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ORIGINAL ARTICLE
Hypertension

Hypertension-mediated organ damage involving multiple sites is an independent risk factor for cardiovascular events

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Aims

Chronic pressure overload determines functional and structural alterations, leading to hypertension-mediated organ damage (HMOD), affecting multiple districts. We aim at evaluating the prognostic impact of the absence vs. presence of HMOD in one or more sites and of blood pressure (BP) and metabolic control in hypertensive patients.

Methods and results

The study included 7237 hypertensive patients from the Campania Salute Network Registry, followed up for 5.3 ± 4.5 years. As HMOD, we analysed the presence of left ventricular hypertrophy, carotid plaques, and chronic kidney disease (CKD-EPI ≥3 stage) and evaluated the impact of zero vs. one vs. two vs. three sites of HMOD on the occurrence of major adverse cardiovascular events (MACEs). Blood pressure control and Metabolic Score for Insulin Resistance (METS-IR) were also considered. Optimal BP control was achieved in 57.3% patients. Major adverse cardiovascular events occurred in 351 (4.8%) patients. The MACE rate in patients without HMOD was 2.7%, whereas it was 4.7, 7.9, and 9.8% in patients with one, two, and three sites with HMOD, respectively. By using Cox multivariate models, adjusted for age, BP control, mean heart rate, mean METS-IR, number of HMOD sites, and drugs, MACE was found to be significantly associated with ageing, mean METS-IR, anti-platelet therapy, and multiple sites with HMOD, whereas a negative association was found with renin–angiotensin system inhibitor drugs.

Conclusion

In hypertensive patients, the risk of MACE increases with the incremental number of districts involved by HMOD, independent of BP control and despite the significant impact of metabolic dysregulation. Hypertension-mediated organ damage involving multiple sites is the deleterious consequence of hypertension and dysmetabolism but, when established, it represents an independent cardiovascular risk factor for MACE occurrence.

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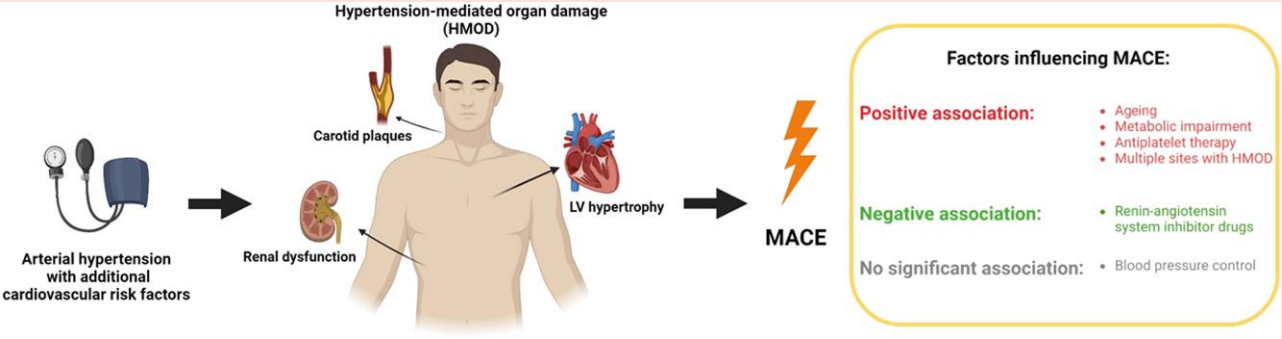
Graphical Abstract



Keywords Arterial hypertension • Major adverse cardiovascular events • Renin–angiotensin system inhibitor drugs

Introduction

Arterial hypertension (AH), especially when combined with other cardiovascular risk factors, is responsible for functional and structural abnormalities involving multiple organs, defined as hypertension-mediated organ damage (HMOD),[1–3] including left ventricular (LV) hypertrophy, carotid atherosclerosis, and renal functional impairment, possibly impacting patient prognosis.[4–6] Insulin resistance and metabolic dysfunction have shown a synergic deleterious effect with hypertension, in both the development and the progression of HMOD.[7]

Early control of blood pressure (BP) values is recommended to prevent the progression of hypertensive disease and further cardiovascular complications,[4] as also suggested by several studies, which demonstrated a decrease in the rate of major adverse cardiovascular events (MACEs) in patients achieving precocious BP control.[8,9] However, when multiple districts are involved in HMOD, a deeply rooted injury may already be established, and it should be elucidated whether the presence of several sites with HMOD could influence a poor prognosis and MACE occurrence.

Indeed, according to the current guidelines on AH, the presence of HMOD is important to define cardiovascular risk stratification in hypertensive patients; however, common scores, established with the aim of outlining cardiovascular risk, do not take into account the impact of the number of involved sites.[4,10] In other words, could the screening of HMOD and its extension modify the cardiovascular risk score and therapeutic approach of hypertensive patients?

Despite little evidence suggesting that the relationship between HMOD and outcomes seems to be graded, with a more adverse prognosis in patients with multiple sites of HMOD involvement, the real impact of the presence of one vs. several districts with HMOD on MACE is still not well defined.[11,12] Furthermore, it is still unclear which classes of anti-hypertensive drugs may have a favourable effect on helping to prevent the occurrence of MACE in hypertensive patients with HMOD. Therefore, we aim at evaluating the prognostic impact of the absence vs. the presence of HMOD involving one or more districts, and the effect of BP and metabolic control as well as of anti-hypertensive treatment on a population of patients affected by AH.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study population

Patients affected by AH with a long-term follow-up, enrolled in the Campania Salute Network, were evaluated. The Campania Salute Network is an open electronic registry that received approval from the Federico II University Hospital Ethics Committee (ClinicalTrials.gov Identifier: NCT02211365) and was previously described in detail.[13,14] All patients signed a written informed consent to participate in clinical studies.[15,16]

The study population included patients with available follow-up ≥12 months, echo and serum creatinine assessment, and without a history of prevalent cardiovascular disease at baseline, including congestive heart failure, myocardial infarction, angina pectoris, coronary or carotid revascularization procedures, transitory ischaemic attack, stroke, clinically relevant heart valvular disease (more than mild valve regurgitation or any stenosis), known renal diseases not mediated by AH, and chronic kidney disease (CKD) more than Stage 3.

The diagnosis of AH was confirmed according to current ESC/ESH guidelines.[4] At baseline and at each follow-up visit, systolic and diastolic BP and heart rate were collected in the sitting position after 2 min of resting, using a semi-automatic oscillometric sphygmomanometer with cuffs of appropriate size (average of three measurements at 1 min interval). The calibration of the devices was performed by yearly checks from the manufacturer. Optimal office BP control during the follow-up was defined for average values <140/90 mmHg during the follow-up visits, in accordance with ESC/ESH guidelines for the management of AH.[4] Pulse pressure was computed as the difference between systolic BP and diastolic BP values.[17]

Diabetes was defined as a history of diabetes, use of any specific anti-diabetic treatment, or for values of fasting plasma glucose >126 mg/dL confirmed on two different occasions.[18] Obesity was established for values of body mass index ≥30 kg/m^2.

Glomerular filtration rate was estimated by using the CKD epidemiology collaboration (CKD-EPI) equation, as previously reported.[19]

Metabolic evaluation was assessed by using the Metabolic Score for Insulin Resistance (METS-IR), an insulin resistance surrogate, measured according to the following formula: METS-IR = {ln [2 × fasting plasma glucose (mg/dL) + triglycerides (mg/dL)] × body mass index (kg/m^2)/ln [HDL-cholesterol (mg/dL)]}.[15,20]

The rate of MACE developed during the follow-up was related to the first occurrence. Major adverse cardiovascular events during the follow-up period included myocardial infarction, stroke, and transitory ischaemic attack, coronary or carotid revascularization procedures, hospitalization due to heart failure symptoms, and the development of life-threatening arrhythmias or atrial fibrillation.

Three-point MACE (3P-MACE) was also considered, which constituted a less broad definition of MACE and including just the occurrence of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke during the follow-up.

Ultrasound assessment

Ultrasound cardiac and carotid assessment was performed at the Hypertension Outpatient Clinic of the Federico II University in Naples, using a standardized protocol.[21] All measurements were evaluated according to the latest consolidated convention and according to the standards of our laboratory.[22,23] Echocardiographic examinations were digitally recorded and read offline by a trained expert reader under the supervision of a senior faculty member, using dedicated workstations.

Left ventricular mass was estimated from a necropsy-validated formula and normalized for height in metres to the power of 2.7 (LV mass index).[24,25] Left ventricular hypertrophy was defined for values of LV mass index >47 g/m$^{2.7}$ in women and >50 g/m$^{2.7}$ in men.[26,27]

Left ventricular ejection fraction and stroke volume were computed as the difference between LV end-diastolic and end-systolic volume by the z-derived method and indexed for height to the power of 2.04.[28,29]

Left atrial volume was estimated according to the previously validated formula and indexed for height powered to 2.[30]

Carotid ultrasound was evaluated in the supine position. The intima–media thickness was measured as the distance between the lumen–intima and the media–adventitia interface in up to two arterial walls, on both the near and the far walls of the distal common carotid (1 cm), bulb and the proximal internal carotid artery of both sides, and carotid plaques were identified for intima–media thickness values >1.5 mm.[14]

As sites with HMOD, we considered the presence of LV hypertrophy, carotid plaques, and/or CKD-EPI ≥3 at baseline and evaluated the impact of one vs. two vs. three districts involved by HMOD vs. the absence of HMOD on the occurrence of MACE.

Statistical analysis

Categorical variables were expressed as frequency (percentage) and continuous variables as mean ± standard deviation. Simple Cox regression models were used to evaluate the association between the measured variables and the occurrence of MACE. Predictors that were significant in the simple regression models were added, along with the variable of interest (sites with HMOD), to a multiple Cox regression model. *P*-values and hazard ratios for all combinations of sites with HMOD with different references were estimated using separate multiple Cox models. The proportional hazard assumption was tested using the Schoenfeld residuals.

In all analyses, a *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using R Statistical Software version 4.0.3 and SPSS Statistics 26 software (IBM Corp.).

Results

The study population included 7237 hypertensive patients followed up for a period of 5.3 ± 4.5 years. *Table 1* summarizes the clinical and ultrasound characteristics of the study population. At baseline, the prevalence of diabetes and obesity was of 10.2 and 25.5%, respectively. At basal evaluation, 35.6% patients did not have any HMOD, whereas 38.8, 21.7, and 3.9% patients presented one, two, or three sites with HMOD, respectively. Among districts with HMOD, LV hypertrophy was recorded in 2761 patients (38.2%), carotid plaques in 3325 patients (45.9%), and CKD-EPI >3 in 706 (9.7%).

The average number of visits was 6.15 (±5.40). At baseline, 27% (n = 1987) of patients were already in therapy with a single anti-hypertensive drug, 36% (n = 2640) were under combination therapy, and 37% (n = 2610) were not under any anti-hypertensive drug and were referred to our centre to verify their hypertensive state and start an appropriate therapy. During the follow-up, 32% (n = 2293) were treated with a single anti-hypertensive drug, 55% (n = 3977) received a combination therapy, and 13% (n = 967) continued to not receive any anti-hypertensive drug. The latter group included patients without HMOD and with Grade I hypertension and low cardiovascular risk who received as first instance just lifestyle advice, according to current guidelines.

During the follow-up, MACE occurred in 351 patients with a prevalence rate of 4.8% in the whole study population. The rate of MACE in patients without HMOD was 2.6% (67/2580), 4.7% (132/2806) in patients with one site with HMOD, 7.9% (124/1567) in patients with two sites with HMOD, and 9.8% (28/284) in patients with three districts affected by HMOD (*P*-value 0 vs. 1 <0.001; 0 vs. 2 <0.001; 0 vs. 3 <0.001; 1 vs. 2 <0.001; 1 vs. 3 <0.001; 2 vs. 3 = 0.309).

By simple Cox regressions (*Table 2*), MACE was found to be associated with ageing, mean heart rate, mean METS-IR, LV hypertrophy,

Table 1 Clinical and ultrasound data of the study population

Parameter	Mean ± SD or *n* (%)
Age, years	53.8 ± 11.4
Female sex	3079 (42.5)
Baseline systolic BP, mmHg	142.7 ± 18.4
Baseline diastolic BP, mmHg	88.8 ± 11.1
Baseline pulse pressure, mmHg	61.7 ± 15.9
Baseline heart rate, b.p.m.	74.4 ± 11.5
Baseline body mass index, kg/m^2	27.8 ± 4.2
Baseline fasting glycaemia, mg/dL	99.2 ± 24.2
Baseline total cholesterol, mg/dL	206.1 ± 39.2
Baseline triglycerides, mg/dL	132.2 ± 75.2
Baseline HDL-cholesterol, mg/dL	50.6 ± 13.1
Baseline METS-IR	41.6 ± 8.0
Diabetes	738 (10.2)
Obesity	1846 (25.5)
Smoking habit	1465 (20.2)
Baseline LV mass index, g/m$^{2.7}$	47.2 ± 9.3
Baseline left atrial volume index, mL/m^2	13.2 ± 2.7
Baseline ejection fraction, %	63.1 ± 4.1
Baseline stroke volume index, mL/m$^{2.04}$	25.9 ± 3.4
Baseline intima media thickness, mm	1.6 ± 0.7
LV hypertrophy	2761 (38.2)
Carotid plaque	3325 (45.9)
CKD-EPI >3	706 (9.8)
No HMOD	2580 (35.6)
One HMOD	2806 (38.8)
Two HMOD	1567 (21.7)
Three HMOD	284 (3.9)
Optimal BP control during the follow-up	4147 (57.3)
Mean systolic BP, mmHg during the follow-up	137.2 ± 12.7
Mean diastolic BP, mmHg during the follow-up	84.2 ± 7.3
Mean heart rate	73.68 ± 8.43
MACEs during the follow-up	351 (4.8)
Mean METS-IR	41.4 ± 8.0
Number of medications in at least 50% of control visits	1.7 ± 1.0
Anti-renin–angiotensin system[a]	5917 (81.8)
Dihydropyridine calcium channel blockers[a]	1891 (26.1)
Diuretics[a]	3150 (43.5)
Beta-blockers[a]	1914 (26.4)
Anti-platelet therapy[a]	1313 (18.1)
Statins[a]	1371 (18.9)

BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology collaboration; HMOD, hypertension-mediated organ damage; LV, left ventricular.
[a]Medications used for >50% of control visits.

Table 2 Univariate simple regression to test the correlations of variables with the occurrence of major adverse cardiovascular events

Variable	HR	95% CI	*P*-value
Sex (female vs. male)	0.87	0.70–1.08	0.202
Age	1.06	1.05–1.08	**<0.001**
Obesity	1.23	0.97–1.56	0.090
Smoking habits	0.97	0.74–1.29	0.857
Mean heart rate	0.98	0.96–1.00	**0.011**
Mean METS-IR	1.01	1.00–1.03	**0.034**
BP control	0.78	0.63–0.97	**0.025**
Anti-renin–angiotensin system drugs	0.63	0.48–0.83	**<0.001**
Beta-blockers	1.24	0.99–1.55	0.063
Dihydropyridine calcium channel blockers	1.48	1.19–1.85	**<0.001**
Diuretics	1.27	1.03–1.57	**0.025**
Statins	1.38	1.03–1.85	**0.032**
Anti-platelet therapy	2.84	2.29–3.53	**<0.001**
LV hypertrophy	2.04	1.66–2.52	**<0.001**
Carotid plaque	2.19	1.76–2.72	**<0.001**
CKD-EPI >3	1.93	1.43–2.60	**<0.001**
LV hypertrophy + carotid plaque	1.92	1.67–2.21	**<0.001**
CKD-EPI >3 + carotid plaque	1.97	1.67–2.32	**<0.001**
LV hypertrophy + CKD-EPI >3	1.85	1.58–2.17	**<0.001**
HMOD 1 vs. 0	1.78	1.33–2.38	**<0.001**
HMOD 2 vs. 0	3.40	2.53–4.57	**<0.001**
HMOD 3 vs. 0	5.19	3.34–8.05	**<0.001**
HMOD 2 vs. 1	1.91	1.49–2.44	**<0.001**
HMOD 3 vs. 1	2.91	1.93–4.38	**<0.001**
HMOD 3 vs. 2	1.53	1.01–2.30	**0.044**

The bold values represent statistical significant difference.
Abbreviations as in *Table 1*.

carotid plaque, CKD-EPI >3, and the number of sites with HMOD, whereas optimal BP control represented a good prognostic factor. Simple Cox models evaluating the effect of coupled combinations of sites with HMOD, including LV hypertrophy + carotid plaque vs. LV hypertrophy + CKD-EPI >3 vs. carotid plaque + CKD-EPI >3, showed a substantially superimposable impact on MACE occurrence. Among therapeutic pharmacological approaches, only renin–angiotensin system inhibitor drugs showed a negative association with the occurrence of MACE during the follow-up, whereas statins, anti-platelet therapy, dihydropyridine calcium channel blockers, and diuretics showed a positive association with MACE.

Mean METS-IR was significantly lower in patients without HMOD than in those with any HMOD combination [95% confidence interval of mean METS-IR in patients with HMOD = 0 (40,40), HMOD = 1 (41,42), HMOD = 2 (43,44), HMOD = 3 (42,43)]. Mean METS-IR was also significantly higher in patients with two sites with HMOD than in patients with one HMOD district, whereas it did not differ in patients with one vs. three and in those with two vs. three sites with HMOD.

By using multiple Cox regression models (*Table 3* and *Figure 1*) after adjusting for age, BP control, mean heart rate, mean METS-IR, number of sites with HMOD, and drugs, a significant association was confirmed between MACE and ageing, mean METS-IR, anti-platelet therapy, and multiple HMOD sites, with the risk increasing with the number of districts involved also increasing, whereas BP control did not gain entry into the model. On the other hand, renin–angiotensin system inhibitor drugs proved to be the only class of drugs that were negatively associated with MACE occurrence. The adjusted survival plot of the multiple model comparing HMOD absence with its presence in one, two, or three districts showed a decreasing probability in MACE-free survival in patients with an increasing number of districts involved by HMOD. The difference in these survival curves revealed a significant impact of HMOD presence in two and three districts vs. none, and of one vs. two and one vs. three sites with HMOD, whereas the difference between zero vs. one and two vs. three HMOD districts did not reach statistical significance (*Figure 2*).

When considering a less broad definition of MACE, 3P-MACE occurred in 125 patients (1.7%) during the follow-up. By simple Cox regressions (see Supplementary material online, *Table S1*), 3P-MACE resulted in a positive association with ageing, mean heart rate, LV hypertrophy, carotid plaque, CKD-EPI >3, the number of sites with HMOD, anti-platelet therapy, and dihydropyridine calcium channel blockers, whereas it was negatively associated with BP control, female sex, and renin–angiotensin system inhibitor drugs. Metabolic Score for Insulin Resistance did not result in an association with 3P-MACE. In addition, by using a multiple Cox regression model (see Supplementary material online, *Table S2*), a significant association was confirmed between 3P-MACE and female sex, ageing, anti-platelet therapy, renin–angiotensin system inhibitor drugs, and multiple HMOD sites, while BP control did not gain entry into the model.

Table 3 Cox regression multivariate model to test the possible predictors of major adverse cardiovascular events in the hypertensive population

Variable	aHR	95% CI	*P*-value
Age	1.04	1.02–1.05	**<0.001**
BP control	1.09	0.82–1.45	0.543
Mean heart rate	0.99	0.97–1.01	0.534
Mean METS-IR	1.02	1.00–1.03	**0.032**
Anti-renin–angiotensin system drugs	0.32	0.23–0.44	**<0.001**
Dihydropyridine calcium channel blockers	1.11	0.83–1.48	0.490
Diuretics	0.95	0.71–1.26	0.701
Statins	0.89	0.65–1.22	0.468
Anti-platelet therapy	2.20	1.62–2.99	**<0.001**
HMOD 1 vs. 0	1.39	0.94–2.07	0.099
HMOD 2 vs. 0	2.14	1.39–3.31	**<0.001**
HMOD 3 vs. 0	2.61	1.39–4.93	**0.003**
HMOD 2 vs. 1[a]	1.54	1.11–2.13	**0.010**
HMOD 3 vs. 1[a]	1.87	1.09–3.24	**0.024**
HMOD 3 vs. 2[a]	1.22	0.72–2.06	0.459

The bold values represent statistical significant difference.
Abbreviations as in *Table 1*.
aHR, adjusted hazard ratio.
[a]These coefficients were estimated by using separate models.

Discussion

The present study demonstrates that in a population of hypertensive patients with a long-term follow-up, (i) HMOD extension in terms of the number of involved sites impacts MACE occurrence; (ii) by multiple Cox regression, adjusting for age, BP control, mean heart rate, mean METS-IR, and therapy, the risk of MACE occurrence increases with the incremental number of districts with HMOD, independently of BP control and despite the significant impact of metabolic impairment; and (iii) among anti-hypertensive therapies, only renin–angiotensin system inhibitor drugs show a negative association with MACE occurrence.

Arterial hypertension is a systemic disease, causing functional and structural alterations in multiple organs.[4,5,31] Hypertension-mediated organ damage represents the result of the direct and indirect effect of chronic pressure overload, intensified by the harmful impact of additional cardiovascular risk factors possibly coexisting, with a negative impact on cardiovascular prognosis.[32] Hypertension-mediated organ damage often clusters together, reflecting the extension of the hypertensive burden.[12]

In the present study, we found that different expressions of HMOD (LV hypertrophy, carotid plaques, and renal dysfunction) were associated with the rate of MACE occurrence during the follow-up.

By using the Cox regression model after adjusting for age, mean heart rate, mean METS-IR, BP control, the number of sites with HMOD and therapy, the occurrence of MACE was found to be associated with ageing, mean METS-IR, and a wider extension of the hypertensive damage in terms of the higher number of districts with HMOD. The association of ageing with cardiovascular risk and MACE is well documented in the literature.[33]

Metabolic dysregulation and insulin resistance are well-known prognosticators of cardiovascular risk, even when expressed in terms of METS-IR.[34,35] Metabolic Score for Insulin Resistance represents a validated index for the evaluation of insulin resistance.[20] In the present study, we demonstrated that metabolic dysregulation in terms of mean METS-IR was related to the occurrence of MACE in a hypertensive population.

More importantly, we showed that the presence of multiple sites with HMOD could impact MACE occurrence independently of optimal BP control and despite the significant impact of metabolic impairment.

Indeed, BP control, even if having a positive impact on cardiovascular events in the simple model, was not associated with the occurrence of MACE in the multiple Cox regression model. This phenomenon entails that in hypertensive patients with a severe degree of HMOD, BP control could no longer be the crucial player in the development of MACE, since in these conditions, HMOD represents itself a determinant for the occurrence of events. Thus, when HMOD is extensive and involves multiple sites, cardiovascular injury is automatically boosted and it could act itself as an independent risk factor for the development of MACE occurrence. Our conclusions are also supported by considering the model with 3P-MACE, where female gender was additionally protective for cardiovascular events, whereas metabolic control, in terms of METS-IR, did not.

We demonstrate that the increasing number of districts involved in the hypertensive disease impacts on cardiovascular prognosis by favouring MACE occurrence. Previous studies showed a higher risk of MACE and death in patients affected by LV hypertrophy and microalbuminuria, and increased rate of cerebrovascular events in patients presenting carotid plaques.[36,37] In addition, the simultaneous presence of LV hypertrophy and renal dysfunction was associated with an increased MACE rate than observed when only one of the two sites with HMOD was involved.[38]

As also evident from the survival curves in *Figure 2*, the presence of at least two sites with HMOD vs. the absence of HMOD represents a major shift in terms of MACE-free survival impairment, reflecting the extent of AH-mediated detrimental effect. Thus, multiple districts involved by HMOD represent a significant cardiovascular risk for the occurrence of MACE, with a progressively higher risk with an increase in the number of affected sites.

The effect of the absence vs. the presence of one site with HMOD on MACE was not statistically significant in the multiple Cox model, probably reflecting an early stage of hypertensive injury, without the involvement of multiple districts. On the other hand, the impact of two vs. three sites with HMOD on MACE did not attain statistical significance in the multivariate Cox regression model, probably on the account of the relatively small sample of patients in the group with three sites affected by HMOD, when compared with the number of patients present in the other three groups. Nonetheless, there is a trend in increasing percentage of MACE in hypertensive groups when moving either from zero to one (2.6 vs. 4.7%) or from two to three sites with HMOD (7.9 vs. 9.8%) in the hypertensive groups.

Furthermore, with regard to therapeutic approaches, the association between anti-platelet therapy and MACE occurrence could be linked to a possible confounding by indication and is likely due to a more frequent administration of this class of drugs in patients with worse clinical conditions related to endothelial dysfunction and exacerbated atherosclerotic process induced by AH in combination with other risk factors.[39,40] In contrast, only anti-renin–angiotensin system drugs were found to have a significant negative association with MACE, thus helping to prevent their occurrence.

Our results suggest, in hypertensive patients with multiple districts involved by HMOD, the possible activation of further mechanisms triggered by AH in association with other cardiovascular risk factors and metabolic dysregulation, perpetuating hypertensive disease progression even in the presence of BP control, thus transforming HMOD from the consequence of risk factors into a risk factor *per se*.

We could speculate that one common denominator of the ongoing cardiovascular impairment may be represented by the activation of an inflammatory response, elicited by pressure overload, and maintained by bioactive molecules released in response to structural changes

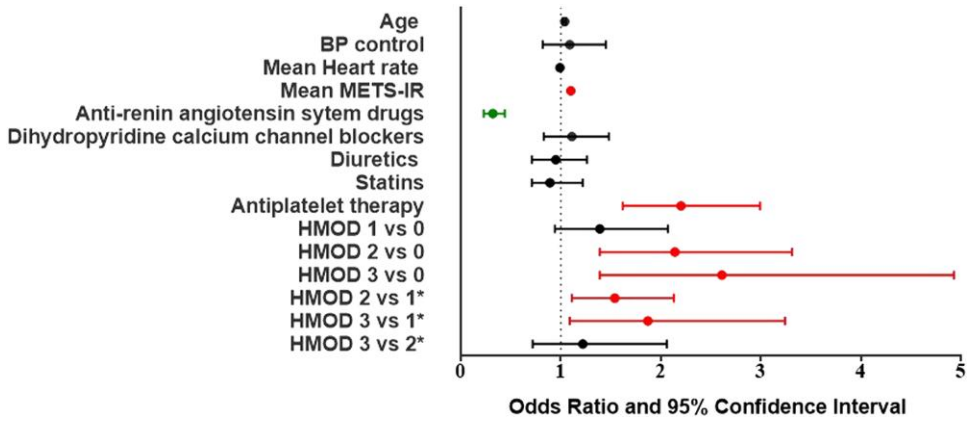


Figure 1 Adjusted hazard ratio and 95% confidence interval of parameters associated with major adverse cardiovascular event occurrence. BP, blood pressure; HMOD, hypertension-mediated organ damage; MACE, major adverse cardiovascular event.

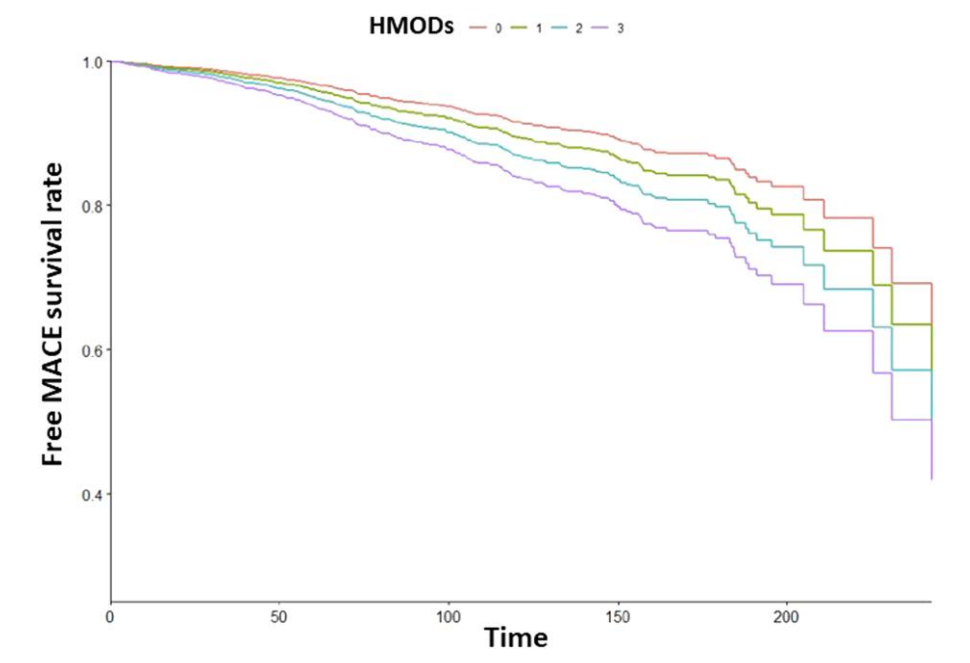


Figure 2 Adjusted major adverse cardiovascular event–free survival plot of the multivariate model presented in *Table 3* describing the difference in survival in patients with none (0), one (1), two (2), or three (3) sites with hypertension-mediated organ damage. HMODs, hypertension-mediated organ damage; MACE, major adverse cardiovascular event.

related to the establishment of HMOD.[41,42] It is well known, for instance, that once carotid plaques are shaped, they produce chemotactic and pro-inflammatory molecules, which, by a vicious path, may be responsible for cerebrovascular events.[43–45] In addition, recent evidence highlights that a 'residual risk' exists, since several patients continue to suffer from cardiovascular events despite optimal medical therapy and achievement of clinical targets.[46] Such evidence suggests that this 'residual inflammatory risk' could represent an important pharmacologic target.[46,47]

This hypothesis may be corroborated by the observation that renin–angiotensin system inhibitor drugs, interestingly, had a negative association with MACE occurrence. Indeed, this class of medications was demonstrated to provide an anti-inflammatory and immunomodulatory effect, by regulating free radical production and cellular synthesis of cytokines, chemokines, and transcription factors, which also results in positive cardiac and vascular remodelling.[48,49] In addition, anti-renin–angiotensin system therapy was demonstrated to also have an impact on the areas of the brain, empowering its effect in modulating the immune response to the hypertensive stimuli and its related damage.[50]

Of course, the control of cardiovascular risk factors is important as a strategy for preventing first-line functional and structural cardiovascular

injury,[4] but, as suggested by the current study, it could not be enough to reduce the burden of MACE occurrence when multiple sites affected by HMOD are concomitantly recruited. Therefore, the presence of HMOD and its extension can represent a predictor of MACE occurrence, thus affecting patient prognosis.

Further studies are needed to investigate whether other mechanisms recruited by organ injury, such as enhanced inflammation, could be the target of therapeutic approaches reducing HMOD impact on MACE occurrence in hypertensive patients.

Limitations

Our results derive from a retrospective study, based on an observational registry. However, the design of a randomized trial for the evaluation of MACE occurrence in patients with and without BP control would be ideal but not ethically appropriate, considering that multiple evidence had highlighted the importance of aiming at early BP control as a prompt approach to reduce the risk of HMOD formation as a progression of hypertensive disease and MACE evolution.[4,51,52] Thus, the employment of an observational real-life registry as the present one could still provide important information under these circumstances.

The present study was performed on a hypertensive population followed up for a limited period. A longer follow-up period could have strengthened the outcomes and results of the present study.

Further sites of HMOD were not investigated in the present study, such as retinopathy or brain magnetic resonance abnormalities. Nonetheless, LV hypertrophy, carotid plaques, and renal impairment seem to provide an enough comprehensive scenario for the extension of HMOD.

Additional preclinical echocardiographic parameters preceding HMOD, such as LV global longitudinal strain, were not explored for the evaluation of LV systolic function, but the main focus of the study was the evaluation of established HMOD and their extension as possible predictors of MACE. Another limitation is the lack of information about inflammatory markers that could possibly support our hypothesis of the role of inflammation in the progression of HMOD and its translation into a risk factor for the occurrence of events. However, the association between inflammation and HMOD is well documented in the literature.[41]

Conclusions

In a population of hypertensive patients, the presence of multiple sites affected by HMOD could represent not only the result of the impact of risk factors on the cardiovascular system but a risk factor *per se* for MACE occurrence, despite the significant association with metabolic impairment and independently of BP control. In hypertensive patients with HMOD, therapy with the anti-renin–angiotensin system could improve cardiovascular prognosis, providing a potential protective effect on the occurrence of MACE.

Lead author biography

Maria Lembo, MD, PhD, is a clinical cardiologist and researcher at the Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy. She has focused her research activity on the application of standard and advanced cardiovascular imaging methods, particularly for the assessment of cardiovascular organ damage in multiple settings, including hypertensive heart disease. This activity is testified by a valid scientific production and participation as speaker at national and international conferences. Currently, she also collaborates with the British Heart Foundation Centre of Cardiovascular Science of Edinburgh, UK, on the topic of non-invasive cardiac imaging.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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