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THE VOBARNO study

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ABSTRACT

Introduction. The Vobarno study represents the first observational study aimed to assess in a general population sample the relationship between parameters of cardiac and vascular structure (and function) and blood pressure values, measured in the clinic and during the 24 hours.

Evidence acquisition and synthesis. In the frame of the Vobarno study blood samples for hematochemistry and DNA extraction, clinic and 24-hour blood pressure measurements, cardiac and carotid ultrasound, and aortic stiffness were measured in all subjects, living in a small town (Vobarno) between Brescia and the Garda lake, and randomly selected from electoral roles. In this sample of a general population an extensive evaluation of organ damage, including left ventricular (LV) mass and hypertrophy, LV systolic function, left atrial dimensions and aortic root diameters, carotid intima media thickness (IMT) and carotid plaques, carotid and aortic stiffness were performed. In this study subjects were included in a long follow-up, lasting 25 years, and cardiovascular morbility and mortality were assessed up to 2019. This will allow to update the information related to cardiovascular morbidity and mortality in the study cohort.

Conclusions. The present paper will report the results of some analyses performed, exploring epidemiological and clinical aspects of target organ damage.

Key words: Hypertension, organ damage, epidemiology, morbidity and mortality, cardiovascular.

INTRODUCTION

The Vobarno study represents an epidemiological research, originally aimed to assess the relationship between parameters of cardiac and vascular structure (and function) and blood pressure values, measured in the clinic and during the 24 hour ambulatory BP recordings (1). The study started in 1992, including a large sample of subjects, representative of the general population of Vobarno (a town in a rural/urban area between Brescia and the Garda lake, Italy) for gender and decades of ages. A total of 585 individuals were recruited, starting with a first group of 284 subjects aged 50 to 65 years in 1992 and a second group of 301 subjects aged 35-50 in 1999 (approximately 2/3 of the population in that range of age) agreed to take part in the study. The study design and protocol (1,2) included the collection of a detailed medical history, with special reference to family and personal history of cardiovascular risk factors and events, including drug therapy. In addition, in each subject anthropometric parameters, clinic and ambulatory BP and heart rate were recorded; a transthoracic echocardiography (for LV mass and geometry, systolic function, atrial dimension and aortic root diameter) and a carotid ultrasound (for intima-media thickness, IMT, and intima-media thickening and plaque identification) were performed.

Blood samples for a genetic profile were also collected at baseline.

During follow up visits, the same protocol at first visit and evaluation was repeated, adding the assessment of carotid and aortic stiffness by local and carotid femoral pulse wave velocity (PWV), and central blood pressure measurement, by radial artery tonometry (3). Furthermore, a questionnaire for headache evaluation was obtained in the younger group of subjects in 1999 (4).

Two follow-up studies were planned during the years, allowing to obtain longitudinal information on a number of items. The first and second follow-up were performed

about 5 and 10 years after the original survey, starting in 1998 and 2004 for the first group and in 2006 and 2011 for the second group with the participation about 70% of the original sample. The last follow-up was carried out just few years ago, between 2017 and 2018, on 200 subjects who underwent the same measurements performed in the first two surveys and an extensive cognitive function assessment. Information on fatal and non-fatal cardiovascular events (stroke, myocardial infarction and heart failure) were collected by telephone calls, a fiscal-code record linkage procedure using the admission database of the Brescia and Gavardo Hospitals and validation of events using a standardized procedure for each medical record.

Data collected in the Vobarno study focus in 2 main research fields: a) the relationship between cardiac and vascular target organ damage and CV risk and b).the genetic profile as related to BP and cardiovascular phenotypes

The data collected in the frame of the Vobarno study have been included in several multicentre databases, aimed to assess reference values for cardiac anatomic parameters (5) and aortic stiffness (6). The Vobarno data collected during the 2nd follow up were also included in the MARE (Metabolic syndrome and Artery REsearch) Consortium aimed to study clustering of metabolic syndrome, its altered components and associations with arterial ageing (7,8). Data from subjects enrolled into the Vobarno study have been considered in the referent (control group) of the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study (9).

Cardiac and carotid artery damage prevalence and relationship with BP

The earliest publication on this issue (1) documented the presence of early carotid and cardiac structural changes in 225 untreated apparently healthy, middle aged men and women. In the Vobarno study 19% of hypertensives and 13 % of

normotensives fulfilled criteria for LVH (i.e. 134 g/m^2 in men 110 g/m^2 in women). LV mass index was positively related to all 24 hour systolic and diastolic BP means, to sex, to body mass index. In addition, a significant correlation was observed between LV mass index and IMT in the common carotid (r=0.19, p< 0.01) and at the bifurcation (r=0.19, p< 0.01) and average IMT at all sites (r=0.23, p=0,001). This correlation did not remain statistically significant at multivariate analysis, and only sex, body mass index and 24-hour mean BP were independent predictors of LV mass index.

IMT was significantly related to clinic and to 24 hour BP and was slightly thicker in hypertensives as compared to normotensives. In 38 % of subjects a plaque was observed. At logistic regression analysis the association between the presence of plaque and age, mean night-time systolic BP and cigarette smoking was observed. These findings add the notion that 24-hour measurement are more tightly related to target organ damage, especially those measured during the night-time.

This aspect was further investigated in a further publication (10), aimed to assess the increase in intima-media thickness or the presence of a plaque according to the degree of blood pressure reduction (dipping). In the group of 225 untreated and 59 treated individuals the thickness of carotid IMT and the prevalence of plaque were greater in those untreated without a 10 % decrease in BP values during the night; no differences were observed between dipper and no dipper treated subjects, possibly due to the effect of long-term hypertensive and cardiovascular drugs on vascular alterations.

The association between cardiac and carotid structural changes was further evaluated, according to LV geometry (2). The results of this analysis showed that those with concentric LV hypertrophy have a greater increase in the intima–media thickness and cross-sectional area of the common carotid artery than subjects with

different geometric patterns of the left ventricle. In subjects with both concentric and eccentric LV hypertrophy an increased number of plaques in the carotid tree was reported. These differences remained significant when differences in age, sex distribution, body size and blood pressure were considered. We also found that in subjects with concentric hypertrophy, the arterial thickness was increased not only in the common carotid artery, but also at the artery bifurcation site. The average intima–media thickness, which may represent an index of the extent of structural alterations, in the carotid arteries, was increased in both groups of subjects with LV hypertrophy and reached statistical significance for subjects with concentric hypertrophy. These results further indicated that a greater degree of involvement in carotid arteries, characterized by wall thickening and/or plaque occurrence, might explain, at least in part, the association between LV concentric hypertrophy and cardiovascular prognosis reported in the Framingham population and in hypertensive patients, also by our group (11).

The Vobarno study added new information on a controversial issue, i.e.the more appropriate formula to use for the calculation of LV mass (12). According to the recommendations of the American society of Echocardiography the calculation of LV mass is based on the assumption that the left ventricle may be represented as a prolate ellipsoid with both the internal and external long axes twice the short axis. In 1997 Wikstrand (13) raised concern about the 'correct' calculation of LVM using the prolate ellipsoidal model like in the ASE method and in the Penn convention. Wikstrand proposed that a precise estimate of LVM might be obtained by using an alternate formula that considers the wall thickness constant around the ellipsoidal cavity. Therefore we have compared the thin wall and the thickwall models for the calculation of LV mass in the population enrolled in the Vobarno Study. We found a close relationship between values of LV mass calculated by using a thin-wall

ellipsoidal model (Wikstrand formula) and those calculated using a thick-wall model with Penn convention or ASE left ventricle measurements (r = 0.99, for the Vobarno populations). LVH was observed in 88 subjects in the Vobarno population according to the thin-wall model, in 87 according to the ASE adjusted thick-wall model, and in 89 according to the Penn convention. Highest values of Penn left ventricle mass were slightly underestimated by use of the thin-wall formula.

Target organ damage in prehypertensive subjects and in resistant hypertensive patients

The extensive phenotyping of target organ damage performed in the Vobarno study allowed us to assess the impact of different forms of subclinical alterations in patients with different degree and severity of BP increase, for the assessment of global cardiovascular risk.

Patients with High normal BP (or pre-hypertension)

We assessed the prevalence of high-normal (HN) BP and of associated cardiovascular target organ damage (TOD) in 420 subjects (age 50 ± 8 years, 46% males) of the whole sample (14, 15). Normotension was defined as a SBP/DBP <130/85 mmHg, HN BP was defined as SBP/DBP ≥130/85 and <140/90 mmHg and hypertension (HT) as SBP/DBP ≥140/90 mmHg. A follow-up (FU) visit, laboratory examinations, echocardiography and carotid intima-media thickness (IMT) measurement were performed after 9 years.

At baseline 34% of subjects were normotensives (NT), 36% were hypertensives and 30% (n = 126) of subjects were classified as HN. As compared to NT, subjects with HN BP were older, were more often male, and had a greater body mass index. Furthermore, as compared to NT subjects, those with HN BP had greater plasma glucose values, creatinine and uric acid levels (all p < 0.05). The prevalence of

metabolic syndrome was 3.5% in NT, 29.4% in HN and 34% in HT ($p < 0.05$ vs. NT for both HT and HN; p = ns for the comparison between HN and HT). LV mass index and relative wall thickness progressively increased form NT to HN to HT and, in particular, LV mass index and relative wall thickness were significantly greater in HN as compared to NT (ANOVA p, with Bonferroni correction, <0.05). Carotid IMT was greater in HT as compared to NT and HN (all $p < 0.05$). No significant difference in IMT was observed between HN and NT.

At the follow-up visit, performed after 8.6 ± 2.2 years, among subjects classified as NT at baseline, 34% had progressed to HT, 23% had HN BP, while 43% had normal BP. Among those classified as HT at baseline, most (84%) were classified as hypertensive at FU visit, 11% had HN BP and 5% were NT. Interestingly, among the 126 subjects classified as HN at baseline, at follow-up visit 71% had progressed to HT, 18% had HN BP and only 11% had BP values within the normal range.

When cardiac organ damage was analysed at FU, subjects classified as having HN BP at baseline had a LV mass index and a relative wall thickness that were significantly greater than those classified as NT at baseline, ($p < 0.05$), indicating the development of a more concentric geometry in these subjects. Some parameters derived from the transmitral flow velocity measurement and left atrial dimensions indicated a tendency to an earlier development of diastolic dysfunction in this group, as compared to normotensives. Also vascular damage was more prominent in subjects classified as having HN BP at baseline. In particular, both Meanmax and CBMMax (mean max of carotid and bifurcation) IMT were significantly greater in subjects who had HN BP at baseline as compared to those classified as NT and the greatest values were observed in patients classified as hypertensives at baseline (p at least <0.05 for all comparisons).

Finally, when changes over time (during the long follow-up) in cardiac and vascular measures of TOD were analysed, in subjects classified as HN BP at the baseline visit the progression of IMT was progressively greater from patients classified as NT, as HN BP and as HT at baseline (p for trend <0.01). A similar trend was also observed for LV mass index, but the finding did not reach statistical difference. When the analysis was limited to untreated patients (*n* = 295), the results remained substantially unchanged for IMT, and reached statistical significance for the change of LV mass index over time. In conclusion, this analysis showed that a significant proportion (30%) of apparently healthy subjects have HN BP, associated to a higher BMI, to a worst cardiovascular risk profile as compared to normotensives (higher plasma glucose, creatinine and uric acid) and to metabolic syndrome in a third of them. The progression from HN hypertension (or pre-hypertension) was frequent (71 % in about 9 years), while only 11% showed BP values within the normal range. In addition, the progression of organ damage is more rapid in patients with high-normal blood pressure, with an increase in carotid intima-media thickness and in LV mass index, which is intermediate between that observed in normotensives and in hypertensives, possibly explaining the increase in the risk of cardiovascular events observed in subjects with high-normal blood pressure and prehypertension.

Resistant hypertension

We also assessed the prevalence of resistant hypertension and of associated cardiac, vascular and renal TOD in 317 hypertensive individuals (173 treated) selected from the larger general population living in Vobarno (16). We used the definition for resistant hypertension proposed by Calhoun et al (17). that is, the presence of BP values > 140/90mmHg despite adherence to lifestyle measures and to pharmacological treatment with full doses of at least three antihypertensive

medications, including one diuretic. The prevalence of resistant hypertension was 17.3%. Resistant hypertension patients were older, more often females and exhibited higher fasting glycemia. Lower values of estimated glomerular filtration rate (eGFR) (72±17 vs. 80±16 ml min_1 per 173m2; P<0.01) and a higher prevalence of chronic kidney disease (eGFR o60ml min_1 per 173m2; 27% vs. 8.5%, P<0.01) were observed in patients with resistant hypertension than in patients with controlled BP values. In resistant hypertensive patients, a significantly higher LV mass index was observed, compared with that in controlled patients using two different indexations of LV mass Accordingly, the prevalence of LV hypertrophy was twofold higher in resistant hypertension patients (40% vs. 21%; P< 0.05) as well as concentric geometry (concentric geometry 40% vs. 22% in RH and controlled hypertensive patients, respectively, P<0.04). The prevalence of carotid plaques was quite high in the entire population, but was greater in the group of RH patients (97% vs. 83%, P<0.04). Finally, aortic stiffness (according to the measurement of carotidofemoral PWV) was increased in RH patients compared with subjects with satisfactory BP control (13.3±2.8 vs. 11.8±2.6ms_1; P< 0.03), and the prevalence of PWV 49.6ms_1 was 71%, and 44%, P<0.04, respectively. Our data confirmed that RH is not a rare clinical condition, and we were able to detect an increase in the prevalence and severity of TOD in the heart, kidney and macrovasculature, possibly reflecting the differences in age, glycemia and body mass index, but also the longer duration and severity of arterial hypertension (Figure 2) (16).

Risk stratification of target organ damage

In addition to routine work-up, based on the detection of classical risk factors, we added the identification of LV hypertrophy, carotid intima–media thickness, or plaque, albuminuria, and carotid–femoral PWV. Carotido-femoral PWV represents an

accurate parameter of aortic stiffness, measured by a relatively simple non-invasive procedure. The contribution of PWV measurement, in addition to echocardiography, carotid ultrasound and measurement of eGFR, albuminuria or both, on cardiovascular risk stratification was assessed in 385 subjects (mean age 57±10 years, 44% men) of the general population sample in Northern Italy, examined between 2002 and 2005 (3). Twenty-three patients were identified at average risk and 131 patients were identified at high or very high-added cardiovascular risk (n = 3) by routine clinical workup, because of the presence of grade 3 hypertension, more than three additional risk factors, TOD or associated clinical disease, 136 subjects were at low and 95 at moderate added cardiovascular risk, as a result of the routine clinical workup.

Among all patients, echocardiographic LVH overall prevalence was 9%, that increased when the indexation to the height to the 2.7 power of LV mass was used (11%). Renal TOD, based on the identification of sex-specific eGFR measurements, had an overall prevalence of 8.3% (32 subjects), while the prevalence of concomitant microalbuminuria and reduced eGFR was 18%.

At least one carotid plaque or common carotid thickening was observed in 238 individuals (61.8%), whereas an increase in PWV was detected in 122 (31.7%).

Overall, at least one manifestation of organ damage was found in 278 patients (72%), whereas two, three and all four manifestations of TOD were observed in 36, 28, 10 and 2% of patients, respectively.

The reclassification of patients at low or moderate in high-added cardiovascular risk in different grades of BP elevation was based on the presence of TOD in 32 subjects (26%) with BP values in the high-normal range, in 66 (54%) in grade 1 hypertension group, in 22 (18%) in grade 2 hypertension group and in two patients (2%) in the grade hypertension 3 group. This was the first study that analyzed, in a

general population sample, the impact of the simultaneous assessment of different forms of organ damage, including PWV, on cardiovascular risk stratification as recommended by ESH–ESC guidelines (18). The number of subjects reclassified as being at high risk was high, in particular, when vascular damage was assessed, including both carotid IMT (30%) and PWV (14%) measurements. The results of this study reinforced the concept that the evaluation of different forms of TOD may differently affect the accuracy of global cardiovascular risk assessment

Headache

In order to explore the controversial association of headache and arterial hypertension we aimed to evaluate the prevalence of headache in a general population sample and the relationship with arterial hypertension. The diagnosis of hypertension was based on office measurements and 24-hour ambulatory monitoring of blood pressure (BP) (4). We administered a structured standardized headache questionnaire to the "younger" group of subjects (n= 301, 126 males and 175 females, age range 35-50 years) and in the same day measured office and 24-h ambulatory BP. Prevalence of lifetime headache and of migraine was greater in females than in males. Office and 24-h BP values did not differ between subjects without or with headache. No differences in headache prevalence (58% vs 55%), migraine prevalence (32% vs 28%) and use of analgesic drugs in the presence of headache (82% vs 78%) were observed between hypertensive patients (93.5% newly diagnosed, 6.5% treated) and normotensive subjects, confirming that in a general population sample, the diagnosis of hypertension (diagnosed by office and/or 24-h BP) is not associated with headache.

GENETIC PROFILE

The genetic variability of some polymorphisms was proposed as a marker of a genetic predisposition for the increase of blood pressure values and /or the development of target organ damage (alpha-adducin, ACE, Angiotensinogen, Angiotensin II receptors, aldosterone synthase, sympathetic nervous system).

In the Vobarno study it was observed that IMT was greater in subjects with a DD allele polymorphism of the Angiotensin Converting Enzyme (ACE) (19).

On the opposite no differences were observed according to the different Angiotensin II type 1 receptor A/C 1166 and aldosterone synthase polymorphisms (20, 21).

A slight, although statistically significant association, was reported between BP values measured by 24-hour monitoring and the presence of at least one allele Trp 460 (P= 0.066) of alpha adducin polymorphism, a cytoskeleton protein (22). Finally, the beta-2 adrenoceptor gene polymorphism was investigated and the influence of age on the relationship between the different alleles and cardiovascular phenotypes was reported (23).

CONCLUSIONS

As mentioned in the introduction, the investigators involved in the Vobarno study are now working in the analysis of the data collected during the follow-up, focusing on the relationship of 24 hour BP values, TOD and the impairment of cognitive function.

All Authors read and approved the final version of the manuscript

AUTHORS CONTRIBUTION SECTION

Prof Agabiti Rosei conceived the Vobarno Study, all other authos wrote different parts of the manuscript and Prof Agabiti Rosei revised it.

REFERENCES

1) Muiesan ML, Pasini G, Salvetti M, Calebich S, Zulli R, Castellano M, Rizzoni,D, Bettoni G, Cinelli A, Porteri E, Corsetti V, Agabiti-Rosei E. Cardiac and vascular structural changes. Prevalence and relation to ambulatory blood pressure in a middle-aged general population in northern Italy: the Vobarno Study. Hypertension. 1996 May;27(5):1046-52. doi: 10.1161/01.hyp.27.5.1046. PMID: 8621195.

2) Muiesan ML, Salvetti M, Zulli R, Pasini GF, Bettoni G, Monteduro C, Rizzoni D, Castellano M, Agabiti-Rosei E. Structural association between the carotid artery and the left ventricle in a general population in Northern Italy: the Vobarno study. J Hypertens. 1998 Dec;16(12 Pt 1):1805-12. doi: 10.1097/00004872-199816120-00014. PMID: 9869015.

3) Muiesan ML, Salvetti M, Paini A, Monteduro C, Rosei CA, Aggiusti C, Belotti E, Bertacchini F, Galbassini G, Stassaldi D, Castellano M, Rosei EA. Pulse wave velocity and cardiovascular risk stratification in a general population: the Vobarno study. J Hypertens. 2010 Sep;28(9):1935-43. doi: 10.1097/HJH.0b013e32833b4a55. PMID: 20520574.

4) Muiesan ML, Padovani A, Salvetti M, Monteduro C, Poisa P, Bonzi B, Paini A, Cottini E, Agosti C, Castellano M, Rizzoni D, Vignolo A, Agabiti-Rosei E. Headache: Prevalence and relationship with office or ambulatory blood pressure in a general population sample (the Vobarno Study). Blood Press. 2006;15(1):14-9. doi: 10.1080/08037050500436089. PMID: 16492611.

5) Echocardiographic Normal Ranges Meta-Analysis of the Left heart (EchoNoRMAL) Collaboration A meta-analysis of echocardiographic measurements of the left heart for the development of normative reference ranges in a large international cohort: the EchoNoRMAL study. .Eur Heart J Cardiovasc Imaging. 2014 Mar;15(3):341-8. doi: 10.1093/ehjci/jet240. Epub 2013 Nov 17.

6) Reference Values for Arterial Stiffness' Collaboration Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. .Eur Heart J. 2010 Oct;31(19):2338-50

7) Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Mañas LR, Mattace Raso FU, Muiesan ML, Ryliškytė L, Rietzschel E, Strait J, Vlachopoulos C, Völzke H, Lakatta EG, Nilsson PM; Metabolic Syndrome and Arteries Research (MARE) ConsortiumMetabolic syndrome across Europe: different clusters of risk factors.
.Eur J Prev Cardiol. 2015 Apr;22(4):486-91. doi: 10.1177/2047487314525529. Epub 2014 Mar 19.PMID: 24647805

8) Scuteri A, Cunha PG, Agabiti Rosei E, Badariere J, Bekaert S, Cockcroft JR, Cotter J, Cucca F, De Buyzere ML, De Meyer T, Ferrucci L, Franco O, Gale N, Gillebert TC, Hofman A, Langlois M, Laucevicius A, Laurent S, Mattace Raso FUS, Morrell CH, Muiesan ML, Munnery MM, Navickas R, Oliveira P, Orru' M, Pilia MG, Rietzschel ER, Ryliskyte L, Salvetti M, Schlessinger D, Sousa N, Stefanadis C, Strait J, Van Daele C, Villa I, Vlachopoulos C, Witteman J, Xaplanteris P, Nilsson P, Lakatta EG; MARE Consortium. Arterial stiffness and influences of the metabolic syndrome: a cross-countries study. Atherosclerosis. 2014 Apr;233(2):654-660. doi: 10.1016/j.atherosclerosis.2014.01.041. Epub 2014 Jan 30.PMID: 24561493

9) Debette S, Metso T, Pezzini A, Abboud S, Metso A, Leys D, Bersano A, Louillet F, Caso V, Lamy C, Medeiros E, Samson Y, Grond-Ginsbach C, Engelter ST, Thijs V, Beretta S, Béjot Y, Sessa M, Lorenza Muiesan M, Amouyel P, Castellano M, Arveiler D, Tatlisumak T, Dallongeville J; Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) Group.Association of vascular risk factors with cervical artery dissection and ischemic stroke in young adults. Circulation. 2011 Apr 12;123(14):1537-44.

10) Salvetti M, Muiesan ML, Rizzoni D, Bettoni G, Monteduro C, Corbellini C, Viola S, Agabiti-Rosei E. Night time blood pressure and cardiovascular structure in a middle-aged general population in northern Italy: the Vobarno Study. J Hum Hypertens. 2001 Dec;15(12):879-85. doi: 10.1038/sj.jhh.1001286. PMID: 11773992.

11) Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E.Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. J Hypertens. 1995 Oct;13(10):1091-5. doi: 10.1097/00004872-199510000-00003.

12) Muiesan ML, Salvetti M, Monteduro C, Donato F, Rizzoni D, Agabiti-Rosei E. Various ways of calculating echocardiographic left ventricular mass and their relative prognostic values. J Hypertens. 1998 Aug;16(8):1201-6. doi:10.1097/00004872-199816080-00014. PMID: 9794725.

13) Wikstrand J. Calculation of left ventricular mass in man [comment]. *J Hypertens* 1997; 15:811–813

14) Agabiti-Rosei E, Paini A,Salvetti M. Subclinical Vascular Damage in Prehypertension in R. Zimlichman et al. (eds.), *Prehypertension and Cardiometabolic Syndrome*, Updates in Hypertension and Cardiovascular Protection, Springer International Publishing AG, part of Springer Nature 2019 25 https://doi.org/10.1007/978-3-319-75310-2_18

15) M.L. Muiesan, M. Salvetti, M. Castellano, C. Monteduro, S. Viola, S. Comini, C. Perani, D. Rizzoni, E. Agabiti-Rosei. Cardiac and vascular structure in subjects with high normal blood pressure Abstracts from 23th Congress of the European Society of Cardiology, ESC Congress, Stockholm 1-4 september 2001. European Heart Journal, vol 22, 189, pag. 23.

16) Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, Agabiti Rosei Resistant hypertension and target organ damage. E.Hypertens Res. 2013 Jun;36(6):485-91.

17) Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008; 117: e510–e526

Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al . 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial

Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013 Jul;31(7):1281-357.

19) Castellano M, Muiesan ML, Rizzoni D, Beschi M, Pasini GF, Cinelli A, Salvetti M, Porteri E, Bettoni G, Kreutz R, Lindpainter K, Agabiti-Rosei E. Angiotensin converting enzyme I/D polimorphism and arterial wall thickness in a general population. Circulation 1995, 91;11:2721-2724

20) Castellano M, Muiesan ML, Beschi M, Rizzoni D, Cinelli A, Salvetti M, Pasini G, Porteri E, Bettoni G, Zulli R, Agabiti-Rosei E.Angiotensin II type 1 receptor A/C1166 polymorphism. Relationships with blood pressure and cardiovascular structure.
Hypertension. 1996 Dec;28(6):1076-80. doi: 10.1161/01.hyp.28.6.1076.

21) M. Castellano, F. Rossi, F. Rivadossi, C. Perani, M. Giacchè, M.L. Muiesan, M. Beschi, D. Rizzoni, E. Agabiti-Rosei. Relationship of an aldosterone synthase gene polymorphism with cardiovascular hypertrophic changes. Abstracts from the Tenth European Meeting on Hypertension, Goteborg, 29 May -3 June 2000. J Hypertens, 2000, 18 (Suppl.2): p S116, n. P2.107

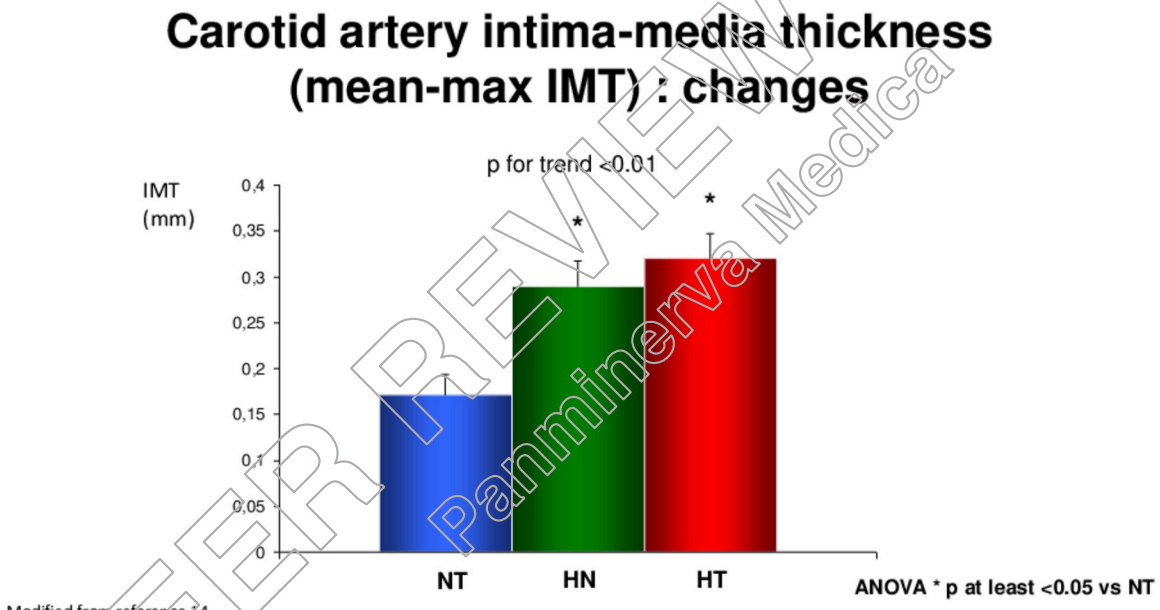
22) Castellano M, Barlassina C, Muiesan ML, Beschi M, Cinelli A, Rossi F, Rizzoni D, Cusi D, Agabiti-Rosei E. Alpha-adducin gene polymorphism and cardiovascular phenotypes in a general population.J Hypertens. 1997 Dec;15(12 Pt 2):1707-10. doi: 10.1097/00004872-199715120-00076.

23) Castellano M, Rossi F, Giacchè M, Perani C, Rivadossi F, Muiesan ML, Salvetti M, Beschi M, Rizzoni D, Agabiti-Rosei E.Beta(2)-adrenergic receptor gene polymorphism, age, and cardiovascular phenotypes. Hypertension. 2003 Feb;41(2):361-7. doi: 10.1161/01.hyp.0000052831.85600.79

LEGENDS

Figure 1. Prevalence of target organ damage in Resistant Hypertension and non resistant hypertension subjects . CKD = Chronic Kidney Disease , ie estimated glomerular filtration rate < 60 ml/min/1.73 m^2

Figure 2. Progression of target organ damage in normotensives, in high normal blood pressure subjects, and in hypertensive patients



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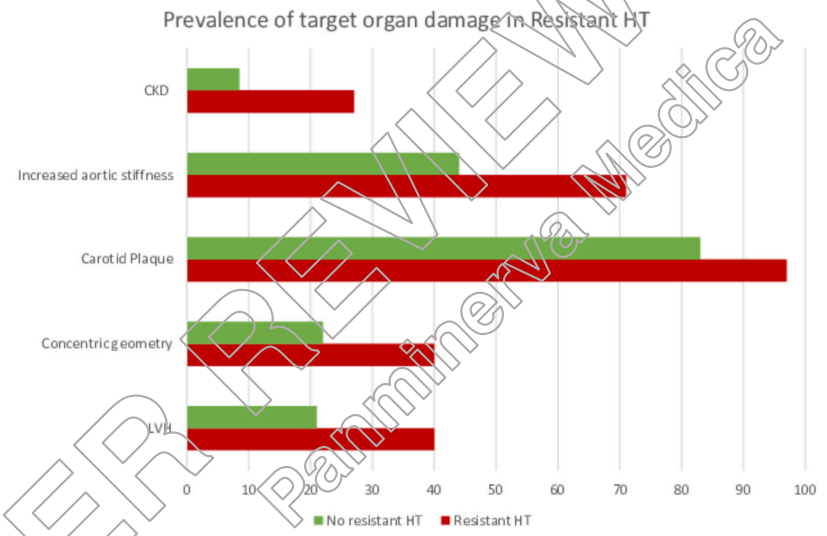

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