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**PRIMARY PREVENTION OF CARDIOVASCULAR RISK IN OCTOGENARIANS
BY RISK FACTORS CONTROL**

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INTRODUCTION

Primary prevention of cardiovascular events in older adults is a relevant problem, because of lack of evidence for safe and efficacious therapy, its costs and elderly quality of life, Italy's aging population is constantly increasing, so cardiovascular disease (CVD) primary prevention in the elderly is a prime objective. Life expectancy has dramatically increased over the last 2 decades, the proportion of individuals aged 80 years and older has grown rapidly in Europe and United States, but cost / effective ratio of CVD prevention through risk factors control is debated [1 - 2].

The aim of our paper is to assess if, when and how to perform CVD primary prevention on octogenarians, through a critical analysis of the guide lines recommendations in the lights of evidences on treatment.

METHODS

Our review was performed using the following keyword: octogenarians; arterial hypertension; cardiovascular risk, searching on 2 engines: Pubmed and Medlin. We considered 50 articles. Inclusion and exclusion criteria are assessed in CONSORT Flow Diagram, FIGURE 1

OCTOGENARIANS AND HYPERTENSION

Blood pressure increases with age, and there is an higher prevalence of hypertension in the elderly [3-4], and high systolic blood pressure (SBP) may be the most important risk factor for cardiovascular events [5]. Many large clinical trials suggest that prescription of antihypertensive drugs, to reach a value of blood pressure required by current guidelines, may reduce cardiovascular morbidity and mortality in the elderly. In HYVET (Hypertension in the Very Elderly Trial) [6] concerning antihypertensive treatment on people over 80 years aged, a lowering in blood pressure was associated with 30% reduction in stroke, 21% reduction in all-cause mortality, and 64% reduction in heart failure. In SPRINT (Systolic Blood Pressure Intervention Trial) [7], concerning over 80 years aged, a SBP to a target value lower than 120 mmHg was associated with 34% reduction in cardiovascular

events and 33% reduction in all-cause mortality. These results from clinical trials lead to delivering more intensive drug therapy to lower SBP among very old people. Nevertheless although both American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) support that all physicians must treat hypertension in the elderly, they suggest a target of BP of 150/90 mm Hg, that substantially improves health outcomes in this setting of subjects. There is less consistent evidence to suggest to lower SBP, less than 120 mm Hg, that also if did not increase falls or cognitive decline is however associated with hypotension, syncope, and greater medication burden, so it appears reasonable to focus our attention on the benefits and harms of an aggressive or more moderate approach, discussing about the benefits and harms of specific blood pressure targets with the single patients [8-9]. Our position is derived from randomized clinical trials regarding primary objectives, and from observational studies regarding harms due to excessive treatment [10-14]. The key-points of our position are:

- a) Elderly hypertensive patients need for receive a pharmacological treatment for a SBP greater than 160 mmHg
- b) The absolute risk reduction (ARR) estimated by reduction of SBP from greater of 160 mmHg to lower than 150 mmHg, comparing treated and untreated, was for all causes mortality: 1.64, for incidence of stroke: 1.13 and for all cardiac events: 1.25.
- c) A more aggressive treatment, with target of SBP lower than 140 mmHg, does not significantly reduce all causes mortality or cardiac events, but ensures only a small reduction in the incidence of stroke (ARR 0.49).
- d) Many of the more aggressive treatment studies cannot be taken into account because the SBP target, lower than 140 mmHg, has not been achieved, therefore there are no reliable data about potential harms of this kind of treatment.

- e) Patients who have already suffered a stroke or a TIA, if submitted to an aggressive treatment, to achieve a SBP of 130-140 mmHg, present a decreased risk of recurrence (ARR 3.02) but the risk of cardiac events or all causes mortality remain unchanged.
- f) There are no evidence to support the treatment of patients with isolated diastolic hypertension.
- g) There is a low-quality evidence suggesting that aggressive treatment to achieve SBP between 121.5 and 143 mmHg increases the risk of syncope.
- h) There is a good-quality evidence to treat elderly people with SBP constantly greater than 150 mmHg.
- i) There is a modest-quality evidence that suggest to consider a target of treatment lower than 140 mmHg, only for elderly people with a previous stroke or TIA, to reduce the risk of recurrence
- j) There is a low-quality evidence that in the elderly, on patients with high cardiovascular risk, a target of treatment lower than 140 mmHg may decrease the risk of stroke or cardiac events, where for elderly patients with high cardiovascular risk we mean those affected by peripheral vascular disease, diabetes, chronic renal failure, metabolic syndrome, 10 years CV risk greater than 15% on patients aged ≥ 75 years.

Joint National Committee 8 (JNC-8) [15] has spark off a debate about the target of hypertensive in the elderly and the same controversy is reported in these guidelines: over 60 years SBP target values must be lower than 150 mmHg, a target of 140 mmHg is suggested for patients with a previous stroke or with a high cardiovascular risk. However, considering the reachability of the target, potential therapy harms, patient's adherence to the therapy itself, a reasonable position is to detect a personalized targets for each individual patient according to his clinical conditions and comorbidities, without consider the target value suggested by guidelines an objective to be achieved at any cost. .

OCTOGENARIANS AND DYSLIPIDEMIA

Clinical trials suggest in the elderly people with high levels of total Cholesterol (TC) or LDL-cholesterol are likely to benefit by lowering these levels. This is also supported by the National Cholesterol Education Program (NCEP) guidelines [16]. Nevertheless we need of caution in lowering cholesterol to excessively low levels (TC <145 mg/dL) in the elderly because of subclinical frailty of these patients [17]. An interesting study recruited elderly subjects, aged 85-100 years, carrier of a CETP gene polymorphism, a low ApoB / ApoA1 ratio, condition associated with the detection of circulating “buoyant LDL”, LDL less dense and larger that float to the ultracentrifuge analysis. This lipoprotein structure is associated with a low prevalence of atherosclerosis and CV events [18]. On the contrary the detection of circulating pathogenic, dense and small LDLs, according to Morley [19], justifies the pharmacological treatment of hypercholesterolemia even in very elderly subjects.

Arterio Sclerotic Cardiovascular Diseases (ASCVD) are common in the elderly, but the optimal blood level of total cholesterol and/or LDL- cholesterol to prevent them is still unclear. Observational studies on U.S. subjects assess a correlation curve between both total and LDL cholesterol levels with incidence of coronary artery diseases (FIGURE 2 and FIGURE 3) [17]. The relationship between hypercholesterolemia and CV events is complex in elderly; with aging, the absolute risk of CV events, due to hypercholesterolemia increases, while the relative risk, which assess the strength of the association of hypercholesterolemia with CV events, decreases. The increase of absolute risk is due to high prevalence of hypercholesterolemia and high incidence CV events in elderly population, the mortality rate so increases [20]. The relative risk decrease is instead due to the “harvest effect”: the association between total blood cholesterol levels and CV morbidity and mortality weakens with age, however, because age itself is a major risk factor for CVD, treatment of hypercholesterolemia in the elderly may bring about a greater reduction in absolute risk than it is possible to obtain in younger subjects [21-22]. The most severe patterns of dyslipidemia occur in younger persons and may cause

early death. Moreover, in the elderly, the death probability increases for different causes than CVD: the coexisting diseases that represent the polyopathy of the elderly [23]. Therefore it seems that statin treatment in the elderly, as primary prevention, does not prolong the survival but only modifies the cause of death [24], so there is no evidence that statin treatment is useful in primary prevention in elderly, until a randomized trial will be realized prescribing patterns will be not part of clinical practice [25-26]. In elderly subjects without known CVD, but with high-risk, statins significantly reduce the incidence of myocardial infarction and stroke, but do not significantly prolong short-term survival [27]. The use of statins in elderly patients with known CVD is recommended by the Guidelines [28], but the benefits of these drugs in patients without CVD are still unclear. It is interesting to compare the randomized studies between statins and placebo that assessed all-cause mortality, CV mortality, myocardial infarction (MI), stroke and new onset of cancer in elderly patients (over 65 years) without known cardiovascular disease. Eight studies that enrolled a total of 24.674 subjects (42.7% females, mean age 73.0 + 2.9; mean follow-up 3.5 + 1.5 years) were included in the analysis. Statins, compared to placebo, significantly reduced the risk of myocardial infarction by 39.4% (relative risk [RR]: 0.606, p = 0.003), so as the risk of stroke of 23.8% (RR: 0.762, p = 0.006), conversely, the risk of death for all causes (RR: 0.941, p = 0.210) and cardiovascular death (RR: 0.907, p = 0.493) were not significantly reduced. The new onset of cancer did not differ between statins compared to subjects treated with placebo (RR: 0.989, p = 0.890).

OCTOGENARIANS AND DIABETES MELLITUS

More than 25% of the U.S. population aged over 65 years is diabetic [29], and the aging of overall population is a significant driver of the diabetes epidemic. Although the burden of diabetes is often debated because of its impact on working-age adults, diabetes in older adults is linked to higher mortality, impaired functional status, and increased risk of institutionalization [30]. Older adults with diabetes are at high risk for to develop acute and chronic microvascular and macrovascular complications of the disease. American Diabetes Association (ADA) convened a Consensus

Development Conference on Diabetes and Older Adults (defined as those aged >65 years) since February 2012. The European Diabetes Working Party for Older People recently published guidelines for treating people with diabetes aged over 70 years [31]. These extensive guidelines recommend that the decision to treat must take into account the benefit/risk ratio of the prescription, on an individual basis, considering concurrent factors such as: ability to therapy self-management, risk of hypoglycemia, cognitive status, life expectancy and possible existence of other chronic disabling pathologies. Other recommendation is to perform annual evaluations of functional status, including global/physical, cognitive and affective aspects, using validated instruments, avoiding the use of drugs with high risk of hypoglycemia in this population. Further recommendation is to estimate CV risk in all patients less than 85 years of age, suggesting that beyond this is age the CV risk estimation is less relevant for CV prevention. Glycosylated haemoglobin (HbA1c) targets to be reached in elderly are based on age and comorbidity, so a range of 7–7.5% is suggested for patients with type 2 diabetes without major comorbidities and 7.6–8.5% for frail patients affected by multisystem disease or home care residency including those with dementia, where hypoglycemia risk may be high and the likelihood of benefit low. Management of type 2 diabetes in the elderly must follow specific rules: a strategy focused on physical activity and diet is a leading factor in health and well-being, drugs should be prescribed paying attention to renal function; glycemic targets must be the above mentioned. Indeed, if a poorly controlled diabetes increases by 48% the risk of dementia, particularly fearful in this age setting, hypoglycemia, as values below 70 mg/dl, can cause falls, bone fractures, increase in cognitive impairment, high risk hospitalization. Mediterranean diet and aerobic physical activity are also necessary avoiding a sedentary lifestyle. Glycaemia self-monitoring education is also very important in this age setting, but glucometers with large displays or voice messages for people with vision problems should be chosen. Metformin remains the drug of choice, unless there is a high-grade renal failure or a high NYHA Class heart failure. Among other oral anti-diabetics drugs, we have to choose those without risk of hypoglycaemia, such as DPP-4 inhibitors, avoiding repaglinide and sulphonylureas, because of their side effect severe hypoglycaemia, especially for glibenclamide.

Italian Society of Diabetology (SID) and Italian Society of Gerontology and Geriatrics (SIGG) drafted a position paper “Customizing the treatment of hyperglycemia in the elderly with type 2 diabetes” with a series of recommendations for an appropriate clinical management of elderly diabetic patients [32], 65 % of people with diabetes are over 65 years aged and 20% are over 80. Diabetes treatment in older men and in oldest too must follow special rules. WHO estimates that by 2040 one in 10 people in the world will suffer from diabetes, with a greater prevalence in men than women. The advice of above mentioned diabetologists and geriatricians for optimal management of diabetes in the elderly patient are [32]:

- a) Routinely carry out a nutritional assessment with a standard tool, such as the “Mini Nutritional Assessment”, a survey on physical and behavioral aspects concerning the nutritional status. It takes 10 minutes and is very useful. The elderly person is at high risk of malnutrition, a condition that may lead to reduction of bone and muscle mass and water content, increase in fat mass and finally to sarcopenic obesity.
- b) Interventions on nutrition and physical activity. All elderly patients with diabetes and their caregivers should receive a counseling about nutrition and physical activity. The nutritional plan must be personalized according to individual preferences and habits, physical and mental health and current therapy. Mediterranean diet must be preferred; protein intake should not exceed 10-20 percent of total calories when renal failure occurs. When diet alone fail to meet nutritional needs, it is useful to add: protein supplements, vitamin B12, vitamin D and calcium. An adequate supply of fluids must be guaranteed to avoid dehydration. Older diabetic people in good clinical conditions should also be encouraged to exercise, with a minimum of 150 minutes in a week, of moderate-intensity aerobic exercise divided on three days, combined with resistance and stretching exercises, reducing periods of sedentariness. After 90 minutes of sitting or lying down it is good to move a little. The diet is useful only when associated to physical activity: otherwise it increases the risk of loss of bone and muscle mass.

- c) Impact of other diseases on elderly diabetics. The elderly with type 2 diabetes needs of a multidimensional geriatric assessment of global / physical, cognitive and affective functions, checking for geriatric syndromes and early detection of difficulty on managing anti-diabetes therapy and for occurrence of depression or cognitive impairment, being diabetes associated with an increased risk of dementia by 47% and Alzheimer's by 39%. The dosage of drugs should be determinate according to renal function. The annual screening of the elderly diabetic must include checks for incontinence and/or fall, often due to hypoglycemia, but sometime to peripheral neuropathy or to disorders of vision.
- d) Glycemic goals. In elderly diabetics, the glycemic targets to be achieved with treatment should be modulated on the basis of the drug used and its risk of hypoglycemia. For drugs at low risk of hypoglycaemia (metformin, DPP-4 inhibitors, pioglitazone, SGLT-2 inhibitors, GLP-1 agonists and acarbose) the target of glycated hemoglobin may be lower than 7 %. In case it is necessary to administer drugs at risk of hypoglycaemia, as sulphonylureas, repaglinide, insulin or its analogs, it is better a less restrictive target, glycated hemoglobin 7.0 /7.5% or even higher 7,5/8.0%) for frail patients.
- e) The glucometer, a device for self-monitoring of blood glucose, must be easy to use and read, with large characters or with voice response for patients with vision problems. The importance of glucose monitoring should always be emphasized. The elder must know how to manage hypoglycemia and always carry sugar sachets with him.
- f) Non-insulin therapy. Metformin is the first choice drug in the elderly as long as there is no severe renal impairment, with glomerular filtrate lower than 30 ml/min, severe heart failure as NYHA Class III /IV, respiratory or hepatic failure. When metformin is contraindicated, the first line of treatment are drugs that don't induce hypoglycemia as acarbose, GLP-1 receptor agonist, DPP-4 inhibitor, SGLT-2 inhibitor and pioglitazone. If target of HbA1c is not reached a second, third or fourth drug can be added. DPP-4 inhibitors are preferable to sulphonylureas

and repaglinide in elderly patients due to efficacy, high safety, easy of use, and cardiovascular favorable profile.

OCTOGENARIANS AND HYPERURICEMIA

Age is one of the factors contributing to increased level of uric acid in the blood serum determining hyperuricemia. Gout is today common in the elderly, its pathogenesis and its risk factors are well defined. Despite this, only a minority of patients receive adequate treatment today, mainly due to a lack of awareness concerning many doctors and patients, about clinical relevance of this condition[33]. Hyperuricemia and gout, during the recent years, are increasingly developing in patients of older age, because of the endogenic synthesis of purines, on one side, and the reduced excretion of uric acid, on the other side[34]. Hyperuricemia is detectable not only in gout, but also in other morbid conditions as well; in particular, high level of uric acid correlates with the development of metabolic syndrome, obesity, insulin resistance, arterial hypertension, intake of diuretics and a low-dosed acetylsalicylic acid, alcohol abuse, elderly age and renal failure[35]. Often the therapeutic management is limited to acute attacks treatment, while little attention is paid to the chronic character pathology which, if not adequately treated, leads to the progressive extension of lesions by urate deposits[36]. This happens especially in the geriatric population because in elderly gout is often unrecognised, because of its presentation often atypical, and in any case not adequately treated, with consequent increased risk of morbidity and disability[37-38]. There is an increasingly convincing evidence of a possible cardio-nfro-metabolic injury due to chronic hyperuricemia, it represents a further element for the clinician to treat persistently high levels of uricemia to avoid the hyperuricemia-related pathology not depending by deposition of urate deposits[39]. We need to pay more attention to hyperuricemia in elderly, especially because of the possible iatrogenic nature of this condition and of a possible joint lesion due to urate deposits that could underlie it. There are specific criteria to formulate the diagnosis of gout and effective and well-tolerated therapies even in the

elderly[40]. Furthermore the lesion due to urate deposits is paucisymptomatic or asymptomatic and requires an high level of attention towards this pathology[39]. A reduced content of uric acid at the age of 80 is an evidence of an age-specific selection: patients with a lower content of uric acid may have a longer life[41].

DISCUSSION

Aging of elderly population is constantly growing and people over 80 years are destined to more than double between 2015 and 2080, increasing from 5.3% to 12.3%, this leads to an increase of age dependency ratio from 28.8% in 2015 to 51% in 2080, where we mean the ratio of the elderly population to the working age population [15-64 years] [42]. Istat 2016 data assessed that Italy was in third place in Europe for longevity, with a life expectancy of 84.7 years for women and 80.1 years for men, with the forecast for 2065 to reach 91.5 years for women and 86.6 years for men [43]. Healthy life expectancy (HALE) is a global health indicator in a population, it is the number of healthy years that a newborn could expect to live, considering age-specific mortality rates and age-specific levels of health status [44]. It was estimated that in 2015 the HALE, worldwide, was 63.1 years for both sexes. The gap between life expectancy (LE) and HALE matches the years spent with disability and comorbidity as chronic degenerative diseases as like depression, neurological diseases, loss of vision and hearing, cardiovascular disease and diabetes. All these conditions increase with age, so the increase in HALE is slower than the increase in LE [45]. In 2016 the WHO assessed that HALE was 61.5 years for men and 64.6 years for women. In 2016, according to WHO data, chronic non-communicable diseases were the main cause of health loss in over half of the cases [46]. It is therefore important to implement cardiovascular risk factors estimation in the elderly to maximize quality of life of patients and to lengthen their HALE, choosing the better treatment for each patient sharing the

choice with himself when it is possible, always remembering that elderly patients often have multiple co-morbidities that require a high number of concurrent medications; this may increase the risk for drug-drug interactions, thereby reducing the potential benefits of CVD prevention therapy [47]. Anyway CVD are not an inevitable concomitant of aging. Sometimes autopsy in the elderly reveals atheroma-free coronary arteries, a normal-sized heart and unscarred valves [48]. **We support that primary prevention strategy decisions should consider estimated life expectancy and overall function not only cardiovascular event risks, magnitude and time to benefit or harm, potentially altered adverse effect profiles, and informed patient preferences, so to be an individualized prevention, tailored for single patients.** This strategy is supported by others authors too [49]. So CVD primary prevention need to be more implemented in the elderly [50], this might contribute to improve health status and quality of life in this growing population if correctly performed.

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FIGURES

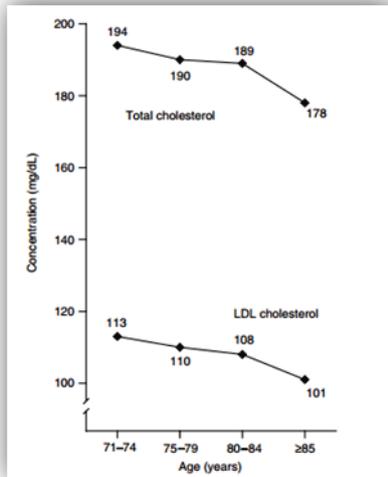


FIGURE 2: Mean level of serum total and low-density lipoprotein (LDL) cholesterol at baseline in each 5-year age group. Both cholesterol measures declined significantly with age ($P < 0.001$).

Taken from [Curb JD et al. Prospective association between low and high total and low-density lipoprotein cholesterol and coronary heart disease in elderly men. *J Am Geriatr Soc* 2004;52:1975-80.]

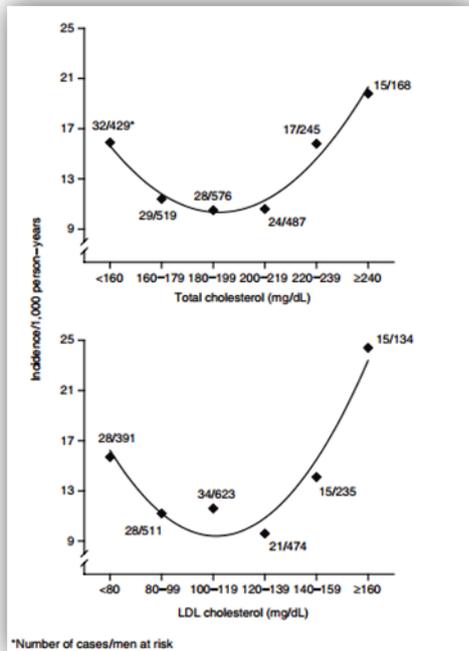


FIGURE 3: Age adjusted coronary heart disease (CHD) incidence rates by clinically relevant categories of total and low-density lipoprotein (LDL) cholesterol. The quadratic relationship between each cholesterol measure and CHD is statistically significant ($P < 0.05$). CHD is defined as unequivocal findings of nonfatal myocardial infarction, coronary death, or sudden death within an hour that could not be attributed to another cause.

Taken from [Curb JD et al. Prospective association between low and high total and low-density lipoprotein cholesterol and coronary heart disease in elderly men. *J Am Geriatr Soc* 2004;52:1975-80.]