Ms. G, 62, is admitted to the ED after experiencing a transient ischemic attack (TIA). Her sister reported that Ms. G’s speech was slow and garbled. Ms. G’s health history includes an ischemic stroke diagnosed 3 years ago, hypertension, type 2 diabetes mellitus (T2DM), and dyslipidemia. She has no known drug allergies. Medications include daily aspirin, amlodipine, losartan, atorvastatin, ezetimibe, metformin, and empagliflozin. Pertinent family history includes Ms. G’s mother, who is alive at age 84 with hypertension; Ms. G’s father had hypertension and T2DM and died at age 60 from a myocardial infarction (MI). Ms. G smokes half a pack of cigarettes daily.

Computed tomography (CT) of the head showed no blood or other abnormalities. A 12-lead ECG showed normal sinus rhythm with no signs of myocardial ischemia or infarct. Labwork done in the ED, including a finger-stick blood glucose, complete blood cell count, coagulation profile, basic metabolic panel, and erythrocyte sedimentation rate were all within normal limits. Results of a fasting lipid panel completed 2 weeks prior to admission demonstrated a total serum cholesterol, 165 mg/dL (normal, 140-199 mg/dL); low-density lipoprotein cholesterol (LDL-C), 89 mg/dL (normal, <100 mg/dL); high-density lipoprotein cholesterol (HDL-C), 48 mg/dL (normal, 35-80 mg/dL); and triglycerides, 140 mg/dL (normal, <150 mg/dL).¹

This article explores the pharmacology of alirocumab and evolocumab, two new proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors approved by the FDA for subcutaneous administration to reduce LDL-C and reviews the clinical trial evidence supporting these drugs, their nursing implications, and patient education for optimal safety.

**TIA and stroke**

A TIA is a high-risk event, and 12% of patients who experience a stroke have a TIA preceding the stroke.² TIA is currently defined as a transient episode of neurologic dysfunction caused by focal brain ischemia, spinal cord, or retinal ischemia without acute infarction. Ischemic stroke is diagnosed by the presence of infarcted brain tissue and may cause persistent cognitive, language, motor, or sensory deficits. Stroke is the fifth leading cause of death in the US, with an estimated 795,000 strokes reported annually.²³ Acute ischemic stroke (87%) is more common than intracerebral hemorrhage (10%) or subarachnoid hemorrhage (3%).²

The ABCD² score can be used to estimate the risk of ischemic stroke in the first 2 days after a TIA.⁴ Patients age 60 or older, with a systolic BP of at least 140 mm Hg or diastolic BP of at least 90 mm Hg, unilateral weakness, diabetes, and a duration of TIA symptoms for at least 60 minutes have the greatest risk of stroke heralded by a TIA.⁴

ABCD² scores are interpreted as follows:
• 6 to 7: High 3-month stroke risk (8%)
• 4 to 5: Moderate 3-month stroke risk (4%)
• 0 to 3: Low 3-month stroke risk (1%)

Ms. G’s ABCD² score was 6 (high 3-month stroke risk). Ms. G’s risk factors included her age, hypertension, T2DM, dyslipidemia, and smoking. Cigarette smoking is associated with an increased risk for all stroke subtypes. The likelihood of a stroke event is 1.45 times greater in someone with diabetes as compared with someone without diabetes.² For women and men with diabetes, the relative risk of stroke is 2.28 and 1.83 times greater than healthy individuals, respectively.² The burden of stroke has a substantial impact on patients and their caregivers. Within 6 months, 50% of older
adults surviving an acute ischemic stroke have residual hemiparesis, and 30% need assistance with walking and other activities of daily living. The financial impact to survivors and the health system is astounding; the collective estimated annual cost of long-term disability is over $30 billion. Fortunately, there are new lipid-lowering drug therapies being examined for cardiovascular prevention, including stroke prevention.

**Pharmacology**

LDL-C, a lipoprotein, circulates within the blood, oxidizes, and adds to arterial plaque in vulnerable arteries, such as coronary and carotid arteries. Plaque builds to critical levels to diminish or occlude blood flow in the intimal lining, or may break off to occlude cerebral arteries.

PCSK9 is an enzyme, encoded by the PCSK9 gene, predominantly produced in the liver. PCSK9 binds to the LDL receptor (LDL-R) on the surface of hepatocytes, leading to the degradation of the LDL-R and higher plasma LDL-C levels. Antibodies to PCSK9 interfere with its binding of the LDL-R leading to higher hepatic LDL-R expression and lower plasma LDL-C levels.

In summary, the mechanism of action of PCSK9 inhibitors is halting the metabolic breakdown of LDL-Rs resulting in increased clearance of LDL-C. This mechanism is distinctly different from statins, which inhibit cholesterol synthesis in the liver. The mean percentage change in LDL-C levels decreased by 50% or more from baseline in patients receiving the PCSK9 inhibitors alirocumab and evolocumab. Apolipoprotein B, a marker of cardiovascular risk, also declined significantly. Therefore, the potential to prescribe potent nonstatin lipid-lowering drugs together with statins has generated significant interest.

PCSK9 inhibitors are bioengineered monoclonal antibodies directed against PCSK9. Alirocumab and evolocumab are PCSK9 inhibitors approved by the FDA for subcutaneous administration and are effective in reducing LDL-C. Clinical trials are revealing promising results for the prevention of atherosclerotic cardiovascular disease (ASCVD), including nonembolic ischemic stroke.

**Clinical trial evidence**

PCSK9 inhibitors have been studied in secondary and primary prevention populations to mitigate or prevent ASCVD (see *Statin and nonstatin management of ASCVD*). The 2018 guidelines on blood cholesterol management describe the place in therapy of PCSK9 inhibitors and other nonstatin drugs for specific populations. Secondary prevention applies to individuals with clinical ASCVD, including a past ischemic stroke/TIA. Clinical ASCVD also applies to individuals with a history of MI, acute coronary syndromes (ACS), stable angina, coronary artery or carotid arterial revascularization, or peripheral artery disease. The common pathophysiologic process arises from the presence of arterial plaque accompanied by inflammation and thrombosis.

Primary Prevention applies to individuals without clinical ASCVD who have dyslipidemias stemming from a genetic mutation or inherited defect. Familial hyperlipidemias are associated with defective lipoprotein metabolism predominantly affecting LDL-C levels. Adults with heterozygous or homozygous familial hypercholesterolemia are included in the population with severe hypercholesterolemia (LDL-C of 190 mg/dL or higher).

Several clinical trials assessed the change in lipid values when PCSK9 inhibitors were added to moderate- to high-intensity statin therapy, and also assessed major adverse cardiovascular events.
(MACE) as a composite endpoint. (See Clinical trial results.)

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial evaluated evolocumab on the composite of MACE as a primary endpoint.11 FOURIER was a randomized, double-blind, placebo-controlled trial enrolling adults ages 40 to 85 who had clinically evident ASCVD. Patients had a history of MI, nonhemorrhagic stroke, and/or peripheral artery disease.11 They must be receiving an optimized lipid-lowering regimen that included high-intensity statins with or without ezetimibe.11

The Long Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY long term) trial evaluated MACE events in a post-hoc analysis of secondary endpoints.10 The study enrolled adults with heterozygous familial hyperlipidemia, or hypercholesterolemia with or without established coronary heart disease (CHD) or CHD risk equivalents. The primary endpoint was the ODYSSEY long term trial was the change in LDL-C over time.

The Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during treatment with Alirocumab (ODYSSEY OUTCOMES) trial completed enrollment, and a summary of the preliminary results are available.14-16 ODYSSEY OUTCOMES evaluated patients recently hospitalized for ACS occurring 4 to 52 weeks before randomization.14-16 Adults age 40 or older were inadequately controlled on high-dose or maximally tolerated statins. The primary endpoint was the composite of MACE events.

### Statin and nonstatin management of ASCVD

| Secondary prevention | Statins | Nonstatin lipid-lowering drugs |
|----------------------|---------|-------------------------------|
| Secondary ASCVD prevention | Age ≤75: high-intensity statins | Persistently elevated LDL-C > 70 mg/dL |
|                       | Age >75: moderate-intensity statins | Option 1: ezetimibe |
|                       |                              | Option 2: PCSK9 inhibitors***, *** |

| Primary prevention without ASCVD | Statins | Nonstatin lipid-lowering drugs |
|----------------------------------|---------|-------------------------------|
| Severe hypercholesterolemia with LDL-C ≥190 mg/dL | High-intensity statins to achieve at least a 50% reduction in LDL-C* | Persistently elevated LDL-C > 190 mg/dL on maximally tolerated statins and ezetimibe, consider adding PCSK9 inhibitors***, *** |
| Diabetes with LDL-C 70-189 mg/dL | Moderate-intensity statins If 10-year ASCVD risk estimate ≥7.5%: high-intensity statins | Ezetimibe (No primary prevention role for PCSK9 inhibitors) |
| Moderate to high 10-year ASCVD risk estimate ≥7.5% with LDL-C 70-189 mg/dL | Statin dosing based on 10-year ASCVD risk estimate ≥7.5%: moderate- or high-intensity statin 5% to <7.5%: moderate-intensity statin (Additional risk factors should be evaluated) | Option 1: Ezetimibe Option 2: Bile acid sequestrant (No primary prevention role for PCSK9 inhibitors) (Additional risk factors should be evaluated) |

---

*Applies to individuals age ≥21

**Alirocumab indicated in patients with heterozygous familial hyperlipidemia, and clinical ASCVD (limitations: the effect on cardiovascular morbidity and mortality has not been determined)15

***Evolocumab indicated in patients with established cardiovascular disease to reduce the risk of MI, stroke, and coronary revascularization, primary hyperlipidemia (including heterozygous familial dyslipidemia), and homozygous familial dyslipidemia18

± Applies to individuals ages 40 to 79; ≠ excludes statin benefit group 3 (diabetes ages 40 to 79)

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9
Safety

Patients should be informed about injection site reactions, which occurred more frequently with alirocumab (3.8% versus placebo 2.1%) and evolocumab (2.1% versus placebo 1.6%) as compared with placebo administration.10,11

Most individuals who are prescribed PCSK9 inhibitors will also take moderate- to high-intensity statins. Statin-induced myopathy is characterized as a potential adverse reaction causing muscle tenderness, pain, and weakness.19 Myopathy occurred in 5.4% of patients taking alirocumab versus 2.9% getting placebo ($P < .006$).10 In FOURIER, muscle-related events were not significantly different between evolocumab (5%) versus placebo (4.8%) ($P = $ nonsignificant [NS]).11 Patients should be counseled to report persistent muscle symptoms.

There are concerns that substantial reductions in LDL-C may be associated with memory impairment or more serious cognitive effects [amnesia or confusion].7 This theory is based on the role of cholesterol in maintaining central nervous system function and development of neurons.7 Neurocognitive event rates were similar between alirocumab (1.2% versus placebo 0.5%, $P = .17$) and evolocumab versus placebo arms (1.6% versus placebo 1.5%, $P = $ NS).10,11 New-onset diabetes has been reported with statin use and may result in symptomatic hyperglycemia and elevations in hemoglobin A1C.9 Pancreatic beta-cell function involves expression of PCSK9, and evidence from preclinical studies points to diminished beta-cell function and glucose intolerance in animals.7 New-onset diabetes occurred less frequently in the alirocumab arm (1.8%) versus placebo arm (2%) ($P = .84$).10 There was no difference in cases of new-onset diabetes with evolocumab versus placebo arms (8.1% versus 7.7%, $P = $ NS).11 In both studies, investigators distinguished preexisting versus new-onset reports of diabetes.

Drug therapy selection

With the introduction of new evidence on PCSK9 inhibitors, the American College of Cardiology 2017 focused update is organized by statin benefit groups that may benefit from nonstatin lipid-lowering drug therapy.12 PCSK9 inhibitors are recommended in very high-risk patients who have either multiple major ASCVD events, or 1 major ASCVD event and...
multiple high-risk conditions. The guidelines support prescribing of maximally tolerated statins in these patient groups. There is a net benefit to additional lowering of LDL-C with the addition of ezetimibe and PCSK9 inhibitors. Clinicians should engage patients in discussing net benefits, safety, and cost of therapies.

Nonstatin lipid-lowering therapy is indicated for severe hypercholesterolemia. Ezetimibe is recommended as first-line agents, whereas PCSK9 inhibitors are recommended as second-line agents. The control of hereditary primary dyslipidemias typically requires combination drug therapy and aggressive lifestyle modifications. The treatment goal for high-intensity statins is to achieve an LDL-C reduction of 50% from baseline. The availability of PCSK9 inhibitors now results in lowering LDL-C by an additional 40 to 50 mg/dL when used in combination with statins.

At this time, PCSK9 inhibitors are not recommended in the statin benefit groups affecting individuals with diabetes or in patients with an elevated 10-year risk for ASCVD.

Discussion
The case study outlined earlier in this article depicts a patient with a recent TIA who has clinical ASCVD, and ASCVD comorbidities and risk factors that should be aggressively managed, including treatment of dyslipidemia, hypertension, diabetes, and smoking. The patient should be fully evaluated to determine if a carotid vascular intervention is indicated, and to confirm the TIA was not caused by a cardioembolic source. The patient may be referred to a lipid specialist. Because this patient is at high risk for developing an acute ischemic stroke or other ASCVD event, a high-intensity statin, aspirin (an antiplatelet agent for noncardioembolic stroke prevention) should be continued.

Before clinicians modify her drug therapy, they should assess the patient’s pattern of medication adherence and adherence to healthy lifestyles. An interprofessional collaborative approach to care can engage nurses and pharmacists in verifying medication use using documentation from hospital or pharmacy records. Patients not adhering to statins need additional counseling and can be referred to a medication therapy management service. A registered dietitian-nutritionist can evaluate the patient’s diet and provide recommendations for food choices low in saturated fat. The 2018 guideline is an excellent source with clear algorithms that outline steps to optimize statin dosing and lifestyle intensification.

There are other options for modifying the patients’ therapy based on the 2018 guidelines, which address nonstatin lipid-lowering drug therapy. The decision to use nonstatins must weigh patient factors such as their underlying diagnosis, potential for impairment and disability due to stroke, and affordability. In this patient with multiple major ASCVD events, a PCSK9 inhibitor can be added to the statin and ezetimibe combination. Ezetimibe is a once-daily oral medication that is an affordable alternative available in a generic form. When ezetimibe was administered along with simvastatin in the IMPROVE-IT Stroke Analysis, there was a significant reduction in MACE events in adults older than 50 with a recent ACS hospitalization. There was no difference on total stroke events with ezetimibe/simvastatin (4.2%) versus simvastatin alone (4.8%; *P* = .052). Statin dosing is based on prescribing fixed-dose moderate- or high-intensity statins to achieve an anticipated reduction in LDL-C by 25% to 50%. Patient LDL-C levels decrease substantially while taking combination statin and PCSK9 inhibitor. Blinded dose adjustments were made during one trial to achieve LDL-C levels between 25 and 50 mg/dL. The PCSK9 trials were not designed with a specific LDL-C target level in mind; however, it is prudent to monitor LDL-C levels in 4-12 weeks to evaluate the response.

However, Ms. G has recurrent TIA with an LDL-C above 70 mg/dL and additional risk factors; therefore, the guideline recommends that the healthcare provider discuss the advantages and disadvantages of adding a PCSK9 inhibitor to high-dose statins and ezetimibe. The FOURIER trial included subjects with nonhemorrhagic stroke and provided evidence for significantly reducing MACE composite endpoints, ischemic stroke, and nonfatal MI. This
A case study illustrates a patient with TIs and multiple ASCVD comorbidities is a candidate for a PCSK9 inhibitor, such as evolocumab.11,12

**Nursing implications**

Nurses should be aware of the place in therapy and benefits of PCSK9 inhibitors for treatment in individuals experiencing ASCVD progression despite optimal management with medications (see Nursing considerations). PCSK9 inhibitors are an option for specific statin benefit groups. In the case study, the patient experienced repeated TIs, which places them at high risk for an ischemic stroke, and places them within the clinical ASCVD statin benefit group. The patient’s health history and recent head CT results should be carefully evaluated to rule out hemorrhagic stroke. Patients with a history of hemorrhagic stroke may be at a greater risk for experiencing further bleeding with high-intensity statins.9 This was an exclusion criterion in the PCSK9 trials.10,11

**Patient education**

Alirocumab and evolocumab are administered subcutaneously every 2 weeks; and evolocumab can also be given once monthly.17,18 Adherence tools, such as calendars, can be effective reminders for scheduling doses. Videos are available on the manufacturer website for instructing patients on subcutaneous administration of the drug, which can be injected in the upper arm, thigh, or abdomen.17,18 Evolocumab is available with an autoinjector and prefilled syringe, which is used to administer the drug subcutaneously. Also, the needle cover of the evolocumab prefilled syringe and prefilled autoinjector contains latex and poses a risk for individuals with a latex allergy.17 The higher dose of evolocumab is delivered subcutaneously with a single-use on-body infuser with prefilled cartridge, which delivers the drug over the course of 9 minutes.17 The evolocumab single-use on-body infuser with prefilled cartridge is not made with natural rubber latex.17 The alirocumab pens and syringes do not contain rubber latex.17 These products are stored under refrigeration and should be disposed of in a sharps container.17,18 Direct patients to remove the medication from refrigeration to warm at room temperature for 30 minutes before administration.17,18

Injection site reactions were reported with PCSK9 inhibitors and the frequency was less than 4%.9,17,18 Injection site reactions could lead to patient dissatisfaction with the therapy and precipitate medication nonadherence. Patients should return for a follow-up visit within 4 weeks to evaluate the response to therapy and resolve any problems with dose administration. Hypersensitivity reactions causing urticaria, rash, and pruritus have been reported, as well as serious hypersensitivity and vasculitis reactions resulting in hospitalization.17 Individuals taking a PCSK9 inhibitor and experiencing a life-threatening hypersensitivity reaction should immediately stop taking the drug and seek emergency treatment.

**Conclusion**

The 2018 guideline supports the use of PCSK9 inhibitors as an alternative for use in certain

### Nursing considerations

- Assess for a history of TIA, ischemic stroke, hemorrhagic stroke, and dysrhythmias.22
- Ensure optimal management using statins, antiplatelet agents, and other therapies for prevention of ASCVD.22
- Ensure optimal management for comorbidities (including hypertension, hyperlipidemia, diabetes, obstructive sleep apnea).23
- Use motivational interviewing skills in supporting the patient in making healthy lifestyle changes (smoking cessation, saturated dietary fats and total cholesterol reduction, limit alcohol intake, increase physical activity).23
- Assess the following in patients not responding to maximally tolerated statins and optimal lifestyle modifications:12
  - 1) Do they meet the criteria for one of these statin benefit groups: secondary ASCVD or severe hypercholesterolemia?
  - 2) Do they meet the criteria for nonstatin lipid-lowering drugs: on maximally tolerated statins with or without ezetimibe?
- Provide training and instructions for self-administration of injectable drugs.
- Refer patients to a registered dietitian for medical nutrition therapy, and to a pharmacist for adherence support and smoking cessation counseling.12,24
patient populations with secondary ASCVD and severe hypercholesterolemia who are not responding to maximally tolerated statins. There is also emerging evidence on the effectiveness of alirocumab use following a recent ACS. Currently, fixed-dosed statins are the definitive management strategy for these indications for prevention of MACE. Statins are generally well-tolerated and, with the availability of generic formulations, are affordable. PCSK9 inhibitors are new lipid-lowering agents with a unique mechanism of action that causes significant LDL-reductions when used in combination with statins. At this time, the cost of the two FDA-approved products, alirocumab and evolocumab, may be prohibitive to individuals without health insurance, and managed-care policies place them on a restricted tier. Nurses can play an important role in ensuring optimal management of statin therapy and address healthy lifestyles by identifying potentially modifiable risk factors such as smoking, diet, and medication adherence. Patients who are started on a PCSK9 inhibitor will need instructions on administration of subcutaneous injections using a syringe, autoinjector, or infuser.

**REFERENCES**

1. Fischbach F, Dunning MB. *A Manual of Laboratory and Diagnostic Tests*. 9th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation. 2018;137(12):e67-e492.
3. Furie KL, Ay H. Initial evaluation and management of transient ischemic attack and minor ischemic stroke. UpToDate. 2018. www.uptodate.com.
4. Johnston SC, Rothwell PM, Nguyen-Huy nh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischemic attack. *Lancet*. 2007;369(9558):283-292.
5. Gershkoff A, Moon D, Fincke A, Dangaria H. Stroke rehabilitation. In: Mintin I, ed. *Current Diagnosis and Treatment: Physical Medicine and Rehabilitation*. 1st ed. New York, NY: McGraw-Hill Education, Inc.; 2015:209-236.
6. Yang Q, Tong X, Schich L, et al. Vital signs: recent trends in stroke death rates—United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(53):993-999.
7. Bergeron N, Phan BA, Ding Y, Fong A, Krauss RM. Proprotein convertase subtilisin/ kexin type 9 inhibition: a new therapeutic mechanism for reducing cardiovascular disease risk. *Circulation*. 2015;132(17):1648-1666.
8. Malley MJ, Kane JP. Agents used in dyslipidemia. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. 14th ed. New York, NY: McGraw-Hill, Inc.; 2018:620.
9. Lexicomp online. *Lexi-Drugs Online*. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; 2018.
10. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-1499.
11. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.
12. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPEN/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018.
13. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S154-S.
14. Schwartz GG, Besac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168(5):682-689.
15. Sanofi-Aventis. U.S. Letter. (P. Shah, letter, June 18, 2018.)
16. U.S. National Library of Medicine. ODYSSEY outcomes: evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab. https://clinicaltrials.gov/ct2/show/NCT01663402. Published August 13, 2012. Accessed Sep 5, 2018.
17. Sanofi US and Regeneron Pharmaceuticals, Inc. Praluent prescribing information. 2018. www.praluenthcp.com.
18. Amgen, Inc. Repatha prescribing information. 2018. www.repathahcp.com.
19. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2550-2561.
20. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754-3832.
21. Smith WS, Claiborne Johnston S, Hemphill JC. Ischemic stroke. In: Jamieson JL, Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, eds. *Harrison’s Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill Education; 2018.
22. Powers WJ, Babineau AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-e110.
23. Oza R, Rudell K, Garcelano M. Recurrent ischemic stroke: strategies for prevention. *Am Fam Physician*. 2017;96(7):456-460.
24. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The effectiveness of pharmacist interventions on cardiovascular risk: the multicenter randomized controlled RxEACH trial. *J Am Coll Cardiol*. 2016;67(24):2846-2854.
25. Bohula EA, Wiviott SD, Giugliano RP, et al. Prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT. *Circulation*. 2017;136(25):2440-2450.

Grace Earl is an associate professor at the University of the Sciences Department of Pharmacy Practice and Administration, Philadelphia, Pa.

The author has disclosed no financial relationships related to this article.

Unless otherwise specified, the information above applies to adults, not children. Consult a pharmacist, the prescribing information, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions.

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBYNC ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI:10.1097/01.CCN.0000549635.52054.56