Targets for Body Fat, Blood Pressure, Lipids, and Glucose-Lowering Interventions in Healthy Older People

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I mproving cardiovascular (CV) risk profile, by lowering elevated body weight, blood pressure (BP), plasma cholesterol, and blood glucose (BG) levels, is of relevance for decreasing fatal and nonfatal CV events in young and middle-aged patients (1–4). Evidence also exists that the above-mentioned interventions are also highly effective in older patients, i.e., in subjects >65 years of age (3–6). However, it is unclear whether the same therapeutic approaches should be always used to treat old patients, taking into account on one hand the heterogeneity of the aged population and on the other the fact that frequently there is a discrepancy between chronological and biological age values. In addition, it is still undefined whether the threshold values used for initiating treatment of patients of younger ages should also apply to the older patients. Finally, it is debated whether the targets for treatment used for younger patients should be used for the older ones.

Here, we aim to provide a general review on the above-mentioned issues, giving, whenever possible, indications useful for current clinical practice and having as a specific target the general population of healthy older patients. The review will be focused on aged individuals without

major disabilities, such as multiple comorbidities, severe cognitive impairment, and in general, systemic diseases that will require continuous medical and nursing assistance. With this aim, the information available for the various variables, such as BMI, BP, blood cholesterol (BC), and BG, will be analyzed separately in the following sections.

BMI in healthy older subjects

Obesity is becoming a global epidemic, causing a sharp rise in many chronic diseases including diabetes, hyperlipidemia, and hypertension (7). Among older adults, the rate of obesity has also risen dramatically over the last few decades, independent of sex, race, and educational level (8). Obesity has significant implications on the health status of the older subjects, since excess body weight in the aged population correlates strongly with chronic sicknesses, poor quality of life, functional decline, disability, and dependency (9,10).

However, there is evidence suggesting that obesity in aged individuals does not carry the same risk as in younger people and in certain aspects can even be protective. In addition, weight loss in older subjects appears to carry risks related to

loss of lean body mass and potential nutritional deficiencies (9,10).

Definition of obesity and "healthy weight" in aged subjects. BMI values are calculated as the weight in kilograms divided by the square of height in meters. Currently, obesity is defined as a BMI >30 kg/m^2. Definitions of "healthy" body weight rely on incidence rates of associated diseases and on total mortality data, which vary across the age spectrum (2). In aged individuals, "healthy" body weight is even more difficult to define owing to physiological changes related to aging, primarily in body composition and stature. Thus, BMI can either underestimate the degree of obesity in old individuals because of an increase in the proportion of body fat with age or overestimate it as a result of loss of height, secondary to narrowed intervertebral disc spaces, vertebral compression, and kyphosis. As a result, the accuracy of BMI as an indicator of adiposity decreases with increasing age, and its relationship with disease risk weakens (11,12). Longitudinal studies have shown that there is a significant mean increase in waist circumference (WC) with age per year, which continues during the advancing years (13). Thus, WC, which correlates highly with intra-abdominal fat and is an independent risk factor for cardiovascular disease (CVD), might be a better predictor of adverse health effects in the aged population. However, there are insufficient data to define appropriate cutoff points for WC in older subjects with different thresholds used based on sex and ethnicity (12). Therefore, emaciation and low lean body mass is better evaluated by BMI where a low BMI reflects more accurately the associated risks of being underweight, whereas obesity and adiposity are better evaluated by measurements of WC, where WC reflects more accurately the associated risks of obesity (14).

It also appears that the cutoff point above which BMI confers mortality risk is higher in the older individuals (BMI >30 kg/m^2) than in the younger adults (BMI >25 kg/m^2). Indeed, a meta-analysis of all studies on the association between

BMI and all-cause mortality in subjects >65 years of age as well as several longitudinal studies published during the past few years confirmed that overweight (BMI 25–29.9 kg/m^2) was not associated with an increased risk and that a BMI in the moderately obese range (30–35 kg/m^2) carries only a modest increased risk (15–18). These findings do not deny the evidence that obesity is harmful in the old population, as the absolute mortality risk increases with increasing BMI until the age of 75 years.

Health consequences of obesity in aged subjects. Adipose tissue accumulation, especially visceral and ectopic (e.g., intramuscular, hepatic), induces a spectrum of metabolic and hormonal changes, which progressively impair insulin signaling. These changes manifest as increased insulin resistance in the adipose tissue, liver, skeletal muscle, and vascular endothelium (9,10). Additionally, obesity alters adipokine production increasing tumor necrosis factor-α and decreasing adiponectin secretion, thus increasing the inflammatory load. In addition, obesity appears to be key in pathogenetic mechanisms of cardiometabolic complications including glucose intolerance, type 2 diabetes, hypertension, dyslipidemia, and atherosclerosis. Obesity also increases the risk of heart failure, with the risk doubling at BMI >30 kg/m^2. Other common obesity-related disorders are osteoarthritis, pulmonary dysfunction (hypoventilation syndrome and obstructive sleep apnea syndrome), reduced cognitive skills, sexual dysfunction, urinary incontinence, and certain cancer types (5). The obese aged subjects are also likely to display functional limitations and impaired quality of life because of decreased muscle mass and strength and increased joint dysfunction, frailty and chronic pain. On the other hand, there may be some beneficial effects to obesity, such as preserved or higher bone mineral density and a lower risk of hip fractures through the anabolic effects of insulin, leptin, and estrogens on the bone, as well as through the cushioning effect of fat around the hips (19).

Who should lose weight: benefits and risks of weight loss. Effective treatment of obesity with sustained weight loss improves the cardiometabolic profile and decreases the risk for the development and progression of related complications (20). Furthermore, weight loss and increased fitness may slow down the loss of mobility with progressive aging and improve quality of life (21). However, adverse effects of intentional weight loss, such as the loss of bone and muscle mass, may influence the risk-to-benefit ratio in old subjects (9,22) (Table 1). Weight loss has been associated with an increased risk of hip fractures in this age-group (10,23). Moreover, the age-related physiological changes, which induce primarily a decline in lean (muscle and bone) body mass and a parallel increase of fat mass, may result in "sarcopenic obesity" (in ~5–10% of cases) (24). Sarcopenic obesity describes the process of muscle loss combined with increased body fat, as people age, resulting in a low proportion of muscle mass relative to total weight (24). Loss of muscle tissue and a decrease in the synthesis of muscle proteins leads to a decreased functional capacity, an increase in the risk of frailty and falls, and loss of independency ultimately leading to disability, morbidity, and mortality (24). Therefore, identifying aged subjects with sarcopenic obesity, albeit difficult, is clinically important (24,25). Toward this purpose, muscle strength can be measured by handgrip dynamometry, an easy and cheap method, which is also clinically more relevant than measuring muscle mass by dual-energy X-ray absorptiometry or computed tomography scan (26). Bioelectrical impedance analysis can also be easily used to assess body composition, using age- and sex-specific prediction equations (26). Sarcopenia may be aggravated by weight loss (24). In conclusion, weight loss interventions may not always necessarily be beneficial in aged subjects with obesity (BMI >30 kg/m^2), unless they display functional limitations or metabolic complications that are expected to improve with weight loss.

The current therapeutic tools available for weight management in the aged individuals do not substantially differ from those routinely used for the general population. These include lifestyle interventions (diet, physical activity, and behavioral modifications), pharmacotherapy, and bariatric surgery. Dietary restriction in older adults holds greater risk of insufficient macro- and micronutrient intake that can result in specific protein and vitamin deficiencies (10,27). Thus, dietary interventions in this age-group should address their specific nutritional requirements. Balanced protein intake (1.0 g/kg body wt of high-quality proteins) is crucial in order to maintain levels that help preserve muscle and bone mass and at the same time do not increase the risk of renal impairment (e.g., excessive protein intake in older adults is associated with glomerular sclerosis) (28). Supplementation with specific vitamins and minerals, such as calcium (1,000 mg/day) and vitamin D (10–20 µg/day), should be required, as they protect against bone mineral loss and reduce the risk of bone fractures. Caution may be needed, however, with calcium supplementation, because in some clinical trials this intervention has been associated with an increased risk of cardiovascular disease (29). Other micronutrients that should be supplemented in patients in whom deficiencies have been documented include iron, vitamin B$_{12}$, and zinc (24).

It is also essential that weight-management interventions in aged obese patients additionally aim at minimizing lean body mass loss. Physical activity is crucial for this goal (10). Elements of aerobic exercise, resistance training, balance, and

Table 1—*Potential benefits and risks related to weight loss in older adults*

Health benefits of weight loss
- Reduced risk of developing type 2 diabetes in subjects with impaired glucose tolerance.
- Reduced cardiovascular risk: improved glycemic, lipid, and blood pressure control.
- Possible reduction in mortality risk from CVD.
- Improved respiratory function and reduction in obstructive sleep apnea.
- Improved functional capacity and reduced musculoskeletal comorbidities.
- Fewer depressive symptoms and a sense of well-being along with a better quality of life.

Health risks of weight loss
- Potentially increased mortality risk with unintentional weight loss (less with intentional weight loss).
- Loss of muscle mass (sarcopenia) if not combined with regular exercise.
- Loss of bone mineral density: osteoporosis and increased risk for fractures.
- Increased risk of specific protein and vitamin deficiencies.
- Increased risk of gallstone formation and cholecystitis (in rapid weight loss).

Table modified with permission from Mathus-Vliegen et al. (10).

flexibility training may be of particular benefit in older people, as these exercises improve physical function. Behavioral therapy can also be beneficial, including goal setting, self-monitoring, social support, stimulus control, and relapse prevention.

Older subjects have been excluded from most clinical trials of pharmacological agents for weight loss (30,31). Orlistat, a pancreatic lipase inhibitor, is the only antiobesity drug available in current clinical practice. However, only a few months ago the U.S. Food and Drug Administration approved two new weight loss drugs: lorcaserine, a selective serotonin 2c receptor activator, and a drug combining two old drugs, phentermine and topiramate (21). For both orlistat and these two newly developed compounds, however, outcome data in aged subjects are still lacking. It should be emphasized that many drugs used to treat diabetes cause weight gain. Therefore, weight-neutral alternatives (such as metformin, dipeptidyl peptidase [DPP]-4 inhibitors, and glucagon-like peptide [GLP]-1 receptor agonists) should be preferred in the obese older patients. Other drugs that can cause weight gain (e.g., tricyclic antidepressants, β-blockers, etc.) should also be avoided in the elderly or substituted with weight-neutral equivalents (10). Laparoscopic bariatric surgery can be safely performed and be clinically effective in aged individuals if properly indicated and with a careful patients selection (32). Complications rates appear to be low and mainly related to the underlying disease rather than to the surgical technique adopted. However, no clear benefit for long-term survival has been demonstrated thus far. In addition, there are no data available to determine the optimal procedure(s) for this age-group. Taken together, these two factors prevent clear determination of the risk-to-benefit ratio.
Conclusions. The following epidemiological, clinical, and therapeutic considerations should be taken into account in current clinical practices:

1. The prevalence of obesity is increasing in the healthy older population, and late-life obesity constitutes a growing threat to public health in developed countries.
2. WC, which reflects visceral fat redistribution, appears to have greater prognostic value than BMI for characterizing obesity and associated risks in healthy older people.

3. Weight loss is recommended in aged individuals only in cases of obesity (BMI >30 kg/m^2) combined with weight-related comorbidities or functional limitations that could benefit from weight loss.
4. Intentional weight loss has beneficial effects in healthy older subjects. However, there are detrimental effects as well, including the risk of sarcopenic obesity, the loss of bone mass, and the risk of hip fractures.
5. Weight-management interventions in healthy older people should be done cautiously. Individualized plans for the elderly patients should be devised in order to limit lean body mass loss and avoid nutritional deficiencies.

Blood pressure control in healthy older subjects

Meta-analyses of data collected over the past 20 years from several randomized clinical trials (33,34) have conclusively shown that antihypertensive drugs are effective in reducing fatal and nonfatal CV events in hypertensive patients of all ages including the elderly (6). The beneficial effects of treatment, particularly on CV morbidity, have recently been documented also in patients ≥80 years of age recruited for the HYpertension in the Very Elderly Trial (HYVET) (35) and in the 1-year open-label treatment extension substudy of the same trial (36). The benefits of treatment were detectable with the different drug classes recommended by the latest guidelines for the management of hypertension in the general population (1) and in the elderly as well (6). These benefits were detectable in both systo-diastolic and isolated systolic hypertensive states, i.e., in a high cardiovascular risk condition typical of elderly people characterized by an elevated pulse pressure value (6). We can conclude that the BP-lowering effects of antihypertensive treatment are associated with a reduction in CV events in aged hypertensive patients as well. These beneficial effects can be detected independently for both of the classes of drug(s) used to reduce BP, and they are recommended for the systolic or systodiastolic type of elevated BP.

Despite the evidence collected over the years on the beneficial effects of high BP treatment in the old population, two major issues related to the BP-lowering intervention in the old and very old hypertensive patients are still unresolved. The first issue is the lower limit for

initiating antihypertensive therapy and the second issue is defining the BP goal to be achieved during treatment. These two issues will be separately addressed in the following paragraphs.
Blood pressure threshold for initiating treatment in aged subjects. As far as a BP threshold for treatment initiation is concerned, the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommend BP ≥140/90 mmHg as values at which the antihypertensive pharmacological approach has to be started in older hypertensives, resembling the recommended threshold in young and middle-age patients (1), as emphasized in the reappraisal guidelines document recently issued by the ESH (37). However, this recommendation is not supported by any trial result. There have been no clinical studies published with the aim of determining the effects of antihypertensive treatment on morbidity and mortality in elderly patients with systolic and diastolic BP values ranging from 140 to 160 mmHg and 90 to 95 mmHg, respectively. In the absence of any trial-based evidence, the decision to initiate a BP-lowering treatment in the aged hypertensive patients showing a grade 1 hypertensive state is based on the detection of one or more of the following conditions: associated clinical conditions that increase "per se" total CV risk, such as obesity, diabetes, and metabolic syndrome; target organ damage at the level of the heart, large vessels (particularly carotid arteries), and kidney (including microalbuminuria); previous CV events (myocardial infarction, stroke) or concomitant CVD (angina, heart failure, renal insufficiency, etc.); and a high or a very high CV risk profile (1,6).
Blood pressure treatment targets in aged subjects. Figure 1 summarizes the results of the published trials that assessed the effects of lowering elevated BP values in aged hypertensive patients. The vast majority of the studies confirmed the beneficial effects of BP lowering on CV outcomes. In these studies, the BP values achieved during treatment were well above 140 mmHg for systolic BP. It is unknown, however, whether more tight BP reductions in aged hypertensive patients would lead to additional benefits in terms of decrease in CV events. Therefore, we cannot recommend a specific BP target in treated older hypertensive subjects. The JApanese Trial assessing Optimal Systolic BP in elderly hypertensive patients (JATOS) reduced systolic BP to 138 mmHg. There
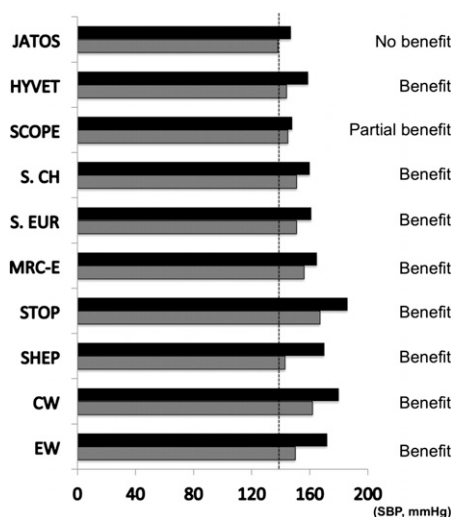
Figure 1—*Achieved systolic BP (SBP) in different clinical trials, identified by the acronyms, performed in elderly hypertensive patients randomized to either active treatment (dotted bars) or placebo treatment (black bars). Note, the only trial in which systolic BP values <140 mmHg were achieved did not show any benefit of treatment.*

was, however, no clear-cut evidence of any further reduction of CV events in these patients (38). Future clinical trials are needed to provide conclusive evidence on whether and to what extent lowering BP values below 140 mmHg is beneficial in older hypertensive subjects.

There is some evidence that antihypertension treatment regimens reducing systolic BP to values close to or below 120–125 mmHg and diastolic BP below 70–75 mmHg may be accompanied by an increase (rather than by a further reduction) in the incidence of coronary and cerebrovascular events. This is known as the so-called "J-curve" phenomenon (39). The issue may be of particular relevance in old and very old patients, where age-related physiologic or pathophysiologic alterations in cerebral and coronary tissue perfusion pressure may indeed promote paradoxical increases in vascular events when the systolic BP is <130 mmHg. No study, however, is available addressing this issue by comparing, particularly in aged hypertensive patients, the effects of different BP targets achieved by antihypertensive treatment on CV events.

Conclusions. In the absence of information, ESH/ESC guidelines suggest starting treatment in healthy older patients with BP values between 140 and 160 mmHg when there is the presence of target organ damage or associated clinical conditions capable of increasing the cardiovascular risk profile of the individual (1). As far as treatment targets are concerned, the

recommendation is to avoid, particularly in very old people, a drastic lowering of BP (1,6). These reductions are capable of doing harm to a fragile patient such as the aged individual. It remains unclear whether the target systolic BP should be the same for patients ranging from 65 to 80 years as it is for patients over the age of 80 years (6).

Blood lipids control in healthy older subjects

High LDL BC levels are considered a significant risk factor for CVD. It is generally agreed that the decision to start statin therapy should rely on the individual absolute risk, as determined by models such as the Framingham risk score (40) or the European Systematic COronary Risk Evaluation (SCORE) (41). Older people may require special attention in that regard. At the age of 75 years, the Framingham risk score assigns 13 points to a man and 16 points to a woman, requiring an LDL BC level of ≤130 mg/dL. Moreover, most risk assessment models stop at age 65 years (SCORE) or 79 years (Framingham) (40,41); they cannot be used to assess the risk in octogenarians. The following section will summarize the current data concerning LDL BC as a risk factor in old people, as well as the efficacy, safety, and cost-effectiveness of statins in aged individuals.

Is cholesterol a risk factor in aged subjects? A meta-analysis of data from 61 prospective studies consisting of almost 900,000 apparently healthy adults found

that total BC was positively associated with ischemic heart disease mortality in both middle- and old age. However, the association was much weaker in elderly people. Each 1 mmol/L lower value of total BC was associated with a hazard ratio of 0.44 at ages 40–49 years compared with a hazard ratio of only 0.83 at the ages of 70–89 years (42).

Moreover, some epidemiological studies suggest that in the old population, low BC levels are associated with greater total mortality (43). How can this be explained? The most reasonable explanation is that the apparent adverse effects associated with low BC levels are secondary to overt or occult comorbidity and frailty. For example, in one study people with the lowest total BC levels had the highest rate of death from coronary heart disease in an unadjusted analysis. However, after adjustment for established risk factors for coronary heart disease and markers of poor health and exclusion of deaths from coronary heart disease that occurred within the first year of follow-up, elevated total BC levels reemerged as a predictor for increased risk for coronary heart disease death (44).

Is statin therapy effective in aged subjects? Most retrospective cohort studies have demonstrated that statin use is associated with a lower risk of CHD morbidity and mortality in the old population. For example, a study was conducted in Sweden between 1999 and 2003 that included 21,410 patients ≥80 years of age who were admitted with the diagnosis of an acute myocardial infarction. The study showed that CV incidence and coronary mortality were significantly lower in patients who received statins at discharge (45). Since retrospective studies may be confounded by the "healthy patient bias" (i.e., by the administration of statins to relatively healthy aged patients), prospective randomized trials are needed. However, in many prospective randomized clinical trials, older patients are frequently underrepresented (Table 2). Many studies have excluded people over the age of 75 years, and the others included only small numbers of old individuals.

Despite these caveats, some conclusions can be drawn from these studies. In almost all of them, post hoc analyses have shown a reduction in CV events in patients aged ≥65 years who were taking statins. The studies that included the largest numbers of old people were the Heart Protection Study (HPS) (46,47) and the

Table 2—*Elderly patients in major statin prospective trials (identified by the trial acronym)*

Study	Mean age (years)	Maximal age (years)	Elderly patients
4S	59	70	23% >65 years
LIPID	62	75	15% >70 years
CARE	59	75	31% >65 years
WOSCOPS	55	64	0% >65 years
AFCAPS/TexCAPS	58	73	21% >65 years
ALLHAT-LLT	66	No limit	55% >65 years
ASCOT-LLA	63	79	64% >60 years
HPS	64	80	28% >70 years
CARDS	61	75	12% >70 years
PROVE-IT	58	No limit	30% >65 years
TNT	61	75	No data
JUPITER	66	No limit	32% >70 years
CORONA	73	No limit	41% >75 years
4D	66	80	14% >75 years
AURORA	64	80	49% >65 years
A to Z	61	80	25% >69 years
SEARCH	64	80	30% >70 years
IDEAL	62	80	42% >65 years
SPARCL	63	No limit	No data
GREACE	59	75	No data
Post-CABG	61	74	No data
GISSI-P	60	No limit	15% >70 years
LIPS	60	80	No data
PROSPER	75	82	100% >70 years
ALERT	50	75	No data
ALLIANCE	61	No limit	No data
ASPEN	61	75	36% >65 years
MEGA	58	70	No data
GISSI-HF	68	No limit	44% >70 years
CTT meta-analysis	63	—	No data

Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (48).

In the HPS, almost 6,000 participants were ≥70 years old at the beginning of the study. These participants displayed the same risk reduction using simvastatin as younger patients. The proportional reduction in the rate of major vascular events with simvastatin was approximately one-quarter irrespective of the age of the participants. Indeed, even among the 1,263 individuals aged 75–80 years at entry, the reduction in the event rate was substantial and definite (23.1% vs. 32.3%; $P = 0.0002$) (46). Treatment with statins remained cost-saving or cost-effective in people as old as 85 years, with 5-year risks of a major vascular event as low as 5% at the start of treatment (47).

In the JUPITER trial, 5,695 participants were aged ≥70 years at the beginning of the study (48). These patients had the same magnitude of risk reduction in CV events with rosuvastatin as the

younger patients (hazard ratio 0.61; $P < 0.001$). Moreover, since the absolute risk of CV events is greater in older people, the absolute reduction in the first CV event associated with rosuvastatin was greater among older than among younger participants (48).

The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study was the only trial to exclusively evaluate older people prospectively. A total of 5,804 patients, between the ages of 70 and 82 years, who had risk factors for vascular diseases, were randomized to receive pravastatin 40 mg/day or a placebo. After 3 years of follow-up, pravastatin reduced the risk from coronary death, nonfatal myocardial infarction, and stroke by 15% but did not reduce total mortality (49).

A meta-analysis including nine trials enrolling 19,569 patients with an age range of 65 to 82 years found that statin therapy was associated with a 30% reduction in coronary mortality with a

number needed to treat to save 1 life of 28 (50). In the cholesterol treatment trialists' collaboration meta-analysis, there was a significant risk reduction in major vascular events of 16% per 1 mmol/L reduction in LDL BC in people older than 75 years at study entry—a reduction similar to that seen in younger participants (51).

Are statins safe for aged subjects? In the PROSPER study, there was no difference in serious adverse events, myalgia, or elevated liver enzymes between the patients receiving statins and those receiving placebo, and there were no cases of rhabdomyolysis (49). Other randomized clinical trials did not find an increase of serious side effects, either (47,48,51). However, in the PROSPER study cancer was 25% more frequent in the pravastatin group (49). This seems to be a chance finding, since there are no reports about excess incidence of cancer due to statin use (47,48,51). In contrast, a recent study has shown that statins may reduce cancer mortality (52).

Conclusions. According to the limited data at hand, healthy older people should not be denied statins solely because of their age. According to the American Heart Association scientific statement on secondary prevention of coronary heart disease in the elderly, these patients may derive greater benefits from therapy because of their greater absolute risk (53). Since there is 1–2 years lag time before the benefit of statin emerges, such a lag time should not represent too large a proportion of remaining life expectancy.

The recent ESC/European Atherosclerosis Society guidelines for the management of dyslipidemias also state that statins are recommended for elderly patients with established CVD similarly as for younger patients and should be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age (3). It is recommended to start at a low dose and titrate with caution to the same target levels as in younger subjects.

Blood glucose control in healthy older subjects

The prevalence of type 2 diabetes is steadily increasing as more people live longer and grow heavier (4). As people with diabetes age, their disease may become more difficult to control owing to its progressive nature and the increase in complications (54). The aged population poses new challenges in diabetes control,

with increased comorbidities on the one hand and an increased susceptibility to medication side effects on the other. This calls for a different approach in setting glycemic targets in this population and specifying the means recommended to attaining them.

Aged patients are at high risk for polypharmacy, physical, and functional disabilities; cognitive impairment and dementia; depression; urinary incontinence; and falls. Progressive deterioration of organ function occurs with increasing age including a decline in renal function, decreased cardiac output, increased systolic hypertension, and visual changes. Hypoglycemia is a major safety concern in the old population. The diabetic population with an advanced age is heterogeneous, including people residing independently in the community, those residing in assisted care facilities, and nursing home residents. They may be fit and healthy or frail with multiple comorbidities and functional disabilities. The overall goals of diabetes management are to take into account frailty and life expectancy as well as coexisting medical conditions and the ability to perform self-management.

Glucose targets in aged subjects. There are sparse data specifically addressing optimal glycemic goals in elderly patients; thus, guidelines are mostly based on expert opinions. Recently, the International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People, and the International Task Force of Experts in Diabetes collaborated on a position paper on the effective management of older patients with diabetes (55). The following advice was given:

1. BG targets must be individualized taking into account individual comorbidities and cognitive and functional status and should have the consent of the patient or caregiver.
2. Glucose-lowering therapy should be initiated if fasting BG levels are consistently >7 mmol/L.
3. Target HbA_{1c} levels should be 7.0–7.5%.
4. Target fasting BG levels should be >6.0 mmol/L.
5. Avoid BG levels <5 mmol/L.
6. Avoid random BG >11 mmol/L.

When setting glycemic goals, life expectancy should be taken into account and we should balance short-term versus long-term risks and benefits. In the short-term, side effects of diabetes treatment, most notably hypoglycemia, can result in traumatic falls and the exacerbation of comorbid conditions. Hyperglycemia increases dehydration and impairs vision and cognition.

In the long-term, BG control may prevent the development of microvascular complications. However, it may take several years for this benefit to be realized. It took 3–4 years of intensive glycemic control to begin to perceive a reduction in new onset of retinopathy or microalbuminuria (56,57). It may take >10 years of intensive glycemic control from disease onset to see improved CV outcomes (58) and ≥20 years to prevent end-stage renal disease (59). Macrovascular benefits of glycemic control in well-established diabetic patients are unclear.

One may consider more stringent diabetes control goals, similar to those of young adults (HbA_{1c} <7%), in fit aged patients who have a life expectancy of >10 years. The target should be somewhat higher (≤8.0%) in frail older adults with medical and functional comorbidities. Individualized targets for the very elderly may be even higher and should

include efforts to preserve quality of life and avoid hypoglycemia and related complications.

Specific treatment issues in aged subjects. Figure 2 displays an algorithm of recommended treatment for the older diabetic population, based on recent guidelines, on clinical experience, and on the position statement document issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (60). As also emphasized by the recent consensus report of the ADA for diabetes in older adults (61), some considerations should be done when comparing the ADA/EASD general algorithm of treatment (60) to the one proposed for older adults. The first consideration refers to the use of metformin, which according to ADA/EASD general algorithm should be regarded as the optimal first-line treatment drug (60). Indeed, in patients above the age of 80 years, in agreement with the consensus report for diabetes in older adults (61), we suggest not using it unless normal renal function is present. Metformin should be avoided in patients with hepatic impairment, since it increases the risk of lactic acidosis. Patients should be warned
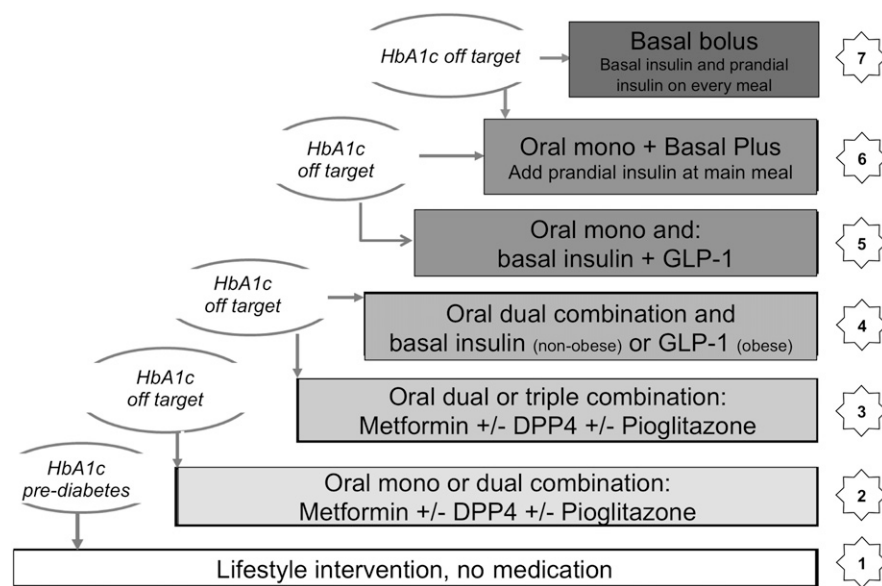
Figure 2—*This seven-step algorithm is a guide to glucose optimization in the elderly striving for minimal hypoglycemic events. Note that the use of sulfonylureas is not recommended. HbA_{1c} should be measured every 3–6 months and treatment adjusted accordingly. Glucose targets should be individualized as specified in the text. No medications are recommended for prediabetes. If glucose control deteriorates, interventions are gradually increased from monotherapy (mono) to dual and triple oral therapy. Once injections are being used, the number of oral medicines should be gradually decreased in order to minimize polypharmacy. If metformin and pioglitazone are contraindicated, the recommended first-line oral therapy is a DPP-4 inhibitor, and the next step is long-acting basal insulin in the nonobese and GLP-1 agonist in the obese. The full basal-bolus protocol should seldom be used in the elderly when appropriate.*

against excessive alcohol intake, acute or chronic, as ethanol produces NADH, which increases the conversion of pyruvate to lactate. However, despite early concerns, the evidence for an increase in the risk of lactic acidosis is minimal. The recent evaluation of metformin associated lactic acidosis cases from 347 trials by Salpeter and coworkers (62) showed that the risk of lactic acidosis with metformin was not significantly increased compared with other antiglycemic agents. The dose should be reduced if estimated glomerular filtration rate is 30–60 mL/min, and the drug should not be used if estimated glomerular filtration rate is <30 mL/min (63,64).

The second consideration relates to the use of pioglitazone. The recommendation is to use the drug in patients who are not at high risk of weight gain, heart failure, or bone loss; do not display the tendency to develop edema; and do not have a history of osteoporosis or bladder cancer (the relative risk is ~3.42 among thiazolidinedione users with >5 years since treatment initiation) (65). Patients without peripheral artery disease at baseline seemed to benefit more from pioglitazone treatment, as shown in the PROspective pioglitAzone Clinical Trial In macrovascular eVEnts (PROACTIVE) study (66). A further consideration should be done for sulfonylureas and meglitinides, which should be used with caution in older adults, given the increased risk of hypoglycemia. In the elderly population, these drugs should generally be avoided. A final comment deserves to be made for DPP-4s and GLP-1 mimetic, for which clinical trials did not show overall differences in safety, tolerability, or effectiveness between subjects ≥65–75 years old and younger subjects (55). These drugs are known to be substantially excreted by the kidney, except for linagliptin and liraglutide, which have no renal elimination (67). Because aged patients are more likely to have decreased renal function, care should be taken in dose selection in the older population.

Other recommendations include the following. First, in nursing home patients and those with severe cognitive impairment, in whom medication intake is erratic and not easily monitored, basal insulin should be the preferred therapy. Second, in order to avoid triple oral therapy (because of polypharmacy), add instead an injection of either insulin or a glucagon-like peptide 1 receptor (GLP-1R) as applicable to dual oral treatment. Third, the use of a basal-bolus protocol in

the older patients should be reserved for those who remain very hyperglycemic on basal insulin doses and oral medications because of their sporadic and unpredictable eating patterns along with a long history of diabetes with resultant very low β-cell function.

Patient safety and conclusions. A comprehensive geriatric assessment should be applied to identify functional loss and the impact of the disability. The physician should evaluate the healthy older patient within the patient's environment and assess the patient's self-management ability and supportive surroundings prior to proposing a treatment and monitoring plan.

Polypharmacy should be avoided; simplified treatment regimens are preferred. Evaluate the medication list, and justify the use of each and every medication periodically. The priority list of medications should include a statin, an ACE inhibitor, and a glucose-lowering agent. Hypoglycemia is a major safety concern in the elderly. Healthy older patients have reduced awareness of the autonomic symptoms of impending hypoglycemia and are at an increased risk of fall and injury due to hypoglycemia. Advanced age; polypharmacy; use of sulfonylureas, meglitinides, or insulin; poor nutrition; intercurrent illnesses; and chronic liver, renal, or CV diseases all increase the risk of the patient suffering significant hypoglycemic events.

Hypoglycemic episodes in healthy older individuals may also increase the risk of adverse CV events and cardiac autonomic dysfunction (68). In addition, severe hypoglycemia requiring hospitalization has been associated with an increased risk of developing dementia, which was found to be higher in patients with repeated episodes, although the direction of causality, if any, remains undefined (69).

References

1. Mancia G, De Backer G, Dominiczak A, et al.; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–1187

2. Tsigos C, Hainer V, Basdevant A, et al.; Obesity Management Task Force of the European Association for the Study of Obesity. Management of obesity in adults: European clinical practice guidelines. Obes Facts 2008;1:106–116

3. Reiner Z, Catapano AL, De Backer G, et al.; European Association for Cardiovascular Prevention & Rehabilitation; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769–1818

4. Centers for Disease Control and Prevention. National diabetes fact sheet 2011 [article online]. Available from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed 31 January 2013

5. Villareal DT, Apovian CM, Kushner RF, Klein S; American Society for Nutrition; NAASO, The Obesity Society. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am J Clin Nutr 2005;82:923–934

6. Aronow WS, Fleg JL, Pepine CJ, et al.; ACCF Task Force. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2011;123:2434–2506

7. James WP. The epidemiology of obesity: the size of the problem. J Intern Med 2008;263:336–352

8. Arterburn DE, Crane PK, Sullivan SD. The coming epidemic of obesity in elderly Americans. J Am Geriatr Soc 2004;52:1907–1912

9. Kyrou I, Tsigos C. Obesity in the elderly diabetic patient: is weight loss beneficial? No. Diabetes Care 2009;32(Suppl. 2):S403–S409

10. Mathus-Vliegen EM; Obesity Management Task Force of the European Association for the Study of Obesity. Prevalence, pathophysiology, health consequences and treatment options of obesity in the elderly: a guideline. Obes Facts 2012;5:460–483

11. Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? Am J Epidemiol 1996;143:228–239

12. Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. Int J Obes Relat Metab Disord 2001;25:1730–1735

13. Shimokata H, Andres R, Coon PJ, Elahi D, Muller DC, Tobin JD. Studies in the distribution of body fat. II. Longitudinal effects of change in weight. Int J Obes 1989; 13:455–464

14. Seidell JC, Visscher TL. Body weight and weight change and their health implications for the elderly. Eur J Clin Nutr 2000;54(Suppl. 3):S33–S39

15. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. Obes Rev 2007;8:41–59

16. Lang IA, Llewellyn DJ, Alexander K, Melzer D. Obesity, physical function, and mortality in older adults. J Am Geriatr Soc 2008;56:1474–1478

17. Kuk JL, Ardern CI. Influence of age on the association between various measures of obesity and all-cause mortality. J Am Geriatr Soc 2009;57:2077–2084

18. Stessman J, Jacobs JM, Ein-Mor E, Bursztyn M. Normal body mass index rather than obesity predicts greater mortality in elderly people: the Jerusalem longitudinal study. J Am Geriatr Soc 2009;57:2232–2238

19. Han TS, Tajar A, Lean ME. Obesity and weight management in the elderly. Br Med Bull 2011;97:169–196

20. Caterson ID, Finer N, Coutinho W, et al.; SCOUT Investigators. Maintained intentional weight loss reduces cardiovascular outcomes: results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. Diabetes Obes Metab 2012;14:523–530

21. Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. N Engl J Med 2012;367: 1577–1579

22. Ensrud KE, Cauley J, Lipschutz R, Cummings SR; Study of Osteoporotic Fractures Research Group. Weight change and fractures in older women. Arch Intern Med 1997;157:857–863

23. Villareal DT, Shah K, Banks MR, Sinacore DR, Klein S. Effect of weight loss and exercise therapy on bone metabolism and mass in obese older adults: a one-year randomized controlled trial. J Clin Endocrinol Metab 2008;93:2181–2187

24. Bales CW, Ritchie CS. Sarcopenia, weight loss, and nutritional frailty in the elderly. Annu Rev Nutr 2002;22:309–323

25. Li Z, Heber D. Sarcopenic obesity in the elderly and strategies for weight management. Nutr Rev 2012;70:57–64

26. Wagner DR, Heyward VH. Techniques of body composition assessment: a review of laboratory and field methods. Res Q Exerc Sport 1999;70:135–149

27. Miller SL, Wolfe RR. The danger of weight loss in the elderly. J Nutr Health Aging 2008;12:487–491

28. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652–659

29. Lutsey PL, Michos ED. Vitamin D, calcium, and atherosclerotic risk: evidence from serum levels and supplementation studies. Curr Atheroscler Rep 2013;15: 293

30. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med 2005;142:532–546

31. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 2007;335:1194–1199

32. Fried M, Hainer V, Basdevant A, et al. Inter-disciplinary European guidelines on surgery of severe obesity. Int J Obes (Lond) 2007;31:569–577

33. Turnbull F, Neal B, Ninomiya T, et al.; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ 2008;336:1121–1123

34. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. J Hypertens 2010;28:1366–1372

35. Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898

36. Beckett N, Peters R, Tuomilehto J, et al.; HYVET Study Group. Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. BMJ 2012;344:d7541

37. Mancia G, Laurent S, Agabiti-Rosei E, et al.; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121–2158

38. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008; 31:2115–2127

39. Grassi G, Quarti-Trevano F, Dell'Oro R, Mancia G. The "J curve" problem revisited: old and new findings. Curr Hypertens Rep 2010;12:290–295

40. D'Agostino RB, Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–187

41. Conroy RM, Pyörälä K, Fitzgerald AP, et al.; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003

42. Lewington S, Whitlock G, Clarke R, et al.; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829–1839

43. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med 1993;153:1065–1073

44. Corti MC, Guralnik JM, Salive ME, et al. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. Ann Intern Med 1997;126:753–760

45. Gränsbo K, Melander O, Wallentin L, et al. Cardiovascular and cancer mortality in very elderly post-myocardial infarction patients receiving statin treatment. J Am Coll Cardiol 2010;55:1362–1369

46. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22

47. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R; Heart Protection Study Collaborative. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. BMJ 2006;333:1145–1149

48. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med 2010;152: 488–496, W174

49. Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360: 1623–1630

50. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol 2008;51:37–45

51. Baigent C, Blackwell L, Emberson J, et al.; Cholesterol Treatment Trialists' (CTT)

Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–1681

52. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367:1792–1802

53. Williams MA, Fleg JL, Ades PA, et al.; American Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients > or =75 years of age): an American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2002;105:1735–1743

54. Bethel MA, Sloan FA, Belsky D, Feinglos MN. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med 2007;167:921–927

55. Sinclair A, Morley JE, Rodriguez-Mañas L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc 2012;13:497–502

56. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995;102:647–661

57. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853

58. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589

59. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med 2012;172:761–769

60. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379

61. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664

62. Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010;1:CD002967

63. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–1437

64. National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes [article online], 2009. Available from http://www.nice.org.uk/nicemedia/live/12165/44320/44320.pdf. Accessed 31 January 2013

65. Mamtani R, Haynes K, Bilker WB, et al. Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study. J Natl Cancer Inst 2012;104:1411–1421

66. Dormandy JA, Betteridge DJ, Schernthaner G, Pirags V, Norgren L; PROactive investigators. Impact of peripheral arterial disease in patients with diabetes—results from PROactive (PROactive 11). Atherosclerosis 2009;202:272–281

67. Nicholson G, Hall GM. Diabetes mellitus: new drugs for a new epidemic. Br J Anaesth 2011;107:65–73

68. Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, Freeman R. Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes 2009;58:360–366

69. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572