Executive Summary of the 2018 Joint Consensus Document on Cardiovascular Disease Prevention in Italy

High Blood Pressure & Cardiovascular Prevention
https://doi.org/10.1007/s40292-018-0278-8

CONSENSUS DOCUMENT

Executive Summary of the 2018 Joint Consensus Document on Cardiovascular Disease Prevention in Italy

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Received: 1 August 2018 / Accepted: 29 August 2018

Abstract
Cardiovascular diseases (CVDs) are the leading cause of death, disability and hospitalization in Italy. Primary prevention strategies are able to prevent clinically evident CVDs, mostly by early identifying asymptomatic, otherwise healthy individuals at risk of developing CVDs. A more modern approach recommended for effective CVD prevention is based on "4P", that is: *Predictive*, *Preventive*, *Personalized* and *Participative*. This executive document reflects the key points of a consensus paper on CV prevention in Italy, realized though the contribution of different Italian Scientific Societies and the National Research Council, and coordinated by the Italian Society of Cardiovascular Prevention (SIPREC), published in 2018. The need for such document relies on the difficulty to apply "sic et simpliciter" European guidelines, to which this document is largely inspired, to national, regional and local realities, in this Mediterranean country, namely Italy. Indeed, our Country has specific features in terms of demography, socio-cultural habits, distribution and prevalence of risk factors, organization, policy and access to National Health Service compared to other European countries.

Keywords Cardiovascular prevention · Cardiovascular risk factors · Cardiovascular mortality · Hypertension · Dyslipidaemia · Diabetes · Smoking · Obesity · Vaccination

1 Introduction

This executive document reflects the key points of a consensus paper on cardiovascular (CV) prevention in Italy, realized though the contribution of different Italian Scientific Societies and the National Research Council, and coordinated by the Italian Society of Cardiovascular Prevention (SIPREC), published in 2018 [1]. The need for such document relies on the difficulty to apply "sic et simpliciter" European guidelines, to which this document is largely inspired, to national, regional and local realities, in this Mediterranean country, namely Italy. Indeed, our Country has specific features in terms of demography, socio-cultural habits, distribution and prevalence of risk factors, organization, policy and access to National Health Service compared to other European countries [2].

CV prevention is defined as combined and integrated interventions directed to either entire population or individuals, with the aim of reducing or minimizing the impact of CV diseases (CVDs) and their consequences in terms of morbidity and mortality. Although the natural history of CVDs from risk factors to clinical onset is indeed a "continuum", CV prevention has been traditionally distinguished into either primary prevention, when the intervention precedes any clinical manifestation of an underlying pathology, or secondary prevention, which reflects the preventive measures following a clinically manifest event. In this document, the aspects concerning primary prevention are mainly discussed (Fig. 1) [1].

Primary prevention strategies are able to prevent clinically evident CVDs, mostly by early identifying asymptomatic, otherwise healthy individuals at risk of developing CVDs. A more modern and comprehensive view of CV

All collaborators for the Writing Commitee and the Scientific Societies are listed in the Acknowledgements.

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Published online: 20 September 2018

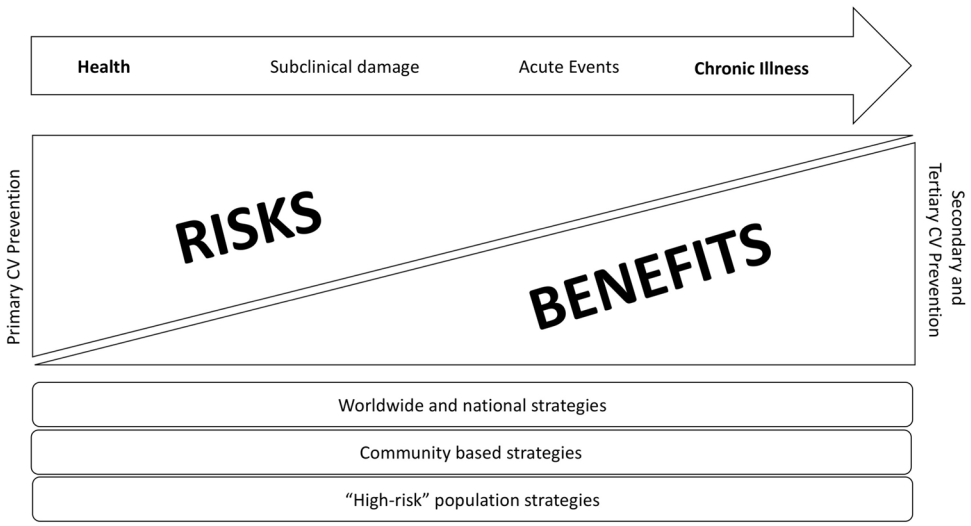

Fig. 1 Schematic representation of cardiovascular continuum and possible interventions for primary, secondary and tertiary cardiovascular prevention. Derived from Volpe et al. [1]

prevention should include the ability of estimating how many years of "healthy life" are earned by adhering to specific preventive interventions. The promotion of health policies aimed at earning healthy years through CVD prevention and, therefore, the interruption of the transition from health to acute or chronic illness, should be based on different levels of intervention: global, national, community, family and individual levels [3]. A novel approach recommended for effective CVD prevention is based on "4P", that is: *Predictive*, *Preventive*, *Personalized* and *Participative*. *Predictive* of disease precursors at an early stage; *Preventive*, for the early elimination of risk factors; *Personalized*, based on the information available for everyone; *Participative*, which reflects the integration of multiple professionals and technologies available today with the involvement of patients [4]. The present consensus is largely based on this multifaceted conceptual approach to CV prevention.

2 Cardiovascular Diseases and Risk Factors in Italy

CVDs are the leading cause of death, disability and hospitalization in Italy. According to the 2016 Italian Agency of Statistics (ISTAT) data, 367 deaths from CVDs are recorded every year per 100,000 inhabitants. In our country, 220,200 deaths due to CVDs occurred in 2014. Of these, 69,653 deaths were attributed to ischemic heart disease, in particular acute coronary syndromes (ACS) (35,714 in men and 33,939 in women) and 57,230 to cerebrovascular diseases, mainly stroke (22,609 in men and 34,621 in women). The rate of hospitalization for CVDs in men is more than double of that in women, although a significant progressive increase in CVDs in females has been observed in the latest decades. The analysis of the trends between 1998–2002 and 2008–2012, shows that cardiac diseases (myocardial infarction, angina pectoris, atrial fibrillation, left ventricular hypertrophy), cerebrovascular diseases (cerebrovascular accidents, transient ischemic attacks) and interventional procedures (coronary bypass or coronary angioplasty) increased over the years. In men, there was a slight decrease in prevalence of coronary heart diseases (6.7% in 2008–2012), and a decrease of cerebrovascular diseases (1.5% in 2008–2012). In contrast, a marked increase of coronary revascularization procedures (from 2.2% in 1998–2002 to 4.2% in 2008–2012) was observed in male individuals. In women, the prevalence of coronary heart disease slightly increased (from 5.9% to 1998–2002 to 6.2% in 2008–2012), whilst that of cerebrovascular diseases decreased (from 1.6% in 1998–2002 to 1.3% in 2008–2012) and, similarly to what observed in men, the revascularization procedures doubled (from 0.4% in 1998–2002 to 0.8% in 2008–2012). Therefore, the growing burden of CVDs may seriously affect the sustainability and the socio-economic capacity of the Health Care System in Italy [5, 6]

The efforts aimed at antagonising these trends by improving strategies for effective CV prevention at both population and individual levels do not seem to have been implemented sufficiently. Prevalence of some CV risk factors (i.e. hypertension, hypercholesterolemia, overweight, and obesity) is continuously increasing as well [7]. The comparison of the data on the prevalence of such CV risk factors collected in adults aged 35–74 years by the Epidemiological Cardiovascular Observatory within the CUORE Project of the Istituto Superiore di Sanità (ISS), between two surveys performed in 1998–2002 and in 2008–2012, respectively, reported that the prevalence of hypertension has remained almost unchanged (from 52.2 to 51.0%) in men, whereas it decreased in women

Table 1 Trends in cholesterol levels in Italy according to ISS data. Derived from Volpe et al. [1]

Parameters	1998–2002	2008–2012	Δ%
Men			
Total cholesterol ≥ 240 mg/dl	20.8	34.3	+ 13.5
LDL cholesterol ≥ 115 mg/dl	63.4	68.0	+ 7.3
Women			
Total cholesterol ≥ 240 mg/dl	34.3	36.6	+ 6.7
LDL cholesterol ≥ 115 mg/dl	60.9	67.3	+ 10.5

Table 2 Trends in hyperglycemia and diabetes in Italy according to ISS data. Derived from Volpe et al. [1]

Parameters	1998–2002	2008–2012	Δ%
Men			
Glycemia ≥ 100 to ≤ 125 mg/dl	9.9	10.8	+ 9.1
Glycemia ≥ 126 mg/dl	11.4	11.2	− 1.8
Women			
Glycemia ≥ 110 to ≤ 125 mg/dl	5.2	5.3	+ 1.9
Glycemia ≥ 126 mg/dl	7.8	7.6	− 2.6

Table 3 Trends in metabolic syndrome prevalence in Italy according to ISS data. Derived from Volpe et al. [1]

Parameters	1998–2002	2008-2012	Δ%
Men	29.2	23.5	− 19.5
Women	29.6	18.5	− 37.5

Table 4 Trends in body mass index in Italy according to ISS data. Derived from Volpe et al. [1]

Parameters	1998–2002	2008–2012	Δ%
Men			
BMI < 18.5 kg/m^2	0.6	0.2	− 66.7
BMI 18.5–24.9 kg/m^2	32.2	27.8	− 13.7
BMI 25–29.9 kg/m^2	49.7	47.5	− 4.4
BMI ≥ 30 kg/m^2	17.5	24.5	+ 40.0
Women			
BMI < 18.5 kg/m^2	1.5	1.3	− 13.3
BMI 18.5–24.9 kg/m^2	42.3	42.0	− 0.7
BMI 25–29.9 kg/m^2	34.2	31.8	− 7.0
BMI ≥ 30 kg/m^2	22.0	24.9	+ 13.2

(from 44.3 to 37.2%). Prevalence of hypercholesterolemia increased both in men (from 20.8 to 34.3%) and in women (from 24.6 to 36.6%) (Table 1). Similarly, abdominal obesity increased in men (from 22.5 to 26.6%) and in women (from 35.9 to 40.3%). It is interesting to note that the prevalence of diabetes has remained almost unchanged both in men (from 11.4 to 11.2%) and in women (from 7.8 to 7.6%), while there was an increase of hyperglycaemia [8] (Table 2). Prevalence of obesity and metabolic syndrome tended to increase, especially in men (Tables 3, 4). Both habit of cigarette smoking and sedentariness remained steadily high [8]. The effects of the law banning smoking from public inner spaces has produced positive effects, although less relevant than expected. There has been a positive trend with a better control of hypertension [9], although this remains suboptimal [10]. Hypercholesterolemia showed a better control in men than in women, whilst diabetes showed an opposite trend [8].

3 Global Cardiovascular Risk and Integrated Cardiovascular Prevention

The modern approach to CV prevention must overcome a vision based on the treatment of individual risk factors, by promoting an approach based on integrated and multidisciplinary management of total CV risk [11] (Fig. 2). In this line, the main target of therapeutic intervention should be the reduction of total CV risk rather than the absolute levels of single risk factors. This document fully agrees the recommendations from the European Guidelines and supports the integrated approach to global CV risk estimation and prevention.

The estimation of global CV risk in primary prevention is recommended in subjects aged > 40 years who have not been already classified at high or very high risk [2]. The use of risk charts and scores is recommended in this population. In subjects aged < 40 years, a reasonable and more reliable estimate of CV risk can be obtained with the use of "relative risk", "risk-age", "lifetime risk" [12].

A recent Italian study, involving a cohort of about 7000 subjects aged between 49 and 70 years, followed by general practitioners, showed that 15.1% individuals have high CV risk and 19.9% were at very high CV risk, according to the CUORE Project algorithm. When translating these data to the general population, this would mean that about 4.68 million subjects are at high CV risk and 6.17 million are at very high CV risk. According to the ISS data, the average overall CV risk at 10 years, estimated with the equation of the CUORE Project, decreased between 1998–2002 and 2008–2012 both in men and, particularly, in women aged 35–74 years. The prevalence of high CV risk subjects (> 20% to 10 years) also decreased in both men and women (Table 5).

To better estimate the overall CV risk in individuals, markers of target organ damage (i.e. left ventricular hypertrophy, increased intima-media thickness of carotid arteries,

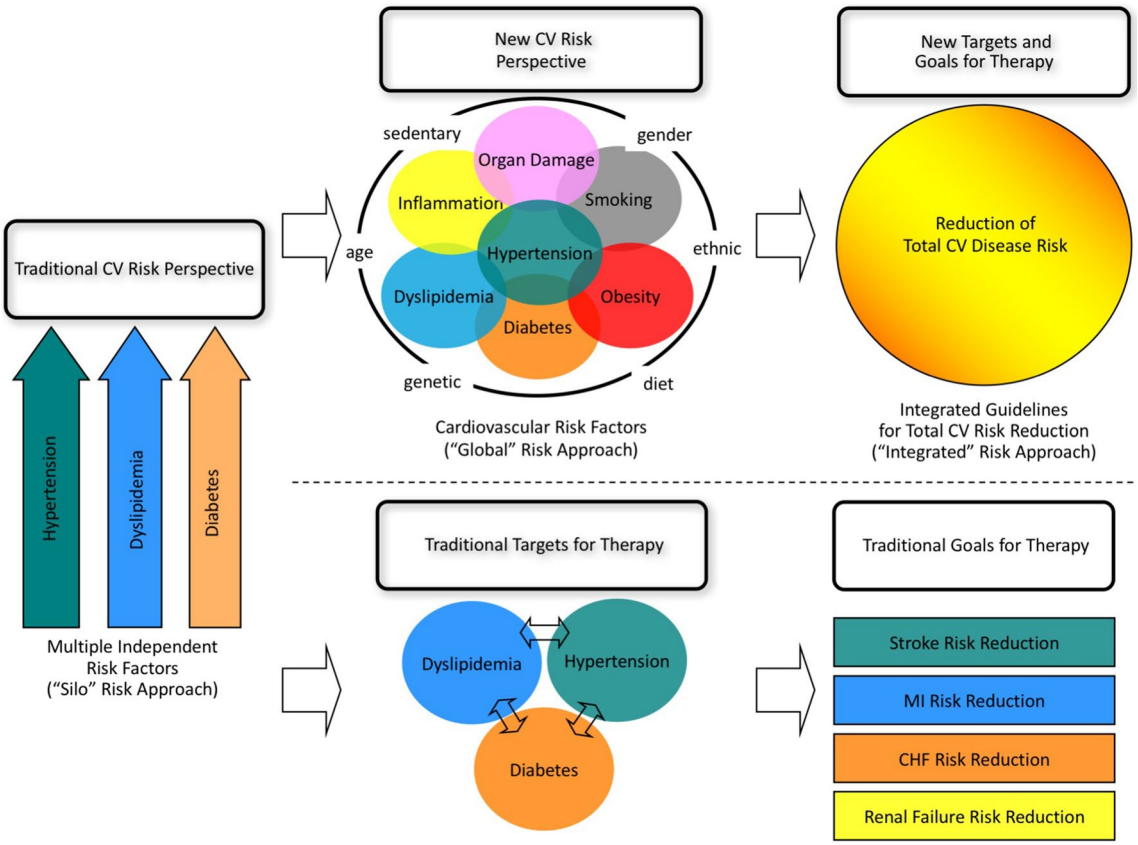

Fig. 2 Schematic representation of integrated cardiovascular prevention. Modified from Volpe et al. [11]

Table 5 Trends in cardiovascular risk, according CUORE project (%). Derived from Volpe et al. [1]

Parameters	1998–2002	2008–2012	Δ%
Men			
<5%	51.5	53.2	+3.3
5–9.9%	21.2	19.9	−6.1
10–14.9%	11.3	11.6	+2.7
15–19.9	6.4	6.8	+6.3
≥20%	9.6	8.5	−11.5
Women			
<5%	78.9	82.7	+4.8
5–9.9%	14.0	12.8	−8.6
10–14.9%	4.5	2.8	−37.8
15–19.9	1.8	1.1	−38.9
≥20%	0.8	0.6	−25.0

changes in the renal function) may provide useful additional information and they may be integrated in the risk evaluation at least in specialized clinical settings [2]. Moreover, the measurement of biomarkers such as natriuretic peptide plasma levels (i.e. BNP, NT-pro-BNP), could reveal useful in future preventive strategies [13].

4 Dietary Habits and Cardiovascular Risk

International guidelines on CVD prevention agreed in emphasizing the importance of an integrated therapeutic approach, based not only on the use of drugs for treating single CV risk factor, but mostly on lifestyle interventions aimed at correcting potentially harmful habits for individuals. There are several interventions that can be applied to maintain a healthy nutrition [2, 14–18]

- To reduce saturated fatty acids to less than 10% of the total energy supply, or replace them with mono (olive oil) and polyunsaturated ones (bluefish, salmon, walnuts, almonds, etc.).
- To eliminate hydrogenated fatty acids or reduce to less than 1%.
- To take no more than 5 g of salt per day.
- To encourage the consumption of vegetables, fruit, legumes and cereals, preferably integral and favour the consumption of fish at least 1–2 times a week, because this food is rich in minerals, omega-3 fatty acids and low in cholesterol.
- To discourage the consumption of sugary drinks.
- To reduce alcohol consumption.

The Mediterranean diet, which is largely adopted in Italy, is an expression of proper nutrition because it combines groups of good nutrients, in such proportions as to make it complete from the point of view of the nutritional needs. It includes a high consumption of vegetables, fruit, cereals, fish, olive oil, moderate consumption of alcohol and a very low consumption of red meat and saturated fats. The greater the adherence to the fundamentals of the Mediterranean diet the better are the advantages in terms of CVD prevention. Indeed, a good adherence to the Mediterranean diet is associated with a 9% reduction in mortality for CVDs, a 6% reduction of cancers, and a 13% decrease in the incidence of Alzheimer and Parkinson diseases [19, 20].

5 Physical Activity and Cardiovascular Risk

According to the World Health Organization (WHO) definition, physical activity means any movement produced by skeletal muscles that requires an energy expenditure. Physical inactivity is identifiable as the fourth global mortality risk factor (responsible for 6% of all deaths) [21]. The WHO, aligning with the United States guidelines, defined the levels of physical activity recommended for three age groups [22]:

- For children (5–17 years): at least 60 min a day of moderate-vigorous activity, including at least 3 times a week isotonic exercises, which may consist of games or sports;
- For adults (18–64 years): at least 150 min per week of moderate activity or 75 min of vigorous activity (or equivalent combinations of the two) in sessions of at least 10 min at a time, with reinforcement of the major muscle groups to be performed at least twice a week;
- For elderly (≥ 65 years): the indications are the same as for adults, with the warning to prevent falls.

Those who are unable to follow the recommendations should exercise at least 3 times a week and adopt an active lifestyle.

The correct prescription of an exercise program provides the following parameters: type of exercise, intensity, duration and frequency (number of sessions over time) and training modalities.

5.1 Type of Exercise

The selection of the activity will depend on the preferences of the subject, the target, any co-morbidity, costs and other individual and situational variables.

5.2 Intensity

This is commonly defined using parameters such as: percentage of maximum heart rate (HR_{max}), usually estimated with the formula: 220 − age of the subject; percentage of the heart rate reserve ("heart rate reserve", HRR) + resting HR; percentage of maximum oxygen consumption (VO_{2max}); workload; perceived level of effort. However, it is necessary to specify that in subjects affected by CVDs the effective HR should be used (the one reached during a stress test in optimized pharmacological therapy). Moreover, it would be preferable to use HRR which is the difference between the max HR (reached during the exercise test) and the HR at rest (measured before taking any physical effort and in conditions of absolute relaxation), which is more correlated with the parameters derived from the VO_{2max}. This applies for the VO_2 as well.

The levels commonly used for the prescription of physical exercise are the following ones [23]. 1. *Mild intensity:* 35–55% of the theoretical or real HR max (or 20–40% of HRR + HR at rest, or 20–40% of peak or reserve VO_2 or 10–11 on the Borg scale 6/20); 2. *moderate intensity:* 55–70% of the theoretical or real HR_{max} (or 40–60% of HRR + HR at rest, or 40–60% of peak or reserve VO_2, or 12–13 of the Borg scale 6/20; 3. *vigorous intensity:* 70–89% of the theoretical or real HR_{max}, (or 60–84% of HRR + HR at rest, or 60–84% of peak or reserve VO_2, *or* 14–16 on the Borg scale 6/20).

Furthermore, the intensity can be evaluated in absolute terms, as a quantity of energy consumed per minute of activity, distinguishing it in: *mild*: 1.1–2.9 times resting energy consumption (or MET, metabolic equivalent); *moderate*: 3.0–5.9 times the energy consumption at rest; vigorous: > 6.0 times the energy consumption at rest.

5.3 Duration and Frequency

According to the European guidelines for primary prevention, it is recommended at least 2.5 h per week of moderate intensity activity or at least 1.25 h of vigorous activity a week or a combination of the two (remembering that 2 min of moderate activity correspond roughly 1 min of intense activity). In secondary prevention, instead, aerobic activity of moderate to vigorous intensity is recommended, for at least 30 min per session with a frequency of at least 3 weekly sessions [2].

5.4 Training Mode

Traditionally, the most widespread training method used is the one based on constant load. However, the scientific literature now agrees in considering the interval work as effective and safe. Compared to standard constant load training protocols,

this type of activity would produce similar or slightly higher results in terms of increased VO_{2max} and reduced myocardial oxygen consumption for sub-maximal workloads, while it would improve the anaerobic threshold. This would allow the execution of many activities of daily life more easily, generally performed at an intensity of work, which, for ischemic subjects, may be precisely that of the anaerobic threshold [24]. While recognizing the results achievable with interval training, constant-load training should be preferred. It gives greater certainty that patients can effectively perform it after discharge, safely maintaining the intensity of the exercise within the levels tested and verified during the supervised period.

6 Overweight and Obesity and Cardiovascular Risk

Overweight/obesity is defined as a chronic condition characterized by excessive body weight due to accumulation of adipose tissue to an extent that negatively affects the state of health [25]. The pyramid for the treatment of overweight/obesity is based on lifestyle changes, through programs of proper eating behaviour associated with a proper physical activity programme. However, the application of these measures is difficult, especially in the long term. When changes in lifestyle do not produce satisfactory results, as well as in case of severe obesity, the possibility of drug therapy or bariatric surgery should be considered. Currently, there are three drugs approved for the treatment of obesity in the adult and on the market in Italy: orlistat 120 mg (available since 1999) [26], liraglutide 3.0 mg (available since 2015) [27] and the fixed association naltrexone/bupropion (approved in March 2015, but available only from November 2017) [28]. The indications for drug therapy include patients with BMI > 30 kg/m^2 even in the absence of risk factors or concomitant diseases, and in those with BMI > 27 kg/m^2 in the presence of risk factors (e.g., arterial hypertension, dyslipidaemia, type 2 diabetes mellitus, etc.). Current indications for bariatric surgery in obese patients include: (1) patients aged between 18 and 65; (2) BMI > 40 kg/m^2 even in the absence of co-morbidity or BMI > 35 kg/m^2 in the presence of comorbidities; (3) duration of obesity over 5 years; (4) previous demonstrated failure to attempt to weight loss and/or to maintain weight loss with non-surgical techniques; (5) full availability of the patient to a prolonged post-operative follow-up [29].

7 Smoking and Cardiovascular Risk

According to a recent epidemiological ISS survey, there are 11.7 millions of smokers (22.3% of the population) in Italy. Whereas smoking has decreased among men, it rose from 4.6 million in 2016 to 5.7 million among women. All types of tobacco are harmful, without a lower limit below which no harmful effects occur [30]. Smoking is harmful at any age, but the risk associated of developing a disease (CV, oncological, respiratory) is strictly dependent on the age of the beginning of this habit [31]. Former smokers have an intermediate CV risk between smokers and non-smokers. Randomized studies have shown that in the case of 10–15 years the risk of CVDs is approaching (even if it is not equivalent) to that of those who have never smoked. Quitting smoking after a heart attack is potentially the most effective intervention among all secondary prevention measures [32]. All smokers should be advised to stop smoking and exposure to second-hand smoke should be avoided. Nicotine replacement therapy (NRT) in the form of chewing gum, patches, nasal sprays, inhalation preparations, bupropion and varenicline can help in smoking cessation, but are not recommended [33].

8 Therapeutic Management of Hypertension

Blood pressure (BP) level measurement represents a primary goal in the population and should be encouraged in all adult individuals. Life-style interventions including salt, alcohol and saturated fatty acids restriction, abstinence from smoking, regular physical activity and weight control may contribute to prevent the development of hypertension and contribute to better control BP levels, so they should be advised in all patients with hypertension [34–38]. However, in most cases pharmacological therapy is required to control BP and reach the recommended therapeutic goals in patients with grade 1–3 of hypertension, independently of age, and in subjects within the high-normal BP range with high CV risk.

An adequate therapeutic management of hypertension may significantly reduce the risk of major CV events, which represents the main goal of every prevention strategy, also reverting subclinical target organ damage. Pharmacological therapy should be immediately started in grade 2 and 3 hypertension and in subjects with grade 1 hypertension and overt organ damage or high CV risk levels (diabetes, chronic kidney disease, previous CV events). Pharmacological treatment should be also considered in patients with grade 1 hypertension at low-to-moderate CV risk when office BP levels remain elevated after adequate lifestyle modifications or in case of elevated ambulatory BP. An antihypertensive treatment is not indicated in young patients with isolated increase of brachial systolic BP, but a strict follow up is strongly advised. A systolic BP < 140 mmHg is recommended in patients at low-to-moderate CV risk and diabetic patients, and should be considered in patients with history of stroke, transitory ischemic attack, coronary artery disease and nephropathy. In elderly patients aged < 80 years

and with systolic BP ≥ 160 mmHg, a target BP between 140 and 150 mmHg has demonstrated beneficial effects and should be considered. In fit elderly, a target of systolic BP < 140 mmHg may be considered, whereas in frail ones the therapeutic goals should be adapted to individual tolerability. The target of diastolic BP < 90 mmHg is always recommended. Diabetic patients should reach diastolic BP values < 85 mmHg if well tolerated without side effects. New European guidelines, presented in a preliminary version during the 28th Congress of the European Society of Hypertension, suggest the new systolic BP target of 130 mmHg or lower, if tolerated, whatever the level of estimated CV risk. In older patients, systolic BP levels between 130 and 140 mmHg should be reached, with a close monitoring of adverse effects. A diastolic BP target of < 80 mmHg will be recommended for all hypertensive patients, independent of the level of risk and comorbidities [2]. Benefits of drug treatment in individuals with high-normal BP are not univocally established, but several studies have demonstrated its potential role in delaying the development of hypertension [39, 40]. Indications about starting antihypertension drugs have been addressed in the last guidelines on management of hypertension presented worldwide last June 2018. Moreover, additional studies are still necessary to clearly define optimal ambulatory, home BP levels and corresponding therapeutic targets especially in the presence of some pathological conditions, such as diabetes mellitus, previous coronary events or peripheral artery disease. How much the addition of ambulatory or home BP to office BP measurement improves quantification of CV is not fully established, and it is unclear if home BP (HBPM)- or ambulatory BP (ABPM)-guided therapy results in greater reductions in morbidity and mortality than conventional office BP-guided treatment. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers and thiazide diuretics are indifferently recommended as first line therapies by European guidelines. Combination therapies, especially those based on renin-angiotensin system (RAS) blockers and calcium channel blockers and/or thiazide diuretics, preferably in single pill, are currently encouraged because of the difficulty to control BP in more than 70% of patients. Newer European guidelines support an early use of single-pill combination therapy even as a starting treatment.

9 Therapeutic Management of Hypercholesterolemia

Another fundamental intervention for CV prevention consists in the treatment of dyslipidaemias (mostly hypercholesterolemia), since the linear relationship between the reduction of low density lipoproteins cholesterol (LDL-c) and CV risk levels has been well established. The intensity of lipid lowering treatments should depend on the presence of concomitant CV risk factors, on the baseline CV risk estimation and on the severity of hypercholesterolemia [41].

LDL-c should be considered the main target of any lipid lowering strategy. Non-high-density lipoprotein cholesterol (non-HDL-C) should represent only a secondary therapeutic target, whereas there is no evidence of a beneficial role of increasing HDL-C levels. In patients at very-high CV risk, LDL-C levels < 70 mg/dl are recommended. A reduction of at least 50% is recommended in case of baseline LDL-c levels between 70 and 135 mg/dl. In patients at high CV risk, LDL-c levels < 100 mg/dl are recommended. A reduction of at least 50% is recommended in case of baseline LDL-C levels between 100 and 200 mg/dl. In patients at low-to-moderate CV risk, LDL-C levels < 115 mg/dl may be considered. HDL-C levels do not represent a therapeutic target. However, HDL-C levels > 40 mg/dl in men and > 48 mg/dl in women have a protective CV role. There are not recommended triglycerides targets. However, levels < 150 mg/dl are strongly encouraged. The presence of adjunctive CV risk factors should be investigated in case of triglycerides levels > 150 mg/dl. In addition to diet and lifestyle interventions, a supervised prescription of specific nutraceutical with proven lipid lowering efficacy may be considered in patients with low CV risk and only mildly elevated LDL levels. Statins with different power and at different dosages, depending on baseline LDL-c levels and estimated CV risk, represent the first line drug strategy. These drugs (pravastatin, simvastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin, etc.) decrease the hepatic biosynthesis of cholesterol by a reversible inhibition of the hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase [42]. Therefore, there is an increase in receptors for LDL on cell surface with an enhanced metabolism, so that LDL-C levels may decrease by 50%. This translates in a reduction of CV mortality, morbidity and atherosclerotic plaque progression. Side effects of statins may include: increased liver enzymes, pharmacological interactions, nausea, head pain, and myopathy. Ezetimibe, by inhibiting intestinal cholesterol absorption, may decrease cholesterol by 20% on top of statins. Recently, antibodies against the proprotein convertase subtilisin/kexin type 9 (PCSK9), such as evolucumab and alirocumab, showed to reduce LDL cholesterol by 60–70% by inhibiting the degradation of LDL receptors. They are allowed in Italy in the presence of homozygous and heterozygous familial hypercholesterolemia, statin intolerance or inability to reach optimal targets with first and second line therapies with the use of an electronic, web-based therapeutic plan. These concepts have been extensively discussed in the SIPREC position paper (REF), dealing with the diagnostic and therapeutic management of patients with dyslipidaemia, with a multidimensional and integrated evidence-based approach adapted and updated from recent guidelines of the European

Society of Cardiology and the most recent results of randomized clinical trials [43].

10 Therapeutic Management of Diabetes Mellitus

The efficacy of lifestyle changes and regular physical activity in primary prevention has been largely demonstrated in individuals at high risk of developing diabetes. Predefined glycemic targets, which have been demonstrated as beneficial effects in terms of improvement in quality of life and free-event survival, should be reached in type 1 diabetic patients with a correct management of insulin therapy also using insulin pumps and novel techniques of continuous glucose monitoring in association with the assessment of carbohydrates intake, pre-prandial blood sugar and carried out on planned physical activity. A HbA1c target < 53 mmol/l (< 7%), with an individual goal < 6.5%, should be recommended with all the efforts to avoid hypoglycemic events. Therapeutic goals are represented by fasting or pre-meal blood sugar between 70 and 130 mg/dl and post-meal blood sugar < 160 mg/dl.

In patients with type 2 diabetes in addition to the lifestyle intervention and metformin [44, 45], pioglitazone, inhibitors of the sodium-glucose cotransporter 2 (SGLT2) and glucagon-like peptide 1 receptor agonists (GLP1-RA) may be used for a dual therapy, meanwhile sulfonylureas and acarbose are suggested only for triple therapeutic regimen. Insulin may be used at any stage of the natural history of the disease. These recommendations are related to RCTs supporting CV safety (DPPIV-i) or prevention (Pioglitazone, SGLT2-I, GLP1-RA long acting) in patients with a previous history of CV events (tertiary prevention) [46–54]. As a further crucial advantage of these drugs, they bear low risk of hypoglycemia. In particular, DPPIV-I and GLP1-RA induce post-prandial insulin secretion on a glucose dependent effect and SGLT2-i reduce blood sugar levels blocking glucose tubular reabsorption with an insulin independent glycosuric effect. A strict glycemic control is essential to prevent microvascular complications, such as retinopathy, nephropathy and autonomic neuropathy and CV complications. In Italy prescription of the newer antidiabetic drugs is still restricted to diabetologists, whereas our position encourages the possibility of a wider prescription.

11 Antiplatelet Therapy in Primary Prevention

The benefits of antiplatelet drugs, aspirin and P2Y12 inhibitors, are unquestionable in patients with history of CV events (secondary prevention), significantly reducing mortality rate and incidence of further acute events, with an acceptable bleeding risk [55, 56]. However, the assumption of aspirin in primary prevention is not systematically recommended, because the absolute CV event reduction may be similar to the absolute excess in major bleedings. Recently, several studies have demonstrated that aspirin, when assumed for more than 5 years at 75–300 mg daily dosage, may play a role in colorectal cancer prevention, by inhibiting specific pathways of carcinogenesis mediated by cyclooxygenases 1 and 2. In addition, aspirin seems to reduce colorectal cancer mortality and the development of metastasis. These data could encourage the use of aspirin also in primary prevention, but definite evidence is still lacking while waiting for further results of prospective and randomized trials. Since CV risk should be considered as a continuum from primary prevention in otherwise healthy subjects through prevention in high CV risk individuals, to secondary prevention, dychotomic recommendations are not conceivable. Thus, a careful clinical judgment, analysing the net clinical benefit based on a reliable estimation of risk of both ischemic and haemorrhagic events, is essential and is strongly recommended. In this context, the reduction of cancer mortality could be of extreme importance in extending indications for aspirin treatment [57, 58]. It seems reasonable to recommend the use of aspirin in primary prevention, for subjects with a risk of major CV events ≥ 2/100 patient-years (equivalent to a SCORE risk of 7–10% at 10 years), especially if male patients aged between 50–60 years [59]. A position paper of the Italian Society for Cardiovascular Prevention has investigated the current evidence about the potential effect of aspirin to reduce the incidence of mortality, CV events and cancer in primary prevention, by analysing the balance between risks and benefits of the treatment (Fig. 3). Currently ongoing prospective studies will probably be able to address the lack of data and will drive future medical choices.

12 Strategies to Improve Compliance to Prescribed Drugs

Among the different factors that contribute to a full therapeutic success, patients' compliance, including correct assumption, adherence and persistence to the therapy, plays an essential role. However, only a small percentage (40–45%) of high-risk patients, is sufficiently adherent to the prescribed therapies (assumption of drugs > 80%). Many studies have demonstrated that the pill burden is strongly associated with higher levels of nonadherence, independent of age, sex and drug classes. For each additional prescribed medication, the proportion of adherent patients decreases by about 85%. The simplification of treatment, based on fixed dose combination (FDC) therapies, may surely improve adherence and may represent a key element to achieve therapeutic

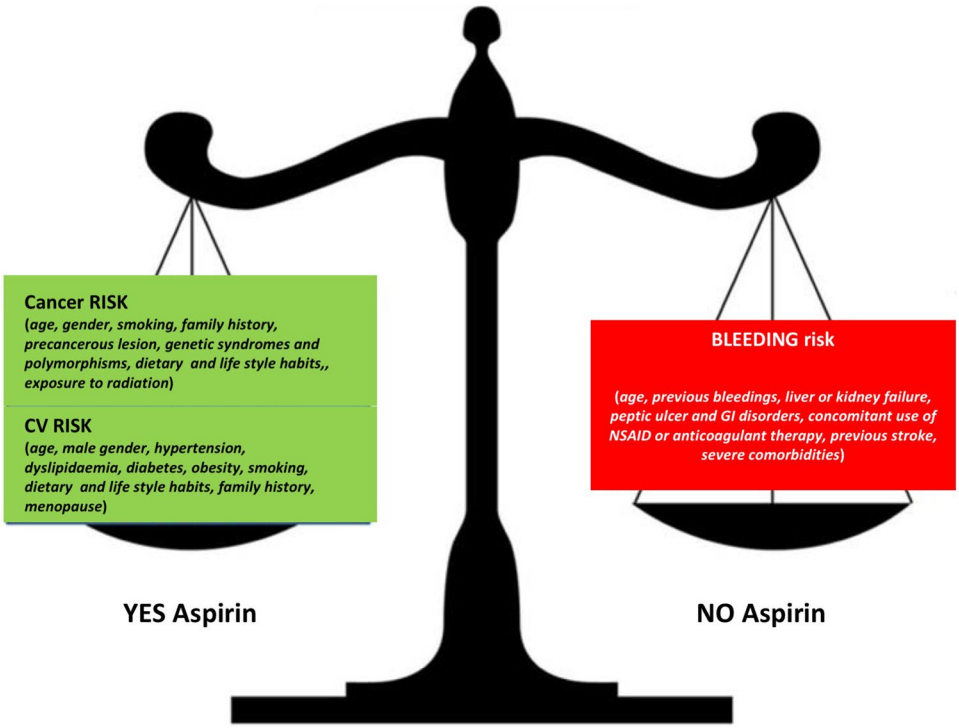

Fig. 3 Risk/benefit ratio for aspirin use in primary prevention. Modified from Volpe et al. [43]

objectives and better clinical results, since it allows the use of lower dosages of individual components with a consequent reduction of dose-dependent adverse effects. Preferable FDCs are those available with single components at flexible dosages and with long-lasting drugs, so that they can be administered once a day. Other patient-specific barriers responsible for adherence reduction may and must be identified, such as depression, medication cost, and inadequate social support, lack of incentive for self-care and low costs sustained by the Health Care System. Once one or more of these risks factors for poor-compliance have been recognized multidisciplinary interventions must be put in place. Several approaches have been proposed to investigate adherence to drugs, such as self-reported questionnaires, pill counts and prescription refills. Patients should be consulted about this topic and should have the opportunity to always discuss with their physicians about the aspects of the treatment that they consider with worry [60].

13 Vaccination Strategies

Vaccination programs are often misread as a measure limited to prevent infective disease, but this simplification underestimate their large beneficial role in a more complex and integrated preventive strategy. A conscious popular adhesion could guarantee a wide and consolidated vaccination coverage, especially in high-risk categories such as subjects aged > 65 years and children or adults affected by chronic pathological conditions. The 90% of deaths and hospitalizations due to influenza virus occurs in older patients, especially with comorbidities, such as CVDs who are more susceptible to lower respiratory tract complications, like viral and secondary bacterial pneumonia. In addition, influenza virus may exacerbate a pre-existing CV pathology. Therefore, the acceptable target of high-risk subjects aged > 65 years exposed to the anti-flue vaccination should be at least 75%, with an optimal goal of 95% [61]. The annual immunization program should be considered as an important tool of secondary prevention in patients affected by coronary artery disease and other atherosclerotic conditions. A recent meta-analysis of 5 randomized trials in patients with CVDs has demonstrated a significant 50% mortality reduction in the group exposed to anti influenza vaccination compared to controls [62]. Moreover, ant influenza vaccination is a highly cost-effective intervention in reducing acute CV events [2]. A relationship also exists between CV disease and pneumococcal pneumonia, since patients with CV history have a higher incidence of pneumococcal infections and subjects with pneumonia have a higher rate of cardiac complications (overall incidence 17%, 14% heart failure, 5.3% acute coronary syndromes, 4.7% arrhythmias) [63–65]. Anti-pneumococcal vaccination is now offered to infants with less than 2 years in a three dose schedule with PCV (pneumococcal conjugate vaccine) and to subjects aged > 65 years, as well as to all the subjects with known risk factors at least 2 years old, with the possibility to schedule sequential PCV and PPV (polysaccharide pneumococcal

vaccine) administrations after at least 8 weeks. Another pathological condition that largely affects the elderly and also patients with CVDs is herpes zoster (or shingles), an acute viral disease due to a reactivation of varicella zoster virus (VZV) from its latent state in a posterior dorsal root ganglion [66]. The clinical relevance of herpes zoster disease is confirmed by the positive correlation between an episode of herpes zoster, in particular herpes zoster ophthalmicus, and CVDs, in particular ischemic stroke, transient ischemic attack and myocardial infarction [67–70]. Anti-zoster vaccine, approved by both U.S. Food and Drug Administration and European Medicine Agency, represents an important preventive option against a disease with a high impact on the population and potentially very disabling, being able to contribute to an improved level of health and quality of life of adults and the elderly.

13.1 Preventive Strategies in Childhood and Adolescence

There is an increasing evidence that exposure to CV risk starts early, even during the first years of life [71]. According to this consideration, it is essential to promptly identify children at increased CV risk based on concomitant risk factors (Table 6), to refer them to specific programs aimed at correction of lifestyle habits and eventually drug therapy. Obesity is a warning phenomenon during childhood and adolescence, thus its early diagnosis and prompt treatment is strongly advised with careful and close metabolic evaluations [72]. The diet is the main factor affecting the increase of obesity. In Italy, 9% of children do not have breakfast, whereas 30.2% of them have not balanced breakfast consisting in taking proteins (milk, eggs, yogurt and cheese) or carbohydrates (bread, baked foods and fruit only). Only a minority of 27.5% of children has an adequate mid-morning snack, whereas 68.2% of children take energy-dense foods, mostly those children who do not have breakfast (74.3%) [73]. Repeated office BP measurements should be performed in obese children, along with the lipid profile and glycaemic assessment [74]. Dietetic advises and daily physical activity are recommended in all children and adolescent categories, independent of their lifetime estimated risk, with a caloric intake adequate to the metabolic demand typical of young age, independently from the distribution of the main macronutrients [75]. In addition, physical activity should be part of the daily educational programs [76]. In Italy, only 25% of children carry out physical activity with continuity, from 4 to 7 days per week. The children defined "active" (83%) attends schools where there are initiatives promoting physical activity. However, 62% of children dedicate up to 2 h and 30 min per day, 30% dedicate from 3 to 4 h and 30 min, and 7% dedicate over 5 h per day to sedentary activities, such as watching TV and playing videogames. Physicians should strongly motivate parents and children to perform daily aerobic exercise, such as swimming, walking and cycling, of moderate intensity ($\leq$65% of the theoretical maximum heart rate or $\leq$55% of maximum oxygen extraction) for at least 30 min per day.

14 Preventive Strategies in the Elderly

In this population, non-pharmacological interventions have a pivotal role and are strongly suggested, although a full adherence to lifestyle measures is hard to be obtained in elderly patients, especially when affected by cognitive and motor disorders. In elderly, drug related adverse events occur more frequently, especially in "frail" individuals older than 70 years, often affected by many comorbidities. Physicians should tailor therapeutic strategies based on the functional status of the patient and of the presence and severity of comorbidities (Fig. 4).

According to Ferri et al, a systematic screening for frailty should be performed in old hypertensive patients to allow

Table 6 Risk categories in paediatric age. Derived from Volpe et al. [1]

Risk category	Conditions	Physiopathology
High risk	Coronary artery disease at age < 30 years	Homozygous familial hypercholesterolemia
		Type 1 diabetes mellitus
		Chronic kidney disease/end stage renal disease
		Orthotopic cardiac transplant
		Post Kawasaki coronary aneurisms
Moderate risk	Accelerated atherosclerosis	Heterozygous familial hypercholesterolemia
		Solved post Kawasaki coronary aneurisms
		Type 2 diabetes mellitus
		Chronic inflammatory diseases
Low risk	Predisposing conditions to accelerated atherosclerosis	Chemotherapy
		Congenital cardiopathies
		Kawasaki disease without coronary involvement

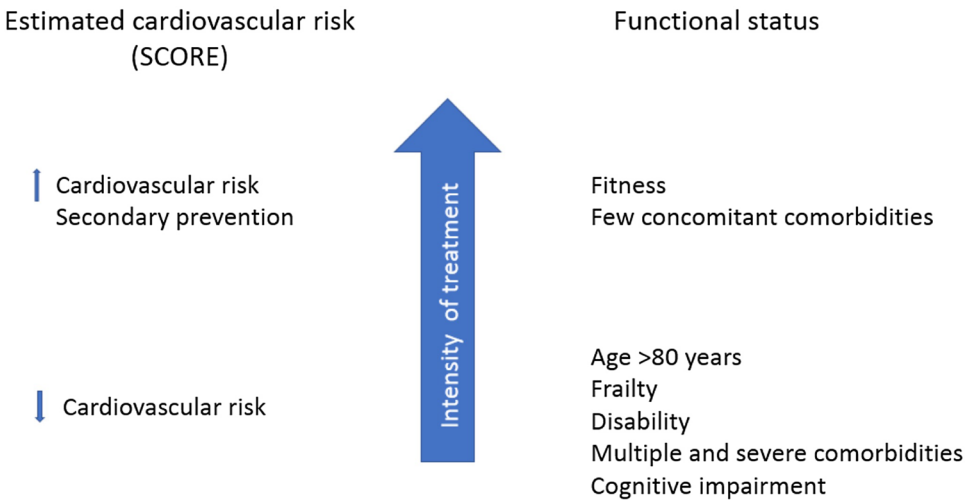

Fig. 4 Factors to be considered for starting/modifying therapeutic interventions in elderly patients. Risk SCORE estimation can be based on SOCRE OD in those elderly individuals aged more than 65 years. Derived from Volpe et al. [1]

Table 7 Glycaemic targets in the elderly. Derived from Volpe et al. [1]

Functional status	Prognosis	Target HbA1C (%)	Fasting blood sugar	"Bedtime" blood sugar
"Healthy" (few comorbidities, good cognitive status)	Long life expectancy	< 7[a]	90–130 mg/dl	90–150 mg/dl
"Complex/Intermediate" (multiple comorbidities, low-to-moderate cognitive impairment, ≥ 2 compromised instrumental daily activities)	Intermediate life expectancy	< 7.5	90–150 mg/dl	100–180 mg/dl
"Compromised or very compromised" (long-term care, end stage disease, moderate-to-severe cognitive impairment, ≥ 2 compromised basic daily activities)	Limited life expectancy	< 8	100–180 mg/dl	110–200 mg/dl

[a]Only using drugs with low risk of hypoglycemia (metformin, DPP4 inhibitors, pioglitazone, SGLT2-i, GLP1-RA and acarbose or these drugs in combinations)

Table 8 Strategies for an adequate glycaemic control in the elderly. Derived from Volpe et al. [1]

Metformin should be prescribed as first line therapy in patients who do not reach therapeutic targets with lifestyle modifications, excluding those with chronic kidney disease at IV stage, advanced heart failure, hepatic and respiratory insufficiency
If metformin is contraindicated or not well tolerated, DPP4 inhibitors, GLP-1 agonists and SGLT2 inhibitors should be prescribed in monotherapy
If an adequate glycemic control is not obtained with monotherapies, other drugs which do not cause hypoglycemia should be added, considering the functional status and concomitant comorbidities
If non-insulin drugs are insufficient to reach adequate targets, insulin therapy should be started, initially with long-acting insulin analogues plus oral hypoglycemic agents and subsequently with a basal bolus approach (long-acting insulin once a day plus rapid acting insulin analogues at each meal)

DPP 4 dipeptidyl peptidase 4, *GLP1 RA* glucagon-like peptide 1 receptor agonist, *SGLT2* sodium-glucose cotransporter 2

the perfect balance between treatment benefits and potential harms [77]. The benefits of antihypertensive and lipid lowering therapies are not clearly established in these subjects, since they have not been usually enrolled in randomized clinical trials. According to ESC/ESH guidelines in elderly patients aged < 80 years and with SBP ≥ 160 mmHg, a target between 140 and 150 mmHg has demonstrated beneficial effects and should be considered. In fit elderly, a target of SBP < 140 mmHg may be considered, whereas in frail ones the therapeutic goals should be adapted to individual tolerability. The most recent American guidelines on hypertension management suggest a systolic blood pressure target < 130 mmHg for fit patients aged > 65 years, whereas an individual evaluation by physicians is advised in frail patients with a reduced life expectancy [78]. These recommendations are supported by the results of the Systolic

Blood Pressure Intervention Trial (SPRINT) which have demonstrated a significant reduction of MACEs and CV mortality in patients aged > 75 years who reached systolic blood pressure < 120 mmHg [79]. The decision to start a statin therapy should consider the presence of frailty and comorbidities, the age and functional status of the patient [80]. Hydrophilic statins, such as pravastatin and fluvastatin should be preferred in elderly patients, based on their pharmacokinetics and metabolic characteristics [81]. A rational approach could be represented by combination therapies of low dose statin plus ezetimibe [82]

Regarding glycaemic control, different targets are suggested according to functional status, concomitant comorbidities and life expectancy (Table 7).

Pharmacological classes which do not cause hypoglycaemia should be preferred, choosing insulin based strategies only if glycaemic targets are not reached with combinations of two or more non-insulin drugs (Table 8).

15 Preventive Strategies for Women

Female sex hormones have a pivotal protective role during childbearing age, delaying the development of CV events of about 10 years compared with men, with a mechanism probably related to a minor atherosclerotic burden.

Women who develop hypertension, pre-eclampsia, diabetes mellitus during the pregnancy or with history of multiple spontaneous abortions have a higher incidence of coronary events, probably due to an increased inflammatory and prothrombotic status [83, 84]. In addition, chronic autoimmune diseases, mainly treated with steroids and nonsteroidal anti-inflammatory drugs which increase the risk of hypertension and diabetes, are more common among women [85].The clinical management of CV disease in women is comparable to that adopted in men, considering the same pathological mechanisms and the same occurrence of complications.

16 Preventive Strategies for Ethnical Minorities

Immigrant populations are characterized by a complex status of vulnerability, health needs, risk of social exclusion and poverty. Several studies have demonstrated that the prevalence of CV risk factors, such as hypertension, dyslipidaemias and diabetes, is higher among ethnical minorities compared to populations of the host countries [86] and this phenomenon is rapidly increasing [87]. For these reasons, the estimation of CV risk with the European SCORE system should be corrected when applied to immigrants, multiplying the risk by 1.4 for immigrants from Southern Asia and by 1.3 for those from Sub-Saharan Africa and Caribbean. Moreover, the World Health Organization recommends to consider different cut offs of BMI to assess overweight, depending on different ethnicities and their related CV risk. Specific preventive strategies, addressed to minorities, are necessary even if compromised by the difficulties to maintain lasting clinical relationships with the migrants and to perform adequate programs of screening and follow up. Such strategies should be targeted to the entire ethnical communities, during all phases of prevention and treatment and adapted to their cultural background [88].

17 Conclusions

CVD prevention should be actually considered as an integrated, comprehensive and multidisciplinary approach aimed at promoting healthy life-style and better control of major CV risk factors, such as hypertension, dyslipidaemia, obesity and diabetes. Such approach, based on total CV risk reduction rather than separate treatment of single CV risk factors, has demonstrated to be effective in reducing the burden of CVDs and improving event-free survival rates in different clinical settings, different CV risk levels and populations. More recently, the use of FDC has provided additional benefits by ensuring high level of adherence and better tolerability to prescribed medications in both asymptomatic individuals and high CV risk patients.

Acknowledgements On behalf of the Writing Committee: Domenico Accettura (Bari), Simonetta Bellone (Novara), Paolo Bellotti (Savona), Marco Bertolotti (Modena), Claudio Borghi (Bologna), Maurizio Casasco (Brescia), Agostino Consoli (Chieti), Raffaele Coppini (Firenze), Alberto Corsini (Milano), Gianfranco Costanzo (Roma), Giovambattista Desideri (L'Aquila), Claudio Ferri (L'Aquila), Giorgio Galanti (Firenze), Franco Giada (Venezia), Giancarlo Icardi (Genova), Niccolò Lombardi (Firenze), Maria Grazia Modena (Modena), Pietro Amedeo Modesti (Firenze), Giorgio Monti (Voghera), Alessandro Mugelli (Firenze), Andrea Orsi (Genova), Gianfranco Parati (Milano), Roberto F.E. Pedretti (Pavia), Gianluca Perseghin (Monza), Matteo Pirro (Perugia), Roberta Ricotti (Novara), Damiano Rizzoni (Brescia), Carlo Rotella (Firenze), Guido Salvetti (Pisa), Patrizio Sarto (Treviso), Federico Tassinari (Genova), Bruno Trimarco (Napoli), Saula Vigili de Kreutzenberg (Padova), Roberto Volpe (Roma).

On behalf of the Scientific Societies: SIMI, Società Italiana di Medicina Interna; SID Società Italiana di Diabetologia; SIIA, Società Italiana dell'Ipertensione Arteriosa; SISA Società Italiana per lo Studio dell'Aterosclerosi; CNR, Consiglio Nazionale delle Ricerche; FMSI, Federazione Medico Sportiva Italiana; GICR-IACPR, Gruppo Italiano di Cardiologia Riabilitativa e Preventiva - Italian Association for Cardiovascular Prevention, Rehabilitation and Epidemiology; SIF, Società Italiana di Farmacologia; SItI, Società Italiana di Igiene Medicina Preventiva e Sanità Pubblica.

Compliance with Ethical Standards

Funding None.

Conflict of interest Authors have no conflict of interest to disclose.

Ethical approval This article does not contain data derived by any current studies with human participants performed by any of the authors. The clinical studies mentioned were provided with specific ethical approval.

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