FRAILTY IN CARDIOLOGY: DEFINITION, ASSESSMENT AND CLINICAL IMPLICATIONS FOR GENERAL CARDIOLOGY

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SUPPLEMENTARY DATA

Supplementary Data (online Annexe 1).

5.1) Frailty and cardiovascular prevention

The risk of frailty appears to be reduced in healthy ageing (86) while the frailty and pre-frailty status are associated with increased prevalence of several CV risk factors in older people (87). Moreover, though greater all-cause and CV disease mortality was confirmed in prefrailty and frailty, being physically active was linked to lower mortality both in prefrail and frail individuals from a cohort of 4,008 non-institutionalized population aged 60 and older, partially reversing the increased frailty-associated risk (88). Although these findings strengthen the need for CV prevention in all stages of frailty, frailty has long affected negatively the implementation of preventive strategies.

CV diseases linked to arterial hypertension and dyslipidaemia contribute to increase frailty (89). Moreover, antihypertensive (90), as well as lipid lowering drugs (91), even if proven to be effective and safe in older patients, may have a direct effect on frailty.

5.1.1) Arterial Hypertension

Frailty is common in people with hypertension (92). Orthostatic hypotension affects the prognosis in older people by increasing the risk of syncope and falls, leading to hospitalization and functional impairment, and increasing CV disease and all-cause mortality (93-96).

Carefully titrated antihypertensive therapy, not only based on measurement of blood pressure in recumbent, but also standing position, which should form part of the standard evaluation in elderly and frail people, has positive effects on functional status and may have a positive effect on orthostatic hypotension and cognitive function (97-99). In these patients, specific recommendations of the current ESC guidelines are to maintain a 130 to 140 mmHg systolic target and 80 to 90 mmHg diastolic target, if tolerated, and to consider monotherapy as a first-line strategy in older and frail patients (100).

5.2.1) Dyslipidaemia

Longstanding dyslipidaemia may cause CV complications which may increase frailty as well as common geriatric conditions, including dementia (101). In 945 subjects from the British Regional Heart Study, high fat/low fibres intake was associated with incident frailty after a 3 years follow-up, independently of established CV disease in older British men (102).

Low cholesterol in the elderly has been shown to be associated with the highest risk of death in patients not taking lipid-lowering medications, possibly low serum values being a marker of chronic diseases, cachexia, malnutrition and inflammation (103).

Statins may increase frailty in some people by side effects such as muscle pain. Nevertheless, the use of statins is associated with reduced development of dementia (104) and reduced mortality (91,105,106) in older patients with vascular disease.

The 2019 ESC guidelines on Dyslipidaemias recommend treating older patients with atherosclerotic CV disease to targets just similar to younger patients. In primary prevention, people ≤ 75 years old should be treated according to the level of risk whereas older subjects may be considered for initiation of statin treatment if at high or very high risk. The recommendation is to start with lower doses due to comorbidities - in particular renal impairment - altering pharmacokinetics, with potential accumulation and drug-drug interaction, and then titrate to target with caution (107).

5.2) Chronic coronary syndrome

Elderly patients have the greatest mortality and morbidity risk attributable to chronic coronary syndrome (CCS) and associated multimorbidity (108).

Beyond the cross-sectional association between frailty and coronary artery disease, the Women's Health Initiative Study revealed that women with coronary artery disease were more likely to develop frailty over a 6 year period (12% vs. 5%) (109) and the Health ABC study showed that older adults with objectively-measured frailty were more likely to develop coronary events (3.6% vs. 2.8% per year) (110).

The decision to treat invasively (especially surgically) a frail chronic coronary artery disease patient is always a difficult task. The two most widely used models of perioperative risk assessment in

cardiac surgery are the EuroSCORE II and the STS score, but both are inaccurate in estimating individual risk (111) and in both frailty per se is not represented. The updated EuroSCORE II includes 'poor mobility' as a risk factor. This allows a representation of frailty and improves the accuracy of the score, even if mobility alone does not necessarily equate to frailty.

Singh et al. assessed frailty, comorbidity and QoL in 628 patients over the age of 65 years who underwent percutaneous coronary intervention (PCI). Three-year mortality was 28% for frail patients compared to 6% in non-frail (112). The addition of frailty to the Mayo clinic risk score increased the accuracy for mortality prediction (113). In a secondary analysis from the Surgical Treatment for Ischemic Heart Failure trial which compared coronary artery bypass graft (CABG) with medical therapy in patients with ischemic left ventricular dysfunction, patients with low exercise capacity, a marker of frailty, had a higher early surgery-related mortality if randomized to CABG, and no significant benefit at follow-up. In contrast, patients with better exercise capacity had a lower risk from surgery and lower mortality (HR 0.77, 95% CI 0.59 to 0.99, p=0.038) if randomized to CABG compared with medical therapy (114).

Freiheit et al. (115) observed 347 frail subjects post coronary angiography for 30 months. CABG was chosen for 128 of them, PCI for 150 and medical therapy only for 96. When the frailty trajectories were evaluated during follow-up, the pattern of frailty index variations upon time differed by age and treatment, with worse frailty progression seen in patients ≥ 75 years with major frailty burden at baseline who were submitted to CABG.

In conclusion, frail patients are less aggressively managed as compared to non-frail counterparts, but the outcomes associated with this management remains unclear. Frail subjects are less likely to be referred for cardiac catheterization or CABG. When frail patients undergo revascularization, the 2018 ESC/EACTS guidelines recommend choosing the least invasive procedure (ie PCI vs CABG) (116).

Recently, the interest of revascularization for angina has been challenged in non-frail patients (117) and it is therefore judicious to limit revascularization in frail patients in this setting, unless other factors (e.g. left ventricular dysfunction) are present. These cases must be then discussed in a

multidisciplinary heart team, and if revascularization is indicated, patients should procede thorough pre-operative optimization of the frailty status and heightened post-operative surveillance (6,118).

The recently published ESC guidelines on CCS (119) underline specific points in elderly and frail people. Atypical symptoms and complications of both invasive and medical treatments may occur more frequently in older patients. Class I recommendations include: a) consider side effects of drugs, intolerance, and overdosing in elderly patients, b) prefer a radial access whenever possible to reduce complications, c) use drug eluting stents (DES) and a shorter duration of dual antiplatelet therapy (DAPT) rather than bare metal stents, and d) weigh carefully the decision for diagnostic tests and revascularization choices.

Guidelines on CCS recommend caution for antithrombotic drugs in frail subjects due to their high bleeding risk similarly to other conditions such as a prior history of intracerebral hemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding.

5.3) Arrhythmias

The main arrhythmic issues in cardiology practice with specific aspects for frail patients are essentially atrial fibrillation (AF) and the evaluation of the implant of electronic devices.

5.3.1) Atrial fibrillation

AF is the most frequent sustained arrhythmia in elderly people, with a prevalence of 23% in subjects older than 84 years (120). Its incidence starts rising after 50 years of age (121) and, interestingly, it progressively increased from 1998 to 2010 with a higher number of cases observed in people ≥75 years (122).

AF subjects are usually more complex, with more comorbidities than the sinus rhythm population. In particular, not only traditional CV risk factors, but also arthritis, cancer, chronic kidney disease, chronic obstructive pulmonary disease and diabetes are more frequent (123). A population-based study revealed a mortality and disability excess in older individuals with AF (124,125). Possible explanations are the link of AF with HF, chronic inflammation and a prothrombotic status. All these factors can lead, through cerebral hypoperfusion, to cognitive decline and dementia (126). Indeed, brain MRI demonstrated a progressive decrease in total cerebral blood flow correlated with AF (127),

and the Cardiovascular Health Study, after a 7-year follow-up, found an increased incidence of dementia after AF onset (128). More recently, in a large registry of subjects ≥ 60 years, the incidence of both the Alzheimer's and the vascular form of dementia was significantly higher in those with incident AF, independent of clinical stroke (129). The development of AF may have a negative impact on the predicted trajectory of physical performance in the Health Aging, and Body Composition study (130).

Together these data explain how AF can be considered as a marker of a frail condition in the elderly (5) and when frailty and AF coexist, mortality risk is twice as higher than in age-matched robust subjects with AF (131). In the ORBIT AF registry, frail arrhythmic patients are older, with a higher CHA_2DS_2-VASc score, more frequently need to live with assistance, and are more often severely symptomatic with a worse EHRA score (132).

In AF management, rhythm-control could be more effective than rate-control strategy to reduce 12-month mortality, stroke incidence and cognitive performance changes (133-135). However, the EORP-AF General Pilot Registry results clearly demonstrated that such a strategy is less frequently adopted in the elderly (136).

Appropriate management of risk factors of both CV diseases and of cognitive and functional decay is therefore mandatory. Several studies have focused on the relative benefits of a rhythm- or rate-control strategy for the management of AF, looking at mortality and the incidence of frailty, disability, and dementia (137), and in particular considering the high incidence of adverse drug reactions that digoxin and anti-arrhythmic drugs can cause in the elderly frail population (138,139).

When required due to the severity of the clinical condition or symptoms, advanced age *per se* does not impair the immediate and long-term efficacy of electrical cardioversion, which allows a prompt improvement of left ventricular performance (140). Some preliminary observations also seem to demonstrate the efficacy and safety of AF ablation in advanced age (141). The procedure may be associated with a reduced rate of hospitalizations and dementia development (142).

According to the 2016 ESC guidelines, all available rate and rhythm control interventions should not be denied to older patients, although their QoL can be impaired by other comorbidities than by the AF itself (143). Thus frail patients should not be excluded from evidence-based medical therapies,

but estimated life-expectancy, ischaemic and bleeding risk assessment, comorbidities, QoL and patient preferences should be considered in a fully integrated approach (144).

Antithrombotic therapy deserves specific considerations in frail subjects with AF (see antithrombotic therapy section).

5.3.2) Cardiac Implantable Electronic Devices

The high incidence of sinus node dysfunction, atrioventricular block and carotid sinus hypersensitivity, and the high prevalence of chronic HF in elderly subjects justifies the significant use of cardiac implantable electronic devices (CIEDs) at an advanced age (145).

Patients >75 years, in particular with an anti-bradyarrhythmia device, represent the majority of those receiving a CIED (146). They are more often followed-up with face-to-face visits as remote monitoring seems to be less attractive than the traditional approach (146). Older patients infrequently self refer with CIED-related difficulties and limitations in their usual activities. Consequently, it seems that the elderly derive a greater benefit in QoL from this therapy (146).

The benefit of cardiac resynchronization therapy (CRT) on QoL is particularly evident (147). The advantage of CRT is greater than that observed after ICD implantation alone (148). Even in AF subjects with moderate to severe left ventricular dysfunction, CRT after atrioventricular node ablation offers a significant improvement in HF hospitalizations and QoL, when compared with optimal medical therapy (149). These results can be attributed to the age-independent positive influence of CRT on left ventricular dimensions and systolic performance, with consequent reduction of NYHA class (150).

Importantly, after only 6 months of therapy, CRT improved both cognitive and functional profile (151), and therefore could be considered an anti-frailty therapy. In this regard, the MADIT-CRT trial showed that the benefits of CRT and Defibrillator versus ICD alone are particularly evident when comorbidities are present (152). In octogenarians with severe cardiac dysfunction, most of clinical events seems to be due to non-cardiac conditions, explaining the lack of superiority of CRT-Defibrillator versus CRT-Pacemaker only therapy (153).

After ICD implantation, the vast majority of patients, irrespective of age, do not receive any information about what to do with their device when end of life is approaching (146,154). This issue

is particularly relevant because of the high proportion of ICD recipients experiencing arrhythmic storms and multiple shocks in the last days of life (155). Interestingly, when specifically asked about what they would want to do with their device at end of life, the majority of patients, independently of age, admitted to have never thought about this topic, and some of the interviewed subjects refused to give an answer (146).

In accordance with the EHRA Consensus Statement on the management of CIEDs in patients nearing the end of life, and the AHA/ACC/HRS guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, pacemakers and CRT devices preventing symptomatic bradycardia remain essential during palliative care and should not be de-activated. Conversely, in the same situation, ICD shocks can be physically painful and psychologically stressful, without prolonging life of acceptable quality (156,157).

5.4) Valvular heart diseases

Valvular heart disease is increasingly prevalent – approximately 13.3 million in the ESC member countries (158). The rapid development of less invasive transcatheter repair and replacement techniques in recent years has increased candidates for intervention. The choice between surgery or a transcatheter procedure in an individual should always be evaluated by the Heart Team. The Heart Team will usually calculate the EuroScore II and the Society of Thoracic Surgery scores, but important risk factors, such as frailty or mood disorders, are not included in these risk scores. Transcatheter aortic valve replacement (TAVR) is now alternative to surgery in high, intermediate and low-risk patients and the recognition of frailty is a key step in the pre-operative evaluation, as recommended (class I) in the 2017 ESC guidelines for the management of valvular heart disease (159), to predict outcome and to avoid futility (160,161).

A recent nationwide cohort in the USA including data on 28,531 patients submitted to TAVR and 3,746 patients who underwent mitral edge-to-edge repair (162) was assessed by an electronic data-base score, the Hospital Frailty Risk Score. Patients were classified as low, intermediate or high-risk for frailty with similar distribution of risk categories between TAVR and transcatheter mitral valve repair. One-year mortality was 12.8% in low-risk patients, 29.7% in intermediate risk and 40.9% in

high-risk frail patients. The Hospital Frailty Risk Score, also predicted rehospitalization for any cause, acute myocardial infarction, acute HF, acute renal failure, stroke and post-haemorrhagic anaemia. Although the ideal method of assessment is still unclear, the utility of frailty indices to predict short- and long-term outcome in valvular disease has been clearly demonstrated, regardless of the method used to assess the condition, both for surgical or transcatheter mitral and aortic valve interventions (56,162-170).

When various indices of frailty have been compared, analyzing the discrimination power on outcomes after TAVR or surgical valve replacement therapy (SAVR) in the FRAILTY-AVR study, all the frailty scales improved 1-year mortality prediction, with the simple composite Essential Frailty Toolset (figure 2S) performing better (56).

Frailty is a dynamic condition, which may become more severe if the waiting time for TAVR is prolonged, or alternatively may be improved, especially with focussed intervention. It is therefore important during pretreatment evaluation to identify any aspects of frailty which could potentially be improved. For example, the relevance of nutritional status in pretreatment evaluation has been recently underlined in multicentre registry data on 1,613 patients from Japan and in 1,158 patients from the FRAILTY-AVR population, in which the Geriatric Nutritional Risk Index and the Mini Nutritional Assessment-Short Form were associated with 1-year mortality in the two studies, respectively (171,172). Moreover, the nutritional status correlated with other measures of frailty (Clinical Frailty Scale) or physical frailty components such as gait speed, grip strength and the SPPB scores (171,172). A new CGA-derived score recently introduced, the Erasmus frailty score, focusing on cognition, nutritional status, muscle strength and inactivity, has been associated with delirium and 1-year mortality after TARV in older patients (173).

For office-based cardiology practice, an initial evaluation with a very simple and rapid assessment including the Essential Frailty Toolset, malnutrition screen, depression and disability evaluation has been proposed recently for patients being considered for a TAVR (figure 3) (160). This can then be followed by a targeted deeper assessment of the specific domains of frailty identified, or at least by simple physical measures of frailty, followed by a more extensive evaluation by CGA when required (160,169).

To facilitate screening, a practical smartphone app assessing the essential frailty toolset score and additional geriatric domains has been recently proposed (160).

5.5) Chronic heart failure

Frailty increases the likelihood of acute HF and overt HF accelerates the emergence of frailty. Chronic HF may impair body composition and induces sarcopenia (174-177).

The prevalence of frailty among HF patients varies according to the clinical setting (community-dwellers vs hospitalized patients and, among these, in cardiology vs internal medicine and geriatric setting) and the diagnostic tools used for frailty screening (frailty phenotype vs accumulation of deficits). Very recently, the ESC HFA evidenced that techniques to assess frailty in HF should involve a multidomain frailty evaluation. A new frailty score for HF should reflect this holistic approach (9).

In a recent review, Denfeld et al. reported a prevalence of frailty of 44.5% in HF patients, slightly lower when frailty was identified according to the "frailty phenotype" compared with "multidimensional" frailty tools (178). In the TOPCAT study (mean age 71.5 years, 49% female) 94% of HF patients with preserved ejection fraction were deemed frail according to a modified multidimensional Frailty Index (179). When directly comparing screening and assessment techniques to detect frailty, the prevalence of frailty among HF patients varied from 30% to 52%. Among the screening tools used, the Clinical Frailty Scale had the strongest correlation with the frailty assessment tools, with the highest sensitivity and specificity (180).

Frail patients with HF have increased risk of mortality, hospitalization and worsening disability, compared with non-frail HF patients (80,179,181-186). In a population-based observational study on a large electronic health data record using an electronic frailty index based upon the concept of deficit accumulation, frailty was found to predict the first unplanned hospitalization for HF or all-cause admission after diagnosis (187). In two recent meta-analysis in HF patients (188,189), frailty was found to be a predictor of both all-cause mortality (HR 1.54, 95% CI 1.34–1.75; P<0.001 in one study and HR 1.59, 95% CI 1.39-1.82, P < .0001 in the other study) and hospitalizations (HR 1.56; 95% CI, 1.36–1.78; P<0.001, and HR 1.31, 95% CI 1.21- 1.42, P < .0001). Frailty was also associated with all-cause mortality in HF patients undergoing ventricular assist device implantation (189).

Moreover, even prefrailty (3 studies) was associated with increased risk of hospital readmission and higher mortality (190).

In the meta-analysis by Zhang Y et al., among the individual frailty components, physical exhaustion, weight loss, low physical activity and grip strength were associated with mortality (189). The comprehensive Multidimensional Prognostic Index was predictive of mortality and adverse clinical outcomes in older patients with HF (40, 191). Physical measures such as Gait speed have been demonstrated to be a simple and reliable predictor of hospitalization (192), and a low SPPB score was associated with prolonged length of hospital stay, whereas a low score at discharge was associated with a higher risk of basic functional disability, mortality, or re-hospitalization (193-195).

There is no consensus on which method should be used in HF for operational definition of frailty (9). In the McDonagh review the most commonly used instruments were the frailty phenotype assessment and the CGA (12). Moreover, though a substantial heterogeneity was perceived by physicians from the geriatric cardiology community regarding the subdomains that were evaluated by the various assessment tools (57), there is an increasing awareness of the need to assess the individual multidomains of frailty to address specific clinical challenges in HF patients (26,196).

Frail patients may derive less mortality benefit from some interventional procedures due to increasing number of competing causes of death and may have increased risk of complications from certain medical treatments and interventional procedures (197-202). Therefore, in frail patients, particularly those with HF in whom standard treatment includes a significant number of drugs, appropriate use of medical therapies and reduction of polypharmacy, avoidance of drugs of uncertain benefit, slow titration and careful monitoring of HF medications should be recommended. Careful surveillance should be in place to improve frailty trajectories in HF in order to prevent decompensation and hospitalization via multidisciplinary management programs, together with adequate transitional and tailored rehabilitation care packages after discharge (203-205). Relatively new approaches such as Home Telemonitoring and Nurse Telephone Support could be cost-effective (206).

5.6) Peripheral vascular disease

Patients with lower-extremity artery disease (LEAD) are known to have widespread atherosclerosis, and are at risk of limb loss as well as mortality and CV events, including myocardial infarction and stroke (207). The physical deterioration and CV risk increase are present even before the diagnosis of symptomatic LEAD (207,208). Frailty is a frequent condition among patients with LEAD; in a geriatric population-based study, frailty was much more frequently found in the presence of subclinical LEAD, detected by the ankle-brachial index measurement (odd ratio 3.17, 95% CI 1.80–5.57, p<0.001) (209).

High levels of frailty are found in 15% of patients with intermittent claudication (210).This rate is even higher in patients with chronic limb threatening ischaemia (CLTI): in a series of 643 patients revascularized for CLTI, over 33% were severely or very severely frail (211). This is not only because LEAD mostly affects elder people with frequent comorbidities (e.g. diabetes, renal failure, other CV conditions…), but also because of direct LEAD contribution to frailty through walking and gait disturbances, lower physical activity and increased sarcopenia. Using a lumbar CT-scan to assess sarcopenia (i.e. in other regions than lower-extremities) in patients hospitalized for CLTI, Matsubara et al. reported sarcopenia in 44% of these patients, with poorer survival rates during follow-up (212). The rates of cognitive impairment and dementia are higher than age-adjusted counterpart without LEAD, at least partly because of generalized atherosclerosis (213).

The estimation of frailty, using validated scores, may be difficult in patients with severe LEAD due to mobility loss related to the condition (214). Also, the use of different frailty scales may lead to important disparities in the prevalence of this condition: in a series of 148 patients with severe LEAD requiring revascularization, the rates of frailty ranged from 16% to 70% according to different scores (215). When looking at mortality and major disability at 12 months, the head to head comparison showed that the best predictors were the Groningen Frailty Indicator, and the modified Essential Frailty Toolset, both being non-physical performance-based frailty scales and therefore suitable to be used in these patients with severely impaired mobility, constituting a starting point to identify patients in whom further geriatric assessment should be considered.

Frailty has a major prognostic impact in patients with LEAD. In claudicants, high frailty scores were associated with increased risk of major adverse cardiac events (210).

The modified Frailty Scale was predictive of 30-day mortality and secondary events in patients undergoing amputation (216). Indeed, the prognostic importance of frailty is reported even after revascularization. Using the data from 72,106 patients in a large database in the US, the predictive ability of the modified Frailty Index surpassed the regular CV predictive scores (e.g. the Lee Cardiac Index) to stratify the perioperative risk of patients undergoing vascular surgery (217). In another series of patients revascularized for CLTI, severe frailty, defined by the Canadian Study of Health and Aging clinical frailty scale, was associated with +134% higher risk of death or major amputation within 2 years, independently of age, type of revascularization and renal failure (211).

However, the presence of significant frailty should not be considered as a contra-indication to revascularization, but rather be integrated with other aspects of the assessment, including revascularization feasibility and operability, in order to use it in the discussion of the patients' management by a multidisciplinary team.

Beyond revascularization, the management of pain and CV risk factors and comorbidities, walking rehabilitation, nutritional support and wound care are all key pillars for the optimal management of frail patients with LEAD.

5.7) Coagulation and antithrombotic therapy

Ageing per se increases both the risk of thromboembolic and bleeding complications (218) and studies measuring individual coagulation factors suggest that frailty is associated with both pro-coagulant and fibrinolytic changes.

Studies on coagulation factors like fibrinogen, factor (F)VIII, D-dimer and FXI, (219-221) showed conflicting results. The heterogeneity in frailty definition and scores may explain some inconsistencies in coagulation factor levels among these different cohorts (222). The increase in fibrinogen is often associated with an increase in C-reactive protein (219-221) and interpreted as an index of the 'inflammageing' that characterizes frailty (84,223).

High D-dimer levels independently predict mortality and vascular complications (both venous and arterial) across multiple vascular diseases (224) and predict functional decline specifically in older people (225).

Clinically, frailty has been associated with ≈30% increased risk of idiopathic venous thromboembolism in the Cardiovascular Health Study (226). On the other hand, clinical studies suggest that frail people on oral anticoagulant therapy, both vitamine K antagonists (VKA) and direct oral anticoagulants (DOACs), may be at an increased risk of major bleeding compared to robust subjects (227,228) probably due to high prevalence of low body size (229).

After an acute coronary syndrome, frailty is associated with ≈4-fold increase in mortality rate within 12 months (230,231), increase in any CV disease event (230) and 51% increase in major bleeding (230) versus robust older subjects, independently of the score used to grade frailty (231). Thus, it may be worth testing whether frailty assessment integrated into current thrombosis and bleeding scores may improve the comprehensive evaluation of the prognosis and appropriate management strategies including invasive therapy and antithrombotic medication.

Perhaps the most difficult decisions about antithrombotic management in the frail patients are related to acute coronary syndrome occurring in a patient already on DOACs or warfarin, in relation to the addition of anti-platelet treatment. The general principles outlined in the ESC focused update on DAPT are therefore highly relevant for frail patients: assess the relative ischaemic and bleeding risks carefully using validated risk predictors, minimize the duration of triple therapy, consider whether dual therapy with clopidogrel and DOAC might suffice, use a DOAC rather than warfarin where possible, use the lowest proven dose of the DOAC, consider standard low dose aspirin if used and use a proton pump inhibitor in all patients (232).

Trials testing the optimal antiplatelet therapy in frail patients are lacking (233). Recent guidelines do not include specific antiplatelet therapy recommendations for frail subjects, in whom the least invasive procedure seems safe (233-235).

Along with the words of caution in treating frail subjects, the 2019 ESC guidelines on CCS suggest to treat the subjects using strategies allowing the shorter duration of DAPT to minimize the high risk of bleeding (see the CCS section).

Antithrombotic treatment in AF is a key step in stroke prevention. Although recent data support a great net clinical benefit for anticoagulation, under-treatment with oral anticoagulant therapy is common in elderly patients with AF, due to the fear of bleeding complications, and attention should

be paid to avoid inappropriate dosage reduction. However, stroke avoidance is the key and there are data to suggest that patients are prepared to endure four major bleeds to avoid one stroke (236). The optimal antithrombotic treatment strategy for AF in frailty remains undefined due to the small number of frail subjects included in the phase III trials (218,237). Whilst DOACs provide a therapeutic option, evidence in frail subjects is limited as they were excluded from trials because of expected short life-expectancy and high comorbities (238).

A recent observational study on a large cohort showed that DOACs were similar to warfarin in protecting from stroke, systemic embolism, or ischemic stroke at 1 year, while at 2 years rivaroxaban was associated with a reduced hazard of stroke or systemic embolism, and ischemic stroke versus warfarin by 32% and 31%, respectively (239). No significant differences were reported between any DOAC and warfarin in rates of any major bleeding including hemorrhagic stroke, intracranial hemorrhage and gastrointestinal bleeding at 2 years (239). Overall in AF, physicians seem to over-estimate the risk of bleeding and under-prescribe oral anticoagulation, although recent data show that this trend is lower than in the past, especially for community-based subjects (238,240,241).

The alternative option of aspirin which is often discussed with patients is inappropriate as evidence would suggest that it is not safer than anticoagulant therapy and has fewer protective effects (242). In spite of this, general practice data from the United Kingdom would suggest that older patients were more likely to receive prophylaxis with aspirin rather than oral anticoagulant therapy, or no treatment (243). Renal function should be carefully considered, when eGFR is <30 ml/min/1.73m² dabigatan is contraindicated, while apixaban and edoxaban should be used at reduced dose.

In conclusion oral anticoagulant therapy in the majority of frail patients with AF should be administrated unless there is a prohibitive haemorrhagic risk, very short life expectancy or very poor expected net clinical benefit. Moreover, before considering an AF patient at high risk of bleeding because of a frail condition, this state should be evidenced using proper assessment tools.

According to the 2019 ESC Guidelines on Acute Pulmonary Embolism (244) age and immobility are risk factors for pulmonary embolism and are also common in the frail. Although there are no specific recommendations for frail patients, it would seem wise to anti-coagulate for the shortest suitable

period (3 months) in frail patients with pulmonary embolism to reduce the risk of bleeding complications.

SUPPLEMENTARY DATA

Supplementary Data (online Annexe 2).

8.1) Special role for General Cardiologists

The general cardiologist should be aware of the association between frailty and CV disease and address these considerations in clinical practice in frail patients.

8.1.1) Prevention of cardiovascular disease

CV risk factors should be treated to target, though with caution, and specific measures for frailty management should be reinforced.

8.1.2) Clinical evaluation of frailty and use of tools addressing specific issues

Patients being evaluated by general cardiologists in out-patient clinics (for planned visits, primary or secondary prevention of CV disease or prior to scheduled interventions) tend to have a lower burden of social-associated components of frailty and lower cognitive impairment than long-stay hospitalized patients, and are generally self-caring with support from their families if required. In these patients, the physical frailty domain components such as weakness or slowness and the medical domain components such as multi-morbidity or deficient nutritional status, may determine the outcomes. The general cardiologist should use simple measures that mainly consider those items that seem to be more appropriate for an initial out-patient evaluation and then procede with an in depth assessment with the help of specialists (geriatric cardiologist or geriatrician) when needed.

Few studies have reported frailty measures to be associated with post-intervention outcomes in out-of-hospital patients, particularly in relation to planned PCI or TAVR. The use of these evaluations should be recommended if and when the available literature in the specific context showed incremental benefit.

8.1.3) Specific cardiovascular disease treatment aspects

Specific aspects of pathophysiology of CV disease, QoL, particular presentations, the presence of co-morbidities, therapeutic aspects and prognosis, should be taken into account when choosing diagnostic and therapeutic interventions in older and frail subjects. Treatment strategies rely on specific outcome measures and goals defined on a tailored base in the individual.

8.1.4) Improvement of cardiovascular protocols impacting on frailty

Besides interventions on diet, exercise and social support, the development of new protocols, particularly linked to health technology and home support (video-cameras, activity tracking, wearable devices, etc) need to be studied for evaluating and treating pre-frail and frail subjects to support sufficient degree of self-care.

8.2) **Special role for General Practitioners**

The role of General Practitioners (GPs) and other primary care physicians has been widely recognized in frailty management. The main areas for consideration are:

8.2.1) Assessment tools and the initial contact

For GPs, a key question is what patient should receive screening for frailty. Although there is no consensus, screening for frailty and the available screening tools have been previously highlighted.

8.2.2.) Informing the patient and meeting the patient's family

Informing the patient about any diagnosis and its prognosis is always an important task. This is particularly the case for frailty conditions: frailty is not a disease but a status indicating a decreased capacity to react to stressors, with many manifestations across various systems and functions enhancing the probability of hospital admission and death. This concept can be difficult for patients to understand, particularly with respect to the implications for disease management. Motivational, compassionate skills are essential for an effective communication with patient and family members.

8.2.3) Patient and family support: the interface with the primary care team

There are several domains of physical, medical, mental and spiritual health, as well as social and daily life that GPs should monitor after a diagnosis of frailty. These include functionality, physical activity, exercise tolerance, appetite changes, memory loss, depressive feelings, sleep disorders, weight loss, control of co-morbidities, review of medication adherence, and non-prescription intake.

Three important goals are 1) to reduce symptoms that frequently occur due to the underlying conditions and morbidities and 2) to reduce the risk of complications from medical procedures, inappropriate prescribing and overdosing, risk of falls, and offering long term support after any discharge at the patient level, and 3) to empower and support family members and caregivers at the family level.

8.3) **Special role for Nurses**

8.3.1) Person-centred approach

Nurses use a holistic, individualized, person-centred approach to caring for a person including their physical, psychosocial and spiritual needs. Thus, nurses have a key role in the care of frail CV patients.

8.3.2) Intervention impacting on frailty aimed at maintenance of homeostasis

Nursing care plans are good at identifying issues where intervention may help to prevent or diminish frailty, and prevent or delay its adverse outcomes, for example assessment of nutrition, pharmacotherapy, adherence to treatment, falls risk, exercise, and mood and cognitive impairment (292,293). The goal of the care provided is to minimize further weight loss, loss of muscle mass and strength, and reduce fall risk factors to help maintain a state of homeostasis.

8.3.3) Case/care management

Nurses may also play the role of case/care manager or coordinator of the interdisciplinary care provided (292,294-296). This role includes: comprehensive assessment, care planning, information and referral, direct nursing care services and coordination and monitoring of services (296). Given the dynamic, multidimensional aspects of frailty and disability, a coordination of primary care practitioners, GPs, social workers, psychologists and several medical specialists and nurses is needed to take into consideration the person's individual circumstances and to tailor treatment recommendations to realistically attainable healthcare goals.

SUPPLEMENTARY DATA

Supplementary Data (online Annexe 3).

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