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BRINGING PREVENTION IN GERIATRICS : EVIDENCES FROM CARDIOVASCULAR MEDICINE SUPPORTING THE NEW CHALLENGE

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Abstract

Aging is a *dynamic* and *systemic* process, with high inter-individual *heterogeneity*, likely partially *adaptiv*e. Cardiovascular disease and hypertension are among the leading conditions causing disabilities in older subjects. If, in accordance with most recent definition, prevention is any intervention before the patient receives a diagnosis, prevention is possible at any age. Additionally, disability and CV disease in the elderly may be prevented by targeting factors underlying and modulating the arterial aging process. Cross-talk between arterial and brain aging will be discussed in this context as a paradigmatic clinical model fostering prevention in older subjects.

Keywords

arterial aging; arterial stiffness; prevention; cardiovascular disease; dementia; cognitive impairment

The world population is getting older and older. In 2000, there were 600 million people aged 60 and over who will become 1.2 billion by 2025 and 2 billion by 2050. The older population is also getting older with the number of subjects 80 and older rapidly increasing (Centers for Disease Control and Prevention, 2003).

Prevalent and incident cardiovascular (CV) diseases are projected to increase-predominantly in older subjects - by approximately 26% in the next 30 years. Yet, the number of cases in 75- to 84-year-olds will double in the same period (Odden et al, 2011).

CV disease in older subjects and traditional risk factors control

The aforementioned trends in CV disease in older persons may reflect inadequate control of population-wide traditional CV risk factor levels (Ford et al. 2003, Wang et al 2007, Scuteri et al. 2009b). Indeed, traditional CV risk factors are more risky at older age (MRC Working Party 1992, Bertoni et al 2002, Saydah et al 2002): for instance, the same elevation in blood pressure level is accompanied by a significantly greater risk of CV events in older subjects

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(MRC Working Party 1992). Therefore, a proper therapy should be of great effectiveness in the prevention – as currently intended - of CV morbidity and disability at older ages. Conversely, several studies suggest that drug prescription and monitoring remains a key issue in older subjects.

In fact, a substantial proportion of traditional CV risk factors (hypertension, dyslipi- demia, diabetes) are not diagnosed and result undertreated, particularly at older ages. For instance, data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that only 53.6% of hypertensive subjects were treated and only 27.4% were controlled to goal levels of <140 mm Hg systolic and <90 mm Hg diastolic (The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 1997). The situation is not better in more recent survey across countries (Wang et al 2007) nor in older subjects (Scuteri et al. 2009a).

Another factor contributing to the inadequate control of CV risk factors in older subjects may be the adoption of “the lower the better” strategy also in older subjects. Recently, it has been reported that in older groups a more aggressive control of traditional CV risk factors is not accompanied by a reduction in CV events (Gerstein et al 2008, The ACCORD Study Group 2010); conversely, an increase in iatrogenic effects may be observed (Gerstein et al 2008, The ACCORD Study Group 2010). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study compared an intensive treatment strategy with standard treatment in a population with a mean age of 62 years and a baseline duration of diabetes of 10 years in whom the primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes (The ACCORD Study Group 2010). Despite a non significant difference in the occurrence of the composite outcome, 257 patients in the intensive-treatment group (Glycated Hemoglobin - HbA1c - goal <6.0%) and 203 patients in the standard-treatment group (HbA1c goal of 7.0% to 7.9%) died during the follow-up period (HR =1.22; 95% CI, 1.01–1.46; P = 0.04). This increased risk of death was hypothesized to be the result of a higher incidence of hypoglycemia in the intensive treatment arm. A similar report concerned target BP levels in older subjects. In fact, a Systolic Blood Pressure (SBP) of <120 mmHg was not associated with a lower rate of CV events than in subjects attaining SBP<140 mmHg; additionally, serious adverse events attributable to medications were more common in the group with SBP<120 mmHg (11). Of note, a recent study remarked that episodes of SBP hypotension are extremely common in older subjects – affecting approximately 50% of this population (Scuteri et al 2012).

While increasing evidence is emerging against the strategy “the lower the better” in older subjects, novel threshold values for CV risk factors control in subjects over 75 years are welcome. For instance, most recent Guidelines of European Diabetes Working Party on diabetes in the elderly suggested different glycemic targets for older diabetic subjects without severe disability and comorbidities (suggested target: HbA1c <7% and/or fasting glucose levels 90–126 mg/dl) or for older subjects with severe comorbid disabling conditions exposing them to a high risk of hypoglycemia (suggested target: HbA1c < 8% and/or fasting glucose levels 108–144 mg/dl) (Sinclair).

Beyond the considerations above, it has been estimated that even by controlling blood pressure or LDL cholesterol levels a significant increase in the projected incidence of CV disease will occur in the next 30 years (Odden et al 2011). Additionally, in subjects with subclinical arterial disease, such as increased arterial stiffness or thickness (arterial aging), the control of established CV risk factors appears lower than in? (Scuteri et al. 2009a, Sutton-Tyrrell et al. 2003).

The traditional approach of reducing the burden of CV disease predominantly by lowering traditional CV risk factors levels appears to be more complex and less successful in older subjects. Thus in order to implement effective prevention strategies for older subjects the paradigm should be shifted from traditional CV risk factors to arterial aging.

Aging as the field in which CV diseases flourish and grow

Aging is a *dynamic* and *systemic* process that progressively limits our normal functions and makes us more vulnerable to disease and more likely to die (Comfort 1968). Aging or functional decline begin early in life, after sexual maturity (age 19) for several functions – for instance, hearing and flexibility (Bowen et al 2004).

> Subjects age at different rates so that the incidence of most age-related changes vary considerably between individuals. Thus, aging is an *heterogeneous* process; heterogeneity means also that greater variations around the mean are observable with advancing age (Hughes 1969). Arterial aging, measured as aorta Pulse Wave Velocity (PWV) or Common Carotid Artery Intima Media Thickenss (CCA IMT), exhibits greater variation with advancing age (Pilia et al 2006).

The heterogeneity of the ageing process represents a great opportunity for prevention: identifying, assessing, and following-up more intensively older subjects with a “greater than average” rate of aging will offer a tremendous opportunity for an effective prevention of CV disease and disability, with dramatic benefits in terms of quality of life and health care costs.

Targeting arterial aging to prevent CV disease and disability in older subjects: the case of cognitive impairment

Moving towards preventive strategies in older subjects requires a major shift in our cultural paradigm as clinicians and as researchers. The first novelty (in language and paradigm) proposed is the *shift from traditional CV risk factors to arterial aging*. The second step consists of a progressive *re-definition of clinical outcomes* in CV geriatric patients. The last novelty deals with *the definition of prevention*. Beyond the 1957 classification of primary, secondary, and tertiary prevention (Caplan 1964), we suggest the more recent definition of prevention as intervention before the patient receives a diagnosis (Committee on Prevention of Mental Disorders; Division of Biobehavioral Sciences and Mental Disorders, 1994) - where treatment is an intervention for patients already with a diagnosis.

Arterial aging is a continuum that can be identified and followed at different stages. The most prominent features of clinical relevance are stiffening and thickening of large arteries (Najjar et al 2005). Both large artery stiffening and thickening can be measured non-

invasively and in a highly reproducible manner as PWV and CCA IMT, respectively (Najjar et al 2005, Laurent et al 2006).

Amongst the determinants of arterial aging, the metabolic syndrome (MetS) supports the concept that prevention is possible at any age. Metabolic syndrome (MetS) is defined by the simultaneous occurrence of at least three of five CV risk factors of predominantly metabolic origin (abdominal obesity, elevated fasting glucose, low high-density cholesterol, elevated triglycerides, and high blood pressure) commonly exhibiting clustering that cannot be explained by chance alone (Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III), 2001). MetS has been recognized as a major risk factor for CV disease, even in older subjects in whom MetS confers a 38% higher risk of myocardial infarction and stroke (Scuteri et al 2005a). Early vascular aging, clinically measurable as increased large artery stiffness and/or thickness, has been associated with MetS in different populations (Scuteri et al. 2004a, 2010a) - independently of proinflammatory cytokines (Scuteri et al 2011a). Moreover, accelerated arterial aging is still evident in persons older than 65 years with MetS– indicating out that MetS associated CV burden is relevant, and thus preventable, even in older subjects.

Recent findings in the SardiNIA Study suggested that not all the combinations of altered MetS components that dramatically increasing age-associated arterial changes carry the same CV burden (Scuteri et al 2010a). Abdominal obesity was common to the cluster of altered MetS components associated with extremely thick and stiff arteries in the SardiNIA Study (Scuteri et al 2010a) as well as to the cluster of MetS components reported to confer higher risk of CV events in the Framingham Study (Franco et al 2009). Of note, abdominal obesity showed a non linear relationship with arterial aging, that differed with advancing age (Scuteri et al 2011c).

Cognitive decline and dementia never represented one of the *primary outcomes* in CV medicine. Yet, the prevalence of dementia increases with advancing age - affecting around 7% of subjects over 65 years and 30% of those over 80 (Jellinger et al 2008, Kalaria et al 2008) – and it is expected to double over the next 30 years (Melzer et al 1997).

Cognitive function declines with advancing age (Scuteri et al 2005b). The age-associated decline in cognitive functions is also characterized by a great *heterogeneity* and its apparently linear trajectory masks the presence of fast and slow decliners (Lamar et al 2003). To simplify, the trajectories of cognitive decline in populations suggest that at least three major groups of subjects can be identified: subjects with a steady decline of cognition over time; subjects with an accelerated cognitive decline with age, and subjects with marked decline in cognitive function without any acceleration over time (Terrera et al 2010).

In the present context, we specifically propose cognitive impairment up to the onset of dementia as an outcome of primary relevance in older subjects. We suggest the cross-talk between arterial and brain aging as a target (and, likely, as a “living model” of) for prevention in older age.

Both large artery stiffness or thickness have been significantly and inversely associated with cognitive function in cross-sectional and in longitudinal studies; the greater the arterial stiffness or thickness, the lower the cognitive performance (Gorelick et al 2011). Macro- and micro- vascular remodelling are likely major pathophysiological mechanisms leading to cognitive impairment (Scuteri et al 2011b). Arterial aging has also been involved in left ventricular remodelling that, in turn, has been linked to cognitive impairment (Scuteri et al 2009a), cerebral white matter lesions (Selvetella et al 2003), and depression (Scuteri et al 2010b)

Therefore, if arterial aging is significantly associated with cognitive impairment it may be possible to decrease the progress of cognitive impairment – before and after the onset of clinical overt dementia – by modifying factors known to modulate arterial aging.

For example, obesity, a key component of the MetS - a major determinant of accelerated arterial aging (see above) -, also has been associated with brain atrophy in cognitively normal elderly persons (Raji et al 2010). The significant relationship between obesity and cortical brain atrophy applied not just in healthy older persons but even to those with Mild Cognitive Impairment or dementia (Hoa et al. 2010). After controlling for age, sex, and education, every unit increase in Body Mass Index (BMI) is associated with approximately 1%–2% average brain tissue reduction in the frontal, temporal, and occipital lobes, brainstem, and cerebellum and an approximately 3% expansion of ventricles in subjects with mild to moderate Alzheimer type dementia (Hoa et al 2010). In other terms, the significant positive association between obesity and brain loss forms a continuum that is observable even when dementia became clinically evident. This suggests that it is never too late to prevent further deterioration of cognitive impairment by improving arterial properties/ slowing arterial aging.

Specific effective therapeutical interventions are more beneficial than other ones with respect to improving arterial properties (London et al. 2004, The CAFÉ Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators 2006) and left ventricular remodelling (Klingbeil et al 2003). Of note, the same treatments have been associated with a reduced burden on cerebral white matter lesions (Hatazawa et al 2004) and, somehow, with lower occurrence of dementia (Dufouil et al 2005, Forette et al 1998, Gorelick et al 2011, Lu et al. 2007). Thus, if it is plausible that pathophysiological mechanisms support the concept that prevention is needed and possible even at older ages, and that targeting arterial aging and its determinants may result effective in decreasing the progression of cognitive deterioration (at any stage), yet we lack clear evidence regarding interventions specifically designed to verify improvement in the rate of cognitive impairment by modifying arterial aging (Gorelick et al 2011, Scuteri 2007). We look forward clinical trials that will adopt a set of standardized combination of measurements of arterial aging and a set of standardized neuropsychological tests and neuroimaging data to answer this question.

Bringing prevention in geriatric medicine: from bedside to bench

The heterogeneity of the ageing process is the result of long-lasting complex interactions between genetic and environmental factors. Therefore, a more detailed profiling of the phenotype “arterial aging” at different levels of resolution (blood markers, molecules, cells, genetically-modified animal models, etc) may contribute to identify those combinations of specific factors resulting in a greater individual risk of CV disease and dementia. This is the conceptual relevance of the so called “Human Phenome Project”(Freimer and Sabatti 2003). At this point, the bedside interrogates the bench, expecting not only more detailed identification of pathophysiological pathways leading to “greater than average” rate of arterial aging, not only for novel therapeutic agents with more specific targets, but also expecting a novel classification of clinical conditions. For instance, PWV represents the gold standard for measuring arterial stiffness in clinical setting. Yet, as discussed above, there is tremendous variation of this parameter with advancing age (Pilia et al 2006). In the near future, combinations of PWV measurement with circulating cytokines, oxidative stress markers, genetic polymorphysm(s), metabolomic and proteomic, should help to identify those older subjects with stiff arteries at a greater risk of disease or a greater rate of progression from health to subclinical damage to clinical overt disease and disability. Angiotensin II affects an example of the aforementioned perspective. Angiotensin II accelerates aging in the aorta from old monkeys and humans (Wang et al 2005, 2010) and chronic pharmacological inhibition of the renin-angiotensin system significantly slows down arterial aging (Basso et al 2007). Pharmacological blockage of angiotensin type1 receptors decreased cognitive dysfunction in experimental model of Alzheimer’s disease (Takeda et al 2009). Thus, the related bedside to bench “phenomic hypothesis”: can alteration in the –omics of angitonesin II signalling identify subjects with stiff arteries who more rapidly develop dementia or progress to clinical overt CV event?

Another example is provided by the observation that the same elevation in blood pressure level is accompanied by a significantly greater risk of CV events in older subjects (MRC Working Party, 1992). Additionally, older subjects generally also have higher blood pressure variability (Convanico et al 1990). Experimental models showed that arterial aging magnified oxygen radical production in response to increased blood pressure (for the same increase in intravascular pressure, younger rats presented a threefold increase in oxygen radical production, whereas old rats presented a sixfold oxygen radical production) (Jacobson et al 2007).

Novel evidences have been cumulating regarding the differential regulation of steady and pulsatile stretch in the aorta (Lehoux et al 2005a). A better characterization of pathways involved in the abovementioned reactions and therapeutical novel agents interfering with those mechanisms may become powerful weapons to slow down arterial aging.

Similarly, a better characterization of age-associated changes in the organization and composition of vascular extracellular matrix (Lehoux et al 2005b, Pauly et al 1994) may be helpful to slow down and prevent the clinical consequences of aging, ending-up with ***maladaptive*** *CV remodelling* observable in large artery (Scuteri et al 2001, 2004b), small artery (Jacobsen et al 2008, Scuteri et al 1995), and left ventricular (Ganau et al 1995,

Scuteri et al 2010b, Selvetella et al 2003, Slotwine et al 1998) level that is risky for CV events as well as for brain diseases (Scuteri et al 2004b, 2010b, Selvetella et al 2003).

Conclusions

Geriatric medicine and gerontological research have become increasingly relevant. Yet, in the recent years the dominant paradigm has relegated (and reduced) the geriatric medicine to the role of “the better management” of disability, when not of instituzionalized patients. In such a context, remarking the dimension of prevention is dramatically urgent. Prevention is a critical goal to which clinicians should aspire because it reduces morbidity, may alleviate suffering by reducing disability, and reduces the cost of health care. We propose that prevention is possible in geriatric patients at any age.

This working hypothesis requires a major shift in our paradigm to be proven true: from traditional CV risk factors to arterial aging; defining prevention as any intervention occurring prior to a diagnosis; a progressive re-definition of clinical outcomes for older subjects. However, it should be acknowledged that its strong background is not yet supported by clinical trials clearly showing its effectiveness and its public health impact.

Nonetheless, no evidence will ever be available if geriatric medicine won’t give credit to this novel paradigm. Consistently, greater resources should be allocated to verify whether a better phenotypic characterization of arterial aging and its inter-individual variability (heterogeneity) will significantly improve the accuracy of prevention in older subjects and will allow significant reduction in healthcare and social costs.

Meanwhile, it should be promoted and diffused the concept that arterial aging – similar to any other aging process – is a continuous phenomenon that can be identified and followed at different stages, even in subjects with normal levels of traditional CV risk factors, like blood glucose and blood pressure (Najjar et al 2008, Scuteri et al 2008). Therefore, prevention should progressively focus more and more on arterial aging even in younger subjects, as indicated by the emerging concept of Early Vascular Ageing syndrome (Nilsson et al 2008, 2009).

Aging –whether we welcome it as a blessing or we fear it as a curse – is an inevitable process. The rate of aging and, thus, the clinical impact of aging is modifiable - likely at any age.

ABBREVIATIONS

BMI	Body Mass Index
CCA	Common Carotid Artery
CV	Cardiovascular
HbA1c	Glycated Hemoglobin
IMT	Intima-Media Thickness

MetS	Metabolic Syndrome
PWV	Pulse Wave Velocity
SBP	Systolic Blood Pressure

References

Basso N, Cini Pietrelli AR, Ferder L, Terragno NA, Inserra F. Protective effect of long-term angiotensin II inhibition. Am J Physiol Heart Circ Physiol. 2007; 293:H1351–H1358. [PubMed: 17557916]

Bertoni AG, Krop JS, Anderson GF, Brancati FL. Diabetes-Related Morbidity and Mortality in a National Sample of U.S. Elders. Diabetes Care. 2002; 25:471–475. [PubMed: 11874932]

Bowen RL, Atwood CS. Living and dying for sex. A theory of aging based on the modulation of cell cycle signaling by reproductive hormones. Gerontology. 2004; 50:265–290. [PubMed: 15331856]

Caplan, GA. A Conceptual Model for Primary Prevention: Principles of Preventive Psychiatry. New York NY: Basic Books; 1964.

Centers for Disease Control and Prevention. Trends in aging—United States and worldwide. MMWR Morb Mortal Wkly Rep. 2003; 52:101–106. [PubMed: 12645839]

Mrazek, PJ.; Haggerty, RJ., editors. Committee on Prevention of Mental Disorders; Division of Biobehavioral Sciences and Mental Disorders. Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research. Washington, DC: National Academy Press; 1994.

Comfort A. Feasibility in age research. Nature. 1968; 217:320–322. [PubMed: 5639145]

Convanico V, De Caprio L, Vigorito C, et al. Differences in blood pressure profile between young and elderly hypertensive patients. J Hum Hypertens. 1990; 4:405–9. [PubMed: 2258885]

Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. Circulation. 2005; 112:1644–1650. [PubMed: 16145004]

Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III), . Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA. 2001; 285:2486–97. [PubMed: 11368702]

Ford ES, Mokdad AH, Giles WH, Mensah GA. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults: findings from the National Health and Nutrition Examination Survey, 1999 to 2000. Circulation. 2003; 107:2185–9. [PubMed: 12719276]

Forette F, Seux MI, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double- blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998; 352:1347–1351. [PubMed: 9802273]

Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino R. Trajectoreis of entering the metabolic syndrome. The Framingham Heart Study. Circulation. 2009; 120:1943–1950. [PubMed: 19884471]

Freimer N, Sabatti C. The Human Phenome Project. Nature Genet. 2003; 34:15–21. [PubMed: 12721547]

Ganau A, Saba PS, Roman MJ, de Simone G, Realdi G, Devereux RB. Aging induces left ventricular concentric remodelling in normotensive subjects. J Hypertens. 1995; 13:1818–1822. [PubMed: 8903659]

Gerstein HC, Miller ME, Byington RP, et al. for the Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358:2545–2559. [PubMed: 18539917]

Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. on behalf of the American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular Contributions to Cognitive Impairment and Dementia. A Statement for Healthcare Professionals From the American Heart Association/ American Stroke Association. Stroke. 2011; 42:2672–713. Epub 2011 Jul 21. [PubMed: 21778438]

Hatazawa J, Shimosegawa E, Osaki Y, Ibaraki M, Oku N, Hasegawa S, Nagata K, Hirata Y, Miura Y. Long-term angiotensin-converting enzyme inhibitor perindopril therapy improves cerebral perfusion reserve in patients with previous minor stroke. Stroke. 2004; 35:2117–22. [PubMed: 15256675]

Hoa AJ, Rajib CA, Beckerd JT, Lopezf OL, Kuller LH, Hua X, Lee S, Hibar D, Dinov ID, Stein JL, Jack CRJ, Weiner MJ, Toga AW, Thompson PM. the Cardiovascular Health Study, and the ADNI. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiology of Aging. 2010; 31:1326–1339. [PubMed: 20570405]

Hughes G. Changes in taste sensitivity with advancing age. Gerontol Clin (Basel). 1969; 11:224–30. [PubMed: 5796812]

Jacobsen JC, Mulvany MJ, Holstein-Rathlou NH. A mechanism for arteriolar remodeling based on maintenance of smooth muscle cell activation. Am J Physiol Regul Integr Comp Physiol. 2008; 294:R1379–R1389. [PubMed: 18184768]

Jacobson A, Yan C, Gao Q, Rincon-Skinner T, Rivera A, Edwards J, Huang A, Kaley G, Sun D. Aging enhances pressure-induced arterial superoxide formation. Am J Physiol Heart Circ Physiol. 2007; 293:H1344–H1350. [PubMed: 17557915]

Jellinger KA. Morphologic diagnosis of “vascular dementia” - a critical update. J Neurol Sci. 2008; 270:1–12. [PubMed: 18455191]

Kalaria RN, Maetre GE, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA, Ogunniyi A, Perry EK, Potocnik F, Stewart R, Wimo A, Zhang Z, Antuono P. Alzheimer’s disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol. 2008; 7:812–826. [PubMed: 18667359]

Kannel WB. Coronary heart disease risk factors in the elderly. Am J Geriatr Cardiol. 2002; 11:101–7. [PubMed: 11872968]

Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003; 115:41–6. [PubMed: 12867233]

Lamar M, Resnick SM, Zonderman AB. Longitudinal changes in verbal memory in older adults: Distinguishing the effects of age from repeat testing. Neurology. 2003; 60:82–86. [PubMed: 12525723]

Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27:2588–605. [PubMed: 17000623]

Lehoux S, Esposito B, Merval R, Tedgui A. Differential Regulation of Vascular Focal Adhesion Kinase by Steady Stretch and Pulsatility. Circulation. 2005A; 111:643–649.10.1161/01.CIR. 0000154548.16191.2F [PubMed: 15668343]

Lehoux S, Tedgui A. Making Up and Breaking Up : The Tortuous Ways of the Vascular Wall. Arterioscler Thromb Vasc Biol. 2005b; 25:892–894. [PubMed: 15863721]

London GM, Asmar RG, O’Rourke MF, Safar ME. REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. J Am Coll Cardiol. 2004; 43:92–9. [PubMed: 14715189]

Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS One. 2009; 4:e4144. [PubMed: 19127292]

Melzer D, Ely M, Brayne C. Cognitive impairment in elderly people: population based estimate of the future in England, Scotland, and Wales. BMJ. 1997; 315:462. [PubMed: 9284665]

MRC Working Party. Medical Research Council trial of treatmeant of hypertension in older adults: principal results. Br Med J. 1992; 304:405–412. [PubMed: 1445513]

Najjar SS, Scuteri A, Lakatta EG. Arterial Aging: Is it an Immutable Cardiovascular Risk Factor? Hypertension. 2005; 46:454–462. [PubMed: 16103272]

Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol. 2008; 51:1377–83. [PubMed: 18387440]

Nilsson PM, Lurbe E, Laurent S. The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. J Hypertens. 2008; 26:1049–57. [PubMed: 18475139]

Nilsson PM, Boutouyrie P, Laurent S. Vascular aging: A tale of EVA and ADAM in cardiovascular risk assessment and prevention. Hypertension. 2009; 54:3–10. [PubMed: 19487587]

Odden MC, Coxson PG, Moran A, Lightwood JM, Goldman L, Bibbins-Domingo K. The impact of the aging population on coronary heart disease in the United States. Am J Med. 2011; 124:827–833. [PubMed: 21722862]

Pauly RR, Passaniti A, Bilato C, Monticone R, Cheng L, Papadopoulos N, Gluzband YA, Smith L, Weinstein C, Lakatta EG, Crow MT. Migration of cultured vascular smooth muscle cells through a basement membrane barrier requires type iv collagenase activity and is inhibited by cellular differentiation. Circ Res. 1994; 75:41–54. [PubMed: 8013081]

Pilia G, Chen WM, Scuteri A, Orru M, Albai G, Dei M, Lai S, Usala G, Lai M, Loi P, Mameli C, Vacca L, Deiana M, Olla N, Masala M, Cao A, Najjar SS, Terracciano A, Nedorezov T, Sharov A, Zonderman AB, Abecasis GR, Costa P, Lakatta EG, Schlessinger D. Heritability of Cardiovascular and Personality Traits in 6,148 Sardinians. PLoS Genet. 2006; 2:e132–e148. [PubMed: 16934002]

Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, Hua X, Leow AD, Toga AW, Thompson PM. Brain structure and obesity. Hum Brain Mapp. 2010; 31:353–364. [PubMed: 19662657]

Saydah SH, Eberhardt MS, Loria CM, Brancati FL. Age and the Burden of Death Attributable to Diabetes in the United States. Am J Epidemiol. 2002; 156:714–719. [PubMed: 12370159]

Scuteri A, Jensen PE, Aalkjaer C. Regulation of intracellular pH in resistance arteries of WKY and SHR - Role of bicarbonate. J Hypertens. 1995; 13:523–528. [PubMed: 7561009]

Scuteri A, Chen CH, Yin FCP, Chih TT, Spurgeon HA, Lakatta EG. Functional correlates of central arterial geometric phenotypes. Hypertension. 2001; 38:1471–1475. [PubMed: 11751738]

Scuteri A, Najjar SS, Muller DC, Andres R, Hougaku H, Metter EJ, Lakatta EG. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. JACC. 2004a; 43:1388–1395. [PubMed: 15093872]

Scuteri A, Manolio TA, Marino EK, Arnold AM, Lakatta EG. Prevalence of specific variant carotid geometric patterns and incidence of cardiovascular events in older persons. The Cardiovascular Health Study. JACC. 2004b; 43:187–93. [PubMed: 14736436]

Scuteri A, Najjar SS, Morrell CH, Lakatta EG. The metabolic syndrome in older individuals: prevalence and prediction of cardiovascular events: the Cardiovascular Health Study. Diabetes Care. 2005a; 28:882–7. [PubMed: 15793190]

Scuteri A, Palmieri L, Lo Noce C, Giampaoli S. Age-related changes in brain functions: cognition, executive process, and motor speed. A population-based study. Aging Clin Exp Res. 2005b; 17:367–373. [PubMed: 16392410]

Scuteri A. Slowing arterial aging: how far have we progressed? J Hypertens. 2007; 25:509–10. [PubMed: 17278963]

Scuteri A, Tesauro M, Rizza S, Iantorno M, Federici M, Lauro D, Campia U, Turriziani M, Fusco A, Cocciolillo G, Lauro R. Endothelial dysfunction and arterial stiffness in normotensive

normoglycemic first degree relatives of diabetic patients are independent of the metabolic syndrome. Nutr Metab Cardiovasc Dis. 2008; 18:349–56. [PubMed: 17935958]

Scuteri A, Coluccia R, Castello L, Nevola E, Brancati AM, Volpe M. Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure. Eur Heart J. 2009a; 30:1525–9. [PubMed: 19406864]

Scuteri A, Najjar SS, Orru' M, Albai G, Strait J, Tarasov KV, Piras MG, Cao A, Schlessinger D, Uda M, Lakatta EG. Age- and gender-specific awareness, treatment, and control of cardiovascular risk factors and subclinical vascular lesions in a founder population: The SardiNIA Study. Nutr Metab Cardiovasc Dis. 2009b; 19:532–41. [PubMed: 19321325]

Scuteri A, Najjar SS, Orru' M, Usala G, Piras MG, Ferrucci L, Cao A, Schlessinger D, Uda M, Lakatta EG. The central arterial burden of the metabolic syndrome is similar in men and women: the SardiNIA Study. Eur Heart J. 2010a; 31:602–13. [PubMed: 19942601]

Scuteri A, Castello L, Coluccia R, Modestino A, Nevola E, Volpe M. Depression is associated with increased occurrence of left ventricle concentric geometry in older subjects independently of blood pressure levels. Nutr Metab Cardiovasc Dis. 2010b Jul 29.

Scuteri A, Orru' M, Morrell CH, Piras MG, Taub D, Schlessinger D, Uda M, Lakatta EG. Independent and additive effects of cytokine patterns and the metabolic syndrome on arterial aging in the SardiNIA Study. Atherosclerosis. 2011a; 215:459–64. [PubMed: 21241986]

Scuteri A, Nilsson PM, Tzourio C, Redon J, Laurent S. Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications. J Hypertens. 2011b; 29:1469–77. [PubMed: 21577138]

Scuteri A, Orru' M, Morrell CH, Tarasov K, Schlessinger D, Uda M, Lakatta EG. Associations of large artery structure and function with adiposity: Effects of age, gender, and hypertension. The SardiNIA Study. Atherosclerosis. 2011c Dec 14. Epub ahead of print.

Scuteri A, Modestino A, Frattari A, DiDaniele N, Tesauro M. Occurrence of Hypotension in Older Participants. Which 24-hour ABPM Parameter Better Correlate With? J Gerontol A Biol Sci Med Sci. 2012 Jan 6. Epub ahead of print.

Selvetella G, Notte A, Maffei A, Calistri V, Scamardella V, Frati G, Trimarco B, Colonnese C, Lembo G. Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. Stroke. 2003; 34:1766–1770. [PubMed: 12805496]

Sinclair, A. Available at: http://www.instituteofdiabetes.org/wp-content/themes/IDOP/other/diabetes_guidelines_for_older_people.pdf

Slotwiner DJ, Devereux RB, Schwartz JE, Pickering TG, de Simone G, Ganau A, Saba PS, Roman MJ. Relation of age to left ventricular function in clinically normal adults. Am J Cardiol. 1998; 82:621–6. [PubMed: 9732891]

Sutton-Tyrrell K, Wildman R, Newman A, Kuller LH. Extent of cardiovascular risk reduction associated with treatment of isolated systolic hypertension. Arch Intern Med. 2003; 163:2728–2731. [PubMed: 14662626]

Takeda S, Sato N, Takeuchi D, Kurinami H, Shinohara M, Niisato K, et al. Angiotensin receptor blocker prevented beta-amyloid induced cognitive impairment associated with recovery of neurovascular coupling. Hypertension. 2009; 54:1345–1352. [PubMed: 19805638]

Terrera GM, Brayne C, Matthews F. and the CC75C Study Collaboration Group. 2, 2010. One size fits all? Why we need more sophisticated analytical methods in the explanation of trajectories of cognition in older age and their potential risk factors. International Psychogeriatrics. 22:291–299. [PubMed: 19906326]

The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 201010.1056/NEJMoa1001286

The CAFÉ Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. Principal results of the Conduit Artery Function Evaluation (CAFÉ) Study. Circulation. 2006; 113:1213–1225. [PubMed: 16476843]

The Sixth Report of the Joint National Committee on Prevention. Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med. 1997; 157:2413–2446. [PubMed: 9385294]

Wang M, Zhang J, Spinetti G, Jiang LQ, Monticone R, Zhao D, et al. Angiotensin II activates matrix metalloproteinase type II and mimics age-associated carotid arterial remodeling in young rats. Am J Pathol. 2005; 167:1429–42. [PubMed: 16251426]

Wang M, Khazan B, Lakatta EG. Central Arterial Aging and Angiotensin II Signaling. Curr Hypertens Rev. 2010; 6:266–281. [PubMed: 21423831]

Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. Arch Intern Med. 2007; 167:141–7. [PubMed: 17242314]