UNIVERSITY OF TORINO DEPARTMENT OF MEDICAL SCIENCE

DOCTORAL SCHOOL IN LIFE AND HEALTH SCIENCES

PHD PROGRAMME IN MEDICAL PHYSIOPATHOLOGY XXXV CYCLE

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THE CLINICAL OR SUBCLINICAL TARGET ORGAN DAMAGE IN HYPERTENSIVE EMERGENCIES: A RANDOMISED CONTROLLED CLINICAL TRIAL

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2019 – 2022

LIST OF CONTENTS **Page**

LIST OF TABLES AND FIGURES

1. BACKGROUND

Acute blood pressure (BP) disorders are a major challenge for the Emergency Department (ED). The prevalence of acute BP disorders considerably differs among studies, even depending on the definition used, but it ranges from 0.24% to 2.4% of ED admissions for hypertensive urgencies (HU) and from 0.08% to 0.76% for hypertensive emergencies (HE) [1]. These prevalences seem comparable across continents [2], although with some differences probably due to ethnic disparities, medication adherence, and insurance status [3]. Although HU do not appear to be associated with short-term adverse outcomes [4] [5], or at least have significantly lower in-hospital mortality compared to HE [6], long-term implications, such as risk of stroke and fatal or non-fatal cardiovascular events, are relevant [7] [8] [9].

Despite the significant clinical and epidemiological impact, the management of patients with acute BP disorders is still very uneven among professionals of critical areas, as pointed out by a recent Italian surveys [10] [11]. The lack of good-quality evidence makes it difficult to propose strong recommendations for clinical practice. The therapeutic management is very uneven, especially for HU. The timing of follow-up, when present, is heterogeneous and it is not clear whether a referral to a Hypertension Centre could have a prognostic role compared to standard care.

In order to obtain more and more accurate information on this category of patients, we are conducting the ERIDANO (EmeRgenze Ipertensive e DANno d'Organo) prospective multicenter cohort study on behalf of the Italian Society of Hypertension (SIIA: Società Italiana dell'Ipertensione Arteriosa). The aims of the ERIDANO study are detailed below; the present thesis is intended to be a preliminary, mainly descriptive, report of the first patients enrolled, focusing on the clinical and demographic characteristics, on the management in the ED, on BP control within 72 hours of discharge, and on the prevalence of hypertension-mediated subclinical organ damage (HMOD).

2. EXPERIMENTAL STUDY

2.1 Aims of the Study

Primary aims

- To assess the prevalence of *acute* organ damage and *subclinical* HMOD (cardiac, renal, vascular, cerebral, and ocular) in patients presenting to the ED with symptomatic BP ≥ 180/110 mmHg (observational analysis).
- To assess the relative prognostic impact of the two conditions, *acute* organ damage and *subclinical* HMOD (prospective analysis).

Secondary aims

- To assess the prevalence of secondary hypertension in patients presenting to the ED with symptomatic hypertensive disorders.
- To assess the prognostic impact of high specialist management at a Third Level Hypertension Center after ED discharge, compared to standard management of hypertensive disorders (dependent on the general practitioner).

[As randomization after discharge from the ED was not accepted by the ethics committee of all participating centers, this secondary aim will be verified by comparison with historical cohorts].

Aim of the present report

The COVID-19 pandemic, which has severely affected Italian hospitals and especially ED and internal medicine wards, has not allowed patients to be enrolled for several months over the last 3 years. For this reason, the current thesis is not able to meet all the aims of the ERIDANO study; it will be a descriptive report, focusing on the clinical and demographic characteristics of the cohort, on the management in the ED, on BP control within 72 hours of discharge, and on the prevalence of hypertension-mediated subclinical organ damage (HMOD).

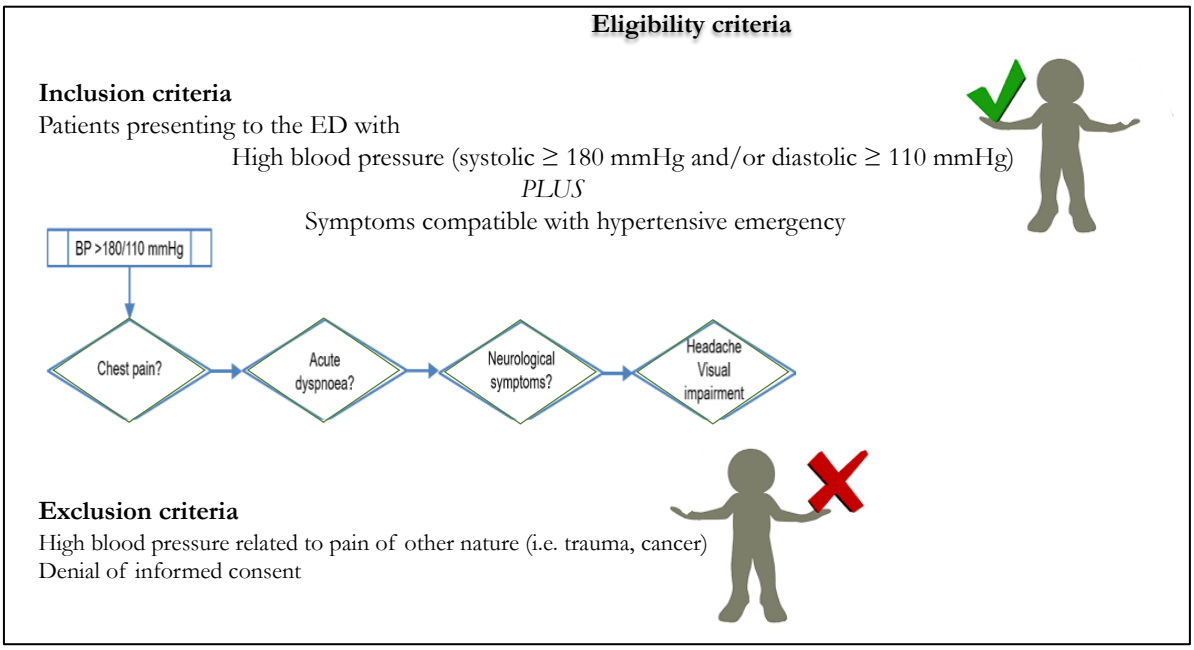
2.2 Materials and Methods

The current enrolment has involved 6 Italian hospitals (see page 27), officially starting in Turin, the main center, in January 2020.

Consecutive patients, aged 18 years and over, admitted to the ED with a symptomatic BP rise, defined as systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg associated to at least one symptom consistent with suspected HE as defined by latest guidelines [12], were enrolled. BP measurements were performed according to the current European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommendations [13], with validated automatic sphygmomanometers (e.g., Omron, M10-IT models, Matsusaka, Kyoto, Japan), with patients in the sitting position whenever possible. Three BP measurement were performed, and the mean value was used for subsequent analysis.

Patients with BP rise due to traumatic causes or known neoplastic pain, or with BP rise without any associated symptoms were excluded, as were those who withheld their informed consent (Figure 1).

Figure 1. Summary of inclusion/exclusion criteria

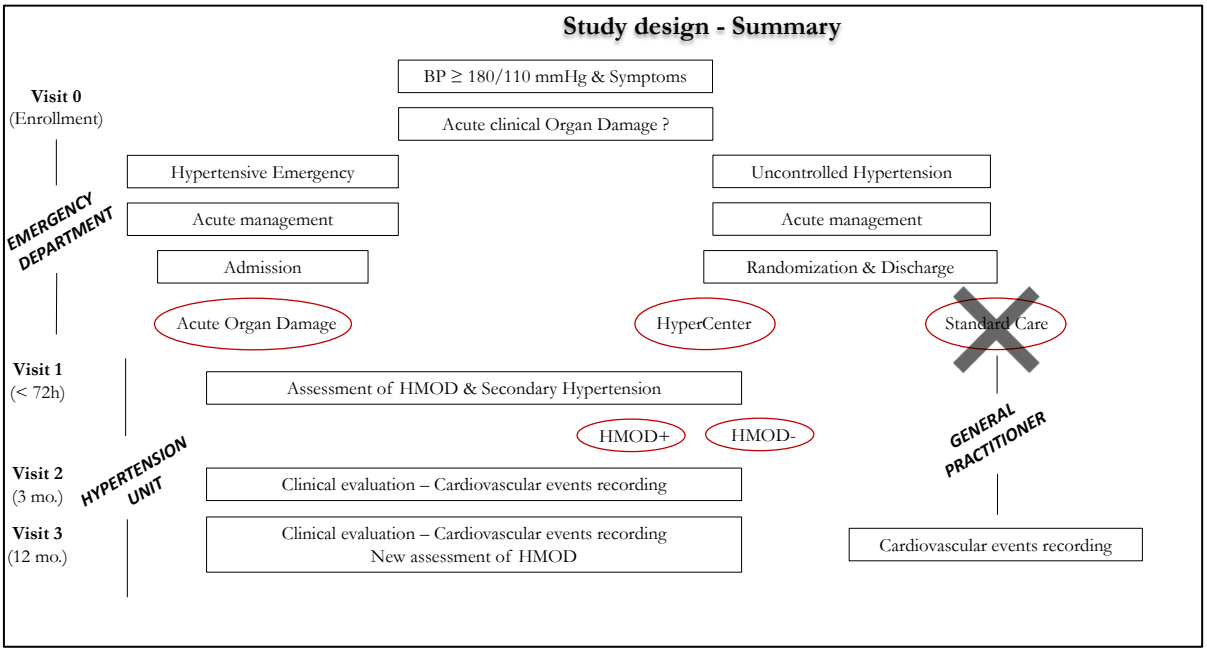


Enrolled patients were managed by the emergency physicians in the ED, according to their clinical presentations, as suggested in the current European position paper [12]. After appropriate work-up, in

the presence of acute organ damage (coronary ischemia, acute cardiogenic pulmonary oedema, acute ischemic or hemorrhagic stroke, hypertensive encephalopathy, acute aortic disease) as defined by current guidelines [12] (HE), patients were admitted to an appropriate hospital specialist setting; in the absence of acute organ damage (HU or HyperCenter group), they were discharged after a period of observation. In any case, an evaluation at a Third Level Hypertension Centre was performed within 72 hours of enrolment. Subsequent therapeutic modifications, or indications for further diagnostic investigations, related to the detection of subclinical organ damage (which may be present independently of the acute organ damage) or secondary hypertension, have been left to the discretion of the hypertension specialist, always guided by current guidelines [13].

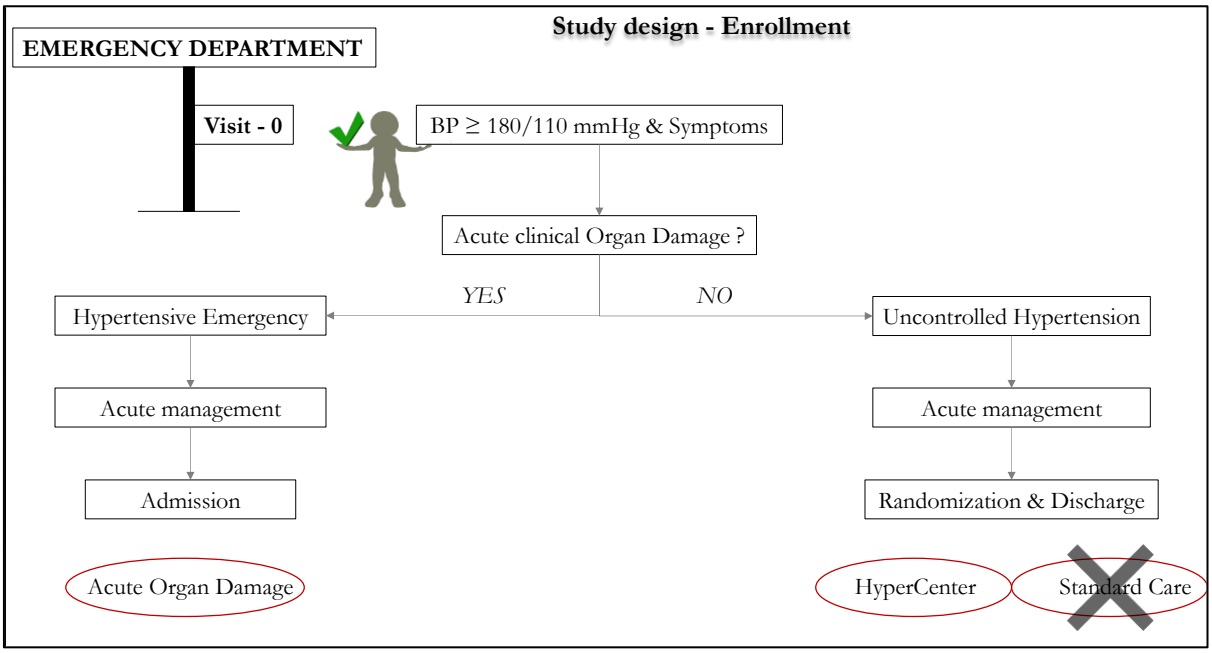
Figures 2-6 summarize the study protocol, although data from visit 2 and visit 3 have not yet been considered in the present Thesis.

Figure 2. Summary of the study design



In accordance with the advice of the ethics committee of some hospital boards, randomization will not take place for the HyperCenter group (black cross in the figure). All patients discharged from the ED will be referred to the Hypertension center. The prognostic outcome, relating to the number of major cardiovascular events developed within one year of enrollment, will be compared with the prognostic outcome of similar historical cohorts.

Figure 3. Enrollment



In accordance with the advice of the ethics committee of some hospital boards, randomization will not take place for the HyperCenter group (black cross in the figure). All patients discharged from the ED will be referred to the Hypertension center.

Figure 4. Follow-up

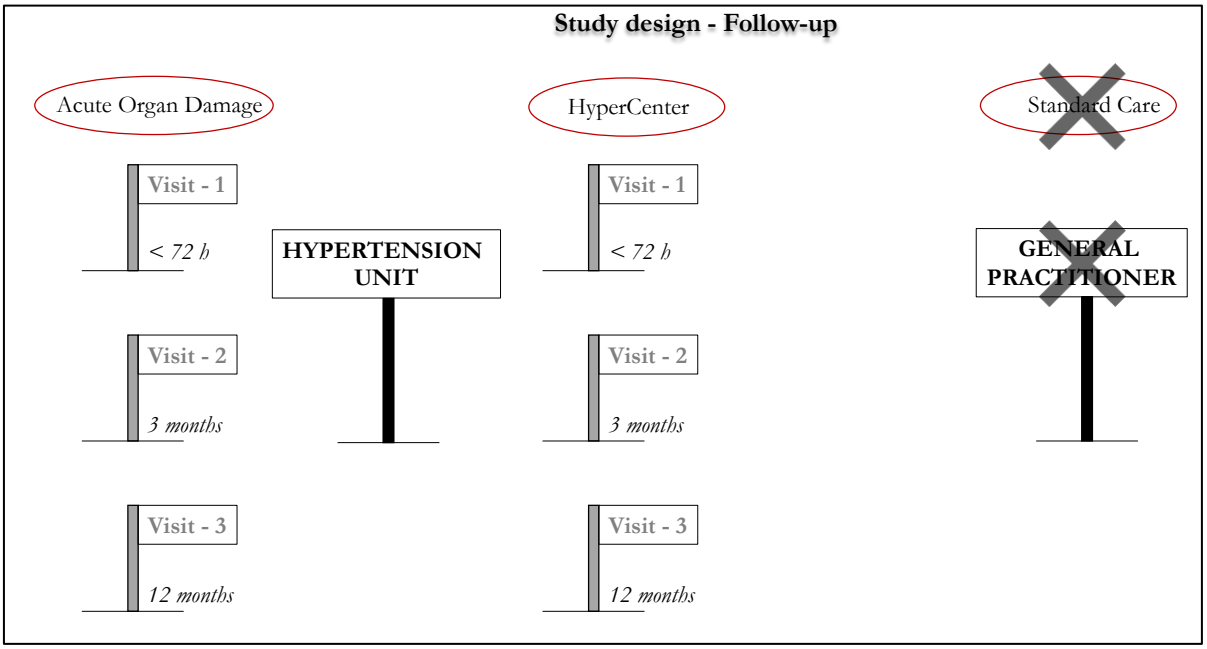


Figure 5. First visit

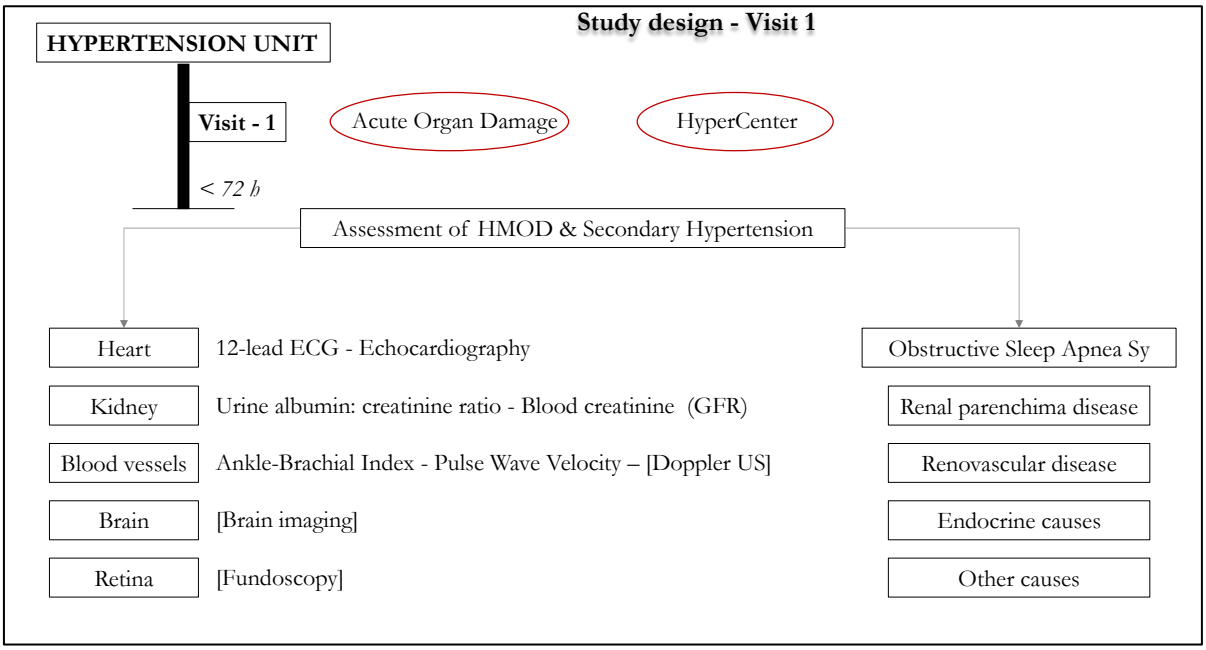
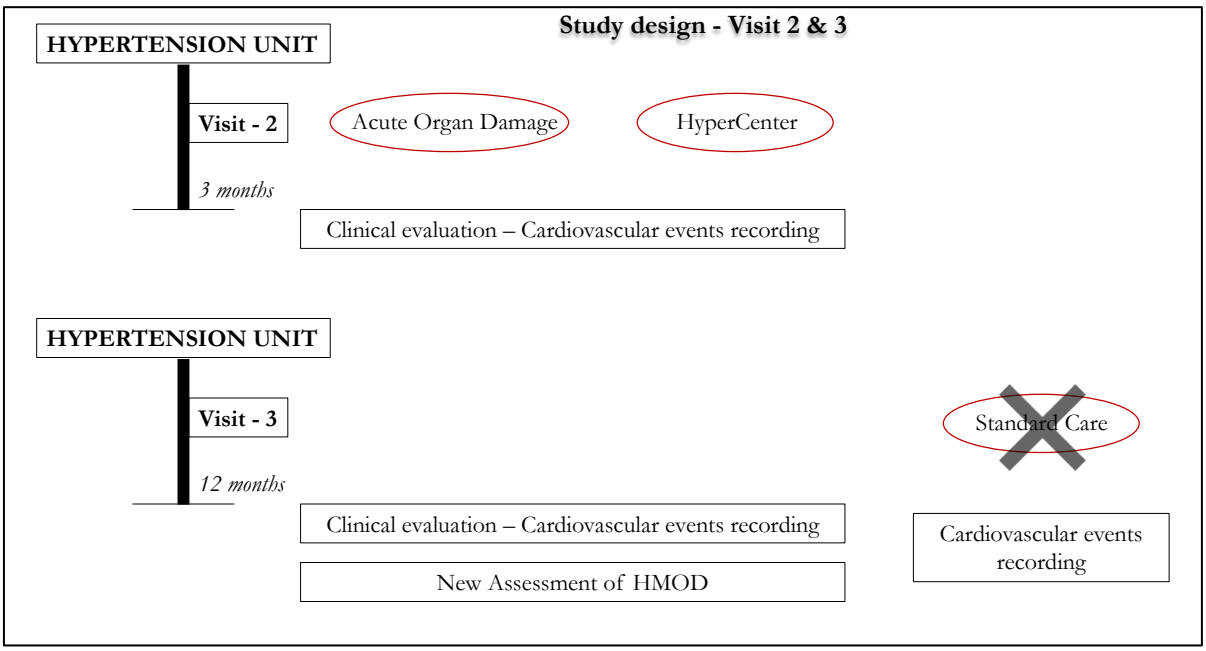


Figure 6. Second and third visit



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Subclinical HMOD criteria

Subclinical cardiac HMOD - Echocardiography

Standard two-dimensional transthoracic echocardiographic (TTE) images were acquired by expert accredited staff with commercially available ultrasound machines (e.g., IE33, Phillips Medical Systems, Andover, Massachusetts, USA). Conventional parameters were assessed according to the current guidelines [14]. Left ventricular (LV) mass was estimated. Devereux's formula was used to calculate body surface area (BSA) and LV mass values were indexed for BSA (LVMi). LV volumes and ejection fraction, and left atrial volume were assessed using Simpson's Biplane technique from apical two and four-chamber views. LV diastolic function was estimated through the evaluation of left atrial volume, mitral inflow peak systolic velocities of early (E) and late (A) diastolic filling on pulsed-wave Doppler, color-tissue Doppler imaging of the septal and lateral mitral annulus (E'), according to current international recommendations [15].

Alterations of LV mass and geometry, increased left atrial volume, and diastolic dysfunction were considered subclinical cardiac HMOD [13 16]. LV hypertrophy (LVH) was defined by LVMi > 115 g/m2 in men and > 95 g/m2 in women [14 13]. Relative wall thickness (RWT) was defined as two-times inferolateral wall thickness divided by the LV diastolic diameter and was used to classify LV remodeling as either concentric (RWT > 0.42) or eccentric (RWT ≤ 0.42). Left atrial enlargement (LAe) was considered as left atrial volume indexed to BSA (LAVi) > 34 ml/m2 [14].

Subclinical vascular HMOD

Arterial stiffness was quantified using carotid-femoral pulse wave velocity (PWV). Pressure waveforms at the carotid and femoral artery were obtained non-invasively by applanation tonometry with validated instruments (e.g., Sphygmocor, AtCor Medical - Sydney, Australia) [17].

Carotid artery imaging assessment was performed by experienced staff using available ultrasound machines, equipped with 4–12 MHz linear-array ultrasound transducer. The common carotid artery (CCA) intima-media thickness (IMT) was detected by validated software (e.g., Q-lab, Philips) on

longitudinal bidimensional imaging. When clinically indicated patients underwent further imaging investigation.

PWV > 10 m/s and CCA IMT > 0.9 mm or the presence of carotid plaques (identified by an IMT ≥1.5 mm, or by a focal increase in thickness of 0.5 mm or 50% of the surrounding carotid IMT value) were considered subclinical vascular HMOD [17] [13].

Subclinical renal HMOD

Estimated glomerular filtration rate (eGFR) was assessed with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on serum creatinine measured within 3 months from ED presentation [18]. Moreover, patients underwent microalbuminuria assessment. eGFR <60 ml/min/1.73m^2, urinary albumin/creatinine ratio > 30 mg/g, and albuminuria > 30 mg/24h were considered endpoints of significant renal HMOD [13] [19].

Subclinical cerebral HMOD

When clinically indicated, according to ED presentations, patients underwent brain imaging, either by computed tomography or magnetic resonance imaging. The presence of white matter lesions, microinfarcts (e.g., lacunar infarctions), microbleeds, and brain atrophy identified by experienced radiologists were considered cerebral HMOD [13] [20] [21].

2.3 Statistical analysis

Statistical analysis was performed by a dedicated software (R: A Language and Environment for Statistical Computing, v4.0.0 for Mac OSX, R Core Team., Vienna, Austria). Continuous variables were expressed as mean ± standard deviation. Qualitative variables were expressed as absolute values of frequency and percentage values. Normal distribution of variables was tested using the Kolmogorov-Smirnov and residual analysis tests. Differences between independent groups were evaluated using a t-test for continuous variables with normal distribution and the Mann-Whitney or Kruskal-Wallis test for continuous variables with non-normal distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was considered for p values < 0.05.

The present study was firstly approved by the Institutional Review Committee of Turin (Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino – A.O. Ordine Mauriziano, CS2/1075), as well as by the local ethics committees of each participating center. All subjects gave their written informed consent.

3. RESULTS

A total of 122 patients (52.5% female) with a mean age of 60.7±13.9 years were enrolled until July 2022 and thus included in the present report. A total of 18 patients (14.8%) had *acute* organ damage at ED presentation (HE), whereas the remaining 104 (85.2%) patients were diagnosed as HU. The acute organ damages detected were heart failure (n. 7, 39%), stroke (n. 6, 33%), acute coronary syndrome (n. 2, 11%), hypertensive encephalopathy (n. 2, 11%), aortic dissection (n. 1, 6%).

No significant difference emerged between HE and HU groups in terms of gender, BMI, cardiovascular comorbidities (Table 1). Hypertensive therapy ongoing at ED admission is listed in Table 2.

At ED presentation mean systolic BP was 201±20 mmHg and mean diastolic BP was 113±13 mmHg, without significant difference between HE and HU patients. The most common clinical presentation was headache (46.7%), followed by chest pain (23.8%), dyspnea (14.8%), and neurological symptoms (6.6%), while other non-specific symptoms were present in 68.9% of patients.

A silent medical history was present in 20 patients (16.4%). Moreover, 94 patients (77%) had previously known arterial hypertension and 85 (69.7%) were on antihypertensive medical therapy, with a median number of medications of 1.0 [IQ range 0.0;2.0]; 23 patients (18.9%) were on ≥3 hypertensive drugs.

Table 1. Demographic and clinical characteristics of study population.

	Total *N=122*	**HE** *N=18*	**HU** *N=104*	**p value**
Male Sex [n. (%)]	58 (47.5%)	9 (50.0%)	49 (47.1%)	0.821
Age (y)	60.7±13.9	66.5±15.9	60.0±13.5	0.134
Height (cm)	165±10	166±9	165±11	0.644
Weight (kg)	79.6±19.4	78±25	79±19	0.883
BMI (kg/m^2)	28.9±5.78	28.6±7.2	28.9±5.6	0.826
ED SBP (mmHg)	201±20	205±18	200±20	0.372
ED DBP (mmHg)	113±13	110±14	113±13	0.357
Discharge SBP (mmHg)	152±21	155±25	151±20	0.669
Discharge DBP (mmHg)	88±12	87±14	88±12	0.820
ED Stay (h) [IQ range]	7.2 [4.7;12.8]	5.6 [4.7;18.7]	7.2 [4.7;12.2]	0.900
BP <180/110 at ED discharge [n. (%)]	96 (78.7%)	8 (44.4%)	88 (84.6%)	0.003
Office SBP (mmHg)	147±22	149±22	147±23	0.680
Office DBP (mmHg)	87±15	88±15	87±16	0.746
Difference ED-Office SBP (mmHg)	54±28	56±34	53±27	0.770
Difference ED-Office DBP (mmHg)	26±17	22±19	26±17	0.322
Silent medical history [n. (%)]	20 (16.4%)	1 (5.6%)	19 (18.3%)	0.179
Arterial Hypertension [n. (%)]	94 (77.0%)	17 (94.4%)	77 (74.0%)	0.057
Hypertension duration (y) [IQ range]	10.0 [5.0;18.0]	15.5 [10.0;28.5]	10.0 [5.0;16.0]	0.066
Diabetes [n. (%)]	24 (19.7%)	4 (22.2%)	20 (19.2%)	0.768
Dyslipidemia [n. (%)]	36 (29.5%)	8 (44.4%)	28 (26.9%)	0.132
CAD [n. (%)]	15 (12.3%)	4 (22.2%)	11 (10.6%)	0.165
Heart failure [n. (%)]	5 (4.1%)	2 (11.1%)	3 (2.9%)	0.104
Atrial fibrillation [n. (%)]	7 (5.7%)	1 (5.6%)	6 (5.8%)	0.971
Previous stroke [n. (%)]	5 (4.1%)	2 (11.1%)	3 (2.9%)	0.104
CKD [n. (%)]	8 (6.6%)	2 (11.1%)	6 (5.8%)	0.398

Abbreviations: BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CKD: chronic kidney disease; ED: emergency department; HE: hypertensive emergencies; HU: hypertensive urgencies; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Ongoing hypertensive therapy and medications of study population at ED admission.

Previous Hypertensive Therapy	Total *N=122*	HE *N=18*	HU *N=104*	p value
Previous Hyp therapy [n. (%)]	85 (69.7%)	15 (83.3%)	70 (67.3%)	0.172
Nr. Previous Hyp drugs [IQ range]	1.0 [0.0;2.0]	1.0 [1.0;2.0]	1.0 [0.0;2.0]	0.471
Previous Hyp drugs ≥ 3 [n. (%)]	23 (18.9%)	2 (11.1%)	21 (20.2%)	0.363
ACE-Inhibitors [n. (%)]	33 (27.0%)	8 (44.4%)	25 (24.0%)	0.072
ARB [n. (%)]	30 (24.6%)	1 (5.6%)	29 (27.9%)	0.042
CCB [n. (%)]	27 (22.1%)	6 (33.3%)	21 (20.2%)	0.215
CCB NDH [n. (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Beta-blockers [n. (%)]	44 (36.1%)	7 (38.9%)	37 (35.6%)	0.787
Alfa-blockers [n. (%)]	9 (7.4%)	0 (0.0%)	9 (8.7%)	0.195
Alfa2-agonist [n. (%)]	2 (1.6%)	0 (0.0%)	2 (1.9%)	0.553
MRA [n. (%)]	1 (0.8%)	0 (0.0%)	1 (1.0%)	0.676
Thiazides [n. (%)]	14 (11.5%)	2 (11.1%)	12 (11.5%)	0.958
Loop diuretics [n. (%)]	8 (6.6%)	1 (5.6%)	7 (6.7%)	0.852
Potassium sparing [n. (%)]	1 (0.8%)	0 (0.0%)	1 (1.0%)	0.676
Nitrates [n. (%)]	3 (2.5%)	1 (5.6%)	2 (1.9%)	0.358
Others hyp drugs [n. (%)]	2 (1.6%)	1 (5.6%)	1 (1.0%)	0.156
Benzodiazepines [n. (%)]	7 (5.7%)	1 (5.6%)	6 (5.8%)	0.971

Abbreviations: ACE-Inhibitors: inhibitors of angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CCB: calcium channel blockers; CCB-NDH: non-dihydropyridine CCB; ED: emergency department; HE: hypertensive emergencies; HU: hypertensive urgencies; Hyp: hypertension; MRA: mineralocorticoid receptor antagonists.

3.1 Hypertensive therapy and BP control during ED stay

Among patients enrolled, 61.1% and 94.2% of HE and HU group (p<0.001) received antihypertensive therapy during ED stay (89.3% of total population), with more drugs administered in the latter group (1.0 [0.0;2.0] vs. 2.0 [1.0;2.0] in HE and HU patients, respectively, p=0.003). A total of 25 patients (24%) of HU group received 3 or more antihypertensive medications. Intravenous antihypertensive drugs were given to 27.8% and 15.4% of patients in HE and HU group (p=0.198).

The most used class of medication was calcium channel blockers (CCB), administered to 74 patients (60.7%) (22.2% vs. 67.3% in HE and HU group, respectively, p<0.001), followed by benzodiazepines, administered to 57 patients (46.7%) (16.7% vs. 51.9%, in HE and HU group, respectively, p=0.006) and ACE-Inhibitors, given to 53 patients (43.4%) (16.7% vs. 48.1%, in HE and HU group, respectively, p=0.013). The remaining classes of drugs administered during ED stay are listed in Table 3.

After 1 hour from ED admission, 50.0% of HE patients and 76.7% of HU patients had BP values <180/110 mmHg. At the time of ED discharge, these percentages increased to 66.7% of and 93.6%, respectively (p=0.003) (90.6% of total population), with a median ED stay of 7.2 hours [IQ range 4.7;12.8]. At ED discharge mean systolic BP was 152±21 mmHg and diastolic BP was 88±12 mmHg.

No drugs were significantly associated with successful BP control during ED stay (data not shown).

Table 3. Hypertensive therapy and medications administered during ED stay

Hypertensive therapy administered in ED	Total *N=122*	HE *N=18*	HU *N=104*	p value
Hyp therapy in ED [n. (%)]	109 (89.3%)	11 (61.1%)	98 (94.2%)	< 0.001
Nr. Hyp drugs in ED [IQ range]	2.0 [1.0;2.0]	1.0 [0.0;2.0]	2.0 [1.0;2.0]	0.003
Hyp drugs in ED ≥ 3 [n. (%)]	25 (20.5%)	0 (0.0%)	25 (24.0%)	0.020
IV Hyp drugs in ED [n. (%)]	21 (17.2%)	5 (27.8%)	16 (15.4%)	0.198
ACE-Inhibitors [n. (%)]	53 (43.4%)	3 (16.7%)	50 (48.1%)	0.013
ARB [n. (%)]	13 (10.7%)	2 (11.1%)	11 (10.6%)	0.946
CCB [n. (%)]	74 (60.7%)	4 (22.2%)	70 (67.3%)	< 0.001
CCB NDH [n. (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Beta-blockers [n. (%)]	26 (21.3%)	2 (11.1%)	24 (23.1%)	0.252
Alfa-blockers [n. (%)]	14 (11.5%)	0 (0.0%)	14 (13.5%)	0.098
Alfa2-agonist [n. (%)]	11 (9.0%)	1 (5.6%)	10 (9.6%)	0.579
MRA [n. (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Thiazides [n. (%)]	6 (4.9%)	0 (0.0%)	6 (5.8%)	0.296
Loop diuretics [n. (%)]	11 (9.0%)	2 (11.1%)	9 (8.7%)	0.737
Potassium sparing [n. (%)]	1 (0.8%)	0 (0.0%)	1 (1.0%)	0.676
Nitrates [n. (%)]	8 (6.6%)	2 (11.1%)	6 (5.8%)	0.398
Other vasodilators [n. (%)]	1 (0.8%)	0 (0.0%)	1 (1.0%)	0.676
Others hyp drugs [n. (%)]	2 (1.6%)	1 (5.6%)	1 (1.0%)	0.156
Benzodiazepines [n. (%)]	57 (46.7%)	3 (16.7%)	54 (51.9%)	0.006

Abbreviations as in Table 2.

3.2 Office BP control at first visit (72 hours after ED discharge)

At 72 hours visit patients had mean systolic BP of 148±22 mmHg (p=0.037, compared to BP at ED discharge) and diastolic BP of 88±16 (p=0.944).

BP control was achieved in 42 patients (34.4%) who resulted normotensive at 72 hours visit (22.2% and 36.5% of HE and HU patients, p=0.238). 43 patients (35.2%) had grade 1 hypertension, 27 (22.1%) had grade 2 hypertension, and 10 (8.2%) had grade 3 hypertension, with no differences between HE and HU patients (p=0.592).

Patients with uncontrolled BP were more frequently males (56.3% vs. 31.0%, p=0.008), but there were no other significant differences in terms of age, body size, and cardiovascular comorbidities. Moreover, patients with uncontrolled BP had higher mean PWV (10.1±2.3 vs. 8.9±2.2 m/s, p=0.017) and higher prevalence of PWV > 10 m/s (49.1 vs. 25.9%, p=0.045), even after adjusting for heart rate and mean BP (data not shown). Hypertensive therapy prescribed at 72 hours visit is depicted in Table 4.

Table 4. Hypertensive therapy and medications prescribed at 72 hours visit

Hypertensive therapy prescribed at 72h visit	Total *N=122*	HE *N=18*	HU *N=104*	p value
Hyp therapy at 72h [n. (%)]	105 (86.0%)	10 (55.6%)	95 (91.3%)	< 0.001
Hyp drugs at 72h (n) [IQ range]	3.0 [2.0;4.0]	2.0 [0.0;2.75]	3.0 [2.0;4.0]	0.023
Hyp drugs at 72h ≥ 3 [n. (%)]	65 (53.3%)	5 (27.8%)	60 (57.7%)	0.019
ACE-Inhibitors [n. (%)]	30 (24.6%)	5 (27.8%)	25 (24.0%)	0.734
ARB [n. (%)]	56 (45.9%)	4 (22.2%)	52 (50.0%)	0.029
CCB [n. (%)]	85 (69.7%)	7 (38.9%)	78 (75%)	0.002
CCB NDH [n. (%)]	15 (12.3%)	0 (0.0%)	15 (14.4%)	0.085
Beta-blockers [n. (%)]	39 (32.0%)	6 (33.3%)	33 (31.7%)	0.893
Alfa-blockers [n. (%)]	30 (24.6%)	1 (5.6%)	29 (27.9%)	0.042
Alfa2-agonist [n. (%)]	2 (1.6%)	0 (0.0%)	2 (1.9%)	0.553
MRA [n. (%)]	8 (6.6%)	2 (11.1%)	6 (5.8%)	0.398
Thiazides [n. (%)]	25 (20.5%)	2 (11.1%)	23 (22.1%)	0.286
Loop diuretics [n. (%)]	9 (7.4%)	3 (16.7%)	6 (5.8%)	0.102
Potassium sparing [n. (%)]	2 (1.6%)	0 (0.0%)	2 (1.9%)	0.553
Nitrates [n. (%)]	10 (8.2%)	1 (5.6%)	9 (8.7%)	0.658
Others hyp drugs [n. (%)]	1 (0.8%)	1 (5.6%)	0 (0.0%)	0.016
Benzodiazepines [n. (%)]	2 (1.6%)	1 (5.6%)	1 (1.0%)	0.156

Abbreviations as in Table 2.

3.3 Hypertension-mediated subclinical organ damage (HMOD) at first visit (72 hours after ED discharge)

LVH was present in 41 patients (33.6% of total population; 50% and 30.8% of HE and HU patients, respectively, p=0.0.54). HE group showed higher LVMi compared to HU group (110.9±36.0 vs. 93.0±26.4 g/m^2, p=0.023).

LAe was detected in 26 patients (21.3%); no difference in LAe prevalence was found between HE and HU group (22.2% vs. 21.2%, p=0.836), but the former group had significant higher LAVi (37.8±17.4 vs. 28.2±10.0, p=0.014). Systolic and diastolic function was similar between the two groups.

Subclinical vascular HMOD was assessed in 86 patients, and was detected in 45 patients (52.3%), with 34 (41.5%) having PWV >10 m/s. Indices of subclinical vascular HMOD were proved to be comparable between the two groups (Table 5).

Subclinical renal HMOD was observed in 15 patients (12.3%). HE patients had higher prevalence of renal damage than HU patients (27.8% vs. 9.6%, p=0.010).

Brain damage was detected in 16 patients (34.8% of 46 patients who underwent brain imaging during ED evaluation), and it was detected in all HE patients who underwent brain imaging (100% vs. 21.1%, p<0.001).

In summary, subclinical HMOD was detected in 82 patients (67.2% of total population), 100% of HE patients and 61.5% of HU patients (p=0.001). Patients with detected subclinical HMOD were older than patients without HMOD (64.4±13 vs. 53.3±12 years, p<0.001), and had more likely history of diabetes (p<0.001), dyslipidemia (p=0.042), coronary artery disease (p=0.021), and chronic kidney disease (p=0.041). Patients with detected subclinical HMOD were also taking higher median number of hypertensive drugs at ED admission (1.0 [0.0;1.0] vs. 1.0 [0.0;2.0], p=0.004), and had higher mean systolic BP values at ED admission (204±18 vs. 194±20 mmHg, p=0.007) and at 72h visit (150±23 vs. 140±19 mmHg, p=0.016).

Table 5. Subclinical hypertension mediated organ damage characteristics of study population.

	Total *N=122*	**HE** *N=18*	**HU** *N=104*	**p value**
LVMi (g/m^2)	95.5±28.4	110.9±36.0	93.0±26.4	0.023
LVH [n. (%)]	41 (33.6%)	9 (50.0%)	32 (30.8%)	0.054
EF (%)	61.3±7.9	57.9±5.0	61.9±7.0	0.067
LAVi (ml/m^2)	29.2±11.2	37.8±17.4	28.2±10.0	0.014
LAe [n. (%)]	26 (21.3%)	4 (22.2%)	22 (21.2%)	0.836
Ascending aorta (mm)	34.4±4.9	36.2±5.0	34.1±4.8	0.171
E/E' ratio	9.28±4.57	9.91±3.34	9.21±4.71	0.634
E/E' ratio > 14 [n. (%)]	12 (9.8%)	3 (16.7%)	9 (8.7%)	0.081
TR max vel (m/s)	2.32±0.43	2.51±0.33	2.31±0.44	0.380
PWV (m/s)	9.71±2.30	9.83±1.54	9.68±2.41	0.847
PWV > 10 m/s [n. (%)] §	34 (39.5%) §	4 (33.3%)	30 (40.5%)	0.536
Vascular HMOD [n. (%)] §	45 (52.3%) §	7 (58.3%)	38 (51.4%)	0.629
Renal HMOD [n. (%)]	15 (12.3%)	5 (27.8%)	10 (9.6%)	0.010
Cerebral HMOD [n. (%)] *	16 (34.8%) *	8 (100%)	8 (21.1%)	<0.001

§ Data available for 86 patients (12 patients among HE, 74 patients among HU).

** Data available for 46 patients (8 patients among HE, 38 patients among HU).*

Abbreviations: E/E' ratio: mean transmitral inflow early wave on pulsed-wave Doppler to mitral annulus (lateral/septal) early wave on tissue-doppler imaging ratio; EF: ejection fraction; HMOD: hypertension mediated organ damage; LAe: left atrial enlargement; LAVi: left atrial volume indexed for body surface area; LVH: left ventricular hypertrophy; LVMi: left ventricular mass indexed for body surface area; PWV: pulse wave velocity

4. DISCUSSION

This thesis described around the first hundred patients with acute hypertensive disorders enrolled within the Italian multicenter prospective study called Eridano. ERIDANO study has an ambitious prognostic aim, but, at present, only descriptive data from the first visits have been presented, specifically the ED enrolment and the office evaluation within 72 hours of ED discharge.

Acute hypertensive disorders are serious medical conditions, with a combined prevalence of 1.2% of total admission in the ED, in the most recent meta-analysis on the topic [1]. In the present prospective study, it is difficult to estimate the true prevalence of these conditions, considering the changes in the ED admissions dictated by the COVID-19 pandemic [22 23].

However, the ratio between HE and HU is similar to those of previous studies [24 25 26 27 28 29 30]. Some differences are at least in part explained by the different HE/HU definitions, in terms of BP cut-off or diagnostic coding; in a large retrospective study, the prevalence of HE in the United States between 2006 and 2013 was lower, probably due to the strict definition, based on acute BP elevation together with a diagnosis of acute organ damage based on the ICD-9 code [2].

Our population is younger than the previous Italian multicenter study, whose enrolment was held in 2009, by about 10 years [27], but with similar age of an Asian study from the most recent recruitment [31]. Although we need to increase the sample size to confirm these data, no differences in age, sex and cardiovascular comorbidities are currently present between HE and HU. This seems to disagree with previous findings, in which HE was associated with male sex [24 27], older age, and comorbidities [29].

Pharmacological management in ED confirms for the umpteenth time the great inconsistency among professionals concerning the treatment of acute BP disorders, as well pointed out by the GEAR project [10]. Frequently, antihypertensive drugs are used with the goal of acutely reducing BP in HU, while there is no benefits to support this practice [32 4]. In contrast, there are data on the possible damage from rapid BP reduction in patients without organ damage [33].

Although mostly based on expert opinion, there are official recommendations on the treatment of HE [12]; moreover, a reasoned pharmacological approach has recently been proposed, starting from the pathophysiology of HE [34 35]. Indeed, the major problem seems to be represented by patients with HU, where the greatest discrepancies in treatment approach are found. The current European position paper [12] suggests that HU should be treated in the same way as asymptomatic uncontrolled hypertension, by modifying home therapy without claiming rapid BP reduction in the emergency room. In these patients, oral administration of antihypertensive drugs, aimed at gradual BP reduction over the following days, is the best approach [36 37 38].

In our cohort, CCBs were the most widely used class; in particular, amlodipine, the most available drug in the class in Italian ED, was used in 99% of cases (73 out of 74 patients); nifedipine was used in only one case. These data are fortunately a marked improvement from the frequent use shown in the survey cited above [10], where 22% of participants (and 23% of those working in the ED) were inclined to use sublingual nifedipine to reduce BP, although its use has been discouraged for years because of possible deleterious effects [39]. Long-acting CCBs are also encouraged in this context because they do not interfere with diagnostics, and consequently allow the search for secondary causes of hypertension when indicated [34].

Captopril remains by far the most widely used drug within the class of ACE inhibitors (31 out of 53 patients treated with this class in our cohort). Compared to nifedipine, captopril has been shown to be equally effective in terms of BP reduction, but with fewer side effects [40]; however, considerations must be taken even with this drug due to the possible sudden hypotension [41].

A special consideration should be given to benzodiazepines, class not officially suggested but widely used in clinical practice, as evidenced by previous studies [10 29 24]. Administered in almost half of the cases in our cohort, benzodiazepines are definitely recommended medication in adrenergic hyperactivity BP disorders, such as cocaine abuse [37 42], but their use outside this context would merit more in-depth studies. Patients with HU treated with benzodiazepines demonstrated greater reductions in systolic BP values, than patients not treated with anxiolytic therapy [43]. In a randomized

clinical trial, diazepam demonstrated the same pressor effect as nifedipine and propranolol [44]; in another trial, the same pressor effect of captopril [45].

The fact that not all patients with HE were treated in our cohort is surprising, but this data could be distorted by rapid admission to the intensive or semi-intensive units with treatment initiated outside the ED. Furthermore, in ischemic strokes (n. 5 in our cohort), the cut-off for starting acute antihypertensive treatment is higher than that of HE diagnosis.

To our knowledge, this study is currently the only one that prospectively and systematically assesses short-term (72 hours) BP control in office setting after ED discharge, except for a small study on 21 hypertensive patients in which 24h-ABPM immediately after discharge from the ED [46]. Approximately 90% of patients in our study were discharged from the ED with BP < 180/110 mmHg, thus no longer meeting the criteria for HU, for those without organ damage; a similar rate has been described in recent studies [47] [48]. In about one-third of the cases, normal office BP was present at 72 hours after ED discharge; similar outcome than that reported, of about 20% at 2 weeks after discharge, in a retrospective study conducted in the Thai population [48], but very different from the previously cited Israeli report in which 17 out of 21 patients remained with a SBP > 180 mmHg 24 hours after ED discharge [46].

The median number of hypertensive drugs prescribed increased from 1.0 [IQR 0.0;2.0] before ED admission, to 2.0 [IQR 1.0;2.0] during ED stay, and eventually to 3.0 [IQR 2.0;4.0] at 72h visit. These data confirm both the high BP variability in this population and the need for aggressive treatment.

Finally, we presented some data on subclinical HMOD: to our knowledge this is the first study to assess subclinical HMOD in HE and HU patients immediately after ED discharge.

In general, HE patients had worse subclinical HMOD profile than HU patients, particularly cardiac, renal, and cerebral HMOD, while vascular HMOD was comparable. At 72h visit, patients with uncontrolled BP had worse PWV, suggesting a possible role of aortic stiffness in impeding proper BP control, or possibly grater vascular damage in patients with short-term uncontrolled BP. A recent study showed that HU patients had subclinical HMOD profile midway between patients with

asymptomatic grade 3 hypertension and patients with various grade hypertension, matched for office BP [49]. The higher prevalence of subclinical HMOD in HE patients found in the present study underlines that HE patients have worse baseline CV risk profile than HU patients, leading to more severe manifestations of acute BP rise. Moreover, this difference in subclinical HMOD was not observed when comparing patients with controlled and uncontrolled BP at 72h visit, somehow indicating that some patients could represent a special high-risk population, irrespectively of acute and short-term BP control. Ongoing follow-up is needed to better define this aspect.

4.1 Study limitations

The present thesis has a purely descriptive nature, impaired by the relatively small total number and the numerical discrepancy between the two groups analyzed (HE and HU); this must make comparisons interpreted with caution. At the same time, it has the advantages of describing short-term BP control and the investigation of subclinical HMOD immediately after discharge from the ED.

Follow-up data are not present due to the difficulties already outlined in the previous sections; we estimate to be able to collect a reasonable sample size within 2-3 years, including prognostic data.

Moreover, it was not possible to provide reliable data on the prevalence of secondary hypertension also due to the reduced access to diagnostic medical services during the COVID-19 pandemic. We preferred not to provide data at our disposal that could be affected by such biases; we are gradually restoring this information, which will be present in future manuscripts.

5. CONCLUSIONS

Acute BP disorders are a major challenge for the ED. The lack of good-quality evidence makes it difficult to propose strong recommendations for clinical practice. In this first report about the ongoing prospective Italian multicenter study ERIDANO, we showed that great inconsistency is present in acute BP disorder management. Up to one third of patients resulted normotensive after 72h after ED discharge. HE patients showed greater cardiac, renal, and cerebral subclinical HMOD, compared to HU patients. 72h BP control is not associated with different subclinical HMOD, except for vascular HMOD; therefore, proper comprehensive examination after discharge from the ED could provide added value in cardiovascular risk stratification of such patients.

Acknowledgement

We are grateful to staff physicians and fellows of the Emergency departments and Hypertensive centers for their work.

6. RESEARCH STATUS AND FUTURE PERSPECTIVES

In this thesis, we were forced to consider patients enrolled up to July 2022, taking the following months to enter the data into the common online database (REDCAP Electronic Data Capture). However, the enrolment went ahead and by 31 November 2022 we had enrolled a total number of 182 patients. The following table (Table 6) summarizes the recruitment and follow-up status of the participating centers, listed below:

1) Division of Internal Medicine, Hypertension Unit, Città della Salute e della Scienza Hospital, Department of Medical Sciences, University of Turin, Turin, Italy;

2) Department of Internal Medicine, ASST Spedali Civili of Brescia, University of Brescia, Brescia, Italy;

3) Clinic of Emergency Medicine, Department of Internal Medicine, IRCCS Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy;

4) Cardiothoracovascular Department, Cardiology 4 Unit, Grande Ospedale Metropolitano Niguarda Ca Granda, University of Milan-Bicocca, Milan, Italy;

5) Department of Advanced Biomedical Science, Hypertension Research Center, "Federico II" University Hospital of Naples, Naples, Italy;

6) Department of Medical Specialties, AUSL Toscana Centro, Internal Medicine Unit, San Marcello e San Jacopo I Hospital, Pistoia, Italy.

Table 6. Research status

Recruiting Center	**Total patients** ***N=182***	**3-mo. Visit** ***N=117***	**12-mo. Visit** ***N=19***
Torino	99	65	11
Milano	16	8	4
Brescia	3	3	0
Genova	29	24	0
Pistoia	5	2	0
Napoli	30	15	4

The ERIDANO study has great potential, so future perspectives, in a still very broad and open field of research such as acute hypertensive disorders, are many and various.

It will be crucial to complete follow-up in order to obtain prognostic information on these patients; this is the real primary aim of the study. This will help us to understand whether subclinical HMOD plays a role in predicting an adverse prognosis; if so, as we expect, then an early screening might be warranted in all patients discharged from the ED for an acute hypertensive disorder.

Having the prognostic data, comparing it with that of comparable historical cohorts, will allow us to understand the added value of the Hypertension center compared to follow-up at the expense of the general practitioner. There will inevitably be a bias against the randomization proposed in the original study protocol, but it may be the only compromise at the moment, pending different decisions by the ethics committee for future studies.

Hopefully, the ERIDANO study will also be the stimulus for designing ad-hoc studies on pharmacological treatment, which is still very disparate among emergency physicians especially for HU. The role of benzodiazepines may deserve to be given space in the same way as other pharmacological treatments, but more evidence is needed than just clinical practice.

We are attempting to get approved an extension of the ERIDANO study, that aims to evaluate the psychological profile of the enrolled patients; this might also introduce the idea of treatment as a more holistic care of patients with acute hypertensive disorders.

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8. ABSTRACT

Background. Hypertensive urgencies (HU) and hypertensive emergencies (HE) are challenges for the Emergency Department (ED). A prospective multicentre study is ongoing to characterize patients with acute hypertensive disorders, prevalence of subclinical hypertension-mediated organ damage (HMOD), short- and long-term prognosis; this is a preliminary report.

Methods. Patients admitted to the ED with symptomatic blood pressure (BP) ≥180/110 mmHg were enrolled. They were managed by ED personnel according to their clinical presentations. Subsequently they underwent clinical evaluation and subclinical HMOD assessment at a Hypertension Centre within 72h from enrolment.

Results. 122 patients were included in this report. Mean age was 60.7±13.9 years, 52.5% were females. 18 (14.8%) patients were diagnosed with HE, 108 (88.5%) with HU. There were no differences in gender, BMI, and cardiovascular comorbidities between groups. At ED discharge, 66.7% and 93.6% (p=0.003) of HE and HU patients, respectively, had BP <180/110 mmHg. After 72h, 34.4% of patients resulted normotensive; 35.2%, 22.1%, and 8.2% had hypertension grade 1, 2, and 3, respectively. Patients with uncontrolled BP at office evaluation had higher vascular HMOD (49.1 vs. 25.9%, p=0.045). Cardiac (60 vs. 34%, p=0.049), renal (27.8 vs. 9.6%, p=0.010) and cerebral (100 vs. 21%, p<0.001) HMOD was more frequent in HE compared to HU group.

Conclusions. HE showed greater cardiac, renal, and cerebral subclinical HMOD, compared to HU. 72-hours BP control is not associated with different HMOD, except for vascular HMOD; therefore, proper comprehensive examination after discharge from the ED could provide added value in cardiovascular risk stratification of such patients.

9. GRAPHICAL ABSTRACT