Journal of the American Heart Association

MINI-REVIEW

High Prevalence of Geriatric Conditions Among Older Adults With Cardiovascular Disease

Amal Aïdoud, MD; Wassim Gana, MD; Fanny Poitau, MD; Camille Debacq, MD; Victoire Leroy, MD; Jacques-Alexis Nkodo, MD; Pierre Poupin, MD; Denis Angoulvant, MD-PhD; Bertrand Fougère, MD-PhD

ABSTRACT: As the population ages, the global cardiovascular disease burden will continue to increase, particularly among older adults. Increases in life expectancy and better cardiovascular care have significantly reshaped the epidemiology of cardiovascular disease and have created new patient profiles. The combination of older age, multiple comorbidities, polypharmacy, frailty, and adverse noncardiovascular outcomes is challenging our routine clinical practice in this field. In this review, we examine noncardiovascular factors that statistically interact in a relevant way with health status and quality of life in older people with cardiovascular disease. We focused on specific geriatric conditions (multimorbidity, polypharmacy, geriatric syndromes, and frailty) that are responsible for a major risk of functional decline and have an important impact on the overall prognosis in this patient population.

Key Words: aging; older adults ■ cardiovascular disease ■ clinical decision-making ■ frailty ■ geriatric cardiology ■ geriatric syndrome ■ polypharmacy

Revolutionary therapeutic advances (eg, the combination of myocardial revascularization and better drug treatment) have gradually reshaped the clinical course of cardiovascular disease (CVD). In the 1990s, most patients with CVD died of cardiac causes. Since then, improvements in care have led to an increase in noncardiac mortality, irrespective of the severity of CVD.[1] Once fatal, CVD has become a chronic disease. These advances have been so significant that the mortality rate in patients with CVD is now much the same as in the general population.[2] As a result, the number of patients with chronic CVD has increased and the profile of current CVD survivors has changed: they are more likely to be old and frail and to have multiple comorbidities.[3] Given that mortality has long been the most common CVD outcome, survival has been the primary criterion for assessing the effect of cardiac care. However, survival does not necessarily constitute a return *ad integrum*, and additional determinants (such as quality of life) must be considered. Cardiac care with more technical interventions in complex, heterogeneous, frail patients thus faces a conundrum: how can we both improve life expectancy and maintain quality of life? One can hypothesize that comprehensive care will be facilitated by taking account of aging phenotypic profile and geriatric factors that can interact with overall cardiac outcomes to base medical decisions on an accurate assessment of the risks and benefits of an intervention. Older people with CVD are particularly likely to develop geriatric conditions, which are powerful but often overlooked noncardiovascular prognostic factors that are responsible for a range of adverse events.

In this review, we describe the aging-related burden in 4 common geriatric conditions: multiple comorbidities, polypharmacy, geriatric syndromes (GSs), and frailty, all of which statistically contribute to adverse noncardiac outcomes in older people with CVD. We hypothesized that a better understanding of geriatric conditions and their prevalence would help to resolve

Correspondence to: Amal Aïdoud, MD, Division of Geriatric Medicine, Tours University Hospital, 2 Blvd Tonnellé, F-37000 Tours, France. Email: amal.aidoud@univ-tours.fr

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms	
GS	geriatric syndrome

the dilemma faced when managing older patients with CVD. Our ultimate goal is to help clinicians deal with complex cases among older patients and thus choose or continue the most appropriate management approach.

AGING, CVD, AND THE OVERLAP WITH GERIATRIC CONDITIONS

Most definitions of aging refer to a progressive decline with age. It may be tempting to imagine that the decline is always linear (ie, a scenario in which very old adults are "highly damaged" and younger ones are "minimally damaged"). This simplistic view can affect the choice of optimal care by causing the physician to ignore important aspects of biological aging.

Although the biological causes of aging have not yet been clearly elucidated, 9 cellular and molecular hallmark factors have been identified: the accumulation of DNA damage, telomere shortening, epigenetic alterations, loss of proteostasis, deregulation of nutrient sensing, mitochondrial dysfunction (responsible for oxidative stress), cellular senescence, stem cell depletion, and impaired intercellular communication. These damaging events are associated with a chronic, low-grade inflammatory state referred to as "inflamm-aging".[4] In unhealthy aging, the body fails to compensate for this inflammatory burden effectively. In contrast, healthy aging is linked to a lower frequency of inflammatory responses and more effective anti-inflammatory strategies. This overall imbalance towards persistent chronic inflammation results in insufficient tissue repair and tissue degeneration. The resulting phenotypic changes are characterized by increased susceptibility to aging-related diseases (including CVD), a high risk of concomitant age-related chronic diseases, decreased stress tolerance, the emergence of GSs, a worse response to treatment, and low functional capacity.

It is now widely accepted that chronic, low-grade inflammation contributes to the pathogenesis of CVD and atherosclerosis, independently of other cardiovascular risk factors.[5] From this perspective, CVD in the older adult is consistent with the concept of compromised biological aging (ie, a high basal level of inflammation associated with pathological phenotypic changes). These issues have long been left to geriatricians but—given the current profile of patients with CVD—need to be highlighted. We provide an overview of the burden of geriatric disorders in patients with CVD versus those in the general population.

PREVALENCE OF GERIATRIC CONDITIONS IN OLDER PATIENTS WITH CVD

Older adults with CVD usually have other chronic or multimorbid conditions, which is responsible for a significant drug burden.[6] Furthermore, functional decline and complex GSs are major concerns in the management of older adults with CVD.[7] Given that current CVD management is being structured to respond more specifically to the health needs of older adults, we shall suggest a number of guidelines on what to look for when managing an older patient with CVD. The prevalence and prognosis of each index geriatric condition are summarized in Table 1.

Chronic Diseases and Multimorbidity

It has been estimated that between 55% and 98% of older adults aged 60 years and over have at least 2 chronic diseases (ie, multimorbidity).[8,9] CVDs are the most common conditions in multimorbid patients, and ischemic heart disease is among the most prevalent individual chronic diseases.[8,10,11] Almost all older adults with CVD have multiple comorbidities. In 1 study, only 17% of older patients with coronary heart disease had no other chronic diseases.[12] It is estimated that 70% of people over 70 years old will develop CVD and that more than two thirds will also have associated noncardiovascular comorbidities.[6] In a large national survey of Medicare beneficiaries aged 65 years, CVD frequently coexisted with diabetes (37%–47%), anemia (39%–51%), and arthritis (41%–46%).[13] Clinicians caring for old patients with CVD are therefore more likely to encounter CVD as part of a constellation of chronic diseases.

Polypharmacy

The treatment of multiple comorbidities often leads to polypharmacy (defined typically as taking 5 or more medications). The results of the Survey of Health, Ageing, and Retirement in Europe study showed that the prevalence of polypharmacy among adults aged 65 or over in Europe and Israel ranged from 26.3% to 39.9%.[14] Despite significant progress in CVD prevention, drug-based approaches still constitute the cornerstone of CVD management. Based on the combination of 4 drug classes (statins, antiplatelets, β-blockers, and angiotensin-converting enzyme inhibitors), strict adherence to clinical guidelines will bring individuals closer to polypharmacy. Cardiovascular drugs are the most frequently prescribed treatments in older people. Having

Table 1. Overview of Common Health Problems Affecting Older Adults With CVD

Geriatric conditions	Definition	Prevalence in adults ≥65 y	Relevant epidemiology data in older adults	Prognosis and clinical implication
Multimorbidity	Coexistence of 2 or more chronic diseases	30% to 83%	• Various combinations of chronic diseases • Cardiovascular comorbidities are the most frequently reported	↓ Functional status and QOL ↑ Polypharmacy ↑ Falls ↑ Use of care ↑ Mortality
Polypharmacy	Simultaneous use of ≥5 medications Excessive polypharmacy: ≥10 drugs	26.3% to 40%	• Excessive polypharmacy ≈ 10% • Incidence at 3 y: 53%–87% • Cardiovascular medications are the most frequently reported	↑ Adverse drug reactions ↑ Institutionalization Exacerbation of other medical conditions ↑ Hospital admissions ↑ Mortality
Geriatric syndrome	Impaired function because of cumulative, synergistic effects on multiple organ systems	10% to 60% (at least 1 GS)	• Prevalence in inpatients with acute CVD: 60%	↑ Frailty ↓ Functional status and QOL ↑ Hospital admission ↑ Mortality
Frailty	A state of reduced physiological reserve in multiorgan systems, increasing susceptibility to stressful events	10%	• CVD: 10%– 60%; severe CAD: 50% • An important prognostic determinant in older patients with CVD	↓ Functional status and QOL ↑ Falls ↑ Hospital admission ↑ Mortality

CAD indicates coronary artery disease; CVD, cardiovascular disease; GS, geriatric syndrome; and QOL, quality of life.

CVD is associated with the highest levels of drug prescription. In a retrospective study of older patients with CVD and who were admitted to a cardiology department, the prevalence of polypharmacy (95%, and even 69% for excessive polypharmacy [≥10 drugs]) far exceeded that observed in the general population. On average, patients were treated with 11.6±4.5 drugs at home.[15] Clinicians face new challenges, including the interplay between individual chronic disease strategies that can compete with each other and create barriers to the provision of coordinated care.

Geriatric Syndromes

The GS concept requires a shift from the conventional medical use of the term "syndrome" (ie, a set of symptoms with a single underlying cause). GSs result from the cumulative, synergistic effects of discrete diseases on multiple organ systems; when the body can no longer compensate, the effects are finally expressed as a single symptom[16] (Figure 1). Just as heart failure is an expression of the heart's limited ability to tolerate additional stress, GS is the failure of postural status for falls or failure of brain function for delirium. GSs commonly include gait disorders, falls, cognitive syndromes, delirium, depression, pressure ulcers, sarcopenia, sensory impairments, chronic pain, sleep disorders, urinary incontinence, and frailty (discussed individually in the next paragraph).[16]

The effects of GS on health care are well documented. Table 2 summarizes the main results for the GSs that have been most studied in cardiovascular research. Older patients with CVD are particularly at risk.[17,18] In a large US Health and Retirement Study survey of adults aged 65 years or over, 25% of those with congestive heart failure or CVD had severe urinary incontinence or at least 1 fall.[19] The prevalence of GS is linearly related to the number of comorbidities, particularly in older adults with CVD. Patients with ischemic heart disease and heart failure have an average of 2 GSs (particularly pain, urinary incontinence, and falls). Older adults with CVD and 2 or more other diseases were twice as likely to develop GS as those with CVD alone.[18] Conversely, clinical data have also suggested that the presence of GS increases the CVD risk.[20] Despite the contributory role of GSs in older people with CVD, these syndromes are still underrecognized and often overlooked.

Frailty

Frailty is a complex and emerging GS that is increasingly used in primary, acute, and specialist care. Frailty is a condition of particular interest that may represent a transitional phase between successful aging and disability, a new, more accurate and tailored approach to biological age. In this sense, we propose to address this GS in a more precise way.

Frailty is a vulnerable state characterized by the accumulation of impairments in several interdependent systems, a decrease in physiological reserves, and the failure of homeostatic mechanisms in response to low-level stress.[21] In other words, frailty corresponds to a premorbid state that reflects "precompromised" biological aging (Figure 1).[16] The concept of frailty has been widely integrated into guidelines on CVD management. As a result, the European Society of Cardiology's 2021 guidelines placed particular emphasis on frailty

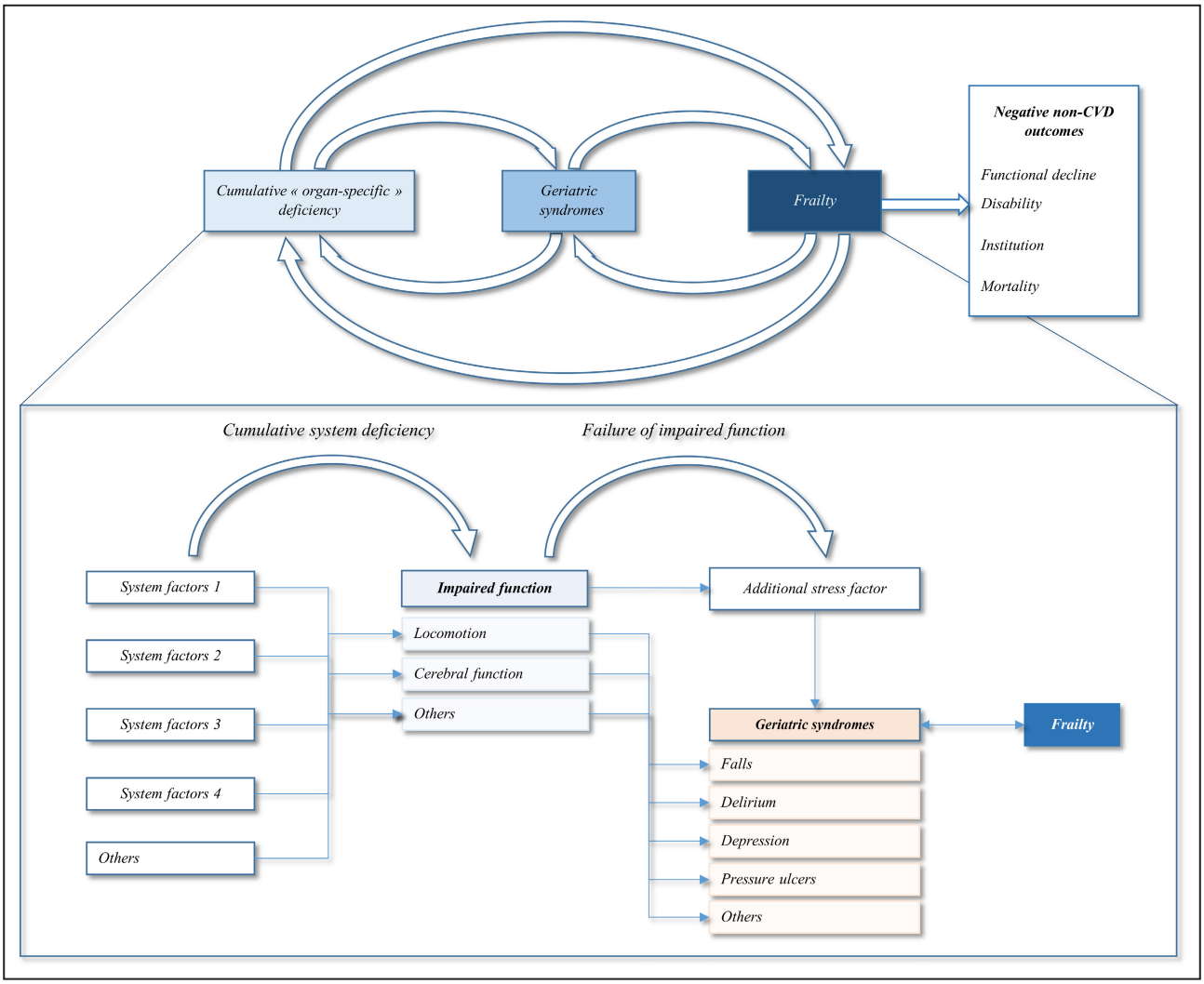

Figure 1. Conceptual Definition of Geriatric Syndrome.
Geriatric syndromes result from the cumulative, synergistic effects of discrete diseases on multiple organ systems; when the body can no longer compensate, the effects are finally expressed as a single symptom. The cumulative system impairments result in impaired function. When these impairments accumulate or when additional stress is present, function is lost and a geriatric syndrome develops. The accumulation of geriatric syndromes leads to an overall premorbid state (ie, frailty).

conditions in adults with atherosclerotic CVD and thus demonstrated the growing concern and need for individualized actions.[22]

Numerous tools have been developed to account for frailty in clinical practice, some focusing on physical frailty (eg, the Fried frailty scale), and others based on the accumulation of deficits that place individuals at increased risk for adverse outcomes (eg, the Rockwood frailty index). Both of these scores have additional prognostic value in patients at high risk for CVD because they are associated with increased CVD events and mortality, independent of CVD risk factors.[23,24] Nevertheless, these scales do not necessarily identify the same individuals. The frailty phenotype does not require prior clinical assessment, making it a relevant tool for stratifying the profile of older patients with CVD at baseline. However, it does not provide guidance for interventions, unlike the Rockwood frailty score, which identifies the underlying causes of the risk state as a modifiable exposure. Depending on the definition and scale used, the overall prevalence of frailty is ≈10% among community-dwelling people aged 65 years and over[25] and 10% to 60% among older patients with CVD.[26,27] Sex differences have been identified in the prevalence of frailty and its prognostic impact. The clinical literature shows that women almost always have a higher prevalence and risk of frailty, a more compromised state, whereas they have a lower risk of mortality, the so-called male–female healthy survival paradox. Frailty is highly prevalent in older women with CVD, ≈1.6 times more than in men.[28] Nevertheless, the factors responsible for this frailty-mortality paradox

Table 2. Epidemiology of Geriatric Syndromes

Geriatric syndromes	Definition	Prevalence in adults ≥65 y*	Prevalence in hospital	Relevant data on CVD in older adults
Delirium	Acute impairment of attention and awareness	2%–10% (4%–38%)	10%–30%	• Common in ICU patients (70%–87%) • 15%–50% had delirium on admission or during the hospital stay • Delirium: a 7-fold increased risk of mortality
Dementia (all types)	Severe loss memory that interferes with daily life and causes a loss of functional independence	2% (≈50%)	25%–30%	• Delirium at admission associated with dementia ≈50% • Prevalent CHD: a 27% increase in the risk of dementia. • Incident CHD (MI or angina pectoris): accelerated cognitive decline at 1 y
Depression	Severe mood disorder	0.6%–2% (≈10%–45%)	5%–60%	• MI, a specific risk factor for depression onset ≈20% • Associated with poor adherence to care
Falls	Inadvertently ending up on the ground	20%–40% (50%–75% of people fall each y)	30%–40%	• The most common adverse event in hospital • Older adults with CVD have a 57% risk of falling. • Specific CVD risk factor for fall-related mortality: MI, AF, and congestive HF
Pressure ulcers	Injury to the skin and underlying tissue, caused by prolonged pressure	3%–10% (7%–23%)	8%–14%	• CVD patients in the ICU (postsurgical or not): 23% • Mortality rate because of pressure ulcers and its associated secondary complications: 68%.
Urinary incontinence	Any involuntary urine loss	2%–25% (≈50%)	22%	• Prevalence in acute cardiac disease ≈50%
Sarcopenia	Progressive loss of muscle mass and function	10% (31%–51%)	24%	• Prevalence in older patients with MI: 64.6% • Independently related to prevalent CVD, such as MI, HF, AF, and atherosclerosis • Associated with a higher cardiovascular risk score in MI.
Chronic pain	Pain for at least 3 mo	35%–60% (≈50%)	50%	• Prevalence in older patients with CVD: 50% • People with chronic pain are more likely to have CVD (reductions in physical activity and deterioration in mental health, sleep, and diet quality).

AF indicates atrial fibrillation, CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; ICU, intensive care unit; and MI, myocardial infarction.

*Indicates the prevalence in community-dwelling adults aged 65 years or over; the specific prevalence in adults aged 65 years or over living in nursing homes is given in brackets.

are not yet well understood. A combination of behavioral, social, and biological factors has been proposed. Classically, one can cite the protective effect of estrogen against female mortality, particularly in terms of CVD. Many studies have found a statistical overlap between frailty and CVD.[4,26,28] A meta-analysis showed that prevalent frailty was associated with an elevated risk of any type of CVD (odds ratio [OR] 95% CI, 2.85 [2.29–3.53]), and with specific CVDs (coronary heart disease: 2.86 [2.20–3.71]; stroke/transient ischemic attack: 3.38 [2.37–4.81]; and peripheral vascular disease: 3.45 [1.79–6.64]), with an almost 9-fold greater risk of heart failure than in robust individuals.[29] Frailty was also an independent predictor of a wide range of incident CVDs and was associated with an increased risk of developing any cardiovascular condition during follow-up (median: 4.4 years) versus robust patients (OR=1.70; *P*=0.004).[29] There is a growing body of evidence for a bidirectional, colinear relationship between frailty and CVD. CVDs are also a potential modulator of the overall frailty risk. In the longitudinal cohort in the Cardiovascular Health of Community-Dwelling Older People Study, CVD (including ischemic heart disease, stroke, and congestive heart failure) was statistically associated with incident frailty.[30]

GERIATRIC CONDITIONS CHALLENGE THE PROVISION OF CARE FOR PATIENTS WITH CVD

Although living longer is certainly an important goal, most older people are also concerned about their overall quality of life and their independence. After arthritis, CVD is the second most common cause of disability in older people and is a major cause of self-reported poor health.[31] It has been shown that CVD in adults aged 65 years or over was associated with a loss of 6.5 years

of "successful" life (ie, life with good health and function) in women and 5.6 years in men.[32]

Beyond traditional risk factors, geriatric conditions may add prognostic information. Interestingly, Vaes et al found that frailty (but not a set of conventional cardiovascular risk factors) was statistically predictive of all-cause and specific cardiovascular mortality in very old adults with prevalent CVD.[33] Geriatric conditions negatively affect the presentation and course of CVD, so that diagnosis, prognosis, and management are worsened by the presence of these conditions. They are important predictive factors of adverse noncardiovascular outcomes, including an increased risk of death, disability, institutionalization, greater use of health resources, lower quality of life, and higher frequencies of adverse drug reactions in older patients with CVD[16,34] (Table 1). Notably, functional decline, defined as reduced activities of daily living, is a prevalent yet preventable complication during hospitalization affecting 33% of older patients with acute CVD.[35]

By evaluating CVD as an independent condition in a single organ system, our clinical care initially ignored the interorgan interactions necessary for good general health. Noncardiovascular conditions are sometimes ignored, even when they have a relevant impact on overall outcomes or a negative impact on self-management (eg, cognitive impairment). Further efforts to defragment care, encompass noncardiovascular conditions, and apply team-based care are important steps in managing older people with CVD. Care provision for the geriatric patient must integrate all the contributory risks: (1) the diagnosis and treatment of not only CVD but also other chronic diseases, (2) targeted prevention of noncardiovascular event and cardiovascular complications, and (3) efficient assessment of the functional impact of cardiovascular conditions on the patient's quality of life and independence (Figure 2).

As a result, geriatric medicine has gradually become an imperative for clinical cardiologists. In addition to longer survival for older patients with CVD, optimized

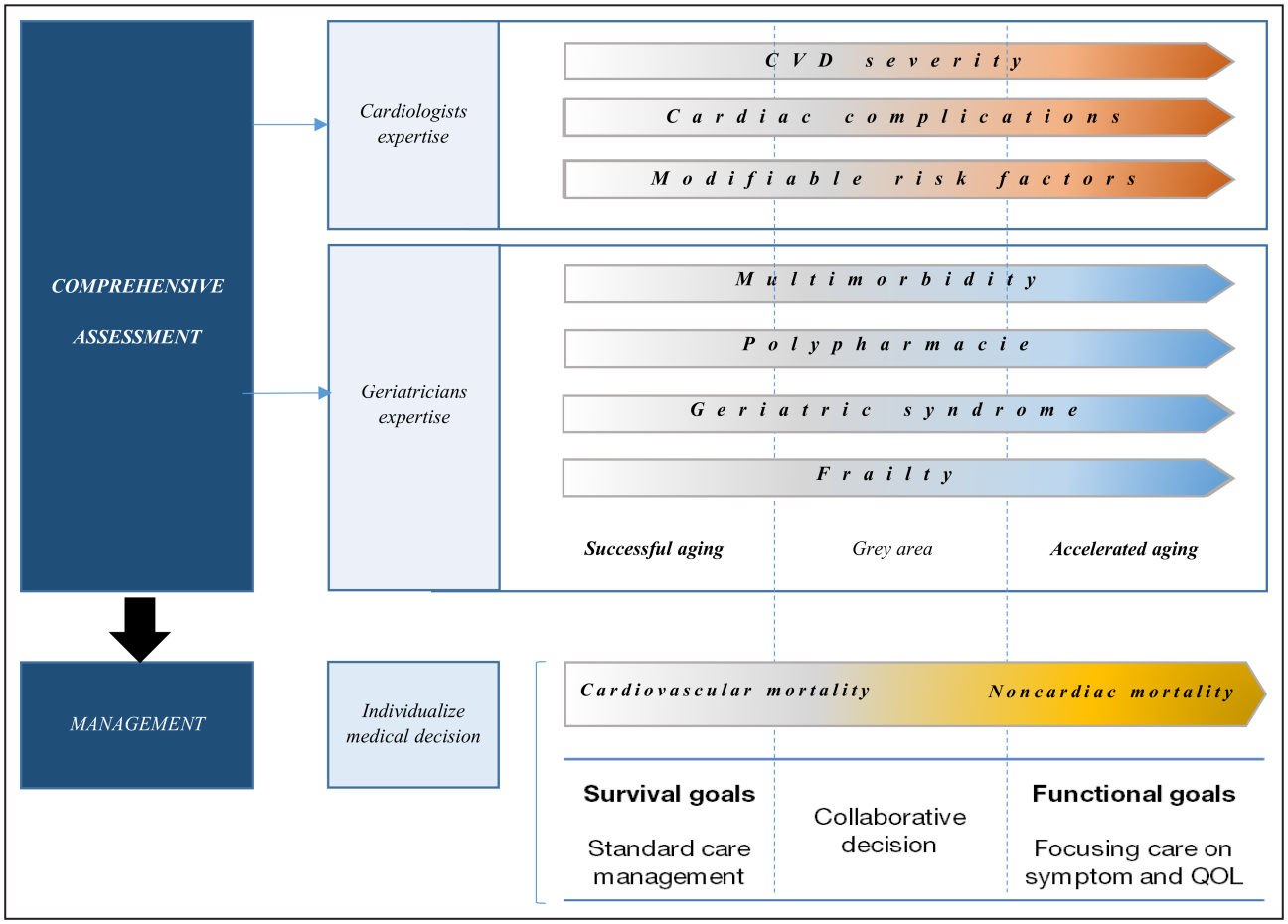

Figure 2. Factors Involved in the Management of CVD in Older Adults.
Care of older patients with CVD should include a comprehensive assessment and risk stratification: (1) management of the CVD (not just the diagnosis and treatment of cardiac complications), and (2) identification, prevention, and treatment of noncardiovascular geriatric conditions. Older patients who might benefit from more invasive interventions could be identified by leveraging the wealth of experience accumulated by geriatricians. CVD indicates cardiovascular disease; and QOL, quality of life.

quality of life, functional status, and independence have become common challenges. This type of holistic approach could build on the wealth of experience accumulated by geriatricians. As Robert J. Havighurst wrote in 1952: "In considering the needs of older people it is well, first, to remember that older people have the needs that are common to all people, and, second, that they have special needs due to the fact they are old people".[36] New tools are being developed to support this holistic vision of care and to guide clinical decisions. Most CVD risk scores have been developed and validated in middle-aged adults with no significant comorbidities. However, in the population of older adults, discriminatory abilities of the scores are biased by the complexity of the cumulative disease processes and the failure to account for the negative outcomes predicted by geriatric functions. Furthermore, health care goals have long focused on prolonging life expectancy: clinical scores have been validated for the prediction of 10-year mortality rates, which are less important in patients with advanced age and are overshadowed by the value of quality of life and independence. With current technical advances in cardiological medicine, older patients eligible for the more invasive interventions could be identified by leveraging the cumulative experience of geriatricians (Figure 2).

To determine the aging profile of older people, one method is to assess their biological age (ie, to determine whether a person is younger or older than expected, based on observable manifestations of biological aging processes). To this end, the World Health Organization has developed the concept of intrinsic capacity, defined as the combination of a person's physical and mental abilities and their interaction with relevant environmental characteristics that define the individual's functional capacity. It involves the measurement of 5 critical domains for older adults (cognitive, psychological, sensory, locomotor, and vitality). Geriatric expertise, based on the determination of functional capacity, contributes to a better understanding of these different trajectories of aging and thus to identify groups at higher risk of death and disease.

Multidimensional scales for the evaluation of geriatric factors might be relevant tools for facilitating this shift towards geriatric considerations in cardiology. The scale has value per se but also encourages the clinician to integrate geriatric management into his/her clinical routine. The implementation of these scales would standardize the rapid collection of the main geriatric functions and prevent them from being ignored or forgotten. For example, the Short Emergency Geriatric Assessment grid is dedicated to the rapid evaluation of frailty by combining the geriatric profile and risk factors.

To go further in this direction and to accurately predict the subsequent risk of death in older patients with CVD, we would need more complex scores (based on a comprehensive geriatric assessment). In this respect, we wish to highlight the Multidimensional Prognostic Index (MPI) as a score that progressively integrates cardiological management and calls on the geriatrician's expertise. The MPI is based on a standardized assessment of geriatric conditions, with 6 geriatric scales commonly used to explore cognitive, functional, nutritional, and clinical status, together with information on medications taken and the patient's level of social support.[37] The MPI can accurately predict not only in-hospital and long-term mortality but also institutionalization, hospital readmission, and the use of home care services by older adults with acute diseases. Pilotto et al validated the MPI's short- and long-term predictive value in older patients hospitalized for (among other diseases) heart failure,[38] transient ischemic attack,[39] and acute myocardial infarction.[40] More importantly, the MPI also accurately identifies patients who could benefit (in terms of a reduction in the mortality rate) from specific therapies (eg, statins for coronary heart disease, or anticoagulants for atrial fibrillation).[41] The MPI score is now widely used with older patients requiring complex procedures, such as transcatheter aortic valve implantation. The MPI's application to other cardiovascular conditions is ongoing and should be encouraged for a better understanding of optimal care.

CONCLUSIONS

Our narrative review provided further evidence of so-called "accelerated aging" in older patients with CVD. The observation of high comorbidity burden among older people with CVD suggests that our care models should be adopted to better meet the needs of this particularly vulnerable patient population. The high prevalence of geriatric conditions associated with CVD undoubtedly emphasizes the need for an integrated, multisystem approach.

Since individual health trajectories are currently difficult to predict in older adults, our review is intended to stimulate the development of new ways to elucidate the complexity of aging and to address the lack of consensus on CVD management in very elderly people. In view of the data summarized above, we believe that a comprehensive, specific approach to caring for older patients with CVD is essential and that geriatric medicine is a valuable, complementary ally in the physician's decision-making process.

ARTICLE INFORMATION

Affiliations

Division of Geriatric Medicine, Tours University Hospital, Tours, France (A.P.A., W.G., F.P., C.D., V.L., J.N., B.F.); EA4245 Transplantation, Immunologie, Inflammation, Tours University, Tours, France (A.P.A., D.A.); Cardiology Unit, Trousseau Hospital, Tours University Hospital, Tours, France (D.A.);

EA 7505 Education, Ethics, Health, Tours University, Tours, France (V.L., B.F.); INSERM CIC 1415, Tours University Hospital, Tours, France (P.P.); and INSERM, SPHERE U1246, Tours University, Nantes University, Tours, France (P.P.).

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Spoon DB, Psaltis PJ, Singh M, Holmes DR, Gersh BJ, Rihal CS, Lennon RJ, Moussa ID, Simari RD, Gulati R. Trends in cause of death after percutaneous coronary intervention. *Circulation*. 2014;129:1286–1294. doi: 10.1161/CIRCULATIONAHA.113.006518
2. Bauters C, Deneve M, Tricot O, Meurice T, Lamblin N; CORONOR Investigators. Prognosis of patients with stable coronary artery disease (from the CORONOR study). *Am J Cardiol*. 2014;113:1142–1145. doi: 10.1016/j.amjcard.2013.12.019
3. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J*. 2014;35:1726–1731. doi: 10.1093/eurheartj/ehu197
4. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018;15:505–522. doi: 10.1038/s41569-018-0064-2
5. Libby P. Inflammation in atherosclerosis-No longer a theory. *Clin Chem*. 2021;67:131–142. doi: 10.1093/clinchem/hvaa275
6. Dunlay SM, Chamberlain AM. Multimorbidity in older patients with cardiovascular disease. *Curr Cardiovasc Risk Rep*. 2016;10:3. doi: 10.1007/s12170-016-0491-8
7. Trtica Majnarić L, Bosnić Z, Kurevija T, Wittlinger T. Cardiovascular risk and aging: the need for a more comprehensive understanding. *J Geriatr Cardiol*. 2021;18:462–478. doi: 10.11909/j.issn.1671-5411.2021.06.004
8. Marengoni A, Angleman S, Meinow B, Santoni G, Mangialasche F, Rizzuto D, Fastbom J, Melis R, Parker M, Johnell K, et al. Coexisting chronic conditions in the older population: variation by health indicators. *Eur J Intern Med*. 2016;31:29–34. doi: 10.1016/j.ejim.2016.02.014
9. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, Meinow B, Fratiglioni L. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10:430–439. doi: 10.1016/j.arr.2011.03.003
10. St Sauver JL, Boyd CM, Grossardt BR, Bobo WV, Finney Rutten LJ, Roger VL, Ebbert JO, Therneau TM, Yawn BP, Rocca WA. Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity. *BMJ Open*. 2015;5:e006413. doi: 10.1136/bmjopen-2014-006413
11. van den Bussche H, Koller D, Kolonko T, Hansen H, Wegscheider K, Glaeske G, von Leitner E-C, Schäfer I, Schön G. Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. *BMC Public Health*. 2011;11:101. doi: 10.1186/1471-2458-11-101
12. Weiss CO, Boyd CM, Yu Q, Wolff JL, Leff B. Patterns of prevalent major chronic disease among older adults in the United States. *JAMA*. 2007;298:1160–1162. doi: 10.1001/jama.298.10.1160-b
13. Arnett DK, Goodman RA, Halperin JL, Anderson JL, Parekh AK, Zoghbi WA. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions. *Circulation*. 2014;130:1662–1667. doi: 10.1161/CIR.0000000000000128
14. Midão L, Giardini A, Menditto E, Kardas P, Costa E. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. *Arch Gerontol Geriatr*. 2018;78:213–220. doi: 10.1016/j.archger.2018.06.018
15. Sheikh-Taha M, Asmar M. Polypharmacy and severe potential drug-drug interactions among older adults with cardiovascular disease in the United States. *BMC Geriatr*. 2021;21:233. doi: 10.1186/s12877-021-02183-0
16. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research and policy implications of a core geriatric concept. *J Am Geriatr Soc*. 2007;55:780–791. doi: 10.1111/j.1532-5415.2007.01156.x
17. Li C-L, Chiu Y-C, Chang H-Y, Hsu K-H, Bai Y-B, Wang H-H. Association of geriatric conditions and cardiovascular diseases with disability in older adults with diabetes: findings from a nationally representative survey. *Geriatr Gerontol Int*. 2013;13:563–570. doi: 10.1111/j.1447-0594.2012.00935.x
18. Vetrano DL, Foebel AD, Marengoni A, Brandi V, Collamati A, Heckman GA, Hirdes J, Bernabei R, Onder G. Chronic diseases and geriatric syndromes: the different weight of comorbidity. *Eur J Intern Med*. 2016;27:62–67. doi: 10.1016/j.ejim.2015.10.025
19. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study. *J Am Geriatr Soc*. 2009;57:511–516. doi: 10.1111/j.1532-5415.2008.02150.x
20. Rausch C, van Zon SKR, Liang Y, Laflamme L, Möller J, de Rooij SE, Bültmann U. Geriatric syndromes and incident chronic health conditions among 9094 older community-dwellers: findings from the lifelines cohort study. *J Am Med Dir Assoc*. 2021;23:54–59. Available from: https://www.jamda.com/article/S1525-8610(21)00250-4/abstract
21. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The Lancet*. 2013;381(9868):752–762. doi: 10.1016/s0140-6736(12)62167-9
22. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2021;42:3227–3337. doi: 10.1093/eurheartj/ehab484
23. Damluji AA, Chung S-E, Xue Q-L, Hasan RK, Moscucci M, Forman DE, Bandeen-Roche K, Batchelor W, Walston JD, Resar JR, et al. Frailty and cardiovascular outcomes in the national health and aging trends study. *Eur Heart J*. 2021;42:3856–3865. doi: 10.1093/eurheartj/ehab468
24. Farooqi MAM, Gerstein H, Yusuf S, Leong DP. Accumulation of deficits as a key risk factor for cardiovascular morbidity and mortality: a pooled analysis of 154 000 individuals. *J Am Heart Assoc*. 2020;9:e014686. doi: 10.1161/JAHA.119.014686
25. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc*. 2012;60:1487–1492. doi: 10.1111/j.1532-5415.2012.04054.x
26. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. *Am J Cardiol*. 2009;103:1616–1621. doi: 10.1016/j.amjcard.2009.01.375
27. Liperoti R, Vetrano DL, Palmer K, Targowski T, Cipriani MC, Lo Monaco MR, Giovannini S, Acampora N, Villani ER, Bernabei R, et al. Association between frailty and ischemic heart disease: a systematic review and meta-analysis. *BMC Geriatr*. 2021;21:357. doi: 10.1186/s12877-021-02304-9
28. Marinus N, Vigorito C, Giallauria F, Haenen L, Jansegers T, Dendale P, Feys P, Meesen R, Timmermans A, Spildooren J, et al. Frailty is highly prevalent in specific cardiovascular diseases and females, but significantly worsens prognosis in all affected patients: a systematic review. *Ageing Res Rev*. 2021;66:101233. doi: 10.1016/j.arr.2020.101233
29. Veronese N, Cereda E, Stubbs B, Solmi M, Luchini C, Manzato E, Sergi G, Manu P, Harris T, Fontana L, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: results from a meta-analysis and exploratory meta-regression analysis. *Ageing Res Rev*. 2017;35:63–73. doi: 10.1016/j.arr.2017.01.003
30. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB, Initiative WH. Frailty: emergence and consequences in women aged 65 and older in the women's health initiative observational study. *J Am Geriatr Soc*. 2005;53:1321–1330. doi: 10.1111/j.1532-5415.2005.53405.x
31. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, Yusuf S. The burden of disease in older people and implications for health policy and practice. *Lancet*. 2015;385:549–562. doi: 10.1016/S0140-6736(14)61347-7
32. Newman AB, Arnold AM, Naydeck BL, Fried LP, Burke GL, Enright P, Gottdiener J, Hirsch C, O'Leary D, Tracy R, et al. "Successful aging": effect of subclinical cardiovascular disease. *Arch Intern Med*. 2003;163:2315–2322. doi: 10.1001/archinte.163.19.2315
33. Vaes B, Depoortere D, Van Pottelbergh G, Matheï C, Neto J, Degryse J. Association between traditional cardiovascular risk factors and mortality in the oldest old: untangling the role of frailty. *BMC Geriatr*. 2017;17:234. doi: 10.1186/s12877-017-0626-x

34. Anpalahan M, Gibson SJ. Geriatric syndromes as predictors of adverse outcomes of hospitalization. *Intern Med J*. 2008;38:16–23.
35. Van Grootven B, Jeuris A, Jonckers M, Devriendt E, Dierckx de Casterlé B, Dubois C, Fagard K, Herregods M-C, Hornikx M, Meuris B, et al. Predicting hospitalisation-associated functional decline in older patients admitted to a cardiac care unit with cardiovascular disease: a prospective cohort study. *BMC Geriatr*. 2020;20:1–7. doi: 10.1186/s12877-020-01510-1
36. Havighurst RJ. Social and psychological needs of the aging. *The ANNALS of the American Academy of Political and Social Science*. 1952;279(1):11–17. doi: 10.1177/000271625227900102
37. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L. A multidimensional approach to frailty in older people. *Ageing Res Rev*. 2020;60:101047. doi: 10.1016/j.arr.2020.101047
38. Pilotto A, Addante F, Franceschi M, Leandro G, Rengo G, D'Ambrosio P, Longo MG, Rengo F, Pellegrini F, Dallapiccola B, et al. Multidimensional prognostic index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. *Circ Heart Fail*. 2010;3:14–20. doi: 10.1161/CIRCHEARTFAILURE.109.865022
39. Sancarlo D, Pilotto A, Panza F, Copetti M, Longo MG, D'Ambrosio P, D'Onofrio G, Ferrucci L, Pilotto A. A multidimensional prognostic index (MPI) based on a comprehensive geriatric assessment predicts short- and long-term all-cause mortality in older hospitalized patients with transient ischemic attack. *J Neurol*. 2012;259:670–678. doi: 10.1007/s00415-011-6241-4
40. Cammalleri V, Bonanni M, Bueti FM, Matteucci A, Cammalleri L, Stifano G, Muscoli S, Romeo F. Multidimensional prognostic index (MPI) in elderly patients with acute myocardial infarction. *Aging Clin Exp Res*. 2021;33:1875–1883. doi: 10.1007/s40520-020-01718-6
41. Cruz-Jentoft AJ, Daragjati J, Fratiglioni L, Maggi S, Mangoni AA, Mattace-Raso F, Paccalin M, Polidori MC, Topinkova E, Ferrucci L, et al. Using the multidimensional prognostic index (MPI) to improve cost-effectiveness of interventions in multimorbid frail older persons: results and final recommendations from the MPI_AGE European project. *Aging Clin Exp Res*. 2020;32:861–868. doi: 10.1007/s40520-020-01516-0