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Clinical research

Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery?

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Aims To analyse decision-making in elderly patients with severe, symptomatic aortic stenosis (AS).
Methods and results In the Euro Heart Survey on valvular heart disease, 216 patients aged ≥75 had severe AS (valve area ≤0.6 cm^2/m^2 body surface area or mean gradient ≥50 mmHg) and angina or New York Heart Association class III or IV. Patient characteristics were analysed according to the decision to operate or not. A decision not to operate was taken in 72 patients (33%). In multivariable analysis, left ventricular (LV) ejection fraction [OR = 2.27, 95% CI (1.32–3.97) for ejection fraction 30–50, OR = 5.15, 95% CI (1.73–15.35) for ejection fraction ≤30 vs. >50%, $P = 0.003$] and age [OR = 1.84, 95% CI (1.18–2.89) for 80–85 years, OR = 3.38, 95% CI (1.38–8.27) for ≥85 vs. 75–80 years, $P = 0.008$] were significantly associated with the decision not to operate; however, the Charlson comorbidity index was not [OR = 1.72, 95% CI (0.83–3.50), $P = 0.14$ for index ≥2 vs. <2]. Neurological dysfunction was the only comorbidity significantly linked with the decision not to operate.
Conclusion Surgery was denied in 33% of elderly patients with severe, symptomatic AS. Older age and LV dysfunction were the most striking characteristics of patients who were denied surgery, whereas comorbidity played a less important role.

Introduction

Aortic stenosis (AS) is the most frequent heart valve disease in Western countries, where its prevalence steadily increases with age.[1,2] Indications for aortic valve replacement (AVR) are well defined in guidelines and there is a consensus that intervention should be advised in patients with severe, symptomatic AS.[3] Decision to operate raises specific problems in the elderly, in particular, because of the increase in operative mortality and morbidity.[4–17] However, little is known regarding the proportion of elderly patients with AS who are denied intervention and, in particular, the reasons leading to contraindicate it.[17–19]

To address this issue, we used the data from the Euro Heart Survey on valvular heart disease, the purpose of which was to assess contemporary practices in Europe. An important feature of this prospective survey was to include consecutive patients regardless of the therapeutic decision. This made it possible to evaluate the proportion of patients with severe, symptomatic AS who were denied surgery and to compare their characteristics and 1-year outcome with those in whom a decision to operate was taken.

Methods

Study population

The Euro Heart Survey on valvular heart disease was conducted between April and July 2001 in 92 centres from 25 European countries and it included 5001 patients. Details on inclusion and data collection have been previously described.[2] Isolated AS was defined by a maximum aortic velocity as assessed by Doppler echocardiography ≥2.5 m/s without significant associated valve disease, i.e. aortic or mitral regurgitation more than grade 2/4 or mitral stenosis with a valve area ≤2 cm^2.

Isolated AS was encountered in 1197 patients, among whom 408 were aged ≥75. Of them, 284 had severe AS, as defined by a valve area ≤0.6 cm^2/m^2 of body surface area and/or a mean aortic gradient ≥50 mmHg. Seventy-eight patients had a mean aortic gradient <50 mmHg and a valve area >0.6 cm^2/m^2 of body surface area. Neither mean gradient nor aortic valve area was available in 46 patients.

Functional status was missing in one patient, 26 were asymptomatic [New York Heart Association (NYHA) class I and no angina], 41 were in NYHA class II and had no angina, and 216 had severe symptoms, i.e. either singly or in combination: dyspnoea NYHA

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class III in 105 patients (49%), class IV in 35 (16%), and angina pectoris in 147 (68%) (*Figure 1*).

These 216 elderly patients presenting with severe isolated AS and severe symptoms form the basis of the present study. Twenty-nine (13%) were recruited from the outpatient clinics, 127 (59%) from medical cardiology departments, and 60 (28%) from cardiac surgery departments. Follow-up started from the inclusion date in the survey. One-year follow-up was available in 190 of the 216 patients (88%).

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation. Patient characteristics were compared according to whether or not a decision to operate was taken by the attending practitioner. Predictive factors of the decision not to operate were analysed by comparing patient characteristics related to demographics, risk factors, comorbidity, symptoms, and investigations as listed in *Table 1*. Definitions of risk factors and comorbidities are detailed in the appendix. Comorbidities were analysed individually and combined using the Charlson comorbidity index.[20] Because the aim of the Euroscore is to evaluate the risk of surgery, we calculated the Euroscore as if all patients would have undergone valve surgery, thereby enabling the global risk of surgery to be assessed, regardless of the actual decision.[21] Univariable comparisons used the unpaired Student's *t*-test for quantitative variables and the χ^2 test for qualitative variables.

Two multivariable models were elaborated to estimate the respective weights of cardiac and non-cardiac characteristics in the decision to operate. In the first model, comorbidities were combined using the Charlson comorbidity index, the second model included separate comorbidities listed in *Table 1*.

Variables with $P < 0.25$ were entered in each multivariable logistic model. Quantitative variables included in the multivariable models were transformed into qualitative variables of which the cutpoints were chosen according to risk progression in univariable analysis. Variables were selected using a backward procedure with a threshold of $P = 0.05$, except for the Charlson comorbidity index which was forced in the model.

One-year survival was analysed using the Kaplan–Meier method. Univariable analysis of the predictive factors of 1-year mortality used a Cox model. Variables with $P < 0.25$ were entered into a multivariable Cox model and selected by a backward procedure with a threshold of $P = 0.05$, except for the variable 'decision to operate' which was forced in the model. The assumption of proportional hazard hypothesis was verified graphically. All tests were two-sided. A *P*-value <0.05 was considered significant. Analysis was performed with SAS statistical software (SAS Institute Inc. release 8.2).

Results

Patient characteristics

Mean age of the 216 patients was 80.3 ± 4.2 years (range 75–92), 124 (57%) patients were aged between 75 and 80, 58 (27%) between 80 and 85, 29 (14%) between 85 and 90, and five (2%) were aged ≥90. At least one non-cardiac comorbidity was present in 95 patients (44%). Coronary angiography was performed in 163 patients (75%), 99 (61%) of whom had significant coronary artery disease: 1-vessel disease in 37, 2-vessel disease in 31, 3-vessel disease in 28, and left main stenosis in three. Medical therapy used, either singly or in combination, aspirin in 116 patients (54%), diuretics in 133 (62%), beta-blockers in 83 (38%), nitrates in 79 (37%), ACE-inhibitors in 74 (34%), and calcium-blockers in 56 (26%).

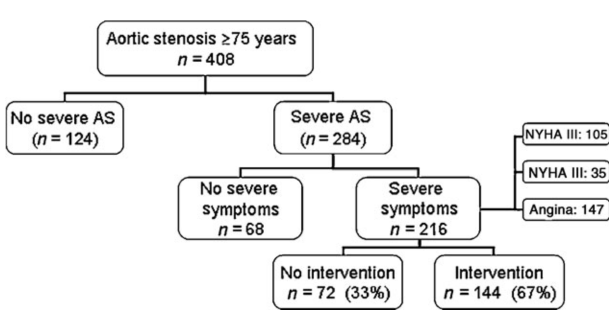

Figure 1 Details of study population.

Analysis of therapeutic decision

Surgery was decided against by the attending practitioner in 72 patients (33%). A decision to operate was taken in 144 patients (67%): 100 underwent AVR during the study period in a centre participating in the Euro Heart Survey and 44 were scheduled for intervention, 36 of whom being on a waiting list with a mean duration 6.1 ± 2.7 weeks (range 3–12).

In univariable analysis, patients in whom intervention was decided against by the attending practitioner were older, more frequently had neurological dysfunction, heart failure, atrial fibrillation, and left ventricular (LV) dysfunction than patients in whom a decision to operate was taken (*Table 1*). The Charlson comorbidity index was higher in patients in whom intervention was decided against (*Table 1*). Decision to operate according to age, LV ejection fraction, and Charlson comorbidity index are detailed in *Figures 2–4*. There was no significant difference between the four European regions regarding the proportion of decision to operate, which was 65% in Northern Europe, 57% in Eastern Europe, 73% in Western Europe, and 63% in Mediterranean Europe ($P = 0.35$). Surgery was not decided upon in seven patients (10%) because of patient refusal.

In multivariable analysis, the two significant factors linked with the decision not to operate were older age and lower LV ejection fraction, whereas the Charlson comorbidity index did not reach statistical significance (*Table 2*). When including individual comorbidities instead of the Charlson comorbidity index in the multivariable analysis, the three factors significantly linked with the decision not to operate were older age, lower LV ejection fraction <50%, and neurological dysfunction (*Table 3*).

Of the 100 patients who underwent AVR during the study period in a centre participating in the Euro Heart Survey, five (5%) died during the post-operative period (30 days). The mean Euroscore was 8.0 ± 1.7 in patients who survived vs. 9.4 ± 2.6 in the patients who died post-operatively ($P = 0.076$). A bioprosthesis was used in 93 patients and a mechanical prosthesis in seven. An associated procedure was performed in 41 patients, it was coronary artery bypass grafting in 37 and partial replacement of the ascending aorta in five (both procedures in one patient). There were no cases of balloon aortic valvuloplasty.

One-year outcome

One-year follow-up was available in 123 patients (85%) with a decision to operate and 67 patients (93%) with a decision not to operate ($P = 0.11$).

Of the 72 patients in whom the initial decision was not to operate, four underwent subsequent AVR after 1–9 months.

Table 1 Predictive factors of therapeutic decision

Factors	Decision not to operate ($n = 72$) mean $\pm$ SD or n (%)	Decision to operate ($n = 144$) mean $\pm$ SD or n (%)	*P*-value
Demographics			
Age	81.7 $\pm$ 4.8	79.5 $\pm$ 3.7	0.0004
Gender (male)	31 (43.1)	70 (48.6)	0.44
Previous percutaneous coronary intervention	1 (1.4)	8 (5.6)	0.15
Previous coronary bypass grafting	5 (6.9)	4 (2.8)	0.15
Previously known valve disease	57 (79.2)	102 (70.8)	0.19
Risk factors			
Smoking (current)	1 (1.4)	10 (6.9)	0.11
Hypertension	42 (59.1)	92 (63.9)	0.50
Diabetes	17 (23.6)	27 (18.8)	0.40
Insulin treated	5 (6.9)	10 (6.9)	1.0
Dyslipidaemia	22 (31.0)	56 (38.9)	0.26
Family history	10/57 (25.6)	29/118 (24.6)	0.30
Comorbidity			
Previous myocardial infarction	16 (22.2)	22 (15.3)	0.21
Carotid atherosclerosis	5 (6.9)	8 (5.6)	0.76
Lower limb atherosclerosis	8 (11.1)	9 (6.3)	0.28
Creatinine >200 μmol/L	5 (7.0)	4 (2.8)	0.16
Neurological dysfunction	12 (16.9)	7 (4.9)	0.009
Chronic obstructive pulmonary disease	14 (19.4)	23 (16.0)	0.52
≥1 comorbidity	37 (51.4)	58 (40.3)	0.15
Charlson comorbidity index			0.01
0	20 (27.8)	60 (41.7)	
1	18 (25.0)	48 (33.3)	
2	17 (23.6)	20 (13.9)	
3	10 (13.9)	13 (9.0)	
>3	7 (9.7)	3 (2.1)	
Symptoms			
Angina pectoris	49 (69.0)	98 (69.1)	0.98
NYHA class IV	15 (20.8)	20 (13.8)	0.19
Congestive heart failure at admission	23 (31.9)	28 (19.6)	0.04
Atrial fibrillation	18 (25.3)	21 (14.6)	0.05
Investigations			
LV ejection fraction (%)	51.5 $\pm$ 17.6	59.0 $\pm$ 12.2	0.001
< 50%	24/57 (42.1)	21/127 (16.5)	
LV end-diastolic dimension (mm)	49.6 $\pm$ 7.6	49.7 $\pm$ 6.4	0.97
Systolic pulmonary artery pressure (mmHg)	37.9 $\pm$ 23.0	39.4 $\pm$ 18.2	0.72
Aortic valve area (cm^2)	0.73 $\pm$ 0.23	0.68 $\pm$ 0.55	0.40
Indexed aortic valve area (cm^2/m^2)	0.42 $\pm$ 0.13	0.38 $\pm$ 0.25	0.24
Mean aortic gradient	52.4 $\pm$ 19.8	56.3 $\pm$ 18.2	0.17
Aortic regurgitation grade 2/4	12/68 (17.6)	26/134 (19.4)	0.76
Coronary artery disease	17/23 (73.9)	82/140 (58.6)	0.18
Euroscore	9.4 $\pm$ 2.9	8.1 $\pm$ 1.8	0.0006

Univariable analysis. In case of missing data, the number of patients with available data is specified at the denominator. Definitions of risk factors and comorbidities are detailed in the appendix.

One-year survival was higher in the 144 patients who had a decision to operate than in the other 72 (90.4 $\pm$ 2.6 vs. 84.8 $\pm$ 4.8%, $P = 0.057$). In multivariable analysis, the decision to operate was not associated with 1-year survival ($P = 0.94$) and the three significant predictors of 1-year mortality were a higher Charlson comorbidity index, male gender, and NYHA class IV functional class (*Table 4*).

Discussion

This contemporary pan-European survey is the first prospective study, which was specifically designed to evaluate the management of patients with valvular heart disease in a wide range of centres. One-third of elderly patients with severe, symptomatic AS were denied surgery by the attending practitioner. Patients in whom intervention was decided against were older and more frequently had LV ejection fraction <50% and comorbidities. However, the results of multivariable analysis suggest that age and LV function have a heavier weight in the decision to operate than the combination of comorbidities. When considering comorbidities individually, neurological dysfunction was the only one associated with a decision not to operate.

Population

The presence of primary care centres and the inclusion of patients from outpatient clinics, as well as medical and

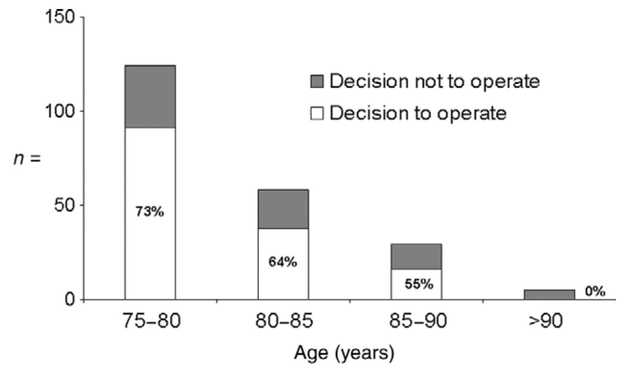

Figure 2 Decision to operate according to age range.

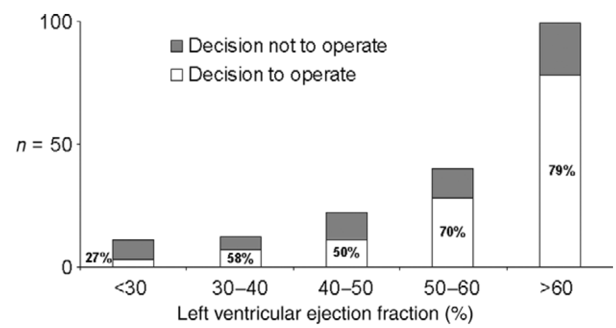

Figure 3 Decision to operate according to left ventricular ejection fraction.

surgical wards, enabled a wide spectrum of elderly patients with AS to be considered and reduced selection bias. We deliberately chose to consider only patients who had severe AS associated with severe symptoms, i.e. patients for whom there is a clear-cut indication for surgery according to guidelines.[3] Cardiovascular risk factors and comorbidities were frequently associated. Patients were managed at a relatively advanced stage of their disease, as attested by the 24% presenting with congestive heart failure and the frequent use of medical therapy.

Decision against surgery: frequency and associated patient characteristics

Decision-making is particularly complex in the elderly who represent a heterogeneous population, resulting in a wide range of operative risk, as well as life expectancy, according to individual cardiac and non-cardiac patient characteristics.

In the Euro Heart Survey, despite severe AS and severe symptoms, intervention was denied in as many as 33% of patients. In the only other series addressing this issue, the corresponding figure was 41% in patients aged >70 with AS and severe symptoms.[17] Besides patient characteristics, the proportion of patients in whom a decision not to operate is taken is also influenced by referral patterns and it could be expected to be higher in general practice.

To analyse decision-making, we chose to compare objective patient characteristics rather than reasons given by the attending practitioner to limit the subjective component in patient evaluation. The two most striking characteristics of patients who were denied surgery were older age and LV dysfunction. Age and LV dysfunction are associated

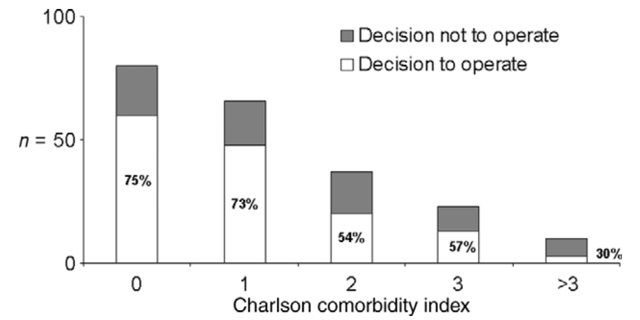

Figure 4 Decision to operate according to comorbidities.

with an increased operative risk and a poor late outcome after surgery, which may explain the reluctancy to operate on such patients. However, decision-making should rely not only on estimation of operative risk, but also on estimation of the risk–benefit ratio, requiring outcome after surgery to be compared with spontaneous evolution.

Age is a strong predictor of operative risk and poor late survival in cardiovascular surgery, in particular, in the case of AS.[15,21–25] Nevertheless, age is not a predictor of poor late outcome when considering relative survival, i.e. compared with expected survival in an age-matched population.[4,12,26] These findings led guidelines to state that age *per se* is not a contraindication to valve replacement and that the decision depends on many factors.[3]

The decrease in LV ejection fraction is a predictor of operative mortality in cardiovascular surgery and in certain series studying elderly with AS.[6,9,15,21] However, the increase in operative risk is most marked in patients who have severe ventricular dysfunction, such as LV ejection fraction <30%, which was seldom encountered in the present study. Conversely, studies on natural history have pointed out that congestive heart failure and LV dysfunction are strong predictors of poor outcome in non-operated patients with AS,[17,27,29] and patients with LV dysfunction seem to derive a particular benefit from surgery.[17,19] Therefore, in the present study, the decrease in the proportion of decisions to operate on patients with an LV ejection fraction between 30 and 50% is neither substantiated by the analysis of risk–benefit ratio nor supported by the guidelines.[3]

Of course, according to clinical judgement, surgery is more likely to be denied in very old patients or those with major LV dysfunction. However, there were very few patients aged >90 or with an LV ejection fraction <30% in the present series.

Comorbidities are frequent in the elderly and are expected to affect the risk–benefit analysis because they influence life expectancy regardless of the valvular disease, as well as the operative risk and late outcome after AVR. The combination of comorbidities is also a strong determinant of operative risk.[21,23,24]

As expected, the proportion of patients in whom a decision to operate was taken decreased for higher levels of the Charlson comorbidity index. However, it was no longer significantly associated with the therapeutic decision in multivariable analysis, suggesting that age and LV function were stronger determinants of the choice than comorbidities. When considered individually, the only comorbidity associated with the decision not to operate was neurological

Table 2 Factors associated with a decision not to operate

	P-value	Odds ratio	95% CI
LV ejection fraction	0.003		
>50%		1	
30–50%		2.27	1.32–3.97
≤30%		5.15	1.73–15.35
Age (years)	0.008		
75–80		1	
80–85		1.84	1.18–2.89
≥85		3.38	1.38–8.27
Charlson comorbidity index	0.14		
0–1		1	
≥2		1.72	0.83–3.50

Multivariable analysis including the Charlson comorbidity index as a forced variable. Hosmer–Lemeshow goodness-of-fit $\chi^2 = 2.65$ (df = 5), $P = 0.75$, *c*-index 0.72.

dysfunction. Renal failure or chronic obstructive pulmonary disease is a predictor of life expectancy as well as operative mortality, in particular in AS in the elderly, but they were not associated with the decision not to operate in the present series.[9,10,14]

Coronary disease is a particular comorbidity. It increases operative risk, but its weight in the decision to operate cannot be objectively assessed because the performance of coronary angiography is closely linked with the decision to operate.[4,5,8,13] This leads to an obvious bias in the evaluation of the prevalence of coronary disease in non-operated patients.

Our findings from observed practice are consistent with an analysis using a different approach based on case vignettes describing different patient profiles.[18] Age and LV function were the most important factors of the decision to operate or not on elderly patients with AS for the majority of questioned cardiologists, whereas comorbidity played a less important role.

Multivariable scores estimating operative mortality can be helpful in decision-making in this particular heterogeneous population. However, such scores have limitations when attempting to analyse therapeutic decisions. The Euroscore includes variables related to the timing and modalities of surgery, and the comparison of the Euroscore between operated and non-operated patients, i.e. the comparison of the estimated risk of surgery, needs to consider that all patients would have undergone valve surgery. The strength of the Charlson comorbidity index is that it is a global and validated evaluation of the impact of comorbidities, which are frequently associated in the elderly. No scoring system enables spontaneous outcome to be weighted against the outcome of surgery. Finally, predictive value of scores can be lower in specific cases, such as patients operated on for AS or the elderly.[25] This explains why guidelines state that there is no reliable method to identify elderly patients who will derive the greatest benefit from AVR, and that clinical judgement remains the main determinant of the therapeutic decision in the individual patient.[3] Patient refusal was seldom mentioned as a reason for deciding against AVR. Although patient's preference contributes to the therapeutic decision, this is likely to be influence by the responsible practitioner.

Table 3 Factors associated with a decision not to operate

	P-value	Odds ratio	95% CI
LV ejection fraction	0.004		
>50%		1	
30–50%		2.66	1.57–4.64
≤30%		7.09	2.42–20.82
Age (years)	0.005		
75–80		1	
80–85		1.90	1.22–2.99
≥85		3.60	1.47–8.82
Neurological dysfunction	0.02	3.82	1.23–12.27

Multivariable analysis including separate comorbidities. Hosmer–Lemeshow goodness-of-fit $\chi^2 = 5.48$ (df = 4), $P = 0.24$, *c*-index 0.73.

Table 4 Predictive factors of 1-year mortality

	P-value	Hazard ratio	95% CI
Charlson comorbidity index	0.001	1.54	1.18–1.99
NYHA class IV vs. III	0.05	2.37	1.02–5.55
Gender (male vs. female)	0.04	2.34	1.05–5.23
Decision to operate	0.94	0.97	0.41–2.27

Multivariable analysis.

Patient outcome

In this survey including a large number of centres, operative mortality was relatively low (5%) given the patient risk profile, as reported in certain series.[10,11,17] One-year survival was in the high range of reported outcome in non-operated elderly patients with AS.[17,19,28,29] This may be partly related to the inclusion of patients from outpatient clinics, as series comprising only hospitalized patients are more likely to select patients who have more advanced diseases.

In multivariable analysis, decision to operate was no longer linked with the outcome, and predictive factors were consistent with surgical series.[9,10,14,22] This is an illustration of confounding factors between decision for surgery and patient characteristics, because non-operated patients have a worse clinical profile. This contributes to a worse outcome as attested by the strong predictive value of the Charlson comorbidity index. Moreover, 1-year follow-up is probably too short to perceive the benefit of AVR, because 1-year survival is partly determined by operative mortality, and most of the difference between surgical and medical therapies in AS appears after the first year.[17,19]

Study limitations

Such an observational survey does not enable the appropriateness of the therapeutic decision to be fully assessed for an individual patient. Nevertheless, this survey enables for the first time decision for surgery to be prospectively analysed and put into perspective with cardiac as well as non-cardiac patient characteristics in a population of elderly patients with severe and symptomatic AS.

Because of the number of patients in each participating centre, it was not possible to adjust the analysis of therapeutic decision or outcome on each centre. However, there was no significant difference when comparing European regions.

The lack of external validation limits the accuracy of the factors linked with the decision not to operate. However, the aim of the present study is not to elaborate a model to be used in clinical practice, but to analyse decision-making.

Conclusion

In this prospective survey including a wide range of patients, intervention was decided against in as much as one-third of the elderly presenting with severe, symptomatic AS. The analysis of patient characteristics linked with the therapeutic decision suggests that the weight of cardiac variables is overstressed when compared with comorbidities in denying surgery.

These findings underline particular difficulties regarding decision-making in the elderly, in whom current guidelines provide limited recommendations as a consequence of the low level of evidence from the literature. Randomized trials are unlikely to be conducted in this field, thus further prospective studies including quantification of comorbidities are necessary to enable risk–benefit ratio to be better evaluated and, therefore, guidelines to be refined.

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Conflict of interest: none declared.

Appendix: definitions

Smoking: cigarette, cigar, pipe.

Hyperlipidaemia: diagnosis previously made by physician, receiving lipid-lowering therapy or total cholesterol $>$190 mg/dL or $>$5 mmol/L, HDL $<$40 mg/dL or $<$1 mmol/L, TG $>$190 mg/dL or $>$2 mmol/L.

Hypertension: diagnosis previously made by physician, receiving medications to lower blood pressure, or known blood pressure values of $\geq$140 mmHg systolic or $\geq$90 mmHg diastolic on more than two occasions.

Diabetes: fasting blood glucose level $\geq$7 mM/L on more than two samples or previous diagnosis of diabetes, whatever the treatment.

Family history of premature coronary artery disease: history of angina pectoris, myocardial infarction, or sudden death among first-degree relatives before the age of 55 years.

Chronic obstructive pulmonary disease: diagnosis previously made by physician, or patient receiving bronchodilators, or values of forced expiratory volume $<$75% of expected value, arterial pO_2 $<$60 mmHg, or arterial pCO_2 $>$50 mmHg in prior studies.

Carotid atherosclerosis: stenosis $>$50%, previous or planned surgery.

Lower limbs atherosclerosis: claudication, previous or planned surgery.

Neurological dysfunction: neurological disease severely affecting ambulation or day-to-day functioning.

Coronary artery disease: more than one stenosis $>$50% of vessel diameter on coronary angiography.

Congestive heart failure: clinical sign of congestive heart failure at admission.

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