JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 17, 2024

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Malignant Hypertension: A Systemic Cardiovascular Disease

JACC Review Topic of the Week

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ABSTRACT

Malignant hypertension (MHT) is a hypertensive emergency with excessive blood pressure (BP) elevation and accelerated disease progression. MHT is characterized by acute microvascular damage and autoregulation failure affecting the retina, brain, heart, kidney, and vascular tree. BP must be lowered within hours to mitigate patient risk. Both absolute BP levels and the pace of BP rise determine risk of target-organ damage. Nonadherence to the antihypertensive regimen remains the most common cause for MHT, although antiangiogenic and immunosuppressant therapy can also trigger hypertensive emergencies. Depending on the clinical presentation, parenteral or oral therapy can be used to initiate BP lowering. Evidence-based outcome data are spotty or lacking in MHT. With effective treatment, the prognosis for MHT has improved; however, patients remain at high risk of adverse cardiovascular and kidney outcomes. In this review, we summarize current viewpoints on the epidemiology, pathogenesis, and management of MHT; highlight research gaps; and propose strategies to improve outcomes. (J Am Coll Cardiol 2024;83:1688-1701) © 2024 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 14, 2023; revised manuscript received January 30, 2024, accepted February 5, 2024.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2024.02.037

HIGHLIGHTS

- There has been a recent resurgence in the incidence of MHT, although it remains underdiagnosed.
- MHT provokes a vicious cycle of cardiovascular, cerebral, and renal complications.
- Strategies for BP lowering should be tailored to account for comorbidities.
- Very limited evidence-based outcome data are available to guide management of patients with MHT.

Malignant hypertension is a medical emergency which demands reduction of arterial pressure—not tomorrow or next week, but now!

— Sir George Pickering, 1955[1]

HISTORICAL BACKGROUND

Malignant hypertension (MHT) is a textbook example where a simple risk factor progresses to a disease requiring emergency treatment. In MHT, hypertension itself is the driving force of the clinical complications. This situation contrasts with other hypertensive emergencies that are caused by the coexistence of (severe) hypertension and acute cerebral or cardiovascular complications, including acute coronary syndrome, acute cardiogenic pulmonary edema, ischemic stroke, intracranial hemorrhage, and acute aortic aneurysm or dissection. MHT originally was defined by the concomitant presence of severe hypertension and bilateral retinopathy. This terminology was based on studies showing limited survival in patients with severe hypertension and advanced retinopathy (retinal hemorrhages and cotton wools spots with or without papilledema) at a time when drug therapy was not available. The arrival of effective antihypertensive medication and screening methods to monitor the risk of cardiovascular disease has improved the prognosis of MHT considerably. Despite such improvements, MHT should still be considered an emergency given its life-threatening progression of target organ damage. The retinal lesions associated with MHT are an important indicator of vascular damage elsewhere as can be documented by the coexistence of acute kidney injury and thrombotic microangiopathy (TMA). Because systemic microcirculatory damage is the pathological hallmark of MHT and retinal lesions can be absent in patients with acute kidney injury, the term acute hypertensive microangiopathy may be more informative. The excessive cardiovascular risk associated with the presence of acute and chronic hypertension mediated organ damage requires additional therapeutic stratification based on clinical findings in these patients.[2]

EPIDEMIOLOGY

The success in decreasing the prevalence of cardiovascular diseases has also led to a decrease in the prevalence of MHT. Yet, MHT remains relatively common in areas where blood pressure (BP) control or the availability of BP-lowering drugs is limited. In 2 European cohorts in Birmingham and Amsterdam,[3] the overall incidence rates were of 2 new cases per 100,000 individuals per year, with rates up to 4 times higher (7.3 per 100,000 per year) for subjects of self-reported Black African/Afro-Caribbean ethnicity (Table 1). Conceivably, however, MHT remains significantly underdiagnosed. Between September 2019 and May 2023, the multicenter HAMA (Hypertension Arterielle MAligne) registry enrolled 425 patients with MHT, and hypertensive encephalopathy, a hypertensive complication closely associated with MHT was reported in 7,781 French patients over an 8-year period.[4] Of concern is recent evidence suggesting that the number of incident cases of MHT is increasing.[5,6] This resurgence may be partly explained by the increase in number of migrants and the poor access to medical care in some countries.

CAUSES AND TRIGGERING FACTORS

The fact that no specific BP threshold can be used to define MHT poses a challenge to the diagnosis. As a result of microvascular adaptations, patients with longstanding high BPs can tolerate much higher BP levels, whereas patients who have a sudden rise in BP may have emergency symptoms at considerably lower BP values. In most cases, however, MHT rarely occurs below diastolic BP values of 120 mm Hg. In principle, any trigger that acutely increases BP can elicit MHT, provided the stimulus is sufficiently powerful and sustained. Secondary hypertension, including renal artery stenosis, mineralocorticoid excess, and pheochromocytoma have been associated with MHT, but are uncommon as a single cause. More recently, cytotoxic and antiangiogenic drugs also have been associated with severe hypertension and TMA.[7] Antiangiogenic (vascular endothelial growth factor and tyrosine kinase inhibitors) and immunosuppressant drugs, including calcineurin inhibitors

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

MHT = malignant hypertension

MRI = magnetic resonance imaging

PRES = posterior reversible encephalopathy syndrome

TMA = thrombotic microangiopathy

TABLE 1 Highlights for Clinicians: When to Think of MHT in Daily Care

Severely hypertensive patient who exhibits a high-risk profile, young (age 30-60 y), male, of African descent, living in disadvantaged conditions.
Known triggering factors such as therapeutic nonadherence or use of prohypertensive substances (eg, cytotoxic drugs, antiangiogenic drugs, NSAIDs, or cocaine).
Severe, unusual, and persistent hypertension accompanied by headache and visual disturbances, and low normal potassium levels.
Severe hypertension with signs of target organ damage on routine assessments, such as subacute kidney injury and/or disproportionate left ventricular hypertrophy on echocardiogram/electrocardiogram.
Inappropriate hypertension, when BP levels are inappropriately suddenly elevated in a hitherto well controlled patient.

BP = blood pressure; MHT = malignant hypertension; NSAID = nonsteroidal anti-inflammatory drug.

like cyclosporine, sirolimus, and tacrolimus, are known to be associated with the development of severe hypertension and there are various case reports and case series that have associated these drugs with the development of MHT and posterior reversible encephalopathy syndrome (PRES). The pathophysiology concerns both a direct vasoconstrictive effect (and in the case of calcineurin inhibitors also sodium retaining effects) combined with endothelial damage leading to severe hypertension with and without TMA. MHT has been associated with IgA nephropathy and other kidney diseases including glomerulonephritis, although the distinction can be difficult in the acute phase because MHT-associated kidney failure is frequently accompanied by proteinuria and hematuria.

The odds of finding an underlying cause in MHT is higher compared with non-MHT hypertension, but prevalence rates of secondary hypertension vary between 10% and 40% in cohorts. Still, most patients present with a history of poorly controlled or untreated essential hypertension.[3,5] Nonadherence to usual oral therapy and abrupt withdrawal of medication (especially sympathicolytics) can result in severe hypertension. However, although many hypertensive patients are uncontrolled, progression to MHT is uncommon. The exact reason why some patients progress to an accelerated phase is incompletely understood. Among factors that directly increase BP, genetic variations in the renin-angiotensin and complement systems may contribute to the vascular injury and facilitate progression to MHT.[8,9]

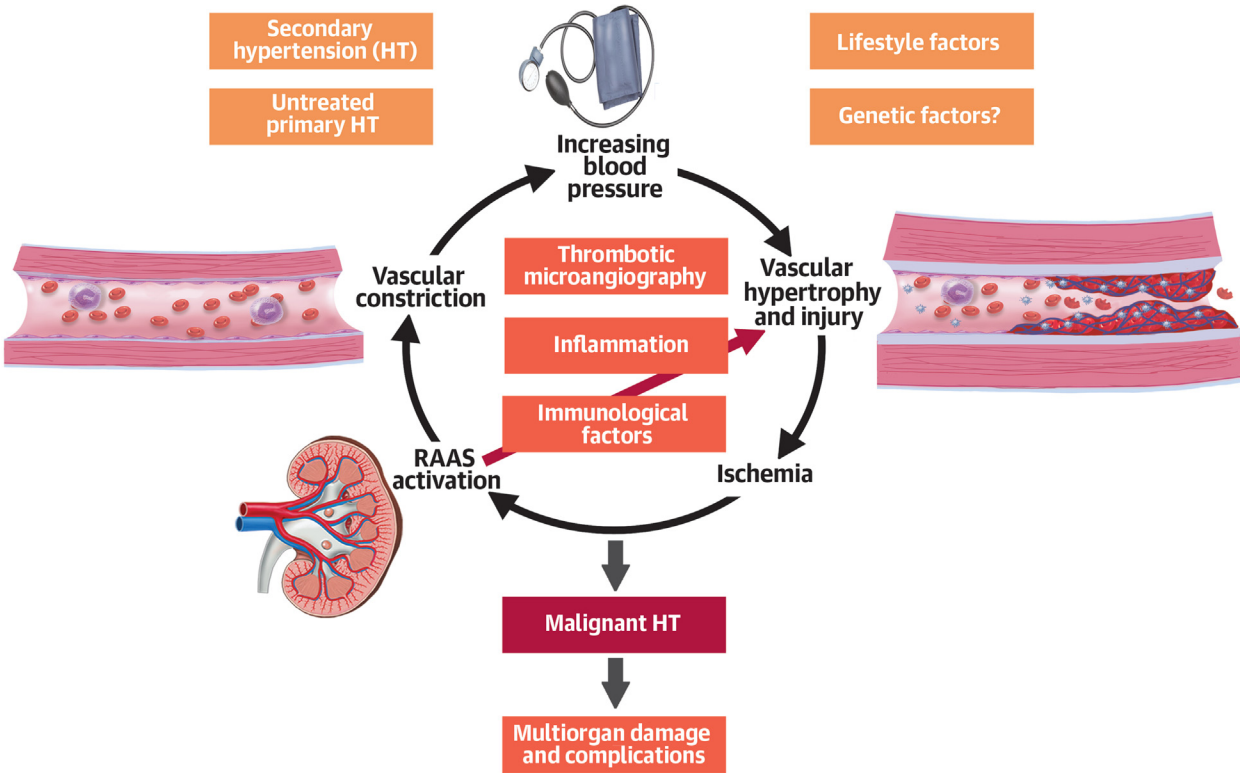
PATHOPHYSIOLOGY

Experimental evidence has shown that MHT most often is an angiotensin-mediated type of hypertension with marked activation of the renin-angiotensin system.[10] The degree of renin-angiotensin system activation is highly variable and linked to the severity of vascular injury and the presence of TMA.[11,12] Activation of the renin-angiotensin system has shown to be a secondary event triggered by ischemic nephropathy and hypertension-induced vascular injury (**Central Illustration**).[13,14] Hallmarks of MHT are the presence of myointimal proliferation of arterioles and fibrinoid necrosis caused by leakage of fibrin (and other serum proteins) through a necrotic vessel wall. In the kidney, myointimal thickening of afferent arterioles results in luminal narrowing and activation of the renin-angiotensin system, which further increases BP and aggravates vascular injury (**Figure 1**). Although renin-angiotensin system activation often is causal in MHT, angiotensin II-mediated aldosterone secretion and sympathetic activation further accelerate the BP increase. Experimental evidence has shown marked upregulation of adhesion molecules, followed by monocyte and macrophage infiltration. A key regulator in MHT induced vascular injury is nuclear factor-κB, a transcription factor that regulates the expression of adhesion molecules and proinflammatory cytokines, that is stimulated via mechanoreceptors and angiotensin II. This is further demonstrated by the finding that either BP-lowering treatment or direct inhibition of nuclear factor κB, a key regulator of adhesion molecules and proinflammatory cytokines, can attenuate the vascular changes and inflammation associated with MHT.[15,16] To what extent the influx of immune cells, including monocytes, lymphocytes, and their derived cytokines contribute to the progression of MHT, is unknown. Experimental studies have suggested a causal role for lymphocytes and monocytes in the development of hypertension, vascular remodeling, and endothelial function. In kidney biopsies of patients with MHT, there is a marked influx of monocytes and evidence of increased complement activation,[17] suggesting that anti-inflammatory therapies might mitigate MHT-induced kidney injury.

WORKUP OF PATIENTS WITH MHT

MHT is a hypertensive emergency requiring immediate BP lowering; however, its workup should not delay treatment in any way. History and physical examination should comprise a careful search for

CENTRAL ILLUSTRATION Pathophysiology of Malignant Hypertension



Boulestreau R, et al. J Am Coll Cardiol. 2024;83(17):1688–1701.

Sustained and prominent increases in BP, whether attributed to a singular factor or a combination of factors, can lead to vascular hypertrophy and endothelial injury. In the kidneys, this cascade can culminate in ischemia and RAAS-activation, initiating a vicious cycle marked by heightened vascular constriction, further elevation of BP, and ongoing endothelial injury. The activation of prothrombotic and proinflammatory pathways, as a result of endothelial injury, may give rise to thrombotic microangiopathy. This, in turn, contributes to the development of cardiovascular, cerebral, and renal complications that are characteristic of MHT. BP = blood pressure; MHT = malignant hypertension; RAAS = renin-angiotensin-aldosterone system.

target organ damage and features of various identifiable causes of hypertension.[2]

Fundoscopy is helpful in all patients with suspicion of MHT (Table 2).[18,19] However, patients with MHT may lack retinal lesions and present with target organ damage other than the eyes, including to the brain, heart, and kidney.[20,21] Fundoscopy may also serve to discriminate TMA associated with MHT from TMA associated with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.

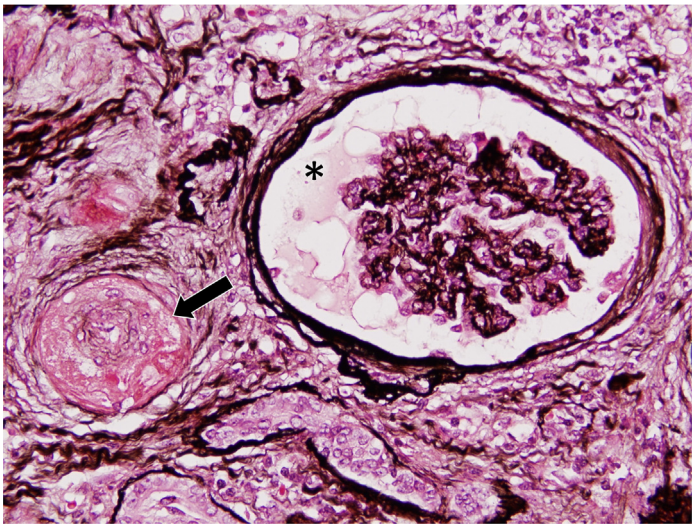
Acute kidney failure with oliguria may be the presenting manifestation. Creatinine is elevated in 60% to 70% of cases, suggesting progressive kidney dysfunction with excessive renin-angiotensin system activation.[22] Often it is impossible to discriminate kidney injury caused by MHT from kidney injury by other causes in the acute phase.

Despite kidney injury, hypokalemia is observed in approximately 50% of patients with MHT. It results from activation of the renin-angiotensin-aldosterone cascade induced by intrarenal ischemia. Hyponatremia is frequently present as a result of angiotensin II-medicated ADH stimulation and may be severe.

Laboratory analysis should include a full blood cell count and peripheral smear, lactic dehydrogenase, haptoglobin, and fibrinogen to rule out TMA.[23] TMA may comprise a number of acute syndromes with microangiopathic hemolytic uremia, thrombocytopenia, and organ injury, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.[24]

Hypertensive encephalopathy with or without PRES can be diagnosed by brain magnetic resonance imaging (MRI).[20,21,25] Transthoracic echocardiography

FIGURE 1 Kidney Biopsy (A 47-Year-Old Woman) With MHT, Kidney Insufficiency, and TMA



Microscopy shows myointimal hyperplasia with fibrinoid necrosis and near occlusion of an arteriole (arrow) and ischemic wrinkling of the glomerulus with widening of Bowman's space (asterisk). MHT = malignant hypertension; TMA = thrombotic microangiopathy.

has replaced the electrocardiogram as primary tool in the cardiac evaluation of MHT. Cardiac MR, N-terminal pro-B-type natriuretic peptide, and troponin may be helpful to assess the degree of cardiac dysfunction and/or damage. A workup for secondary hypertension should be deferred until the patient is clinically stable.

TABLE 2 Highlights for Clinicians: Which Diagnostic Workup Is Useful in Patients With Suspected MHT and What to Expect?

Fundus examination should be part of the initial assessment, as its results might suffice to establish diagnosis of MHT. To clarify target organ damage, additional evaluations of other organs should be considered.
TTE or 12-lead electrocardiogram to assess the degree of left ventricular hypertrophy. Troponin and BNP should be measured if there are abnormalities, to assess microvascular cardiac injury.
Creatinine levels, eGFR, electrolytes, urine albumin-to-creatinine ratio, and urine microscopy for red blood cells to identify acute kidney injury.
LDH, haptoglobin, schistocytes, hemoglobin, and platelet counts to detect TMA. In severe TMA, uremic and hemolytic syndromes or thrombotic thrombocytopenic purpura need to be ruled out.
Brain MRI preferably, or CT scan to assess cerebral injuries such as PRES, stroke, or cerebral hematoma, as well as cerebral microangiopathy.
Urine screening, if available, for substances like cocaine, methamphetamine, or for assessing therapeutic adherence.
Screening for secondary hypertension should be conducted after managing the acute crisis, if possible, without interrupting BP-lowering therapy.

BNP = B-type natriuretic peptide; CT = computed tomography; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PRES = posterior reversible encephalopathy syndrome; TMA = thrombotic microangiopathy; TTE = transthoracic echocardiogram; other abbreviations as in Table 1.

ORGAN DAMAGE

BRAIN. Hypertensive encephalopathy is one of the most life-threatening emergencies. With an accelerated pace of BP rise, it may occur without the classic retinal lesions that define MHT.[26] In patients with MHT and retinal abnormalities, encephalopathy is present in approximately 1 in every 10 patients. However, brain MRI alterations, including PRES, may be observed even without neurological symptoms, further attesting to the excessive risk of cerebrovascular outcomes in this population.[27] Key clinical symptoms include altered consciousness, including delirium and bradyphrenia, and loss of consciousness with or without preceding tonic-clonic seizures. The immediate threat of hypertensive encephalopathy is cerebral hemorrhage and intracranial herniation.

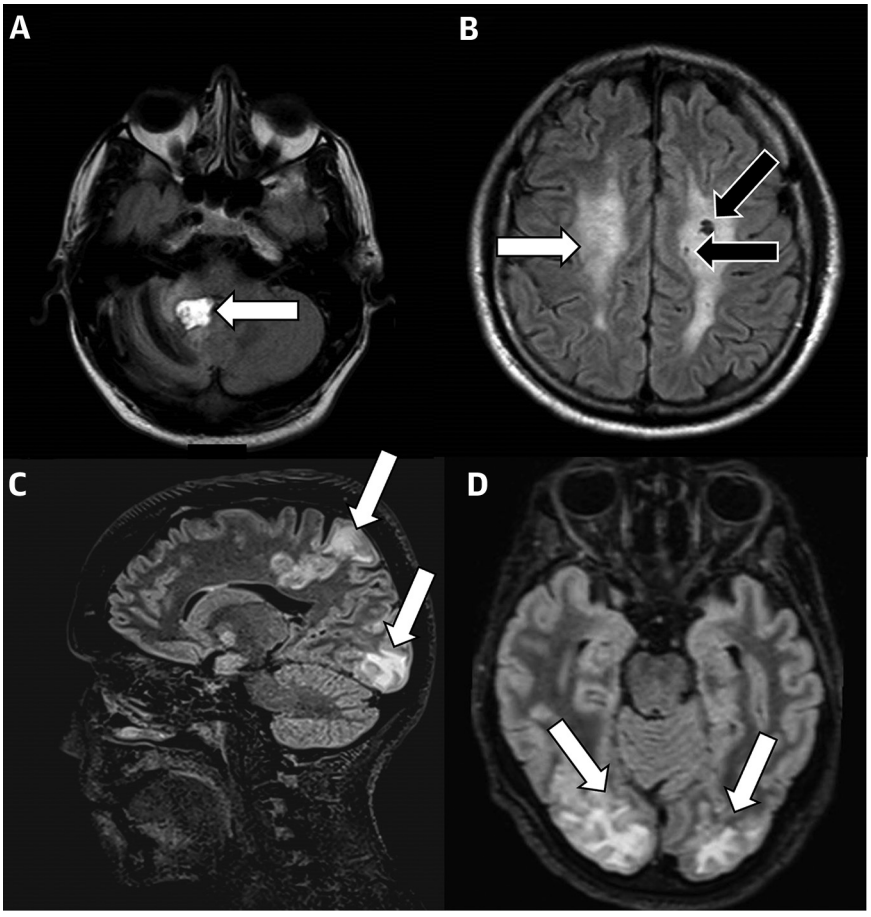
Hypertensive encephalopathy is one of the causes of PRES.[20,27,28] PRES is characterized by focal intracerebral edema resulting from systemic microcirculatory damage and autonomic failure. Its main clinical manifestations are headache, encephalopathy, seizures, or visual disturbances in various combinations. For diagnosis, MRI is superior to a CT scan because it may reveal vasogenic edema in the parieto-occipital regions of both cerebral hemispheres (Figure 2). The subcortical white matter regions are always involved. MRI has been suggested as a diagnostic tool for the systematic evaluation of all patients with MHT because it may impact patient management.[3] In the acute phase, an MRI may detect asymptomatic stroke, cerebral hematoma, or PRES. In the chronic phase, the detection of asymptomatic sequalae and/or severe cerebral microangiopathy may modify the therapeutic strategy.

When treatment is initiated promptly, PRES is generally radiographically and clinically reversible and has a favorable prognosis. Although Immink et al[29] showed that, during immediate BP lowering, cerebral blood flow may be better maintained with labetalol than with sodium nitroprusside, no studies have documented the superiority of specific antihypertensive agents.

EYE. Excessive BP elevation causes disruption of the blood-retina barrier and failure of autoregulatory mechanisms. The injury of arteries in the superficial or inner retinal layers manifests itself as flame-shaped and dot-blot hemorrhages. Any exudation of lipids can be seen as hard exudates and intraretinal edema. Cotton wool spots are signs of retinal nerve fiber layer ischemia (Figure 3).

Elevated intracranial pressure causes optic nerve ischemia and disc swelling. The clinical picture

FIGURE 2 **Brain MRI**



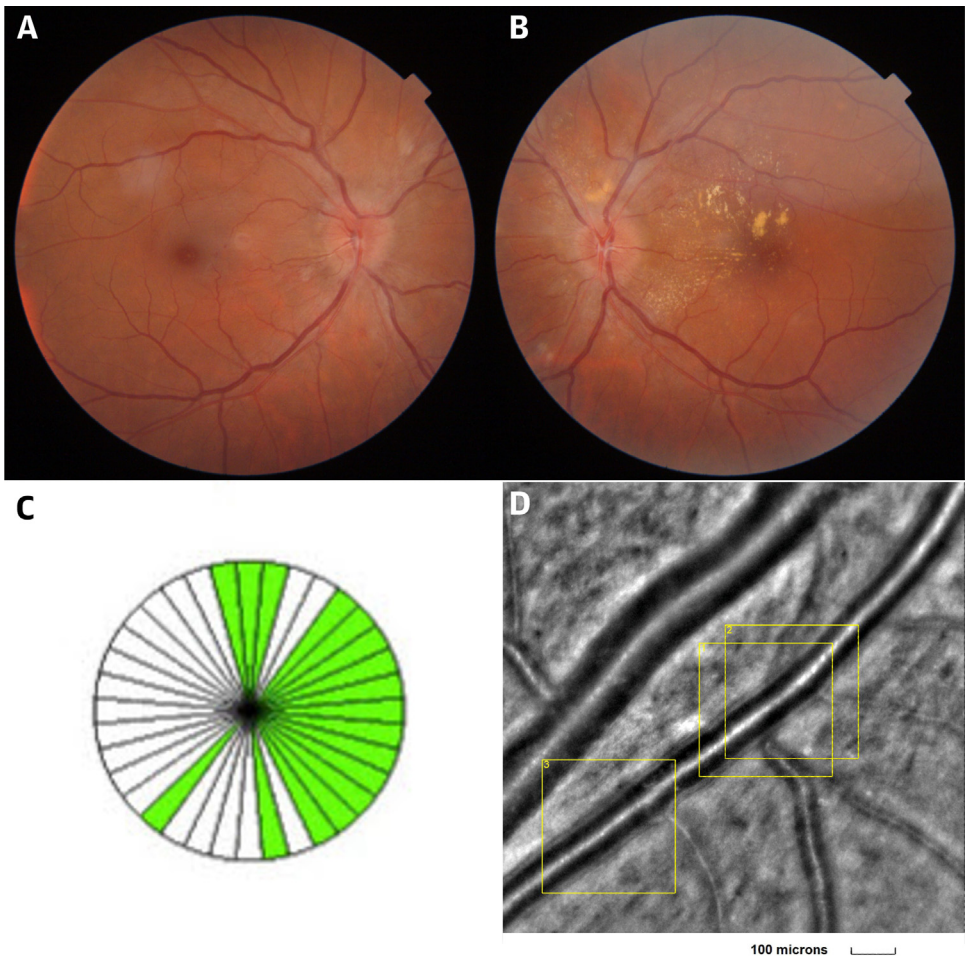
(A, B) A 32-year-old man admitted with MHT. (A) FLAIR sequence, axial view, brain hemorrhage (white arrow). (B) Flair sequence, axial view, severe leukoaraiosis (extensive white matter hyperintensities, white arrow), and sequels of past brain hemorrhage (black arrows). (C, D) A 52-year-old woman with MHT and typical posterior reversible encephalopathy syndrome (white arrows), identified by bilateral white matter edema in the parieto-occipital regions. FLAIR sequence, sagittal view (C), and axial view (D). FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; other abbreviations as in **Figure 1**.

includes papilledema, with flame-shaped hemorrhages at the disc margin, disc edema, congested retinal veins, and macular exudates with a macular star sign. Retinal hemorrhages are mostly located in the peripapillary area where radial capillaries are distributed.[30,31]

MHT can also cause choroidopathy owing to fibrinoid necrosis of the choroidal arterioles. Excessively elevated BP is directly transmitted to choriocapillaries because their autoregulation is not as effective as the one in retinal vessels. This leads to nonperfusion of the overlying choriocapillaries and focal ischemic damage to the retinal pigment epithelium, manifested as Elschnig spots. They represent necrosis of choroidal arterioles and capillaries secondary to acute increases in the BP. Retinal pigment epithelium pump failure owing to choroidopathy can result in subretinal fluid accumulation and, in severe cases, exudative retinal detachment. Resolution of Elschnig spots appear as pale-yellow atrophic areas with pigmented margins. Most often, the fundus findings in MHT are bilateral.[30]

Based on current progress, diagnostic procedures in MHT retinopathy may include not only fundus examination with color fundus photography, but also fluorescein angiography, optical coherence tomography or angiography, and adaptive optics.

FIGURE 3 A 36-Year-Old Male Patient With MHT

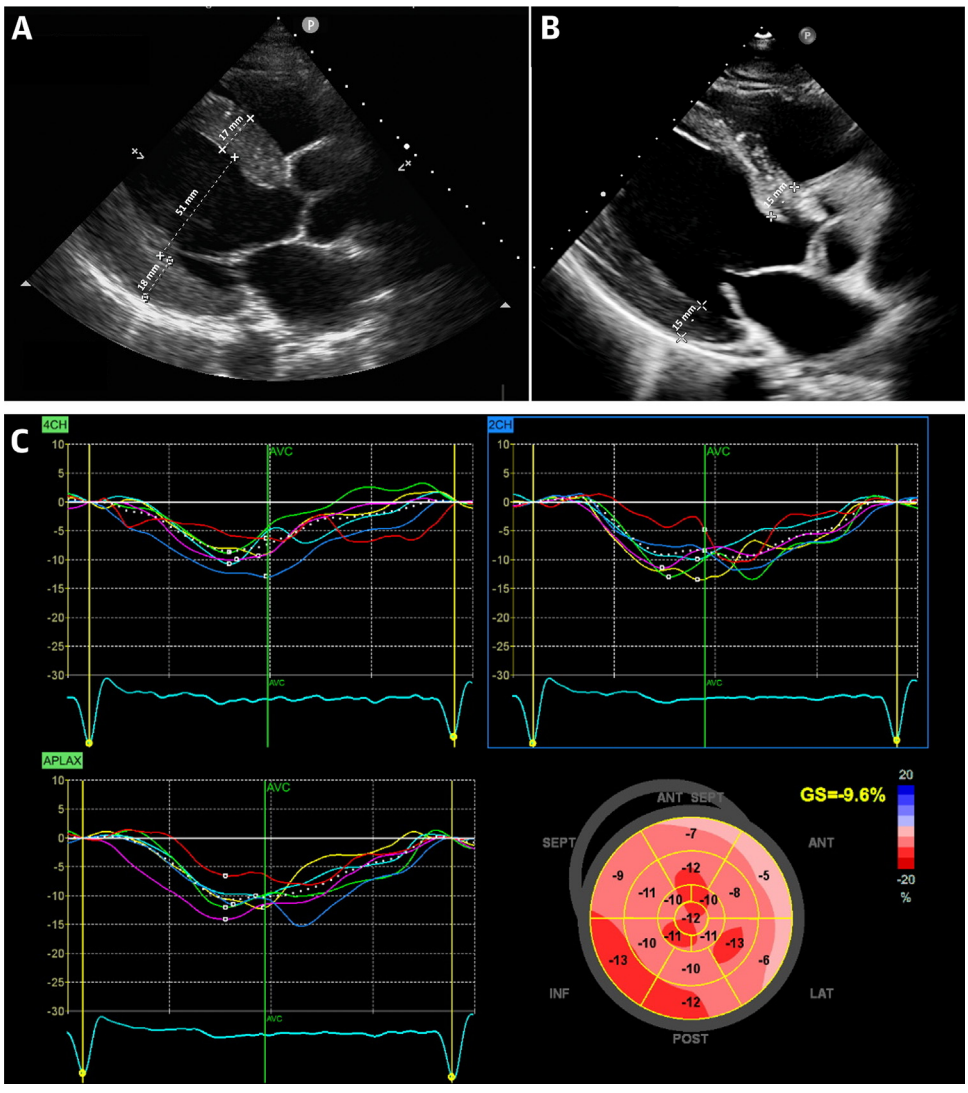


(A) Right eye color fundus photography—edema of the optic disc, blurred margins, dilated capillaries, and filled cup. (B) Left eye color fundus photography—edema of the optic disc, blurred margins, hard exudates in posterior pole and in the macula ("figure star"). (C) Right eye optical coherence tomography—thickening of retinal nerve fiber layer (RNFL, white areas) owing optic disc swelling. Green represents normal retinal nerve fibers. (D) Right eye adaptive optics rtx1—high abnormal values of wall-to-lumen ratio; the mean (taken from 3 measurements) wall-to-lumen ratio of the right eye is 0.37.

HEART. Increased left ventricular (LV) mass and progressively severe hypertrophy, as well as increased dimensions of the left ventricle, left atrium, and aortic root, as well as decreased LV ejection fraction, have been shown on transthoracic echocardiography in patients with MHT as compared with those with controlled nonmalignant essential hypertension (**Figure 4**). There is a paucity of studies exploring more modern imaging methods, namely, speckle tracking echocardiography or cardiac MR; few studies and single case reports have used global longitudinal strain assessment, demonstrating decreased function of LV longitudinal fibers in patients with MHT.[5,32,33]

Cardiac MR demonstrated symmetric LV hypertrophy, as well as myocardial fibrosis and edema, although there is inconsistency in the documentation of the latter.[34] Echocardiography demonstrated regression of LV hypertrophy and cardiac dimensions together with improvement of cardiac systolic function as early as 1 to 3 months after treatment (**Figure 5**).[32] However, despite long-term adequate BP control, some degree of LV hypertrophy and functional changes persist in patients with MHT.[32,35] In addition, in former patients with MHT with fairly well-controlled BP, cardiac and arterial elastance were comparable with those patients with high-risk hypertension.

FIGURE 4 Echocardiography

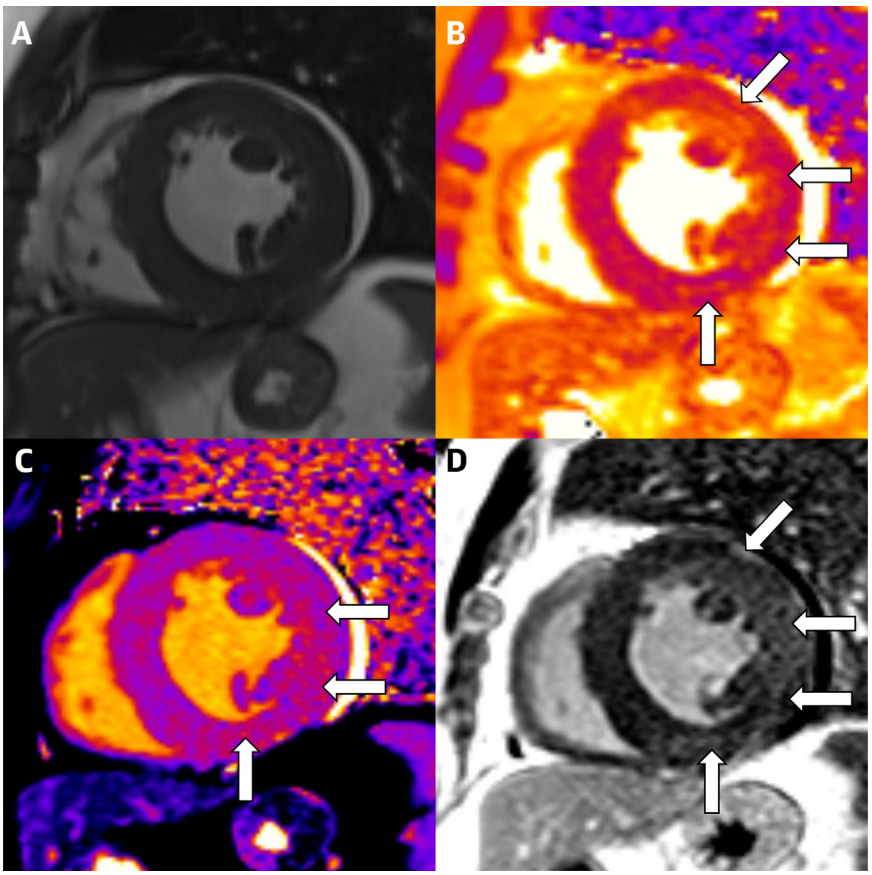


(A, B) A 21-year-old man with MHT. (A) Two-dimensional (2D) image showing concentric LVH (baseline). (B) A 2D image demonstrating partial regression of LVH after 7 months of treatment. (C) A 36-year-old male patient. Speckle tracking echocardiography demonstrating reduced global longitudinal strain of the left ventricle. (Courtesy of Dr Ewa Kowalik, National Institute of Cardiology). LVH = left ventricular hypertrophy.

Very few data are available on coronary macro- and microcirculation, despite its relevance in contributing to possible myocardial hypoperfusion during acute and chronic treatment.[36,37] Of note, in the Bordeaux cohort, 75.6% of patients exhibited at admission elevated B-type natriuretic peptide levels, whereas 55.6% of them showed a mild and temporary increase in troponin levels (median pic troponin 0.14 ng/mL [Q1-Q3: 0.1-0.34 ng/mL]; reference value, <0.04 ng/mL). Importantly, there was no evidence of epicardial coronary stenosis, indicating transient myocardial microvascular and/or functional ischemia during hypertensive crisis.

TMA. MHT is frequently associated with a (Coombs-negative) hemolysis, which is characterized by low platelets and increased lactic dehydrogenase and schistocytes in a peripheral blood smear (**Figure 6**). Experimental evidence has shown that the origin of TMA in MHT is endothelial injury and detachment caused by shear stress-induced and angiotensin II-mediated activation of proinflammatory and procoagulant pathways. In humans with MHT, circulating

FIGURE 5 Cardiac MR of a 36-Year-Old Male Patient

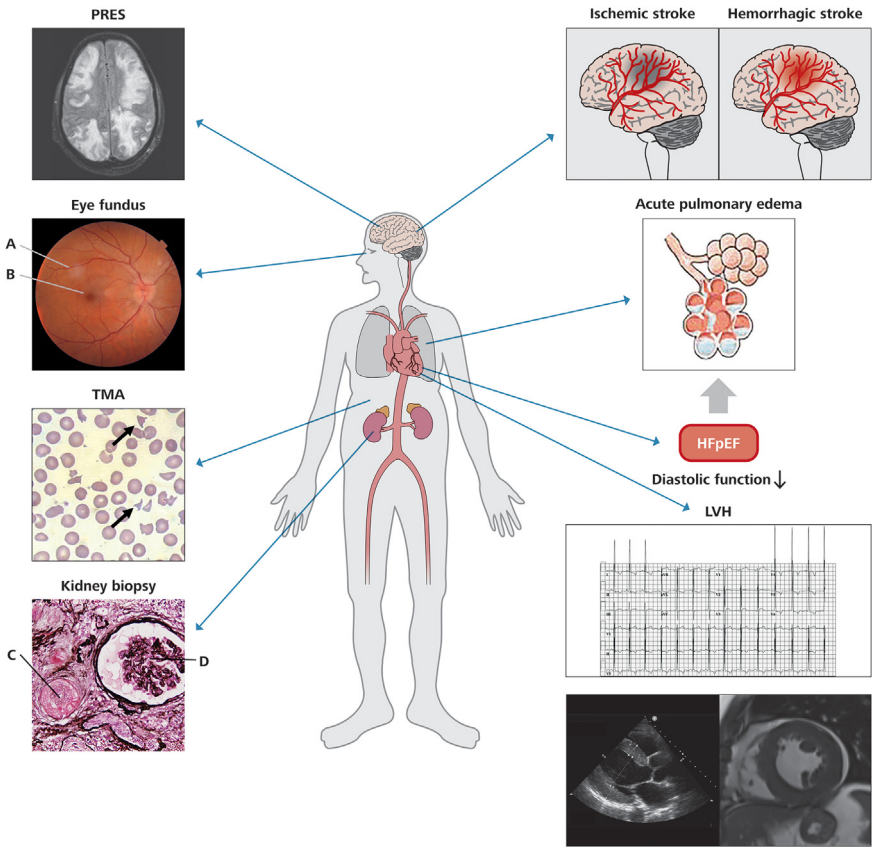


(A) Balanced steady-state free precession (cine) image demonstrating concentric LVH. (B) T2-mapping image. Edema of the lateral and inferior LV wall (arrows). (C) Native T1-mapping image demonstrating fibrosis of the lateral and inferior LV wall (arrows). (D) Late gadolinium enhancement image. Diffuse patchy foci of fibrosis are seen (arrows). LV = left ventricular; other abbreviations as in Figures 2 and 4.

levels of adhesion molecules and von Willebrand factor are markedly elevated. This finding is further demonstrated by the strong correlation between the severity of TMA and von Willebrand factor, a marker of endothelial injury, and (soluble) tissue factor that is present in the subendothelial space.[38] von Willebrand factor adheres to collagen in the subendothelial space, where it can propagate platelet adhesion and stimulate platelet activation. This process can lead to fibrin crosslink formation, where platelets and red blood cells can be trapped and destroyed. A decrease in the platelet count and intravascular hemolysis ensue with the appearance of schistocytes in the peripheral blood.

KIDNEYS. Between one-half and two-thirds of the patients presenting with MHT have decreased kidney function with proteinuria at presentation,[5,23,39] and some may present with acute kidney failure requiring emergency dialysis.[17] The typical structural changes associated with MHT-associated kidney injury include myointimal proliferation and onion skin appearance of small arteries and arterioles; fibrinoid necrosis is less common. The vessel wall abnormalities coincide with ischemic wrinkling of glomerular capillaries and atrophic tubuli (Figure 1). In a subset of patients presenting with MHT, improvement in kidney function can be observed with adequate BP control. These patients more often present with acute kidney injury and oliguria and have normal-sized kidneys and TMA at initial presentation. The reason why the presence of TMA in patients presenting with MHT and kidney insufficiency is a favorable indicator for future recovery of kidney function is unknown, even when initially dialysis was needed.[17,23] Given

FIGURE 6 Complications of MHT



Complications specific for MHT (left side) or commonly associated with MHT (right side). (From top left down) Hypertensive encephalopathy with PRES on MRI, retinal photograph showing cotton wool spots (A) and flame-shaped hemorrhages (B), TMA with arrows depicted fragmented red blood cells, a kidney biopsy in a patient with acute kidney injury with hematuria and proteinuria showing thrombotic occlusion of an afferent arteriole (C) and ischemic glomerular wrinklage (D). (From top right down) Neurological sequalae associated with MHT include ischemic and hemorrhagic stroke, acute pulmonary edema in a patient with heart failure with preserved ejection fraction, diastolic dysfunction, and LVH. HFpEF = heart failure with preserved ejection fraction; PRES = posterior reversible encephalopathy syndrome; other abbreviations as in Figures 2 to 4.

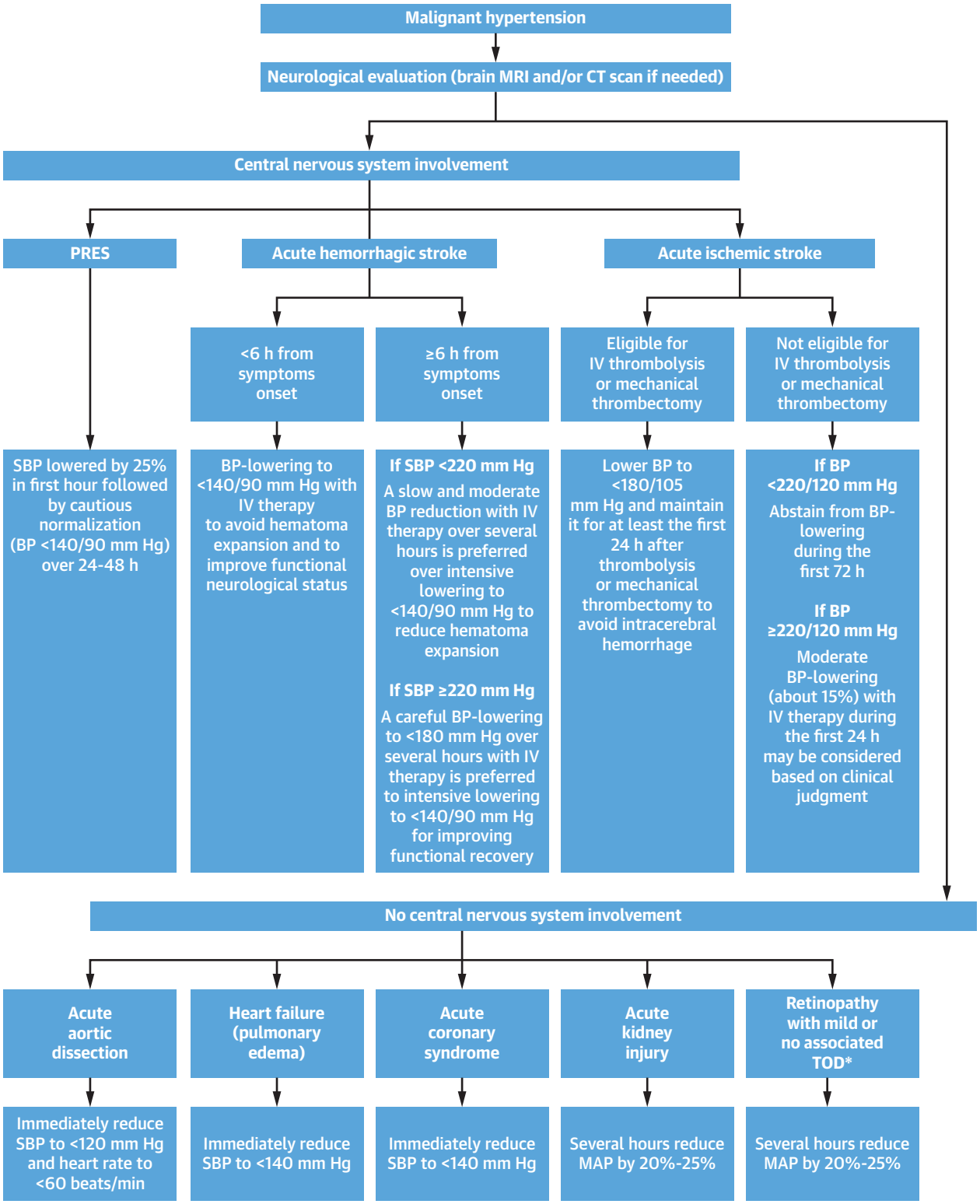
that recovery of kidney function usually occurs within several weeks, recovery from acute tubular necrosis is the most likely mechanism.

MANAGEMENT OF MHT

The management of MHT encompasses 2 distinct situations, depending on whether it is associated with vital target organ damage or not.[2] In MHT with a compelling condition, the specific treatment of this condition should take priority, and the presence of MHT should not alter the management. This strategy applies to situations such as ischemic and hemorrhagic stroke, hypertensive encephalopathy, aortic dissection, acute heart failure, acute coronary syndrome, and preeclampsia.[18] Under these circumstances, BP treatment should be rapid, but controlled with intravenous medication under strict hemodynamic monitoring, preferentially in a coronary care or intensive care unit. Because patients with MHT display an impaired cerebral autoregulation with the risk of cerebrovascular hypoperfusion, the therapeutic challenge consists in reducing BP without jeopardizing the cerebral circulation (Figure 7, Table 3).

Recent hypertension guidelines advocate the use of intravenous antihypertensive therapy with the objective of reducing mean BP by not >25% in the first hours to avoid cerebral hypoperfusion.[18] Depending

FIGURE 7 **BP Control in Patients With MHT and Various Clinical Scenarios**



*Mild TOD should be highlighted, which encompasses target organ damage associated with MHT that does not significantly affect short-term prognosis. Examples include severe LVH without evident heart failure, isolated severe cerebral microangiopathy, and/or nonsevere acute kidney injury (stage 1 or 2 according to Kidney Disease: Improving Global Outcomes guidelines). BP = blood pressure; CT = computed tomography; MAP = mean arterial pressure; SBP = systolic blood pressure; TOD = target organ damage; other abbreviations as in Figures 2 and 4.

TABLE 3 Highlights for Clinicians

Hypertensive emergencies associated with vital organ damage (such as stroke, aortic dissection, or heart failure) should be treated with intravenous therapy tailored to the specific condition, independent of the presence of the complications associated with MHT (retinopathy, TMA).
MHT with isolated ocular involvement, or noncritical associated kidney, brain, or heart damage (eg, extensive LVH) can be managed with either intravenous or oral therapy, depending on the center's experience and expertise.

LVH = left ventricular hypertrophy; other abbreviations as in Tables 1 and 2.

on availability, labetalol, nicardipine, nitroglycerine, enalaprilat, fenoldopam, hydralazine, and urapidil are the most commonly used intravenous antihypertensive drugs.[18] In the absence of data on morbidity and mortality outcomes, there is no evidence to prefer one of these drugs over another.[18] However, simple hemodynamic and pharmacological considerations indicate that hydralazine is not the drug of choice in a patient after myocardial infarction, whereas labetalol may not be prudent in the case of suspected underlying pheochromocytoma, because the alpha antagonistic activity is insufficient in relation to the beta-blocking effect.[2] This strategy may result in a paradoxical BP increase after labetalol administration because beta-adrenergic vasodilatation is blocked.[40] After 24 to 48 hours, oral antihypertensive medication can be slowly instituted, and intravenous medication can be tapered.

In 45% of cases, patients may present with severe hypertension and advanced retinopathy with no signs of acute target organ damage (without symptomatic heart failure, TMA and kidney injury-KDIGO [Kidney Disease Improving Global Outcomes] stage 3 or higher) (Boulestreau, personal communication, October 2023). For these patients, starting oral treatment with rapid titration without prior intravenous therapy may be considered.[19,41]

The arguments in favor of oral medication without intravenous therapy are that the risks of BP lability and worsening of target organ function associated with intravenous treatment do not justify immediate BP reduction.[42] Early use of blockers of the renin-angiotensin system may be indicated in MHT to decrease organ damage and deterioration of kidney function. Treatment should start with a low dose and be uptitrated every 6 hours as tolerated. Alternatively, treatment with a long-acting calcium channel blocker can be initiated. Patients need to be monitored during ≥2 days after uptitration to prevent precipitous BP drops. Short-acting drugs such as sublingual nifedipine are contraindicated because of their unpredictable effects.[43] So-called clonidine loading should be avoided because the adverse effects of clonidine such as lethargy, confusion, and somnolence can be misinterpreted as MHT encephalopathy. There are no specific data as to the optimal BP target with oral therapy in MHT. Initially, we advise to decrease the mean BP by not >25% within the first few hours and consider subsequent adjustments over the subsequent 24 to 48 hours.

When patients are admitted for intravenous treatment, intra-arterial monitoring is usually preferred because repetitive oscillatory BP measurements triggered by excessive BP values are uncomfortable to the patient and frequently generate error warnings.

Regardless of the mode of therapy, the consensus is to lower BP to acceptable but not normal levels during hospitalization. The risks of hypotension upon discharge should be discussed with the patient and instructions provided accordingly.

PROGNOSIS

Before 1970, the median survival time in patients with MHT was 39.2 months with kidney failure, stroke, heart failure, and myocardial infarction as the most common causes of death.[44] Since then, mortality has decreased with 5-year survival increasing to >90% in high-income countries.[45,46] Despite effective BP-lowering medications, patients with MHT remain at increased risk of cardiovascular and kidney complications. In the Bordeaux cohort, 18% had either end-stage kidney disease, a major cardiovascular event, or had died after 4 years.[5] In the Amsterdam cohort, 15% had died and 24% needed kidney replacement therapy after a median follow-up of 67 months.[46] These results are of particular concern because the average age was 40 to 50 years in both cohorts. The degree of kidney dysfunction at presentation and BP levels during follow-up remain the principal predictors of kidney failure,[46] emphasizing the importance of good BP control. In a subset of patients with MHT with oliguric kidney failure, normal-sized kidneys and evidence of TMA the impaired kidney function may recover after adequate BP control.[17,23] Mortality from MHT is especially high in socioeconomically disadvantaged communities, where screening for hypertension, availability of BP treatment, and adherence are suboptimal.[8,45,47] Given the efficacy of BP-lowering medications in both the prevention of MHT and its cardiovascular and kidney complications, better awareness, treatment, and control of hypertension in the population at large will not only decrease the burden of

cardiovascular disease, but also decrease the burden of MHT. Ensuring adherence to therapy is of vital importance to avert deterioration of end-organ function and prevent recurrence of MHT.

CURRENT PERSPECTIVES AND CHALLENGES

As an extreme phenotype of angiotensin-mediated hypertension, MHT is of interest both from the patient and research perspectives. To decrease the prevalence of MHT and improve prognosis, we need contemporary, credible, and interdisciplinary epidemiological data concerning its prevalence, incidence, population, and subgroups characteristics. Current treatment is based on consensus and pathophysiological reasoning. There is little if any outcome evidence in MHT, and it seems unlikely that there will be in the near future. We know that, with prompt BP-lowering treatment in a critical care unit, short-term survival has improved distinctly; clinical trials are ongoing to assess whether oral treatment is safe and efficacious for less severe cases. In addition, other therapeutic strategies to limit target organ damage, including possible anticoagulant, anti-inflammatory, or antifibrotic treatments remain to be explored. After the acute phase, many questions remain, including thresholds for BP-lowering treatment, transition to oral therapy, and subsequent monitoring.

CONCLUSIONS

Uncovering why some patients develop MHT while others do not, and why there is a cardiac, kidney, or cerebral form, could facilitate the identification of risk factors and diagnostic biomarkers. This understanding might pave the way for individualized therapeutic strategies based on acute crisis pathophysiology, thereby transcending simple BP treatment. The European HAMA registry, established in September 2019, has enrolled >450 patients already and is expected to help overcome these challenges by providing more precise insight in the epidemiology and pathophysiology of MHT and its complications.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Pickering GW. *High Blood Pressure*. 1st ed. J & A Churchill; 1955.

2. Elliott W. In: Bakris GLSM, Laffin LJ, eds. *Hypertension: A Companion to Braunwald's Heart Disease*. 4th ed. Elsevier; 2024:556-554.

3. van den Born BJ, Koopmans RP, Groeneveld JO, van Montfrans GA. Ethnic disparities in the incidence, presentation and complications of malignant hypertension. *J Hypertens*. 2006;24:2299-2304.

4. Halimi JM, de Fréminville JB, Gatault P, et al. Characteristics and prognosis of patients with hypertensive encephalopathy: a French nationwide cohort study. *Hypertension*. 2023;80:1716-1727.

5. Rubin S, Cremer A, Boulestreau R, Rigothier C, Kuntz S, Gosse P. Malignant hypertension: diagnosis, treatment and prognosis with experience from the Bordeaux cohort. *J Hypertens*. 2019;37:316-324.

6. Polgreen LA, Suneja M, Tang F, Carter BL, Polgreen PM. Increasing trend in admissions for malignant hypertension and hypertensive encephalopathy in the United States. *Hypertension*. 2015;65:1002-1007.

7. Mazzierli T, Allegretta F, Maffini E, Allinovi M. Drug-induced thrombotic microangiopathy: an updated review of causative drugs, pathophysiology, and management. *Front Pharmacol*. 2022;13:1088031.

8. van den Born BJ, van Montfrans GA, Uitterlinden AG, Zwinderman AH, Koopmans RP. The M235T polymorphism in the angiotensinogen gene is associated with the risk of malignant hypertension in white patients. *J Hypertens*. 2007;25:2227-2233.

9. Timmermans S, Abdul-Hamid MA, Potjewijd J, et al. C5b9 Formation on endothelial cells reflects complement defects among patients with renal thrombotic microangiopathy and severe hypertension. *J Am Soc Nephrol*. 2018;29:2234-2243.

10. Laragh JH, Ulick S, Januszewicz V, Deming QB, Kelly WG, Lieberman S. Aldosterone secretion and primary and malignant hypertension. *J Clin Invest*. 1960;39:1091-1106.

11. Hollenberg NK, Epstein M, Basch RI, Merrill JP, Hickler RB. Renin secretion in the patient with hypertension. Relationship to intrarenal blood flow distribution. *Circ Res*. 1969;24:113-122.

12. van den Born BJ, Koopmans RP, van Montfrans GA. The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. *Am J Hypertens*. 2007;20:900-906.

13. Möhring J, Petri M, Szokol M, Haack D, Möhring B. Effects of saline drinking on malignant course of renal hypertension in rats. *Am J Physiol*. 1976;230:849-857.

14. Lohmeier TE, Tillman LJ, Carroll RG, Brown AJ, Guyton AC. Malignant hypertensive crisis induced by chronic intrarenal norepinephrine infusion. *Hypertension*. 1984;6:I177-I182.

15. Mervaala EM, Müller DN, Park JK, et al. Monocyte infiltration and adhesion molecules in a rat model of high human renin hypertension. *Hypertension*. 1999;33:389-395.

16. Muller DN, Dechend R, Mervaala EM, et al. NF-kappaB inhibition ameliorates angiotensin II-induced inflammatory damage in rats. *Hypertension*. 2000;35:193-201.

17. Bureau C, Jamme M, Schurder J, et al. Nephrosclerosis in young patients with malignant

hypertension. *Nephrol Dial Transplant*. 2023;38:1848–1856.

18. van den Born BH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. *Eur Heart J Cardiovasc Pharmacother*. 2019;5:37–46.

19. Kulkarni S, Glover M, Kapil V, et al. Management of hypertensive crisis: British and Irish Hypertension Society Position document. *J Hum Hypertens*. 2023;37(10):863–879.

20. Cremer A, Amraoui F, Lip GY, et al. From malignant hypertension to hypertension-MOD: a modern definition for an old but still dangerous emergency. *J Hum Hypertens*. 2016;30:463–466.

21. Mishima E, Funayama Y, Suzuki T, et al. Concurrent analogous organ damage in the brain, eyes, and kidneys in malignant hypertension: reversible encephalopathy, serous retinal detachment, and proteinuria. *Hypertens Res*. 2021;44:88–97.

22. Shantsila A, Lane DA, Beevers DG, Lip GY. Lack of impact of pulse pressure on outcomes in patients with malignant phase hypertension: the West Birmingham Malignant Hypertension study. *J Hypertens*. 2012;30:974–979.

23. van den Born BJ, Honnebier UP, Koopmans RP, van Montfrans GA. Microangiopathic hemolysis and renal failure in malignant hypertension. *Hypertension*. 2005;45:246–251.

24. Shatzel JJ, Taylor JA. Syndromes of thrombotic microangiopathy. *Med Clin North Am*. 2017;101:395–415.

25. Healton EB, Brust JC, Feinfeld DA, Thomson GE. Hypertensive encephalopathy and the neurologic manifestations of malignant hypertension. *Neurology*. 1982;32:127–132.

26. Amraoui F, van Montfrans GA, van den Born BJ. Value of retinal examination in hypertensive encephalopathy. *J Hum Hypertens*. 2010;24:274–279.

27. Boulestreau R, Lucas L, Cremer A, et al. Neurologically asymptomatic patients frequently present cerebral injuries during malignant hypertension: a MRI study. *J Hypertens*. 2021;39:2463–2469.

28. Geocadin RG. Posterior reversible encephalopathy syndrome. *N Engl J Med*. 2023;388:2171–2178.

29. Immink RV, van den Born BJ, van Montfrans GA, Kim YS, Hollmann MW, van Lieshout JJ. Cerebral hemodynamics during treatment with sodium nitroprusside versus labetalol in malignant hypertension. *Hypertension*. 2008;52:236–240.

30. Mishra P, Dash N, Sahu SK, Kanaujia V, Sharma K. Malignant hypertension and the role of ophthalmologists: a review article. *Cureus*. 2022;14:e27140.

31. Ahn SJ, Woo SJ, Park KH. Retinal and choroidal changes with severe hypertension and their association with visual outcome. *Invest Ophthalmol Vis Sci*. 2014;55:7775–7785.

32. Gosse P, Coulon P, Papaioannou G, Litalien J, Lemetayer P. Impact of malignant arterial hypertension on the heart. *J Hypertens*. 2011;29:798–802.

33. Prejbisz A, Klisiewicz A, Januszewicz A, et al. 22-Year-old patient with malignant hypertension associated with primary aldosteronism. *J Hum Hypertens*. 2013;27:138–140.

34. Misumi I, Fukushima M, Wada K, et al. A case of malignant hypertension with multi-organ injury. *Radiol Case Rep*. 2022;17:455–461.

35. Shantsila A, Dwivedi G, Shantsila E, Butt M, Beevers DG, Lip GY. A comprehensive assessment of cardiac structure and function in patients with treated malignant phase hypertension: the West Birmingham Malignant Hypertension project. *Int J Cardiol*. 2013;167:67–72.

36. Bosisio FG, Mingardi D, Moretti E, et al. Case report: area of focus in a case of malignant hypertension. *Front Cardiovasc Med*. 2022;9:1108666.

37. Shantsila A, Dwivedi G, Shantsila E, Butt M, Beevers DG, Lip GY. Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension*. 2011;57:490–496.

38. van den Born BJ, Löwenberg EC, van der Hoeven NV, et al. Endothelial dysfunction, platelet activation, thrombogenesis and fibrinolysis in patients with hypertensive crisis. *J Hypertens*. 2011;29:922–927.

39. González R, Morales E, Segura J, Ruilope LM, Praga M. Long-term renal survival in malignant hypertension. *Nephrol Dial Transplant*. 2010;25:3266–3272.

40. Fang F, Ding L, He Q, Liu M. Preoperative management of pheochromocytoma and paraganglioma. *Front Endocrinol (Lausanne)*. 2020;11:586795.

41. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, et al. 2023 ESH guidelines for the management of arterial hypertension The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). *J Hypertens*. 2023;41:1874–2071.

42. Gosse P, Boulestreau R, Brockers C, Puel C, Rubin S, Cremer A. The pharmacological management of malignant hypertension. *J Hypertens*. 2020;38:2325–2330.

43. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA*. 1996;276:1328–1331.

44. Lane DA, Lip GY, Beevers DG. Improving survival of malignant hypertension patients over 40 years. *Am J Hypertens*. 2009;22:1199–1204.

45. Shantsila A, Shantsila E, Beevers DG, Lip GYH. Predictors of 5-year outcomes in malignant phase hypertension: the West Birmingham Malignant Hypertension Registry. *J Hypertens*. 2017;35:2310–2314.

46. Amraoui F, Bos S, Vogt L, van den Born BJ. Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study. *BMC Nephrol*. 2012;13:71.

47. Reis KG, Wilson R, Kalokola F, et al. Hypertensive urgency in Tanzanian adults: a 1-year prospective study. *Am J Hypertens*. 2020;33:1087–1091.

KEY WORDS hypertension, malignant, systemic