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Review

Known–Unknowns in Geriatric Cardiology

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Abstract

The present article summarizes the current state of understanding in geriatric cardiology in terms of the main developments in the field. The focus of the present review is on the therapeutics, into the specific characteristics of the elderly patients dealing with the prevention of arterial hypertension, bradycardic arrhythmias, atrial fibrillation, coronary artery syndromes, valve heart diseases, and heart failure. Progress in the field of medicine has rendered possible to treat lethal cardiac diseases in the extremely old patients. Nonetheless, data regarding the very old cardiac patients are limited, and it is dangerous to directly extrapolate the experience with the young patients to the old ones. ● Preventive therapies are important in the old cardiac patients, although these therapies differ from those for young patients. ● Very old patients with arterial hypertension benefit from antihypertensive treatment, although the therapeutic strategy of one-size-fits-all cannot be applied. ● Elderly patients often require a cardiac pacemaker. In the case of patients with sinus node dysfunction, pacing modes capable of preserving atrioventricular synchrony are associated with a reduced incidence of atrial fibrillation. In the case of patients with atrioventricular block, the importance of synchronization is debatable. Implantable cardioverter-defibrillators may be used in very old patients, although a limited number of

studies evidencing this in elderly patients are available. ● In very old patients with atrial fibrillation, ablative therapies are seldom used. OAC is useful in such cases, although the HAS-BLED score is inadequate for assessing the real bleeding risk in the old people. ● Patients who are ≥80 years old and exhibit acute coronary syndromes would benefit more from a myocardial revascularization compared to a medical therapy, while in the patients who are ≥90 years old, revascularization and medical therapy are equivalent. ● In the very old patients with severe aortic stenosis, transcatheter valve replacement is safe and efficient, while antithrombotic therapy is problematic. The treatment of mitral regurgitation is different in the very old and the young patients; the mortality is high and there is no consensus on the best therapy. Tricuspid regurgitation is recognized as a serious problem in certain old cardiac patients; however, the best therapeutic approach to this problem has not been discovered so far. ● Information regarding the geriatric patients with heart failure is inadequate due to lack of clinical details in the population-based studies and because clinical trials typically enroll younger patients. Elderly patients with heart failure constitute a heterogeneous group and differ substantially from the younger patients enrolled in the clinical trials. The limited data indicate that a proven therapy for heart failure that reduces mortality and morbidity in the younger patients is also beneficial in elderly patients. However, elderly patients exhibit different responses to the pharmacotherapy in comparison to the younger patients, as the former are susceptible to adverse events, such as orthostatic hypotension, renal dysfunction, electrolyte disturbances, and interactions with the medications prescribed for the treatment of comorbidities. Close monitoring of elderly patients undergoing HeFa treatment is essential to ensure optimal outcomes. The number of old people is large, and progress in the field of medicine has made it possible to treat lethal cardiac diseases in very old patients. Certain individuals are biologically younger in comparison to their anagraphic age; however, geriatric patients are often frail and exhibit much comorbidities. The demand for invasive therapies and novel drugs has led to rapidly increasing expenditures. Practicing cardiologists are encountering increasing number of consultations for very old patients. This creates a requirement for training a greater number of geriatric cardiologists to offer the best of care to the old patients. Owing to the comorbidities, several of which are critical in nature, in the elderly patients, the geriatric cardiologists must be, first of all, master internists at all times. Old patients, with their peculiar pharmacokinetics and multiple illnesses, are also oversensitive to drugs. Several aspects of geriatric cardiology are unknown even now. There is a necessity to understand the effects exerted by the aging process on the human heart. Studies in this direction should command priority in the financial as well as the other forms of support.

Keywords
Geriatric cardiology; old cardiac patients; geriatric cardiac diseases

1. Introduction

G. Bernard Shaw once wrote, "Do not try to live forever, you will not succeed". Certain people are biologically younger in comparison to their anagraphic age, and there is no globally accepted definition for the geriatric age [1-3]. However, conventionally, people ≥65 years of age are referred to as 'old', the people with age ranging between 65 and 74 years as referred to as 'early old', and those ≥75 years of age are referred to as 'late elderly' [4]. Modern medicine has contributed largely to the increase in the life-span of humans. A recent Swiss study [5] reported that between the years 1995 and 2014, the mortality rate associated with the cardiovascular diseases decreased by 20%; since 1990, the medial life-expectancy increased by 7.5 years for men and by 4.5 years for women; at the end of the year 2018, the median life-span was 83 years and 20% of the Swiss people were ≥65 years old. Statistics predict that in 2065, 30% of the Swiss people shall be ≥65 years old. In the USA, the elderly population is expected to have an increase of 126% by 2050, rendering those older than 65 years of age as the most rapidly growing segment in the population [6]. The scenario is similar in most of the developed countries as well. All these aspects form a domain of geriatrics. However, in the developed countries, cardiac patients are now older and further complex in comparison to the situation a decade ago, and practicing cardiologists are encountering patients with a higher number of comorbidities as well as geriatric conditions, such as cognitive impairment and frailty, which complicate the disease management and influence the outcomes. A recent American Heart Association Scientific Statement [7] considered four commonly encountered geriatric syndromes, namely, multimorbidity, polypharmacy, cognitive decline and delirium, and frailty, and laid a strong emphasis on integrating these syndromes into the cardiovascular care for older patients. The complex interplay between each geriatric syndrome and acute cardiovascular illness gives rise to novel healthcare issues that are partially independent of the underlying disease, creating novel challenges for the involved doctors, the cardiologists in particular.

Technological advances in the field of cardiac disease management have widened the range of available therapeutic options for patients with the most advanced diseases. The demand for advanced therapeutics is increasing expenditures. Therefore, in most developed countries, the costs of the healthcare systems are already unsustainable, and it is no longer sure that technological advances would be able to align with the shifts in the patients and the payers [8-10]. Consequently, therapeutics ought to be used rationally and adapted to the individual necessities and comorbidities [11, 12]. It is noteworthy that the priorities and necessities of the senior patients differ from those of the young patients and also from those of their relatives and the medical personnel. The seniors wish to maintain independence, adequate dealing with the daily necessities, and good quality of life. For instance, it is most important for seniors to be living in a familiar space without suffering. In this context, geriatric cardiology has emerged as a discipline that aims to adopt the principles of geriatric medicine into everyday cardiology practice. Accordingly, the responsibilities of a geriatric cardiologist may include traditional evidence-based cardiac management plus a comprehensive geriatric assessment, medication reduction, team-based coordination of care, and explicit incorporation of patient goals into the management of the disease [13].

The present article provides a review of the recent developments in the field of geriatric cardiology, with focus on the specific characteristics of the elderly in the prevention of

cardiovascular events, arterial hypertension (AH), bradycardic arrhythmias, atrial fibrillation (AF), coronary artery syndromes (CAS), valve heart diseases (VHDs), and heart failure (HeFa).

2. Prevention of Cardiovascular Events

Preventive therapy in primary care is guided by the risk thresholds for future cardiovascular events. Common sense and evidence-based medicine recommend a balanced diet suitable to the age and the physical necessities of the seniors. A central role should be assigned to the appropriate treatment of the comorbidities, particularly by avoiding unnecessary drugs, pharmacological interactions, and side-effects.

In recent years, it has been accepted that LDL-C plays a central role in the development of arteriosclerosis and the associated complications; therefore, a high priority has been assigned to the treatment of high LDL-C. The 2019 ESC/EAS Guidelines [14] recommend a ≥50% reduction in LDL-C from the baseline and a treatment goal of achieving an absolute LDL-C of <55 mg/dL (<1.4 mmol/L) for the very high-risk patients. In regard to the patients at high risk, a ≥50% reduction in LDL-C and a goal of achieving LDL-C <70 mg/dL (<1.8 mmol/L) are recommended. Several risk calculators have been developed for the assessment of the risk thresholds for future cardiovascular events. The most frequently used ones are SCORE, SCORE-HDL, PROCAM, AGLA, FRAM, and PCE [15]. However, all these have been used only in the patients of age up to 75 years, and are not valid for older patients. Therefore, at present, there are no globally accepted guidelines and recommendations for therapy for the treatment of high LDL-C in very old patients.

It has been demonstrated that a significant number of elderly patients with CAD are resistant to aspirin therapy, and that fasting blood glucose levels are closely related to aspirin resistance in the elderly patients with CAD [16]. A total of 22,781 elderly people in retirement communities were inquired regarding aspirin usage, and it was revealed that daily use of aspirin increased the risk of kidney cancer and almost doubled the risk of CAD; in addition, small, non-significant increased risks of stroke were observed in both males and females [17]. A previous study [18] has reported the effects of low-dose aspirin for primary prevention in 400 healthy ≥70-years-old seniors. In comparison to the placebo, aspirin was observed to induce significantly more adverse gastrointestinal symptoms, clinical gastrointestinal bleeding in 3% of the patients, and a significant decrease in the mean hemoglobin levels. The authors of the study suggested that caution should be exercised when aspirin is used for primary prevention in the case of cardiovascular diseases in the elderly. Another study [19] reported that low-dose aspirin exerted no effect on the cognitive function in middle-aged to elderly people who were at increased cardiovascular risk. Furthermore, the recent ASPREE study [20] has also confirmed that the use of low-dose aspirin as a primary prevention strategy in older adults results in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease in comparison to the placebo. Therefore, it is inferred that low-dose aspirin plays no significant role in the primary prevention of cardiovascular diseases in the elderly.

In secondary prevention, aspirin has been demonstrated to be effective in reducing ischemic events, although little is known regarding the bleeding risks in the elderly. Two previous studies [21, 22] estimated the bleeding risks in elderly patients associated with the use of aspirin for secondary prevention, and both the studies reported a significant risk for bleeding. Therefore, the use of aspirin for secondary prevention in the elderly is indicated, although with close monitoring

of the patients for aspirin-related adverse events, such as gastrointestinal irritability or bleeding risk, owing to the increased vulnerability of this subgroup, particularly in the context of polypharmacy, comorbidities, and frailty.

3. Arterial Hypertension

The prevalence of AH, systolic hypertension, in particular, is continuously rising throughout the world. AH is mainly the clinical expression of arterial stiffening that occurs as a consequence of aging. It is established that in geriatric patients, AH represents a major risk factor for cardiovascular morbidity and mortality, as well as for cognitive decline and loss of autonomy occurring later in life [23]. Older patients with AF are at the greatest risk of catastrophic complications, particularly stroke, as well as for intracranial hemorrhage (ICH) [24]. In Switzerland, 47% of the men and 38% of the women between the age of 65 and 74, and greater than 50% of the ≥75-years-old AF patients are treated for AH [25]. The 2018 ESC Guidelines for AH [26] recommend that in the patients with age ≥65 years, systolic pressure should be reduced to 130–139 mmHg, and that these values should be reached independent of the comorbidities. Indeed, the real evidence obtained in the community-dwelling older people with few comorbidities and preserved autonomy corroborates the beneficial effects of lowering the blood pressure in older hypertensive subjects even after the age of 80, and the observational studies conducted with frail older individuals treated for AH have reported higher morbidity and mortality rates compared to those with lower blood pressure levels [26]. Despite this, even though AH is, in practice, among the most common reasons for an outpatient medical visit, several hypertensive patients, especially the seniors, have poorly controlled blood pressure levels [27]. Clearly, in the very old subjects, the therapeutic strategy of one-size-fits-all is not applicable, owing to the enormous functional heterogeneity among these individuals. Geriatric medicine, therefore, recommends considering the function/frailty/autonomy status of older people as well as frequent assessments for possible symptomatic hypotonic blood values, orthostatic symptoms, worsening of the renal function, and occurrence of electrolyte disturbances [28, 29].

4. Cardiac Pacemakers and Implantable Cardioverter Defibrillators

Cardiac pacemakers and implantable cardioverter defibrillators (ICD) are important therapies with expanding indications for their application. Aging is associated with progressive fibrosis in both the sinus node and the atrioventricular (AV) conduction system (AV node, right and left bundles, and His bundles). Consequently, bradycardia due to sinus node and AV dysfunction is common in the elderly. In the presence of irreversible causes, implantation of a permanent cardiac pacemaker is often required in patients with symptomatic bradycardia. In the case of elderly patients with sinus node dysfunction, pacing modes capable of preserving AV synchrony are associated with a reduced incidence of AF and an improved quality of life. In the patients with AV block, the importance of preserving AV in the elderly remains debatable and is being evaluated presently [30].

The feasibility of ICD implantation in elderly patients has not been studied sufficiently. Recent data [6] suggest that older age, by itself, is not associated with a significant increase in the rates of complications arising from these devices. Noseworthy et al. [31] assessed the feasibility and safety of ICD therapy in the patients with age >80 years. The patients were divided on the basis of age

into the following two groups: group 1: 70–79-years-old, and group 2: ≥80-years-old. The two groups were similar in gender distribution, NYHA class, and the indication for implantation. Survival and complication rates were observed to be similar in the two groups. Therefore, age alone may not be sufficient as a suitable criterion for excluding ICD implantation, and the current consensus guidelines for ICD implantation appear to be generalizable for treating the octogenarians who are otherwise medically fit [31]. Notably, a recent DANISH Trial [32] demonstrated that ICD in non-ischemic HeFa does not result in a reduction in the long-term mortality.

5. Atrial Fibrillation

Aging is associated with progressive fibrosis in the atria. Several pathologies, such as renal insufficiency, AH, VHDs, diabetes mellitus, sleep apnea, obesity, and unhealthy lifestyle habits such as tobacco, alcohol, and reduced physical activity are the predisposing factors for AF, and contribute to the occurrence of its complications [33-35]. There is evidence that non-steroid antirheumatic drugs not only worsen the renal function, they also increase the risk for AF [36-38]. A strong correlation has been observed between age and the occurrence of AF, and being fueled by the aging of the population, this arrhythmia has become an epidemic. As a matter of fact, at present, the physicians are regularly encountering challenges in the management of AF in old patients. Currently, in the patients of age ≥65 years, the prevalence of AF is approximately 5%, and in 1.4% of these cases, AF remains undetected; 25% of the patients with age ≥40 years shall have AF in their lifetime [38]. Furthermore, the prevalence of AF is expected to double in the next four decades, and the 2016 ESC guidelines for the management of AF [34] recommend an "opportunistic" screening for the patients aged ≥65 years.

AF is responsible for up to 30% of the cerebrovascular strokes [36-42], and the treatment relies heavily on the prevention of stroke through the use of oral anticoagulation (OAC). Ischemic (CHA_2DS_2-VASc) and hemorrhagic (HAS-BLED) scores are used for guiding the OAC. These scores incorporate age as a factor, although unfortunately, there exist several limitations when these scores are applied to very old patients; currently, no scoring systems specifically developed and validated for guiding OAC in the elderly are available [41]. The HAS-BLED score mainly predicts the major bleeds, at least 80% of which are extracranial hemorrhages, particularly gastrointestinal, that carry low (<6%) mortality rates, are rarely the cause of the disability, and are manageable; however, this score does not provide specific assessment of the risk of ICH, which is possibly the greatest concern in the older patients. Therefore, it is not possible to identify the old patients with AF, in whom the risk of ICH plus fatal or disabling extracranial hemorrhage is likely to exceed the risk of fatal and disabling ischemic stroke, through the HAS-BLED scoring system. Therefore, Belmonte et al. [41] believes that it would be beneficial to develop a novel scoring system dedicated to the older patients with AF, which would encompass all the risk factors specific to this subset of the population.

OAC remains underused in the patients with age ≥80 years, due to the concerns of bleeding complications, comorbidities (renal dysfunction mainly), and poor functional autonomy [41-43]. However, age and frailty per se do not form absolute exclusion criteria for OAC in patients with AF who require OAC. A study [42] conducted with ≥90-year-old patients who were treated with OAC revealed that, compared to the patients without AF, the AF patients exhibited an increased risk of

ischemic stroke and similar risks of ICH. Among the AF patients, the use of warfarin, compared with no antithrombotic therapy, was associated with a positive net clinical benefit, a lower risk of stroke, and no difference in the ICH risk. The use of non-vitamin K antagonists (NOACs), compared with no antithrombotic therapy, was associated with a lower risk of ICH, with no difference in the risk for ischemic stroke. Therefore, OAC may be considered a thromboprophylaxis for very old patients, while NOACs would be the more favorable choice. However, there are no one-size-fits-all NOACs, and this also applies to elderly, particularly the vulnerable patients [43]. Furthermore, a significant proportion of geriatric patients cannot be treated with the necessary OAC because of the comorbidities, and in these patients, occlusion of the left atrial appendage may be a valuable choice [44].

Radiofrequency ablation is emerging as an effective therapy in the treatment of AF [45]. In reality, this therapy is rarely used in the old patients, partially because AF is sustained and mostly because of the comorbidities. Rhythm-control is also rarely indicated in the geriatric patients, who are generally treated using heart rate-control, usually through a β-blocker or diltiazem or verapamil [46]. In drug-resistant, poorly-tolerated AF, AV junction catheter ablation and pacemaker implantation has been used as the final option and has proven to be quite effective [47].

6. Coronary Artery Syndromes

The 2019 ESC-Guidelines for CAS [48] recommend the use of a pretest propensity risk of disease (PPRD), which is calculated using the age and sex of the patient, clinical presentation of the myocardial ischemia, and the Canadian Cardiovascular Society (CCS) grading of AP. The PPRD would assist in saving medical resources by allowing an effective selection of appropriate diagnostic procedures (non-invasive versus invasive) and therapeutic treatment (invasive-surgical versus conservative-pharmacological). The non-invasive approach is suitable for the patients with a medial (<85%) PPRD, while the invasive approach would be suitable for those with high (>85%) PPRD or severe AP (CCS grade > III). The PPRD is always higher in the old compared to the young patients as age is an important factor for its computation. A necessary invasive approach for treating potentially lethal and treatable conditions should not be avoided in old patients, although with the consideration of comorbidities and frailty. Notably, old patients with CAS often present with atypical symptoms, e.g., they present more often with dyspnea rather than pain, or with atypical localization of AP. In addition, such patients usually present with either an unstable AP or a non-ST-segment elevation myocardial infarction, and present less frequently with ST-segment elevation myocardial infarction [49].

In previous years, the interventional risk of coronarography and revascularization has reduced, and the related techniques have been improved. Therefore, it is possible to perform further invasive interventions in the old patients compared to previous times. Recent data [50] demonstrate that patients with age ≥80 years would benefit more from a myocardial revascularization compared to intensive pharmacological therapy. However, medical therapy and revascularization is not inferior to revascularization in the ≥90-year-old patients. Indeed, modern pharmacological therapy is better compared to previous times, and may reduce symptoms and improve the life-quality and survival, at least in the patients without acute ischemic conditions, rendering it not inferior to revascularization [50]. A conservative approach is followed in the cases

for which revascularization is not indicated or is technically impossible, which may also serve as a valid opportunity for the old patients who refuse an intervention. It is understandable why an old patient may refuse an invasive therapy and a polytherapy. However, currently, cardiologists are also encountering old patients who would rather favor an intervention to a polytherapy. Treatment of old cardiac patients must be individualized and presumes adequate information from the patients and their relatives [51-53].

7. Valve Heart Diseases

VHDs are associated with high morbidity and high mortality [54]. Since the incidence of VHDs increases with age, the number of patients presenting with VHDs is increasing with the aging of the population. A Euro Heart Survey on VHDs [55] conducted in 2003 reported that the incidence of VHDs for both mitral and aortic valves was <1% in the old patients with age <64 years and 6% in the ≥75-year-old patients. Notably, 30% of the patients with severe, symptomatic, single VHDs, usually the elderly with relevant comorbidities, did not undergo surgery. A 2015 European VHDs survey [56] revealed that despite the high prevalence and morbidity associated with VHDs, the awareness and knowledge regarding them in the general population were alarmingly low, with only 3.8% of the population understanding what aortic stenosis (AS) was. Another survey conducted in [57] reported a small improvement in the general knowledge regarding the VHDs, while the detailed understanding of AS remained low.

In the elderly, the etiology of AS is degenerative in the majority of the cases [52-57]. However, large-scale surveys [58-60] have reported that 22% of the octogenarians presenting for surgery for isolated AS had bicuspid valve disease. Isolated aortic regurgitation, reported in 2.0%–2.5% of the 70–83-year-old patients [without gender differences], is significantly less common compared to AS [61-63].

In developed countries, mitral regurgitation (MR) is the most frequent VHD in the ≥65-year-old patients, while geriatric patients account for approximately 40% of all the patients with MR, among which 4.5% are ≥80 years old [54]. In the Framingham study, the prevalence of moderate MR in 70–83-year-old men was 11.1% [61]. In the elderly, MR occurs mostly due to degenerative and ischemic pathologies [54, 62], and is associated with concomitant AS in 22%–48% of the cases.

In the general population, tricuspid regurgitation (TR) has an incidence of 1.2%–1.5% [54, 64]. The prevalence of TR increases with age, particularly in females; in the 70–83-year-old patients, the incidence of TR is 5.6% in women and just 1.5% in men [59]. In young patients, TR is usually associated with congenital, infectious, traumatic, and rheumatic pathologies, and rarely culminates in implantation for pacing or leaflet damage due to biopsy [64, 65]. On the other hand, in geriatric patients, TR usually develops due to left heart disease [62]. Severe TR is associated with higher mortality and poorer outcomes, regardless of patient age and other comorbidities [65].

In geriatric patients, VHDs are often associated with CAD [54, 66]. Data regarding the elderly subjects are limited, although it is proven that the coexistence of AS and CAD leads to a worse prognosis compared to that for an AS of comparable severity occurring alone [54, 66]. Moreover, significant MR is observed in one-fifth of the octogenarians with non-ST elevation myocardial infarction, with poor prognosis [67, 68].

The concept of transcatheter aortic valve replacement (TAVR) for the treatment of AS emerged in the early 1990s. In 2002, Cribier [69] performed TAVR in humans using femoral vein access and

a trans-septal approach. The associated techniques and valves are undergoing continual improvement. Since 2005, aortic valves are being implanted using the transfemoral artery, and a trans-apical approach is used only in patients with unsuitable vascular access [70]. The surgical risk is assessed using scores, usually the STS score or the European System for Cardiac Operative Risk Evaluation score [54]. Currently available data present TAVR as safe and efficient, and it is now recommended for the patients at intermediate risk; it is expected that newer data being generated may enable the expansion of the indication for TAVR to low-risk patients as well [70-72]. However, the risk scores may be misleading in the ≥80-year-old patients, as peri-operative complications exist beyond the scores, owing to frailty and very old age per se [71-73]. Nonetheless, the current data demonstrate that TAVR is beneficial in octogenarians [70-77] as well as in >90-year-old patients [75, 76]. Furthermore, a recent study [76] conducted with asymptomatic patients with very severe AS aged between 20 and 80 years has proven that the incidence of operative mortality or death from a cardiovascular cause was significantly lower in those treated with early surgical aortic valve replacement compared to those who received conservative care.

Recent data report the effect of antithrombotic therapy in TAVR-treated patients. The GALILEO trial [77] report stated that in patients without an established indication for OAC after successful TAVR, a treatment strategy including rivaroxaban at a daily dose of 10 mg was associated with a higher risk of death or thromboembolic complication as well as a higher risk of bleeding compared to an anti-platelet-based strategy. In a sub-study of the GALILEO trial [78], it was revealed that in the patients without an indication for long-term OAC after successful TAVR, a rivaroxaban-based antithrombotic strategy was more effective in preventing sub-clinical leaflet motion abnormalities compared to an anti-platelet-based strategy, although the former was also associated with a higher risk of death or thromboembolic complications as well as a higher risk of bleeding. These data demonstrate that a rivaroxaban-based antithrombotic strategy cannot be recommended for the patients who have undergone a successful TAVR.

The etiology of MR plays an important role in the therapy, particularly in old patients. In developed countries, the etiology of MR in geriatric patients is usually secondary [54, 61, 79, 80]; in this clinical setting, the clinical benefit of surgery remains uncertain. The ESC Guidelines [79] provide no recommendations for the therapy of secondary MR, while the American Guidelines [80] propose individualized approaches. Currently, mitral valve repair (MVR) is the generally accepted "gold standard" treatment for degenerative MR [81-83], while surgical mitral valve replacement (SMVR) is indicated only in cases where the expected clinical improvements exceed the increased operative risk associated with aging and comorbidities [80-85]. MVR has a high short-term mortality of 25%–30%, and the limited life-expectancy of old patients, the lower technical complexity of SMVR with shorter cardio-pulmonary bypass times, and a decreased risk of failure with a requirement for reintervention may explain the lower-than-expected rate of MVR [80]. Nonetheless, in octogenarian patients, 15% operative mortality has been reported for SMVR [76]. At present, according to the administrative American databases, MVR was performed in less than 50% of the elderly patient cases [81-87]. Especially when a concomitant coronary bypass surgery is not planned, most cardiologists are inclined to opt for an optimal pharmacological, and if indicated, cardiac resynchronization therapy [54]. The recent availability of percutaneous devices for the treatment of mitral valve diseases may offer an alternative approach for the management of MR [81, 82]. However, the evidence for treatment of MVR with MitraClip is not extensive, and the only

transcatheter therapy recommended at present is the one with MitraClip for the high-risk surgical patients; however, it is considered that the treatment is unlikely to improve the quality of life and survival [54, 72].

Previously, the approach to TR treatment was rather conservative. However, the understanding of the etiologies and effects of TR have changed, and nowadays, pathology is often being considered for a repair [54]. In elderly patients with long-standing disease, TR frequently raises a challenging treatment dilemma [88, 89]. Transcatheter therapies are being tested in feasibility trials, and among these, the Tri-align system has been delivered percutaneously through the right internal jugular vein [54].

8. Heart Failure

The incidence and prevalence of HeFa increase with age, owing to the physio-pathological changes and the increasing frequency of predisposing comorbidities that occur with aging. Indeed, over 80% of HeFa patients are older than 65 years [90-93]. Despite that, information regarding geriatric HeFa patients is limited because of lack of clinical trials in population-based studies and because clinical trials typically enroll younger patients. Havranek et al. [90] studied the charts of Medicare patients hospitalized in the period between 1998 and 1999 with a principal diagnosis of HeFa. After excluding the patients who were <65 years of age, those who were either discharged to other acute-care facilities or discharged with medical advice, or the ones who were receiving long-term hemodialysis, the authors collected data from 34,587 patients. More than half of these patients had CAD and a history of AH, approximately 40% had diabetes, and approximately one-third had chronic obstructive pulmonary disease. Left ventricular ejection fraction was <40% in only 50.4% of the patients in whom it was assessed. Renal insufficiency was more common with advancing age. This study evidenced that elderly HeFa patients are a heterogeneous group and differ substantially from the younger patients enrolled in the clinical trials. The authors of the study suggested that there is an urgent requirement for evidence-based guidance for the treatment in the context of comorbidities, poor renal function, HeFa with preserved left ventricular systolic function (HFpEF), and residence in long-term care facilities. Weir et al. [91] reported similar data, stating that the prevalence of HeFa increases with age and that the majority of the HeFa patients in the future would be the elderly. Despite these reports, most of the current evidence for the management of this serious condition is provided by the trials that have largely excluded the older patients. As a consequence, older patients who may derive the greatest benefit from the treatments known to reduce morbidity and mortality in HeFa are being treated without any specific recommendations.

Furthermore, the diagnosis and management of HeFa in older adults could be challenging. Therefore, Ahmed [92] proposed a mnemonic DEFEAT–HeFa approach (**D**iagnosis, **E**tiology, **F**luid, **E**jection fr**A**cion, and **T**reatment), which would simplify the diagnosis and therapy in HeFa in the geriatric patients.

The PREDICT study [93] confirmed that much clinical research that is of relevance to elderly patients examines individuals who are younger in comparison to those who have the disease in question, and this is particularly true for HeFa. In the World Health Organization Clinical Trials Registry Platform of HeFa clinical trials, almost all the studies excluded geriatric patients, either by an arbitrary upper age limit or by other exclusion criteria that might indirectly cause limited

recruitment of the older individuals. Exclusion criteria were classified into two categories: justified or poorly justified. Among the 251 trials investigating the treatments for HeFa, 64 (25.5%) excluded patients by an arbitrary upper age limit. Such exclusion was significantly more common in the trials conducted in the European Union compared to those conducted in the USA [31/96 (32.3%) versus 17/105 (16.2%)] and in the drug trials sponsored by public institutions compared to the ones organized by private entities [21/59 (35.6%) versus 5/36 (13.9%)]. Overall, 109 trials (43.4%) on HeFa had one or more poorly justified exclusion criteria that could limit the inclusion of older individuals. A similar percentage of clinical trials with poorly justified exclusion criteria was obtained in pharmacological and non-pharmacologic trials. The authors concluded that despite the recommendations of national as well as international regulatory agencies, exclusion of older individuals from the ongoing trials for HeFa continues to be widespread.

In 2009, Cheng and Nayar [94] reviewed 40 clinical studies on HeFa. The drugs used were angiotensin-converting enzymes inhibitors, angiotensin-II receptor blockers (also referred to as angiotensin II receptor antagonists or AT_1 receptor antagonists), β-blockers, diuretics, aldosterone antagonists, digoxin, and [in Afro-Americans] a combination of hydralazine and nitrates. The authors reported that no clinical trials assessing the effects of HeFa treatment exclusively in elderly patients has been conducted. Most clinical trials did not specify the number of included elderly patients or had included 30%–50% elderly patients, usually less than 70 years in age. The insufficient data that are currently available appear to confirm that HeFa therapy, which reduces mortality and morbidity in the non-elderly patients, is also beneficial in elderly patients. However, elderly patients exhibit different responses to HeFa pharmacotherapy compared to the younger patients and are also susceptible to adverse events, such as orthostatic hypotension, renal dysfunction, electrolyte disturbances, and interactions with medications received for the treatment of the comorbidities. Therefore, close monitoring of elderly patients undergoing HeFa treatment is essential to ensure optimal outcomes.

Despite the use of β-blockers for more than 40 years, no study has so far demonstrated that these reduce morbidity and mortality in the elderly, and therefore, β-blockers should not be considered first-line therapy in the treatment of AH in geriatric people [95]. Despite having gained an indisputable status in the therapy of HeFa, β-blockers may exhibit several unknowns when used in elderly patients. Previous epidemiological studies have demonstrated failure in reaching the guideline-recommended β-blocker dose in more than one-half of the old HeFa patients, even in those managed by cardiologists [96]. It is plausible not to withhold treatment with β-blockers when discharging the elderly HeFa patients with left ventricular systolic dysfunction, although a less-tight up-titration than that dictated by the major trials is advisable; moreover, it remains unclear whether to pursue the published target doses or that clinical benefit could be gained with lower doses as well [96].

Ivabradine has been approved for use as an adjunct in the treatment of selected patients having symptomatic HeFa with reduced ejection fraction (HFrEF), those who are in sinus rhythm, and the ones with resting heart rate of at least 70 beats per minute despite treatment with an evidence-based dose of a β blocker (or the maximal tolerated dose below that), angiotensin-converting enzymes or angiotensin-II receptor blockers, or aldosterone antagonists. Certain authors suggest, although, without evidence, that ivabradine might also be useful in patients with HFpEF [97, 98]. Indeed, it has been observed that the safety and efficacy of ivabradine are comparable in young and old patients [99]. However, a recent study confirmed that the evidence

for treating elderly HeFa patients is generally extrapolated from the cohorts who are up to 2 decades younger, while the real-life therapy requires extrapolation of findings from the trials conducted in much younger populations; as such, little is known regarding the tolerability and the side-effect profile of evidence-based ivabradine therapy in the elderly patients [100]. Furthermore, most of the geriatric HeFa patients have AF (ivabradine is ineffective in AF), several have a sick-sinus dysfunction (a contraindication for ivabradine), and at least 50% of the geriatric HeFa patients have CAD (role of ivabradine in CAD is not yet elucidated beyond doubts). Therefore, in a real-life cardiology practice, ivabradine is rarely used in geriatric HeFa patients. Prescribing patterns and potential benefits in the elderly are influenced heavily by polypharmacy and the comorbidities. Increasing longevity may become less relevant in the frail elderly, while improving the quality of life is almost always the priority; improving wellbeing, maintaining independence for a longer period, and delaying institutionalization come as bonus. These unknowns have encouraged a recently commenced study [101] for the assessment of the beneficial and harmful effects of ivabradine in the treatment of CAD and/or HeFa. Unfortunately, data shall again be collected from the currently available publications, in which the data on geriatric patients remains scarce.

Sacubitril/valsartan has been recently approved for the treatment of HFrEF. Since it has been recently introduced in the armamentarium for HeFa treatment, "field-practice" evidence is scarce. A case report [102] described the effect of sacubitril/valsartan therapy in a hypertensive geriatric patient with HFrEF. Sacubitril/valsartan could reduce dyspnea and blood pressure, and improved the left ventricular pathologic changes as assessed by echocardiography. Another study [103] reported the effect of sacubitril/valsartan versus olmesartan in 588 hypertensive Asian patients with a mean age of 70.7 years. Sacubitril/valsartan exhibited greater lowering of blood pressure compared to olmesartan, and no relevant side-effects were reported. These data should be considered hypothesis-generating, although they are insufficient for deciding whether the use of sacubitril/valsartan is safe in the geriatric patients with HFrEF.

Lastly, the EMPA-REG OUTCOME trial [104] demonstrated that empagliflozin, an inhibitor of sodium-glucose cotransporter 2, significantly reduced the risk of cardiovascular deaths, non-fatal myocardial infarction, or non-fatal stroke in subjects with type 2 diabetes mellitus and established CAD, with a greater benefit in those over 65 years of age. In addition, empagliflozin was associated with a reduction in the risk of secondary composite endpoint of HeFa hospitalization or cardiovascular death, with a consistent benefit across the subgroup age as well as in the patients with or without baseline HeFa [105]. Although several factors, including osmotic diuresis, reduction in plasma volume, and sodium retention, may explain the effects of empagliflozin on HeFa and cardiovascular death, the actual underlying mechanism remains uncertain. Empagliflozin has exhibited a good safety profile. However, a higher risk of volume deletion-related adverse events and urinary infections in the elderly patients is expected [106].

9. Discussion

Since the proportion of older people in the population is increasing, practicing cardiologists are encountering an increasing number of consultations from very old patients. Although certain individuals are biologically younger than their anagraphic age, the geriatric patients in general are frail and have several comorbidities. Progress in the field of medicine has rendered it possible to

treat lethal cardiac diseases in very old patients. This is certainly good, although the demand for invasive therapies and novel drugs has created a rapid increase in the expenditures.

Geriatric cardiology has become a necessity. Owing to the comorbidities, several of which are critical, in the elderly patients, it is imperative for the geriatric cardiologists to be, first of all, master internists at all times. Old patients, with their peculiar pharmacokinetics and multiple illnesses, are also oversensitive to drugs. The former USA Secretary of Defense, *Donald Rumsfeld* once wrote, "There are known knowns; the things we know that we know; then there are known unknowns; the things that we know that we do not know; however, there are also the unknown unknowns; the things we do not know that we do not know". This holds true for geriatric cardiology. It is impossible to directly extrapolate the experience with the young patients to the old people. Given the increasing proportion of the old in the population, there is a necessity to train a large number of geriatric cardiologists to offer the best of care to the old patients. There is also a requirement to understand the effects exerted by the aging process on the human heart, and the studies exploring this should command priorities in the financial as well as other forms of support.

Abbreviations

AF: Atrial fibrillation; AP: Angina pectoris; AS: Aortic stenosis; AR: Aortic regurgitation; AV: Atrioventricular; CAD: Coronary artery disease; CCS: Canadian cardiovascular society; HeFa: Heart failure; HfpEF: Heart failure with a preserved ejection fraction; HfrEF: Heart failure with a reduced ejection fraction; ICD: Implantable cardioverter defibrillators; ICH: Intracerebral hemorrhage; NOACs: Non-vitamin K antagonists; MR: Mitral regurgitation; MVR: Mitral valve repair; OAC: Oral anticoagulation; PPRD: Pretest propensity risk of disease; SMVR: Surgical mitral valve replacement; TAVR: Transcatheter aortic valve replacement; TR: Tricuspid regurgitation; VHDs: Valve heart diseases.

Author Contributions

G. Cocco collected and analyzed the references, and wrote the paper. Ph. Amiet checked the collection and completness of data, and together with Cocco agreed on the printed data.

Competing Interests

The authors have declared that no competing interests exist.

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