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Review

Acute blood pressure elevation: Therapeutic approach

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ABSTRACT

International guidelines have suggested to avoid the term "hypertensive crisis" for the description of an acute and severe increase in blood pressure (BP) and to consider the definition of 'hypertensive emergencies' or 'hypertensive urgencies'. These two clinical presentations are characterized by the presence of high BP values but imply a different diagnostic and therapeutic approach.

Hypertension awareness, treatment and control are slightly increased in the last years mostly in the United States and in some European nations. Nevertheless the prevalence of hypertensive emergencies is still high and remains associated to a higher mortality.

International Guidelines have also given some recommendations regarding the target BP during treatment and the use of antihypertensive drugs in hypertensive emergencies, although the adherence to these indications is frequently suboptimal.

The present paper is aimed to update the currently available data on the treatment of hypertensive emergencies.

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1. Introduction

The management of an acute increase in BP in a patient with a critical clinical condition is often difficult, because clinicians need to balance the negative impact of BP rise on wall tension in arterial vessels and in the left ventricle and the danger of a too rapid reduction in organ perfusion.

Few randomized clinical trials have been performed in order to establish the adequate approach in the acute hypertensive setting [1–4], as opposed to the large number of observational and interventional studies, on which guidelines indications for treatment of hypertensive patients are based [1,5,6]. Some pathophysiogical aspects could guide the therapeutic approach, but the precise mechanisms underlying the acute increase in BP remain still unknown and unpredictable [7–10]. Another complex issue is represented by the large number of patients with longstanding hypertension admitted to the emergency department (ED), that do not need an acute intervention, but only a closer follow-up in the outpatient clinic [11,12]. For these reasons the use of antihypertensive drugs in the ED is still based on individual clinical experience.

The present paper is aimed to update the currently available data on the treatment of hypertensive emergencies.

2. Definition

International guidelines have suggested to avoid the term "hypertensive crisis" for the description of an acute and severe increase in blood pressure (BP) and to consider the definition of 'hypertensive emergencies' or 'hypertensive urgencies' [1,5,6]. These two clinical presentations are characterized by the presence of high BP values but imply a different diagnostic and therapeutic approach. An hypertensive emergency is an acute increase in BP associated with severe, potentially life-threatening target organ damage (TOD), requiring rapid BP control by the use of intravenous antihypertensive drugs and hospitalization (preferably in an intensive care unit) (Table 1). The most common presentations of hypertensive emergencies are acute stroke, hypertensive encephalopathy, acute hypertensive heart failure, acute coronary syndromes, aortic dissection, sympathetic crises (cocaine toxicity/pheochromocytoma), eclampsia and malignant hypertension. In all these conditions the main objective is to stop the worsening of organ damage and avoid the long-term complications [2,7,13–15].

On the opposite, in the presence of a hypertensive urgency, BP is acutely increased without symptoms suggesting acute organ damage; the reduction of BP values may be reached in hours or even days by oral antihypertensive drugs and patients do not need hospitalization and may be discharged from the ED after a short period of observation.

None of the terms hypertensive emergencies or urgencies corresponds to ICD system codes or implies a reimbursement, while other old terms (malignant and accelerated hypertension) may be still used for reimbursement and coding [16]. It has been suggested that these definitions might be responsible, at least in part, for the increase in hospital admissions for malignant hypertension [17].

An increase in BP above 180 mmHg and/or 120 mmHg may indicate the presence of an hypertensive emergency or urgency, although in some cases the distinction is not strict, since the unrecognized or undertreated hypertensive urgency may evolve into an emergency.

The value of systolic and diastolic BP for the definition of these conditions are not generally accepted and slightly different thresholds have been used. In the "Studying the Treatment of Acute hypertension" (STAT) registry, hypertensive emergency or urgency were defined if SBP and or DBP were >180/110 mmHg, or if SBP and/or DBP were ≥140/ ≥ 90 mmHg only in patients with subarachnoid hemorrhage [18].

In non-stroke patients [19], mean BP of patients receiving intravenous antihypertensive drugs was 180.9 (range 105–220) mmHg as observed in a survey examining the management of acute BP rise by a large group of physician and pharmacists, all members of the Society of Critical Care Medicine and the American College of Clinical Pharmacy.

The distinction between an hypertensive urgency and 'uncontrolled hypertension' may be particularly difficult, if the velocity of the rise in BP remains unknown. Moreover, in several patients with chronic elevation of BP values, often due to poor antihypertensive treatment adherence, a sudden increase in BP may be induced by anxiety, alcohol withdrawal, pain, venous epistaxis.

Table 1
Hypertensive emergencies.

Hypertensive emergencies
√ **Hypertensive encephalopathy**
√ **Severe hypertension associated to acute target organ damage:**
- acute coronary syndromes
- pulmonary edema
- acute aortic dissection
- intracerebral hemorrage
- subaracnoid hemorrage
- acute brain infarction
- acute or rapidly progressing renal failure
√ **Severe hypertension after thrombolysis for ischemic stroke**
√ **Pheochromocytoma crisis**
√ **Drugs related hypertension** (sympathomymetics, cocaine, phencyclidine, phenylpropanolamine, lysergic acid diethylamide, cyclosporin, antihypertensive treatment withdrawal, interaction with MAO inhibitors)
√ **Guillain Barrè syndrome**
√ **Spinal cord injury**
√ **Postoperative bleeding**
√ **Post coronary artery bypass hypertension**
√ **Eclampsia**

3. Epidemiology

Available data indicate that the prevalence of hypertensive emergencies ranges from 2 to 3% of hypertensive patients [20–22] while the mortality rate associated to this condition has declined in the past 40 years. The prevalence ratio of hypertensive emergencies and urgencies is about 1–3/1–4, respectively.

The incidence of cardiovascular events is high in both hypertensive emergencies and urgencies [21,23,24]. In the United States the incidence of hospitalization for a hypertensive emergency has increased in the year interval 2000–2007, but a decline in mortality has been reported. The stronger predictors of mortality for these patients were older age, male sex and Charlson comorbidity index [25]. In the "Studying the Treatment of Acute hypertension" (STAT) registry hospital mortality and 90 day readmission rate were, 6.9% and 37%, respectively [18], being the last mainly associated to low adherence to antihypertensive drugs, substance abuse and end-stage renal disease [26].

A recent study has evaluated 58 535 patients (mean age 63.1 years, 57.7% women and 76% were white) with an hypertensive urgency [27]. No significant difference in the occurrence of major cardiovascular events at 7 days nor at 6 months were observed as compared with the general population of hypertensive patients, and Authors concluded that hypertensive urgency is common, with a low rate of major cardiovascular events. The study also showed that patients referred to the ED were more frequently hospitalized, without an improvement in outcome; in addition the prevalence of uncontrolled hypertension was 65%, when evaluated 6 months after admission.

Table 2
Management of hypertensive emergencies and urgencies in 2013 ESH/ESC and 2017 ACC/AHA hypertension guidelines.

	Hypertensive urgency (asymptomatic acute BP elevation)	BP lowering target/timing in hypertensive emergency
European Society of Hypertension & European Society of Cardiology, 2013	• Isolated large blood pressure elevations without acute organ damage should not be considered an emergency but treated by reinstitution or intensification of drug therapy and treatment for anxiety. • No specific agents mentioned for hypertensive urgency.	• Reduce blood pressure by <25% during "first hours" and then subsequent cautious reduction. • Intravenous agents most usually employed: labetalol, sodium nitroprusside, nicardipine, nitrates, and furosemide • Treatment should be individualized
AHA/ACC, 2017	• In the absence of new/progressive/worsening target organ damage reinstitute/intensify oral antihypertensive drug therapy and arrange follow-up	• Admission to an intensive Care Unit, Continuous BP and target organ damage monitoring • Parental treatment of appropriate drugs • (clevipine, nicardipine, sodium nitroprussiate, nitroglycerin, esmolol, labetalol, fenoldopam, enalaprilat, phentolamine) • Target SBP <140 mmHg during the first hour and <120 mm Hg in aortic dissection for adults with aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis • SBP reduction by maximum 25% over the first hour; then, if stable, to 160/100 mmHg within the next 2–6 h; and then to normal during the following 24–48 h for adults without a compelling condition,

It remains to be determined what are the best approaches for the early evaluation and follow-up intervals, as related to long/short term clinical outcomes [12].

4. Initial management

The initial evaluation of a patient with an acute increase in BP should include careful investigation about alcohol consumption, some food ingestion (cheese with high tyramine content), the use of illicit substances (cocaine) [28] and concomitant drug treatment with corticosteroids and mineralocorticoids, oestrogens, NSAID, cyclosporine, carbamazepine or metoclopramide. Most recently, a particular attention has been given to the acute rise in BP secondary to treatment with angiogenesis inhibitors in patients with solid neoplasms. *Patients with acute BP elevation due to cocaine abuse should receive a benzodiazepine to resolve anxiety; if sedation is not sufficient to control hypertension, BP may be reduced by sodium nitroprusside, nitroglycerin, or intravenous phentolamine. Unopposed a-stimulation during b-blocker use in patients with cocaine abuse/intoxication was considered an absolute contraindication, suggesting the alternative use of non-dihydropiridinic calcium-channel blockers.*

The optimal screening includes repeated measurements of BP, few laboratory examinations (urine-analysis, creatinine, urea, electrolytes and a full blood count), an electrocardiogram and fundoscopy [18,29]. Other investigations, such as echocardiography [30,31], brain CT scan, thoracic and abdominal ultrasound or CT scan and vascular ultrasound are usually performed in patients with hypertensive emergencies according to the clinical presentation.

A systematic review [32] aimed to examine guidelines addressing acute hypertension management has identified three guidelines, issued by the American College of Emergency Physicians (ACEP), the National Heart, Lung, and Blood Institute (NHLBI), and the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) respectively. In hypertensive emergencies, a similar approach was proposed by the NHLBI and the ESH/ESC guidelines, both recommending to reduce mean arterial pressure by $\leq$25% from baseline during the first hour. ESH/ESC Guidelines suggest a "subsequent cautious reduction", while NHLBI suggests to reach BP values equal to 160/100–110 mmHg during the subsequent 2–6 h and obtain progressive BP normalization in 1 or 2 days. This last recommendation is also reported in the recently published multisocietary guidelines issued by the American Heart Association (AHA) and the American College of Cardiology (ACC) in 2017 (Table 2).

Most patients with severe BP increase complain no or very mild symptoms and have a hypertensive urgency; in some of these subjects, the presence of elevated BP values may partially reflect inadequate control of chronic hypertension. In these patients the oral administration of antihypertensive drugs, aimed to lower BP gradually over 24–48 h, is the best approach. Clinical surveillance in a short-stay observation unit is usually appropriate, without the need of hospital admission, and a short-term outpatient visit by hypertension specialist is strongly suggested. The gradual reduction in BP is beneficial, while potential harm may derive from a rapid BP decrease, due to an impairment of coronary, cerebral and renal autoregulation [33–36].

All guidelines recommend against the sublingual administration of nifedipine; the degree of BP decrease cannot be anticipated and often is too fast and larger than desirable [37,38].

For the initial approach the use of a calcium antagonist or of combinations of different antihypertensive agents, can be considered.

Very recently, in a small group of patients with an hypertensive urgency the use of a low dose telmisartan was compared to bed rest, showing no significant difference between resting and antihypertensive medication in reducing BP [39]; this result and other findings [40,41] underline the clinical efficacy of resting in managing hypertensive urgency, mainly in those with emotional stress or sympathetic overactivity.

Admission to an intensive or semi-intensive unit for strict observation and BP monitoring is strongly recommended for patients with a hypertensive emergency. The administration of drugs with a short onset of action should allow to obtain in few minutes a BP reduction of about 15–25% of the initial values, that should be maintained during the first hours. BP normalization (<140/90 mmHg) should be progressively obtained in a longer period of time, at least 48 h, in patients with ischemic stroke [5]. Only in patients with aortic dissection is mandatory to reach rapidly a target BP < 100–120/80 mmHg [42].

Despite Guidelines advice against an excessive speed of BP reduction, the rate of change of BP is frequently greater than recommended [43], even in acute stroke patients, in whom the AHA recommended treatment criteria are applied only in 30% of cases [44]. In the STAT (Studying the Treatment of Acute hyperTension) registry, iatrogenic hypotension was reported in 4% of patients

Table 3
Drugs used in hypertensive emergencies.

DRUG	INDICATION	DOSE	ADVERSE EFFECTS
Sodium nitroprussiate	Acute HF(systolic), ACS, aortic dissection, ischemic stroke (only if DBP >140 mmHg)	0.25–10 mg/kg/min	Vomiting, cyanate toxicity
Labetalol	ACS, aortic dissection, stroke (ischemic & hemorrhagic), hypertensive encephalopathy, eclampsia, perioperative hypertension, (sympathetic crisis, pheochromocytoma)	20–80 mg bolus 1–2 mg/min infusion	Bradycardia, heart block, bronchospasm, nausea, vomiting
Esmolol	ACS, aortic dissection, stroke (ischemic & hemorrhagic), perioperative hypertension, hypertensive encephalopathy, eclampsia	Bolus I mg/kg/min over 1 min, than 50–300 mcg/kg/min	Bradycardia, heart block, bronchospasm, nausea, vomiting
Nitroglycerin	ACS, acute HF(systolic & diastolic), ischemic stroke, sympathetic crisis, pheochromocytoma, perioperative hypertension	5–100 mg/min	Headache, vomiting
Enalaprilat	(in patients already treated with ACE-Inhibitors): perioperative hypertension	1.25–5.00 mg bolus	Renal failure, angioedema, relatively slow onset of action
Furosemide	Acute HF(systolic & diastolic), acute renal failure, volume overload	40–60 mg	Hypokalemia, ↑ creatinine, fluid depletion
Fenoldopam	acute renal failure, acute HF(systolic & diastolic), ACS, stroke (ischemic & hemorrhagic), hypertensive encephalopathy, aortic dissection, perioperative hypertension	0.1–0.8 mg/kg/min	Headache, flushing, nausea
Nicardipine	ACS, acute HF(systolic & diastolic), aortic dissection, acute stroke (ischemic & hemorrhagic), hypertensive encephalopathy, sympathetic crisis, acute renal failure, perioperative hypertension	2–15 mg/h	Reflex tachycardia, flushing
Clevipine	ACS, acute HF(systolic & diastolic), stroke (ischemic & hemorrhagic), hypertensive encephalopathy, aortic dissection, sympathetic crisis, acute renal failure, perioperative hypertension	1–32 mg/hour	Reflex tachycardia, flushing
Urapidil	acute stroke (ischemic & hemorrhagic), perioperative hypertension, sympathetic crisis, pheochromocytoma, eclampsia,	25–50 mg bolus	Sedation
Hydralazine	Eclampsia, perioperative hypertension	10–20 mg bolus	Reflex tachycardia; unpredictable response, long duration of action
Phentolamine	sympathetic crisis, pheochromocytoma	5 mg bolus; infusion 5–50 mcg/kg/min.	Reflex tachycardia

with hypertensive emergencies, and parenteral therapy was re-started in 29% because of recurrent and severe hypertension [45]. In another observational study conducted in Europe (Euro-STAT) evaluating 'real-world' management of acute hypertension not only in the ED but also in ICU or in the perioperative period, the prevalence of hypotension induced by intravenous nitroglycerin, urapidil or furosemide was 10% [46].

5. Drug treatment

A systematic Cochrane review, including about 1000 patients, has compared each antihypertensive drug with placebo, no treatment, or another agent of a different class, and the results have shown that all drugs similarly reduce BP and do not differ in the effect on morbidity and mortality. In the 15 clinical trials examined nitrates were most frequently used, with fewest adverse effects [47].

Therefore, being the decision of physicians not supported by randomized clinical trial [4], the choice of the best drug(s) with the best benefit–risk ratio depends on the correct recognition of the clinical picture and the consideration of comorbidities (Table 3).

5.1. Acute heart failure

The ESC guidelines on heart failure have underscored the presence of a phenotype of acute heart failure due to an acute increase in BP [2,5,48]. According to guidelines, hypertensive acute heart failure (H-AHF) is defined as the rapid onset of pulmonary edema in the presence of SBP values >140 mm Hg, and often >160 mmHg [49]; frequently these patients present with a long-standing poor control of hypertension. The analysis of BP values in four cohorts of patients hospitalized for acute heart failure from 1995 to 2012 has shown that the portion of patients with SBP value higher than 160 mmHg significantly declined from one-third to one-fifth of the whole population [50].

Despite about 50% of patients with AHF have elevated BP at the ED admission, it is important to underline that SBP higher than 140 mmHg in patients hospitalized for acute heart failure is associated to a favorable survival, as shown by the ESC-HF-LT Registry [51]; on the opposite, the decline in BP below 120 mmHg during treatment is associated with an increased number of adverse events [52].

In patients presenting with dyspnea and the suspicion of acute heart failure, it should be considered, in addition to the ECG, an echocardiogram for the evaluation of left ventricular systolic and diastolic function and valvular regurgitation [30]. The use of thoracic ultrasound is becoming increasingly indicated during a hypertensive emergency and signs or symptoms of congestive heart failure in order to assess the presence of comet tails. Brain natriuretic peptide (BNP) or NT-proBNP may be particularly useful for the diagnosis of new onset or acute heart failure in the ED [53]; measurement of BNP/NT-proBNP may also improve prognosis or risk stratification [54].

Guidelines suggest the use of a loop diuretic and of a vasodilator for the aggressive reduction of BP in hypertensive acute heart failure [49]. Among loop diuretics [55,56], furosemide is the most frequently used and should be administered intravenously in all patients as soon as possible [57]. The results of a prospective, multicenter, observational cohort study, conducted to assess the effect of time to loop diuretic treatment in patients with AHF admitted through the emergency department [58] have confirmed that earlier is the administration of furosemide, the better will be the outcome. The REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure), has shown that early treatment (defined as the time from patient arrival at the ED to the first intravenous furosemide injec-

tion <1 h) with intravenous loop diuretics was associated with a 60% lower mortality during hospital stay, confirming a previous retrospective analysis of the ADHERE registry [58]. The DOSE study has shown no differences between bolus every 12 h or continuous infusion of furosemide [59].

Nitroglycerin is mainly a venodilator and induces arteriolar dilatation only when high doses are given. Nitroglycerin acts by reducing preload and increasing venous capacitance, while at higher doses may be effective also by decreasing afterload [60]. These hemodynamic effects represent the main reason why it is preferred for patients with hypertensive emergencies, especially those with hypertensive acute heart failure.

In the treatment of H-AHF in ED and ED-like settings, an improvement in dyspnea may be obtained by intravenous administration of nitroglycerin, isosorbide dinitrate or nitroprusside, but do not influence mortality. These agents have few side effects [61], provided hypotension is carefully avoided by continuous BP monitoring, especially when nitroprusside is chosen [62].

Few data support the efficacy and safety of other vasodilators such as enalaprilat. Ayaz et al. [63] have shown a progressive reduction of BP values during the first 60 min after IV bolus enalaprilat administration without adverse effect in more than 100 patients with hypertensive acute heart failure.

Clevidipine is a new dihydropyridinic calcium antagonist, approved in 2008 by the United States Federal Food and Drug Administration and available for intravenous administration [64,65]. The use of clevidipine is indicated to patients in whom oral therapy is not indicated or feasible, and BP needs to be reduced in a short time [48,55]. Clevipine inhibits the influx of extracellular calcium through the L-type channel, causes smooth muscle of small arteries relaxation, thus decreasing peripheral vascular resistance [64,65]. This third-generation calcium antagonist has no effect on venous vessels tone or on myocardial contractility [60], and no relevant changes in stroke volume, heart rate and cardiac output have been reported during its administration.

The novel features that characterize this new compound are the rapid blood metabolism and the extra-short half-life of 1 min, allowing rapid titration.

In a randomized trial clevipine was compared to standard of care therapy, showing a significantly greater reduction in BP and improvement of dyspnea in patients receiving clevipine as compared to standard treatment, with similar safety profile [66]; moreover the resolution of dyspnea speed paralleled the reduction in BP induced by clevipine, with a reduction in the need of additional IV antihypertensive drugs and in the total dose of furosemide [66].

Other new drugs are currently proposed for the treatment of hypertensive acute heart failure. The use of a vasodilator drug, as tested in more recent studies, would be aimed to counteract the wall stress and myocardial damage induced by an acute increase in afterload, being advantageous in patients with acute BP increase.

Ularitide is a synthetic compound derived from a natriuretic peptide named urodilatin. Ularitide induces vasodilation both at systemic and renal level, may enhance diuresis and natriuresis and is able to inhibit the renin-angiotensin system. Based on the favorable effects of ularitide infusion on hemodynamic profile and clinical tolerability observed in previous smaller trials, a large placebo-controlled trial named the TRUE-AHF study [67] was performed. In the TRUE-AHF trial, including more than 2000 patients, no differences were observed in cardiovascular mortality in patients treated with ularitide as compared to placebo, despite ularitide treatment was associated to a significantly greater reduction of intravascular congestion and to a short-term persistence or worsening of HF [67].

Serelaxin is derived by recombinant DNA from the human protein relaxin-2, that plays a central role in the cardiovascular and renal adaptations to pregnancy in humans. The binding of relaxin to the G-protein-coupled receptor RXFP1, in the myocardium, in the kidneys and in the systemic vasculature leads to nitric oxide production. Relaxin regulates collagen synthesis by upregulation of metalloproteinases and has antifibrotic properties, decreases systemic resistances and improves arterial compliance [68]. In the RELAX-HF study treatment with serelaxin was associated with significant improvement in dyspnea and 6 months survival and with a decrease of biomarkers suggesting end-organ damage; in addition worsening of heart failure during admission and the duration of hospital stay were lower in patients treated with serelaxin infusion [69]. The potential beneficial effects of serelaxin have not been confirmed by the RELAX-AHF-2 study, including more than 6500 patients [70].

The use of morphine is controversial despite the evidence that morphine may act as a venodilator and may reduce preload and the sympathetic drive also because it decreases dyspnea and anxiety.

Symptoms relief may be obtained by noninvasive ventilation (NIV) in patients with pulmonary edema and severe respiratory distress, after failure of improvement by pharmacological therapy [71]. BP reduction induced by NIV may be particularly useful in H-AHF.

5.2. Acute stroke

Severe BP elevation is a common early finding in patients who have experienced an acute ischemic or hemorrhagic stroke and is considered as a hypertensive emergency. Despite this, a rapid fall in BP values in hemorrhagic and ischemic stroke is not always useful to prevent death and disability.

Antihypertensive treatment may have a different impact in ischemic and haemorrhagic stroke, which need to be considered separately [72,73].

5.2.1. Ischemic stroke

Acute ischemic stroke represents 85% of total strokes in western countries [74]. Studies have shown that blood pressure values are elevated in most patients with acute ischemic stroke; this has been observed in previously hypertensive patients (treated or untreated) and in normotensive subjects; the increase in BP is usually transient and often BP values spontaneously decline within 24–48 h.

Several mechanisms may contribute to the acute elevation of BP; among them a significant role may be related to increased sympathetic drive, reflex response to cerebral ischemia, impaired neurogenic cardiovascular control, autonomic dysregulation and baroreflex failure; pain and stress may further increase BP values in these patients. High BP values during the first hours after an acute ischemic stroke may not always represent a deleterious phenomenon. It has been shown that patients with lacunar infarctions have a significantly greater BP elevation as compared to patients with atherothrombotic and cardioembolic strokes of the anterior and posterior circulation; despite this, clinical outcomes were more favorable in the former group [75]. In the CATIS trial ['China Antihypertensive Trial in Acute Ischemic Stroke' (CATIS)] the use of antihypertensive drugs and consequent decrease in BP did not reduce the occurrence of death and major disability at 14 days or hospital discharge compared with no antihypertensive treatment in patients with acute ischemic stroke [73].

Therefore the use of antihypertensive drugs for BP reduction is not always advisable in patients with acute ischemic stroke [76]. The early (the first 24–48 h) and the late phase changes in BP are influenced by the rapid changes of the protective mechanism called 'cerebral blood flow autoregulation' that occur after stroke.

After an acute ischemic stroke, the autoregulation of cerebral perfusion is lost in the area around the infarct core, called "penumbra", exposing the cerebral tissue to potential injury. Due to the loss of autoregulation, the cerebral perfusion in the 'penumbra' is

driven by the perfusion pressure. A BP fall during this early phase may be critical, reducing cerebral perfusion, extending the ischemic area and inducing irreversible damage; therefore, during the first 24–48 h, a high BP may be seen as a compensatory mechanism, until the autoregulation is restored. On the opposite, in the latter phase, *if BP decline is obtained at a slower rate, the risk of cerebral edema, hemorrhagic transformation and stroke recurrence is reduced and the incidence of other cardiovascular complications is lower.*

Unfortunately, in acute ischemic stroke it is very difficult to anticipate the effect of BP changes on cerebral perfusion, even when a thrombolytic agent is administered.

The American Stroke Association (ASA) recommend treatment with intravenous labetalol or nitroprusside only in the presence of severely elevated BP, i.e. values repeatedly above 220/120 mmHg. The threshold for the treatment could be lower only if the patient has other concomitant clinical conditions congestive heart failure, myocardial infarction, or aortic dissection [76].

Antihypertensive treatment should not administered in previously untreated hypertensive patients for the first 48 h after an ischemic stroke, unless BP is higher than 220/120 mmHg or thrombolytic therapy is indicated. On the contrary, in patients previously treated with baseline BP > 220/120 mmHg, antihypertensive therapy should be given to avoid rebound hypertension.

Guidelines suggest to maintain BP around 180/105 mmHg and 160–180/90–100 mmHg in previously hypertensive or normotensive patients, during the acute phase of an ischemic stroke respectively [76]; in other words, a reduction of 15% in respect to baseline BP values could be considered a reasonable target during the first 24 h after onset of stroke.

A systematic metanalysis of studies evaluating the effect of BP lowering in early ischemic stroke [77] has included 13 clinical trials, and has shown no differences in the primary outcome (unfavorable outcome at 3 months or at trial endpoint); in addition BP reduction did not influence secondary outcomes, both at short (modified Rankin scale 3–6 and 2–6, all-cause death and serious adverse events) and long term (recurrent stroke, recurrent vascular events, modified Rankin score 2–6, all-cause death).

A sub-analysis of the CATIS trial [78] has compared the clinical outcome in 4071 acute ischemic stroke patients with elevated systolic BP who received antihypertensive treatment or discontinued all antihypertensive medications during hospitalization. The results show that the primary (death and major disability) and secondary outcomes (modified Rankin score, recurrent stroke, vascular disease events, and all-cause death) were not significantly different between the treatment and control groups, both 2 weeks after the stroke or at hospital discharge. It is important to underline that only patients who received antihypertensive treatment between 24 and 48 hours after the stroke had a benefit, showing a significant reduction in death or major disability, recurrent stroke, and vascular events at the 3-month follow-up.

In patients eligible for treatment with intravenous thrombolytics or other acute reperfusion intervention, BP should be lowered to less than 185 mmHg, before the intervention [76], and if BP is persistently elevated (SBP > 185 mmHg or DBP > 110 mmHg) intravenous thrombolytic therapy is contraindicated. After reperfusion therapy, it is necessary to keep SBP < 180 mmHg and DBP < 105 mmHg for at least 24 h. The Safe Implementation of Thrombolysis in Stroke (SITS) registry showed that baseline high SBP was associated with symptomatic intracranial hemorrhage and baseline DBP > 90 mmHg was associated with poor outcome [79]. To this regard the currently ongoing study ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) is evaluating the effects of early BP-lowering treatment and compares SBP 130–140 mmHg vs. SBP < 180 mm Hg in patients treated with IV-TPA [80].

5.2.2. Haemorrhagic stroke

Haemorrhagic strokes represent 15% of strokes. The occurrence of intracerebral haemorrhage (ICH) is often associated with elevated BP and high BP is related to an increased risk of death, disability or neurological deterioration. Hematoma expansion is a frequent complication of ICH, occurring mainly in the first 24 h in about 30% of patients. It has been calculated that for each 1 ml increase in hematoma expansion, the risk of death and dependency will increase by 5% and hematoma volumes >30 ml are related to increased mortality rates (60%–90%) at 1 month after ICH.

Hematoma growth is related to increased BP [81] and early reduction in BP may mitigate hematoma volume expansion. Two pilot trials (INTERACT1 and ATACH1) indicated that intensive BP lowering in the setting of acute ICH is safe and may be associated with reduced hematoma growth. In addition the ICH ADAPT study [82] showed no relationship between the absolute change in systolic BP and the perihematoma relative cerebral blood flow both in patients with target SBP < 150 mmHg or <180 mm Hg, suggesting that rapid BP lowering after a ICH does not reduce perihematoma cerebral blood flow and does not precipitate cerebral ischemia.

The INTERACT-2 study has demonstrated that intensive lowering of BP is not associated with a reduction in the rate of the primary outcome (death or major disability), but with significantly lower modified Rankin scores and quality of life improvement in patients with ICH [72]. *In this study, a greater SBP reduction achieved quickly and maintained consistently in the intensive arm, was able to avoid hematoma growth for 24 h* [83]. The multicenter ATACH-2 (Antihypertensive Treatment in Acute Cerebral Hemorrhage 2) trial has randomized ICH patients to the same BP targets proposed in the INTERACT 2, but treatment was started earlier and nicardipine was predefined as the first antihypertensive agent to be administered [84]. The results of the ATACH-2 trial *have* shown that intensive SBP reduction does not provide an incremental clinical benefit, while serious adverse events may occur more frequently within 3 months after randomization among participants randomly assigned to intensive treatment as compared to standard treatment.

The results of the INTERACT-2 and ATACH-2 also suggest that the blunting fluctuations in SBP in patients with intracerebral hemorrhage and an acute hypertensive response may confer a treatment benefit, independently of the magnitude of SBP lowering.

According to these evidences, AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage [85] state that if SBP is higher than 220 mmHg, aggressive reduction of BP should be considered, using intravenous drugs; a reduction of SBP to 140 mmHg is also considered safe in patients with SBP between 150 and 220 mmHg at admission.

In patients with subaracnoidal hemorrhage (SAH), the major cause of morbidity and mortality is aneurysmal rebleeding. *In the past, a relationship between SBP in the range of 160–200 mmHg and aneurysmal rebleeding was observed.* The AHA/ASA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [86] suggest, while awaiting for the prompt obliteration of the aneurism, a cautious reduction of SBP values to below 160 mmHg, with careful monitoring of BP values and neurologic status in order to minimize the risk of both ischemic and hemorrhagic complications.

There is no consensus about the best drugs for BP reduction in ischemic or hemorrhagic stroke. The choice should be based on few principles, including rapidity of action, titration and lack of fluctuations on cerebral blood flow.

To this regard some studies have reported that nitrate transdermal agents have inconsistent absorption and efficacy, although stable cerebral perfusion has been observed during glyceryl trinitrate administration [87]. A randomized, controlled study is currently ongoing, testing the use of transdermal glyceryl-trinitrate

(The Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial-2 (RIGHT-2)) [88] given in the ambulance during the first 4 h after the onset of an acute ischemic stroke [89].

Nitroprusside is rarely used in acute stroke for BP reduction in the ED setting, since, despite the rapid onset of action, it needs careful and continuous monitoring; it carries a small risk of thiocyanate and cyanide toxicity, although this side effect is seen more commonly with excessive dosing and prolonged use.

Other intravenous agents such as hydralazine or enalapril have been included as treatment options in stroke guidelines. Hydralazine, however may be difficult to titrate with unpredictable effects [90] and may reduce cerebral perfusion through systemic vasodilatation [91]. Intravenous enalapril was first-line therapy in the CATIS trial, without an increase in adverse events [92].

Intravenous labetalol (a dual b and a adrenergic receptor blocker) is indicated as first-line agent for BP control in ischemic or hemorrhagic stroke, because it has a rapid onset of action, a rapidly reversible effect and is associated with stable cerebral perfusion; by blocking b and a receptors, with a ratio of b to a antagonism of 3:1, it induces peripheral vascular resistance decrease, without significant changes in heart rate and cardiac output. Labetalol was used in the CHHIPS trial [93] and induced a small fall in SBP (7 mmHg) at 24 h without increase in serious adverse events, early neurological deterioration or death. *This drug has been shown to be safe also in patients with other comorbidities such as acute left ventricular failure, myocardial infarction, stable congestive heart failure, atrial fibrillation, angina pectoris.*

Urapidil, is an α–receptor blocker and stimulates serotonin 5HT1A receptors, and has a sympatholytic effect, mediated via antagonism of peripheral adrenergic system and stimulation in the central nervous system. *No randomized trials have evaluated the effect of urapidil in acute stroke treatment, although intravenous urapidil was used in 47% of patients randomized to intensive BP reduction in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT) study* [94]. BP reduction with urapidil is generally not associated with an increase in intracranial pressure and impairment of cerebral perfusion pressure [95].

Nicardipine is a dihydropyridinic calcium antagonist that may be administered intravenously, has many ideal characteristics for managing the acute hypertensive response in the ED and has been included in recent guidelines for stroke management [76]. Nicardipine was used in the ATACH-2 study and it has been shown to decrease blood pressure more smoothly than sodium nitroprusside or even labetalol; brain oxygen tension measurements showed stable values during treatment with nicardipine [96–98].

The treatment with labetalol and nicardipine in hypertensive emergencies has been compared in 10 studies, analysed in a systematic review; both drugs had comparable efficacy and safety, but a more predictable and consistent BP control was obtained with nicardipine than with labetalol [65]. Some new data indicate that BP variability may be better controlled by nicardipine than by labetalol, in addition to absolute BP reduction [99].

The onset of action of nicardipine is between 5 and 15 min after starting infusion and the clinical offset of activity within 30 min after stopping infusion (defined as a 10 mmHg increase in SBP or DBP); the patient's weight has no influence on drug dosage. The infusion can be started at the initial rate of 5 mg/h, and increased by 2.5 mg/h every 5 min to a maximum of 15 mg/h until the desired BP reduction is achieved. The high vascular selectivity as well as the increase in stroke volume and in coronary blood flow, render this drug also useful in patients with coronary artery disease and systolic heart failure.

Clevidipine has not been extensively studied for the treatment of patients with acute stroke, but could represent an alternative to nicardipine for ED management of acute hypertension [100]. Again, it is important to stress that sublingual nifedipine is not recommended [38,101,102].

Available data indicate that oral nimodipine may improve neurological outcome after SAH (ref LG SAH).

5.3. Acute aortic dissection

Aortic dissection true prevalence and incidence are difficult to establish; it has been reported that aortic dissection prevalence ranges from 5000 to 10 000 cases per year in the United States [103,104] and the incidence is approximately less than 1 in 10.000 patients. The death rate is very high (1–2% per hour in patients who do not receive treatment), reaches 40% during the first 24 h [105] and 90% overall after 1-year [106]; even in patients that may reach the hospital and receive treatment a hospital mortality of 25% has been reported. The risk for acute aortic dissection is higher in several genetic syndromes, in arterial inflammatory diseases and in the presence of hypertension [107]. The diagnosis of acute aortic dissection is often delayed and sometimes missed in the ED, since only 25% of patients present with the classical main 3 symptoms (thoracic pain of sudden onset, increased inter-arm difference in BP and mediastinum widening on chest radiograph) [106]. Signs and symptoms may be influenced by the initial site and the progression of the aortic wall dissection and by the dimensions of the false lumen and frequently overlap with the clinical presentation of an acute coronary syndrome. The Stanford classification has defined as Type A dissections the involvement of the ascending aorta, and Type B dissections the one of the descending aorta [107]. Acute aortic syndromes may also include the presence of aortic intramural hemorrhage and penetrating aortic ulcer.

In the clinical suspicion of acute aortic dissection, imaging by *trans*-oesophageal echocardiography, CT scan with intravenous contrast or MRI should be promptly performed confirm (or reasonably exclude) the diagnosis [107]. A surgical team consultation might be lifesaving, but at the same time medical therapy is mandatory to control heart rate (goal <60 beats/min), systolic BP (target between 100 and 120 mmHg) and pain (intravenous opiate analgesia), in an attempt to minimize further tension and damage to the aortic wall, while waiting for surgery [108].

Treatment with intravenous rapid-acting and titratable beta-blockers (propranolol, metoprolol, labetalol, or esmolol) is needed to first lower heart rate; in asthmatic patients non-dihydropyridine calcium channel antagonists (verapamil and diltiazem) may be used as alternative. Labetalol might have some advantage on other beta-blockers because of the dual alpha and beta receptor blockade, favoring arterial vasodilation.

In order to more rapidly and effectively reduce BP, the combination with a vasodilator (intravenous sodium nitroprusside or nitroglycerin) may be necessary; nevertheless beta-blockers should be initiated first to counteract reflex tachycardia and increased inotropy secondary to the vasodilator administration.

5.4. Eclampsia

Pre-eclampsia and eclampsia are still the most important disorders associated with increased maternal and fetal morbidity and mortality and potentially preventable. An increase of BP > 160/110 mmHg, sustained for more than 15 min, is considered an obstetric emergency and should receive appropriate attention and treatment. Eclampsia is characterized by the new-onset of seizures, attributable to the hypertensive disorder. In these obstetric emergencies/urgencies BP should be reduced below 160/110 mm Hg, ideally to 140–150/90–100 mmHg, in order to avoid hypoprfusion of the fetus and mother organs. The administration of intravenous labetalol, intravenous hydralazine or oral nifedipine are suggested for immediate BP control; second-line

drug treatment include intravenous esmolol, nicardipine, labetalol or sodium nitroprusside. In eclampsia magnesium sulfate is given for seizure prophylaxis, but not for BP reduction.

6. Conclusions

Despite the increasing prevalence and the high mortality rate of hypertensive emergencies, the best approach in patients presenting with acute hypertension in the ED is still not well established. A prompt and rapid evaluation of the clinical presentation is crucial for the optimal management of these conditions. In fact, the initial presentation and the associated organ damage strongly influence the thresholds and targets of antihypertensive treatment. Also the choice of the most adequate drug (or combination of drugs) may be different according to a patient's clinical picture and comorbidities. Due to the paucity of data derived from randomized studies management of hypertensive emergencies is still based on experience rather than on evidence-based recommendations and further studies are warranted.

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