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EXPERT PANEL

Comprehensive Geriatric Assessment to Optimize the Management of Older Patients With Transthyretin Cardiac Amyloidosis

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ABSTRACT

Transthyretin cardiac amyloidosis (ATTR-CA) predominantly affects older adults with multiple chronic conditions, leading to significant physical, cognitive, and emotional challenges. New disease-modifying drugs are effective in early stages, prompting a shift toward comprehensive assessments, including functional capacity and quality of life. However, these assessments may not fully capture the complexity of older ATTR-CA patients, especially regarding frailty and mood disorders, which can influence symptom reporting. Thus, integrating comprehensive geriatric assessment tools into routine clinical practice may be crucial to detect early signs of frailty or functional impairment that could impact outcomes and mitigate futility and ageism in the decision-making process. This review highlights the importance of evaluating multimorbidity, disability, and frailty in older patients with ATTR-CA to optimize management strategies. (JACC Adv 2024;3:101123) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walking test

AF = atrial fibrillation

ATTR-CA = Transthyretin cardiac amyloidosis

CA = cardiac amyloidosis

CFS = Clinical Frailty Scale

CGA = comprehensive geriatric assessment

HF = heart failure

SPPB = Short Physical Performance Battery

TRANSTHYRETIN CARDIAC AMYLOIDOSIS: THE NEED FOR AN INTEGRATED APPROACH

Transthyretin cardiac amyloidosis (ATTR-CA) derives by the deposition of misfolded transthyretin (TTR) as amyloid fibrils in the heart interstitium. While wild-type ATTR is sporadic, aging-associated, and observed mostly in older men[1-4] and accounts for up to 15% of all cases of heart failure (HF) after the age of 80 years, hereditary ATTR is heterogeneous in presentation (from exclusively cardiac to neurologic or to a mixed phenotype).[2] Whenever red flags are present in a HF patient, the diagnosis must be promptly suspected to facilitate early diagnosis and improve outcomes.[5]

ATTR-CA is the quintessential form of HF with preserved ejection fraction in older individuals with upward and leftward shifts in the end-diastolic pressure volume relation leading to small ventricular chambers with high filling pressures: these patients present with multiple geriatric competing risks[3] such as ischemic heart disease, atrial fibrillation (AF), hypertension, diabetes, and stroke, which contribute to a higher risk of disability or functional impairment.[6,7] Multimorbidity and related polypharmacy increase the risk of drug-drug interactions with adverse events. Furthermore, advanced disease stage may be associated with worse neuro-autonomic dysfunction (particularly in hereditary ATTR) and need for diuretics, which are predictors of adverse outcomes[8,9] and are linked to increased risk of syncope and falls. Means of assessing the degree of this complexity and its long-term outcome is currently an unmet need. As such, patients with ATTR-CA may benefit from a tailored management strategy based on the comprehensive geriatric assessment (CGA), which takes into consideration a broad spectrum of clinical and functional domains (**Figures 1 and 2**).[3,10]

With the dawn of disease-modifying drugs[11] that are more effective in the early course of the disease, conventional clinical, instrumental, and laboratory data are nowadays integrated with functional capacity (typically, with the 6-minute walking test [6MWT]) and quality of life (with the Kansas City Cardiomyopathy Questionnaire). These tools, however, may not capture the complexity of older patients with ATTR-CA. Conditions such as sarcopenia, cerebrovascular disease, or osteo-muscular disease may reduce the walking distance, but with probably different prognostic impact.[12] The recent demonstration that concurrent frailty, depression, and anxiety also influence the way ATTR-CA patients perceive and report quality of life and their symptoms reinforce the need for routinely adopting a CGA to identify those elements that may affect clinical management and outcomes.[13-17]

HIGHLIGHTS

- Patients with ATTR-CA are almost exclusively older adults at diagnosis with multiple chronic conditions.
- A routine CGA is useful to delineate the clinical complexity (ie geriatric syndromes) of older ATTR-CA patients.
- A CGA that incorporates the expertise of geriatricians, cardiologists, neurologists, palliative care specialists, and others may help reduce ageism and futility and could be integrated in future clinical trials.

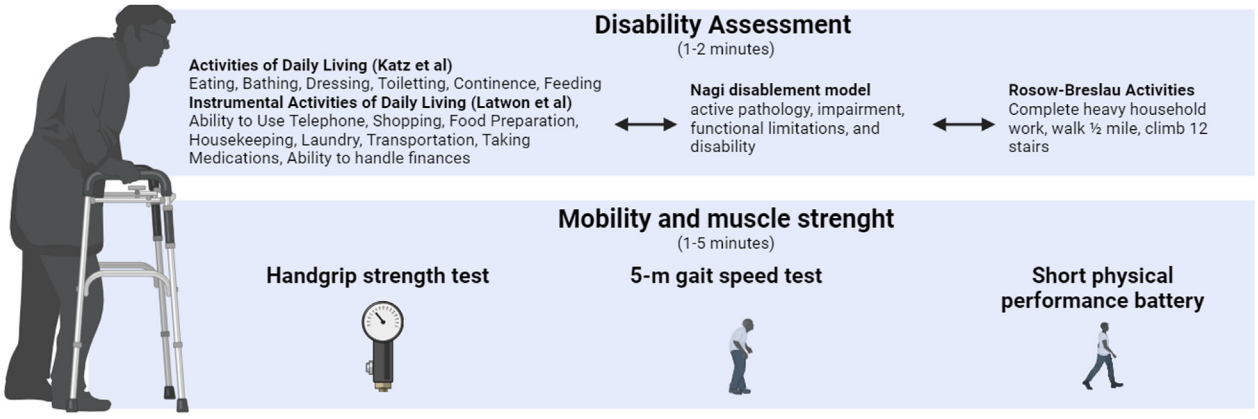
In this document, we aim to review the current knowledge on the 3 domains of multimorbidity, disability, and frailty, which may impact on the general health status of older patients and can be evaluated with CGA, and to speculate on how their routine evaluation may improve the management of patients with ATTR-CA.

THE CGA ESSENTIAL ITEMS

MULTIMORBIDITY AND DISABILITY. Multimorbidity (the coexistence of multiple health conditions[18]) and disability (defined by the U.S. Center for Disease Control and Prevention as any condition of the body or mind that makes it more difficult for persons to do certain activities and interact with the world around them)[19] represent 2 entities which are frequently associated with, but are not equivalent to, physical frailty (a decline of functional reserve of multiple physiological systems, resulting in impaired homeostasis with increased vulnerability to stressors).[20,21]

Multimorbidity, disability, and frailty are distinct concepts. Data from the Cardiovascular Health Study reported a stepwise increase of multimorbidity and decrease in functional status with worsening frailty phenotype, with an overall prevalence of frailty of 7%, with some degree of overlap, but not concordance, in the co-occurrence of frailty, multimorbidity, and disability.[20] Preliminary data on ATTR-CA suggest that overt disability ranges from 6.5% to 15% depending on the tools adopted (eg modified frailty index-11 item or Clinical Frailty Scale [CFS]),[17,22] but can rise to 69% if self-reported deficits

FIGURE 1 Functional and Disability Assessment in Older Patients Diagnosed With ATTR-CA



The figure illustrates the components of functional and disability assessment for older patients diagnosed with transthyretin cardiac amyloidosis (ATTR-CA). The assessment is divided into 2 main categories: disability assessment and physical performance. Created with BioRender.com.

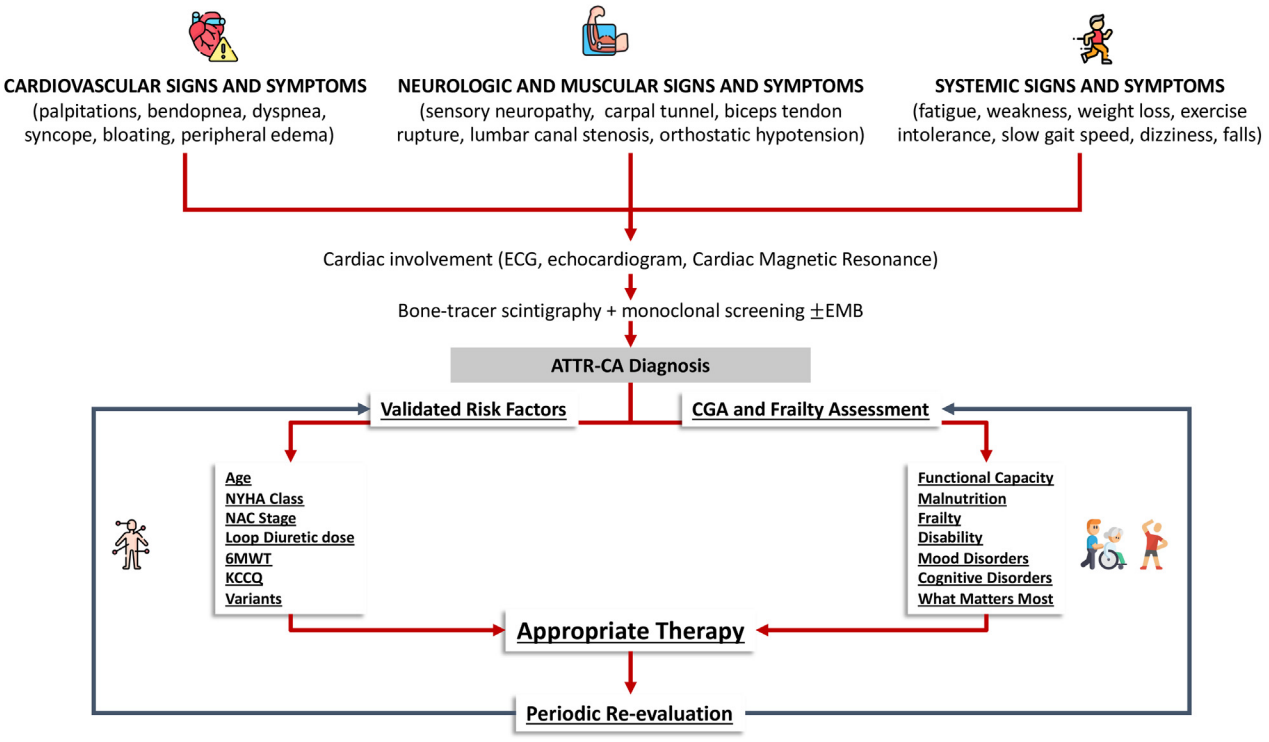
in instrumental activities are recorded.[23] Similarly, >50% of CA patients may have >3 cardiovascular risk factors.[23]

A functional assessment is warranted in older patients, irrespective of past medical history.[15] Patients with disability are at increased risk of death both in the presence and absence of multimorbidity[24] and are at increased risk for admission to a long-term care facility. Traditional assessment of functional status relies on self-reported ability to perform basic activities of daily living (bathing, dressing, transferring within one's home, using the toilet, maintaining continence, and feeding),[25] which are essential for maintaining independence at home, and instrumental activities of daily living, which explore higher-level abilities (using public transportations and telephone, managing finances and drug therapy, housekeeping, shopping, and preparing meals) and are essential to maintain independence out-of-home and in social life.[26] Other tools that can be used to assess functional performance are the activities identified by Nagi.[27] and by Rosow-Breslau[28] as summarized in **Figure 1**. However, use of competence in basic activities of daily living/instrumental activities of daily living has several limitations, including the fact that they are not objectively assessed—but self-reported or reported by caregivers—and that they have a "ceiling effect"—as they do best at identifying the most disabled minority.[29] Therefore, they may be unable to detect more subtle, preclinical forms of functional impairment, which pertain to the domain of physical frailty and can be identified by objective measures of physical performance.

FRAILTY ASSESSMENT. Frailty assessment has become an important topic for clinical research due to the aging of the population, its major implications for clinical practice and health care system, and the opportunity to slow or even reverse an accelerated functional decline.[6,30] Frailty is a decline of functional reserve of multiple physiological systems, resulting in impaired homeostasis with increased vulnerability to stressors.[20,21] Two main conceptual models of frailty have, so far, been identified:

1) Frailty phenotype,[20] which is defined by 5 key elements: weakness (grip strength in lowest quintile stratified by sex and body mass index), slow gait speed (gait speed in lowest quintile stratified by sex and height), low physical activity (low energy expenditure, based on physical activity questionnaire); rapid exhaustion (self-reported, based on 2 items from the Center for Epidemiological Studies Depression scale); unintentional weight loss (weight loss ≥5 kg over the past year). Frailty status is classified as non-frail (0 criteria present), pre-frail (1-2 criteria present), and frail (≥3 criteria present).
2) Frailty index,[31] which counts health deficits such as: signs, symptoms, diseases, disabilities, abnormal test results (eg, laboratory, imaging, electrocardiogram). A frailty classification is provided by the sum of health deficits present divided

FIGURE 2 Framework Proposal for the Integration of the CGA in the Management of ATTR-CA With a Detailed Overview of the Key Stages of ATTR-CA Management, From Work-Up to Diagnosis to Follow-Up Evaluation



6MWT = 6-minute walking test; ATTR-CA = transthyretin cardiac amyloidosis; CGA = comprehensive geriatric assessment; KCCQ = Kansas City Cardiomyopathy Questionnaire; NAC = National Amyloidosis Centre; EMB = endomyocardial biopsy; ECG = electrocardiogram.

by total number of deficits assessed, resulting in a continuous score between 0 and 1, with higher scores indicating greater frailty. Current cutoffs are controversial, although ≥0.25 has been proposed to indicate frailty.

Although more prevalent among older patients, frailty can affect individuals of any age, especially when a chronic condition is present.[6] Frailty is an independent risk factor for mortality across various settings and subpopulations, especially in patients with CV diseases.[6,32,33] The strong association may in part be explained because frailty and CV diseases share several risk factors, such as chronic inflammation.[33] In HF, frailty is also associated with a reduced probability of receiving guideline-directed medical therapy[34] and with increased health care costs.[6] Therefore, a routine assessment of frailty may help deliver tailored care, improve outcomes, and assist in driving primary and secondary prevention. Two recent studies confirmed a negative prognostic impact of frailty also in patients with ATTR-CA using the CFS,[22,23] independently of disease-modifying therapy.[22] The reported prevalence of frailty in community-dwelling adults ranges between 12 and 24%, depending on the different tools adopted,[35] with higher prevalence among women,[35] low-income individuals, or ethnic minorities.[6] The results of frailty assessments or CGA in general are usually handled in a dichotomous fashion (eg futility or proceeding with a treatment). While evidence on ATTR-CA is still missing, especially on the possibility to restratify prognosis based on functional status to drive new treatments, useful considerations may be derived from neighboring clinical contexts such as valvular heart disease (eg aortic stenosis[36]). Older patients with advanced disease stage may limit their physical activities to lower intensity levels and appear asymptomatic at common basic tasks but be highly symptomatic (and even limited by dyspnea) on exertion. Lower extremity performance, or disability in the activities of daily living, could thus be useful markers to restratify disease stage on the opposite sides of the disease spectrum to reduce ageism or

TABLE 1 Example of Major Tools to Assess for Frailty, Disability, and Perform a Comprehensive Geriatric Assessment

	Assessed Characteristics	Reference Values	Resources	Time Required to Perform
Standardized Comorbidity Assessment				
Charlson comorbidity index	A comorbidity index based on age and 16 comorbidities	Higher scores are associated with higher number of comorbidities	Trained healthcare personnel Or caregiver Specific questionnaires	2-3 min
Elixhauser Comorbidity Index	A comorbidity index based on 30 comorbidities	Higher scores are associated with higher number of comorbidities	Trained healthcare personnel Or caregiver Specific questionnaires	2-3 min
Frailty (preclinical disability)				
Frailty phenotype	Weakness, slow gait speed, low physical activity, exhaustion, unintentional weight loss	Non-frail (0 criteria present), pre-frail (1-2 criteria present), and frail (≥3 criteria present)	Trained healthcare personnel Specific questionnaires	10 min
Short Physical Performance Battery (SPPB)	Balance, weakness (chair raise), gate (4 m distance)	0 (worst)-12 (best) ≥10 excellent performer 7-9 intermediate performer 0-6 poor performer	Trained healthcare personnel Chronometer	5-6 min
5-m gait speed test	Gate (5 m distance)	>0.83 m/s: good performance	Trained healthcare personnel Chronometer	1-2 min
Handgrip strength test	Handgrip assessment with dedicated tools	Men:>30 kg; women: >20 kg	Trained nurse dynamometer	<1 min
FRAIL scale	Assessment of fatigue, resistance, ambulation, illnesses, loss of weight	≥3/5 criteria met indicates frailty; 1-2/5 indicates pre- or intermediate-frailty; 0/5 indicates non-frail	Trained healthcare personnel Specific questionnaires	10 min
Frailty index (deficit model)	Counts health deficits: signs, symptoms, diseases, disabilities, abnormal test results	Sum of health deficits present divided by total number of deficits measured. It is a continuous score between 0 and 1	Trained healthcare personnel Or caregiver Specific questionnaires	10 min
Clinical Frailty Scale (CFS)	Semiquantitave scale	From 1 (very fit) to 9 (terminally ill). Frailty: CFS≥4	Trained healthcare personnel Or caregiver Specific questionnaires	1-2 min

Continued on the next page

futility (eg functionally limited patients in early stages vs robust patients at advanced stage). Factors potentially useful in frailty assessment are:

Lower extremity function and physical performance. Lower extremity function can be considered a proxy for frailty. Gait speed and other physical performance tasks have a prognostic power in older patients and enrich the health assessment beyond cardiovascular (CV) risk factors,[37] chronic comorbidity, and disability.[25] The Short Physical Performance Battery (SPPB) measures lower extremity physical function with 3 performance tasks that generate a 0 to 12 score, with higher values indicating better functioning. The SPPB is an independent predictor of the incident risk of disability in nondisabled, community-living individuals >70 years of age and could thus be considered as a marker of "preclinical" disability.[38] Moreover, SPPB scores <6 double the risk of all-cause mortality and of adverse CV outcomes.[39,40] Gait speed alone is a powerful predictor of outcome in CV diseases, with slow walkers[41] at increased risk of mortality during the follow-up of with coronary artery disease[42] or after elective cardiac surgery.[43] The 6MWT is often used to assess functional capacity in a wide variety of CV conditions, such as chronic HF, coronary artery disease, and elective cardiac surgery.[44,45] However, measurement of the 6MWT requires a long walking path, not always achievable in hospital. In addition, there is only a signal toward worse 6MWT in frail patients with HF and preserved ejection fraction.[46] The recently observed good correlation between gait speed and 6MWT in patients referred to cardiac rehabilitation[47] suggests that gait speed may be an alternative to the 6MWT. A list of tools to assess lower extremity function is summarized in **Table 1**.

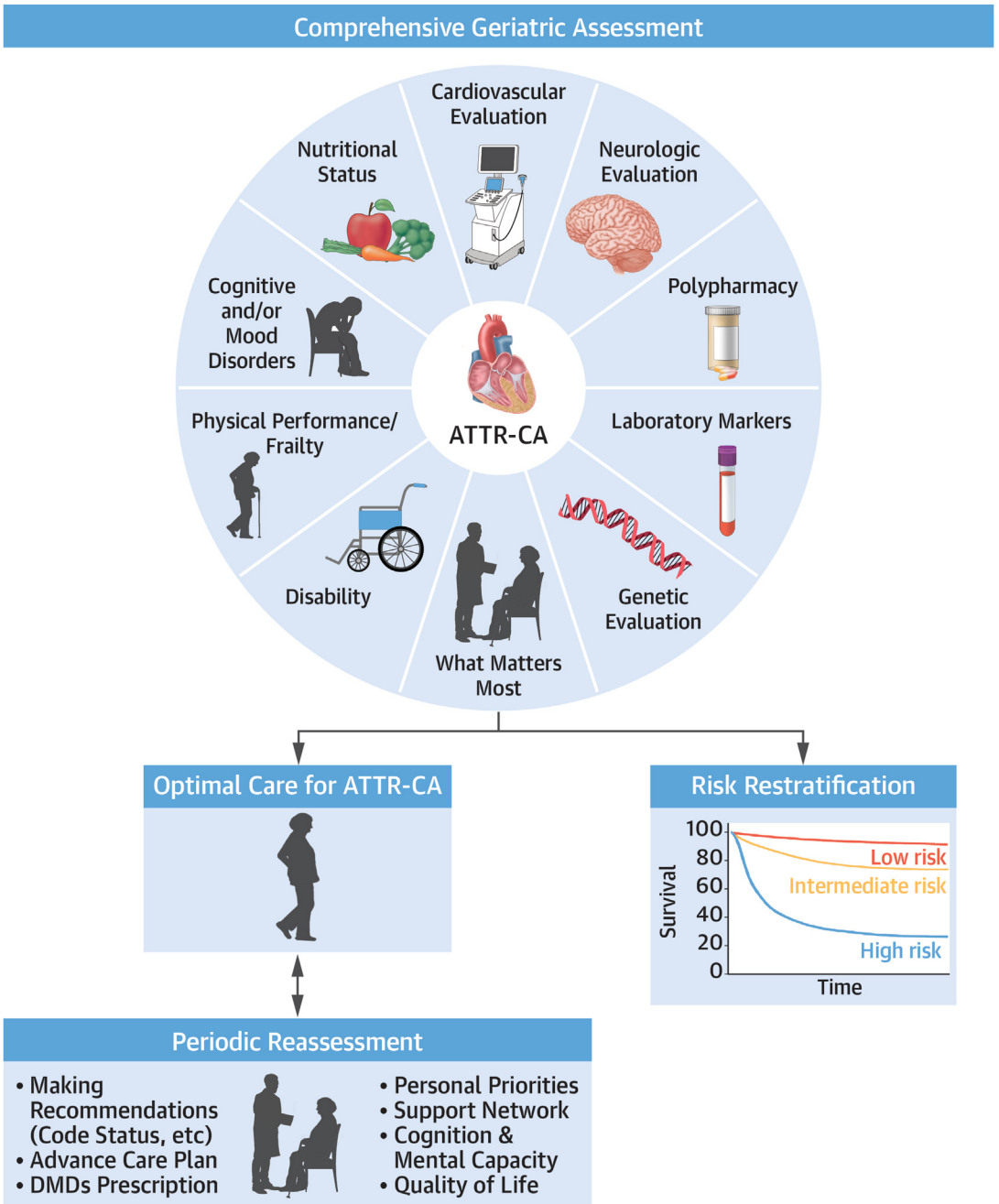
Malnutrition. The diagnosis of malnutrition is made when unintentional weight loss (>5% within past 6 months), or low body mass index (<22 kg/m^2 if >70 years), or reduced muscle mass (from body composition analysis), coexists with reduced food intake or assimilation or inflammation (acute or chronic disease-related).[48]

Prevalence of overt malnutrition is around 3% in community-dwelling adults[49] but can rise to more than 60% in ATTR-CA,[23] where it is associated with a

TABLE 1 Continued

	Assessed Characteristics	Reference Values	Resources	Time Required to Perform
Malnutrition				
Global Leadership Initiative on Malnutrition (GLIM)	Unintentional weight loss (>5% within past 6 mo, or >10% beyond 6 mo), Low body mass index (BMI) (<20 kg/m^2 if <70 y, or <22 kg/m^2 if >70 y), reduced muscle mass (according to validated body composition techniques), and 2 etiologic criteria: reduced food intake or assimilation (≤50% of energy requirements >1 week, or any reduction for >2 weeks, or any chronic gastrointestinal condition that adversely impacts food assimilation or absorption), and inflammation (acute disease/injury or chronic disease-related)	It is proposed that the diagnosis of malnutrition is based upon at least 1 phenotypic and 1 etiologic criterion.	Trained healthcare personnel Or caregiver Specific questionnaires	3 min
Mini Nutritional Assessment – short form (MNA-SF)	Based on appetite, weight loss, mobility, acute illnesses, neuro/psychologic disease, BMI, calf circumference https://doi.org/10.1007/s12603-021-1601-y	Scores 12-14: no malnutrition 8-11: at risk of malnutrition 0-7: malnutrition present	Trained healthcare personnel Or caregiver Specific questionnaires	3 min
Geriatric Nutritional Risk Index (GNRI)	GNRI = 14.89 × serum albumin (g/dL) + 41.7 × (present body weight/ideal body weight)	No risk (GNRI >98), low risk (GNRI 98-92), moderate risk (GNRI <92-82), or major risk (GNRI <82)	Trained healthcare personnel Or caregiver Specific questionnaires	<1 min
Cognitive decline and mood disorders				
Montreal Cognitive Assessment (MoCA)	Domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.	Sum all subscores. Add +1 for a person who has had 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal. A final total score below 26 is indicative of mild cognitive impairment	Trained healthcare personnel Specific questionnaires	10-15 min
Mini Mental State Examination (MMSE)	Three domain structure: executive functioning, memory, and attention	Scores of >25/30 are considered normal, 21-25 as mild, 10-20 as moderate and below 10 as severe impairment. Can be corrected by education	Trained healthcare personnel Specific questionnaires	7-10 min
Saint Louis University Mental Status Exam	Attention and working memory Cognition, executive functioning Language, mental health Reasoning/Problem solving	The maximum score is 30 points, cutoff scores for dementia or mild neurocognitive impairment are based on the education level of the patient (high school and above or less than high school), ≥ 27 normal.	Trained healthcare personnel	7 min
Mini-Cog	Memory and visuoconstructional skills	Word recall: 0-3 points Clock drawing: 0-2 points Total score: 0-5 points (<3 has been validated for dementia screening)	Trained healthcare personnel Specific questionnaire	5 min
Geriatric Depression Scale (GDS)	Depression	Depending on the version, depression has different cutoff values. In the 15-item GDS, a score >5 points is suggestive of depression.	Trained healthcare personnel Or caregiver	3-5 min
Comprehensive geriatric assessment				
Multidimensional Prognostic Index	8-item score	Low risk: ≤0.33; intermediate risk: 0.34-0.66; high risk ≥0.67	Trained healthcare personnel Specific questionnaires	25-30 min
Short Emergency Geriatric Assessment	13-item score	Not frail: score ≤8; frail 9-11, very frail: score >11	Trained healthcare personnel Specific questionnaires	10 min
Vulnerable Elders Survey 13 scale	Age, self-rated health, activities of daily living, difficulty in special activities	Score ≥3: vulnerable elderly	Trained healthcare personnel Specific questionnaires	5 min

CENTRAL ILLUSTRATION **Providing Optimal Medical Care for Patients With ATTR-CA From Diagnosis, to Risk Stratification, and Follow-Up**



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Includes key elements of the multidisciplinary evaluation with the comprehensive geriatric assessment (CGA). DMD = disease-modifying drug.

TABLE 2 Factors Which Should Support Consideration of Medication Deprescription

Clinical scenarios which may lead to medication deprescription [70]
Onset of adverse drug reaction
Polypharmacy (≥5 drugs)
Prescription of drugs following adverse drug reactions (prescription cascade) which are interpreted as a new medical condition
Reduced life expectancy (new precipitating event, diagnosis of another terminal condition [eg cancer])
Tool to assist choice of deprescription [71]
Screening Tool of Older Persons Prescriptions in Frail criteria
1) End-stage irreversible pathology
2) Less than 1-y survival
3) Severe functional impairment or severe cognitive impairment or both
4) Symptom control is the priority rather than prevention of disease progression
The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:
1) Risk of the medication outweighing the benefit
2) Administration of the medication is challenging
3) Monitoring of the medication effect is challenging
4) Drug adherence/compliance is difficult

worse prognosis.[50,51] Thus, malnutrition should be systematically screened for and managed with a dietitian support.

Cognitive and mood disorders. The prevalence of cognitive impairment increases with age. Recognizing cognitive disorders is central in health assessment of older patients since they have several clinical implications, including adherence to prescriptions as well as the risk of delirium, which may have a substantial impact in case of hospitalization. Recently, cognitive impairment has been found associated with mortality and risk of rehospitalization in HF patients.[52] Therefore, cognitive performance should be assessed objectively with a validated instrument, such as the Mini Mental State Examination or Montreal Cognitive Assessment.[53]

Mood disorders in the elderly are a serious and common health concern leading to unnecessary suffering, impaired functional status, increased CV morbidity and mortality, and health care resources consumption.[54] Chronic diseases, chronic pain, socioeconomic disadvantage, or recent widowing are all risk factors for depression with relative increase in CV risk.[55] In ATTR-CA, depressive symptoms are linked to worse perceived quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire.[13,14]

TABLE 3 Investigations and Interventions Which May Help Improve a Comprehensive Assessment

Cardiopulmonary exercise test	Better assessment of symptoms. Define the cardiac and pulmonary contributions to exercise intolerance.
Cardiac rehabilitation or prehabilitation	Interventions targeting mobility, balance, strength, resistance, and endurance. Early evidence on prehabilitation (home- or center-based multidomain interventions started before treatment) is increasing especially is surgical/interventional settings, but data are lacking in ATTR-CA patients.
Drug prescription or deprescription	Optimization of pharmacological therapy based on the CGA to increase benefit (clinical, quality of life, etc.) while reducing potential adverse drug reactions.
Dietary interventions	Interventions aimed at addressing malnutrition, sarcopenia, cachexia, sarcopenic obesity etc.
Mood and cognition	Dedicated intervention to treat depression, mood disorders related to primary diagnosis, social frailty or behavioral disorders related to cognitive impairment.

ATTR-CA = transthyretin cardiac amyloidosis; CGA = comprehensive geriatric assessment.

THE CGA IN OLDER PATIENTS WITH ATTR-CA TO OPTIMIZE MANAGEMENT

Almost all patients with CGA are older adults and ATTR-CA almost exclusively affects adults over the age of 60 years. As such, patients with ATTR-CA may benefit from a CGA.[56-58] Prompt recognition of geriatric syndromes (functional decline, explained and unexplained falls, pressure ulcers, malnutrition, incontinence, cognitive impairment, or depressive symptoms) and of polypharmacy allow for earlier tailored care, with improved quality of life and outcome.[59-62] Although the CGA is a diagnostic process, the term is often used to include both evaluation, management, and follow-up.[63] The CGA and Multidimensional Prognostic Index,[64] as well as other frailty tools,[33,65] help identify patients who may benefit as opposed to those who are at high risk of futility or potential harm from treatment in several CV diseases.[33,66] (Table 1).

Management of ATTR-CA should be customized according to an interdisciplinary evaluation and considering functional status, life expectancy, patient's priorities, with the primary aims of preventing functional decline and improving quality of life and outcome (Central Illustration).[66] Different health care plans can be developed, including medication deprescription and early access to palliative care services (the latter endorsed by current European and American HF guidelines).[54] Adverse drug reactions, polypharmacy (≥5 drugs), prescription cascade, and reduced life expectancy (due to a precipitating event or diagnosis of another terminal condition [eg cancer]) may lead to therapy re-evaluation, deprescription, and advance care planning (Table 2).[67] Screening Tool of Older Persons Prescriptions in Frail (Table 2) is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients, once they are all met.[68]

Identifying polypharmacy is crucial, especially in older frail or functionally impaired populations. Strategies like medication review, education, and digital tools effectively reduce polypharmacy. However, the impact of deprescribing on outcomes remains uncertain, with mixed findings on quality of life and hospitalizations.[69] ATTR-CA patients, particularly at advances stage, may have reduced ejection fraction, AF, and compensatory higher heart rate, and be symptomatic for dyspnea; given the low and fixed stroke volume irrespective of their ejection fraction, the cardiac output is often low and as a result so is their blood pressure. This limits the ability to prescribe typical HF medications and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor or beta-blockers, which are usually not well tolerated: for instance, the use of beta-blockers remains controversial[70] and is not necessarily associated with improved outcome.[71] In addition, orthopedic manifestations (eg lumbar spinal stenosis and joint involvement or replacement) can often be more debilitating than the cardiac issues especially when concomitant with neuropathy which impairs patients' gait and can lead to falls irrespective of blood pressure or medications. Finally, the prevalence and incidence of AF is higher than in other cardiomyopathies, in part attributable to large atria, atrial infiltration by amyloid, and advanced age of patients.[7,72] Given the high incidence of thromboembolism, patients are recommended to take anticoagulation irrespective of their $CHA_2DS\text{-}VASC_2$ score. However, given their gait disturbances and risk for falls, bleeding risk may be increased. For this reason, common medications currently approved for the management of HF may not always be prescribed in this setting.[73] Tailoring therapy is crucial, especially at advanced stages, for adequate symptom control and quality of life.

Management of ATTR-CA aims to relieve the generally severe symptoms of disease and, whenever feasible and possible, to modify its course using newer ATTR disease-modifying therapies. Among these, tafamidis—an oral TTR stabilizer that reduces TTR tetramer dissociation—was proven to reduce mortality, CV hospitalizations, decline in 6MWT distance and in quality of life after 30 months in ATTR-CA.[11] Moreover, although tafamidis can slow the decline in various clinical parameters and quality of life, many patients may still experience disease-related symptoms and limitations while on treatment. Therefore, the cost-effectiveness of tafamidis is still a matter of debate and in some countries, reimbursement has been excluded for patient in advanced disease stage (New York Heart Association 3). Similar concerns exist for other drugs for ATTR-CA, such as acoramidis,[73-75] or others under investigation like vutrisiran[76,77] and eplontersen.[78]

TABLE 4 General Recommendations for Older Patients Diagnosed WithATTR-CA

Patients with either hereditary (v) or wild-type (wt) ATTR-CA should receive a comprehensive geriatric assessment (CGA). Multidomain health status, including frailty, should be assessed irrespective of age at diagnosis and is to be used to monitor disease evolution and the potential benefits of therapy.
Submaximal functional capacity should be assessed at diagnosis with the 6-min walking test as distance walked and as gait speed in m/s (either within the Short Physical Performance Battery [SPPB] test or equivalent); which can be used preferentially in environments with limited spaces.
Malnutrition should be routinely assessed with validated tools as part of CGA, to identify and possibly correct precipitating factors for frailty (eg sarcopenia).
Mood disorder domain should be explored both in v- and wt ATTR-CA to detect cognitive impairment and/or depressive symptoms that negatively impact on adherence to disease-modifying therapy, reduce health status (KCCQ) and are independent risk factors for increased cardiovascular morbidity and mortality.
Patients may be screened also for early disability (eg, loss of ADLs), to provide better support to help them maintain their independence (eg, rehabilitation), or for advanced and potentially irreversible frailty/disability, to provide optimal advance care plans, including palliative care.

ADLs = activities of daily living; KCCQ = Kansas City Cardiomyopathy Questionnaire.

Therefore, beyond shared communication with patients and caregivers, a formal and comprehensive CGA (**Table 1**) to provide information on residual life-expectancy and the potential for therapeutic benefit, is necessary to help specialists select the most appropriate patients for the new, but expensive, therapeutic regimens, avoiding 2 opposing risks: on one hand, futility of interventions not justified by a reasonable survival and adequate quality of life and, on the other hand, ageism, ie, the adoption of the stereotypes, prejudice, and discrimination based simply on chronological age.[79] As an example, since CFS is independently associated with outcomes, frailty assessment could usefully restratify the clinical outcomes in patients either 80+ years of age or highly symptomatic (NYHA functional class >III), for whom disease-modifying therapy may not achieve the benefits deemed important to the patients and thus be considered futile. Indeed, beyond the personal suffering, the public costs of ageism should not be underestimated.[80] Moreover, since clinical trials on ATTR-CA will likely recruit progressively older patients, inclusion of functional parameters and related patient-reported outcomes in trial design may help generalize results to real-world patients.[81]

Advanced HF requiring high-dose diuretics is characterized by frequent hospitalizations, poor quality of life, and a prognosis comparable to malignant diseases[82]: in this condition, advance care planning and indicated palliative care are still an unmet need. Given that physically frail HF patients often have palliative care needs,[83] advanced frailty

and disability could be used as a screening tool to advocate referral for palliative care.[53]

Table 3 summarizes potentially useful interventions stemming from the CGA (cardiac rehabilitation or prehabilitation,[30,84] drug intervention,[85] nutrition interventions[86] etc). A framework for CGA that might drive the therapeutic management and might be used as a follow-up toolkit is outlined in **Figure 2** and **Table 4**.

CONCLUSIONS

The diagnosis rate of ATTR-CA is likely to increase soon, thanks to increasing disease awareness and application of noninvasive diagnostic tools with superior sensitivity and specificity. ATTR-CA specialists and geriatricians should be part of the same team to assess this condition: although there is a signal for lower disease severity at first medical contact, older age at diagnosis, multimorbidity, and potential disability are a call to screen for geriatric syndromes and frailty. Overall, a CGA integrated within the baseline medical assessment (irrespective of the tools used) might provide further information regarding the status of patients diagnosed with ATTR-CA and help guide appropriate therapy initiation and monitoring.

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