

News in Review

COMMENTARY AND PERSPECTIVE

HYPERTENSION

Medication Linked With Glaucoma

CALCIUM CHANNEL BLOCKER USE

is associated with glaucoma, according to researchers from the U.K.'s National Institute for Health and Care Research's Biomedical Research Centre, in London, and colleagues. The scientists found that people who used calcium channel blockers—commonly prescribed for hypertension—had, on average, 39% higher odds of glaucoma compared with people who did not take them.¹

Calcium channel blocker use was also associated with thinner macular retinal nerve fiber layer (mRNFL) and macular ganglion cell–inner plexiform layer (mGCIPL)—both objective, structural glaucoma-related parameters. There was no link found between calcium channel blocker use and IOP.

The cross-sectional study findings suggest that calcium channel blockers may represent a modifiable risk factor for glaucoma, the authors wrote.

Study details. For their investigation, the scientists analyzed data drawn from 427,480 patient records from the UK Biobank with an ICD code for open-angle or other form of glaucoma. Of these participants, 41,023 had macular spectral-domain OCT imaging and 97,100 had IOP findings. The median age of participants whose records were analyzed was 58, 54% were women, 94.8% were White, and 7.8% used calcium channel blockers. The researchers adjusted for various factors including

sociodemographic, lifestyle, medical, and other factors. They reported that dihydropyridines, the class of calcium channel blockers that includes amlodipine, were the most commonly used subtype (88.4%), followed by benzothiazepines (9.1%). Both medications were associated with higher odds of glaucoma, but not of elevated IOP.

The researchers' analysis of OCT-derived inner retinal layer thicknesses also supports the association between calcium channel blocker use and glaucoma. OCT data revealed that calcium channel blockers were linked to thinner mRNFL thickness ($-0.16\text{ }\mu\text{m}$) and thinner mGCIPL thickness ($-0.34\text{ }\mu\text{m}$) compared with nonusers. Dihydropyridine use in particular was associated with thinner mRNFL and mGCIPL. This finding runs counter to some previous research that suggests calcium channel blockers are neuroprotective, said lead study author Alan Kastner, MD, MSc, at the Clínica Oftalmología Pasteur, in Santiago, Chile.

No associations were found with other classes of antihypertensive agents and glaucoma, including diuretics, renin-angiotensin system inhibitors, and systemic beta-blockers. Dr. Kastner said additional analysis of IOP data from close to 100,000 participants revealed no link between calcium channel blocker use and IOP, suggesting that other IOP-independent mechanisms of glaucomatous neurodegeneration may be



PILL CHECK. Hypertension drugs are associated with glaucoma, according to a new study.

involved. “These mechanisms may be related to the effects of calcium channel blockers on the vasculature of the optic nerve head,” he said.

Reflections on the research. In an accompanying editorial, Paula Anne Newman-Casey, MD, MS, and Rithambara Ramachandran, MD, at the University of Michigan, Ann Arbor, noted the debate over the use of calcium channel blockers as a potential treatment for normal-tension glaucoma. They also pointed to contradictory evidence over calcium channel blockers' impact on IOP and open-angle glaucoma. They wrote that analyses of data from publicly funded and publicly available datasets, like the UK Biobank, can provide critical new information as aging global and U.S. demographics lead to rising glaucoma cases—helping ophthalmologists better understand the unintended consequences to eye health of prescription medicines taken by people with multiple chronic conditions.²

Are Rx changes needed? The adverse association of calcium chan-

nel blockers with glaucoma should not affect care for most patients, Dr. Kastner said. “However, for patients whose glaucoma is worsening despite a very low IOP, we need to think about other factors playing a role. If those patients are on calcium channel blockers, ophthalmologists should discuss the evidence of our study with them and with their general physician and consider changing their antihypertensives.”

—Miriam Karmel

1 Kastner A et al. *JAMA Ophthalmol.* 2023;141(10):956-964.

2 Newman-Casey PA, Ramachandran R. *JAMA Ophthalmol.* 2023;141(10):964-965.

Relevant financial disclosures—Dr. Kastner: None.

DIABETES

Cholesterol Crystals May Play Role in DR

RESEARCHERS SAY THEY’VE DEEP-ened their understanding about the relationship between cholesterol crystal formation in the retina and diabetic retinopathy.

“This study transforms our understanding of what drives diabetic retinopathy,” said study coauthor Maria B. Grant, MD, FARVO, at the University of Alabama at Birmingham. Dr. Grant said the findings suggest that “repurposing existing cholesterol-lowering drugs to remove cholesterol crystals” in the retina may hold promise as a possible avenue to stopping disease progression.¹

Background. Studies suggest an association between diabetes and cholesterol accumulation in the retina in the form of crystals—similar to the cholesterol crystals found in atherosclerotic plaques that can form in arteries and cause heart attacks. These “hyper-reflective crystalline deposits found in retinal lesions have been suggested to predict the progression of diabetic retinopathy” in other studies, the authors wrote. So, they set out to take a closer look at the crystalline deposits, hoping their findings might help explain the mechanisms underlying retinal damage in diabetes, which to date have been unclear.

Electron microscopy. One challenge

to studying cholesterol crystals is that “traditional techniques for fixing and staining tissues for microscopy involve reagents that dissolve lipids, such as cholesterol,” said lead investigator Julia V. Busik, PhD, at Michigan State University in East Lansing. This masks the potential involvement of cholesterol crystals in pathogenic mechanisms. “We used a novel methodology that does not use ethanol or organic solvents and, thus, preserves lipids in the tissues,” Dr. Busik said.

Using scanning electron microscopy, the researchers identified cholesterol crystals in donor human tissue—the same type of deposits seen on retinal images of patients with diabetes, the authors wrote. They also detected cholesterol crystals in diabetic retina from pig and mouse models.

In vitro tests. The researchers then conducted in vitro experiments to explore how cholesterol crystals affected the blood-retinal barrier breakdown in retinal endothelial and retinal pigment epithelial cells, and to see whether certain treatments affected cholesterol crystal-induced cell damage. Treatment of retinal endothelial cells with cholesterol crystals caused diabetic retina-like damage, including inflammation, cell death, and blood-retina barrier breakdown. “The fact that cholesterol crystals damage the blood-retina barrier and induce vessel leakage at an even higher degree than vascular endothelial growth factor (VEGF), a well-known barrier-disrupting agent, was a surprise,” said Dr. Busik.

Next, after treating the damaged cells with the cholesterol-lowering drug fenofibrate, the researchers noted that it significantly prevented cholesterol crystal-induced upregulation of inflammation. Additionally, treatment with the cholesterol-binding agent α -cyclodextrin dissolved cholesterol crystals, reduced retinal inflammation, and prevented diabetic retinopathy in diabetic mice. However, fenofibrate was more effective at dissolving cholesterol crystals, and it prevented breakdown of retinal cell membrane integrity and restored vascular barrier function, the researchers wrote. “The ability of α -cyclodextrin to mitigate retinal dam-

age is proof-of-concept that clearing cholesterol crystals may stop disease progression,” said Dr. Grant. “This opens entirely new therapeutic angles for diabetic retinopathy.”

Looking ahead. Dr. Busik said that although cholesterol accumulation in the retina could lead to cholesterol crystal formation, more research is needed to understand the mechanisms underlying cholesterol crystal formation in the diabetic retina and to confirm the benefits of treatments targeting these crystals. “Cholesterol crystals may be the missing link that could unlock more effective management of this blinding complication,” she said. “We are currently looking for treatments to dissolve cholesterol crystals in the retina and examining if these can help stop disease progression and vision loss.”

—Christos Evangelou, PhD

1 Hammer SS et al. *Diabetologia.* 2023;66(9):1705-1718.

Relevant financial disclosures: Dr. Grant—None. Dr. Busik—None.

GLAUCOMA

Risks Identified for Flat Anterior Chamber After BGI

A POSTOPERATIVE FLAT ANTERIOR chamber following Baerveldt Glaucoma Implant (BGI) surgery can result in serious complications, with the potential to permanently damage ocular structures.

“Understanding the risk factors associated with the development of complications will help glaucoma surgeons in selecting the best surgical intervention for their patients,” said Huda Sheheitli, MD, at the University of Minnesota, Minneapolis, and lead author of a study that identified three key risk factors for flat anterior chamber after BGI surgery.¹

Methodology. Dr. Sheheitli and colleagues reviewed data on 42 eyes that underwent BGI surgery and went on to develop flat anterior chamber requiring surgical intervention within a 90-day period after the procedure. Cases were treated at Anne Bates Leach Eye

Hospital in Miami between 2011 and 2019. For their study, the researchers matched each case with two controls. The variables assessed in the study included the individual's sex, diagnosis, the presence of diabetes and hypertension, the administration of pre- and postoperative glaucoma medications, other ocular conditions, and IOP.

Results. Patients who developed a flat anterior chamber were more likely to be female (69.1% versus 41.7% controls), to have a history of taking oral carbonic anhydrase inhibitors (CAIs) at tube opening (21.4% versus 7.1%), and to have pseudoexfoliation syndrome (23.8% versus 6.0%). Patients participating in the study were less likely to be using cholinergic agonists (0.0% versus 11.9%) at baseline and were less likely to have primary open-angle glaucoma (42.9% versus 64.3%). They were also older (mean age 75.9 versus 64.9 years) and had an earlier tube opening time (5.6 versus 6.2 weeks) and lower IOP after tube opening (7.2 mm Hg versus 14.4 mm Hg). However, their IOP before opening was higher (24.7 versus 19.5 mm Hg), the authors reported.

Takeaways. The researchers reported that those patients most likely to require additional intervention in the 90-day period after BGI surgery were older, prescribed CAIs at tube opening, and more likely to have higher IOP prior to tube opening.

Dr. Sheheitli said the findings paint a more complete picture of the risks for flat anterior chamber after BGI surgery. "Our study highlights the risk factors that could contribute to the development of this complication," she said.

She recommended that surgeons consider alternatives to BGI "in patients with significantly elevated preoperative IOP requiring the use of oral CAI." She also said the findings lead to the recommendation that surgeons consider the use of flow-restricting glaucoma implants in older patients. She also suggested glaucoma specialists consider holding off on the use of oral CAI medications one to two weeks before opening the tube (the tube is typically tied off at the time of surgery and then

opened up six weeks after surgery).

The study can be a guidepost for colleagues, said Dr. Sheheitli, stressing that trabectomy and glaucoma drainage implants are among the most commonly performed surgical procedures worldwide for glaucoma and "remain the standard of care for glaucomatous neuropathy resistant to medical therapy."

That said, while these procedures lower IOP, all surgical options should be weighed for patients with risk factors for complications. —*Brian Mastroianni*

1 Sheheitli H et al. *Am J Ophthalmol.* 2023;256:39-45.

Relevant financial disclosures: Dr. Sheheitli—None.

RETINA

Macular Thickness Maps for Monitoring Wet AMD

TO PRESERVE VISION IN PATIENTS

receiving anti-VEGF therapy for exudative age-related macular degeneration (eAMD), clinicians rely on in-office OCT scans to detect new onset or recurrent exudation over time. Because interruptions in monitoring can have devastating effects on vision in eAMD patients, Bascom Palmer Eye Institute researchers wanted to explore the effectiveness of and potential for remote monitoring using macular thickness maps (MTMs)—a technique shown in previous research to effectively determine the presence of macular fluid in eyes with eAMD. They report that MTMs are an effective way to monitor disease progression remotely and may help identify patients who need treatment in clinic while minimizing unnecessary visits for stable patients.¹

"Our findings suggest that MTMs provide sufficient information to accurately identify new or recurrent fluid in patients with eAMD," said lead study author Omer Trivizki, MD, MBA, at Tel Aviv Medical Center, and a senior researcher at Bascom Palmer Eye Center. "By enabling timely detection and treatment, remote monitoring with



OCT. Macular thickness maps may help monitor eAMD.

MTMs could preserve vision for AMD patients," he said.

Approach. The researchers performed a retrospective analysis using data from 53 eyes—including a total of 45 patients being treated in at least one eye for eAMD with anti-VEGF therapy. They compared different imaging strategies, including MTMs alone, selective OCT B-scans alone, and the entire OCT data set. "Although the cohort size was relatively small, our analysis included data from over 1,380 imaging sessions acquired over 12 years, which allowed us to confidently draw conclusions," said Dr. Trivizki.

MTMs. While performing full OCT scans to identify fluid changes can be complex and time consuming, MTMs are generated using a macular thickness algorithm available on the OCT scanner. The macular thickness analysis is calculated using the distance between the inner limiting membrane and the retinal pigment epithelium.

Results. Five retinal specialists evaluated the imaging results. The majority consensus based on full OCT data was used as "the ground truth." On average, the evaluations by the graders of the MTM images agreed with their full OCT assessments in 90% of cases across graders. This was higher than the agreement rate for central B-scans (88%). The results suggest MTMs simplify monitoring and may allow for remote patient self-assessment to identify early fluid changes needing treatment, but more research is required.

—*Christos Evangelou, PhD*

1 Trivizki O et al. *Am J Ophthalmol.* 2023;256:1-8.
Relevant financial disclosures: Dr. Trivizki—None.

See the financial disclosure key, page 9. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.