GUIDELINES

Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of atrial fibrillation in elderly people

Consensus d'experts de la Société française de gériatrie et gérontologie et de la société française de cardiologie, sur la prise en charge de la fibrillation atriale du sujet âgé

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Abbreviations: AF, atrial fibrillation; CGA, comprehensive geriatric assessment; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; ESC, European Society of Cardiology; INR, international normalized ratio; MCI, mild cognitive impairment; MMSE, Mini Mental Status Examination; NOAC, novel oral anticoagulant; RR, relative risk; VKA, vitamin K antagonists.

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Summary Atrial fibrillation (AF) is a common and serious condition in the elderly. AF affects between 600,000 and one million patients in France, two-thirds of whom are aged above 75 years. AF is a predictive factor for mortality in the elderly and a major risk factor for stroke. Co-morbidities are frequent and worsen the prognosis. The management of AF in the elderly should involve a comprehensive geriatric assessment (CGA), which analyses both medical and psychosocial elements, enabling evaluation of the patient's functional status and social situation and the identification of co-morbidities. The CGA enables the detection of ''frailty'' using screening tools assessing cognitive function, risk of falls, nutritional status, mood disorders, autonomy and social environment. The objectives of AF treatment in the elderly are to prevent AF complications, particularly stroke, and improve quality of life. Specific precautions for treatment must be taken because of the co-morbidities and age-related changes in pharmacokinetics or pharmacodynamics. Preventing AF complications relies mainly on anticoagulant therapy. Anticoagulants are recommended in patients with AF aged 75 years or above after assessing the bleeding risk using the HEMORR$_2$HAGES or HAS-BLED scores. Novel oral anticoagulants (NOACs) are promising treatments, especially due to a lower risk of intracerebral haemorrhage. However, their prescriptions should take into account renal function (creatinine clearance assessed with Cockcroft formula) and cognitive function (for adherence to treatment). Studies including frail patients in ''real life'' are necessary to evaluate tolerance of NOACs. Management of AF also involves the treatment of underlying cardiomyopathy and heart rate control rather than a rhythm-control strategy as first-line therapy for elderly patients, especially if they are paucisymptomatic. Antiarrhythmic drugs should be used carefully in elderly patients because of the frequency of metabolic abnormalities and higher risk of drug interactions and bradycardia.
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Résumé La fibrillation atriale (FA) constitue un problème de santé publique avec entre 600 000 à un million de patients concernés en France dont les deux-tiers sont âgés de plus de 75 ans. La FA majore de risque mortalité et représente un facteur majeur de risque d'accident vasculaire cérébral ischémique (AVC). Chez la personne âgée en FA, les comorbidités sont fréquentes et aggravent le pronostic. La prise en charge de la FA du sujet âgé doit s'accompagner d'une évaluation gériatrique standardisée (EGS) qui apprécie les éléments médicaux, psychosociaux et permet une évaluation fonctionnelle du patient et de sa situation sociale. Elle conduit à identifier certaines comorbidités ou syndromes gériatriques (troubles cognitifs, chutes, dénutrition, dépression). Pour rendre l'évaluation gériatrique plus facile dans la pratique clinique, des tests courts de *screening* sont proposés, ils peuvent être complétés par une exploration plus complète réalisée par des équipes spécialisées de gériatrie. Les objectifs généraux du traitement restent applicables au sujet âgé : prévention des complications en particulier l'AVC, amélioration de la qualité de vie, réduction de la mortalité et des hospitalisations. Des précautions particulières d'utilisation des médicaments sont nécessaires en raison des comorbidités et de modifications pharmacocinétiques ou pharmacodynamiques liées au vieillissement. La prévention des complications repose essentiellement sur le traitement anticoagulant. Les anticoagulants sont recommandés après 75 ans en cas de FA après évaluation du risque hémorragique en utilisant les scores HEMORR$_2$HAGES ou HAS-BLED. Les nouveaux anticoagulants sont prometteurs pour la prise en charge des malades âgés en FA non valvulaire, en particulier en raison du moindre risque d'hémorragie cérébrale. Toutefois, leur utilisation nécessite la prise en compte la fonction rénale (clairance de la créatinine selon la formule de Cockcroft) et du fonctionnement cognitif (observance thérapeutique). La réalisation d'études menées spécifiquement dans les populations de patients très âgés polypathologiques est nécessaire pour évaluer leur

tolérance en situation de « vie réelle ». La prise en charge comprend aussi le traitement de la cardiopathie sous-jacente et la gestion du rythme cardiaque. Chez les personnes âgées, la stratégie du contrôle de fréquence cardiaque doit être privilégiée par rapport à celle du contrôle du rythme dans la majorité des cas. L'emploi des anti-arythmiques doit être prudent du fait des anomalies métaboliques fréquentes et d'un plus grand risque d'interaction médicamenteuse et de bradycardie.

Definition

Atrial fibrillation (AF) is an arrhythmia characterized by disorganized atrial activation with consequent deterioration of atrial mechanical function [1]. Clinically, AF is suspected in case of irregularity in pulse and heart rate. The diagnosis is made by means of an electrocardiogram (ECG) showing the absence of P wave undulating baseline and irregular ventricular response when atrioventricular conduction is normal.

The underlying mechanism usually involves multiple micro—re-entry circuits. In some cases, AF is due to abnormal ectopic foci located in the pulmonary veins [2]. Other atrial arrhythmias can occur in patients with AF, such as atrial tachycardia or atrial flutter.

Classification

Several classifications of AF have been proposed, based on ECG features or clinical presentation. The ''three-P'' classification is consensual: paroxysmal, persistent and permanent. AF is paroxysmal if it is self-terminating, usually within 48 hours; AF paroxysms may continue for up to 7 days. AF is persistent if the episode lasts for more than 7 days and is not terminated spontaneously. AF is permanent if all recorded ECGs show AF over an extended period (in general > 1 year). Persistent AF becomes permanent AF when cardioversion is not attempted or is unsuccessful.

When a patient is seen for the first time for AF and the arrhythmia was not previously known, it is called first-detected AF. The evolution of first-detected AF to a paroxysmal, persistent or permanent pattern is unpredictable (Fig. 1). Paroxysmal AF is often recurrent.

Epidemiology

AF constitutes a public health problem. It affects between 600,000 and 1 million patients in France, two-thirds of whom (i.e. 400,000 to 660,000 people) are aged above 75 years [3]. The average annual cost per patient with AF is estimated to be 3000 euros [4]. The total cost of the disease is about 2.5 billion euros, half of which is related to hospital expenses.

The prevalence of AF increases with age; it doubles each decade after the age of 50 years (Fig. 2) [5—14] and increases from less than 0.5% for those aged 40—50 years to 10—20% for those aged 80 years or above [8,10,15]. Thus, 70% of AF patients are aged 75 years or above [3]. This prevalence is probably underestimated because the methods used in epidemiological studies poorly detect paroxysmal AF [16].

The prevalence of AF is higher among men than women. However, the number of women with AF appears to be higher due to the longer life expectancy for women [17]. Lastly, AF prevalence has increased in the past decades independent of population ageing [8,10,18]. In the USA, the age- and sex-adjusted AF incidence was 3.04 per 1000 person-years in 1981, increasing to 3.68 in 2000 [19]. Extrapolation to the French population yields a number of 200,000 new cases per year. Based on these elements, the number of patients with AF is expected to double or triple in the next decades.

Aetiologies and co-morbidities

Cardiac ageing is often associated with myocardial fibrosis and atrial dilation, which favour the occurrence of AF. All cardiac diseases (in particular ischaemic, valvular or hypertensive heart diseases) may be complicated by AF, especially at an advanced stage of their evolution. Main cardiovascular risk factors are also associated with the risk of AF [12]. Among these factors, age and hypertension play a leading role. Lastly, a search for an extracardiac cause, such as bronchopneumonia, chronic obstructive pulmonary disease (COPD), pulmonary embolism, iatrogenic event, hypokalaemia, hyperthyroidism or sleep apnoea syndrome, should be carried out systematically.
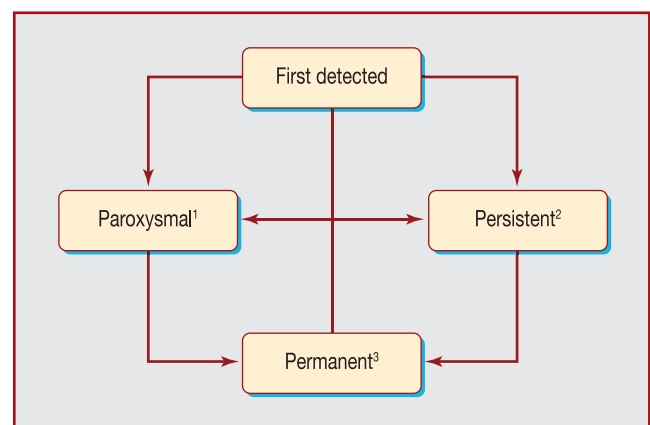

Figure 1. Classification of atrial fibrillation. 1: an episode that lasts less than or 7 days (often < 24 hours); 2: an episode that lasts more than 7 days; 3: cardioversion is unsuccessful or it is not attempted. Note that paroxysmal and persistent fibrillations may be recurrent.
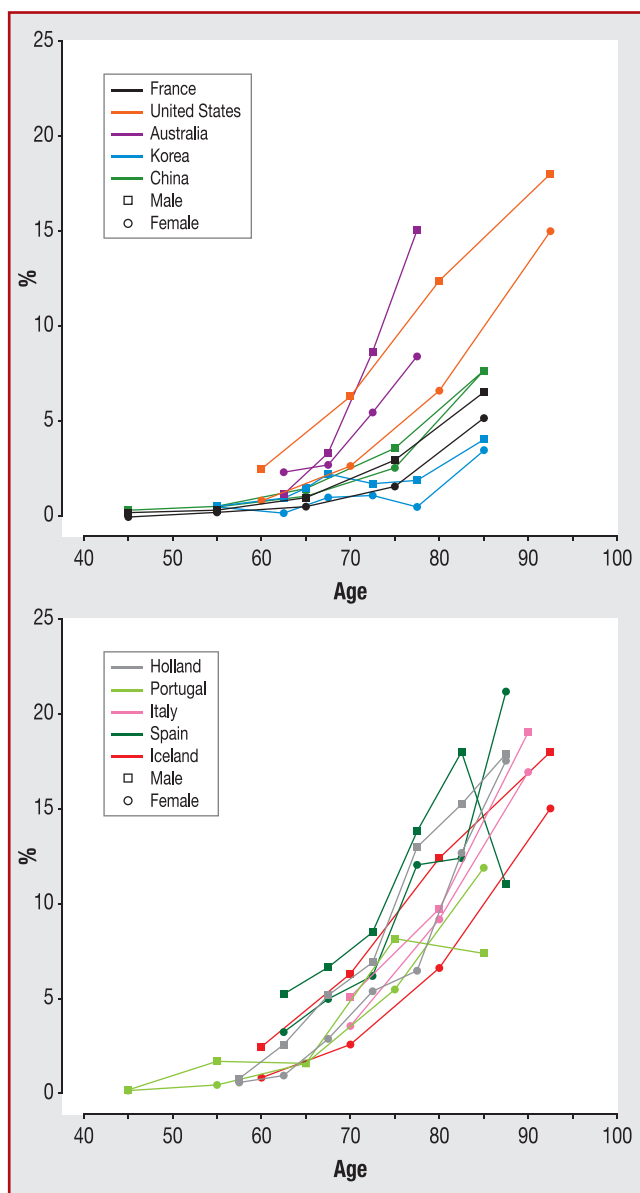
Figure 2. Prevalence of atrial fibrillation stratified by age and sex in published studies since 1991: 1: [9]; 2: [8]; 3: [13]; 4: [12]; 5: [11]; 6: [10]; 7: [6]; 8: [5]; 9: [7]; 10: [14].

In elderly people, co-morbidities are frequent and worsen the prognosis of AF. They can be the cause or the consequence of AF and their management is a major therapeutic objective.

Hypertension

Hypertension is the most frequent co-morbidity factor associated with AF in the elderly, with a prevalence varying from 40% to 70% [20]. Hypertension significantly raises the incidence of AF and thromboembolic events [15,21]. Recent works [22] demonstrate the role of pulse pressure as a predictive factor for AF; they highlight the impact of arterial ageing on left ventricular hypertrophy in the mechanisms of electrophysiological alterations.

Blood pressure control seems to reduce the incidence of AF [23,24]. Several meta-analyses [25,26] suggest a protective effect of renin-angiotensin system blockers (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) on AF occurrence. However, this class-effect on reducing the incidence of AF recurrences has not been confirmed in a randomized trial [27]. In any case, blood pressure control in patients with AF and hypertension is a major goal for the prevention of complications, particularly cerebral strokes.

Heart failure

The occurrence of heart failure modifies the prognosis of AF, with an increased risk of mortality and stroke [28], even in cases of heart failure with preserved ejection fraction. After the age of 75 years, the prevalence of AF is about 40% in patients with heart failure [29,30].

The interaction between AF and heart failure is complex and is a vicious circle [31]. AF favours heart failure and heart failure raises the risk of AF development. Heart failure increases atrial pressures and volumes and thus increases atrial stretch; it also leads to neurohormonal activation, which generates electrical and anatomical remodelling responsible for modifications of atrial electrophysiological properties. On the other hand, AF favours heart failure because of the loss of atrial systole leading to a decrease in diastolic ventricular filling. Lastly, tachycardia and irregularity of ventricular cycles contribute to alterations of cardiac output.

Coronary heart disease

Coronary heart disease is a risk factor for AF [15,21]; it also presents a risk factor for stroke [20] in the presence of AF. Particularly, the acceleration of heart rate and the irregularity of cycles increase myocardial oxygen consumption and may alter coronary output.

Diabetes mellitus

Diabetes mellitus constitutes a risk factor for AF and a risk factor for stroke in the presence of AF [21,32]. The explanatory factors of this association are numerous: arterial hypertension, coronary heart disease, altered sympathetic tone, ''direct toxicity'' of glucose on atrial structure, deterioration of diastolic function, alteration of atrial endothelial function and more frequent acute stress situations (infections, electrolyte anomalies, renal failure, etc.).

Obesity

Obesity is a risk factor for AF [33] due to left atrial dilation, presence of high blood pressure or ventricular hypertrophy.

Respiratory insufficiency, COPD and sleep apnoea

Respiratory diseases, particularly sleep apnoea, are associated with AF due to oxygen desaturation episodes,

Table 1 CHADS$_2$ and CHA$_2$DS$_2$-VASc scores.

	CHADS$_2$ score	CHA$_2$DS$_2$-VASc score
Items		
Age $\geq$ 75 years	1	2
Age 65—74 years	0	1
Arterial hypertension	1	1
Diabetes	1	1
Heart failure or left ventricular dysfunction	1	1
Previous stroke or transient ischaemic attack	2	2
Female sex (if age > 65 years)		1
Vascular diseases (prior myocardial infarction, peripheral artery disease, aortic plaque)		1
Anticoagulation		
No therapy		0
Aspirin[a]	0	
Aspirin[a] or anticoagulant therapy	1	
Anticoagulant therapy	$\geq$ 2	1 or $\geq$ 2

Adapted from Camm et al. [43,65].
[a] 75—325 mg daily.

fluctuations in sympathetic activity or modifications of intrathoracic pressure [34].

Prognosis and outcome

Mortality

AF is a predictive factor for mortality. Several observational studies show an increase in the risk of death from 50% to 90% in patients with AF compared with subjects of the same age in sinus rhythm [35,36]. In the Euro Heart Survey (mean age, 66 years), the 1-year mortality of patients with AF was 5% (50% of deaths were due to cardiovascular causes) [37]. In the BAFTA study (subjects aged > 75 years), the annual death rate was 8% (50% of deaths were due to cardiovascular causes) [38]. The risk is higher among women, especially when cardiomyopathy or underlying heart failure is associated. Nevertheless, the increase in AF-related mortality seems to lower beyond the age of 75 years due to overmortality related to other causes [39].

Stroke

Stroke presents the main AF complication and accounts for 85% of embolic accidents due to AF. The annual incidence of stroke is similar in paroxysmal AF and permanent AF, varying from 1.5% to 3.3% [37,40]. The main risk factors for the occurrence of stroke in AF patients [41] are included in the CHADS$_2$ score [42] (Table 1): congestive heart failure, hypertension, age 75 years or above, diabetes (one point for each item) and prior stroke or transient ischaemic attack (two
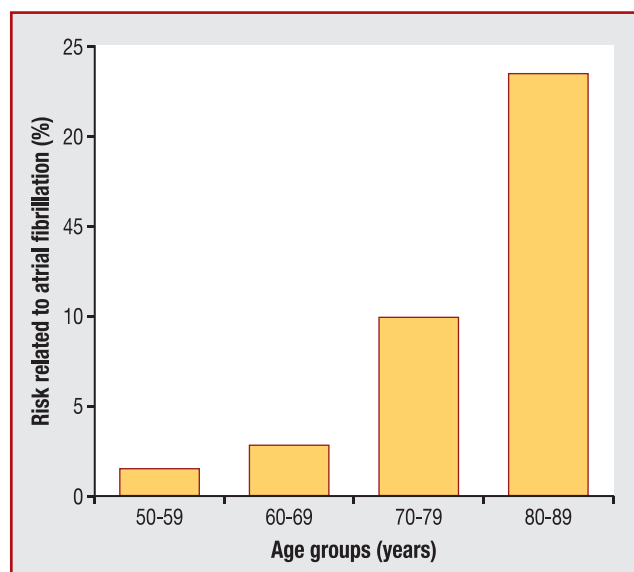

Figure 3. Risk of atrial fibrillation-related stroke according to age.
Adapted from Wolf et al. [40].

points). This score allows the evaluation of thromboembolic risk in AF.

The European Society of Cardiology (ESC) guidelines 2012 focused update [43] recommended use of the CHA$_2$DS$_2$-VASc risk score [44] (Table 1) to assess stroke risk in patients with AF. This score includes three further risk factors: female sex, age 65—74 years and history of cardiovascular diseases (Table 1).

The risk of stroke increases with age, which is an item in the CHADS$_2$ score ($\geq$ 75 years) as well as in the CHA$_2$DS$_2$-VASc score (moderate risk from 65—74 years, high risk if aged $\geq$ 75 years). AF is a major risk factor for stroke in the elderly: the risk of stroke related to AF is 2% for age less than 70 years, 24% for age 80—89 years and 35% for age above 90 years (Fig. 3) [40]. In the elderly, 80% of strokes are ischaemic and 20% are haemorrhagic [40].

AF-related strokes seem to be more severe than those unrelated to AF, with an increased 30-day mortality of 27—57%, 2-fold mortality and recurrences at 1 year and more severe disability at 3 months (75% of patients with AF are dependent compared with 36% of those without AF) [45—48].

Other cardiovascular events

AF is associated with a high annual incidence of cardiovascular events. In the Euro Heart Survey [37], 11% of AF patients had heart failure (one-third of whom had new onset heart failure), 6% had coronary events and 49% of cases needed hospitalization, 75% for cardiovascular causes.

Hospitalizations

In France in 2008, an analysis of the database of the electronic medical record system (PMSI) showed that AF was the main diagnosis in 84,000 hospitalizations and one of the associated diagnoses in 349,000 hospitalizations. This accounts for a total of 412,000 patients and a total of

610,198 hospitalizations [3]. The number of AF hospitalizations has increased by 26% over a 3-year period. Most of these patients (92%) were aged 60 years or above. Pathologies associated with AF were hypertension, cardiac diseases, heart failure, stroke, syncope and renal dialysis. The death rate among these patients was 5.6%. It has been estimated that each year, 41% of AF patients are hospitalized; of these, 8% are hospitalized for a direct AF-related problem.

Cognitive disorders

Several epidemiological studies suggest that AF increases the risk of cognitive disorders and dementias [5,49,50]. A recent meta-analysis, including 21 studies and 95,427 subjects, showed a significant association between AF and cognitive impairment or dementia (relative risk 1.40, 95% CI 1.19−1.64), both in patients with or without history of stroke [51]. This cognitive alteration could be due to common risk factors (hypertension, diabetes), the occurrence of cerebral microemboli or fluctuations of cerebral perfusion. Cognitive disorders in elderly patients with AF must be detected and assessed because of their impact on prognosis, autonomy, understanding instructions and adherence to treatment (cf. paragraph on comprehensive geriatric assessment [CGA]).

Quality of life

Elderly patients with AF have a poorer quality of life compared with other people of the same age. Rhythm- or rate-control strategies allow significant improvement in quality of life [52].

Diagnosis

Clinical presentations

In the elderly, AF is often asymptomatic and an incidental finding [53,54]. Palpitations are less frequent in elderly patients compared with younger adults [55]. When present, AF symptoms are diverse [56,57]: dyspnoea, palpitations, thoracic pain, faintnesses, falls, syncope, asthenia, anxiety, etc. AF can also be discovered when a complication, such as an embolic accident or heart failure, occurs.

AF in the elderly is often of acute onset during the course of stress secondary to an infectious episode (particularly bronchopneumonia), a surgical procedure and cardiac or respiratory decompensation. The occurrence of AF in the elderly indicates a high probability of an underlying cardiovascular disease and a higher risk of AF recurrence compared with that in younger people.

Clinical assessment

The aim of the clinical assessment is to define the type of AF (paroxysmal, persistent or permanent), to specify the illness history and to evaluate symptoms, trigger factors, cardiovascular diseases, complications, co-morbidities and current therapeutics.

History of atrial fibrillation

The history of AF in elderly patients is often difficult to reconstitute; questioning the patient's family circle and/or general practitioner may be necessary. A trigger factor must be systematically sought: infectious episode, cardiac or respiratory decompensation, myocardial ischaemia, electrolyte disorders (hypokalaemia), hyperthyroidism, iatrogenic factors, diuretics, theophylline, salbutamol, etc.

Ventricular rate

Searching for pulse irregularity should be done systematically. Pulse palpation has a high sensitivity but low specificity for AF [54,58]. The diagnosis of AF must be confirmed by an ECG. A very rapid ventricular rate suggests an associated extracardiac factor, especially in case of well-tolerated permanent AF. Bradyarrhythmia may be due to an iatrogenic effect (antiarrhythmic drugs, digitalis, calcium channel antagonists, inhibitors of cholinesterase, beta-blockers) or an associated conduction disorder.

Comprehensive assessment of the elderly subject with atrial fibrillation

It is necessary to look for co-morbidities and complications of AF, evaluate the thromboembolic and haemorrhagic risks and carry out a CGA.

Diagnostic tests

Twelve-lead ECG

A 12-lead ECG is indispensable to confirm the diagnosis (Table 2). When paroxysmal AF is suspected, repeated ECG monitoring or long-term recordings should be considered. When AF is associated with a slow ventricular rate, an atrioventricular block should be suspected.

Chest X-ray

A chest X-ray allows heart size measurement and analysis of the pulmonary parenchyma (interstitial oedema, pneumonia, pulmonary sequelae); it helps detection of interstitial pneumonia due to long-term amiodarone therapy.

Ambulatory long-term ECG recordings

Ambulatory long-term ECG recordings can be useful to confirm paroxysmal AF or in case of symptoms that can be related to a slow ventricular rate (syncope, faintness) or a very rapid ventricular rate despite treatment.

Transthoracic echocardiography

Transthoracic echocardiography is recommended in all AF patients; it is used to detect ventricular, valvular and atrial disease. The presence or absence of an underlying cardiomyopathy is important for the choice of antiarrhythmic and antithrombotic drugs.

Transoesophageal echocardiography

Transoesophageal echocardiography is the only examination that enables the analysis of intra-atrial thrombosis; it is,

Table 2 Diagnostic tests in elderly people with atrial fibrillation (AF).

Tests	Indication	Awaited result
ECG	Systematic	Diagnosis of AF
ECG Holter recording	Non-systematic unless syncope, faintness, unexplained heart failure	Searching for bradycardia, heart pauses, rapid ventricular rate
Transthoracic echocardiography	Systematic	Searching for heart disease, left atrium dimensions, left ventricular function
Transoesophageal echocardiography	Non-systematic unless rapid cardioversion is indicated	Intracavitary thrombus
Chest X-ray	Non-systematic	Cardiomegaly, signs of pulmonary oedema
BNP, troponin	Non-systematic	
Blood cell count, serum electrolytes, creatinine, glycaemia, haemostasis test	Systematic	Searching for anaemia, creatinine clearance calculation, potassium disorders, diabetes, haemostasis disorder
Thyroid-stimulating hormone	Systematic	Hyperthyroidism
Serum digoxin level	Non-systematic unless overdose is suspected	
Liver function tests, CRP	Non-systematic unless clinical suspicions	

BNP: B-type natriuretic protein; CRP: C-reactive protein; ECG: electrocardiogram.

however, rarely carried out in the elderly. The two main indications are: reversion to sinus rhythm without prior effective anticoagulation (for at least 3 weeks); and a search for the underlying cause in case of recurrent stroke or transient ischaemic attack of unknown aetiology.

Blood tests

A systematic work-up must be carried out: complete blood count, international normalized ratio (INR) for patients on a vitamin K antagonist, partial thromboplastin time, serum electrolytes, creatinine (with its clearance calculated by the Cockcroft formula), glycaemia and thyroid-stimulating hormone. According to the clinical picture, the following tests can be added: troponin assay, C-reactive protein, liver function tests, serum albumin and urine test strip ± urine culture. This work-up is necessary for the detection of trigger factors and for therapeutic management.

Comprehensive geriatric assessment

The management of AF in an elderly subject should involve a CGA, which analyses both medical and psychosocial elements, enabling evaluation of the patient's functional status and social situation and identification of co-morbidities.

The CGA enables the detection of ''frailty'', which is characterized by decreased physiological adaptation to stress or environmental changes, whether associated with organ failure. Short screening tools are proposed to make CGA easier and quicker to complete in clinical practice. If screening tests are abnormal, an intensive exploration by specialized geriatric teams must be launched (Table 3). The principal elements of the CGA are outlined below.

Assessment of cognitive function

Evaluation of cognitive function is important in elderly AF patients for several reasons: it assesses the quality of the information obtained from the subjects (regarding memory disorders and the absence of functional complaint in anosognosic patients), the ability to understand instructions and the potential for therapeutic observance and adherence to treatment, particularly antithrombotics. Medical history and clinical examination are not enough to detect mild cognitive impairment (MCI); only cognitive assessment using a test can reveal MCI. The Mini Mental State Examination (MMSE) [59] is a simple and brief standardized 30-point test that is used for screening cognitive disorders (Appendix 1). The threshold value depends on the age and educational level of the patient. A score greater than 27 is considered normal. A score less than 24 is abnormal and should lead to a more detailed evaluation of the cognitive functions in a specialized setting. A score between 24 and 27 has to be considered abnormal, especially when the patient is not very old (age < 80 years), has a high educational level and has symptoms involving the memory or other cognitive functions. An abnormal MMSE score indicates cognitive dysfunction not necessarily related to dementia. This is why an abnormal score is not enough to confirm the diagnosis and further specialized assessment is required. More rapid tests can be used to detect cognitive disorders in the elderly, such as the Memory Impairment Screen (MIS) (Appendix 2), CODEX (Appendix 3), the five-word test, the clock test, etc. Whatever the test used, abnormal results indicate a strong probability of

Table 3 Geriatric assessment of elderly people with atrial fibrillation.

Dimension	Brief screening	More complete assessment	Interpretation
Cognitive function	MIS (score 0—8) Clock test (normal/abnormal) CODEX (normal/abnormal)	MMSE (score 0—30) Neuropsychological tests	Cognitive disorders if: immediate and/or delayed MIS $\leq$ 6; or five words < 9; or clock test abnormal; or abnormal CODEX; or MMSE $\leq$ 27 (or $\leq$ 24 if low educational level)
Dependency	Four-item IADL (score 0—4)	IADL (score 0—14) ADL (score 0—6)	Possible dependency if four-item IADL < 4 Dependency if IADL < 14 Severe dependency if ADL < 6
Depressive symptoms	Mini GDS (score 0—4)	GDS (score 0—30)	Possible depression if Mini GDS $\geq$ 1 Probable depression if GDS $\geq$ 15
Nutritional status	Weight variation	MNA (score 0—30) Serum albumin	Malnutrition if: weight loss > 5% in 1 month; or > 10% in 6 months; or MNA < 17; or serum albumin < 35 g/L
Risk of fall	One-leg balance test	TUG test	High risk of fall if; one-leg balance test < 5 s; and/or TUG > 20 s
Living condition	Interview with patient and family		Social isolation, safety of the treatment and follow-up organization

ADL: Activities of Daily Living; CODEX: Cognitive Disorders Examination; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily Living; MIS: Memory Impairment Screen; MMSE: Mini Mental State Examination; MNA: Mini Nutritional Assessment; TUG: Timed Up and Go.

cognitive disorders and indicate the need for a specialized assessment.

Assessment of dependency

Dependency is defined as the need for support by a third person to carry out activities of daily living. Autonomy can be evaluated by scales that assess activities of daily life (Instrumental Activities of Daily Living [60] and Activities of Daily Living (Appendix 4)) through questioning the patient and their relatives. The short form of the Instrumental Activities of Daily Living scale (Appendix 5) includes the following four items: ability to use telephone, mode of transportation, responsibility for own medication and ability to handle finances. The Activities of Daily Living scale gives information about personal hygiene and grooming, dressing, ability to go to the toilet, transferring, continence and feeding autonomy. A subject is considered dependent when they need personal assistance in performing a given activity.

Gait disorders and risk of falls

The risk of fall related to postural instability plays a role in the therapeutic choice (cf. paragraph on falls and vitamin K antagonists). The assessment of the risk of fall is based on taking a history (history of falls), physical examination (general health status, neuromuscular status, joint status, vision and neurological and cardiovascular examination, searching for orthostatic hypotension in particular) and simple tests such as the one-leg balance test, which evaluates the ability to stand unaided for 5 seconds on one leg, and the Timed Up and Go test, which measures the time taken to stand up from a standard armchair, walk 3 m, turn around, walk back

to the chair and sit down again. A time more than 20 seconds indicates a risk of falls.

Assessment of nutritional status

A systematic measurement of weight should be taken in elderly subjects. Malnutrition is defined as weight loss of above 5% in 1 month or above 10% in 6 months; it indicates the presence of an at-risk situation. Weight interpretation should consider clinical and biological elements of fluid retention or dehydration. The nutritional assessment can also be done by means of a validated scale (Mini Nutritional Assessment) and serum albumin. A Mini Nutritional Assessment score less than 17 or a serum albumin concentration less than 35 g/L indicates malnutrition.

Assessment of mood disorders

The Mini Geriatric Depression Scale is a rapid four-question screening test (Appendix 6). In case of abnormal result, the complete Geriatric Depression Scale allows collection of depressive symptoms. A score of 15/30 or more indicates possible depression and a score greater than 22/30 indicates possible major depression. Depression in the elderly subject is associated with worse cardiovascular prognosis and lower compliance with treatment [61].

Assessment of living conditions

Assessment of living conditions aims to determine compliance with prescribed treatment. If patients cannot manage their own treatments, it is important to organize the administration of medication (purchase, preparation, use of a pill dispenser, involvement of family members, nurse or social

worker). It is also important to determine the state of isolation of the patients and to consider the involvement of caregivers, as well access to various care services. Educating and informing patients and families about the disease is required in order to ensure medication administration and an understanding of the complications.

Treatment

The objectives of AF treatment in the elderly are to: prevent AF complications, particularly stroke and thromboembolism; reduce mortality; reduce the number of hospitalizations; reduce symptoms; and improve quality of life.

Preventing AF complications relies mainly on anticoagulant therapy. Management also involves the treatment of underlying cardiomyopathy and heart rate control.

Stroke prevention: antithrombotic therapy

Antithrombotics are used in the prevention of systemic embolisms.

Stroke prevention: the place of oral anticoagulants

Vitamin K antagonists (VKAs)

The benefits of VKAs have been largely shown in patients with AF and appear to be even more important among elderly people [62]. VKAs reduce the risk of stroke by 64% compared with placebo and by 39% compared with aspirin, whereas aspirin only reduces the risk by 22% [63] compared with placebo. A randomized trial (the BAFTA study) [38] was specifically conducted in subjects aged 75 years or more with AF. The results confirmed the benefit of VKAs, with a significant reduction of 52% (relative risk [RR] 0.48, 95% confidence interval [CI] 0.28–0.80; $P = 0.003$) in the embolic risk (cerebral/systemic) for warfarin compared with aspirin. Another randomized study that included very old patients (> 80 years) [64] showed a reduction in cardiovascular events for VKAs compared with aspirin after a 1-year follow-up period (6% vs 13%; $P < 0.01$). These benefits were also confirmed in an observational study (ATRIA) [8]. Concerning the target INR, values must range between 2.0 and 3.0. Prevention is insufficient with an INR level less than 2.0, and an INR greater than 3.0 does not give any additional benefits, while significantly increasing the risk of bleeding.

Assessment of embolic risk and the indication for vitamin K antagonists in the elderly

The embolic risk of stroke is evaluated with the $CHADS_2$ score (Table 1), which includes age of 75 years or more. In 2006, it was recommended to use VKAs when the $CHADS_2$ score is greater than or equal to 2 [1], as is the case with most patients aged 75 years or more. With a $CHADS_2$ of 1, the choice between VKA and aspirin was to be made according to patient context and preferences.

In 2010, the ESC proposed a new score (the CHA_2DS_2-VASc score; Table 1) [44]. This score gives greater importance to the age factor when determining the indications for anticoagulant therapy (Table 1). On the basis of this score, anticoagulant therapy is recommended in all patients aged 75 years or more with AF, after considering the bleeding risk [43,65].

Modalities of vitamin K antagonist prescription

In the elderly, the use of warfarin is recommended because it has a higher level of evidence and is easy to titrate. A validated scheme for warfarin initiation in elderly people is shown in Table 4 [66,67].

Once the patient is stable, an INR is performed every 15–21 days. INR monitoring should also to be done in case of an acute event and within 48–72 hours after discontinuation or introduction of a new drug, especially antibiotics or antimycotics.

Other than in cases of a very labile INR, it is not recommended to follow a specific diet by avoiding foods rich in vitamin K. The education of patients and/or their caregivers is necessary. Every patient should use a treatment diary to record their INR results. The French version is available at the French Federation of Cardiology: infos@fedecardio.com.

Novel oral anticoagulants (NOACS)

New prospects have been opened up with the NOACs, which do not require monitoring of coagulation factors or platelets: the oral direct thrombin inhibitor dabigatran [68] and the oral factor Xa inhibitors rivaroxaban [69], apixaban [70] and edoxaban [71]. The recent ESC update [43] proposes that NOACs be considered as first-line treatment because of their net clinical benefit versus VKAs, after assessment of haemorrhagic risk and renal function (calculation of creatinine clearance with the Cockcroft formula).

Oral direct thrombin inhibitor (dabigatran)

In the RE-LY study, which included 18,113 patients (mean age of 71.5 years) with non-valvular AF and at least one additional embolic risk factor, the incidence of stroke or systemic embolism was significantly lower with dabigatran 150 mg twice a day than with warfarin (34% relative risk reduction) [68]. Similar incidences were found in the dabigatran 110 mg twice a day group and the warfarin group. Compared with the warfarin group, the risk of major bleeding was statistically lower with dabigatran 110 mg twice a day (20% relative risk reduction) but was not different with dabigatran 150 mg twice a day. The risk of cerebral haemorrhage was significantly lower with both doses of dabigatran compared with warfarin (60% reduction risk with dabigatran 150 mg twice a day and 69% reduction risk with dabigatran 110 mg twice a day). In the subgroup of subjects aged 75 years or more ($n = 7258$), the reduction of thromboembolic risk remained similar to that observed in those aged less than 75 years. On the other hand, the risk of major bleeding increased with age: after age 75 years, it was higher than that for VKAs with the 150 mg twice a day dose and similar to that for VKAs with 110 mg twice a day dose. After the age of 75 years, the dabigatran group still showed a reduced cerebral haemorrhage risk [72].

The use of dabigatran in the elderly requires some precautions because it is mainly eliminated by the kidneys (80% renal elimination). Dabigatran is contraindicated if creatinine clearance calculated according to Cockcroft formula is less than 30 mL/min.

Table 4 Initiation of warfarin therapy in elderly people.

Day	INR in the morning	Daily dose of warfarin
First dose = day 0	No measure	4 mg
Second dose = day 1	No measure	4 mg
Third dose = day 2	No measure	4 mg
Day 3 (the day after the third dose)	< 1.3	5 mg
	$1.3 \leq INR < 1.5$	4 mg
	$1.5 \leq INR < 1.7$	3 mg
	$1.7 \leq INR < 1.9$	2 mg
	$1.9 \leq INR < 2.5$	1 mg
	$INR \geq 2.5$	Measure INR daily and omit doses until INR < 2.5 then give 1 mg
Day 6 ± 1	$INR \leq 1.6$	1 mg increase
	$1.6 < INR \leq 2.5$	Maintain the day 3 dose
	$2.5 < INR \leq 3.5$	If dose $\geq$ 2 mg: 1 mg reduction
		If dose = 1 mg: maintain same dose (1 mg)
	INR > 3.5	Manage according to overdose guidelines (HAS 2008[a])

Adapted from Siguret et al. and Gouin-Thibault et al. [66,67].
HAS: Haute Autorité de Santé; INR: international normalized ratio. Further control 48—72 hours after IRN stability has been reached.
[a] http://www.has-sante.fr/portail/upload/docs/application/pdf/2008-09/surdosage_en_avk_situations_a_risque_et_accidents_hemorragiques_-_synthese_des_recommandations_v2.pdf.

In summary, a lower dose of dabigatran (110 mg twice a day) is recommended after the age of 80 years or after the age of 75 years in case of high haemorrhagic risk: creatinine clearance 30—50 mL/min (Cockcroft formula) or low weight (< 50 kg) or HAS-BLED score greater than or equal to 3.

Oral direct factor Xa inhibitors
Other antithrombotic drugs targeting factor Xa have been developed (rivaroxaban, apixaban, and edoxaban); their renal elimination is about 30%.

Rivaroxaban. The double-blind ROCKET AF study [69] was designed as a non-inferiority trial comparing rivaroxaban with warfarin for the prevention of stroke or systemic embolism in non-valvular AF patients. Rivaroxaban was used in 14,264 patients with a median age of 73 years, at a dose of 20 mg once daily or 15 mg once daily for patients with creatinine clearance 30—50 mL/min. Patients included in this study had higher $CHADS_2$ scores compared with those in the RE-LY study. Rivaroxaban was non-inferior to warfarin for the prevention of ischaemic and haemorrhagic stroke and systemic embolism. Moreover the risk of major and non major clinically relevant bleeding was similar between Rivaroxaban and warfarin. A significant reduction in intracranial haemorrhage was observed compared with warfarin (reduction of 33%). The analysis of subgroups of patients aged 75 years or more (n = 6164), as well as those with moderate renal failure (clearance 30—49 mL/min; n = 2950), showed results similar to those in the general population, with non-inferiority of rivaroxaban compared with warfarin for the prevention of thromboembolic and haemorrhagic strokes [73]. In summary, the dose of 15 mg once a day is recommended in elderly patients with a creatinine clearance of 30—50 mL/min (Cockcroft formula). Rivaroxaban is not recommended in the elderly if creatinine clearance calculated according to the Cockcroft formula is less than 30 mL/min.

Apixaban. Apixaban, used in the AVERROES trial at the dose of 5 mg twice a day, was compared using a double-blind design with aspirin in 5599 patients with a mean age of 70 years, who were unsuitable for VKA therapy [74]. The AVERROES trial was stopped early because of the benefits of apixaban compared with aspirin (55% reduction of stroke or systemic embolism; $P < 0.001$). Apixaban (5 mg twice a day) has also been compared with warfarin in the double-blind ARISTOTLE trial, conducted in 18 201 AF patients, median age of 70 years [70]. The results indicated superiority of apixaban compared with warfarin, characterized by a significant reduction in thromboembolic events (21%), major bleedings (31%) and total mortality (11%). As in the RE-LY and ROCKET studies, a significant reduction in intracranial haemorrhage was observed (58% reduction). Similarly, the analysis of subgroups of patients aged above 75 years (n = 5678) found a significant benefit for apixaban in the reduction of thromboembolic events and major bleedings. Apixaban was used at a dose of 5 mg twice a day or 2.5 mg twice a day in patients with at least two of the following criteria: aged above 80 years; creatinine greater than 133 μmol/L; weight less than 60 kg. Apixaban is not recommended in the elderly if creatinine clearance calculated according to the Cockcroft formula is less than 30 mL/min.

Other oral direct factor Xa inhibitors have been developed, such as edoxaban, which is currently being studied in the ongoing ENGAGES AF TIMI 48 trial, which is in the follow-up phase.

A meta-analysis [75] of the RE-LY, ROCKET and ARISTOTLE trials, which included 44,563 subjects, found better efficacy with the NOACs compared with warfarin for stroke prevention (RR 0.78, 95% CI 0.67—0.92), associated with a lower risk of intracranial haemorrhage (RR = 0.49, 95% CI 0.36—0.66).

In summary, NOACs are promising treatments for the management of non-valvular AF in elderly people, especially due to a lower risk of intracerebral haemorrhage. However, their prescription should take into account some important elements, such as their renal elimination and the absence of monitoring; they are contraindicated in case of severe

renal failure defined by a creatinine clearance less than 30 mL/min. The Cockcroft formula has to be systematically used for renal function assessment because this formula was used in all the trials that evaluated these new drugs. Adherence to treatment is important due to the short elimination half-life of these molecules compared with VKAs, as well as the absence of therapeutic monitoring, so their use requires an assessment of cognitive function. Lastly, although the RE-LY, ROCKET and ARISTOTLE trials included about 19,000 subjects aged above 75 years, a relatively small number of frail patients aged above 80 years were included in these trials. Studies including frail patients (age > 80 years, renal failure) are thus necessary to evaluate tolerance in ''real life''. In the future, the reversal of the anticoagulant effect and the development of specific biological tests in case of acute severe bleeding are important challenges in elderly patients.

Antiplatelet agents

In the latest update in 2012, the ESC guidelines for the management of AF [43] no longer recommend aspirin unless patients refuse the use of any oral anticoagulant (VKAs or NOACs). Indeed, the evidence for stroke prevention with aspirin in AF is weak and the risk of major bleeding or intracranial haemorrhage with aspirin is not significantly different to that of oral anticoagulants, especially in the elderly. Indeed, in the ATRIA cohort, the annual incidence of intracerebral haemorrhage after the age of 80 years was similar with VKAs (0.70%) and aspirin (0.69%) [8]. Moreover, in BAFTA study, the annual incidence of major bleeding in patients aged above 85 years was 2.9% with VKAs and 3.7% with aspirin [38].

Clopidogrel monotherapy is not indicated in AF in the absence of documented study. The combination of aspirin 75 mg/day with clopidogrel 75 mg/day was superior to aspirin alone for stroke prevention but with a higher haemorrhagic risk [76]. Moreover, no positive effect on thromboembolic risk was observed in the subgroup of patients aged above 75 years.

In the elderly, the association of an anticoagulant with an antiplatelet agent raises the bleeding risk, so the use of this combination is restricted to particular cases (acute coronary syndrome, stents; cf. paragraph on coronary patients). The combination of anticoagulant plus aspirin plus clopidogrel, if unavoidable, should be used for as short a time as possible [77].

In the patient with coronary artery disease

The selection of antithrombotic therapy depends on three main factors: the clinical context (acute coronary syndrome or stable patient); the revascularization by angioplasty (in particular the type of stent); and the bleeding risk. In elderly patients aged above 75 years, who are generally considered to be at high bleeding risk, the use of drug-eluting stents should be avoided and triple therapy (combination of an oral anticoagulant with two antiplatelet agents) should be used for as short a time as possible. Table 5, based on expert assessment and not on published randomized studies assessing benefit-risk balance, shows the main clinical situations.

Atrial fibrillation patient aged 75 years or more with stable coronary artery disease

In the absence of recent revascularization by angioplasty, long-term treatment with an oral anticoagulant (VKA or probably NOAC) without an antiplatelet drug is sufficient.

In case of recent revascularization by stent, triple therapy (aspirin plus clopidogrel plus oral anticoagulant) is recommended for 2—4 weeks, then the combination of an oral anticoagulant with only one antiplatelet drug is necessary for 1—12 months after stent placement (according to bleeding risk). Beyond that, oral anticoagulant monotherapy is sufficient.

Atrial fibrillation patient aged 75 years or more following an acute coronary syndrome

In the absence of revascularization procedure, the duration of use of triple therapy (aspirin plus clopidogrel plus oral anticoagulant) should be kept as short as possible (maximum 1 month [2—4 weeks]). It is preferable to continue the combination of an oral anticoagulant plus one antiplatelet agent for 12 months. The duration varies according to the bleeding risk (1 month minimum). Beyond that, an oral anticoagulant as monotherapy is sufficient.

In case of revascularization by angioplasty, initial triple therapy (oral anticoagulant plus aspirin plus clopidogrel) is recommended for a period of 4 weeks to 6 months. However, because the bleeding risk is increased after the age of 75 years, the duration of the triple therapy is usually not longer than 4 weeks. After triple therapy, combination therapy (oral anticoagulant plus one antiplatelet agent) is recommended for a maximum of 12 months. Beyond that, oral anticoagulant monotherapy is sufficient. The continuation of the combination therapy beyond this period, however, varies according to the bleeding and thrombotic risks.

The use of a bare-metal stent is preferred due to the fact that triple therapy in this case is limited to 4 weeks. Exceptionally, drug-eluting stents can be used in complex situations (intrastent restenosis) and require much longer triple therapy (3—6 months) or, if needed, dual antiplatelet therapy with temporary oral anticoagulant discontinuation. The WOEST study (not yet published), which was presented to the ESC Congress in 2012, showed that in subjects with oral anticoagulation and coronary stenting, treatment with clopidogrel plus VKA was significantly less associated with haemorrhagic events than clopidogrel plus aspirin plus VKA, with no more stent thromboses.

Bleeding risk related to vitamin K antagonists

VKAs are underused in elderly people with AF [78,79] who have no contraindication for such medications. The main reason is the fear of bleeding among the majority of physicians. This risk is often overestimated despite an acceptable risk—benefit ratio reported by many randomized trials. This risk perception is related to the fact that elderly patients enrolled in these trials are not representative of all patients in whom VKAs are indicated, particularly very old people with multiple co-morbidities and/or cognitive disorders.

Table 5   Antithrombotic treatment in subjects aged 75 years or above with coronary heart disease and atrial fibrillation.

	Clinical situation	Treatment
Coronary patient without stent	Stable coronary artery disease Unstable coronary artery	Long-term OAC[a] therapy Triple therapy 2—4 weeks Then OAC + aspirin or clopidogrel up to 12 months[a] Then OAC alone
Coronary patient with stent[b]	Stable	Triple therapy 2—4 weeks if bare-metal stent Then OAC + aspirin or clopidogrel up to 12 months Then OAC alone
	Unstable	Triple therapy 4 weeks if bare-metal stent Then OAC + aspirin or clopidogrel up to 12 months[a] Then OAC alone[c]

INR: international normalized ratio; OAC: oral anticoagulant; VKA: vitamin K antagonist. OAC: VKA or probably novel oral anticoagulant.
VKA with double or triple therapy: INR between 2 and 2.5. VKA used alone: target INR between 2 and 3.
[a] 1—12-month duration according to stability of coronary heart disease, thrombotic risk of stent and bleeding risk of subject.
[b] The use of a bare-metal stent is preferred for subjects aged $\geq$ 75 years.
[c] The continuation of double therapy beyond 12 months can be discussed depending on the bleeding and thrombotic risks.

Safety of vitamin K antagonist treatment in the elderly

The incidence of major bleedings related to VKAs varies from 1% to 13% per year [80—84] and clearly increases in the frail elderly and in very old people [82,85,86]. The risk of major bleeding is higher in the first months following treatment initiation [82], then decreases during long-term treatment but does not completely disappear. In France, VKA-related bleeding events are mainly due to serious iatrogenic accidents requiring emergency hospitalization [87]. A better knowledge of VKA-related bleeding risk factors [88—90] enables detection of patients in whom the risk of bleeding outweighs the benefit of VKAs. On the other hand, a more objective evaluation of the risk can lead to VKA prescription in patients untreated because of an excessive fear of bleeding risk.

Assessment of bleeding risk in patients treated with vitamin K antagonists

Several scores are available for assessing the bleeding risk in patients who are being or will be treated with VKAs [91—95]. These scores are based on the identification of certain factors known to increase the bleeding risk. The most used scores are HEMORR$_2$HAGES [92] and HAS-BLED [94]. The HEMORR$_2$HAGES score was studied in elderly patients with a mean age of 80 years, so it is the most suitable score to assess bleeding risk in elderly patients receiving VKAs (Table 6). The HAS-BLED score, recently proposed by the ESC, is simple to carry out but was based on a population with a mean age of 66 years and includes fewer items concerning elderly co-morbidities, such as falls or cognitive disorders (Table 7).

The increase in VKA-related bleeding risk with age is still not well understood. The bleeding risk increases with age independent of the overdose risk. Potential reasons are listed below.

The modifications to VKA pharmacodynamics that occur during the process of ageing explain the difficulty in obtaining long-term INR stability in this population, with a risk of

an INR that exceeds the therapeutic range. It is preferable, therefore, to undertake more frequent INR monitoring compared with that in younger adults (every 15 or 21 days once the treatment is adjusted).

Vascular fragility or potentially unknown haemorrhagic lesions may be present.

There may be co-prescription of medications that lead to INR modifications (some antibiotic and antifungal drugs, amiodarone, statins, fibrates, paracetamol, tramadol, thyroid hormones, serotonin reuptake inhibitors) or drugs that raise the bleeding risk without modifying INR (heparin,

Table 6   HEMORR$_2$HAGES scores for bleeding risk assessment in patients receiving vitamin K antagonists.

Item	Score
Hepatic or renal disease	1
Ethanol abuse	1
Malignancy	1
Older (age > 75 years)	1
Reduced platelet count or function	1
Rebleeding risk	2
Hypertension uncontrolled	1
Anemia	1
Genetic factors (CYP 2C9)	1
Excessive fall risk or neuropsychiatric disease	1
Stroke	1
HEMORR$_2$HAGES total score	Bleeds per 100 patient-years
0	1.9
1	2.5
2	5.3
3	8.4
4	10.4
$\geq$ 5	12.5

Adapted from Gage et al. [92].

Table 7 HAS-BLED score for bleeding risk assessment in patients receiving vitamin K antagonists.

Item	Points
Hypertension (SBP > 160 mmHg)	1
Abnormal renal[a] or liver[b] function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly (age > 65 years)	1
Drugs with bleeding risk[c] or alcohol (1 point each)	1 or 2

Adapted from Pisters et al. [94].
INR: international normalized ratio; SBP: systolic blood pressure.
[a] Serum creatinine ≥ 200 μmol/L.
[b] Chronic liver diseases (cirrhosis) or abnormal liver blood tests (bilirubin 2 × normal limits; aspartate aminotransferase/alanine aminotransferase 3 × normal limits; etc.)
[c] Antiplatelet drugs, non-steroidal anti-inflammatory drugs.

antiplatelets, non-steroidal anti-inflammatory drugs). When a new medication is started, it is essential to monitor INR for 48—72 hours after drug initiation.

The incidence of recurrent falls increases with age and these are often considered to be a bleeding risk factor. In fact, few studies have documented and quantified this risk. In a retrospective study [96], the risk—benefit ratio was in favour of VKA prescription despite a twofold increased intracranial haemorrhage risk in recurrent fallers. Another observational study, conducted in 4093 patients aged above 80 years treated with VKAs, showed a threefold increased risk of major bleeding in fallers [97]. In case of recurrent falls without modifiable underlying cause, VKA prescription should be avoided, especially if life expectancy is reduced. In addition, geriatric assessment and preventive management are needed to avoid the occurrence of new falls.

Cognitive disorders are associated with poorer INR control and therefore with an increased bleeding risk. Memory disorders can result in errors in medication intake, e.g. the patient forgets to take their medication or takes it twice. These mistakes must be prevented. To do so, cognitive disorders must be sought when an anticoagulant treatment is being considered (see geriatric assessment). Anticoagulant therapy in cognitively impaired patients requires the involvement of the caregiver for the administration of medications as well as the therapeutic education of patients' relatives.

Protein-energy malnutrition is frequent in the elderly. In case of sudden-onset malnutrition, particularly in the setting of inflammation, serum albumin level can fall rapidly. With VKAs being strongly bound to serum albumin, the risk of a VKA overdose is high and so INR monitoring and dose adjustment are necessary.

Renal insufficiency is frequent in the elderly and raises the bleeding risk. In this situation, a careful INR monitoring is particularly needed.

Elderly subjects often combine major identified bleeding risk factors [98], especially impaired renal function and use of antiplatelet drugs, explaining, at least partly, their susceptibility to haemorrhagic complications with VKA therapy.

Assessment of bleeding risk in patients treated with novel oral anticoagulants

There are currently no specific bleeding risk scores for NOACs. The usual risk factors for bleeding (HAS-BLED or HEMORR$_2$HAGES scores), especially age above 75 years, low weight, creatinine clearance 30—50 mL/min and associated treatment with antiplatelet or drugs inhibiting P-Gp or CY3A4 inhibitors/inducers (verapamil, azole antifungal drugs, rifampicin, etc.), can be considered as risk factors for NOACs while awaiting results from specific studies. Severe renal insufficiency (creatinine clearance < 30 mL/min according to the Cockcroft formula) contraindicates the use of NOACs.

In elderly patients taking NOACs, renal function should be assessed three times each year or in the case of an acute event (e.g. dehydration, fever).

Antiarrhythmic drugs

Therapeutic strategies

The therapeutic strategy in elderly AF patients does not differ basically from that applied in the younger population. The main discussion about pharmacological treatment is focused on the choice between rhythm-control and rate-control strategies [65,99,100].

The rhythm-control strategy aims to restore and maintain normal sinus rhythm. The objective of the rate-control strategy is to control the ventricular rate by avoiding rapid ventricular response without specific therapy for restoring or maintaining sinus rhythm. Each strategy is mainly based on pharmacological treatments; however non-pharmacological interventions and hybrid therapeutic procedures can also be used. To date, few data are available concerning non-pharmacological interventions, particularly radiofrequency ablation of AF in elderly patients [65].

Many prospective and randomized trials have compared rhythm- and rate-control strategies: PIAF, AFFIRM, RACE, STAT, HOT CAFE, AF-CHF, etc. [65] Patients included in these trials had a mean age of 70 years, 60% were men, 75—80% had persistent AF and 90% were asymptomatic. Few patients had heart failure, except in the AF-CHF study. The results of these trials are consistent and showed no difference in mortality rate between patients assigned to one strategy or the other [65]. Nevertheless, a prespecified analysis of the AFFIRM study among patients aged above 65 years showed that the rate-control strategy was superior to the rhythm-control strategy for mortality and stroke criteria [101]. Ancillary studies suggested that increased stroke incidence in the rhythm-control group is probably related to the underuse of oral anticoagulants [99,101].

Finally, the AFFIRM study focused on the impact of both strategies on symptoms and cost effectiveness. There was no difference between both strategies for quality of life and the 6-minute walk test [102]. On the contrary, it was shown that rate control is a cost-effective strategy compared with rhythm control, mainly due to a reduction in hospitalizations [102]. The RACE II study, which compared a strict rate control strategy (resting heart rate < 80 beats
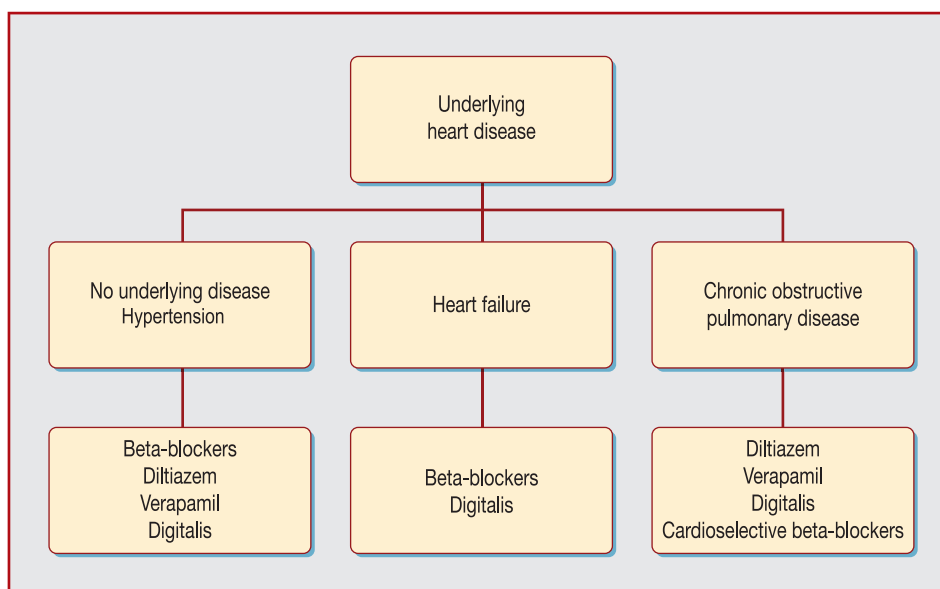
Figure 4.   Heart rate control according to underlying heart disease.

per minute) with a ''lenient'' rate control strategy (heart rate < 110 beats per minute), did not show any difference in a composite primary outcome that included cardiovascular mortality, hospitalizations for heart failure and stroke, systemic embolism, bleeding and life-threatening arrhythmic events [103].

In summary, in elderly patients, the rate control strategy should be used preferentially in most cases. However, the choice of the ''return to normal sinus rhythm'' strategy can be considered in case of severe persistent symptoms and in the absence of advanced cardiomyopathy or contraindication to the use of antiarrhythmic drugs.

Pharmacological treatment

Rate control

The latest ESC guidelines recommend the rate-control strategy as first-line therapy for elderly patients, especially if they are paucisymptomatic [65].

In case of haemodynamic intolerance or severe symptoms related to a rapid ventricular rate, a rate-control therapy can be carried out by the intravenous route (beta-blockers, non-dihydropyridine calcium channel antagonists, digoxin). In case of acute heart failure, digoxin is recommended [65].

In the long-term rate control strategy, the choice of the drug should take into account the presence of associated heart diseases (Fig. 4). In the absence of heart disease, beta-blockers, non-dihydropyridine calcium channel antagonists and digoxin can be used. In patients with heart failure, beta-blockers and digoxin are recommended. In patients with COPD, small doses of cardioselective beta-blockers may be used, as well as non-dihydropyridine calcium channel antagonists. In acute congestive heart failure, beta-blockers and non-dihydropyridine calcium channel antagonists (verapamil and diltiazem) are contraindicated. Amiodarone is also effective at rate control but is rarely used in this indication due to its extracardiac side-effects [99,100]. Lastly, the combination of drugs causing bradycardia should be used cautiously and under careful monitoring.

As a general rule, in the absence of contraindication, it is recommended to use beta-blockers as first-line therapy in AF elderly patients, especially in case of underlying heart failure and/or coronary artery disease. The AFFIRM substudy showed that beta-blockers are the most effective at rate control [104]. On the other hand, digoxin is found to be an independent risk factor for death in AF patients without heart failure [105]. Thus, the use of digoxin in elderly patients is complex due to its renal elimination and the need for careful monitoring.

A less strict rate control therapy can be sufficient in patients without severe symptoms. Strict rate control will be needed in case of disabling symptoms or suspicion of rhythmic cardiomyopathy. If pharmacological therapy fails, rate control can be achieved by atrioventricular node ablation associated with the insertion of a pacemaker or sometimes an automated implantable defibrillator. In case of left ventricular dysfunction and heart failure, a biventricular pacemaker is needed.

Rhythm control: cardioversion

Cardioversion, whether electrical or pharmacological, is less frequently used in elderly patients due to higher prevalence of permanent AF and the difficulty in maintaining sinus rhythm; the rate-control strategy is therefore preferred in this population. Moreover, both types of cardioversion can have serious side-effects, especially in the elderly population. Electrical cardioversion requires general anaesthesia and pharmacological cardioversion requires drugs that can be contraindicated and/or have adverse events, particularly in case of left ventricular dysfunction or heart failure. Oral amiodarone is often used in this situation in elderly patients [65,99,100]. Documented anticoagulation for 3 weeks (or AF < 48 hours) is recommended before both electrical and pharmacological cardioversion [65].

Maintenance of sinus rhythm

Rhythm control is difficult to obtain in elderly patients. Maintaining sinus rhythm involves pharmacological therapy,
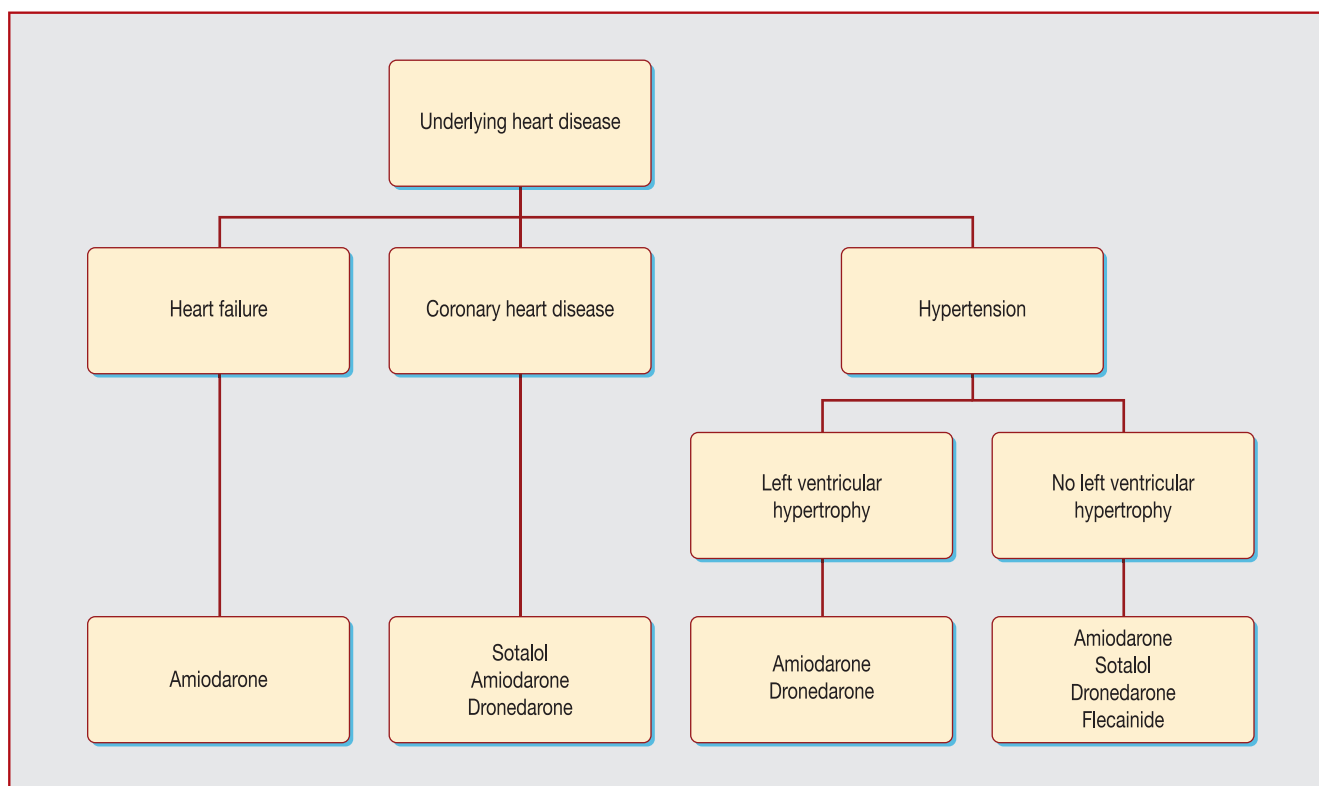
Figure 5.   Heart rhythm control according to underlying heart disease.

as in the younger population, and must follow ESC recommendations [65]. The use of antiarrhythmic drugs in the elderly is limited because of the frequently associated heart diseases and the high prevalence of renal and hepatic conditions that modify the pharmacokinetics of the drug used. Few data are available concerning the use of antiarrhythmic drugs in this specific population.

The choice of the antiarrhythmic therapy depends on the underlying heart disease (Fig. 5): for coronary heart disease, sotalol, amiodarone and dronedarone are recommended [65]; for left ventricular hypertrophy, amiodarone and dronedarone are advised [65]; for heart failure (current or prior) or left ventricular dysfunction, only amiodarone is recommended.

Class I antiarrhythmic drugs are not recommended in case of heart disease, so their use is very limited in the elderly. Lastly, it is difficult to reach the effective doses of sotalol in elderly patients because of poor tolerance and risk of torsades de pointes [65]. Dronedarone has been shown to improve cardiovascular morbimortality (ATHENA study) [106], especially in patients aged above 75 years with paroxysmal or persistent AF. On the other hand, in the ANDROMEDA study, the use of dronedarone in patients with heart failure was associated with increased mortality [107], and in the PALLAS study, its use in patients with permanent AF was associated with increased cardiovascular events [108]. Consequently, dronedarone is contraindicated in these two situations: permanent AF and heart failure.

Tolerance to antiarrhythmic drugs and patient follow-up

Antiarrhythmic drugs should be used with caution in elderly patients because of the frequent metabolic abnormalities

and because of a higher risk of drug interactions and bradycardia. All antiarrhythmic drugs require regular monitoring of ECGs, serum potassium and renal function (in particular digoxin, class I agents, sotalol). Amiodarone requires specific monitoring (thyroid-stimulating hormone, liver transaminases, chest X-ray). In patients treated with dronedarone, health authorities recommend regular monitoring of liver transaminases after the notification of two serious cases of drug-induced hepatitis in January 2011. Pulmonary (dyspnoea, dry cough, crackles, chest X-ray) and renal function (creatinine clearance) monitoring are also recommended for dronedarone.

Non-pharmacological interventions are limited in elderly patients, particularly AF ablation. AF is often permanent, needing complex procedures other than pulmonary vein isolation, which is less successful in the treatment of AF in the elderly. This procedure is carried out rarely in elderly patients when atrioventricular node ablation is contraindicated [65].

In conclusion, a rate-control strategy is the treatment of choice for AF in almost all elderly patients.

Disclosure of interest

O.H. reports consulting and/or lecture fees from Boehringer Ingelheim, sanofi-aventis, Daichi-Sankyo, Bayer-Schering Pharma, Bristol-Myers Squibb, Servier, Abbott and Novartis.

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Appendix 1. Mini Mental State Examination (MMSE) [59].

Orientation

''*I am going to ask you some questions to evaluate your memory. Some questions are very easy while others are not so simple. Try to give the best answer.*''

Score/5 ☐

1.	What is today's year?...........	☐
2.	What season it is?...............	☐
3.	What is the month?............	☐
4.	What day is today?.............	☐
5.	What is the week?..............	☐

''*I am going to ask you now some questions about the place we are in.*''

Score/5 ☐

6.	What is the name of this hospital?..........	☐
7.	What city are we in?...........	☐
8.	In what department is this city situated?………………………..	☐
9.	In what region is this department situated?...........	☐
10.	What floor are we on?.........	☐

Immediate recall

''*I am going to say three words. Listen carefully. You say them back after I stop. Ready? Here they are.*''

Score/3 ☐

11.	Cigar................	☐
12.	Flower..........	☐
13.	Door...........	☐

Now repeat those words back to me.

Attention and calculation

''*I would like you to count backwards from 100 by 7.*''

Score/5 ☐

14.	93..............	☐
15.	86..............	☐
16.	79..............	☐
17.	72..............	☐
18.	65..............	☐

For all subjects, even those who obtained the maximum of points, ask them to spell the word ''WORLD'' backwards: DLROW.

The score corresponds to the number of good responses (this figure should not be noted in the final score).

Recall

''*Earlier I told you the names of three things. Can you tell me what those were?*''

Score/3 ☐

19.	Cigar............	☐
20.	Flower...........	☐
21.	Door.............	☐

Language

Score/9 ☐

22.	Show a pencil. '*What is the name of this subject?*'.........................	☐
23.	Show a wristwatch. '*What is the name of this subject?*'...............	☐
24.	'*Listen carefully and repeat the phrase: 'no ifs, ands or buts'.*'.......	☐

Put a sheet of blank paper on the desk, show it to the subject and then say '*Listen carefully and do what I say.*'

25.	'*Take the paper in your right hand*'.............	☐
26.	'*Fold it in half*'.........	☐
27.	'*And put it on the floor*'............	☐
28.	Hold up the card that reads 'Close your eyes' and say to the subject:	
	'*Read it and do what it says*'.............	☐
29.	Give the subject a sheet of blank paper and a pencil and ask him to write a sentence; it should contain a subject and a verb, and is sensible.	☐

Constructive praxia

30.   Show the subject the drawing of the intersecting pentagons.
            '*Would you like to copy this drawing?*'   ☐
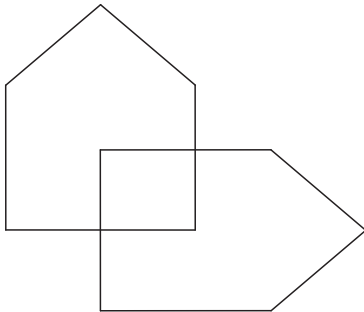
         Total score (0 to 30): ☐
         Score ≤ 27, suspicion of cognitive impairment; score ≤ 24, suspicion of dementia.

Appendix 2. Memory Impairment Screen (MIS) test [109].

'*I am going to show you some words written on this sheet of paper. Please read each word and try to remember it.*'

LEEK   PLANE TREE   WHITING   DAHLIA

         '*Now, I would like you to count from 1 to 20.*'
         When the patient has counted, the examiner says: '*Can you tell me the four words you remember, in any order.*' (free recall)
         If the patient misses a word, the examiner cues the patient with the category: e.g. '*There was also a tree, what was this tree?*' (cued recall)

Immediate MIS

Count 2 points for each item recalled without cueing (free recall) and one point for each item recalled with cueing (cued recall). The score equals the sum of free + cued recall.

|	Free recall (2 points per recalled word)	Cued recall (if no response in free recall, 1 point per recalled word)
Word		
Leek		
Plane		
Whiting		
Dahlia		
Score		

Total score = free recall + cued recall (maximum score = 8).
Cognitive disorder if score ≤ 6.

Delayed MIS

About 10 minutes later, re-ask the patient once more '*Can you tell me the four words you remember, in any order.*'

	Free recall (2 points per recalled word)	Cued recall (if no response in free recall, 1 point per recalled word)
Word		
Leek		
Plane		
Whiting		
Dahlia		
Score		

Total score = free recall + cued recall (maximum score = 8).
Cognitive disorder if score ≤ 6.

Appendix 3. Cognitive Disorders Examination (CODEX) [110].

CODEX is a simple and brief test for detecting dementia. It requires at least 3 minutes to administer. It can be conducted by non-specialized persons in the cognitive assessment.
         The subject is asked to repeat and remember three words (cigar, flower and door).
         The evaluator then gives the subject a sheet of paper on which is drawn a large circle (symbolizing a watch face) and asks him to write the numbers of hours and then draw the hands indicating a given hour. The subject is then asked to repeat the three previously memorized words.
         Lastly, the evaluator asks five questions about spatial orientation: '*What street (or hospital) are we in? In what city? In which department? In which region? On what floor?*'
         The quotation is simple and a binary decisional tree allows conclusion: normal CODEX makes the likelihood of dementia very low; conversely if CODEX is abnormal the probability of dementia is very strong.
         For more information visit the website: www. testcodex.org.

Appendix 4. Katz Activities of Daily Living (ADL) scale [111].

Bathing

(washbasin, tub or shower and body care)
1	☐	Needs no personal assistance
½	☐	Needs partial assistance
0	☐	Dependency

Dressing

(get clothes from closets and drawers and put on clothes and outer garments complete with fasteners)
1	☐	Needs no personal assistance
½	☐	Gets and puts clothes without help, needs help with tying shoes.
0	☐	Dependency

Toileting

(goes to toilet, gets on and off, cleans genital area)
1	☐	Without help
½	☐	Should be assisted or needs help for getting on and off
0	☐	Needs help transferring to the toilet or uses bedpan or commode.

Transferring

1	☐	Moves in and out of bed or chair unassisted. Mechanical transferring aids are acceptable
½	☐	Needs help
0	☐	Is confined to bed (bedridden)

Continence

1	☐	Exercises complete self control over urination and defecation
½	☐	Is partially incontinent
0	☐	Is totally incontinent

Feeding

1	☐	Without help
½	☐	Needs help for the preparation of food
0	☐	needs total help

Score/6: ☐

(Normal score = 6/6)

Appendix 5. Four-item Instrumental Activities of Daily Living (IADL) scale [112].

1. Ability to use telephone
    ☐ Operates telephone on own initiative; looks up and dials numbers

2. Mode of transportation
    ☐ Travels independently on public transportation or drives own car

3. Responsibility for own medications
    ☐ Is responsible for taking medication in correct dosages at correct time

4. Ability to handle finances
    ☐ Manages financial matters independently (writes cheques, pays rent, bills, goes to bank)

Each item is scored (0) dependency or (1) independency, according to response.

Score/4: ☐

(Normal score = 4/4)

Appendix 6. Mini Geriatric Depression Scale (GDS) [113].

The patient is asked to choose the best answer for how they have felt over the past week.

1. Do you often feel sad or depressed?	Yes = 1, no = 0
2. Do you feel that your life is empty?	Yes = 1, no = 0
3. Do you feel happy most of the time?	Yes = 0, no = 1
4. Are you afraid that something bad is going to happen to you?	Yes = 1, no = 0

Results

If total score = 0, high probability of absence of depression.
If total score ≥ 1, high probability of depression.

References

[1] Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e257–354.

[2] Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.

[3] Charlemagne A, Blacher J, Cohen A, et al. Epidemiology of atrial fibrillation in France: extrapolation of international epidemiological data to France and analysis of French hospitalization data. Arch Cardiovasc Dis 2011;104:115–24.

[4] Le Heuzey JY, Paziaud O, Piot O, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am Heart J 2004;147:121–6.

[5] Bilato C, Corti MC, Baggio G, et al. Prevalence, functional impact, and mortality of atrial fibrillation in an older Italian population (from the Pro.V.A. study). Am J Cardiol 2009;104:1092–7.

[6] Bonhorst D, Mendes M, Adragao P, et al. Prevalence of atrial fibrillation in the Portuguese population aged 40 and over: the FAMA study. Rev Port Cardiol 2010;29:331–50.

[7] Cea-Calvo L, Redon J, Lozano JV, et al. [Prevalence of atrial fibrillation in the Spanish population aged 60 years or more, The PREV-ICTUS study]. Rev Esp Cardiol 2007;60:616–24.

[8] Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5.

[9] Guize L, Thomas F, Bean K, Benetos A, Pannier B. [Atrial fibrillation: prevalence, risk factors and mortality in a large French population with 15 years of follow-up]. Bull Acad Natl Med 2007;191:791–803 [discussion 03–5].

[10] Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949–53.

[11] Hu D, Sun Y. Epidemiology, risk factors for stroke, and management of atrial fibrillation in China. J Am Coll Cardiol 2008;52:865–8.

[12] Jeong JH. Prevalence of and risk factors for atrial fibrillation in Korean adults older than 40 years. J Korean Med Sci 2005;20:26–30.

[13] Lake FR, Cullen KJ, de Klerk NH, McCall MG, Rosman DL. Atrial fibrillation and mortality in an elderly population. Aust N Z J Med 1989;19:321—6.

[14] Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. Europace 2011;13:1110—7.

[15] Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455—61.

[16] Kirchhof P, Auricchio A, Bax J, et al. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. Europace 2007;9:1006—23.

[17] Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26:2422—34.

[18] Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart 2001;86:516—21.

[19] Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119—25.

[20] Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation 2003;108:711—6.

[21] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840—4.

[22] Mitchell GF, Vasan RS, Keyes MJ, et al. Pulse pressure and risk of new-onset atrial fibrillation. JAMA 2007;297:709—15.

[23] Thomas MC, Dublin S, Kaplan RC, et al. Blood pressure control and risk of incident atrial fibrillation. Am J Hypertens 2008;21:1111—6.

[24] Verdecchia P, Staessen JA, Angeli F, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet 2009;374:525—33.

[25] Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005;45:1832—9.

[26] Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. J Am Coll Cardiol 2010;55:2299—307.

[27] Disertori M, Latini R, Barlera S, et al. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med 2009;360:1606—17.

[28] Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920—5.

[29] Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215—25.

[30] Komajda M, Hanon O, Hochadel M, et al. Management of octogenarians hospitalized for heart failure in Euro Heart Failure Survey I. Eur Heart J 2007;28:1310—8.

[31] Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N—9N.

[32] Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity — results of a meta-analysis. Am Heart J 2008;155:310—5.

[33] Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol 2007;49:565—71.

[34] Forti P, Maioli F, Pisacane N, Rietti E, Montesi F, Ravaglia G. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). Arch Gerontol Geriatr 2007;44(Suppl. 1):155—65.

[35] Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946—52.

[36] Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359—64.

[37] Nieuwlaat R, Prins MH, Le Heuzey JY, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. Eur Heart J 2008;29:1181—9.

[38] Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493—503.

[39] Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998;158:229—34.

[40] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983—8.

[41] Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449—57.

[42] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864—70.

[43] Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719—47.

[44] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest 2010;137:263—72.

[45] Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. Stroke 2003;34:122—6.

[46] Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27:1760—4.

[47] Miyasaka Y, Barnes ME, Gersh BJ, et al. Time trends of ischemic stroke incidence and mortality in patients diagnosed with first atrial fibrillation in 1980 to 2000: report of a community-based study. Stroke 2005;36:2362—6.

[48] Schwammenthal Y, Bornstein N, Schwammenthal E, et al. Relation of effective anticoagulation in patients with atrial fibrillation to stroke severity and survival (from the National Acute Stroke Israeli Survey [NASIS]). Am J Cardiol 2010;105:411—6.

[49] Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J 2008;29:2125—32.

[50] Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 1997;28:316–21.

[51] Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med 2013;158:338–46.

[52] Lane DA, Lip GY. Quality of life in older people with atrial fibrillation. J Interv Card Electrophysiol 2009;25:37–42.

[53] Mehall JR, Kohut Jr RM, Schneeberger EW, Merrill WH, Wolf RK. Absence of correlation between symptoms and rhythm in ''symptomatic'' atrial fibrillation. Ann Thorac Surg 2007;83:2118–21.

[54] Nergardh A, Frick M. Perceived heart rhythm in relation to ECG findings after direct current cardioversion of atrial fibrillation. Heart 2006;92:1244–7.

[55] Kerr C, Boone J, Connolly S, et al. Follow-up of atrial fibrillation: the initial experience of the Canadian Registry of Atrial Fibrillation. Eur Heart J 1996;17(Suppl. C):48–51.

[56] Dagres N, Nieuwlaat R, Vardas PE, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. J Am Coll Cardiol 2007;49:572–7.

[57] Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation 1999;99:3028–35.

[58] Cooke G, Doust J, Sanders S. Is pulse palpation helpful in detecting atrial fibrillation? A systematic review. J Fam Pract 2006;55:130–4.

[59] Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[60] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.

[61] Nemeroff CB. The curiously strong relationship between cardiovascular disease and depression in the elderly. Am J Geriatr Psychiatry 2008;16:857–60.

[62] Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. Circulation 2001;104:2118–50.

[63] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.

[64] Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age Ageing 2007;36:151–6.

[65] Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.

[66] Gouin-Thibault I, Levy C, Pautas E, et al. Improving anticoagulation control in hospitalized elderly patients on warfarin. J Am Geriatr Soc 2010;58:242–7.

[67] Siguret V, Gouin I, Debray M, et al. Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. Am J Med 2005;118:137–42.

[68] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

[69] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

[70] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

[71] Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010;160: 635–41.

[72] Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363–72.

[73] Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32:2387–94.

[74] Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806–17.

[75] Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol 2012;110:453–60.

[76] Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066–78.

[77] Ruiz-Nodar JM, Marin F, Hurtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. J Am Coll Cardiol 2008;51:818–25.

[78] Lau E, Bungard TJ, Tsuyuki RT. Stroke prophylaxis in institutionalized elderly patients with atrial fibrillation. J Am Geriatr Soc 2004;52:428–33.

[79] Tilly-Gentric A. [Anticoagulation in permanent atrial fibrillation after 75 years of age]. Rev Med Interne 2002;23:834–9.

[80] Douketis JD, Arneklev K, Goldhaber SZ, Spandorfer J, Halperin F, Horrow J. Comparison of bleeding in patients with nonvalvular atrial fibrillation treated with ximelagatran or warfarin: assessment of incidence, case-fatality rate, time course and sites of bleeding, and risk factors for bleeding. Arch Intern Med 2006;166:853–9.

[81] Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120:700–5.

[82] Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689–96.

[83] Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996;348:423–8.

[84] Schulman S, Clinical practice. Care of patients receiving long-term anticoagulant therapy. N Engl J Med 2003;349:675–83.

[85] Jacobs LG. Warfarin pharmacology, clinical management, and evaluation of hemorrhagic risk for the elderly. Cardiol Clin 2008;26:157–67, v.

[86] Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med 2005;165:1527–32.

[87] Pouyanne P, Haramburu F, Imbs JL, Begaud B. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance Centres. BMJ 2000;320:1036.

[88] Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019—26.

[89] Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897—902.

[90] Pautas E, Gouin-Thibault I, Debray M, Gaussem P, Siguret V. Haemorrhagic complications of vitamin K antagonists in the elderly: risk factors and management. Drugs Aging 2006;23:13—25.

[91] Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998;105:91—9.

[92] Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006;151:713—9.

[93] Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med 1999;159:457—60.

[94] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093—100.

[95] Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. Chest 2006;130:1390—6.

[96] Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. Am J Med 2005;118:612—7.

[97] Poli D, Antonucci E, Testa S, Tosetto A, Ageno W, Palareti G. Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. Circulation 2011;124:824—9.

[98] Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol 2011;57:173—80.

[99] Aronow WS. Management of atrial fibrillation in the elderly. Minerva Med 2009;100:3—24.

[100] Wyse DG. Pharmacotherapy for rhythm management in elderly patients with atrial fibrillation. J Interv Card Electrophysiol 2009;25:25—9.

[101] Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825—33.

[102] Marshall DA, Levy AR, Vidaillet H, et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. Ann Intern Med 2004;141:653—61.

[103] Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363—73.

[104] Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. J Am Coll Cardiol 2004;43:1201—8.

[105] Hallberg P, Lindback J, Lindahl B, Stenestrand U, Melhus H. Digoxin and mortality in atrial fibrillation: a prospective cohort study. Eur J Clin Pharmacol 2007;63:959—71.

[106] Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668—78.

[107] Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678—87.

[108] Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011;365:2268—76.

[109] de Rotrou J, Battal-Merlet L, Wenisch E, et al. Relevance of 10-min delayed recall in dementia screening. Eur J Neurol 2007;14:144—9.

[110] Belmin J, Pariel-Madjlessi S, Surun P, et al. The cognitive disorders examination (Codex) is a reliable 3-minute test for detection of dementia in the elderly (validation study on 323 subjects). Presse Med 2007;36:1183—90.

[111] Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The Index of Adl: a standardized measure of biological and psychosocial function. JAMA 1963;185:914—9.

[112] Barberger-Gateau P, Dartigues JF, Letenneur L. Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia. Age Ageing 1993;22:457—63.

[113] Clement JP, Nassif RF, Leger JM, Marchan F. [Development and contribution to the validation of a brief French version of the Yesavage Geriatric Depression Scale]. Encephale 1997;23:91—9.