# Coronary imaging in elderly population

**Abstract**

**Keywords**
*aging, atherosclerosis, coronary imaging, coronary CT angiography, elderly population*

**Sections:**

1. **Aging and frailty**
2. **Atherosclerosis: pathophysiology of ageing**
3. **Coronary ageing: imaging features of the elderly**
4. **Discussion**

## 1. Aging and frailty

Age is a well-known non-modifiable cardiovascular risk factor and represents a strong independent marker of endothelial dysfunction [1]. With demographic changes, occurring worldwide, such as prolongation of life expectancy, the elderly population is increasing. According to World Health Organization (WHO) [2], between 2015 and 2050, the proportion of the world's population > 60 years will nearly double, outnumbering children < 5 years, the number of people > 80 years is expected to triple and by 2050, 80% of older people will be living in low/middle income countries. These changes have relevant financial and public health implications. Population aging is associated with higher healthcare costs and resources' consumption: costs of care for individuals aged 85 and over is on average twice as much as that for the "young-old" (65-84 years) [3]. Thus, all countries should address this demographic shift and frame public health policies accordingly. Aging is also associated with increasing incidence of chronic disease, which are one of the leading causes of death and disability in high-income countries, and it is estimated that approximately 80% of people over 65 years has at least one chronic condition, with coronary artery disease (CAD) being the most common [4].

Ageing, an inevitable process that occurs during our whole life, is commonly measured by chronological criteria: a person aged 65 years or more is often referred as elderly and, as such, can be referred to a geriatrician. Conventionally, those from 65 to 74 years old are considered "early elderly" while people over 75 years of age are "late elderly". However, such definition of elderly might be no longer appropriate for this era with longer and healthier life expectancy [5]. Chronological age also fails to address the heterogeneity of the elderly, not taking into consideration exogenous factors, such as lifestyle and environment, and endogenous factors, such as genetics, which both influence the ageing process [6]. Thus, a broader concept of elderly has been defined: frailty.

Frailty is an expression of aging and it is a consequence of age-related decline in homeostasis following stress and decline of multiple physiological systems. This process results in increased vulnerability and increased risk of adverse outcomes, such as falls, delirium and disability [7]. As a broad concept, in order to be applied to clinical practice and trials, frailty has to be standardized. For this purpose, different reliable frailty models have been assessed. The two principal models are the phenotype model, which includes patients over 65 years old and variables such as weight loss, weakness, slow gait speed, exhaustion and low physical activity [8] and the cumulative deficit model that defines frailty on the basis of ninety-two baseline parameters, referred as deficits, including

symptoms, signs, disabilities, disease state and laboratory values [9]. The latter model demonstrated greater discriminatory ability among moderate to severe frailty and facilitates more precise identification of vulnerable old people [10].

Thus, ageing leads to increased risk of developing chronic conditions, such as CAD, which leads to increased frailty and consequent higher risk of disability. From a pathophysiological standpoint, aging is the result of lifelong accumulation of molecular and cellular damage, which occur under the influence of genetic, epigenetic and environmental factors, leading to loss of physiological reserve of multiple organ systems [11]. The cardiovascular system for example is deeply affected by ageing, which represents a major risk factor for atherosclerosis and development of CAD. Indeed, advancing age is linked to significant morphological structure changes of the coronary arteries, and even in the absence of other cardiovascular risk factors it can produce modifications that can be seen at a microscopic and macroscopic level [12].

## 2. Atherosclerosis: pathophysiology of ageing

Aging promotes atherosclerosis in various vascular districts and, while consequences differ depending on the district affected, the underlying mechanisms are similar. Coronary ageing is caused by molecular and cellular mechanisms, each of whom has pathophysiologic consequences on the vasculature itself responsible, in the long-term, for heart structural and functional changes and alterations. In particular, there are mechanisms that are both extrinsic and intrinsic to the vasculature. The former includes bone marrow age-related modification. Ageing affects the development of myeloid cells, promoting the expansion of certain clones that show an increased production of pro-inflammatory interleukins, such as IL-6, accelerating atherosclerosis [13]. Among the intrinsic factors there are several contributors of vascular ageing of the coronary tree: increased oxidative stress, mitochondrial dysfunction, inflammation, loss of proteostasis, increased apoptosis, genomic instability and epigenetic factors. These factors can be divided in three main categories of alterations: mitochondrial dysfunction, vascular smooth muscle cells (VSMCs) modification and endothelial dysfunction.

With ageing, even before the initiation of atherogenesis [14], mitochondria show signs of reduced function, mitochondrial genomic instability and increased mitochondrial DNA damage. These altered mitochondrial functions are associated with increased oxidative stress (higher levels of reactive oxygen species ROS) and promote atherosclerosis and necrotic core formation [15]. Impaired mitochondrial function in endothelial and VSMCs leads also to less ATP generation and

impaired cellular energy metabolism; this alteration is responsible for impaired membrane transport and barrier function, which lead to a loss of vascular functional integrity [16]. It is been demonstrated that with ageing occurs a pro-inflammatory shift in the gene expression profile of both endothelial cells and VSMCs [17]; inflammation is associated with extracellular matrix (ECM) changes in the vessel wall, altered cellular metabolism and increased apoptosis, collectively contributing to CAD. ECM changes are then responsible for arterial remodeling and stiffening, responsible for decreased ability to dilate and tolerate blood pressure variations, resulting in increased pulse wave velocity, pulse pressure and systolic pressure, which promotes left ventricular remodeling and diastolic dysfunction, and decreased diastolic pressure, resulting in a decline in coronary blood flow and reserve [18-19] .

Indeed, as the CANTOS study [20] suggested, chronic inflammation is a major contributor of age-related atherosclerosis: mitochondrial injury and altered function, throughout a series of chain reactions, promote an inflammatory state within the vessels, creating a pro-atherogenic environment that favors plaque formation. Inflammation is also associated with age-related pro-inflammatory shift in the VSMCs [21]. In fact, with ageing VSMCs show increased proliferation and secondary intimal thickening, contributing to arterial stiffness, but also phenotype change from contractile to secretory [22]. This shift promotes migration, proliferation and secretion of several pro-inflammatory, pro-apoptotic, pro-atherogenic cytokines, resulting in lipid accumulation, altered matrix production and calcification of the arterial wall [23]. With ageing there is also a loss of proteostasis, indicating protein homeostasis, with a decline of ubiquitin-proteasome system activity [24], which may lead to dysregulated autophagy and endothelial cells and VSMCs senescence. Senescence contributes to progression and destabilization of atherosclerotic plaques by promoting inflammation/necrosis within the plaque and by reducing VSMCs content of the fibrous cap which results in its thinning [25].

Lastly, progressive reduction in the endothelial function contributes to age-related atherogenesis as well. With age there is an increased oxidative stress, due to increased production of ROS and decreased endothelium-derived nitric oxide (NO), which is an anti-oxidant, which leads to a decline of vasomotor reactivity, reduction in endothelium dependent vasodilation, enhancing vasoconstriction, leading to impaired coronary dilation and dysregulation of tissue perfusion which might cause myocardial ischemia, and platelet activation [26].

Taken together, these pathophysiological changes that occur at a molecular and cellular level correspond to histological/structural alterations, which are thus responsible for microvascular and

macrovascular structural alterations, which progressively lead to tissue and organ damage, especially if not treated. Indeed, in aged coronary arteries there are immune cells infiltrating the adventitia and perivascular tissues, with macrophages and lymphocytes accumulating in these arterial layers; there is an increase of collagen content, which contributes to vascular fibrosis, and decrease of elastin in the ECM, responsible for impaired elasticity and resilience of the coronary wall; there is microvascular rarefaction due to apoptosis; there is vascular calcification due to VSMCs phenotype shift toward a secretory one [27]. To summarize, the main structural changes occurring in older coronary arteries are thicker walls, larger diameters and stiffer walls, while the main changes occurring with age in atherosclerotic plaques are increased vulnerability, necrotic lipidic core and calcification [28-29].

The advent of non-invasive imaging techniques, such as coronary-CT angiography (CCTA), allowed to study the anatomy of the coronary vasculature and to characterize the atherosclerotic plaque phenotype. The aim of this review is to analyze the current literature regarding non-invasive coronary imaging techniques applied to the elderly population and to describe the main features of atherosclerotic plaque in these specific set of patients.

## 3. Coronary ageing: imaging features of the elderly

Changes occurring with age to the coronary vasculature are responsible for age-related atherosclerosis and consequent higher risk of CAD. Changes in structure have functional counterparts, and they can be studied and evaluated using imaging techniques that may add prognostic information helpful for clinical and therapeutic decisions. In this setting, CCTA represents a useful diagnostic tool. In fact, CCTA is a non-invasive imaging technique in which, throughout the use of contrast media agent and post-processing analysis, we can study the coronary vasculature. It allows the identification, localization and grade of coronary stenoses, the composition of the plaque, the presence of high-risk features, and the quantification of calcium in the vessel (coronary artery calcium, CAC). Thus, it can help to diagnose extent and severity of nonobstructive and obstructive CAD. CCTA is indicated and recommended (class 1 level A) by the American Heart Association [30] for patients at an intermediate risk of ACS, presenting with acute chest pain, no history of CAD and negative or inconclusive evaluation of ACS. Similarly, ESC guidelines [31] recommend CCTA as an alternative to invasive coronary angiography (ICA) to exclude ACS when there is low-to intermediate likelihood of CAD. These recommendations are based on CCTA's high diagnostic efficiency and high negative predictive value (NPV), as demonstrated by the VERDICT trial [32], where upfront CCTA in

NSTE-ACS patients, had a NPV of 90.9% for clinically significant (>50% stenosis) CAD. Thus, CCTA allows to avoid invasive, riskier and more expensive tests, such as ICA, leading to a more appropriate selection of patients who should be sent to ICA [33]. As the CONFIRM registry [34] suggests, CCTA may be used effectively as a gatekeeper to ICA. In the CT-STAT trial [35] CCTA resulted in improved efficiency, with a prompt discharge from emergency department, and cost reduction. Indeed, CCTA can guide treatment strategy and as the CATCH trial [36] showed, it improves outcome of patients with recent acute chest pain. Moreover, according to the PROMISE trial [37], CCTA has a significantly better discriminatory ability compared to functional tests, providing a better prognostic information on CAD, and, as suggested by the SCOT-HEART trial [38], the addition of CCTA to standard of care resulted in a reduction in 5-year CAD death or myocardial infarction (MI).

While for NSTE-ACS ESC guidelines [31] recommend (class I level B) to apply the same diagnostic and interventional strategies in older people as for younger patients, in case of chronic coronary syndromes (CCS) the strategy can be tailored [39]. In the elderly population age-specific approaches to noninvasive evaluation of CAD should be considered. In the PROMISE substudy, Lowenstern et al. [40] hypothesized that, among patients with stable symptoms, suggestive of CAD, the likelihood of a positive test result would differ among older and younger patients and that the association between a positive test and clinical event would be influenced by patient age and test type, either anatomic (CCTA) or functional (stress test). They found that age was associated with higher proportion of positive non-invasive test results, regardless of type, of obstructive CAD on CCTA and higher CAC score, overall indicating age-related increased prevalence of CAD. Moreover, they found that among different age groups (younger or older than 65 years of age), there were different prognostic values of stress test and CCTA, suggesting that age should be taken into consideration when choosing a test modality. Similarly, as shown by the CRESCENT and CRESCENT 2 trials [41-42], CCTA confidently ruled out CAD and, compared to functional tests, it was associated with fewer invasive angiograms of nonobstructive CAD. Additionally, incorporating CAC score into the diagnostic workup resulted in lower diagnostic expenses and radiation exposure and, by including dynamic perfusion imaging in the protocol, CCTA provided a comprehensive assessment of anatomy and function, reducing time for diagnosis and removing the need for additional non-invasive tests.

Calcium in the arterial wall is a well-known predictor of arterial ageing. Indeed, it has been demonstrated that long-term nondevelopment of coronary calcification, with persistent CAC score = 0, is a marker of healthy ageing and that maintenance of low CV risk factor burden is associated with increased likelihood of CAC = 0 [43]. Conversely, increased CAC score is a marker of ageing and

frailty and in older patients there is a shift toward calcified atherosclerotic plaque (CAP). As shown by Tota-Maharaj et al. [44], with ageing there is a 40-fold increase in mixed calcified atherosclerotic plaque (MCAP) and 16-fold increase in CAP, which can be easily assessed with CCTA. Moreover, MCAP is proven to be more prone to rupture, with occurrence of subsequent acute events: this explains the increased rate of thrombosis and coronary occlusion and the higher risk of adverse clinical events in the elderly and underlines the importance of early detection of MCAP by CCTA [45]. Thus, it has been reported that there is a relationship between frailty and coronary plaque phenotype. As Gu et al. [46] suggested in their study, frailty was strongly and independently associated with the presence of high-risk plaque features: thin cap fibroatheroma, minimum lumen area < 4 $mm^2$ and plaque burden > 70%. Similarly, other atherosclerotic plaque features in the elderly include lipid-rich plaque, presence of cholesterol crystal and calcification and greater stenosis severity [47]. Another recent study, a PARADIGM substudy [48], which included a large cohort of patients who underwent serial CCTA, also showed that age is significantly associated with the growth of coronary plaque burden, mainly driven by an increase of calcified plaque. Also, since age is proven to be an independent predictor for adverse cardiovascular events and the elderly are more likely to show a rapid plaque progression, Kim et al. [48] suggested this as a possible underlying mechanism that links age, atherosclerosis progression and clinical events. Naoum et al. [49] developed age-specific nomograms of CAD extent, quantifying global plaque burden using CCTA, and the age-specific segment involvement score percentile (SIS%) derived from it was shown to predict annualized event rates and relative major adverse CV event (MACE) risk, independent of traditional Framingham risk, in older patients. Hence, CCTA demonstrated great prognostic utility and it represents a useful tool to assess CV risk, and even the simple quantification of CAD segmental involvement alone seemed to provide prognostically useful information, highlighting the prognostic importance of global plaque burden.

Changes in the global coronary vasculature were documented also in experimental Fischer rat model of ageing. As demonstrated by Sangaralingham et al. [50], age is associated with decrease of total and intramyocardial vessel volumes and increase of epicardial vessel volumes indexed to left ventricular mass, and the reduction in intramyocardial coronary volume occurred in the setting of left ventricular fibrosis and mild dysfunction. They hypothesized that these changes might be an adaptive response to natural myocardial growth associated with ageing in order to assure sufficient blood supply. More recently, Ramandika et al. [51] tested the hypothesis that ageing impacts coronary flow velocities and coronary flow reserve, which is the functional capacity of coronary

vasculature to adapt to oxygen demand, even in patients without myocardial perfusion abnormalities on single-photon emission computed tomography (SPECT). They found that elderly patients seemed to have increased resting coronary flow velocity, that ageing was a determinant for hyperemic coronary flow velocity and that it was associated with impaired CFR.

## 4. Discussion

Despite the prolongation of life expectancy and the increase of elderly population, and even though age is a well-known, non-modifiable CV risk factor that predisposes to a high incidence and prevalence of CAD, elderly patients are still under-represented in clinical trials, misdiagnosed and undertreated for cardiovascular diseases [52]. With regards to NSTE-ACS, it is known that age is a predictor of in-hospital and 6-month mortality for patients with these clinical presentation [53], however there are limited trial data regarding elderly population, resulting in discrepancies of treatment among those patients [54]. Indeed, older patients are often managed conservatively, while younger patients receive more often invasive treatment, but despite an increased risk for major bleeding, an invasive strategy improves ischemic outcomes also in the elderly presenting with unstable angina and NSTEMI [55, 56]. Another factor that should be taken into consideration when evaluating elderly patients with NSTE-ACS is that they tend to have mild elevation of sensitive serum cardiac troponin level, even in the absence of MI [57]. Thus, different cut-off levels should be considered in different age-groups in order to avoid overdiagnosis of MI and misdiagnosis of other pathological entities [58]. Taken together, this data emphasizes the growing importance of including the elderly population in clinical trials in order to avoid treatment discrepancies among patients. Similarly, this discrepancy is seen also in patient with CCS, where the elderly population is undertreated, underdiagnosed and under-represented in clinical trials because their eligibility criteria for research studies often exclude patients with comorbidities, such as the elderly. Older patients present more often with atypical symptoms, including absence or different perception of chest pain, dyspnea as the only presenting symptom, general symptoms like confusion and malaise, leading to prolongation of diagnostic time and higher risk of misdiagnosis [59, 60].

As the number of elderly patients requiring diagnostic assessment for CAD increases, accurate, non-invasive imaging techniques applicable to this age group have become more important. In this setting, functional and anatomical tests gained relevance and clinical importance, especially considering their prognostic added value. While exercise testing remains a useful tool, it is not applicable to the entire elderly population, because it requires patients capable of performing

treadmill or bicycle exercise. Pharmacological stress testing in combination with myocardial perfusion SPECT imaging represent a valid alternative, which also improves specificity and adds prognostic information [61].

As a screening tool for CAD, CAC score has shown to be a powerful predictor, with greater predictive value than conventional cardiac risk factors in asymptomatic patients, including the elderly [62]. More importantly, CCTA represents a useful non-invasive imaging technique, with high NPV [63], which can be used as an advanced screening tool for CAD, because it provides anatomical and functional assessment of coronary artery vasculature and it is suitable for a larger portion of the elderly population. Moreover, CCTA showed better long-term prognostic value for MACE than CAC score and conventional risk factors in asymptomatic elderly patients, indicating that it might give more reliable clinical guidance to prevent and delay future cardiac events that other traditional methods [64]. As shown by Hoffmann et al. [65], in patients in stable condition, with known or suspected CAD, presenting to the emergency department with acute chest pain, suggestive of ACS, the early use of CCTA safely improves efficiency of clinical decision making, as compared to standard evaluation, shortening the length of stay in the hospital.

Regarding plaque characterization and features assessment using CCTA, coronary findings are different in young patients with CAD compared with the elderly. Particularly, in the elderly population there is a predominance of MCAP and CAP; as Moon et al. [64] observed in their study, among an asymptomatic elderly population, calcified plaques were present in 38.5% and mixed plaques in 32.4%, while noncalcified plaques were observed only in 9.1% of participants. Moreover, they found that 47.7% of participants had nonobstructive CAD, while 16.2% had obstructive CAD and among the latter group there was a significantly higher rate of patients with CAC score > 400, who exhibited a poor 8-year event-free survival rate, confirming the good negative predictiveness of CCTA. Similarly, Han et al. [63] found that, among elderly asymptomatic patients with CAC score > 400, most patients who had MACE during follow-up had obstructive CAD. Thus, they concluded that CCTA improves risk prediction for MACE and correctly reclassify patients above and beyond conventional risk classification and CAC score. Additionally, CCTA showed improvement in prediction, discrimination and reclassification for risk of future events particularly among older asymptomatic patients at moderate-to-high risk, such as those with CAC score between 100 and 400, indicating that CCTA added prognostic value would be particularly proven in this subset of individuals [66].

More recently, Sagris et al. [67] mentioned other atherosclerotic plaque features that can be found more often among the elderly: greater number of lesions, higher number of affected vessels and greater lesion complexity, as estimated by Gensini score, which is a predictor of successful myocardial reperfusion, of adverse cardiac events and of long-term mortality in the elderly [68]. Additionally, in the elderly population it is less likely to detect eccentric lesions, the inflammatory response within the plaque decreases and there is a lower rate of plaque erosion and a higher rate of intraplaque hemorrhage leading to thin cap fibroatheroma formation and rupture, which seemed to be the main mechanism of MI in older patients and one of the reasons why elderly have a worse prognosis than young patients with MI [69, 70].

With ageing and with the improvement of survival rates after ACS, there is also an increase of older patients with CVD and comorbidities. Multimorbidity impacts the diagnosis, management, outcome, prognosis, healthcare costs and clinical presentation of these patients, and special effort should be made, and it is already being made [71], to shift the approach from disease-centered to patient-centered care. Similarly, the shift toward frailty, rather than the mere chronological ageing, is focusing on the patient and his/her vulnerability. Frailty screening is indicated in every elderly patient, but it should also be assessed in every individual at risk of accelerated ageing, regardless of age [72]; frailty represents a prognostic marker but it can also influence treatment, in order to build individualized care plans. For example, as Ekerstad et al. [73] suggested, quantification of frailty, according to the Canadian Study of Health and Aging Clinical Frailty Scale [74], predicts short-term outcomes for elderly NSTEMI patients. Particularly, they included patients over or 75 years of age, with diagnosed NSTEMI, and they found that frailty is strongly and independently associated with in-hospital and 1-month mortality, prolonged hospital care and primary composite outcome. Altogether, taken into account the demographic changes occurring worldwide, with the increase of the elderly population, the undoubtable role of ageing in atherosclerosis and CAD, the different presentation of atherosclerosis among the elderly and the particular characteristics of this type of population, customization of diagnostic and therapeutic strategies should be considered and it would be desirable. Future effort should be made to include elderly patients in clinical trials.

**References**


1. Grundy SM. Age as a risk factor: you are as old as your arteries. *Am J Cardiol*. 1999;83(10):1455-A7. doi:10.1016/s0002-9149(99)00125-3
2. *Aging and Health,* World Health Organization (WHO) Updated October 4, 2021. Accessed September 6, 2022 https://www.who.int/news-room/fact-sheets/detail/ageing-and-health
3. Zolotor AJ, Tippett R. Running the Numbers: Aging and Cost of Health Care in North Carolina. *N C Med J*. 2018;79(1):66-69. doi:10.18043/ncm.79.1.66
4. Rich PB, Adams SD. Health care: economic impact of caring for geriatric patients. *Surg Clin North Am*. 2015;95(1):11-21. doi:10.1016/j.suc.2014.09.011
5. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly" Geriatrics & gerontology international. 2006;6(3):149-158. doi:10.1111/j.1447-0594.2006.00341.x.
6. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. *Pharm Pract (Granada)*. 2014;12(4):489. doi:10.4321/s1886-36552014000400007
7. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people [published correction appears in Lancet. 2013 Oct 19;382(9901):1328]. *Lancet*. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9
8. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156. doi:10.1093/gerona/56.3.m146
9. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489-495. doi:10.1503/cmaj.050051
10. Kulminski AM, Ukraintseva SV, Kulminskaya IV, Arbeev KG, Land K, Yashin AI. Cumulative deficits better characterize susceptibility to death in elderly people than phenotypic frailty: lessons from the Cardiovascular Health Study. *J Am Geriatr Soc*. 2008;56(5):898-903. doi:10.1111/j.1532-5415.2008.01656.x
11. Kirkwood TB. Understanding the odd science of aging. *Cell*. 2005;120(4):437-447. doi:10.1016/j.cell.2005.01.027
12. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*. 2012;111(2):245-259. doi:10.1161/CIRCRESAHA.111.261388
13. Tyrrell DJ, Goldstein DR. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. *Nat Rev Cardiol*. 2021;18(1):58-68. doi:10.1038/s41569-020-0431-7
14. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217. doi:10.1016/j.cell.2013.05.039
15. Yu EPK, Reinhold J, Yu H, et al. Mitochondrial Respiration Is Reduced in Atherosclerosis, Promoting Necrotic Core Formation and Reducing Relative Fibrous Cap Thickness [published correction appears in Arterioscler Thromb Vasc Biol. 2018 Jul;38(7):e135]. *Arterioscler Thromb Vasc Biol*. 2017;37(12):2322-2332. doi:10.1161/ATVBAHA.117.310042
16. Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of Vascular Aging. *Circ Res*. 2018;123(7):849-867. doi:10.1161/CIRCRESAHA.118.311378
17. Csiszar A, Ungvari Z, Koller A, Edwards JG, Kaley G. Proinflammatory phenotype of coronary arteries promotes endothelial apoptosis in aging. *Physiol Genomics*. 2004;17(1):21-30. Published 2004 Mar 12. doi:10.1152/physiolgenomics.00136.2003
18. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of Dysfunction in the Aging Vasculature and Role in Age-Related Disease. *Circ Res*. 2018;123(7):825-848. doi:10.1161/CIRCRESAHA.118.312563
19. Scuteri A, Morrell CH, Orrù M, et al. Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging. *Hypertension*. 2014;64(6):1219-1227. doi:10.1161/HYPERTENSIONAHA.114.04127
20. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med*. 2017;377(12):1119-1131. doi:10.1056/NEJMoa1707914
21. Csiszar A, Sosnowska D, Wang M, Lakatta EG, Sonntag WE, Ungvari Z. Age-associated proinflammatory secretory phenotype in vascular smooth muscle cells from the non-human primate

Macaca mulatta: reversal by resveratrol treatment. *J Gerontol A Biol Sci Med Sci*. 2012;67(8):811-820. doi:10.1093/gerona/glr228

22. Alexander MR, Owens GK. Epigenetic control of smooth muscle cell differentiation and phenotypic switching in vascular development and disease. *Annu Rev Physiol*. 2012;74:13-40. doi:10.1146/annurev-physiol-012110-142315
23. Piccirillo F, Carpenito M, Verolino G, et al. Changes of the coronary arteries and cardiac microvasculature with aging: Implications for translational research and clinical practice. *Mech Ageing Dev*. 2019;184:111161. doi:10.1016/j.mad.2019.111161
24. Kaushik S, Cuervo AM. Proteostasis and aging. *Nat Med*. 2015;21(12):1406-1415. doi:10.1038/nm.4001
25. Grootaert MOJ, Moulis M, Roth L, et al. Vascular smooth muscle cell death, autophagy and senescence in atherosclerosis. *Cardiovasc Res*. 2018;114(4):622-634. doi:10.1093/cvr/cvy007
26. Xu S, Ilyas I, Little PJ, et al. Endothelial Dysfunction in Atherosclerotic Cardiovascular Diseases and Beyond: From Mechanism to Pharmacotherapies. *Pharmacol Rev*. 2021;73(3):924-967. doi:10.1124/pharmrev.120.000096
27. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. *Cardiovasc Res*. 2018;114(4):590-600. doi:10.1093/cvr/cvy010
28. Thijssen DH, Carter SE, Green DJ. Arterial structure and function in vascular ageing: are you as old as your arteries?. *J Physiol*. 2016;594(8):2275-2284. doi:10.1113/JP270597
29. Tesauro M, Mauriello A, Rovella V, Annicchiarico-Petruzzelli M, Cardillo C, Melino G, Di Daniele N. Arterial ageing: from endothelial dysfunction to vascular calcification. J Intern Med. 2017 May;281(5):471-482. doi: 10.1111/joim.12605. Epub 2017 Mar 27. PMID: 28345303.
30. Writing Committee Members, Gulati M, Levy PD, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;78(22):e187-e285. doi:10.1016/j.jacc.2021.07.053
31. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [published correction appears in Eur Heart J. 2021 May 14;42(19):1908] [published correction appears in Eur Heart J. 2021 May 14;42(19):1925] [published correction appears in Eur Heart J. 2021 May 13;:]. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
32. Linde JJ, Kelbæk H, Hansen TF, et al. Coronary CT Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *J Am Coll Cardiol*. 2020;75(5):453-463. doi:10.1016/j.jacc.2019.12.012
33. Smulders MW, Kietselaer BLJH, Wildberger JE, et al. Initial Imaging-Guided Strategy Versus Routine Care in Patients With Non-ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2019;74(20):2466-2477. doi:10.1016/j.jacc.2019.09.027
34. Shaw LJ, Hausleiter J, Achenbach S, et al. Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry. *J Am Coll Cardiol*. 2012;60(20):2103-2114. doi:10.1016/j.jacc.2012.05.062
35. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. *J Am Coll Cardiol*. 2011;58(14):1414-1422. doi:10.1016/j.jacc.2011.03.068
36. Linde JJ, Hove JD, Sørgaard M, et al. Long-Term Clinical Impact of Coronary CT Angiography in Patients With Recent Acute-Onset Chest Pain: The Randomized Controlled CATCH Trial. *JACC Cardiovasc Imaging*. 2015;8(12):1404-1413. doi:10.1016/j.jcmg.2015.07.015
37. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic Value of Noninvasive Cardiovascular Testing in Patients With Stable Chest Pain: Insights From the PROMISE Trial (Prospective Multicenter Imaging

Study for Evaluation of Chest Pain). *Circulation*. 2017;135(24):2320-2332. doi:10.1161/CIRCULATIONAHA.116.024360

38. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. *N Engl J Med*. 2018;379(10):924-933. doi:10.1056/NEJMoa1805971
39. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [published correction appears in Eur Heart J. 2020 Nov 21;41(44):4242]. *Eur Heart J*. 2020;41(3):407-477. doi:10.1093/eurheartj/ehz425
40. Lowenstern A, Alexander KP, Hill CL, et al. Age-Related Differences in the Noninvasive Evaluation for Possible Coronary Artery Disease: Insights From the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial. *JAMA Cardiol*. 2020;5(2):193-201. doi:10.1001/jamacardio.2019.4973
41. Lubbers M, Dedic A, Coenen A, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J*. 2016;37(15):1232-1243. doi:10.1093/eurheartj/ehv700
42. Lubbers M, Coenen A, Kofflard M, et al. Comprehensive Cardiac CT With Myocardial Perfusion Imaging Versus Functional Testing in Suspected Coronary Artery Disease: The Multicenter, Randomized CRESCENT-II Trial. *JACC Cardiovasc Imaging*. 2018;11(11):1625-1636. doi:10.1016/j.jcmg.2017.10.010
43. Whelton SP, Silverman MG, McEvoy JW, et al. Predictors of Long-Term Healthy Arterial Aging: Coronary Artery Calcium Nondevelopment in the MESA Study [published correction appears in JACC Cardiovasc Imaging. 2016 Feb;9(2):217]. *JACC Cardiovasc Imaging*. 2015;8(12):1393-1400. doi:10.1016/j.jcmg.2015.06.019
44. Tota-Maharaj R, Blaha MJ, Rivera JJ, et al. Differences in coronary plaque composition with aging measured by coronary computed tomography angiography. *Int J Cardiol*. 2012;158(2):240-245. doi:10.1016/j.ijcard.2011.01.041
45. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol*. 2004;24(7):1161-1170. doi:10.1161/01.ATV.0000133194.94939.42
46. Gu SZ, Qiu W, Batty JA, et al. Coronary artery lesion phenotype in frail older patients with non-ST-elevation acute coronary syndrome undergoing invasive care. *EuroIntervention*. 2019;15(3):e261-e268. Published 2019 Jun 12. doi:10.4244/EIJ-D-18-00848
47. Araki M, Yonetsu T, Kurihara O, et al. Age and Phenotype of Patients With Plaque Erosion. *J Am Heart Assoc*. 2021;10(19):e020691. doi:10.1161/JAHA.120.020691
48. Kim M, Lee SP, Kwak S, et al. Impact of age on coronary artery plaque progression and clinical outcome: A PARADIGM substudy. *J Cardiovasc Comput Tomogr*. 2021;15(3):232-239. doi:10.1016/j.jcct.2020.09.009
49. Naoum C, Berman DS, Ahmadi A, et al. Predictive Value of Age- and Sex-Specific Nomograms of Global Plaque Burden on Coronary Computed Tomography Angiography for Major Cardiac Events. *Circ Cardiovasc Imaging*. 2017;10(3):e004896. doi:10.1161/CIRCIMAGING.116.004896
50. Sangaralingham SJ, Ritman EL, McKie PM, et al. Cardiac micro-computed tomography imaging of the aging coronary vasculature. *Circ Cardiovasc Imaging*. 2012;5(4):518-524. doi:10.1161/CIRCIMAGING.112.973057
51. Ramandika E, Kurisu S, Nitta K, et al. Effects of aging on coronary flow reserve in patients with no evidence of myocardial perfusion abnormality. *Heart Vessels*. 2020;35(12):1633-1639. doi:10.1007/s00380-020-01643-8
52. Skinner TR, Scott IA, Martin JH. Diagnostic errors in older patients: a systematic review of incidence and potential causes in seven prevalent diseases. *Int J Gen Med*. 2016;9:137-146. Published 2016 May 20. doi:10.2147/IJGM.S96741

53. Rosengren A, Wallentin L, Simoons M, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. *Eur Heart J*. 2006;27(7):789-795. doi:10.1093/eurheartj/ehi774
54. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation*. 2007;115(19):2549-2569. doi:10.1161/CIRCULATIONAHA.107.182615
55. Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med*. 2004;141(3):186-195. doi:10.7326/0003-4819-141-3-200408030-00007
56. Bauer T, Koeth O, Jünger C, et al. Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. *Eur Heart J*. 2007;28(23):2873-2878. doi:10.1093/eurheartj/ehm464
57. Chenevier-Gobeaux C, Meune C, Freund Y, et al. Influence of age and renal function on high-sensitivity cardiac troponin T diagnostic accuracy for the diagnosis of acute myocardial infarction. *Am J Cardiol*. 2013;111(12):1701-1707. doi:10.1016/j.amjcard.2013.02.024
58. Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. *Eur Heart J*. 2011;32(11):1379-1389. doi:10.1093/eurheartj/ehr033
59. Gupta R, Munoz R. Evaluation and Management of Chest Pain in the Elderly. *Emerg Med Clin North Am*. 2016;34(3):523-542. doi:10.1016/j.emc.2016.04.006
60. Grosmaitre P, Le Vavasseur O, Yachouh E, et al. Significance of atypical symptoms for the diagnosis and management of myocardial infarction in elderly patients admitted to emergency departments. *Arch Cardiovasc Dis*. 2013;106(11):586-592. doi:10.1016/j.acvd.2013.04.010
61. De Winter O, Van de Veire N, Gemmel F, Goethals I, De Sutter J. Myocardial perfusion imaging in the elderly: a review. *Nucl Med Commun*. 2006;27(6):529-534. doi:10.1097/00006231-200606000-00009
62. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation*. 2005;112(4):572-577. doi:10.1161/CIRCULATIONAHA.104.488916
63. Han D, Hartaigh BÓ, Gransar H, et al. Incremental prognostic value of coronary computed tomography angiography over coronary calcium scoring for major adverse cardiac events in elderly asymptomatic individuals. *Eur Heart J Cardiovasc Imaging*. 2018;19(6):675-683. doi:10.1093/ehjci/jex150
64. Moon SJ, Chun EJ, Yoon YE, Park KS, Jang HC, Lim S. Long-Term Prognostic Value of Coronary Computed Tomography Angiography in an Asymptomatic Elderly Population. *J Am Heart Assoc*. 2019;8(23):e013523. doi:10.1161/JAHA.119.013523
65. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med*. 2012;367(4):299-308. doi:10.1056/NEJMoa1201161
66. Cho I, Chang HJ, Ó Hartaigh B, et al. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study [published correction appears in Eur Heart J. 2015 Dec 7;36(46):3287]. *Eur Heart J*. 2015;36(8):501-508. doi:10.1093/eurheartj/ehu358
67. Sagris M, Antonopoulos AS, Theofilis P, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res*. 2022;118(10):2281-2292. doi:10.1093/cvr/cvab264
68. Sinning C, Lillpopp L, Appelbaum S, et al. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. *Clin Res Cardiol*. 2013;102(7):495-503. doi:10.1007/s00392-013-0555-4

69. Kitulwatte ID, Pollanen MS. A Comparative Study of Coronary Atherosclerosis in Young and Old. *Am J Forensic Med Pathol*. 2015;36(4):323-326. doi:10.1097/PAF.0000000000000203
70. Niccoli G, Montone RA, Di Vito L, et al. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J*. 2015;36(22):1377-1384. doi:10.1093/eurheartj/ehv029
71. Forman DE, Maurer MS, Boyd C, et al. Multimorbidity in Older Adults With Cardiovascular Disease. *J Am Coll Cardiol*. 2018;71(19):2149-2161. doi:10.1016/j.jacc.2018.03.022
72. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice [published correction appears in Eur Heart J. 2022 Sep 09;:]. *Eur Heart J*. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
73. Ekerstad N, Swahn E, Janzon M, et al. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. *Circulation*. 2011;124(22):2397-2404. doi:10.1161/CIRCULATIONAHA.111.025452
74. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489-495. doi:10.1503/cmaj.050051

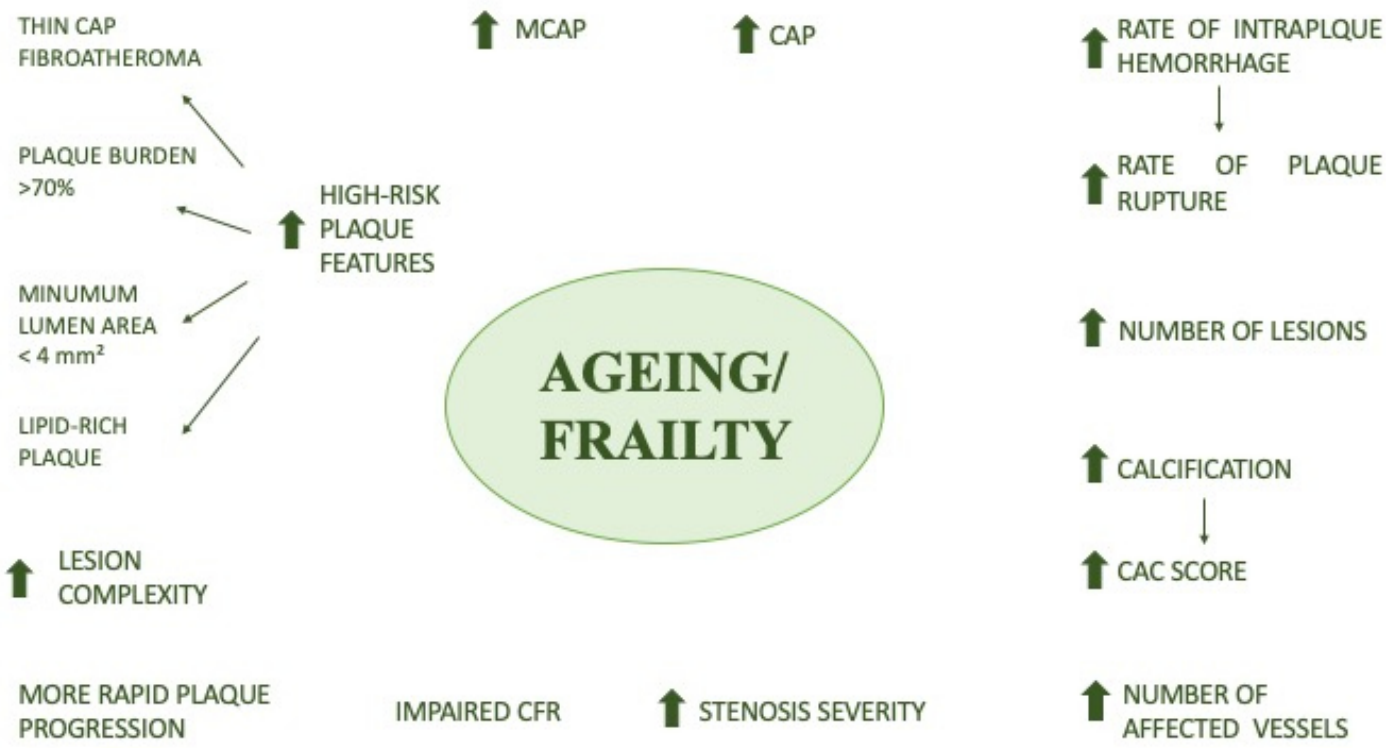
**Table 1**

| Reference | Year of publication | Population included | Results |
|---|---|---|---|
| Lowenstern et al. (40) | 2020 | Patients without known history of CAD but with symptoms suggestive of CAD, divided in three age-groups from <65 to >75 | Older patients more likely to have obstructive CAD, CACS> 400 and MACE |
| Tota-Maharaj et al. (44) | 2012 | 49 ± 10 years old asymptomatic patients | 40x increase in MCAP<br>16x increase in CAP<br>2,5x increase in NCAP<br>with ageing |
| Gu et al. (46) | 2019 | >75 years NSTE-ACS patients | Frailty (assessed with phenotype model/Fried criteria) associated with high-risk plaque phenotype |
| Araki et al. (47) | 2021 | Patients with ACS divided in five age-group from <45 years to >75 years | Increase of stenosis severity, presence of lipid-rich plaque and calcification were associated with age |
| Kim et al. (48) | 2020 | 61 ± 5 years patients who underwent serial CCTA | Rate of whole-heart plaque progression and dense classification increases with age |
| Nouman et al. (49) | 2017 | 40-79 years without known history of CAD | Global plaque burden measured using SIS increases with age and predicts MACE |
| Ramandika et al. (51) | 2020 | Patients without myocardial perfusion abnormality; three age-groups from <70 to >80 years | Age is a determinant for hyperemic CFV and it is associated with impaired CFR |
| Han et al. (63) | 2018 | Asymptomatic patients, without known history of CAD in age-groups from <52 to >62 years | Prevalence of CAD and number of vessels with coronary stenosis increased with age |
| Moon et al. (64) | 2019 | Asymptomatic patients, without known history of CAD, >65 years | 16.2% of patients had obstructive CAD, of which 4.5% had 3-vessel disease; 63.8% had any kind of plaque, of which 38.5% CAP and 32.4% MCAP; 41% of patients had CACS >100 |

*CAD: coronary artery disease; SIS: segment involvement score; CACS: coronary artery calcium score; MACE: major adverse cardiovascular events; MCAP: mixed calcified atherosclerotic plaque; CAP: calcified atherosclerotic plaque; NCAP: non-calcified atherosclerotic plaque; NSTE-ACS: non-ST elevation acute coronary syndromes; CFV: coronary flow velocity; CFR: coronary flow reserve;*

**Table 1:** literature regarding coronary ageing and atherosclerosis in elderly population

**Graph 1**




**Graph 1:** atherosclerotic plaque features and coronary artery changes occurring with ageing in elderly patients