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In Memoriam:

Michael J. Hennessy Sr.

MICHAEL J. HENNESSY SR, founder and chairman of MJH Life Sciences™, died on November 21, 2021. He leaves behind a successful legacy of innovation and entrepreneurial spirit that continues to drive his company to deliver a “white-glove experience” as the largest privately held medical media company in North America.

He spent his career turning his passion for building businesses and creating jobs into a run of successful ventures and brands. Following Hennessy’s graduation from Rider University in 1982, he started his career in medical publishing as a sales trainee, eventually advancing to the position of chief operating officer. In 1986, he became chief operating officer of Medical World Business Press, which was part of the launch of medical newspapers and other media products. The company prospered and was eventually sold to a Boston, Massachusetts–based venture capital firm.

Hennessy launched MultiMedia Healthcare, LLC, in 1993 and built a portfolio of award-winning clinical journals. In 2001, Freedom Communications, Inc, acquired MultiMedia HealthCare about the time that Hennessy was pioneering a new approach to print and digital publishing with Intellisphere®, LLC (now part of MJH Life Sciences™). Guided by the principles of innovation and entrepreneurial spirit and reflecting its founder’s dedication to improving quality of life through health care research and education, Intellisphere® publishes a variety of integrated print and digital products on a range of topics in clinical medicine and research.
To build a comprehensive multimedia and education platform, Hennessy added companies and capabilities to the MJH Life Sciences™ portfolio. In 2004, he acquired HRA® (Healthcare Research & Analytics), which has been the leader in health care market research for more than 30 years. In 2005, Hennessy acquired ArcMesa Educators®, LLC, leaders in online certification for physicians, pharmacists, nurses, and other health care professionals. Reflecting his lifelong interest in politics, Hennessy acquired Campaigns & Elections magazine in 2005, publishing the journal through Political World Communications, LLC. He sold the publication to Biteback Publishing in 2011.

In February 2008, Hennessy acquired the rights to the journals Pharmacy Times® and The American Journal of Managed Care®, both recognized in their respective markets as authoritative, trusted media platforms that provide essential information to a large audience of health care professionals.

In April 2011, MJH Life Sciences™ acquired Physicians’ Education Resource®, LLC (PER®), an accredited continuing medical education company that is an industry leader in producing high-quality, first-rate oncology and hematology meetings and conferences. The PER® acquisition included a variety of multichannel educational activities, as well as the rights to legacy medical meetings such as the annual Miami Breast Cancer Conference®.

Hennessy’s commitment to improving the lives of patients with cancer is deeply rooted within the halls of MJH Life Sciences™. As a complement to the industry-leading OneLive® platform, he developed the Giants of Cancer Care® awards to recognize the leaders and pioneers who often go unrecognized for their contributions to advancing oncology care. He further strengthened his commitment to education by acquiring CURE Media Group in 2014, followed by the purchase of the Chemotherapy Foundation Symposium, in his quest to provide oncology professionals with focused education on innovative cancer therapy.

In 2019, MJH Life Sciences™ made its largest acquisition to date when it acquired the health care and industry sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as Medical Economics® to its already impressive portfolio. This acquisition made the organization the largest independently owned medical communications company in North America. In addition to acquisitions, Hennessy organically developed ancillary in-house agency divisions with Proximyl Health®, Truth Serum NTWK®, and MJH Global Medical Affairs. Later in 2019, Hennessy elevated his role to chairman and named Mike Hennessy Jr to assume the leadership role of the organization and carry on the family legacy. The company enhanced its global potential by entering into a long-term partnership with BDT Capital Partners, LLC, in November 2021.

Because of his broad business and educational experience, Hennessy’s counsel and insight had been sought out by several organizations, including his alma mater, Rider University, where he served on the board of trustees and was elected to the executive committee. In addition to being active in New Jersey and national politics, Hennessy also had a long record of service at the local level, where he was a strong advocate for veterans and environmental issues.

Hennessy’s true passion was his relationship with his wife, Patrice “Patti” Hennessy. After meeting her in college, Hennessy devoted his life to Patti and raising their 4 children. Hennessy was Patti’s rock as she bravely battled cancer for almost 10 years until her death in January 2020. Hennessy recently honored Patti by making a donation to Rider University to expand the Science and Technology Center at their alma mater. The Mike and Patti Hennessy Science and Technology Center is set to be completed in 2022.

Hennessy’s legacy and “family first” mantra will live on through his children, their spouses, and his 10 grandchildren. He will be greatly missed by his family, his friends, and his MJH Life Sciences™ family.
WE DO NOT need to go much farther than the local diner, grocery store, or retail location to recognize that there is a widespread labor shortage. The media have reported for months on the so-called Great Resignation during the COVID-19 pandemic.

The health care sector, including pharmacy, has been no exception to staffing shortages. The US Bureau of Labor Statistics indicated in its December 2021 employment report that employment in the health care sector for November 2021 was down by 450,000 individuals since February 2020, an improvement from more than 500,000 in August 2021.

However, the results of a recent survey showed that 18% of health care workers quit their jobs during the pandemic and another 12% were laid off. Of those still employed, more than 30% said that they have considered leaving their jobs, and approximately 80% of health care workers said that the national workforce shortage has negatively affected them and their place of employment.

The impact of this level of attrition is further exacerbated by a lack of qualified applicants seeking employment; long training lead times; loss of highly skilled and more senior health care workers, who are also needed to train others; and surging demand for health care in both the ambulatory and acute care settings. Increased need for health care services is caused by a combination of COVID-19 and non–COVID-19 illnesses that have led to unprecedented rates of hospital admissions, primary care workload, and urgent-care visits. Patients presenting with non–COVID-19 illnesses are often more acutely ill with more advanced disease processes, which is thought to result from the avoidance of health care and deferral of care since the start of the pandemic. Understaffing at long-term-care facilities (LTCFs) limits the number of patients they can accept, leading to a backup in hospitals who are medically ready for transfer to a LTCF but have no place to go, further exacerbating the critically high census at many hospitals. All of this leads to
severe overcrowding of emergency departments, which also are understaffed.

Add to the mix another significant surge of COVID-19 illness, affecting mostly the unvaccinated, and most hospitals are facing a true crisis. If we experience a significant influenza season for the 2021-2022 season, because of lower-than-usual vaccination rates, open schools, and a return to large public gatherings, there will likely be severe, widespread shortages of access to acute health care. The combination of staff shortages, very high demand, an increased severity of illness, lack of available beds, and more inexperienced health care workers providing often fragmented and rushed care is negatively affecting the quality of that care. The term perfect storm seems appropriate.

Health system pharmacies are no exception to the workforce shortages, with the pharmacy technician ranks most significantly affected. I recently attended a virtual meeting of health system pharmacy executives, and to a person everyone listed technician shortages as one of the top 2 challenges their departments face.

As another indicator that the problem is widespread, the American Society of Health-System Pharmacists’ 2021 survey of hospital pharmacies included specific questions relative to the severity of and measures being taken to deal with technician shortages. This is not a new problem but it has certainly been exacerbated by the pandemic. The causes include concerns about COVID-19 infection, general health issues associated with the pandemic, lack of recognition and reward, perceived lack of advancement opportunities, relatively low wages, undesirable schedules associated with 24/7 operations, workload stressors, and, for some, health system and state vaccine mandates. Of course, worsening staffing shortages only increase the schedule disruptions, stress, and workload for those remaining, fueling greater risk of attrition due to anger, anxiety, and burnout. Although there are many suggestions about how to improve employee engagement, increase retention, and introduce greater workplace flexibility, they seem a bit absurd to try to implement while the house is burning down. Perhaps the aphorism of trying to “build the plane while flying it” is appropriate?

The overworked, underappreciated, and underpaid technician crisis has been brewing for years, but it took a pandemic to expose the potential severity of the issue. In the short term, health system pharmacy leaders are reassigning pharmacists to tasks normally completed by technicians, pulling back pharmacists to support greater operational burdens, and spending money on contract labor and overtime. These are necessary patches, which are probably contributing to decrements in the quality of care, but we all recognize that it will do nothing to solve the issue long term.

What is perplexing is where have all the workers gone? And what are they living on? We find ourselves in a position of more proactively reaching out to potential employment pipelines and trying to sell a career as a technician—and maybe we should have been doing this all along. Long term, we are only going to be successful if we make an investment in accredited technician training programs to provide real vocational training leading to board certification, greater advocacy efforts to increase recognition through continuing education and licensure, meaningful career ladders that represent true job growth opportunities, and salary structures that provide a livable wage. Technicians are critical to providing safe medication use systems, and the pandemic has exposed how tenuous technician support can be. Health system pharmacy leaders should act now to ensure that when individuals are ready to return to the workforce, being a technician is an appealing career choice. Patients deserve nothing less.

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COVID-19–Related Stress Is Linked to Poorer Cognitive Ability, Risk-Taking Behavior

Stress from the COVID-19 pandemic may have had a negative impact on cognitive abilities and risk perception among the public, according to results of a study published in PLoS ONE. “The impact of stress and of worry on cognitive function are well known but are typically studied in the laboratory setting,” Madeleine Sharp, MD, assistant professor, Department of Neurology and Neurosurgery at the Neuro (Montreal Neurological Institute-Hospital) in Canada, said in a statement.

“Here, we’re able to extend these findings by studying the effects of a real-world stressor in a large sample,” she said. “An important future direction will be to examine why some [individuals] are more sensitive than others to stress and to identify coping strategies that help to protect from the effects of stress.”

The investigators surveyed more than 1500 Americans between April and June 2020. To conduct the study, participants were asked to rate their level of worry about the COVID-19 pandemic before completing a set of psychological tests measuring basic cognitive ability and risk assessment. For example, participants completed an information processing test in which they were asked to match pairs of digits and symbols according to a fixed rule.

For the assessment of risk attitudes, participants were asked to make a series of hypothetical economic choices between certain options and riskier alternatives. These data were then compared with results from the same tests given before the start of the pandemic.

Those who experienced greater stress from the pandemic had decreased information retention, heightened sensitivity to the odds given when taking risks, and reduced processing speed, according to investigators. The pandemic group performed more poorly on simple cognitive tasks the prepandemic group. Further, participants in the last wave of data collection showed higher risk sensitivity than those in the first wave, lower ability to keep goals in mind, and slower processing speed.

The study results also suggest that pandemic worry could be an effective predictor of a participant’s tendency to distort described levels of risk, overweighting unlikely probabilities and underweighting likely ones. This shows that worries related to COVID-19 have affected decision-making styles, which could influence choices about getting vaccinated against COVID-19, according to the investigators.—Skylar Kenney

Vaccinated Individuals Show Lower Non–COVID-19 Death Rates

Individuals who received a COVID-19 vaccination had lower non–COVID-19 death rates than individuals who were unvaccinated, according to results of a Kaiser Permanente study. Individuals who had the Pfizer vaccine had a mortality rate of 4.2 deaths per 1000 vaccinated individuals per year after the first dose and 3.5 deaths after the second dose compared with 11.1 deaths per 1000 unvaccinated individuals. Individuals who received the Moderna vaccine had a mortality rate of 3.7 deaths per 1000 vaccinated individuals per year after the first dose and 3.4 after the second compared with 11.1 deaths per 1000 unvaccinated individuals. Individuals who received the 1-dose Johnson & Johnson vaccine had 8.4 deaths per 1000 individuals per year compared with 14.7 deaths per 1000 unvaccinated individuals.

There were different comparison groups because of when the vaccines were available and potential demographic differences among those choosing the various vaccines. To determine mortality risk, investigators evaluated the electronic health records of 6.4 million individuals who received a vaccination compared with 4.6 million unvaccinated individuals from December 14, 2020, to July 31, 2021.—Ashley Gallagher

Vaccination Rates Among Individuals With HIV Vary by Geography

The overall global COVID-19 vaccination rate among individuals living with HIV is approximately 55%, with rates varying significantly by geography, according to results of a study published in the Journal of Infectious Diseases. Immunocompromised individuals are at higher risk of developing severe symptoms and dying from COVID-19, making vaccination in this population critical.

“To our knowledge, COVID-19 vaccination rates among [individuals] with HIV have not yet been reported,” Steven Grinspoon, MD, chief of the Metabolism Unit at Massachusetts General Hospital in Boston, said in a statement.

Vaccination rates across participants in REPRIEVE—a cardiovascular prevention study being conducted in individuals living with HIV in multiple countries—were examined in different Global Burden of Disease superregions that exhibit similar cause-of-death patterns. These regions included the Caribbean and Latin America (Brazil, Haiti, Peru, and Puerto Rico), East/Southeast Asia (Thailand), high-income regions (Canada, Spain, and the United States), South Asia (India), and sub-Saharan Africa (Botswana, South Africa, Uganda, and Zimbabwe). Additionally, vaccination rates in REPRIEVE participants were compared with those from the general populations of their regions.

Among the 6952 REPRIEVE participants active in the study as of January 1, 2021, the overall vaccination rate was 55%, according to investigators.

Rates were highest in the high-income superregion at 71%, followed by the Caribbean and Latin America at 59%, South Asia at 49%, East/Southeast Asia at 41%, and sub-Saharan Africa at 18%.

Vaccination rates among REPRIEVE participants were similar to the general populations in most of the superregions.—Skylar Kenney

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PHARMACY TIMES® HEALTH-SYSTEM EDITION® JANUARY 2022
Immune-Boosting Antibody Treatment Meets Primary End Point for Multiple Myeloma

Patients who received the anti-CD38 monoclonal antibody isatuximab (Sarclisa) in addition to the standard 3-component induction therapy of lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVd) for newly diagnosed multiple myeloma were significantly more likely to achieve minimal residual disease negativity, with no evidence of cancer in the bone marrow compared with those receiving RVd alone, according to a phase 3 trial presented at the 63rd American Society of Clinical Pharmacy at the University of California, San Francisco, said during the presentation.

The therapy is a monthly intramuscular injection of 400 mg of cabotegravir and 600 mg of rilpivirine. There is a loading dose of 600 mg and 900 mg, respectively.

There is also a 1-month, daily oral lead-in therapy of a 30-mg cabotegravir tablet and 25-mg tablet of rilpivirine before the loading injection.

Cocohoba discussed 4 clinical trials of the injectable cabotegravir LA with rilpivirine LA: ATLAS, (NCT02951052) for maintenance therapy; ATLAS 2M (NCT03299049), for extended interval; FLAIR (NCT02938520), for the treatment-naïve; and LATITUDE (NCT03635788), for use in individuals with medication adherence challenges.

The ATLAS and FLAIR studies directly contributed to the FDA approval of cabotegravir with rilpivirine in January 2021. The FLAIR study was an open-label, phase 3, randomized study that included individuals who were treatment-naïve. All the participants were started on a 20-week regimen of a daily oral treatment regimen of abacavir (Ziagen), dolutegravir (Tivicay), lamivudine, or dolutegravir plus 2 other nucleoside reverse transcriptase inhibitors if the participant was positive for HLA-B*5701.

—Ashley Gallagher

Flu Vaccine Rates Are Lowest for Those Without Regular Health Care Providers

Vaccination rates for influenza are low for those who have regular health care providers but are still more than twice as high for those without health care providers, according to research results presented at the American Society of Health-System Pharmacists 2021 Midyear Clinical Meeting & Exhibition.

Results showed that approximately 44.5% of individuals with health care providers were vaccinated for the flu, but only approximately 20.5% of individuals without health care providers were vaccinated.

“This research reminds us that undervaccination and vaccine hesitancy are not limited to COVID-19,” Simmileoluwa Okegbile, a PharmD candidate at Midwestern University in Glendale, Arizona, said in a statement.

Investigators started the study to help identify predictors of flu vaccinations, which will help pharmacists tailor efforts to increase vaccination rates.

The study results show that demographic characteristics and risk perceptions are most likely to influence vaccine hesitancy.

To determine the rates of flu vaccination, investigators analyzed more than 2.5 million health survey records from the CDC’s 2015, 2017, and 2019 Behavior Risk Factor Surveillance System. All individuals included in the study were from the United States and 18 years or older.

The findings showed that flu vaccinations were lowest among Black and Latino individuals at 32% and 31%, respectively, compared with 41% of White individuals.

The vaccination rates rose with the number of medical conditions an individual had. Approximately 82% of those with 4 or more obesity-related conditions had been vaccinated for the flu.

The rates also steadily increased with age, and approximately 60% of individuals 65 years or older were vaccinated compared with less than one-third of those aged 18 to 25 years.

—Ashley Gallagher
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Disparities in Chronic Disease Outcomes Require Solutions
Finding Ways to Eliminate Barriers to Care Helps Narrow the Gap for At-Risk Populations

BY NEIL A. GILCHRIST, PHARMD, MBA, BCPS, DPLA

SIX IN 10 Americans have a chronic disease, and 4 in 10 have received a diagnosis of 2 or more chronic diseases.1 Millions of Americans live with and manage cancer; diabetes; epilepsy; Alzheimer disease; heart, lung, and kidney disease; rheumatoid arthritis; and other conditions. Many participate in ongoing medication therapy, prescribed regimens, and regular medical support.

However, best outcomes are out of reach for some of them. For myriad reasons, health care professionals may be unable, unaware, or unsure of how to manage their illnesses, resulting in outcome disparity.2

A 2017 publication by the National Academies of Science, Engineering, and Medicine cited 2 root causes for inequitable health outcomes: systemic mechanisms that organize power and resources unevenly across class, gender, and race; and an unequal allocation of power and resources that manifest as unequal economic, environmental, and social conditions.3

Other factors may include patients downplaying or ignoring symptoms, having to travel long distances to doctors or hospitals, living alone without support, being financially insecure, and having unreliable transportation.

Health system–owned integrated specialty pharmacies (ISPs) have experience managing and improving outcomes with complex diseases4 and are poised to lead the change necessary to address chronic disease outcome disparities. As a collaborative team that includes traditional dispensing pharmacists, drug contracting access experts, health outcomes managers, in-clinic liaisons, and payer contracting experts, ISPs are fully embedded in integrated care teams. They have the access, desire, knowledge, and structure to help bridge the gap between diagnosis and outcome.

Community Outreach
UMass Memorial Health is the largest not-for-profit health care system in central Massachusetts with more than 15,500 employees and 2100 physicians, many of whom are members of Harrington Physician Services and UMass Memorial Medical Group. The health care system is the clinical partner of the UMass Chan Medical School. The health care system makes health and wellness services available to everyone in the community whether at the clinic or at home, advocates for social equality, and provides economic stability and opportunity.

UMass Memorial Health has many services and tools to increase visibility and reduce barriers to access by being flexible and meeting patients where they are.5 These include a hospital-at-home program; vaccination mobile; and e-visit, telehealth, and telemonitoring programs, which have been expanded for patients because of the COVID-19 pandemic.6 Early evidence shows that telehealth is a win-win scenario, decreasing costs for hospitals while improving outcomes for at-risk patients.7

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NEIL A. GILCHRIST, PHARMD, MBA, BCPS, DPLA, is chief pharmacy officer at UMass Memorial Medical Center in Worcester, Massachusetts, and a board member of the Health System Owned Specialty Pharmacy Alliance.
Access
Pharmacists are consistently viewed as some of the most accessible health care providers. In addition to community pharmacies, there are pharmacies embedded within health system organizations that offer mail-order services, provide discharge prescriptions for patients as they leave the hospital, and support employee prescription programs. Pharmacists serve a critical role in patient care with access, education on therapies, medication review and verification, and targeted care services for conditions such as asthma and diabetes.

The ISP focuses more of its care model on access to specialty medications that are more complex regimens with higher costs and significant education requirements. Although there are not specialty pharmacies in every neighborhood or town, it is critical to have local access to health system–owned specialty pharmacies where patients benefit from higher acuity care and specialty clinicians. A patient’s specialty medication should come from local health care providers and not be shipped by large fulfillment centers across the United States.

The ISP has additional resources beyond the traditional community pharmacy, including access to the electronic medical record documenting pharmaceutical care into the patient’s care plan and direct interaction with provider colleagues at the health system, including embedded clinical pharmacists and pharmacy liaisons who work with patients directly during their appointments. The integration of pharmacy services and medical care is proving successful. Evidence already shows better outcomes, improved medication adherence, and reduced costs, specifically with Medicaid patients. Because of accreditation requirements, payer and limited drug distribution contracting, and other complexities of specialty pharmacy services, the infrastructure on this model is much greater than at a community pharmacy. The model provides resources that focus on health outcomes and further evaluate access to care in the scope of health disparities. The Health System Owned Specialty Pharmacy Alliance offers more information on this topic.

Advocacy
After more than a decade of debates and discussions, the right pieces for integrated, whole-person care are in place. There is still work to be done, however, to ensure that the parts work together effectively and that efforts to expand the approach to health care grow in the right direction. Pharmacists must resist the easy tendency to become routinized and siloed. If internal teams constantly seek and have access to the bigger picture, then pharmacists may realize that their biggest problem is not the department down the hall, but the data showing that millions of individuals deserve and need better outcomes. Advocacy, improvement, and innovation must be normalized.

Do not sit back and wait for hospital leadership to guide the way. Specialty pharmacy leadership can formulate goals and advocate within their own systems, demonstrating new ways to be involved, and resolving outcome disparity.

Strong communication can oil the new gears of integrated care. For example, team members, both within the specialty pharmacy and as part of the larger care team, should use the same language and terms to describe patient problems and solutions. Make sure that terminology does not cause confusion but increases clarity.

When data in specific departments show that certain chronic disease states disproportionately affect non-White or underinsured populations, recognize the opportunity. Seek creative ways to engage with the team and educate disassociated patients. For example, are there any start-ups or technology companies offering beta programs for more affordable smart watches and other wearables? Research from the American Diabetes Association shows the benefits of continuous glucose monitoring. Educate health care team members and patients with engagement to optimize care.

Find ways to proactively eliminate barriers to care with at-risk populations. Adopting a spirit of innovation makes it easier to envision possibility and find new solutions to familiar problems.

Patient-centered models within UMass Memorial Health and other systems have an opportunity to narrow and close the disparity gap. At each postdiagnosis patient interaction, there are on-the-ground and philosophical opportunities for specialty pharmacies to improve outcomes by educating at-risk individuals about the benefits of following courses of care, encouraging the filling and taking of prescribed medications, and establishing and taking pride in ease of access and a supportive “Care is there” environment.
ALZHEIMER DISEASE (AD) is the most common type of dementia and affects an estimated 6 million individuals in the United States.\(^1,2\)

Characterized by symptoms of behavioral and cognitive impairment, it is not just a disease of older adults. Up to 200,000 individuals younger than 65 years have early-onset AD.\(^2\) AD is the fifth-leading cause of death in those 65 years or older and has an estimated annual cost of $355 billion.\(^2,3\)

Most approved medications for the treatment of AD are symptomatic therapies that work on the acetylcholine or glutamate neurotransmitters. The standard medical treatment for AD includes cholinesterase inhibitors and a partial N-methyl-D-aspartate (NMDA) antagonist that aid the symptoms of learning and memory.\(^4\) Most recently, Biogen’s aducanumab (Aduhelm) received FDA approval for patients with AD with mild cognitive impairment or mild dementia, although it has been the subject of controversy. There are no treatments that delay, prevent, or stop disease progression.

AD is a progressive neurodegenerative disorder, and the risk of developing AD doubles every 5 years after an individual turns 65 years old.\(^1,2\) It is characterized by a continuous decline in completion of familiar tasks, memory loss, and thinking.\(^1,3\)

Risk factors include aging, brain trauma, diabetes, family history, high blood pressure, and smoking.\(^2,3\)

Most experts acknowledge that development of AD occurs through several mechanisms in the brain. Neuropathological changes include the appearance of extracellular amyloid plaques, neuritic plaques associated with neural injury, and neurofibrillary degeneration exemplified by neurofibrillary tangles. The pathogenesis also involves tau protein, which aids in microtubule assembly. The formation of neurofibrillary tangles involving tau protein lead to neuronal injury and the progressive loss of neurons results in cognitive impairment.\(^5\)

Treatment

The standard of care continues to focus on the symptoms of AD. For treatment of mild to moderate AD, first-line cholinesterase inhibitors give small improvements in cognition, daily activities, and neuropsychiatric symptoms. For moderate to severe disease, the NMDA receptor antagonist memantine is recommended in combination with a cholinesterase inhibitor.\(^4,6\)

Aducanumab, a recombinant monoclonal antibody directed against amyloid-β, obtained approval in June 2021 to a mixed response from neurologists and investigators. Although aducanumab demonstrated the ability to reduce brain amyloid-β levels in research trials, other clinical end point benefits have been inconsistent and small. With controversial results and a steep price, clinical practice has been varied to date and will likely evolve over time.\(^7\)

Aducanumab is indicated for mild AD and is administered intravenously every 4 weeks. A recent brain MRI study is required prior to initiating treatment, and additional MRIs are required during dose escalation.\(^8\) Adverse effects include amyloid-β–related imaging abnormalities, confusion, diarrhea, falls, headaches, and hypersensitivity.\(^9\) No clear guidance has been given regarding treatment duration. Other treatments studied for their antioxidant effects in AD are vitamin E and the monoamine oxidase inhibitor selegiline. Vitamin E at a dose of 2000 IU per day has shown modest but inconclusive benefits for
delaying progression in patients with mild to moderate AD. However, some studies suggest additional AD risk in patients with cardiovascular disease.\textsuperscript{10,11} Selegiline does not have strong long-term evidence of benefit in clinical research and is significantly more costly.\textsuperscript{11}

**On the Horizon**

The AD pipeline continues to be robust, with 126 agents in development and 28 of those in phase 3 trials. Most of these drugs target the underlying biology of the disease.\textsuperscript{12} For example, donanemab, lecanemab, and solanezumab are monoclonal antibodies that target amyloid-β plaque and are in phase 2 and 3 trials. The remaining targets focus on enhancing cognitive abilities and reducing neuropsychiatric symptoms. New biomarker technologies are also transforming the epidemiologic study of AD. Future research will target the tau protein and brain waves and will include an antibody and vaccine.\textsuperscript{13}

**Lifestyle Factors**

A healthy lifestyle that includes exercise, mentally stimulating pursuits, a nutritious diet, quality sleep, and social engagement has shown to benefit individuals as they age and may also help reduce cognitive decline in AD.\textsuperscript{14} The CDC recommends that individuals 65 years or older get 30 minutes of moderate-intensity activity 5 days a week to improve their overall health.\textsuperscript{15}

Not only does good nutrition help with chronic disease risk factors such as cardiovascular disease and diabetes, it also may protect the brain through anti-inflammatory and antioxidant processes. So far there is no hard evidence that avoiding or eating certain foods lowers AD risk, but there are clues that show that eating fish and green, leafy vegetables, as well as following a low-salt and low-sugar diet, may lower the risk of developing dementia.

Although investigators are still debating whether dementia leads to poor sleep or poor sleep exacerbates dementia, they agree that there is a link.

In 2018, the National Institutes of Health reported that sleep deficits might increase the amyloid-β proteins in the brain linked to AD.\textsuperscript{16}

The results of another study that followed individuals 25 years and older showed a 30% increased dementia risk in 50-, 60-, and 70-year-old participants who slept 6 or less hours a night.\textsuperscript{17}

Lifelong learning and social interaction also show evidence of slowing cognitive decline. However, most of these trials need longer term follow-up.\textsuperscript{18}

**What Can Pharmacists Do?**

Pharmacists should stay up-to-date on the research. Early identification is a priority. Screening patients and identifying AD earlier can have a lasting impact. Finally, there are lifestyle factors that may reduce the risk of developing AD. Pharmacists should promote healthy choices, such as cognitive engagement, diet, and exercise.

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**REFERENCES**


C OVID-19 VACCINE–RELATED ERRORS have demonstrated the importance of ensuring a safe medication-use process.\(^1\)

Insufficient training, multiple manufacturers, and noninterchangeable products increase the risk of vaccine-related errors. Increasing the complexity are the addition of boosters with different doses, personnel new to the vaccine administration process, changes in dosing, easily misidentified labeling or products, vaccines given together, and the interchanging of booster products.\(^2,3\) As a result, there is an increased need to be alert in safety efforts with vaccine administration and storage. Pharmacy staff members must work together to improve safety and prevent vaccine-related errors.

Supply Chain
As staff members dispense and administer more vaccines, the probability that a mix-up can occur increases. Pharmacy staff members should proactively assess areas in the pharmacy where vaccines have been handled and stored and develop a safety plan. Signing up for CDC and drug manufacturer newsletters to stay abreast of safety warnings can help. Staff members should

### TABLE. WHAT PHARMACISTS SHOULD CONSIDER\(^4,5\)

<table>
<thead>
<tr>
<th>ITEM OF CONCERN</th>
<th>CONSIDERATION</th>
</tr>
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| Adult and pediatric formulations (not interchangeable): COVID-19 vaccine | Pfizer-BioNTech adult and pediatric formulations are different and cannot be interchanged. Consider separating and color coding bins and products.  
  • Adult formulation (aged ≥ 12 years): (purple cap)  
  • Pediatric formulation (aged 5-11 years): (orange cap) |
| Predrawn syringes not labeled                                       | • Label syringes if drawn up and not administered with product name, dose, and purpose.  
  • Double-check by keeping the empty vial with syringe when possible. |
| Maximum punctures for Moderna vial: 20                             | Note each dose with an X and each booster with a Y to track punctures and calculate waste. |
| Orange-capped Pfizer-BioNTech vials for pediatric patients aged 5-11 years: expiration date mix-up | Train staff; label with manufacture date. |
| Mix-ups between influenza vaccine and COVID-19 vaccines             | • Have patient read syringe label and vial back, if possible, prior to administration.  
  • Limit vaccines taken to administration area to only those being given to prevent a mix-up. |
label and segregate high-risk inventory to prevent errors. Many experts recommend using baskets and/or color coding on refrigerators and shelves based on whether the vaccines are used for adults or children. Prepackaging and labeling kits for high-risk vaccines can distinguish among booster, pediatric, or standard doses. All pediatric vaccines should be stored in a separate area of the pharmacy and administration areas away from the adult doses.

Implementing safety recommendations into the pharmacy’s workflow decreases risk. Mix-ups have recently occurred, and the TABLE highlights items that pharmacy personnel should consider when assessing the system and training staff members.

Preparation
During dose preparation, pharmacy staff members should get into the habit of using charts, checklists, guides, and other tools to ensure that there is a multiple check process. Do not rely solely on the cap color when drawing up products, as these often get separated from vials. Best practices include instituting a double or triple check of the label and dose when drawing up a product, immediately labeling syringes not administered, and training team members to not rely on memory. For example, the Moderna COVID-19 vaccine is 0.5 mL for a series dose and 0.25 mL for the booster dose. Recommendations include labeling predrawn syringes for the purpose they are intended, such as an adult series or booster or pediatric dose. In addition, designating a staff member specifically to make updates to workflow documents and communicate changes to staff members immediately upon release is crucial to ensure a safer process.

Patient Administration
Setting up a designated area for administration can minimize distractions. Verify the product the patient will receive as a third check prior to administration, showing the patient the vaccine vial and syringe. Engaging the patient is a final critical step in the process.

Reporting
If a vaccine error is identified, follow policies and procedures for documenting and reporting the error. Report administration errors and serious adverse events to the Vaccine Adverse Event Reporting System (VAERS). To file an electronic report, visit the VAERS website (https://vaers.hhs.gov/reportevent.html). The Institute for Safe Medication Practices (ISMP) also requests that providers report vaccine errors to the ISMP National Vaccine Errors Reporting Program (www.ismp.org/report-medication-error).

Conclusion
It is essential to stay abreast of changes in vaccine formulations and recommendations. Communicating with all staff members and being proactive in planning helps ensure that risk in the pharmacy is reduced. When situations do arise, develop a plan to prevent future mix-ups and adverse events.

REFERENCES
CERVICAL CANCER is a rare type of cancer that originates from the cellular lining of the cervix, representing approximately 0.8% of all new cancer cases and 0.7% of all cancer deaths each year in the United States.¹

In 2021, there were 14,440 new cases of cervical cancer and approximately 4290 deaths from cervical cancer in the United States, according to data from the National Cancer Institute.¹ The 5-year relative survival rate for patients with cervical cancer is 66.3%, with a lower 5-year survival rate of 17.6% for patients with distant metastatic disease.¹

Along with lower survival rates, recurrence rates for metastatic cervical cancer remain high, despite the implementation of newer therapies. Platinum-doublet chemotherapy alone was initially seen as a preferred first-line treatment option for patients with metastatic cervical cancer. Over time, however, the addition of newer agents such as the VEGF inhibitor bevacizumab (Avastin, Genentech) to first-line cervical cancer regimens has improved overall survival for patients who have metastatic cervical cancer. Over time, however, the addition of newer agents such as the VEGF inhibitor bevacizumab (Avastin, Genentech) to first-line cervical cancer regimens has improved overall survival for patients who have metastatic cervical cancer.² Regardless, patients with metastatic disease will ultimately fail treatment in the first-line setting because of chemotherapy intolerance or disease progression. National Comprehensive Cancer Network guidelines recommend numerous second- and subsequent-line therapies for metastatic cervical cancer.² Therefore, there has been a general push for the development of newer, more effective, and safer treatments in this setting.

Antibody-drug conjugates (ADCs) are targeted agents that have shown promise in the treatment of certain cancers, including acute leukemias, breast cancer, and Hodgkin lymphoma. An ADC comprises a cytotoxic drug (“payload”) that has been artificially combined with a monoclonal antibody designed to carry, selectively target, and bind to tumor antigens. It then delivers the cytotoxic payload to the tumor sites, which results in cell death. Once the payload is internalized by a tumor cell, a phenomenon known as “bystander killing” can occur, where the cytotoxic payload is diffused to adjacent cells. By itself, the cytotoxic payload is incredibly potent. ADCs have been theorized to be more efficacious and safer than standard chemotherapy because of the lower incidence of systemic chemotherapy exposure through localized delivery.³ Even though ADCs are more selective than other chemotherapy agents, risks for off-target toxicities exist, oftentimes involving major organs.

Tissue factor (TF), also known as platelet coagulation factor III, is normally found within the body and is involved with the initiation of the coagulation cascade.⁴ Unfortunately, in cervical and many other cancers, malignant cells have developed mechanisms to manipulate TF. Some cancer cells can increase overall TF levels in the bloodstream, resulting in surges of tumor cell angiogenesis, metastasis, growth, and risks for thrombosis.⁴ Specifically in cervical cancer, higher levels of TF expression have been associated with higher-stage disease and an increased rate of invasion and metastasis.⁵

FDA Approves Newest Antibody-Drug Conjugate for Cervical Cancer
Tisotumab Vedotin-tftv Is Used as Antitumor Therapy for Patients With Disease Progression During or After Chemotherapy

BY DON V. SCIGLIANO AND BRYAN FITZGERALD, PHARMD, BCOP

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Antibody-drug conjugates (ADCs) are targeted agents that have shown promise in the treatment of certain cancers, including acute leukemias, breast cancer, and Hodgkin lymphoma. An ADC comprises a cytotoxic drug (“payload”) that has been artificially combined with a monoclonal antibody designed to carry, selectively target, and bind to tumor antigens. It then delivers the cytotoxic payload to the tumor sites, which results in cell death. Once the payload is internalized by a tumor cell, a phenomenon known as “bystander killing” can occur, where the cytotoxic payload is diffused to adjacent cells. By itself, the cytotoxic payload is incredibly potent. ADCs have been theorized to be more efficacious and safer than standard chemotherapy because of the lower incidence of systemic chemotherapy exposure through localized delivery.³ Even though ADCs are more selective than other chemotherapy agents, risks for off-target toxicities exist, oftentimes involving major organs.

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The FDA approved tisotumab vedotin-tftv (Tivdak, Seagen/Genmab) in September 2021 for patients with metastatic or recurrent cervical cancer with disease progression during or after prior treatment with chemotherapy. As the first ADC approved to target TF on tumor cells, tisotumab vedotin comprises a TF-directed antibody attached to a cytotoxic microtubule inhibitor, monomethyl auristatin E (MMAE). After selectively binding to extracellular TF, the ADC complex becomes internalized and MMAE is released intracellularly, leading to cell death.

The innovaTV 204 clinical trial (NCT03438396) was a multicentered, open-label, single-arm, phase 2 trial where 101 patients with either metastatic or recurrent cervical cancer were treated with tisotumab vedotin. Eligible patients had to have disease progression either during or after treatment involving doublet chemotherapy (paclitaxel, plus either platinum or topotecan) plus bevacizumab. Patients received tisotumab vedotin at a dose of 2 mg/kg (maximum 200 mg/dose) intravenously every 3 weeks until either disease progression or unacceptable toxicities.

After a median follow-up of 10 months at the time of data cutoff, 24% of patients had a confirmed disease response. The data were supported by a 6-month survival rate of 79% and a median overall survival rate of 12.1 months. With approximately 79% of patients having reductions in target lesion size and a median time to response of 1.4 months, the rapid antitumor effects of tisotumab vedotin may be clinically attractive as a subsequent-line treatment option.

Numerous toxicities were seen in the innovaTV 204 trial, including alopecia, bleeding events, fatigue, nausea, and peripheral neuropathy. Ocular toxicities have been seen with tisotumab vedotin, as well, reported in 53% of patients in the trial. These ocular toxicities include conjunctivitis, dry eye, keratitis, and vision changes, with rare cases of corneal ulceration and severe vision loss. The FDA label for tisotumab vedotin includes a boxed warning for ocular toxicities, and it is recommended that patients undergo ophthalmic exams at baseline and prior to each cycle. In addition, it is recommended that patients premedicate each infusion of tisotumab vedotin with corticosteroid and vasoconstrictor eye drops and ocular lubricants and use cooling eye pads during the infusion.

Tisotumab vedotin is one of the newest subsequent-line treatment options for patients with recurrent metastatic cervical cancer, who have generally poorer prognoses. As an ADC, tisotumab vedotin is among a growing class of antitumor therapies with more than 100 others under investigation.

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Therapeutics Treat Patients Who Test Positive for COVID-19
Monoclonal Antibodies and Emerging Agents May Avert Severe Illness, Especially for High-Risk Individuals

BY SARA LEE, PHARMD

ALTHOUGH VACCINES REMAIN the best preventive strategy for COVID-19, there is still a need for therapies to help avert progression to severe illness, especially for high-risk patients.

**Monoclonal Antibodies**

Monoclonal antibodies (mAbs) have the potential to prevent and treat COVID-19 by binding to an epitope in the SARS-CoV-2 spike protein to neutralize the virus. It is expected such therapies that directly target SARS-CoV-2 would have the greatest effect earlier in the disease course when pathogenesis is primarily driven by viral replication. Therefore, treatment should be started as soon as possible in those who test positive. Three anti–SARS-CoV-2 mAbs have received emergency use authorizations (EUAs) for mild to moderate COVID-19 in those who are at high risk for progression (see the Table). Tixagevimab and cilgavimab (Evusheld) is a fourth anti–SARS-CoV-2 mAb under EUA for COVID-19. However, it is only authorized as pre-exposure prophylaxis for immuno-compromised patients who may not mount an adequate immune response to vaccination or those with a history of severe adverse reactions to available vaccines. Its efficacy against the omicron variant is being determined.

Bamlanivimab and etesevimab are neutralizing mAbs that bind to different but overlapping, epitopes of the spike protein. A phase 3 trial in 1035 patients showed a 4.8% absolute risk reduction (ARR) in death or hospitalization in those who received the combination compared with a placebo. They are the only mAbs available for younger pediatric patients, including neonates, largely based on pharmacokinetic studies. However, efficacy may vary based on the dominant circulating strain.

Casirivimab and imdevimab are recombinant mAbs that bind to nonoverlapping epitopes of the spike protein. Also known as the cocktail REGEN-CoV, a single intravenous infusion was associated with a 2.2% ARR in death or hospitalization compared with a placebo. REGEN-COV, a combination of the mAbs casirivimab and imdevimab, reduced the viral load and number of medical visits in patients with COVID 2019 (COVID-19 REGEN-CoV is also available as a subcutaneous injection, which has the propensity to increase access and administration to outside clinic and hospital settings. However, 1-hour monitoring is still required).

Sotrovimab is a pan-sarbecovirus mAb that has demonstrated a 4.5% ARR in death or hospitalizations compared with a placebo. Sotrovimab is expected to have a higher barrier to resistance, because it targets an epitope that lies outside the rapidly evolving motif and thus could retain activity against emerging variants of concern. In a study evaluating in vitro neutralizing activity of anti–SARS-CoV-2 mAbs, sotrovimab was the only agent authorized for treatment that has retained activity against the omicron variant.

**Emerging Agents**

Although mAbs represent a milestone in COVID-19 management, because of challenges in accessibility, administration, and monitoring requirements, new oral antivirals such as molnupiravir nirmatrelvir, and ritonavir (Paxlovid) are welcome interventions to prevent disease progression.

Molnupiravir is a prodrug that introduces transcription errors into viral RNA to impair SARS-CoV-2 replication. Results from a phase 3 trial in 1433 patients...
showed a 3% ARR in death and hospitalizations with molnupiravir compared with the placebo (95% CI, –5.9 to –0.1).\(^9\) Paxlovid is a protease inhibitor that also targets viral replication. Results from a phase 2/3 trial in 2246 patients showed a death or hospitalization rate of 0.8% with Paxlovid compared with 6.3% for the placebo when administered within 5 days of symptom onset.\(^1\) Paxlovid contains ritonavir to slow nirmatrelvir’s metabolism via cytochrome P450 inhibition. However, that also makes it prone to drug interactions requiring pharmacists to be very vigilant upon dispensing. Both agents have been issued an EUA to be initiated as soon as possible after diagnosis and within 5 days of symptom onset to prevent progression in high-risk patients with mild to moderate COVID-19.\(^1,10\) Paxlovid is authorized in patients aged 12 years and older weighing at least 40 kg. However, molnupiravir is not recommended in children or pregnant women, because of the potential risk of embryofetal toxicity and impaired bone and cartilage growth seen in nonclinical studies. There are no available data to support the use of Paxlovid during pregnancy.\(^10,11\)

Repurposing existing drugs is another approach to identify potential agents for COVID-19. Fluvoxamine is the first of many repurposed agents that has shown a mortality benefit.\(^12\) As an oral selective serotonin reuptake inhibitor and an alpha-1 receptor (S1R) agonist, a potential mechanism against COVID-19 is via S1R’s regulation of cytokine production in response to inflammatory triggers. Results from an adaptive platform trial in 1497 patients showed a 5% ARR in hospitalizations with fluvoxamine compared with the placebo.\(^12\)

### Conclusion

The therapeutic management of COVID-19 has evolved with our understanding of its clinical course of infection. As studies continue to emphasize the importance of early intervention in mild to moderate disease, pharmacists should remain up-to-date on information regarding therapies used to control, prevent, and treat COVID-19 infection. ■

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### TABLE. MONOCLONAL ANTIBODIES FOR THE TREATMENT OF MILD TO MODERATE COVID-19 IN PATIENTS AT HIGH RISK FOR PROGRESSING TO SEVERE DISEASE AND/OR HOSPITALIZATION\(^1\)

<table>
<thead>
<tr>
<th>MONOCLONAL ANTIBODY</th>
<th>EMERGENCY USE AUTHORIZATION</th>
<th>SELECT VARIANT(S)(^a)</th>
<th>ADMINISTRATION(^b)</th>
</tr>
</thead>
</table>
| Bamlanivimab and etesevimab | Adults and pediatric patients, including neonates\(^d\) | • Alpha (B.1.1.7)  
• Delta (B.1.617.2, non-AY.1/AY.2)  
• Epsilon (B.1.427, B.1.429)\(^j\) | • Intravenous infusion  
• 700 mg bamlanivimab and 1400 mg of etesevimab\(^d\) |
| Casirivimab and imdevimab | Patients aged 12 years and older who weigh at least 40 kg | • Alpha (B.1.1.7)  
• Beta (B.1.351)  
• Gamma (P.1)  
• Delta (B.1.617.2)  
• Epsilon (B.1.427, B.1.429) | • Intravenous infusion or subcutaneous injection  
• 600 mg casirivimab and 600 mg imdevimab |
| Sotrovimab | Patients aged 12 years and older who weigh at least 40 kg | • Alpha (B.1.1.7)  
• Beta (B.1.351)  
• Gamma (P.1)  
• Delta (B.1.617.2, non-AY.1/AY.2)  
• Epsilon (B.1.427, B.1.429)  
• Omicron (B.1.529) | • Intravenous infusion  
• 500 mg sotrovimab |

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\(^a\)CDC’s designated variant of concern with no change in susceptibility to monoclonal antibody  
\(^b\)Within 10 days of symptom onset  
\(^c\)Etesevimab retains activity against this variant.  
\(^d\)Dosage for pediatric patients weighing less than 40 kg varies depending on body weight.
The FDA has approved zanubrutinib (Brukinsa, BeiGene) for the treatment of adults with Waldenström macroglobulinemia (WM).\(^1\)

Zanubrutinib also received approval for adults with relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 anti-CD20-based regimen. The MZL indication was approved under accelerated approval based on overall response rate, and its continued approval may be contingent upon description and verification of clinical benefit in a confirmatory trial.\(^2\)

**Pharmacology and Pharmacokinetics**

Zanubrutinib is a small molecule inhibitor of Bruton tyrosine kinase. After oral administration, the median time to maximum concentration is 2 hours, and the elimination half-life is approximately 2 to 4 hours. Zanubrutinib is metabolized primarily by cytochrome P450 (CYP) 3A.\(^2\)

**Dosage and Administration**

The recommended dose of zanubrutinib is 160 mg orally twice daily or 320 mg orally once daily. Patients with severe hepatic impairment should use 80 mg orally twice daily. The dose for patients who are concomitantly using a strong CYP3A inhibitor is 80 mg orally once daily. Patients concomitantly using a moderate CYP3A inhibitor should use 80 mg orally twice daily. Zanubrutinib should not be coadministered with a moderate or strong CYP3A inducer. Discontinuation, dose reduction, or interruption of treatment may be required if a grade 3 or higher adverse reaction occurs. The medication should be swallowed whole with water, with or without food.\(^2\)

**Clinical Trials**

The efficacy of zanubrutinib in WM was evaluated in an active control, open-label, randomized trial (ASPIN; NCT03053440). Participants were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity occurred. The major efficacy outcome was the response rate, which was 78% with zanubrutinib and 78% with ibrutinib. An additional efficacy outcome measure was duration of response, which at 12 months was 94% with zanubrutinib and 88% with ibrutinib.\(^2,3\)

The efficacy of zanubrutinib in MZL was assessed in a multicenter, open-label, single-arm trial of 66 patients who had received at least 1 prior anti-CD20-based therapy. Participants received zanubrutinib 160 mg orally twice daily until disease progression or unacceptable toxicity occurred. Efficacy was based on overall response rate (ORR) and the duration of response. The ORR based on CT scan assessment was 56% with a complete response (CR) rate of 20%. The ORR based on prioritizing positron emission tomography–CT scan was 67%, with a CR rate of 26%. The duration of response was not reached at the median follow-up of 8.3 months. At 12 months, 85% of the responders were still in remission.

Zanubrutinib was also evaluated in a multicenter, open-label, single-arm trial (NCT02343120) of 20 patients with previously treated MZL. Participants received zanubrutinib 160 mg orally twice daily or 320 mg once daily. The ORR based on CT scan assessment was 80%, with a CR rate of 20%. The median duration of response was not reached at the median follow-up time of 31.4 months. At 12 months, 72% of the responders were still in remission.\(^1,2\)

**Contraindications, Warnings, and Precautions**

There are no contraindications to treatment with zanubrutinib. Patients using zanubrutinib should be monitored for bleeding, and the medication should be discontinued if
any grade of intracranial hemorrhage occurs. Fatal and serious infections have occurred during treatment with zanubrutinib. Because grade 3 or 4 cytopenias have occurred in patients using zanubrutinib monotherapy, complete blood counts should be monitored regularly during treatment. Second primary malignancies, including nonskin carcinoma, have occurred in patients taking zanubrutinib. Patients should be counseled to use sun protection during treatment. Atrial fibrillation and atrial flutter have been reported in patients receiving zanubrutinib monotherapy. Because zanubrutinib can cause fetal harm, both men and women should use effective contraception during treatment and for 1 week after the last dose. Women should not breastfeed while using zanubrutinib.

The most common adverse reactions are decreased lymphocyte count, decreased neutrophil count, decreased platelet count, hemorrhage, musculoskeletal pain, rash, and upper-respiratory tract infection.

REFERENCES
340B Program Helps Reduce Health Care Disparities
Drug Manufacturers Participating in Medicaid Offer Lower Prices, Stretching Resources and Providing Comprehensive Services to a More Patients

BY JUSTIN LINDHORST, MBA

A RECENT REPORT FROM the Commonwealth Fund puts the US health care system in last place compared with 11 other high-income countries.1

Despite spending the highest proportion of its gross domestic product on health care, the United States performed the worst in terms of access to care, administrative efficiency, health equity, and outcomes.1 Although the performance of the US health system affects all Americans, certain populations are at greater risk for health disparities based on their age, disability, ethnicity, gender, race, sexual identity, and socioeconomic status.2 Health disparities include, but are not limited to, differences in access to care, disease burden, life expectancy, mental health, and mortality.3

Health disparities have long been documented in the United States, evidenced by poorer outcomes for at-risk populations across a wide range of health conditions and indicators.4 Beyond the avoidable negative health outcomes, health disparities create an unnecessary financial burden on both the health care system and the patients. A study commissioned by the Joint Center for Political and Economic Studies and conducted by investigators at Johns Hopkins University and the University of Maryland examined the costs associated with health disparities over a 4-year period.5 The investigators analyzed economic burden across 3 measures: costs of premature death, direct medical cost of health inequalities, and indirect cost of health inequalities. The total direct and indirect costs over the 4-year period totaled $1.24 trillion.5

The COVID-19 pandemic has brought health disparities into sharper focus. Health systems, nonprofit agencies, pharmacies, and the US government are working to promote health equity and reduce disparities. “Health equity is achieved when everyone can attain their full potential for health and well-being,” according to the World Health Organization.6

For qualified health systems, cost savings generated through the 340B pharmacy program provide significant opportunities to reduce health disparities.

Health Systems
The 340B program was designed to “stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services,” according to the Health Resources & Services Administration.7

The program works by requiring drug manufacturers participating in Medicaid to provide outpatient drugs at a reduced price for qualified health care organizations. Eligible health organizations are referred to as covered entities (CEs). They are defined by statute and include certain health centers, hospitals, Ryan White HIV/AIDS program grantees, and specialized clinics that serve at-risk or vulnerable populations.7 The difference between what a CE pays for 340B drugs and what they are reimbursed by third-party payers generates cost savings that can be used to expand services, invest in community health initiatives, provide care for individuals who are underinsured or uninsured, and offer discounted or free medications.

Promoting Health Equity
CEs often care for low-income, minority, underserved, or vulnerable populations. 340B disproportionate share hospitals...
Improving Outcomes, Reducing Disparities

340B cost savings allow CEs to enhance services and stretch resources. In addition to financing essential community support services, funding critical salaries, and keeping doors open, the support provided at the 340B pharmacy level can promote equity and reduce disparities. The 340B program permits CEs to use an in-house pharmacy, contract with external pharmacies, or use a combination of both to expand access and better serve unique patient communities. There is no cap to the number of contract pharmacy arrangements that a CE can deploy. This flexibility allows CEs the ability to maximize cost savings, better meeting the needs of the communities and patients they serve. CEs can leverage their 340B pharmacy staff members to enhance the clinical and support services provided to patients.

CEs often use cost savings to develop programs integrating pharmacists as central members of the care team. Deploying integrated pharmacy services has been shown to improve outcomes and patient satisfaction while reducing health care costs. Many 340B hospitals have used cost savings to integrate members of the pharmacy team, increasing adherence, providing targeted services for unique patient populations, and reducing hospital readmissions. Many programs dispense specialty drugs for patients with chronic or difficult-to-treat health conditions.

“Contracting with a specialty pharmacy that has specific therapeutic experience can enhance clinical support, improve patient engagement, and assist with other critical aspects of care, such as timely medication access and connection to financial assistance programs,” Enright said. “Highly trained, culturally competent staff add an additional layer of support at the individual patient level, reducing disparities and enhancing the patient’s overall health care experience.”

Contract pharmacy arrangements help CEs extend the geographic reach of their programs. In urban areas, pharmacy deserts leave Black and Hispanic patients with fewer options to access medication. In rural areas, an increase in hospital closures threatens to place vulnerable communities at even greater risk. Contract pharmacy partnerships can help solve that problem.

“Contract pharmacy arrangements help extend program reach to benefit a larger population of patients, often whom reside in rural or economically challenged areas,” said Pete Pecoraro, national account manager for 340B program and client services at BioMatrix Specialty Pharmacy. “These partnerships are critical in expanding both medication access and clinical support for patients residing in at-risk and underserved communities.”

Toward a More Equitable Health System

The 340B program is not without controversy. Recent research questions the amount of uncompensated care that some hospitals participating in the program provide. (DSHs) treat a significantly higher number of low-income and Medicaid patients than non-340B acute-care hospitals. Additionally, 340B DSHs are more likely to provide “essential community services” that are considered “low-margin” or not always reimbursed by third-party payers.

These services often focus on at-risk patients and include community health programs addressing behavioral health, health care access, and social determinants influencing health. In its 2021 340B Hospital Community Benefit Analysis, the American Hospital Association examined public tax records of tax-exempt 340B hospitals. The analysis shows that cost savings generated by the 340B program provided $67.9 billion in total community health benefits.

“340B savings are used to provide a wide range of support for underserved communities, including diagnostics, counseling, transportation, and translation services,” said Sabine Enright, PharmD, director of 340B services at BioMatrix Specialty Pharmacy. “These services are a critical resource helping to address disparities and promote health equity.”

In addition to making up for low-margin or non-reimbursable services, some hospitals rely on 340B cost savings to support staff salaries and, in some cases, keep their doors open.

Hemophilia treatment centers provide specialized support for patients with bleeding disorders. 340B cost savings provided up to 90% of funding for critical staff, including nurses, physical therapists, and social workers at these centers, according to a 2018 report.

Critical access hospitals (CAH) are 340B-eligible organizations serving rural populations, which often face health disparities such as less access to care and poorer outcomes. CAH provide essential support for at-risk communities, but they face significant financial challenges that often threaten their ability to remain open. In a survey of more than 500 hospitals that were 340B-eligible, three-fourths of CAH respondents indicated that the 340B program is essential to staying open.

Improving Outcomes, Reducing Disparities

340B cost savings allow CEs to enhance services and stretch resources. In addition to financing essential community support services, funding critical salaries, and keeping doors open, the support provided at the 340B pharmacy level can promote equity and reduce disparities. The 340B program permits CEs to use an in-house pharmacy, contract with external pharmacies, or use a combination of both to expand access and better serve unique patient communities. There is no cap to the number of contract pharmacy arrangements that a CE can deploy. This flexibility allows CEs the ability to maximize cost savings, better meeting the needs of the communities and patients they serve. CEs can leverage their 340B pharmacy staff members to enhance the clinical and support services provided to patients.

CEs often use cost savings to develop programs integrating pharmacists as central members of the care team. Deploying integrated pharmacy services has been shown to improve outcomes and patient satisfaction while reducing health care costs. Many 340B hospitals have used cost savings to integrate members of the pharmacy team, increasing adherence, providing targeted services for unique patient populations, and reducing hospital readmissions. Many programs dispense specialty drugs for patients with chronic or difficult-to-treat health conditions.

“Contracting with a specialty pharmacy that has specific therapeutic experience can enhance clinical support, improve patient engagement, and assist with other critical aspects of care, such as timely medication access and connection to financial assistance programs,” Enright said. “Highly trained, culturally competent staff add an additional layer of support at the individual patient level, reducing disparities and enhancing the patient’s overall health care experience.”

Contract pharmacy arrangements help CEs extend the geographic reach of their programs. In urban areas, pharmacy deserts leave Black and Hispanic patients with fewer options to access medication. In rural areas, an increase in hospital closures threatens to place vulnerable communities at even greater risk. Contract pharmacy partnerships can help solve that problem.

“Contract pharmacy arrangements help extend program reach to benefit a larger population of patients, often whom reside in rural or economically challenged areas,” said Pete Pecoraro, national account manager for 340B program and client services at BioMatrix Specialty Pharmacy. “These partnerships are critical in expanding both medication access and clinical support for patients residing in at-risk and underserved communities.”

Toward a More Equitable Health System

The 340B program is not without controversy. Recent research questions the amount of uncompensated care that some hospitals participating in the program provide.
Debate continues, but achieving health equity will require an all-hands-on-deck approach to identify and systematically address the health disparities negatively affecting US communities.

Several drug manufacturers are pushing back against providing discounts for contract pharmacies. But organizations such as the American Hospital Association and 340B Health maintain that the program is working as intended. They cite the multitude of unique ways that hospitals use 340B funds to enhance services, expand access, support patients, and ultimately create healthier communities. The 340B program still has a high level of support. In February 2021, a large bipartisan group of lawmakers voiced their support for protecting the program. Debate continues but achieving health equity will require an all-hands-on-deck approach to identify and systematically address the health disparities negatively affecting US communities.

“There is no single program in existence today that does more to promote health equity than the 340B drug pricing program,” Pecoraro said. “Whether increasing access to care, expanding operations, or financing community services, 340B extends critical support to patients who would not have access to similar resources in the absence of the program.”

As the US moves toward a more health care equitable system, a broad coalition of community health workers, health systems, lawmakers, pharmacies, and professional health agencies agree that the 340B program will continue to play a critical role in promoting healthier communities and reducing health disparities.

**REFERENCES**


Current Good Manufacturing Practices Are Reliable Safeguard
Properly Implemented CGMP Should Not Be Seen as a Regulatory Burden but a Remedy to Poorly Compounded Drugs

By Gary E. Ritchie

In the minds of many pharmacists, the FDA’s Current Good Manufacturing Practices (CGMP) have unduly raised the bar of compliance under the authority and jurisdiction of state boards of pharmacies (SBOP).

But compared with the potential financial- and safety-related consequences of noncompliance, CGMPs should not be seen as a regulatory burden but as a reliable safeguard against disastrous outcomes, a point made clear in 2012 when improper compounding at the New England Compounding Pharmacy sparked an outbreak of fungal meningitis. The outbreak resulted in 64 deaths and 751 injuries.1 As of November 2017, no studies had been published that provided financial data on the impact of CGMPs on drug-compounding pharmacies’ compliance or the significance to protecting the health of the public. But the FDA’s SBOP data provide compelling evidence that, for the most part, compounding pharmacies do not realize the importance that CGMPs have on sustaining compounded medicines as a viable resource to patients.2

Although much work still needs to be done to eliminate the risk of exposing the public to poorly compounded drugs, education is the best mechanism for changing risky behavior by compounding pharmacists. With the right knowledge about what the FDA and the public require from quality compounded drug products, the FDA’s mission can be realized in a way that works to everyone’s benefit. Compounding pharmacists should consider these questions to understand the risks of failing to adopt CGMPs throughout their organizations: How do CGMPs apply to compounding? How does a compounding pharmacy comply with CGMPs? How does the FDA assess the state of CGMP compliance once implemented? Rather than contending that regulators are misapplying the rules and that the FDA, in the words of Congress, is “overstepping” its regulatory authority, educating and implementing appropriate strategies that enhance patient safety while making economic sense will best serve compounding pharmacies in the long run.

The Law and Compounding Pharmacies

A debate has been brewing between compounding pharmacists and the FDA. Following the New England Compounding Center tragedy in 2012, Congress acted quickly to promulgate new rules codified in the Drug Quality
and Security Act (DQSA) that gave the FDA regulatory oversight of drug compounding activity in the United States and its territories.

Since then, some statutory practices that had evolved over the past 25 years are being questioned when applied to drug compounding. These concerns have been further accelerated by an FDA now more proactive in its initiative to bring its operations into the 21st century. CGMPs are the cornerstone of the Food, Drug and Cosmetic (FD&C) Act. CGMPs provide a mechanism for drug manufacturers to produce effective, pure, and safe drug products and for the FDA to inspect and issue observations, warnings, injunctions, and consent decrees to drug manufacturers that fail to comply with the CGMP rules.

Since the DQSA was passed in 2013, the FD&C Act has been extended to additional drugs for humans and for veterinary compounding.

The FDA’s list of inspections, recalls, and other enforcement actions shows that regulators not only intend to make good on this initiative but are actively doing so. With many pharmacies not registered as outsourcing facilities, it is certain that the FDA will continue to leverage its enforcement of CGMPs on compounding pharmacies to protect the public from poorly compounded drugs.

REFERENCES
Overcoming Barriers to Influenza Vaccination: Examining Available Vaccines for 2021-2022 and Addressing Hesitancy During the COVID-19 Pandemic

**EDUCATIONAL OBJECTIVES**

At the completion of this activity, the participant will be able to:

- Examine the epidemiology of the influenza virus and the challenge of increasing influenza vaccination rates during the era of COVID-19
- Determine the patient populations at elevated risk of complications related to influenza and COVID-19 and the need to improve vaccination rates during the pandemic
- Explore the recommendations, safety, and efficacy of the available influenza vaccines for the 2021-2022 influenza season
- Investigate the growing presence of pharmacies as a site of care to improve influenza and COVID-19 vaccination rates especially during the ongoing pandemic and the role of the pharmacist as patient identifier, educator, and vaccine administrator

**TARGET AUDIENCE:** Pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** December 15, 2021

**EXPIRATION DATE:** January 15, 2023

**ESTIMATED TIME TO COMPLETE ACTIVITY:** 2.5 hours

**FEE:** This lesson is offered for free at www.pharmacytimes.org.

**Introduction**

In 1918, the influenza A (H1N1), Spanish flu, killed 50 million to 100 million people worldwide, and was called “the mother of all pandemics.”

Influenza vaccines have been available for more than 80 years with the first-generation live-attenuated vaccine developed in 1933. Due to the predominant use of embryonated chicken eggs for their production and the continuous antigenic changes in the influenza viruses, they had challenges with effectiveness. In 1973, the World Health Organization (WHO) issued annual recommendations for the composition of the vaccine based on surveillance cultures and in 1978, the first trivalent vaccine was produced, resulting in improved responses.

Vaccination is a powerful tool for limiting the progression and dissemination of infectious diseases, as vaccines save lives and are one of the greatest achievements in the history of public health. It is estimated that vaccines save more than 9 million lives per year worldwide. Thanks to extensive vaccination, smallpox, a deadly disease, has been eradicated with the WHO proclaiming the disease to be eliminated worldwide in 1980.

It was an unprecedented achievement in public health. Despite this progress, some diseases that were almost eliminated by vaccines are slowly increasing. For example, cases of measles in the United States have been on the rise even though endemic measles were declared eliminated in 2000. This increase was related to an antivaccination trend that started following a 1997 study suggesting that the measles, mumps, rubella (MMR) vaccine was causing autism; however, this study was disproven and retracted.

As vaccine hesitance continues to present a challenge, it is imperative that pharmacists address potential misconceptions to increase vaccination rates for all vaccines, including the influenza vaccine.
This is of utmost importance given the continued burden respiratory illnesses impose on the health care system.

In December 2019, a group of patients in Wuhan, China, experienced shortness of breath and fever resulting in isolation of a novel coronavirus, SARS-CoV-2, as the causative agent. In January of the following year, the Centers for Disease Control and Prevention (CDC) confirmed the first laboratory-confirmed case of COVID-19, the illness caused by SARS-CoV-2. The WHO declared the coronavirus outbreak a Public Health Emergency of International Concern at the end of the month, and a COVID-19 pandemic on March 11, 2020, with most US states reporting widespread cases by the next month. Elective surgeries were put on hold and routine health care was delayed, including vaccinations. In 2020, routine vaccination rates declined significantly across all populations in the United States due to fears of contracting COVID-19 and overwhelmed US health care systems. Several COVID-19 vaccines were developed about 10 months later. Unfortunately, due to various reasons including fear, distrust, and confusion, there has been hesitation for people to receive the COVID-19 vaccine, adding to the vaccine hesitancy issue. This article will focus on a review of influenza and its complications and a selection of available influenza vaccines as well as the impact of the COVID-19 pandemic on immunizations, objections to vaccination, and overcoming barriers to improve immunization rates.

### Review of Influenza

Influenza is an acute infection caused by the virus of the Orthomyxoviridae family involving both the type A and type B viruses. As the influenza virus has a high mutation rate, the WHO serologically monitors the yearly changes and recommends the strains that need to be included in next year’s vaccine to the FDA, which makes the final decision. Influenza A viruses are classified by...
their envelope glycoproteins, hemagglutinin (HA) and neuraminidase (NA). The 3 major HA subtypes (H1, H2, and H3) and 2 NA subtypes (N1 and N2) are commonly associated with disease in humans. Influenza B viruses have 2 genetic lineages, B/Victoria/2/87-like and B/Yamagata/16/88-like. Minor changes in these viruses are defined as antigenic drifts, while major changes are antigenic shifts. Only influenza A viruses have antigenic shifts, which can result in a pandemic.

In 2019 and 2020, influenza and pneumonia were the ninth most common cause of death in the United States. Fatilities from influenza begin to rise in midlife and are highest in persons with chronic disease. The number of cases fluctuate each year (FIGURE 1) and vary by age (FIGURE 2). Measures available to reduce the incidence of influenza include immunoprophylaxis with inactivated or live influenza vaccine and chemoprophylaxis. Vaccination of people at risk and those likely to transmit influenza to at-risk populations is the most effective measure. In addition, healthy practices of avoiding others who are ill, using proper handwashing, and covering one’s mouth properly when coughing or sneezing will help stop the spread of germs and prevent respiratory illnesses. The impact of these practices reducing influenza can be seen on FIGURE 1 for the 2020-2021 season when the COVID-19 pandemic restrictions were in place.

The influenza vaccine provides protection from influenza and decreases potential complications and health care costs. It is estimated that in the United States, vaccines prevented 1.6 million to 6.7 million illnesses, 790,000 to 3.1 million outpatient medical visits, 39,000 to 87,000 hospitalizations, and 3000 to 10,000 respiratory and circulatory deaths during the influenza seasons between 2010 and 2016. The 2017-2018 season was cited as particularly severe due to elevated influenza activity. Despite a vaccine efficacy of 38%, it was estimated that vaccination prevented 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8000 deaths.

As of November 3, 2021, approximately 45.6 million cases of COVID-19 had been reported in the United States, including
approximately 740,000 deaths. There were 400,000 influenza-like illness hospitalizations in the 2019-2020 influenza season. Although influenza activity during the 2020-2021 season was low throughout the United States (FIGURE 1)3, fewer influenza vaccinations did not result in more influenza. Masking, social distancing, increased handwashing, and decreased travel led to a significant reduction in influenza for 2020-2021.13,17

The timing and intensity of the 2021-2022 influenza season cannot be predicted. Influenza vaccination remains an important tool for the prevention of potentially severe respiratory illness, which might decrease stress on the US health care system during the COVID-19 pandemic.13,17

Healthy People 2030 is a group that continues to promote the movement throughout the United States to increase immunization rates and reduce preventable infectious diseases.19 They also address vaccine hesitancy and continue to have a significant impact on preventing communicable diseases, reducing preventable complications, and improving clinical outcomes. A goal target of 70% was set for individuals to receive the influenza vaccine. They have not met their goal as only 49.2% of persons aged 6 months and older were vaccinated against seasonal influenza for the 2017-2018 season. However, adult vaccination coverage remains low for most routinely recommended vaccines and below the Healthy People 2030 target.19

It is important to note that the effectiveness of the influenza vaccine is dependent on factors such as a patient’s age and health status, circulating strains, and type of vaccine. For this reason, the overall effectiveness varies from season to season ranging from 19% to 60%.4 A key point for patients to remember is that they could still get the flu if vaccinated, but vaccination significantly reduces the incidence and severity of influenza and risk of serious complications, hospitalizations, and death to both themselves and others.4 Influenza vaccine is recommended for all people aged 6 months or older without contraindications.8 This is particularly important to reduce complications during the current COVID-19 pandemic.

Patients need to be reminded that cold, influenza, and COVID-19 symptoms can be similar. Most people understand that COVID-19 has caused many deaths, but they need to understand that infections with influenza can cause mild to severe illness that can also lead to death. Both COVID-19 and flu usually have a sudden onset with symptoms consisting of fever or chills, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, and fatigue. Change in or loss of taste or smell may occur, but this is more frequent with COVID-19. See TABLE 1 for a comparison of symptoms.

Patients need to be assessed and tested to determine which infection is present and provide the proper management. Individuals can be infected with both viruses and have symptoms of both influenza and COVID-19. Both are transmitted through inhalation and surface contact, with COVID-19 being more contagious than influenza. Also, the COVID-19 virus can spread much faster to large numbers of people. COVID-19 mortality rate is higher in the elderly population and in those with preexisting chronic medical conditions.22

Typically, most people who get the flu will recover in 3 to 14 days. Both COVID-19 and flu can result in complications, including pneumonia, respiratory failure, acute respiratory distress syndrome, sepsis, heart attack, inflammation of the heart (myocarditis), encephalitis, myositis, worsening of chronic medical conditions, and multiple-organ failure that could cause a long recovery. Secondary bacterial infections are more common with influenza. These complications can be severe, requiring hospitalization.20 Reye syndrome, a complication that occurs almost exclusively in children, presents with severe vomiting and confusion, which may progress to coma because of swelling of the brain. To decrease this from occurring, infants, children, and teenagers should not be given aspirin for fever reduction or pain relief.5

Zanettini et al examined the effects of influenza vaccination in elderly individuals on COVID-19 mortality. They found that overall, a 10% increase of influenza vaccination rates was associated with a statistically significant 5% average decrease in the COVID-19 death rate. Their findings suggest that influenza vaccination can play a protective role in COVID-19.21 Huang et al reviewed 56 million health records of older adults (>65 years) to determine if influenza vaccine had an impact on COVID-19 infections. Those who had received an influenza vaccination had a 24% decreased risk of getting a COVID-19 infection and a 28% decreased risk of developing a severe COVID-19 illness, compared with others who had not received influenza vaccination. The authors similarly concluded that an influenza vaccination seems to have a protective effect against COVID-19 infection.24 Other studies continue to show the importance of receiving the influenza vaccine during the COVID-19 pandemic.

**STAR**

How do you differentiate influenza from COVID-19?

*S = Stop; T = Think; A = Assess; R = Review

**STAR**

What populations are at a higher risk of developing complications if they contract influenza?
High-Risk Groups

Certain conditions put patients at much higher risk of developing complications if they contract influenza. Older adults and individuals who have severe underlying medical conditions such as heart or lung disease or diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness, so it is important that they receive both the influenza and COVID-19 vaccines. Pharmacists should be aware that some high-risk groups vary according to recommendations from the Advisory Committee on Immunization Practices (ACIP) or the CDC. People who are at increased risk for influenza-related complications include the following:

- Persons aged 50 years or older (per ACIP) versus persons aged 65 and older (per CDC)
  - The age varies based on the underlying health and comorbidities of the patient
- Children aged 5 through 59 months
- Women who are or will be pregnant during the influenza season (per ACIP) versus women who are pregnant and women up to 2 weeks after the end of pregnancy (per CDC)
- Residents of nursing homes and other long-term care facilities
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who are immunocompromised due to any cause (including but not limited to immunosuppression caused by medications or HIV infection)
- Children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza infection
- American Indians and Alaska Natives (per ACIP) versus non-Hispanic Black, Hispanic or Latinos, American Indian or Alaska Natives, non-Hispanic Asian or Pacific Islander (per CDC)
- Persons who are extremely obese (body mass index [BMI] ≥40 kg/m² for adults)

Unfortunately, the risk factors putting people at developing complications from influenza are similar to risk factors for contracting severe COVID-19 disease. Age is the strongest risk factor for COVID-19. As of September 2021, the mortality rate for people 65 years or older residing in the United States was 80 times more than the rate of 18- to 29-year-olds. Individuals living in long-term care facilities comprised more than 35% of all COVID-19 deaths. Cancer, cerebrovascular disease, chronic kidney disease, certain chronic lung and liver diseases, diabetes, heart conditions (heart failure, coronary artery disease, or cardio-

### TABLE 1. COMPARISON OF COLD, INFLUENZA, AND COVID-19 SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom onset</th>
<th>Cold</th>
<th>Influenza (flu)</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Gradual</td>
<td>Abrupt (1-4 days after exposure)</td>
<td>Abrupt (2-14 days after exposure)</td>
</tr>
<tr>
<td>Aches</td>
<td>Rare</td>
<td>Fairly common; lasts 3-4 days</td>
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</tr>
<tr>
<td>Chills</td>
<td>Slight</td>
<td>Common; often severe</td>
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</tr>
<tr>
<td>Fatigue, weakness</td>
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<td>Common</td>
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<tr>
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<td>Mild to moderate; hacking cough</td>
<td>Common; can be severe</td>
<td>Common; typically dry cough</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Common</td>
<td>Sometimes</td>
<td>Possible</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>Common</td>
<td>Sometimes</td>
<td>Common; can have runny nose</td>
</tr>
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<td>Common</td>
<td>Sometimes</td>
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<td>Change in or loss of taste and smell</td>
<td>Rare</td>
<td>Possible</td>
<td>Common</td>
</tr>
<tr>
<td>Shortness of breath or difficulty breathing</td>
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<td>Common</td>
<td>Common (can be severe)</td>
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<tr>
<td>Nausea, vomiting, and diarrhea</td>
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### TABLE 2. COMPARISON OF COLD, INFLUENZA, AND COVID-19 SYMPTOMS

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myopathies), depression or schizophrenia, obesity (BMI ≥30 kg/m²), pregnancy or recent pregnancy, smoking (current or former) and tuberculosis are comorbidities with the strongest evidence of causing greater complications with COVID-19 infections. The risk of COVID-19 increases at any age as a person has a higher number of underlying medical conditions. People with disabilities or those who live in a congregate setting or face more barriers to health care have a higher risk of serious COVID-19 disease as well. Black or African American, Hispanic and Latino people are less likely to get the COVID-19 vaccine and more likely to get seriously ill and die from COVID-19 and its complications. These individuals may have different economic, social, environmental, and geographic factors that cause challenges to vaccine acceptance and access.

Patients need to understand the value of getting both the influenza vaccine yearly and staying up-to-date with COVID-19 recommendations and the potential consequences if these recommendations are not followed. Vaccination remains the best way to protect against influenza. Pharmacists have a responsibility to instruct patients that while there is still a potential chance they could contract influenza after vaccination, it will be a much less severe case if they receive the influenza vaccine. Educating patients on the potential for life-changing complications due to influenza or COVID-19 infections and the importance of avoiding this burden could help improve immunization rates.

Overview of Influenza Vaccines

Recommendations for the 2021-2022 Season

The ACIP makes yearly recommendations for routine influenza vaccination. Routine annual influenza immunization is recommended for all persons aged 6 months or older who do not have contraindications. The available vaccines include the standard-dose inactivated influenza vaccine, quadrivalent (IIV4); high-dose inactivated influenza vaccine, quadrivalent (HIIV4); standard-dose adjuvanted inactivated influenza vaccine, quadrivalent (aIIV4); standard-dose cell-culture-based inactivated influenza vaccine, quadrivalent (cIIV4); recombinant inactivated influenza vaccine, quadrivalent (RIV4); and live-attenuated influenza vaccine quadrivalent (LAIV4). No specific vaccine is preferred in persons for whom more than one formulation is appropriate. Select vaccines will be covered in more detail, with an emphasis on available vaccines indicated specifically for older adults.

There were 6 recommendations made for the 2021-2022 season. The biggest update is that trivalent vaccines are no longer available as all US-licensed influenza vaccines are quadrivalent. This should provide patients with expanded coverage and protection against influenza.

Additionally, while the B strains did not change, the A strains included in the 2021-2022 influenza vaccines available in the United States have been changed from the previous season and include:

- **Influenza A**
  - H1N1
    - A/Victoria/2570/2019 (H1N1) pdm09-like virus (for egg-based vaccines) **OR**
    - A/Wisconsin/588/2019 (H1N1) pdm09-like virus (for cell culture–based and recombinant vaccines)
  - H3N2
    - A/Cambodia/e0826360/2020 (H3N2)-like virus

- **Influenza B**
  - B/Washington/02/2019 (Victoria lineage)-like virus
  - B/Phuket/3073/2013 (Yamagata lineage)-like virus

A third change is the approved age indication for cIIV4 (Flucelvax) from older than 4 years to older than 2 years. Fourth, providers should use the ACIP and CDC recommendations for guidance and consideration for coadministration of influenza vaccines and COVID-19 vaccines. Pregnant women should ideally receive the influenza vaccination in September or October. However, pregnant women in the third trimester should receive it as soon as the vaccine becomes available (July or August). Children 6 months through 8 years who are flu vaccine naïve or who have not had 2 lifetime total doses should receive their first dose as soon as possible. The second dose should be administered at least 4 weeks later. The remaining population ideally should receive the vaccine by the end of October, avoiding vaccination in July and August unless there is concern that later vaccination is not possible.

There have also been modifications to the contraindications and precautions associated with the use of cIIV4 (Flucelvax) and RIV4 (Flublok). A precaution to the use of cIIV4 or RIV4 is a history of a severe allergic reaction to a previous dose of an egg-based vaccine; in these patients, the vaccines should be administered in a medical setting (eg, doctor’s office or clinic) under supervision of a provider who can recognize and manage a severe allergic reaction. Providers may consider an allergist consultation to assist with determining which vaccine component was responsible for the reaction. A contraindication to future use of cIIV4 includes a history of a severe allergic reaction such as anaphylaxis.
TABLE 2. INFLUENZA VACCINES AVAILABLE IN THE UNITED STATES FOR THE 2021-2022 INFLUENZA SEASON

<table>
<thead>
<tr>
<th>Brand name (manufacturer)</th>
<th>Dose</th>
<th>Recommended age</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated influenza vaccine, quadrivalent (IIV4), standard-dose, egg-based vaccines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afluria Quadrivalent (Seqirus)</td>
<td>0.25 mL, PFS</td>
<td>6 through 35 months</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, PFS</td>
<td>≥3 years</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, 5 mL MDV*</td>
<td>≥6 months (needle/syringe); 18-64 years (jet injector)</td>
<td>IM</td>
</tr>
<tr>
<td>Fluarix Quadrivalent (GlaxoSmithKline)</td>
<td>0.5 mL, PFS</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td>FluLaval Quadrivalent (GlaxoSmithKline)</td>
<td>0.5 mL, PFS</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td>Fluzone Quadrivalent (Sanofi Pasteur)</td>
<td>0.5 mL, PFS</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, SDV</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, 5 mL MDV*</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td>High-dose inactivated influenza vaccine, quadrivalent (HD-IIV4), egg-based vaccine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fluzone High-dose Quadrivalent (Sanofi Pasteur)</td>
<td>0.7 mL, PFS</td>
<td>≥65 years</td>
<td>IM</td>
</tr>
<tr>
<td>Adjuvanted inactivated influenza vaccine, quadrivalent (aIIV4), standard-dose, egg-based vaccine with MF59 adjuvant</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fluad Quadrivalent (Seqirus)</td>
<td>0.5 mL, PFS</td>
<td>≥65 years</td>
<td>IM</td>
</tr>
<tr>
<td>Cell-culture-based inactivated influenza vaccine, quadrivalent (ccIIV4), standard-dose vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucelvax Quadrivalent (Seqirus)</td>
<td>0.5 mL, PFS</td>
<td>≥2 years</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, 5 mL MDV*</td>
<td>≥2 years</td>
<td>IM</td>
</tr>
<tr>
<td>Recombinant influenza vaccine, quadrivalent (RIV4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flublok Quadrivalent (Sanofi Pasteur)</td>
<td>0.5 mL PFS</td>
<td>≥18 years</td>
<td>IM</td>
</tr>
<tr>
<td>Live attenuated influenza vaccine, quadrivalent (LAIV4), egg-based vaccine</td>
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</tr>
<tr>
<td>FluMist Quadrivalent (AstraZeneca)</td>
<td>0.2 mL prefilled single-use intranasal sprayer</td>
<td>2-49 years</td>
<td>Nasal</td>
</tr>
</tbody>
</table>

IM, intramuscular; MDV, multidose vial; PFS, prefilled syringe; SDV, single-dose vial.
*MDVs have approximately 25 mcg/0.5 mL mercury (from thimerosal).

Vaccines Specifically for Patients 65 Years and Older

There are 2 influenza vaccines this year, HD-IIV4 (Fluzone High-Dose) and aIIV4 (Fluad), that are indicated for persons 65 years or older. This is because, as patients grow older, their immune system is not as robust so they typically have weaker immunogenic responses (antibody production) to influenza vaccination than younger persons, and their antibody levels may decline more rapidly. This leads to decreased vaccine effectiveness.

Recombinant, high-dose, and adjuvanted influenza vaccines result in higher antibody production. Cowling and colleagues immunized community-dwelling adults aged 65 to 82 years residing in Hong Kong, with either recombinant, high-dose, adjuvanted vaccines or standard-dose inactivated influenza vaccine. The patients receiving any of the 3 enhanced vaccines showed greater humoral and cell-mediated immune responses, compared with the standard-dose vaccine subjects.9

to any ccIIV vaccine or component of ccIIV4. Similarly for RIV4, history of a severe allergic reaction to any RIV vaccine or component of RIV4 is a contraindication.8

Available Vaccines in the 2021-2022 Season

TABLE 2 lists the specific influenza vaccines that all provide protection against influenza A and B for the 2021-2022 season. The generic vaccine names are included in the section headers with brand and manufacturer names included to assist with minimizing confusion between the vaccines. All influenza vaccines need to be designed each year to match the identified circulating strains. This is a drawback for the traditional vaccines as the production process takes approximately 6 months when embryonated eggs are used.28 The 2 vaccine formulations not produced in eggs include ccIIV4 and RIV4. The non–egg-based methods use Madin-Darby canine kidney cells instead of eggs and are less laborious to produce as they have a shorter production time and do not depend on a supply of eggs.5,8
During the 2018-2019 influenza season, Pelton et al performed a retrospective cohort study of individuals in the United States who were 65 years or older and vaccinated with either adjuvanted trivalent influenza vaccine (aTIV, Fluad) or trivalent influenza vaccine—high dose (TIV-HD, Fluzone) to assess relative effectiveness. The final unadjusted sample included 561,243 aTIV and 1,672,797 TIV-HD recipients. Influenza-related hospitalization/emergency department visits and associated costs among people aged 65 and older were comparable between the 2 vaccines. The aTIV had a higher relative vaccine effectiveness in preventing influenza-related office visits as compared with TIV-HD. Both vaccines appear to provide comparable clinical and economic benefits in providing protection against influenza and associated complications among the older population. Other studies have shown similar responses but there is a need for additional clinical trials comparing the recombinant, adjuvanted, and high-dose vaccines in older adults. Currently there are no studies comparing the new HD-IIV4 and aIIV4 to standard-dose IIV4 due to the recent availability of these formulations.

High-dose Inactivated Influenza Vaccine
HD-IIV4 (Fluzone High-dose) contains 4 times the amount of antigen that is included in standard-dose inactivated influenza vaccines. This is the second season that it is a quadrivalent preparation. Several studies in adults 65 years or older have shown a reduced risk of respiratory-related and all-cause hospitalization and death in patients receiving the high-dose inactivated trivalent vaccine compared with standard-dose inactivated trivalent vaccines. In a randomized, double-blind trial of almost 32,000 adults 65 years or older, the high-dose inactivated trivalent vaccine induced significantly greater antibody responses than the standard-dose inactivated trivalent vaccine and was 24% more effective in preventing laboratory-confirmed influenza illness.

Adjuvanted Inactivated Influenza Vaccine
The aIIV4 (Fluad) contains MF59, an oil-in-water emulsion of squalene oil that increases the immune response by recruiting antigen-presenting cells to the injection site and promoting uptake of influenza virus antigens. In a randomized trial in adults 65 years or older, an adjuvanted inactivated trivalent vaccine produced significantly greater antibody responses against all 3 influenza strains than a nonadjuvanted inactivated trivalent vaccine. Other studies have shown that older adults who received an adjuvanted inactivated trivalent vaccine were less likely to develop symptomatic influenza illness or to be hospitalized for influenza or pneumonia compared with those who received a nonadjuvanted inactivated trivalent vaccine. McCongehy et al examined the use of adjuvanted versus nonadjuvanted trivalent influenza vaccine in 823 nursing homes throughout the United States. This cluster-randomized trial supports the use of adjuvanted influenza vaccine over nonadjuvanted, standard-dose, egg-based vaccines to prevent nursing home resident hospitalizations during the influenza season. The adjuvanted trivalent vaccine was more effective in preventing hospitalizations during an A/H3N2-predominant season that exhibited low trivalent influenza vaccine effectiveness.

Select Additional Vaccines

Recombinant Influenza Vaccine
RIV4 (Flublok) is produced without the use of influenza virus or chicken eggs. It contains 3 times the amount of antigen compared with the standard-dose inactivated influenza vaccines. It is approved for individuals 18 years or older. The vaccine is made using recombinant DNA technology and a baculovirus expression system that produces virus-like particles. In a randomized, double-blind trial in 8604 adults 50 years or older during the A/H3N2-predominant 2014-2015 season, the recombinant quadrivalent vaccine was 30% more effective than a nonadjuvanted standard-dose inactivated quadrivalent vaccine in preventing laboratory-confirmed influenza illness.

Live-attenuated Influenza Vaccine
LAI4 (Flumist) was developed as a quadrivalent vaccine for individuals aged 2 to 49 years that is administered intranasally. It was not recommended to be used from 2015 to 2018 due to its low effectiveness against H1N1 influenza among children during the 2013-2014 and 2015-2016 seasons. The manufacturer subsequently determined that the H1N1 strain had poor replicative fitness during the seasons in which LAIV was poorly effective. Data from the manufacturer indicate that the H1N1 strain used in the newer vaccine has improved replicative fitness and induces higher antibody responses than the earlier strain.

Because it is a live vaccine, there are several contraindications and precautions that needed to be considered. It should not be given to pregnant women, children and adults who are immunocompromised, those who have a history of severe allergic reaction (eg, anaphylaxis) to any component or to a previous dose of any influenza vaccine, or if one has close contact or are a caretaker of severely immunosuppressed individuals. It is important to note that influenza antiviral use might interfere with LAIV. Use
of oseltamivir (Tamiflu) or zanamivir (Relenza) within 48 hours before, peramivir (Rapivab) within 5 days before, or baloxavir marboxil (Xofluza) within 17 days before or if any of these are given within 2 weeks after vaccination could inhibit antibody production and reduce efficacy.8 If this occurs, patients should be revaccinated with the appropriate IIV or RIV4.53

Considerations for Vaccine Selection
While the ACIP provides no preference for vaccine type based on efficacy, patient-specific and vaccine-specific factors such as age or contraindications should be taken into consideration for vaccine selection. Studies have illustrated potential benefits of specific vaccines in different populations such as older adults. If a specific vaccine is unavailable, influenza vaccination should not be delayed.8

There are other scenarios where specific vaccine types should be avoided. Although most influenza vaccines contain trace amounts of egg protein (ovalbumin), numerous studies have demonstrated that patients with an egg allergy are not at increased risk for a reaction to any influenza vaccine.44 The ACIP states that persons with egg allergy of any severity can receive any age-appropriate influenza vaccine. However, patients with a history of a severe egg allergy (angioedema, respiratory distress, lightheadedness, recurrent vomiting, or requiring epinephrine or another emergency medical intervention) who receive an egg-based vaccine should be vaccinated in a medical setting supervised by a clinician experienced in managing severe allergic reactions. The recombinant vaccine and the cell culture-based vaccine do not contain egg protein.8 The Joint Task Force on Practice Parameters comprised of members from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology state that no special precautions are necessary for patients with egg allergy of any severity.44

STAR
What are some management strategies for vaccine adverse effects?

Adverse Effects
Injection site pain is the major adverse effect that occurs with inactivated influenza vaccines and other adverse effects are less common. In clinical trials, the incidence of injection site pain with the HD-IIV4 and aIIV4 in participants 65 years and older were 41% and 16%, respectively. The most common systemic reactions with HD-IIV4 were myalgia (22.7%), headache (14.4%), and malaise (13.2%) versus headache (10.8%) and fatigue (10.5%) with aIIV4.37,45

The most common adverse reactions associated with the LAIV are runny nose, nasal congestion, fever, and sore throat. LAIV can increase the risk of wheezing, especially in children younger than 5 years with recurrent wheezing and in persons of any age with asthma. Influenza vaccination has been associated with Guillain-Barré syndrome, but the absolute risk is very low (about 1-2 additional cases per million persons vaccinated).4 Influenza infection itself has also been associated with Guillain-Barré syndrome.46

Patients should remain in a seated position for at least 15 minutes after receiving a vaccine to prevent injury from a syncopal episode. Patients should refrain from taking prophylactic ibuprofen, acetaminophen, or aspirin; these medications are only recommended to be taken post-vaccination to relieve adverse effects.

Use of and physical activity with the arm that received a vaccine has been shown to reduce pain and discomfort following vaccination. Patients should be educated to use their arms throughout the day or use a cool, damp washcloth over the area to minimize arm pain. Sometimes patients feel feverish and will feel better by drinking plenty of fluids and wearing lighter clothing until the fever passes. Fatigue might occur but should only last for up to a few days. The patient should be advised to call the pharmacy if these adverse effects do not go away within 48 hours.

Patients need to be reminded that the vaccine does not cause the flu. They might experience illness shortly after receiving the flu vaccine for several reasons, including illness due to other respiratory viruses, such as rhinoviruses, that cause similar symptoms; exposure to flu viruses shortly before, or during the 2-week period after vaccination; composition of seasonal flu vaccine poorly matched to circulating strains of virus; and variability in the effectiveness of vaccine response among individuals.

STAR
What are some strategies to address vaccine hesitancy?

Role of the Pharmacist
Pharmacists have a professional responsibility to promote vaccines that will save lives and prevent disease. The COVID-19 pandemic offers an important opportunity for pharmacists to have a continued impact on patient care. Patients need to be reminded not only of the value of influenza and COVID-19 vaccines, but other vaccines such as pneumococcal, zoster, and pertussis. This could possibly assist with managing the impact of COVID-19
on health care systems by reducing morbidity and mortality and associated health complications or hospitalizations due to non-COVID-19 respiratory infections as well as bacterial infections during a COVID-19 infection. This would reduce the resources needed to care for patients without COVID-19.27-49

Pharmacists’ involvement in immunization as educators, facilitators, or administrators of vaccines improves immunization rates.50-52

Pharmacies are an accessible option for patients seeking vaccinations with the most common setting of influenza vaccination for adults in the 2020-2021 season including a pharmacy or store.53 Educating patients regarding the availability of various types of influenza vaccines and nuances in their recommendations is important.

Patel et al examined the national individual immunization data for influenza and pneumococcal immunizations. Five years after

<table>
<thead>
<tr>
<th>Condition</th>
<th>Suggested Patient Discussion Points</th>
<th>Takeaways for Getting Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>As you grow older, your immune system is not as strong to fight off infections and you are at a higher risk of getting the flu which will put you at risk to develop other medical problems. Between 50% and 70% of flu-related hospitalizations and 70%-85% of flu-related deaths occur in people 65 years and older.</td>
<td>Although immune responses may be lower in older people, studies have shown that the flu vaccine reduces medical visits, hospitalizations, and deaths associated with flu.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Your diabetes puts you at a big risk for developing serious flu complications including sinus and ear infections, pneumonia, bronchitis, and death. The flu can also make it harder for you to control your blood glucose.</td>
<td>Getting the influenza vaccine can significantly decrease your risk of getting the flu and being admitted to the hospital. It can also decrease the risk of worsening of your diabetes and having other complications.</td>
</tr>
<tr>
<td>Heart disease and stroke (excludes isolated hypertension)</td>
<td>Cardiovascular disease (CVD) puts you at a higher risk for developing serious flu complications. If you get the flu, you have an increased risk of a stroke or heart attack.</td>
<td>Getting the influenza vaccine can significantly decrease your risk of getting the flu and being admitted to the hospital. It can also decrease the risk of worsening your current health. Vaccination can reduce the risk of major cardiac events among adults with existing CVD.</td>
</tr>
<tr>
<td>Patients with cancer, chronic kidney disease, dialysis, HIV, or transplant</td>
<td>You have a weaker immune response, due to your condition, which can make the immune system less able to fight infections. This puts you at a much higher risk of getting the flu, which can result in worsening of your current illness, hospitalization, and even death.</td>
<td>Receiving the influenza vaccine can significantly decrease your risk of getting the flu and being admitted to the hospital.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Pregnant women are more susceptible to the flu and are more likely to have more severe cases compared to non-pregnant women. Fever, a common symptom of flu, may be associated with negative outcomes for a fetus.</td>
<td>Getting the influenza vaccine can reduce your risk of getting the flu, being admitted to the hospital, and protect your baby from flu illness. Get the inactivated vaccine ideally in September or October. Earlier vaccination can be considered for women in their third trimester.</td>
</tr>
<tr>
<td>Respiratory disease (asthma and chronic obstructive pulmonary disease [COPD])</td>
<td>Respiratory disease puts you at a higher risk for developing serious flu complications. The flu can cause inflammation of the airways and trigger an asthma attack or COPD exacerbation. The flu can also lead to pneumonia and other respiratory complications. People with respiratory disease are more likely to develop pneumonia if they get the flu than people who do not.</td>
<td>Getting the influenza vaccine can decrease your risk of getting the flu and prevent having an asthma attack, COPD exacerbation, or getting bacterial pneumonia. Influenza vaccination has been associated with reduced hospitalizations for adults with chronic lung disease.</td>
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</table>
national implementation, they estimated that 6.2 million additional influenza immunizations and 3.5 million additional pneumococcal immunizations were attributable to pharmacy-delivered immunization services. Pharmacists have played a key role in COVID-19 vaccine administration through their involvement with the Federal Retail Pharmacy Program for COVID-19 vaccination. As of October 2021, more than 141 million doses were administered by retail pharmacies across the United States, including 8 million doses administered at long-term care facilities, which highlights the potential reach of pharmacists.

Pharmacists need to take advantage of every patient encounter to increase vaccination rates. Data from the 2020-2021 influenza season in the United States demonstrate that influenza vaccination coverage among adults aged 65 years or older was higher (75.2%) than coverage among adults aged 18 to 49 years (37.7%) and 50 to 64 years (54.2%), although there is room for improvement in all age groups. There are even lower immunization rates in the socioeconomically disadvantaged and various ethnicities.

Patients can be reminded about the importance of obtaining an annual influenza vaccine at multiple encounters. Video or audio recordings while patients are waiting in the pharmacy or on the phone are great ways to inform patients. Providing immunization histories periodically and keeping these updated in the patient profile system both for inpatients and outpatients in the hospital, clinic, or pharmacy are key. Reminders should be sent to patients through postcards or text messages. Many pharmacies are using automated phone or computer systems to allow patients to schedule their COVID-19 vaccine appointments; this strategy can be used for influenza vaccines and other vaccines as well. Patient vaccine screening questionnaires at the time of immunization should contain questions to determine if a patient qualifies for other vaccines as well. When vaccines are needed, patients should be educated on their value and be immunized. Combining multiple strategies across different settings and addressing patient barriers may offer the best approach to optimize vaccine administration.

While nearly all individuals would be appropriate candidates for the influenza vaccine, it is especially important to promote vaccination in individuals who are high risk, such as older adults. Table 3 includes some key education and talking points for patients at high risk for influenza-associated complications who also have a higher risk of COVID-19 infection. Furthermore, pharmacists should educate high-risk patients to call their physician immediately if they start to have flu symptoms so antiviral therapy can be initiated, which could help reduce the severity and duration of influenza regardless of their vaccination status.

Influenza vaccination has been associated with reduced hospitalizations for adults (including those >65 years) with diabetes and chronic lung disease. Vaccination reduced the risk of major cardiac events among adults with existing CVD. Additionally, among adults hospitalized with the flu, intensive care unit (ICU) admissions decreased, and fewer days were spent in the ICU.

Addressing Vaccine Hesitancy

Despite the proven value and promotion of vaccination, vaccine hesitancy, the belief that a vaccine may be unnecessary, ineffective, or unsafe, is a growing problem. In 2019, the WHO named vaccine hesitancy as one of the 10 threats to global health. The first international systematic endeavor that examined this problem was a working group of a WHO advisory body, the Strategic Advisory Group of Experts on Immunization (SAGE). The SAGE Working Group on Vaccine Hesitancy defined vaccine hesitancy as the delay in acceptance or refusal of vaccination despite availability of vaccination services.

The SAGE group created “3 Cs” model to describe and understand vaccine hesitancy. It included the following factors:

- **Confidence:** lack of trust in safety and effectiveness of vaccines
  - This includes the reliability and competence of health care professionals, health services, and/or the motivation of policy makers who make decisions about vaccines.

- **Complacency:** not perceiving diseases as high risk and vaccination as necessary
  - Low perceived risk of vaccine-preventable diseases, leading to an assumption that vaccines are not needed. It is affected by many factors, including other life/health responsibilities that seem more important at that point in time.

- **Convenience:** practical barriers
  - The ability to access, understand (language and health literacy), and afford the vaccination services as well as quality of the service (real and/or perceived).

Vaccine hesitancy reduces vaccine uptake, compromises herd immunity, and undermines the effectiveness and success of immunization programs. When herd immunity is compromised, disease outbreaks among the unvaccinated population are likely. Vaccine hesitancy represents a threat that can seriously jeopardize success of past vaccination campaigns as well as the control of the COVID-19 pandemic and implementation of new vaccines in the future. These factors are context specific and multidimensional; they overlap and interact. While high levels of hesitancy lead to low vaccine demand, low levels of hesitancy do not necessarily
mean high vaccine demand. Hesitancy describes a continuum between complete acceptance and complete refusal.64

Others have expanded on the 3C model as they feel additional factors play a role in vaccine hesitancy. Betsch and colleagues developed the 5C scale to include psychological factors of vaccination. They replaced convenience with constraints, and added calculation and collective responsibility for the 5C model65:

- **Confidence**: having trust in safety and effectiveness of vaccines and the health care team and services who deliver them
- **Complacency**: not perceiving diseases as high risk and vaccination is not necessary as a preventive action
- **Constraints**: structural (ability to access, afford, geographical factors) and psychological barriers (language and health literacy issues)
- **Calculation**: engagement in extensive information searching
  - Related to perceived vaccination and disease risks
- **Collective responsibility**: willingness to protect others by getting vaccinated and promoting herd immunity

Pharmacists should be aware of the various factors that can affect vaccination behavior and assess the relative importance of psychological factors and previous experiences. These could assist in a patient’s decision to be vaccinated.

**Communication Strategies**

Pharmacists have opportunities to provide advice and recommendation to vaccine-hesitant persons. To adequately address vaccine hesitancy, it is important for pharmacists to understand the factors that contribute to vaccine hesitancy and how to support patients in their decision-making process to guide them toward vaccine acceptance. Potential reasons why people are vaccine hesitant involve lack of understanding or information, concern about adverse effects, effect of additives, mistrust in the health care system, religious beliefs, or thinking the vaccines can overwhelm the immune system.52,59-61,64

When talking to vaccine-hesitant patients, there are many structured approaches to help providers manage vaccine conversations. The most important factor is to have a deep knowledge of the issues and come across as being truly interested and genuine. Developing connections with patients is key. The following are some useful strategies to use:

1. **Listen and communicate effectively.** As vaccine hesitancy is highly variable and context specific, pharmacists need to determine the concerns of the patient to provide the appropriate information and advice. Pharmacists should inform, educate, and correct vaccine-related misinformation raised by the patient and be empathetic. It is very important not to overload the patient with detailed technical information, use strong risk negation, or repeat vaccine myths.

2. **Be proactive.** Addressing vaccine hesitancy needs to be an ongoing dialogue. If a patient does not agree to vaccination at your first discussion, it is important to leave the door open for more information. Continued positive messages could help them recognize misinformation.

3. **Be prepared.** The internet and digital technologies spread information quickly and are the source for patient information. Patients can have misinformation or be drawing conclusions based on wrong facts or disinformation or deliberately spreading false information to promote an agenda. Pharmacists need to keep up-to-date with scientific information, the available vaccines, and provide the correct information to patients. Information on vaccine safety and efficacy are effective strategies for addressing vaccine hesitancy by community pharmacists. (The Additional Resources at the end of this activity contains useful references for keeping updated.)

4. **Be aware of cultural concerns.** Vaccine hesitancy is greater among ethnic minorities. Barriers include perception of risk, low confidence in vaccines, distrust of public services due to historical issues and racism, access barriers, language and religious factors, and fear and mistrust of authority. Involving community leaders or trusted members of the community can lead to greater levels of acceptance. Clearly communicating evidence and advice in a tailored message is important and most effective to the targeted community. It is also extremely important to be respectful of all cultural and religious beliefs.

When talking to patients, motivational interviewing has been shown to be an effective means of reversing vaccine hesitancy. Motivational interviewing is a counseling method that helps people resolve ambivalent feelings and insecurities to find the internal motivation they need to change their behavior. There are 4 principles in motivational interviewing: open-ended questions, affirmations, reflective listening, and summary (OARS).66,67 Pharmacists should use this method along with the key talking points discussed to try to improve patients’ perceptions on vaccinations.

**Educational Points for Vaccines During COVID-19**

Pharmacists and other health care professionals have challenges ahead to dispel negative beliefs in promoting immunization with the influenza vaccine, as well as the COVID-19 vaccine. The COVID-19 vaccines were developed quickly and there are ongoing changes that pharmacists need to educate patients about. As the qualified age for administration expands, new opportuni-
ties for patients to be immunized will expand. Recommending influenza vaccines as appropriate when individuals are seeking COVID-19 vaccines can be helpful. Previously COVID-19 vaccines were recommended to be administered alone, with a minimum interval of 14 days before or after administration of any other vaccines. However, this has changed, and COVID-19 vaccines may be coadministered at the same time as other vaccines such as the influenza vaccine. Extensive experience has shown immunogenicity and adverse effects are similar when vaccines are administered simultaneously. Many patients are unaware of this change and are unnecessarily putting off important vaccines.

Some patients think that since they had a SARS-CoV-2 infection or had a very mild case or still have symptoms, they are now immune to future infections, which is a myth. People should be offered vaccination regardless of their history of symptomatic or asymptomatic SARS-CoV-2 infection, including individuals with prolonged post-COVID-19 symptoms. They should not receive the COVID-19 vaccine until they have recovered from acute illness and met all criteria for discontinuing isolation. Viral or serologic testing for acute or prior infection is not recommended for the purpose of deciding whether to vaccinate. Similar misconceptions may be seen with the influenza vaccines. Influenza vaccination should generally be deferred in individuals with moderate or severe COVID-19 until they have recovered. While there are no data regarding the optimal timing of influenza vaccination in patients with or recovering from COVID-19, timing of influenza vaccination for these individuals should take multiple factors into consideration, including the degree of influenza circulation in the community and the patient’s underlying risk of complications.

The WHO, CDC, and other organizations have identified common misconceptions of vaccinations that pharmacists should be prepared to address.Some of these myths and educational points to discuss with patients are listed in the SIDEBAR. Pharmacists can assist with addressing common questions, clarify any confusion surrounding vaccines, and direct patients to additional educational resources for information about vaccines if needed.

**Conclusion**

It remains important to receive an influenza vaccination to reduce the risk of a co-infection of influenza and COVID-19. Because influenza and COVID-19 present with similar symptomatology and occupy the same medical resources, the influenza vaccine is crucial in reducing the number of patients with severe influenza to free up resources that may be necessary to handle another wave of patients with COVID-19. Maximizing the number of people immunized, especially older adults and/or adults at risk, with seasonal influenza and other vaccines can reduce the burden of the targeted diseases, but also prevent a proportion of COVID-19 morbidity and mortality.

There are many ways that pharmacists can promote vaccination; one of the most important contributions is by administering vaccines. Pharmacists can assess patients and vaccination records to help identify high-risk patients to be immunized and provide recommendations to patients. Using the appropriate motivational interviewing, pharmacists can inform patients of their risk of infection when delaying or refusing vaccination, address concerns about vaccine safety and efficacy, and encourage vaccination. When counseling a patient, it is important to ask about any concerns they may have to identify any opportunities to address vaccine hesitancy by correcting misinformation and providing statistical facts demonstrating the benefits of vaccination.

Pharmacists need to advocate for patients to receive the influenza vaccine as well as other required vaccines. Pharmacists are essential members of the health care team and are key to improving health care through promotion and delivery of immunization to patients during the current COVID-19 pandemic.
REFERENCES


6. Godlee F, Smith J, Marcovitch H. Wakefield’s article linking MMR vaccine and autism was fraudulent. BMJ. 2011;342:c7452. doi:10.1136/bmj.c7452


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.
Go to www.pharmacytimes.org/influenza-vaccines to access the online version of this activity.
Click “Proceed,” then complete the online pretest.
Once completed, click “Next” until reaching the activity posttest.
After successful completion of the online interactive patient simulation, posttest, and activity evaluation, your credit will be uploaded into CPE Monitor. You must complete these steps before the activity expires in order to receive your credit.
You may view your credit within 48 hours at www.mycpemonitor.net.

NOTE: Your CE credit will be automatically uploaded to CPE Monitor. Please ensure that your Pharmacy Times® account is updated with your NABP e-profile ID number and your date of birth. Participation data will not be uploaded into CPE Monitor if you do not have your NABP e-profile ID number and date of birth entered into your profile on www.pharmacytimes.org.

SYSTEM REQUIREMENTS FOR COMPLETION:
Computer or smartphone with internet-access web browser (IE7.0+ or Webkit-/Mozilla-compatible) with JavaScript enabled.

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POSTTEST QUESTIONS

1. Which statement is correct regarding the influenza vaccine for 2021-2022?
   A. If a patient has received the influenza vaccine last flu season, they can skip receiving one this flu season.
   B. The influenza vaccines in the United States are trivalent and quadrivalent.
   C. Adjuvanted inactivated influenza vaccine, quadrivalent (Fluad) is an influenza vaccine approved for patients 65 years and older.
   D. The Advisory Committee on Immunization Practices (ACIP) strongly recommends patients receive the recombinant influenza vaccine as it produces the highest antibody response.

2. According to the Centers for Disease Control and Prevention, which patient is considered the highest risk for complications related to influenza and COVID-19?
   A. A 60-year-old patient with no comorbidities
   B. A 62-year-old patient with hypertension
   C. A 68-year-old patient with diabetes
   D. A 55-year-old patient with osteoarthritis

3. Jake is an 18-year-old college student who presents to your pharmacy. He has no underlying diseases, takes no medication, and has an egg allergy (rash). He received his second COVID-19 vaccine 7 days ago because he needed it to attend college; he does not like needles and almost passed out when he got the COVID-19 vaccine. He also tells you that his sister underwent a bone marrow transplant 1 month ago and he is going home to see her this weekend. Based on this information, what action should you take?
   A. Jake should be scheduled to be immunized with the recombinant influenza vaccine in a medical setting this week.
   B. Jake should wait another week to get the inactivated influenza vaccine (IIV4) because he received the COVID-19 vaccine just 7 days ago.
   C. Jake should receive the LAIV4 intranasal spray today because he does not like needles.
   D. Jake should receive any of the inactivated influenza vaccine (IIV4), standard dose today.

4. Which statement is correct regarding influenza and the COVID-19 pandemic?
   A. COVID-19 infections increased the number of influenza cases seen in 2020-2021.
   B. In 2020-2021, routine vaccination rates increased significantly across all populations in the United States due to fears of getting COVID-19.
   C. Studies in the elderly population have concluded that an influenza vaccination seems to have a protective effect against COVID-19 infection.
   D. There were fewer influenza vaccinations given in 2020-2021 resulting in a higher rate of influenza.

5. Which of the following is an example of how pharmacists can improve influenza and COVID-19 vaccination rates?
   A. Tell the patient to receive the influenza and COVID-19 vaccines 2 weeks apart to minimize adverse effects.
   B. Tell patients who were hospitalized for influenza that they have antibodies and will not need the flu vaccine this year.
   C. Clearly communicate evidence and advice in a tailored message.
   D. Avoid discussing adverse drug effects so you do not scare the patient.
Addressing the Challenges of Managing CAD/PAD and Associated Comorbidities: The Role of Antithrombotic Therapy

EDUCATIONAL OBJECTIVES
At the completion of this activity, the participant will be able to:
• Explain the unmet need and clinical burden of coronary artery disease/peripheral artery disease (CAD/PAD)
• Examine the evidence-based treatment guidelines for patients with CAD/PAD
• Analyze clinical data exploring therapies with the potential to improve patient outcomes and reduce complications
• Identify the role of the pharmacist in making clinical recommendations, counseling and educating patients, and managing associated comorbidities of CAD/PAD

TARGET AUDIENCE: Pharmacists

PHARMACY TIMES® EDITORIAL STAFF
Davy James
An anonymous peer reviewer was part of the content validation and conflict resolution and has no relevant financial relationships with commercial interests to disclose.

Background
Atherosclerosis is a major vascular disease, characterized by plaque formation in arteries and capillary beds that can lead to significant morbidity and mortality. Atherosclerosis develops over time as lipid material deposits in the subendothelial space of blood vessels. As pathological lipid material accumulates, inflammation, driven by cells such as macrophages, T-helper cells, and lymphocytes, further upregulates lipid deposition and development of the atherosclerotic plaque.1,2 As the atheroma increases in depth, the vessel narrows and can restrict blood flow to muscles and major organs such as the heart or brain. As these vessels narrow, specifically in the myocardial vascular bed, oxygen supply may not adequately meet the demands of the downstream target.3 Coronary artery disease (CAD) is defined by the development of atherosclerosis in the major coronary arteries, whereas peripheral artery disease (PAD) is defined as the presence of atherosclerosis in the peripheral vasculature.3,4 As lipid accumulation progresses, the intimal layer of the endothelium can undergo erosion, consequently causing platelet activation, aggregation, and ultimately occlusion of the artery.5 Severe narrowing or complete occlusion of these vessels blocks oxygen delivery to downstream targets such as the myocardium, leading to acute coronary syndrome (ACS), acute limb ischemia in patients with PAD, or noncardioembolic ischemic stroke.1,3 With thrombus formation playing a significant role in the progression of atherosclerotic disease, antithrombotic therapies such as antiplatelet agents and anticoagulants have been a major target for reducing morbidity and mortality associated with CAD and PAD. This article will focus on not only the management of antithrombotic therapies, but also the comorbidities and risk factors associated with the development of CAD and PAD in high-risk patient populations.

Interactive Simulation of Patient Cases

This article includes a unique and interactive patient simulation activity that will guide you through clinical decision making regarding anticoagulation and comorbidity management for patients with CAD and PAD. Access the simulation at www.pharmacytimes.org/CAD-PAD

Pharmacy Times Continuing Education™ is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. This activity is approved for 3.0 contact hours (0.30 CEU) under the ACPE universal activity number 0290-0000-21-407-H01-P. The activity is available for CE credit through December 6, 2022.

This article is supported by an educational grant from Janssen Pharmaceuticals, Inc., administered by Janssen Scientific Affairs, LLC.
TABLE 1. PHARMACOLOGIC MANAGEMENT OF COMORBID DISEASE STATES

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>General management</th>
<th>Treatment goals</th>
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</thead>
<tbody>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Lifestyle modifications</td>
<td>Moderate-intensity statin goal: 30%-49% reduction from baseline LDL-C values</td>
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<tr>
<td></td>
<td>• Pharmacologic therapies</td>
<td>High-intensity statin goal: at least 50% reduction from baseline LDL-C values</td>
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<tr>
<td></td>
<td>• Moderate-intensity statin in patients with T2D aged 40-75; or patients aged 40-75, LDL-C 70-189 mg/dL and ASCVD risk ≥7.5%-20%</td>
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<td>• Atorvastatin 10-20 mg/day or rosuvastatin 5-10 mg/day</td>
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<td></td>
<td></td>
<td>• High-intensity statin in patients if LDL-C ≥190 mg/dL, ASCVD risk ≥20%, T2D and high ASCVD risk, or established ASCVD</td>
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<tr>
<td></td>
<td></td>
<td>• Atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day</td>
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<td></td>
<td></td>
<td>• Ezetimibe 10 mg/day or PCSK9 inhibitor (alirocumab or evolocumab) may be reasonable for patients who have progression of CAD or PAD while on maximally tolerated statin therapy.</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td></td>
<td>• Lifestyle modifications</td>
<td>• Target blood pressure &lt;140/90 mm Hg in patients &gt;65 years</td>
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<tr>
<td></td>
<td>• Pharmacologic therapies in CAD or PAD</td>
<td>• Target blood pressure &lt;130/80 mm Hg in patients &lt;65 years, those with high risk of ASCVD events (score ≥10%), or established ASCVD</td>
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<tr>
<td></td>
<td></td>
<td>• First-line therapies: ACEi or ARB, thiazide or thiazide-like diuretics, and DHP CCB</td>
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<td></td>
<td></td>
<td>• Adjunctive therapies for specific indications or refractory hypertension: β-blockers, non-DHP CCB, spironolactone or nitrates</td>
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<tr>
<td><strong>T2D</strong></td>
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<tr>
<td></td>
<td>• Lifestyle modifications</td>
<td>Target hemoglobin A1c &lt;7%-8%</td>
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<tr>
<td></td>
<td>• Pharmacologic therapies</td>
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<tr>
<td></td>
<td></td>
<td>• First-line: metformin</td>
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<tr>
<td></td>
<td></td>
<td>• Preferred therapies in CAD/PAD*</td>
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<tr>
<td></td>
<td></td>
<td>• Dulaglutide 0.75 mg SC weekly</td>
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<td></td>
<td>• Liraglutide 0.6 mg SC daily x1 week, then 1.2 mg SC daily</td>
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<td></td>
<td>• Semaglutide 0.25 mg SC weekly</td>
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<td></td>
<td>• Empagliflozin 10 mg/day</td>
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<td></td>
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<td>• Canagliflozin 100 mg/day</td>
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<td></td>
<td></td>
<td>• Preferred therapies in CHF*</td>
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<td></td>
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<td>• Empagliflozin 10 mg/day</td>
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<td>• Canagliflozin 100 mg/day</td>
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<td></td>
<td></td>
<td>• Dapagliflozin 10 mg/day</td>
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<tr>
<td><strong>Tobacco use</strong></td>
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<tr>
<td></td>
<td>• 5 A’s – Ask, Advise, Assess, Assist, and Arrange</td>
<td>Sustained cessation</td>
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<tr>
<td></td>
<td>• NRT</td>
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<td></td>
<td></td>
<td>• Patch*– 21 mg daily for ≥10 cigarettes/day; 14 mg daily for &lt;10 cigarettes/day</td>
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<td></td>
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<td>• Gum or lozenge – 4 mg if first tobacco use is ≤30 minutes from awakening; 2 mg if first tobacco use is &gt;30 minutes from awakening</td>
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<td></td>
<td></td>
<td>• Bupropion SR 150 mg daily for 3 days, then 150 mg twice daily (in combination with NRT)</td>
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<tr>
<td></td>
<td></td>
<td>• Varenicline 0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily for 3-6 months</td>
</tr>
</tbody>
</table>

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; DHP, dihydropyridine; GLP-1, glucagon-like peptide-1; LDL-C, low-density lipoprotein cholesterol; NRT, nicotine replacement therapy; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin 9; SGLT2, sodium-glucose cotransporter-2; SC, subcutaneous; SR, sustained release; T2D, type 2 diabetes.

*Initial doses are listed for reference. Further dose modifications are required for continuation of treatment.

The Burden of CAD and PAD

CAD remains the leading cause of mortality in the United States with more than 650,000 deaths each year. In 2017, 18 million people older than 20 years had been diagnosed with CAD in the United States. Each year, it is estimated that myocardial infarction (MI) occurs in approximately 605,000 patients, with 200,000 of those occurring in someone who has already had a previous MI. After an initial MI, patients are not only at risk for a recurrent MI at a rate of 16.2% within 7 years, but for patients over age 65 years,
one in 40 will develop a stroke within the first 6 months after an initial MI, and nearly 20% of patients will die of cardiac causes within the first year. CAD also remains a significant economic burden, costing nearly $220 billion annually from direct costs associated with health care utilization, medication, and indirect costs such as loss of productivity. The average cost for each MI averages $18,931, with an additional $8037 added during the first year for repeat hospitalizations and emergency department visits.

**PAD**

Although CAD is often the focus of atherosclerosis, PAD is also a large burden on the US health care system. Approximately 8.5 million Americans older than 40 years and more than 200 million individuals worldwide have some degree of PAD. PAD predominantly affects older individuals; approximately 6% to 7% of people older than 40 years have PAD, whereas 29% of those 70 years or older are affected. Significant racial differences are also seen in the prevalence of PAD; just 5.5% of Caucasians are affected, but more than 10% of non-Hispanic Blacks have PAD. Although PAD is the direct cause of death in a small number of those affected (57,000 deaths in 2018), patients with PAD are 2.5 times more likely to develop an MI than those without PAD. Additionally, patients with PAD have a 35% higher risk of having a stroke. One of the most traumatic complications of PAD occurs in the setting of acute limb ischemia requiring lower extremity amputation. Between 2000 and 2008, 186,338 amputations occurred in patients hospitalized with PAD. These patients experience almost a 2 times higher rate of mortality than those who do not require an amputation for PAD.

The evaluation for PAD is completed by obtaining the patient’s brachial and ankle artery blood pressure and determining the ratio of ankle to brachial blood pressure or ankle-brachial index (ABI). The diagnosis of PAD is confirmed when the ABI is lower than 0.9.

**Risk Factors and Prevention of Atherosclerotic Cardiovascular Disease (ASCVD) Events**

The presence of CAD, PAD, previous MI, or stroke are collectively referred to as clinical ASCVD. Major modifiable risk factors for the development of atherosclerosis include elevated blood lipid levels, specifically low-density lipoprotein cholesterol (LDL-C), hypertension, tobacco use, elevated body mass index (BMI), and type 2 diabetes (T2D). Additionally, alcohol, premature family history of heart disease, and sedentary lifestyle are also predictors for the development of atherosclerosis.

**Hyperlipidemia**

Due to the significant role LDL-C plays in the development and progression of ASCVD, statin therapy remains a cornerstone for reducing the risk of ASCVD events. In patients without ASCVD, statin therapy is indicated in 4 high-risk groups, as listed in TABLE 1. The most recent guidelines for secondary prevention and risk reduction of ASCVD recommend initiating high-intensity...
Hypertension

Hypertension is strongly associated with the development of vascular injury in CAD and PAD. Definitions of hypertension vary slightly among different guidelines but generally fall between greater than 130-140/80-90 mm Hg during at least 2 separate occasions. Over time, hypertension leads to endothelial hypertrophy and vascular smooth muscle growth, ultimately causing a reduction in the vascular lumen diameter. These pathological changes cause damage to vascular walls and further increase the risk of MI, stroke, and arterial thrombosis.

The American College of Cardiology (ACC) and American Heart Association (AHA) 2017 guidelines identify a blood pressure of greater than 130/80 mm Hg along with either clinical ASCVD or an ASCVD 10-year risk of greater than or equal to 10% as the threshold for initiating pharmacologic therapy, whereas the International Society of Hypertension (ISH) 2020 guidelines recommend pharmacologic therapy once blood pressure is greater than or equal to 140/90 mm Hg. Blood pressure goals in patients with CAD and PAD also vary according to the presence of comorbidities. In patients with stable CAD and PAD, ISH and ACC/AHA guidelines recommend a blood pressure target of at least lower than 130/90 mm Hg in patients without compelling indications, and a goal of lower than 130/80 mm Hg for patients with ASCVD, chronic kidney disease (CKD), or diabetes, as more stringent blood pressure targets have been shown to reduce the risk of CV complications by 25%. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) are a cornerstone of antihypertensive therapies in all patients and are strongly recommended as first-line therapy in patients with stable CAD and PAD. Gradual titration to the maximum recommended dose should occur to achieve the target blood pressure within 3 months. β-blockers and non-dihydropyridine calcium channel blockers (CCBs) (verapamil and diltiazem) may be indicated and necessary for patients with stable CAD who develop or continue to experience angina after maximizing first-line antihypertensive therapies. In the absence of angina or other compelling indications, thiazide or thiazide-like diuretics and dihydropyridine CCBs such as amlopidine or nifedipine are additional first-line therapies if target blood pressure is not achieved. Both the ACC/AHA and ISH guidelines recommend initiating combination drug therapy consisting of 2 first-line treatment agents for patients with severely uncontrolled blood pressure (>160/90 mm Hg) and a history of CAD or PAD, although cautious application of this approach should be used in elderly patients or those at risk for developing significant adverse effects. All patients should be educated on lifestyle modifications to achieve target blood pressure goals.

T2D

It is estimated that approximately 26 million adults in the United States have a diagnosis of T2D, and in 2018, 1.5 million adults were newly diagnosed with T2D. T2D is associated with a 67% to 85% increased risk of CV death due to stroke, MI, or heart failure compared with patients without diabetes. Since the late 1990s, the rate of atherosclerotic complications of diabetes has decreased substantially, yet diabetes remains one of the strongest predictors of MI, stroke, or need for amputation in patients with PAD.

Hyperglycemia, even in the “prediabetes” stage, augments lipid deposition in the endothelium of vascular smooth muscle, even in the setting of well-controlled lipid levels. Over time, as diabetes progresses, increased oxidative stress and inflammation cause accelerated atheroma calcification and destabilization of atherosclerotic plaques, increasing the likelihood of atherothrombosis. These pathological changes highlight the importance of aggressive lipid control in patients with T2D. For patients aged 40 to 75 years with T2D with low-ASCVD risk (<7.5%), moderate-intensity statin therapy should be used in addition to lifestyle modifications. In high-ASCVD risk (≥20%) patients with T2D, high-intensity statin therapy is reasonable for the prevention of CV events. All patients with T2D and a history of ASCVD events should receive high-intensity statin therapy and if target LDL-C level of lower than 70 mg/dL cannot be achieved with statin therapy alone, the use of ezetimibe or PCSK9 inhibitors (alirocumab or evolocumab) may be considered.

For patients with T2D and ASCVD, a target hemoglobin A1c of lower than 7% to 8% should be achieved by implementation of lifestyle changes, and the use of pharmacologic therapies with proven CV risk-reducing qualities.
TABLE 3. ANTI THROMBOTIC THERAPY LANDMARK TRIALS25-34

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Outcomes (HR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRIVE</td>
<td>ASCVD primary prophylaxis Men aged ≥65 years with 2-4 ASCVD risk factors or women aged ≥60 years with ≥3 ASCVD risk factors Excluded patients with ASCVD history or high bleeding risk</td>
<td>Aspirin daily vs placebo</td>
<td>• MACE: 0.81 (0.64-1.02) • MI: 0.53 (0.36-0.79) • GI bleeding: 2.1 (1.36-3.28)</td>
</tr>
<tr>
<td>ASCEND</td>
<td>ASCVD primary prophylaxis T2D without known ASCVD</td>
<td>Aspirin daily vs placebo</td>
<td>• MACE: 0.88 (0.79-0.97) • Major bleeding: 1.29 (1.09-1.52)</td>
</tr>
<tr>
<td>ASPREE</td>
<td>Healthy patients aged ≥70 years without a history of CAD or ASCVD</td>
<td>Aspirin daily vs placebo</td>
<td>• All-cause death: 1.14 (1.01-1.29) • CV death: 0.82 (0.62-1.08) • Major hemorrhage causing death: 1.13 (0.66-1.94)</td>
</tr>
<tr>
<td>CHANCE</td>
<td>Patients aged ≥40 years and acute minor ischemic stroke or TIA</td>
<td>Clopidogrel-based DAPT x21 days then aspirin until day 90 vs aspirin x90 days</td>
<td>• Stroke: 0.67 (0.57-0.81) • MACE: 0.69 (0.58-0.82) • GLUSTO severe bleeding: 0.94 (0.24-3.79) • Any bleeding: 1.41 (0.95-2.10)</td>
</tr>
<tr>
<td>COMPASS</td>
<td>Patients with stable CAD aged ≥65 years, or &lt;65 years with at least 2 additional risk factors: smoking, diabetes, CKD, HF, or non-lacunar ischemic stroke ≥1 month prior Excluded patients at a high risk of bleeding, recent stroke, or indications for DAPT, anticoagulation, or other antithrombotic therapies</td>
<td>Rivaroxaban 5 mg twice daily vs rivaroxaban 2.5 mg twice daily plus aspirin vs aspirin alone</td>
<td>• MACE (rivaroxaban 2.5 and aspirin vs aspirin alone): 0.76 (0.66-0.86) • Major bleeding (rivaroxaban 2.5 and aspirin vs aspirin alone): 1.70 (1.40-2.05) • Nonfatal, non-ICH, symptomatic major bleeding (rivaroxaban 2.5 and aspirin vs aspirin alone): 1.43 (0.89-2.29) • Net clinical benefit (rivaroxaban 2.5 and aspirin vs aspirin alone): 0.80 (0.70-0.91)</td>
</tr>
<tr>
<td>GLOBAL LEADERS</td>
<td>Patients with CAD requiring PCI ≥47% of patients presenting with ACS</td>
<td>Ticagrelor-based DAPT x1 month then ticagrelor x23 months vs DAPT x12 months, then aspirin x12 months</td>
<td>• All-cause death or MI: 0.87 (0.75-1.01) • BARC bleeding ≥3: 0.97 (0.78-1.20)</td>
</tr>
<tr>
<td>HOST-EXAM</td>
<td>Patients with PCI and stable on DAPT for 6-18 months</td>
<td>Clopidogrel 75 mg daily vs aspirin 100 mg daily</td>
<td>• MACE: 0.73 (0.59-0.90) • BARC bleeding ≥2: 0.70 (0.51-0.98)</td>
</tr>
<tr>
<td>MASTER DAPT</td>
<td>Patients with CAD requiring PCI at high risk for bleeding based on history of bleeding, indication for OAC, or PRECISE-DAPT score ≥25 Biodegradable stents used ≥60% of patients presenting with ACS</td>
<td>DAPT x1 month vs DAPT for at least 3 months</td>
<td>• MACE: 1.0 (0.76-1.52) • Any BARC bleeding: 0.64 (0.54-0.76) • Net adverse clinical events: 0.94 (0.76-1.15)</td>
</tr>
<tr>
<td>PEGASUS-TIMI S4</td>
<td>Patients with an MI within 3 years aged ≥50 years and 1 additional high-risk feature: age ≥65 years, diabetes, recurrent MI, multivessel CAD or CKD</td>
<td>Ticagrelor 90 mg twice daily and aspirin vs ticagrelor 60 mg twice daily and aspirin vs aspirin alone</td>
<td>• MACE (ticagrelor 60 and aspirin vs aspirin alone): 0.84 (0.74-0.95) • TIMI major bleeding (ticagrelor 60 and aspirin vs aspirin alone): 2.32 (1.68-3.21) • TIMI minor bleeding (ticagrelor 60 and aspirin vs aspirin alone): 3.31 (1.94-5.63) • Fatal bleeding or nonfatal ICH (ticagrelor 60 and aspirin vs aspirin alone): 1.20 (0.73-1.97)</td>
</tr>
<tr>
<td>POINT</td>
<td>Patients with minor ischemic stroke or high-risk TIA</td>
<td>Clopidogrel-based DAPT x90 days vs aspirin x90 days</td>
<td>• MACE: 0.75 (0.59-0.95) • Major hemorrhage: 2.32 (1.40-3.47) • Minor hemorrhage: 3.21 (1.8-5.53)</td>
</tr>
<tr>
<td>SMART-CHOICE</td>
<td>Patients with CAD requiring PCI Most patients with stable angina, small proportion with ACS</td>
<td>DAPT x3 months, then P2Y12 vs DAPT x12 months</td>
<td>• MACE: 0.40 (0.36-0.92)</td>
</tr>
<tr>
<td>THALES</td>
<td>Patients aged ≥40 years and acute minor to moderate ischemic stroke or TIA</td>
<td>Ticagrelor-based DAPT x30 days vs aspirin x30 days</td>
<td>• Stroke or death: 0.83 (0.71-0.96) • Stroke: 0.81 (0.69-0.95) • Severe bleeding: 3.99 (1.74-9.14) • ICH or fatal bleeding: 3.66 (1.48-9.02)</td>
</tr>
<tr>
<td>THEMIS</td>
<td>Patients with T2D and stable CAD aged ≥50 years Excluded patients with history of MI or stroke ≥80% of patients had received either PCI and/or CABG</td>
<td>Ticagrelor 60 mg twice daily vs aspirin x12 months</td>
<td>• MACE: 0.90 (0.81-0.99) • BARC bleeding ≥3: 2.36 (1.96-2.84)</td>
</tr>
<tr>
<td>TWILIGHT</td>
<td>Patients with CAD requiring PCI ≥63% of patients presenting with ACS</td>
<td>Ticagrelor-based DAPT x3 months, then ticagrelor vs ticagrelor-based DAPT x12 months</td>
<td>• MACE: 0.97 (0.76-1.24) • BARC bleeding ≥2: 0.56 (0.45-0.68)</td>
</tr>
<tr>
<td>VOYAGER</td>
<td>Patients aged ≥50 years with documented symptomatic PAD requiring revascularization Excluded patients at heightened bleeding risk or duration of clopidogrel therapy expected to extend past 6 months</td>
<td>Rivaroxaban 2.5 mg twice daily plus aspirin vs aspirin alone</td>
<td>• ALI, major amputation for vascular cause, MI, ischemic stroke, or CV death: 0.85 (0.76-0.96) • TIMI major bleeding: 1.43 (0.97-2.10) • ISTH major bleeding: 1.42 (1.10-1.84) • BARC bleeding ≥2: 0.91 (0.75-1.14)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; ALI, acute limb ischemia; ASCVD, atherosclerotic cardiovascular disease; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; GI, gastrointestinal; GUSTO, Global Use of Strategies to Open Occluded Arteries; HF, heart failure; ICH, intracranial hemorrhage; ISTH, International Society of Thrombosis and Haemostasis; MACE, major adverse cardiovascular event; MI, myocardial infarction; OAC, oral anticoagulation; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; T2D, type 2 diabetes.
oral formulation did not show a lower rate of MACE compared with placebo, and is not indicated for reduction of CV events in patients with T2D. Lixisenatide and exenatide have not been shown to reduce cardiovascular events in patients with T2D.

**Antithrombotic Therapies**

Antiplatelet therapies are a cornerstone of medical therapy in patients with CAD and PAD due to the significant role platelet activity has in causing MI, stroke, and arterial thrombus formation. The timing, combination of agents, and duration of their use are highly complex due to the interplay of various patient risk factors and populations. TABLE 2 includes a summary of the major trials discussed in the following sections.

**CAD**

For several decades, aspirin therapy has been recommended for the primary prevention of ASCVD events primarily due to its well-documented efficacy in secondary prevention; however, a more critical evaluation of aspirin for primary prevention has developed on the basis of several recent randomized controlled trials showing an increased risk of adverse effects that may outweigh benefits.

The 2019 Primary Prevention of Cardiovascular Disease guidelines recommends metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as first-line treatment options for patients with T2D and ASCVD. The SGLT2 inhibitors empagliflozin and canagliflozin, but not dapagliflozin, have been shown to reduce the risk of major adverse cardiac event (MACE) outcomes. Only empagliflozin was shown to explicitly reduce the risk of CV and all-cause mortality when compared with placebo.

The primary benefit of the SGLT2 inhibitors is the reduced risk of hospitalization for heart failure in patients with T2D. While all of these specific GLP-1 RAs require a daily injection, semaglutide is also available as an injectable formulation of semaglutide was associated with a reduction of CV events compared with placebo, and is not indicated for reduction of CV events in patients with T2D. Lixisenatide and exenatide have not been shown to reduce cardiovascular events in patients with T2D.

**STAR**

What antithrombotic therapies have demonstrated benefit in reducing major adverse CV events in patients with established CAD or PAD?

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**Figure 1. Antithrombotic Therapy for Primary Prevention in CAD and PAD**

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease.

1. The addition of low-dose rivaroxaban for patients with PAD is based on the results of the VOYAGER PAD trial. It is not addressed in the most current AHA/ACC guideline on the management of patients with lower-extremity PAD.

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**Table 3**

<table>
<thead>
<tr>
<th>Antithrombotic Therapy</th>
<th>Primary Prevention</th>
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<tbody>
<tr>
<td>Aspirin 75-100 mg daily is reasonable in high ASCVD risk (&gt;10%) and low-bleed risk patients (IIb)</td>
<td>CAD</td>
</tr>
<tr>
<td>Aspirin 75-325 mg or clopidogrel 75 mg daily for symptomatic PAD is recommended (Ia)</td>
<td>PAD</td>
</tr>
<tr>
<td>Avoid aspirin for primary prevention in patients &gt;70 years old with high-bleed risk (III)</td>
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</tr>
<tr>
<td>DAPT for symptomatic PAD to reduce ASCVD events is not well established (IIb)</td>
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<tr>
<td>Low dose rivaroxaban in addition to aspirin may be reasonable to reduce the risk of major adverse cardiovascular events in patients with low-risk of bleeding</td>
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</table>

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**Notes:**

- It is possible that aspirin is not the right choice for patients with an increased risk of adverse effects that may outweigh benefits.
- The timing, combination of agents, and duration of their use are highly complex due to the interplay of various patient risk factors and populations.
- **FIGURE 2:** The addition of low-dose rivaroxaban for patients with PAD is based on the results of the VOYAGER PAD trial. It is not addressed in the most current AHA/ACC guideline on the management of patients with lower-extremity PAD.
- **TABLE 2:** Includes a summary of the major trials discussed in the following sections.

---

**Antithrombotic Therapies**

Antiplatelet therapies are a cornerstone of medical therapy in patients with CAD and PAD due to the significant role platelet activity has in causing MI, stroke, and arterial thrombus formation. The timing, combination of agents, and duration of their use are highly complex due to the interplay of various patient risk factors and populations. TABLE 2 includes a summary of the major trials discussed in the following sections.

**CAD**

For several decades, aspirin therapy has been recommended for the primary prevention of ASCVD events primarily due to its well-documented efficacy in secondary prevention; however, a more critical evaluation of aspirin for primary prevention has developed on the basis of several recent randomized controlled trials showing an increased risk of adverse effects that may outweigh benefits. The 2019 Primary Prevention of Cardiovascular Disease guidelines include low-dose aspirin for primary prevention as a IIb recommendation to patients aged 40 to 70 years who have a greater than 10% estimated risk of ASCVD and do not have increased risk of bleeding. Recently, the US Preventive Services Task Force (USPSTF) released draft recommendations limiting the use of aspirin for primary prevention to patients aged 40 to 59 years with a greater than or equal to 10% ASCVD risk score. Specifically, they suggest not initiating aspirin therapy for primary prevention in patients 60 years or older due to the increased risk of bleeding.

Despite appropriate medical therapy, a significant proportion of patients with CAD or PAD may experience an ACS event. For patients who develop ACS and are medically managed without percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor (clopidogrel or ticagrelor) is recommended for 12 months. Patients with ACS who undergo PCI with stenting are also indicated to receive DAPT for 12 months, although the P2Y12 inhibitor prasugrel can be used in these settings (FIGURE 2). For patients who require CABG in the setting of...
ACS, DAPT with clopidogrel for 12 months is listed as a Ia recommendation. Continuation of DAPT past 1 year is supported by a IIb recommendation in current guidelines specifically in those who received a drug-eluting stent, but careful patient selection should be conducted to avoid use in patients at an elevated risk of bleeding. At the completion of DAPT therapy, it is recommended to discontinue the P2Y\textsubscript{12} inhibitor therapy, while aspirin is continued indefinitely (FIGURE 2). Indefinite aspirin therapy is recommended by the AHA and ACC for all patients with stable CAD to prevent the development of MI or stroke. Alternatively, clopidogrel is recommended for those with a contraindication to aspirin.

Although DAPT reduces the risk of cardiovascular death and recurrent MI within the first year of PCI and stenting, it also carries a relatively high risk of bleeding. New approaches to the management of DAPT and antiplatelet therapy have produced promising results to maximize the efficacy and minimize the bleeding risks in several phases of CAD management.

**P2Y\textsubscript{12} monotherapy**

Recently, several trials have addressed alternative DAPT regimens aimed at reducing bleeding events while still preventing ischemic events. The TWILIGHT trial evaluated the use of ticagrelor monotherapy after 3 months of DAPT, compared with continuation of DAPT after PCI in a high-risk patient population. The results of this simple, yet novel approach showed a noninferior rate of ischemic outcomes but a significantly lower rate of minor and major bleeding in patients randomized to ticagrelor monotherapy. The SMART-CHOICE, GLOBAL LEADERS, and MASTER DAPT trials also evaluated P2Y\textsubscript{12} inhibitor monotherapy after 1-3 months of DAPT, revealing similar rates of MACE outcomes and similar or lower rates of bleeding compared with continuation of DAPT.

The CHARISMA trial failed to show any meaningful benefit in ischemic or CV death with the addition of clopidogrel to aspirin over aspirin alone (6.8% with DAPT, 7.3% with aspirin; \( P = .22 \)) in patients with stable CAD. Moderate bleeding was increased by 38% in the DAPT-treated patients.

The CHARISMA trial, in the PEGASUS-TIMI 54 trial, patients with a history of MI who were at high risk for recurrent ACS were randomized to either 2 doses of ticagrelor and aspirin or aspirin alone. In this study of high CV risk patients, the use of either dose of ticagrelor significantly lowered the incidence of CV death, MI, or stroke compared with aspirin monotherapy.
While major bleeding was similar between treatment groups, more patients discontinued ticagrelor due to bleeding compared with the placebo group. There was no significant difference in the rates of fatal bleeding or nonfatal intracranial hemorrhage (ICH). While ticagrelor displayed beneficial effects on ischemic events, the elevated bleeding risk observed diminished the overall benefit seen with using ticagrelor and aspirin long term, even at a reduced dose of 60 mg twice daily. Preference for this approach may be used in patients at a particularly high risk of CV events with a low bleeding risk based on a validated scoring tool such as the DAPT-Score.30,43

Alternatively, the HOST-EXAM trial studied the effect of clopidogrel 75 mg monotherapy compared with aspirin 100 mg monotherapy in patients with stable CAD after receiving PCI. During the 24-month follow-up period, all-cause death, nonfatal MI, stroke, readmission for ACS, and serious bleeding were significantly lower in those treated with clopidogrel compared with those treated with aspirin (P = .003). Interestingly, although clopidogrel may exert greater antiplatelet effects leading to increased bleeding, the incidence of serious bleeding and minor gastrointestinal bleeding were also significantly lower in the clopidogrel treatment arm. While no difference in all-cause or CV death was observed in this trial, the results suggest clopidogrel may be a reasonable maintenance antiplatelet therapy regimen in patients who are categorized as high CV risk who prioritize avoidance of ischemic events.29

**PAD**

The AHA/ACC guidelines for the management of PAD provide a Ia recommendation for aspirin at a dose of 75 to 325 mg daily or clopidogrel 75 mg daily for the treatment of symptomatic patients (FIGURE 9).9,3035 The use of these agents in patients with symptomatic PAD has shown a significant reduction in the risk of developing stroke, MI, and vascular death. For patients with asymptomatic PAD, antiplatelet therapy is given a slightly lower recommendation, as limited data suggest that it provides similar benefit. DAPT is often initiated in patients with PAD, particularly after endovascular intervention to prevent morbidity and mortality, although its use remains a point of controversy due to inconsistent results across several trials, thus it is only provided a IIa recommendation.9 In a subgroup analysis of the CHARISMA trial, 3096 patients with PAD, most of whom were symptomatic, were evaluated for the development of CV death, MI, or stroke. The primary composite outcome occurred in 7.6% of patients treated with DAPT versus 8.9% in patients treated with aspirin monotherapy (P = .18). The rate of fatal and nonfatal MI was significantly reduced by approximately 38% (P = .028) and the rate of hospitalization for unstable angina, transient ischemic attack (TIA), or need for revascularization was reduced by about 18% (P = .011). Minor bleeding was substantially increased by the addition of clopidogrel. Although there was no significant benefit of DAPT in the primary outcome, the reduction of MI may outweigh the increased observance of minor bleeding in patients with PAD.44

Ticagrelor has also been evaluated in patients with PAD. The EUCLID study compared the effectiveness of ticagrelor compared with clopidogrel as monotherapy for patients with an ABI of lower than or equal to 0.80 or who had previously received revascularization of the lower limbs. No significant difference was observed in the primary outcome of cardiovascular death, MI, or stroke between ticagrelor- and clopidogrel-treated patients.45 Notably, current AHA/ACC PAD guidelines do not address ticagrelor for antiplatelet treatment in patients with PAD.9

**Anticoagulation in CAD and PAD**

Although anticoagulation with vitamin K antagonists has been used in patients with CAD and PAD for a number of years, several trials highlighted the adverse risks associated with their use. While in several large-scale trials, the addition of warfarin provided a reduction in MACE, these benefits were strongly outweighed by the upwards of 50% relative risk increase in major bleeding and is not routinely recommended.46

With the advent of the direct acting oral anticoagulants (DOACs), a re-emergence of interest in the role of anticoagulation has surfaced over the past decade. Two trials, the APPRAISE-2 trial and the ATLAS AC 2-TIMI 51 trial, evaluated the use of apixaban and rivaroxaban, respectively, in addition to DAPT in patients with ACS.47,48 In both trials, rates of bleeding were significantly higher in patients receiving DAPT and DOAC therapy. While apixaban did not lead to any CV benefit, low-dose rivaroxaban was associated with a lower rate of CV death, MI, or stroke.48 Ultimately, due to risk of bleeding with the addition of apixaban or rivaroxaban, this antithrombotic approach was not incorporated into the treatment of patients during the acute and late phase (<12 months from event) management of ACS.47,48 Follow-up studies would be required to determine whether rivaroxaban could demonstrate similar CV benefits with lower rates of bleeding in patients who had stable CAD.

COMPASS was a large, randomized, double-blinded, placebo-controlled trial evaluating the addition of rivaroxaban in 27,395 patients with stable CAD and/or PAD.23 Patients with CAD were included, but patients younger than 65 years were required to have additional ASCVD risk factors (TABLE 3).23 The primary efficacy composite outcome of CV death, MI, or stroke was lowered by 15% with the combination of rivaroxaban 2.5 mg twice daily and aspirin compared with aspirin alone (P = .007).
Rivaroxaban 5 mg twice daily did not provide significant benefit over the aspirin monotherapy. Each of the individual outcomes of the composite, with the exception of MI, was statistically lower with the addition of low-dose rivaroxaban. There were statistically more major bleeds in patients treated with a combination of rivaroxaban and aspirin (3.1%) compared with aspirin alone (1.9%). Fatal bleeding, nonfatal symptomatic ICH, or symptomatic bleeding into a critical organ did not differ in those receiving rivaroxaban and aspirin versus aspirin alone. With any study evaluating augmented antithrombotic regimens, there will always be a need for careful examination of the benefit from the addition of an additional agent to reduce ischemic events and how this compares to increases in clinically important bleeding episodes. When looking at the net clinical benefit outcome in the COMPASS trial, there is a net 20% relative risk reduction in overall adverse effects (ischemic outcomes and bleeding events). While this may seem impressive, some experts suggest the overall benefit derived from the addition of rivaroxaban is not robust enough to treat a large proportion of this patient population. While the net clinical benefit outcome attempts to include bleeding events (fatal or bleeding into critical organs) that share a similar severity to CV death, MI, or stroke, this approach may minimize the impact on quality of life that patients experience from minor bleeding episodes. Additionally, in instances where patients had multiple major bleeding episodes, only the most severe form of bleed was included, thus minimizing the impact of bleeding in the overall net clinical benefit analysis. Despite the critiques and controversies presented, clinicians have been provided with an additional therapeutic agent that can provide benefit in reducing the morbidity and mortality associated with CAD. A discussion with patients sharing the risk and benefit of low-dose rivaroxaban can help guide the decision-making process as some patients may find the increased risk of bleeding reasonable to prevent the ischemic events that have a high rate of fatal and nonfatal sequelae.

In a subgroup analysis of the COMPASS trial including patients with symptomatic PAD or carotid artery disease, similar CV benefits were observed as the original trial. Because the complications of PAD are not confined to an MI, CV death, and stroke, an additional composite outcome of major adverse limb events (MALEs) including acute and chronic limb ischemia and major amputations was evaluated. Use of rivaroxaban 5 mg twice daily alone in comparison to aspirin alone did not reduce the risk of CV death, stroke, or MI but did significantly lower the risk of MALE events. In addition to reducing CV death, stroke, or MI, rivaroxaban 2.5 mg twice daily and aspirin also reduced the risk of MALE events by 46%. Specifically, major amputations, although rare in this subgroup, were reduced by 70%. With the addition of MALE events, the net clinical benefit was slightly higher than seen in the overall COMPASS population at 22%. The VOYAGER PAD trial further measured the potential benefits of rivaroxaban. Patients were required to have had lower extremity revascularization within 10 days of randomization. Of the patients randomized to rivaroxaban plus aspirin, 15.5% experienced the primary outcome of acute limb ischemic, major amputation, MI, stroke, or CV death, compared with 17.8% of patients receiving aspirin only ($P = .009$). Of these individual outcomes, only major amputation was statistically lower in the rivaroxaban- plus aspirin-treated patients. Additional outcomes associated with lower extremity ischemia or revascularization were also significantly lower in patients randomized to rivaroxaban plus aspirin. Unsurprisingly, major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) and the Bleeding Academic Research Consortium (BARC) were significantly higher in the rivaroxaban and aspirin group compared with the aspirin group. Currently, the AHA/ACC and European Society of Cardiology (ESC) guidelines for the management of PAD do not include recommendations for the use of rivaroxaban, but it has gained FDA approval to reduce the risk of major CV events in patients with CAD or PAD.

**Antithrombotic Therapies in Specific Patient Populations**

**CAD/PAD and Diabetes**

**Mechanisms of Platelet Dysfunction**

Diabetes is associated with upregulation of platelet activity during vascular injury. This occurs through several mechanisms such as increased platelet adhesion molecules, von Willebrand factor antigen, and clotting factors. Insulin resistance can cause upregulation of the adenosine diphosphate P2Y$_{12}$ pathway and impaired fibrinolysis. The combination of these effects leads to platelet hyperreactivity and increases the incidence of platelet-mediated thrombosis, the cause of MI, stroke, and arterial thrombosis in patients with CAD and PAD, and may contribute to the increased risk of MI, stroke, and CV death in patients with T2D compared with the general population.

**Antithrombotic Therapy**

Due to the significant interplay of diabetes and platelet function, extensive research has been conducted evaluating various antithrombotic regimens in patients with diabetes. Similar to primary prevention in the general population, aspirin use in patients with diabetes but without prior vascular events has yielded underwhelming outcomes, resulting in varying national guideline recommendations. The ADA provides a level C recommendation for

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**Insulin resistance can cause upregulation of**

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aspirin as a primary preventive strategy for patients with diabetes who have an elevated ASCVD risk such as those aged 50 years or older with at least 1 additional ASCVD risk factor (hypertension, family history of premature ASCVD, smoker, CKD, or hyperlipidemia) only if the risk of bleeding is low due to increased risk of bleeding seen in more recent studies.19,20 The ACC/AHA guidelines do not provide any specific recommendations for aspirin in patients with diabetes without CAD as a primary preventive measure, but do recommend aspirin as a reasonable strategy for select patients who are at an elevated risk for ASCVD events.10 The ESC guidelines also provide IIb recommendation for aspirin therapy in patients with diabetes at high or very high ASCVD risk in absence of any contraindications.54 High-risk patients are defined as those who have had diabetes for 10 or more years and have at least 1 other risk factor such as hypertension, hyperlipidemia, active smoker, or obesity. Very-high risk encompasses patients with diabetes who have 3 or more of the previous risk factors, or evidence of end-organ dysfunction such as left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) less than or equal to 30 mL/min/1.73m², proteinuria, or retinopathy.24

Due to the enhanced platelet activity associated with diabetes, a number of trials have evaluated various antiplatelet regimens at different stages of CAD. THEMIS was one of the largest studies evaluating an augmented antiplatelet regimen in patients with diabetes and CAD.32 Patients with a history of known MI or stroke were excluded. The composite outcome of CV death, MI, or stroke was not reduced in the ticagrelor treatment group, but MI and stroke were statistically lower in those receiving ticagrelor compared with placebo. Conversely, major bleeding according to TIMI, PLATO, and BARC criteria were all significantly higher in patients receiving ticagrelor. Although small, a significantly higher incidence of trauma-related ICH was also noted in those receiving ticagrelor.32 Collectively, the lack of benefit in the composite ischemic outcome, the small difference in reduced ischemic events did not outweigh the increased rate of adverse effects, thus ticagrelor cannot be recommended for primary prevention even in patients with diabetes who have an increased risk of MI and stroke.

In a subgroup analysis of the TWILIGHT trial, patients with diabetes treated with ticagrelor were significantly less likely to experience a major bleeding event compared with those who continued to receive DAPT (1.1% vs 3.1%, respectively; \( P = .001 \)). Additionally, no significant difference was observed in the composite ischemic end point of CV death, MI, or stroke.55 This approach may be a suitable alternative regimen for those patients who are at a particularly high risk of bleeding to ensure ongoing antiplatelet therapy is provided to patients after PCI.

Another decision point occurs after 12 months of antiplatelet therapy from PCI. Two large-scale trials found clopidogrel monotherapy to be a reasonable antiplatelet strategy for patients with diabetes and stable CAD. In CAPRIE, patients were randomized to receive clopidogrel 75 mg daily or aspirin 325 mg daily after either an MI or stroke, or those with symptomatic PAD.56 In the patients with diabetes, those who received clopidogrel had an improved net clinical benefit compared with those who received aspirin.57 Unfortunately, patients with diabetes only represented about 20% of the trial population, and the use of higher dose aspirin limits conclusions regarding the safety and efficacy in current day practice. In the HOST-EXAM trial’s prespecified analysis of patients with diabetes treated with clopidogrel, the composite of all-cause death, nonfatal MI, stroke, readmission for ACS, and major bleeding was lower compared with those treated with aspirin.29 The ESC guidelines provide a IIb recommendation for the use of clopidogrel for secondary prevention over aspirin in patients with ASCVD.54

Although a focus on antiplatelet therapies predominates the anti-thrombotic interest in patients with diabetes, anticoagulation may still be a therapeutic option to minimize ischemic outcomes. In the COMPASS trial, CV death, stroke, and MI were 21.5% lower in patients with diabetes treated with rivaroxaban and aspirin, and the incidence of stroke was statistically lower in those treated with rivaroxaban and aspirin (1.2%) versus those only receiving aspirin (2.1%). While major bleeding was significantly higher in the rivaroxaban-treated patients \( (P = .0006) \), no significant difference in fatal bleeding was observed. When fatal bleeding or bleeding into a critical site was included in the net clinical benefit outcome, the addition of rivaroxaban showed a 22% benefit, whereas when major bleeding was included, no significant benefit was observed.58 This again suggests patients should be informed about the overall risk-benefit profile from the addition of rivaroxaban and should play a role in the decision to initiate this therapy.

**CAD/PAD and Stroke**

**Mechanisms of Platelet Dysfunction**

Patients with CAD and PAD are at a heightened risk for noncardioembolic ischemic stroke.6 Intracranial and carotid artery stenosis follows a similar pathophysiological process as in CAD and PAD. As the carotid arteries and intracranial arteries supply specific areas of the brain, blockage of these vessels can cause catastrophic neurologic consequences.29 Neurologic symptoms of stroke (eg, facial or limb numbness or weakness, altered mental status, aphasia, vision changes) can develop within seconds to minutes of artery occlusion. More than 7.6 million adult Americans have had a stroke and rates...
are expected to increase to nearly 11 million adults by the year 2030. After an initial stroke, 16% to 21% of patients will experience a recurrent stroke. Unsurprisingly, the risk factors for CAD and PAD are also predictors for the development of stroke. Glycemic, blood pressure, and lipid control as outlined previously can significantly reduce the risk of an initial and recurrent ischemic stroke by 25% to 65%. 

**Antithrombotic therapy**

As the pathophysiology of ischemic stroke closely resembles that of CAD and PAD, the use of antiplatelet therapies remains a mainstay of treatment in patients with noncardioembolic stroke. DAPT has shown greater efficacy than aspirin monotherapy in patients with TIA or minor ischemic stroke. In the CHANCE and POINT trials, patients were randomized to either early DAPT with clopidogrel for 21 to 90 days, respectively, or aspirin monotherapy for 90 days. Patients receiving only aspirin had a higher rate of ischemic stroke compared with those receiving initial DAPT in both trials. A small but significant difference in major bleeding was observed in the POINT trial and may be related to the longer duration of DAPT compared to only 21 days of DAPT in the CHANCE study.

Although prasugrel has been limitedly evaluated in the setting of ischemic stroke, the results from the TRITON-TIMI 38 trial identified a higher risk of major bleeding and CV death in patients with a history of ischemic stroke or TIA and thus should be avoided in these patients. Ticagrelor-based DAPT for 30 days after a mild to moderate stroke (National Institutes of Health Stroke Scale score ≤5) was found to reduce the incidence of stroke or death by 17% compared with patients treated with only aspirin in the THALES study. While severe bleeding was rare, the incidence of ICH or fatal bleeding was significantly higher in those receiving ticagrelor. While direct comparisons cannot be made between clopidogrel- and ticagrelor-containing DAPT regimens, clopidogrel-based DAPT, particularly when used for a short time period, appears to be the most optimal DAPT regimen to avoid adverse safety events.

Patients with a minor, noncardioembolic ischemic stroke or high-risk TIA should be initiated on clopidogrel-based DAPT within 12 to 24 hours of symptom onset based on the AHA and American Stroke Association 2021 guidelines for secondary prevention of ischemic stroke. DAPT should be continued for 21 to 90 days, although no specific duration within this time period is recommended and should depend on overall bleeding risk. Ticagrelor-based DAPT may be considered for patients with minor-moderate stroke or high-risk TIA but carries a slightly weaker IIb recommendation due to the increased risk of ICH and serious bleeding. After completion of DAPT, indefinite single antiplatelet therapy with either aspirin or clopidogrel is recommended by current guidelines. The use of aspirin 25 mg and dipyridamole 200 mg twice daily is also reasonable for the secondary prevention of ischemic stroke.

In patients with significant but stable CAD, rivaroxaban may be a suitable antithrombotic agent to prevent a first or recurrent stroke. A sub-analysis of the COMPASS trial found rivaroxaban 2.5 mg twice daily and aspirin was associated with a 42% lower risk of stroke and 49% lower risk of ischemic stroke when compared with aspirin alone. In patients with a previous history of stroke, the combination of rivaroxaban and aspirin was found to reduce the incidence of ischemic or unknown stroke by 67%. Unfortunately, the beneficial effect on stroke reduction was not observed in the VOYAGER PAD trial and with just 27% of patients in the COMPASS trial having PAD, the use of rivaroxaban in these patients cannot be recommended specifically for stroke prevention in patients with PAD.

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**STAR**

What interventions from a pharmacist are most impactful in helping patients achieve optimal control of comorbid disease states and reducing cardiovascular risks?

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**Optimizing Outcomes in the Management of CAD/PAD and Associated Comorbidities**

**Role of the Pharmacist**

Pharmacists can play an imperative role in the management of patients with CAD and PAD. Given the risk of bleeding events associated with antithrombotic therapies, pharmacists should regularly inform patients about the potential for bleeding and assess them for significant bleeding such as epistaxis, genitourinary bleeding, or melena. Additionally, due to the potential for drug–drug interactions that may cause enhanced or diminished effects of the antithrombotic therapies discussed, pharmacists should regularly assess patients for any changes to their prescribed medications and appropriate use of over-the-counter products.

Despite the demonstrable evidence for using therapies such as lipid-lowering agents, some studies have shown shockingly low rates of statin usage. Even when initiated, just 25% of patients with clinical ASCVD have been reported to attain appropriate LDL-C goals. Regular contact with patients allows pharmacists in the community setting to regularly assess and educate patients through medication therapy management (MTM) services. MTM is a wide-ranging array of services centered on optimization of therapeutic outcomes through the review of medication profiles, creation of a medication treatment plan, monitoring of effectiveness, and provision of education and support services. Community pharmacy-based education for patients with diabetes has directly
demonstrated improvement in medication usage, adherence to clinical practice guideline recommendations, attainment of goal A1c, LDL-C, and blood pressure targets.66-69

Additionally, several studies have documented the direct impact the community pharmacist has in early disease state recognition through initial and follow-up monitoring. Over the past 2 decades, community-based screening has grown and produced a substantial evidence base for the positive impact pharmacists can have in early recognition of hypertension, diabetes, hyperlipidemia, and increasing rates of sustained smoking cessation.66-70 These programs help not only identify patients with modifiable risk factors but can also lead to initiation of appropriate medications to reduce ischemic events.

Pharmacists working in the hospital setting also have the opportunity to recognize risk factors and optimize the medication therapy regimens patients receive. Unfortunately, more than 25% of Americans do not have a primary care physician.71 A hospital admission may be a patient’s first encounter with a health care system and the transitions of care (TOC) period may serve as an optimal time to educate patients about indications for various medications and initiate life-saving guideline-directed medical therapies. Various TOC programs have not only demonstrated reduction in hospital readmissions but have also been shown to improve medication adherence and patients’ understanding of their therapies.72,73 The optimization of antithrombotic therapy by pharmacists for patients with CAD and PAD is an area in need of attention and further evaluation.

**Pharmacist Interventions**

Although various interventions may be appropriate for a patient, it may be difficult to determine those that have the most significant impact. The CDC’s Million Hearts 2022 Campaign has sought to reduce the number of MIs and strokes by 1 million in the next 5 years. The ABCS of heart health center around 4 primary recommendations: taking aspirin as directed, controlling blood pressure, managing cholesterol, and smoking cessation.74 Pharmacists, with their frequent patient interactions, can identify patients who may benefit from aspirin therapy based on comorbid disease states. Additionally, for patients who require DAPT therapy after PCI, several tools, such as the DAPT Score and PRECISE-DAPT Score, are available to assess the likelihood of benefit from prolonged duration of DAPT.75,76 While these calculators may provide an estimate of whether patients may benefit from longer periods of DAPT, it is important to recognize that these tools have limitations in their ability to predict bleeding events.

The Million Hearts campaign has created a blood pressure log and educational pamphlet that pharmacists can provide to any patient. Assisting patients with control of blood pressure and understanding their therapies is pivotal; of the 116 million adults with hypertension in the United States, more than 73% of them have not met guideline blood pressure targets.77 Pharmacists can also provide blood pressure measurement services for those who may not be able to afford in-home blood pressure monitors. Pharmacists are also perfectly poised to assist with medication adherence and identify opportunities for medication consolidation and reducing polypharmacy. With the risk factors for CAD and PAD addressed earlier, many medication therapies are available as single-pill combinations. While these products may not be suitable during episodes of medication titration, once stable doses are obtained, adherence may be improved by up to 20% by switching to single-pill combination therapies.78,79 Pharmacists should also identify medication products with extended or sustained-release formulations so once-daily medication administration can be achieved.

Similarly, pharmacists can help recognize patients who may be candidates for statin therapies and discuss with the patient’s provider to recommend initiating therapy. Collaborative practice agreements may also serve as an avenue for pharmacists to increase their scope of practice and initiate and monitor therapies, such as statins or antihypertensive therapies, in conjunction with medical practices and physicians. Lastly, tobacco cessation plays a tremendous role in reducing CV events in patients with CAD, PAD, or high-risk patients. Community pharmacists are key players in helping patients avoid tobacco products. Fourteen states have statutes or regulations that allow pharmacists to prescribe tobacco cessation therapies.80 Again, due to frequent contact with a community pharmacy, the pharmacist can assist with not only helping patients decide when and which therapies would be most effective, they can regularly follow up with patients regarding relapses and potential modification of therapeutic regimens to achieve sustained cessation. Several resources through national and state pharmacy organizations are available to help navigate implementing smoking cessation and other CV risk reduction services.

**Conclusion**

As CAD and PAD continue to cause significant morbidity and mortality in the United States, the pharmacist’s role continues to evolve and expand. It is important for all pharmacists to recognize the importance of antithrombotic therapies available for patients with a variety of comorbidities. At a minimum, single antiplatelet therapy should be used for all patients with stable CAD or PAD in the absence of contraindications. For patients requiring PCI with stent placement, innovative DAPT regimens may become
more common to improve the safety profile and ensure patients are able to remain on beneficial antplatelet therapies for the appropriate durations. Anticoagulation with rivaroxaban may also provide benefits to select patients who have stable CAD or PAD with additional CV events, although identifying patients at high risk of bleeding remains an important aspect in determining the overall clinical benefit. Outside of antithrombotic therapy management, pharmacists should regularly engage with patients to identify therapeutic opportunities for medication optimization for those with hypertension, hyperlipidemia, diabetes, and those who are active tobacco users.

**REFERENCES**


**ADDITIONAL RESOURCES**

American College of Cardiology: www.acc.org/clinical-topics/acute-coronary-syndromes/atherosclerotic-disease-cad-pad

Take a Stand Against Amputation: https://standagainstamputation.com/resources-for-physicians/

Tobacco Cessation: quitassist.com

Million Hearts Campaign: https://millionhearts.hhs.gov

This article includes a unique and interactive patient simulation activity that will guide you through clinical decision making regarding anticoagulation and comorbidity management for patients with CAD and PAD. Access the simulation at: www.pharmacytimes.org/CAD-PAD

**INTERACTIVE SIMULATION OF PATIENT CASES**

This article includes a unique and interactive patient simulation activity that will guide you through clinical decision making regarding anticoagulation and comorbidity management for patients with CAD and PAD. Access the simulation at: www.pharmacytimes.org/CAD-PAD


lines on the Diagnosis and Management of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extra-


58. Bhatt DL, Eikelboom JW, Connolly SJ, et al; COMPASS Steering Committee and Investi-


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/CAD-PAD to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

Once completed, click “Next” until reaching the activity posttest.

After successful completion of the online interactive patient simulation, posttest, and activity evaluation, your credit will be uploaded into CPE Monitor. You must complete these steps before the activity expires in order to receive your credit.

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POSTTEST QUESTIONS

1. JB, a 66-year-old woman, was recently discharged from the hospital after experiencing a myocardial infarction (MI) and receiving percutaneous coronary intervention (PCI) with stent placement. She has a past medical history significant for hypertension and hyperlipidemia, and a gastrointestinal bleed that occurred 2 years ago. She reports her physician prescribed her aspirin 81 mg daily and ticagrelor 90 mg twice daily for 3 months and is planning to have her continue ticagrelor after that for an additional 9 months. She reports her husband was on aspirin and clopidogrel for an entire year and is wondering why her regimen is different. Which of the responses related to the TWILIGHT trial is correct related to JB’s regimen?
   A. In high-risk patients, ticagrelor monotherapy reduced the risk of ischemic events and had a similar risk of bleeding.
   B. In high-risk patients, ticagrelor monotherapy had a similar risk of ischemic events and a lower risk of bleeding.
   C. In low-risk patients, ticagrelor monotherapy had a similar risk of ischemic events and had a similar risk of bleeding.
   D. In low-risk patients, ticagrelor monotherapy had a similar risk of ischemic events and a lower risk of bleeding.

2. Which of the following goals of therapy is the most appropriate for patients with hypertension with established coronary artery disease (CAD) and history of MI?
   A. Blood pressure of <150/90 mm Hg
   B. Blood pressure of <120/80 mm Hg
   C. Blood pressure of <130/80 mm Hg
   D. Blood pressure of <140/90 mm Hg

3. Which of the following antithrombotic regimens is appropriate for a patient with stable CAD and low risk of bleeding?
   A. Aspirin 81 mg daily and rivaroxaban 5 mg twice daily
   B. Aspirin 81 mg daily and warfarin titrated to a goal international normalized ratio of 2-3
   C. Aspirin 81 mg daily and apixaban 5 mg twice daily
   D. Aspirin 81 mg daily and rivaroxaban 2.5 mg twice daily

4. Which of the following P2Y₁₂ inhibitors is reasonable to initiate based on the results of the PEGASUS-TIMI 54 trial?
   A. Ticagrelor 60 mg twice daily
   B. Prasugrel 5 mg daily
   C. Clopidogrel 75 mg daily
   D. Ticagrelor 90 mg twice daily

5. Which of the following events are patients at risk for after an MI?
   A. Cardiovascular (CV) death
   B. CV death and MI
   C. Stroke and MI
   D. MI, stroke, and CV death

6. In the VOYAGER trial, the addition of rivaroxaban to aspirin specifically reduced the rate of which of the following outcomes?
   A. Major amputation for vascular causes
   B. Acute limb ischemia
   C. CV death
   D. Stroke
POSTTEST QUESTIONS (CONTINUED)

7. Which patient would most benefit from high-intensity statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD)?
   A. 52-year-old man with a past medical history significant for MI
   B. 40-year-old woman with a past medical history of type 2 diabetes with an ASCVD risk score of 6%
   C. 90-year-old man with an ASCVD risk score of 5%
   D. 60-year-old woman with peripheral artery disease (PAD) and an ASCVD risk score of 22%

8. Which initial antithrombotic regimen would be most appropriate for a patient presenting with a minor acute noncardioembolic ischemic stroke?
   A. Aspirin 81 mg daily and prasugrel 10 mg daily for 21 days
   B. Aspirin 81 mg daily and clopidogrel 75 mg daily for 30 days
   C. Aspirin 81 mg daily and rivaroxaban 2.5 mg twice daily indefinitely
   D. Ticagrelor 90 mg twice daily for 30 days

9. Which of the following antihyperglycemic medications is most likely to reduce the risk of major cardiac adverse event outcomes in a patient already taking metformin and a history of MI and a hemoglobin A1c of 8.8%?
   A. Sitagliptin
   B. Dulaglutide
   C. Dapagliflozin
   D. Lixisenatide

10. Which statement is correct related to the benefits of adding rivaroxaban to aspirin for patients with stable CAD?
    A. Significantly reduces the composite ischemic outcome and all the individual components of MI, stroke, and CV death
    B. The decrease in ischemic events outweighed the increased risk of bleeding.
    C. There was no significant difference in any bleeding between those treated with rivaroxaban 2.5 mg twice daily compared with those treated with aspirin only.
    D. In young patients (<65 years old) with low ischemic risk, the addition of rivaroxaban 2.5 mg twice daily to aspirin significantly reduces the risk of ischemic events and CV death.
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