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# Cardiovascular Risk Factors in the Elderly

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## 1. Introduction

The twenty-first century is often called the age of aging. Old age, though one of the most difficult concept to define, is frequently used to describe those older than 60 years of age. Ages can also be divided according to decade: sexagenarian (60 to 69 years), septuagenarian (70 to 79 years), octogenarian (80 to 89 years), nonagenarian 90 to 99 years and centenarian (>100 years) etc. Today, with improved quality of life resulting in longer life spans, the percentage of elderly in the total population is increasing. Because they live longer than men, women constitute the majority of older persons. Since 1950, the proportion of the world's population aged 60 and over has changed from one in thirteen to one in ten, with some developing countries aging faster than developed countries. Marked differences exist between regions. In Europe, one in five people are aged 60 and over as compared to one in 20 in Africa. According to the United Nations Population Division, one in every ten persons is now aged 60 and over. It is projected that by the year 2050 this figure will increase to one in five and by 2150 it will be one in three (**Figure 1**, United Nations Department of Economic and Social Affairs Population Division Report, 2009). The older population is also aging in itself. Currently, octogenarians constitute 11 percent of the world's older population. By 2050, 27 percent of the older population will be 80 years and over (Troisi, 2005).

## 2. Information on aging, atherogenesis and risk factors

**Markers of cardiovascular aging** in humans are the progressive **rise** of systolic blood pressure, pulse pressure, pressure pulse rate, left ventricular mass, coronary artery disease and atrial fibrillation prevalence. In parallel with aging a **decrease** can be seen in early diastolic filling rate, maximal heart rate, maximal cardiac output, maximum aerobic capacity, left ventricular contractility index, maximal O<sub>2</sub> consumption, ejection fraction and reflex heart rate augmentation during exercise, heart rate variability, vasodilator response to beta-adrenergic stimulation, endothelium-mediated vasodilatation.

With aging, cardiovascular (CV) diseases become more frequent and complicated. They are usually not isolated, but are associated with other medical problems (Ulucam & Muderrisoglu, 2008) and they continue to be the most important cause of morbidity and mortality in the elderly. More than 15% of deaths in the world are due to CV diseases (Ozturk & Kutlu, 2010) for both women and men >65 years of age (Ulucam & Muderrisoglu, 2008). Among CV diseases, more than 75-80% of the population aged 65 and over die from

vascular diseases, in particular coronary heart disease. The most important pathologic cause is atherosclerosis, which results in coronary and cerebrovascular events and other major health problems (Ozturk & Kutlu, 2010). Thus, the prevention of CV disease and atherosclerosis plays a key role in the formation of a healthy elderly population (Packard et al., 2005). Maintaining an optimized cardiovascular risk profile seems likely to improve the chance of becoming a centenarian, especially for males (Benatti et al., 2010).

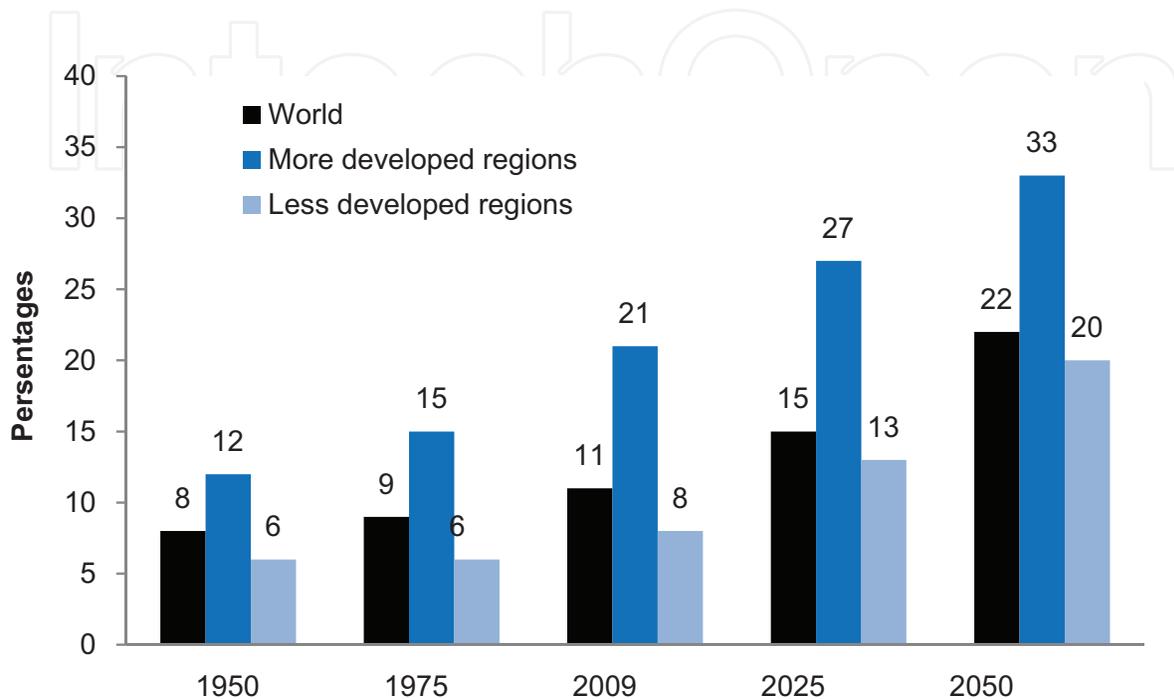


Fig. 1. Population aged 60 or over: world and development regions, 1950-2050 (United Nations Department of Economic and Social Affairs Population Division Report, 2009)

### 3. Cardiovascular risk factors in the elderly

The most well known **CV risk factors in the elderly** are high blood pressure (BP), wide pulse pressure, age (male > 55, women > 65), smoking, dyslipidemia (total cholesterol >190 mg/dL, or LDL cholesterol >115 mg/dL, or HDL cholesterol in men <40 mg/dL, female <46 mg/dL, triglyceride >150 mg/dL), fasting glucose 102-125 mg/dL, abnormal glucose tolerance test, diabetes mellitus, abdominal obesity (abdominal circumference: M > 102 cm, F > 88 cm), and a family history of premature CV disease (Mancia et al., 2007).

There are of course some major difficulties associated with identifying subjects with a higher CV risk in the elderly populations; every old person may have different nutritional, coagulative, renal, psychogenic, cognitive, and immunity disorders, which all affect CV risk factors and make every old person unique (Redgrave, 2004).

### 4. Hypertension in the elderly

The European Society of Cardiology describes hypertension (HT) as systolic and diastolic BP values that are over 140 and 90 mm Hg respectively and isolated systolic hypertension (ISH) as systolic BP at  $\geq 140$  mm Hg and diastolic BP <90 mm Hg respectively. Both types of HT

can be divided into 3 phases according to severity (Mancia et al., 2007, 2009). Based on this definition, >50% of elderly people are hypertensive and 30% of the population over age 80 suffers from ISH (Staessen et al., 2000). Given the increasing life span of the older population, this poses a higher risk for the elderly, as indicated by the Framingham study which suggested that the lifetime probability of an elderly person developing HT is as high as 90% (Splansky et al., 2007).

#### 4.1 Blood pressure in the elderly

The **pathophysiological reasons for HT in the elderly** are stiffness and compliance reduction of the aorta and great vessels, the increase in systemic vascular resistance, weakness of baroreceptor reflexes, reduction of CV beta-receptor activity, and low plasma renin activity despite a fall in volume reduction and environmental factors (diet, stress, inactivity, and obesity). As a result, systolic BP increases, diastolic BP decreases and pulse pressure rises. All of these combine to create ISH, a natural result of aging (Izzo, 2005; Hajjar et al. 2001). Although ISH is the most frequent type of HT in the elderly, systolic and diastolic HT can also be seen, albeit to a lesser extent (**Figure 2**, Chobanian, 2007).

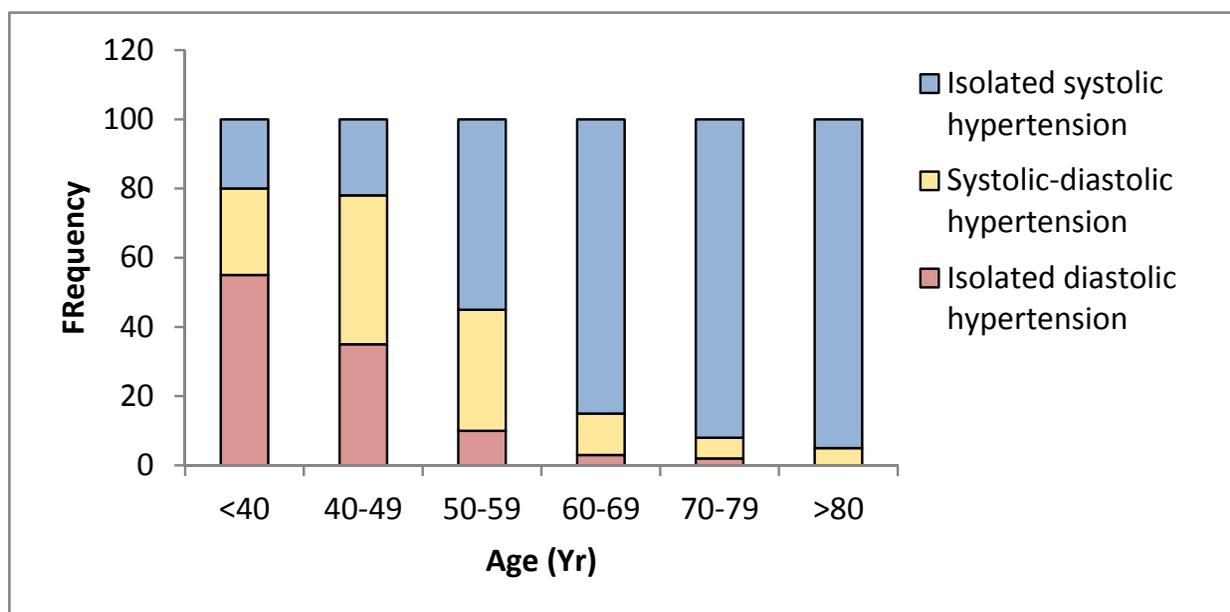


Fig. 2. Frequency of hypertension according to subtype and age (Chobanian, 2007).

ISH creates different clinical manifestations in the elderly and young people. In **young people**, aortic regurgitation, high output states, hyperkinetic circulation, tachycardia, high left ventricular ejection rate, high cardiac index, normal systemic vascular resistance accompanied by high plasma volume are components of **ISH** whereas the main characteristics of the **ISH in the elderly** are loss of aortic compliance, normokinetic circulation, normal heart rate, decreased left ventricular ejection rate and cardiac index, increased systemic vascular resistance and low plasma volume (Adamopoulos et al., 1975).

The specifics of HT in the elderly have been described abundantly in the literature. Baroreflex sensitivity decreases with age, leading to an impaired baroreflex-mediated increase in the heart rate and total systemic vascular resistance in response to decreased BP

(Gribbin et al., 1971). Therefore, elderly people are more likely than younger people to develop **orthostatic and postprandial hypotension** when treated with antihypertensive medications. Another specific condition called **pseudohypertension** is a frequent finding in the elderly, and refers to a falsely high systolic BP resulting from markedly sclerotic arteries that do not collapse during inflation of the BP cuff. Pseudohypertension can be confirmed by measuring intra-arterial pressure.

The importance of hypertension lies in its being an independent and strong risk factor for atherosclerotic cardiovascular disease (CVD), heart failure, stroke, kidney failure, and death in all age groups. The relationship between HT and risk of CVD is linear, progressive and continuous, in that the higher the BP, the greater the risk of CVD (Mancia et al., 2009). However, compared with diastolic BP, systolic BP is a much more accurate predictor of cardiovascular morbidity and mortality (Mancia et al., 2007).

In the elderly, combined HT and ISH increase the risk of congestive heart failure, coronary artery disease, transient ischemic attacks, and incidences of strokes and death (Joint National Committee, 1993). Even with the same BP values, elderly people with HT are 3-4 times more likely than younger hypertensives to suffer from CVD. (Chobanian et al., 2003). Although BP control rates are lower in elderly hypertensives (Hyman & Pavlik, 2001), the results of treatment are better in the elderly (Staessen, 2000). Another striking finding shows that in same age normotensives both type of HT increase the risks of congestive heart failure 6 times and CV mortality 8 times in women and 2 times in men (Sowers, 1987).

#### 4.2 Clinical studies about hypertension in the elderly

Many studies have examined the **benefits of pharmacological treatment of systolic and/or diastolic HT** in the elderly, and have demonstrated a positive effect of medication on the prevention of strokes, coronary artery disease, heart failure, and all CVD (Amery et al., 1982; Ekblom et al., 1992; Hypertension Detection and Follow-up Program Cooperative Group, 1988; Medical Research Council Working Party, 1985; Thijs et al., 1992).

Studies have also compared the **effectiveness of different antihypertensive drugs in elderly hypertensive** patients, and have shown that diuretics, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers all have similar effects (Brown et al., 2000; Hansson et al., 1999). Subgroup analysis of another study showed that alpha-blocker increases heart failure in older hypertensives and chlortalidon is shown to be superior to other pharmacological agents (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group, 2003). In studies dealing with the **ISH in the elderly**, thiazide diuretics and dihydropyridine calcium channel blockers were shown to have similar effects (SHEP Cooperative Research Group, 1991; Staessen et al., 1997; Wang et al., 2000). Both decreased the incidence of strokes by 30%, the risk of CV events by 23%, and the total number of mortality cases by 13%. Those who were shown to benefit most from this treatment were males of an age > 70 years, and who suffered from wide pulse pressure and CV complications.

All of these studies are compatible with the conclusion that treatment of elderly hypertensives reduces cardiac and cerebral mortality and morbidity. Treatment compliance was good and drugs were well tolerated. These studies also show us that diuretics, calcium

channel blockers, as well as beta-blockers, angiotensin receptor blockers and angiotensin converting enzyme inhibitors may be started as an initial drug, but alpha-blockers should not be used as the first drug and/or as monotherapy.

In studies on **very old** (80-99 years) hypertensives, treatment was shown to severely reduced stroke, fatal and nonfatal CV disease, but total mortality did not change (Staessen et al., 2000). In a pilot study, the risk of strokes decreased by 53% and the risk of fatal strokes decreased by 43% in the combined treatment groups, as compared with the placebo group; however, there was an unexpected increase in total mortality (Bulpitt et al., 2003). However, the study Hypertension in the Very Elderly (HYVET) has shown that antihypertensive treatment caused a reduction in heart failure, strokes and also total mortality (**Figure 3**, Beckett et al., 2008). The prevalence of CV disease was only 12% at baseline in HYVET patients. Therefore, the absolute reduction in CV events resulting from antihypertensive drug therapy in an elderly population with a high prevalence of CV disease could be much greater than observed in HYVET. In conclusion, for hypertensive patients older than 80 years, if there is adequate quality of life and a life expectancy of more than 2 years, it makes sense to apply the same guidelines for younger hypertensives.

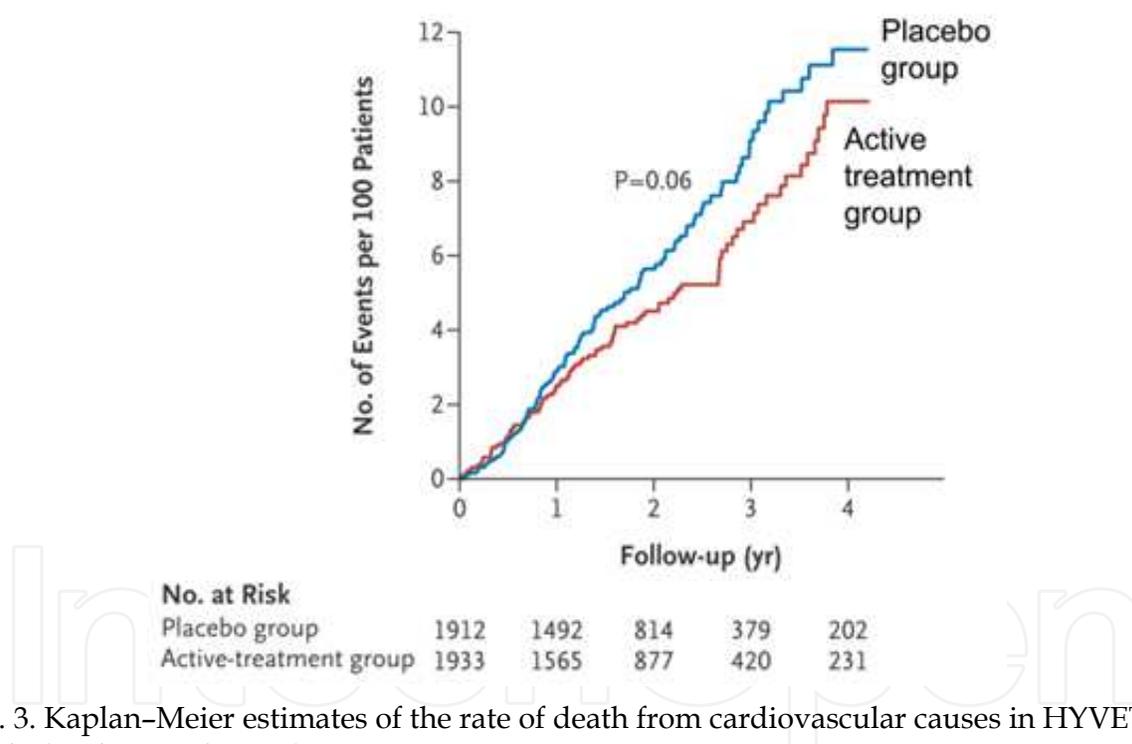


Fig. 3. Kaplan–Meier estimates of the rate of death from cardiovascular causes in HYVET study (Beckett et al., 2008).

In the first observational studies of **hormone replacement therapy (HRT)** in postmenopausal women, it was shown that HRT prevents the development of CVD. However, in the Heart and Estrogen/Progestin Replacement Study (HERS) (Hulley et al., 1998) and Heart and Estrogen/Progestin Study II (HERS II) (Grady et al., 2002) studies, performed some years later, no long- or short-term benefits of HRT were observed. In the Women's Health Initiative WHI (Wassertheil-Smoller et al., 2004) study of patients being treated with HRT, deaths resulting from coronary heart disease, strokes, pulmonary embolisms, venous thromboembolisms, and risk of ischemic strokes increased and BP rose

slightly. For these reasons, HRT should not be given to prevent CV endpoints, without knowing the baseline BP, if any, and patients should be monitored closely.

### 4.3 Treatment rules of hypertension in the elderly

Factors to be taken into account in deciding when to start treatment in elderly and young hypertensives are not fundamentally different. The decision is based on both BP level and the patient's CV risk factors (Mancia et al., 2007, 2009). For a hypertensive patient in stage 1, who does not display any risk factors, it is possible to monitor him or her for several months with non-drug therapies, whereas non drug therapies must be started immediately in patients with established CV or renal disease (Mancia et al., 2007., 2009).

**Non-drug treatments**, such as sodium restriction, maintaining ideal weight, regular exercise, smoking cessation, reducing dietary fat content, etc., have proven efficacy and should be administered before pharmacological treatment, or with it. Lifestyle changes are the first, primary, and permanent treatment recommendations in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Chobanian et al., 2003), as well as the European Society of Cardiology (ESC) hypertension guidelines (Mancia et al., 2007). In the Tone study (Trial of Non Pharmacologic Interventions in the Elderly) (Kostis et al., 2002) salt restriction, weight loss, or both were attempted in 985 patients between the ages of 60-80. Each method alone reduced BP, but the combination of the two methods had the most successful results.

In elderly hypertensives, there is no evidence that any drug dramatically affects combined HT or ISH. Most elderly hypertensives suffer from other health problems (target organ damage and associated CV cases), and so the choice of drug should be based on each patients personal requirements. Although there is no clear difference in the results, tolerability, cost, compatibility with other drugs and patient preference affects the choice of the initial antihypertensive drug. A recently published meta-analysis (Staessen et al., 2000), showed that drug selection is less important than the reduction BP for the prevention of CV outcomes (Mancia et al., 2007). It is difficult to lower BP below 140 mm Hg in many old patients, so often two or more drugs are required (Fagard et al., 2002; Mancia et al., 2002). In such cases, the general rules about which drugs may be combined with each other will guide the selection of agents (Mancia et al., 2007).

Compared with younger patients, however, older patients are at an increased risk for serious adverse effects, including effects of drug interactions related to the use of multiple medications. Drug dosage is half that prescribed to young people, and it is important that BP be lowered at a slow pace. Syncope in elderly persons may be caused by orthostatic or postprandial hypotension, and frail elderly persons are at an increased risk for these adverse consequences of antihypertensive therapy. Blood pressure should be measured regularly, especially after eating, with the patient sitting in an upright position. Marked orthostatic or postprandial hypotension should prompt a reduction in drug dosage or substitution to another antihypertensive agent.

According to hypertension guidelines, the goal of treatment of hypertension in elderly persons is to reduce the blood pressure to less than 140/90 mm Hg and to less than 130/80

mm Hg in those with diabetes mellitus or chronic renal insufficiency (Chobanian et al., 2003; Mancia et al., 2007). There is sufficient evidence to recommend that SBP be lowered below 140 mm Hg (and DBP below 90 mm Hg) in all hypertensive patients, both those at low moderate risk and those at high risk. Evidence is less available for elderly hypertensive patients, in whom the benefit of lowering SBP below 140 and 130 mmHg has never been tested in randomized trials. The optimum diastolic blood pressure goal in elderly persons is unclear (Aronow, 2010). Based on current data, it may be prudent to recommend lowering systolic and diastolic BP values within the range 130–139/80–85 mmHg, and possibly close to the lower values in this range, in all hypertensive patients. More critical evidence from specific-randomized trials is needed for more specific conclusions (Mancia et al., 2009).

## 5. Dyslipidemia in the elderly

Atherosclerosis is a continuous degenerative process, and its burden increases progressively with aging. The pathology consists of chronic remodeling of the vascular wall and participation of the calcification process. Hyperlipidaemia is one of the most important risk factors in the development of atherosclerosis. Older studies indicated that serum cholesterol was related to CV disease, but the relationship between serum cholesterol and CV mortality was not clear. A few decades later, a study gave us the first scientific clue showing that lowering serum cholesterol decreases the CV morbidity by decreasing atherosclerosis (The Lipid Research Clinics, 1984). Significant reduction in cholesterol levels and CV disease morbidity can be achieved through lifestyle changes and drug therapy. Our information and knowledge on the importance of cholesterol plaque stability and its relationship with lipid lowering drugs developed subsequently. The current accepted theory is that the main mechanism of action of lipid lowering drugs is to ensure a more stable formation of atherosclerotic plaques (Streja, D. & Streja, E., 2011).

### 5.1 Atherogenic particles and aging

**Atherogenic particles** are defined as total cholesterol, low-density lipoprotein (LDL) cholesterol, non-high density lipoprotein (HDL) cholesterol (Total cholesterol-HDL cholesterol) or Apolipoprotein B (Apo B). Their role in CV diseases is shared by other risk factors, such as high BP, obesity, smoking and alcohol.

Elderly individuals have different properties of lipid metabolism compared with younger individuals, as **physiological changes can be seen in the lipid profile** of the elderly. In general, **atherogenic particles increase with age**. Age-related changes in the total serum cholesterol concentration primarily result from an increase in LDL cholesterol levels. Apolipoprotein B and LDL cholesterol show a progressive increase with age (Aslam et al., 2009). The mechanisms responsible for the progressive age-related elevation in LDL cholesterol have not been fully explained; however, various data suggest a decrease in the fractional catabolic rate of LDL cholesterol as playing a primary role. This reduction in LDL cholesterol catabolism is believed to result from diminished activity of hepatic LDL cholesterol receptors (Ericsson et al., 1991). Triglycerides (TG) increase with age, and reaches maximum values in men at age 50-59 and in women at 60-69. In contrast, HDL cholesterol levels do not vary much with age, being approximately 10 mg/dL higher in women than men throughout their lifetime (Aslam et al., 2009).

## 5.2 Clinical studies about atherogenic particles and cardiovascular risk

Numerous studies, including those with elderly subjects, reported a high risk of coronary artery disease in subjects with only high, but also low, **total cholesterol** concentrations (Abbott et al., 2002, Higgins & Keller, 1992; Manolio et al., 1992; Tyroler & Ford, 1992). However, there are some confusing data, in that a meta-analysis about the relationship between total cholesterol and coronary events shows a significant association for men aged 65-80 years, but none for women over 65 years or men over 80 years (Anum & Adera, 2004). This suggests that total cholesterol may not be a good parameter to predict coronary events in the elderly (Krumholz et al., 1994). This lack of association is especially valid for elderly women (Barrett-Connor, 1992).

One meta-analysis showed that high **triglyceride** levels are strongly associated with a significantly higher CV risk in middle age cohorts (Sarwar et al., 2007). Another study reported that in the highest TG quintile an 80% increase in the risk of coronary events, a 70% increased risk of coronary death and a 50% increased risk of stroke was observed in all age groups and genders (Patel et al., 2004). A specific study for participants aged 65 years and older showed a gender specific risk of triglycerides, which were shown to be powerful independent predictors of CVD in women only (Mazza et al., 2005). Therefore, it seems that high TG levels increase CVD in the elderly, but women are more affected.

**HDL cholesterol** is the parameter of strongest association with CV risk in lipid particles, especially for middle-aged men and women. Subjects with high HDL cholesterol are more likely to have long life expectancy (Arai & Hirose, 2004; Barter, 2004). In The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Study, it is reported that low HDL cholesterol in elderly people determines both the risk of fatal and nonfatal coronary and cerebrovascular events and the efficiency of statin therapy (Packard et al., 2005).

**Non-HDL cholesterol** does not appear to be a reliable predictor of CV risk in older subjects. Some studies have reported that **Apo B and Apo A1** might be superior to the measurement of standard lipid parameters (Bruno et al., 2006).

Randomized controlled trials of the last 30 years used groups of older individuals, which was often not the case in earlier studies. Most of these recent studies have shown that lipid-lowering **statine therapy for both primary and secondary prevention reduced CV events in elderly individuals**.

Two randomized **primary prevention clinical trials** (CARDS, Neil et al., 2006 and ASCOT, Sever et al., 2003) reported separately that elderly and young individuals showed similar results after lipid-lowering drug therapy. Cardiovascular event rates in treated individuals in both groups were significantly less frequently observed. In other words, the treatment of hyperlipidemia, are useful in both younger and elderly individuals. However, data on primary prevention in the elderly are less clear. There is a significant reduction in coronary events, coronary deaths and all cause mortality but numbers needed to treat are higher than in secondary prevention (Berthold et al., 2011).

Cholesterol And Recurrent Events (CARE) (Sacks et al., 1996), Scandinavian Simvastatin Survival Study (4S) (The Scandinavian Simvastatin Survival Study Group, 1994), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) (LIPID Study Group, 1998) are three large **secondary prevention clinical trials**. They include large numbers of elderly

patient subgroups and analyses of these studies have demonstrated similar results. In not only the middle aged, but also in the elderly, CV events were seen less in treated cases, (Lewis et al., 1998).

Some current studies are designed specifically for elderly patients. The PROSPER trial (Packard et al., 2005), was designed to determine whether pravastatin 40 mg/d reduces coronary and cerebral events in older patients aged 70-82 years who have preexisting vascular disease or who are at high risk for vascular disease and stroke. This double-blind randomized trial included 5804 patients on either placebo or 40 mg of pravastatin. The primary composite endpoint was definite or suspected death from coronary heart disease, nonfatal myocardial infarction, or fatal or nonfatal stroke. After 3 years, coronary events were significantly reduced by 19%, and coronary mortality was reduced by 24% in patients on pravastatin; however, this therapy had no effect on stroke or cognitive function. The PROSPER study clearly showed that the benefits of statin therapy observed among middle-aged adults can also be extended to older patients (>70 years). Study Assessing Goals in the Elderly (SAGE) trial (Deedwania et al., 2007), enrolled 893 people aged 65-85 who had coronary heart disease and one or more past episodes of myocardial ischemia. They were randomized according to intensive (atorvastatin 80 mg/day) vs. moderate (pravastatin 40 mg/day) lipid-lowering therapy. After one year, intensive therapy was shown to reduce cardiac events by 28%, indicating the benefit of intensive statin therapy in older men and women.

It is widely accepted that age is not a factor affecting the benefits of lipid-lowering drugs. Therefore, today's guidelines for the prevention and treatment of CV diseases, recommend lipid-lowering drugs without specifying an age limit. Despite the satisfactory results obtained from the statin trials that included elderly patients, there are still knowledge gaps regarding the benefits of therapy with other hypolipidemic agents, such as fibrates and niacin, in the elderly.

### 5.3 Treatment rules of dyslipidemia in the elderly

The National Cholesterol Education Program Adult Treatment Panel 3 (**Table 1**, The National Cholesterol Education Program expert panel, 2001) and the American Heart Association (AHA) and American College of Cardiology (ACC) (Smith et al, 2006) suggest LDL cholesterol goals for lipid lowering therapy. For all patients with coronary artery disease, ACC/AHA recommends LDL set the goal at <70 mg/dL.

Not all guidelines accept old age as a parameter affecting treatment methods of dyslipidemia, but they suggest evaluating and treating every old person individually. This is because guidelines are based on risk scoring, but most of the risk assessment tools are not adaptable to the elderly. So, when deciding which drug (especially statin) therapy to use in the elderly, instead of applying the algorithms routinely prescribed for persons with multiple risk factors, the physician's decision must be based on the HDL cholesterol level, other vascular diseases, accompanying chronic diseases, frailty, benefit/cost assessment, safety, tolerability, and patient preference. The AHA Evidence-based Guidelines for Cardiovascular Disease Prevention in Women (Mosca et al., 2007) also declares that treatment rules are not clear for the treatment of very elderly women, because of the exclusion criteria of many studies. Uncertainty about the benefits of hypolipidemic treatment

in these patient groups and the resulting question marks indicate the need for more clinical trials that included men and women patients at a very advanced age.

Risk Level	LDL Goal
Coronary heart disease and coronary heart disease risk equivalent*	<100 mg/dl
Multiple (2+) risk factors	<130 mg/dl**
0-1 risk factor	<160 mg/dl

\*Diabetes, chronic kidney disease

\*\*LDL cholesterol goal for multiple risk factors and 10 year risk >20 percent is 100 mg/dL.

Table 1. Low-density lipoprotein goals for three risk levels (The National Cholesterol Education Program expert panel, 2001).

Most guidelines for CV prevention recommend **lifestyle change** as an important measure for therapy of dyslipidemia in all age groups. Their suggestions are based on several randomized clinical trials. There is no specific advice for the elderly in these trials. Beyond the randomized clinical trials, there are many positive observations about the use of grains, nuts (Hu et al., 1999), the Mediterranean diet (particularly walnuts), monounsaturated fat (olive oil), smoking cessation, and strong negativities about foods with high glycemic index or containing trans fatty acids (Lemaitre et al., 2006).

**Statins** decrease cholesterol synthesis by inhibiting HMG CoA Reductase, the most important enzyme in the synthesis of cholesterol. All statins also perform anti-inflammatory and anti-proliferative functions in other metabolic ways. These properties, referred to as "pleiotropic effects," (Arnaud & Mach, 2005; Athyros et al., 2009; Gotto & Farmer, 2001; Liao & Laufs, 2005) are improvement in endothelial function, decreased smooth muscle cell proliferation and prevention of vascular remodeling. Statins also reduce the level of anti-inflammatory markers such as C-reactive protein (CRP) (Jialal et al., 2001). **Fibrates** increase fatty acid oxidation and reduce very light density lipoprotein (VLDL) and Apo C3 concentration (Chinetti-Gbaguidi et al., 2005; Robillard et al., 2005). A process of activation of lipoprotein lipase increases VLDL catabolism. Fibrates have pleiotropic effects too. Other lipid lowering drugs are **bile acid binding resins, niacin, cholesterol absorption inhibitors,** and **omega-3 fatty acids**. **Serum antioxidants** have been associated with a reduced CV mortality in the elderly, however, the benefit of antioxidant therapy on CV mortality is yet to be proven (Buijsse et al., 2005; Fletcher et al., 2003).

#### 5.4 Safety and toxic effects of lipid-lowering drugs in elderly individuals

The safety of using lipid-lowering drugs is diminished in the older age group. With age, the glomerular filtration rate, hepatic blood flow, and elimination of drugs can decrease (Redgrave, 2004). All of these may result in the drugs, including statins, causing **augmented toxic effect**. In addition, aging increases the number of co-morbidities requiring pharmacologic intervention and this in turn results in polypharmacy. All these factors contribute to a modification of the risk/benefit ratio of preventative interventions. This further decreases the safety of lipid lowering drugs.

The most important side effects of statins are **rhabdomyolysis**. Although it has been suggested, it has not yet been definitively proven that statins cause decreased cognitive

function. Meta analyses of statins have not confirmed the hypothesis that they may increase cancer prevalence. Some studies recorded decreased colorectal cancer frequency (Poynter et al., 2005), but other studies were not able to confirm this (Bailey et al., 2007; Bouchard et al., 2007; Gibson et al., 2006; Goodpaster et al., 2006; Ho et al., 2006; Fonarow GC, 2005; Naughton et al., 2007). Another study (Setoguchi et al., 2007) concluded that it is unlikely that statins have any relationship with cancer incidence. Larger studies are needed to be performed in order to use statins for the prevention of cancer in medical practice. An old study that compared fibrates (Committee of Principal Investigators, 1978) showed a decrease in the risk of myocardial infarction, but an increase in the risk gastro-intestinal cancer. There is no such indication in currently used fibrates.

## 6. Smoking in the elderly

Smoking in old age has been a subject of much attention in past years. In studies across the board, smoking was seen to jeopardize the health of individuals in every age group. The risks were caused not only by smoking in elderly individuals, but also by exposure to passive smoke.

Many health problems are likely to occur in old age. Hypertension, heart and vascular diseases, cancer, chronic diseases are associated with, and more frequently experienced during this period. Smoking tobacco products increases the risk of each of these conditions, and if they occur at the same time, the risk greatly increases. Smoking cessation decreases the associated risks for each organ, and increases physical capacity, which results in a decrease in the threats to the health of the heart and blood vessels.

The relationship between smoking and adverse cardiovascular events and death is well established. Numerous studies have demonstrated that cigarette smoking increases CV morbidity and mortality in elderly patients with CAD. Smoking also aggravates angina pectoris and precipitates silent myocardial ischemia in older patients who have CAD. At 40 month follow-up of 644 older men, mean age 80 years, and at 48-month follow up of 1488 older women, mean age 82 years, current cigarette smoking increased the relative risk of new coronary events (nonfatal or fatal myocardial infarction [MI], or sudden cardiac death) by a factor of 2.2 in older men and 2.0 in older women (Aronow & Ahn, 1996).

There are three main approaches for smoking cessation: to never begin smoking, to quit smoking, and to prevent passive smoking. From a prevention standpoint, goals should be the same for each age group, but abstinence by never beginning to smoke remains the best method of preventing the adverse CV effects of smoking. However, if it is not possible, based on the available data, older men and women who smoke cigarettes should be strongly encouraged to stop smoking because cessation of smoking will reduce CV and all-cause mortality after MI. However, changes in an individual's perception of health in old age may create difficulty in an attempt at smoking cessation. The elderly are often more resistant to changing their behavior patterns than younger patients. There is a widely accepted perception in old age that, "there is little point to quitting smoking at this age." This perception is not based on reality, as stopping smoking is beneficial at all ages. In order to change such false perceptions, a smoking cessation program should be instituted (Smith et al., 2006). They are frequently applied toward young people, adults and the elderly quite successfully. Intervention programs that use behavioral approaches, physician counseling,

close clinical follow-up, and pharmacologic therapy are recommended to help older adults who are tobacco dependent (Williams et al., 2002).

Quitting smoking has an early impact on mortality risk, reducing mortality by as much as 50% in those with prior MI, with most of this mortality benefit occurring in the first year (Sparrow & Dawber, 1978). In patients over the age of 70 years with CAD, participating in the Coronary Artery Surgery Study (CASS) registry, morbidity and mortality rates were reduced among those who stopped smoking, with risk reductions similar to those seen among younger patients (Hermanson et al., 1988). The risk of new coronary events falls immediately after cessation of smoking, returning to that of non-smoking elderly persons within 5 years.

## 7. Inflammation and heart in the elderly

Inflammation markers related to CV risk have been known for a long time. Some **meta-analyses** clearly show that high sensitivity C-reactive protein (hs-CRP) is useful in predicting CV risk. It is believed that hsCRP gives information about intravascular inflammation and unstable atherosclerotic plaque (Kubo et al., 2009). hs-CRP represents the atherosclerotic burden like ankle brachial index, increased carotid intima-media thickness or vascular calcifications (Cao et al., 2003) not only in young but also old patients.

A prospective big **study** has shown that hs-CRP accurately predicts CV mortality (Clarke et al., 2008). However, it is suggested that high CRP is also a good independent marker for nonvascular mortality. In another study, mortality risk was much greater if there was more than one inflammatory marker (Wang et al., 2006). Results of these **studies** suggest to measure hs-CRP levels in order to measure the benefit of statin therapy. The AHA suggests to measure hs-CRP in order to determine higher risk of CV events and to limit the use of hypolipidemic therapy in specific groups of patients. Some **cardiovascular risk estimation models** have added hs-CRP to their parameters (Cook et al., 2006; Ridker et al., 2008). These models are suggested to be used in patients up to 79 years of age.

Most data detailing the importance of hs-CRP in the **elderly** uses The Cardiovascular Health Study as its main source. This study implicated that CRP is a strong and independent predictor of 10-year coronary artery disease risk in patients over age 65 (Cushman et al., 2005).

hs-CRP indicates the risk of CV events and other causes of mortality for all ages (Kaptoge et al., 2010). But its specificity decreases with increasing age. hs-CRP increase is a part of the aging process and high hs-CRP values are frequent in healthy older people (Streja, 2011). It not only increases progressively with healthy aging, it may also be due to of the higher number of disease in the elderly, so the specificity of CRP for CV risk is lower than younger patients. Furthermore, according to some studies, well-known traditional risk factors predict CV risk but hs-CRP adds only a few, or it does not change the risk status. Because of the abovementioned reasons, there are still hesitations about adding hs-CRP to the process of CV risk determination in the elderly.

Other inflammatory parameters are also found to be related with mortality but we do not have too much information about them compared with CRP. Some studies compare interleukin 6 (IL-6) and hs-CRP and conclude that the ability of IL-6 to estimate risk is

modest, while the ability of hs-CRP is only borderline (Rodondi et al., 2010). Furthermore, there are some close associations between inflammatory markers, Factor VIII, and D-dimer, which are the risk factors for increased risk of death in the elderly (Zakai et al., 2007).

## 8. References

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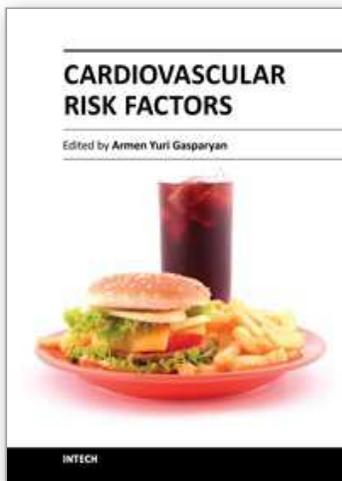
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## **Cardiovascular Risk Factors**

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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