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Fibrates and Drug-Induced Liver Injury

By: Sarah Plummer, Pharm D.

The FDA recently released safety-related labeling changes to include warnings of drug-induced liver injury (DILI) associated with fenofibrate. Fibrates are indicated for the treatment of severe hypertriglyceridemia (HTG), primary hypercholesterolemia, or mixed dyslipidemia. Along with fibrates, there are several pharmacologic agents proven to reduce hypertriglyceridemia (HTG) including statins, omega-3 fatty acids, and to a lesser extent niacin. Fibrates may be considered in situations where attempts to reduce HTG with diet and lifestyle modifications fail to lower triglycerides adequately and when statins and omega-3 fatty acids produce inadequate triglyceride lowering or intolerance is reported. Statins, omega-3 fatty acids, and fibrates, including fenofibrate, are options for treating severe, persistent HTG. However, clear evidence is lacking to support reducing the risk for pancreatitis in patients with severe HTG (e.g., HTG >500 mg/d) using any of the available agents.

Existing evidence does not support adding fenofibrate to a statin for the primary or secondary prevention of ASCVD. In prespecified subgroup analyses from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, possible benefit from fenofibrate versus placebo was observed in patients on statins with both a high baseline TG level (>200mg/dl) and low high density lipoprotein cholesterol (HDL-C) level (<40m/dL) as well as possible harm in women.[1]

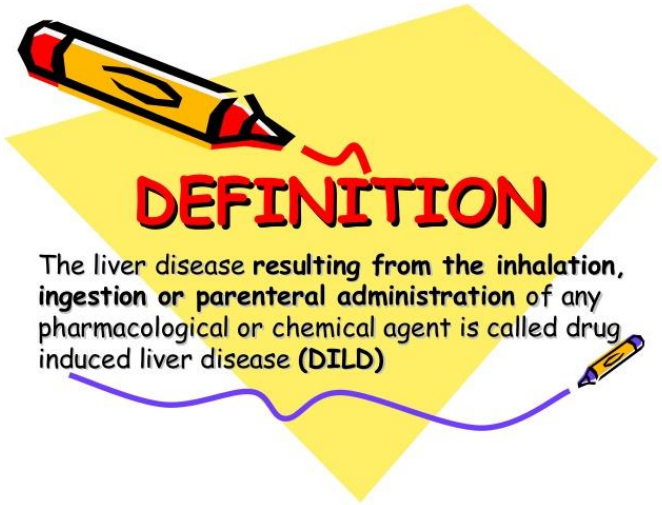
According to revised product labeling[2], providers should:

- Avoid fenofibrate use in patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities (contraindication).
- Monitor patient's liver function, including serum ALT, AST, and total bilirubin, at baseline and periodically for the duration of therapy fenofibrate.
- Discontinue fenofibrate therapy if signs or symptoms of liver injury develop or if elevated enzyme levels persist (ALT or AST > 3 times the upper limit of normal, or if accompanied by elevation of bilirubin).
- Do not restart fenofibrate treatment in these patients if there is no alternative explanation for the liver injury.

Adverse events should be reported, as appropriate, to the FDA MedWatch program.

References:

1. The ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med 2010; 362:1563-1574.
2. FDA Drug Safety-Related Labeling Changes (SrLC). Tricor (fenobirate) 6/17/2021. Available at: Drug Safety-related Labeling Changes (SrLC) (fda.gov). Accessed 6/17/2021.



Definition: Resistant Hypertension

The standard definition of resistant hypertension is a blood pressure >140/ 90 mmHg despite treatment with three antihypertensive drugs of different classes, including an appropriate diuretic.

Managing Resistant Hypertension

By: Craig Kimble, PharmD, MBA, MS, BCACP, TTS

This newsletter article will focus on strategies for patients known as "treatment resistant", patients with resistant hypertension, or frankly the "hard to manage" hypertension patients. There are currently two good consensus documents that focus on the treatment of resistant hypertension. The first is the 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[1] The second is the AHA Scientific Statement from the American Heart Association: Resistant Hypertension: Detection, Evaluation, and Management. The scientific statement was released in 2018.[2]

There has been change over the years on the standard for treating hypertension with changes occurring with how hypertension is defined and the stages of hypertension. The diagnosis and treatment for hypertension was lowered with the last set of guidelines to SBP of ≥130 or a DBP of ≥80 (Stage I hypertension) in 2017 guideline.[1] Table 1 outlines the current categories under these guidelines.

Table 1: Blood Pressure Categories in Adult Patients*

Category of BP	SBP		DBP
Normal	<120 mmHg	and	<80 mmHg
Elevated	120-129 mmHg	and	<80 mmHg
Stage 1 HTN	130-139 mmHg	or	80-89 mmHg
Stage 2 HTN	≥140 mmHg	or	≥90 mmHG

**If patient is elevated in 2 categories (SBP and DBP), use the highest category for diagnosis.*

In these guidelines, the goal was set to achieve a goal blood pressure of < 130/80 for most patients (previously it was 140/90). This recommendation is really age independent but applies to the majority of healthy elderly patients ≥65 years old. Co-morbidities and ASCVD risk can affect this goal. This is important in the context of achieving a goal in a difficult to manage patient. When the guidelines were first released, some clinicians and organizations were not comfortable with the lower blood pressure goal initially at least. Now, more seem comfortable with the goal but a result of these changes was a larger population that fits into the category of "uncontrolled hypertension," as a result of these lower blood pressure goals. Patients that fall into stage 2 hypertension are more at risk for developing resistant hypertension.

The ACC guidelines have a good flow chart on the management of hypertension that walks through each scenario giving recommendations on how to manage and follow up on patients based on their category, ASCVD risk, and other considerations.[1] The biggest problem identified associated with management of hypertension and achieving goal blood pressure is usually noted as clinical inertia. Often before pharmacological interventions, there are suggested lifestyle or nonpharmacological

interventions. All of these have scientific evidence to improve blood pressure at least some. These include:

- Weight loss in adults that are overweight or obese
- Healthy diet (e.g., DASH diet) that facilitates achieving desirable weight
- Sodium reduction
- Potassium supplementation (preferably diet) if not contraindicated
- Increase in physical activity via structured exercise program
- Limit alcoholic drinks per day to ≤ 2 (men) or ≤ 1 (women)

For pharmacological interventions, the 2017 ACC/AHA guidelines summarized in table 2 below break this out as initial medication, initial monotherapy versus combination therapy, and race and ethnicity considerations. For initial drug initiation, clinicians can select from one of the 4 listed classes. In addition, most patients eventually end up using multiple medications to reach goals.

Table 2: 2017 ACC/AHA Medication Selection for Hypertension:[1]
First Line: Thiazide diuretics, CCBs, and ACE inhibitors or ARBs
Initial Monotherapy versus Combination Therapy: 2 first-line agents of different classes in stage 2 hypertension and BP > 20/10 mmHg above goal
Race and Ethnicity Considerations: • African American patients without HF or CKD (with or without diabetes), initial treatment should include a thiazide diuretic or CCB • 2+ medications are recommended to achieve a BP < 130/80 mmHg in most adults, especially in African American patients.

Resistant hypertension was defined in the 2017 ACC/AHA guidelines. It is defined as patients not at their goal BP despite concurrent use of 3 antihypertensive drug classes, commonly including a long-acting CCB, ACEi or ARB, and a diuretic. Should be at maximum or maximally tolerated daily doses or a patient at BP target on 4 or more antihypertensive medications would be classified as resistant as well.

Before we consider different approaches to treatment, we must consider causes of resistant hypertension. There are several both pharmacologic and nonpharmacologic causes. The items in table 3 are examples of the most common medications and conditions that can contribute to elevated blood pressure or hypertension. If you identify any of these in a patient with resistant hypertension, you may consider eliminating one of these drugs as a contributing factor in your management approach. A prime example is that NSAIDs work well for pain but can increase your blood pressure and are readily available over the counter. Sometimes prescribers do not know patients are taking them and NSAIDs are one of the most common problematic drugs you should look for. One option would be to consider acetaminophen or topical NSAIDs (do not have the same systemic side effects) if possible, in patients with resistant hypertension taking an NSAID. The most common secondary cause of resistant hypertension is kidney disease. It is not always reversible but acknowledging kidney disease might be a contributing factor may open the door for other treatment strategies or all clinicians to use an alternative approach to treatment.

Table 3: Common Causes of Resistant Hypertension[2]	
Drugs with Potential to Induce or Exacerbate Elevated BP or Hypertension	**Secondary Causes of Resistant Hypertension**
NSAIDS	Primary aldosteronism
Oral Contraceptives	Renal parenchymal disease
Cyclosporine, tacrolimus	Renal Artery Stenosis (RAS)
Erythropoietin	Pheochromocytoma/Paraganglioma
Alcohol	Cushing Syndrome
Cocaine	Coarctation of the aorta
Sympathomimetics	Other (e.g., hypo/hyperthyroidism, mineralocorticoid excess syndromes, acromegaly)
Amphetamines	
Antidepressants	
Vascular endothelial growth factor (VEGF) inhibitors	
Glucocorticoids, mineralocorticoids	

Some patients have a condition known as "pseudo-resistant hypertension". They do not really meet the definition of resistant hypertension but sure appear like they are. The most common causes of this condition are inaccurate BP measurement, white-coat effect, under-treatment or clinical inertia, or medication non-adherence. A fair number of patient's cause of resistant hypertension may be one of these. About 70% of patients that do not meet definition are in the undertreated or clinical inertia category. There are a few key suggestions to address obtaining accurate blood pressure measurement. They are summarized in table 4 and include:

Table 4: Suggestions to Ensure Accurate Blood Pressure Measurement[1]		
Step 1	Properly prepare the patient	• Have patient relax with feet on floor and back supported for > 5 minutes before taking reading • Patient should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement • Ensure patient has emptied their bladder • Do not talk during reading • Remove all clothing covering cuff contact point
Step 2	Use proper technique for BP measurements	• Use validated and calibrated device • Position middle of cuff on upper arm at level of right atrium (midpoint) • Support the patient's arm • Use the correct cuff size for the patient's arm
Step 3	Take the proper measurements needed for diagnosis and treatment	• Avoid clinical inertia
Step 4	Properly document accurate BP readings	• Having the patient keep a log is also helpful
Step 5	Average the readings	• Gives more accurate representation
Step 6	Provide BP readings to the patient	

The biggest mistake reported in the literature technique wise is not having patient sit in position that you are going to measure for at least 5 minutes. Ensuring this is done will affect the readings. This may unfortunately crimp busy workflows but needs to be done for accurate readings. Cuff size also causes problems and using the cuff over clothing can give an inaccurate reading as well. Ensure if large arm, we use large cuff and if small arm we use small cuff.

There are several treatment options to manage resistant hypertension. Strategies recommended include maximizing lifestyle modifications, using a long-acting thiazide-like diuretic (chlorthalidone or indapamide), adding a mineralocorticoid receptor antagonist (eplerenone or spironolactone). Stepwise addition of antihypertensive drugs with complementary mechanisms of action is also recommended to lower blood pressure.[2]

The AHA published the stepwise approach to resistant HTN in the Journal of Hypertension.
It uses a series of 6 steps as outlined below[1]**:**

- *Step 1*: exclude other causes, ensure low-sodium DASH style diet, maximize lifestyle intervention, and optimize 3-drug regimen
- *Step 2*: Substitute optimally dosed thiazide-like diuretic (chlorthalidone or indapamide) for the prior used diuretic
- *Step 3*: Add a mineralocorticoid receptor antagonist (spironolactone or eplerenone) – use caution if eGFR <30 mL/min/1.73m^2
- *Step 4*: Add a beta-blocker or a alpha/beta-blocker if HR is $\geq$70 BPM
    - If contraindicated, consider centrally acting alpha-agonist (clonidine patch weekly or guanfacine at bedtime)
    - If not tolerated, consider once daily diltiazem
- *Step 5*: Add hydralazine 25 mg three times daily and titrate up
- *Step 6*: Switch hydralazine to minoxidil 2.5 mg two to three times daily and titrate up.
- *Step 7*: If still not at BP target, may need hypertension specialist or experimental studies

In the guidelines you will note that there is a recommendation for switching from thiazide type diuretic like hydrochlorothiazide (HCTZ) to a thiazide-like diuretic (chlorthalidone). The landmark cardiovascular studies mostly used chlorthalidone and it is more potent and has a longer half-life. There is not a big difference in side effects between the two. As a result of recent recommendations, we have seen uptake in chlorthalidone. Data supports switching in resistant HTN patients from HCTZ to chlorthalidone.
In resistant HTN, when patients given spironolactone, the decrease in SBP was significantly more in these patients than with all other studied agents. Efficacy is there with spironolactone more so than doxazosin and bisoprolol but there is a small number of patients that see an increased risk of hyperkalemia so need to monitor when you do use it.

There are a few strategies to promote adherence with medications that clinicians can use.
We all must engage in meaningful conversations to treat a disease that is mostly asymptomatic. As corny as it sounds, we must get patients to take drugs for them to work and antihypertensives are proven to reduce morbidity and mortality when taken appropriately. Effective strategies include[1]:

- **Follow-up after initiating drug therapy** – ensure patient has remained adherent and seeing response at monthly intervals until control is achieved
- **Monitoring strategies to improve control of BP** – follow-up and monitoring should include systematic strategies including home based blood pressure monitoring, team-based care, and telehealth where possible.
- **Promote medication adherence** – use once daily medications where possible instead of multiple times daily, use combination pills instead of free individual components when possible. Anytime we are making adjustments we should look at adherence.
    a. Use telephone, text, and email reminders
    b. Have the patient keep a diary
    c. May consider unit-dose packaging
    d. Counsel the patient
    e. Automated refill reminders from the pharmacy
    f. Ensure patient can afford the medication

The 2018 AHA Scientific Statement provides in-depth recommendations regarding resistant hypertension, including the clinical definition. In addition the 2020 International Society of Hypertension Global Hypertension Practice Guidelines supports these guidelines with additional commentary around secondary causes but no major changes as it relates to resistant hypertension.[3] It should be noted that there are several causes of elevated BP discussed here that should be assessed in all patients with resistant hypertension There are many treatment options available for the proper management of resistant hypertension, many of which are optimizing medications in addition to adding medications Effective patient counseling can also be used to promote adherence to antihypertensive medications.

References:

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018 May, 71 (19) e127–e248
2. Carey RM, Calhoun DA, Bakris GL, et al. American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement from the American Heart Association. *Hypertension*. 2018 Nov;72(5):e53-e90. doi: 10.1161/HYP.0000000000000084. PMID: 30354828; PMCID: PMC6530990.
3. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global

FDA Approval of Novel Alzheimer's Disease Medication

Casey Fitzpatrick, PharmD, BCPS

The United States (US) Food and Drug Administration (FDA) has approved Biogen's new Alzheimer's disease (AD) medication, aducanumab-avwa (Aduhelm®). This first-in-class therapy was granted accelerated approval based on data from clinical trials demonstrating a reduction of amyloid beta plaque in the brain.[1] The FDA is requiring Biogen to conduct a post-approval clinical trial to verify the drug's clinical benefit.[2]

Approval of aducanumab-avwa was based on findings in two phase 3 clinical trials that evaluated over 3000 patients with early stages of AD with confirmed presence of amyloid pathology. The effects of aducanumab-avwa were supported by a double-blind, randomized, placebo-controlled, dose ranging study. The results of these trials showed that aducanumab-avwa consistently reduced the level of amyloid plaques in the brain in a dose- and time-dependent manner.[3,4,]

FDA approval of aducanumab-avwa was accompanied with significant controversy. Many experts cited a lack of evidence for the drug's effectiveness. Although clinical trials did show that aducanumab-avwa reduced the level of amyloid plaques, no clinical benefit was observed. The FDA argued that reducing amyloid beta plaques, a hallmark finding the brain of patients with AD, is expected to lead to a reduction in clinical decline.[2] To add to the controversy, the monthly infusion will reportedly cost $56,000 per year, in addition to required brain imaging and monitoring for anyone who is prescribed the medication.

A dose titration is required for initiation of aducanumab-avwa administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart. After initiation, the recommended maintenance dose is 10 mg/kg. Aducanumab-avwa does not carry any contraindications for use but can cause amyloid-related imaging abnormalities (ARIA). ARIA can take form of edema (ARIA-E) and/or microhemorrhage (ARIA-H). These adverse reactions are monitored by brain magnetic resonance imaging (MRI) while therapy is continued. Other serious adverse reactions reported in clinical trials include fall (15%), diarrhea (9%) and confusion/delirium/altered mental status/disorientation (8%).[1]

1. Aduhelm (aducanumab) [prescribing information]. Cambridge, MA: Biogen Inc; June 2021.
2. U.S. Food and Drug Administration (2021, June 07). FDA Grants Accelerated Approval for Alzheimer's Drug [Press release]. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug
3. Alexander GC, Emerson, S, Kesselheim AS. Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility. *JAMA* 2021;325(17)171-1718.
4. Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*. 2016;537(7618):50-56.

ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease.

Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

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