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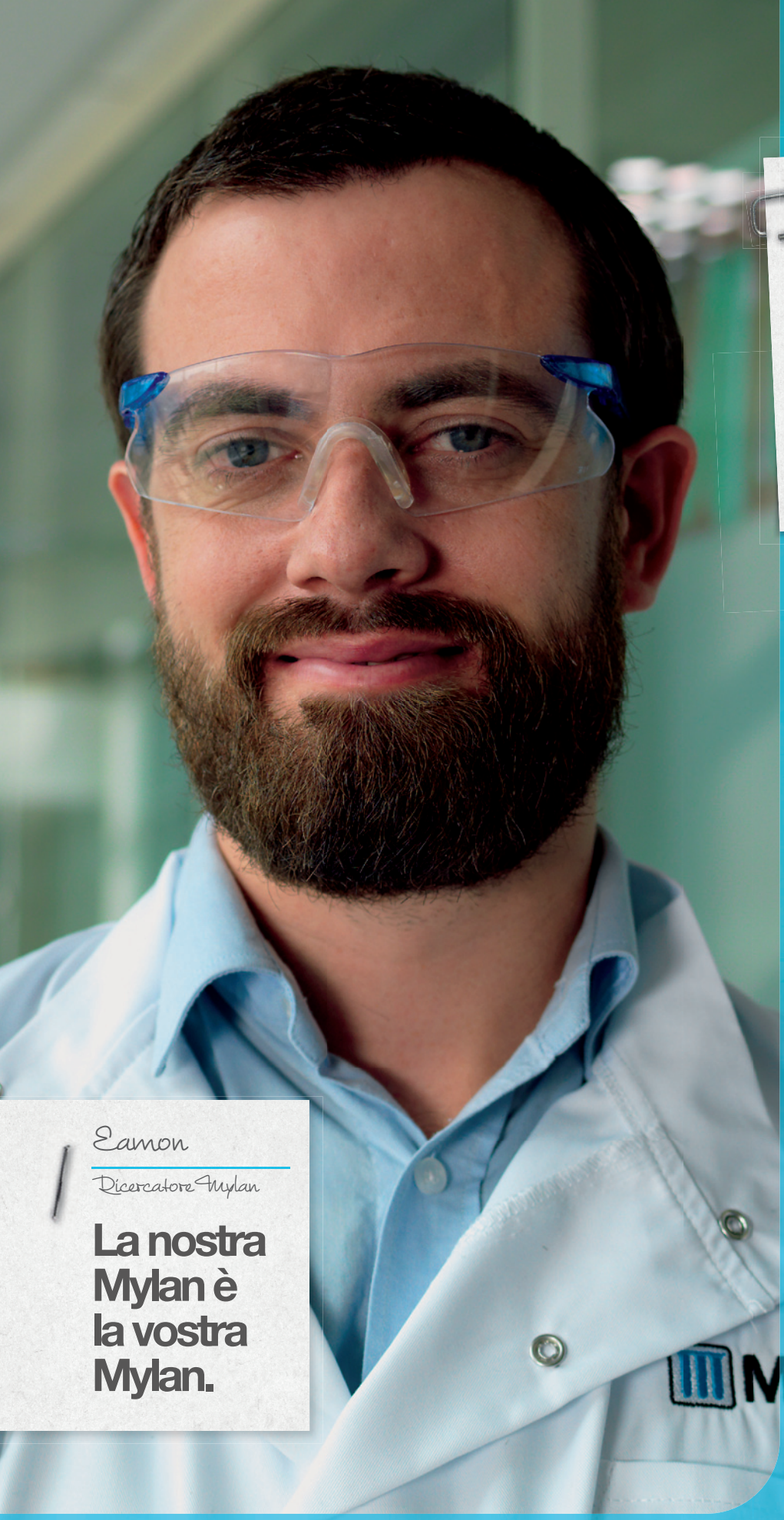

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*Autorizzazione per modifica degli astucci con inserimento dei pittogrammi.

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Contents • Sommario

NEW CHALLENGES FOR THE MANAGEMENT OF CARDIOVASCULAR AND NEUROLOGICAL DISORDERS IN THE ELDERLY

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Novel instruments for risk stratification of elderly patients with cardiovascular diseases

Nuovi strumenti di valutazione prognostica del paziente anziano con patologia cardiovascolare

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Le malattie cardiovascolari rappresentano la causa principale di mortalità e morbidità nella popolazione geriatrica e uno dei capitoli più importanti della spesa socio-sanitaria. Le condizioni di salute dell'anziano presentano aspetti complessi che vanno al di là dei criteri cronologici e dei fattori di rischio legati alla singola malattia. Inoltre, gli obiettivi terapeutici nel paziente geriatrico devono considerare non solo la riduzione della mortalità ma anche lo stato funzionale e la qualità della vita rendendo necessaria un'accurata valutazione di tutti i fattori di potenziale impatto sulla prognosi. A tal riguardo, la maggior parte dei modelli tradizionali adottati per la stratificazione del rischio nelle patologie cardiovascolari, ideati e applicati nella popolazione adulta, non considerano in maniera adeguata la complessità dell'anziano e risultano non appropriati in tale popolazione. La fragilità, una condizione legata ad una riduzione fisiologica età-correlata delle riserve d'organo e all'incremento della vulnerabilità, è un predittore indipendente di outcome avversi e mortalità nel paziente geriatrico. Le misure di performance fisica e di assessment multidimensionale geriatrico sono state recentemente esaminate allo scopo di migliorare la stratificazione prognostica del paziente anziano con patologie cardiovascolari. In questo articolo viene presentata una rassegna dei più comuni strumenti prognostici adottati in pazienti con malattie cardiovascolari; vengono inoltre illustrati i nuovi strumenti di stratificazione del rischio che tengono conto delle correlazioni tra la condizione di fragilità e le malattie cardiache, con particolare riferimento alla valutazione funzionale ed alla recente introduzione nella pratica clinica del "Multidimensional Prognostic Index".

***Parole chiave*: Malattie cardiovascolari, Valutazione multidimensionale geriatrica, Anziano, Fragilità, Multidimensional prognostic index, Prognosi**

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality among the adults aged 65 and older, affecting approximately 40 million of older subjects only in the United States. For individuals over the age of 80 years the prevalence of CVD reaches 83% of men and 87% of women [1]. Nowadays, due to evolving technical innovations, a wide number of older patients, previously considered as "ineligible", can be treated with devices, procedures and pharmacological therapies [2]. Uncertainty regarding individual benefit from such treatments has been coupled with growing economic constraints on healthcare systems, such that the issue of appropriate patient selection has increased. On the one hand there is need of avoiding the under-treatment of older adults just for a "chronological age" criterion, while on

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the other hand it is more and more important to optimize resource allocation to prevent patients from receiving costly but futile interventions [3]. The majority of standardized scores for risk stratification in CVD have been developed and validated in middle aged adults; however, in the very elderly subjects their value in discrimination of who will benefit rather than be harmed by a specific management strategy or intervention is unreliable. Moreover, standardized guidelines are often not useful in the very old adult with significant multi-morbidity, polypharmacy, and in which goals of care should be focused not on mortality only but also on quality of life and in maintaining individual's independence [4]. Hence the importance of assessment tools accounting of the complexity of older individuals, able to measure the multiple determinants of frailty and to stratify risks due not only to the severity of CVD itself but also on the global and functional status of older persons [5 6].

DISEASE-SPECIFIC PROGNOSTIC TOOLS

Heart failure

Heart failure (HF) is the leading medical cause of hospitalization among people aged 65 years or older in the developed countries and imposes a substantial burden on individuals and society in terms of mortality, morbidity, and associated healthcare costs. The most commonly used classification system of severity of HF, in relation to functional limitation, is that developed by the New York Heart Association (NYHA). The NYHA functional classification assigns patients to 1 of 4 classes depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels that would limit normal individuals (class I) [7]. Studies have shown a very poor post-discharge prognosis in patients admitted to hospital for acute HF, with high risk of re-hospitalization (about 40% at 6 months) and death (11% and 33% at 1 and 12 months respectively) [8]. Predictive models for short- and long-term mortality in patients with HF have been described. The EFFECT risk score, based on clinical signs [systolic blood pressure (SBP) and respiratory rate], laboratory tests [blood urea nitrogen level (BUN) and serum sodium concentration], and five comorbid conditions (cerebrovascular disease, chronic obstructive pulmonary disease, hepatic cirrhosis, dementia and cancer), predicted mortality at 30-days and 1 year [9]. The ADHERE risk tool, thought to be more practical and applicable bedside, was able to predict in-hospital mortality in HF combining BUN, heart rate, SBP and age in two cohort of over 32.000 subjects [10]. More recently another simple four-item risk score based on BUN, hyponatremia, SBP and peripheral arterial disease, showed to identify older patients with HF at high risk of death within 6 months [11]. Finally, 1-, 2-, and 3-year survival of patients with HF could be predicted by the Seattle Heart Failure Model, a score based on clinical, pharmacological, device and laboratory characteristics [12].

Aortic stenosis

Aortic valve stenosis is the most frequently acquired native valve disease, and its prevalence is increasing with age. Surgical aortic valve replacement (SAVR) has been for long time the mainstay of therapy for severe aortic stenosis. However, trans-catheter aortic valve implantation (TAVI) is now generally accepted as the new standard of care for patients with symptomatic aortic stenosis with contraindications to surgery or those considered to be at high surgical risk [13]. In order to assess patient surgical risk, several scoring systems have been traditionally and widely used. The European System for Cardiac Operative Risk Evaluation (EuroSCORE), and the updated EuroSCORE II [14 15], use cardiac-related factors, such as Left Ventricular Eject Fraction (LVEF), previous angina or cardiac surgery, as well as patient-related factors, like age, comorbidity and laboratory tests, for predicting risk of death in patients undergoing SAVR. The other broadly used prognostic measure is the Society of Thoracic Surgeon (STS) risk score, which has been developed using clinical and demographical data from a large database and allow to have different risk models for operative mortality as well as possible post-operative complications [16]. Recently, a mainly Italian project was aimed to develop and validate a score for mortality risk in TAVI. The Survival posT-TAVI (STT) score consider previous stroke, inverse of renal clearance and systolic pulmonary blood pressure ≥ 50 mmHg. In a population of older subjects (mean age 81 years) STT score was superior to STS and EuroSCORE to predict 1-year all-cause death [17].

Coronary artery disease

Despite one-third of patients hospitalized for acute myocardial infarction (AMI) are 75 years or older, this peculiar age group has been generally excluded or at best under-represented in AMI clinical trials and epidemiological studies. Traditional risk stratification scores in ischemic cardiac disease include clinical, laboratory and instrumental data such as heart rate, blood pressure, cardiac biomarkers, ECG characteristics, LVEF, etc. [18]. None of the currently available risk stratification tools for AMI consider the weight of other conditions such as burden of comorbidities, cognitive and functional status and incorporate these geriatric conditions. In this perspective the Comprehensive Evaluation of Risk Factors in Older Patients with AMI (SILVER-AMI) study, a currently ongoing prospective cohort study, has been designed with the purpose of creating a more personalized assessment of risk (included as outcome readmission, all-causes mortality and decline in functional status) and identifying potential targets for interventions in older ischemic cardiac patients [19].

PROGNOSIS IN OLDER ADULTS: THE ROLE OF FRAILTY

Frailty is a biological syndrome that reflects a state of reduced physiological reserve and increased vulnerability to stressors such as illness, drugs, life events [20]. When exposed to such stressors, frail patients are at risk for marked and often disproportionate decompensation, adverse events, procedural complications, prolonged recovery, functional decline, disability and mortality [21]. Nowadays it is widely accepted that frailty is determined by disorders in multiple domains, including neuromuscular, metabolic, immune, mobility, strength, endurance, nutrition and cognition [22]. In particular, abnormalities involving endocrine, immune and neuromuscular systems lead to the final common pathways of sarcopenia, considered a key component of frailty and characterized by progressive and generalized loss of skeletal muscle mass, strength and performance [23]. CVD and frailty seem to share several features as chronic low-level inflammatory status that may represent a common pathophysiologic basis for both conditions, due to lifelong antigen exposure, obesity, insulin resistance and imbalance in redox. Markers of inflammation such as activation of neutrophils and monocytes, elevations in high sensitivity C-reactive protein, interleukin 6 and thrombotic markers are found in frail patients and in those with CVD [24]. Very recently, even a condition of pre-frailty, defined as the presence of 1 or 2 among low energy expenditure, exhaustion and slow gait speed, has been strongly associated to a higher risk of developing CVD (over a 4.4-year follow-up period) in a cohort of community-dwelling older individuals with no disabilities and CVD at baseline [25]. Understanding the relationship between frailty and CVD remains challenging. It seems possible a bidirectional causal relationship between these two conditions, like a vicious cycle. In this perspective, interventions aimed to break this vicious cycle earlier in the diseases course would be able to enhance global physiologic reserve and to improve outcomes [26]. On the other hand, in a clinically manifest stage of disease, in order to better assess benefits and risks, avoiding over- or under-utilization of therapeutic interventions and resources, recent guidelines recommend including life expectancy in clinical decision-making paths. The recognition of frail older subjects may enable to better estimate prognosis and consequently to avoid potentially useless time- and cost-consuming medical interventions in such population [27].

NOVEL INSTRUMENTS FOR PROGNOSTIC STRATIFICATION IN OLDER SUBJECTS WITH CVD

Physical performance

Clinical approach to older patients with CVD cannot be limited to a traditional, purely cardiologic paradigm, but should also consider peculiarities of these syndromes in late life, which encompass problems in the physical, psychosocial and cognitive domains. Complex clinical pictures and highly unstable health trajectories distinguish older ill adults, for whom a traditional clinical approach based just on disease-specific guidelines can be equivocal and misleading with regard to prognosis, resulting in poor quality of care and negative outcomes [28]. In the last years, physical performance has been shown to contribute to functional evaluation and to provide valuable prognostic information in older subjects, in a variety of settings and

Tab. I. Summary of prognostic instruments in older adults with CVD.

Index	Variables	Authors
Disease-specific risk stratification tools		
NYHA Functional Classification	Limitation of physical activity due to symptoms. Class I: no limitation of ordinary physical activity. Class II: no symptoms at rest; slight limitation of ordinary physical activity. Class III: no symptoms at rest; marked limitation in less than ordinary physical activity. Class IV: symptoms at rest; unable to carry on any physical activity without discomfort.	New York Heart Association Criteria Committee 1964
EFFECT	SBP, BUN, respiratory rate, serum sodium concentration; comorbidity	Lee et al. 2003
ADHERE	SBP, BUN, heart rate, age	Fonarow et al. 2005
4-item RISK SCORE	SBP, BUN, serum sodium concentration, peripheral arterial disease	Huynh et al. 2008
SEATTLE HEART FAILURE MODEL	Clinical status, therapy (drugs and devices), laboratory parameters	Levy et al. 2006
STS RISK SCORE	Clinical and demographical data	O'Brien et al. 2009
EuroSCORE	Cardiac-related factors and patient-related factors	Nashef et al. 1999
STT SCORE	Previous stroke, renal clearance, systolic pulmonary blood pressure	D'Ascenzo et al. 2014
Novel instruments for risk stratification, no disease-specific		
GAIT SPEED	Gait speed at subject's usual velocity on 4 m	Studenski et al. 2003
SPPB	Balance, gait speed, lower limb performance	Guralnik et al. 1994
CHS FRAILTY SCALE	Unintentional weight loss, low physical activity level, weakness, exhaustion, slow gait speed	Fried et al. 2001
MPI	Basic and Instrumental Activities of Daily Living; Short Portable Mental Status Questionnaire; Cumulative Illness Rating Scale; Exton-Smith Scale; Mini Nutritional Assessment; social status; number of drugs	Pilotto et al. 2008

Abbreviations: NYHA=New York Heart Association; EFFECT=Enhanced Feedback for Effective Cardiac Treatment; ADHERE=Acute Decompensated Heart Failure National Registry; STS=Society of Thoracic Surgeon; EuroSCORE=European System for Cardiac Operative Risk Evaluation; STT=Survival posT-TAVI; SPPB=Short Physical Performance Battery; CHS=Cardiovascular Health Study; MPI=Multidimensional Prognostic Index; SPB=systolic blood pressure; BUN=blood urea nitrogen level

clinical conditions. One of the most used tools is the Short Physical Performance Battery (SPPB), which includes 3 tests exploring balance, gait and indirectly, via repeated chair standing, lower limb strength [29]. A score from 0 (worst performance) to 4 (best performance) is attributed at each test, based on quartile distribution of the performance in a reference population. The final score (range 0-12) is obtained by summing the three individual scores. Population-based cohort studies have demonstrated that the SPPB is a strong, independent predictor of mortality, institutionalization, and incident disability in old age. In subjects older than 65 years living in the community, the risk of death and disability increased 7% to 9% for every point reduction in SPPB score, even after adjustment for complex measures of comorbidity [30]. The validity of SPPB has been demonstrated also in clinical settings. SPPB is able to predict hospitalization, declining health status and physical functioning in outpatients [31]. In patient hospitalized for an acute medical event (in most cases congestive HF), SPBB is a powerful short- and long-term predictor of global clinical and functional status, length of stay, re-hospitalization or death [32]. SPPB has been applied to elderly patients being discharged from hospital after an episode of worsening HF: the battery accurately predicted 1-year survival independently of demographics, comorbidity and, notably, also of ejection fraction and NYHA classification, both measures which are recognized as cornerstones of risk stratification in cardiac patients [33].

Another widely used measure of physical performance, more simple than the multi-item SPPB, is gait speed, that has been claimed as a novel "vital sign" for older person [31] and that has demonstrated to be a good predictor of survival and other strong outcome in aged population [34]. Gait speed is usually evaluated on a short distance (4 or 5 m), walking at a usual, comfortable velocity. Accepted cut-off varies between 0.8 and 1 m/s. In cardiology gait speed has shown to improve risk stratification for adverse outcome after cardiac surgery, percutaneous coronary intervention and

TAVI [35 36]. In particular in assessing surgical risk for SAVR, physical performance evaluated by gait speed seems to increase the prognostic value of a traditional validated score as the STS risk score. For a given STS score, predicted mortality or major morbidity were 2-3 times greater in patients with slow gait speed vs. normal [37].

Multidimensional Prognostic Index

It is more and more evident that the prognosis of older patients with chronic medical conditions is strongly affected by comorbidity, functional status, body composition, treatments, and other factors not directly related to the index disease. Comprehensive Geriatric Assessment (CGA) is a broadly used instrument in geriatric practice, that allow to encompass the complexity of older adults and to evaluate frailty [38]. The Multidimensional Prognostic Index (MPI) is a prognostic tools, based on a standardized CGA, that has been developed and validated for 1-month and 1-year mortality in two wide cohorts of hospitalized patients older than 65 years [39]. The CGA included clinical, cognitive, functional, nutritional, and social parameters and was carried out using six standardized scales and information on medications and social support network, for a total of 63 items in eight domains. Functional status was evaluated by Basic and Instrumental Activities of Daily Living scales [40 41]. Cognitive status was assessed by the Short Portable Mental Status Questionnaire, a 10-item questionnaire that assesses orientation, memory, attention, calculation, and language [42]. Co-morbidity was examined using the Cumulative Illness Rating Scale [43]. Nutritional status was explored with the Mini Nutritional Assessment [44]. The Exton-Smith Scale was used to evaluate the risk of developing pressure sores [45]. Finally, number of drugs used by patient at admission and social background were also included in the predictive model. MPI was developed from CGA data by aggregating the total scores of the these eight domains and expressing it as a score from 0 to 1. Three grades of MPI were identified: low (0.0–0.33), moderate (0.34–0.66) and severe risk (0.67-1.0), progressively and significantly associated with higher mortality after both 6 (grade 1, 4.2%; grade 2, 17.1%; grade 3, 36.9%; $p = 0.001$) and 12 months (grade 1, 5.7%; grade 2, 23.2%; grade 3, 45.1%; $p = 0.001$) (37). Subsequently MPI has been studied in older patients hospitalized for various acute and chronic disorders, such as pneumonia and dementia [46 47], confirming its role as short-term and long-term predictor of mortality, as well as predictor of length of stay and intra-hospital mortality [48]. Compared to other three frailty instruments in a large cohort of hospitalized older patients, MPI has demonstrated a significant higher predictive power for short-term and long-term all-cause mortality [49]. The role of MPI as prognostic tool for 30-days mortality has been tested even in older adults discharged after hospitalization for HF [50]. In a cohort of 376 over65 patients admitted to a geriatric unit with a diagnosis of HF, increasing MPI grades were associated to progressively higher 30-day mortality rates both in men (MPI-12.8%, MPI-215.3%; MPI-347.4%; $p < 0.001$) and in women (MPI-10%, MPI-26.5%; MPI-314.6%; $p = 0.011$). The discrimination of MPI was also very good, with a ROC area for mortality of 0.83 (95% CI, 0.76 to 0.90) in men and of 0.80 (95% CI, 0.71 to 0.89) in women. In the same study MPI has been compared with other "traditional" prognostic scores: the predictive value of MPI was significantly higher than that of the NYHA, EFFECT, and ADHERE models in men and in women (Fig. 1). Thus, it appears more evident that prognosis of HF in older patients is maybe "not (only) an affair of the heart" [51]. A sensitive measure of the multidimensional impairment such as MPI might be useful in identifying elderly patients with HF with different risk of mortality, who could then be directed to the most appropriate management depending on the individual situation. Finally, very recently MPI has been included as a key prognostic tool in the ongoing European CGA-TAVI Registry of older patients who are undergoing TAVI [52]. Further studies could evaluate the reliability and the usefulness of MPI in prognostic stratification of other cardiovascular disorders.

CONCLUSIONS

In time of evolving therapeutic strategies and spending review in healthcare systems, predicting outcomes in older subjects with CVD is fundamental for the subsequent decision making process. Due to the peculiar health trajectories in older adults and the role of frailty in determining prognosis, it is very important to have multidimensional assessment tools able to identify both high- and low-risk patients, so that specific interventions can be eventually targeted to each group. This could be important in particular for identifying those older low-risk patients who can benefit from screening and/or prevention programs and

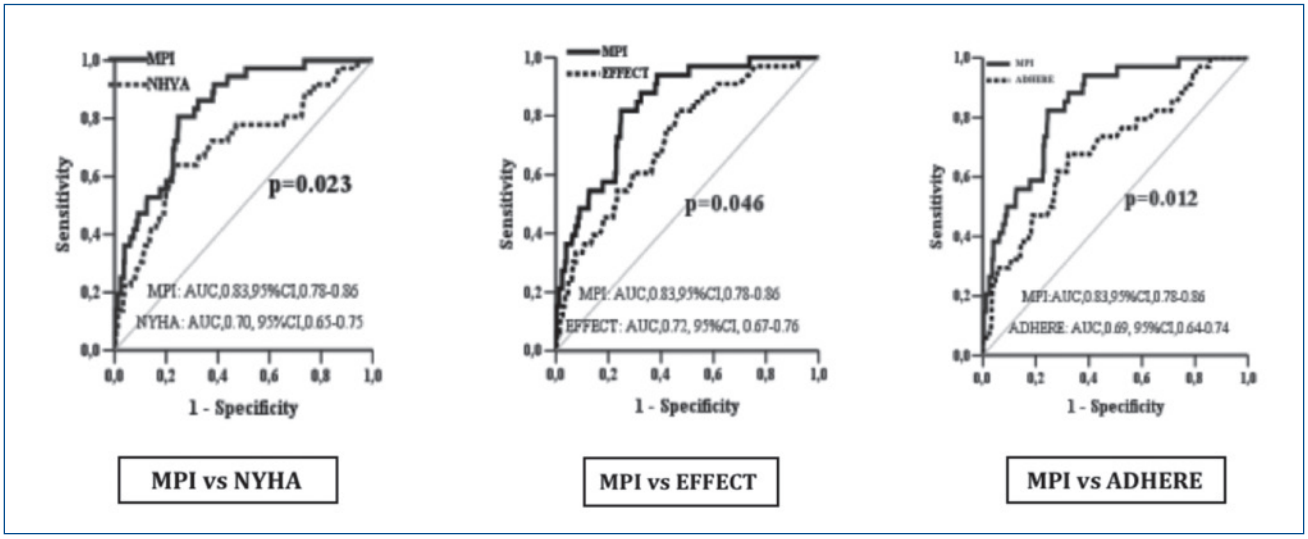

Fig. 1. Accuracy of Multidimensional Prognostic Index (MPI) compared to NYHA, EFFECT and ADHERE in 376 older patients with heart failure. Male = 163, Female = 213, mean age = 80.5 ± 7.3, range = 65-100 years (from Pilotto et al., 2010 [50], mod.).

who are actually excluded because of a "chronological age" criterion. Conversely, for high-risk patients advanced care assistance programs could be appropriate and cost effective. In the perspective of the best management of older individuals with CVD, the role of geriatric assessment and management is fundamental for: a) performing an accurate and reliable multidimensional diagnostic process and b) to design patient-tailored interventions based on residual reserves and deficits resulting from the CGA. The final aim is to provide the best management, to prevent complications and to promote functional recovery and quality of life in older patients.

Cardiovascular diseases (CVD) are the main cause of mortality and morbidity among older adults, representing a high burden in terms of social and health costs. Health trajectories of older adults are very complex, surpassing the only chronological criterion and the single disease-specific risk factors. Moreover, goals of care in advanced age require to take into account not only survival but also functional status and quality of life, so that careful consideration of prognosis is particularly important for clinical decision making in the elderly. In this perspective, the majority of traditional risk stratification models in CVD, developed and broadly used in middle age adults, do not consider adequately the peculiarities of older age, resulting not appropriate in this population. Frailty, a dynamic geriatric condition of reduced physiological reserve and increased vulnerability, is an independent predictor of poor outcomes and mortality in older individuals. It seems to be associated with CVD, although the relationship between these two conditions is still not clear. Some specific geriatric assessment tools have been recently applied in studies aimed to evaluate prognostic stratification in older subjects with CVD. In particular nowadays evidences are available regarding the role of physical performance measures and multidimensional geriatric assessment. In this article some of the most common traditional prognostic tools for CVD will be considered, the relationship between frailty and CVD will be examined and the novel instruments for cardiac risk stratification in older patients will be illustrated, with particular regard to functional evaluation and to Multidimensional Prognostic Index.

***Key words*: Cardiovascular diseases, Comprehensive geriatric assessment, Elderly, Frailty, Multidimensional prognostic index, Prognosis**

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Beta-blockers for the treatment of elderly patients with coexisting heart failure and chronic obstructive pulmonary disease

I beta-bloccanti nel trattamento degli anziani con insufficienza cardiaca e broncopneumopatia cronica ostruttiva

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La broncopneumopatia cronica ostruttiva (BPCO) e l'insufficienza cardiaca (IC) sono tra le principali cause di morte in tutto il mondo. La mortalità e l'incidenza di queste patologie aumenta con l'età. Queste due patologie spesso coesistono e condividono meccanismi fisiopatologici comuni. Nonostante il beneficio indiscusso sulla mortalità e morbilità cardiovascolare in pazienti anziani affetti da IC e BPCO, l'uso di beta-bloccanti è spesso evitato. I trial clinici e i studi di meta-analisi indicano che i beta-bloccanti cardioselettivi non dovrebbero essere evitati nei pazienti con BPCO. Il beneficio che deriva del trattamento con beta-bloccanti sembra superare i loro possibili effetti collaterali. In questo manoscritto descriviamo i meccanismi fisiopatologici comuni coinvolti nello sviluppo della BPCO e IC, e riportiamo le evidenze sull'utilizzo, la sicurezza e il beneficio della terapia con beta-bloccanti nei pazienti anziani.

***Parole chiave*: Broncopneumopatia cronica ostruttiva, Insufficienza cardiaca, Anziani, Beta-bloccanti, mortalità, Recupero funzionale**

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are leading causes of mortality worldwide [1 2]. The incidences of both COPD and HF increase with age [3-5]. These chronic diseased frequently coexist among elderly patients and share common pathophysiological mechanisms [6]. HF is characterized by sympathetic nervous system hyperactivity, due to enhanced catecholamine secretion from sympathetic nerve endings and from the adrenal medulla [7-11]. Accordingly, plasma catecholamine levels may be utilized as circulating biomarkers together with other well known biomarkers in HF, as well as in COPD patients [13-16]. It is widely recognized that chronic stimulation of the beta-adrenergic receptors by catecholamine exerts toxic effects on the heart and other organs and this deregulation plays a key role in HF pathogenesis and progression [17-19]. Further, enhanced extrinsic sympathetic nerve activity occurring in HF could induce a simultaneous activation of sympathetic fibers of cardiac visceral fat which might contribute to the adrenergic nerve derangement observed in the failing heart [20-23]. Despite administration of beta adrenergic receptor agonists induces immediate hemodynamic advantages, long-term treatment with these drugs do not increase survival of HF patients [24]. On the other side, beta-blocker treatment is known to counteract HF progression and to significantly reduce HF-related morbidity and mortality, with positive effects also on right ventricular function [25-27]. These therapeutic effects are mainly attribute to the ability of beta-blockers to protect the heart from the noxious effects of elevated SNS activity [28-30]. Moreover, beta-blocker therapy, as well as physical activity [31-35], ameliorates adrenergic inotropic response in the failing heart by preventing beta-adrenergic receptor

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desensitization and down-regulation and reduces myocardial oxygen consumption, cardiac interstitial fibrosis, myocyte apoptosis and cardiac adverse remodeling [36-40]. However, despite these well-recognized therapeutic effects, there is still a general concern among physician in using beta-blocker therapy in COPD patients [41-43]. One of the most important goal in COPD is the prevention of exacerbations. In animal studies report that treatment with beta-blockers has a protective effect on airway responsiveness, reduces the levels of cytokines like IL-13, IL-10, IL-5, TGF, inflammatory cells in the lung tissue and beta-blocker therapy leads to an up-regulation of $beta_2$-adrenergic receptors in the lung, improving the effectiveness of beta-agonists [44-47]. In this vein, it is important to mention that preservation of $beta_2$-adrenergic receptor signaling and function is protective also in the heart [48 49]. The evidence from trials and meta-analyses indicate that cardio-selective beta-blockers should not be avoided in patients with COPD, since the benefit derived from their use seems to outweigh the possible side effects, however this class of drugs remains underused especially in old patients with comorbidities [50-54]. In the present article we will discuss common pathophysiological mechanisms involved in the development of COPD and HF and we will review evidence derived from trial on beta-blocker use, safety and benefits among elderly patients.

DEFINITIONS AND EPIDEMIOLOGY

HF is defined as an abnormality of cardiac structure and function leading to instability between tissues oxygen demand and the ability of heart to deliver oxygen to tissues. The main clinical manifestations of this complex syndrome are: dyspnea, fatigue and fluid retention which result in limited exercise tolerance, pulmonary congestion and peripheral edema. Epidemiological studies have shown a high prevalence and incidence of HF among the elderly population [2 5]. About 50% of HF cases are reported in patients older than 70 years and, with each decade of life, its prevalence doubles and its incidence rises up to 10 % in elderly subjects over 70 years and is associated with high incidence of HF-related tromboembolisms [55 56]. COPD is defined as a condition characterized by airflow limitation that is not completely reversible, resulting a post-bronchodilator ratio FEV1/FVC < 70%. Worldwide prevalence of COPD ranges from 7,8% to 26,1% and becomes higher in the geriatric population [1]. COPD is the fourth leading cause of death in Europe and USA. Frequent symptoms in COPD patients are represented by cough, dyspnea and sputum production. The prevalence of HF in COPD patients is reported to be 21-31% [57]. On the other side, the prevalence of COPD in HF patients varies from 7% to 13% in HF outpatients population and from 9% to 51% in hospitalized HF patients [58].

CARDIOPULMONARY CONTINUUM

The major risk factor for COPD is tobacco-smoking which causes pulmonary inflammation by inducing pulmonary mucus hypersecretion, influx of neutrophils in the lung tissue, oxidative stress and pro-inflammatory cytokines secretion (i.e. IL-1b, IL-6, IL-18) [59-61]. However, these pro-inflammatory changes do not affect exclusively the lung but the entire body through the induction of a systemic low-grade inflammatory status. Mild leukocytosis and elevated fibrinogen and CRP levels characterize this systemic inflammation. This low grade systemic inflammation represents a common characteristic between COPD, coronary artery disease, coronary artery remodeling after revascularization, and HF [62-65]. Moreover, COPD is associated with development of pulmonary artery hypertension, which in turn may lead to right ventricle dysfunction and HF. Furthermore, obesity and diabetes mellitus which are established determinants of coronary artery disease reduce the ventilatory mechanics and lung function [66 67]. Finally, SNS hyperactivity, which is a pivotal characteristic of chronic HF, is present also in COPD patients [68-70]. Based on these common inflammatory pathways and the evidence of frequent coexistence of COPD and HF, the concept of cardiopulmonary continuum has been described [59 71]. Tumor Necrosis Factor (TNF) appears to have an important role in this common pathway. Indeed, increased levels of TNF, CRP and IL-6, observed in COPD patients, are associated with poor survival, increased hospitalization rates and worsening of general conditions also in HF patients [72-74]. However, additional studies are needed to better clarify the common pathophysiological mechanism involving COPD and HF in order to improve the treatment strategies in patients affected by both these chronic diseases.

BETA-BLOCKERS USE IN COPD

The use of beta-blockers is often avoided in elderly patients with concomitant HF and COPD despite the well-known benefit on cardiovascular mortality and morbidity recognized also in this population. The main reason is based on the possible side effects of beta-blockers on airways, since these drugs are known to facilitate bronchospasm, by blocking beta2 adrenergic receptors in the lung. Gottlieb et al. [75] reported that in elderly patients with myocardial infarction, treatment with beta-blockers reduced mortality during a follow-up of 24 months. The overall reduction in mortality was 40% in the overall population and 32% among elderly over 80 years. A similar trend was observed in patients with a history of COPD. Thus, taking into consideration the elevated mortality rate observed in these groups of patients, the use of beta-blockers is strongly supported in elderly HF patients with concomitant COPD. However, it is important to underline that in this study different classes of beta-blockers were not compared, COPD patients were not stratified according to the severity of disease, and the mortality rate ratio was not adjusted for any confounders. The use and the efficacy of beta-blockers therapy in elderly patients with COPD or asthma was evaluated by Chen et al. [76]. The study sample size was of 54962 patients divided in three sub-groups: patients with COPD or asthma without beta-agonist treatment (12,1%), patients with COPD or asthma under beta-agonist therapy (5,2%) and patients with severe COPD or asthma, treated with beta-agonists and steroids and presenting respiratory exacerbation within one year before acute myocardial infarction (2,7%). The remaining 80% of patients did not present any history of COPD or asthma. Beta-blockers were prescribed in 31,1% of patients with COPD or asthma that were not under beta-agonists therapy, in 21,1% of patients treated with beta-agonists and only in 9,3% of patients with severe COPD or asthma. Patients with COPD or asthma were significantly less likely to be treated with beta-blockers therapy after myocardial infarction. Importantly, this study reported that treatment with beta-blocker was associated with a significant reduction in mortality rate over one year of follow-up also in the subgroup of patients with COPD or asthma who were not under beta-agonist therapy (RR = 0.86, 95% CI 0,73 to 1,00 p = 0,048). Based on these results, the authors concluded that in elderly patients without severe COPD or asthma the use of beta-blockers may be beneficial. In another population of elderly patients with HF the association between beta-blocker use and mortality was examined [77]. Patients who received beta-blockers showed a 28% reduction in all-cause mortality and a 35% reduction in HF-related mortality compared to patients not treated with beta-blockers. Importantly, the subgroup of elderly patients with COPD showed even a lower all-cause mortality rate (HR = 0,78; 95% CI: 0,63 to 0,95). Moreover, a trend towards greater therapeutic benefit was reported in patients receiving the highest doses of beta-blockers. However, in this study the authors did not report whether patients presented systolic or diastolic HF and the population was not stratified according to COPD severity. In a 10-year retrospective observational study, a higher mortality risk during hospitalization and 30 days after hospital discharge was observed during hospitalization and was observed in COPD patients with myocardial infarction [78]. Recently, Mentz RJ et al. [79] explored the interaction between beta-blocker selectivity and outcome in patients with COPD and systolic left ventricle dysfunction. In the overall population, there were 725 patients with a history of COPD (27%). In line with the results of the other studies, COPD patients were less likely to receive beta-blockers than patients without COPD. Among patients receiving beta-blockers, 40% received a cardioselective beta-blockers and 60% a non-cardioselective one. Within cardioselective beta-blockers, metoprolol and atenolol were more used, while carvedilol was the non-cardioselective beta-blocker more frequently prescribed. Both cardioselective and non-cardioselective agents were associated with lower mortality rate among patients with COPD and, in the overall population, there were no differences between cardioselective and non-cardioselective beta-blockers on mortality rates. However, this study presented a relative short-term follow-up (60 to 90 days). Thus, this study reported that the outcome was not affected by the selectivity of the beta-blocker used in patients with concomitant COPD and HF. Probably, beta-blockers may attenuate the adverse effects of beta-agonists on the heart, such as the facilitation of ischemia and arrhythmia induction. Moreover, there are some non-canonical effects of beta-blockers: some beta-blockers (i.e. carvediolol) have been shown to own same antioxidant effects and to counteract insulin-

resistance. Probably, these beneficial effects of beta-blockers may overweight the potential adverse pulmonary effects. Lee et al. [80] published a cohort study reporting interesting results on the effects of beta-blocker therapy on cardiopulmonary outcomes and mortality in elderly patients with heart disease. The study included 1062 patients over 65 years with COPD or asthma and concomitant coronary artery disease with follow-up of 4 years. Fifteen percent of these patients were under beta-blocker therapy and, within 389 patients presenting a pulmonary exacerbation, 199 were treated with beta-blockers. Interestingly, over a total of 255 deaths 126 were under beta-blocker treatment. Thus, in this study beta-blocker use was not associated with any benefit on mortality. Anyway, it is important to underline that the adherence to beta-blocker therapy has not been considered and the possibility that beta-blocker users were at higher cardiovascular risk could not be excluded. In a Cochrane review [81] of controlled randomized trials long-term administration of cardioselective beta-blockers was not associated with pulmonary symptoms or changes in FEV1, even in a subgroup of patients with severe COPD. However in this review the mean age of patients was 53.8 ± 11.1 years and the trials were of short duration. Recently, another meta-analysis, including 15 observational cohort-studies with a mean follow-up ranging from 1 to 7.2 years, reveled that beta-blocker therapy was associated with a significant reduction in all-cause mortality (RR 0.72; 95% CI = 0.63 to 0.83) and exacerbation of COPD (RR 0.63; 95% CI = 0.57 to 0.71). In subgroup analysis of COPD patients with HF the risk of overall mortality was significantly decreased (RR 0.74; 95% CI = 0.58 to 0.93). However, in this meta-analysis a marked heterogeneity in study size, follow-up and patient mean ages was found. Moreover, COPD diagnosis was exclusively based on clinical criteria, most of the studies did not provide stratification for COPD severity and type or dose of beta-blocker used was not reported. Despite these limitations the meta-analysis supported the safety of beta-blocker in patients with concomitant COPD [82].
However both the American and European guidelines do not indicate a contraindication of beta-blockers use in HF patients with coexistent COPD. However, the management of elderly patients needs expertise and frequent controls in initiating, up titrating and maintaining the beta-blockers therapy.

CONCLUSIONS

The low grade systemic inflammation may be a possible interaction between HF and COPD coexistence. This common pathophysiological mechanism is complex and not completely clarified. From the evidence derived from trials beta-blockers therapy is safe in elderly patients with HF and comorbidities, such as COPD. The overall benefit of beta-blocker treatment in elderly patients with HF and COPD overweight the possible side effects derived from this therapy.

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are leading causes of mortality worldwide. COPD and HF incidence and related mortality increase with age. These chronic diseases frequently coexist especially among elderly patients and share common pathophysiological mechanisms. Despite the well-recognized benefit of beta-blockers on cardiovascular mortality and morbidity, this class of dugs is often underused in elderly patients with concomitant HF and COPD. Evidences derived from trials and meta-analyses suggest that cardio-selective beta-blockers should not be avoided in patients with COPD, since the benefit of beta-blockers treatment seems to outweigh the possible side effects. In this review we will discuss common pathophysiological mechanisms involved in the development of COPD and HF and we will review the evidence derived from trials on beta-blocker use, safety and benefits among elderly patients.

***Key words*: Chronic obstructive pulmonary disease, Heart failure, Elderly, Beta-blocker, Mortality, Functional recovery**

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Modulation of pro-inflammatory status of visceral fat: a novel therapeutic perspective for cardiovascular disease

Modulazione dello stato pro-infiammatorio del grasso viscerale: una nuova prospettiva terapeutica per le malattie cardiovascolari

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La prevalenza dell'obesità è aumentata nelle ultime decadi raggiungendo proporzioni epidemiologiamente significative nel mondo occidentale. È ampiamente riconosciuto che l'obesità rappresenta un fattore di rischio indipendente per le malattie metaboliche, quali insulino resistenza, diabete tipo 2, dislipidemia, e per le malattie cardiovascolari. Il tessuto adiposo è un organo dinamico la cui espansione nell'obesità porta al rilascio di lipidi aberranti e alla produzione di citochine che determinano la cosiddetta "chronic low grade inflammation". Inoltre, l'età influenza l'omeostasi del tessuto adiposo con un significativo incremento età correlato della massa grassa e della redistribuzione del grasso corporeo con aumento del tessuto adiposo viscerale, una diminuzione del tessuto adiposo sottocutaneo ed un incremento dei depositi ectopici di grasso. Tutti questi cambiamenti età-correlati contribuiscono al peggioramento dello stato di salute nell'anziano. Numerosi studi sperimentali ed epidemiologici hanno mostrato che il link tra l'obesità, in particolare l'obesità viscerale, e le malattie cardiovascolari potrebbe essere rappresentato dallo stato pro-infiammatorio sistemico correlato all'obesità. A tal riguardo, differenti strategie sono state disegnate avendo come target l'infiammazione correlata all'obesità e, di conseguenza, la riduzione del rischio cardiovascolare. In questa review vengono illustrate le correnti strategie che potrebbero controllare il rischio cardiovascolare attraverso la modulazione dell'infiammazione.

***Parole chiave*: Obesità, Grasso viscerale, Infiammazione, Invecchiamento, Rischio cardiovascolare**

VISCERAL OBESITY AND AGING

Normal aging is associated with a progressive increase in fat mass [1]. It has been shown that adipose tissue (AT) accumulation with age is mainly distributed at visceral level. Aging is associated not only with visceral fat increase, but also with a decrease in subcutaneous fat in other regions of the body (abdomen, and in particular thigh, calves), with a simultaneous ectopic fat accumulation [1]. Modifications in body fat distribution dramatically change the endocrine properties of AT, determining a dysregulation in adipokines production. Adipokines derived from visceral AT exert pro-inflammatory effects in a paracrine and/or autocrine matter on several systems representing a common ground for insulin resistance, metabolic syndrome and cardiovascular diseases' (CVD) morbidity and mortality [2-4]. These signals support an influx of pro-inflammatory leukocytes, especially type M1 macrophages, and might therefore contribute to the physiopathological consequences of obesity [5]. AT-associated macrophages (ATM)

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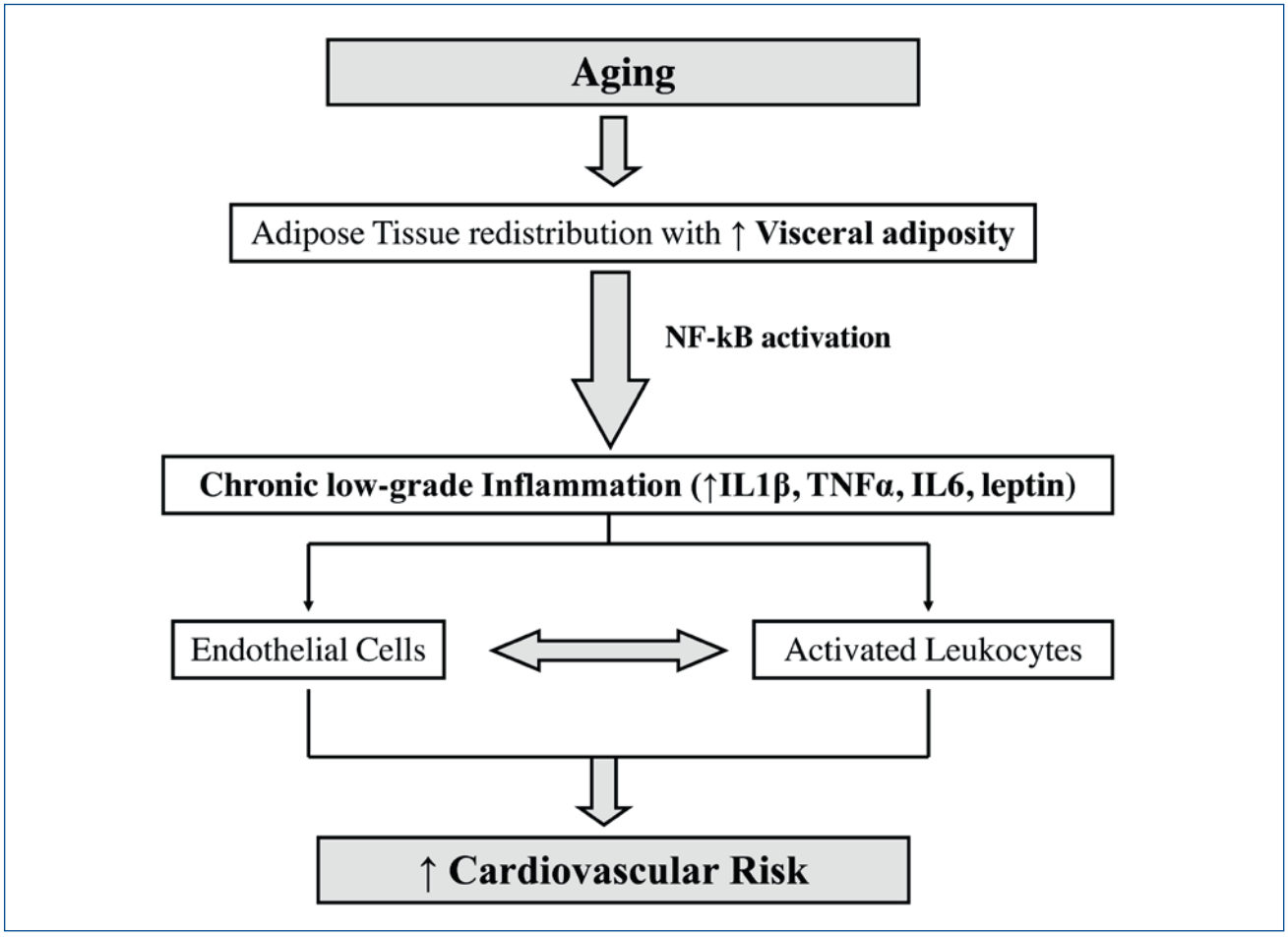

Fig. 1. The possible link between aging, adipose tissue accumulation and increased cardiovascular risk.

are the most abundant leukocytes ranging from 10% in normal weight subjects to almost 50% in obese subjects [6].

Interestingly, it seems that not only AT amount and distribution may change with age, but also the endocrine function of adipocytes as older adipocytes display reduced gene expression of adiponectin and leptin, and increased insulin resistance, when compared to young mature adipocytes [5]. In a mouse model of aging, Lumeng et al. demonstrated that visceral AT presented a decreased anti-inflammatory macrophages (M2) infiltration, with a decreased ratio between anti-inflammatory and inflammatory (M2/M1) macrophages [6]. All together these results suggest that AT in older ages presents a greater inflammatory profile with ATM polarization and lymphocytes expansion, that together with adipocytes dysregulation fuel a chronic low-grade AT inflammation that contributes to obesity-related comorbidities.

VISCERAL OBESITY – ONE OF THE MAJOR CVD RISK FACTOR IN OLD INDIVIDUALS

Although age-related changes in AT distribution and quality have been clearly shown to be linked to higher risk of diabetes, dyslipidaemia and CVD in old subjects [7], the underlying mechanisms remain elusive. Nevertheless, accumulating evidence from animal studies proved that the pathogenesis of obesity-related CV dysfunction involves the development of a systemic, low-grade inflammatory state (Fig. 1). A strong association has been reported between visceral fat and several cytokines, such as interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and leptin which have been shown to be related also to endothelial dysfunction [5]. In particular, the activation of inflammatory signalling by adipokines, like tumor necrosis factor alpha (TNFα), leptin, PAI-1, has been suggested to contribute

Tab. I. Adipokines involved in CVD (from Taube et al., 2012 [8], mod.).

Adipokines	In vitro studies	Animal studies (KO models)	Clinical studies
Adiponectin	↓ Inflammatory cytokines ↑ NO production, ↓ NO inactivation in EC	↑ Leukocyte-endothelial cell interactions; ↑ E-Selectin and VCAM-1	Inversely associated with markers of endothelial function and inflammation, and with the risk of MI in healthy men ↓ Levels in patients with CAS and ACS
Leptin	↑ PAI and CRP ↑ NO production in EC	↑ Plasma cholesterol and TG; extensive atherosclerotic lesion in the aorta.	↑ Plasma levels in patients with ACS Conflicting results on the association with CAD risk
IL-1β	↑ VCAM-1 and MCP-1 in EC ↑ VCAM-1 and MCP-1 in VSMC	↓ VCAM-1 and MCP-1 ↓ aortic lesion and lesion area	↑ Levels in patients with unstable angina ↑ Expression in coronary arteries of patients with MI
IL-6	↑ MCP-1 and ↑ adhesion molecules	Mature-onset obesity with ↑ cholesterol, TG and accelerated atherosclerosis.	Chronic ↑ levels correlate with the progression of IMT ↑ CRP
TNFα	↑ Apotosis in EC, ↑ Migration and proliferation in VSMC	↓ Pro-atherosclerotic factors; ↓ Fatty-streak lesions.	↑ Plasma levels in patients with premature coronary disease Positive correlation with IMT.

CVD: cardiovascular disease; EC: endothelial cells; NO: nitric oxide; CAS: coronary atherosclerosis; MI: myocardic infarction; ACS: acute coronary syndrome; CRP: C reactive protein; TG: triglycerides; IMT: intima-media thickness; VSCM: vascular smooth muscle cells

to the development of CVD by stimulating the generation of endothelial adhesion molecules, proteases and other mediators, which may act locally or also enter the circulation in soluble form [8].

The current evidence of the roles of various adipokines in the progression of CVD is resumed in Table I. Leptin, the first adipokine identified, present circulating levels increasing as the accumulation of visceral AT increases. Moreover some studies proved a direct association between circulating leptin levels and the risk of coronary artery disease, while other experimental observations revealed that leptin determines an increased expression of PAI-1 and C-reactive protein (CRP) in human vascular endothelial cells [8]. Besides, leptin-deficient mice seem to be protected from atherosclerosis, despite a higher metabolic risk related to the development of a severe obesity phenotype [9]. Visceral fat has also been shown to be negatively associated with adiponectin levels, whose protective effect on arteries has been well documented. For example, in macrophages and endothelial cells, adiponectin acts as a TNF-α suppressor and directly ameliorates endothelial dysfunction by increasing nitric oxide production, while in transgenic mice adiponectin over-expression exerts an improved lipid profile [10]. Low levels of adiponectin were observed even in patient with coronary atherosclerosis and have been associated with biomarkers of insulin resistance, inflammation and endothelial dysfunction, which are independent risk factors for CVD [8]. At a molecular level, the central player of this scenario seems to be the transcriptional factor NF-kB that activates a multitude of genes controlling immune cells adherence, diapedesis and accumulation, further contributing to the pro-inflammatory status central in CVD pathogenesis and progression [8]. Further translational studies are needed in order to fully understand the mechanisms that link AT accumulation, its low-grade inflammation and the augmented CVD risk in elderly adults.

OBESITY-TARGETED TREATMENT STRATEGIES FOR LOWERING CVD RISK IN THE ELDERLY

Weight loss is associated with CVD risk improvement, with consequent reduction in obesity-related morbidity and mortality rates, providing the rationale that interventions targeting even modest weight loss might reduce CVD risk.

HEALTHY LIFE STYLE

It is broadly known that dietary patterns in old age are very important for health maintaining and for preventing disease-related complications, considering the complexity of age-related pathology and physiopathology. Nevertheless, managing overweight or obesity in elderly per-

sons should consider the fact that obese old subjects lose weight in similar proportion as young people, even though they start with less lean mass as a result of age-related changes in muscle mass and strength. Several studies investigated the benefits in old age of the adherence to various dietary recommendations, generally based on a Mediterranean Diet (MedDiet) type. For example, the EPIC-elderly study proved that people (age > 60 years) following a dietary pattern similar to MedDiet for 89 months presented a lower overall death rate [11]. Furthermore, Anderson et al. showed that a dietary pattern high in low-fat dairy products, fruit, whole grains, poultry, fish and vegetables may be associated with greater insulin sensitivity and lower systemic inflammation in older adults [12].

Some studies demonstrated that physical activity may directly reduced inflammation, while others reported that the anti-inflammatory effects of physical activity can be only indirectly caused by reduced visceral adiposity and consequent reduction in fat-derived inflammatory adipokines [13]. Moreover, it has been recently shown that in frail, obese older adults, lifestyle interventions associated with weight loss improved CVD risk factors, but continued improvement was only achieved when exercise training was added to dietary interventions [14].

Lately, there is a growing interest in caloric restriction (CR) in animal studies as a valid approach to enhance survival. The overall data from animal studies showed that the benefits of CR described a linear decline trend if plotted as a function of the age at onset. Furthermore, translating the results achieved in small rodents to human subjects, Speakman et al. sustained that late-onset CR seems unlikely to provide significant benefits in terms of increased lifespan [15].

DIET SUPPLEMENTATION

It has been shown that nutrients may also influence AT distribution and function, even if evidences are sparse and quite controversial with only a few studies performed in older subjects. In Table II, we presented the most commonly used types of dietary supplementations that have been proved to have an important effect in regulating AT-related inflammation. In the Framingham Heart Study, whole-grain intake was inversely associated with subcutaneous and visceral AT, while refined-grain was positively associated with both subcutaneous and visceral AT [16]. Moreover, whole grain intake appeared to be inversely associated with markers of low-grade inflammation [17]. This negative association between whole grains consumption and both the AT amount and distribution could be dependent on their capability to determine satiety by delaying gastric emptying, or on their effects on gut hormones, whilst anti-inflammatory activity may be explained by plant-specific constituents of fruit and vegetables such as phytochemicals. Indeed, several components present in fruit and vegetables seem to have anti-inflammatory effects on AT. In particular, some studies concentrated on the role of dietary polyphenols in the prevention of obesity and obesity-related diseases. It had been largely proved that commonly consumed polyphenols, including green tea catechins, epigallocatechin, resveratrol and curcumin, reduce viability of adipocytes and proliferation of preadipocytes, suppress adipocytes differentiation and triglyceride accumulation, stimulate lipolysis and fatty acid beta-oxidation, reducing inflammation [18]. In particular, *in vitro* studies proved that resveratrol significantly reduced NF-kB activation and the expression and release of IL-6 and TNF-α in a co-culture model of macrophages and 3T3-L1 adipocytes. Moreover, *in vivo* studies demonstrated that resveratrol anti-obesity effect was mediated through stimulation of fat oxidation and inhibition of obesity-induced chronic inflammation as it down-regulated the expression of TNF-α, interferon-gamma (IFNγ) and IL-6 along with downstream signaling molecules. Although, a few clinical studies had been made, some demonstrated that resveratrol supplementation to patients resulted in an increased serum adiponectin and decreased PAI-1, by modulating various pathways involved in inflammation, cell migration and T-cell interaction signals [18].

In vitro and *in vivo* studies demonstrated that polyunsaturated fatty acids (PUFAn-3) have beneficial effects on the inflammatory profile [17]. The anti-inflammatory effects of PUFAn-3 appear to be mediated by the increase in adiponectin secretion by a PPAR-γ dependent pathway as well as by the decrease of pro-inflammatory cytokines such as TNF-α, IL-6, MCP-1. Moreover, it has been suggested that PUFAn-3 reduce the production of adipocytes-derived eicosanoids, which have pro-inflammatory actions. PUFAn-3 supplementation may determine a fat mass de-

Tab. II. Dietary Supplementation and the risk for CVD (from Calder et al., 2011 [17] and Wang et al., 2014 [18], mod.).

Supplements	In vitro studies	In vivo studies	Clinical trials
Green tea catechins	↓ Inflammation ↓ Resistin in 3T3-L1 cells	↓ Weight, ↓ adiposity, ↓ cholesterol and TG ↓ Pro-inflammatory signals (TNF-α, TLR4) ↓ Pro-inflammatory cytokines (MCP-1, CRP, IL6) ↑ Adiponectin level and expression	Inconsistent outcome Modest weight loss ↓ Bioavailability ↓ Pro-inflammatory markers (TNF-α, IL-6, CRP) Multiple confounders (ethnicity, genetic effects, habitual caffeine, different intake)
Resveratrol	↓ TNFα-induced IL6 and PAI production in 3T3-L1 ↓ LPS-induced TNFα and IL6 production in 3T3-L1 ↓ Adipokines expressions ↓ TNFα-induced NF-kB activation	↓ Body weight and fat deposition in diet-induced obese rats ↓ TNFα in liver ↓ Pro-inflammatory cytokines (TNF-α, IFN-α, IFN-β,IL-6) and triglycerides molecules (TLR2/4, MyD88, Tirap, TRIF, TRAF6, IRF5, p-IRF3, NF-κB) in leptin KO mice	↓ Inflammation (↓ hs-CRP, TNF-α, PAI-1, IL-6/IL-10 ratio, sICAM-1), ↑ Anti-inflammation (↑ IL-10) ↑ Adiponectin in subjects on statin and high CV risk (supplemented for 6 months) ↔ Blood pressure, resting energy expenditure, oxidation Rates of lipids, ectopic or visceral fat content, inflammatory and metabolic biomarkers in healthy obese
Curcumin	↓ NF-κB activation in 3T3-L1 cells ↓ Expression of IL-6, TNF-a and COX2 on 3T3-L1 cells ↓ Migration of macrophages in co-culture with 3T3 cells	↓ IFN-γ and IL-2 mRNA levels ↔ mRNA expression of TNF-α, IL-1β, IL-4, IL-5, IL-10, IL-12, IL-18, TGF-β on obese cats supplemented for 8 weeks ↓ Body weight and ↓ inflammatory markers in diet-induced obese mice ↓ NF-κB pathway ↓ Proinflammatory cytokines (↓ TNF, IL-6; ↑ IL-4) ↑ Insulin sensitivity (↓ fasting glucose and insulin, HOMA-IR) and ↑ Serum adiponectin in ob/ob mice.	Improved lipid profile in healthy subjects supplemented for 30 days ↔ Serum lipid profile (TAG, total, LDL-C, HDL-C) in elderly healthy subjects supplemented for 6 months
PUFA n3	↑ Adiponectin, ↓ Inflammatory cytokine by inactivating NF-kB pathway	↓ Fat mass ↓ AT inflammation ↓ Macrophage infiltration ↓ NF-kB activation	↓ IL-18 in elderly subjects supplemented for 3 years. ↓ Visceral adiposity ↓ CV risk

PUFA n3: polyunsaturated fatty acids n3; TNF-α: tumor necrosis factor alpha; IL: interleukin; MCP-1: monocyte chemotactic protein 1; TGF-β: transforming growth factor beta; IFN-α: interferon alpha; TLR4: Toll-like receptor 4; CRP: C reactive protein; LPS: lipopolisacharide; PAI-1: plasminogen activator inhibitor-1; CV: cardiovascular; TAG: triacilglicerol; LDL-C: low density lipoprotein cholesterol; HDL-C: high level density lipoprotein cholesterol; HOMA-IR: homeostasis assessment model- insulin resistance; AT: adipose tissue; TG: triglyceride; KO: knock out

cline, as well as a decline in AT inflammation and macrophage infiltration [19]. Although the preliminary data are very encouraging, translational studies from animal observation to human clinical trials are needed to further confirm the anti-obesity benefits of specific dietary supplementations in old adults and to set-up community interventions.

NEW PHARMACOLOGICAL INTERVENTIONS IN OBESITY

A limited number of medicine are approved at the present time as pharmacological intervention in obesity. Drug therapy had many setbacks over the past 20 years, basically because of serious adverse effects. In Table III we present the drugs currently approved by the US Food and Drug Association (FDA) for short or long-term obesity treatment [20]. The only obesity drug approved both in Europe and USA, for long-term therapy in conjunction with reduced-caloric diet, is Orlistat, a selective pancreatic lipase's inhibitor that inhibits 30% of fat absorption. Orlistat appears to be modestly effective in promoting weight loss, as a recent meta-analysis showed, and averages greater weight reduction of 2,9% in patients who received orlistat as an adjunct to lifestyle modifications compared with placebo, with equivalent weight gain over time. Regarding the improvement in CVD risk factors, Orlistat treatment seems associated to a decrease in systolic and diastolic blood pressure, and in

Tab. III. Pharmacotherapy for Obesity (from Joo et al., 2014 [20], mod.).

Treatment	Action	Clinical trials
Noradrenergic drugs (*Phentermine*) (short term use-12 weeks)	Inhibitors of the re-uptake of noradrenalin	↓ Weight ↓ Waist circumference ↑ Blood pressure and heart rate
Orlistat (*Xenical*)	Selective inhibitor of pancreatic lipase	↓ Weight ↓ Diabetes ↓ Blood pressure ↓ Cholesterol ↓ Glucose
Lorcaserin (*Belviq*)	Serotonin type 2C receptor agonist	↓ Food intake ↓ Weight ↓ Glucose Potential valvulopathy
Phentermine/TopiramateER (*Qsymia*)	Combination of a sympatomimetic drug and anticonvulsant drug	↓ Weight ↓ Blood pressure ↓ Glucose levels ↓ Cholesterol and TG
Bupropion/naltrexone (*Contrave*)	Combination of a dopamine, noradrenaline reuptake inhibitor and an opioid antagonist	↓ Weight CV safety No data on cardiovascular risk ↑ Suicide risk

CV: cardiovascular; TG: triglyceride

serum levels of total cholesterol, LDL-colesterol and glucose [21]. Moreover, it seems that orlistat can be effective in older as in younger adults, with no significant increase in adverse effects [22]. Among sympathomimetic drugs approved for short-term obesity treatment (12 weeks), phentermine, an appetite-suppressant, is the most often prescribed. It has been proven to lower significantly body weight and waist circumference, compared to the placebo group [23]. As it may increase heart rate and blood pressure, it is not recommended for individuals with history of CVD, which narrows the indication in elderly patients. Moreover there is no data on its long-term efficacy and safety in older subjects.

Lorcaserin, a serotonin type 2C receptor agonist, was approved by the US FDA in 2012 for long-term obesity therapy, in association with lifestyle intervention. The drug was associated with moderate weight loss after 2 years of treatment, while the data regarding CVD risk factors were inconclusive, as the initial improvement in cardiometabolic risk factors (glycemic and lipid levels) after 1 year of treatment, was no longer significantly maintained by the end of the study, reflecting maybe the effects of weight regain [24].

Phentermine/Topiramate extended-release (ER) medication was approved in 2012 for long-term obesity treatment and till this date there were only a few clinical trials that investigated its efficacy and safety. One of them, the CONQUER study, assessed also its impact on cardiometabolic risk factors [25]. This clinical trial enrolled patients aged between 18 and 70 years old and the subgroup analyses of age proved that the combined therapy phetermine plus topiramte resulted in greater weight loss than placebo, with no age-related hazards. It was demonstrated that phentermine/topiramate ER treatment significantly decreased systolic and diastolic blood pressure and improved lipid and glycemic profile [25].

The latest drug approved by the FDA and introduced in the US is bupropion/naltrexone, a combination of a dopamine/noradrenaline reuptake inhibitor and an opioid antagonist. Although, initially rejected for lack of convincing CVD safety data, in 2014 this drug association was accepted by the US authorities, although there is a warning alert for suicide thoughts in long-term users. No data had been published so far about the safety of bupropion/naltrexone treatment in elderly subjects.

BARIATRIC SURGERY

Bariatric surgery (BS) represent an effective therapeutic option in accurately selected severely

obese patients, although it remains a demanding procedure, applicable only to a limited number of patients [26]. Additionally, it has been demonstrated that BS is associated with restoration of normal serum profiles of adipokines and gut hormones. In a recent study, Vest et al. [27] analysed 58 studies with a mean follow-up of 57,8 months after BS and demonstrated a substantial resolution or improvement of their baseline hypertension (62%), diabetes (73,2%) and hyperlipidaemia (65,2%), with a reduction in 10-year coronary heart disease Framingham risk score from 5,9% to 3,3%. In parallel, the same meta-analysis showed that among the 12 studies reporting the effect of BS on inflammatory status for CVD, CRP levels decreased by 73% after surgical procedure. Furthermore, after 6 months from BS, the registered weight loss in a group of clinically severely obese patients at a very high risk was especially effective in the reduction of CVD risk and related mortality [28].
Recently it had been observed an increase in the number of bariatric procedures performed also in the elderly, reaching 10% of all bariatric operations in academic centres in the USA. Moreover, it seems that the in-hospital mortality in BS in the elderly has improved so much that it is now even lower than that of nonelderly BS patients [29]. Although, older adults seem to experience less weight loss, it seems that the surgical intervention has potential benefits also for these patients, as it has been observed a significant improvement in hypertension, diabetes, and, to a lesser extent in dyslipidemia also in older patients undergoing BS; however no data is available regarding the changes in inflammatory profile in these studies [30]. It should be noted that all these studies concern only short-term outcomes of BS in the elderly, so that long-term trials are needed to better evaluate the benefits of BS in aging obese patients.

CONCLUSIONS

Visceral obesity is a major risk factor for CVD, as it is associated with AT dysfunction, aberrant adipokines release and chronic low-grade inflammation. The most important ethiopathogenetic link between obesity and CVD has been shown to be represented by different adipokines, as leptin, adiponectin, TNF-alpha and other interleukins whose levels profoundly changes with AT expansion. Even a modest weight loss of 5-10% has been proved to ameliorate cardiometabolic risk factors and improve health outcomes [31]. Understanding the molecular mechanisms linking visceral obesity, inflammation and CVD appears still to be essential to identify possible therapeutic strategies.

Obesity's prevalence worldwide has steadily increased over the past decades, reaching epidemiological proportions in Western Countries. Obesity has been recognised as an independent risk factor for metabolic disorders including insulin resistance, type 2 diabetes, dyslipidemia as well as for cardiovascular diseases (CVD). Adipose tissue (AT) is a dynamic organ which expansion in obesity leads to aberrant lipid release and cytokines production, that ultimately determine a low-grade chronic inflammatory state. Moreover, aging influences AT homeostasis with a significant age-related increase in fat mass, redistribution of body fat with increase in visceral AT and decline in subcutaneous AT, as well as ectopic fat deposition. All these age-related AT changes contribute to worse health conditions in the elderly. Several experimental and epidemiological studies showed that the link between obesity, especially visceral obesity, and CVD might be represented by the systemic pro-inflammatory status triggered by obesity. Different approaches had been designed to target obesity-related inflammation and, consecutively, to lower the CVD associated risk. In this review we highlight the present strategies that might control CVD risk by lowering visceral AT depots, throughout regulating AT inflammation.

***Key words*: Obesity, Visceral fat, Inflammation, Aging, Cardiovascular risk**

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Calcific aortic stenosis: novel insights in pathophysiology, diagnosis and management

Stenosi aortica calcifica: nuovi approfondimenti in fisiopatologia, diagnosi e gestione

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La stenosi aortica calcifica rappresenta la più comune valvulopatia cardiaca nella popolazione anziana. Recenti evidenze hanno dimostrato che la progressiva degenerazione calcifica dei lembi valvolari è determinata da eventi biologici attivi prevalentemente regolati dai lipidi e da fenomeni infiammatori. Le manifestazioni cliniche della stenosi aortica severa sono spesso confondenti e presentano un'alta variabilità nella popolazione. Comunque, l'insorgenza dei sintomi rappresenta un'indicazione assoluta all'intervento chirurgico di sostituzione valvolare.
L'ecocardiografia svolge un ruolo essenziale nella diagnosi e nella valutazione del grado di severità della stenosi aortica.
Nonostante le numerose evidenze che supportano l'efficacia dell'intervento chirurgico di sostituzione valvolare aortica nella popolazione anziana, circa il 30-40% dei pazienti con indicazione alla chirurgia non vengono operati a causa dell'età avanzata e della comorbidità. Crescenti evidenze provenienti da studi clinici controllati indicano che la tecnica di sostituzione valvolare aortica transcatetere rappresenta una valida alternativa alla chirurgia tradizionale per i pazienti inoperabili con eccellenti risultati sulla qualità di vita e sulla sopravvivenza.

***Parole chiave*: Stenosi aortica, Lipidi, Anziano, Protesi valvolari**

PATHOPHYSIOLOGY

Calcific aortic stenosis (AS) is a common heart disorder in the elderly and the most prevalent valvular heart disease in the Western world representing one of the main causes of cardiovascular morbidity and mortality [1]. It is important to strengthen that the severity of AS in elderly patients is worsened by the coexistence of several structural and functional cardiac alterations leading to a rapid deterioration of the hemodynamic status [2-4]. AS was previously considered a passive, degenerative disorder of aging, but recent evidences have demonstrated that active biological events lead to a progressive degeneration of aortic valve (AV) leaflets mainly regulated by lipids and inflammation [5]. It is now established that atherogenesis and inflammation generate biologically active calcification of AV leading to bone deposition [6 7].

ROLE OF LIPIDS IN THE PATHOGENESIS OF AS

In hypercholesterolemic mice, it has been demonstrated an enhanced oxidative state in the AV endothelium associated to increased levels of

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Ox-LDL inflammatory cell infiltrates, containing mast cells, macrophage and T lymphocytes [8]. Accordingly, human stenotic AV contains oxidized LDLs, T-cells and macrophages [9 10]. At this regard, in vitro studies show that oxidized LDLs strongly promote mineralization when assessed in isolated AV interstitial cells [11]. The clinical association between LDLs and AS has been recently evaluated in 6942 patients of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium [12]. In this study, genetic elevation in LDL-C, but not in HDL-C or triglycerides, was associated with increased prevalence of AV calcium and incident AS at a follow-up of 15 years. Yet, the role of HDL in AS remains controversial, but because of their anti-atherogenic and anti-inflammatory properties, a protective role in AS pathogenesis and progression would be expected. In this regard, an high total cholesterol/HDL ratio and low serum HDL-cholesterol levels have been found to be associated with a rapid rate of AS progression [13]. Although the amount of valvular HDL is reduced in human stenotic AV [14], recent evidences suggest that also HDL might promote AS. In fact, in explanted stenotic human AV, apolipoprotein A1 of HDL has been found close to calcific nodules and contributes to the production of amyloid proteins which promote the transition of isolated valvular interstitial cells (VICs) toward an osteoblast phenotype [15].

ROLE OF EXERCISE FOR PREVENTION OF AV DEGENERATION

Regular physical exercise training plays an important role in primary and secondary prevention of atherosclerotic cardiovascular diseases . Exercise improves endothelial function, attenuates oxidative stress, restores cardiac and vascular beta-adrenergic receptor system and has a significant impact on blood lipids and lipoprotein profiles [16-21]. All these factors are known to be involved in AV degeneration and in AS development. This represented the rationale to test exercise training to prevent the progression of AV disease. In LDLR deficient mice, an experimental animal model which is largely used to mimic human atherosclerosis, a regular exercise training program prevented the development of AV sclerosis [22]. Interestingly, in this study, the cellular and molecular mechanisms by which exercise counteracted the processes of AV degeneration were: i) preservation of the integrity of valvular endothelium; ii) attenuation of oxidative stress and reduction in ox-LDL; iii) attenuation of proosteogenic signaling pathways.

AS AND ALTERED BONE TURNOVER: THE ROLE OF LIPIDS

It is widely accepted that bone deposition within the AV is inversely correlated with bone mineralization [23]. This phenomenon has been observed in osteoporosis, in patients with chronic kidney disease (CKD) [24] and in less frequent bone disorders such as Paget's disease [25]. The relationship between ectopic calcification and reduced bone mineral density is commonly defined as "bone paradox" [26 27]. This phenomenon has been largely demonstrated for vascular calcification and several evidences indicate that it could be also involved in the progression of AS [27]. In a recent experimental study conducted in apoE-/- mice, a murine model of atherosclerosis, an association between AV calcification, arterial calcification and bone mineral loss has been demonstrated [28]. These results add new insights in the pathogenesis of calcific AS, indicating that inflammation and atherosclerosis could represent both the initiating process and the link between valvular calcification and altered bone metabolism . Interestingly, the described association between atherosclerosis, inflammation and ectopic calcification/bone demineralization seems to be enhanced in the presence of CKD. Hjortnaes et al. [27], described increased osteogenic activity in the femurs and greater arterial and aortic valve osteogenic signal intensity in apoE -/- mice with CKD when compared to animals with normal renal function. These findings are in line with the clinical evidence of bone demineralization and arterial calcifications in patients with CKD [29].

ROLE OF LIPIDS IN THE ACTIVATION OF MOLECULAR PATHWAYS INVOLVED IN AV CALCIFICATION

a) The Lipoprotein-associated phospholipase A2/LDL/lysophosphatidylcholine axis

We have previously emphasized the role of ox-LDL in the pathogenesis of AS. Interestingly, ox-LDL are converted into lysophosphatidylcholine (LPC) by the lipoprotein associated phospholi-

pase A2 (Lp-PLA2) that is upregulated in calcified AV [30]. In vitro studies indicate that LPC is a strong promoter of mineralization in isolated aortic VICs through a cyclic adenosine monophosphate (cAMP)/protein kinase A pathway. Lp-PLA2 is produced within the AV by macrophages and/or is transported in the aortic valve by LDL, particularly by small, dense LDL. Lipoprotein (a) represents a vector for oxidized phospholipids transport into the AV [31] and its plasma levels have been found to be associated with increased risk of AS [31].

b) Renin-angiotensin system activation in AS

Activation of the renin-angiotensin system (RAS) is also implicated in AS pathogenesis and RAS inhibition slowers AS progression [32]. In explanted human stenotic AV, angiotensin-converting enzyme (ACE) is expressed and colocalized with angiotensin II [32]. Notably, ACE can be transported in the aortic valve by LDL, thus promoting local production of angiotensin II and triggering the process of tissue fibrosis which represents an hallmark of AV remodeling.

c) Wnt/Lrp5 signaling pathway

The upregulation of the Wnt/lipoprotein receptor-related protein 5 (Lrp5) signaling pathway is considered a relevant molecular phenomenon that can trigger calcification (28). Lipids and other cardiovascular risk factors induce oxidative stress [33] in the AV endothelium which in turn activates the secretion of cytokines and growth factors activating cell signaling. Wnt3 secretion from valvular endothelium and the activation of Wnt canonical pathway through the Lrp5 are largely dependent on the abnormal oxidative stress environment promoted by atherosclerosis [34]. Lrp5 is a member of the family of structurally closely related cell surface LDLRs (receptors involved in the LDL metabolism) that have diverse biological functions in different organs, tissues and cell types [35]. In the AV, Wnt is secreted from endothelial cells into the subendothelial space and binds to his receptor on the myofibroblast extracellular membrane forming the complex Lrp5/Wnt3/Frizzled, which triggers the phenotypic transition of these cells toward osteoblasts [36 37].

d) Osteoprotegerin (OPG)/RANKL/RANK

OPG/RANKL/RANK pathway is considered to be involved in vascular and AV calcification [38]. In addition, opposite regulation of this pathway in bone and vasculature may explain, at least in part, the calcification paradox [25]. It has been demonstrated that the osteoblastic transition of AV myofibroblasts may be promoted by RANKL, produced by lymphocytes and macrophages [39 40]. In calcified AV, RANKL expression is highly increased while OPG expression is not detectable with the net result of a decrease of the calcification inhibition potentially associated with OPG [41]. Furthermore, in cultured AV myofibroblasts, exogenous RANKL accelerates the transition toward an osteogenic phenotype. Comprehensively, these data point to common molecular pathways that characterize vascular and valvular atherosclerosis as well as bone resorption.

POTENTIAL ROLE OF EPICARDIAL ADIPOSE TISSUE IN THE PATHOGENESIS OF AS

Epicardial adipose tissue is the visceral fat depopt of the heart and in physiologic conditions exerts several protective functions for the myocardium. However, it has been also demonstrated that cardial visceral fat may play an unfavourable activity through secretion of numerous pro-inflammatory factors that are correlated with the presence and the extent of several cardiac disorders. In this regard, we have recently demonstrated that echocardiographic thickness of epicardial adipose tissue is correlated with the presence of severe AS [42]. Moreover, further studies from our group have suggested that cardiac visceral fat represents a source of catecholamines, thus potentially contributing to the adrenergic overdrive occurring in AS-related heart decompensation and cardiac adrenergic dysfunction [43-49].

DIAGNOSIS

Typical symptoms of AS are angina, syncope, and heart failure [50]. However, clinical manifestation is frequently insidious at the onset and can be highly variable among patients with similar degrees of valve stenosis. Many patients note a subtle decrease in exercise tolerance as the first symptom of AS [51]. This element is crucial in the evaluation of AS severity in the elderly because the limitation of the daily life activity due to comorbidity and disability would hardly elicit the symptoms in these patients with the consequence that AS tends to be asymptomatic for a long time. The onset of symptoms represents an

indication to surgical replacement. Echocardiography has become the key tool for the diagnosis and evaluation of aortic valve disease, and is the primary non-invasive imaging method for aortic valve stenosis assessment. Clinical decision-making is based on echocardiographic evaluation of aortic stenosis (AS) severity [52]. The primary haemodynamic parameters recommended for clinical evaluation of AS severity are: AS jet velocity, mean transaortic gradient and valve area by continuity equation. Severe AS is usually defined by a mean gradient > 40 mmHg, aortic valve area (AVA) < 1 cm^2 and peak aortic jet velocity > 4.0 m/sec. However, discrepancies are frequently observed between the mean gradient and the valve area in the single patient. For this reason it has been imperative an underclassification of the general severe AS pattern, in terms of transvalvular flow rate and pressure gradient [53]. In severe AS with an AVA < 1cm^2, four flow gradient AS cathegories can be identified: Normal flow/Low gradient (NF/LG), Normal flow/High gradient (NF/HG), Low flow/High gradient (LF/HG) and Low flow/Low gradient (LF/LG). LF is defined through the Stoke Volume index (SVI) (Normal value > 35 ml/m^2) and LG as a mean transaortic pressure gradient < 40 mmHg.

Exercise testing may add important informations in asymptomatic patients allowing to recognize normal exercise limitations from abnormal symptoms due to AS, even though patients with symptoms evoked by exercise testing should be considered symptomatic. In particular in old sedentary patients, exercise-induced angina, early excessive dyspnea, dizziness or syncope are compatible with symptoms of AS. It is important to underline that the risk of exercise testing is low in asymptomatic patients with AS as reported in numerous prospective and retrospective studies. Exercise testing should not be performed in symptomatic patients with AS when the aortic velocity is ≥4.0 m/sec or mean pressure gradient ≥40 mm Hg, due to high risk of complications, comprising syncope, ventricular tachycardia, and death [54 55].

MANAGEMENT

For patients with low to moderate, international guidelines reccomend medical therapy with the use of drugs which can reduce cardiac workload and sympathetic overactivity and restore cardiac adrenergic impairment related to HF, such as beta-blockers [56-58]. In this regard, targeting cardiac beta-adrenergic receptor system has been demonstrated a valid strategy for treatment of HF of different etiologies, including AS and of other diseases that recognize autonomic dysfunction as an important patogenetic mechanism [59-65]. In patients with AS related heart failure in sinus rithm, left atrial enlargement and high tromboembolic risk, the use of anticoagulants could be taken in account [66].

Patients with a pattern of “normal flow low gradient” represent 31-38% of patients with severe AS. They have a preserved longitudinal myocardial function and a less severe degree of AS. The prognosis in these patients seems to be relatively better then the others cathegories. Patients with “normal flow high gradient” represent the 39-72% of patients with severe AS. The longitudinal function is still preserved but the exposition to the disease seems to be longer. The cardiac event-free survival rate is reduced. Patients with a model of “low flow high gradient” represent the 8% of patients [67-70]. It is characherized by a low SVI despite a preserved LVEF due to the compromission of the LV longitudinal function. It is the result of a concentric remodelling of LV that ensures a normal LVEF, thus underestimating the extent of myocardial impairment. The transvalvular gradient is high but lower than expected because of intrinsic myocardial disfunction and significant LV remodelling. The outcome in this patients is similar to patients with NF/HG. It is important to underline that AS outcome is strongly conditioned by the coexistence of coronary artery disease which in turn shows a worse behaviour in elderly patients with cardiac valvulopathy [71-74].

Patients with a pattern of “low flow low gradient” have a low transaortic volume flow rate due to LV systolic dysfunction with a low LV ejection fraction (LVEF). In general 7% of symptomatic patients and 15-35% of asymptomatic patients have this pattern. So actually when LV systolic dysfunction co-exists with severe AS, the AS velocity and gradient may be low, despite a small valve area. However, LVEF can be paradoxically preserved. In this case the small and hypertrophied LV ejects a small SV so that, even when severe stenosis is present, the AS velocity and mean gradient may be lower than expected for a given valve area.

Indication for AVR should be limited to patients in whom symptoms can clearly be attributed to AS. When asymptomatic, individual risk stratification

can support the identification of patients who may benefit from early surgery. In these patients, evaluation of circulating cathecolamines, which are expression of adrenergic activity, may be useful for prognostic stratification togheter with other well recognized circulating biomarkers [75-79]. Exercise echocardiography may be important in revealing patients with limited valve compliance and/or exhausted LV contractile reserve [52, 80-82]. In adults with severe symptomatic AS, AVR is the only effective treatment considered with a Class I recommendation by ACCF/AHA and ESC guidelines [83-85]. Current AVR options include mechanical, bioprosthetic,and in specific situations homograft and autograft techniques. Each has its advantages and drawbacks, but the trend in some centers in the recent era has been toward tissue valve replacement in a majority of patients because of improved durability and the lack of requirement for anticoagulation therapy [84 86].

Minimally invasive AVR through a ministernotomy has been developed as an alternative approach to conventional full sternotomy AVR. The technique was developed to reduce surgical trauma and studies have demonstrated favourable postoperative outcomes compared with full sternotomy AVR [87].

Mortality and morbidity outcomes of mini-AVR are equivalent to conventional AVR. Mini-AVR is associated with decreased ventilator time, blood product use, early discharge, and reduced total hospital cost. In contemporary clinical practice, mini-AVR is safe and cost-effective [87].

Current data from the Society of Thoracic Surgeons (STS) registry documents a mortality that is under 3% for all patients undergoing AVR. As with any procedure, operative mortality is strongly correlated with the severity of the disease and comorbidity.

However, despite substantial contemporary experience with successful AVR in elderly patients, multiple series have documented that 30% to 40% of patients with severe AS do not undergo surgery owing to advanced age [88 89]. In summary, a substantial percentage of patients with AS are judged to be inoperable for surgery based primarily on the physician's or surgeon's determination of operative risk and survivability without an adequate multidimensional geriatric assessment [90]. Although some patients may be found to be inoperable for technical and surgical reasons, most inoperable patients are felt to be too ill from associated comorbid conditions. When considered inoperable, patients may undergo alternative procedures. Balloon aortic valvuloplasty has been considered to be a less invasive and safe alternative to AVR for a long time, particularly in high surgical risk patients with multiple medical comorbidities. Although balloon aortic valvuloplasty results in immediate hemodynamic improvement with a significant decrease in transvalvular gradients resulting in larger valve area, it does not result in sustained clinical improvement because of high recurrence rates of restenosis or recoil of the aortic valve usually occurs within 6 months [91]. Balloon aortic valvuloplasty, therefore, should not be used as a substitute for AVR in patients who are candidates for surgical AVR. Even as a palliative treatment, balloon aortic valvuloplasty data suggest that there is much uncertainty regarding improved longevity or quality of life after the procedure with a mean duration of symptom improvement of only 1 year [92 93]. Although balloon aortic valvuloplasty as a stand-alone treatment is not recommended [94-96], it may still be used in contemporary practice as a bridge to subsequent AVR (both Class IIb, Level of Evidence C recommendation) [91-93]. In the current era of TAVR, there has been increased interest in balloon aortic valvuloplasty. In this setting, balloon aortic valvuloplasty may be used to assess whether there is initial clinical improvement, in which case, then the patient may be a candidate for transcatheter aortic valve replacement (TAVR) [85].

TAVR

Background and History

Given the increased mortality and morbidity of AVR for high-risk patients and the poor long-term results of balloon aortic valvuloplasty, there has been interest in the development of a percutaneously delivered aortic heart valve [97]. The concepts of frailty, an important and frequent condition in elderly patients, will assume central importance in patient selection for TAVR by virtue of the extensive comorbidities present in this population [98 99]. To the extent that AS may contribute to the declining health state, AVR or TAVR may reverse frailty. In this case, frailty may be a marker for treatment benefit. Conversely, if the individual is frail from multiple other organ system declines, frailty may be a marker of treatment risk.

The initial hemodynamic performance of TAVR valves must be similar or superior to that ob-

tained with surgical AVR. This is crucial because high residual transprosthetic gradients result in less symptomatic improvement and poorer regression of left ventricular mass [85 100]. Transprosthetic gradients are a function of prosthetic size as well as the specific type of prosthesis and can result in patient–prosthesis mismatch. There are only limited clinical data on the durability of TAVR valves – up to 2 years – in the PARTNER trial and up to 5 years in other registry experiences. The fundamental clinical need for durability may depend in part on the specific patient population. In the PARTNER trial, the mean age at implant was 83 years, and serious comorbidities were frequent. In this setting, the need for durability of 20 years is less important than if the patient selection criteria are broadened to include patients in their early to mid 60s who have isolated AS without comorbid conditions. In this latter group, the TAVR valve must have at least equivalent clinical durability to currently available surgically implanted valves.

Quality of life is a key patient-centered outcome especially in the old patient. Although death is the lowest possible functional status, for many, survival marked by reduced physical function in a background of previous disability may be worse than death. The PARTNER study highlights that all patients improved, with no significant differences in NYHA functional class improvement. Improvements following TAVR in vitality, physical functioning, and general and mental health scores have been identified with physical function demonstrating the greatest improvement. Patients who do not experience improvement are more likely to have comorbidities that contribute to continued symptoms and impair quality of life, such as COPD and reduced EF [85 101 102].

Medical therapy

There are no proven medical treatments to prevent or delay the disease process in the aortic valve leaflets. However, evaluation and modification of cardiac risk factors is important in patients with aortic valve disease to prevent concurrent coronary artery disease (CAD). The association of AS with risk factors similar to those associated with atherosclerosis [5 103-105] had suggested that intervention may be possible to slow or prevent disease progression in the valve leaflet [106 107]. Anyway the medical therapy is the real challenge of the AV stenosis and the aim of the future research especially in the elderly, often charachterized by high surgical risk, where a medical therapy could avoid an intervention and improve prognosis.

Calcfic aortic stenosis represents the most common heart valve disease in the elderly population. Recent evidence have demonstrated that active biological events lead to a progressive degeneration of aortic valve leaflets mainly regulated by lipids and inflammation. Clinical manifestation is frequently insidious at the onset and can be highly variable among patients with similar degrees of valve stenosis. The onset of symptoms represents an indication to surgical replacement. Echocardiography has become the key tool for the diagnosis and evaluation of aortic valve disease, and is the primary non-invasive imaging method for aortic valve stenosis assessment. Despite substantial contemporary experience with successful aortic valve replacement in elderly patients, multiple series have documented that 30% to 40% of patients with severe AS do not undergo surgery owing to advanced age. In summary, a substantial percentage of patients with AS are judged to be inoperable for surgery based primarily on the physician's or surgeon's determination of operative risk and survivability. Growing evidence indicate that in unoperable patients, transcatheter aortic valve implantation may represent a valid alternative to surgery with excellent results in terms of quality of life and survival.

***Key words*: Aortic stenosis, Lipids, Elderly, Prosthetic valve**

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Targeting oxidative stress for improving cardiovascular performance in the elderly

La modulazione dello stress ossidativo: un nuovo target per migliorare le prestazioni cardiovascolari nell'anziano

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Lo stress ossidativo è implicato nella fisiopatologia di diverse malattie cardiovascolari, come dimostra la correlazione tra i marcatori di stress ossidativo e d'insufficienza cardiaca (HF).
Le specie reattive dell'ossigeno (ROS) giocano un ruolo importante nei processi di signaling, ma la loro sovrapproduzione genera stress ossidativo. Studi precedenti hanno dimostrato che l'HF è associato a deficit di antiossidanti ed aumento dello stress ossidativo. Inoltre, tali cambiamenti si correlano alla funzione emodinamica, suggerendo il loro ruolo nella patogenesi della disfunzione cardiaca. Un meccanismo importante coinvolto nella risposta cellulare cardiovascolare è rappresentato dalle sirtuine. L'inibizione di SIRT1 determina la soppressione dei geni attivati dall'esposizione ad uno shock termico, mentre la sua attivazione ne migliora la risposta. Quindi, la capacità di SIRT1 di modulare la resistenza allo stress è multiforme e non solo legata allo stress ossidativo, ma anche ad altri stimoli stressanti. Recentemente diversi studi hanno dimostrato la capacità dell'attività fisica di indurre attivazione di SIRT1 che, a sua volta, ha la capacità di mediare gli effetti antiossidanti favorevoli dell'allenamento. Anche altri agenti in grado di attivare SIRT1 hanno dimostrato effetti sulla funzione cardiaca. La supplementazione con resveratrolo ha dimostrato di ridurre i fattori di rischio cardiovascolare, ed il suo effetto positivo sulla risposta all'esercizio e sulla capacità aerobica nei ratti sembra essere mediato da SIRT1. Il futuro della ricerca deve essere indirizzato a chiarire il possibile ruolo della terapia antiossidante negli studi clinici, in particolare alla definizione di una standardizzazione delle procedure, delle dosi e della durata del trattamento.

***Parole chiave*: Stress ossidativo, Sirtuine, Resveratrolo, Curcumina, Antiossidanti**

In the last decades the worldwide population has exhibited an increasing life expectancy with a consequent raise in elderlies, with resultant impact on the prevalence of age-related diseases, with the cardiovascular conditions as the most prevalent illnesses [1].
Increasing evidence suggests that chronic systemic inflammation and accumulating oxidative stress are related to the aging process and play a role in developing many chronic diseases such as atherosclerosis, hypertension, COPD [2-8]. At the same time metabolic changes show high influence in to prevent or to reduce the severity of age-related pathologies, suggesting that management of these factors could have an effect on the progression of the diseases [9-11].

OXIDATIVE STRESS AND CARDIOVASCULAR DISEASES

Oxidative stress is implicated in the pathophysiology of several cardiovascular diseases, such as heart failure (HF), hypertension and myocardial

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infarction, as evidenced by a correlation between oxidative stress markers and HF in human and animal studies [12 13] and by direct molecular evidence for an etiological role of reactive oxygen species (ROS) [14]. During life, cardiovascular system is constantly exposed to oxidative stress, which occurs when ROS are produced in excess of the endogenous antioxidants [15]. The balance between the production of ROS and the activation of the antioxidant defence system is crucial for the human physiology and the control of cellular homeostasis. ROS play an important role in signalling processes, but their overproduction generates oxidative stress. In fact, ROS can regulate cellular functions; in turn their overproduction causes damage to cellular constituents, including DNA, proteins, and lipids, especially when occurs with insufficient antioxidant enzyme activity.

Several in vitro and in vivo studies have demonstrated ROS activation in the cardiovascular system in response to various stressors, and animal studies have also suggested that antioxidants and ROS defence pathways can ameliorate ROS-mediated cardiac abnormalities [16].

The importance of oxidative stress, as well as adrenergic nervous system hyperactivity [17-34] is increasingly emerging with respect to a pathophysiological mechanism responsible of cardiac hypertrophy, cardiomyocyte apoptosis, development and progression of HF [35]. Moreover, an increased production of ROS in the vascular wall and a reduction in nitric oxide bioavailability lead to endothelial dysfunction in atherogenesis [35].

Specifically, ROS can directly impair contractile function by modifying proteins central to excitation-contraction coupling, by activation of hypertrophy signalling kinases and transcription factors and mediating apoptosis. They also stimulate cardiac fibroblast proliferation and activate the matrix metalloproteinases, leading to the extracellular matrix remodelling. These cellular events are involved in the development and progression of maladaptive myocardial remodelling and failure [36 37].

ROS overproduction also occurs in response to several stressors, including chemicals, drugs, pollutants, high-caloric diets, and exercise. Physical exercise can increase oxidative stress, eventually causing a perturbation of homeostasis that is dependent on training specificity [38-42] and workload [43], but in turn it is also able to counterbalance the deleterious effects of ROS by activation of several antioxidant systems, such as Super Oxide Dismutases (SODs), Heat Shock Proteins (HSPs) and catalase [43-46]. The mechanisms by which ROS mediate these different biologic responses are not fully understood, but in many cases involve activation of specific redox-sensitive signalling molecules [45].

SYSTEMS INVOLVED IN CARDIOVASCULAR ANTIOXIDANT RESPONSE

Previous studies demonstrated that HF subsequent to myocardial infarction was associated with antioxidant deficit as well as increased oxidative stress. Furthermore, these changes correlated with the hemodynamic function, suggesting their role in the pathogenesis of cardiac dysfunction.

The main protective systems involved in antioxidant cellular defence are represented by Glutathione peroxidase (GSHPx), superoxide dismutases (SOD), and catalase.

GSHPx catalyses the reduction of H2O2 and hydroperoxides, which results in prevention of the more toxic radicals formation. It has been demonstrated that overexpression of the GSHPx gene attenuated myocardial remodelling and preserved diastolic function in diabetic heart [47], suggesting that therapies designed to interfere with oxidative stress by using GSHPx could be beneficial to prevent myocardial remodelling and failure [48].

The SOD catalyse the dismutation of superoxide into oxygen and hydrogen peroxide during physiological and pathological conditions. Manganese superoxide dismutase (MnSOD) is the primary mitochondrial antioxidant enzyme and is essential for maintaining normal cell development and function. Overexpression of the MnSOD gene has been shown to be beneficial in various animal models of cardiac diseases [49]. Recently, Shen et al. [50] demonstrated that protection of cardiac mitochondria by overexpression of the MnSOD gene reduced the severity of diabetic cardiomyopathy, and completely normalized contractility in diabetic myocytes. Results from this study and from other authors [51] showed that elevating levels of MnSOD provided extensive protection to diabetic mitochondria and provided overall protection to the diabetic heart, as well as to the brain. Interestingly, MnSOD gene overexpression also elevated levels of myocyte catalase and mitochondrial GSHPx, which might also act together with MnSOD against oxidative stress. On the contrary, Nojiri

Tab. I. Classes of Sirtuins, their localization and prevalent activity.

	Localization	Activity
SIRT1	Nuclear and cytoplasmic	NAD-dependent Deacetylase
SIRT2	Cytoplasmic and nuclear	NAD-dependent Deacetylase
SIRT3	Mitochondrial, nuclear and cytoplasmic	NAD-dependent Deacetylase
SIRT4	Mitochondrial	ADP-ribosyl transferase
SIRT5	Mitochondrial	NAD-dependent Deacetylase, Desuccinylase, Demalonylase
SIRT6	Nuclear	NAD-dependent Deacetylase, ADP-ribosyl transferase, defatty-acylase
SIRT7	Nucleolar	NAD-dependent Deacetylase

et al. [52] reported that heart/muscle-specific Mn-SOD-deficient mice developed progressive HF with specific molecular defects in mitochondrial respiration in association with excess formation of superoxide and transcriptional alterations of genes associated with HF. Catalase, which reduces hydrogen peroxide to water, represents a primary safeguard of the antioxidant system and some recent studies have suggested that this enzyme might play an important role in the pathophysiology of HF [53]. Recently Kumar et al. [54] showed that subjects with ischaemic heart disease, myocardial infarction and unstable angina had increased TBARS levels and reduced SOD, catalase, and ascorbic acid levels. These findings are in accord to meta-analyses that identified strong and statistically significant inverse associations of GSH-Px, SOD, and catalase activities with coronary heart disease outcomes [55]. This supports a role of oxidative stress in the pathogenesis of coronary artery disease and in the outcome of patients undergone to coronary revascularization procedures [56-61].

REGULATOR OF CARDIOVASCULAR ANTIOXIDANT RESPONSE

An important mechanism involved in cellular cardiovascular response is represented by family of sirtuins (Tab. I, Fig. 1), a cluster of proteins composed by seven homologues regulating cellular biology and metabolism through deacetylation of histones and other cellular factors such as NFkB, HSF1, p53, FOXOs, and PGC- 1. Sirtuins are found in different subcellular locations, including the nucleus, cytosol, and mitochondria. The regulation of mammalian lifespan by sirtuins has important therapeutic implications for age-related diseases.

SIRT1, the best characterized member of the family, is involved in many functions of human physiology, including DNA repair, cell cycle regulation, apoptosis, gene expression, and aging [62]. SIRT1 can modulate the cellular stress response directly deacetylating some proteins and regulating their expression. Furthermore, this enzyme modulates the threshold of cell death in the setting of exogenous stress, including oxidative damage, and regulation of other targets linked to cell death. Then the ability of SIRT1 to modulate stress resistance is multifaceted and it is not only linked to oxidative stress, but also to other stressful stimuli. It also seems to be implicated in processes of morphological

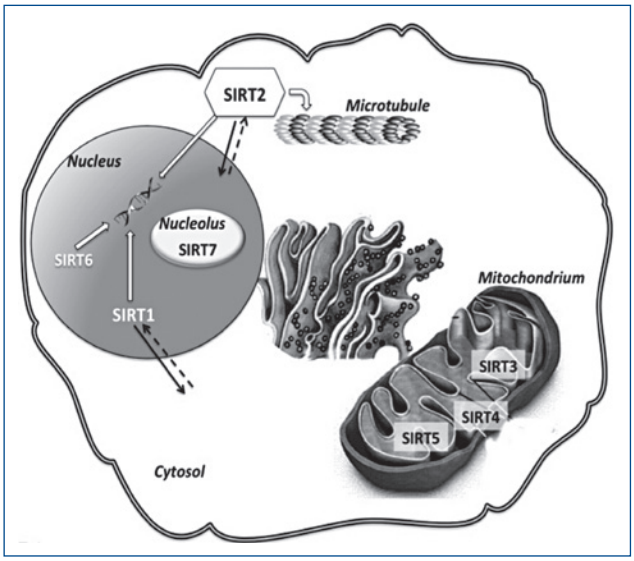

Fig. 1. Sirtuins localization in the cell. In the figure the main localization of sirtuins is showed. The solid line indicates the shift from the primary to the secondary location; the broken line demonstrates the shift from the secondary to the primary location.

heart development. In fact, the full-body SIRT1 knockout mouse displays ventricular adult heart abnormalities [63], but a severe developmental phenotype, together with high neonatal mortality rates make use of it difficult to study the physiological role of SIRT1 in the adult heart. Interestingly, high levels of SIRT1 expression (> 9-fold) in the heart cause hypertrophy, loss of cardiac function, and elevated apoptosis [63]. On the other hand, moderate overexpression (2.5 to 7-fold) of SIRT1 in transgenic mouse hearts protects against oxidative stress, and results in increased expression of antioxidants [64].
SIRT3 modulates mitochondrial gene expression and function via a general deacetylation of mitochondrial proteins involved in oxidative phosphorylation [65], or ROS handling [66].

TARGETING ANTIOXIDANT REGULATORS

Recently it has been demonstrated that by acting on this mechanism other factors could influence cardiac performance.
In particular, physical activity has been demonstrated able to reduce generation of oxidants during ischemia-reperfusion damage and to have a calcium-protective role via activation of the ROS scavenger, MnSOD. This better oxidative status consequent to a correct program of physical activity is partially responsible for some benefits (such as decreased arterial stiffness, improved endothelial function and metabolic and clotting setting, and reduced body weight) [67-71]. In part, it seems that positive effects of the physical exercise on heart in terms of antioxidant activity could be ascribable to a greater expression and activity of SOD and HSPs.
An 8-week training period has been shown to reduce body weight and cardiac abnormalities characteristic of senescence heart, such as structural changes, ventricular systolic pressure, left ventricle weight/body weight ratio, and heart rate [71], suggesting that exercise training antioxidant effects might be also mediated by mechanisms involving metabolic pathways.
In fact, both exercise training and caloric restriction improve the antioxidant system, and this could also explain the analogy between benefits derived by these tools [72].
In another study the exercise training increased SIRT3 and MnSOD levels in quadriceps muscle of wild-type, but not AMPK α2 kinase dead mice, suggesting an important role for AMPK in regulating mitochondrial function and ROS handling in skeletal muscle in response to exercise training [73]. Then the possibility to act on this mechanism has induced several researcher to test the efficacy of sirtuins' activator other then physical activity.
Resveratrol is a polyphenol found in the skin of grapes, berries and peanuts that can activate AMPK and sirtuins. In rodents resveratrol supplementation has been shown to decrease cardiovascular risk factors, including blood lipids [74] and VCAM-1 [75], to improve cardiovascular function and physical capacity, and to decrease inflammation in the vasculature of aged animals leading to improved vascular function [76]. Specifically, the positive effect of resveratrol on training response and aerobic capacity in rats has been shown to be mediated via SIRT1 [77 78].
Recently Meng et al. [79] found that resveratrol administration had improved the enzymatic and non-enzymatic antioxidant system against the atherogenic diet as well as in normal condition. These effects were similar in both heart tissue and haemolysate which is consistent with the previous study, treatment of apoE knockout mice with resveratrol for 7 days results in the upregulation of superoxide dismutase, glutathione peroxidase, and catalase in heart tissue [79]. The authors hypothesized that resveratrol activated the SIRT1, eNOS and regulated the phosphorylation of AMPK against the atherogenic diet [80]. SIRT1 binds directly to eNOS and has been shown to target eNOS for deacetylation, thereby stimulating nitric oxide production and promoting vascular relaxation [80].
In another study a Resveratrol treatment protected rats against diet induced Insulin Resistance, increased SIRT1 and SIRT3 expressions, mtDNA, and mitochondrial biogenesis. Moreover, the activities of mitochondrial antioxidant enzymes were increased, suggesting that Resveratrol ameliorates insulin sensitivity consistent with improved SIRT3 expressions and rebalance between subsarcolemmal mitochondrial oxidative stress and antioxidant competence in high-fat diet rats [81 82].
In another interesting study, Gliemann et al. [83] tested the hypothesis that oral resveratrol supplementation enhances the positive cardiovascular adaptations to exercise training in aged subjects by increasing SIRT1-mediated signalling and by promoting the endogenous antioxidant system. The authors showed that high-intensity exercise training potently improves a number of parameters related to vascular function and cardiovascular health in aged men, but that concomitant

oral resveratrol supplementation blunts several of these positive effects of exercise training. Specifically, resveratrol had adverse effects on improvements in maximal oxygen uptake, on blood pressure reduction and on the lowering of blood lipids induced by exercise training, rejecting the hypothesis that resveratrol improves cardiovascular health by enhanced SIRT1-dependent signalling and improved antioxidant defence. Furthermore, the authors concluded that training enhances the capacity for ROS formation via increased levels of NOX and that removal of ROS via resveratrol treatment may limit training-induced adaptations [83].

On the other hand, other studies showed as a regular ingestion of a different antioxidant, as curcumin, significantly increased carotid arterial compliance in postmenopausal women. In the study by Akazawa et al. [84], the magnitude of improvement by curcumin was similar to that of exercise training alone. Moreover, the combination of exercise training and curcumin ingestion led to a greater improvement in arterial compliance compared to that achieved with either treatment alone. These results suggested that a combination of exercise and curcumin could have a strong positive effect on arterial compliance [84].

Other antioxidants (e.g. vitamin E, vitamin C, coenzyme Q10, etc.) have been tested in several experimental and clinical models with mixed success.

Lane et al. conducted a population-based study to examine the association between consumption of certain nutrients and prevalence of peripheral arterial disease, and they found that increased consumption of antioxidants, vitamin E and C was associated with reduced odds of peripheral arterial disease [85]. Other studies demonstrated the importance of vitamin E for protection against cardiac ischemia-reperfusion injury using vitamin E deficient animal models. These observations indicate that the modulation of oxidative stress by antioxidants appears to have a positive outcome in the prevention of CVDs. Despite this, the protective effects of vitamin E remain controversial, because it requires prolonged and very high levels of oral treatment to achieve cardiac concentrations that are protective from reperfusion injury.

Recently Takahashi et al. demonstrated that a 12-week supervised walking program improved oxidative stress status in postmenopausal women, but combining the exercise program and vitamin E supplementation showed no additive effects on the improvement of oxidative stress status [86].

On the large differences in results it should probably be considered that in these studies antioxidant agents might have been tested at different doses, or durations, or that the wrong drug or combination of drugs has been used. Therefore, regardless of these controversial data from clinical studies, oxidative stress still remains a potential attractive target for CVDs prevention and therapy. Possible future therapies aimed at decreasing mitochondrial either than nuclear oxidative damage should also be considered [87].

Recently Klishadi et al. [88] showed that SIRT3 decreased levels induced by ischemia reperfusion can be reverted by Losartan at non-hypotensive dose which exerts anti-ischemic effects in part by normalizing the SIRT3 protein level and upregulating the survival factors encoding genes transcription in ischemic tissue of the heart.

CONCLUSIONS

Surely the oxidative stress represents one of the most important and intriguing mechanism involved in the genesis, development and progression of several cardiovascular diseases, and still many pathways involving oxidant and antioxidant response should be better clarify. The future research should be addressed to better clarify the possible role of the antioxidants therapy in clinical studies, in particular defining a standardization of procedures, doses and duration of treatment in order to make comparable the various data and to understand the real effectiveness of antioxidants in the prevention and treatment of cardiovascular diseases.

Oxidative stress is implicated in the pathophysiology of several cardiovascular diseases, as evidenced by correlation between oxidative stress markers and Heart Failure (HF) and by direct molecular evidence for an etiological role of reactive oxygen species (ROS).

ROS play an important role in signalling processes, but their overproduction generates oxidative stress. Previous studies demonstrated that HF was associated with antioxidant deficit as well as increased oxidative stress. Furthermore, these changes correlated with the hemodynamic function, suggesting their role in the pathogenesis of cardiac dysfunction. An important mechanism involved in cellular cardiovascular response is represented by sirtuins. SIRT1 inhibition determines suppression of genes ac-

tivated by exposure to heat shock, on the contrary, SIRT1 activation enhances the heat shock response. Then the ability of SIRT1 to modulate stress resistance is multifaceted and not only linked to oxidative stress, but also to other stressful stimuli. Recently several studies have demonstrated the capability of physical activity to induce SIRT1 activity and, in turn, the ability of this enzyme to mediate the favourable antioxidant effects of the exercise training. Other agents able to induce SIRT1 activity have demonstrated some effects on cardiac function. Resveratrol supplementation has been shown to decrease cardiovascular risk factors, and the positive effect of resveratrol on training response and aerobic capacity in rats to be mediated via SIRT1. The future research should be addressed to better clarify the possible role of the antioxidants therapy in clinical studies, in particular defining a standardization of procedures, doses and duration of treatment.

***Key words*: Oxidative stress, Sirtuins, Resveratrol, Curcumin, Antioxidants**

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Oral anticoagulation therapy in the elderly

La terapia anticoagulante orale negli anziani

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I pazienti anziani sono a maggior rischio di tromboembolia a causa della presenza di comorbidità, di polifarmacoterapia e dell'invecchiamento. Gli anziani presentano un aumentato rischio sia tromboembolico, arterioso e venoso, che emorragico per tale motivo risulta difficile la scelta della miglior terapia da parte del medico. Negli ultimi anni sono stati creati dei sistemi di punteggio per la valutazione del rischio di stroke e di quello emorragico che potessero aiutare il medico nella scelta della miglior terapia anticoagulante. Le evidenze scientifiche indicano che i nuovi anticoagulanti orali (NAO) non sono associati ad un maggiore sanguinamento rispetto alla terapia convenzionale negli anziani. Viceversa i NAO riducono significativamente il rischio di ictus e di embolia sistemica negli anziani con fibrillazione atriale e sono anche più efficaci della terapia convenzionale per la riduzione del rischio di tromboembolismo venoso o di morte correlata a tromboembolismo venoso. Tuttavia, sebbene numerose evidenze scientifiche abbiano chiaramente affermato che i pazienti anziani con scompenso cardiaco hanno un elevato rischio intrinseco di eventi trombotici, le linee guida non suggeriscono l'utilizzo routinario di anticoagulanti, se non nei pazienti con fibrillazione atriale e/o portatori di valvola protesica e/o storia di tromboembolismo. La relazione tra scompenso cardiaco, fibrillazione atriale e asse sistema nervoso simpatico-emostasi dovrebbe essere approfondita in studi che focalizzano ed integrano l'approccio clinico con le nuove conoscenze biochimiche e biologiche degli anticoagulanti.

***Parole chiave*: Anticoagulazione, Anziano, Nuovi anticoagulanti orali, Insufficienza cardiaca, Fibrillazione atriale e tromboembolismo venoso**

Older adults have an increased risk of thromboembolism, due to the presence of many comorbidities, polipharmacotherapies and of the age process itself [1-4]. Both venous and arterial thromboembolic diseases have an high impact in elderly patients. Aging is regarded as one of the strongest and most prevalent risk factors for venous thromboembolism (VTE) [2 4]. Previous studies have showed that conventional risk factors, malignant disease, and the presence of comorbidities in elderly adults increase the risk of VTE and bleeding and might complicate anticoagulation treatment [2 5 6]. For arterial thrombosis, one of the main causes, for individuals aged 80 to 90, is atrial fibrillation (AF). AF related stroke also increases with age; in the Framingham Study, 23.5% of strokes in individuals aged 80 and older were attributable to AF [7]. Age 75 and older is considered a risk factor in stroke risk stratification scores and contributes 1 point toward a maximum risk score of 6 in the cardiac failure, hypertension, age, diabetes, stroke (CHADS2) score [8 9]. In the CHA2DS2-VASc score, aged 75 and older contributes 2 points toward a maxi-

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mum score of 9 [8,10]. In addition, other risk factors, such as hypertension, prior stroke, diabetes mellitus and heart failure have an higher prevalence in older adults [11]. Anticoagulants such as heparin and vitamin K antagonists remain the mainstay for the treatment of arterial and venous thromboembolic diseases, although they have potential limitations [12,13]. Recently, new oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban have been developed as an alternative to conventional anticoagulants [14,15] but the efficacy and safety profiles of NOACs have not been established in elderly adults [1,16] and there are particular concerns regarding bleeding with NOACs in elderly adults. The suggested predisposing factors are low body mass index in frail and in adults over 85 years, altered body composition of muscle and fatty tissue and high frequency of renal impairment [3,16].
Recent reports suggest an higher potential risk of bleeding with NOACs in older individuals [17,18]. No randomized trial has specifically randomized elderly adults to compare NOACs with vitamin K antagonists (VKA), or low-molecular-weight heparin (LMWH) as the population of primary interest.
This review has focused on a proposed physiopathological link between coagulation and the ageing process in order to analyze the role of anticoagulation in HF without AF and the role of NOACs in elderly adults for stroke prevention in individuals with AF and for VTE in acutely medically ill patients.

PHYSIOPATHOLOGICAL LINK BETWEEN COAGULATION AND AGEING

Hemostatic processes contribute to gradual fibrin deposition within atherosclerotic plaques and over thrombus formation subsequent to plaque disruption [19]. It is still debated whether hypercoagulability indicates an underlying atherosclerotic process or is cause of atherosclerosis and thrombosis [20]. Stimulation of sympathetic nervous system (SNS) increases blood clotting (by V, VIII, and Von Willebrand factors) and platelet activation with raised risk for atherothrombotic events [21-37] and major cardiovascular events after coronary revascularization procedures [38-41]. In addition, the phenomena may be exacerbated in the elderly since the well recognized age-related autonomic dysfunction [42,43]. The SNS regulates several homeostatic functions (e.g. cardiac, respiratory, digestion, urination and sexual arousal) and induces physiological changes during the "fight-or-flight response"(also called the acute stress response), that is a physiological reaction occurring in response to a perceived harmful event, attack, or threat to survival. During acute stress response or prolonged exercise, catecholamines (adrenaline and noradrenaline) facilitate immediate physical reactions associated with a preparation for violent muscular action and increased strength and speed in anticipation of fighting or running [44-50]. These physiological changes include: increased blood flow to the muscles, raised blood pressure, heart rate, blood sugars and fats, increased muscle tension, dilation of pupil, enhanced perspiration, increased the blood clotting function of the body speeds up, and changes of circulating biomarkers [51-57]. Although hastened blood coagulation the impact of SNS activation on hemostasis is not still clearly understood. Given the significance of increased hemostatic activity in atherosclerosis and the important role of the SNS in cardiovascular disease, SNS activation might contribute to arterial thrombus formation. Several studies have demonstrated that SNS activation induced procoagulant responses in patients with atherosclerotic plaques and endothelial dysfunction [58-63]. Adrenaline infusion induces platelet activity and it is higher in hypertensive individuals than in normotensive controls [59]. Moreover behavioral stressors, such as mental arithmetic and cold test, led to increase in fibrinogen and platelet activity as well as to impaired fibrinolysis in hypertensive individuals compared with normotensive controls. In patients with heart failure, there is an higher platelet activity with acute mental stress than normal controls [60].
Chronic stimulation of the SNS and concomitant hypercoagulable changes could contribute to gradual fibrin deposition at sites of atherosclerotic lesions. Once hemodynamic stress for instance emotional arousal has triggered rupture of an atherosclerotic plaque [61], hypercoagulability due to catecholamine spillover with both activation of the hypothalamic-pituitary-adrenal axis [62] and myocardial ischemia may promote coronary thrombus growth. These evidence raise the hypothesis that targeting the beta-adrenergic receptor system might be advantageous also for the control of blood coagulation [64-71]. Also, hypercoagulable changes with morning surge in catecholamine levels due to both circadian

variation in catecholamine activity and postural change may be related to increased morning frequencies of thrombotic vascular events [72-78].
In conclusion, future studies on the effects of SNS function on hemostasis mechanisms may further help integrating arduously achieved biochemical and biological knowledge for understanding the regulation of the SNS-hemostasis axis [79].

NOACS IN ELDERLY PEOPLE WITH AF/VTE

A recent meta-analysis of Lip G showed that NOACs did not cause greater major or clinically relevant bleeding than conventional therapy in individuals aged 75 and older (6.4% with NOACs vs 6.3% with conventional anticoagulants) [80]. Similar results were observed with NOACs and pharmacologically active agents (6.4% vs 6.3%). NOACs also did not cause extra bleeding for treatment of acute VTE or pulmonary embolism, extended treatment of VTE, or AF except thromboprophylaxis for acutely ill medical individuals. Risk of stroke and systemic embolism was significantly lower with NOACs than conventional therapy or pharmacologically active agents (3.3% vs 4.7%; absolute risk reduction = 1.4%). NOACs also resulted in a significantly lower risk of VTE or VTE-related death than conventional therapy (3.7% vs 7.0%) and pharmacologically active agents (3.9% vs 6.6%). In particular, regarding each NOACs: rivaroxaban did not cause greater major or clinically relevant bleeding than conventional therapy in elderly adults (4.5% vs 4.5%). Rivaroxaban was noninferior to or more effective than conventional therapy in prevention of stroke or systemic embolism and VTE or VTE-related death. The risk of major or clinically relevant bleeding was not higher with apixaban (5.1% vs 7.3%). Risk of stroke or systemic embolism and VTE or VTE-related death with apixaban was equal to or lower than conventional therapy. Safety data on dabigatran were more limited. Major or clinically relevant bleeding was similar with dabigatran and conventional therapy (9.3% vs 8.7%). Dabigatran was more effective than conventional agents in the prevention stroke or systemic embolism (3.2% vs 4.3%). NOACs did not cause greater bleeding than warfarin (6.5% vs 7.1%) or LMWH or LMWH followed by VKA (6.9% vs 5.3%).
These data suggest that NOACs did not lead to greater major or clinically relevant bleeding than conventional therapy and pharmacologically active agents in elderly adults. NOACs significantly reduced the risk of stroke or systemic embolism in elderly adults with AF. NOACs were also more effective than conventional therapy for the reduction of the risk of VTE or VTE-related death. A similar profile was also found for the effectiveness of the individual NOACs. Dabigatran, rivaroxaban and apixaban were more or as effective and safe as conventional therapy or pharmacologically active agents. However, the main concerns of geriatricians are about the bleeding risk. Several recent reports have raised concerns regarding the safety profile of NOACs in the elderly population [17 18]. Reports initially suggested that NOACs may cause more bleeding events, including life-threatening or fatal bleeding in elderly adults [17]. A 2 months audit conducted by the Haematology Society of Australia and New Zealand identified 78 episodes of bleeding in dabigatran treated individuals and participant age was one of the four major factors that contributed to these episodes [17]. Two thirds of the participants were aged 80 and older and 58% had moderate or severe renal impairment. One of the major arguments for the findings [17] was that the mean age of the trial population (RE-LY trial) was lower, and data from that trial may not be extrapolated into clinical practice in this case, but the current analysis for individuals aged 75 and older, including data from ten randomized controlled trials (RCTs), did not show excess bleeding with NOACs or with dabigatran specifically (data pooled from 2 RCTs). The data also showed that NOACs are significantly more effective than conventional therapy in this population.
Recent detailed analysis of bleeding related to apixaban and rivaroxaban in elderly adults in two large randomized trials also did not show excess bleeding with these drugs [81 82]. The reasons frequently suggested for the greater risk of bleeding in elderly adults are renal function impairment, low body weight, drug interactions, and unavailability of reliable coagulation tests to monitor blood level of NOACs [1 16]. Almost all previous articles reporting greater bleeding in elderly adults included individuals who had comorbidities, mainly coexisting renal failure [17], but all of the reports were from small observational studies or case reports and no randomized data are available. A possible explanation for the contrasting results of the current study might be that the chances of bleeding with NOACs are more related to associated comorbidi-

ties than the age of the individual per se. At the moment for edoxaban there are no publication about elderly patients.
The key message for clinicians is that the benefit of antithrombotic therapy is well established in elderly adults, including those who are at high risk of falling or bleeding [12 13]. The Lip study [80] suggests that NOACs are more effective than conventional anticoagulants in elderly adults. Old age per se should not be a criterion for withholding anticoagulation with NOACs. The recommended dose of apixaban is lower (2.5 vs 5 mg) in elderly adults with at least one comorbidity in addition to older age (i.e., a lower dose is recommended in those with ≥ 2 of aged ≥ 80, body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL). For individuals with AF, 110 mg of dabigatran twice a day is recommended for aged 80 and older in the European Union, rather than a 150 mg twice a day regular dose, although the Food and Drug Administration (FDA) does not recommend a routine dose modification for dabigatran in elderly adults. Dose modification for rivaroxaban is also not recommended for elderly adults, but a lower dose of dabigatran and rivaroxaban is recommended in individuals with moderate renal impairment [83].
A recent FDA postmarketing report of bleeding with dabigatran did not identify any unrecognized risk factors for bleeding [84]. A large propensity score matched nationwide cohort study from Denmark supports the FDA report (which does not adjust for comorbidities) [85]. Another report showed no greater risk of bleeding with dabigatran in VKA-naive individuals [86]. These arguments do not contradict the fact that caution should still be taken with NOACs in elderly adults with other comorbidities (mainly renal impairment) and very low body weight. Lack of a reversal agent for the anticoagulant effects of NOACs should also be kept in mind while prescribing these agents. Thus, an individualized case by case approach might be best for elderly adults, with proper judgment of risk of bleeding and associated comorbidities rather than a generalized "one drug fits all" approach. Prospective, randomized controlled trials of NOACs in elderly populations are also needed. In conclusion, bleeding with NOACs was not different from that with conventional anticoagulants in elderly adults enrolled in randomized trials. NOACs might be more effective than conventional agents in this population. An individualized approach matching the particular NOACs to the participant profile, taking into consideration the risk of bleeding and other comorbidities, should be taken rather than a generalized "one drug fits all" approach in elderly adults.

ANTICOAGULATION IN HF WITHOUT AF

Although it has been a topic of investigation for more than 50 years, the use of anticoagulants in patients with heart failure (HF) in sinus rhythm remains an argument of controversy and clinical debate [87]. Increased risk of thromboembolism, cardioembolic stroke and sudden death due to coronary occlusion occurs in about one third of HF patients, contributing to the high mortality and morbidity rates of the disease [88 89].
A Cochrane systematic review compared antiplatelet treatment versus oral anticoagulation therapies (OATs) in HF patients without AF and included three RCTs [90]. The rates of death, myocardial infarction (MI) and stroke were similar across OATs versus antiplatelet treatment. In pooled analyses there was no difference between warfarin and aspirin in all cause deaths or cardiovascular deaths. Although aspirin is of proven benefit in post-MI patients, there is inadequate evidence from long term studies to recommend its routine use in HF patients. Again, there is also no evidence to indicate superior beneficial effects from oral anticoagulation, when compared to aspirin, in HF patients, and there was some evidence of greater risk of bleeding events in warfarin as compared to aspirin. In conclusion, anticoagulation/antiplatelet therapy should be reserved for HF patients with other comorbidities (such as AF or underlying coronary artery disease) who may further benefit from these therapies.
A recent meta-analysis has explored the potential role of anticoagulation for HF in sinus rhythm [72], showing that OATs might reduce the entire cardiovascular thromboembolic risk also in HF patients without AF. This meta-analysis included four randomized controlled studies of oral anticoagulation (the same three of Cochrane systematic review and WARCEF trial) involving overall 1825 HF patients treated with warfarin who were compared to 1838 HF patients treated with aspirin. There was no significant difference in mortality between OATs group and antiplatelet drug group. OATs have reduced ischemic stroke risk, but have increased major bleeding risk compared to antiplatelet

treatment. In all trials included, the primary outcome was cardiovascular death (stroke, MI, pulmonary embolism, peripheral arterial embolism) and sudden death [91-94]. The WASH pilot study randomized 279 HF patients to treatment with either aspirin, warfarin or no antithrombotic therapy and showed no difference in mortality among these interventions [91]. However, compared to the other two groups, more patients randomized to aspirin were hospitalized for worsening HF. The HELAS trial separated 197 patients according to the etiology of their HF [92]. Only patients in the ischemic cardiomyopathy group (n = 115) were randomized to receive warfarin (target INR 2-3) or aspirin (325 mg), while patients in the non-ischemic group (n = 82) were randomized to receive warfarin or placebo. The incidence of the primary endpoint (composite endpoint of non fatal stroke, peripheral or pulmonary embolism, MI, re-hospitalization, exacerbation of heart failure or death from any cause) was not different between the groups. Major bleeding only occurred in the warfarin groups and was usually due to over anticoagulation but no case led to death. The WATCH trial included 1587 HF patients receiving aspirin (162 mg), clopidogrel (75 mg) or warfarin (target INR 2-3.5) [93]. Unfortunately, this trial was terminated early due to poor recruitment and was therefore underpowered to make any firm conclusion on antithrombotic therapy. Furthermore, this study did not have a placebo arm to show the effectiveness of antithrombotic therapy compared with no treatment. There was no difference among the three treatment groups for the primary endpoint (all cause mortality, non fatal MI or non fatal stroke). However, the data show a significant decrease in hospitalization rate in the warfarin group compared to aspirin and suggest that up to one third of all hospitalizations for HF could be attributed to the use of aspirin, which is consistent with the findings of the WASH study. Deaths and vascular events were similar on aspirin and clopidogrel. There were fewer hospitalizations for HF in the clopidogrel group. The safety data showed, as expected, a greater incidence of bleeding complications in the warfarin group. The WARCEF trial randomized 2305 HF patients to receive aspirin (325 mg) or warfarin (target INR 2.5-3.5) [94]. The rates of the primary endpoint (composite endpoint of ischemic stroke, intracerebral hemorrhage or death from any cause) were 7.47 events per 100 patient-years in the warfarin group and 7.93 per 100 patient-years in the aspirin group, with no significant difference between the two groups. The rates of MI and hospitalization for heart failure did not differ significantly between the two groups, although there was a trend toward a higher rate of hospitalization for heart failure in the warfarin group. Major bleeding was significantly higher with warfarin than with aspirin (1.78 events with warfarin versus 0.87 with aspirin per 100 patient-years). However, intracerebral and intracranial bleeding did not differ significantly according to treatment group (0.27 events in the warfarin group and 0.22 in the aspirin group per 100 patient-years). Despite the reduction in stroke events observed with anticoagulants compared to control, this evidence needs to be interpreted with caution. In fact, nowadays OATs are indicated only in HF patients with AF, since the overall data available do not support its use in HF patients who are in sinus rhythm because, despite the reduction of stroke, increased bleeding is observed.

The main cause of death in HF patients is attributed to refractory HF or sudden cardiac death and the latter is frequently due to new coronary (thrombotic) occlusion causing arrhythmic events. Systemic thromboembolism is common in HF patients, even in the absence of AF [95-110]. Moreover, several studies indicate that patients with previous stroke or peripheral thromboembolism have depressed left ventricular (LV) function [111 112]. In an analysis of > 600 deaths in a community long-term study comparing HF patients with depressed LV function versus those with preserved LV function, sudden death occurred in 21% and 16% respectively. New coronary occlusions (as reflected by MI) occurred in 50% of the patients within the first month during follow-up of 1.5 year in the depressed LV group [113]. In fact, it is well established that patients with HF in sinus rhythm are burdened with a moderate risk of thromboembolism and frequent comorbid conditions such as AF, valvular disease and atherosclerotic vascular disease that predispose to thrombosis only add to intrinsic thromboembolic risk. Moreover, a recent study demonstrated similar levels of platelet activation in both AF and non-AF patients with cardiovascular comorbidities, suggesting that platelet activation in AF may be caused by underlying cardiovascular disease rather than AF itself [114]. Thus, the increased risk of thromboembolism in HF may be related to the fulfillment of Virchow's triad for thrombogenesis in HF and its pathogenesis is multifactorial: low cardiac

output through dilated cavities of poor contractility, regional wall motion abnormalities and atrial fibrillation are the main factors [115]. Abnormal endocardial surface after MI or inflammatory/infiltrative cardiomyopathy may also favor the formation of clots. It has also been recently suggested that patients with HF may be in a hypercoagulable state. Indeed, the pathophysiology of thrombosis in HF is complex and the underlying mechanisms are only partially known.
Despite several evidence demonstrating the increased thromboembolic risk in HF patients, current guidelines from the American Heart Association and American College of Cardiology, the American College of Chest Physicians, and the European Society of Cardiology (ESC) do not support the routine use of warfarin in cardiomyopathy in sinus rhythm [116-118]. In ESC Guidelines for the diagnosis and treatment of acute and chronic HF, warfarin (or an alternative anticoagulant) is recommended in patients with HF and permanent, persistent or paroxysmal AF without controindications to anticoagulation (Class of recommendation I, level of evidence A). It is also recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism (Class of recommendation I, level of evidence C). The key evidence reports that warfarin is more effective in reducing the risk of stroke with respect to antiplatelet therapy and is preferred over antiplatelet therapy in patients at high risk for stroke [130]. The same issue is addressed in the American Guide to Warfarin Therapy indicating that "*warfarin is used frequently in patients with dilated cardiomyopathy, although no randomized trial has confirmed the benefit of anticoagulation*" [116]. A Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis, which reviewed the published evidence, summarized 'best practice' and put forward consensus statements that may assist management decisions in clinical practice [119]. This Consensus Document states "*Given no overall benefit of warfarin on rates of death and stroke, with an increase in major bleeding – despite the potential for a reduction in ischemic stroke – there is currently no compelling reason to routinely use warfarin for all HF patients in sinus rhythm*". Thus, whilst there is no doubt about whether HF patients in AF should receive OATs, the routine use of OATs cannot be recommended in those patients in sinus rhythm without any previous AF.

NOACs

Recently, the therapeutic armamentarium for anticoagulation has been expanded thanks to the evidence arising from RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF studies [120-123]. These trials have evaluated the non inferiority of new anticoagulant molecules compared to warfarin in patients with AF. For more than 50 years, warfarin has been the primary medication used to reduce the thromboembolic risk events in patients with AF. Despite its clinical efficacy, warfarin has several limitations, including interactions with other drugs and food, a narrow therapeutic range, the need for frequent laboratory monitoring and frequent bleeding. Therefore, it is often not used and when it is, rates of discontinuation are high. Moreover, many patients receiving warfarin might still have inadequate anticoagulation. Thus, physicians and patients may favorably take new oral anticoagulants into account for the management of thromboembolic risk in AF.
In the RE-LY trial, patients with AF and high risk of stroke were randomized to receive dabigatran, a competitive inhibitor of thrombin, in blinded fashion at the doses of 110 mg or 150 mg twice daily, or adjusted-dose warfarin, in unblinded fashion. The study demonstrates that both dabigatran doses were non-inferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150 mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism and the 110 mg dose was superior to warfarin with respect to major bleeding [120]. In the ROCKET-AF trial the investigators compared rivaroxaban, a direct factor Xa inhibitor, with warfarin for the prevention of stroke or systemic embolism among patients with nonvalvular atrial fibrillation who were at moderate to high risk for stroke. The study shows that rivaroxaban was non inferior to warfarin in the prevention of subsequent stroke or systemic embolism. Although there were no significant differences in rates of major and clinically relevant non major bleeding between the two study groups, intracranial and fatal bleeding occurred less frequently in the rivaroxaban group [121]. In the ARISTOTLE trial, the authors compared apixaban, a direct oral factor Xa inhibitor, with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke [122]. The use of apixaban, as compared with warfarin, significantly reduced

the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% in patients enrolled in the study. In the ENGAGE-AF TIMI 48 trial, the efficacy and safety of edoxaban, a direct oral factor Xa inhibitor, was compared with warfarin in patients with moderate to high risk atrial fibrillation for the prevention of stroke or systemic embolism. Both once a day regimens of edoxaban (60 mg and 30 mg) were non inferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding (significantly reduced risk of major bleeding by 20% with edoxaban 60 mg and 53% with edoxaban 30 mg) and death from cardiovascular causes [123].

These trials have similar conclusions: dabigatran, rivaroxaban, apixaban and edoxaban compared with warfarin, all significantly reduce the risk of hemorrhagic stroke. However, there are also some differences among the four trials, regarding patients' risk profile, modalities of drug administration and the study design especially for statistical analysis plans and power. However, head-to-head trials (superiority trial) are needed to further assess the therapeutic potential of this novel compounds and, possibly, test their use in pathologic conditions other than AF, such as in HF patients in sinus rhythm. In conclusion, at present, there are no guidelines indicating the use of prophylactic anticoagulation in elderly patients with HF except in those affected by AF and/or carriers of prosthetic valve and/or history of thromboembolism, despite the fact that numerous evidences have clearly stated that HF has an intrinsic risk of thrombotic events. From the randomized studies carried out thus far, there is a beneficial trend in favor of anticoagulation therapy, with less hospitalization for HF compared with patients taking aspirin but the questionable benefit of anticoagulation needs to be weighed against the potential for hemorrhagic complications caused by this therapy. The available data collectively suggest that the risk of using warfarin in patients with reduced ejection fraction may outweigh any possible benefit, if one exists at all, in HF patients in sinus rhythm. In addition to that, new anticoagulant molecules, that have fewer complications compared to warfarin, are currently being evaluated at reducing thromboembolic risk in different clinical contexts. In AF, direct thrombin inhibitors have already demonstrated their non inferiority to warfarin and recent trials have evaluated possible benefits of rivaroxaban in acute coronary syndromes. In light of these evidence, we can hypothesize that the time has come to further refine the thin balance between potential benefits and harms of anticoagulation in HF, a severe clinical condition whose mortality rates are still high.

CONCLUSIONS

Evidence suggests that NOACs do not lead to greater major or clinically relevant bleeding than conventional therapy and pharmacologically active agents in elderly adults. NOACs significantly reduce the risk of stroke or systemic embolism in elderly adults with AF. NOACs are also more effective than conventional therapy for the reduction of the risk of VTE or VTE related death. While numerous evidence have clearly stated that elderly patients with HF have an intrinsic risk of thrombotic events, no guidelines indicating the use of prophylactic anticoagulation in HF except in those affected by AF and/or carriers of prosthetic valve and/or history of thromboembolism. The SNS-hemostasis axis should be investigated better in further studies integrating biochemical and biological knowledge.

Older adults have an increased risk of thromboembolism, due to many comorbidities, polipharmacotherapies and the aging. Both venous and arterial thromboembolic risk have an high impact in elderly patients but they also have an increased risk of bleeding so for the physicians it is difficult to choose the best anticoagulation treatment. Over the last years some scores for risk stratification of stroke and bleeding have been created to help physicians, since new oral anticoagulants (NOACs) were introduced. Evidence suggests that NOACs do not lead to greater major or clinically relevant bleeding than conventional therapy in elderly patients. NOACs significantly reduce the risk of stroke or systemic embolism in elderly adults with AF and are also more effective than conventional therapy for the reduction of the risk of venous thromboembolism (VTE) or VTE-related death. However, while numerous evidence have clearly stated that elderly patients with heart failure (HF) have an intrinsic risk of thrombotic events, no guidelines indicating the use of prophylactic anticoagulation in HF except in those affected by atrial fibrillation (AF) and/or carriers of prosthetic valve and/or history of thromboembolism. The

sympathetic nervous system-hemostasis axis should be investigated deeply in further studies integrating clinical approach with the novel biochemical and biological knowledge.

***Key words*: Anticoagulation, Elderly, NOACs, Heart failure, Atrial fibrillation and venous thromboembolism**

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The syncope in the elders: how to diagnose and treat

La sincope nell'anziano: diagnosi e trattamento

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La diagnosi e il trattamento della sincope nell'anziano può risultare complessa causa la coesistenza di comorbidità e impairment cognitivo. L'approccio basato sulle linee guida può consentire una diagnosi certa in oltre il 90% dei pazienti anziani e ridurre il ricorso a superflue procedure diagnostiche e ospedalizzazioni. La valutazione iniziale dovrebbe prevedere: a) anamnesi clinica, supportata dalla testimonianza di familiari o caregivers in considerazione della possibilità di amnesia retrograda correlata alla perdita di coscienza; b) esame obiettivo generale, neurologico, valutazione dell'apparato locomotore e standing test, data l'alta incidenza di ipotensione ortostatica nell'anziano; c) un ECG a 12 derivazioni. Il massaggio del seno carotideo potrebbe anche essere eseguito durante l'iniziale valutazione clinica in considerazione dell'alta prevalenza di ipersensibilità e sindrome senocarotidea del seno carotideo nell'anziano. Il Tilt Test è ben tollerato e risulta estremamente utile nel discriminare la sincope neuromediata, dall'ipotensione ortostatica, soprattutto quando iniziale o tardiva e nella diagnosi differenziale delle cadute non spiegate o di crisi comiziali farmacoresistenti. Il Loop Recorder Impiantabile è un dispositivo utile nell'identificazione di possibili meccanismi aritmici sia in fase diagnostica iniziale, sia tardiva. Non esistono differenze nell'approccio terapeutico tra anziani e giovani. Trattamenti mirati ed eziologici sono necessari in caso di ipotensione ortostatica o bradiaritmie.

***Parole chiave*: Sincope, Ipotensione ortostatica, Sindrome senocarotidea, Loop Recorder Impiantabile, Anziano**

DIAGNOSIS

The diagnostic protocol proposed by the European Society of Cardiology (ESC) guidelines on syncope [1] (Fig. 1), is well enforceable in older patients and the rate of unexplained syncope decreases to 10.4% [2].

Initial evaluation

The collection of the clinical history should include any association between the loss of consciousness and food or drugs consumption, type of the treatment and time-relationship between the former and the latter. The physician should search for diurnal or nocturnal syncope, body position during the event, changes between supine and standing position, as well as any relation with micturition or efforts. The clinical history should also include association with physical frailty, neurological and loco-motor causes of disabilities as Parkinson's disease, arthritis, cerebrovascular disease or other conditions and respective treatments, which could be responsible for hypotension or dysautonomia as

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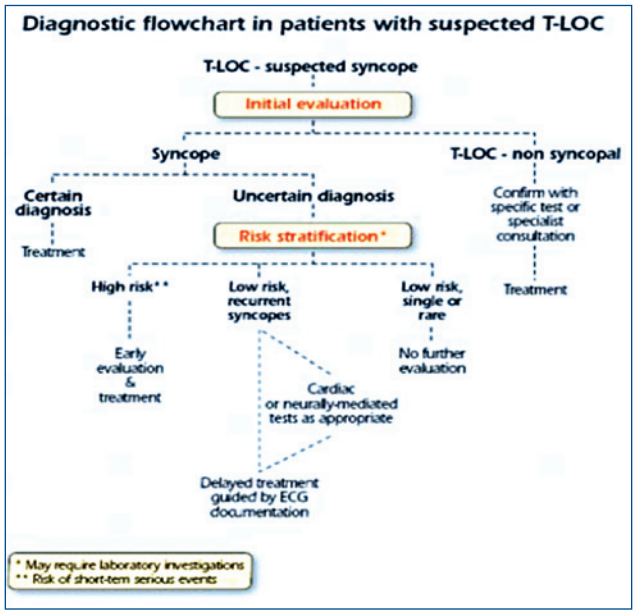

Fig. 1. Diagnostic flowchart of suspected transient loss of consciousness (T-LOC) (from Moya et al., 2009 [1], mod.).

T-LOC = transient loss of consciousness

anaemia, ischemic heart disease, heart failure or diabetes and hypertension. Older adults frequently experience retrograde amnesia for the loss of consciousness, therefore a witness's account of the episodes is mandatory, when available. However, considering the limited value of the medical history in the differential diagnosis between cardiac and neurally-mediated cause of syncope in older patients [3], the neuro-autonomic evaluation, through TT and CSM, becomes an essential step of the diagnostic pathway.

As part of a geriatric multidimensional assessment, the cognitive status should be evaluated and the Mini Mental State Examination, a 30 item internationally validated tool, is adequate for this purpose. Details of social circumstances, injuries, impact of the event on confidence and ability to carry out basal/instrumental activities of daily living independently, should be recorded [1].

There are some findings in the 12-leads ECG that can be considered diagnostic of the cause of syncope, permit no further evaluation and institution of treatment, as persistent sinus bradycardia < 40 bpm in awake or repetitive sinus-atrial block or sinus pauses > 3 s, Mobitz II 2nd or 3rd degree atrio-ventricular block, alternating left and right bundle branch block, ventricular tachycardia (VT) or rapid paroxysmal supra-ventricular tachycardia, non-sustained episodes of polymorphic VT and long or short QT interval, evidence of acute ischaemia with or without myocardial infarction [1].

The physical examination in the older patient should include cardiovascular and neurological assessment, searching for Parkinson's disease or other neurodegenerative conditions related to autonomic dysfunction [4-8]. A careful observation of gait and standing balance is useful in the evaluation of the loco-motor system and the consequent risk of falling, which can be a tremendous consequence of a syncope. The active standing test, which consists in the measurement of blood pressure first in the supine position and then immediately after changing from the supine to the upright position and after 1 and 3 minutes of orthostatic position, is a relevant diagnostic step, especially in older patients, given the age-related increased rate of OH, 24.3% in the VIII decade and 30.9% in the IX decade [9]. The test is diagnostic when there is a symptomatic fall in systolic blood pressure (BP) from a baseline value ≥ 20 mmHg or diastolic BP ≥ 10 mmHg or a decrease in systolic BP to < 90 mmHg [1]. Since the magnitude of blood pressure drop also depends on baseline values, it was suggested that a drop of 30 mmHg may be a more appropriate criterion for OH in patients with supine hypertension [10]. Passive TT, with beat-to-beat BP monitoring is necessary for the diagnosis of "Initial" OH, which lasts roughly 30 s with a prompt spontaneous recovery of baseline BP value and "Delayed" OH, characterized by a slow and progressive decrease of systolic BP which becomes clinically manifest up to 30 minutes after the achievement of the upright position. Alpha-receptor blockers, nitrates or benzodiazepines, frequently used in older people, were found to be predictors of OH, therefore attention should be paid in the re-evaluation of drugs regimen in the presence of OH, in order to reduce the syncope recurrence [9].

In a sample of 242 older patients with syncope, a possible cause of loss of consciousness was identified in 40.1% of the cases, after the proposed initial evaluation. In only 2% of the cases no diagnosis was made at the first assessment; cardiac syncope was subsequently confirmed in 43.7% of the cases and neurally-mediated syncope in 83.5% of the cases. Only one cardiac syncope was not suspected or diagnosed after the first level evaluation [2].

Neuro-autonomic evaluation

It has been recently demonstrated that the neuro-autonomic evaluation through TT and CSM is similarly diagnostic in young and older patients, also in those older than 80 years old. TT positivity was the same across the age groups, except in the second decade, where the rate of TT positivity was 90%. Positivity of CSM increased with advancing age, reaching a rate of 20% in the X decade, as OH. Patients ≥ 65 years old showed a higher rate of "complex diagnosis", namely the presence of more than one diagnosis, most frequently OH and vasovagal syncope on TT [9].

TT and CSM are safe and well tolerated even in older adults. Data not already published on 1401 patients (mean age of 72 ± 16 years) who underwent neuro-autonomic evaluation, showed that complications after TT occurred in 4.5% of older patients and in 2.1% of the younger ones (p = 0.01). All complications were minor to moderate, as prolonged hypotension and were observed in about 3% of patients ≥ 80 years. No complications occurred after CSM.

Carotid Sinus Massage

Exerting pressure at the site of the neck, where the common carotid artery bifurcates, produces a slowing in the heart rate and a fall in blood pressure (BP). In some individuals, this reflex induced by CSM could result in an abnormal response, with a ventricular pause lasting more than 3 s and/or a fall in systolic BP of > 50 mmHg, defining the carotid sinus hypersensitivity (CSH).

CSH is very frequent in older patients and has been found to be a predictor of spontaneous asystolic syncope in patients with recurrent syncope, who underwent ILR insertion, suggesting that pacing would be useful to prevent the recurrence of syncope. It has to be underlined that in older adults with only one episode of syncope, CSH is not diagnostic [11]. CSH associated with spontaneous syncope defines CSS, but this latter's definite diagnosis requires the reproduction of symptoms during 10 s sequential right and left CSM performed as syncope supine and erect, under continuous monitoring of heart rate and periodic measurement of blood pressure, allowing a better evaluation of the vasodepressor (VD) component [12]. In order to assess the contribution of the VD component, CSM may be repeated after intravenous administration of 0.02 mg/Kg of atropine, which eliminates vagally-induced asystolic pauses, thereby unmasking the VD phenomenon [13]. This quantification of the VD component is clinically relevant, because it has been shown that pacemaker therapy is less effective when the VD effect is large, compared with predominant cardio-inhibition [14]. Transient ischemic attack or stroke in the 3 months beforehand or critical carotid artery stenosis on Doppler ultrasounds performed in the presence of carotid bruits, represent contraindications to CSM [15]. The ESC guidelines on syncope propose CSM as part of the initial evaluation, given the high prevalence of CSS as a cause of syncope and unexplained falls in the elderly. In patients ≥80 years old carotid sinus massage is positive in 41% of the cases, maintaining a high efficacy and safety [1].

Tilt Testing

TT is the most validated test for the clinical assessment of neurally-mediated reflexes, particularly for the diagnosis of vasovagal syncope of undetermined origin after the initial evaluation. It has been validated in older subjects using the Italian Protocol (400 mcg of sublingual nitroglycerine) [16]. The test is well tolerated even in the elderly with a similar positivity rate and specificity to that observed in younger patients. The test should be performed in the morning, in fasting state, in a quiet and dimly-lighted place. Briefly the test consists of 20 minutes of passive orthostatic position at an angle of 60° that is potentiated, if syncope does not occur, on administration of sublingual nitroglycerine (400 µg) with a further 15 minutes of observation at the same angle. The test is considered positive if symptoms reproducing those reported by the patient during the spontaneous syncope are associated with hypotension, bradycardia, or both [17]. In a recent meta-analysis TT demonstrated a good overall ability to discriminate between symptomatic patients and asymptomatic control subjects, with an elevated specificity in most of the protocols investigated and widely variable sensitivity. Pharmacological protocols had higher sensitivity and lower specificity than passive protocols. Moreover, nitroglycerine-stimulated TT had greater diagnostic capability in comparison to isoproterenol-stimulated TT [18]. However there is an inability to apply the test to populations with syncope of uncertain cause, as the TT was positive in 56% of presumed neurally-mediated syncope and in 43% of non-neurally-mediated syncope patients and in 45-47% of those with true cardiac arrhythmic

Tab. I. Tilt Testing in patients with unexplained fall and syncope [18].

	Unexplained falls n = 298	Unexplained syncope n = 989	p
Performed (n, %)	275 (92.2)	944 (99.4)	0.001
Diagnostic (n, %)	99 (36.0)	485 (51.3)	0.001
VASIS I (n, %)	25 (25.2)	115 (23.7)	0.743
VASIS 2A (n, %)	1 (1.0)	17 (3.5)	0. 190
VASIS 2B (n, %)	7 (7.0)	72 (14.8)	0. 039
VASIS 3 (n, %)	60 (60.6)	261 (53.6)	0. 202
Disautonomic (n,%)	6 (6.0)	20 (4.1)	0.394

syncope [19]. A possible explanation of this discrepancy comes from a recent reinterpretation of TT, according to which the test could reveal a susceptibility to vertical posture stress as a "hypotensive susceptibility", which could cause syncope irrespectively of the aetiology and the mechanism of syncope itself [20]. The identification of hypotensive susceptibility makes TT a risk stratification tool, rather than a diagnostic one, for patients with recurrent, traumatic syncope and ECG documentation of spontaneous asystolic reflex syncope, as showed in the ISSUE 3 Study [21], who could greatly benefit from pacing, especially when TT is negative, because of a pure asystolic mechanism [22].

TT can also be useful in guiding the differential diagnosis between syncope and unexplained falls, as recently confirmed that the positivity prevalence of TT and CSM were similar in patients who presented with these two conditions, suggesting that neuro-autonomic evaluation should be routinely performed in older patients with unexplained falls [23] (Tab. I).

Implantable Loop Recorder

ILR was developed to provide an ECG documentation of events that occur sporadically, as other technologies (ambulatory ECG and external event recorder) have a low rate of diagnosis due to the infrequent nature of events such as syncope. The device is placed subcutaneously, has a retrospective (loop) memory which continuously records and deletes the patient's ECG, including a manual function, through which the patient can activate the ECG storage as a result of symptoms and an automatic feature, that allows the capture of arrhythmic events without relying on patient's compliance or perception of symptoms. ILR appears to provide an ECG-syncope correlation in about 35% of patients during the lifetime of the device. Of these, 56% had asystole or severe bradycardia. Similar findings were observed when ILR was inserted in patients with suspected neurally-mediated syncope in an early phase after the initial evaluation or in unexplained syncope at the end of the conventional work-up [24]. One of the newest devices has such a small size that can be injected with a minimally invasive procedure and is able to send wireless transmissions automatically to a central server, allowing a continuous patient's monitoring. Krahn has previously shown that age was the only independent variable that predicted bradyarrhythmic syncope and the need for pacing [25], as recently confirmed [26]. Older patients are indeed more likely to receive an ILR implantation than younger patients, because of the need for a precise diagnosis in case of structural heart disease or bundle branch block, which are almost exclusively present in patients ≥65 years, because of the limited value of the clinical history in the diagnosis of the causes of syncope and finally because in the elderly the onset of syncope is sudden, with little or no prodromes and a consequent higher risk of trauma, justifying the need for ILR to detect the underlying mechanism and start a precise treatment [27]. ILR has a high diagnostic value also in those conditions in which an initial diagnosis is only suspected and the demonstration of an arrhythmic mechanism could definitively guide the therapy. It has been demonstrated in a population of highly selected patients, with a mean age of 71 years old and an initial diagnosis of either likely epilepsy or unexplained fall that the device gave a documentation of a relapse of their index attack and that, in about a quarter of patients, the final diagnosis was of arrhythmic syncope. Moreover, when the arrhythmia was not documented at the time of a spontaneous

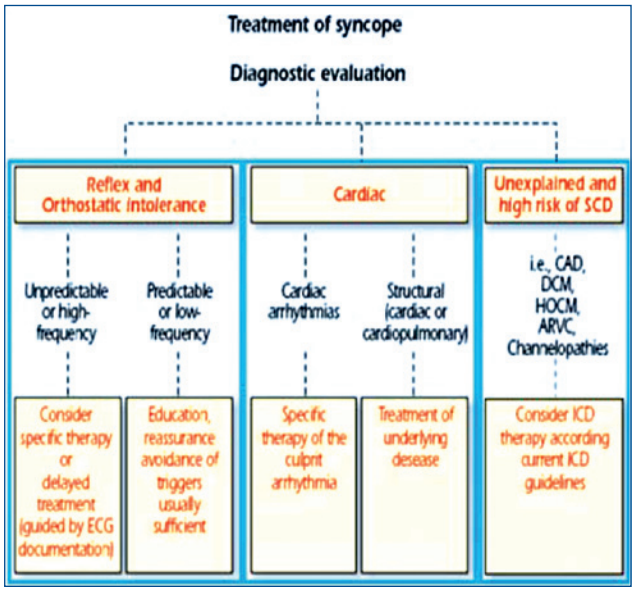

Fig. 2. Treatment of syncope (from Moya et al., 2009 [1], mod.).

ARVC = arrythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; DCM = dilated cardiomyopathy; ECG=electrocardiographic; HOCM = hypertrophic obstructive cardiomyopathy; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death

attack, ILR monitoring definitely excluded an arrhythmic cause [28].

TREATMENT

The treatment of patients with syncope is directed to the mechanisms leading to global cerebral hypoperfusion and is based on risk stratification and identification of specific mechanisms, consequently an arrhythmic syncope would benefit from cardiac pacing, implantable cardioverter-defibrillators and/or catheter ablation as well as in case of structural cardiac or cardiopulmonary disease, the treatment would be best directed at amelioration of the specific structural lesion or its consequences (Fig. 2) [1].

Therapeutic options in neurally-mediated syncope

Physical treatments as leg crossing, hand grip or arm tensing are able to induce a significant BP increase during impending reflex syncope, but given the frequent absence of prodromes, often brief when present in older adults, this maneuvers are hard to be applied in this group of age. Education and reassurance, modification or discontinuation of hypotensive drug, avoidance of triggering situations are cornerstones of behavioral strategies. Disappointing results have been obtained by the use of various drugs in the context of neurally-mediated syncope.
Cardiac pacing should be considered in patients with dominant cardioinihibitory CSS (class 2a, level B) [1]. The efficacy of pacing in patients with neurally-mediated syncope has been controversial, until the results of the ISSUE3 study have been published, showing that pacing was effective in reducing the recurrence of syncope in patients ≥ 40 years with severe asystolic neurally mediated syncope, previously documented by an ILR [21]. Nevertheless 25% of the patients had syncopal recurrence after 2 years, despite pacemaker therapy. The benefit of pacemaker therapy was not substantial in patients with a positive TT, speculating an hypotensive mechanism that cannot be prevented by cardiac pacing [22].

Therapeutic options in Orthostatic Hypotension and orthostatic intolerance syndromes

The principal treatment strategy is characterized by the elimination of hypotensive drugs, expansion of extracellular volume, salt and water intake, in the absence of hypertension. The elevation of the head of the bed ameliorates nocturnal hypertension, maintains a more favourable distribution of body fluids and prevents nocturnal polyuria. Gravitational venous pooling in older patients can be treated with abdominal binders or compression stockings [1]. If non-pharmacological measures do not attenuate symptoms sufficiently, pharmacological interventions may become necessary. Nevertheless, supine hypertension has to be taken into consideration in pharmacological treatment. Volume expansion may be achieved with 9-α-fluorohydrocortison, a synthetic mineralocorticoid, indicated in order to increase plasma volume by renal sodium retention. Peripheral vascular resistance is the limiting factor of 9-α-fluorohydrocortison treatment, resulting in dose-dependent supine hypertension. Alpha-agonist midodrine has been used, achieving a proper vasoconstriction of the peripheral vessels; nevertheless its limitation is represented by a short half-life, which requires frequent dosing and limits a long-term compliance. Furthermore its use is related to adverse effects on urinary outflow, which requires special caution in older males [29]. Pyridostigmine, a cholinesterase inhibitor, improves ganglionic transmission and vascular adrenergic tone in primarily upright position, mediating a slight increase in diastolic blood

pressure during standing without worsening supine hypertension [30]. Droxidopa, is an orally administered artificial amino-acid converted both peripherally and centrally into norepinephrine. The enzyme responsible for the conversion, aromatic amino acid decarboxylase, is widely expressed and so the administration of droxidopa increases norepinephrine even if postganglionic sympathetic neurons are not intact. The drug has received accelerated Food and Drug Administration (FDA) approval for the treatment of symptomatic OH. It has been recently demonstrated that droxidopa improved symptoms and symptom impact on daily activities, with an associated increase in standing systolic BP in patients with symptomatic OH due to different orthostatic intolerance syndromes, without worsening supine hypertension [31].

The diagnostic pathway and the consequent management of syncope in older patients may be difficult for the coexistence of comorbidities and cognitive impairment. A guidelines-based approach may guide a definite diagnosis in more than 90% of the older patients with syncope and reduce the usage of diagnostic investigations and hospital admissions.
The initial evaluation should include clinical history supported by a witness's account, considering the relevant presence of retrograde amnesia for the loss of consciousness, physical examination comprising the assessment of the neurological and loco-motor system, active standing test, as the rate of orthostatic hypotension (OH) increases with advancing age and 12-leads electrocardiogram (ECG). The Carotid Sinus Massage (CSM) could also be performed during the first line evaluation, because of the high prevalence of Carotid Sinus Syndrome (CSS) in older adults. Tilt Testing (TT) is well tolerated and useful in differentiating between neurally-mediated syncope, orthostatic intolerance and between syncope and unexplained falls or epileptic seizures. The Implantable Loop Recorder (ILR) is widely acknowledged as an important diagnostic device both at the beginning or at the ending of the syncope's diagnostic workup, because its diagnostic yield is pretty similar, as the percentage of asystole and bradyarrhythmia detected. There are no consistent differences in the treatment of syncope between older and younger population, but a specific approach is necessary for OH, drug therapy and pacemaker implantation.

***Key words*:** Syncope, Orthostatic Hypotension, Carotid Sinus Syndrome, Implantable Loop Recorder, Elderly

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Adrenergic system in Alzheimer's disease

Il sistema adrenergico nella malattia di Alzheimer

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La malattia di Alzheimer (MA) è la più frequente forma di demenza per la quale è necessario promuovere lo sviluppo di nuove strategie terapeutiche che agiscano sui diversi meccanismi patogenetici coinvolti nell'insorgenza e nella progressione della patologia stessa. Uno dei possibili bersagli è il sistema adrenergico. Evidenze di studi clinici e preclinici indicano che il sistema adrenergico è alterato in corso di MA ed è implicato nella formazione della beta-amiloide. Inoltre, alcuni dati indicano che i bloccanti dei recettori adrenergici possano avere un effetto favorevole nella MA. Pertanto, è necessario che ulteriori studi valutino la relazione tra sistema adrenergico e MA allo scopo di sviluppare nuovi target terapeutici efficaci.

***Parole chiave*: Malattia di Alzheimer, Sistema adrenergico, Chinasi dei recettori accoppiati a proteine G, Beta-bloccanti**

Alzheimer's disease (AD) is the most common form of dementia in the elderly. As of 2013, there were an estimated 44.4 million people with dementia worldwide. AD is a neurodegenerative disorder characterized by progressive memory loss and cognitive dysfunction [1]. The treatment options currently available are only able to slow disease progression, thus the identification of novel therapeutic targets is of primary importance [2].

AD is neuropathologcally characterized by the extracellular deposition of amyloid-β (Aβ) plaques, intracellular tau neurofibrillary tangles, and neuronal death [3 4]. In AD neurodegeneration affects mainly the entorhinal cortex, hippocampus, and basal forebrain, however it has been demonstrated that also locus coeruleus (LC) degeneration and loss of forebrain norepinephrine (NE) is ubiquitous in AD and occurs early [5 6].

ADRENERGIC SYSTEM IN AD

The LC, situated in the pons, is the main norepinephrine source in the central nervous system, and it is connected to all major brain regions, including the neocortex and hippocampus [7]. Recent evidence suggests that LC degeneration could be implicated in AD pathogenesis [8]. Indeed, it has been demonstrated that LC degeneration occurs early during the course of AD, with neurofibrillary tangles detected at the stage of mild cognitive impairment (MCI) [9-12]. Moreover, animal studies using a mouse model of selective LC degeneration have demonstrated that neuronal loss significantly increased, together with increased memory deficits, reduced cerebral glucose metabolism and altered neuronal integrity, indicating that LC degeneration contributes to AD development [7 13 14].

The effects of LC-derived NE in brain are medi-

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ated by the modulation of adrenergic receptors (AR) in brain, with both α- and β-AR playing a crucial role in neurotransmission [15-17].
The ARs belong to the family of G-protein-coupled receptors (GPCR) and both α- and β-AR all highly expressed in brain. Imaging studies have indicated that AR are distributed in different brain regions, such as the neocortex and striatum, but also in the amygdala, hippocampus and cerebellum, at lower density [18 19]. Moreover, it has been demonstrated that both β_1- and β_2AR are present on rat microglial cells [20-22].
The stimulation of the AR by their specific ligands (NE and epinephrine) has different effects depending on the cellular type they are expressed on [23-25]. Typically, their agonist-mediated activation induces the exchange of GTP for GDP on the Gα-subunit of the associated G proteins, resulting in the dissociation of the heterotrimer into active Gα- and Gβγ-subunits, which activate independent signaling pathways [26-28]. The Gα-subunit is able to either stimulate (Gs) or inhibit (Gi) adenylyl cyclase, therefore modulating the intracellular amount of cyclic AMP [23 29-31]. On the other hand, the dissociation of the Gβγ subunit induces the interaction of AR with G-protein receptor kinases (GRKs), which ultimately mediate the phosphorylation of AR [32, 33]. GRK-mediated phosphorylation results in AR desensitization (homologous desensitization) and promotes the binding of the cytosolic proteins arrestins. Arrestins binding prevents further G-protein coupling and targets the activated receptor for endocytosis (downregulation) [34 35].
Several lines of evidence indicate that there is an association between AR signaling and AD pathogenesis.
Studies from Kalaria et al reported a change in number of β-ARs in different brain regions in AD, paralleled by reduction in the number of LC cells and norepinephrine concentrations in putamen and frontal cortex [36]. Also, lower levels of β2-AR and of β2-AR-stimulated cAMP have been found in lymphocytes of patients with AD, when compared to controls [37] and the β-AR-stimulated cAMP levels were reduced of approximately 80% in fibroblasts from AD compared with age-matched controls [38].
β-ARs have also been implicated in Aβ formation in AD. Indeed, norepinephrine stimulation of AR resulted in amyloid precursor protein overexpression in rat astrocytes, which was inhibited by pre-treatment the β-AR antagonist propranolol [39].
Ni and colleagues further investigated the role of β-AR in amyloid formation, showing that the activation of β_2-AR increases Aβ production in vitro and amyloid plaque formation in vivo by enhancing γ-secretase activity. These authors proposed that this mechanism involves the association of β_2-AR with presenilin-1 and requires agonist-induced endocytosis of β_2-AR. They also demonstrated that chronic treatment with β_2-AR agonists increased cerebral amyloid plaques, while administration of a β_2-AR–selective antagonist ameliorated amyloid plaque pathology in mouse models of AD, suggesting that impaired β_2-AR function might contribute to Aβ formation in AD [40]. Data from subsequent studies have demonstrated that in primary cortical neurons Aβ is able to bind to β_2AR and induce receptors internalization and degradation, a process which seems dependent on GRK2-mediated receptor phosphorylation [41].
Moreover, genetic studies have shown a correlation between β-AR polymorphisms and AD. In particular, Yu and colleagues reported that two polymorphisms in the β_2-AR gene (Gly16Arg and Gln27Glu) were associated with an increased risk of late onset AD in a Chinese population. They also showed a significant correlation of these two variants with the apolipoprotein E ε4 allele, suggesting an interaction with apolipoprotein E ε4 status [42].

GRK2 AND AD

The GRKs are a family of cytosolic serine/threonine kinases whose primary function is GPCRs desensitization and promotion of internalization. Several lines of evidence have indicated that besides ARs alterations, there is also a diffuse alteration in post-receptor components of GPCR signaling in AD brain, particularly at the receptor-G protein interface, that is the site of action of GRKs [19 43 44].
GRK2, also known as β-AR kinase 1 (βARK1), is the most abundant GRK in the heart, and its levels are increased in different cardiovascular diseases associated with impaired cardiac signaling and function [45-51]. Indeed, in heart failure adrenergic system hyperactivity is associated with myocardial overexpression of GRK2 and AR downregulation and desensitization [45 52-55]; in myocardial infarction, AR hyperstimulation is associated with poor outcome after revascularization procedures [56-62]. Moreover, therapeutic

modalities such as exercise training and beta-blocker treatment have been demonstrated to ameliorate the impairment of beta-adrenergic receptor signaling and enhance cardiac responsiveness to adrenergic stimulation in cardiovascular and metabolic diseases [63-72]. In brain, GRK2 is also widely distributed, as it is found in both postsynaptic densities and presynaptic axon terminals consistent with the role of GRK2 in the desensitization of synaptic receptors [73-75]. In a study by Suo et al the role of GRK2 in AD was investigated in both murine microglial cells and in AD transgenic mouse model. They discovered that soluble Aβ can dose-dependently potentiate the release of inflammatory cytokines from microglial cells and, more importantly, that subthreshold Aβ treatment of microglial cells in vitro decreased membrane-bound levels of GRK2, leading to cytosol accumulation. This process resulted in retarded GPCR desensitization and prolonged GPCR signaling, leading to receptors hyperactivity. Also, in an early-onset AD transgenic mice it was demonstrated that while total brain GRK2 levels increased, the kinase in the membrane fractions was significantly reduced; this was associated with the early increase of brain soluble Aβ levels and occurred before the onset of cognitive decline. These observations globally suggest that the GRK abnormality may be an early event in the pathogenesis of AD, detectable at prodromal and early stages of the disease [76 77].

Leosco et al examined for the first time the role of lymphocyte GRK2 in patients with AD. These authors evaluated GRK2 mRNA levels and protein expression in peripheral blood lymphocytes of AD patients with mild or moderate/severe cognitive impairment and in age-matched healthy subjects, finding that both GRK2 mRNA and protein expression were significantly higher in AD patients compared to controls. Furthermore, lymphocyte GRK2 levels were significantly correlated with cognitive status, giving further credence to the role of lymphocyte GRK2 as a biomarker in AD [78].

POTENTIAL OF ADRENERGIC BLOCKERS IN AD

Beta-blockers, also known as β-AR blocking agents, are widely used to treat cardiovascular diseases such as angina, heart failure and hypertension [79-81]; however, preclinical and clinical data have suggested that blocking AR might also have beneficial effects in AD pathogenesis [82 83]. In transgenic mouse models of AD, the administration of propranolol was able to reduce cognitive impairment and to counteract the increases of hippocampal Aβ in. Propranolol treatment also resulted in reduction of tau hyperphosphorylation [84]. Other authors have demonstrated that chronic administration of the nonselective β-AR blocker carvedilol, significantly reduced brain Aβ content and cognitive impairment in two AD mouse models, improving neuronal transmissio [85]. Moreover, treatment with the selective β1-AR antagonist nebivolol resulted in a significant reduction of amyloid pathology in mouse brains after three weeks of treatment, although it failed to improve cognitive function [86]. As mentioned before, Ni and colleagues demonstrated the β2-AR–selective antagonist ICI-118,551 ameliorated amyloid plaque pathology in mouse models of AD [40]. Moreover, it has been demonstrated that in primary cortical neurons Aβ is able to bind to β2AR and induce receptors internalization and degradation, and pretreatment with β-AR antagonist timolol is able to prevent this effect [41].

Further evidence on the potential role of adrenergic blockers derives from clinical studies evaluating the association of cardiovascular medication use and AD incidence [87-89]. The Dementia Progression Study of the Cache County Study has indicated that use of statins and β-blockers was associated with a slower annual rate of functional decline in the AD population, while other cardiovascular drugs did not affect the functional decline [90]. Moreover, data from the Honolulu-Asia Aging Study indicated that β-blockers were the only anti-hypertensive drugs associated with a lower risk of developing cognitive impairment, even after adjusting for other confounding factors [91 92].

CONCLUSIONS

AD is a growing public health problem and there is an urgent need for the development of new therapeutic strategies targeting the different pathogenic mechanisms involved in its onset and progression, as well as new, easily accessible biomarkers for early diagnosis and progression monitoring. AR signaling modulation may represent a potentially valuable and novel therapeutic target for the treatment of AD. Also, biomarkers of AR function, such as circu-

lating catecholamines, might be of potential use in AD as they are in cardiovascular diseases [93-96]. So far, studies evaluating the use of AR blockers have proven interesting results, however further preclinical and clinical studies that could further explore this hypothesis are needed in view of the development of a multitarget approach to treat AD.

Alzheimer's disease (AD) is the most prevalent form of dementia and there is an urgent need for the development of new therapeutic strategies targeting the different pathogenic mechanisms involved in its onset and progression. One of the candidates to possibly contribute to AD pathogenesis is the adrenergic receptor (AR) system. The central noradrenergic system undergoes substantial changes in the course of AD and both AR and downstream components of their signalling pathway have been implicated in amyloid formation and in amyloid-induced neurotoxicity. Moreover, clinical data indicate that the use of AR blockers might be beneficial on AD onset. Thus, further preclinical and clinical studies that could explore the relationship between AD and AR are needed in view of the development of a multi-target approach to treat AD.

***Key words*: Alzheimer's disease, Adrenergic system, G-protein receptor kinases, Beta-blockers**

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