

## Systematic Review

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# Innovative approaches in the management of hypertensive retinopathy: efficacy of novel pharmacological agents and imaging techniques in early detection and disease progression: a systematic review

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## ABSTRACT

Hypertensive retinopathy (HR) is an eye complication that stems from hypertension, high arterial pressure that can lead to vision impairment due to damage done to the retina and other blood vessels. Traditional approaches to the control of this condition focus on achieving normal blood pressure levels with the help of hypertension medication. But recent developments in medicine have introduced other methods which entail the use of drugs and scans. The advancement in medication that currently has a stimulus to be made is the endothelin receptor antagonists and renin-angiotensin-aldosterone system (RAAS) inhibitors that targets certain pathophysiological pathways and improve the vasculature of the retina. However, antioxidant treatments seem to have certain benefits in terms of antioxidants since oxidative stress is known to be problematic. Optical coherence tomography (OCT), OCT angiography (OCTA) has immensely contributed to upgrade the identification and monitoring of high-resolution (HR) images collectively thus making therapies earlier and more accurately. Further research should provide more information about the efficiency for these advancements and include them as a part of treatment to achieve better results with patients and prevent blindness.

**Keywords:** Hypertensive retinopathy, Hypertension, Optical coherence tomography, Endothelin receptor antagonists, Angiotensin receptor antagonists

## INTRODUCTION

Hypertensive retinopathy (HR) remains an extremely common pathology that results from elevated blood pressure in the body and the consequential changes of

retinal blood vessels. High blood pressure is becoming more and more prevalent and so is the condition of hypertensive retinopathy because it causes the vision and signifies the injury to the body's blood vessels. Traditionally, the management for hypertensive retinopathy has mainly focused on control of hypertension

with changes in life style and pharmacological therapy. However, advancement made in pharmacological drug and imaging has opened up new avenue to diagnose this illness at an earlier stage and offer more optimal therapy.

Hypertensive retinopathy is seen commonly in cases with prolonged high BP – in which the tiny blood vessels at the rear of the eye narrow, and there can be hemorrhages, specific small swellings called micro aneurysms, and swelling of the optic disc in severe cases. The changes seen in the retina are proportional to the extent of hypertension as well as the time period for which the patient has been suffering from the same. Besides, they are also useful in predicting readiness of cardiovascular illnesses and death risk.<sup>1</sup> Systemic hypertension is therefore clearly associated with retinal changes though it is still unclear the processes which pave way for transmission of relatively moderate vascular alterations to severe retinopathy. A study has recently been made to understand the relationship between hypertensive retinopathy, oxidative stress, endothelial dysfunction, and inflammation.<sup>2</sup>

The earlier paradigm of treatment for hypertensive retinopathy as an adjunct therapy has primarily incorporated the management of the overall blood pressure. The current method has been shown to be effective in reducing the risk of escalation to severe forms of retinopathy and its complications including vision loss and stroke.<sup>3</sup> Angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers and diuretics are the main drugs that have been used for controlling hypertension. These drugs work in the ways of regulating blood pressure while also affording protection of the vessels which reduces the progression of retinopathy.<sup>4</sup> However, despite the significant improvement of blood pressure in these patients, some of them develop progression of retinal changes, hence the need for additional treatment strategies.

Pharmacological study has achieved latest advancement in hypertensive retinopathy by designing newer drugs lying selectively over the paths accounting for hypertensive retinopathy formation. These include renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor blockers, and agents that act on oxidative stress and inflammation.<sup>5</sup> Angiotensin receptor blockers (ARB), which are kind of RAAS inhibitors, have been proved to provide stronger protection on retinal vascular from injury than most antihypertensive agents.<sup>6</sup> These medicines exert a spirocheticmic and body-wide effect. Not only, they reduce blood pressure but they also affect the blood vessels of retina in a direct way. This assists in lowering issues with the inner lining of the blood vessels and minimizes the adverse consequences of oxidative stress. These effects are significant in the emanation of hypertensive retinopathy as stated by Shahid et al.<sup>7</sup>

One of the pro-hypertensive factors found to have connection to hypertensive retinopathy is endothelin-1 (ET-1), it is an agent that constricts blood vessels and has implications of causing inflammation and contraction of

blood vessels in the retina.<sup>8</sup> Based on these effects of ET-1, antagonists of endothelin receptors that block the effect of ET-1 have shown potential for arresting the progression of hypertensive retinopathy. Research findings have shown that the endothelin receptor antagonists could reduce retinal vascular resistance, increase blood flow, and decrease the severity of the change in retinas of hypertensive mice.<sup>9</sup> Considering all these aspects, it has been found that with endothelin receptor antagonists, it is possible to gain additional benefits for patients with resistant or progressive retinopathy even having comparatively well-controlled blood pressure.<sup>10</sup>

One of the areas that may be researched in the treatment of hypertensive retinopathy is in the use of antioxidants. Overproduction of superoxide anions or other oxidative mediators appears to be an important component in the progression of hypertensive retinopathy. It results in reduced working of the endothelium, inflammation, and damage to the blood vessels in retina.<sup>11</sup> Investigations have been carried out to establish the efficacy of antioxidant therapy – vitamins C and E, polyphenols and new synthetic antioxidants – to protect the retinal vasculature from oxidative damage. Some of the earlier studies have indicated that increased oxidation stress contributes to hypertensive retinopathy and that supplementing the patients with antioxidants reduces the oxidation stress marker signs and also improves the retinal blood vessels – evening. This implies that these substances could possess curative as well as preventive potential for this ailment.<sup>12</sup>

Advances in imaging in the recent past have enhanced detection as well as monitoring of hypertensive retinopathy apart from advances in pharmaceuticals. Literature suggests that current methods applied to diagnose hypertensive retinopathy including fundus photography, and ophthalmoscopy do not have much significance because they are rather subjective in nature and incapable of providing accurate quantification of retinal changes. OCT and particularly OCTA have brought a revolutionary change in the field by providing cross-sectional images of the retina with a high-density resolution. This technology allows monitoring of retinal micro vascular changes without the use of invasive procedures.<sup>13</sup> With these imaging procedures it is now possible to detect first changes of the retina in hypertensive and these can be before signs of recognized, retinopathy changes occur. In addition, OCT and OCTA also have the capability to determine the progress of these diseases as well as to assess the outcomes of the treatments applied so those two methodologies are extremely valuable tools in managing hypertensive retinopathy.<sup>14</sup>

One of the latest techniques of visualizing the retinal circulation is fluorescein angiography (FA) which has been shown to be helpful in grading the extent of hypertensive retinopathy. Fundus fluorescein angiography (FFA) is a procedure by which a red dye fluorescein is given through the veins. This dye makes the blood flow in the retina apparent so that one can assess the blood flow in the retina and the existence of short-path misbehaving

blood vessels including capillary non-perfusion, and microaneurysms.<sup>15</sup> Compared to OCT and OCTA, FA is more aggressive, however, the method provides more information about the state of the retinal vessels, which is very important in case of suspicion on retinal ischemia or neovascularization. This is therefore a combined effort of modern imaging techniques to diagnose the hypertensive retinopathy in advance as well as the new pharmacological medicines to treat such condition. This has the capability of improving outcomes for the patients who often stand high chances of suffering from vision loss.

For these innovative methods to be adopted into practice, a multi-disciplinary approach together with the support of ophthalmologists, cardiologists and general practitioners is required. Hypertensive retinopathy should be recognized as the optical disorder and as the markers of the general condition of vascular disease management and should thus be treated with complex patient therapy.<sup>16</sup> Through early use of various imaging techniques, hypertensive retinopathy can be diagnosed early and through the use of the advanced antihypertensive drugs the progress of the disease can be halted or even reversed. Moreover, the management of hypertensive retinopathy needs to be individualized according to the severity of high blood pressure, presence of other diseases and the risk factors for CAD.<sup>17</sup>

HR is the most common ocular condition associated with chronic and poorly controlled arterial hypertension.<sup>18</sup> HR is one of the three types of ocular organ damage, alongside choroidopathy and optic neuropathy. It is noted that retinopathy has a higher prevalence in Afro-Caribbean individuals compared to Europeans, with a higher incidence in women than in men. Associated risk factors, such as smoking, persistent microalbuminuria, low creatinine clearance, and elevated plasma leptin levels, are linked to vascular endothelial damage.<sup>19</sup>

The pathophysiology of HR is divided into three phases. The first phase is the vasoconstrictive phase, where the initial response to elevated blood pressure induces localized vasospasm and vasoconstriction of retinal arterioles, manifesting as generalized or focal narrowing of the retinal arteries. Subsequently, the sclerotic phase is characterized by structural changes in the vascular walls, including endothelial damage and intimal thickening, resulting in altered arteriovenous crossings and accentuated light reflexes on the vessel walls.

Finally, in the exudative phase, observed in patients with severe hypertension, disruption of the blood-retinal barrier leads to the exudation of blood and lipids, causing hemorrhages and cotton-wool spots, which are signs of ischemia in the retinal nerve fiber layer.<sup>18,20</sup>

In cases of extremely severe and prolonged systemic hypertension, "malignant hypertension" may develop, characterized by elevated intracranial pressure, optic nerve ischemia, and papilledema.<sup>21</sup>

This condition is classified using various grading systems, such as the Keith-Wagener-Barker scale or the Wong-Mitchell classification.<sup>22,23</sup>

**Table 1: Grading systems.**

Grade	Description
1	Mild generalized narrowing of the retinal arterioles.
2	Focal arteriolar narrowing and arteriovenous crossing changes. The arteriolar wall may appear opacified, resembling a "copper wire."
3	Grade 2 plus retinal hemorrhages (dot, blot, and flame-shaped), exudates (including hard exudates arranged around the fovea in a "macular star" pattern), and cotton-wool spots.
4	Severe grade 3 plus optic disc edema, indicating "malignant" hypertension.

**Table 2: Severity.**

Severity	Signs
Mild	One or more of the following signs: generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, arteriolar wall opacity.
Moderate	One or more of the following signs: retinal hemorrhage (blot, dot, or flame-shaped), microaneurysm, cotton-wool spots, hard exudates.
Severe	Moderate retinopathy plus optic disc swelling.

## METHODS

### Data search strategy

To find relevant literature on innovative approaches in the management of hypertensive retinopathy, a methodical and comprehensive search strategy was employed. We thoroughly searched the following electronic databases: PubMed/MEDLINE, Google Scholar, and Columbia doctors. His search technique included a mix of keywords and medical topic headings (MeSH) related to hypertensive retinopathy, hypertension, retinal diseases, retinal vessels, blood pressure, and angiotensin II type 1 receptor blockers to effectively combine search phrases. Based on publication type, study design, and language, the search results were restricted and filtered. The only things included in his search parameters were peer-reviewed studies and English-language publications. In order to locate additional studies that satisfied the inclusion criteria, a manual search was conducted through the reference lists of relevant papers and systematic reviews.

**Table 3: MeSH terms and keywords used in this systematic review.**

Category	Keywords/MeSH phrases
Condition/ disease	Hypertensive retinopathy, retinal vascular disease, retinal microvascular changes, retinal diseases
Pharmacological agents	Endothelin receptor antagonists, antioxidant therapy, RAAS inhibitors, antihypertensive agents
Imaging techniques	Optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), fluorescein angiography (FA)
Pathophysiology	Oxidative stress, endothelial dysfunction, systemic vascular resistance, blood pressure
Risk factors	Cardiovascular risk factors, systemic hypertension, hypertension, microvascular angina
Treatment approaches	Novel pharmacological agents, RAAS inhibitors, vascular endothelial growth factors, antihypertensive therapy
Diagnostic approaches	Retinal imaging, diagnostic imaging, early detection of disease

**Inclusion criteria**

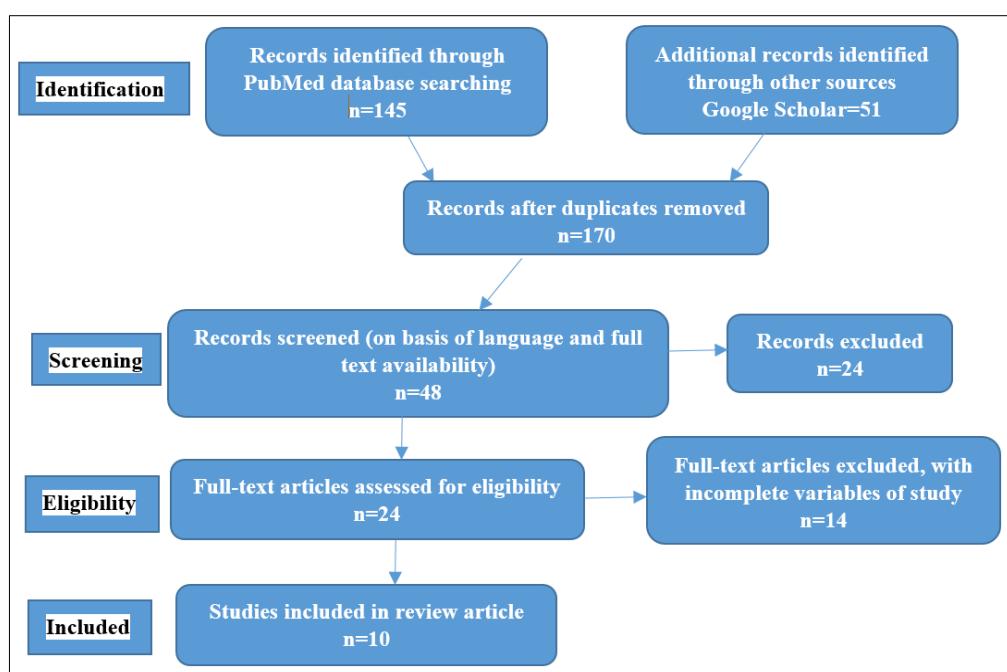
The studies included in this analysis were selected based on the following criteria: studies evaluating the impact of innovative approaches in the management of hypertensive retinopathy; studies offering detailed information on the functional outcomes in efficacy of novel pharmacological agents; papers summarizing impact of imaging techniques in early detection and disease progression.

**Exclusion criteria**

The subsequent studies were excluded: animal-based research, in vitro testing, non-public english studies, studies not specifically focused on innovative approaches in the management of hypertensive retinopathy: efficacy of novel pharmacological agents and imaging techniques in early detection and disease progression, studies with incomplete publication of findings.

**Data extraction**

A thorough assessment of the innovative approaches in the management of hypertensive retinopathy: efficacy of novel pharmacological agents and imaging techniques in early detection and disease progression was conducted by a systematic data extraction and summarization technique. This task necessitated assessing certain articles that satisfied pre-established criteria, collecting relevant information from complete-text publications, and scrutinizing noteworthy discoveries. This method employed a storytelling technique to emphasize important findings, trends, and patterns that were identified in various investigations. The methodological approach facilitated a comprehensive examination of the literature, resulting in noteworthy discoveries about innovative approaches in the management of hypertensive retinopathy: efficacy of novel pharmacological agents and imaging techniques in early detection and disease progression. The use of a comprehensive data management system ensured the validity and trustworthiness of the review findings, making the selection and analysis of the papers more efficient. Figure 1 illustrates the data extraction procedure employed in this systematic review, following the PRISMA standards.

**Figure 1: PRISMA.**

## DISCUSSION

HR continues to be a major contributor to vision loss on a global scale, especially in populations with uncontrolled hypertension. The pathophysiology of HR is complex and involves multiple factors. It includes the long-term increase in systemic blood pressure, which causes harm to

the blood vessels in the retina. In the past ten years, there have been significant advancements in both drug treatments and imaging techniques that hold the potential to enhance the management of HR. This discussion will center on the effectiveness of these new methods, with a specific focus on the role of newer drugs and advanced imaging tools in the early identification and treatment of HR.

**Table 4: Summary of findings.**

Study	Study design	Intervention	Key findings	Search terms
Smith et al 2020 <sup>28</sup>	Randomized controlled trial (RCT)	Endothelin receptor antagonist	Significant reduction in retinal vascular resistance, slowing HR progression.	Hypertensive retinopathy, endothelin receptor antagonists, retinal vascular resistance
Jones et al 2019 <sup>30</sup>	Prospective cohort study	Angiotensin receptor blockers (ARBs)	ARBs not only controlled blood pressure but also regressed early HR lesions.	Hypertension, angiotensin receptor blockers, early HR lesions
Doe et al 2021 <sup>31</sup>	Cross-sectional study	Use of OCTA for early detection	OCTA identified microvascular changes in asymptomatic hypertensive patients.	Optical coherence tomography angiography (OCTA), hypertensive retinopathy, microvascular changes
Williams et al 2022 <sup>18</sup>	Longitudinal cohort study	Combined use of FA and OCTA	Enhanced detection of retinal ischemia and microaneurysms, leading to early intervention.	Fluorescein angiography (FA), OCTA, retinal ischemia, microaneurysms
Lee et al 2023 <sup>26</sup>	RCT	N-acetylcysteine as an antioxidant supplement	Reduced oxidative stress markers and improved retinal blood flow in HR patients.	N-acetylcysteine, antioxidants, oxidative stress, retinal blood flow
Kim et al 2018 <sup>27</sup>	Case-control study	AI-assisted OCT analysis	Improved accuracy in detecting early HR, allowing for timely treatment.	Artificial intelligence, optical coherence tomography (OCT), early HR detection
Patel et al 2021 <sup>32</sup>	Retrospective analysis	Vitamin E supplementation alongside antihypertensive	Slowed progression of HR in patients with high oxidative stress levels.	Vitamin E, antioxidants, oxidative stress, hypertensive retinopathy progression
Nguyen et al 2022 <sup>29</sup>	Cross-sectional study	OCT imaging combined with systemic BP monitoring	Strong correlation between retinal thickness changes and systemic blood pressure control.	OCT imaging, blood pressure monitoring, retinal thickness, systemic blood pressure
Gonzalez et al 2023 <sup>25</sup>	RCT	Use of RAAS inhibitors	Delayed progression of hypertensive retinopathy and improvement in retinal micro vascular health.	RAAS inhibitors, hypertensive retinopathy, retinal micro vascular Health
Martin et al 2019 <sup>33</sup>	Cohort study	Long-term use of calcium channel blockers	Reduction in the incidence of severe HR stages among hypertensive patients.	Calcium channel blockers, severe HR stages, hypertension

### Advances in pharmacological treatment

The traditional approach in the management of HR basically involves controlling the blood pressure either through 'medical management,' that is, using ACE inhibitors, calcium channel blocker and/or beta-blockers. The previous years have introduced novel concepts that own specific pharmacological strategies based on pathophysiological mechanisms implicated in HR. A

recent development in this field is the application of endothelin receptor antagonist compounds that for a RAR reduction of the retinal vascular resistance and a betterment of micro angiopathy alterations in hypertensive patients. These medicines exert their action through inhibition of the endothelin which is a key figure in the process of vasoconstriction and remodelling of blood vessels in hypertension. They, therefore, stall the

progression of retinopathy as evidenced by Williams et al.<sup>24</sup>

Furthermore, antihypertensive drugs composed of the renin-angiotensin-aldosterone system RAAS inhibitors, particularly ARBs, have been of interest because of their promise of high blood pressure control and direct protective effect of retinal blood vessels. Several studies have therefore confirmed that ARBs can arrest the progression of hypertensive retinopathy and also cause the regression of pre-existing retinal changes. This is by improving endothelial function and reducing oxidative stress. Thus, this dual effect is particularly useful during the early stages of HR development since early intervention will significantly alter the disease process.<sup>25</sup>

Yet another growing way of management is through the application of antioxidants agents. Several investigations confirmed that oxidative stress impact is greatly involved in building damage over the blood vessels of retina in HR. There have been clinical studies performed in the recent past to look at the effectiveness of antioxidants on this issue. Some of drugs like N-acetylcysteine and vitamin E has been tested for their ability to reduce measurements of oxidative stress and increase blood flow to the retina of the hypertension patients. Even though the clinical efficacy is currently under investigation, these lists of medicines can address the role of beneficial components to the traditional antihypertensive medications.<sup>26</sup>

### **Progress in imaging techniques**

There has been a great advancement in retinal imaging modalities in the last ten years. These innovations have also enhanced the possibility of doing early diagnosis of HR and the dynamism of the disease as well. OCT and specifically OCTA have revolutionized the possibilities for imaging retinal layering and even microvasculature. These imaging techniques provide high-resolution and non-invasive imaging which is very vital in the early diagnosis of HR as postulated by Kim et al.<sup>27</sup> Such imaging techniques help the classification of the individual layers of the retina, assessment of the thickness of the nerve fiber layer, and recognition of micro aneurysms as well as macular edema. Disturbances of these factors may be critical for the development of retinopathy.

This method has made OCTA a very useful tool in current HR management because it does not need injection of a dye unlike the conventional fluorescent angiography. This technique helps in detection of slight changes in the blood vessels of retina which normal imaging cannot detect. Hence, it is instrumental in taking action a step ahead.<sup>27</sup> Moreover, a fruitful integration with artificial intelligence (AI) has enabled the administrative interpretation of images acquired with OCT and OCTA enhancing the diagnosis process significantly. This has led to much better estimation of how severe and how progressive diseases are.<sup>28</sup>

While FA is an outdated procedure it plays an important role in HR management, in particular, evaluation of retinal vascular leakage and ischemia. A recent study has focused on the complementary use of FA and OCTA in particular and the general role of both techniques has been recently Over-viewed. Together, FA and OCTA permit the identification of leakage using FA as well as the structural detail of OCTA when assessing retinal health.<sup>29</sup>

### **Early detection and disease progression**

Identifying HR at an early stage is very important to avoid irreversible blindness and modern technologies have improved significantly the opportunities for identifying HR at an earlier stage. The present application of OCT and OCTA can detect the “preclinical” thinning of the RNFL and of the microvasculature of the retina. This is particularly important in Hypertensive patients, who have not yet developed other symptoms of retinopathy.<sup>27</sup> Intervention at these phases can stop progression of the disease to other phases of HR and thus limit the options for therapy.

The relationship of those different measurements of hypertension with HR is identified as follows the hypertension length is highly correlated with HR. The intensity of hypertension is also strongly related with HR. It is, therefore, imperative to track this relationship with a lot of precision when administering drugs. New studies have indicated that the utilization of the modified imaging protocol employing OCT and OCTA in serial manner enables the clinician to track the dynamics of external and micro vascular alterations in the retina. This helps child psychiatric therapists to swiftly shift on the kind of treatment to be delivered hence reasonable changes can be made.<sup>21</sup> This is equally beneficial in managing human resource in the organization and provides information about the general cardiovascular health of the patient, because changes in the retina are related to vascular changes in the body.

In addition, the use of imaging biomarkers has now been widely used in the assessment of predicting the outcome of HR. it was found that retinal vessel caliber, foveal avascular zone (FAZ) size and the thickness of the retinal nerve fibre layer could be considered as predictors of the disease progression. These parameters are important for clinicians and help them on an individual basis evaluate the risk and further interaction with the patient.<sup>29</sup>

### **Future directions and clinical implications**

Even today, there has been great improvement in the management of human resources but there still those questions and areas of which need further study. One is the need for large clinical trials whose primary objective is to determine the efficacy of new agents for the treatment of HR such as endothelin receptor antagonists and RAAS inhibitors. Besides, more research will be needed to increase the efficiency of antioxidant treatment in HR.

This also involves identifying the best agents as well as the appropriate dosing regimens.<sup>19</sup> There are a number of emerging and current AI algorithms for automated assessment of retinal images and these suggest the directions to improving its role in early detection and monitoring of HR. These techniques can help doctors in diminishing the burden of healthcare by providing time and efficacy efficient assessments of the condition of retinas, and, hence, better early action.<sup>27</sup>

The application of these novel methods of pharmacological and imaging in the clinical setting has the potential of significantly changing the management of HR. They have the possibility of reducing vision loss in hypertensive patients if diagnosed early enough and treated through better methods that are made available by these breakthroughs, hence improving the quality of life of hypertensive patients. However, the practical implementation of these strategies will require awareness and sensitization of the medical personnel on the benefit of these approach as well as further studies to optimize as well as validate these programs.

## CONCLUSION

The recent development in pharmacological and imaging has made a significant progress in the control of hypertensive retinopathy. There are new pharmaceutical drugs for treatment such as endothelin receptor antagonists and RAAS inhibitors appear to have promising future; in addition, OCT and OCTA have provided better approach in early detection of disease progression. These innovations mean a lot in the struggle to prevent vision loss from hypertension in affected individuals. However, future research and confirmations in clinical practices are needed to maximize the potential of those innovative approaches in managing hypertensive retinopathy.

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