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New challenges of geriatric cardiology: from clinical to preclinical research

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Abstract

The field of geriatric cardiology reflects the evolving medical approaches tailored to address the needs of the growing population of oldest old with cardiovascular diseases (CVD). The burden of CVD is expected to increase particularly for the most common types of chronic heart disease of the elderly including coronary artery disease, heart failure and atrial fibrillation. In this context of dramatic demographic changes, geriatric cardiologists are facing important challenges. In this review, we outline the basic concepts of geriatric cardiology and describe these challenges as well as the unmet needs around this discipline with also a focus on the translation from basic research.

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1 Introduction

According to the most recent statistics, the world global life expectancy at birth for both sexes is increased from 65.3 years in 1990 to 71.5 years in 2013.[1] Reduced fertility and the demographic change of the world's population to older ages has led to a shift of the mean age of death to approximately 60 years. In high-income regions, including central Europe, this global change is reflected by a substantial fell in child death and a strong increase in the number of deaths of people older than 80 years. However, while the average life expectancy of Europeans has increased, the number of healthy life years (HLY) seems to be slightly affected thus suggesting that Europeans still spend 20%–25% of their lives in poor health.[2] Indeed, most of deaths and causes of disability are the consequence of age-related non communicable diseases (NCD) such as cardiovascular diseases (CVD), cancers and chronic respiratory diseases. Indeed, NCD account for nearly 86% of deaths and 77% of the disease burden, putting increasing strain on health systems, economic development and the well-being of large parts of the population, in particular people aged 65 years and older.

CVD account for most NCD deaths and still remains US and European number one cause of death (approximately 50% of all deaths in high income countries) and illness. In these regions more than one third of people above 65 years and more than half above 85 shows clinically significant CVD usually accompanied by several co-morbidities.[3] The huge efforts in prevention strategies (action on food habits and preference, quit smoking, promotion of physical activity) have produced a decline in the overall cardiovascular mortality rates for CVD in industrialized countries,[3,4] but the total numbers of people with chronic CVD is likely to increase substantially in the next years as a consequence of population aging. Indeed, while the preventive strategies have to be able to reduce the number of adult population with CVD, this action can just shift cardiovascular problems towards the oldest old (i.e., above 80 years), which in turn are exponentially increasing as relative numbers in the industrialized countries. As a consequence, the future continuing burden of cardiovascular disease will increasingly affect older groups and will stress healthcare systems, even in the wealthiest countries.[5,6]

The field of geriatric cardiology reflects the evolving approaches tailored to address the needs of this growing population. This approach consists in considering the whole medical, physical and mental profile of the patients in order

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to achieve a sort of individualized therapy, based not just on a given cardiovascular diagnosis but with respect to each patient's aging experience. Here we describe the medical needs that have contributed to the raise of geriatric cardiology and the great challenges that these physicians are facing during this dramatic demographic change. One of the most important challenges regards the adoption of medical treatments in a context where very few randomized placebo-controlled trials have been performed in the oldest population. Therefore, evidence of efficacy of treatments is mostly based on personal experience and on extrapolation of results from studies performed in the younger groups.

2 Increasing burden of CVD in geriatric patients

The economic burden of CVD is huge. It is estimated around €196 billion a year, including direct health expenditure, productivity losses and informal care of people with CVD. The impact on national health care systems in European Union is estimated around €212 per year per person.[7] This is the reason while lot of efforts have been spent in the last decades to reinforce prevention strategies. The range of initiatives taken, including lowering blood pressure and cholesterol levels as well as highlighting the dangers of smoking has led to a considerable decline in CVD mortality in high income countries.[8] Since the 2008 report there has been a substantial drop in the number of deaths attributed to heart disease in Europe. CVD is now responsible for four million European deaths annually, down from 4.3 million in 2008 (which represents a drop from 48% to 47% of total European deaths).[9] This mean that a small reduction in risk in a large number of people may prevent many more cases, such as cardiovascular events and deaths, than treating a small number at higher risk.[10] Nonetheless, CVD is still the leading cause of deaths worldwide and it is not clear if the downward trend in CVD can be extended to the oldest old. Indeed, it has been already observed that the rate of improvement can reach a plateau with age.[11] If we consider for example the age effect on ischemic heart disease (IHD) mortality (the leading cause of death worldwide), this is so strong that high income countries, which have older and ageing populations, have a total mortality burden which remains high and is falling only slowly over time.[12] Hence, the combined effect of population growth and ageing is so strong that despite all current efforts, total numbers of IHD deaths worldwide are increasing. Moreover, emerging data suggests that the proportion of the oldest old on chronically prescribed medication for CVD is markedly increasing.[13,14] The burden of CVD is expected to increase particularly for the most common types of chronic heart disease of the elderly including coronary artery disease (CAD), heart failure (HF) and atrial fibrillation (AF).

3 CAD and coronary heart disease

CAD involves impairment of blood flow through the coronary arteries, most commonly by atheromas. Clinical presentations include silent ischemia, angina pectoris, acute coronary syndromes (ACS, i.e., unstable angina and myocardial infarction), and sudden cardiac death. CAD accounts for the primary diagnosis at admission in up to a quarter of nursing-home residents older than age 65. In US population, it is expected a considerable increase in CAD incidence, prevalence and mortality during the next 30 years.[15] A similar scenario with an increase of coronary heart disease (CHD, a consequence of CAD deaths from 56% to 62% as been proposed also for the UK.[16] As treatment outcomes of CAD continue to improve, more patients survive the acute phase and remain for many years in a state of chronic diseases. This cause a steadily increasing population with CAD. In this scenario, it is important to consider that approximately 30% of patients aged ≥ 70 years with significant CAD at hospitalization display evidence of frailty,[17] which parameters represent the strongest predictors of mortality in this population. A particular consideration should be deserved to the decreased prevalence of CAD with age observed in patients above 85 years in a recent study performed in Canada.[18] This is likely the consequence of a survivor effect. Indeed, it is reasonable to assume that the patients who survived the longest were the least likely to be afflicted by this condition. However, in the same study it was observed a stable prevalence of hypertension, which in turn could indicate subclinical presence of CAD. The Cardiovascular Health Study (CHS), the first major epidemiological study specifically focused on the elderly population, reported an association between blood-pressure patterns (such as isolated systolic hypertension) and subclinical CVD, in particular with increased intima-media thickness of the carotid artery.[19] This could be particular important in the oldest old as the severity of CAD in patients above 90 years seems to correlate poorly with the prevalence of established traditional cardiovascular risk factors (smoking, dyslipidaemia, diabetes and age) with the exclusion of hypertension.[20]

4 HF

With population aging, HF is becoming a very serious

medical issue. It has been estimated that there are currently 6.5 million HF patients in Europe and 5 million in the USA. While around one in 35 people aged 65–74 years has HF, this prevalence increases to about 1 in 15 of those aged 75–84 years, and just over 1 in 7 of those aged 85 and above. Although recent advances in the diagnosis and treatment of HF have led to improved survival rates,[21] the number of patients with HF is increasing and is estimated to increase in future. Projections reported by the American Heart Association show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age with HF in the USA.[4] But the numbers that deserve more attention regards the prevalence of patients of 65 years or older in the overall number of patients with HF, being 78% of men and 85% of women. These numbers clearly describe the strong relationship existing between age and HF. In addition, older patients with HF have a high prevalence of comorbidities including additional multiple cardiovascular problems such as hypertension and atrial fibrillation. Therefore, it is not surprising that HF accounts for 36% of CVD deaths in US and represent also a major cause of re-hospitalization.

5 AF

AF is another cardiovascular disease which prevalence is expected to rise worldwide in the foreseeable future as a consequence of population ageing and increased survival from conditions associated with AF.[22] AF is the most common arrhythmia in the elderly. The prevalence of AF also roughly doubles with each advancing decade of age, from 0.5% at age 50–59 years to almost 9% at age 80–89 years. In the USA, the prevalence of AF is 3%–4% in apparent healthy people over 60 years of age, 10 times higher than that in the younger population.[23] Over the past decade, both the incidence and prevalence of AF has markedly increased and prevention of stroke in elderly patients with this condition require increasing attention.[24] In a recent European study, of the newly diagnosed AF cases, only 58.2% received antithrombotic drugs. Antithrombotic drugs were more often prescribed to men (61.8%) than to women (51.6%). Interestingly, the proportion of incident AF cases receiving antithrombotic drug therapy declined with advancing age in a German study.[25] These data suggest that antithrombotic management of AF cases in elderly population deserve particular consideration in future clinical studies.

6 Senile cardiac amyloidosis

In the last years, senile cardiac amyloidosis (SCA) has been recognized as an important underdiagnosed condition in the oldest old[26] that can lead to congestive HF, AF and death. This disease results from massive cardiac deposition of wild-type transthyretin (TTR) and is one of the commonest forms of cardiac amyloidosis, but the diagnosis is often missed, either because the physician is unaware of the disease or because symptoms are attributed to other forms of heart disease.[27] With population aging this condition is increasingly being considered much more common than previously. SCA has a clear association with aging and is almost exclusively seen in men older than 65 years of age.[28] In a Finnish population older than 85 years, one-quarter had amyloid deposition in the heart on post-mortem examination.[29] In a US community-based sample, approximately 30% of subjects over the age of 75 years with congestive HF and a preserved ejection fraction have cardiac deposits of wild-type TTR.[30] Confirmed cases of SCA by cardiac biopsy have a typical clinical presentation and affected individuals commonly develop AF or require permanent pacing during follow up.[26] The diagnosis of SCA has become easier in recent years with advances in cardiac imaging.[31] This could be important for the care and management of geriatric patients with CVD and eventually to plan "ad hoc" clinical trials as certain cardiac medications, such as digoxin, calcium channel blocker and beta-blocker, have been proposed to worsen the disease.[32]

7 Aortic stenosis

Aortic stenosis (AS) is the most common valvular heart disease in developed countries. In a recent meta-analysis,[33] the prevalence in the elderly (> 75 years) of severe AS was 3.4%, with 1.0 million elderly patients with severe AS in the European countries and 540,000 in North America. If we consider data from moderate to severe valvular heart disease the prevalence in the elderly above 75 years is approximately one in eight people, and this data could even be still underestimated.[34] With the progressively ageing population, there will be an estimated 1.3 million and 2.1 million patients with symptomatic severe AS in the 19 European countries in 2025 and 2050, respectively. Among elderly patients with severe AS, 75.6% are symptomatic, and 40.5% of these patients are not treated surgically. In elderly patients, the most common cause of AS is the degenerative-calcific stenosis (senile AS), rarely rheumatic, as opposed to young people in which the genesis is almost congenital.[35]

If the diagnosis and drug therapy are similar, the timing and type of valve repair are the current problem for the

management of the elderly patient with AS, compared to young adult. A third of elderly patients are not screened for surgical valve replacement,[36] due mainly to age and presence of comorbidity ("frail" patients) and disability.[37] Fortunately, unlike other clinical areas, numerous studies have been performed on the aortic valve replacement (AVR) in this setting of patients (> 75 years); consequently there are numerous data to properly treat these patients. Some authors have shown the efficacy and safety of isolated aortic replacement in patients above 80 years and it remains the "gold standard treatment" in patients without surgical contraindications.[38–42] Transcatheter aortic valve implantation (TAVI) is indicated in inoperable patients at high surgical risk and it is a safe and effective procedure with similar outcomes than surgical AVR.[43–48] In any case, as for young and adult patients, the elderly with AS, when possible, should be always subjected to the AVR, because the medical therapy alone has shown a significant increase in mortality compared to valve repair.[37,49]

8 The approach of "Geriatric Cardiology"

The field of Geriatric Cardiology reflects some evolving approaches tailored to address the needs of this growing population. Geriatric Cardiology can be referred to the care of CVD in "old age" patients, i.e., those above 65 years of age or older. However, the practical approach of a geriatric cardiologists consists in taking decisions not on age alone but on the whole medical, physical and mental profile of the patients in order to achieve a sort of individualization, based not just on a given cardiovascular diagnosis, but with respect to each patient's aging experience.[50,51] This kind of approach enclose the knowledge of comprehensive geriatric assessment, altered pharmacokinetics in aging, and the concept of frailty that should ensure to adopt a therapy that take into account for age-associated changes.[52–54] These changes may include a complex mix of cognitive deficits, sarcopenia, diminished resiliency, altered pharmacodynamics and pharmacokinetics, falls, delirium, incontinence, pain and fatigue which may strongly affect the key priority and the modalities of the therapeutic approach. Additional aspects regarding the management of a geriatric patient should be also considered such as multi-morbidity, polypharmacy, functional decrements, as well as visual and auditory limitations.

Hence, people above 70s with cardiovascular disease display also a number of non-cardiac illnesses that make the application of traditional cardiology challenging. One of the most common examples are related to the interaction among medications that are prescribed for various conditions that may increase the risks of adverse effects in older adults. This picture is also complicated by "geriatric syndromes" such as cognitive impairment, muscle loss and other functional impairment that may affect the recovery after cardiac interventions as well as the quality of life after hospital discharge. Hence, beyond taking a complete medical history of the patient, geriatric cardiologists have to look for frailty by measuring things like gait and grip strength and have to administer tests for cognitive ability which conventional cardiologists mostly don't. This required additional expertise, resources and lot of time to be spent with just a single patient. Patients above 80s are usually also coping with several other chronic conditions and disabilities, including diabetes and chronic respiratory diseases as well as visual and hearing impairments, which bring them to use several drugs, thus increasing the risk to take inappropriate drugs. For this reason, it is not uncommon that very old patients can take redundant or wrong medications. Thus, it is not enough to ask the patients which prescription they are taking, but it is usually necessary to ask them to show directly during the visit their prescriptions. It is also common that very old patients are not able to cope well with medical procedures and regimens that are effective for younger patients. For example, the patient could be impaired to remember the drugs that he is taking thus making ineffective the conventional approach.

Finally, procedure to diagnosis cardiac diseases that specifically affect very old patients (i.e., SCA) should be taken into account during the clinical management of the patients or eventually before taking decisions on treatments.

The diagnosis and identification of comorbidities appears to be particularly critical in view of the new advances in treatments that are being made in the field of geriatric cardiology.

9 Treating elderly patients in geriatric cardiology

A common misconception that is currently changing in the field of geriatric cardiology is that treating elderly patients in advanced age precludes aggressive interventions, including surgical therapies. Indeed, the advances in cardiovascular surgery have led to the possibility that a growing number of elderly patients can be operated safely and with a satisfactory outcome.[55] In the field of CAD, for example, elderly patients seem to benefit from surgical revascularization more than from conservative medical treatment.[56–58] Coronary artery bypass grafting (CABG) has been demonstrated to achieve excellent intermediate survival in octagenarians.[59–61] At the same time, percutaneous

coronary interventions (PCI) display low operative mortality[62] that combined with its minimal invasive nature make it valuable in high-risk patients. The increasing use of early PCI and newer anticoagulants (low molecular weight heparin and fondaparinux) as well as recommended medication is likely the factors that contributed to the decrease in one year mortality of elderly patients with ACS. However, the best option for CAD in patients aged above 80 is still not completely known due to the paucity of "elderly-focused" clinical trials and the absence of randomized controlled trial comparing PCI and CABG. In the recent European Guidelines on myocardial revascularization the word "elderly" appears only 6 times, in relation to the TIME trial (Trial of Invasive Medical Therapy in Elderly),[56] the choice of the treatment of patients presenting with cardiogenic shock and the choice of invasive approach according to the bleeding risk. Therefore the management of elderly patients with ACS is largely based on data from trials performed on young adults. The presence of comorbidities strongly increase the risk of these interventions thus making usually acceptable an invasive procedure only in a limited number of patients that are free from renal dysfunction, cerebrovascular disease and other clinical state associated with a worse outcome. An observational study of 100193 patients with ACS performed in Poland reported that in elderly patients undergoing PCI, hospital complications (stroke, re-infarction and death) were less frequent for the invasive treatments, with the exception of major bleeding, which occurred almost three times more frequently (2.9% *vs*. 1.1%).[63] Elderly patients tend to present greater technical challenges in relation to PCI owing to heavier coronary calcification, tortuous anatomy in both coronary and peripheral arteries and reduced tolerance to bleeding problems. They also tend to have a greater risk profile owing to more severe coronary disease and multiple vessel disease. Hence, PCI strategy in elderly could be performed with extensive use of radial approach, moderate use of intravenous anticoagulant and prevalent use of bare metal stent (reduce of bleeding events).[64] Recently, TAVI was demonstrated to provide good clinical and hemodynamic outcomes both in inoperable patients and in high-risk elderly patients, and during the last few years the number of procedures, as well as performing centers and performing physicians, has rapidly increased.[65,66] The first studies on this procedure suggest that TAVI with either one of the prosthesis is feasible, safe, improves hemodynamics and, therefore, might be an alternative to conventional AVR in very high-risk patients. However, all of the available transcatheter heart valves currently available have certain disadvantages, thus still limiting their use in daily clinical practice. Another poor invasive emerging procedure that demonstrated safeness in surgical myocardial revascularization is the off-pump coronary artery bypass (OPCAB). OPCAB can offer potential benefit to elderly patients requiring surgical myocardial revascularization by avoiding the deleterious effects of cardiopulmonary bypass.[67]

In general, it emerges that very old patients presenting with IHD who are functional should not be treated in a different way as compared with younger, although, when clinical decision making is difficult, the assessment of frailty, physical and mental functioning autonomy may be helpful for tailoring treatments to individual patients.[68]

10 Evolving changes in biomarkers related to Geriatric Cardiology

In the recent years we have observed a great improvement of our knowledge around the use and limits of biomarkers in Geriatric Cardiology. The relevance of most traditional CVD risk factors, including systolic blood pressure (BP), LDL-C, HDL-C, obesity, and diabetes seems to be minimal in the oldest old.[69] Sometimes, this association can be even reversed compared to the finding observed in the youngest elderly, such as in the case of high BP,[70] or cholesterol.[71]

The use of biomarkers has received considerable attention also in the diagnosis and prognosis of patients with HF and worsening renal function, which is the most frequent comorbidity associated with high mortality in elderly HF patients.[72,73]

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the gold standard biomarkers in determining the diagnosis and prognosis of HF.[74] The concentration of both peptides is increased with myocardial stretch (ventricular, and to a lesser extent, atrial), and particularly in elderly patients without diagnosis of HF could indicate the presence of a silent cardiac damage,[75] and AF.[76] However, deterioration in kidney function and other comorbidities (e.g., cognitive deficits), as it may occur frequently in geriatric patients, may affect BNP and NT-proBNP levels thus complicating the diagnosis,[77] and their clinical management.[78] Recent studies suggest that risk stratification in elderly patients with acute HF (AHF) could be performed on the basis of simple parameters, such as respiratory rate and albumin.[79] In agreement with these findings, few predictive factors for mortality have been identified in nonagenarians with AHF. These factors functional deterioration, basal kidney disease, hyponatremia and respiratory insufficiency on arrival at the emergency department.[80]

Patients aged 80 and above that are admitted with tro-

ponin positive chest pain are increasingly common in Geriatric Cardiology. However, the absence of clinical trial data and the poor relevance of risk stratification in this group of subjects cause that clinical management is often at the discretion of the treating physician.[81] In this case, serial testing of cardiac troponins (cTs) with high sensitivity assay could be useful to discriminate myocardial infarction from HF.[82]

Hence, it emerges that most biomarkers, although associated with in-hospital mortality, do not have independent predictive significance when a comprehensive and multidimensional evaluation is conducted. The main clinical implication is that indiscriminate recourse to measurement of cardiac and inflammatory biomarkers, at least in older medical inpatients, could be avoided thus reducing a patient's hospital cost and potentially minimizing further unnecessary diagnostic procedures.[83]

Recently, it has been demonstrated that miRNAs have significant association with ageing heart.[84,85] Based on their rapid release and stability in plasma, some circulating miRNAs such as miR-208b, miR-499, miR-1, and miR-133 have been demonstrated as novel diagnostic biomarkers in patients with acute myocardial infarction and acute coronary syndrome. Some work performed in geriatric CAD patients propose miR-765 and miR-149 as potential non-invasive biomarkers for diagnosis of CAD patients.[86] This could ensure urgent initiation of reperfusion therapy to potentially decrease the morbidity and mortality rate of CAD. However, measurement of plasma miRNAs requires qRT-PCR, which is expensive and time-consuming. Therefore, less expensive and newer techniques to detect plasma miRNA levels are needed before effective translation into clinical practice may occur.

11 Unmet research needs “in and for” Geriatric Cardiology

While there have been lots of progress around research in the field of biomarkers in Geriatric Cardiology, there is still poor if any progress in the field of new medications for major cardiovascular disease, especially in the oldest old. Current pharmacological therapies are only targeted to alleviate the symptoms associated with cardiac deterioration, thus there is a pressing need for novel therapeutic modalities. It is frustrating to know that the only therapy available for advanced HF is heart transplantation, which in turn involve clinical and ethical issues in elderly patients.[87]

The lack of randomized clinical trial data to guide acute care in elderly patients contributes to slow the progress towards appropriate therapies. Appropriate selection of elderly patients for specific therapies and medication regimens is usually not based on solid published data,[88] but the benefits that might be achieved with the design of therapies specifically suited to the needs of the oldest old are well known. For example, the increasing use of revascularization therapy has led to a reduction in 30-day adjusted mortality rate in elderly patients with non-ST elevation myocardial infarction.[89]

At the same time, there is a problem in the translation of findings from basic research. Basic researchers investigate cardiovascular disease in animal models that are specifically modified to develop early cardiac dysfunctions,[90] and atherosclerosis.[91]

However, providing new treatments for heart dysfunction in aged humans require the creation of a common ground between animal studies and clinical assessments. Lots of functional and clinical tests (hand grip and other physical performance, non-invasive measurements of blood pressure and electrocardiograms) as well as imaging technologies (i.e., echocardiographic data, magnetic resonance imaging, High- resolution X-ray computed tomography) that have been established in humans have been scarcely (if not) measured in aged animals.[92] The first comprehensive and longitudinal paper on evaluating cardiovascular function in ageing mice was published few years ago.[93] This paper show that cardiac aging in the mouse closely recapitulates human aging. The authors found that wild-type mice undergo age-dependent left ventricular hypertrophy and a decline in cardiac performance (especially diastolic function), concomitant with increased ventricular fibrosis, cardiomyocyte hypertrophy and various molecular changes.

There is also a lack of knowledge around the changes that affect cardiac aging and comorbidities in very old mice as, in analogy with human studies, most published basic research studies are focused on early development of specific pathologies. Hence, new research methods are needed to characterize cardiovascular function and comorbidities in the same animals as they age as well as to assess non-invasively the results of interventions in very old mice with specific cardiac dysfunction. A promising target in this context appears the development of drugs or natural compounds that are able to target senescent cells,[94] which accumulation in different tissues is considered an hallmark of aging and pathology.[95] In old mice, cardiac function and carotid vascular reactivity were improved five days after a single dose of a senolytic drug (a drug that selectively kills senescent cells) consisting in a combination of dasatinib and quercetin.[96] This measurement was also associated with the improvement of a comprehensive measurement of the age functional status of old mice.

These results confirm that current technologies allows to measure comprehensive geriatric assessment and other tools commonly adopted in geriatric cardiology in mouse models, thus allowing to track survival and functional changes. This approach could be important to investigate the promises or to demonstrate the pitfalls of innovative treatments based on the hypothesis that mammalian heart possesses an innate regenerative capacity.[97,98] This kind of translational approach in basic research could be also useful to verify if a drug can improve cardiac function in the oldest mice without affecting the function of other organs (i.e., cognitive function) or reducing survival (i.e., due to increased cancer incidence), thus increasing the chances to be translated in geriatric cardiology. However, few if any laboratories are currently adopting these protocols. Moreover, investigators studying ageing in model organisms should collaborate with geriatric cardiologists to plan joint programs and adapting new tools that can be reasonably translated in treatments for cardiac dysfunctions in the oldest old. This clearly need new strategies for communication and interaction between clinics and basic researchers.

12 Conclusions

Currently, we are facing the challenge to ensure that all older adults can have access to quality healthcare that meets their unique needs. In the field of cardiology, this means the necessity to improve the knowledge around the emerging field of Geriatric Cardiology. This mean that physicians should be educated about the special healthcare needs of older adults as well as about advances in aging research that helps to identify new diseases affecting the oldest old and understand their pathology. In parallel, clinical care for older people should be enhanced while advocating for public policy that ensure that they can have access to high quality and appropriate cost effective care.

At the same time, there are urgent research needs that need to be addressed in order to accelerate the progress towards appropriate therapies for CVD of the oldest old. On one side, there is still a dramatic lack of clinical trials in the elderly, particularly in the oldest old. New randomized clinical trials are needed to verify the effects of the Geriatric Cardiology approach in elderly with CVD affected by additional geriatric syndromes and age-related diseases. On the other side, the problem in the translation of findings from basic research to Geriatric Cardiology should be afforded with new strategies for communication and interaction between clinics and basic researchers as well as by improving the interventions in heterogeneous old mice characterized before and after intervention with a comprehensive non-invasive phenotyping that is more similar to the approach of geriatric cardiologists in humans.

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