomarkers. Hemodynamic measurements encompass various techniques, such as arterial blood pressure monitoring, echocardiography, cardiac catheterization, pulse wave velocity measurement and plethysmography.

As described in 1.2.3, hypertension is a major risk factor for CVD. Hypertension is present if a patient's systolic blood pressure is ≥140 Hg or diastolic blood pressure ≥90 Hg. The diagnosis should, wherever possible, not be made during a single office visit. To confirm the diagnosis of hypertension, typically 2-3 office visits at 1-4-week intervals are needed. If the blood pressure is above 180/110 mm Hg and signs of CVD are present, the diagnosis may be made in a single visit. It is important to use both office blood measurements and out-of-office

measurements to rule out patients with white-coat hypertension, which is a non-permanent elevation of blood pressure. White coat hypertension affects 10% to 30% of patients visiting clinics because of elevated blood pressure. High blood pressure, can be categorized into two main types, primary hypertension, which has no identifiable cause, and secondary hypertension, which is caused by an underlying medical condition such as renal parenchymal disease, renovascular hypertension, primary aldosteronism, chronic sleep apnea or certain medications. In 5-10% of patients, a secondary cause can be identified. Secondary causes should be considered in patients with early-onset hypertension, lack of other risk factors, hypertension resistant to treatment, family history and hypertensive emergencies (19). To accurately measure the blood pressure, the patient should be placed in a sitting position for at least five minutes with the arm supported at the level of the heart. Then the cuff should be filled to a pressure that is approximately 30 mmHg higher compared to the systolic pressure. Next, the pressure is slowly released under palpitation of the pulse on the radial artery or under auscultation of the brachial artery. The systolic pressure is read from the manometer when a pulse is first palpated or auscultated. As soon as the pulse sound is muffled or disappears the diastolic pressure is read from the manometer (27).

Diabetes is another major risk factor for CVD. As described in 1.2.3, diabetes can be categorized into four groups. Since diabetes type 2 accounts for 90-95% of diabetes cases, the following will focus on the diagnosis of type 2 patients. Diabetes type 2 can be diagnosed by fasting plasma glucose, A1C, 2-hour plasma glucose during 75-g OGTT or random plasma glucose. The diagnostic criteria for diabetes, according to the American Association of Diabetes, include A1C levels of ≥6.5% (48 mmol/mol), fasting plasma glucose (FPG) levels of ≥126 mg/dL (7.0 mmol/L), 2-hour plasma glucose during 75-g OGTT ≥200 mg/dL (11.1 mmol/L) and a random plasma glucose level of ≥200 mg/dL (11.1 mmol/L). One elevated value is sufficient to secure the diagnosis of diabetes. The term prediabetes describes a patient group that does not meet the diagnostic criteria for diabetes yet, but signs of abnormal carbohydrate metabolisms are already present(28). The fasting plasma glucose test is performed by measuring the glucose levels in a person's blood sample after a fast of at least 8 hours, typically in the morning before any food or drink is consumed. The measurement of Hemoglobin A1C gives information about the mean blood sugar of the last two months (22).

As described in 1.2.3 obesity is a CVD risk factor and further a crucial element in the development of other CVD-causing diseases, including hypertension, insulin resistance and

dyslipidemia. It can be diagnosed by measuring the body mass index, waist-to-hip ratio or waist circumference. The waist-to-hip ratio compares the size of the waist to that of the hips, indicating the distribution of abdominal fat. The body mass index is a commonly used measurement that assesses body fat based on weight and height. By the American Journal of Managed Care, Class 1 obesity is defined by a BMI of 30 kg/m$^2$ to 34.9 kg/m$^2$, class 2 obesity is defined by a BMI of 35 kg/m to 39.9 kg/m$^2$, and class 3 obesity is defined by a BMI of at least 40 kg/m$^2$. A normal BMI ranges between 18.5 to 24.9 kg/m (24). In European men the waist circumference should not be above 94cm, in females it should not be above 80(29). Abdominal distribution of fat is expected to play a leading role as a risk factor for the development of insulin resistance and metabolic syndrome (25). Therefore the measurement of waist circumference and waist-to-hip ratio are better predictors of cardiovascular disease since it takes the distribution of fat into account compared to the BMI (30).

In the form of lipoproteins, lipids are transported to the tissue for energy utilization, deposition, creation of steroid hormones and bile acid synthesis. Chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, Lp(a), and high-density lipoproteins (HDL) are the six main lipoproteins in the blood. The size and lipid content of lipoproteins vary. LDLs are smaller and denser and contain a higher amount of cholesterol. HDL is the smallest and most dense and includes more proteins and less cholesterol. VLDL and chylomicrons are larger and transport mostly triglycerides. VLDL, IDL and LDL can cross the endothelial barrier and deposit(31). Out of these, the major form of atherogenic cholesterol is LDL-C. Therefore LDL-C is the main target for therapeutic options(32). The American Heart Society describes the total Cholesterol levels to reach ideal cardiovascular health as <200 mg/dL (33).

### 1.1.5 Treatment and prevention

Through a variety of strategies, cardiovascular disease can be effectively treated and prevented. Treatment strategies seek to regulate symptoms, manage risk factors, and slow the progression of the disease (33).

In 2010 the American Heart Association published a strategic impact goal for 2020 and beyond, with the target to improve cardiovascular health of all Americans by 20 % and to reduce the deaths by CVD and stroke by 20 %. To reach this goal the Life´s Simple 7 were created, composed of seven key factors for optimal cardiovascular health. It includes four modifiable

behaviors: no smoking, healthy weight, healthy diet and physical activity. The missing three are biometric measures, including blood pressure, blood glucose and blood cholesterol (33). In the category of modifiable behaviors, smoking should be stopped and a healthy weight can be reached by diet and physical activity. In terms of diet, the American Heart Association recommends eating 4.5 cups of vegetables and fruits in a single day, two meals of fish per week and three portions of whole grains of at least 1 ounce every day. The recommended daily sodium intake should be less than 1500 mg and the recommended weekly intake of sugar-containing drinks is less than 450 kcal. Physical activity should be either 150 minutes of moderate-intensity or 75 minutes of intense exercise per week (33).

Since the non-modifiable risk factors are influenced by smoking, diet and physical activity as well, Life´s Simple 7 and cardiovascular prevention, in general, can be broken down into these three simple components(33)

It may be necessary to consider medications for effective management if a patient's risk factors prove to be resistant to lifestyle modifications or if the patient is unable to adopt healthier habits. For the management of hypertension, β-Blockers, Angiotensin-Converting Enzyme Inhibitors (ACE-I), angiotensin receptor blockers  (ARBs), calcium channel blockers, and diuretics have been shown to be beneficial in the prevention of CVD occurrences(17). Statins are highly effective at preventing CVD as they lower cholesterol, particularly LDL cholesterol (33).

## 1.2  Ankle-Brachial Pressure Index

### 1.2.1  Definition

The Ankle-Brachial Pressure Index (ABPI) is a quick and non-invasive test, mostly used in the diagnostics of peripheral artery disease (PAD). To calculate the ABPI, the systolic blood pressure measured at the ankle is divided by the pressure of the arm. A decreased systolic pressure in the ankle indicates stenosis at an artery below the aorta. Therefore an ABPI below or equal to 0.9 is considered diagnostic for PAD. Normal ABPI values typically range between 1.0 and 1.30, values between 0.9 and 1.0 are considered to be borderline. An ABPI between 0.9 and 0.5 indicates a narrowing of one or more arteries and may be accompanied by the clinical sign of claudication. Patients with severe narrowing, ABPI of 0.5 to 0.3, often present with persistent wounds due to the compromised blood flow in the affected areas (34).

### 1.2.2 Measurement of ABPI

While ABPI is a relatively simple measurement, it is important to bear in mind certain considerations and adhere to specific guidelines to obtain precise and reliable results. A blood pressure cuff, a Doppler ultrasound device, and a sphygmomanometer are used in the ABPI measuring process. The patient should be placed in the supine position for at least 10 minutes (35).

The brachial systolic blood pressure is first determined. The upper arm is wrapped in a cuff of the proper size. The Doppler probe should be placed at a 45-degree angle above the brachial artery and the pulse is detected. Then the cuff is filled until the pulse signal is lost. Next, the pressure is slowly released to the point at which the signal returns. That point is read from the manometer as the systolic pressure. This procedure is repeated for both arms, and the higher of the two values is used for ABPI calculation (35).

Subsequently, the blood pressure in the ankle is measured. The cuff is placed at the ankle, right above the malleoli. The ultrasound probe is placed on the dorsalis pedis or anterior tibial artery. The same procedure used for measuring the brachial pressure is followed. The measurement needs to be repeated at the posterior tibial artery and the highest reading obtained among these sites is used to calculate the ABPI for that specific leg. The ABPI can then be calculated as the ratio between the highest obtained value from the legs to the highest value of the arm. (35).

### 1.2.3 Role of ABPI in cardiovascular risk predictions

The Ankle-Brachial Pressure Index (ABPI) is a diagnostic tool primarily used for assessing Peripheral Artery Disease (PAD), which is a prevalent disease caused by atherosclerosis. Since the ABPI measures the presence of atherosclerosis in the legs, we might be able to estimate the presence of atherosclerosis in other locations and therefore might be able to predict cardiovascular risk in general.

Beyond its use for the assessment of PAD, studies were able to prove its association with other cardiovascular events. In the Strong Heart Study ABPI values outside the range of 0.90 and 1.40 were linked to higher all-cause cardiovascular disease mortality in a population-based investigation(36). In a systematic review, the sensitivity of a low ABPI was found to be 16,0 % in predicting coronary heart disease and 16,5 % for stroke. Therefore only 16 % and 16,5 % of

individuals that experience cardiovascular events in the future were correctly identified. The specificity on the other hand was found to be 92,7 % and 92,2%, therefore enabling the accurate identification of individuals who did not experience cardiovascular events in the future(37). Yet studies show when paired with the Framingham risk score (FRS), the ankle-brachial index has been shown to improve cardiovascular risk estimation while making it easier to reclassify risk categories enabling more effective therapy choices (38). In conclusion, the ABPI lacks the criteria of a good screening tool that combines high sensitivity and high specificity, yet in combination with other measurements or risk calculations, it may be a useful tool in predicting the risk of cardiovascular disease.

# 2. OBJECTIVES

The objectives of this thesis are to investigate the patterns of ankle-brachial pressure index (ABPI) in the population of two Adriatic islands and the city of Split and to determine the relationship between ABPI and key cardiovascular risk factors including blood pressure, serum lipids, and sedentary lifestyle.

# 3. MATERIALS AND METHODS

This thesis uses data from the 10,001 Dalmatians project. In this project, health and disease in the Croatian Adriatic islands were examined by focusing on the development of a large-scale research biobank capable of providing a wide range of clinically relevant measurements. For the purposes of this study, people from the two islands of Korcula and Vis were involved. Additionally, the third subsample included inhabitants from the city Split.

The entire project was approved by the Ethics Board of the University of Split School of Medicine.

The Huntleigh Dopplex ABPI Ankle Brachial Pressure Index Kit (Huntleigh, US) was used to take all ABPI measurements. All subjects were first instructed to lie still for five to ten minutes. Subsequently, the cuff was wrapped around the patient's arm and the probe was used to determine the pulse. Afterward, the cuff was inflated till the puls was lost, indicating the systolic pressure. While slowly releasing the pressure, diastolic pressure was read from the manometer at the point of signal return at the manometer. Measurements were recorded from both arms, at the brachial artery, as well as at both legs at the dorsalis pedis artery and the posterior tibial artery. The ABPI was then calculated as the ratio between the highest obtained value from the legs to the highest value of the arm. The normal expected normal range was defined to be between 1.0 and 1.2

Categorical data were represented by using percentages, numerical data are summarized using the mean and the standard deviation. Statistical analyses in this study utilized the chi-square test for categorical data and the t-test was used for numerical data that met the distribution criterion. All statistical analyses were conducted using the statistical software IBM SPSS (version 18, IBM SPSS), with a significance level set at $P<0.05$.

# 4. RESULTS

This thesis included data from 2,921 subjects, 991 from the island of Vis, 918 from Korčula and 1,012 from the city Split. Regarding gender composition, a marginal statistical difference was observed, with the smallest deviation from an equal distribution of men and women found in the group from Vis (Table 1). The age composition suggested significant differences at the level of the entire sample, while conducting pair-wise comparisons, there was no significant difference between Vis and Korčula. However, when comparing Split to the preceding two, a significant difference was evident (Table 1). The remaining indicators of general cardiovascular health were comparable among the three subgroups (Table 1).

**Table 1.** Sociodemographic comparative data among regions: Vis, Korčula and Split

| Measurement | Vis (n=991) | Korčula (n=918) | Split (1,012) | P |
|---|---|---|---|---|
| Gender | | | | |
| Men | 412 (41.6) | 326 (35.5) | 395 (39.0) | 0.025 |
| Women | 579 (58.4) | 592 (64.5) | 617 (61.0) | |
| Age | 55.4±15.4 | 55.8±13.6 | 50.3±14.4 | <0.001* [$P_{VK}$:0.548; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Years of schooling | 10.1±3.6 | 10.9±3.4 | 13.1±3.0 | <0.001* [$P_{VK}$:<0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Subjective material status | 3.0±0.8 | 3.1±0.7 | 3.3±0.7 | <0.001* [$P_{VK}$:<0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Objective material status (salary) | n/a | 3.2±.1.4 | 4.3±1.4 | <0.001* [$P_{VK}$:<0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Objective material status (household) | 9.5±2.7 | 10.5±2.8 | 11.3±2.5 | <0.001* [$P_{VK}$:<0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |

*ANOVA for the entire sample level, with the LSD *post-hoc* tests for pair-wise comparisons (P values in square brackets for every pair-wise comparison).

When comparing the systolic and diastolic blood pressure measurements, the Vis and Korčula groups showed marginal differences, while the Split group displayed either significant or insignificant differences (Table 2).

**Table 2.** Blood pressure data among regions: Vis, Korčula and Split

| Measurement | Vis (n=991) | Korčula (n=918) | Split (1,012) | P |
|---|---|---|---|---|
| Systolic blood pressure, $1^{st}$ measurement | 137.8±23.8 | 139.5±21.7 | 130.2±19.4 | <0.001* [$P_{VK}$:0.084; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Diastolic blood pressure, $1^{st}$ measurement | 80.6±11.2 | 81.8±9.9 | 76.8±10.3 | <0.001* [$P_{VK}$:<0.013; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Systolic blood pressure, $2^{nd}$ measurement | 136.1±23.5 | 138.1±21.9 | 125.8±17.5 | <0.001* [$P_{VK}$:<0.045; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| Diastolic blood pressure, $2^{nd}$ measurement | 80.0±11.2 | 80.1±9.9 | 76.6±10.8 | <0.001* [$P_{VK}$:0.102; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| White-coat effect** | SBP:<0.001 DBP:0.003 | SBP:<0.001 DBP:<0.001 | SBP:<0.001 DBP:0.151 | - |

*ANOVA for the entire sample level, with the LSD *post-hoc* tests for pair-wise comparisons (P values in square brackets for every pair-wise comparison).
**Pair-wise comparison of the first and second measurement, performed for both systolic and diastolic pressure in all three sub-groups

The analysis of the blood pressures measured in the six designated ABPI locations suggested that all three sub-samples were significantly different, except for several instances of pair-wise comparisons between Vis and Korčula (Table 3).

**Table 3.** Comparison of ABPI among regions: Vis, Korčula and Split

| Measurement | Vis (n=991) | Korčula (n=918) | Split (1,012) | P |
|---|---|---|---|---|
| ABPI/right brachial artery | 153.8±28.0 | 143.5±25.8 | 126.7±18.1 | <0.001* [$P_{VK}$: <0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| ABPI/right posterior tibial artery | 154.4±28.5 | 155.4±29.1 | 136.3±19.5 | <0.001* [$P_{VK}$:<0.421; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| ABPI/right dorsal plantar artery | 152.0±28.0 | 155.1±29.5 | 132.4±19.1 | <0.001* [$P_{VK}$:<0.009; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| ABPI/left brachial artery | 151.2±28.5 | 138.6±24.5 | 124.6±17.2 | <0.001* [$P_{VK}$: <0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| ABPI/left posterior tibial artery | 141.4±23.9 | 151.7±29.0 | 134.5±19.0 | <0.001* [$P_{VK}$: <0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| ABPI/left dorsal plantar artery | 143.5±24.2 | 151.7±29.6 | 133.0±19.3 | <0.001* [$P_{VK}$: <0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |
| ABPI | 0.98±0.08 | 0.90±0.13 | 0.92±0.08 | <0.001* [$P_{VK}$: <0.001; $P_{VS}$:<0.001; $P_{VK}$:<0.001] |

The analysis of the ABPI in comparison with age suggested that the vast majority of subjects had good ABPI, close to 1, and that there were two subgroups that deviated from this pattern (Figure 4).
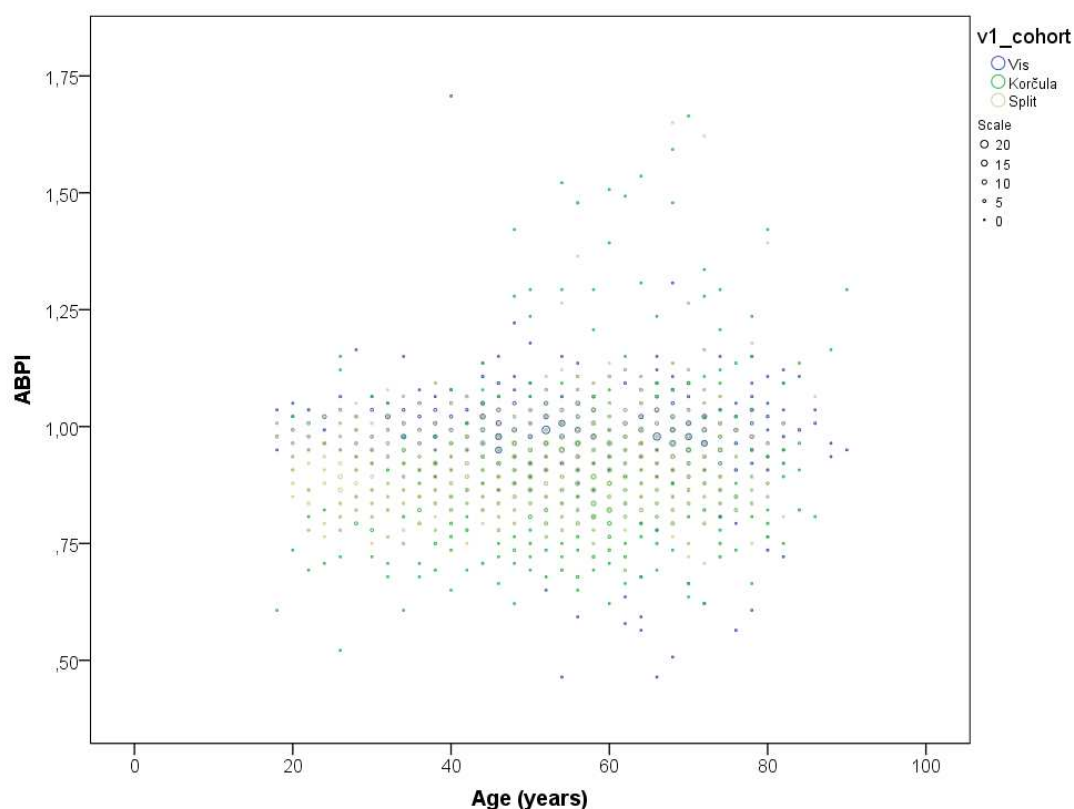
**Figure 4.** Comparison between ABPI and age

Further analysis, including only subjects with ABPI that was 0.2 away from the value of 1, had suggested that there were 235 (4.8%) subjects with values of 0.8 or lesser, compared to 35 (0.7%) who had ABPI over 1.2. The sub-analysis suggested that lower ABPI was more prevalent among men (121; 10.7% vs 114; 6.4% in women; P<0.001). Higher ABPI was equally prevalent in both groups (12 men; 1.1% vs 23 women; 1.3%; P=0.582). In terms of age, lower ABPI was not significantly different from normal ABPI (52.82±14.7 in the lower ABPI group vs 53.11±15.6 in normal ABPI; P=0.476), while higher ABPI values were more prevalent among the elderly (63.2±10.9 for higher ABPI vs 53.7±14.7 for normal ABPI; P<0.001).

The analysis of the high and low ABPI groups across the three subsamples indicated that the subjects from the island of Korčula were the most prevalent in both groups, with a strong excess in case of lower ABPI values (Table 4)

**Table 4.** Prevalence of low and high ABPI among regions: Vis, Korčula and Split

| Measurement | Vis (n=991) | Korčula (n=918) | Split (1,012) | P |
|---|---|---|---|---|
| Low ABPI (0.8 or less) | 23 (2.3) | 167 (18.2) | 45 (4.4) | <0.001 |
| High ABPI (1.2 or more) | 3 (0.3) | 26 (2.8) | 6 (0.6) | <0.001 |

Interestingly, the correlation between the ABPI and the common cardiovascular risks did not suggest any significant result, except for physical activity during leisure hours (Table 5).

**Table 5.** Correlation of serum lipids and ABPI

| Measurement | Correlation with ABPI |
|---|---|
| Serum cholesterol | r=-0.05, P=0.464 |
| Serum triglycerides | r=0.02, P=0.751 |
| HDL | r=-0.04, P=0.677 |
| LDL | r=-0.05, P=0.391 |
| Daily physical activity | r=0.08, P<0.001 |

# 5. DISCUSSION

The results of this Thesis show that the ABPI is a useful measurement of peripheral atherosclerosis. It is a quick and easy procedure, which can be widely used in screening, and then further explored by more sophisticated examinations.

The ABPI in this study exhibited interesting differences across the analyzed groups. The lowest values were recorded in Korčula and the highest in Vis. Interestingly, when analyzing the two groups, 0.8 or lower and 1.2 or higher, most of the subjects originated from Korčula. These results suggested that the population of Korčula exhibits greater variance than the remaining two. This could be a result of the founder effect, which is described as the deviation of a measurement from the isolated population, related to the demographic structure of the isolated population. The term refers to the island founders, who were ancestors of the modern-day populations. If some of these founders had an increased risk of a specific disease, they could introduce a much higher frequency of deleterious genes, which could lead to an increased rate of that exact disease over time. This was already described for several diseases in the Croatian islands, including gout (39). The results of that study confirmed that the frequency of the gene involved in the development of gout was much higher on the island of Vis, leading to a nearly ten-fold greater risk of the island population developing gout, compared to the population of Split.

The lack of correlation between ABPI and other measures of cardiovascular health is interesting, and could also suggest that there are substantial differences in the cardiovascular risks definition across the islands. Unfortunately, it is difficult to compare these in terms of mortality (40). The differences between the islands could very well be a result of the methodological differences in death reporting, meaning that such results might not be compared directly to one another.

The provided data gives us valuable insights into the distribution of ABPI values and cardiovascular indicators among different subgroups. However, it is important to note that we cannot draw conclusions about the connection between ABPI and cardiovascular risk since crucial data is missing.

Firstly, the absence of follow-up data limits our ability to determine the predictive capacity of ABPI for future cardiovascular events. Data on cardiovascular events in general, such as stroke or heart attacks, are missing. Further, the analyzed data lack information about other risk factors data such as smoking status or blood glucose. In addition to that, the data

revealed differences between the islands suggesting notable variations in population characteristics, which therefore may not be accurate in the entire population.

In conclusion, the ABPI is not yet a validated tool to asses cardiovascular risk, yet, due to its simplicity and its noninvasive nature it might be a useful tool in combination with other techniques.

# 6. CONCLUSION

Based on the study results, we can conclude the following:

1. The vast majority of patients presented with a good ABPI, close to 1.0.

2. A low ABPI, below 0.8, was more prevalent among men.

3. A higher ABPI, above 1.2, was more prevalent in the elderly.

4. Blood pressures measured in the six designated ABPI locations indicated significant differences among the three sub-samples, with some exceptions in pair-wise comparisons between Vis and Korčula.

5. The correlation between ABPI and serum lipids was not significant.

6. The ABPI correlated significantly with physical activity during leisure hours.

7. The prevalence of low ABPI shows a significant difference between the islands.

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# 8. SUMMARY

**Objectives:** The objectives of this thesis are to investigate the patterns of ankle-brachial pressure index (ABPI) in the population of two Adriatic islands and the city of Split, and to determine the relationship between ABPI and key cardiovascular risk factors including blood pressure, serum lipids, and sedentary lifestyle.

**Methods:** This thesis uses data from the 10,001 Dalmatians project and in total included data from 2,921 subjects. Of these, 991 subjects originated from the island of Vis, 918 from the island of Korčula and 1,012 from the city of Split.

**Results:** The vast majority of patients presented with a good ABPI, close to 1.0. There were 235 (4.8%) subjects with values of 0.8 or lesser, compared to 35 (0.7%) with an ABPI above 1.2. A low ABPI, below 0.8, was more prevalent among men (121; 10.7% vs 114; 6.4% in women; $P<0.001$), while a higher ABPI, above 1.2, was more prevalent in the elderly ($63.2\pm10.9$ for higher ABPI vs $53.7\pm14.7$ for normal ABPI; $P<0.001$). The systolic blood pressure for the Vis group was $137.8\pm23.8$ mmHg, for the Korčula group was $139.5\pm21.7$ mmHg, and for the Split group was $130.2\pm19.4$ mmHg. The diastolic blood pressure for the Vis group was $80.6\pm11.2$ mmHg, for the Korčula group was $81.8\pm9.9$ mmHg, and for the Split group was $76.8\pm10.3$ mmHg. The correlation between ABPI and serum lipids was not significant (serum cholesterol: $r=-0.05$, $P=0.464$; serum triglycerides: $r=0.02$, $P=0.751$; HDL: $r=-0.04$, $P=0.677$; LDL: $r=-0.05$, $P=0.391$). The ABPI demonstrated a significant correlation with physical activity ($r=0.08$, $P<0.001$).

**Conclusion:** A low ABPI, below 0.8, was more prevalent among men, on the other hand, a higher ABPI, above 1.2, was more prevalent in the elderly. Blood pressures measured in the six designated ABPI locations indicated significant differences among the three sub-samples, with some exceptions in pair-wise comparisons between Vis and Korčula. The correlation between ABPI and serum lipids was not significant. The ABPI correlated significantly with physical activity. Since further crucial data is missing, we cannot draw conclusions about the connection between ABPI as a predictor of cardiovascular risk. Additional studies are needed to explore the use of ABPI as a tool in cardiovascular risk assessment.

# 9. CROATIAN SUMMARY

**Ciljevi:** Ciljevi ovog diplomskog rada su istražiti obrasce gležanj-brahijalnog indeksa tlaka (ABPI) u populaciji dva jadranska otoka i grada Splita, te utvrditi odnos između ABPI i ključnih čimbenika kardiovaskularnog rizika uključujući krvni tlak, serumske lipide i sjedilački način života.

**Metode:** Ovaj rad koristi podatke iz projekta 10.001 Dalmatinac i ukupno uključuje podatke od 2.921 ispitanika. Od toga je 991 subjekt podrijetlom s otoka Visa, 918 s otoka Korčule i 1012 s područja grada Splita.

**Rezultati:** velika većina pacijenata imala je dobar ABPI, blizu 1,0. Bilo je 235 (4,8%) ispitanika s vrijednostima 0,8 ili manjim, u usporedbi s 35 (0,7%) s ABPI iznad 1,2. Nizak ABPI, ispod 0,8, bio je zastupljeniji među muškarcima (121; 10,7% naspram 114; 6,4% kod žena; P<0,001), dok je viši ABPI, iznad 1,2, bio zastupljeniji u starijih osoba (63,2±10,9 za viši ABPI naspram 53,7±14,7 za normalan ABPI; P<0,001). Sistolički krvni tlak za višku skupinu bio je 137,8±23,8 mmHg, za korčulansku 139,5±21,7 mmHg, a za splitsku 130,2±19,4 mmHg. Dijastolički krvni tlak za višku skupinu bio je 80,6±11,2 mmHg, za korčulansku 81,8±9,9 mmHg, a za splitsku 76,8±10,3 mmHg. Korelacija između ABPI i serumskih lipida nije bila značajna (serumski kolesterol: r=-0,05, P=0,464; serumski trigliceridi: r=0,02, P=0,751; HDL: r=-0,04, P=0,677; LDL: r=-0,05, P=0,391). ABPI je pokazao značajnu korelaciju s tjelesnom aktivnošću (r=0,08, P<0,001).

**Zaključak:** Nizak ABPI, ispod 0,8, bio je zastupljeniji kod muškaraca, s druge strane, viši ABPI, iznad 1,2, bio je zastupljeniji kod starijih osoba. Krvni tlakovi izmjereni na šest označenih ABPI lokacija ukazali su na značajne razlike između tri poduzorka, uz neke iznimke u usporedbama parova između Visa i Korčule. Korelacija između ABPI i lipida u serumu nije bila značajna. ABPI je značajno korelirao s tjelesnom aktivnošću. Budući da nedostaju daljnji ključni podaci, ne možemo donositi zaključke o povezanosti između ABPI kao prediktora kardiovaskularnog rizika. Potrebne su dodatne studije kako bi se istražila upotreba ABPI kao alata u procjeni kardiovaskularnog rizika.

# 10. CURRICULUM VITAE

**Personal Information:**
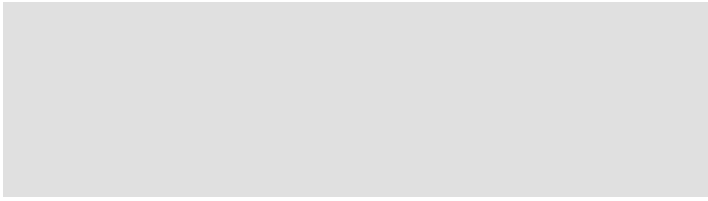
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