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# JGGG

## JOURNAL OF GERONTOLOGY AND GERIATRICS

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and Scopus Elsevier Database

### Regular Issue

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**Elder cardiac diseases:  
new hypothesis for old topics**

*Guest Editor*

*Graziamaría Corbi*



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## ORIGINAL INVESTIGATION

# Quality of life in patients with mild dementia. Validation of the Italian version of the quality of life Alzheimer's disease (QoL-AD) Scale

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**Background and aims:** to investigate possible clinical determinants of quality of life (QoL) in mild dementia

**Methods:** 200 dementia outpatients assessed with the Quality of Life-AD (QoL-AD) scale administered to patients and their caregivers and combined into a QoL-AD composite score (QoL-AD CS). Patients were divided into tertiles according to high, intermediate and low QoL levels. Cognitive status was assessed with the Mini Mental State Examination (MMSE) and depressive symptoms with the Geriatric Depression Scale (GDS). Basic (BADL) and instrumental (IADL) activities of daily living scales were used to assess functional domain. The Neuropsychiatric Inventory (NPI) measured neuropsychiatric symptoms.

**Results:** a strong correlation was found between patient-rated QoL-AD scores and caregiver-rated QoL-AD scores (Pearson correlation coefficient: .353;  $p = .000$ ). High QoL group patients displayed better functional status in BADL and IADL, had lower comorbidity and number of medications. Insight level and cognition were comparable among the three groups. The group with higher QoL had significantly lower depressive and neuropsychiatric symptoms compared to the intermediate and low QoL groups. On linear regression analysis using the QoL-AD CS as the depended variable, the model including GDS, IADL, number of medications and NPI explains nearly 50% of QoL-CS variance ( $R^2 = .495$ ; adjusted  $R^2 = .485$ ).

**Conclusions:** QoL in mild dementia is a broad dominion that goes beyond the cognitive impairment itself and is determined by for the presence of depression, impairment in instrumental activities of daily living, behavioural disturbances and number of medications.

**Key words:** Quality of life, Dementia, Assessment

## INTRODUCTION

Dementia is a chronic and progressive condition that causes decline of cognitive, physical and social functions and the development of behavioural disturbances<sup>1</sup>. Quality of life (QoL) is considered a primary goal of treatment of dementia, even if only few studies distinctively evaluate this domain<sup>2</sup>. The main outcome of clinical trials of anti dementia drugs is prevalently cognition, and, in a limited number of studies, function and behaviour; these domains are frequently assumed as

acceptable surrogates for quality of life<sup>3,4</sup>. In the recent years specific instruments devoted to measure QoL in dementia were developed<sup>5,6</sup>.

Many authors underline that direct assessment of quality of life provides a more reliable mean to evaluate the broad outcomes of dementia care<sup>7,8</sup>. Dementia raises specific challenges to the measurement of QoL: lack of insight, reduction of the ability to recognize change or to make choice among options, difficulty to understand the meaning of abstract notion of QoL. Nevertheless, several recent studies suggested that demented patients

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in mild moderate stage of disease provide a reliable judgement of their QoL<sup>9,10</sup>. One element distinguishing the measures of QoL is whether it is self-rated or proxy rated. Self-rated instruments emphasize on the subjective and individualized nature of QoL measurement. However, cognitive dysfunction may interfere with the perception of QoL and patients may lack the capacity to self-rate. For this reason, other measures of QoL have been developed that are rated by others ("proxy rated")<sup>11</sup>.

Lawton provided a conceptual framework about QoL in patients with dementia based on four components: behavioural competence, objective environment, psychological well-being, and perceived QOL<sup>12</sup>. The Quality of Life-Alzheimer's Disease (QoL-AD) scale, based on Lawton's concepts, provides both caregiver and patient judgment of the QoL of demented subjects, and it has been confirmed a reliable and valid instrument in patients with mild to moderate AD<sup>13-15</sup>. Cross-cultural validity of the QoL-AD questionnaire has been confirmed in various countries<sup>10,16-20</sup>.

Since in Italy, the reliability and the validity of this scale has not yet been established, we developed its Italian version and evaluated its reliability. Using this instrument we investigate the clinical correlates of quality of life in outpatients with mild dementia with the aim to evaluate the effect of decreasing cognition, impaired activities of daily living, behavioural disturbances on perceived QoL in these patients.

## MATERIAL AND METHODS

Participants for this study were recruited among 11 Italian Alzheimer's Evaluation Units (clinics specialized for the diagnosis and treatment of dementia)<sup>21</sup>. Dementia was diagnosed according to DSM IV criteria<sup>22</sup>. Trained geriatric researchers conducted all the interviews to care recipients and caregivers.

The QoL-AD scale was used to assess quality of life<sup>13</sup> (refer to: <https://goo.gl/9GfSWR>). The scale is composed of 13-items that measure the domains of physical condition, mood, memory, functional abilities, interpersonal relationships, ability to participate in meaningful activities, financial situation, and global assessments of self as a whole and QOL as a whole. The items are rated on a four-point scale with a description for each item ranging from 1 (poor) to 4 (excellent). Separate scores are calculated for patients and carers and then combined into a composite score (QoL-AD CS), in which patients' ratings are given twice the weight of the carers.

Cognitive status was assessed with the Mini Mental State Examination (MMSE)<sup>23</sup>, and depressive symptoms with the 30-item version of the Geriatric Depression Scale (GDS)<sup>24</sup>. The Katz basic activities of daily

living (BADL) scale<sup>25</sup> and Lawton instrumental activities of daily living (IADL) scale<sup>26</sup> were used to assess functional domain. Patient behavioural symptoms were assessed with the Italian version of Neuropsychiatric Inventory (NPI)<sup>27</sup>. Comorbidity was evaluated by the Geriatric Index of Comorbidity (GIC) that classifies patients into 4 classes of increasing somatic comorbidity resulting from the number and the severity of chronic diseases<sup>28</sup>. The presence of chronic diseases are taken from the 15 conditions identified by the Greenfield's Individual Disease Severity (IDS)<sup>29</sup>. The IDS grades each condition ranging from 0 (absence of disease) to 4 (life-threatening disease). The GIC score ranges from 1 (low comorbidity) to 4 (high comorbidity). Mean GIC scores have been considered as a continuous variable. Insight was estimated with the semi-structured interview Clinical Insight Rating Scale (CIRS) scoring patients from 0 (full insight) to 8 (absence of insight)<sup>30</sup>. This is a semi-structured interview which examines four items: the reason for medical examination, awareness of cognitive impairment, awareness of functional impairments and progression of disease. Each item is scored 0 (full insight), 1 (partial insight) or 2 (absence of insight). Total CIRS score ranges from 0 to 8. Caregivers depressive symptoms were assessed with the Beck Depression Inventory (BDI)<sup>31</sup>, a 21 question multiple choice self-administered scale. The burden of dementia care was assessed with the Caregiver Burden Inventory (CBI)<sup>32</sup>, a 5 item self-report inventory evaluating objective, psychological, physical, social and emotional burden. The number of drugs currently assumed was recorded.

The exclusion criteria were a MMSE score lower than 18, severe visual or hearing impairment, institutionalization and a history of hospitalization in the previous three months for any reason.

## STATISTICAL ANALYSIS

Differences between mean values or percentages for the groups were assessed using Student's *t* test or  $\chi^2$  test. Analysis of variance (ANOVA) was used to compare groups of continuous variables (i.e.: levels of QoL). Bonferroni's post-hoc analysis was also applied for the groups. Cronbach's  $\alpha$  coefficient was calculated to assess the internal consistency reliability of patient and caregiver reports on the QoL-AD. Pearson correlation coefficients were used to compare agreement between patient and caregiver QoL-AD ratings and reliability on test-retest analyses. A stepwise linear regression analysis was carried out to examine the factors influencing the QoL-AD composite score.

All statistical analyses were performed using the SPSS® package for Windows®, version 11.0 (SPSS Inc., Chicago, IL). A *p* value < .05 was regarded as statistically significant for all analyses.

## RESULTS

### INTERNAL CONSISTENCY AND TEST-RETEST RELIABILITY OF THE ITALIAN VERSION OF THE QoL-AD

QoL-AD was fielded twice (the second after two weeks by the same researcher) in a sample of 32 patients (56% female, mean age was  $77.5 \pm 7.5$ ) and their caregivers (all female, 11 spouses and 21 daughters, mean age  $58.3 \pm 4.7$  years). The internal consistency reliability (Cronbach's alpha coefficient) was good for both patient (0.86) and caregiver (0.83) report. Pearson correlation coefficient for the two-week retest was 0.66 ( $p < .001$ ) for patients and 0.63 ( $p < .005$ ) for caregivers.

### PATIENTS' CHARACTERISTICS

A total of 200 outpatients with a diagnosis of mild dementia were enrolled; 131 (65.5%) had a diagnosis of Alzheimer's disease; 35 (17.5%) had mixed dementia, 26 (13%) vascular dementia and 8 (4%) Lewy body dementia. Mean MMSE score was  $22.1 \pm 3.2$ . Table I shows demographic and clinical characteristics of the subjects (whole sample and subgroups with MMSE score equal or more than 24 and less than 24).

The two groups difference only for educational level and number of IADL functions lost. QoL-AD scores (patient, caregiver and composite score) were not different according to MMSE score.

There was a statistically significant agreement of the patient and caregiver-rated QoL-AD scores ( $r = 0.353$ ;  $p < .001$ ).

### CLINICAL DETERMINANTS OF QoL

To assess the determinants of QoL the sample was stratified into tertiles: low QoL (QoL-AD CS  $< 29$ ; 70 subjects); intermediate QoL (QoL-AD CS between 29 and 33; 60 subjects) and high QoL (QoL-AD CS  $> 33$ ; 70 subjects). One-way ANOVAs testing for differences between the three groups and Bonferroni's post hoc analysis were performed (Tab. II). High QoL group patients showed fewer basic and instrumental functions lost, lower comorbidity and less drugs assumed. Insight level and MMSE score were similar among the three groups.

The patients in the group with higher QoL had significantly lower depressive and neuropsychiatric symptoms compared to the intermediate and low QoL groups. Depressive symptoms of caregivers in the low QoL

**Table I.** Patients' characteristics according to cognitive function.

Variable (range)	Total sample (N = 200)	Sample divided by MMSE values		p
		MMSE < 24 (N = 127)	MMSE $\geq$ 24 (N = 73)	
Gender (% of female)	60.0%	61%	59%	
Age, years (67-88)	$77.3 \pm 6.7$	$77.5 \pm 6.9$	$76.8 \pm 6.3$	.44
Education, years (4-12)	$6.5 \pm 3.7$	$5.8 \pm 2.9$	$7.6 \pm 4.5$	.01
Living alone (%)	32 (15.5)	20 (15.7)	12 (16.5)	.57
Duration of dementia symptoms, months (9-36)	$25.9 \pm 15.8$	$26.4 \pm 16.5$	$24.9 \pm 14.7$	.55
Number of medications (1-8)	$3.7 \pm 2.1$	$3.7 \pm 2.1$	$3.7 \pm 2.0$	.78
GIC (1-4)	$2.0 \pm 0.9$	$2.1 \pm 0.9$	$1.9 \pm 0.9$	.29
BADL, functions lost (0-6)	$0.9 \pm 1.5$	$1.1 \pm 1.6$	$0.6 \pm 1.2$	.05
IADL, functions lost (0-8)	$2.9 \pm 2.3$	$3.2 \pm 2.4$	$2.2 \pm 2.1$	.01
CIRS (0-8)	$3.0 \pm 2.4$	$3.1 \pm 2.3$	$3.0 \pm 2.4$	.78
GDS (0-30)	$10.0 \pm 5.5$	$10.1 \pm 6.0$	$9.9 \pm 5.5$	.87
NPI (0-144)	$18.0 \pm 18.5$	$18.7 \pm 19.3$	$16.8 \pm 17.1$	.49
BDI (0-63)	$7.4 \pm 6.6$	$7.8 \pm 7.0$	$6.7 \pm 5.8$	.25
CBI (0-56)	$17.4 \pm 16.7$	$18.4 \pm 16.8$	$15.7 \pm 16.2$	.27
QoL-AD patient (13-52)	$32.0 \pm 5.9$	$31.9 \pm 6.0$	$32.1 \pm 5.6$	.83
QoL-AD caregiver (13-52)	$28.9 \pm 6.4$	$28.7 \pm 6.5$	$29.3 \pm 6.2$	.56
QoL-AD CS (13-52)	$31.0 \pm 5.1$	$30.9 \pm 5.2$	$31.2 \pm 4.9$	.68

Mean  $\pm$  SD; *t*-test for continuous independent variables, GIC: Geriatric Index of Comorbidity; higher scores indicate higher comorbidity, BADL: Basic Activities of Daily Living, IADL: Instrumental Activities of Daily Living (for male patients, preparing meals, house working and washing clothes were not assessed), CIRS: Clinical Insight Rating Scale; higher scores denote higher insight, MMSE: Mini Mental State Examination; higher scores indicate better cognitive status, GDS: Geriatric Depression Scale; higher scores denote depressive symptoms, NPI: Neuropsychiatry Inventory; the higher the scores, the more severe are behavioural symptoms. QoL-AD: Quality of Life-Alzheimer's Disease; QoL-AD CS: Quality of Life-Alzheimer's disease composite score; Higher scores indicate better QoL, BDI: Beck Depression Inventory; higher scores denote depressive symptoms, CBI: Caregiver Burden Inventory; higher scores indicate higher burden of care.

Data were missing for the following measures and number of participants: education ( $n = 4$ ); number of medication ( $n = 1$ ); duration of dementia symptoms ( $n = 6$ ); CIRS ( $n = 1$ ); NPI ( $n = 2$ ).

**Table II.** Tertiles of QoL-AD CS and demographic variables, clinical characteristics and association on caregivers' burden of care and depressive symptoms.

Variable	Low QoL (N = 70)	Intermediate QoL (N = 60)	High QoL (N = 70)	F	p
Age, years	78.5 ± 6.5	76.3 ± 5.9	76.9 ± 7.5	1.983	.14
Education, years	5.9 ± 3.0	6.3 ± 4.0	7.2 ± 3.9	2.300	.10
Duration of dementia symptoms, months	27.9 ± 17.5	23.4 ± 12.9	25.9 ± 16.2	1.320	.27
Number of medications	4.6 ± 2.4* <sup>†</sup>	3.4 ± 2.0 <sup>†</sup>	2.9 ± 1.7*	11.433	.00
GIC (1-4)	2.3 ± 0.9 <sup>°</sup>	2.0 ± 0.8	1.8 ± 0.9 <sup>°</sup>	5.307	.00
BADL, functions lost (0-6)	1.5 ± 1.7*	0.9 ± 1.4	0.4 ± 1.1*	8.938	.00
IADL, functions lost (0-8)	3.7 ± 2.4*	3.0 ± 2.4 <sup>‡</sup>	1.9 ± 1.8* <sup>‡</sup>	11.095	.00
CIRS (0-8)	2.8 ± 2.2	2.9 ± 2.3	3.2 ± 2.7	.955	.39
MMSE (0-30)	21.8 ± 3.1	22.2 ± 3.3	22.4 ± 3.2	.696	.50
GDS (0-30)	13.8 ± 15.9* <sup>**</sup>	9.8 ± 4.8**	6.5 ± 3.9* <sup>**</sup>	37.755	.00
NPI (0-144)	26.4 ± 21.2* <sup>†</sup>	18.6 ± 18.6 <sup>‡</sup> <sup>#</sup>	9.2 ± 9.7* <sup>#</sup>	17.592	.00
BDI (0-63)	8.9 ± 7.9 <sup>^</sup>	7.3 ± 6.5	5.9 ± 4.8 <sup>^</sup>	3.771	.02
CBI (0-56)	22.9 ± 18.9*	17.5 ± 16.5	11.9 ± 12.1*	8.271	.00

Mean ± SD, ANOVA for continuous variables and post-hoc analysis.

GIC: Geriatric Index of Comorbidity, BADL: Basic Activities of Daily Living, IADL: Instrumental Activities of Daily Living, CIRS: Clinical Insight Rating Scale, MMSE: Mini Mental State Examination, GDS: Geriatric Depression Scale, NPI: Neuropsychiatry Inventory, QoL-AD: Quality of Life-Alzheimer's Disease, QoL-AD CS: Quality of Life-Alzheimer's disease composite score, BDI: Beck Depression Inventory, CBI: Caregiver Burden Inventory.

Bonferroni post-hoc analysis:

\* p < 0.001 for Low QoL VS High QoL, \*\* p < 0.001 for Intermediate QoL VS High QoL and for Intermediate QoL VS Low QoL, † p < 0.01 for Intermediate QoL VS Low QoL, ‡ p < 0.01 for Intermediate QoL VS High QoL, ° p < 0.005 for Low QoL VS High QoL, # p < 0.001 for Intermediate QoL VS High QoL, ^ p < 0.05 for Low QoL VS High QoL.

group resulted significantly higher compared to high QoL group. A difference between these two groups was also found in terms of burden of care.

The linear correlation for QoL-AD CS and the demographic and clinical variables presented in Table II was calculated (Pearson correlation coefficient). The analysis showed a statistically significant correlations between QoL-AD CS and education ( $r = .207$ ;  $p = .004$ ); number of medications ( $r = -.352$ ;  $p = .000$ ); number of BADL ( $r = -.297$ ;  $p = .000$ ) and IADL ( $r = -.364$ ;  $p = .000$ ) lost; GIC ( $r = -.244$ ;  $p = .001$ ); GDS ( $r = -.609$ ;  $p = .000$ ); NPI ( $r = -.414$ ;  $p = .000$ ). A multivariate model was constructed using these variables as predictors and the QoL-AD CS as the depended variable (Tab. III). In the model, depressive symptoms, IADL functions, medications assumed and behavioural symptoms remained statistically significant associated with QoL. Education, BADL and GIC did not enter the model. This model accounted for nearly 50% of the variance of QoL-AD CS.

To better understand the relation between behavioural symptoms and quality of life a univariate correlation between QoL-AD CS and each items of NPI was performed. The analysis revealed a significant correlation with agitation ( $r = -0.294$ ,  $p < 0.02$ ), depression ( $r = -0.245$ ,  $p < 0.02$ ), anxiety ( $r = -0.255$ ;  $p < 0.02$ ), apathy ( $r = -0.239$ ;  $p < 0.01$ ), irritability ( $r = -0.263$ ;  $p < 0.02$ ).

## DISCUSSION

This investigation evaluate the validity of the Italian version of the Quality of Life – Alzheimer's disease scale in the analysis of the clinical determinants of quality of life in outpatients with mild dementia. Internal consistency and test-retest reliability of the Italian version of QoL-AD were good; these values were similar to those reported in international prospective observational studies<sup>15 20 33 34</sup>.

**Table III.** Linear regression of variables related to QoL-AD score.

Variable	B	β	t	p
GDS	-.437	-.495	-8.990	.000
IADL	-.454	-.209	-3.722	.000
Number of medications	-.365	-.156	-2.829	.005
NPI	-.414	-.153	-2.597	.010

Adjusted R<sup>2</sup> = .485, Excluded variables: education, BADL and GIC. GIC: Geriatric Index of Comorbidity, BADL: Basic Activities of Daily Living, IADL: Instrumental Activities of Daily Living, GDS: Geriatric Depression Scale, NPI: Neuropsychiatry Inventory.

QoL-AD scale take in account both caregiver and patient judgment of the QoL in the definition of the composite score. The agreement between patients and caregivers in the judgment of QoL in dementia is widely discussed and the studies report contrasting results; in most cases, patients rate their QoL higher than caregivers<sup>35</sup>. In defining QoL caregivers are influenced by their own emotions, depression, burden of care, needs and perception<sup>6,36</sup>. Caregiver's distress, burden of care, behavioural symptoms are the strong predictor of QoL rating discrepancy between the patient and caregiver<sup>37</sup>. Patients may rate their QoL higher than their informants due to lack of insight, and caregiver ratings are also inversely related with the age of the carer<sup>38</sup>.

In our study the correlation between QoL patient-rated and caregiver-rated is significant, even modest; the result is similar to that obtained in the original presentation of the scale<sup>13</sup>. In different studies the correlation between patients and caregivers rate of QoL range between 0.28 to 0.60<sup>10</sup>. In our study patients have a mild level of cognitive decline and to relatively high level of insight, and all the patients are recruited from specialized clinics offering an elevated level of care, not only pharmacological, and a almost uniform level of educational interventions for caregivers; so important factors of discrepancy from patients and caregivers evaluation of QoL may be attenuated<sup>39</sup>. Gathering information from both patients and informants may be considered an ameliorative element for the interpretation of QoL determinants, since neither source of information has been established to be superior.

Our data demonstrated that in a sample of mild demented subjects QoL is related to depression, impairment in instrumental activities of daily living, behavioural symptoms and number of drugs assumed. In our study cognitive decline is not related to QoL, similarly to those observed in the majority of cross-sectional studies<sup>10,14,15,40</sup>. Data obtained from longitudinal studies are limited; in the Qualidem study a cohort of demented subjects of different level of severity was examined in a 2-year follow-up study and MMSE scores were significant correlated with QoL either at baseline that at follow-up<sup>41</sup>. In a longitudinal study conducted in community-dwelling people with mild cognitive impairment for three years a limited changes in QoL was found during the time, even in patients developing dementia, suggesting that a decline in subjective QoL is not inevitable during the natural history of dementia<sup>42</sup>. In an intervention study, Spector et al. demonstrated that improvement in cognition were positively correlated to improvement in QoL, suggesting a relation between these two domains (Spector et al., 2003). Our data, obtained in a group of patients with mild dementia (MMSE score  $\geq 18$ ), support the hypothesis that, almost in a

relatively small range on MMSE score, QoL is not influenced by cognition.

The association of quality of life with behaviour and psychological symptoms in dementia (BPSD) are analyzed in previous studies, with contrasting results<sup>14,18,36,43</sup>. In our study NPI total score are independently associated with QoL-AD CS and, on univariate analyses, there were statistically significant correlations with 5 of its 12 subscales: agitation, depression, anxiety, apathy, irritability. These symptoms have a negative effects on subjects with dementia and their caregivers and significantly influence patient and caregiver-rated QoL. In the evaluation of the effect of BPSD treatment on QoL each symptoms may be considered separately, since composite scores (such total NPI score) are not informative of the influence of specific behavioural symptoms on QoL.

Depression is central in the concept of quality of life, even when applied to demented subjects<sup>6</sup>. In our study, GDS scores are independently associated with QoL-AD CS. These data are consistent with previous reports<sup>10,38</sup>.

Functional status is one of the dimension of quality of life; our data confirm also in dementia subjects a relationship between impairment in functional status and decreased QoL<sup>44</sup>.

In our sample patients assuming higher number of medication revealed lower QoL-AD CS. The number of drugs assumed may be interpreted as a proxy of general health, suggesting a role of this domain in determining QoL in demented subjects, even previous studies reported contrasting results<sup>10,45</sup>.

In this study, we demonstrate that the QoL-AD is a reliable tool for measurement of patients' QoL in Italy. In mild dementia QoL is a broad domain that goes beyond the cognitive impairment itself and is determined by the presence of depression, the impairment in instrumental activities of daily living, behavioural disturbances and general health.

Even an increasing number of studies addresses the field of quality of life in AD, the conceptual framework need to be progressively deepened and the discrepancies between the studies need to be clarified to effectively increase the chances of significantly affecting the quality of life of patients and families.

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# Use of the Barthel Index, mini mental status examination and discharge status to evaluate a special dementia care unit

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**Background:** when dementia patients are grouped according to their ordinal Barthel Index and Mini Mental Status Examination sum scores, it is not clear which portions of the data should be used when valid classifications are developed. Criteria used for classification of patients must be stochastically independent.

**Objectives:** the relationship between Barthel-Index, Mini-Mental State Examination sum scores and discharge status was investigated to develop subgroups of dementia patients. The developed classification uses stochastically independent information and can be used to evaluate special care units.

**Methods:** we used an unrestricted partial credit model to assess the possible scores on the Barthel-Index. We investigated the individual effects of items on the Barthel sum score by using non-parametric conditional-inference-regression trees. The relationships between Barthel score, Mini Mental Status score, and discharge status, in terms of classifying the dementia patients into subgroups, were investigated using a latent class analysis.

**Results:** an interval scale Barthel-Index did not yield a significant improvement versus the ordinal Barthel-Index sum score. Differences in Barthel-Index were meaningful only in the context of three groups using four items. A classification of dementia patients in latent classes could be developed using three Barthel – and Mini Mental Status-Groups and the discharge status of patients who were living at home before admission. Three Barthel – and Mini Mental Status Groups can be combined with the discharge status of those patients who live at home before admission. A combination of a high Barthel – with a low Mini-Mental-Status-group has the highest probability to live no longer at home after discharge.

**Discussion:** the relative frequency of living at home after discharge in different Barthel and Mini Mental Status subgroups could be compared between different acute hospitals as an indicator of service quality for dementia patients. A high risk group is identified by a combination of a high Barthel- and a low Mini Mental Status Examination Group.

**Key words:** Special Dementia Care Unit, Evaluation, Classification of Dementia Patients, Measurement, Barthel-Index, MMSE

## INTRODUCTION

Several studies have demonstrated that the Barthel Index (BI) sum score is not reliable, because it represents neither interval nor uni-dimensional data<sup>1 2 3</sup>. Furthermore, the simple 'raw data' of each BI item

differs markedly in terms of weighting. Therefore, as highlighted by current research, use of the ordinal total BI sum score is problematic.

Barer et al.<sup>4</sup> reduced the number of answer options for each BI item to two, resulting in a clear hierarchy among the 10 items. Sum scores can then be interpreted as

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representative of a certain pattern of indicators. Several researchers have attempted to develop different versions of the BI with fewer items<sup>5,6</sup>. Others have focused on differences in BI item weights<sup>7</sup>.

We changed the weighting of the items as per Table I, and then examined the overall fit of a partial credit model. The maximum modified raw BI score is 20.

## MATERIAL AND METHODS

We investigated whether BI scores could be combined with Mini-Mental State Examination (MMSE) scores and discharge status to categorise patients in a latent class model. By using these data in combination, a hospital may easily ascertain the percentage of patients who no longer live alone after discharge, even if they lived alone pre-admission; in combination with being in the highest BI and low MMSE groups, such dementia patients might be at risk of poor hospital service. Variability in discharge status was compared among different subgroups of patients (classified according to BI and MMSE scores).

In total, 214 patients in the special dementia care unit of Malteser Hospital, St. Hildegarde, Cologne, Germany between 2014 and 2015 were included in the study. These patients had a primary or secondary diagnosis of dementia and an MMSE sum score below 28. Patients without dementia and those with a MMSE sum score above 27 on discharge were excluded. In terms of patient demographics, 25% of the patients were male and 75% were female; 25% were aged 64-78 years, 25% were 79-84 years, 25% were 85-88 years, and 25% were 89-98 years.

The BI was administered by nursing staff upon both admission and discharge. We used discharge BI scores in analyses.

### RASCH ANALYSIS

We used a partial credit model to analyse data related to items with more than two answer options. This model extends on the probabilistic one-parameter logistic Rasch model discussed by Rost<sup>8</sup> and Strobl<sup>9</sup>, in which the probability of providing a certain answer to a given item depends on the relationship between the item's difficulty and the ability of the responder.

In a Rasch model, the probability that a person with a certain level of ability will score positively on an ADL item is a logistic function of the difference between that person's ability (i.e. their BI sum score) and the difficulty of the ADL to which the item pertains (e.g., the 'toilet' ADL). If the ability of a person is equal to the difficulty of an ADL, the probability of success is 0.5. When the person's ability exceeds the difficulty of the ADL, the

probability that the ADL will be completed successfully increases.

A good global Rasch model fit is indicated by a total-item chi-square probability greater than 0.05.

The Rasch model requires that all BI items are measured using a single underlying construct. All items that are summarised by a sum value are assumed to be one-dimensional. Another assumption is that the items are locally independent; i.e. the answer to one item should not determine the answer to any other item. We tested whether the model residuals were associated, where local dependence is indicated by residuals being highly positively correlated. Furthermore, we analysed the loadings of items in a principal components analysis of the residuals.

We used a pairwise algorithm to estimate Rasch model parameters using the RUMM2020 and RUMM2030 software packages (RUMM Laboratory Pty Ltd., Duncraig, Australia).

The overall model fit was evaluated using the chi-square test of model fit (item-trait interaction). Individual item fit was tested using the item residuals, calculated as the difference between the observed and the expected values for each item. According to Andrich<sup>10</sup>, item residuals should be between -2 and 2. We used the person separation index to assess the extent to which the model distinguished between respondents according to their ability.

We also assessed differences in item functioning (DIF) for subgroups defined according to cognitive status (MMSE scores below 20 *versus* MMSE scores 20 or higher). An additional consideration was the answer option thresholds: if ordinal items are changed to an interval scale, the correct answer option thresholds must also be preserved.

To calculate sample size, we referred to Linacre<sup>11</sup>, who proposed a minimum sample size of 108 cases for precision to 0.5 logits, and a confidence interval of 99%, for tests with less than 30 items during Rasch model testing. We also used the RUMM2030 software for the power calculation.

### REGRESSION TREES

Regression tree algorithms are commonly used and have been applied in recursive partitioning by Strobl, Malley, and Tutz<sup>12</sup>. This technique involves dividing a sample such that the resulting subgroups, with respect to the value of the dependent variable, exhibit maximal in-group homogeneity and maximal between-group heterogeneity. The conditional inference trees of Hothorn, Hornik, and Zeileis<sup>13</sup> represent an alternative to the least squares method, and involve significance tests based on permutations of the items. An exhaustive search was conducted during partitioning of the

**Table 1.** Scoring of Barthel Index items: original versus modified version. All values represent points scored.

Barthel item	Unable to perform	Able to perform with assistance	Able to perform independently
1. Feeding (original)	0	5	10
Feeding (modified)	0	1	2
2. Transfer (chair/bed) (original)	0	5-10	15
Transfer (chair/bed) (modified)	0	1-2	3
3. Grooming (original)	0	0	5
Grooming (modified)	0	0	1
4. Toilet (original)	0	5	10
Toilet (modified)	0	1	2
5. Bathing (original)	0	0	5
Bathing (modified)	0	0	1
6. Walking (original)	0	5-10*	15
Walking (modified)	0	1-2	3
7. Stairs (original)	0	5	10
Stairs (modified)	0	1	2
8. Dressing (original)	0	5	10
Dressing (modified)	0	1	2
9. Bowels (original)	0	5	10
Bowels (modified)	0	1	2
10. Bladder (original)	0	5	10
Bladder (modified)	0	1	2

\* With walker/wheelchair

sample, and the selection for the next split was based on items with the highest significance.

The C-Tree algorithm avoids overfitting of the model to the data. We used those BI items that were detected in a regression analysis of the original BI sum score and the BI groups classified by the regression trees. The R Party software package was used for the analysis <sup>14</sup>.

### LATENT CLASS ANALYSIS (LCA)

The latent class model is one example of mixed distribution or 'mixture' models, which are designed to detect 'unobserved heterogeneity' <sup>15</sup> within a population and classify the data according to a latent variable to derive meaningful groups. It is important to note that this latent variable is not used to structure the data; rather it is constructed only during the process of evaluation <sup>8</sup>. The LCA was used to test whether BI and MMSE scores, as well as discharge status, are useful for differentiating dementia patients into subgroups.

The LCA operates according to the conditional assumption that a person belongs to a certain subgroup when a specific pattern of criteria are met. For the model calculation, four assumptions of the LCA are important <sup>8</sup>: 1. The probability of meeting a criterion is constant among all patients within a group; 2. There is local stochastic independence of criteria within a group; 3. The groups are disjoint and exhaustive; and 4. Homogeneity prevails within a group item.

We used likelihood ratio tests to compare the true likelihood of a particular response pattern with that estimated by the model. Ideally, the ratio of these two values is 1. The double-negative logarithm of the likelihood ratio is chi-square distributed, and can therefore be tested for significance. After applying the model, the chi-square test should be associated with a high P-value. We also used the dissimilarity index (DI), which has a value between 0 and 1 and describes the proportion of patients that must be re-classified to perfectly reproduce the actually observed frequencies. The DI should be as close to 0 as possible. We also used the bivariate residuals to test whether the criteria used to generate the latent classes were stochastically independent. We used Latent GOLD software (ver. 4.5; Statistical Innovations, Belmont, MA, USA) to perform this analysis <sup>16</sup>.

## RESULTS

### TESTING THE PARTIAL CREDIT MODEL

The chi-square statistic of the degree of model fit (item-trait interaction) was not significant (27.8, 20 degrees of freedom; model probability, 11%). The person separation index for the BI items was high (0.87), demonstrating that the model had excellent reliability.

All BI items exhibited a good fit with the partial credit

model, with fit residuals of between -2.0 and 2.5. The chi-square statistics of item fit were not significant (all  $p > 0.05$ ). Items were ordered by threshold.

No differential item functioning (DIF) was observed for the subgroups defined according to the MMSE.

Although a partial credit model could be fitted to the data, the mean sum score of the recalibrated BI, of 54 points or -0.323 logits, could be produced by different scoring patterns across the 10 items (where 0 = *unable to perform activity*; 1/2 = *can perform with assistance*, and 2/3 = *can perform independently*).

Table II shows that there is a high degree of variance in dependency within the mean BI sum score.

There were three clearly dissociable BI-groups (Fig. 1):

- a small 'low' scoring group composed of patients who cannot use the toilet, nor perform any transfer actions, without assistance;
- a large 'middle' scoring group characterised by six different patterns of response across the 'toilet', 'transfer' and 'dressing' items; and
- a small 'high' scoring group composed of patients who can use the toilet, dress themselves, and climb stairs assisted or unassisted.

By combining the BI groups and MMSE groups (MMSE: 'low' = score of 0-16, 'middle' = score of 17-21; and 'high' = score > 21), it could be seen that patients with scores in the 'high' category on both the BI and the MMSE had a 93% probability of being able to live alone after discharge. Among patients scoring in the 'middle' category on both instruments, that probability was reduced to 50%.

The three of BI- and MMSE-groups, in addition to the discharge status of patients who were admitted to the hospital after living alone in their own homes, are stochastically independent criteria that can inform subgroups of dementia patients in acute care hospitals. The LCA, which included the three groups of BI and MMSE as well as the discharge status, had a DI of 0.06 and a chi-square probability value of 0.76; furthermore, none of the bivariate residual values, for any combination of the three criteria, exceeded 1.0. Therefore, the derived latent classes represent a good classification scheme; such classification is not possible with the original (ordinal) or revised (interval scale) BI sum scores (Fig. 2).

**Table II.** Response patterns resulting in the average Barthel Index (BI) sum score: in total, 82% of the change in the revised BI was explained by a combination of up to four variables.

The change in BI groups between admission and discharge was mainly caused by changes from the middle BI group to the high BI group. The three groups differed significantly in both their ordinal and interval BI sum scores.

Average Barthel-logit-score	Transfer	Feeding	Bowels	Toilet	Mobility	Bladder	Grooming	Dressing	Stairs	Bathing
-0.323	2	1	2	1	1	2	1	1	0	0
-0.323	2	2	2	1	1	1	1	1	0	0
-0.323	2	2	1	1	2	1	1	1	0	0
-0.323	2	2	1	1	2	1	1	1	0	0
-0.323	2	1	2	1	2	1	1	1	0	0
-0.323	2	2	2	1	1	2	0	1	0	0
-0.323	2	2	2	1	1	2	0	1	0	0
-0.323	2	1	2	1	2	1	1	1	0	0
-0.323	2	2	0	1	3	0	1	2	0	0
-0.323	2	1	1	1	2	2	0	1	1	0
-0.323	2	2	2	1	1	2	0	1	0	0
-0.323	2	1	2	1	2	1	1	1	0	0
-0.323	2	2	1	1	2	1	1	1	0	0
-0.323	3	2	1	1	1	1	1	1	0	0
-0.323	2	1	2	1	2	0	1	1	1	0
-0.323	2	1	2	1	1	1	1	1	1	0
-0.323	3	2	1	1	2	0	1	1	0	0
-0.323	3	1	2	1	2	1	0	1	0	0
-0.323	2	1	2	1	2	1	0	1	1	0
-0.323	2	1	2	1	2	1	1	1	0	0
-0.323	3	1	1	1	3	1	0	1	0	0

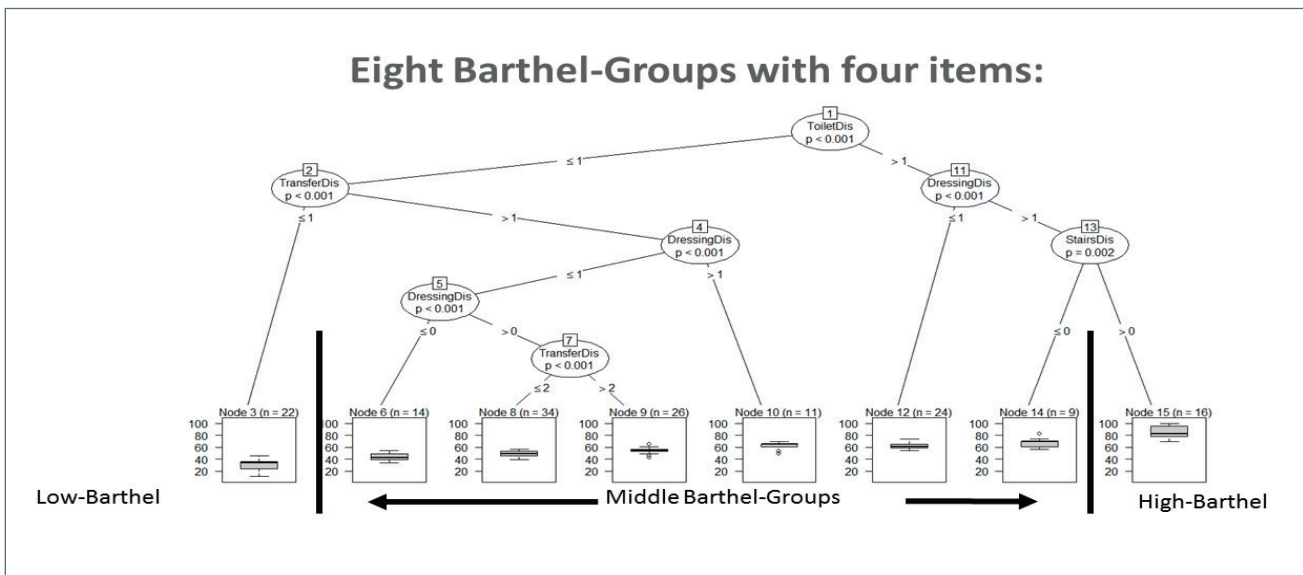


Figure 1. Dementia patients grouped according to scores on the four significant BI items in a regression tree.

April 2016, N= 197		Cluster 1	Cluster 2	Cluster 3
Cluster Size		0.5623	0,3327	0,1051
MMSE				
	low	0.1265	0.7053	0.4923
	middle	0.3778	0.2543	0.3792
	high	0.4958	0.0403	0.1285
Three Barthel-Groups				
	Barthel low	0.0807	0.0611	0.0002
	Barthel middle	0.7694	0.9351	0.5657
	Barthel high	0.2299	0.0039	0.4341
Discharge of patients living at home before admission				
	home	0.9979	0.8224	0.4395
	Assisted living	0.0021	0.1285	0.1738
	Short term care	0.0000	0.0075	0.0256
	Long term care	0.0000	0.0417	0.3811

Figure 2.

## DISCUSSION

The results of the Rasch model revealed that the revised (interval scale) BI sum score did not lead to much improvement over the original (ordinal) BI sum score. Changes in BI sum scores among dementia patients during a stay in an acute care hospital depended mainly only on four items: 'toilet', 'transfer', 'dressing,' and 'stairs'.

Patients who were living at home pre-admission, and had 'high' scores on both the BI and MMSE, had a probability of being able to live alone again after discharge of nearly 1. This probability fell to 0.5 in patients being a member of the high Barthel and the low MMSE group.

Classification of patients according to original (ordinal) BI score, revised (interval scale) BI score, MMSE

score, or discharge status was not possible in an LCA because these measures are stochastically dependent. The LCA demonstrated that use of these BI groups based on combinations of individual items represents a good classification scheme for dementia patients in acute hospitals. Furthermore, these data are routinely collected during normal practice.

The rate of those patients admitted from home and living alone after discharge who are members of the high Barthel-Group (independent toilet, transfer, dressing and partly stairs) and of the low MMSE-group (< 17 points) is a quality criterion for special care units. The rate of those patients living at home who were admitted from home who are members of the low Barthel and the high MMSE Group should be compared between different hospitals.

Grouping of patients with four Barthel-Items and three MMSE score groups identifies a high-risk group for losing the opportunity of living at home. By identifying these subgroup of patients a quality indicator for special care units could be developed, when the rates of those living at home after discharge who were admitted from home are compared.

#### ACKNOWLEDGEMENTS

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## Bisphosphonates and osteoblast function

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Bisphosphonates (BPs) are pharmacological agents widely used in clinical practice for the treatment of diseases characterized by increased bone remodeling, such as osteoporosis. Their main biological effect is the inhibition of osteoclast formation, maturation and activity, resulting in a strong inhibition of bone reabsorption processes. Nevertheless, there is increasing evidence that BPs can act not only through a direct action on osteoclasts, but also by an indirect effect mediated by osteoblasts, which may represent an alternative target and could be required for the complete anti-absorptive effects of these drugs <sup>1</sup>.

The capacity of BPs to modify the osteoblast metabolism is only partially known; moreover, they often exert a contradictory effect on these cells depending on the dosage and the compound types studied. BPs may play a role in osteoblastogenesis, and many studies report that various BPs may modify proliferation, viability and several aspects of osteoblast metabolic activity in normal and pathological conditions <sup>2-4</sup>, supporting the hypothesis that the overall positive effect of this class of compounds on bone mass and strength is due not only to their influence on osteoclast, but also on bone forming cells.

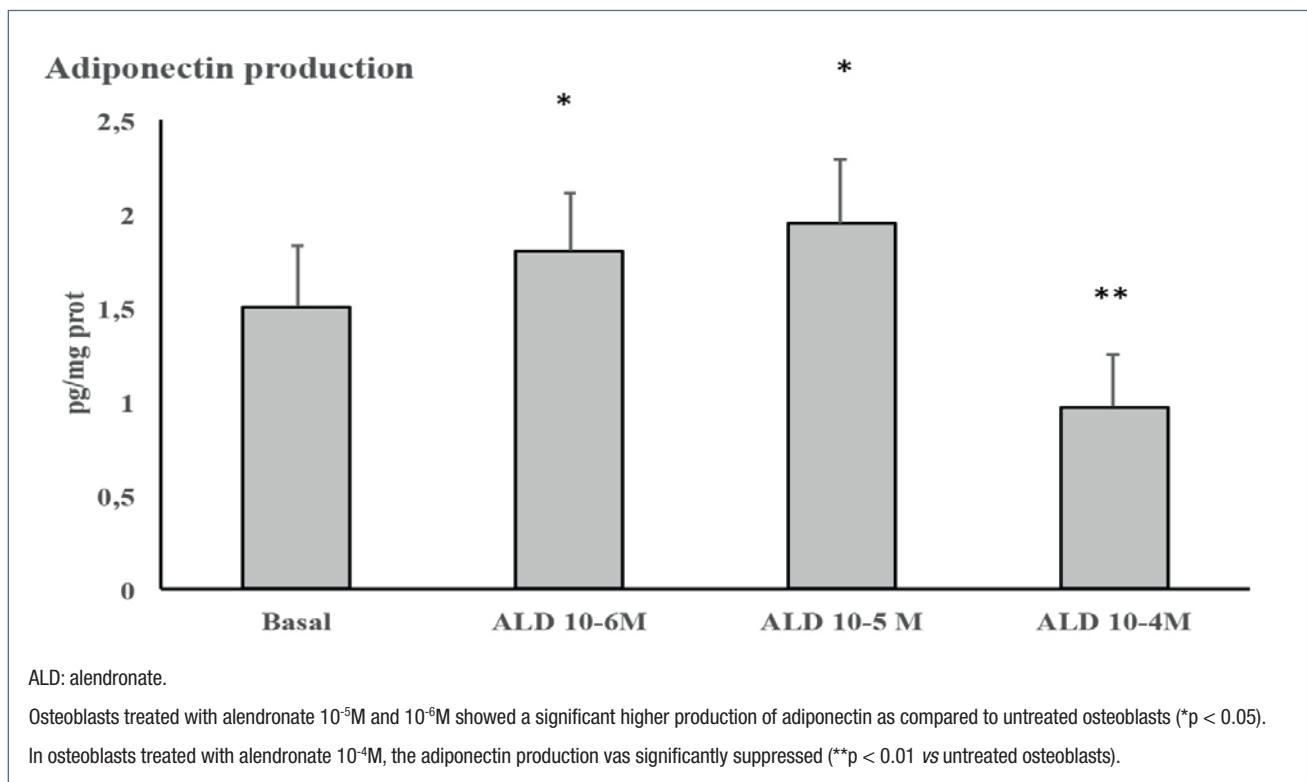
Recently, advances in understanding the physiopathology of bone metabolism have underlined the significant role of adipose tissue as independent endocrine and paracrine factor associated with the production of bioactive molecules, called adipokines, which are able to act as modulators of bone remodeling <sup>5</sup> and have a significant effect on bone structure, presenting both stimulatory or inhibitory effects on osteoblast differentiation, growth, and mineralization <sup>6</sup>. Particularly, experimental data have shown a relationship between plasma levels of adiponectin and body fat, bone mineral density, sex hormones, peri- and postmenopausal

changes, suggesting that this adipokine may modulate bone metabolism. Adiponectin has been observed as a potential factor that may increase osteoblasts proliferation, differentiation and activity <sup>7</sup>. It has previously been shown that adiponectin stimulates bone formation and inhibits bone resorption, advocating a possible positive role as regulator of bone mass. Several *in vitro* studies demonstrate that adiponectin stimulates the differentiation and mineralization of osteoblasts as well as the expression of osteocalcin <sup>6</sup>. Recently, it has been reported that adipokines can be produced by other tissues other than adipose tissue; particularly, human osteoblasts have also been demonstrated to express various adipokines, previously considered adipocyte specific gene products <sup>8,9</sup>, which can act through an autocrine/paracrine mechanism.

Here, we report the preliminary data concerning the effect of the BP alendronate on the production of adiponectin by human osteoblastic cells. Normal human osteoblasts were obtained from fresh bone fragments deriving from 10 adult healthy subjects undergoing surgery for traumatic fractures of limbs. None of the donors had been taking drugs which could interfere with bone metabolism and none was affected by metabolic bone disease. Osteoblast cell culture were obtained as previously described <sup>10</sup>; osteocalcin production and phosphatase alkaline activity were evaluated to confirm the osteoblast lineage of cultured cells. Cell cultures were treated with alendronate at different concentrations (ranging from  $10^{-6}$  M to  $10^{-4}$  M) for 48 hours, before the evaluation of the adiponectin. We found that lower alendronate concentrations significantly increased the adiponectin production compared to untreated cells in a dose-dependent manner, but higher alendronate concentration significantly suppressed adiponectin production (Fig. 1). Also, osteocalcin production and alkaline

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**Figure 1.** Adiponectin production in cultured normal osteoblasts after Alendronate treatment.

phosphatase activity were increased in alendronate-treated cells, but only with lower drug concentrations, whereas they were markedly suppressed by the higher concentration, probably due to a cytotoxic effect.

Our results, although preliminary, further confirm the previously published data showing a direct effect of BPs on the metabolic activity of human osteoblasts and support the hypothesis that these drugs can modify the expression of substances, such as adipokines, that play an essential physiological role in bone metabolism. Additional studies would be useful to establish the effect of various BPs at several concentrations on the production of different adipokines also in pathological cells, particularly in osteoblasts deriving from osteoporotic subjects.

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## Treatment of presbycusis: where do we stand?

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Hearing loss is an important health and social problem in general population. Epidemiological studies suggest that 12.7% of Americans 12 years and older had bilateral hearing loss from 2001 through 2008, and this estimate increases to 48.1 million or 20.3% when also including individuals with unilateral hearing loss<sup>1</sup>. About 8 million Italians (12% of the whole population) suffer from hearing disorders, more than half a million of whom are adults with severe deafness and subsequent social handicap<sup>2</sup>.

Hearing loss is the third most prevalent chronic disease in the elderly, preceded only by arthritis and hypertension. It is estimated that hearing loss which is greater than 25 dB affects 37% of adults between 61 and 70 years of age, 60% of people aged between 71 and 80 years, and over 80% of those aged over 80 years. More than 90% of hearing impaired elderly have a sensorineural hearing loss, which gradually evolves symmetrically and which involves mainly high frequencies<sup>3</sup>. This last condition is commonly defined presbycusis. The elderly may also experience conductive hearing loss, as in the case of chronic ear infections or otosclerosis, or sensorineural hearing loss of other etiologies (eg. Sudden hearing loss).

Such people may not notice mild to moderate hearing loss because of its insidious onset and its progressive nature or because it does not cause difficulties in moderately noisy environments. In particular, it is estimated that only 20% of people over 65 years with moderate to profound hearing loss actually realize to be hearing impaired<sup>4</sup>.

An important recent research topic is represented by the correlation between hearing loss and cognitive impairment. It is now well known that hearing loss is independently associated with accelerated cognitive decline and incident cognitive impairment in community-dwelling older adults<sup>5</sup>. Actual studies are investigating the

potential benefits of an effective prosthetic treatment of presbycusis on cognitive functions.

The recognition of a disabling hearing loss is the prerequisite of therapy that aims at improving communication, cognitive and emotional functions<sup>6</sup>.

However, despite the potential benefits on the quality of life of patients and their families, the lack of adherence to therapy is very common. The reasons are to be found not only in a low initial perception of the hearing loss, but also in the disinclination to the constant use of prosthetic aids, in the excessive expectations, in immediately not satisfactory results, in the high costs and in the negative social stereotypes still associated with the use of hearing aids<sup>7</sup>.

Physicians, particularly audiologists and otolaryngologists, should therefore play an important role in giving advice to hearing-impaired elderly people. In fact, in order to be effective, treatment strategies must be individualized and focused on individual patient characteristics.

The therapeutic approach to the hearing loss should first aim to solve any cause of conductive hearing loss also in the elderly. In fact, a potentially reversible cause of conductive hearing loss can limit the performance of conventional hearing aids when added to presbycusis. For this reason, medical conditions, such as earwax or chronic effusive otitis, or surgical conditions, such as chronic otitis media or otosclerosis, should be solved before any conventional prosthetic treatment.

Traditionally the first prosthetic strategy consists in employing conventional hearing aids. There are various types of hearing aids – behind the ear (BTE), in the ear (ITE), or completely in the canal (CIC) –, but the choice among these models is often made according to the patient's preferences of use and his/her aesthetic sense, rather than for audiological reasons.

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Some practical problems with conventional hearing aids reported by patients are the low comfort at the level of the external acoustic meatus, excessive difficulties in the daily management of the prosthesis, the initial difficulties of adjustment and the presence of possible additional noise.

The result is that only 25% of candidate patients makes use of conventional hearing aids, whereas up to 30% of them do not use such aids. The lack of use of hearing aids correlates neither with age, nor with the degree of hearing loss, nor with the level of education<sup>8</sup>.

In well-motivated patients but with poor compliance with conventional hearing aids, surgically implantable prosthesis can be proposed. These ones provide audiological results comparable to conventional hearing aids and provide greater patient's satisfaction. In particular, in the presence of predominantly conductive hearing loss, the implantable bone conduction prosthesis should also be considered the first choice of treatment in the elderly<sup>9</sup>.

In those elders who continue to have poor verbal comprehension despite a conventional prosthetic treatment, the increasing scientific evidence attributed to the cochlear implant a prominent role.

Despite the long duration of deafness, the age-related degeneration of the spiral ganglion cells and central auditory pathways and the potential learning difficulties in elderly patients, virtually all studies reported in the literature have shown that the cochlear implant improves auditory performance, communication skills, confidence and social interactions in the geriatric population<sup>10</sup>.

Studies to evaluate the benefit/cost ratio have shown that the cochlear implant is a beneficial intervention also in older patients, despite a shorter life expectancy (and, consequently, a reduced duration of use of the device)<sup>11</sup>.

From the surgical point of view, the age does not affect the operating time, the type of surgery or duration of hospital stay. The surgical complication rates are comparable between older and younger cochlear implant receivers. The general state of health seems to be the best predictor of medical complications rather than age alone, although in general patients aged over 80 years are more likely to present non-surgical complications, such as cardiac arrhythmia, delirium, urinary incontinence or retention (2-4%). The result is that advanced age alone is not a contraindication for cochlear implantation, if an accurate assessment of comorbidities before surgery is performed<sup>12</sup>.

This concept of a general nature can be extended to all of prosthetic or otologic surgery aimed at restoring a proper hearing threshold in the elderly.

In conclusion, now there are proven tools for management of every kind and degrees of hearing loss in the geriatric population. In order to undertake an adequate therapy, the following prerequisites are required: the resolution of clinical conditions whose medical or surgical correction can optimize the prosthetic treatment of hearing loss; the knowledge of correct indications of conventional and surgically implantable hearing aids currently available; a targeted rehabilitation therapy with the constant monitoring of the results.

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# Vaccination among the elderly: European state of art and the need for a culture shift

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**Background:** since the development of the first vaccine, immunization has been shown to be one of the most effective public health measures to prevent diseases. Vaccination policy is currently mainly focused on the young (aged below 18), to some extent the old (aged above 65) but, in contrast to childhood immunization programs, adult vaccination is not considered to be a routine health intervention.

**Methods:** a PubMed research was performed using elderly and vaccination policy as key words.

**Conclusions:** vaccination in adults remains an underused public health strategy in the promotion of healthy ageing, and adult vaccination rates are still far below the target. Influenza, pneumococcal pneumonia and pneumococcal invasive disease, pertussis and even HZV (because of a high incidence of post-herpetic neuralgia among the elderly) have been highlighted as the most important diseases for which is important to look after immunization strategies due to their burden related to deaths or disabilities. Investing € 1 in adult immunization can generate over € 4 of future economic revenue for government.

**Key words:** Public health, Herpes Zoster, Post-herpetic neuralgia, Pneumococcal vaccination, Influenza

## BACKGROUND

Since the development of the first vaccine, immunization has been shown to be one of the most effective public health measures to prevent disease. Vaccination policy is currently mainly focused on the young (aged below 18), to some extent the old (aged above 65), especially for seasonal influenza, and those in at-risk groups (e.g. people with medical conditions that put them at increased risk of contracting certain infectious diseases). In contrast to childhood immunization programs, adult vaccination is not considered to be a routine health intervention. Hence, vaccination in adults remains an underused public health strategy in the promotion of healthy ageing, and adult vaccination rates are still far below the target<sup>1</sup> even for seasonal influenza vaccination rates remain limited among adults and in the specific high-priority groups<sup>2,3</sup>. This situation has the following consequences:

- vaccine uptake among adults remains low;
- there is a lack of coordinated programs for vaccination of adults<sup>4</sup>;
- adults are not well protected<sup>5</sup>.

Vaccination, as a prevention strategy, should be part of an age-based approach to health throughout all phases of life.

## HIGHLIGHTS ON INFLUENZA

During the season 2012-2013 more than 3.5 million people were affected among the European countries. There were 724 serious cases requiring intensive care and at least 117 influenza deaths (ages ranged between 5 months and 97 years of age). Among the serious cases, only 11% were known to be vaccinated. Moreover, hospitalization rates peaked at 0.35 per 1000 during the pandemic year of 2009<sup>6</sup>. Diaz Granados et al

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randomized nearly 32,000 adults age 65 and older to receive either the standard-dose or the high-dose vaccine. The primary end point was laboratory-confirmed influenza caused by any influenza viral type or subtype, in association with a protocol-defined influenza-like illness. The primary end point was reached in 1.4% of those with the high-dose vaccine and 1.9% of those with the standard-dose vaccine (relative efficacy 24.2%, 95% confidence interval 9.7-36.5). There was also a 26% reduction in respiratory illness regardless of laboratory confirmation. Mortality rates were similar and low (0.5%) in both groups. In those without laboratory confirmation of respiratory illness, there was a 26% lower rate of pneumonia but no statistical difference in rates of hospitalization, medication use, routine office visits, and emergency department visits <sup>7</sup>. These results can be interpreted as meaning that the high-dose vaccine prevented about a quarter of the laboratory-confirmed influenza cases that would have occurred with the standard-dose vaccine. However, due to the low rate of disease in those given the standard-dose vaccine, the number needed to treat to prevent one influenza infection was about 200 with the high-dose vs the standard dose vaccine; to prevent one case of pneumonia, more than 270 would need to be treated. Vaccination coverage rates (VCRs) among older age groups for the influenza season 2012-13 varied from 1% to 77.4% with the median VCR being 44.7%. The highest VCRs were reported by the Netherlands and the United Kingdom, which achieved, or almost achieved, the 75% EU target <sup>8</sup>.

## **PNEUMOCOCCAL DISEASES: INVASIVE PNEUMOCOCCAL DISEASE (IPD) AND PNEUMONIA**

Globally, an estimated 1.6 million people die of IPD annually <sup>9</sup>. Groups at high risk of contracting IPD include:

- children (1 million deaths annually);
- immunocompromised people (e.g. patients with chronic renal failure);
- the elderly (> 65 years of age).

The rate of elderly patients affected has increased from 9.84 in 2009 to 14.4 in 2010. Diagnosis and treatment can be difficult because diagnosis must be confirmed by laboratory analysis of blood, cerebrospinal fluid, pleural fluid, or peritoneal fluid <sup>10</sup> and multidrug resistance (resistance to three or more antibiotic classes) can occur <sup>9</sup>. Pneumococcal pneumonia is responsible for 2% of hospitalizations in the EU-27, with an average stay of 10 days in 2005 and an average hospitalization rate of 3.3 per 1000 population, with the highest rates in Finland, Lithuania and <sup>6</sup>. To understand the

real extension of the problem, it is recommended to take a look at pneumonia related death: In England and Wales in 2011, 25,696 people died of pneumonia (5.3% of all deaths), compared to 109 with influenza and 316 with pandemic influenza and wide variations in mortality rates are seen between some countries. Mortality could be over 30% in patients requiring intensive care. Also, in all countries the elderly, disabled and those with healthcare-associated pneumonia are at increased risk of multidrug resistance mortality <sup>11</sup>. The aforementioned data is impressive especially because a 23-valent polysaccharide vaccine has been available since 1983 and is recommended in the United States for all adults age 65 and over. It costs 72 \$ per dose. A recent Cochrane Collaboration analysis of 11 randomized trials involving 36,489 participants 16 years or older concluded that PPSV23 was 74% (95% CI, 55-86%) effective against invasive pneumococcal disease and 74% (95% CI, 54-85%) effective against confirmed pneumococcal pneumonia. However, PPSV23 is far from perfect. There have yet to be any high-quality randomized trials focusing on PPSV23 in elderly individuals, and the available data on the elderly population are at times conflicting (although overall, lower-quality observational data suggest 68% [95% CI, 53-78%] effectiveness against invasive pneumococcal disease in elderly individuals) <sup>12</sup>. Furthermore, a 13-valent pneumococcal-diphtheria conjugate vaccine (PCV13) has been available since 2010. It costs 152 \$ per dose and it also contains the conjugated protein which gives a more robust immune response. Up until recent times, the conjugate vaccine was recommended for children; the only adults for whom it was recommended were those age 19 and over who either were immunocompromised or had a cochlear implant, asplenia (anatomic and/or functional, i.e. coeliac disease), a cerebral spinal fluid leak, or renal failure <sup>12</sup>. The CAPiTA (*Community Acquired Pneumonia Immunization Trial in Adults*) trial randomized nearly 85,000 people (most 65 and older, and some children) in the Netherlands to receive either the conjugate vaccine or placebo. It found a 46% reduction in community-acquired pneumonia ( $p = .0006$ ), a 45% reduction in nonbacteremic nonvaccine-type community-acquired pneumonia ( $p = .0067$ ), and a 75% reduction in vaccine-type invasive pneumococcal disease ( $p = .0005$ ) <sup>10 11</sup>. The ACIP correctly points out that PCV13 induces higher antibody levels than PPSV23 in people with weakened immunity, such as individuals 65 years or older. In addition, the clinical efficacy of PPSV23 in that age group is not well established. Nonetheless, this reasoning does not obviate the need for compelling clinical data demonstrating the value of giving PCV13 in addition to PPSV23 <sup>15</sup>. Anyway, rapid uptake and improved PCV13 coverage

among adults might help to close the immunity gap in the short term <sup>16</sup>.

## **PERTUSSIS: A TOUGHER DISEASE THAN EXPECTED**

The global incidence of pertussis is estimated at 48.5 million cases a year with 295,000 deaths <sup>17</sup>. In the US, pertussis has the greatest incidence and mortality of all vaccine-preventable diseases <sup>18</sup> and it continues to be a public health concern, even in countries with high vaccination coverage <sup>9</sup>. The main reasons are that adults may be unaware of having the disease so they may infect vulnerable infants who are not yet vaccinated <sup>9</sup>. As most severe cases and deaths occur in infants <sup>9</sup> policy makers need to reconsider regular pertussis booster vaccinations in adolescents and adults as well as in healthcare workers and pregnant women to reduce the overall incidence and indirectly protect susceptible infants which are called “Cocoon Strategy” <sup>19</sup>. The incidence of pertussis varies widely in Europe due to differences in vaccination policies, levels of awareness, and surveillance procedures. In 2010, confirmed cases were low overall (3.87 per 100,000 population), with the highest rates reported in Estonia and Norway (95.44 and 73.28 per 100,000, respectively) <sup>9</sup>. There is a considerable gap between number of confirmed cases reported in the EU in 2010 (14,000) when compared to epidemiological evidence from the US showing infection rates of 1-6% (800,000 to 1 million cases) during non-epidemic periods <sup>20</sup>. A review <sup>21</sup> indicated 4 different US state-specific studies (in Colorado <sup>22</sup>, Michigan <sup>23</sup>, New York <sup>24</sup> and California <sup>25</sup>, all demonstrated that schools and communities with high vaccine exemption rates also had higher rates of pertussis. The risk for acquiring pertussis was higher even for those who were appropriately vaccinated.

## **HIGHLIGHTS ON HERPES ZOSTER: AN OLD NEW PROBLEM FOR WHICH THERE IS A SOLUTION**

Herpes zoster, commonly referred to as “shingles”, is a serious disease in older people and in the immunocompromised. In the absence of antiviral therapy, up to 45% of patients over 60 years of age experience considerable pain due to post-herpetic neuralgia for 6-12 months <sup>26 27</sup>, severely affecting their quality of life <sup>28</sup>. Herpes Zoster is common in people  $\geq 50$  years of age and they account for 70% of the estimated 1 million new cases per year <sup>29</sup>. The incidence in people

$> 60$  years of age is 10 cases per 1000 population per year <sup>30</sup>. Lifetime risk of developing shingles is approximately 1 in 3 <sup>31 32</sup> and, by the age of 85 years, 50% of people will have had shingles <sup>33</sup>. Shingles is considerably less contagious than Chickenpox but can be transmitted to non-immune people, resulting in a primary varicella infection <sup>34</sup>. Post-herpetic neuralgia is the most common complication of shingles, even though a variety of other complications can occur and could involve nervous system, eyes, skin and even gut <sup>31</sup>. Acute complications such as pneumonia and encephalitis rarely occur, but may lead to persistent complications or even death and hospitalization rates are very low <sup>6</sup>. In 2010 the mortality rates had fallen to an average of 0.03 per 100,000 <sup>11</sup>. It is difficult to eradicate Varicella-Zoster because of its ability to establish latency (i.e. the virus can lie dormant). In the US, universal varicella vaccination was adopted for children in 1995. The vaccination program produced a 90-95% decline in chicken pox in children aged 1-9 and reduced the incidence of zoster in children aged 10 years by 55%. Live attenuated Varicella-Zoster vaccination is recommended for healthy adults aged 60 or more and at risk groups [US children and adult schedules 2012]. Otherwise, in Europe, recommendations suggest vaccinating people aged over 50. There is plenty of evidence in favor of vaccinating against HZV <sup>35</sup>. Schmader 2012 <sup>36</sup> is a continuation of the Oxman 2005 study – Short-Term Persistence Study <sup>37</sup>. The 2012 publication evaluated the effectiveness of the vaccine for up to 7 years after the time of vaccination. Number needed to treat for an additional beneficial outcome (NNTB) = 50. It was the same data found before the update of the review. Since 2006 a live, attenuated varicella zoster virus vaccine, that contains VZV Oka strain, was licensed for the prevention of HZ and PHN in adults aged  $\geq 60$  years. Since 2011, the licensure has been extended to adults between 50 and 59 years. Leroux-Roels 2012 was a phase I/II, open-label, randomized, parallel-group trial that evaluated the safety and immunogenicity of a recombinant adjuvanted vaccine (HZ/su) in comparison with attenuated varicella zoster virus vaccine (OKA). The recombinant adjuvanted vaccine, HZ/su (50  $\mu$ g recombinant varicella zoster virus glycoprotein E antigen in 0.2 mL mixed with 0.5 mL of AS01B adjuvant) (HZ/su) proved to be safe with respect to serious adverse events (including death) when compared with the live attenuated vaccine. There were no reports of vaccine-related serious adverse events and no deaths <sup>38</sup>. The evidence gathered including the most recently published studies suggests that there is benefit in vaccinating elderly people with the herpes zoster vaccine, with no major safety/tolerability concerns <sup>36 37 39</sup>. The available data suggest that the vaccine works for up to 7 years to prevent

herpes zoster in individuals over 60 years of age. There were no statistically significant differences in terms of safety of the herpes zoster vaccine when comparing one versus different two-dose schedules. Anyway, all the aforementioned studies received funding from the pharmaceutical industry.

## COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness evidence of immunization for adults aged 50 years or over in EU Member States was found for at least four of the seven most important vaccine-preventable diseases examined in this report: herpes zoster, seasonal influenza, IPD and pneumococcal pneumonia. These studies showed that immunization is likely to provide a cost-effective strategy for adults aged 50 years or over. Hence, immunization strategies can be recommended for specific age groups:

- Herpes Zoster: the general consensus across studies which compared a vaccination strategy versus no vaccination strategies was that vaccination is a cost-saving or a cost-effective intervention. Existing evidence indicated that if immunization was not cost-effective in the short-term, it did not imply cost-ineffectiveness in the long run<sup>40</sup>. There is evidence that adult vaccination is a valuable preventive option when targeting populations aged 50-54 years<sup>41</sup> and that vaccinating older cohorts (70+) is less cost-effective than vaccinating younger cohorts<sup>42</sup>. In Italy, the annual costs related to the HZ and PHN disease accounted to 41.2 million euros, of which 28.2 million related to direct costs (21.5 million for treatment of acute HZ) and 13 million associated to indirect costs (12.2 in lost productivity related to acute episode of HZ)<sup>43</sup>. A pharmaco-economic evaluation performed in Italy confirmed that vaccination program against HZ and PHN within subjects aged 60-79 years is cost-effective from both societal and third-payer standpoints in the Italian scenario<sup>44</sup>. Related to that, some Italian regions, such as Liguria and Puglia, established to introduce HZ vaccination in the regional immunization plan by the active and free offer of the vaccine to specific age-group;
- IPD: a study<sup>45</sup> conducted a multi-country analysis across 10 EU countries to analyze the cost-effectiveness of pneumococcal vaccination for IPD across those aged > 65 years. The study observed substantial variation in the Incremental Cost-Effectiveness Ratios (ICERs) across the countries, with older populations generally having higher ICERs. A UK based study<sup>46</sup> recommended routine vaccination of all populations aged ≥ 65 years. It was estimated to be the best strategy, with lower cost per

life year gained compared to vaccinating high-risk groups only;

- Pneumococcal pneumonia: a study conducted in the Netherlands concluded that vaccination with pneumococcal conjugate vaccine to be cost-effective when compared with no vaccination<sup>47</sup> for both the general population and high risk populations aged ≥ 65 years;
- Seasonal influenza: the results of the multi-country analysis<sup>48 49</sup> found vaccination for influenza to be cost-effective across all the countries of interest. An Italian study<sup>50</sup> concluded that the economic advantage of extending influenza vaccination to healthy adult workers aged 50-64 years mainly relate to indirect costs such as costs associated with productivity loss.

Investing € 1 in adult immunization can generate over € 4 of future economic revenue for government (case study in the Netherlands). The budget needed for vaccinating a cohort of individuals aged 50 in the year 2012 was estimated to be € 136 million, which includes annual costs for influenza vaccination for the remainder of life. In return, the adult immunization program for the seven main infectious diseases in the Netherlands was projected to:

- prevent 34,528 infectious disease cases over the remaining life span;
- prevent roughly 5,782 premature deaths from infections;
- reduce the number of lost work days by 127,480 days with an estimate of 29 fewer disability cases over the remaining number working years for those vaccinated at 50-years of age;
- generate health cost savings reaching € 6.6 million and an additional € 4.2 million in social insurance savings paid towards disability and sick day payments to workers;
- generate future lifetime tax contributions from implementing adult vaccination, which would result in a revenue gain of € 537 million over the remaining life years of the cohort.

## CONCLUSIONS: POLICY GAPS IN ADULT IMMUNIZATION

Despite the wide spreading of antivaccine movements<sup>51</sup>, vaccination still remains one of the most important public health policy in order to prevent potentially deadly diseases. Moreover, thanks to the development of new policies aimed towards the elderly, there is the possibility to prevent not only life-threatening (e.g. pneumococcal pneumonia) diseases but also the ones which could badly affect quality of life (e.g. HZV).

Another very interesting and important aspect related to the previously stated succeed the cost-effectiveness analysis. There is a strong need to plan international public-health recommendations and also to create awareness about the importance of adult immunization, among the public and the health care professionals. Even though the value of adult vaccination programs is becoming more and more well-known, various critical points have to be solved:

- age-based recommendations, which allow individuals to assess their own status with regards to vaccination, are not applied to all diseases. When they are, the age of recommended vaccination varies across countries, despite an overall consensus towards influenza, pneumococcal and Herpes Zoster vaccinations;
- adult immunization is severely undervalued by the public and by providers<sup>52,53</sup>;
- additionally, significant misinformation, much perpetuated by the anti-vaccine movement, exist surrounding vaccines and vaccination<sup>51</sup>;
- natural boosting of immunity may be decreased because of less frequent exposure to pathogens that cause VPDs and because of immunosenescence due to the decreasing immunization given by the childhood vaccination;
- the failure of primary vaccine series and boosters, may have indirect consequences on certain fragile populations, such as the newborns, infants, immunosuppressed and the elderly;
- the lack of implementation of these recommendations may be linked to limited vaccination reimbursement systems and access to vaccines;
- coupled with limited awareness and promotion of adult vaccination schedules by healthcare professionals and health authorities, this may result in low and inconsistent uptake. According to the data from VENICEII Survey Report, only six countries have a comprehensive summary document or schedule describing all vaccines which are recommended for adults<sup>54</sup>. The Adult Vaccination Campaign in Europe (ADVICE) was developed with an aim to raise awareness for adult vaccination and to understand the dynamics of the vaccination practices and the possible barriers against achieving targeted vaccination rates in Europe<sup>1</sup>.

Eventually, it appears clear that to achieve the worthy success of adult vaccination programs, there needs to be a cultural shift in public health policies.

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## REVIEW

## Age and frailty: are they related in decline of renal function?

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The chronic kidney disease (CKD) is defined as abnormalities of kidney structure and/or function, present for at least 3 months, with implications for health. Incidence and prevalence differ between countries ranging from 10 to 20%. In the Baltimore longitudinal studies, Lindeman et al. reported the rate of decline in renal function with aging. The average decline in clearance of creatinine (CICr) was 0.75 ml/min/year. The prevalence of frailty overall among the Cardiovascular Health Study cohort was 7%, but when restricted to patients with CKD, the prevalence of frailty raised to 15%. However, presence of frailty during CKD was associated with about a twofold higher risk for mortality. Because frailty and CKD are associated with age, poor clinical outcomes, falls, disability, hospitalization and mortality, it is important to identify the subjects at high risk and needing a comprehensive care in order to improve outcome for this vulnerable population.

**Key words:** Renal, Age, Frailty, Elderly

### EPIDEMIOLOGY OF RENAL FUNCTION IN ELDERLY

The chronic kidney disease (CKD) is defined as abnormalities of kidney structure and/or function, present for at least 3 months, with implications for health<sup>1</sup>. Incidence and prevalence differ between countries ranging from 10 to 20%. The prevalence of chronic kidney disease (CKD), defined as persistent kidney damage usually marked by albuminuria or reduced glomerular filtration rate (eGFR < 60 ml/min/1.7 m<sup>2</sup>), significantly increases with advancing age<sup>2</sup>. CKD was independently associated with mortality regardless of age<sup>3</sup>. The prevalence of CKD in the > 65 years old population, according to the literature, was approximately 44%<sup>4</sup>. Age is a main determinant of eGFR, classified as unmodifiable risk factor, which can also be considered as a 'container' consisting of multiple different and specific physiological mechanisms. These include stiffening of the arteries, widening of arterial Pulse Pressure (PP), endothelial dysfunction and others<sup>5</sup>.

### MECHANISMS OF RENAL AGING

Aging is a complex process that negatively impacts the development of different systems and their ability to function<sup>6</sup>. Despite the wealth of phenomenological information on renal aging, the underlying molecular mechanisms are not entirely clear and seem to involve several pathways that affect cellular function<sup>7,8</sup>. Chronic inflammation or parainflammation (i.e. response of the immune system to disturbed tissue homeostasis) belongs to these pathways<sup>9</sup>, resulting in accumulation of macrophages, lymphocytes, inflammatory (e.g. IL-1, IL-6, TNF- $\alpha$ ) and pro-fibrotic factors (e.g. IL-4, IL-13, TGF- $\beta$ , collagen I and IV), that ultimately lead to reactive interstitial fibrosis and declining renal function. In addition, the kidney seems to lose part of its repair ability, due to a decline in the proliferative potential of e.g. proximal tubule cells, enhanced senescence, intensified expression of cell cycle inhibitors (e.g. p21), increased apoptosis and reduced expression of growth factors (e.g. EGF, IGF-1, VEGF). Thereby, minor insults that are

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repaired in younger kidney will accumulate and contribute to reduce functional reserve in aged kidney<sup>10</sup>. As almost every organ, the kidney suffers from increasing oxidative stress with aging and a vascular Nitric Oxide (NO) deficiency. The reduced Nitric Oxide Synthase (NOS) activity impairs the control of renal circulation and contributes to changes in glomerular function. Possibly, Advanced Glycation End products (AGEs), the result of glycation, are important mediators of age-related stress, because the decrease in renal function correlates with circulating AGEs levels<sup>11</sup>. In addition, accumulating mitochondrial damages, with disturbed energy homeostasis, have been suggested as drivers of tissue aging.

## MORPHOLOGICAL CHANGES OF THE AGING KIDNEY

The kidneys are affected by the aging process, which results in numerous effects on the renal system (Fig. 1-2). Renal mass decreases between the ages of 30 and 80 years, with the steepest decline observed after age 50<sup>12</sup>. Fat and fibrosis scarring, which may replace some parenchymal tissue, occurs primarily in the renal cortex and affects the nephrons that are important for maximal urine concentration. Even in normal aging kidneys, 30% of the glomeruli are destroyed and display diffuse glomerular sclerosis by age 75<sup>13</sup> and the remaining glomeruli exhibit impaired filtering ability. The age-related findings on kidney biopsies can be defined by nephrosclerosis, including glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. Previous studies had shown an increased proportion of globally sclerotic glomeruli with aging<sup>14</sup>. The glomerulosclerosis, occurring with aging, has an ischemic appearance with intracapsular fibrosis, suggesting a primary vascular origin for the lesions. Some functional glomeruli show ischemic capillary wrinkling of tufts, thickening of basement membranes, and mild intracapillary fibrosis, all of which are precursors for glomerulosclerosis. Over time, shrinkage of the glomerular tufts with sclerosis and collagen deposition filling Bowman's space develops<sup>15</sup>. Besides glomerulosclerosis, increased arteriosclerosis, medial hypertrophy, and arteriolar hyalinosis occur with aging<sup>14</sup>.

## FUNCTIONAL CHANGES IN RENAL FUNCTION WITH AGING

In the Baltimore longitudinal studies, it has been reported the rate of decline in renal function with aging. The average decline in clearance of creatinine (CICr)

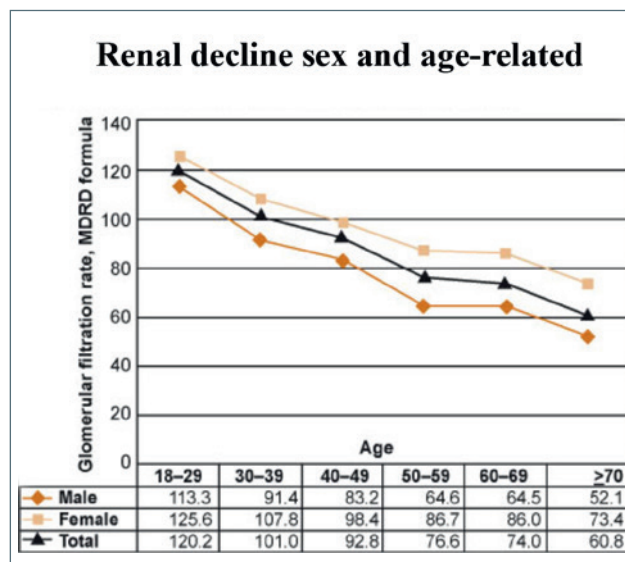


Figure 1. Renal decline by sex and by age.

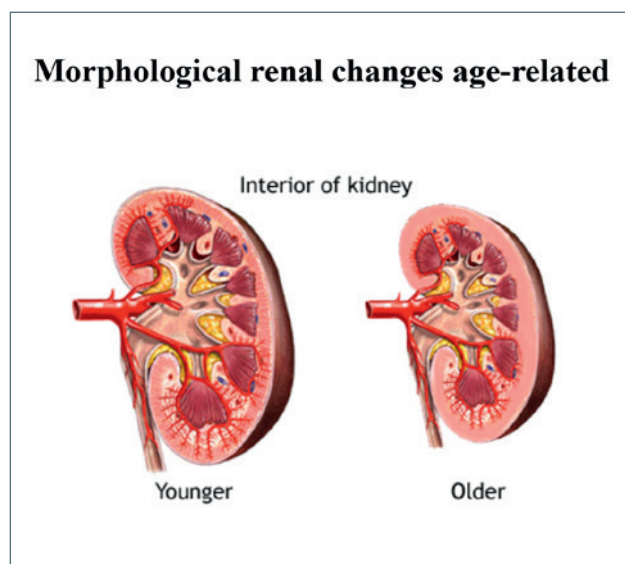


Figure 2. Morphological renal changes age related.

was 0.75 ml/min/year<sup>16</sup>. In adults, the GFR decline per year varies dramatically between studies, ranging from 0.4 to 2.6 ml/min<sup>17</sup>. Fliser et al.<sup>18</sup> suggested that the elderly population was heterogeneous – some having a decline in GFR explained by diseases that complicate aging such as arteriosclerosis with hypertension, whereas in most of healthy adults the decline in GFR is much more modest and not inevitable. Fliser et al. also proposed that the renal functional changes accompanying aging might be the consequence of an altered

responsiveness to vasodilators and vasoconstrictors<sup>19</sup>. This thesis is based on observations that the filtration fraction increases with aging, due to a disproportionate fall in renal plasma flow relative to GFR. The filtration fraction does not begin to increase up to 60 or 70 years, while the decline in GFR begins at age of 30-40 years.  $\text{Na}^+$ -handling is altered in the aged kidney, so that proximal reabsorption is enhanced and distal reabsorption reduced, resulting in a narrow range<sup>20</sup> with consequent reduced response to altered  $\text{Na}^+$ -load. Because sodium is the main determinant of extracellular volume, elderly are at higher risk of volume depletion and salt retention when sodium supply is out of the "normal" range. In addition, there is a reduced activity of the renin-angiotensin-aldosterone system and possibly a partial resistance to atrial natriuretic peptide, both of which contribute to the reduced functional reserve in  $\text{Na}^+$ -homeostasis. In respect to renal  $\text{K}^+$ -handling, renal tubular secretory capacity decreases with age, probably due to reduced  $\text{Na}^+/\text{K}^+$ -ATPase activity<sup>20</sup> in the distal nephron and reduced aldosterone levels. The tendencies to dehydration (lower urine flow rate) and metabolic acidosis in elderly contribute to the reduced functional reserve in  $\text{K}^+$ -homeostasis. Renal concentrating and diluting abilities are reduced, leading to lower maximum urine osmolality, decreased minimum urine flow and worsen free water clearance<sup>21</sup>. Finally, there is also a reduced functional reserve in acid-base homeostasis, with lower renal acid excretion capacity, due to decreased ammonia genesis in the proximal tubule and reduced  $\text{H}^+$ -ATPase activity in the collecting duct, whereas acid excretion is mostly normal<sup>22</sup>. With aging, renal renin release decreases, leading to lower plasma renin activity and consequently decreased angiotensin-II and aldosterone levels, with consequences for electrolyte and volume homeostasis. By contrast, plasma  $1.25(\text{OH})_2\text{D}_3$  levels are in the low-normal range in healthy elderly, with plasma  $25(\text{OH})\text{D}_2$  levels reduced and plasma PTH levels enhanced. This constellation can be interpreted as substrate deficiency for the proximal tubule compensated by enhanced PTH release, stimulating renal  $1.25(\text{OH})_2\text{D}_3$  formation<sup>23 24</sup>. Plasma erythropoietin levels are mostly normal in healthy elderly and only show reduced levels in anaemic subjects, indicating an impaired responsiveness of renal erythropoietin formation. Finally, renal production of the calcio-phospho regulatory hormone<sup>25</sup> decreases with age. However, several studies have shown that renal-synthesized C-type natriuretic peptide (CNP) is correlated with intrarenal regulation of water and electrolyte homeostasis in kidneys of diabetic rats<sup>26</sup>. Importantly, it has also been reported that urinary CNP serves as a marker for increased intravascular and renal interstitial pressure in an animal model of acute intravascular volume overload<sup>27</sup>. In addition,

Segawa et al.<sup>28</sup> and Cannan-Kuhl et al.<sup>29</sup> have demonstrated that CNP inhibits rat mesangial cell proliferation, consistent with antiproliferative properties of CNP in the vasculature<sup>30</sup>. Because abnormal hyperproliferation of mesangial cells is believed to be one of the pathophysiological mechanisms leading to chronic renal failure<sup>31</sup>, it is possible that the antiproliferative actions of CNP could play an important role in patients with progressive renal failure<sup>32</sup>.

## ARTERIAL STIFFNESS AND AGE

Arterial ageing is related to changes in the mechanical and structural properties of the vascular wall, which lead to loss of arterial elasticity and reduced distensibility<sup>33-35</sup>. Arterial stiffness is an important mechanism in the development of age-related renal function decline<sup>36</sup>. The age represents a non-modifiable factor that in healthy adults causes increased arterial stiffness and changes in chromosome replication with telomere shortening<sup>37</sup>. Aging is associated with poorer vascular endothelial function and increased mortality<sup>38-40</sup>. The renal microcirculation of elderly is more vulnerable to the damaging hemodynamic effects of arterial stiffness than in younger people. This could reflect an impaired blood pressure buffering capacity of the vascular wall, caused by arterial stiffening that occurs mainly with advancing age. In CKD, the most common arterial lesions are both occlusive, affecting the intima (atherosclerosis) and remodelling lesions, affecting the media (arteriosclerosis), resulting in an increased arterial stiffness and diameter<sup>41</sup>. Conflicting results have been published about the impact of arterial stiffness on CKD progression. Mitchell et al.<sup>42</sup> demonstrated that central arterial hemodynamic significantly changes from the age of > 60 years, as result of arterial stiffening and, thereby, contributes to increased blood pressure pulsatility. From the age of > 62 years, the correlation between PWV (as indicated as arterial stiffness) and annual change in eGFR becomes stronger<sup>36</sup>.

## ASSESSMENT OF RENAL FUNCTION IN THE ELDERLY

Creatinine is the endogenous marker widely used for estimation of renal function. The Cockcroft-Gault formula, which estimates  $\text{CrCl}$  without adjusting body surface area, and the modification of diet in renal disease (MDRD) formula, which estimates GFR adjusted to standard body of the eGFR<sup>43</sup> use the same variables as the MDRD equation but were developed using a different sample of patients. The inclusion of

age and gender as variables is to provide surrogacy for anticipated endogenous creatinine production rate, which inevitably declines with age due to loss of lean body mass<sup>12</sup>. Assessment of GFR by classical 24-h-clearance (using for example inulin or at least creatinine) or by plasma clearance (using e.g. iohexol) is rarely performed, although these are the gold standards. For practical reasons, GFR is often estimated from serum creatinine using certain formulas (e.g. Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI; Cockcroft-Gault, CG; Modification of Diet in Renal Disease, MDRD). Unfortunately, these formulas are not sufficiently validated for the elderly and are afflicted by great variance and uncertainty. One reason is the hyperbolic relationship of serum creatinine with GFR that limits sensitivity, especially when kidney function is still in the upper 50%. A second reason is the dependence of creatinine formation on muscular mass that changes with age and is affected by age-related modifications, like sarcopenia. To this regard, Giordano et al. reported that in older adults with type 2 diabetes, long-term effects of a moderate protein dietary (MPD) regimen are associated with a significant reduction of decline in renal function, proteinuria, low-grade inflammation, and oxidative stress without a change in fat-free mass<sup>44</sup>. A study from 1997 comparing GFR, of healthy people aged  $68 \pm 7$  years with a group of healthy people aged  $26 \pm 3$  years<sup>23</sup> showed that GFR of the elderly was 85% lower in respect to the value of the young group, but still in the physiological range. The newly developed Berlin Initiative Study (BIS) equation (BIS2: creatinine- and cystatin C-based) may provide more precise and accurate tools for estimating GFR in the elderly group. This equation yielded the smallest bias followed by the creatinine-based BIS1 (BIS1: creatinine-based) and Cockcroft-Gault equations. All other equations considerably overestimated GFR. The BIS equations confirmed a high prevalence of persons older than 70 years with a GFR less than 60 mL/min per  $1.73 \text{ m}^2$ . In Table I we illustrate the bias of existing equations using different statistical parameters. Apart from the BIS2 equation, all other equations had a much larger proportion of false-negatives (wrongly considered  $\geq 60$  mL/min per  $1.73 \text{ m}^2$ ) than false-positives (wrongly considered  $< 60$  mL/min per  $1.73 \text{ m}^2$ )<sup>45</sup>. Thus, there was a decline with age, without threatening homeostasis.

## THE RISK OF END STAGE RENAL DISEASE (ESRD) IN ELDERLY WITH CKD

Elderly patients have become prevalent also in nephrology clinics<sup>46</sup>. This epidemiological finding is critical for three reasons. First, nephrologists represent the

main reference of care for patients with overt non-dialysis CKD. Second, the number of elderly patients referred to a nephrologist has significantly grown in the past decade<sup>47</sup>. Third, worldwide patients followed in the nephrology setting are characterized by more advanced renal disease and higher burdens of CVD comorbidities<sup>48</sup>. It is also still unknown whether and how age influences the predictive role of other risk factors for ESRD and death. De Nicola et al.<sup>49</sup> recently reported the modifying effect of age on the competing risk of ESRD vs death and on the predictive role of the main risk factors in a cohort of patients with non-dialysis CKD under stable nephrology care. Frail patients undergoing haemodialysis had a 2.6 times higher risk of mortality and 1.4 times higher risk of hospitalization, independently by age, gender, comorbidity and disability, compared with no frail patients<sup>50</sup>. Frailty, measured by the original criteria of the frailty phenotype in a haemodialysis population, was found in all ages with an overall prevalence of 42%<sup>50</sup>, compared to the prevalence of 7% in a elderly community-dwelling population<sup>51</sup>.

## CKD AND PRE-CLINICAL FRAILTY

Experts have proposed various definitions of frailty<sup>52</sup>, all of them designed to identify a group of older adults vulnerable to mortality, morbidity, and functional decline in settings of acute stress-stemming from low physiologic reserve. Frailty can precede disability<sup>53</sup>. The Cardiovascular Health Study definition identifies a person as frail if meets three of the following criteria: weight loss, weakness, poor energy or exhaustion, slowness, and low physical activity. For participants identified as frail, the risk of falls and worsening mobility during a period of 3 years was 30% and 50% higher, respectively; the risk of worsening ADL disability and mortality was double that of non-frail participants<sup>51</sup>.

Frailty is currently considered as “primary” or “pre-clinical” when the state is not associated directly with a specific disease, or when there is no substantial disability. Accordingly, the presence of three or more of the five criteria is used to identify pre-clinical frailty (unintentional weight loss, exhaustion, low energy expenditure, slowness, and weakness)<sup>53</sup>. The prevalence of frailty overall among the Cardiovascular Health Study cohort was 7%, but when restricted to patients with CKD, the prevalence of frailty raised to 15%. However, presence of frailty during CKD was associated with about a twofold higher risk for mortality. There is a high prevalence of cognitive impairment among older adults with CKD<sup>54</sup>. A potential link between CKD and impaired levels of physical function and cognition may exist simply because CKD is a common disease state, more

**Table 1.** Bias, precision, and accuracy for eGFR equations in aged 70 y or older (from Schaeffner ES, 2012, mod.)<sup>20</sup>.

Equation	Mean bias*	SD of difference*	Median bias*	First quartile*	Third quartile*	P <sub>30</sub> %†	P <sub>15</sub> %†	Wrongly considered < 60 mL/min per 1.73 m <sup>2</sup> , n (5)	Wrongly considered < 60 mL/min per 1.73 m <sup>2</sup> , n (5)	Total misclassified n (%)	P value ‡
BIS1	0.11	9.20	0.80	-5.03	6.11	95.1	69.5	27 (17.9)	22 (16.4)	49 (17.2)	NA
Cockcroft-Gault adjusted for BSA	2.74	11.66	2.53	-4.06	9.21	87.4	59.3	29 (19.2)	36 (26.9)	65 (22.8)	0.006
MDRD study	11.21	11.38	11.29	3.85	17.68	70.9	39.3	3 (2.0)	63 (47.0)	66 (23.2)	0.035
CKD-EPI	8.94	10.12	9.69	2.45	15.49	77.9	43.5	4 (2.6)	54 (40.3)	58 (20.4)	0.22
BIS2	0.09	8.06	0.87	-4.40	4.98	96.1	78.9	18 (11.9)	15 (11.2)	33 (11.6)	NA
CysC2§	3.22	10.71	2.05	-3.23	8.61	89.1	63.9	15 (9.9)	28 (20.9)	43 (15.1)	0.041
CysC2§	9.32	9.84	9.22	3.46	14.42	81.4	47.0	4 (2.6)	54 (40.3)	58 (20.4)	0.001

likely to be found in older adults who are in ill-health and therefore also suffering from functional<sup>55</sup> and cognitive limitations. For example, CKD may simply be a marker for the frail phenotype – particularly because no prospective studies have still examined whether incidence of frailty is higher in older adults with CKD.

## CKD AND CLINICAL FRAILITY

Frailty is considered “secondary” or “clinical” when it is associated with known comorbidity and/or disability<sup>56</sup>. The characteristics of clinical frailty include not only comorbidity and disability, but also polypharmacy and related adverse drug reactions, hospitalization, health service utilization, age-associated sensory deficits and lack of social support<sup>57</sup>. This condition is associated with higher long-term mortality, both alone and in association with chronic diseases such as chronic heart failure<sup>58</sup>. To this regard it has been reported that the presence of frailty in diabetes subjects strongly influence long-term mortality. Accordingly studies reported long-term mortality was higher in elderly subjects with than in those without COPD<sup>59</sup>.

Other results indicate that mortality at the 12-year follow-up was similar in subjects with and without osteoarthritis (OA)<sup>59</sup>. Clinical frailty strongly influences mortality in subjects with OA. However, CKD may be a potential accelerant of decline in physical and cognitive functions through associated anaemia, mineral-bone disease, or inflammation. Anaemia commonly coexists with CKD, a comorbidity that may be particularly detrimental for older adults because its presence has been linked to adverse outcomes including falls, impaired physical function, and cognitive decline<sup>60</sup>. Cross-sectional analyses from the Women’s Health and Aging Study II<sup>61</sup>

also reported an association between anaemia and poorer scores on tests of executive function and selective attention performance. Disorders of mineral-bone metabolism leading to abnormal bone architecture and fracture may in part explain the relationship between CKD and low physical function. For example, the prevalence of hip fractures among persons with eGFR < 60 ml/min/1.73 m<sup>2</sup> was double that of the general population in NANHES Nutrition Survey III<sup>62</sup>. A complex interplay of hypocalcaemia, hyperphosphataemia, hyperparathyroidism, vitamin D deficiency (both 25-OH and 1,25-OH vitamin D), and metabolic acidosis has been implicated in these processes<sup>63</sup>. Thus, mineral-bone disease associated with CKD leads to increased risk for hip fracture, which in turn is associated with substantial physical disability<sup>64</sup> and could be one important mechanism for the observed indirect correlation between eGFR and physical function. The effect of age on the fate of CKD patients does not represent the only critical issue in contemporary geriatric nephrology research, and in clinical practice as well; attention, in fact, has been recently drawn to the gaps of knowledge on age-related differences in the mechanisms and pathways that contribute to progression to frailty, ESRD and mortality<sup>65</sup>. This information is essential to better delineate the risk profile, and preliminary to the identification of therapeutic goals, in elderly patients. De Nicola et al.<sup>49</sup> found that in the early stages of CKD, the presence of higher proteinuria significantly increased the risk of ESRD in older patients, suggesting that the kidney of elderly is more vulnerable to the ‘nephrotoxic’ effects of proteinuria due to the greater degree of renal fibrosis and ischemia. CKD has been recognized as an important predictor of adverse health outcomes, including increased risk for cardiovascular disease and mortality, and responsible of drugs toxicity<sup>66</sup>. Persons with CKD

also have reduced health-related quality of life, diminished cognitive function, and a high prevalence of such physical symptoms as fatigue, nausea, and anorexia<sup>67</sup>. The authors found that elderly with CKD were 3 times as likely to be frail as those with normal renal function, association that remained significant after multivariate adjustment for demographic characteristics and comorbidity, as well as such potential mediators as inflammation and subclinical atherosclerosis<sup>68</sup>. Inflammatory factors are associated with both CKD and frailty, and inflammation appeared to partially mediate the association between CKD and frailty<sup>69</sup>.

## CONCLUSIONS

Renal function is sufficiently preserved in elderly. Most probably, a minimum functional level to maintain homeostasis under “normal” environmental conditions is undercut only in very old people. Thus, renal aging is first of all characterized by a decreasing regulatory range and not insufficiency under regular conditions and behavioural flexibility. As the population of dialysis and pre-dialysis patients is growing, frailty will become an important issue for clinical care. Because frailty and CKD are associated with age, poor clinical outcomes, falls, disability, hospitalization and mortality, it is important to identify the subjects at high risk and needing a comprehensive care in order to improve outcome for this vulnerable population.

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## CLINICAL OBSERVATION

# Advanced carotid artery disease associated with recurring delirium followed by dementia

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**Background:** delirium and dementia have been defined as different entities in the literature. Knowledge of the relationship between delirium and dementia which are the major causes of cognitive impairment in the elderly is scanty. There has not been any convincing demonstration of altered cognitive function to chronic cerebral ischemia associated with asymptomatic carotid artery disease and remains a concept which is continuously being debated.

**Case presentation:** a 79-year-old man with severe asymptomatic carotid artery disease presented with acute delirium. This was followed by three other episodes over a period of 32 months. He was cognitively and functionally normal prior to the first episode and in between the episodes of delirium. Following the fourth episode he exhibited significant cognitive and functional deterioration consistent with dementia. CT scan had shown a small focal hypodense lesion in the right region following the first episode. A duplex scan of the carotid arteries had shown extensive disease of both common carotids and internal carotid arteries. It is surmised that the dementia that followed was the result of a chronic cerebral ischemia resulting from the bilateral carotid artery disease.

**Conclusions:** if the true role of occlusive carotid artery disease and progressive cognitive decline is acknowledged then early endarterectomy may forestall the disaster. However the optimal treatment choice remains unclear.

**Key words:** Carotid artery stenosis, Chronic cerebral ischemia, Delirium, Dementia, Carotid endarterectomy, Carotid artery stenting

## BACKGROUND

Knowledge of the relationship between delirium and dementia which are the major causes of cognitive impairment in the elderly is scanty. There is growing evidence that delirium occurs across various types of dementia (Alzheimer's diseases, vascular dementia, dementia with Lewy bodies and Parkinson's disease with dementia) and that they overlap, notably in dementia with Lewy bodies<sup>1</sup>. Studies relating to the association between carotid atherosclerosis and dementia are meagre<sup>2</sup>. It has also been documented that cognitive decline

often occur in patients with severe carotid stenosis without clinical evidence of stroke or TIA<sup>3,4</sup>. However, the mechanisms linking altered cognitive function and severe carotid artery disease without symptomatic cerebrovascular events remains less distinct and remains a concept which is continues to be debated. High grade carotid stenosis has been shown to be associated with reduced brain blood perfusion<sup>5</sup>. The likely mechanism of cognitive impairment with advanced carotid disease includes cerebral embolization and chronic hypoperfusion<sup>3,4</sup>.

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## CASE PRESENTATION

A 78-year-old right-handed man presented with acute confusion. He had had a flu-like illness one week prior to this. His wife who was the informant said that normally a talkative person he had become unusually quiet. He had been in good health and was not on any medication. There was no past history of strokes, TIAs, mental illness or chronic alcoholism and his cognitive state was normal. The vital signs were normal and general physical examination was unremarkable other than for bilateral carotid bruits. He was inattentive, easily distracted by external stimuli and was disorientated in all spheres person, place and time. His recent memory and immediate recall were impaired. There were no focal or lateralizing signs. Routine laboratory (haematological and biochemical) tests were normal. A computed tomography (CT) scan of the brain on day 2 revealed no abnormality. The electrocardiogram was normal. A Duplex scan of the carotid arteries revealed more than 80% stenosis of the right internal carotid artery and narrowing of the right common carotid artery. On the left side there was 60-80% stenosis of the internal carotid artery and tight stenosis of the left common carotid artery. The symptoms fluctuated day by day and on day 7 he began to improve and was discharged to his home on day 10. When seen a week later at the Outpatients his mental state was normal on the Mini-Mental State Examination (26/30)(MMSE). A repeat scan of the brain showed a small hypodense area in the right parietal region consistent with a cerebral infarction. In view of the extent of the disease surgical intervention was not offered to the patient. He was commenced on dipyridamole and aspirin. On subsequent follow-ups there was no evidence of cognitive deficits as measured by the MMSE.

The second admission to hospital was 13 months later with acute confusion and was discharged 16 days later. The CT scan showed no new changes. The laboratory investigations were normal including arterial blood gases and blood cultures. He remained well other than for numbness of the left arm which lasted for a day. Surgical intervention was offered but his wife and he declined.

When reviewed three months later his scores on the MMSE was normal and he was functioning normally. Seven months later he was re-admitted to hospital with acute confusion and remained in hospital for 27 days. The CT scan of the brain was normal but for the old hypodense area in the right parietal region. His MMSE score two weeks later was 26/30. Twelve months later he was admitted to hospital for the fourth time and was extremely confused and remained so during the entire stay in hospital for 45 days. He was now dependant for basic self-care and performed poorly on formal memory

tests. His spouse too had noted the marked deterioration. The findings were consistent with a dementing illness and he had to be institutionalised.

## DISCUSSION

Our patient presented with four documented episodes of acute delirium (syn: acute confusional state, acute organic syndrome), duration of which varied from 10 to 45 days over a period of 32 months. In between the episodes, psychometric testing revealed no significant cognitive or memory deficits nor was there any functional impairment. He had severe bilateral occlusive carotid artery disease involving both the internal as well as the common carotid arteries bilaterally. A doubtful TIA occurred during the second episode. The CT scan had shown a small hypodense area in the parietal region of the right cerebral hemisphere with the first episode.

Most patients with acute delirium suffer from reversible toxic, metabolic or infectious disorder and the confusion is caused by a physiological disturbance rather than by structural brain damage. The pathological mechanisms of acute delirium remain unclear and the current view is that they are caused by the disruption of the neurotransmitters, inflammation and acute stress which may all contribute to the disorder. The final common pathway of acute delirium is regarded as a cholinergic deficit combined with dopaminergic hyperactivity<sup>6</sup>. Interaction between the neurotransmitters such as serotonin or noradrenaline with the cholinergic and dopaminergic systems may play a role<sup>6</sup>. Physical stressful events giving rise to increased cortical secretion of cytokines may have a role and some cytokines can influence the activity of the neurotransmitters and these mechanisms can interact<sup>7</sup>. According to MacLulich et al.<sup>8</sup> there are two categories of triggers, namely "direct brain insults" and "aberrant stress responses".

Acute delirium has been reported following focal lesions in the right hemisphere in the territories of the middle cerebral and posterior cerebral arteries and could involve either the cortex or subcortical regions. In both medical and psychiatric literature acute delirium and dementia have been considered as two different disorders. Clinical characteristics and risk factors of acute delirium are different in dementia and non-dementia elderly patients<sup>9</sup>. Acute delirium may be more persistent than generally believed<sup>10</sup> as in our patient. It is generally assumed that the symptoms resolve in 1-2 weeks after appropriate diagnosis and treatment. Distinguishing this from dementia can be difficult. Knowledge of the relationship between acute delirium and dementia, which are the major causes of cognitive impairment in the elderly, is scanty.

In most instances the MMSE has been used as in our patient to stratify the severity of cognitive impairment and dementia. It is requisite that the clinician to look for causes in dementia more so potentially reversible causes such as thyroid disorders, B12 deficiency, normal pressure hydrocephalus among others although the actual reversibility is low. Majority of the patients screened with dementia do not require extensive tests and the testing should be guided by the history and physical examination. Our patient's history, presentation and train of events did not suggest any potentially reversible cause.

It is well documented that occlusion of the carotid arteries could cause dementia either by multifocal infarction or less commonly by haemodynamic mechanism<sup>11</sup> although perfusion insufficiency had been difficult to document as a cause of dementia. It is interesting to speculate that the recurrent episodes of delirium in our patient may be the result of micro-emboli from the diseased carotid arteries resulting in small cerebral infarcts. Trans Doppler ultrasonography has demonstrated high intensity transient signals in patients with symptomatic carotid stenosis and they may present in the territories of the arteries with TIA attacks rather than cerebral infarction<sup>12</sup>. Alternately prolonged hypoxia due to slow flow secondary to bilateral carotid stenosis could result in neuronal death resulting in ischaemic dementia/vascular dementia. The term vascular cognitive impairment is now the preferred term for vascular dementia for it embraces the complex interactions between vascular risk factors, cerebrovascular disease etiology and cellular changes with the brain and cognition<sup>13</sup>. It has been reported that the greatest risk of dementia are in individuals in the upper quintile of carotid intima medial thickness or bilateral carotid plaques<sup>1</sup>.

Although cognitive impairment increases with age some elderly have normal cognitive function whereas others exhibit marked deterioration. However the explanation of the relationship between carotid artery stenosis and cognitive functioning remains unclear and the effect of carotid interventions on cognitive function is not fully understood<sup>4</sup>. Symptomatic and asymptomatic carotid stenosis may be an independent factor for cognitive impairment<sup>3,4</sup>. It is well known that there is substantial overlap between cerebrovascular disease and Alzheimer's disease and hence coexisting Alzheimer's pathology cannot be ruled out.

In asymptomatic patients there is no evidence to support prophylactic endarterectomy or stenting to prevent cognitive decline<sup>4</sup>. Two of the operated patients studied by Gibbs et al.<sup>14</sup> did not show any cognitive improvement but according to Tatemichi et al.<sup>11</sup> delayed neuronal attrition could continue in spite of correcting the cerebral blood flow. In a subgroup of patients in

their 80s the mortality rate was 10.8% following CAS and was attributed to severity of the lesion, calcification, aortic arch elongation, tortuosity and great vessel origin stenosis together with perioperative stroke/myocardial infarction<sup>15</sup>. Age is a risk factor for carotid endarterectomy (CEA) especially in those 80 years and over. Moreover our patient had extensive disease involving the common carotids as well, carrying a high risk. Furthermore, it is generally believed that there are no convincing grounds at present to support the prophylactic carotid endarterectomy or carotid stenting with the intention of preventing cognitive decline in otherwise asymptomatic patients<sup>4</sup> thus posing a problem as to the advisability of any surgical intervention in our patient.

There are some limitations to this study which warrant comment. Firstly imaging with CT perfusion and MRI would have been better at evaluating vascular damage rather than the CT scan. Secondly, the MMSE was used to estimate cognitive function and no other psychometric testing was done. MMSE scores range from 0 to 30 with a score of 24 and above taken as normal function. Although MMSE does not differentiate among specific cognitive functions it is broad and global. Nevertheless we believe this case adds to the concept that severe carotid disease predisposes to delirium and the eventual development of dementia.

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## CLINICAL OBSERVATION

## Rivaroxaban-induced hemorrhage – Acquired hemophilia as a rare cause

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Hemorrhage is a common problem associated with anticoagulation. After introduction of new oral anticoagulants (NOAC) a drug monitoring is no longer necessary. At advanced age, hemorrhage may become a serious side effect of NOAC, especially when other age-associated alterations such as impaired renal function occur. It has been reported that the frequency of fatal or major bleeding is less common under treatment with NOAC compared to Vitamin K antagonists <sup>1</sup>. Here, we report a 88 years old woman with an abdominal hematoma without any accident. The cause of hemorrhage in this case is not due to a new started treatment under NOAC but newly diagnosed acquired hemophilia. Acquired hemophilia A is a rare autoimmune disorder caused by an autoantibody (inhibitor) to factor VIII (FVIII) that interferes with its coagulation function and predisposes to severe, potentially life-threatening hemorrhage <sup>2</sup>. If acquired hemophilia is not detected, the combination with NOAC increases the risk for major potentially life-threatening bleeding.

**Key words:** Rivaroxaban, Acquired hemophilia, Hemorrhage, Bleeding

### INTRODUCTION

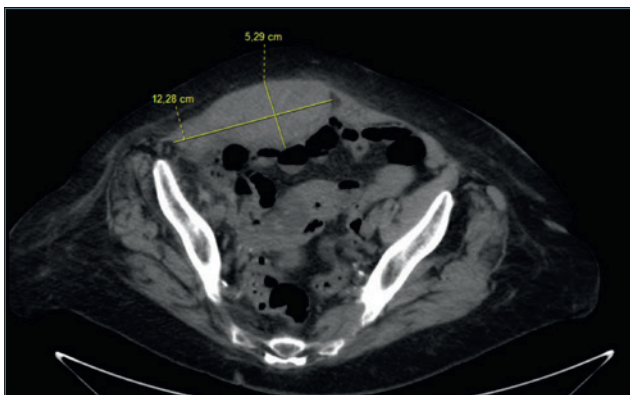
NOACs are getting more and more popular in indications where long-term anticoagulation is necessary. The reasons are their relatively easy use and less common bleeding complications under NOACs in comparison to phenprocoumon/warfarin <sup>1,2</sup>. Therefore, after diagnosis of e.g. atrial fibrillation a new therapy under NOACs will be started and regularly check ups of coagulation are not necessary. Minor bleedings under therapy with NOACs are common and underdiagnosed. Therefore, other diseases causing an increased risk of bleeding <sup>3,4</sup> are not well diagnosed, because treatment under NOACs is expected to be the cause. If other coagulopathies are not being detected treatment with NOACs may cause life-threatening major bleed <sup>5</sup>. In this case report, hemophilia A could be identified for a major risk of bleeding. In most cases the reason for hemophilia is idiopathic <sup>6</sup>. Under treatment along the guidelines <sup>7,8</sup> the hematoma declined.

### CASE PRESENTATION

A 88 years old woman was admitted to our surgery ward with new onset of pain in the lower abdomen. Due to previously diagnosed atrial fibrillation, the cardiologist had put her on NOAC therapy with Rivaroxaban. A recent fall was denied. On admission, she suffered from an upper respiratory tract infection with a slight cough for three days (Geriatric Assessment see table I) Palpation of the abdomen revealed a painful mass in the right abdominal wall. The laboratory tests showed a hemoglobin of 6.4 mg/dl, altered coagulation parameters (INR 1.2, PTT 173 seconds), the signs of impaired renal function (creatinine 1.5 mg/dl, GFR 34.6 ml/min), and slightly elevated infection parameters (CRP 1.43 mg/dl). The remaining laboratory tests were normal. On CT-scan a 12 x 8.5 x 5 cm hematoma was detected in the abdominal wall (Fig. 1).

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**Figure 1.** Hematoma in the right abdominal wall due to acquired hemophilia A and NOAC therapy.

The surgeons recommended a conservative management. The bleeding was interpreted as the result of the newly started NOAC therapy in combination with frequent coughing due to the respiratory tract infection. Therapy with Rivaroxaban was discontinued, and the patient was transferred to our geriatric ward to adjust pain management and to start mobilisation.

During therapy in the geriatric department laboratory findings revealed a persistently increased PTT (> 100 sec.), although the therapy with anticoagulants had been discontinued. The INR has been normalized in the meantime. Extended blood coagulation analysis revealed antibodies against FVIII with significantly decreased FVIII blood levels (< 1%, range of normal values 60-130%) as indication for the diagnosis of an acquired hemophilia A. We further investigated the patient's history which revealed several minor skin hematomas in the past. The patient's opinion was that treatment with acetyl-salicylic acid (ASA) has been the reason for the previous hematomas.

To eliminate the antibodies against FVIII immunosuppressive treatment with prednisolone in combination with cyclophosphamide was initiated according to the current recommendations for the treatment of acquired hemophilia<sup>8</sup>. As the patient's renal function was impaired cyclophosphamide treatment required close monitoring of renal function tests. After two weeks, renal function

decreased further. Therefore, cyclophosphamide treatment was discontinued and steroid monotherapy was continued. Within 6 weeks of therapy, FVIII blood levels returned to normal levels. A new bleeding did not occur and the patient could be discharged home free of symptoms. A further anticoagulation has been started by her general practitioner.

## DISCUSSION

To our knowledge this is the first case report in the literature with hemorrhage caused by acquired hemophilia in combination with NOAC therapy. Acquired hemophilia A is often diagnosed rather late. Although acquired hemophilia rarely occurs in the older age population, the incidence is 1:100,000. In our case the diagnosis was masked by therapies with ASA and NOAC. Persistent prolongation of the PTT despite discontinuation of NOAC therapy led to the diagnosis of FVIII antibodies. Isolated prolongation of the PTT with normal INR values can also be seen in patients with antiphospholipid antibody syndrome, medications such as heparin, or antibodies against factor IX and XII, and deficiency of factor VIII<sup>3,4</sup>.

Acquired hemophilia A is most frequently associated with autoimmune diseases, solid tumors, lymphoproliferative diseases, pregnancy, and drug reactions. However, about 50% are idiopathic<sup>6</sup>. In emergency cases also treatment with recombinant activated FVIII is possible<sup>7</sup>. In our case FVIII substitution was not necessary because of a non life-threatening situation. It should be pointed out that even major bleedings, e.g. with cerebral hemorrhage, may occur spontaneously or due to trauma as cause of acquired hemophilia<sup>5</sup>. The overall mortality of acquired hemophilia-induced hemorrhage has been reported to be 31-33%<sup>9,10</sup>.

## CONCLUSIONS

Analyzing coagulation blood parameters before starting therapy with NOAC is necessary to exclude hemophilia or other coagulation pathologies.

Assessment	Result
Time up and go	Not possible due to pain
Geriatric depression scale	1 (normal)
Clock test	2 (light restrictions)
Mini mental state status	30 (normal)
Time up and go (14 <sup>th</sup> day)	20 seconds
Social assessment	Lives alone, until admission independent, use of walking frame

### CONFLICTS OF INTEREST STATEMENT

Authors disclose that they have no potential conflicts of interest. Authors also ensure that they have no potential financial and nonfinancial conflicts of interest.

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Journal of Gerontology and Geriatrics

## Special Issue Elder cardiac diseases: new hypothesis for old topics

Guest Editor  
Graziamaria Corbi

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## REVIEW

## Cardiac fibrosis in heart failure

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The prevalence of heart failure is rising with poor prognosis and health costs. Cardiac remodeling is a cardinal process mediating the progression to heart failure, and cardiac fibroblasts play a critical role in the regulation of left ventricular remodeling mainly through the excessive extracellular matrix protein deposition and their differentiation to a myofibroblast phenotype with excessive proliferative and migratory properties. All these characteristics are known also as cardiac fibrosis. This process is crucial for the structural integrity of myocardial tissue. After myocardial infarction, are activated two important type of cardiac fibrosis: reparative and reactive cardiac fibrosis. Both of them are mediated by a huge number of inflammatory and hormonal mediators. In this review we will focus on the role of three important systems involved in cardiac fibrosis and described as the great contributors in heart failure: inflammatory, RAA and beta-adrenergic system. The deeper understanding of these great contributors is of interest in the development of new therapeutic strategies toward cardiac fibrosis and heart failure.

**Key words:** Cardiac fibrosis, Cardiac fibroblasts, Cytokines, RAA system, Beta-adrenergic receptors

### INTRODUCTION

The prevalence of Heart Failure (HF) is approximately 1-2% in adult population, rising to more than 10% of elderly over 70 years of age<sup>1,2</sup>. Epidemiological studies show high incidence and prevalence of HF among elderly. The prognosis of HF in this population is poor with rising cases of hospitalization, comorbidity and health costs<sup>3-5</sup>. Cardiac remodeling is a cardinal process mediating the progression to HF. Cardiac fibroblasts (CFs) play a critical role in the regulation of left ventricular remodeling following myocardial infarction<sup>6,7</sup>, mainly through the excessive extracellular matrix (ECM) protein deposition and their differentiation to a myofibroblast phenotype<sup>8</sup> with excessive proliferative and migratory properties. This process known as cardiac fibrosis is crucial for the structural integrity of the myocardial tissue. However in the advanced phases, cardiac fibrosis leads to ventricular stiffness, altered chamber compliance

and contractile dysfunction, in addition cardiac fibrosis impairs the electrical coupling of cardiomyocytes increasing the risk of developing potential arrhythmias and fatal events<sup>9-11</sup>.

Heart tissue is constituted by cardiomyocytes, CFs, endothelial and neuronal cells. Initially it was thought that CFs are the most prevalent cell type accounting for up to 70% of cells<sup>12</sup>, recent studies report that the CFs population is not more than 20% of whole cell population in murine cardiac tissue<sup>13</sup>. Although the numerous CFs markers reported in the present literature, like vimentin, alpha-smooth muscle actin, collagen 1 alpha1, periostin, discoidin domain receptor-2, fibroblast specific protein-1, thymus cell antigen-1, the transcription factor 21, platelet derived growth factor receptor-alpha<sup>14</sup>, a robust specific molecular biomarker of both resident and activated CFs is still lacking. The absence of a universal marker for the detection of CFs can be the explanation to the different interpretation of results on CFs cell number reported till now.

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CFs represent a structural scaffold for the myocardial tissue, responsible for the cardiac ECM homeostasis, distribution of mechanical forces and electric conduction in cardiac tissue. CFs seem to arise mainly from the embryonic epicardium, although other sources have been evaluated in different studies. Linkage tracking studies suggest that vascular endothelial cells contribute to the CFs population even if this contribution is not predominant<sup>15,16</sup>.

Bone marrow-derived progenitor cells are considered an important source of CFs within the cardiac injury. Moreover it is believed that they account for up to 60% of CFs in the post-ischemic injury<sup>17</sup>. Under investigations are also other type of cells like fibrocytes and perivascular cells.

After myocardial infarction injury and cardiomyocytes apoptosis, there is an up-regulation of the inflammatory, paracrine-autocrine profibrotic factors in CFs leading to the increased proliferation and migration process. During this phase CFs differentiate to myofibroblasts, which are not present in the healthy cardiac tissue and represent characteristics of both CFs and smooth muscle cells. They are characterized by migratory, proliferation and contractile properties, thanks to alpha smooth muscle actin, a filament protein<sup>18</sup>. This process is defined as replacement or reparative fibrosis, which is compound by the inflammatory, proliferative and maturation response. Myocardial injury activates the secretion of IL-1, IL-6, TNF-alpha, and beta, CXC chemokines which recruit macrophages and neutrophils in the infarcted area which clear the dead cardiomyocytes cells and trigger the migration of CFs within myocardial injury. CFs produce collagen type I and III, and enhance deposition of collagen in cardiac ECM. After the pro-inflammatory phase the involved inflammatory cells undergo apoptosis, and CFs cells begin the migratory and proliferative phase differentiating toward a myofibroblasts phenotype. Furthermore myofibroblasts produce large amounts of collagen contributing to the scar maturation. At the end of this phase myofibroblasts undergo apoptosis, however a portion of myofibroblasts survive and lead to cardiac remodelling. The activated myofibroblasts expand their collagen deposition, proliferative and migratory properties in the non-infarcted areas of myocardium. This process is called the reactive fibrosis. The exact explanation of this mechanism is not clarified yet. However the activation of myofibroblasts and their profibrotic factors within the infarcted area, might transverse to the remote areas and can lead to cardiac fibrosis activation<sup>19</sup>. The pathophysiological importance of this process is developing further studies in the understanding of profibrotic mechanisms and new potential therapies targeting cardiac fibrosis<sup>20-22</sup>.

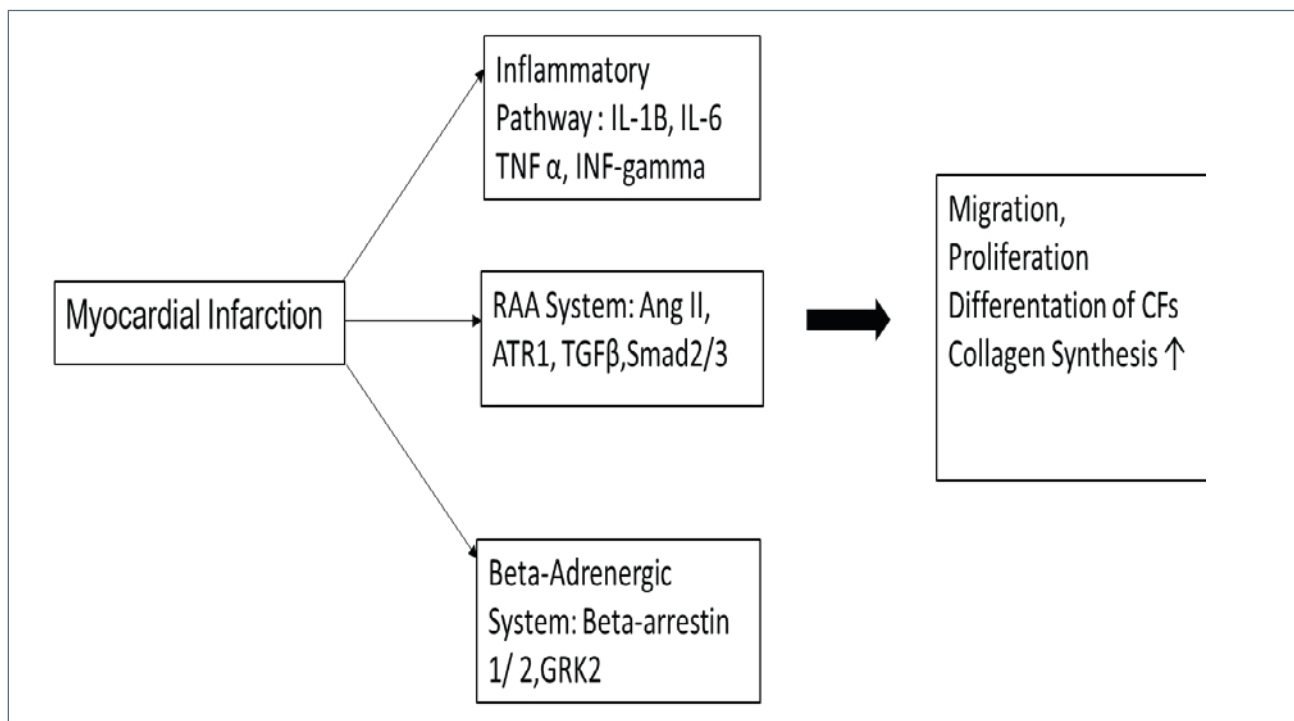
In this review we discuss the role of inflammatory, renin-angiotensin-aldosterone (RAA) axis, and beta-adrenergic system in the development of cardiac fibrosis in heart failure (Fig. 1).

## METHODOLOGY

For the purposes of this review we identified original research articles and other reviews published in English and available in PUBMED from 1997-2016.

## INFLAMMATORY PATHWAY

Inflammatory pathway is a crucial mediator of cardiac fibrosis. Initially its activity is important during the process of reparative fibrosis. The most studied inflammatory factors implicated in the mechanisms of cardiac fibrosis in the present literature are: tumor necrosis alpha, IL-1B, IL-6, IL-18, chemokines like CC, CXC subtype and INF-gamma<sup>23</sup>. Their profibrotic effect is complex and it is quite difficult to define it as a harmful or beneficial effect. After myocardial injury is observed an increase in cytokine expression by CFs like: IL-1B and IL-6. They induce the protein metabolism turnover in cardiac ECM and promote CFs migration and proliferation<sup>24,25</sup>. This inflammatory response seems to include the MAPK and NF-KB pathway. NF-KB is a transcriptional effector of inflammation that as a consequence of its nuclear translocation triggers cytokines, chemokines and adhesion molecules genes. NF-KB is composed of 5 different subunits, which induce different transcriptional response. For example p50 and p52 subunit repress genes transcription, whereas p65, c-Rel and Rel-B contributes to the activation of genes transcription. Importantly, inflammatory components exhibit a paracrine and autocrine response to myocardial tissue cells that express cytokine receptors and are localized in the remote areas. Furthermore, chemokines are responsible for the recruitment of leucocyte population within the infarcted area contributing this way to the basis of reparative cardiac fibrosis. IL-1 receptor type I deficient mice after surgical induced myocardial infarction and reperfusion techniques, present with better adverse left ventricular remodeling signs like: left ventricular chamber size and systolic function. However in this model, IL-1 receptor type I deficiency did not affect infarct size, suggesting that IL-1 modifies the synthesis of pro-fibrotic elements but does not influence cardiomyocyte injury<sup>26</sup>. Also, TNF $\alpha$  KO mice after ischemia/reperfusion surgery showed amelioration of LVEF, minor arrhythmia events and smaller infarct size. Similar results were demonstrated even after intra-coronary



**Figure 1.** Schematic presentation of RAA system, beta-adrenergic system and inflammatory pathway influence on cardiac fibroblasts (CFs).

TNF $\alpha$  antibody use<sup>27</sup>. From the other side, mice deficient for TNF receptors report contrasting results in left ventricular remodeling following myocardial infarction. It seems that type 1 receptor induces the inflammatory response within the infarcted areas inducing left ventricular remodeling, whereas type-2 receptor ameliorates it. Also the circulating levels of IL-1B seem to induce the leukocyte proliferation within infarcted area and are also implicated in the proliferation of bone marrow stem cells after myocardial injury. These findings suggest a possible beneficial role of the inflammatory agents in myocardial tissue repair<sup>28,29</sup>.

Interferon-gamma has an important role in the development of cardiac fibrosis. Mice, knock out for interferon-gamma, reduce the expression of alpha-smooth muscle actin indicating in this way the reduction of CFs differentiation to a myofibroblast phenotype. Importantly, null mice reduce cardiac fibrosis<sup>30,31</sup>.

Recently in a mouse model of pressure overload, was observed that cytokine-like1 mRNA expression was highly elevated. Furthermore, in cytokine-like 1 KO mice, cardiac fibrosis together with other profibrotic proteins as TNF- $\alpha$ , TGF- $\beta$ , and collagen 1 were significantly attenuated. In this study was also reported that this protein is able to induce the trans-differentiation of CFs in myofibroblast phenotype. From the data reported in this study it seems that cytokine-like 1 activity is not

related to C-C chemokine receptor 2 and further research is needed to identify its receptor<sup>32</sup>.

The role of inflammatory pathway in cardiac remodeling adds new perspectives in the therapeutic strategies in heart failure. However the modulation of inflammatory response in myocardial infarction, and the time point where potential modulators of inflammatory components can act by enhancing reparative processes without aggravating the healing process is still challenging.

## RENIN-ANGIOTENSIN-ALDOSTERON SYSTEM (RAA)

Inhibitors of RAA signaling, angiotensin receptor blockers and angiotensin converting enzyme inhibitors have a well-established role in the treatment of HF and in the attenuation of cardiac remodeling. This class of drugs have demonstrated significant efficacy in reducing cardiac fibrosis in either animal or human models of heart failure<sup>33,34</sup>.

After myocardial injury, angiotensin II levels are dramatically increased and the angiotensin II type I receptor (AT1R) expressed in CFs, mediates their proliferation, migration and ECM protein deposition<sup>32</sup>. From one side it is the release of angiotensin II from stressed cardiomyocytes that activates the AT1R, but also as it has

**Table I.** The main factors implicated in the development of cardiac fibrosis. The table summarizes the main factors implicated in the development of cardiac fibrosis, their main mechanism, experimental models where antagonist of these factors were applied and their main results in cardiac remodeling.

Factor	Mechanism	Application	Cardiac remodeling effects	References
IL-1	MAPK and NF $\kappa$ B activation	IL1-R I <sup>-/-</sup> mouse, Ischemia/reperfusion model	LVEDD ↓, LVEDV ↓, FS ↓, collagen expression ↓ Infarct size: no changes	Bujak M et al. <sup>25</sup>
TNF $\alpha$	Proinflammatory cytokine cascade: IL1, IL 6, NF $\kappa$ B activation	TNF $\alpha$ KO mouse, TNF $\alpha$ antibody Ischemia/reperfusion model	Peak LVSP ↑, dP/Dt max ↑, infarct size: ↓, arrhythmia ↓	Maekawa N et al. <sup>26</sup>
INF gamma	MAPK kinase, PKC, jak/stat, mda-9	INF gamma KO mouse Ischemic model	Cardiac Fibrosis ↓, $\alpha$ -SMA ↓	Levick SP et al. <sup>30</sup> , Marko L et al. <sup>32</sup> , Han YL et al. <sup>29</sup>
TGF $\beta$	Activation of ATR1, ERK1/2, Smad 2/3,4.	Oral TGF $\beta$ 1 receptor antagonist, Rat ischemic model	LVEDD ↓, LVESD ↓, FS ↓, LVEF ↑	Tan SM et al. <sup>40</sup>
Angiotensin	RAAS, TGF $\beta$ activation	ACE-inhibitors, Sartans Human and animal models of HFref or HFpEF	Cardiac Fibrosis ↓ IVST ↓, Dec time ↑, LVEF ↑, Collagen ↓	Diez J et al. <sup>33</sup> , Pfeiffer JM et al. <sup>34</sup> , Villareal FJ et al. <sup>35</sup> , Von Lueder TJ et al. <sup>42</sup>
Beta-arrestin 1, 2	Beta-adrenergic System, G-protein	In vitro Beta-arrestin knock down, CFs isolated from human HF samples	Proliferation ↓, Migration ↓, $\alpha$ SMA ↓, Collagen ↓	Li J et al. <sup>54</sup>
GRK2	Beta-adrenergic System, G-protein	Barkct inhibitory peptide, rat model of HF Fibroblasts specific GRK2 KO mouse HF model	Cardiac Fibrosis ↓ Collagen ↓ Infarct size ↓ LVEF ↑ TNF $\alpha$ ↓	Raake et al. <sup>56</sup> Rengo G. et al. <sup>57</sup> Woodall Mc et al. <sup>58</sup>

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; FS: fractional shortening; IVST: intra ventricular septal thickness; HFpEF: heart failure with preserved ejection fraction; HFref: heart failure with reduced ejection fraction.

been observed the mechanical stress due to hemodynamic impairment itself directly stimulates the AT1R in CFs <sup>35 36</sup>.

Indeed, candesartan demonstrated to have antifibrotic role. It is reasonable to think that the reduction of pressure overload reduces the mechanical stretch and as a consequence the profibrotic RAA axis. However, the exact mechanism of this class of drugs on CFs behavior has not been clarified and it is a field of interest <sup>37 38</sup>. From the other hand, it has been reported that losartan reduces cardiac fibrosis blocking the AT1RTGF-beta induced phosphorylation of ERK1/2. As a matter of fact, the activation of AT1R induces the expression of TGF-beta1, which has been reported as the most important profibrotic mediator.

TGF-beta1 binds to its activin receptor-like kinase (ALK 5), induces the phosphorylation of Smad2/3, which binds to Smad 4 and translocate to nucleus. As result, many profibrotic genes are activated. In addition

the activation of TGF-beta II receptor, the activation of TAK1 kinase and p38 protein showed to have an important role in collagen synthesis, cardiac hypertrophy and cardiac fibrosis <sup>39-41</sup>.

Recently a new drug class, angiotensin receptor neprilysin inhibitors have been developed. In an experimental model of myocardial infarction was observed that neprilysin inhibitor component of LCZ696 did not reduce cardiac fibrosis but together with valsartan showed a synergic effect in the reduction of perivascular and interstitial cardiac fibrosis <sup>42</sup>.

Interestingly a recent in vivo and in vitro study revealed that metformin potentiated the inhibitory effects of spironolactone in cardiac fibrosis without effecting systolic blood pressure, restored AMPK activation, and inhibited the migration and proliferation of CFs <sup>43</sup>.

Another component of RAA pro-fibrotic signalling seems to be also prorenin receptor. In this case the activation of this receptor induces the activation of angiotensin II,

intracellular second messengers and finally the activation of pro-fibrotic genes. Then there is an increased expression of collagen fibronectin-1, plasminogen and I activator inhibitor-1<sup>44</sup>. However further studies are necessary to establish the role of RAA axis not only on the overall cardiac fibrosis but also on CFs activation and their phenotypic differentiation. Only in this way it would be possible to explore a more direct therapeutic targeting on CFs activation.

## BETA-ADRENERGIC SIGNALING

The alteration of beta-adrenergic signaling in HF is a central problem associated with important clinical and prognostic implications<sup>45</sup>. The chronic overstimulation of BARs by catecholamines induces their downregulation/internalization. This mechanism is well described, and of great importance is the role of G-protein coupled receptor kinase (GRK2). The agonist-bound state of BARs induces the dissociation of G-protein into beta-gamma and alpha subunit, which triggers the activation of c-AMP and PKA. Consequently GRK2 changes its localization from intracellular to transmembranic, phosphorylating the BARs, which become the target for binding of B-Arrestin proteins that prevent BARs further coupling to G-protein. The final result is the internalization of BARs, their decreased density and desensitization<sup>46-48</sup>. Anyway in cardiomyocytes it has been reported that is present in particular B1AR down-regulation and the HF impaired adrenergic responsiveness is related to GRK2 and Gi up regulation<sup>49-52</sup>. Differently, it has been reported that the predominant B-AR subtype expressed in CFs is the B2AR. Indeed CFs isolated from human atrial tissue expressed only B2AR subtype. It has been showed that a chronic stimulation with isoproterenol in human CFs culture induced their proliferation, migration and collagen synthesis. From the other side the acute stimulation of these receptors increased the levels of c-AMP and reported modulation of either proliferation or migration in *in vitro* CFs culture. In these experiments was noticed a significant reduction of proliferation, migration and collagen synthesis<sup>53-55</sup>.

Beta-arrestins are important signaling molecules involved in BARs desensitization. Beta-arrestin 1 and 2 are significantly up-regulated in CFs isolated from human HF cardiac samples and their knock down led to inhibition of collagen synthesis<sup>56</sup>.

Furthermore, in human failing CFs is reported an up-regulation of GRK2 and un-coupling of BARs signaling. The knock down of GRK2 restored the B-ARs stimulated inhibition of collagen synthesis and reduced the proliferative properties of failing CFs<sup>15</sup>. Indeed the inhibition of GRK2 by using BARKct peptide in animal models

of HF has demonstrated to reduce cardiac fibrosis and to attenuate left ventricular remodeling<sup>57-60</sup>. Recently, fibroblasts-specific GRK2 knock out mice after myocardial ischemia/reperfusion injury showed decreased infarct size, increased LVEF, and decreased infiltration of neutrophils to injured area together with reduction of TNF- $\alpha$  expression<sup>61</sup>.

## OTHER PROMISING MOLECULAR SIGNALING: DAMPS

Damaged myocardial cells and ECM release substances with danger signal properties recently defined as Danger Associated Molecular Patterns (DAMPs). DAMPs include heat shock proteins, S100 protein, HMGB1 protein, hyaluronate fragments, fibronectin, Tenascin C, mitochondrial DNA, IL-1 alfa and advanced glycation end product. Despite the main effector of these proteins are white blood cells, they are able to modulate the function of cardiomyocytes, endothelial cells and CFs. DAMPs activate different receptors like TLR, NLR, IL-1R and RAGE. These receptors even if not well defined are expressed in CFs and it seems that their activation have a pro-fibrotic effect. Recent emerging studies report that CFs are sensitive to ECM protein changes and are a significant sensor of DAMPs contributing in this way to the pathogenesis of cardiac fibrosis. From one side DAMPs-CFs interaction would trigger the proinflammatory pathway via the NF $\kappa$ B, p38 and JNK activation, resulting in ECM degradation, myofibroblasts differentiation. From the other side ERK, AKT, PKC- $\epsilon$  pathway would be induced by CFs proliferation, migration and ECM synthesis. However, little is known about the direct CFs-DAMPs interaction and this could be of great interest for further studies<sup>62</sup>.

## CONCLUSIONS

Cardiac fibrosis is a cardinal process mediating the progression to heart failure. A better understanding of CFs behavior after a myocardial injury, the physiological and pathophysiological pathways of natural reparative processes, the implication of inflammatory response, RAA and Beta-Adrenergic system would be of great interest in the therapeutic interventional strategies targeting cardiac fibrosis as the heart of left ventricular remodeling.

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## Relationship between thyroid dysfunction and heart failure in older people

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Heart failure (HF) is one of the most common chronic diseases, affecting around 8% of older people, with an incidence rate of 10 per 1000 person-years. Besides ageing and classical cardiovascular risk factors, it is well recognized that HF may be worsened by endocrine alterations. The prevalence of thyroid dysfunction, similarly to HF, increases with increasing age and, 5-15% of the entire older population, especially women, suffer from overt or subclinical thyroid dysfunction. Thyroid and heart share a common embryologic origin and an intimate and complex functional relationship and, cardiovascular effects are the most prominent features of thyroid dysfunction. Not only alterations of thyroid hormone synthesis and release are risk factors for cardiac disease, but a mutual relationship has been documented and dysregulation of thyroid hormones represents also a marker for chronic heart disease. Thus, even mild thyroid dysfunction (either in excess or defect) may lead to the development of HF and may increase the risk of cardiovascular events. Consequently, thyroid dysfunction should be ruled out not only in older HF patients with no other identifiable causes but also in those with known cardiovascular risk factors. Nonetheless, the lack of randomized clinical trials leaves us with several unresolved key issues as also stated in the latest guidelines for the treatment of thyroid dysfunction, .key issues regarding specific criteria and goals of treatment, as also stated. Future large randomized intervention studies, balancing the risk and benefits of thyroid therapy according to the degree of serum TSH and TH alteration, are clearly warranted.

**Key words:** Heart failure, Hypothyroidism, Hyperthyroidism, Thyroid hormone, Thyrotropin, Elderly, Atrial fibrillation

### INTRODUCTION

In western countries, epidemiologic data show a continuous shift towards older ages of the demographic distribution. Thus, it has been observed a huge increase of the prevalence of chronic diseases and the need for chronic and acute care services. In this regard, heart failure (HF) is one of the most common chronic diseases, affecting around 8% of people older than 75 years with an incidence rate of 10 per 1000 person-year<sup>1,2</sup>. The five-year mortality rate of patients with HF is around 45-60%, with a high risk of hospitalization for acute decompensated HF. Several risk factors concur for the

development and progression of HF, the most important being represented by coronary heart diseases followed by elevated systolic blood pressure, structural cardiac alteration (valvulopathy), myocardopathy, arrhythmia etc.<sup>3,4</sup>. In addition, even if less frequently, HF may be caused by endocrine alterations<sup>5,6</sup> among which thyroid hormone (TH) excess, as observed in overt hyperthyroidism, is the most undeniable<sup>7</sup>. Given the tight link, at biomolecular level, among cardiac function, endothelial function, intermediate metabolism and thyroid status, even slight serum TH changes (either in excess or defect) have been associated to clinical conditions that may lead to the development of HF, cardiac structural changes, arrhythmia, systemic hypertension (either

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systolic or diastolic) as well as an early atherosclerotic process<sup>7-15</sup>. The effects of the ageing process on heart and vasculature make older people more susceptible to TH variations and consequently more prone to develop cardiovascular alterations, including HF, even in presence of mild thyroid dysfunction<sup>8,9</sup>.

The prevalence of thyroid disease, similarly to HF, increases with the increasing population age<sup>14</sup>. It is estimated that 5-15% of the entire older population (aged > 65 years), especially women, suffer from overt or subclinical thyroid dysfunction<sup>16</sup>. Hyperthyroidism is characterized by the presence of reduced or undetectable serum thyroid-stimulating hormone (TSH) levels and increased (overt disease) or high normal (subclinical disease) TH values and, involves 1% to 7% of the adult population according to age<sup>14,17</sup>. The most common causes of hyperthyroidism in the elderly are represented by nodular goitre (especially in iodine deficient areas) and iatrogenic conditions such as excess iodine (amiodarone, iodine containing drugs etc.) or inappropriate L-thyroxin replacement while, Graves' disease is seldom observed<sup>14,18,19</sup>. The prevalence of hypothyroidism (especially subclinical) is more frequent than hyperthyroidism (up to 10-12% in older women); it's featured by the presence of serum TSH level above normal reference values and reduced (overt disease) or low-normal (subclinical disease) TH levels<sup>14,16,20</sup>. In this setting, it should be outlined that the actual prevalence of subclinical hypothyroidism in older people (especially those older than 80 years) is not clearly defined giving the shift of serum TSH towards upper values in healthy elderly and the lack of epidemiological data obtained by using age specific normal reference ranges for serum TSH<sup>20,21</sup>. The most frequent cause of thyroid failure is represented by autoimmune thyroiditis followed by surgical thyroid removal, concomitant drugs interfering with thyroid function (corticosteroids,  $\beta$ -blockers) etc.<sup>14,21</sup>. In the current study, we focused on the relationship between thyroid dysfunction (either hyperthyroidism or hypothyroidism) and heart failure in older people by reviewing English literature available up to September 2016 on Medline website<sup>®</sup>. We described the main findings on the topic as reported by preclinical to clinical studies, focusing on the combined effect of thyroid dysfunction and the ageing process.

## EFFECT OF THYROID HORMONES ON CARDIAC STRUCTURE AND FUNCTION

It is widely recognized the dose-dependent effect of triiodothyronine (T3) on vasculature and heart function<sup>7,22</sup>. Accordingly, opposite functional thyroid conditions (*i.e.* hypo- and hyperthyroidism) provoke inverse

cardiac function changes that, no matter what they are, lead to cardiovascular disease with consequent increased risk of HF events (Fig. 1)<sup>22</sup>. To clearly explain how thyroid status affects heart function, we should focus on the bio-molecular effects of TH, and what alterations they exert in myocytes, endothelium and vascular muscle cells. In this setting, the concurrent modifications linked to the physiopathology of the ageing process, which involve either the heart or the vasculature (myocardial structural alteration, endothelial dysfunction, coronary stiffness, atherosclerosis development and progression) should be not overlooked<sup>23</sup>. There are two main routes for thyroid hormone action: the transcriptional genomic effects and the non-genomic effects, the last targeting directly different cell structures. As shown in many experimental models, TH has several effects on heart, mainly exerted through the action of T3 on thyroid receptors alpha-1 and beta-1<sup>24</sup>. TH play a role in cardiac function acting as pro-contractile, anti-apoptotic, anti-inflammatory and anti-fibrotic agents thus favoring angiogenesis and regeneration<sup>24</sup>. At biomolecular level, the modification of TH availability may alter cardiac function by reducing or increasing the binding of T3 to the nuclear receptor. In addition to these local actions thyroid hormones exert significant systemic hemodynamic actions, mainly mediated by T3, acting on the cardiovascular system as a whole. Through its action on thermogenesis T3 decreases vascular resistance and cardiac afterload, contributing to regulation of cardiac output and inotropic function. Thus, TH changes lead to myocardial dysfunction either directly through gene expression dysregulation or indirectly, by modifying the sympathetic system response<sup>24-26</sup>. In the presence of chronic excess of TH, the development and progression of HF may be due to tachycardia-mediated cardiomyopathy with high-output HF while in the hypothyroid state, TH deficit results in lower heart rate and weakening of myocardial contraction and relaxation, which firstly gives rise to diastolic, low-output HF<sup>26</sup>.

## HYPOTHYROIDISM

The effects of chronic thyroid failure at cardiovascular level have been well documented in hypothyroid animal models, where maladaptive shape of myocytes along with loss of coronary arterioles and impaired blood flow were observed<sup>27</sup>. Accordingly, TH dose effect studies showed reduced expression of both myosin heavy chains (MHC) and sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase as well as increased expression of its inhibitor phospholamban at lower T3 levels<sup>27,28</sup>. In humans, a report on a hypothyroid patient with dilated cardiomyopathy who underwent endomyocardial biopsies, at baseline and during TH replacement therapy, documented changes in myocardial gene expression with a trend

towards  $\beta$ -to- $\alpha$  MHC shift, which in turn led to cardiac function recovery<sup>29</sup>. Interestingly, treatment with T3 for three days after acute myocardial infarction reduced myocyte apoptosis in the border area, in animal models via complex intracellular signaling<sup>30</sup>.

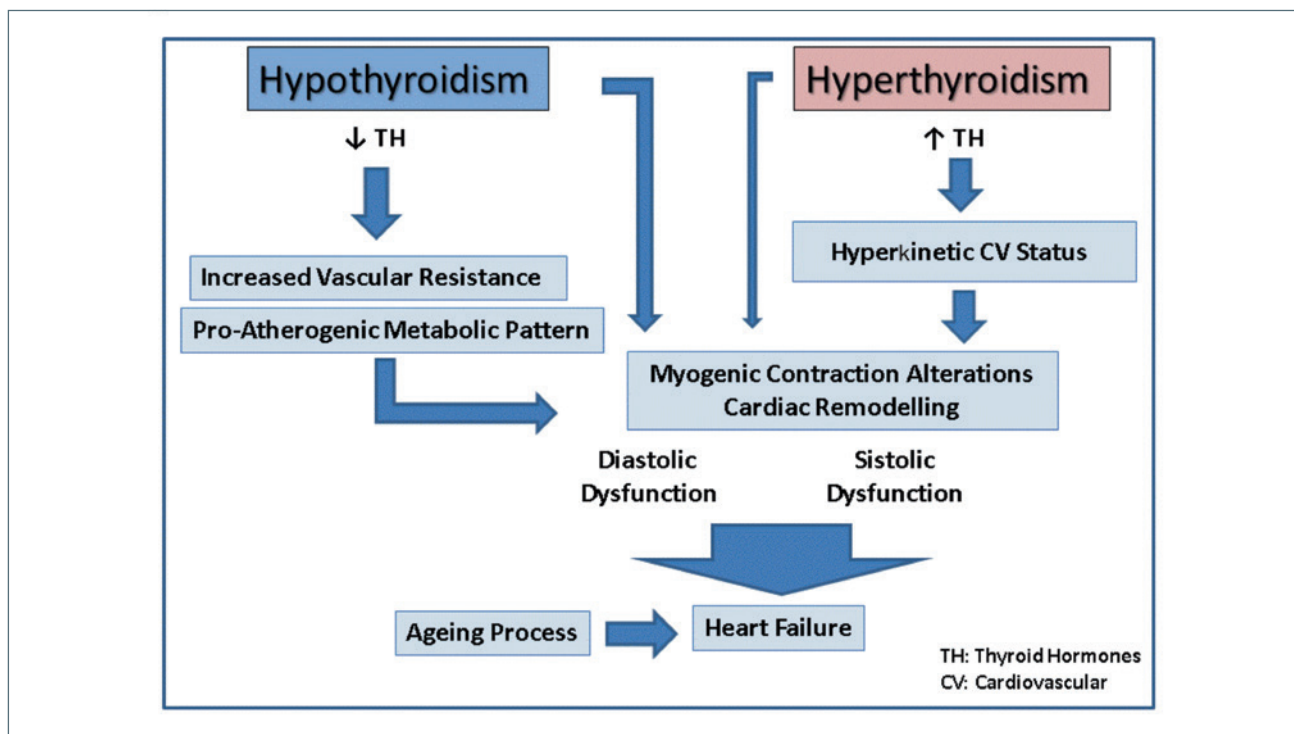
Both overt and subclinical hypothyroidism, according to the extent and time of exposure to TH deficit, may induce bradycardia, decreased ventricular filling, decreased cardiac contractility and oxygen consumption, leading to reduced cardiac output<sup>22 26 31</sup>. Therefore, prolonged isovolumic relaxation time, early reversible diastolic impairment and reduced contractility have been described in subclinical hypothyroid (sHT) patients<sup>32 37</sup>. Systolic function is also altered in sHT subjects as firstly demonstrated by increased pre-ejection/ejection time ratio and subsequently by mean aortic acceleration analysis and video-densitometric evaluation<sup>32 36</sup>. Accordingly, decreased cardiac preload along with increased afterload with consequent reduction in stroke volume and cardiac output was observed in sHT patients by magnetic resonance study, confirming a total impairment of cardiac function that may be worsened by exercise, which further reduce whole cardiorespiratory performance<sup>34 37</sup>. Cardiac modifications associated with hypothyroidism even in the subclinical form, either at rest or during exercise, may be reversed by TH replacement therapy as documented by case-control and placebo-controlled, randomized clinical studies<sup>32 33 37</sup>. TH act at vascular levels as vasodilators through different mechanisms involving both genomic and non-genomic pathways, leading to reduced systemic vascular resistances<sup>14 38 39</sup>. *In vitro* and *in vivo* studies showed different results on TH induced vasodilatation, suggesting that early relaxation may be due to non-genomic effect on vascular smooth muscle cells while delayed vasodilatation mainly depend on nitric oxide increased synthesis and release<sup>14 38</sup>. Accordingly, TH deficit leads to augmented systemic vascular resistances and higher diastolic blood pressure<sup>39-42</sup>. Rarefaction of coronary microvasculature with consequent impaired vasodilatation has been also observed in chronic hypothyroidism, reversible by T3 administration<sup>41</sup>. In this regard, a home dwelling population study of almost 30,000 individuals, without previous known thyroid diseases and serum TSH within the reference range, revealed a linear positive association between TSH level and systemic blood pressure value<sup>42</sup>. In this way, chronic TH deficit may result in aortic stiffness and early atherosclerosis<sup>42 43</sup>. Accordingly, several studies documented significant intermediate metabolism and blood vessel alterations in sHT patients, characteristic of a pro-atherogenic status<sup>11 44 45</sup>. In detail, vascular reactivity and NO release as well as the response to

acetylcholine were significantly impaired in sHT patients as compared to euthyroid controls<sup>13 38</sup>. Besides, flow-mediated vasodilation, a well-known marker of endothelial function, was also significantly altered, thus suggesting abnormalities of the parasympathetic nervous system<sup>46</sup>. Finally, a pro-atherogenic lipid profile with elevation of both total and LDL cholesterol levels, directly related to circulating TSH values, has been described in patients with mild thyroid failure and even in those with high normal serum TSH<sup>11 44-48</sup>. Overall, these findings show that both overt and subclinical hypothyroidism impact on cardiac function via complex mechanisms, including direct effects on myocardium and cardiac vessel reactivity as well as through pro-atherogenic metabolic changes, that may lead to cardiac dysfunction and HF, especially in older people, in whom the ageing process *per se* concurs in determining such modifications (Fig. 1).

#### **HYPERTHYROIDISM**

The long-term exposure to TH excess can exert adverse effects on cardiac structure and function, by increasing left ventricular mass, arterial stiffness and left atrial dimension, which leads to altered left ventricle performance and diastolic dysfunction (Fig. 1). Untreated overt hyperthyroidism is one of the main causes of HF and, also persistent subclinical hyperthyroidism has been associated with the development and progression of HF<sup>14 49</sup>. The mechanism by which TH excess can induce HF is an important issue for both the endocrinologist and the cardiologist. Patients with overt or subclinical hyperthyroidism are at increased risk for cardiac death and, even high normal serum TH levels have been associated with increased risk of sudden death, although the exact mechanism is still not completely defined<sup>15 50</sup>. The increased risk of cardiac mortality, especially in the elderly, may be due to the high prevalence of arrhythmias and HF events associated with hyperthyroidism<sup>50 51</sup>.

Hyperthyroid patients complain of reduced exercise tolerance and exertional dyspnoea due to reduced cardiac output<sup>50 51</sup>. Older patients may develop dyspnoea even while performing minor daily activities and, reduced exercise tolerance may be one of the first signs of HF in hyperthyroid older patients<sup>49</sup>. Orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema and jugular vein turgor are all signs indicating the progression of HF<sup>49</sup>. Nonetheless, the extent and number of clinical manifestations and the severity of HF depend on a variety of factors such as the patient's age, the cause and degree of hyperthyroidism and the presence of pre-existing cardiac disorders<sup>49 51</sup>.



**Figure 1.** Relationship between thyroid dysfunction (hypo and hyperthyroidism) and heart failure (HF) development and progression.

## CLINICAL EXPERIENCES

### HYPOTHYROIDISM AND HEART FAILURE

Several causes and risk factors of HF have been detected in large cohort studies, the most important being represented by cardiovascular (CV) diseases such as elevated systemic blood pressure, coronary heart disease (CHD), structural heart diseases and arrhythmia followed by endocrine disorders. In this regard, hypothyroidism (even the subclinical form) has been correlated with an increased risk of CHD events and some clinical conditions that lead to HF<sup>12 52-55</sup>. Several prospective studies were designed to evaluate the relationship between hypothyroidism and the risk of HF in different clinical settings, among which older population is one of most studied<sup>12 54</sup>. The common ageing modifications of cardiac structure, mainly represented by myocyte loss, interstitial fibrosis, remodeling and hypertrophy, favor the development of cardiac dysfunction, especially diastolic<sup>32 36 56</sup>. Moreover, when age related cardiac modifications are associated to organic disease such as CHD and valvulopathy, the risk of HF becomes highly significant especially in case of concomitant hypothyroidism<sup>56</sup>. In the Prospective Study of Pravastatin in the Elderly at Risk, the persistence of serum TSH values above 10 mIU/L over a 6-month period was associated with increased incident HF events in older

people with previous cardiovascular risk<sup>57</sup>. Indeed, participants with TSH  $\geq 10.0$  mIU/L had a greater incidence of HF events compared to euthyroid participants (41.7 vs 22.9/1000 person/year). An increased risk of HF was observed also in subclinical hypothyroid older patients without history of cardiac disease as shown in the Cardiovascular Health Study<sup>58</sup>. Moreover, mild thyroid failure of the elderly should be considered not only a worsening condition for patients already affected by HF, but also an independent risk factor for developing the disease. Thus, (mild) hypothyroidism is related not only to a greater likelihood of disease progression and hospitalization but also to a poorest prognosis and increased mortality<sup>53 59</sup>.

Hypothyroidism, especially the subclinical form, has been shown to exert an age dependent, biphasic role in CHD development and progression: stronger in young adults (aged < 65 years) while vanishing in the last decade of life<sup>53</sup>. This trend seems not true for HF and, a meta-analysis on community-dwelling older subjects clearly showed that the rate of HF events increased in subclinical hypothyroid patients compared with euthyroid controls, with an incremental risk in those with circulating TSH above 10 mIU/L independently from ageing<sup>54</sup>. Surprisingly, a more recent meta-analysis on 13 longitudinal studies confirmed the association of hypothyroidism with cardiac and all-cause mortality and

hospitalization but, the association disappeared in patients aged < 65 years, suggesting a higher sensitivity of older heart to even mild TH deficit<sup>60</sup>. Moreover, as recently showed in a large naturalistic study of patients with mean age of 61 years, an important factor to be considered when evaluating the relationship between thyroid failure and CV disease or mortality is the duration of the exposure of tissues to TH deficit<sup>61</sup>. Overall, these findings clearly suggest that the potential detrimental effect of (mild) thyroid failure depends on several factors including ageing but also the specific organ or biological system which is analyzed. The concomitant presence of other diseases as well as the degree and duration of TH deficit should be also considered. Furthermore, while discussing on thyroid dysfunction and HF in older people the possible presence of the so called “non-thyroidal illness syndrome (NTIS)” or “low-T3 syndrome” should be not overlooked. Indeed, NTIS is a clinical condition frequently observed in the elderly, generally characterized by reduced circulating T3 and increased level of reverseT3<sup>62</sup>. It is well described the association between NTIS and chronic diseases such as HF, especially during acute events and hospitalization, but it is still unclear whether it represents a protective condition to prevent excessive catabolism or an adjunctive negative illness. Holmager et al. carried out a randomized clinical trial and did not report any effect of T3 administration in older patients with chronic HF while, a previous study showed clinical benefits in terms of both neuroendocrine parameters and systolic function in patients with dilated cardiomyopathy<sup>30 63</sup>. In conclusion, consistent data from large naturalistic studies exploring the relationship between either overt or subclinical hypothyroidism and HF are now available. However, given the lack of evidence of the impact of TH replacement therapy in preventing either the development or progression of HF, especially in older patients with mild thyroid failure, future large randomized studies are warranted to better delineate how to deal with (mild) hypothyroid older patients at risk for or with HF. Nonetheless, thyroid hormone status (not only serum TSH but also TH levels) should be assessed in older HF patients and, in case of certain thyroid failure, the possible usefulness of levothyroxine replacement should be taken into account.

#### **HYPERTHYROIDISM AND HEART FAILURE**

Several case control and naturalistic studies have evaluated the association between hyperthyroidism and HF<sup>49</sup>. In hyperthyroid patients systemic vascular resistances and diastolic blood pressure decrease while mean pulmonary arterial pressure is usually increased, nonetheless the development of right ventricle failure can be underestimated since it is usually reversible after

recovery of euthyroidism<sup>64</sup>. The most frequent form of cardiac disease associated with hyperthyroidism is high output HF, which typically occurs in younger patients suffering from overt hyperthyroidism (Graves' disease) without pre-existing heart disease<sup>56</sup>. Patients suffering from high output HF may have symptoms of shortness of breath at rest and fatigue as well as water retention with peripheral oedema, pleural effusion, hepatic congestion and pulmonary arterial hypertension<sup>56</sup>. The low-output form of HF is seldom observed in hyperthyroid patients, its prevalence ranges from 6% to 15%, and usually affects older people with age related cardiac modifications and pre-existing CV diseases such as systemic arterial hypertension, CHD, valvular disorders and arrhythmia<sup>56</sup>. In these patients cardiac output is low, systemic vascular resistances are increased and left ventricular filling and contractility compromised. Approximately 7-8% of middle-aged hyperthyroid patients develop atrial fibrillation or flutter, the prevalence increases to 10-20% in older patients, up to 20-35% in those with pre-existing CHD or valvular disease<sup>49</sup>. In a study of 591 consecutive young adults (mean age 45 years) suffering from hyperthyroidism, HF was detected in 6% of the cases<sup>65</sup>. Few studies have assessed the risk of HF in older patients with (subclinical) hyperthyroidism. In the Cardiovascular Health Study, a naturalistic study that included 3044 adults older than 65 years without known heart disease, 46 HF patients (mean age 72.6 years) were affected by subclinical hyperthyroidism but, despite cardiac abnormalities at echocardiographic examination, no correlation was found between serum TH values and the risk of developing HF<sup>58</sup>. The authors found that during a 3.2-yr follow-up period, the incidence rate of hospitalization for HF was higher in older people with subclinical hyperthyroidism compared with the euthyroid group, with 31 vs 12 events per 1000 person/year ( $p = 0.01$ ). However, other studies showed that the onset of subclinical hyperthyroidism might exacerbate cardiovascular risk in patients with pre-existing heart disease. Indeed, a recent longitudinal study showed a significant association between subclinical hyperthyroidism (TSH < 0.45 mIU/L) and the rate of HF in older patients (aged 72-82 years) with known CV risk factors or previous CV disease, over 3.2 years of follow-up<sup>57</sup>. Moreover, a large pooled analysis of individual participant data from six prospective cohorts, which included 25,390 participants with 216,248 person-years of follow-up, demonstrated an overall significantly increased risk of HF events in patients suffering from subclinical hyperthyroidism ( $n = 648$ , 2.6%), especially in case of suppressed serum TSH values<sup>54</sup>. Accordingly, a very recent nationwide cohort study, including 35% of subjects older than 70 years, documented increased

all-cause mortality in hyperthyroid patients as compared to euthyroid controls<sup>66</sup>. Also, an increased risk for all examined CV events was observed, with the highest probability in the first three months after diagnosis. The 3-month post-diagnosis risk was highest for atrial fibrillation and arterial embolism, but significantly increased risk was observed also for incident venous thromboembolism, ischemic and non-ischemic stroke and acute myocardial infarction as well as percutaneous coronary interventions<sup>66</sup>. In this setting, a large naturalist study showed that, beside the degree of hyperthyroidism, an important factor affecting patients' clinical outcome and survival is the duration of the exposure of tissues to thyroid hormone excess<sup>61</sup>. Accordingly, data from the Rotterdam Study, in which around 10,000 individuals older than 45 years were enrolled, showed that higher serum free thyroxine (FT4) levels, even in the normal range of thyroid function, were associated with an increased risk of sudden cardiac death, over 9.1 years of follow-up<sup>15</sup>. In this setting, another recent report from the same cohort showed that serum FT4 levels in the highest quartile of the normal range, were associated with higher rate of incident atrial fibrillation. In detail, absolute 10-year risk increased from 1% to 9% in younger participants and from 6% to 12% in those older than 65 years<sup>67</sup>. These two latter studies clearly demonstrate that even small variations of serum TH level, still in the normal range of thyroid function, may have significant impact at CV level, even in individuals younger than 65 years. Overall, these findings suggest that thyroid function tests should be performed not only in (older) patients with no other identifiable causes of HF but also in those with known CV risk factors or previous CV disease.

## CONCLUSIONS

Overall, an increasing body of evidences documented a negative effect of overt thyroid dysfunction on heart function, increasing the risk of HF and mortality. Some experiences also suggested a negative effect of the subclinical form of either hypo- or hyperthyroidism. In detail, both overt and subclinical hypothyroidism impact on cardiac function via complex mechanisms, including direct effects on myocardium and cardiac vessel reactivity as well as through pro-atherogenic vascular changes, that may lead to cardiac dysfunction and HF, especially in the elderly in whom the ageing process *per se* concurs in determining such modifications. It is worth to mention that even subclinical hypothyroidism may increase the risk of hospitalization and death in older HF patients, indicating the extreme susceptibility of the ageing heart to slight TH deficit. Thus, it appears crucial

to assess thyroid function in older patients suffering from HF, even if the lack of randomized clinical trials leaves us with several unresolved key issues regarding specific criteria and goal of treatment, as stated in latest guidelines<sup>20,68</sup>. For this reason, appropriately powered, randomized controlled trials of L-thyroxin replacement in older sHT patients, examining the effect in preventing HF progression and events as well as overall survival, are clearly warranted.

The association between hyperthyroidism and heart failure is well established in older population. Moreover, even small variations of serum TH level, still in the normal range of thyroid function, may have significant impact at cardiovascular level, not only in the elderly. Several mechanisms may directly contribute to HF in patients with hyperthyroidism, as vasculature changes and modification of myocardial contractility. Although high output HF is the most frequently observed in hyperthyroidism, older patients often suffer from low-output HF, especially in case of pre-existing cardiac disease. Approximately 10-20% of older hyperthyroid patients develop AF or flutter and, the prevalence increases up to 20-35% in those with pre-existing CHD or valvular disease. Thus, we should consider AF of the elderly as a possible condition that may worsen and precipitate early phase HF. Overall, these data suggest that hyperthyroidism should be ruled out not only in older patients with no other identifiable causes of HF but also in those with known CV risk factors or previous CV disease. It is important to early recognize (mild) hyperthyroidism in older patients<sup>69</sup> and, depending on the extent and the duration of such alteration, consider anti-thyroid medication<sup>49</sup>. However, future large randomized, intervention studies in elderly balancing the risk and benefits of anti-thyroid medication according to the degree of serum TSH reduction and TH elevation are warranted.

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## Calcific aortic stenosis: a peculiar feature of diastolic heart failure in the elderly

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Calcific aortic stenosis represents the most frequent valvular heart disease and one of the major cause of morbidity and mortality in the elderly. Aortic stenosis results from active biological events, characterized by lipid infiltration, inflammation, neoangiogenesis, endothelial dysfunction and bone deposition. The reduced mobility of aortic valve leaflets produces a fixed obstruction at the outflow, with a consequent remodelling of the left ventricle. The degree of left ventricle hypertrophy and fibrosis results in different degree of diastolic dysfunction and heart failure. Thus, the response of the left ventricle to the pressure overload guides the clinical status and the prognosis of patients with aortic stenosis. After aortic valve replacement hypertrophy and fibrosis partially regress, however the maladaptive LV remodelling strongly impacts the prognosis even after surgery. This review outlines the importance in the evaluation of the left ventricle in patients with severe aortic stenosis, exploring the pathophysiology of the transition from adaptive to maladaptive remodelling.

**Key words:** Aortic stenosis, Elderly, Diastolic dysfunction, Myocardial fibrosis, Left ventricular hypertrophy

### AORTIC STENOSIS: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Aortic stenosis (AS) represents the most prevalent valve heart disease in Western countries<sup>1</sup>. In the elderly, severe AS is a major cause of morbidity and mortality, including sudden death, and its prevalence rises to 3% in patients over age of 80 years<sup>2</sup>. In developed countries, the degenerative aetiology is the most frequent (82%), followed by rheumatic (11%) and congenital (5%)<sup>3</sup>. Nevertheless, it is important to emphasize that calcification of aortic valve (AV) is not only a consequence of aging, but several pro-atherosclerotic factors may account for this degenerative process, such as arterial hypertension, hypercholesterolemia, smoking, etc. Therefore, in the initial phase of the disease, the degeneration of AV leaflets is a part of a diffuse atherosclerotic process<sup>4</sup>. Afterwards, a series of active biological events, such as lipid infiltration, inflammation, neoangiogenesis,

endothelial dysfunction and bone deposition lead to a progressive AV calcification<sup>5-9</sup>. Hemodynamic stress and the consequent endothelial damage with lipid infiltration are probably the first events in the AV calcification process. Microscopic observations in early stenotic valve show the presence of chronic inflammatory cells, lipids, disorganized collagen fibres, proteins of extracellular bone matrix, and bone minerals<sup>10</sup>. Increased levels of oxidized low-density lipoproteins promote inflammatory response and mineralization activity<sup>11</sup>, inducing the transition of valvular fibroblasts to an osteoblastic phenotype<sup>12-13</sup>. Recent evidence suggests that low-grade inflammation, promoted by dysregulation of visceral adiposity, has an important role in the AV atherosclerotic process<sup>14-17</sup>. In this regard, we have recently demonstrated that increased echocardiographic thickness of epicardial adipose tissue, the visceral fat depot of the heart, is correlated with the presence of severe AS and is directly correlated with the secreted levels of inflammatory mediators<sup>18</sup>.

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Epicardial adipose tissue, being a source of both inflammatory mediators and catecholamines<sup>19</sup> may also have an important role in cardiac dysfunction and heart failure (HF) progression.

## THE LEFT VENTRICLE REMODELLING IN AORTIC STENOSIS

The presence of AS induces an abnormal and protract pressure overload upon the left ventricle, that results in systolic and diastolic dysfunction. These abnormalities exacerbate the well known adverse myocardial remodelling occurring with age<sup>20</sup>. In the early phase of AS the main compensatory mechanisms are represented by concentric left ventricular hypertrophy (LV) and elevation of end-diastolic pressure. The protracted pressure overload induces changes in the myocardial extracellular matrix leading to progressive myocardial fibrosis and decreasing LV compliance<sup>21</sup>. Thus, the initial adaptive remodelling becomes maladaptive with increased LV hypertrophy, myocardial fibrosis, heart failure<sup>21</sup>, and worsening prognosis<sup>22-23</sup>. However, the degree of LV hypertrophy appears to be more closely associated to age, male sex, diabetes and obesity rather than severity of AS<sup>24-27</sup>. It is important to underline that in the elderly the presence of comorbidities<sup>28</sup>, such as diabetes, hypertension, increased arterial stiffness, can influence cardiac overload and worse left ventricular response to AS. Myocyte apoptosis and fibrosis are supposed to mark the transition from hypertrophy to heart failure with the consequent onset of symptoms<sup>29</sup>. Interestingly, the degree of myocardial fibrosis secondary to AS seems to condition the presence and the progression of LV systolic dysfunction. Studies exploring the effects of longstanding pressure overload secondary to hypertensive heart disease<sup>30</sup> and AS<sup>29</sup> suggest that fibrosis is increased in patients with reduced LV ejection fraction. Fibrosis occurs after myocyte apoptosis<sup>31</sup>, and areas of fibrosis are observed to co-localize with areas of myocyte loss. Of note, the presence of mid-wall fibrosis is associated with a significant increase in mortality<sup>31-32</sup>. It is reasonable to hypothesize that fibrosis is associated to adverse prognosis not only because it increases LV stiffness but also because it is associated to an increased risk of cardiac arrhythmias<sup>32-33</sup>. Furthermore, the magnitude and chronicity of the increased LV filling pressure are associated with an increase in left atrial size<sup>34-35</sup>, which has been shown to predict postoperative symptomatic improvement<sup>36</sup> and subsequent prognosis in AS patients<sup>37</sup>.

## THE LEFT VENTRICLE: BIOMARKERS OF DECOMPENSATION

The progressive LV decompensation in AS is driven primarily by two processes: myocyte death and myocardial fibrosis<sup>38</sup>. Therefore, biomarkers of LV stress/damage could be helpful in the identification of those patients with more advanced disease. The increased LV wall stress determines an elevation of the circulating levels of brain natriuretic peptide (BNP) and the related N-terminal fragment of proBNP (NT-proBNP) which are widely used in the diagnosis and management of heart failure<sup>39-42</sup>. In particular, several studies in AS patients, demonstrated that BNP levels increase along with the transition from LV hypertrophy to heart failure<sup>43-47</sup>, thus suggesting an important role for natriuretic peptides in the evaluation of patients with severe AS and equivocal symptoms. Myocardial ischemia due to inadequate microcirculation<sup>48-49</sup> promotes myocardial loss. Myocyte death is believed to be one of the key factors driving LV decompensation in AS, thus high-sensitivity troponin T is indicated as a valuable marker of myocardial damage. Some studies<sup>50-51</sup> suggested that troponin levels are correlated with LV mass, myocardial fibrosis, severity of AS, and are predictive of adverse outcome. Furthermore, neurohormonal activation represents a putative additional mechanism of cell death<sup>52-57</sup> and may offer important prognostic indications in heart failure<sup>58</sup>. It is widely established that the presence and the extent of fibrosis are absolutely relevant in the transition from hypertrophy to heart failure. Unfortunately, biomarkers of fibrosis have not an established role in AS patients. Recently, Galectin-3, a member of the lectin family and important mediator of myocardial fibrosis, emerged as a potentially useful prognostic marker in patients with heart failure<sup>59-61</sup>.

## EVALUATION OF SYMPTOMS

Echocardiography is the key tool for the diagnosis and evaluation of AV disease and clinical decision-making is based on echocardiographic evaluation of AS severity<sup>62</sup>.

Once the diagnosis of severe AS is achieved, a careful evaluation of symptoms becomes mandatory. Guidelines clearly establish that the onset of symptoms represents the indication to valve replacement, although, especially in elderly patients, there is often a reluctance to recommend valve replacement due to the supposed high surgical risk. The prognosis of AS dramatically changes with the onset of symptoms such as angina, syncope and dyspnoea<sup>63</sup>. However, clinical manifestation is frequently insidious at the onset and can be

highly variable among patients with similar degrees of valve stenosis. In many patients, the first and subtle symptom is represented by a reduced exercise tolerance<sup>64</sup> and consequently symptoms evaluation is particularly challenging because in this population the daily life activity is strongly conditioned by the presence of comorbidities<sup>65-67</sup>.

Exercise testing may add important information in 'supposed' asymptomatic patients allowing to recognize exercise-related symptoms due to AS and unmask the reduced exercise capacity. 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 mean pressure gradient  $\geq 40$  mmHg, due to high risk of complications, comprising syncope, ventricular tachycardia, and death<sup>68 69</sup>.

## LEFT VENTRICULAR REMODELLING AFTER SURGERY

AV replacement (AVR) is followed by immediate hemodynamic improvement due to afterload reduction and improved active myocardial relaxation. However the regression of hypertrophy and the amelioration of diastolic function require more time<sup>70</sup>. The hypertrophy regression is more precocious and a marked reduction in LV mass usually occurs within 18 months from AVR<sup>71-73</sup>. However, some authors described that a regression of muscular tissue was observed after surgery while fibrous tissue remained unchanged<sup>74</sup>. Consequently, after surgery, there is a relative increase in fibrous content and some authors described a deterioration of LV diastolic function early after AVR. In accordance, it has been described a development of moderate to severe diastolic dysfunction late after AVR, despite a reduction in the LV mass index<sup>70 74</sup>. A late and progressive reduction of LV fibrosis has been described after some years from surgery<sup>74 75</sup>. Of note, the fibrosis regression is predominantly related to the reduction of interstitial fibrosis, while the replacement fibrosis seems to remain unchanged<sup>71-74 77</sup>. Overall, presence of higher grades of myocardial fibrosis increases the risk of congestive heart failure and death<sup>78</sup> while patients with mild diastolic dysfunction have a better prognosis after AVR<sup>79</sup>. As regard the systolic function, a rapid recovery has been described after both surgical and percutaneous AVR<sup>80 81</sup>. Speckle-tracking echocardiography<sup>82</sup> demonstrated improvements in LV systolic function

6 months after AVR. Of interest, there is a significant better recovery of circumferential and radial strain with respect to the longitudinal. Longitudinal strain is particularly affected by the presence of fibrosis, thus its impaired recovery after AVR may reflect the presence of higher degree of fibrosis. Several clinical factors can influence the extent and the duration of LV remodelling after AVR. First of all, the presence of patient-prosthesis mismatch can contribute to the persistence of LV pressure overload and consequently to the persistence of hypertrophy and diastolic dysfunction<sup>83</sup>. Indeed in patients with patient-prosthesis mismatch and hypertension after AVR, an attenuated LV remodelling has been described<sup>84 85</sup>.

## CONCLUSIONS

Aortic stenosis, the most diffuse valve disease in the elderly, is a disease of the valve and the myocardium. After an initial phase of adaptive remodelling, a maladaptive LV remodelling occurs in the advanced stages of the disease. Progressive myocyte death and myocardial fibrosis result in the transition from hypertrophy to heart failure. Markers of left ventricular (LV) decompensation, such as BNP and troponins, may help in the identification of patients who may benefit from early surgery. Preoperative myocardial remodelling conditions survival after surgery and continues after surgery.

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# Chronic obstructive pulmonary disease and heart failure: common diseases of the elderly, frequent non-recognition and the value of specialist referral

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Chronic Obstructive Pulmonary Disease (COPD) and Heart Failure (HF) are major and increasing public health problems worldwide. Both conditions are common diseases of the elderly and often coexist. Unfortunately their coexistence frequently remains unrecognized mainly due to the similarities in clinical presentation and additionally due to a lack of relevant studies addressing the combination of HF and COPD. The coexistence of HF and COPD presents many diagnostic challenges. Several tests can be performed to assist in the diagnosis of each disease. Assessment of left ventricular function by transthoracic echocardiography is mandatory for diagnosing HF, while magnetic resonance imaging is the modality of choice in those with limited acoustic windows. On the other hand, objective evidence of airflow obstruction, demonstrated when clinically euvolemic is mandatory for diagnosing COPD. Greater collaboration is required between cardiologists, pulmonologists, and general practitioners. Both are chronic progressive diseases and their prognosis combined is poorer than for either disease alone, therefore it is really important to recognize the coexistence of both processes early.

**Key words:** Chronic obstructive pulmonary disease, Heart failure, Elderly

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are major and increasing public health problems worldwide. Both conditions are common diseases of the elderly and show high morbidity and mortality rates, contributing enormously to the global burden of disease and result in an economic and social burden<sup>1-3</sup>. Although both diseases have been extensively studied separately, clinicians often fail to recognize one syndrome in the presence of the other, mainly due to the similarities in clinical presentation and additionally due to a lack of relevant studies addressing the combination of HF and COPD<sup>4</sup>.

According to the available evidences, COPD and HF often coexist and their prognosis combined is poorer than for either disease alone, therefore it is really important to recognize the coexistence of both processes early.

The present review focuses mainly on the diagnostic challenges presented by the combination of COPD and HF.

## EPIDEMIOLOGY OF COEXISTING COPD AND HEART FAILURE

The prevalence of the COPD and HF combination is variable, depending on the population studied (community,

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outpatient or hospitalized<sup>5</sup>) and on the diagnostic criteria applied<sup>4</sup>. The coexistence of the two conditions is further supported by shared risk factors, notably age and smoking<sup>4,6,7</sup>.

Epidemiological studies reveal that the incidences of both COPD and HF increase with age<sup>8,9</sup>. Although both can be considered diseases of the elderly, COPD develops on average  $\approx$  10 years earlier than HF (> 55 vs > 65). The incidence of HF doubles with each decades of life. About 50% of HF cases are observed in patients older than 70 years<sup>10</sup>, with a prevalence reaching nearly 10% in patients older than 80 years<sup>11</sup>. Regarding COPD, existing prevalence data ranges from 7,8% to 26,1% and become higher in the elderly population<sup>12</sup>. It was reported that the prevalence of concurrent COPD in patients with HF increases until around 75 years of age, and declines thereafter. This non-linear relationship is probably due to the presence of COPD that may reduce survival beyond this age<sup>4,13-15</sup>.

The prevalence of HF in elderly COPD patients is reported to be 21-31%<sup>16</sup>, while the reported prevalence of COPD in HF varies considerably depending on the population studied, ranging from 7% to 13% in HF outpatients and from 9% to 51% in hospitalized HF patients<sup>17</sup>.

However most studies of the prevalence of coexistent COPD and HF have established diagnosis criteria in a retrospective way and, in most cases, have used a no appropriate definition of both COPD and HF, as they had not been based on GOLD criteria and reproducible echocardiographic parameters<sup>18-20</sup>. Macchia et al., in a prospective cohort study, found a prevalence of 17% of left ventricular dysfunction in patients with clinical and spirometrically confirmed COPD diagnosis and a prevalence of 37,3% of airway obstruction in patients with echocardiographically confirmed HF<sup>21</sup>.

Recently two larger studies have shown that the airflow obstruction observed in patients with HF is dynamic thus spirometry might overestimate the presence of COPD in patients with HF and serial measurements is mandatory in order to minimize the risk of false positive COPD<sup>22,23</sup>. In this regard Dalsgaard et al. examined 593 HF patients with spirometry at their first visit and after optimal medical treatment for HF was achieved. The prevalence of airway obstruction was 39%, although at the baseline spirometry only 12% of patients had a clinical diagnosis of COPD<sup>24</sup>.

## PATHOPHYSIOLOGICAL MECHANISMS

Several studies have shown that patients with COPD are at increased risk of cardiovascular disease<sup>25-27</sup>. The underlying pathophysiological mechanisms that

are responsible for the increased cardiovascular risk in COPD remain unclear but might involve several factors such as: biological (hypoxemia, endothelial dysfunction, arterial stiffness)<sup>27,28</sup>, mechanical and/or functional (emphysema, hyperinflation)<sup>29,30</sup>, neurohumoral<sup>31</sup> and genetic (metalloproteinases, telomere shortening)<sup>32</sup>.

The cardiac abnormality related with COPD has traditionally been right ventricular dysfunction. In the past, heart failure was considered as rather uncommon in COPD, and whenever present was thought to occur as right-sided heart failure<sup>33</sup>. However the prevalence of true "cor pulmonale" or right-sided heart failure in COPD has been shown to be rather low (0.2-0.6%) but might be higher in more severe cases with COPD<sup>34</sup>.

More recent studies have reported that the left ventricle may also be affected in COPD<sup>35-38</sup> and have addressed the coincidence of both COPD and HF and their potential clinical interrelations thereafter<sup>4,12</sup>.

The relationship between COPD and HF is not completely clear, nevertheless the high rate of coexistence of COPD and HF suggests that these two conditions, although aetiologically distinct, share common pathophysiological mechanism.

These chronic diseases share smoking and age as risk factors<sup>39</sup>, and the association of low-grade systemic inflammation<sup>40,41</sup>. A growing body of evidence indicates that systemic inflammation could be the common pathway leading to the high prevalence of multiple chronic diseases in the same patient. Therefore chronic systemic inflammation seems to be a critical link between COPD and HF. High circulatory values of proinflammatory cytokines have been found in patients with COPD and HF, such as tumour-necrosis factor (TNF)- $\alpha$ , interleukin-1 (IL-1), and IL-6; these cytokines might accelerate and perpetuate disease progression and exacerbation of both diseases.

Mechanisms by which systemic inflammation may lead to heart failure in COPD patients include accelerated atherosclerosis (plaque genesis, progression and rupture) leading to the development of ischemic heart disease<sup>42</sup>.

Atherosclerosis and COPD are also associated with premature biological ageing<sup>43</sup>. Atherosclerotic plaques and lungs of COPD patients show features of cellular senescence in terms of reduced cell proliferation, irreversible growth arrest and apoptosis, elevated DNA damage, epigenetic modifications, and telomere shortening and dysfunction<sup>44,45</sup>. Therefore both conditions can be considered – at least partly – as "premature organ ageing".

It has also been shown that the association of obstructive sleep apnoea (OSA) and COPD is associated with vascular endothelial dysfunction, elevated inflammatory mediators, and accelerated atherosclerosis<sup>46,47</sup>.

In epidemiologic studies and clinical cohorts, OSA has also been associated with an increased risk of death, mainly because of cardiovascular causes. Indeed, it has been suggested that the number of cardiovascular deaths in patients with untreated overlap syndrome is higher when compared with overlap treated patients, and also higher than those with COPD only <sup>46</sup>.

It is now recognized that COPD and HF are systemic diseases with profound effects on multiple peripheral tissues including skeletal muscle. Skeletal muscle alterations in patients with COPD and HF include a decrease in muscle mass, size, and diameter. The mechanisms involved in muscular atrophy in both diseases are unknown, although they seem to be related to muscular disease, systemic inflammation, and an increase in oxidative stress, which contributes to reducing protein synthesis and accelerating protein degradation <sup>48</sup>. Particularly both COPD and HF share the same type of metabolic modulation with the cellular metabolism shifting from glucose to lipid metabolism, resulting in generalized muscle dysfunction, and eventually chronic wasting and cachexia in the end stage of both diseases <sup>49 50</sup>.

Muscular atrophy contributes to muscle fatigue during exercise, which causes these patients to interrupt their exercise in spite of not exhausting their cardiac and respiratory reserves. As a result, the maximum oxygen consumption is directly related to skeletal muscle mass in both processes <sup>47-50</sup>.

## PROBLEMS DIAGNOSIS

The coexistence of both COPD and HF remains frequently unrecognized. The diagnosis is problematic for several reasons, especially in the elderly <sup>51-57</sup>.

Both conditions share features such as age of development, smoking as a risk factor and symptoms and signs such as exertion dyspnoea, functional disability, nocturnal cough, peripheral oedema, and jugular venous distension. However these features can be attributed to additional comorbidities <sup>52</sup>, present mainly in the elderly <sup>53</sup>. Therefore clinical symptoms and signs require careful interpretation, in conjunction with objective evidence of each condition. Several tests can be performed to assist in the diagnosis of each disease.

A normal electrocardiogram is useful to exclude HF, nevertheless this tool lacks specificity to undoubtedly assert that diagnosis because abnormalities found frequently overlap with those seen in other conditions, including COPD <sup>58</sup>. The interpretation of chest radiography maybe misleading because chest hyperinflation present in COPD patients can mask an increased cardiothoracic ratio and right ventricular enlargement can

obscure left ventricular dilation <sup>59</sup>. Also, whereas extra shadows commonly seen in lung disease can suggest spurious pulmonary oedema, the remodelling of pulmonary vascular bed may hide the typical alveolar pattern found in acute heart failure <sup>59</sup>.

Assessment of left ventricular function is mandatory for diagnosing HF. Echocardiographic acoustic windows may be impeded by air trapping in pulmonary disease, in addition in elderly patients, changes in echocardiographic parameters associated with ageing, such as reduced early diastolic filling, increased late diastolic filling, and reduced myocardial diastolic velocities, are to considered <sup>60</sup>. To overcome this limitation, the use of cardiac MRI (CMRI) is currently being advocated as an alternative. Apart from providing accurate and reproducible measurements of left ventricular volumes and LVEF that are not affected by lung hyperinflation, this technique is also valuable in the correct valuation of right ventricular volume and function <sup>61</sup>.

On the other hand, objective evidence of airflow obstruction is mandatory for diagnosing COPD. The presence of a post-bronchodilator  $FEV_1/FVC < 0.70$ , at the spirometry, confirms the presence of persistent airflow limitation and thus of COPD <sup>1</sup>.

This criterion in older patients has been repeatedly criticized for not acknowledging the age-associated physiological decline of the  $FEV_1/FVC$  ratio, reaching 70% in those over 75 years of age. Therefore COPD may thus be over diagnosed in elderly patients with HF <sup>56 57</sup>. Alternatively, an age- and sex-adjusted approach was proposed employing the lower limit of normal (LLN) of the  $FEV_1/FVC$  ratio, however the superiority of the LLN over the GOLD definition has not generally been accepted <sup>57</sup>. Although the GOLD guidelines acknowledge these limitations of the current definition, they still adhere to the fixed ratio for its simplicity and applicability to a broader, worldwide range of caregivers <sup>1</sup>. Both the commonly used fixed ratio of  $FEV_1/FVC$  as measured with spirometry, and the LLN approach bear the risk of over- and underdiagnosing true COPD, respectively. Regarding the severity of COPD, until recently it was graded on the reduction of  $FEV_1$ . This approach results in overestimation of COPD severity in patients with heart failure with reduced ejection fraction, because HF itself causes a 20% reduction in  $FEV_1$ . Indeed airflow obstruction is common in patients with decompensated HF <sup>62 63</sup> contrasting with restrictive defects when HF is stable. Interstitial and alveolar oedemas cause compression and obstruction of the airways, compounded by bronchial hyperresponsiveness <sup>64</sup>. With diuresis, mean  $FEV_1$  improves by up to 35% and often returns to normal <sup>62 63</sup>.

Pulmonary function tests are therefore most informative when patients are clinically euvoalaemic.

For routine clinical practice, consultation of a pulmonologist would be both a pragmatic and an adequate approach. It is remarkable that, despite the importance of COPD as comorbidity in HF, the latest HF guidelines do not include spirometry among the complementary tests recommended in the management of this entity.

Natriuretic peptides (NP) are very useful to reliably diagnose or rule out heart failure as the cause of acute dyspnoea in patients without COPD<sup>65-69</sup>. Regarding COPD patients, natriuretic peptides remain accurate, at higher thresholds, in the diagnosis of HF mainly during acute exacerbation<sup>70</sup>. Differently the diagnostic accuracy of BNP in patients with concurrent COPD is less certain. In patients with stable COPD and systolic dysfunction of the left ventricle or pulmonary heart, BNP levels were significantly higher compared to those of patients in whom a diagnosis of heart failure was excluded<sup>71-73</sup>.

During exacerbations, the peptide levels were found to be only modestly higher than in the clinically stable phases, nevertheless in those patients who have comorbidities such as ischemic heart disease, pulmonary embolism, arrhythmias, aortic stenosis, pulmonary hypertension and renal impairment, plasma levels of NP can be raised significantly<sup>74</sup>.

An interesting study has examined the ability to identify HF in elderly COPD patients<sup>75</sup>. Four natriuretic peptide assays produced comparable results in 200 stable elderly patients with a clinical diagnosis of COPD. Although each test excluded HF with reasonable accuracy (all negative predictive values above 0.85), however, the positive predictive value and overall diagnostic accuracy were lower than observed in patients with acute dyspnoea<sup>75</sup>. Different cut-off values apply to COPD patients with acute dyspnoea. A single cut point for BNP to exclude/detect HF was  $< 100$  pg/mL, with a sensitivity of 93% and a specificity of 77%<sup>76</sup>. Although not specifically tested in patients with a history of COPD, it is suggested that BNP levels  $> 500$  pg/mL indicate acute HF in COPD. Finally, in COPD patients with BNP levels of 100-500 pg/mL, cor pulmonale (right ventricular stretch) might be the source (or moderate left ventricular failure)<sup>77</sup>.

In summary, very high and very low concentrations of natriuretic peptides have high positive and negative predictive values for diagnosing HF in those with both conditions.

## BETA-BLOCKERS USE IN ELDERLY PATIENTS WITH COEXISTENT COPD AND HF

According to the ESC HF-guidelines, the HF should be treated even in COPD patients, because there is no evidence that HF should be treated differently in patients with

this comorbidity. However the coexistence of both diseases creates important therapeutic dilemmas, particularly in the elderly patients. A lot of trials show the underutilization of beta-blockers in patients with CHF and coexistent COPD<sup>78-90</sup>. In EVEREST and OPTIMIZE-HF the use of b-blockers was  $\sim 65\%$  vs  $75\%$ , and in HF-ACTION it was  $88\%$  vs  $95\%$ <sup>79-81</sup>. 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 beta 2 adrenergic receptors in the lung.

Existing data support the use of beta-blockers in elderly CHF patients with concomitant COPD. Treatment with beta-blockers was shown to reduce mortality in elderly patients with myocardial infarction during a follow-up of 24 months<sup>86</sup>. The overall reduction in mortality was 40% in the overall population and 32% among elderly over 80 years<sup>86</sup>. Likewise, a reduction of mortality was observed in patients with a history of COPD<sup>86</sup>.

Chen et al. assessed the effectiveness of beta-blocker therapy after acute myocardial infarction in 54,962 patients, of which about 20% was affected by COPD or asthma<sup>87</sup>.

Patients with COPD or asthma were significantly less likely to be treated with beta-blockers therapy after myocardial infarction. Beta-blockers were prescribed only in 9,3% of patients with severe COPD or asthma<sup>87</sup>. 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)<sup>87</sup>.

Differently, in a cohort study, included 1062 patients over 65 years with COPD or asthma and concomitant coronary artery disease, 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<sup>88</sup>.

The interaction between beta-blocker selectivity and outcome in patients with COPD and systolic left ventricle dysfunction was investigated by Mentz et al.<sup>89</sup>. In this study 725 patients had a history of COPD (27%). COPD patients were less likely to receive beta-blockers than patients without COPD<sup>89</sup>. Among patients receiving beta-blockers, 40% received a cardioselective beta-blockers and 60% a non-cardioselective one. Treatment with beta blocker was associated with lower mortality rate among patients with COPD and in the overall population and this outcome was not affected by the selectivity of the beta-blocker used in patients with concomitant COPD and HF. Similar findings have been demonstrated in OPTIMIZE-HF<sup>80</sup>.

A Cochrane meta-analysis concluded that b-1-selective b-blockers are safe: from the b-blockers currently recommended in HF therapy, only carvedilol is not

cardioselective<sup>90</sup>. Metoprolol, bisoprolol and nebivolol are the best candidates in treatment of HF with concomitant COPD<sup>2</sup>.

## PROGNOSTIC IMPLICATIONS OF COEXISTENT COPD AND HF IN ELDERLY PATIENTS

Despite European guidelines indicating COPD as an independent predictor of worse prognosis in HF, contrasting results have been reported in HF studies regarding the impact of COPD on the prognosis. Several studies support worse outcomes in HF patients with COPD, while others have been neutral<sup>88,91,92</sup>. In a study comparing the impact of different comorbidities on prognosis in 2843 patients diagnosed with HF and preserved ejection fraction and 6599 with HF and reduced ejection fraction, COPD was the only comorbidity that acted as an independent variable of mortality for both groups<sup>93</sup>.

In the REPENSAR registry, the presence of airway obstruction in patients with HF did not confer a statistical excess risk of death or hospitalisations during the 2-yr follow-up period. In contrast the presence of ventricular dysfunction in patients with COPD tended to increase the risk of mortality during the follow-up (hazard ratio 2.34, 95% CI 0.99-5.54;  $p=0.053$ )<sup>21</sup>. In HF-ACTION trial, COPD was associated with increased mortality/hospitalization, mortality, and cardiovascular mortality (CV)/HF hospitalization on unadjusted analysis, but not with increased mortality/CV hospitalization. Therefore the primary effect of COPD in HF patients may be increased non-cardiovascular mortality in the acute HF setting<sup>80</sup> with similar outcomes following hospital discharge<sup>81</sup>. Recently, Canepa et al. performed a retrospective analysis of clinical characteristics and outcomes of the 1,533 elderly patients with HF and concurrent COPD (22%)<sup>94</sup>. This study reveals that COPD is an independent predictor of mortality and hospitalizations in ambulatory HF patients. Indeed, COPD carried an independent 28% increased risk of death and 19% increased risk of death or hospitalizations for cardiovascular reasons over 4 years of follow-up<sup>94</sup>.

## CONCLUSIONS

COPD and CHF are common diseases of the elderly that frequently coexist<sup>95</sup>. COPD prevalence is dramatically rising, but reliable figures are not available because many elderly, mostly the ones plagued with disability and multimorbidity, cannot perform a good quality spirometry. Furthermore, atypical presentations contribute to conceal COPD<sup>96</sup>. The combination of HF and COPD presents many diagnostic challenges mainly

due to the similarities in clinical presentation and additionally due to a lack of relevant studies addressing the combination of HF and COPD. Several tests can be performed to assist in the diagnosis of each disease. Assessment of left ventricular function by transthoracic echocardiography is mandatory for diagnosing HF, while magnetic resonance imaging is the modality of choice in those with limited acoustic windows. On the other hand, objective evidence of airflow obstruction, when clinically euvoletic, is mandatory for diagnosis of COPD. Both are chronic progressive diseases and their prognosis combined is poorer than for either disease alone, therefore it is really important to recognize the coexistence of both processes early. Greater collaboration is required between cardiologists, pulmonologists, and general practitioners. Due to the high prevalence of unrecognized HF among patients with COPD, all elderly patients with persistent dyspnoea or functional intolerance despite optimal treatment for COPD should be referred to a cardiologist in order to undergo cardiac imaging to uncover potential coexistence of HF. Likewise, elderly patients with HF and persistent dyspnoea or functional intolerance despite optimal treatment should be referred to a pneumologist in order to undergo investigation including pulmonary function tests to establish or exclude coexistent COPD.

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# Regulation of aldosterone in heart failure and vascular aging: implications for therapy

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Aldosterone mediates a multitude of angiotensin II (AngII)'s effects. Its synthesis and secretion from the zona glomerulosa cells of the adrenal cortex, elevated in chronic heart failure (HF), is induced by AngII type 1 receptors (AT<sub>1</sub>Rs). The AT<sub>1</sub>R is a G protein-coupled receptor, mainly coupled to G<sub>q/11</sub> proteins. However, it also signals through barrestin-1 (barr1) or -2 (barr2), both of which mediate G protein-independent signaling. Over the past decade, a second, G<sub>q/11</sub> protein-independent but barr1-dependent signaling pathway emanating from the adrenocortical AT<sub>1</sub>R and leading to aldosterone production has come to the light, signifying that AT<sub>1</sub>R antagonists that block both G proteins and barrs at the AT<sub>1</sub>R equally well are needed to achieve full suppression of aldosterone. Indeed, although all marketed angiotensin receptor blockers (ARBs, AT<sub>1</sub>R antagonists or sartans) potently inhibit G protein activation, candesartan and valsartan were found to be the most potent agents at blocking also barr activation. Therefore, these two drugs are portended to be the most effective aldosterone suppressors in vitro and in vivo in post-myocardial infarction (MI) HF animals. Finally, in addition to HF, hypertension, and other cardiovascular diseases, aldosterone is implicated also in arterial aging and associated vascular fibrosis, making it a potential therapeutic target for cardiovascular disease treatment in geriatric patients.

**Key words:** Adrenocortical zona glomerulosa cell, Aldosterone, Angiotensin II type 1 Receptor, Barrestin-1, Heart Failure, Vascular aging

## INTRODUCTION

Aldosterone is a mineralocorticoid hormone with several cardio-toxic actions, whose plasma levels are extremely high in chronic heart failure (HF) negatively affecting progression of the disease<sup>1</sup>. Amongst its main actions on the failing myocardium is overall promotion of adverse remodeling via maladaptive hypertrophy, chamber dilatation, collagen deposition and fibrosis<sup>2,3</sup> etc. (Fig. 1). The net result of all of these effects is acceleration of cardiac functional decline<sup>4-6</sup>. The main source of circulating aldosterone is the adrenocortical zona glomerulosa (AZG) cells, which synthesize and secrete it in response to high serum K<sup>+</sup> levels (hyperkalemia), since its main action on the kidneys is K<sup>+</sup> excretion (along with Na<sup>+</sup> and water reabsorption)<sup>7</sup>.

Another powerful physiological stimulus for aldosterone secretion from AZG cells is the octapeptide hormone angiotensin II (AngII), which activates its type 1 receptors (AT<sub>1</sub>Rs), endogenously expressed in AZG cells<sup>7,8</sup>. The AT<sub>1</sub>R is a 7-transmembrane-spanning or G protein-coupled receptor (GPCR); upon agonist activation, it couples primarily to the Gq/11 family of G proteins<sup>8</sup>. Nowadays however, it is known to signal also through other types of G proteins, like Gi/o and Gs, as well as through G protein-independent pathways mediated by the universal GPCR adapter proteins b-arrestin-1 (barr1) and barr2 (also known as Arrestin-2 and -3, respectively)<sup>9-11</sup>. The barrs bind agonist-activated and GPCR-kinase (GRK)-phosphorylated GPCRs to uncouple them from G proteins (receptor desensitization) and to target them to clathrin-coated vesicles for

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internalization (receptor endocytosis). At the same time, they initiate their own, “second wave” of signal transduction independently of G proteins<sup>12-15</sup>.

## A NEW PLAYER IN AT1R SIGNALING TO ALDOSTERONE PRODUCTION: BARR1

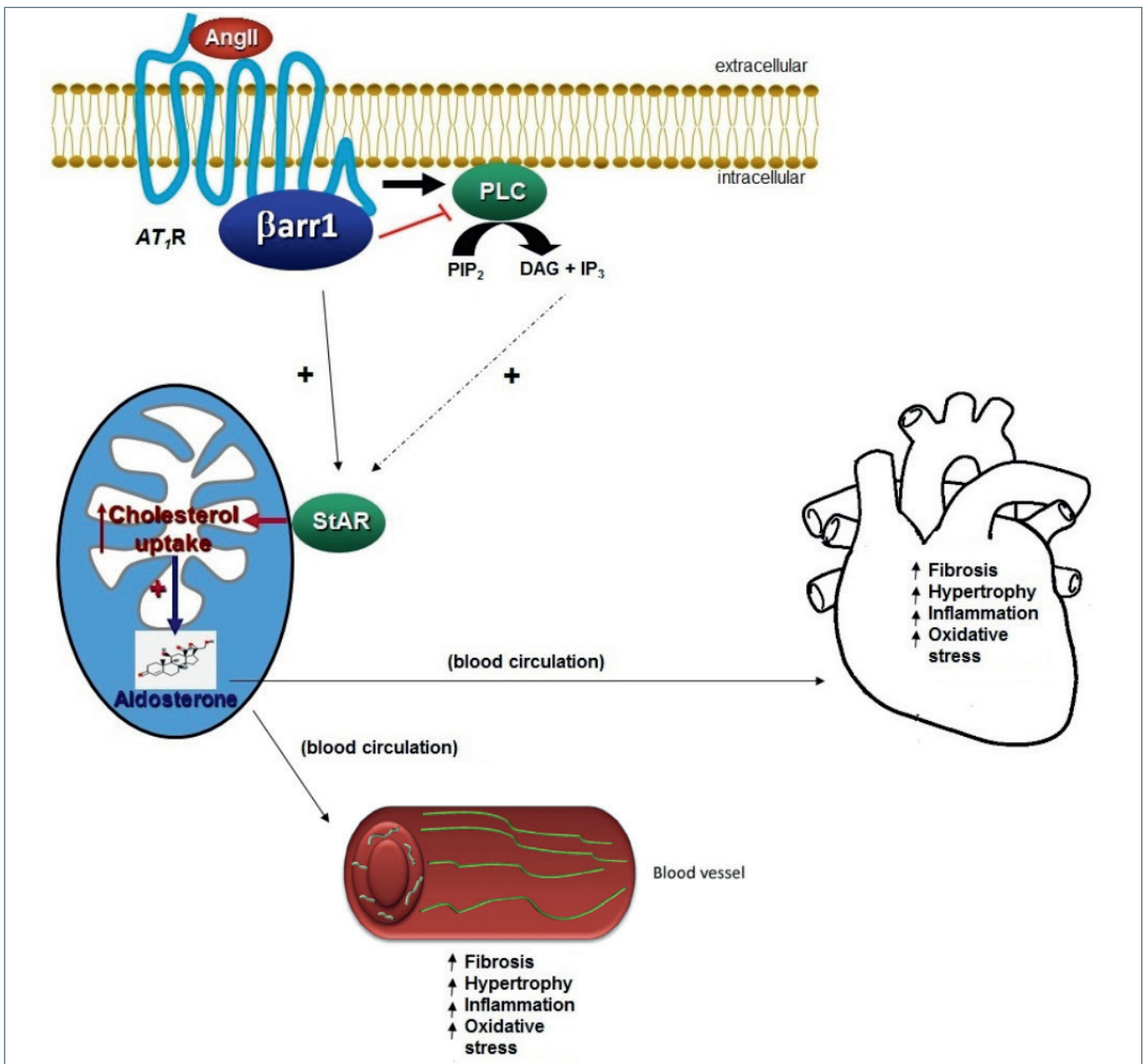
The Gq/11 protein-dependent signaling pathway elicited by the AngII-activated AT1R that culminates in aldosterone synthesis and secretion in AZG cells has been well characterized<sup>16</sup>. More specifically, diacylglycerol (DAG) and inositol trisphosphate (IP3), the two second messengers produced by the Gq-activated phospholipase C (PLC) $\beta$ , ultimately lead to: a) aldosterone secretion, via elevated intracellular free Ca<sup>2+</sup> concentration, which directly stimulates exocytosis and hormonal (in the context of AZG cells, aldosterone) secretion, and b) aldosterone synthesis, via extracellular signal-regulated kinase (ERK) MAPK activation, which, in turn, stimulate aldosterone biosynthesis in AZG cells by transcriptionally upregulating the steroidogenic Acute Regulatory (StAR) protein (Fig. 1)<sup>16</sup>. This protein mediates the mitochondrial uptake of the precursor of all adrenal steroids cholesterol and is the rate-limiting enzyme of aldosterone biosynthesis in AZG cells<sup>16</sup>.

In the chronic HF setting, adrenal GRK2 is upregulated and, along with barr1, hyperphosphorylates and severely desensitizes the sympatho-inhibitory  $\alpha$ 2-adrenergic receptors (ARs) of chromaffin cells in the adrenal medulla<sup>17-23</sup>. The result of this is chronic elevation of adrenal catecholamine secretion, which significantly contributes to the heightened sympathetic nervous system outflow and increased norepinephrine and epinephrine levels that further damage the failing heart<sup>24-29</sup>. Since aldosterone is also increased in HF and its production is stimulated by the AT1Rs of the adrenal cortex<sup>1</sup>, which are also GRK2 and barr1 substrates, it was theorized that the upregulated (in HF) adrenal GRK2 could lead to excessive interaction of barr1 also with the AT1R in the adrenal cortex, thereby modulating aldosterone secretion in the chronic HF setting, as well. Indeed, this was found to be the case<sup>30</sup>. Via a combination of *in vitro* experiments in the human AZG cell line H295R and *in vivo* experiments in experimental rats developing HF following an acute, surgically induced myocardial infarction (MI), we were able to show that adrenal barr1 actually promotes AngII-dependent aldosterone synthesis and secretion by also mediating AT1R signaling to ERK-dependent StAR upregulation independently of G proteins (Fig. 1)<sup>30,31</sup>. This finding was somewhat surprising, given that barr1 would normally be expected to reduce AngII-dependent aldosterone production thanks to desensitizing the AT1R (terminating its G protein-dependent

signaling, see above). Nevertheless, it was discovered that, after abolishing the Gq-dependent signaling by the AT1R in AZG cells, AT1R-bound barr1 initiated its own signaling to aldosterone synthesis by recruiting a DAG-kinase (DGK) to the activated receptor<sup>32</sup>, which converted the second messenger lipid DAG to phosphatidic acid (PA)<sup>30</sup>. PA can directly activate the small (monomeric) G protein Ras at the plasma membrane, which then initiates the cascade that results in ERK phosphorylation and activation<sup>33</sup>. Thus, AT1R-activated barr1 elicits a “second (delayed) wave” of signaling leading to sustained ERK activation in AZG cells in its own right (i.e. independently of G proteins), which, as discussed above, promotes aldosterone production via StAR upregulation<sup>30</sup>. Importantly, since StAR regulates synthesis not only of aldosterone but also of all adrenal steroids throughout the three anatomical zones of the adrenal cortex<sup>16</sup>, adrenal barr1 may also affect the synthesis of glucocorticoids and of androgens in the adrenal cortex.

Notably, adrenal barr1 may not only stimulate the AT1R-dependent aldosterone synthesis via its “second wave” of signaling to ERK-dependent StAR upregulation but also facilitate the acute AT1R-dependent aldosterone secretion at the plasma membrane of AZG cells and in parallel to the G protein-mediated signaling by the receptor (Fig. 1). Recent evidence in transfected heterologous systems suggests such a role in the “first wave” of GPCR signaling for the barrs<sup>34,35</sup> and a very intriguing study, done specifically in the adrenal medulla, suggested an acute stimulation of catecholamine secretion and of Ca<sup>2+</sup>-dependent exocytosis by AT1R-activated barr1 (but interestingly not by barr2) in adrenal chromaffin cells, thanks to its direct interaction with the plasma membrane Ca<sup>2+</sup> channel TRPC3 (short transient receptor potential channel-3)<sup>36</sup>. Thus, it is quite plausible that AT1R-bound barr1 can directly stimulate TRPC3-dependent Ca<sup>2+</sup> currents and hence, exocytosis, also in AZG cells, thereby acutely stimulating AngII-dependent aldosterone secretion within seconds of agonist binding (and in parallel to the Gq-mediated signaling by the AT1R). This interesting possibility of another signaling mechanism by which barr1 can induce aldosterone production in AZG cells is definitely worthy of investigation in future studies.

Most importantly, adrenal barr1-dependent aldosterone production has been documented to occur also *in vivo*, both under physiological (in normal, healthy animals) and pathophysiological (in the post-MI HF setting) conditions<sup>30,31</sup>. Specifically, adrenal-targeted barr1 overexpression increased aldosterone serum levels *in vivo* in normal rats<sup>30</sup>, and caused severe hyperaldosteronism also in post-MI rats on top of the circulating aldosterone elevation normally occurring due to the MI



**Figure 1.**  $\beta$ arr1 and aldosterone production in HF and in vascular aging. Schematic representation of the parallel PLC- and  $\beta$ arr1-mediated, AngII-activated AT<sub>1</sub>R signaling cascades that converge on mitochondrial aldosterone synthesis and secretion from AZG cells. The secreted aldosterone then travels through the bloodstream to exert its various effects on the cardiac and vascular smooth muscles. See text for details and for molecular acronym descriptions. Modified with permission from Ref. 27.

injury<sup>31</sup>. Importantly, in the latter animals, adrenal-specific  $\beta$ arr1 blockade in vivo with a  $\beta$ arr1 C-terminal fragment during post-MI HF progression helped stall the decline of cardiac function and even reversed several aspects/markers of adverse cardiac remodeling courtesy of normalization of circulating aldosterone levels<sup>31</sup>. What's more, aldosterone levels remarkably show no increase in  $\beta$ arr1-knockout mice post-MI, which further highlights the importance of adrenal  $\beta$ arr1 in regulation of circulating aldosterone levels<sup>37</sup>. Together, these *in*

*vivo* studies strongly suggest adrenal  $\beta$ arr1, in conjunction with GRK2, as an attractive therapeutic target for diseases associated with, and aggravated by hyperaldosteronism, such as post-MI HF<sup>9,28</sup>. Adding to its importance as a therapeutic target is also the fact that aldosterone can produce effects independently of its mineralocorticoid receptor (MR) (the so-called "non-genomic" actions of aldosterone)<sup>4</sup>. Obviously, these effects cannot be countered by MR antagonist drugs (e.g. eplerenone, finerenone, spironolactone) and thus,

suppression of aldosterone production at its source, i.e. the adrenal cortex, via adrenal barr1 blockade would be much more preferable from the therapeutic standpoint. Implications for the ARB drug class & HF pharmacotherapy

The involvement of barr1 in AngII-dependent aldosterone production from the adrenal cortex, coupled with the fact that some ARBs appear ineffective at lowering aldosterone in HF, despite their full capacity to block AT1R-G protein coupling<sup>38-41</sup>, prompted investigation of the relative efficacies of the currently available ARBs at suppressing barr1-dependent aldosterone production. The prototypic agent of this class, losartan, was found ineffective at preventing adrenal barr1-dependent aldosterone production and combatting hyperaldosteronism post-MI due to very weak antagonism of barr1 activation by the AT1R<sup>31 42</sup>. Interestingly however, the active metabolite of losartan EXP1374 was found quite effective at blocking AT1R-dependent aldosterone production and barr1 activation<sup>43 44</sup>. Conversely, candesartan and valsartan were the most potent blockers of barr1 activation and the most efficacious aldosterone suppressors *in vitro* and *in vivo*<sup>44 45</sup>. At the opposite end of the spectrum, together with losartan, was irbesartan, which was found to be a very weak barr1 inhibitor and hence, a very ineffective aldosterone suppressor both *in vitro* and *in vivo*, despite its excellent G protein-blocking ability<sup>44 45</sup>. Importantly, effects on cardiac function of post-MI HF animals *in vivo* were in complete concordance with effects on circulating aldosterone levels, i.e. candesartan and valsartan induced significant improvements in cardiac function and remodeling, whereas irbesartan and losartan were not able to halt HF progression<sup>44</sup>.

Given the significant variation in pharmacological and clinical properties, such as improvements in morbidity and mortality of chronic HF, of the ARBs<sup>45-49</sup>, it is quite plausible that their differences in aldosterone-suppressing efficacy may underlie at least some of these pharmacological and clinical differences. In other words, the ARBs that are most effective at blocking the AT1R-barr1-dependent aldosterone production may afford the biggest improvement in HF morbidity and mortality. Indeed, candesartan and valsartan, which are the most efficacious barr1-mediated aldosterone suppressors (see above), have been reported to improve HF patient survival to a larger extent than losartan<sup>46-51</sup>. In contrast, irbesartan, which was found to be very weak at blocking barr1-dependent aldosterone, shows no benefit in HF with preserved ejection fraction (HF-PEF) and appears inferior to candesartan in terms of HF mortality reduction<sup>48 49</sup>. Of course, future trials providing data on the serum aldosterone levels of the

ARB-treated HF patients are needed to confirm such a link between adrenal barr1-dependent aldosterone suppression efficacy and clinical benefit for this important cardiovascular drug class.

On the other hand, failure of these agents to suppress aldosterone, otherwise referred to as "aldosterone breakthrough" or "aldosterone escape", is a clinically well-documented phenomenon<sup>46-49</sup> and the efficacy of each agent at inhibiting barr1-dependent aldosterone production may be inversely proportional to the probability of the ARB to exhibit it.

## IMPLICATIONS FOR AGING

In addition to the heart, aldosterone promotes hypertrophy, fibrosis, inflammation, and oxidative stress also in arteries (Fig. 1)<sup>54-56</sup>. This aldosterone-dependent vascular fibrosis can be quenched by mineralocorticoid receptor blockers, such as spironolactone, eplerenone and finerenone<sup>57</sup>. Interestingly, in aging, aldosterone levels appear to decline rather than increase<sup>58 59</sup>, but vascular mineralocorticoid receptors, which mediate most of the effects of aldosterone, are upregulated in aged intact vessels and in vascular smooth muscle cells isolated from aged animals, correlating with increased vascular fibrosis<sup>60</sup>. Nevertheless, more studies are needed to delineate the precise role of mineralocorticoid receptor signaling in aging-related vascular fibrosis and to validate aldosterone as a therapeutic target for geriatric heart disease.

## CONCLUSIONS & FUTURE PERSPECTIVES

It is now well appreciated that AngII-dependent aldosterone production is a complicated process involving not only G protein signaling but also barr-dependent (G protein-independent) signal transduction. Recent studies have identified candesartan and valsartan as the most potent barr signaling antagonists, hence the most efficacious aldosterone suppressors *in vitro* and *in vivo*. Thus, from a therapeutic standpoint, candesartan and valsartan may be the most preferable agents of the ARB drug class, at least for post-MI HF treatment. On the other hand, the role of aldosterone in vascular fibrosis and hypertension, albeit well established during adulthood, is still under intense investigation in the context of aging. Future studies on aldosterone antagonists and ARBs in animal models of aging and, of course, in geriatric patients will help elucidate the therapeutic potential of targeting this hormone for geriatric cardiovascular therapy.

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## Therapy response variability in elder cardiac patients

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Cardiovascular drugs are among the most prescribed medications in the world and, despite their proven effectiveness, there is a large variability in the therapeutic response in term of both efficacy and tolerability with remarkable clinical consequences especially in elderly patients. Additionally, cardiovascular patients respond in a changing manner also to non-pharmacological therapeutic approaches, such as antioxidants supplementation and exercise training. This review focuses on factors, including biochemical and molecular variables, comorbidity, polypharmacy and life-style that may influence the response to the common cardiovascular pharmacological and non-pharmacological treatments, paying particular attention to the emergent issue of cardiovascular pharmacogenetics.

**Key words:** Cardiovascular drugs, Pharmacogenetics, Anticoagulant, Antiplatelet agents, Non-pharmacological treatments

### INTRODUCTION

Patients with cardiovascular diseases (CVD) show a large variability in the response to cardiovascular treatments. This is true mainly in elder subjects representing a patient population very complicated to treat and manage <sup>1</sup>.

Many and different factors, including molecules in patients' sera and bioavailability of molecules crucial for the maintenance of cardiovascular homeostasis influence onset and progression of chronic diseases as well as the therapeutic response <sup>2</sup>.

In elderly population the management of chronic pathologies, i.e. CVD is strongly influenced by the presence of cardiac and noncardiac comorbidities with consequent polypharmacy <sup>3</sup>, and it is also conditioned by the frailty <sup>4</sup> and cognitive impairment <sup>5</sup> that are very common in the oldest individuals.

Cardiac patients also vary in the response to non-pharmacological therapeutic approaches, such as Salus

Per Aquam (SPA) medicine <sup>6</sup>, antioxidants supplementation and exercise training because also the results of non-drug treatments can be determined by the specific metabolic demand and genetic background of each patient <sup>7,8</sup>.

Nowadays, it is becoming more and more clear that genetic factors can condition the outcomes of the pharmacological treatments <sup>9,10</sup>. In particular, polymorphisms in genes encoding molecules controlling both pharmacodynamics and pharmacokinetics of cardiac drugs may influence the therapeutic response. This is the basic concept of the cardiovascular pharmacogenetics, which recently is attracting great attention from the scientific community <sup>11</sup>.

This review aims to provide a comprehensive overview on the factors influencing the response to both pharmacological and non-pharmacological treatments in elderly cardiac patients, paying particular attention to the emergent issue of cardiovascular pharmacogenetics.

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## BIOCHEMICAL AND MOLECULAR CHARACTERISTICS OF PATIENTS

Several molecules concur to the maintenance of cardiovascular homeostasis and their systemic levels often influence cardiovascular drugs response<sup>12</sup>.

High serum levels of cholinesterase, total cholesterol and albumin have been associated with residual platelet aggregation rate (RPA) during antiplatelet therapy in patients with CVD<sup>13</sup>. Moreover, Hong et al. have showed that coronary heart patients undergoing percutaneous coronary intervention and treated with a standard antiplatelet agent had higher RPA beside increased levels of inflammatory markers such as E-Selectin, metalloproteinase<sup>9</sup> and molecules involved in the platelet aggregation process, including soluble CD40 ligand<sup>14</sup>. Furthermore, it has been observed that aged cardiac patients with higher magnesium levels showed less probability to survive at a 3-year follow-up than patients with lower levels and a strong relationship between hypermagnesemia and laxative/antacid administration was found<sup>15</sup>.

Several studies on the pathways of nitric oxide (NO) have corroborated the idea that the pharmacological treatments are strongly associated to the biochemical and molecular profile of each patient. For instance, the increase of the plasmatic levels of asymmetric dimethyl-arginine (ADMA), a well-known inhibitor of nitric oxide synthase (NOS), may be a predictive factor for cardiovascular events since it contributes to development of the endothelial dysfunction, which is essentially caused by an increase of the oxidant species resulting in oxidative stress and impairment of the NO signalling<sup>16-18</sup>. Hsu et al. demonstrated that ADMA could reduce the capacity of simvastatin to activate endothelial NO synthase (eNOS); notably, the authors subdivided their study population into two tertiles on plasmatic ADMA levels finding that only in patients with lower ADMA the beneficial effects of the statin were preserved<sup>19,20</sup>.

On the other hand, high levels of symmetrical dimethylarginine (SDMA) and ADMA in patients with acute congestive heart failure and impaired renal function have been found increased after a standard therapy as a consequence of the reduced expression and activity of eNOS and increased O<sub>2</sub>- level<sup>21,22</sup>. Furthermore, Angiotensin Converting enzymes inhibitors (ACE-I), especially ramipril, but also statins may improve platelet NO resistance and arterial stiffness, thereby attenuating the risk of coronary events. Such effects are likely to improve therapeutic outcomes and are also helpful to identify patients in whom the pharmacological treatments can be effective<sup>23,24</sup>. The NO pathway has been also referred to explain the reduced response to aspirin (ASA). In this regard, López-Farré have found that

patients with coronary artery disease (CAD) showed low response to ASA probably because of a reduction of the eNOS-derived NO levels in mononuclear cells<sup>25</sup>. The suboptimal response to ASA in CAD patients could also depend on homocysteine levels. Actually, high levels of homocysteine acetylated by ASA have been associated with blood platelet refractoriness to low ASA dose and the serum levels of homocysteine have been found significantly lower in good responders compared to the poor ones<sup>26</sup>. Notably, it was showed that in hypertensive patients with high basal levels of homocysteine,  $\beta$ -blockers and ACE-I may reduce such levels, providing an additional therapeutic effect exemplified by an improvement of the endothelial function<sup>27</sup>. Also the treatment with simvastatin has been found able to decrease homocysteine plasma levels in hyperlipidemic patients and, also in this case, in the subjects with higher homocysteine basal levels<sup>28</sup>.

## COMORBIDITY AND POLYPHARMACY

Patients with CVD are generally elderly subjects and their medical care is often complicated by various, both cardiac and non-cardiac, comorbidities and polypharmacy<sup>29,30</sup>. Braunstein et al. have investigated the relationship between non-cardiac comorbidities and the rates of hospitalizations and total mortality in a large sample of old patients with chronic Heart Failure (HF), finding that chronic disease comorbidities, such as chronic obstructive pulmonary diseases (COPD), renal failure and Alzheimer exerted a huge negative impact on the care of such patients. Of note, the risk of preventable hospitalizations increased with the number of the coexisting diseases<sup>31,32</sup>. These findings are in accordance with those from Muzzarelli and colleagues who have recently reported that a large proportion of early re-hospitalizations in elderly HF patients were due to the presence of non-cardiovascular comorbidities<sup>33</sup>. Unquestionably, the presence of either cardiovascular or non-cardiovascular comorbidities in cardiac patients, especially older ones, invariably leads to polypharmacy that in turn can produce many negative consequences, including the increase of adverse drug reactions and dangerous drug interactions associated with common medications such as thrombolytic, antiplatelet and anticoagulants agents<sup>3,34</sup>.

The inappropriate prescribing represents another important problem. Actually, it has been estimated that a large number of aged patients receives one or more unnecessary medical prescriptions and several drugs are often prescribed even when they are contraindicated or ineffective<sup>3,35,36</sup>.

Importantly, the inappropriate medication is associated

with an increase of both morbidity and mortality and also contributes in expanding health care costs<sup>37</sup>.

Management of the chronic therapies in elderly is complicated also by the presence of frailty that increases the risk of disability, hospitalization, and mortality<sup>4</sup>.

For example, diuretic therapy in frail patients with HF is often associated to urinary incontinence, progression of renal dysfunction, delirium, falls, and vasodilators favor orthostatic hypotension<sup>38</sup>.

Also adherence to medication is an important issue, especially in the elderly patients in whom, besides the aforementioned variables, also psychological and socioeconomic factors must be taken into account<sup>39,40</sup>.

Many and various social barriers contribute to determine the non-adherence to the therapeutic treatments in the elderly. For example, the oldest patients are more likely to be female, often divorced or unmarried and living without caregiver<sup>41</sup>.

Non-adherent patients, often with low incomes and without a sufficient level of education, tend to completely break down their social networks<sup>42</sup>, easily developing psychological impairments such as depressive mood, anxiety symptoms and cognitive impairment<sup>5</sup>.

Campbell et al. found that cognitive decline is one of the most important predictors for poor compliance among the elderly, especially in presence of comorbidity implicating vision and/or hearing impairments. Indeed, the cognitive deficits heavily interfere with all daily activities including the ability to understand and follow physicians' instructions for taking the medications<sup>43</sup>. Cognitive impairment is particularly common in patients affected by CHF with ischemic origin and has been associated with an increased mortality rate<sup>44</sup>. Moreover, the cognitive impairment and dementia appear to increase with the occurrence of atrial fibrillation in elderly regardless of stroke history with a consequent lack of therapy response also to non-pharmacological treatment such as cardiac rehabilitation programs<sup>45</sup>.

## VARIABILITY IN RESPONSE TO NON-PHARMACOLOGICAL TREATMENTS

Management of elder cardiac patients requires a multidisciplinary approach that includes measures of counseling and education, and life-style modifications in dietary regimen and physical activity.

Physical activity, more specifically, exercise training (ET) is an important component of cardiac rehabilitation programs also in the aged patients<sup>46</sup>.

Indeed, sedentary is one of the major risk factors in patients with several chronic diseases, including CVD and the lack of compliance with both physical activity and well-structured ET program is often associated

with higher rates of morbidity and mortality of such individuals<sup>47</sup>.

Many studies have shown that in elder cardiac patients ET improves generic health-related quality of life (HRQOL) and exercise tolerance assessed by the 6-min walking distance (6MWD) test. However, there is a large variability in response to cardiac rehabilitation programs in dependence on several factors, such as age, gender and CVD severity<sup>48</sup>. Moreover, weight loss represents a good response to the exercise also because it favors the improvement of the exercise tolerance as demonstrated in obese men with coronary artery disease<sup>49</sup>; nonetheless, because of CVD population heterogeneity, a proportion of overweight patients, mainly with HF, may experience an attenuated response to the exercise.

Iellamo et al. have suggested that exercise in elder patients with CVD induced an improvement of heart rate variability and baroreflex sensitivity that correlated to individual volume/intensity training load with a significant increase of functional capacity<sup>50</sup>.

Importantly, the effects of ET strongly depend on both type and intensity of the training program<sup>51,52</sup> and, in this framework, great attention has to be paid to worsening of clinical condition possibly associated with an overtraining<sup>52</sup>.

Taking together, these data underline the need to administer a personalized cardiac rehabilitation programs for each patient<sup>53</sup>.

A multicomponent rehabilitation program especially in geriatric population may be helpful in delaying age-associated frailty also thanks to its ability to improve the capacity of antioxidant system, thereby reducing oxidative stress, which is very high in frail patients<sup>54</sup>.

Natural antioxidant compounds, such as vitamins C and E, resveratrol, curcumin and many others have been considered as adjuvant therapy in CVD patients. However, clinical trials involving the use of antioxidants supplementation in several age-associated diseases often show conflicting results and lead to dangerous misconceptions, either too positive or too negative. As a matter of the fact the interplay of both endogenous and exogenous antioxidants with the humans' redox system is very complex and represents an issue that is still under debate<sup>7</sup>.

Actually, a certain level of oxidant molecules, namely free radicals, is physiologically necessary and at same time an excess of the antioxidants might be deleterious<sup>55</sup>.

Thus, the controversial outcomes of the studies on antioxidants supplementation might partially depend on an underestimation of specific metabolic demand and genetic background of the enrolled patients, mainly in the elderly<sup>7</sup>.

## CARDIOVASCULAR PHARMACOGENETICS

Pharmacogenetics is the branch of pharmacology, which studies the genetic basis of the variability in drugs response. Many genetic variations, influencing the response to pharmacological treatments, have been identified; among them, particular attention has focused on Single Nucleotide Polymorphisms (SNPs) that can be responsible for the lack of drug efficacy or the occurrence of dangerous side effects. Nowadays, it is possible to provide the right drug and drug dosage to the right person, thereby maximizing drug efficacy and minimizing drug toxicity<sup>56</sup>.

The application of pharmacogenetics tests is becoming more and more feasible in several medical areas, including oncology<sup>57-58</sup>, immunology<sup>59-60</sup>, rheumatology<sup>61</sup>, endocrinology<sup>62-63</sup>, and many others.

The pharmacogenetics of CVD is of great research interest<sup>11</sup> and, indeed, polymorphisms in genes encoding molecular targets, transport proteins and metabolizing enzymes may influence the response to cardiac drugs encompassing their pharmacodynamics and/or pharmacokinetics<sup>64-66</sup>.

Important pharmacogenetics findings for cardiovascular drugs, such as statins,  $\beta$ -blockers, antiplatelet agents and both old (i.e. warfarin) and new (i.e. dabigatran) oral anticoagulants have been identified<sup>64</sup>.

Several *in vitro* and *in vivo* studies suggest that polymorphisms in genes encoding adrenergic receptors, such as the SNPs resulting in nonsynonymous substitutions Ser49Gly and Arg389Gly in the  $\beta$ 1 adrenergic receptor (ADRB1) gene may influence the therapy response to  $\beta$ -blockers with remarkable clinical consequences in patients with both HF and hypertension<sup>67-69</sup>. In addition, individuals carrying loss of function variant in gene encoding for CYP2D6 P450 enzyme are poor metabolizers for several drugs including  $\beta$ -blockers metoprolol and timolol but this does not result in clinically relevant toxicity. Nevertheless, it has been suggested that in poor metabolizers metoprolol cardioselectivity could be lost<sup>70</sup>.

The most important pharmacogenetics findings and the relative tests currently recommended and entered the clinical practice in the area of CVD concern the anticoagulant warfarin and the antiplatelet clopidogrel<sup>64</sup>.

### WARFARIN PHARMACOGENETICS

Warfarin is the most commonly prescribed oral anticoagulant worldwide for prevention and treatment of thromboembolic events in patients with mechanical heart valves or non-valvular atrial fibrillation (AF). Despite its effectiveness, this drug is associated with a high risk of both thromboembolism and bleeding especially in elderly patients<sup>71-73</sup>.

In particular, bleeding complications depend on a number of concomitant factors, including the reduction of metabolic clearance, the high prevalence of comorbidities, high occurrence of drug interactions and reduced compliance<sup>74</sup>.

Efficacy and safety of warfarin are determined through performing a blood test so called International Normalized Ratio (INR), which checks how long it takes for blood to clot.

An INR between 2.0 and 3.0 is generally accepted for non-valvular AF and venous thromboembolism, but for valve replacements a higher INR between 2.5 and 3.5 is usually recommended. INR levels greater or lower than the target range may result in significant bleeding or stroke respectively, particularly during the first weeks of the therapy<sup>75</sup>.

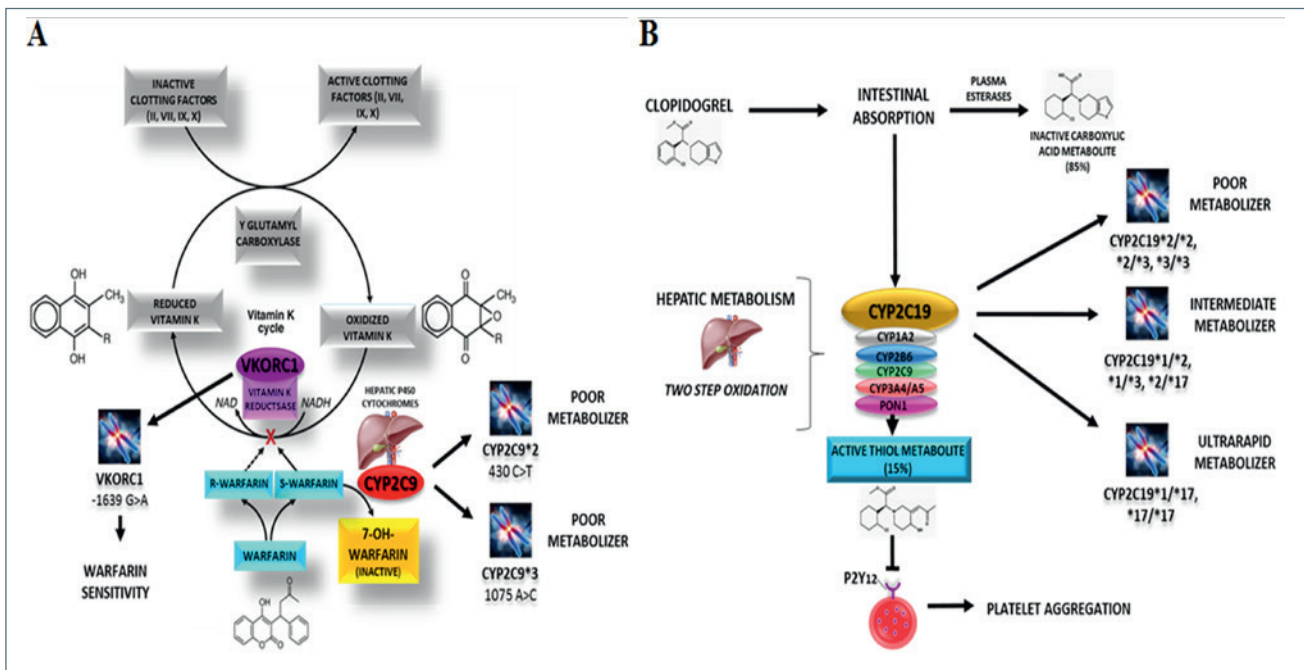
Warfarin acts by inhibiting of vitamin K epoxide reductase complex 1 (VKORC1), thereby limiting the availability of reduced vitamin K and decreasing the synthesis of functionally active vitamin K-dependent clotting factors (II, VII, IX and X). It is administered as a racemic mixture of R- and S-enantiomers and the more potent S-enantiomer is mainly metabolized by the isoform CYP2C9 of CYP450 family (Fig. 1, Panel A).

Patients treated with warfarin vary in the response in terms of both efficacy and safety and, among the numerous genetic factors potentially involved, one SNP in the promoter of the gene encoding warfarin's target vitamin K epoxide reductase complex 1 (VKORC1), indicated as VKORC1 -1639 G > A and two SNPs in the genes encoding the metabolizing enzyme CYP2C9 (e.g. CYP2C9-\*2 and -\*3) have been described as major contributors of dose-response variability. Patients carrying polymorphisms in one or both of these genes require lower or higher warfarin doses to obtain an adequate anticoagulant effect when compared with subjects carrying wild type genes (Fig. 1, Panel A and Tables I and II)<sup>76</sup>.

A pharmacogenetic algorithm, incorporating both clinical and genetic information, has been developed by the International Warfarin Pharmacogenetics Consortium (IWPC) to get a stable warfarin maintenance dose to lower the bleeding risk by personalizing the anticoagulant therapy. Actually, besides clinical and demographic factor, the IWPC algorithm includes the screening of the three aforementioned SNPs that can help to predict warfarin dose requirements<sup>77</sup>.

In 2007 and in 2010, the Food and Drug Administration (FDA) issued guidelines to stress the utility and the importance to analyze CYP2C9-\*2 and -\*3 and VKORC1 -1639 G > A polymorphisms before starting warfarin therapy<sup>78-79</sup>.

Several studies have demonstrated that the pharmacogenetic approach can be considered a feasible and accurate method to establish warfarin dosing and may



**Figure 1.** Schematic representation of pharmacodynamics and pharmacokinetics of warfarin and clopidogrel.

**Panel A:** warfarin produces its pharmacological effect by inhibiting of vitamin K epoxide reductase complex 1 (VKORC1), thereby limiting the availability of reduced vitamin K and decreasing the synthesis of functionally active vitamin K-dependent clotting factors (II, VII, IX and X). It is administered as a racemic mixture of R- and S-enantiomers. The more potent S-enantiomer is metabolized into inactive metabolite, 7-hydroxyl warfarin, by cytochrome *CYP2C9*. The variability in warfarin response depends on the presence of SNPs *VKORC1* -1639 G > A, resulting to a reduced activation of vit. K- dependent clotting factors and *CYP2C9*\*2 (430 C > T) and *CYP2C9*\*3 (1075A > C), that lead to the synthesis of *CYP2C9* isoforms with reduced enzymatic activity. These polymorphisms are associated to warfarin sensitivity, thus patients carrying such variants may require doses of anticoagulant lower than 5 mg/die to achieve the therapeutic INR.

**Panel B:** clopidogrel is a pro-drug that requires hepatic biotransformation to form an active metabolite. When administered, it is largely inactivated (for about 85%) from plasma esterases, while the remaining 15% is activated from several isoforms of cytochrome P450 family. The isoenzymes of the *CYP450* family involved in clopidogrel metabolism are *CYP2C19*, *CYP3A4/A5*, *CYP2C9*, *CYP1A2* and *CYP2B6*. The active metabolite selectively and irreversibly inhibits the purinergic P2Y12 receptor and thus platelet aggregation. Several alleles of *CYP2C19* (mainly *CYP2C19*\*2, *CYP2C19*\*3 and *CYP2C19*\*17) have been recognized as responsible of variable clopidogrel response.

**Table I.** Impact of CYP2C9 and VKORC1 polymorphisms on warfarin pharmacokinetics and pharmacodynamics, respectively.

<i>CYP2C9</i>		
Genotype	Metabolism	Clinical implications
*1/*1	Extensive metabolizer	Normal anticoagulant activity
*1/*2	Intermediate metabolizer	Reduced warfarin metabolism; increased anticoagulant activity
*1/*3	Poor metabolizer	Reduced warfarin metabolism; increased anticoagulant activity; increased risk for bleeding
*2/*2		
*2/*3	Poor metabolizer	Highly reduced warfarin metabolism; increased anticoagulant activity; increased risk for bleeding
*3/*3		
<i>VKORC1</i> (-1639 G > A)		
Genotype	Enzyme expression	Clinical implications
GG	Normal enzyme expression	Normal activation of vit. K- dependent clotting factors
GA	Moderate enzyme expression	Reduced activation of vit. K- dependent clotting factors
AA	Low enzyme expression	Highly reduced activation of vit. K- dependent clotting factors

**Table II.** Recommended daily dose of warfarin (mg/die) based on *CYP2C9* and *VKORC1* genotypes.

<i>VKORC1</i> Genotype (-1639 G > A)	<i>CYP2C9</i> Genotype					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines and FDA-approved warfarin (Coumadin) product label.

be preferred over fixed-dose regimens based on the administration of a starting dose of 5 mg/die<sup>76-80</sup>.

However, it appears that while individuals at the extremes of the dose requirements are undoubtedly advantaged by the application of the genetic-based warfarin treatment regimen, the overall clinical merits of this approach in the entire patient population remain to be assessed in large prospective clinical studies, that indeed are now ongoing<sup>81</sup>.

Nevertheless, it has been recently suggested that specific subgroups have not been included in clinical trials performed until now, likely resulting in underestimation of the pharmacogenetic advantage<sup>82</sup>.

The recent introduction into clinical practice of the New Oral anticoagulants (NOACs), such as the direct thrombin inhibitor, dabigatran etexilate and the direct inhibitors of factor Xa (e.g. rivaroxaban, apixaban) has partially readdressed the oral anticoagulant therapy.

Trials that have compared NOACs with warfarin have substantially demonstrated the non-inferiority of this drugs whit respect to warfarin mainly for stroke prevention<sup>83</sup>.

However, warfarin remains the mainstay of treatment for patients with mechanical heart valves and also in patients with non-valvular AF it is very important to consider both advantages and disadvantages of NOACs in each patient<sup>84</sup>.

Moreover, accumulating evidence suggests that a SNP in gene encoding the hepatic carboxylesterase 1, which

is responsible for the biotransformation of the pro-drug dabigatran etexilate into active metabolite dabigatran may influence the therapeutic response of this drug, suggesting the existence of a pharmacogenetics also for the new anticoagulant agents<sup>85 86</sup>.

#### CLOPIDOGREL PHARMACOGENETICS

Clopidogrel is an oral antiplatelet agent commonly prescribed to prevent thrombotic events in patients undergoing percutaneous coronary interventions (PCI) and/or after acute coronary syndrome (ACS). It is also largely used in secondary prevention in the subjects intolerant to ASA or with atrial fibrillation having contraindication to warfarin<sup>87</sup>.

Clopidogrel is a pro-drug, which requires an activating metabolism mediated by several hepatic cytochrome P450 enzymes, such as *CYP1A2*, *CYP2B6*, *CYP2C9*, *CYP2A4/5* and *CYP2C19*. After intestinal absorption, only 15% of drug is transformed in active thiol metabolite, while remaining 85% is inactivated by plasma esterases. Once activated, it irreversibly inhibits the platelet P2Y<sub>12</sub>-adenosine diphosphate receptor, thus preventing ADP- dependent IIb/IIIa glycoprotein complex activation<sup>88</sup>.

The response to clopidogrel is highly variable depending on drug interactions with metabolic inhibitors and inducers and polymorphisms present in the gene encoding the enzymatic isoform *CP2C19*<sup>89 90</sup>. Nowadays

**Table III.** *CYP2C19* variants and their relationship to clopidogrel antiplatelet action.

<i>CYP2C19</i>		
Genotype	Metabolism	Metabolism
*1/*1	Extensive metabolizer	Normal platelet inhibition; normal residual platelet aggregation
*1/*17 *17/*17	Ultrarapid metabolizer	Increased platelet inhibition; decreased residual platelet aggregation
*1/*2 *1/*3 *2/*17	Intermediate metabolizer	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events
*2/*2 *2/*3 *3/*3	Poor metabolizer	Highly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events

more than 25 variant alleles in the *CYP2C19* gene have been identified but loss-of-function *CYP2C19*\*2, \*3 and gain-of function *CYP2C19*\*17 variants appear to be the major responsible for the variable antiplatelet effect of clopidogrel. From a molecular point of view, \*2 allele causes a splicing defect and the \*3 allele results in the addition of a premature stop codon, while \*17 leads to an increase of *CYP2C19* transcription resulting in a modest gain of function<sup>91</sup>. *CYP2C19* genotypes result in different metabolizer phenotypes; individuals can be extensive metabolizers (EM; \*1/\*1), intermediate metabolizers (IM; \*1/\*2, \*1/\*3, \*2/\*17), poor metabolizer (PM; \*2/\*2, \*2/\*3, \*3/\*3) and ultra-rapid metabolizers (UM; \*1/\*17, \*17/\*17).

According to the *CYP2C19* polymorphic status, about one third of Caucasian patients present high or low on-treatment platelet reactivity, leading to a greater frequency of recurrent thrombotic events or an increased bleeding risk, respectively (Fig. 1, Panel B and Table III). In March 2010, FDA added a black box warning to clopidogrel drug label in order to alert patients and physicians on high risk of treatment failure in *CYP2C19*-poor metabolizers representing up to 14% of patients. Indeed, these patients have a 3.58-times greater risk for major adverse cardiovascular events such as death, heart attack, and stroke<sup>92</sup>.

In addition, both FDA and European Medical Agency (EMA) have issued an alert concerning the risk of very serious adverse events occurring when clopidogrel is co-administered with Proton Pump Inhibitors (PPIs), mainly omeoprazole. PPIs are commonly prescribed in patients receiving clopidogrel plus ASA but such gastro-protectors are potent inhibitors of *CYP2C19* isoform<sup>93</sup>. Moreover, PPIs are both substrate and inhibitor of the *CYP2C19* thus patients that are *CYP2C19*-poor metabolizers may have concomitantly low levels of active clopidogrel and high concentration of PPIs and they could be exposed to a doubled risk of therapeutic failure and toxicity, respectively<sup>94</sup>.

As a matter of fact, clopidogrel is one of the cardiovascular drugs that justifies the use of the term "high risk pharmacokinetics" and, according to the *CYP2C19* status, patients may require dose adjustment or switching to an alternative antiplatelet agent<sup>95</sup>. The standard dose of clopidogrel is 75 mg once daily that could be changed in patients with different genotypes by lowering to 6 mg or increasing to 215 mg but currently, there is not yet a standardized protocol for dose adjustment in the carriers of *CYP2C19* alleles<sup>96</sup>.

The Clinical Pharmacogenetics Implementation Consortium (CPCI) guidelines recommend to switch to alternative antiplatelet agent i.e. prasugrel or ticagrelor in patients who are intermediate or poor metabolizers according to *CYP2C19* genotype<sup>89-91</sup>.

Prasugrel is a new-generation antiplatelet agent, which has been found to be superior to clopidogrel as demonstrated during the phase 3 trial entitled Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI) that has involved patients with ACS undergoing percutaneous coronary intervention (PCI), comparing a regimen of prasugrel with the standard-dose regimen of clopidogrel<sup>97</sup>.

Treatment with prasugrel (a 60 mg loading dose, followed by a 10 mg maintenance dose), thanks to a potent inhibition of the platelet P2Y<sub>12</sub> receptor, led to a greater reduction of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke with respect to clopidogrel therapy. However, this beneficial effect in preventing the ischemic events has been inevitably accompanied by an increase in the occurrence of major bleeding. Indeed, prasugrel may not represent a substitute for clopidogrel in all patients; in fact, some individuals > 75 years old and/or with history of transient ischemic attack, stroke, or intracranial bleeding had an increased risk of fatal and major bleeding<sup>97</sup>.

Importantly, a secondary analysis of the TRITON-TIMI trial have suggested that there was no difference between patients treated with prasugrel or clopidogrel with fully functional *CYP2C19* alleles that are extensive metabolizers<sup>98</sup>.

Prasugrel is a pro-drug as well as clopidogrel, and also this activation strictly depends on the polymorphic *CYP2C19* even if it is less susceptible to genetic variation<sup>99</sup>.

However, recent evidence suggests that prasugrel response could be influenced by the presence of the *CYP2C19*\*17 gain-of-function allele that could be associated with the occurrence of bleeding complications<sup>100</sup>. Platelet function testing might allow measuring the platelet reactivity of individuals and adjusting antiplatelet therapy principally in high-risk patients to improve clinical outcome. However, several randomized trials have failed in demonstrating the clinical efficacy of platelet function monitoring to adjust antiplatelet therapy in ACS/PCI patients<sup>101 102</sup>.

Given the high potential pharmacokinetics risk linked to clopidogrel and since there is no basis for dose adjustment as in the case of the algorithm used to personalize the therapy with warfarin, it would be very important to develop an analytical system to evaluate pharmacogenetics in parallel with measure of platelet function in patients receiving clopidogrel<sup>87 95</sup>.

## CONCLUSIONS

Elder cardiac patients show a large variability in the response to both pharmacological and non-pharmacological therapies. Such variability depends on many

and different factors such as molecular and biochemical variables<sup>103</sup>, comorbidities<sup>104</sup> and polypharmacy and also frailty and cognitive impairment, conditions that are very common in the oldest individuals. The response to cardiac drugs is strongly influenced by the genetic background of each patient and nowadays, cardiovascular pharmacogenetics has an important role in informing therapeutic decisions into the larger context of individualizing care<sup>105</sup>.

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## REVIEW

## Sudden cardiac death in elderly: the post-mortem examination of senile myocardium and myocardial infarction

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Cardiovascular diseases are the main cause of death globally. From a pathological perspective, the causes of sudden cardiac death (SCD) are different in young individuals compared with older ones where chronic degenerative diseases predominate. Most patients with heart disease are elderly, but aging is not synonymous of disease. Many people live past the age of 65 up to 90 and over without evidence of cardiac diseases and in many autopsies of elderly individuals, no specific lesions can be discovered that provide a clear cause of cardiac death. Where age-related changes are observed and no other cardiovascular findings can be related to an arrhythmic or mechanical mechanism of SCD or to myocardial infarction (MI), the senile myocardial degeneration is an inappropriate diagnosis although it is a common expression used by public health physicians and pathologists as cause of death. Age-associated changes in senile myocardium predispose to pathophysiological disease mechanisms and they can be a substantial substrate causing SCD even after acute emotional or physical stress as triggers of myocardial ischemia or arrhythmia. However, distinguishing the age-related physiological processes from the associated pathological changes and their role in a case of SCD is not always possible, since a heart failure (HF) can be the final cardiovascular aging pathway especially in elderly victims. Furthermore, unnatural deaths can be erroneously reported as natural deaths, leaving accidents or homicides undetected. The differentiation between sudden death and fatal elderly abuse is a difficult and critical diagnostic decision that needs a careful post-mortem investigation also in SCDs. To the best of our knowledge, there is no protocol for distinguishing SCD from elderly abuse fatalities. A specific protocol for sudden deaths also in elderly (similar to those already available for infant and child) could enhance the public and professional awareness on elder abuse fatalities as well as on the underlying mechanisms of cardiac deaths. In cases of sudden, unexpected deaths in healthy elderly, it is strongly suggested an accurate post-mortem investigation including a complete examination of clinical signs and medical history, toxicological and/or chemical laboratory tests, circumstantial data related also to the scene-of-the event.

**Key words:** Sudden cardiac death, Senile myocardium, Myocardial infarction, Elder abuse

### INTRODUCTION

Since the middle of the XX century, life expectancy has dramatically increased in developed countries, and for the first time in history most people can actually expect to live past the age of 65<sup>1,2</sup>. The principal causes of death have changed over time mainly due to changing environmental and social conditions and population's disease status<sup>3,4</sup>. Although death rates dropped at all

ages, it has been calculated that three-fourths of all deaths occur at elder age 65 and older. In this regard, data provided by the Center for Disease Control and Prevention (CDC) report that Heart Failure (HF), including heart attacks and chronic ischemic heart disease, is the leading cause of death followed by cancer and other chronic conditions<sup>5</sup>. Although death from atherosclerosis has dropped over 2 decades for all ages and sex, recent trends in elderly mortality suggest that heart

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disease is still the most common cause of death <sup>5</sup>. However, in many autopsies on elderly, no specific lesions can be discovered that provide a clear cause of death <sup>6</sup>. Many old people even of age over 80 can show still healthy vessels with no coronary artery disease or evidence of other cardiac diseases. There are no traceable morphologic signs of the lethal cardiac event, and there is no correlation between autopsy cardiac findings and what we can call a suspected Sudden Cardiac Death (SCD). In fact, SCD can occur even in very old people since ageing is not synonymous of disease.

SCD has been recently defined in 2015 by the Task Force of the European Society of Cardiology (ESC) a “non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event” <sup>7</sup>. The risk of SCD is higher in men than in women, and it increases with age due to the higher prevalence of Coronary Artery Disease (CAD) and, therefore, of myocardial infarction (MI) in older age <sup>8</sup>. In fact, atherosclerosis of the coronary arteries is the most prevalent cause of SCD in adults. Atherosclerotic CAD, commonly asymptomatic or unrecognized, is known to be extremely variable in “quantitative” terms, and findings raising the suspicion of coronary vasospasm (eg, localized or non-occlusive luminal narrowing, typically present in young and adult subjects) are often lacking even in elderly population <sup>9</sup>.

Many cardiovascular diseases can cause SCD, either through an arrhythmic mechanism (electrical SCD) or by compromising the heart’s mechanical function (mechanical SCD), and might affect not only the coronary arteries and the myocardium, but also the cardiac valves, the conducting system, the intra-pericardial aorta or the pulmonary artery, the integrity of which is essential for a regular heart function <sup>10</sup>.

However, cardiac diseases associated with SCD also differ in young versus older individuals <sup>7</sup>. In the young, there is a predominance of channelopathies and cardiomyopathies, myocarditis and drug abuse-induced arrhythmias. In elderly, chronic degenerative diseases, such as CAD, valvular heart disease and HF, predominate. Furthermore, elderly decedents frequently suffer from more than one disorder (the so-called comorbidity) at time of death and, therefore, it is difficult for physicians to identify the originating cause among several pathological conditions <sup>11</sup>. Cardiovascular comorbidity in the elderly can produce serious health consequences so that it becomes difficult to determine which contributed most to SCD. In old people age-related changes in cardiovascular structure and function may lower the threshold for clinically significant signs and symptoms, sometimes occurred as SCD <sup>12</sup>. In these cases, SCD

generally follows arrhythmia (hyperkinetic or hypokinetic) of so severe degree to impair cardiac output and hence cerebral perfusion. In this respect, the main goal of this review is to focus on the difficulties still present in the diagnosis of SCD and its post-mortem examination as well as death certification.

## POST-MORTEM EXAMINATION AND DEATH CERTIFICATION

An accurate diagnosis of SCD is crucial and requires a complete autopsy, investigation of the circumstances of death, and exclusion of other potential cause of deaths. In fact, the incorrect assessment of cause and manner of death can have serious implications for public health and the judicial system. Unnatural deaths can be erroneously reported as natural deaths, leaving accidents or homicides undetected <sup>13</sup>. Negative autopsy can occur in deaths caused by toxic or illicit drug abuse, for example, in case of suicide and/or medical malpractice <sup>14</sup> or by asphyxia suffocation homicides and other types of elder abuse fatalities <sup>15 16</sup>.

There is also considerable variation in the way in which public health physicians and pathologists approach the complex task of the diagnosis of cause of SCD. A uniform method of investigation has been proposed since 2008 by the Association for European Cardiovascular Pathology, in order to improve the minimum standards of practice <sup>10</sup>. The role of the autopsy in SCD has been emphasized to distinguish not only between natural from unnatural deaths but also to establish: 1) whether the death can be referred to cardiac or to other non-cardiac causes of sudden death; 2) the nature of the cardiac disease, and whether the mechanism was arrhythmic or mechanical; 3) whether the cardiac condition causing sudden death may be inherited, requiring screening and counselling of the next of kin.

Unfortunately, the accuracy of death certificates can be questionable for various reasons, including level of expertise and training of the medical practitioner involved in the death investigation, lack of medical records related to the deceased, lack of circumstantial information related to the fatal event, and the perceived lack of importance of the death certificate <sup>13 17</sup>. In the tenth version of the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems (WHO’s ICD-10) <sup>18</sup>, diseases of the circulatory system are inserted in chapter IX. In this section ischemic heart diseases are listed including angina pectoris, acute MI (due to coronary occlusion, thromboembolism, coronary failure, etc.) but also chronic ischemic heart disease mainly related to atherosclerosis and other forms of heart disease among which senile myocardial

degeneration. According to most of the forensic pathology community<sup>6</sup>, where nothing other than general senile atrophy of most organs is found and the history is unhelpful as to a specific manner of death, as long as the physician/pathologist can exclude any unnatural cause and non-cardiac causes of sudden death, then it is quite legitimate to ascribe the death to an acute cardiac death due to senile myocardial degeneration. That means to ascribe the death to a final HF caused by the aging-associated decline of cardiovascular structure and function. In fact, in contrast to other cardiovascular disorders, the prevalence of chronic HF is rapidly growing<sup>19</sup> along with the increasing longevity. The actual version of WHO's ICD-10<sup>18</sup> provides a specific code for such aging-related cardiac changes ("Degeneration of heart or myocardium: senile" – I.51.5), but geriatricians and some pathologists do not totally agree with such expression as cause of death in elderly, preferring the one of an acute cardiac death even when more specific lesions and signs of an ischemic heart disease or MI are not always detected. Under the section of other heart disease, ICD-10 also provides a specific code for SCD ("sudden cardiac death" – I-46.1) with conduction disorder or MI that seem more appropriate to be used also in elderly. In fact, distinguishing the age-related physiological processes from the associated pathological changes is not easy. In this respect, the main macroscopic and microscopic changes of the myocardial degeneration due to senility and to ischemia according to their main functional consequences are discussed as follows.

## THE SENILE MYOCARDIUM

Age-associated changes in senile myocardium can be usually concomitant with pathophysiological disease mechanisms determining the threshold, severity, and prognosis of cardiovascular disease in elderly<sup>20</sup>. Aging cardiovascular changes can be considered the effect of declining cardio-protective systems and increasing disease processes that are the substantial substrate for the development of HF<sup>19</sup>. Therefore, physicians must consider the frailty of the senile myocardium from a structural and functional perspective.

Atherosclerosis, left ventricular hypertrophy, interstitial myocardial fibrosis, atrial fibrillation and cardiac amyloidosis increase dramatically with age. But none of these conditions can be considered an ageing process, as they can be also the sequelae of cardiac adaptation<sup>21</sup> to functional stress or, better, the effect of cardiac structural remodeling<sup>19</sup>.

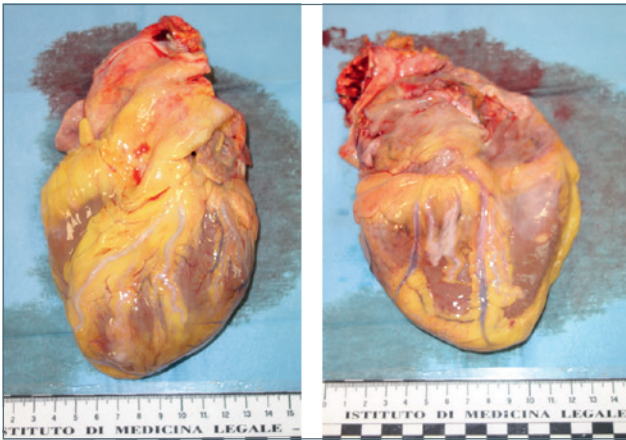
Senile heart changes its overall shape from elliptical to spheroid with an asymmetric increase in the

interventricular septum, more than free wall<sup>22,23</sup>. These structural changes in thickness and shape can have important implications for cardiac wall stress and overall contractile efficacy (Fig. 1). Senile hearts are also usually small, but hypertension may have enlarged the ventricles long ago and the effect of this process may be to sustain the heart at a normal weight<sup>6</sup>. Although in the past a relevant increase of cardiac mass with aging has been illustrated<sup>24</sup>, more recent autopsy-based studies show that the weight may be down to 300 g or even 250 g, if no previous hypertrophy has occurred<sup>6</sup>. Sometimes senile hearts can be brown on the surface. Such appearance (which is also called *brown atrophy* of the myocardium) is mainly related to the gradual increase in lipofuscin pigment and it is considered a true manifestation of biological ageing<sup>21</sup>. On a structural level, the senile heart can also be flabby and soft, the epicardial surface vessels tortuous as a sign of cardiac atrophy and the thumb can be pushed into myocardium without difficulty<sup>6</sup>.

Microscopically, the myocardial fibers generally increase in size and the nuclei of the myocytes can have prominent clumps of lipofuscin pigment at their poles. There may be a fine, diffuse fibrosis, which is not ischemic in origin, because of the loss of cardiomyocytes with aging. However, none of these features is diagnostic of a cardiac cause of death, as other old persons dying of quite unrelated causes, such as trauma, might have equally "poor" heart muscle<sup>6</sup>. On a cellular level, remodeling process involves changes also in the composition of the heart fibrous skeleton and composition of the extracellular matrix. In particular, in the elderly, it has been noted also a partial loss of sinoatrial node pacemaker cells<sup>25</sup>, with formation of fibrous connective tissue in the cardiac conduction system and in LV tissue<sup>26,27</sup>.

Other age related changes concern cusps thickening because of fibrosis both atrial surface of the atrio-ventricular valves and ventricular surface of the aortic valves. Moreover, the line of closure could be eccentrically accentuated and, particularly on the aortic and mitralic valves, the so-called Lambl's excrescences develop. These changes could play an important role in predisposing to some pathological conditions such as infective endocarditis, raised pressure and regurgitant flow<sup>28</sup>. Mitral insufficiency can be a common clinical feature under these circumstances. However, sometimes in elderly aortic valve sclerosis develops usually without much hemodynamic consequences although the term "senile aortic stenosis" is often used in this context<sup>21</sup>.

In old individuals, the most important phenomenon to be considered is also the left ventricular (LV) structural remodeling because of an increase in the thickness of



**Figure 1.** Senile myocardium of a man 94 years old.

the wall as results of the fibrosis due to loss of myocardial fibers and increased cardiomyocyte size<sup>22</sup>. However, LV remodeling from age-related remodeling must be differentiated from LV hypertrophy associated with hypertension. In the first one, LV remodeling begins with an increase in the relative wall thickness (wall thickness/LV radius ratio)<sup>29</sup> within normal limits, explaining the lack of effect on total cardiac mass. In fact, autopsies on subjects free from hypertension, CAD and cardiovascular disease did not show an increase in cardiac mass with aging<sup>30</sup>. Therefore, against previous findings<sup>24</sup>, total cardiac mass does not increase significantly with aging as also supported by autopsy-based and echocardiographic studies<sup>31</sup>.

A progressive decline in LV compliance with age has been also observed and the heart has been found to fill with blood more slowly in older compared with young individuals<sup>19</sup>. Such decline in LV compliance may go unnoticed for many years, but with the occurrence of an acute stress, the subclinical dysfunction can become acutely evident producing a fatal HF<sup>12</sup>. For example, during exercise a mismatch in loading can occur in older individuals because of a failure of LV elastance to increase in proportion to the increase in vascular elastance<sup>12</sup>.

Although LV hypertrophy has been associated with increased risk for CAD and SCD, another interesting aging-related heart remodeling concerns atrial hypertrophy and dilation. In the elderly, atrial contraction can assume a more pronounced role in LV filling during diastole than in the young people<sup>21</sup>, as this structural change can favor the development of atrial fibrillation<sup>32</sup>. Furthermore ageing changes in the right heart are less pronounced than the left sided changes, although they can be enhanced by the presence of other diseases.

At last, another aging-related change in cardiac tissue

is amyloid deposition derived from atrial natriuretic peptide (ANP). The incidence and severity of isolated atrial amyloid deposits increase with age, from 75% incidence in patients aged 51-60 years, to 86% incidence in those aged 81-90 years<sup>33,34</sup>.

In summary, autopsy findings of senile myocardium can show age-associated changes as adaptive pathophysiological mechanisms with unpredictable myocardial functional sequelae. However, distinguishing the age-related physiological processes from the associated pathological changes and their role in a case of SCD is not always possible.

## MYOCARDIAL INFARCTION

A consensus document by an International Joint ESC/ACC Committee defined in 2000 the myocardial infarction (MI) as “myocardial cell death due to prolonged ischemia”, emphasizing that any necrosis in the setting of myocardial ischemia should be labeled as MI<sup>35</sup>.

In 2007, this definition was revised in the light of different conditions that may lead to a MI<sup>36</sup>. But, the development of more sensitive assays for markers of myocardial necrosis pushed the scientific community to an up-dated position. In 2012, the Third Universal Definition of MI consensus document redefined acute MI as “a condition in which there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia”<sup>9</sup>. The new definition recognizes that very small amount of myocardial necrosis can be detected by biochemical markers and/or imaging supporting better the final diagnosis of MI. Therefore in case of MI, a rise and/or fall of a cardiac biomarker values (preferably cardiac troponin – cTn) should be observed, with at least one value above the 99<sup>th</sup> percentile upper reference limit, and with at least one of the following: 1) ischemic symptoms; 2) new or presumed new significant ST-segment or T-wave changes or new left bundle-branch block; 3) development of pathological Q waves in the electrocardiogram (ECG); 4) imaging evidence of new loss of viable myocardium such as a new regional wall motion abnormality; 5) identification of an intracoronary thrombus by means of coronary angiography or autopsy.

Autopsy case studies have suggested that in subjects with CAD, the factor triggering the fatal arrhythmic event causing SCD can be transitory (coronary spasm) or prolonged (occlusive coronary stenosis) myocardial ischemia. However, although most of the elderly people show underlying severe CAD, on occasion they may also have non-obstructive or no CAD at all. Many very old people have excellent coronary arteries and no sign of myocardial ischemia, so that the erroneous clinical

diagnosis of CAD is much over-used by physicians. In this respect, various types of acute MI have been defined based on pathological and clinical differences<sup>7</sup>: type 1 (spontaneous MI related to atherosclerotic plaque rupture, ulceration or coronary thrombosis), type 2 (MI secondary to an ischemic imbalance where a condition other than CAD can contribute to an imbalance between myocardial oxygen supply and/or demand such as in a coronary artery spasm, coronary endothelial dysfunction, hypotension etc.), type 3 (MI resulting in death when biomarker values are unavailable), type 4 and 5 (MI related to percutaneous coronary intervention or coronary artery bypass grafting, respectively). At autopsy, some doubts and difficulties persist mainly concerning the minimum level of lesion compatible with MI and the condition of coronary arteries<sup>37</sup>. In fact, applying the proposed diagnostic criteria, any amount of myocardial necrosis caused by ischemia should be labeled as an infarct. In this respect, there should be continuity from minimal myocardial ischemic damage to classic large MI. In cases of SCD it is therefore extremely important to identify even a small area of myocardial necrosis demonstrating previous ischemia, based on clinical and autopsy findings. In a post-mortem examination, the signs of early myocardial damage must be accurately searched for and documented by all available means including histologic and histochemical stains: *in vivo*<sup>7</sup> by electrocardiograms tracing ischemic modifications, for example, and blood tests studying serologically the level of myocardial necrosis indicators (among them the preferred biomarker is cTn which has high myocardial tissues specificity, as well as high clinical sensitivity). However, public health professionals must keep in mind that myocardial cell death does not occur instantaneously at the onset of ischemia. It takes several hours (at least 4-6 h) before myocardial necrosis can be identified by standard macroscopic or microscopic post-mortem examination depending on the sensitivity of the myocytes, the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, individual demand for oxygen and nutrients<sup>36</sup>. The entire process leading to a healed infarction usually takes at least 5-6 weeks and the reperfusion may alter the macroscopic and microscopic appearance. Therefore, at autopsy the recognition of early myocardial damage using routine histologic techniques such as hematoxylin and eosin staining is possible only if death has occurred at least 4-6 hours after the onset of the ischemic injury. This means that an individual with an ischemic insult has to live for at least 4-6 hours to have detectable histological changes in the myocardium such as necrotic clotting, multifocal patches of wavy

fibers, contraction band lesions, hyper-eosinophilic enucleated myocytes, and marginal rearrangement reactions with early inflammatory infiltrate<sup>38,39</sup>. A period of 1-hour interval or less from the angina attack is not usually enough to produce such histological findings, commonly known as classic morphologic alterations of the MI. In fact, the timing of appearance of the above alterations is strongly affected by various factors such as the efficacy of any collateral blood flow in compensating perfusion of the ischemic area, the duration of the vessel occlusion (persistent or intermittent coronary artery disease or when the vessel lumen could recanalize and regular blood flow resume), and the sensitivity of the myocardial fibers themselves<sup>7,35</sup>. Furthermore, in cases of suspected SCD, whether the autopsy findings deal with "coronary" or "myocardial" lesions, there may be a variety of possible combinations that need to be still investigated before the final diagnosis of MI can be formulated. It is essential to apply adequate study methods of the myocardial morphology, including not only an examination of the various coronary branches but also histologic analysis of the myocardium of both ventricles, by standard and targeted sampling of evident or suspicious lesions<sup>37</sup>. In several cases, scarring of some myocardial areas can cause arrhythmia as well as in cases of MI, the loss of myocytes usually follows prolonged ischemia resulting in cell death (necrosis) as a result of oncosis, and only to a lesser extent of apoptosis<sup>35</sup>. For example, histological evidence of myocardial necrosis may be detectable in clinical conditions associated with predominantly non-ischemic myocardial injury<sup>7</sup>. Small amounts of myocardial injury with necrosis may be detected, which are associated with HF, tachy-brady-arrhythmia, myocarditis, arrhythmias, renal failure, even pulmonary embolism or otherwise uneventful percutaneous or surgical coronary procedures. According to the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology<sup>7</sup>, these entities can also be associated with MI in case of clinical evidence of acute myocardial ischemia with rise and/or fall of cTn. They should not be labeled as MI or a complication of the procedures, but rather as myocardial injury. In fact, elevated cTn values, indicative of myocardial injury with necrosis, may be also observed in cases of non-ischemic HF syndrome<sup>7,40</sup>. In summary, in cases of SCD it is not always easy to differentiate between arrhythmic and non-arrhythmic mechanism of death, as often the pathologists have not enough body of evidence to determine the cardiac cause of death.

## DISCUSSION

Cardiovascular disease is a global health problem and the leading cause of death in elderly<sup>41</sup>. Most patients with HF are elderly, constituting up to 80% of patients suffering from this disease with both incidence and prevalence increasing with age<sup>42</sup>. This can explain the growing interest of the cardiac disease in geriatric medicine as SCD can occur also in elderly individuals without previous symptoms of heart disorders and with excellent coronary arteries.

In this regard, the certification of cause and manner of death is fundamental for legal and epidemiological purposes<sup>13</sup>. In medico-legal setting the incorrect assessment of cause and manner of death can affect not only statistics of mortality but may allow unnatural deaths to go undetected which is an increasing problem in elderly abuse fatalities<sup>16 43 44</sup>. Forgoing forensic autopsies in sudden unexplained deaths is a violation of Recommendation No. R 99 of the Committee of Ministers (Council of Europe) adopted in 1999<sup>36 37</sup> and partially applied in several European countries<sup>45 46</sup>.

It is recommended that all unexplained sudden death victims undergo post-mortem examination to investigate first whether a cardiac origin should be the leading cause, or other non-cardiac causes are involved.

Also based on the 2015 guidelines published recently by the ESC Task Force, an autopsy is recommended to investigate the causes of sudden death and to define whether SCD is secondary to arrhythmic or non-arrhythmic mechanisms (e.g. rupture of an aortic aneurysm or cardiac rupture). Standard histological examination of the heart and the analysis of the blood for toxicology and molecular pathology are also requested. In the elderly, unlike the young, the causes of SCD are mostly related to chronic degenerative disease (CAD, valvular heart disease and HF). However, in most of the SCDs, a clear evidence of the pathological cause cannot be always found. The postmortem diagnosis of acute MI represents still a current challenge for pathologists, particularly when death occurs within minutes to a few hours after the ischemic insult. Unfortunately, despite of the autopsy protocols available and the attention raised in this issue, a proportion of sudden deaths, ranging from 2 to 54%, remain still unexplained<sup>47</sup>. Many elderlies may die suddenly for the so many cardiac and non-cardiac causes. In fact, it is worth of mentioning that aging does not itself cause HF but in elderly, a HF can be the final cardiovascular aging pathway<sup>19</sup> representing the convergence of age-associated changes in cardiovascular structure and function, aging changes in other organ systems, and the progressive increase in cardiovascular diseases<sup>19</sup>.

In this regard, all health professionals should realize

that different degrees of certainty exist in defining the cause–effect relationship between the cardiovascular clinical and pathological findings and the sudden death event. Since 2008 the Association for European Cardiovascular Pathology<sup>10</sup> has summarized the pathological changes related to SCD grouped in three main categories of reliability. Among the certain post-mortem findings of SCD there are of course massive pulmonary embolism, haemopericardium due to aortic or cardiac rupture, mitral valve papillary muscle or chordae tendineae rupture with acute mitral valve incompetence and pulmonary edema, acute coronary occlusion due to thrombosis or embolism, anomalous origin of the coronary artery from the pulmonary trunk, massive acute. Among the highly probable post-mortem findings of SCD there are stable atherosclerotic plaque with luminal stenosis > 75% with or without healed MI, anomalous origin of the left coronary artery, cardiomyopathies (hypertrophic, arrhythmogenic right ventricular etc.), aortic stenosis with left ventricular hypertrophy, ECG anomalies (consistent with a Wolff-Parkinson-White syndrome, Brugada syndrome etc.). Other common post-mortem cardiac findings (such as patent or moderate coronary disease, small foci of inflammatory cells or fatty infiltration of the right ventricle) are considered uncertain cause of SCD. However, both in high probable, and especially in the uncertain categories, it is recommended that each case should be considered unique in its clinical and circumstantial peculiarity. In this regard, the clinical history and the circumstances of death can deeply affect the decision-making process of the diagnosis of cause and manner of death.

In SCDs, doubts and suspects persist mainly concerning the manner of death: natural or unnatural (accidental, homicide, suicide etc.). In elderly, the suspect of unnatural death should always be considered as most of the cases related to elder maltreatment are not reported due to the difficulties and obstacles of identifying the different types of elder abuse (physical, sexual, emotional or psychological, self-neglect etc). Elder abuse is an alarming social problem and a growing public health concern because of the complex area of investigation. Signs of abuse may overlap with symptoms and outcomes of various diseases or side effects of medications<sup>15 16 48</sup>. For example, it is well known that acute emotional stress can have significant adverse effects on the heart and sometimes these latter are fatal even in young adults<sup>49 50</sup>.

An intense emotion can produce left ventricular dysfunction, myocardial ischemia, or cardiac arrhythmia and, therefore, it is widely recognized as trigger of SCD. An acute coronary syndrome can also be the result of such severe stress. From the pathophysiological point of view, an acute emotional stress can cause a

sudden adrenergic discharge, which can also lead to MI by causing plaque destabilization and then coronary thrombosis (type 1 pathophysiology), or by inducing a spasm of epicardial coronary vessels and/or coronary microcirculation (type 2 pathophysiology)<sup>51</sup>. The disequilibrium in the myocardial supply and demand caused by the intense emotional/physical stress related can determine the fatal myocardial ischemia.

Such kind of event (also known as scared to death) should be considered in elderly where the senile myocardial degeneration can represent, due to its structural frailty, the substantial substrate predisposing SCD. There are myocardial diseases where the border between physiological changes and pathological findings is not well defined such as the senile myocardial degeneration. A sort of grey zone where no other pathological evidence is available for a certain diagnosis of SCD even after a careful macroscopic and microscopic examination of the heart and laboratory analyses. In these unexplained cases, the death should be classified as arrhythmic death syndrome according to other authors as the main mechanism involved is the ability of the emotional stress to trigger myocardial ischemia and/or arrhythmia via sympathetic nervous system hyper-responsivity<sup>10 52</sup>.

In every SCD, pathologists and physicians are requested to find enough evidence of a specific cause of death, and in particular to establish whether SCD is secondary to arrhythmic or non-arrhythmic mechanisms or otherwise to HF. However, in elderly, it is not easy to distinguish the aging of the heart by the overlapping of old-age diseases. In the absence of any other cardiac and non-cardiac diseases, old people can eventually die few passing the age of 90 years. Therefore, where age-related changes are observed and no other cardiovascular findings can be related to a MI, it is also author's opinion that senile myocardial degeneration (code I.51.5 of the WHO's ICD-10) is an inappropriate diagnosis of cause of death. Unfortunately, it is a common expression still used by public health physicians and also pathologists. These professionals should realize that aging and senile myocardium is not an acceptable code in death certification just because SCD (code I-46.1 of the WHO's ICD-10) is an appropriate and more specific cause of death even in elderly. SCD should be used especially when there is exclusion of unnatural causes of deaths or no clear evidence of cardiac death has been found post-mortem as well as in the scenario of a fatal event such as scared to death<sup>53 55</sup>. Acute cardiac deaths precipitated by the stress of normal activities and events of daily life can be regarded as natural. But they are different from a scenario with the clear intent to scare of become alarmed which constitutes an assault and, therefore, can be classified as a homicide. In these

cases, it is strongly suggested an accurate post-mortem investigation including a complete examination of clinical signs and medical history, toxicological and/or chemical laboratory tests, circumstantial data related also to the scene-of-the event. The inaccuracy of cause of death determination without an autopsy is well known by the forensic pathology community<sup>56</sup>. The forensic autopsy examination is still a reliable form of quality control to be adopted with strong implications on the public health and judicial systems.

However, to the best of our knowledge, there is no protocol for distinguishing SCD from elderly abuse fatalities. There are several guidelines for distinguishing sudden infant death syndrome (SIDS) or sudden unexpected infant death (SUID) from child abuse fatalities<sup>57 58</sup>, but no one of such post-mortem procedures are dealing with the elderly. The differentiation between sudden death and fatal child/elderly abuse is a difficult and critical diagnostic decision that needs a careful post-mortem investigation. A specific protocol for sudden deaths in elderly could enhance the public and professional awareness on elder abuse fatalities as well as on the underlying mechanisms of cardiac deaths. This knowledge could be also of help for the treatment of the patient with cardiac diseases<sup>59</sup> and improving cardiovascular performance in the elderly<sup>60</sup>.

## CONCLUSIONS

Cardiovascular diseases are the main cause of death internationally. From a pathological perspective, the causes of SCD are different in young individuals compared with older ones where chronic degenerative diseases and CAD predominate.

The aging myocardial changes could predispose SCD. All public health professionals should change old behaviors in classifying elderly deaths as related to senile myocardium in favor of an appropriate diagnosis of cause of death such as SCD even in elderly. In this regard, the hope is that the upcoming revision of WHO's ICD-10 could delete the imprecise code of "Degeneration of heart or myocardium: senile" – I.51.5, according to the clinical and pathophysiological evidence on the physiological nature of senile myocardium. Guidelines for distinguishing SCD in elderly from elder abuse fatalities are needed, similar to those already available for infant and child for SUID and SIDS. It is the time that geriatricians and pathologists think about such a protocol for elderly victims, as aging is not a synonymous of fatal disease. A procedure for the post-mortem examination of elderly deaths could enhance the public and professional awareness on elder abuse fatalities as well as on the underlying mechanisms of cardiac deaths.

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