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# Cardiovascular Risk Factors from Another Point of View

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**ABSTRACT**

Cardiovascular diseases remain the main cause of death in western societies. This contributes to the appearance of new diagnostic and treatment methods addressed to reduce the burden of cardiovascular diseases. In the last decades new imaging methods have emerged, furthermore routine biomarkers where found to be useful in the cardiovascular risk stratification. Date reviewed in this article emphasize the multifactorial etiology of cardiovascular disease. Authors described the role of inflammation in the precipitation and progression of atherosclerosis and atrial fibrillation. Cheap and well knows inflammatory markers can be used alone or in combination with new imaging methods for a better cardiovascular risk stratification. Coronary computed tomographic angiography findings and inflammatory markers are capable to identify patients with high risk of MACE or atrial fibrillation. Furthermore, they also have an important role in the choice of treatment strategy and follow-up.

**Keywords:** cardiovascular diseases, biomarker, risk factor

## INTRODUCTION

Europe's population is getting older. Population ageing is the most significant demographic and social trends of the 21st century, affecting all the countries in the world. The incidence of ischemic heart disease (IHD) and of atherosclerosis increases with age. This appear 6–9 years earlier in men compared with women. Each year, IHD causes millions deaths in the Word. Atherosclerotic disease remains the most common causes of death in developed countries.[1] In the last decades the mortality rate of cardiovascular disease decreases significant due to improved diagnosis and treatment methods and primary prevention.[2] Patients with coronary artery disease can be completely asymptomatic in the early phases, being diagnosed in advanced stages, when the treatment is difficult, and the prognosis can be poor. In most cases the symptoms are caused by heart failure and different types of arrhythmias. In elderly patients, the onset of atrial fibrillation can be the first sign of myocardial hypoperfusion.[3,4] In addition to well-known risk factors, acute or chronic inflammatory states can lead to plaque instability, atherosclerosis progression, and adverse cardio-vas-

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cular events.[5] The most common causes of death in this group of patients are sudden death, acute heart failure and malignant ventricular arrhythmias, caused by acute coronary syndrome, myocardial infarction (MI).[6] These patients are very vulnerable to the slightest internal or external stimulus. For this reason, patients at high risk of atherosclerosis require regular screening, and need to be diagnosed before the acute event. One of the most accurate method is the coronary computed tomography angiography (CTA) which is capable to asses several aspects of coronary atherosclerosis (presence of atherosclerosis, stenosis, markers of potential plaque instability, and atheroma size).[7]

## ASSESSMENT OF CORONARY ARTERY DISEASE

In the last decade the diagnosis of coronary artery disease had become easier, faster, and more accurate. In the past the electrocardiography was the only diagnostic and screening method. The appearance of coronary angiography contributed to the diagnosis of significant coronary stenosis but without giving any information about the structure of the plaques. Nowadays this method is reserved for acute cases, when angioplasty is needed, and it cannot be used widespread for screening and for the assessment of cardiovascular risk. Computed tomography had become an indispensable method in cardiology in the last decade. Numerous large scale randomized studies has demonstrated that this method has an excellent diagnostic accuracy, in both symptomatic and asymptomatic patients.[8,9] Several trials, such as HEART (Scottish Computed Tomography of the Heart), and PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), demonstrated that the rate of MI can be significantly reduced, using CTA guided treatment strategy.[10–13] This non-invasive imaging method is able to diagnose patients with coronary atherosclerosis from the early stages and is able to determine long-term cardiovascular risk.

Another important feature of this investigation is that it is able to provide information about the structure of coronary plaques. This technique is capable to determine vulnerable plaque features, such as: low attenuation plaque, positive remodeling, spotty calcium, and napkin-ring sign.[14–16] In a meta-analysis study, (n = 13,977), Nerlekar *et al.* reported a strong correlation between high-risk plaque features and the incidence of major adverse cardiovascular events (MACE), the presence of two criteria increasing the risk of MACE 9-fold.[17]

## CARDIOVASCULAR RISK IN PATIENT WITH CHRONIC INFLAMMATORY DISEASES

Atherosclerosis is the cause and the consequence of inflammation. This systemic disease is associated with a low-grade inflammation of the arterial wall at the level of medium and large sized arteries.[18] Galkina *et al.*, in their review presented that the inflammation has an important role in all of the phase of atherosclerosis.[19] Several studies demonstrated a positive correlation between chronic inflammatory state and atherosclerosis. In the literature we found several clinical trials dealing with the incidence of cardiovascular disease in patients with chronic inflammatory diseases. Literature reviews described that Chronic inflammatory rheumatic diseases (CIRD), such as systemic lupus erythematosus, rheumatoid arthritis, and seronegative SpA, are associated with a significant CV morbidity and mortality.[20] Aviña-Zubieta *et al.,* in a meta-analysis concluded that CIRD patients have an increased prevalence of cardiovascular (CV) disease.[21] The ATHERODENT clinic trial presented a positive correlation between paradental disease, and atherosclerosis, and plaque vulnerability.[22] The correlation between atherosclerosis and chronic inflammatory disorders of the gastrointestinal tract is not elucidated.[23,24] Multiple cohort studies reported a significantly correlation between inflammatory bowel disease (IBD) and incidence of MACE.[25–27] In a French cohort study (n = 210,162), Kirchgesner *et al.* found an increased risk of acute arterial events, in patients with IBD. Furthermore, they reported a high risk in young patients. In their group, the risk of MACE increased proportional with the number, duration, and severity of acute events.[28] This finding was also confirmed by an Asian and Danish cohort study, where authors described a strong correlation between cardiovascular morbidity and mortality in young patients with IBD.[25,29] Weissman *et al.* concluded in their review that IBD is a risk factor for atherosclerosis and MACE, especially in young and female patients.[30]

## INFLAMMATION AND MAJOR CARDIO-VASCULAR EVENTS

Inflammation has also an important role in the precipitation of acute coronary syndrome. The inflammatory state can leaf to plaque disruption. The correlation between inflammation and MACE is complex, and not fully understood.[31] Many types of inflammatory cells are involved in the mechanism of coronary plaque destabilization. Macrophages and neutrophils play an important role in the plaque disruption and atherosclerosis progression.[32] These

cells secrete matrix metalloproteinase-9 (MMP-9). A disturbance between MMP-9 and tissue inhibitors of matrix metalloproteinase (TIMP-1) ratio lead to arterial extracellular matrix breakdown and trough it to plaque rupture.[33] Several clinical trials demonstrated that patients with ACS have a significantly higher MMP-9 level.[34–36] The authors describe other types of MMPs such as MMP-1, and MMP-2 which are also increased in patients with ACS. Wang H. *et al*, in a recent review, concluded that the acquired immune system also contributes to coronary plaque vulnerability.[31] Helper T cells especially Th1 cells, are characterized by production of pro-inflammatory cytokines, such as interferon-γ and tumor necrosis factor-α, which contributes to plaque disruption in ACS.[37,38] Researchers investigated the correlation between plaque vulnerability and different types of microorganism, but without finding a significantly correlation.[39] Only a few studies reported that infection with Chlamydia and Mycoplasma pneumonia and some viruses may have an additional higher cardiovascular risk.[40–42]

Acute inflammatory state can lead to ACS, without the presence of any coronary artery occlusion. This indirect mechanism of ACS is characterized by increased the oxygen and metabolic needs of myocardium, and it is called demand ischemia or myocardial infarction(MI) type 2.[43,44]

## ROLE OF C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE

The C-reactive protein (CRP) is a widely used inflammatory biomarker. The level of CRP is increased in every type of inflammatory diseases. It is a valuable marker not only for the diagnosis, but for the monitoring too. Determination of CRP is easy, inexpensive and highly availed. Recently, the role of CRP in cardiology it has been demonstrated. In the literature it was demonstrated a strongly correlation between the level of high-sensitivity CRP and MACE.

The role of hs-CRP in primary cardiovascular prevention is not so clear. More large clinical trials demonstrated, that an increased level of hs-CRP is associated with a higher cardiovascular risk. Ridker *et al.*, in more prospective studies, demonstrated that patients with elevated hs-CRP are prone to develop MACE.[45–49] They described that these patients, without cardiovascular disease, have a three times higher risk for myocardial infarction. They also emphasize that hs-CRP was the best predictor of CV risk among female patients after the onset of menopause. Other authors have also demonstrated this correlation.[50,51] However, others did not find a significant correlation.[52–54]

The level of hs-CRP has also an important role in patients with IHD. The authors demonstrated that hs-CRP is a marker of acute events in patients with IHD. Won-Woo *et al.* assessed the correlation between the level of hs-CRP and CTA findings. They concluded that the combination of imaging and inflammatory markers contributes to a better CV risk stratification.[55] Takashi *et al.* found a significantly correlation between the level of hs-CRP and the grade of necrosis of culprit lesion, assessed with IVUS.[56,57] Trans-lesion CRP gradient was calculated by Inoue *et al.*, and they found a higher level, distal to the site of coronary plaque. They reported also a higher level in case of unstable plaques.[58] In VISTA-16 trial (n = 5,145) the authors reported that the elevated hs-CRP level after an acute cardiovascular episode, and subsequent increases of them, is associated with an adverse outcomes.[59] Several trials in literature, confirmed this correlation.[60,61] In 2018, our research group reported that hs-CRP level is in correlation with infarct size in STEMI patients.[62]

## INFLAMMATION AND ATRIAL FIBRILLATION

The inflammation can be either a cause or a consequent of AF. Data from the literature suggest that inflammation have an important role in the structural and electrical remodeling of atrium. Inflammation cause atrial fibrosis, gap junction modulation and calcium homeostasis disturbance. These modifications promote ectopic atrial activity and aberrant impulse conduction.[63] The authors describe a correlation between systemic inflammation and AF. Patients with IBD, CIRD, psoriasis, SLE or sclerosis are more predisposed to AF.[64–67] Local inflammatory conditions, such as myocarditis or pericarditis, are also associated with a high risk of AF.[68]

The determination of the hs-CRP level can be also useful in patients with AF. The authors describe an increased level of this inflammatory marker, in case of persistent AF compared to paroxysmal AF.[69] Wu *et al.* in a meta-analysis study demonstrated that a higher baseline hs-CRP level is associated with a higher risk of AF recurrence after catheter ablation and electrical cardioversion.[70] An elevated white blood cell (WBC) count are also in correlation with the incidence of AF. This positive correlation was confirmed by several studies like Framingham Heart Study.[71] Weymann *et al.*, in a meta-analysis, did not find any correlation between onset of AF and WBC count, but they described the predictive role of WBC in the AF recurrence. Some authors consider that the determination of neutrophil/lymphocyte ratio is more accurate.[72,73]

## CONCLUSIONS

In the last decade, due to increased rate of cardiovascular disease further investigations were conducted to identify novel CV risk factors. Systemic inflammation is directly associated not only with IHD, but also with the risk to develop AF. The pathophysiology of AF is multifactorial, inflammation being both a cause and a consequence of this condition. Inflammation can promote ectopic atrial activity and aberrant impulse conduction, and the level of circulating inflammatory markers may predict the risk of recurrence. Inflammatory biomarkers, especially in combination with imaging markers, can be used for a better stratification of cardiovascular risk.

## CONFLICT OF INTEREST

Nothing to declare.

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