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JANUARY 2022
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MAKE THEIR SHINGLES RISK YOUR RESPONSIBILITY

99.5% OF PEOPLE 50 YEARS AND OLDER ARE INFECTED WITH THE VARICELLA ZOSTER VIRUS[1]

IN 1 OUT OF 3 PEOPLE, THE VIRUS REACTIVATES AND CAUSES SHINGLES[2,3]

SHINGRIX
(ZOSTER VACCINE RECOMBINANT, ADJUVANTED)

Indication

SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

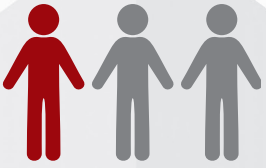
Important Safety Information

SHINGRIX is contraindicated in anyone with a history of a severe allergic reaction (eg, anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX

- Review immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX
- In a postmarketing observational study, an increased risk of Guillain-Barré syndrome was observed during the 42 days following vaccination with SHINGRIX
- Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope

There are certain medical conditions that are normally associated with aging, but **your patients might not even be aware of a potentially serious one—shingles**. And if they're over 50 years of age, the risk is real. Take a closer look to learn more about the risk of shingles:

99.5% of people ≥50 years of age are infected with the varicella zoster virus[1]



In **1 out of 3 people,** the virus reactivates and causes shingles[2,3]

Shingles—**a blistering rash that can be excruciatingly painful**[2,3]

It's time to prioritize shingles in your practice—**are you considering your patients 50 years and older for vaccination with SHINGRIX?**

See a range of potential patient types at **ProfilesSHINGRIX.com**

Important Safety Information (cont'd)

- Solicited local adverse reactions reported in individuals aged 50 years and older were pain (78%), redness (38%), and swelling (26%)
- Solicited general adverse reactions reported in individuals aged 50 years and older were myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%)
- The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women
- It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion
- Vaccination with SHINGRIX may not result in protection of all vaccine recipients

Please see Brief Summary of Prescribing Information for SHINGRIX on the following pages.

References: 1. Kilgore PE, et al. *J Med Virol.* 2003;70(suppl 1):S111-S118. **2.** CDC. *MMWR.* 2008;57(RR-5):1-30. **3.** Kawai K, et al. *BMJ Open.* 2014;4(6):e004833. doi:10.1136/bmjopen-2014-004833.

BRIEF SUMMARY

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

SHINGRIX is a vaccine indicated for prevention of herpes zoster (HZ) (shingles) in adults aged 50 years and older.

Limitations of Use:

- SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

2 DOSAGE AND ADMINISTRATION

2.2 Administration Instructions

For intramuscular injection only.

After reconstitution, administer SHINGRIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours. Discard reconstituted vaccine if not used within 6 hours.

2.3 Dose and Schedule

Two doses (0.5 mL each) administered intramuscularly according to the following schedule:

- A first dose at Month 0 followed by a second dose administered 2 to 6 months later.

4 CONTRAINDICATIONS

Do not administer SHINGRIX to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX *[see Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX.

5.2 Guillain-Barré Syndrome (GBS)

In a postmarketing observational study, an increased risk of GBS was observed during the 42 days following vaccination with SHINGRIX *[see Adverse Reactions (6.2)]*.

5.3 Syncope

Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of SHINGRIX could reveal adverse reactions not observed in clinical trials.

Adults Aged 50 Years and Older

Overall, 17,041 adults aged 50 years and older received at least 1 dose of SHINGRIX in 17 clinical studies.

The safety of SHINGRIX was evaluated by pooling data from 2 placebo-controlled clinical studies (Studies 1 and 2) involving 29,305 subjects aged 50 years and older who received at least 1 dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0- and 2-month schedule. At the time of vaccination, the mean age of the population was 69 years; 7,286 (25%) subjects were aged 50 to 59 years, 4,488 (15%) subjects were aged 60 to 69 years, and 17,531 (60%) subjects were aged 70 years and older. Both studies were conducted in North America, Latin America, Europe, Asia, and Australia. In the overall population, the majority of subjects were White (74%), followed by Asian (18%), Black (1.4%), and other racial/ethnic groups (6%); 58% were female.

Solicited Adverse Reactions: In Studies 1 and 2, data on solicited local and general adverse reactions were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local and general adverse reaction following administration of SHINGRIX (both doses combined) were pain (78%), redness (38%), and swelling (26%); and myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%).

The reported frequencies of specific solicited local adverse reactions and general adverse reactions (overall per subject), by age group, from the 2 studies are presented in Table 1.

Table 1. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Vaccination in Adults Aged 50 to 59 Years, 60 to 69 Years, and 70 Years and Older[b] (Total Vaccinated Cohort with 7-Day Diary Card)

Adverse Reactions	Aged 50-59 Years		Aged 60-69 Years		Aged ≥70 Years	
	SHINGRIX	Placebo[c]	SHINGRIX	Placebo[c]	SHINGRIX	Placebo[c]
Local Adverse Reactions	**n=1,315 %**	**n=1,312 %**	**n=1,311 %**	**n=1,305 %**	**n=2,258 %**	**n=2,263 %**
Pain	88	14	83	11	69	9
Pain, Grade 3[d]	10	1	7	1	4	0.2
Redness	39	1	38	2	38	1
Redness, >100 mm	3	0	3	0	3	0
Swelling	31	1	27	1	23	1
Swelling, >100 mm	1	0	1	0	1	0
General Adverse Reactions	**n=1,315 %**	**n=1,312 %**	**n=1,309 %**	**n=1,305 %**	**n=2,252 %**	**n=2,264 %**
Myalgia	57	15	49	11	35	10
Myalgia, Grade 3[e]	9	1	5	1	3	0.4
Fatigue	57	20	46	17	37	14
Fatigue, Grade 3[e]	9	2	5	1	4	1
Headache	51	22	40	16	29	12
Headache, Grade 3[e]	6	2	4	0.2	2	0.4
Shivering	36	7	30	6	20	5
Shivering, Grade 3[e]	7	0.2	5	0.3	2	0.3
Fever	28	3	24	3	14	3
Fever, Grade 3[f]	0.4	0.2	1	0.2	0.1	0.1
GI[g]	24	11	17	9	14	8
GI, Grade 3[e]	2	1	1	1	1	0.4

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Data for subjects aged 50 to 59 years and 60 to 69 years are based on Study 1. Data for subjects 70 years and older are based on pooled data from Study 1: NCT01165177 and Study 2: NCT01165229.

[c] Placebo was a saline solution.

[d] Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

[e] Grade 3 myalgia, fatigue, headache, shivering, and GI: Defined as preventing normal activity.

[f] Fever defined as ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°F for rectal route; Grade 3 fever defined as >39.0°C/102.2°F.

[g] GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

The incidence of solicited local and general reactions was lower in subjects aged 70 years and older compared with those aged 50 to 69 years.

The local and general adverse reactions seen with SHINGRIX had a median duration of 2 to 3 days.

(continued on next page)

There were no differences in the proportions of subjects reporting any or Grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28% and 21%, respectively) compared with Dose 1 (24% and 14%, respectively). Grade 3 solicited general adverse reactions (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3%, 4%, and 4%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events: Unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded on a diary card by all subjects. In the 2 studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 51% and 32% of subjects who received SHINGRIX (n = 14,645) or placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in ≥1% of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (4% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received SHINGRIX or placebo, respectively, within 30 days of vaccination; available information is insufficient to determine a causal relationship with SHINGRIX.

Serious Adverse Events (SAEs): In the 2 studies, SAEs were reported at similar rates in subjects who received SHINGRIX (2.3%) or placebo (2.2%) from the first administered dose up to 30 days post-last vaccination. SAEs were reported for 10.1% of subjects who received SHINGRIX and for 10.4% of subjects who received placebo from the first administered dose up to 1 year post-last vaccination. One subject (<0.01%) reported lymphadenitis and 1 subject (<0.01%) reported fever greater than 39°C; there was a basis for a causal relationship with SHINGRIX.

Optic ischemic neuropathy was reported in 3 subjects (0.02%) who received SHINGRIX (all within 50 days after vaccination) and 0 subjects who received placebo; available information is insufficient to determine a causal relationship with SHINGRIX.

Deaths: From the first administered dose up to 30 days post-last vaccination, deaths were reported for 0.04% of subjects who received SHINGRIX and 0.05% of subjects who received placebo in the 2 studies. From the first administered dose up to 1 year post-last vaccination, deaths were reported for 0.8% of subjects who received SHINGRIX and for 0.9% of subjects who received placebo. Causes of death among subjects were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases: In the 2 studies, new onset potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 0.6% of subjects who received SHINGRIX and 0.7% of subjects who received placebo from the first administered dose up to 1 year post-last vaccination. The most frequently reported pIMDs occurred with comparable frequencies in the group receiving SHINGRIX and the placebo group.

Dosing Schedule: In an open-label clinical study, 238 subjects 50 years and older received SHINGRIX as a 0- and 2-month or 0- and 6-month schedule. The safety profile of SHINGRIX was similar when administered according to a 0- and 2-month or 0- and 6-month schedule and was consistent with that observed in Studies 1 and 2.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SHINGRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

General Disorders and Administration Site Conditions

Decreased mobility of the injected arm which may persist for 1 or more weeks.

Immune System Disorders

Hypersensitivity reactions, including angioedema, rash, and urticaria.

Nervous System Disorders

Guillain-Barré syndrome.

Postmarketing Observational Study of the Risk of Guillain-Barré Syndrome following Vaccination with SHINGRIX

The association between vaccination with SHINGRIX and GBS was evaluated among Medicare beneficiaries aged 65 years or older. Using Medicare claims data, from October 2017 through February 2020, vaccinations with SHINGRIX among beneficiaries were identified through National Drug Codes, and potential cases of hospitalized GBS among recipients of SHINGRIX were identified through International Classification of Diseases codes.

The risk of GBS following vaccination with SHINGRIX was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 183 days post-vaccination. The primary analysis (claims-based, all doses) found an increased risk of GBS during the 42 days following vaccination with SHINGRIX, with an estimated 3 excess cases of GBS per million doses administered to adults aged 65 years or older. In secondary analyses, an increased risk of GBS was observed during the 42 days following the first dose of SHINGRIX, with an estimated 6 excess cases of GBS per million doses administered to adults aged 65 years or older, and no increased risk of GBS was observed following the second dose of SHINGRIX. These analyses of GBS diagnoses in claims data were supported by analyses of GBS cases confirmed by medical record review. While the results of this observational study suggest a causal association of GBS with SHINGRIX, available evidence is insufficient to establish a causal relationship.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women *[see Use in Specific Populations (8.1) of full prescribing information]*.

8.2 Lactation

Risk Summary

It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion *[see Use in Specific Populations (8.2) of full prescribing information]*.

8.5 Geriatric Use

Adults Aged 60 Years and Older

Of the total number of subjects who received at least 1 dose of SHINGRIX in Studies 1 and 2 (n = 14,645), 2,243 (15%) were aged 60 to 69 years, 6,837 (47%) were aged 70 to 79 years, and 1,921 (13%) were 80 years and older. There were no clinically meaningful differences in efficacy across the age groups *[see Clinical Studies (14.1, 14.2, 14.3) of full prescribing information]*.

The frequencies of solicited local and general adverse reactions in subjects aged 70 years and older were lower than in younger adults (aged 50 through 69 years). *[See Adverse Reactions (6.1).]*

17 PATIENT COUNSELING INFORMATION

- Inform patients of the potential benefits and risks of immunization with SHINGRIX and of the importance of completing the 2-dose immunization series according to the schedule.
- Inform patients about the potential for adverse reactions that have been temporally associated with administration of SHINGRIX.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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IN MEMORIAM

Remembering Michael J. Hennessy Sr.

Michael J. Hennessy Sr., the beloved chairman and founder of MJH Life Sciences™, the parent company of *Medical Economics*®, passed away in November after a lifetime spent turning his passion for building businesses and creating jobs into a run of successful ventures and brands. He was 61.

Following his graduation from Rider College (now Rider University) in Lawrence, New Jersey, in 1982, he started his career in medical publishing as a sales trainee, eventually advancing to the position of chief operating officer. In 1986, Hennessy 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-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 focusing on a range of topics in research and clinical medicine.

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 over 30 years. In 2005, Hennessy acquired ArcMesa Educators, LLC, leaders in online certification for physicians, pharmacists, nurses and other health care professionals.

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 enduring 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 OncLive® 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 Healthcare and Industry Sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as *Medical Economics*® to an already impressive portfolio. This acquisition made the organization the largest independently owned medical communications company in North America.

Later in 2019, Hennessy elevated his own role to chairman while naming his son, Mike Hennessy Jr., to assume the leadership role of the organization and carry on the family legacy. Under Mike Jr.'s leadership, the company enhanced its global potential by entering a long-term partnership with BDT Capital Partners, LLC, in November 2021.

Hennessy's true passion was his relationship with his wife, Patrice "Patti" Hennessy. After they met in college, Hennessy devoted his life to Patti and his family, raising four wonderful children, Shannon, Ashley, Mike Jr., and Chris. 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 & 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, Matt, Phil, Rachel and Jordan; and his 10 grandchildren. He will be greatly missed by his family, friends and MJH Life Sciences™ family. ■

Referenced in MedLine®

Medical Economics®
SMARTER BUSINESS. BETTER PATIENT CARE.

January 2022

Volume 99 Issue 1

MEDICAL ECONOMICS® (USPS 337-480) (Print ISSN: 0025-7206, Digital ISSN: 2150-7155) is published monthly (12 times a year) by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. Subscription rates: one year $108, two years $204 in the United States & Possessions, $170 for one year in Canada and Mexico, all other countries $170 for one year. Singles copies (prepaid only): $18 in US, $22 in Canada & Mexico, and $24 in all other countries. Include $6.50 for U.S. shipping and handling. Periodicals postage paid at Trenton, NJ 08650 and additional mailing offices. Postmaster: Send address changes to *Medical Economics®*, PO Box 457, Cranbury, NJ 08512-0457. Canadian GST Number: R-124213133RT001 Publications Mail Agreement number 40612608. Return undeliverable Canadian addresses to: IMEX Global Solutions, PO Box 25542 London, ON N6C 6B2 CANADA. Printed in the USA.

Cover: Dian Elving/iStock.Adobe.com

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PHYSICIANS FINANCIAL NEWS®

INVESTING INTELLIGENCE *with Dave S. Gilreath, CFP*

Bond alternatives for income amid high inflation

Many physicians on the cusp of retirement are concerned about whether their portfolios will generate enough income now that inflation has hit a 30-year high. Because many physicians are self-employed, they lack corporate pensions pegged to inflation. Instead, they rely largely on their accumulated wealth to fund retirement, so having portfolios structured to generate enough income is critical.

The classic low-risk solution has traditionally been bonds. This may have worked fine for your father's retirement portfolio, which probably used the classic, now-obsolete 60/40 allocation of bonds to stocks.

But this allocation — or any allocation to bonds — has not made sense for years because of withering bond interest rates. Now, with current inflation, bond investors are losing several percentage points annually instead of gaining them.


Gilreath

Now that bonds are a portfolio albatross, the challenge for the retired and nearly retired is how to ensure decent portfolio income during retirement with reasonable risk.

What alternatives can deliver enough income to stay ahead of inflation?

Stocks' surprising role

Some answers involve investment solutions that you may never have heard of, although they are not all that esoteric. After all, they are traded on public markets and plainly visible to inquiring investors who bother to look.

However, one solution is quite familiar — and ironic: stocks themselves. Stocks in general are widely dismissed as being risky in inflationary times, but market history shows that the S&P 500 can provide an effective hedge against inflation. Within this index, dividend-paying stocks can be particularly advantageous as a hedge against inflation over the long term.

All stocks are subject to the ups and downs of the equity market, but reliable dividend payers known as dividend aristocrats—those with 25-plus years of dividend increases—tend to have good long-term records of performance and stability. They pay reliable dividends because they tend to be large, mature companies. Unlike young companies, they do not need to invest a lot in research and development to achieve profitability; most of them have been profitable for decades.

Familiar names

There are several dozen such companies, many with familiar names, including: McDonald's, Colgate-Palmolive, Target, Walmart, Procter & Gamble, PepsiCo, Clorox, PPG Industries, Johnson & Johnson, and 3M. Many are categorized as value stocks, which may be mustering for a performance upswing, according to some indicators. Many of these aristocrats can be found in the holdings of exchange-traded funds (ETFs) like ProShares S&P 500 Dividend Aristocrats (NOBL).

Buying and holding a diversified subportfolio of these stocks long term is a good way to position for income with reasonable risk. During periods of normal inflation, this equity category has frequently beaten bonds for net retirement income.

> ***"The classic low-risk solution has traditionally been bonds. This may have worked fine for your father's retirement portfolio ... but this allocation — or any allocation to bonds — has not made sense for years because of withering bond interest rates."***

Less visible solutions

Other income producers are less well known. Because these are alternative investments (neither bonds nor stocks), they can add needed diversification to equity-heavy portfolios. These investments include the following:

- Real estate investment trusts (REITs). These are landlord companies that own a broad range of rental properties — including billboards, office buildings, medical suites, apartments, marijuana greenhouses, cell towers and data centers. They have a special tax status that requires them to pass along 90% of their profits to investors in the form of dividends. REITs are not usually recommended portfolio allocations upward of 10% or 15% for most individuals. Because many of these companies got beaten up badly by the pandemic in 2020 and still have room to grow after rising this fall, a heftier portfolio allocation of judiciously selected REITs could be a good tactical move these days. Many pay dividends in the 4% or 5% territory, which should keep investors even with or above inflation in 2022, because inflation is expected to decline soon from recently published levels around 6%. If shares increase in price, so much the better.

REITs tend to rise in value during times of inflation and rising interest rates because landlords can increase rents commensurately; many leases include automatic escalator clauses pegged to inflation rates.

Property values tend to rise with prices generally, because higher costs of labor, land and materials used in construction (all current factors) raise the bar for new development. This can constrict the supply of new rental properties, meaning higher occupancy rates for existing properties, which pushes up demand and enables rent increases.

REITs in all categories can be found on the website of the National Association of Real Estate Investment Trusts.

• ETFs of variable-rate preferred stocks (aka floating rate). Preferred stocks are the lesser-known half-sibling of common stocks (the ones referred to simply as stocks). Something of a bond-stock hybrid, preferred shares are bonds in stocks' clothing. They often have less upside than common stocks, but also less downside or volatility.

Variable-rate preferred-share ETFs own shares in which dividend payouts move up and down with market rates. This gives investors protection amid periods of rising interest rates, an attractive feature now that rates appear likely to increase in the coming months. These funds are now typically paying dividends of about 5% annually. With all preferred-share investments, active management is important because many passively managed ETFs track indexes populated by shares that increase risk from a feature known as negative yield-to-call.

Nik_Merkulov/Stock.Adobe.com

Although variable-rate preferred ETFs are a useful portfolio tool, there are not many of these products around. Two examples are Global X Variable Rate Preferred ETF (PFFV) and Invesco Variable Rate Preferred ETF (VRP).

• Options-based ETFs. These trade on the volatility of indexes or set categories of stocks. Volatility is widely feared but as a normal, expected characteristic of the equity market, it should be approached as something to be harnessed for gain. "Risk is not the same as volatility," as Warren Buffett says, "but that lesson has not customarily been taught in business schools, where volatility is almost universally used as a proxy for risk. Though this pedagogic assumption makes for easy teaching, it is dead wrong: volatility is far from synonymous with risk."

Professional and advanced individual investors harness volatility by trading options—bets on whether a stock or group of stocks will rise or fall within a set period. Options' complexity has long made them inaccessible to most individual investors. But over the past few years, about 120 options-based ETFs have come on the market, making options strategies widely accessible.

Some of these funds have posted double-digit share-price gains this year, with annual dividend yields well upward of 5% in many cases. Some use good hedging to potentially reduce risk. Although these products make options strategies highly available to the average investor, caveat emptor applies: Individual investors should take time to evaluate risks, because even the use of options ETFs can be complicated. Investment can be coordinated with existing holdings. For example, if you own shares in a Nasdaq 100 fund, you might want to offset risk by hedging this holding with shares of, for example, Global X Nasdaq 100 Covered Call ETF (QYLD), which tracks the Nasdaq 100 but does not tend to rise as high because of the downside protection it provides.

Though you probably will not hear about these alternative investments often, they might be useful in your portfolio. Lack of public awareness of them can lessen the chance that they will be bid up by your fellow mirth makers. ■

Dave S. Gilreath, CFP, is a 40-year veteran of the financial services industry. He is a partner and chief investment officer of Sheaff Brock Investment Advisors, LLC, a portfolio management company for individual investors, and Innovative Portfolios, LLC, an institutional money management firm. Based in Indianapolis, the firms manage about $1.4 billion in assets nationwide.

Dealing with medical board complaints

by **Keith Loria** Contributing author

Most physicians spend their sleepless nights worrying about malpractice lawsuits but not medical board complaints. However, a complaint to a medical board is a considerable challenge posing as much risk to a physician's career as a malpractice case.

Such a complaint often can be very trying and potentially damaging to one's reputation. Some of the reasons behind medical board complaints involve a doctor's code of ethics. Medical malpractice, misdiagnosis, failure to treat a patient and mismanaging a patient are common allegations in such complaints.

Alex Keoskey, a partner at Mandelbaum Salsburg P.C., a law firm based in Roseland, New Jersey, notes it is essential that legal counsel be retained whenever there is a threat of an adverse action against a physician from any source. "Physicians should take medical board complaints far more seriously than a medical malpractice complaint," he says. "Physicians need to be aware of the reporting requirements enshrined in state and federal law relating to adverse actions by medical boards."

Kevin O'Mahony, an attorney at KOMahony Law in Johns Creek, Georgia, notes disciplinary action resulting from a medical board complaint can include a reprimand, restrictions on a physician's practice, continuing medical education or monitoring requirements, probation and license suspension or revocation. "The adverse consequences of a medical board complaint do not end there," he says. "Physicians generally are required by contract to report disciplinary actions to their professional liability carriers, managed care plans and patients' health insurance plans."

Federal law also requires that discipline be reported to the National Practitioner Data Bank, which hospitals must check before granting or renewing medical staff privileges. "In most states, all public disciplinary actions taken by the medical board are required to be entered on the physician's profile on the board's website," O'Mahony says. "The public board order itself can be viewed online by anyone who wishes."

Public disciplinary actions are also reported to the Federation of State Medical Boards (FSMB), a national clearinghouse whose membership comprises all state medical boards across the country. The FSMB issues periodic reports to all state medical boards informing them of any public actions taken against a physician by another state's board.

If a physician licensed in Georgia, Florida and North Carolina is the subject of a disciplinary action by the Georgia Composite Medical Board, the action will be reported to the FSMB. The FSMB will then report that action to the Florida and North Carolina medical boards, which may initiate their own investigations leading to disciplinary actions in those states as well.

Additional collateral effects of a medical board action may include loss of hospital privileges, loss of participation in preferred provider organizations, loss of enrollment with third-party payers, loss of board certifications, loss of Drug Enforcement Administration registration, and exclusion from participation in Medicare, Medicaid and other government programs.

Attorney Keith Roberts, co-chair of litigation at the Brach Eichler firm in Roseland, New Jersey, has been representing physicians with medical

board complaints for almost two decades. One of the biggest reasons for complaints lately, he shares, involves physicians overprescribing opioids. Others involve crossing patient boundaries and not communicating effectively.

"Physicians need to maintain a high level of ethics and professionalism," he says. "They need to adhere to the standard of care. Don't assume you are up to date. Seek it out. Stay on top of respected journals and attend regional and national conferences — because things evolve."

Avoiding complaints

Medical board complaints can be avoided by following protocol and understanding the patient's expectations. When expectations are not met, empathy and professionalism should be applied.

There are myriad things physicians can do to avoid medical complaints, O'Mahony says, starting with properly training, supervising and utilizing support staff and allied professionals. Other musts include taking time to learn about patients' individual characteristics; identifying their unique needs and accommodating them where possible; being courteous and respectful; being receptive and responsive to questions and complaints; minimizing delays and communicating about anticipated time frame issues as soon as possible; and ensuring proper and thorough medical recordkeeping and billing documentation.

"It's also recommended to avoid inappropriate language in medical record and billing documentation, recognizing that any medical record or bill could later be used as evidence in a medical board or legal proceeding," O'Mahony says.

Additionally, physicians should properly and thoroughly document informed consent, properly refer patients to other qualified health care professionals when appropriate, have a formal policy in place for identifying and resolving complaints, and apologize — without admitting liability or fault — when appropriate.

"Although a physician can take steps to identify and prevent the most common types of complaint, he or she may not be able to avoid a complaint ever being filed," O'Mahony says. "Despite a physician's best efforts, he or she may not be able to please all patients or all parties who could be sources of medical board complaints all the time. Even the finest physician may be the subject of a medical board complaint at some point in his or her career."

Liana Casusi, M.D., a general physician and consultant, notes that medical board complaints and medical malpractice lawsuits stem from almost the same cause — failure to perform primary physician duties within the expected competencies. "Before practicing your medical profession, plan the dynamics thoroughly," she says. "How do you receive a patient? How do you create and keep medical records? How do you issue prescriptions? How do you advise follow-up? And these are just a few considerations. Prepare all your record form templates and have your counsel check them for any missing information."

Her biggest tip for avoiding complaints is to review the rules of one's medical board and let them guide their lifestyle. "On the actual practice aspect, be thorough before arriving at a diagnosis — and, of equal importance, record everything in the chart," Casusi says. "Check and double-check prescriptions before issuing them, to eliminate any errors. Always keep private all information about the patient unless you are legally obliged to share it."

Some practical advice from

9 MISTAKES TO AVOID IF THERE'S A COMPLAINT AGAINST YOU

by **Ike Devji, JD**

Although most doctors are primarily concerned about a medical malpractice suit, a medical board complaint on its own can significantly disrupt your income — and even end a career. As a result, it is vital to handle the complaint in the appropriate manner and avoid making crucial mistakes that can cost you. Here are nine mistakes to avoid if you are dealing with a medical board complaint.

1. Being uninsured for the costs of a medical board complaint defense.

2. Not being represented by experienced legal counsel. Don't represent yourself.

3. Failing to timely inform your insurance carrier about the complaint.

4. Delaying your response to a complaint or ignoring it altogether.

5. Failing to inform your employer, partners or organization about the complaint. You may be contractually obligated to let them know.

6. Responding emotionally rather than in an organized, tactical way. Don't correspond with the patient who lodged the complaint, for example.

7. Deciding to destroy or conceal evidence.

8. Talking about the case with third parties. Even worse, making statements or admissions that can be used against you.

9. Failing to have an asset protection plan in place before the complaint.

Roberts involves becoming engaged in billing practices. "Having to ask the billing department is not an advisable position," he says. "Physicians should know what they're billing (and) why they're billing it, and they should be regularly auditing medical charts on a quarterly basis to make sure they are properly documenting codes."

Dealing with complaints

Whenever a medical board complaint is filed, a physician should consult with qualified legal counsel as soon as possible. "Most physicians are not equipped to represent and defend themselves in a medical board proceeding without the assistance of qualified legal counsel," O'Mahony says. "The damage that can be done to a physician's reputation and livelihood by a professional complaint far outweighs any legitimate concerns he or she may have about retaining the services of an attorney experienced in this area of the law."

Elizabeth Greene, a partner in Mirick O'Connell's litigation and health law groups, Westborough, Massachusetts, notes physicians should check their malpractice insurance to see whether they have coverage for legal counsel for licensing board complaints. Even if they do not have coverage, it is prudent to engage experienced board counsel.

"With the assistance of counsel, physicians are better equipped to protect their license and avoid responding emotionally or inappropriately to a complaint or investigation," she says. "Physicians should never alter or destroy records, including when they are faced with a board complaint or investigation, and they must remember the EMR (electronic medical record) leaves a footprint of all actions—the metadata."

If a physician receives a letter or phone call from a medical board investigator, it is crucial that they not procrastinate or ignore the notice. It is almost never advisable for a physician to meet with or be questioned by a medical board investigator without legal counsel present or on the phone. Once a lawyer has been retained, it is critical that they be promptly provided with all pertinent documents and information, as well as any known grounds for defending the allegations.

"Physicians should take medical board complaints far more seriously than a medical malpractice complaint."

Alex Keoskey, partner, Mandelbaum Salsburg P.C., Roseland, New Jersey.

"It is important that the physician provide the attorney with all information relating to the complaint, including the good, the bad and any 'ugly' facts which may be relevant," O'Mahony says. "A physician does not want his or her lawyer to be unpleasantly surprised by damaging evidence when it is too late for the attorney to consider how best to minimize or deal with its impact."

If the medical board conducts a thorough investigation, all relevant information will almost certainly come to light. Withholding important or potentially damaging evidence from their lawyer because the physician hopes it will not come out will impair the attorney's ability to prepare — or assist the physician in preparing — an appropriate response or defense. Therefore, physicians can best handle medical board complaints by having an experienced lawyer, upholding the code of ethics and behaving professionally.

Casusi recommends keeping all information about the complaint private. "It is actually unnecessary and dangerous for us to share information — especially through letters, SMS or online platforms — because these may be easily leaked and made into evidence in favor of the complainant," she says. "Another tip, trivial as it seems, is to remain calm. Yes, it is human nature to react with anger, and that is valid. However, avoid impulsive acts of rage that may aggravate the condition." Examples are badmouthing the complainant or blaming others.

Resolving a problem

Every case is different, and each case must be examined and evaluated based upon its own facts and circumstances. But a key to resolving medical board complaints successfully — or on terms as favorable as possible — starts with taking the complaint seriously from the get-go.

Roberts notes a physician should never try to take matters into their own hands and contact the complaining party to try to talk them out of it. This will almost always lead to failure and further problems down the line.

If disciplinary action is unavoidable, O'Mahony notes negotiating the most favorable or least damaging resolution possible. Fully complying with all agreed-upon or ordered terms must be accomplished. ■

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5 cryptocurrency investing rules for busy doctors

Cryptocurrencies can be complicated. As a busy medical professional, you likely do not have time to research tokens or the nuances of this specific asset class. As you invest, how will you know whether you are doing the right thing? As prices zoom up and down, it feels like you should do something in response to market movements, but what exactly?

At Makara, the first automated cryptocurrency investment adviser registered with the Securities and Exchange Commission, we believe investing should be smart, inexpensive and simple. We have distilled our philosophy down to five key rules.

1 Stick to your plan

These markets are very volatile and will go up and down frequently. You cannot control that but you can dictate when and how much you invest. Be consistent and focus on what you can control. Investors who chase good performance or run away from poor performance are less likely to be successful.

2 Do not try to time the market

It is difficult to know where cryptocurrency prices will move in the short term. The trick is to not worry about the short-term market. Focus on the long term and invest your money when you can. Do not waste time guessing where prices will go next; instead, focus on longer-term investments.

3 Diversify

Diversification can reduce risk without hurting returns. We have long known about this in the traditional investing world, but it has been slow to arrive in cryptocurrency. Some assets go up in price, others go down. A balanced approach can be beneficial.

4 Invest in yourself while you invest in the market

Learn about what you are investing in along the way. The technology behind cryptocurrency is fascinating, and learning about it can be done in small steps. Developing an appreciation for cryptocurrency's innovations will give you the conviction to stick with the asset during volatile times.

5 Start early

If you believe that cryptocurrency will be valuable over the long term, you benefit by getting started sooner rather than later. The best way to take advantage of the next wave of excitement is to invest today.

If you are already investing or considering investing, the five tenets above serve as a foundation to incorporate cryptocurrency into your larger investment strategy. ■

Jesse Proudman is the co-founder and CEO of Makara as well as the co-founder of Strix Leviathan, a cryptocurrency hedge fund. Prior to Makara and Strix Leviathan, he served as an IBM distinguished engineer focused on blockchain and cryptocurrency.

To learn more about cryptocurrency investing, visit makara.com.

$9 FOR A 90-DAY SUPPLY*

For adults on maximally tolerated statins with TG ≥150 mg/dL and established CVD or diabetes and ≥2 CVD risk factors

Add VASCEPA® (icosapent ethyl) to a statin for **an additional 25%** CV risk reduction[1]

Capsule is not actual size.

INDICATIONS AND LIMITATIONS OF USE

- VASCEPA® (icosapent ethyl) is indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease
- VASCEPA is indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

IMPORTANT SAFETY INFORMATION

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components
- VASCEPA was associated with an increased risk (3% vs 2%) of atrial fibrillation or atrial flutter requiring hospitalization in a double-blind, placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter
- It is not known whether patients with allergies to fish and/or shellfish are at an increased risk of an allergic reaction to VASCEPA. Patients with such allergies should discontinue VASCEPA if any reactions occur

The wholesale price of VASCEPA is $344.22 for 120 1g capsules and $402.73 for 240 0.5g capsules. Commercially insured patients can save with the VASCEPA Savings Card. VASCEPA Savings Card may not be used to obtain prescription drugs paid in part by some Federal or State Programs, or where prohibited by law; see vascepahcp.com for more information. Generic icosapent ethyl capsules available from Hikma Pharmaceuticals do not have an approved indication for cardiovascular risk reduction. Amarin retains exclusivity for cardiovascular risk reduction and the Hikma generic should not be dispensed for this indication.

With the rise of COVID-19 cases nationwide, the Office for Civil Rights (OCR) has temporarily lifted penalties associated with private telehealth communications between health care providers and their patients. For additional information, please visit the temporarily updated guidelines at hhs.gov/hipaa.

AMARIN®

GROUNDBREAKING RESULTS
On top of a statin, VASCEPA is proven to reduce the risk of a life-threatening CV event† by an **additional 25%**[1]

IRRESPECTIVE OF TG LEVELS
VASCEPA showed **robust CV risk reduction** irrespective of achieved TG levels[2]

AVAILABLE COST SAVINGS
With the VASCEPA Savings Card, commercially insured patients can **pay as little as $9 for a 90-day** supply. Subject to eligibility. Restrictions apply*

Indicate "Dispense as written (DAW)" or "Brand medically necessary" to help ensure your patients are getting the benefits of VASCEPA

Scan to see plans that only cover VASCEPA.

IMPORTANT SAFETY INFORMATION (cont'd)

- VASCEPA was associated with an increased risk (12% vs 10%) of bleeding in a double-blind, placebo-controlled trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel or warfarin
- Common adverse reactions in the cardiovascular outcomes trial (incidence ≥3% and ≥1% more frequent than placebo): musculoskeletal pain (4% vs 3%), peripheral edema (7% vs 5%), constipation (5% vs 4%), gout (4% vs 3%) and atrial fibrillation (5% vs 4%)
- Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia (2% vs 1%) and oropharyngeal pain (1% vs 0.3%)
- Adverse Events, Product Complaints, or Special Situations may be reported by contacting AmarinConnect at 1-855-VASCEPA, emailing AmarinConnect@Amarincorp.com, or calling the FDA at 1-800-FDA-1088
- Patients receiving VASCEPA and concomitant anticoagulants and/or anti-platelet agents should be monitored for bleeding

Please see adjacent Brief Summary of full Prescribing Information for VASCEPA or go to www.vascepahcp.com.

*Offer Restrictions: May not be used to obtain prescription drugs paid in part by Federal or State Programs including Medicare, Medicaid, Medicare Advantage, Medicare Part D, Tricare, VA. Most eligible, insured patients will pay as little as $9 of their copay for either each month or a 90 day fill, with a maximum savings of up to $150 per month or $450 on a 90 day fill. Not for use by residents of VT, nor medical professionals licensed in VT. This offer is not valid for those patients under 18 years of age or patients whose plans do not permit use of a copay card. Void where prohibited by law, taxed, or restricted. Eligible patients include those who participate in commercial insurance, through a healthcare exchange, or pay cash. Offer good through December 31, 2021.

†Cardiovascular events including myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization.

References: 1. VASCEPA [package insert]. Bridgewater, NJ: Amarin Pharma, Inc.; 2019. **2.** Bhatt DL, Steg PG, Miller M, et al; for the REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.

Vascepa® (icosapent ethyl)

VASCEPA

THE NEXT LEVEL OF HEART PROTECTION

VASCEPA® (icosapent ethyl) capsules, for oral use
Brief Summary of Prescribing Information

Please see Full Prescribing information for additional information about VASCEPA.

1 INDICATIONS AND USAGE

VASCEPA® (icosapent ethyl) is indicated:

- as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - o established cardiovascular disease or
  - o diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.
- as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Limitations of Use:

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of VASCEPA

- Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate.
- Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA.

2.2 Dosage and Administration

- The daily dose of VASCEPA is 4 grams per day taken as either:
  - o four 0.5 gram capsules twice daily with food; or as
  - o two 1 gram capsules twice daily with food.
- Advise patients to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3 DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied as:

- 0.5 gram amber-colored, oval, soft-gelatin capsules imprinted with V500
- 1 gram amber-colored, oblong, soft-gelatin capsules imprinted with VASCEPA

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Atrial Fibrillation/Flutter

VASCEPA is associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization. In a double-blind, placebo-controlled trial of 8,179 statin-treated subjects with established cardiovascular disease (CVD) or diabetes plus an additional risk factor for CVD, adjudicated atrial fibrillation or atrial flutter requiring hospitalization for 24 or more hours occurred in 127 (3%) patients treated with VASCEPA compared to 84 (2%) patients receiving placebo [HR= 1.5 (95% CI 1.14, 1.98)]. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter.

5.2 Potential for Allergic Reactions in Patients with Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to VASCEPA and advise them to discontinue VASCEPA and seek medical attention if any reactions occur.

5.3 Bleeding

VASCEPA is associated with an increased risk of bleeding. In a double-blind, placebo-controlled cardiovascular outcomes trial of 8,179 patients, 482 (12%) patients receiving VASCEPA experienced a bleeding event compared to 404 (10%) patients receiving placebo. Serious bleeding events occurred in 111 (3%) of patients on VASCEPA vs. 85 (2%) of patients receiving placebo. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Atrial Fibrillation or Atrial Flutter *[see Warnings and Precautions (5.1)]*
- Potential for Allergic Reactions in Patients with Fish Allergy *[see Warnings and Precautions (5.2)]*
- Bleeding *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial, 8,179 statin-stabilized patients were randomized to receive VASCEPA or placebo and followed for a median of 4.9 years *[see Clinical Studies (14.1)]*. The median age at baseline was 64 years, 29% were women, 90% White, 5% Asian, 2% were Black, and 4% identified as Hispanic ethnicity.

Common adverse reactions (incidence ≥3% on VASCEPA and ≥1% more frequent than placebo) included musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation.

Hypertriglyceridemia Trials

In two randomized, double-blind, placebo-controlled trials in patients with triglyceride levels between 200 and 2000 mg/dL treated for 12 weeks, adverse reactions reported with VASCEPA at an incidence ≥1% more frequent than placebo based on pooled data included arthralgia and oropharyngeal pain.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of VASCEPA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Diarrhea
- Blood triglycerides increased
- Abdominal discomfort
- Pain in the extremities

7 DRUG INTERACTIONS

7.1 Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Monitor patients receiving VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published case reports and the pharmacovigilance database on the use of VASCEPA in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies in pregnant rats, non-dose-related imbalances for some minor developmental findings were observed with oral administration of icosapent ethyl during organogenesis at exposures that were equivalent to the clinical exposure at the human dose of 4 g/day, based on body surface area comparisons. In a study in pregnant rabbits orally administered icosapent ethyl during organogenesis, there were no clinically relevant adverse developmental effects at exposures that were 5 times the clinical exposure, based on body surface area comparisons (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had non-dose-related imbalances in visceral and skeletal findings, including 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended, at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons.

In a multigenerational developmental study in pregnant rats given doses of 0.3, 1, 3 g/kg/day icosapent ethyl by oral gavage from gestation day 7-17, icosapent ethyl did not affect viability in fetuses (F_1 or F_2). Non-dose-related imbalances in findings of absent optic nerves and unilateral testes atrophy at human exposures based on the maximum dose of 4 g/day and on body surface area comparisons. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F_2) suggesting potential multigenerational effects of icosapent ethyl at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day icosapent ethyl from gestation through organogenesis, a decrease in body weight and food consumption was observed at the high dose of 1 g/kg/day (5 times the human exposure at the maximum dose of 4 g/day, based on body surface area comparisons). Slight increases in resorbed and dead fetuses were noted in the 1 g/kg/day group, but these were not significantly different from the control group. There were no differences between the icosapent ethyl groups and control group as to the number of *corpora lutea*, number of implantations, number of surviving fetuses, sex ratio, body weight of female fetuses or placental weight. There were no treatment-related malformations or skeletal anomalies.

In pregnant rats given icosapent ethyl from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day no adverse maternal or developmental effects were observed. However, complete litter loss (not dose-related) was noted in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures at a maximum dose of 4 g/day, based on body surface area comparisons.

8.2 Lactation

Risk Summary

Published studies have detected omega-3 fatty acids, including EPA, in human milk. Lactating women receiving oral omega-3 fatty acids for supplementation have resulted in higher levels of omega-3 fatty acids in human milk. There are no data on the effects of omega-3 fatty acid ethyl esters on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VASCEPA and any potential adverse effects on the breastfed child from VASCEPA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in well-controlled clinical studies of VASCEPA, 45% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger groups. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.7 Hepatic Impairment

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling before starting VASCEPA (Patient Information).

Inform patients that VASCEPA may increase their risk for atrial fibrillation or atrial flutter *[see Warnings and Precautions (5.1)]*.

Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to VASCEPA and advise them to discontinue VASCEPA and seek medical attention if any reactions occur *[see Warnings and Precautions (5.2)]*.

Inform patients that VASCEPA may increase their risk for bleeding, especially if they are receiving other antithrombotic agents *[see Warnings and Precautions (5.3)]*.

Advise patients to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA *[see Dosage and Administration (2.2)]*.

Instruct patients to take VASCEPA as prescribed. If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of VASCEPA, they should not double the dose when they take it.

For more information about VASCEPA, go to www.VASCEPA.com or call 1-855-VASCEPA (1-855-827-2372).

AMARIN®

VASCEPA® (icosapent ethyl)

Distributed by:	**Manufactured for:**
Amarin Pharma, Inc.	Amarin Pharmaceuticals Ireland Limited
Bridgewater, NJ, USA	Dublin, Ireland

P00120N Revised: 09/2021

US-VAS-03474 11/21

PRACTICE MANAGEMENT

TOP CHALLENGES FACING PHYSICIANS *in 2022*

by ***Medical Economics*® Staff**

The past year was one of the most challenging on record for U.S. physicians. After the lockdowns and telehealth surge of 2020, the year 2021 has felt strange. Although things went back to "normal" in that most practices resumed seeing patients in person, the COVID-19 pandemic and its challenges have remained. As we do each year, **Medical Economics®** *surveyed our audience to find out what the big challenges were. By far, the top answer was "administrative burdens" including staffing, prior authorizations and electronic health records (EHRs). We decided to take a closer look at what these burdens entail, to help physicians get ready for whatever challenges 2022 will bring.*

INSIDE

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Hiring and retaining staff

A medical practice relies on more than the physicians who see patients, with nonclinical administrative staff being vital to overall success. Between those at the front desk, medical records staff, human resources, billing and other back-of-house employees, it takes a village to run smoothly.

Hiring and retaining staff can be difficult. The recent fears of COVID-19 caused many to stay far away from the health care field, although even before the pandemic, the industry was experiencing a shortage of qualified applicants. Issues such as no room for advancement, generational differences, greater salaries in other industries and interest in working virtually have contributed to employees lack of interest in the field.

Plus, the "Great Resignation" of 2021 — the trend of people quitting their jobs — hit most industries as many employees reexamine their work-life balance.

"This is a big problem for everyone," says Halee Fischer-Wright, M.D., M.M.M., FAAP, FACMPE, president and CEO of Medical Group Management Association (MGMA), a medical practice advocacy organization. "Health care is as much impacted as every industry is across the globe at this time."

A drop in patient volume at the onset of the pandemic led to some medical practice staff being furloughed, and many decided not to return when things picked up. "One of the more interesting statistics is that one-third of nonclinical staff not coming back are not vaccinated," Fischer-Wright says. "The MGMA has heard that 88% of medical practices (have) had difficulties recruiting front-of-office staff."

Practical Solutions

The most obvious way to entice people to take jobs is by offering higher salaries and better benefits, but a practice can use extra incenties to entice prospective employees. Examples include allowing flexible hours, treating employees to lunch twice a week or paying for transportation costs. These perks could make the practice appealing to someone looking for work.

"We recommend being aggressive in recruiting strategies and not waiting until you need staff, so you can start to develop the relationships that help to bring new people in that can contribute immediately when needed," Fischer-Wright says. "Practices also need to optimize their practice to make employees happy."

When it comes to retaining staff, Fischer-Wright believes the key is to alleviate boredom, which often comes down to repetitive tasking. "We recommend that physicians take a look at practice operations and weed out what is necessary versus what is habit," she says.

A good solution is cross-training staff, so different people can take turns doing tasks with less chance of burnout. It is also a good idea to increase communication among the staff, so you can learn of concerns early.

"What we see in workers today is that they want this delightful combination that's almost impossible to achieve — both flexibility and certainty," Fischer-Wright says. "What we find in medical practices is often they work by a need-to-know basis, so we're encouraging a holistic communication strategy so people understand what's going on."

TIPS FOR HIRING AND RETAINING STAFF

Although in September a record number of people resigned from positions in the United States, many experts are optimistic that 2022 will be different. Here are some tips on hiring new staff.

Increase compensation and incentives:
Money talks, but so do benefits and perks. Offer sweeteners that workers will not find anywhere else.

Add flexibility:
The days of the 8 a.m. to 6 p.m. workplace are quickly fading. Although it is unreasonable for a practice to allow employees to work whenever they want, be open to having them work at different times on certain days so they can attend to family and other life issues.

Go digital:
When looking for new employees, utilize job sites like Monster.com on both a local and regional level. Use your internal social media channels for networking and finding worker talent.

Have an open dialogue:
For current staff, ask employees what they want and what issues they are having. Solve problems before they get too big and fix concerns that are reasonable. Employees will appreciate that you listened.

Go beyond health care:
Practices often prefer those with experience in health care, but many qualified people have never worked in a practice. Be open to bringing in bright people from outside the health care arena.

EHRs

Since their introduction, electronic health records have been a perennial issue for physicians across all specialties. From user experience to interoperability, nearly every facet of the computer-based systems has drawn the ire of those using them.

A recent study found that the amount of time spent in the physician's inbox and total time using EHRs were associated with higher physician turnover. However, it was found that less time spent on EHR-based tasks was correlated with a higher rate of physician turnover.

Despite this finding, physician burnout tied to EHR use is greater than initially anticipated. The American Medical Association found that EHRs contribute to between 11% and 60% of the burnout physicians experienced in 2021. With the implementation of new information-blocking rules — aimed to prevent EHR vendors from interfering with record access or exchange — from the Office of the National Coordinator for Health Information Technology on the horizon, 2022 has the potential to be another year of EHR frustration.

Integrating apps

The new frontier of EHRs is the ever-growing number of apps available to be integrated into the systems. There was a 20% increase in the number of EHR-integrated apps available across app galleries operated by Allscripts, athenahealth, Cerner Corporation and Epic Systems Corporation in 2020, according to the Office of the National Coordinator for Health IT.

Of the available apps on these platforms, 42% handle scheduling, check-in and billing; 38% of available apps handle clinical functions; 31% handle care management; and 20% deal with patient engagement.

Micky Tripathi, national coordinator for health information technology at the U.S. Department of Health and Human Services, says these apps are the key to unlocking more functionality from EHR systems and directly addressing physician frustration.

"What (the introduction of these apps says is) that your EHR should be more of a platform than it is a closed software system," he said. "I see my EHR as a conduit to more apps that make life better for me, and that also allows individual providers to tailor their experience a little bit."

Tips to improve EHRs

David Lareau, CEO of Medicomp Systems, says medical practices can combat the burnout associated with EHR use by focusing on these four core areas for improving their systems.

1 **Improve patient care**
Incorporate technological tools that work behind the scenes to capture and interpret billing and coding detail. Streamlining workflow in this area can help physicians quickly find medical information they need to achieve better health outcomes for patients.

2 **Increase physician productivity**
Workflows supporting the automatic identification and interpretation of medical information from previous sessions, inpatient records, laboratory reports and other sources allow physicians to focus on their patients instead of their computers. EHRs should not disrupt the way physicians think and work.

3 **Ensure accurate reimbursements**
Rather than using inefficient, error-prone manual methods, practices should incorporate technologies that prompt the physician at the point of care when patients have potential hierarchical condition category conditions, allowing the doctor to immediately address treatment, documentation or coding gaps while the patient is in the room rather than during a follow-up appointment.

4 **Reduce operational expenses**
EHR systems can lower operational expenses by enhancing clinician productivity and streamlining documentation, coding and billing processes. Documentation tools that support quick, efficient capture of visit information at the point of care can reduce or eliminate the need for transcription services.

Prior authorizations and third-party interference

21%

of prior authorizations were submitted electronically in 2019.

Source: Council for Affordable Quality Healthcare

Doctors want to treat patients using the care they were trained to give but often find themselves arguing with someone from an insurance company about the best course of treatment. This is the main reason physicians consistently rank third-party interference as one of their biggest challenges.

"The problem with a lot of insurance companies is they change what's on their formularies, and one day the insulin NovoLog is covered and then next day it changes to Humalog, and now the patient has to switch, and it's very confusing. And if you want to keep them on the same one, you have to put in the prior authorization, and the insurance company wants them to try the other one first," says Richard Bryce, D.O., a family medicine physician and chief medical officer for the Community Health and Social Services Center in Detroit.

This back-and-forth costs the practice time and money and puts the patient's health at risk.

"Now you've wasted a week or two figuring this process out when a patient needed the medication to take care of their ailment," Bryce says. "The process should be easier."

Although prior authorizations aren't going away, there are some strategies practices can follow to streamline the process.

- Assign a staff member to each payer. This person can become an expert on the payers for which they are responsible, learning their specific expectations and what to avoid. They can also build relationships with their counterparts at the payer, which may help expedite claims and appeals. This person should also create a basic guidebook for each payer that others can follow if needed.
- Maximize the use of technology. Most payers offer online forms for the prior authorization process and some EHRs integrate directly with payer formularies. The more a practice can use these online forms, the more quickly an authorization can be obtained. In many cases, any missing information will be flagged before submission.
- Document all treatment decisions and back them up with evidence-based practices. Payer justification for prior authorizations is that physicians are not always following the latest evidence-based practices, so ensure all treatment decisions are based on the latest guidelines. If a prescription is not following the formulary, make sure all information as to why it is not is included in the prior authorization form.
- Prepopulate forms for each payer. In some cases, you may be able to create a prepopulated form that has common information from the practice already filled in. This just leaves the specific patient information to be added. Although the time savings may be small for each form, it can add up when multiplied over the course of a year.
- Create a spreadsheet outlining what treatments and medications for frequent diagnoses require a prior authorization by payer and what the permitted alternatives are. This quick-reference guide can save physicians time by directing them toward treatments the insurance company will accept.
- Inquire about gold card programs. Some payers offer physicians with a good track record of following clinical best practices a gold card that allows them to skip the prior authorization process for some treatments. Find out whether you are eligible and what it takes to earn eligibility.
- Fight to get rid of the prior authorization burden. Most professional medical societies have come out against prior authorizations and are pushing for legislation to limit their use. Check with your organization to find out how you can help. Write to your state and federal representatives and explain how the process harms patient care and raises health care costs.

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Increased competition

Physicians are not the only option when it comes to primary care services. As venture capital firms, giant tech corporations and pharmacy chains jump into the retail, urgent and primary care space, it is becoming more challenging for traditional practices to stand out.

The competitive landscape is changing quickly. In October, for example, Walgreens announced it was investing $5.2 billion in VillageMD to open primary care clinics in its retail pharmacies. It does not stop there. CVS has MinuteClinic and HealthHUB primary care services in thousands of locations in the United States. Amazon and Walmart have been exploring the landscape as well.

This trend has been exacerbated by the COVID-19 pandemic and patients' increased comfortability with telehealth services. Although the use of telehealth has fallen in 2021 compared to its 2020 highs, patients know what to expect from these services. Physicians will likely have to deal with growing competition from telehealth-only providers. For example, UnitedHealthcare announced earlier this year it is launching a "virtual first" health plan in which a patient is encouraged to choose an online doctor who acts as a first point of contact for most primary care and referral services.

This leaves primary care physicians in a bind. Not only do retail and other alternative care settings steal patients away, but they take mostly the lower-complexity cases, depriving practices of easier revenue and leaving physicians to deal with more complex, difficult cases.

"The expectations on primary care are so overwhelming," says David Boles, D.O., a family physician in Clarksville, Tennessee. "Then you throw on top of that a walk-in clinic right down the street that doesn't deal with any of those things and sees this person for a minor problem and gets paid similar to what we do for an office visit. They get the icing, and the real meat of the issue is left to us."

How can physicians in traditional practices compete? Here are some strategies.

You know telehealth — use it

Patients want convenient services. Telehealth is one way to meet patients when, how and where they want to see their physician. It is something most physicians have had lots of practice with since the pandemic began. If your virtual care program has gone dormant as your practice opened to in-person appointments, dust off the cobwebs and get going again.

Be available

Patients do not get sick only during business hours; offering a few Saturday appointments no longer caters to their busy lifestyles. With urgent care centers and retail clinics offering extended hours daily, if a practice does not adapt its schedule to its patients, they will seek care from a place that does.

Make it easy — and do not make them wait

Patients do not want to spend 15 minutes on hold with your front desk to make an appointment. Practices need to offer online scheduling to make it easier for patients to book an appointment.

When they arrive, patients expect the doctor to see them within about 15 minutes of their appointment time. Consider implementing a system that texts updates on wait times to patients, allowing them to adjust their arrival to reflect the doctor's current schedule.

Streamlined paperwork

The more forms that can be filled out electronically and in advance, the better. No one wants to sit in a waiting room filling out forms on a clipboard that could easily have been done the night before. Checkout should be just as easy, with little or no time spent standing in line.

Quick responses to questions

Patients expect a response to questions posed via email or an EHR portal in 24 hours or less. This time frame is basic business protocol established by the retail and service industry. Medical practices must embrace it as well.

Loss of trust in physicians

Doctors often complain that, like the late comedian Rodney Dangerfield, they "don't get no respect." But when it comes to respect and trust, medicine and its practitioners fare better than many other aspects of American society.

In a 2019 Pew Research Center survey, 74% of respondents said they had a "mostly positive" view of medical doctors.

Still, trust in physicians has been declining. In a 2017 Sermo survey, 87% of doctors said patients trust them less than a decade earlier.

The trend is especially pronounced among younger Americans. A November 2021 Morning Consult survey found that 74% of baby boomers trust the health care system "some" or "a lot," but that number drops to 44% among members of Generation Z — those born between the late 1990s and early 2010s.

What has caused this erosion of trust in doctors, and medicine generally? In part it reflects Americans' ongoing loss of faith in all institutions. But there are also reasons specific to medicine.

Probably the biggest of these is the limited time primary care doctors working for large hospital systems can spend with patients.

Bioethicist Stephen Post, Ph.D., told *Medical Economics*® in 2018 that many hospital systems, where the majority of primary care physicians now practice, require doctors to see an average of eight patients in 30 minutes. "Given that pace, it's extremely difficult to build trust and create meaningful relationships," Post said. Compounding the problem, patients often do not stay with the same doctor long enough to establish trust; doctors leave (or are dropped from) insurance networks, or employers change insurance carriers in search of lower costs.

Another contributor to eroding trust is the ready availability of medical and wellness information, as well as information and ratings for health care providers, on the internet and via social media. A 2015 *Medical Economics*® article noted that about 5% of all Google searches were health-related and the percentage has almost certainly grown since then. "We've seen an explosion in the kind of information that ordinary people can access about their own health and from sources like medical journals and the results of clinical trials," author and patient engagement consultant Jan Oldenburg told *Medical Economics*® in 2019.

Oldenburg and other experts say that although this "patient empowerment" lets patients become more actively involved in their health and wellness, it also means they are less likely to unquestioningly trust a physician's diagnosis or follow a treatment plan than were patients in the era before the internet.

Patients' confidence in their care providers is further weakened by skyrocketing care costs. Although doctors are not primarily responsible for the problem, they often bear the brunt of patient anger. Eighty-seven percent of physician respondents to a 2016 *Medical Economics*® survey said their practices were encountering more angry patients than a year or two earlier, and 56% said financial issues were the main cause of patient anger. Among some patients, that anger takes the form of believing their doctor is recommending unnecessary tests to earn more money.

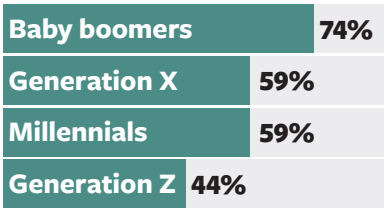
Of course, for large groups within American society — especially people of color — mistrust of doctors and the health care system is longstanding and frequently justified. A 2003 Institute of Medicine report on racial and ethnic disparities in health care found that white clinicians who do not believe they are prejudiced "typically demonstrate unconscious implicit negative racial attitudes and stereotypes." Many public health experts believe this distrust among Black and Hispanic patients contributed to their initial reluctance to get COVID-19 vaccines.

Establishing or rebuilding trust with patients is not easy, especially given the time and financial constraints most doctors face. Nevertheless, it is possible. The process starts with maximizing the time available to spend with patients by, for example, delegating to staff members tasks that reduce time for doctor-patient interactions. Then use the time to listen.

Dhruv Khullar, M.D., M.P.P., a New York City internist and author of a *New York Times* article about trust, reminds doctors that they can no longer expect trust automatically, but "if we work hard to demonstrate that we're trustworthy, patients will come to trust us over time." ■

Trust by generation

Share of American adults who trust the health care system "a lot" or "some" by age demographic:



Source: Morning Consult, "Tracking Trust in U.S. Institutions," Nov. 18, 2021

How 'virtual' scribes can reduce EHR headaches

by **Lisa A. Eramo, M.A.** Contributing Author

Ellen Hight, M.D., a family medicine physician in East Greenwich, Rhode Island, says the electronic health record (EHR) completely changed her practice, and not necessarily in a good way. "When our practice started using an EHR, I began to feel a distance between myself and my patients because I was constantly staring at the computer," she says. Her work-life balance also took a hit as she began to spend Saturday mornings finishing her notes from the previous week.

When the Rhode Island Primary Care Physicians Corporation (RIPCPC), an independent practice association to which her practice belongs, approached her about piloting a virtual scribe program — and said it would pay for the first two months of participation — she jumped at the opportunity. "When I heard about virtual scribes, I thought, 'Well that's a good idea,' " she recalls.

Scribes are someone who works offsite or in a different area of the practice (i.e., not in the exam room) to document important aspects of the encounter so the physician or other provider can focus on providing patient care and working more efficiently.

RIPCPC partnered with an outsourced virtual scribe vendor to launch the two-month pilot program that included Hight, one other physician, and one nurse practitioner. Hight says the pilot was a huge success, prompting her to continue working with the scribe, a dentist in India. "My hands are not on the keyboard and I'm looking directly at the patient," says Hight. "It's more personal. I just feel so much more relaxed."

Greater efficiencies enable Hight to see six or seven additional patients a day without putting in extra hours. She also usually does not take work home at night or on weekends.

The other physician who participated in the pilot continues to use a virtual scribe. Hight's still assessing whether it makes financial sense for the nurse practitioner (who bills under her own national provider identifier rather than incident-to a physician) to continue.

Maximizing efficiency, revenue

Jonathan Weiss, MD, internist in Monticello, New York, has used a domestic virtual scribe for the last four years and says his scribe does just about everything except take vital signs, draw blood, perform electrocardiograms and administer vaccines. For example, in addition to completing all relevant documentation, the scribe listens to the doctor's verbal instructions and then orders tests, initiates referrals, messages relevant office staff to obtain prior authorizations and checks off boxes in the EHR for quality measures. She even navigates to different parts of the record to retrieve information for Weiss upon request.

"To me, virtual scribing is one of the holy grails of making medicine tolerable again," says Weiss. "During a 15-minute established patient visit, I can produce an incredibly well-documented note, get all the tests ordered and stay on schedule. In the majority of cases, I can legitimately obtain a higher E/M (evaluation and management) level because my notes are so robust. Ten minutes after my last patient, I'm in the car and headed home."

Weiss is also able to see an additional three or four patients per day without extending his hours. Previously, he would have stayed until 8 p.m.

and paid his staff overtime. In addition, his medical assistant is not tied to the computer and can engage patients more directly.

"Working with a remote scribe has been the single most work-changing thing I've done in 15 years," he says. "If it was taken away from me, I would quit my job. I could not go back to the way I was doing things before."

Addressing physician burnout, turnover

At UW Health, an integrated health system of the University of Wisconsin-Madison serving more than 700,000 patients each year in the Upper Midwest, working with virtual scribes was part of a deliberate effort to reduce physician burnout, says Christine Williams, director of health information management.

"Providers didn't go to school to document. They went to school to practice medicine and make a difference," says Williams. "With virtual scribes, physicians can stay connected to the patient. This is true whether it's a small practice or a large academic medical center."

Physicians at UW Health have the option of working with a virtual scribe. If they opt in, they are required to see one additional patient per session (i.e., every four hours). This additional revenue covers most of the cost of the scribe, says Williams.

UW Health began its scribe offering with a pilot program in 2019 that subsequently converted into a permanent program focused on ambulatory providers. Williams says she eventually wants to include emergency department physicians and hospitalists. Approximately 150 ambulatory providers currently use virtual scribes with an additional 10 providers joining each month.

Why offer a virtual scribe program? Preventing burnout ultimately reduces costly physician turnover, says Williams. "Physician resignation and needing to fill vacancies is a very large cost, especially for small practices," she adds.

Matthew Malek, M.D., M.P.H., family medicine physician and medical director of provider experience at Thundermist Health Center, a federally qualified health center in Rhode Island, agrees. "If you can prevent one physician from leaving, this is an incredible savings on the order of $300,000 to $500,000," he says.

Why are the costs so high? First, it takes time to find and hire a new provider. "When you consider the lack of billing during this time, that's a big chunk of change," says Malek.

It also takes time for physicians to build a patient panel and maximize efficiency. "At our organization, it takes about a year for a new physician to get to their eventual baseline productivity," he adds.

Using virtual scribes at Thundermist Health Center was a data-driven decision, says Malek, who was instrumental in launching the program. The health center partnered with the American Medical Association to assess physician well-being using the Mini Z 2.0 burnout survey. It also used a set of validated questions about efficiency of practice and teamwork as well as community self-reported data. Finally, the health center tracked an EHR-based metric called the WOW8 to objectively measure work outside of office hours. This metric is defined by time on the EHR outside of scheduled patient hours per eight hours of patient scheduled time.

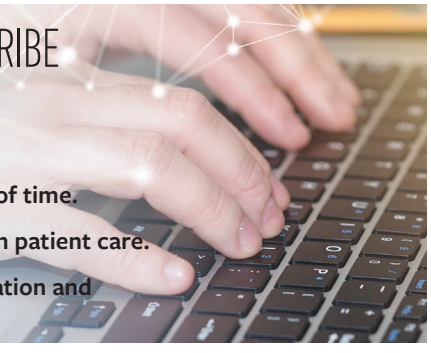
"We realized that our clinicians were spending a lot of time outside of the clinical work doing clinical documentation," he says. "We had the data to bring to leadership to justify the virtual scribes."

The pandemic was the perfect backdrop for a virtual program. "We also use remote scribes in our COVID(-19) evaluation and treatment clinics," he says. "It's nearly impossible to fit three people in an exam room and maintain appropriate distance."

Now that the program is up and running, physicians choose whether to participate. If they do,

5 POTENTIAL BENEFITS OF WORKING WITH A VIRTUAL SCRIBE

1. **Better capture quality measures that can boost bonus payments.**
2. **Elevate role of medical assistants to improve patient experience.**
3. **Generate additional revenue by seeing more patients in same amount of time.**
4. **Improve patient satisfaction by letting physician focus more directly on patient care.**
5. **Produce more detailed documentation that could lead to higher evaluation and management levels.**



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they also decide how many hours they would like to work with the scribe. However, the vendor requires a minimum of four continuous hours and 50 total hours per month. Thundermist requires physicians using scribes to add roughly two visits per day to cover the cost, says Malek.

"The maturation of the scribe market makes it a much more understandable value proposition," he adds. "I think remote scribing is a very scalable intervention to improve physician well-being."

Strategies for success

Think a virtual scribe may be what you're looking for? Industry experts provide six tips to help you succeed.

1 Determine your "why." Are you exploring a virtual scribe program to address burnout concerns and prevent attrition? See additional patients and generate more revenue? See the same number of patients in the same or fewer hours? Improve patient satisfaction?

Knowing the why helps physicians gauge impact and return on investment, says Sean M. Weiss, chief compliance officer at DoctorsManagement, LLC, adding that some physicians work with virtual scribes simply to ensure timely, accurate documentation that establishes medical necessity for services rendered. Your why will determine the key performance indicators necessary to measure the success of the program. Examples might include physician and staff turnover rates, physician self-reported data related to well-being, or patients seen per hour.

2 Vet vendors carefully. Experts recommend asking these questions:

- What type of training or credentials do the virtual scribes have? For example, are they an RN, LPN, or have some other medical training?
- What type of ongoing education for medical specialties, terminology, anatomy, physiology and pharmacology do they receive?
- What is their knowledge of medical coding and clinical documentation requirements (including CPT modifiers and quality measures)?
- What is the vendor's plan if a virtual scribe is suddenly unavailable (e.g., due to sickness, vacation or turnover)? Can it provide immediate backup coverage?

3 Do not overlook cybersecurity. "There's a significant risk of using remote scribes and really any third-party vendor, and it's not getting the attention it should," says Sean Weiss. "That risk is the risk of cyberattack." He says most breaches occur through third-party vendors such as outsourced billing/coding companies, outsourced release of information vendors, virtual scribes and others.

Sean Weiss points to a recent case in Florida in which a hacker fraudulently billed $10 million to Medicare by gaining access to patients' protected financial information, demographics, diagnostic information and the provider's UPIN (unique physician identification number). "The group practice actually had a strong cybersecurity protocol, but this individual was able to hack into the system through the third-party vendor," he says.

Experts agree that practices intending to work with a virtual scribe should ask these questions of the vendor employing the scribe:

- What is the risk management plan in place to test the system, and how often do these tests occur?
- What were the results of the most recent risk assessment?
- What corrective action plan, if any, was implemented?
- Has the vendor ever experienced a cyberattack?
- What is the vendor's plan for business continuity during downtime due to a cyberattack?
- What is the risk management strategy going forward? For example, does each virtual scribe have their own login information? Do they receive ongoing HIPAA (Health Insurance Portability and Accountability Act of 1996) training?

4 Set realistic expectations. "A scribe can be trained by someone else on how to navigate the EMR (electronic medical record), but the provider really needs to train the scribe on their specific dictation style and workflow," says Williams. This process could take a few weeks and physicians need to be on board with the upfront work that's required, she adds.

5 Perform a pilot program. "This ensures it fits within the autonomy of that practice specifically," says Williams. "It ensures you're not interrupting five or 10 clinicians at a time. You have one or two who are really committed to working out some of the kinks. It's not just plug and play." For example, practices will need to ensure processes for patient notification and reviewing documentation for billing and compliance purposes.

6 Think beyond traditional scribing roles. "If physicians are only asking for documentation, they're missing half the boat," says Jonathan Weiss. "They should be pushing scribes to be a virtual medical assistant. You get much more value for your dollar." ■

Pivot to Concierge: Will personalized membership practices redefine medicine in 2022?

There's no minimizing the tumultuous impact of the last two years on every patient, every part of the health care system, and on all physicians. Working harder than ever but feeling threatened by shrinking revenues, an ongoing surge of practice closures, and dwindling options for remaining independent, physicians were experiencing burnout at alarming new levels. A survey published in this magazine just a few months ago painted a vivid picture of a system in crisis, with 4 out of 5 physicians saying they felt burnt out. Even more concerning was that 79% of physicians say their burnout began *before* the pandemic, according to a NIHCM report. Although it may not be surprising, it's not acceptable or sustainable.

Which is why I believe that 2022 will be a year when concierge medicine shifts from niche solution for a few to a mainstream model for many.

The undercurrents have been bubbling up to the surface throughout the pandemic. At Specialdocs, we were deeply gratified to report double-digit increases in both 2020 and 2021 in the number of physicians converting to our concierge medicine model. The resilience of the membership medicine practice has been tested and proven in the most challenging of times. Not one of our physician-clients ever considered having to close their doors due to insufficient operating funds or loss of patients. In fact, they thrived, as an ever more diverse demographic of people actively sought preventive, deeply personalized and readily available care from a physician. The number of concierge medicine patients served in our network swelled significantly in both 2020 and 2021, even during a time of financial uncertainty in the U.S. Also noteworthy is the gradual but consistent lowering of members' average age, a sign of broadening appeal among younger generations realizing the immeasurable value of a long-term relationship with their physician.

What does this mean for 2022? As I write this in late December, we're again being buffeted by the emergence of another COVID-19 variant. It's a potent reminder that the ultimate trajectory of this virus is still unknown, and we simply don't know when we can return to business as usual. While the continued rise of concierge medicine has already sparked a great deal of well-intentioned hand-wringing about exacerbating the shortage of primary care physicians, the facts are somewhat different.

- Physicians struggling in a fee-for-service, volume-based practice have found a path to sustainability. A Specialdocs rheumatologist in Michigan said: "Concierge medicine enabled me to do more than simply keep the doors open — it restored my practice, rejuvenated my staff and allowed me to care for patients exceptionally well."
- Many who intended to close or retire early reversed their plans. Consider this from the head of a now thriving prominent Boston cardiology group: "Making the change to concierge medicine saved our entire organization, including many who had worked with us for their entire careers."
- Work-life balance was realized. Parents reclaimed the sweetest parts of raising their children — as a Massachusetts Specialdocs physician said: "I am finally seeing my kids when they're awake." The spouse of a Specialdocs physician confided: "Concierge medicine has healed our marriage and completely revitalized our family dynamic."
- Virtually every concierge physician regained or, even better, never lost, their overriding passion for medicine. A California OB-GYN who joined our network in 2020 marveled: "Every day I'm fulfilling my mission to completely change the way we care for women's health."

When I first learned about concierge medicine in 1999, it appeared to be a stunning vision of health care's future. Sparked by the cataclysmic events begun 20 months ago, in 2022, I believe the future has arrived. ■

Terry Bauer is CEO of Specialdocs, a concierge medicine pioneer that since 2002 has transformed physicians' professional lives, empowering them to deliver personalized patient care.

Hypothyroidism: Challenges in Optimal Patient Management

In this Medical Economics® *"PrimaryView," Todd Frieze, M.D., FACP, FACE, endocrinologist at the Thyroid Institute of Utah in Lehi, provides insights on hypothyroidism with an overview of the disease; an examination of the clinical manifestations, diagnosis and treatment guidelines; and a review of the importance of accurate dosing of a medication with a narrow therapeutic index (NTI) and its impact on switching therapies. This article summarizes the highlights of the presentation.*

Thyroid Physiology: Defining Thyroid Function and Dysfunction

Hypothyroidism is the most common endocrine disease and can be defined as failure of the thyroid to produce sufficient thyroid hormone to meet the metabolic demands of the body.[1,2] It is estimated that 20 million Americans have thyroid disease in some form, with over 12% of the population developing a thyroid condition in their lifetime.[3] About 13 million Americans have hypothyroidism that is undiagnosed.[2,3]

Overall, hypothyroidism disproportionately affects women and patients above 65 years of age. Women are five to eight times more likely to develop thyroid problems than men.[3] According to one study, the estimated prevalence of hypothyroidism in female patients is between 4% and 21%, whereas the prevalence in male patients is between 3% and 16%.[4] Additionally, in evaluations of thyroid function by age, studies have shown progressively increasing thyroid-stimulating hormone (TSH) concentrations with aging.[5] This is important to note as "hypothyroidism among patients aged 65 and older is associated with significant morbidity," Dr. Frieze explained.[6]

The Etiology of Hypothyroidism

Two main categories of hypothyroidism exist: primary hypothyroidism and central hypothyroidism. Primary hypothyroidism, which presents as a deficiency in thyroid hormone, is far more common.[2,7] Primary hypothyroidism is divided into two subcategories: overt hypothyroidism, which is characterized by elevated TSH with subnormal or low thyroxine (T_4) levels, and subclinical hypothyroidism, which presents with elevated TSH levels with normal T_4 levels.[2]

Central hypothyroidism, which is due to a reduction in the hormones that stimulate the thyroid gland to produce thyroid hormones, presents with low T_4 levels and low TSH levels. Dr. Frieze discussed how central hypothyroidism is also subdivided into two additional subtypes: secondary hypothyroidism, which is the failure of the pituitary gland to secrete TSH and occurs in roughly 5% of cases, and tertiary hypothyroidism, which is the failure of the hypothalamus to secrete thyrotropin-releasing hormone and occurs in 1% of cases or fewer.[2,8]

Clinical Manifestations and Physiological Implications of Hypothyroidism

Insufficient hormonal control can have "a profound effect on all physiological functions by impacting gene

expression, cellular function and growth," Dr. Frieze noted.[9] Hormonal imbalance due to hypothyroidism can adversely affect oxygen use and the body's basal metabolic rate, the synthesis and mobilization of lipids in the blood, and thermogenic/metabolic homeostasis.[9] The clinical presentation of hypothyroidism can be highly variable and includes a broad range of symptoms. Dr. Frieze added that "the most common symptoms that we typically see may be fatigue, weight gain, cold intolerance, dryness of the skin, loss of hair, depression and constipation."[8,10]

During pregnancy, the metabolic system plays a significant role in the development of the fetal central nervous system, muscle, bone and lungs, so the management of hypothyroidism is further complicated in patients of reproductive potential.[3,11] Maternal hypothyroidism has been estimated to affect 2% to 4% of women of reproductive age.[12] If left untreated, hypothyroidism during pregnancy can increase the risk of adverse outcomes for the mother and fetus.[10,13]

Screening and Diagnosing Hypothyroidism

The American Academy of Family Physicians (AAFP), American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE), and American College of Physicians (ACP) all have provided recommendations for screening patients for hypothyroidism. Among these recommendations, it is typically suggested that physicians screen patients over 50 or 60 years of age and women, especially those who are of reproductive potential, are pregnant or have findings suggestive of symptomatic thyroid disease.[7] Dr. Frieze also emphasized how "most professional societies recommend screening for thyroid dysfunction in patients (who) have new-onset cholesterol findings."

Screening should be considered in asymptomatic patients with risk factors such as a history of autoimmune disease, a history of head or neck irradiation, previous radioactive iodine therapy, the presence of a goiter, a family history of thyroid disease, or a history of treatment with agents known to affect the function of the thyroid.[2]

Additionally, Dr. Frieze noted that the preferred laboratory assessment for diagnosing primary hypothyroidism is a serum TSH test and that if the TSH level is elevated, then it should be repeated with a serum free T_4 (FT_4) measurement.[2]

Treating Hypothyroidism

The primary goal of treatment for hypothyroidism is the establishment of euthyroidism, or normal thyroid function, and physicians should consult published guidelines for therapeutic TSH ranges. In 2012, the AACE and ATA clinical practice guidelines for hypothyroidism in adults set forth a TSH target range of 0.45 to 4.12 mIU/L to achieve euthyroidism.[7] In 2014, the ATA established specific guidelines for the treatment of hypothyroidism, recommending a target range of 0.4 to 4.0 mIU/L.[14] In 2017, the ATA revised the guidelines for the management of thyroid disease during pregnancy by recommending a therapeutic target of less than 2.5 mIU/L during the first trimester of pregnancy and less than 3.0 mIU/L during later trimesters.[13] The AACE and ATA recommend measuring TSH levels within four to eight weeks of starting therapy or after adjusting dosage. It may take eight weeks or longer for levels to stabilize with small adjustments, Dr. Frieze pointed out. He added that after the adequate dose is determined and euthyroidism achieved, TSH should be measured after six months and at 12-month intervals thereafter, and possibly more frequently depending on clinical factors.[7]

Thyroid Hormone Replacement Therapy

Most patients with hypothyroidism will require lifelong thyroid hormone therapy. Dr. Frieze stated that levothyroxine is available as brand-name and generic preparations. He added that levothyroxine has an NTI, meaning that even small differences in dosage or blood concentration may affect the efficacy and/or safety of treatment.[15] In 2004, the Food and Drug Administration (FDA) approved the substitution of generic levothyroxine for brand-name levothyroxine. Endocrine medical organizations, including the AACE, the Endocrine Society and the ATA, disagreed with the FDA's conclusion that generic preparations of levothyroxine were equivalent to brand-name levothyroxine. These organizations concluded that the "pharmacokinetic methods used, combined with the lack of TSH measurements to establish bioequivalence, could lead to significant over- or underestimation of generic equivalency compared with brand-name levothyroxine."[2] According to Dr. Frieze, in the past decade, many publications have reviewed the bioequivalence data comparing generic and branded medications.[16] He noted that "the FDA has recommended tighter quality and bioequivalence standards to ensure the safety and efficacy of generic [NTI] medications."[15]

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Levothyroxine Dosing Guidelines

Once they have received a diagnosis of hypothyroidism, patients who are not pregnant can be started at a dose of 1.6 mcg/kg daily. For patients with subclinical hypothyroidism and a TSH of less than 10 mIU/L, Dr. Frieze specified that the starting dose may instead be 50 mcg daily, increasing by 25 mcg every six weeks until the level of TSH falls between the goal range of 0.35 and 5.5 mIU/L. With a TSH of 10 mIU/L or greater, a daily dose of 1.6 mcg/kg should be administered as "these patients may be more toward the overt hypothyroid phase," Dr. Frieze noted.[2] When a patient finds out that she is pregnant, she should take an additional dose on two days each week, totaling nine doses per week, and the patient should be referred to an endocrinologist immediately.[2] In patients who are older or those who have or may have cardiac disease, the initial daily dose administered should be 25 mcg or 50 mcg, increasing by 25 mcg every three to four weeks until the patient has reached a full replacement dosage.[2]

Prevalence of Patients Not Treated According to Guidelines

Roughly half of pregnant patients are not treated according to established guidelines. A retrospective cohort study[a] of data from the Optum Clinformatics database from 2013 through 2015 including 2,340 pregnant women aged 18 to 49 years with hypothyroidism who were treated with levothyroxine demonstrated that 23.9% of patients were undertreated, and 22.5% of patients were not monitored.[12] Another retrospective cohort study[b] of data from the Optum Clinformatics database from 2007 through 2015 including 4,025 patients aged 65 years and older demonstrated that 17.4% of patients were undertreated, and 32.9% were not treated at all.[6]

Case Study: A 66-Year-Old Woman With a History of Hypertension and Type 2 Diabetes[c]

Dr. Frieze presented the patient case of a 66-year-old woman with a history of hypertension and Type 2 diabetes who has been experiencing symptoms that include fatigue, weight gain and constipation for several months. Her current medications include lisinopril 20 mg once daily and metformin 500 mg twice daily. Upon physical examination, she is normotensive with a blood pressure of 120/75 mmHg and a normal pulse rate of 80 beats per minute.

Table 1.
Patient Case Study Initial Laboratory Results

Lipid profile	
Total cholesterol (mg/dL) (normal: < 200 mg/dL)	340
Triglycerides (mg/dL) (normal: < 150 mg/dL)	250
HDL cholesterol (mg/dL) (normal: > 60 mg/dL)	50
LDL cholesterol (mg/dL) (normal: < 100 mg/dL)	250
Thyroid function tests	
TSH (mIU/L) (reference range: 0.4-4.0 mIU/L)	22.0
FT_4 (ng/dL) (reference range: 0.8-1.7 ng/dL)	0.6

FT_4, serum free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

Initial Laboratory Results

Her laboratory results indicate a lipid profile with above-normal levels with evidence of hypercholesterolemia. Her total cholesterol is 340 mg/dL, triglycerides are 250 mg/dL, high-density lipoprotein (HDL) cholesterol is 50 mg/dL, and low-density lipoprotein (LDL) cholesterol is 250 mg/dL. Initial thyroid function test results indicate that TSH is 22.0 mIU/L (reference range: 0.4-4.0 mIU/L) and FT_4 is 0.6 ng/dL (reference range: 0.8-1.7 ng/dL) (**Table 1**).

According to clinical and laboratory workup, this patient meets the diagnosis for primary hypothyroidism. Dr. Frieze explained that "the treatment plan that should be initiated is thyroid hormone replacement therapy." Additionally, treatment of her underlying hypothyroidism has the potential to address secondary changes to her blood lipid levels, Dr. Frieze noted.

Table 2.
Patient Case Study Follow-up Laboratory Results at Two Months, Four Months, Six Months and Nine Months

	Two-month follow-up	Four-month follow-up	Six-month follow-up	Nine-month follow-up
TSH (mIU/L) (reference range: 0.4-4.0 mIU/L)	12	9	3.5	6.6
FT_4 (ng/dL) (reference range: 0.8-1.7 ng/dL)	1.0	1.2	1.3	1.1

FT_4, serum free thyroxine; TSH, thyroid-stimulating hormone.

Follow-up Laboratory Results at Two, Four, Six and Nine Months

After two months of treatment, the patient's follow-up test results demonstrate improvement in TSH (12 mIU/L) and normalization in FT_4 (1.0 ng/dL) (**Table 2**). At this point, her medication is adjusted to further improve TSH levels. At the patient's four-month follow-up, however, the TSH is still high (9.0 mIU/L), but the FT_4 has continued to increase (1.2 ng/dL) (**Table 2**). A discrepancy in the change between TSH and FT_4 levels may occur when inconsistencies exist in medication adherence. Dr. Frieze commented, "This is where we have to look at things clinically and make determinations about patient [adherence]." Patients who may have been nonadherent to treatment may begin taking their medication more regularly as the follow-up testing time approaches. Therefore, FT_4 levels may appear normal because this hormone responds to treatment more quickly, but TSH levels may take longer. Additionally, there may be factors that affect medication absorption.

During the clinical visit, the physician prompts the patient to take her medication more consistently and routinely. The patient agrees to improve treatment adherence, and at the six-month follow-up, TSH has normalized to 3.5 mIU/L, and the FT_4 has remained normal at 1.3 ng/dL (**Table 2**). The TSH reference range of 0.4 mIU/L to 4.0 mIU/L is that for the entire population. This patient is a 66-year-old woman, so this reference range does not represent the age-adjusted population range. Therefore, a level of 3.5 mIU/L would be in the midrange of normal for a 66-year-old woman. The patient is maintained on the same medication dose and is instructed to return in three months. At nine months after initiation of treatment, the laboratory test results once again show an elevated TSH (6.6 mIU/L) (**Table 2**). Dr. Frieze explained that the cause of this rebound in TSH should be explored. The patient indicates 100% medication adherence in recent months; therefore, Dr. Frieze noted that the increase in TSH could instead be attributed to switching between generic and brand-name therapeutic formulations.

Recommendations and Takeaways

Clinicians can take steps to address both adherence and pharmacy challenges in patients being treated for hypothyroidism. Patient adherence can be addressed by emphasizing that hypothyroidism is a chronic condition, requiring a lifelong commitment to hormone replacement therapy; educating the patient on their medical condition and the risks associated with untreated or undertreated disease; providing specific instruction to patients on how to take medication appropriately and consistently; and raising questions around nonadherence in a problem-solving and nonjudgmental manner.

Because bioequivalence does not necessarily exist between all thyroid medication preparations, switching between different preparations could be a possible explanation for the loss of TSH normalization. In that setting, elevation of TSH can lead to levels that reach the thyrotoxic range, potentially causing patients to experience adverse outcomes. As such, Dr. Frieze added that clinicians can address pharmacy challenges in patients being treated for hypothyroidism by asking questions about the patient's experiences at their pharmacy and checking prescription refill data. "This becomes a very pertinent part of the discussion to have with the patient to determine whether or not (they) are getting the same prescribed medication each time (they have) gone to the pharmacy," he concluded.

DISCLOSURES

a This study also examined adherence to the 2012 American Association of Clinical Endocrinologists/American Thyroid Association guidelines, which recommend that pregnant women with hypothyroidism who receive treatment with levothyroxine consult with an endocrinologist and, when treated with levothyroxine, have their thyroid-stimulating hormone levels monitored.

b Key inclusion criteria consisted of patients who had two or more diagnoses of hypothyroidism or at least one diagnosis of hypothyroidism and at least one prescription for levothyroxine over the calendar year 2014, age 18 or older. Adequacy of treatment was assessed from diagnosis in 2014 to one year later.

c This patient case is arbitrary and does not reflect or represent any specific patient profile. This case was designed to engage the audience and provide education around older patients with hypothyroidism.

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Interchangeable insulin biosimilars: A game changer in diabetes management Page 36

Multidisciplinary lipid management for preventing cardiovascular risks

Welcome to this *Medical Economics*® presentation of *Around the Practice*, featuring a panel discussion on multidisciplinary lipid management for prevention of cardiovascular risks.

Let's meet our panel members.

Moderator:
Dhiren Patel, Pharm.D., CDCES, BC-ADM
Adjunct associate professor of pharmacy practice, Massachusetts College of Pharmacy and Health Sciences, Boston

Panelists:
Deepak Bhatt, M.D., M.P.H., FACC, FAHA, FSCAI, FESC
Professor of medicine at Harvard Medical School, Boston

Robert Busch, M.D.
Director of clinical research at Community Endocrine Group, Albany, New York

Jennifer Goldman, Pharm.D., RPh, CDCES, BC-ADM, FCCP
Professor of pharmacy practice, Massachusetts College of Pharmacy and Health Sciences, Boston

Joyce Ross, M.S.N., RNC, CRNP, CS, FNLA, FPCNA
Certified registered nurse practitioner and clinical lipid specialist with concentrated training in preventive cardiology, Philadelphia.

This interactive panel discussion was filmed Dec. 1, 2021, and the following transcript was edited for length and clarity. To view the full video discussion, including panel discussions of two unique patient scenarios, visit:

Around the PRACTICE

Patel: ***Dr. Bhatt, can you walk us through the pathophysiology of hypercholesterolemia and cardiovascular disease?***

Bhatt: This is really an important topic. I recall a time when there was some controversy around the role of cholesterol and atherosclerosis, but that time is well past. At this point, there's no credible voice out there that's debating the point that cholesterol is directly causal in terms of atherosclerosis. There's no question that LDL cholesterol — especially more atherogenic forms, such as when it gets oxidized — is really toxic to blood vessels.

The good news is there's something we can do about that. The first line of attack is lifestyle modification and healthy diets. I would endorse a plant-based diet to the extent one can adhere to that — a diet high in fresh fruit and vegetables and whole grain. Beyond diet, regular daily physical activity, even exercise can be useful in terms of maintaining one's cholesterol, but (there are) other associated risk factors like blood pressure, weight, glucose...and when those

measures aren't enough, pharmacotherapy is certainly indicated. We're lucky that we've got generic statins and relatively safe, well-tolerated, inexpensive ways to lower LDL cholesterol when lifestyle management is not enough.

One concept that's been introduced into the literature is the idea of cholesterol years. Most folks in health care are aware of the concept of pack years of tobacco exposure: The more pack years, the worse off someone is in terms of their cardiovascular health and, in that case, cancer risk. Cholesterol years are similar; it's looking at the number of years that someone has cholesterol elevation and the degree of elevation, and that product or the area under the curve essentially represents their cumulative risk for atherosclerosis, at least attributable to LDL cholesterol. Thinking about it that way, then, forces us to realize that for some people you really do want to start therapy.

At a minimum, lifestyle modification recommendations, but potentially pharmacotherapy much earlier in life if their LDL is extremely high, such as someone with a genetic disorder or familial hypercholesterolemia. Whereas for someone (who) has good LDL cholesterol due to diet, genetics, nature, whatever, that sort of person perhaps [doesn't] need pharmacotherapy until later in life when their cardiovascular risk is higher and their LDL cholesterol has drifted higher.

The pathophysiology and the epidemiology are quite interlinked — and importantly, in a way that's actionable. In cardiology, I'm always thinking about cardiovascular risk, but these are lessons that can apply at the many points where we may touch a patient. They might show up for their screening before their knee surgery at a relatively young age. But if they've got identified cardiovascular risk factors, that provides an opportunity to act even though they're not there at that exact moment to get cholesterol management advice.

"During visit one, you're not giving them the works. You could, but then the patient will put their shoes and socks on and run away. You must choose your battles first and what you're going to be successful with early on."

Robert Busch, M.D.

Patel: ***Dr. Busch, how are you talking to your patients about some of these risk factors?***

Busch: As an endocrinologist, (I see that) most of our patients have diabetes — mainly Type 2 diabetes — but they don't just come in with their diabetes, as Dr. Goldman and others have said. They come in with diabetes, hypertension, hyperlipidemia, obesity. They come in (with) hypertriglyceridemia. Which are we going to tackle first? They've done the lifestyle stuff; they've met with the diabetes educator. You know they're going to end up on six or seven drugs down the line.

During visit one, you're not giving them the works. You could, but then the patient will put their shoes and socks on and run away. You must choose your battles first and what you're going to be successful with early on. Often the LDLs, the easiest thing to control because the statins work — and if they could tolerate the statin, at least you should show success after that first visit (because) you got their LDL at a target, and then try to address the other things.

You must roll out the regimen for the patient. Most of our patients, if you ask what they had for breakfast, their answer is pills, because after a year they're on six or seven medications and some injectables as well. Each thing must be addressed because these are risk multipliers...but it takes about six months to a year to roll out the full regimen that the patient's going to be on. But you're not telling them (on) day one, especially (when) they're coming in (saying), "I don't want medications. I want to treat things the natural way," and you know what you have cooking down the line.

Patel: ***Joyce*** **(*Ross*),** ***from where you sit in a specialty arena where you interact with endocrinologists, pharmacists and cardiologists, how do you go about what Dr. Busch just mentioned — primary and secondary prevention? How do you tackle each of those?***

Ross: I totally agree with Dr. Busch that we can't throw everything at the patient the first time we see them. They will run and won't come back. Communication between the health care providers is critically important because this is a team. Of course, the most important part of the team is that patient. Every time a patient is seen by any (members) of a group, what is very important is for you as a provider, no matter what your (role) is, to communicate with the others about what you saw, what you did (and) how the patient's doing.

Patel: **(*Dr. Goldman*),** ***can you walk us through what***

you tell patients on that first visit? Patient has high cholesterol; what do you walk them through? It's not "you can't eat anything," right? What is your approach there?

Goldman: One of the most important parts of communication is reflective listening. When you meet with a patient you need to ask "what's important to you?" What goals do they have?

When we talk about lifestyle changes, we must be cognizant of the limitations that we have. It's easy to say "go to the gym." Not everyone can afford a gym membership. Not everyone has access to go swimming every day. We have to ask, "What do you do for purposeful exercise? What can you do that might increase that?" It's about listening to them and helping them solve their problems.

We have to hear about food and have that conversation. What's the problem? Are they grazing all day? Are they making good choices? Do they even understand? Speaking of diabetes, are they understanding the role of carbohydrates, fats and protein? In terms of lipids and diabetes and heart disease, are they having the right fish, lean meats, and so forth? Can they afford them? We must work within that, as well as in cultural issues in terms of food. We have to listen. We can't be there finger wagging.

Patel: ***Dr. Busch, we obviously want to start with lifestyle. People want to do things naturally, but we know that's not always going to be the case. When it comes to prescribing that initial statin, we have varying intensities of it. What's your progression? How do you decide what patient goes on what statin and how are you deciding that?***

Busch: If I have an LDL target in mind — if I want to get the LDL below 70 — or if they've had heart disease and diabetes below age 55, you have to know how much efficacy you're going to get from that statin as you titrate up. One of the things we learned early on with statins was the rule of six. If you remember the starting dose of the statin, what it does is you titrate and double and double and double the statin, you get another 6%.

Patel: ***Dr. Bhatt, not all patients are going to get to their goals with just statins. What has the role of ezetimibe been? You've been very involved in some of these pivotal trials.***

Bhatt: Ezetimibe is a really underutilized drug. It's cheap. It's generic now, very safe, very well tolerated; other than the occasional gastrointestinal side effect or discomfort, there's really very little in the way of systemic side effects. For patients who were truly statin intolerant, it's a terrific option. For the patient who's on a statin already where their LDL hasn't gotten (to) the goal...adding ezetimibe can get some additional LDL lowering. It's really a great but unfortunately underutilized tool in our armamentarium.

If that doesn't work, then we can step it up a notch in patients at high risk to a PCSK9 inhibitor. This is applicable to patients in the secondary prevention universe, although in patients (who) have familial hypercholesterolemia it would even be in the primary prevention universe. A PCSK9 inhibitor is currently formulated of injectable agents that are very potent. (It) can lower LDL cholesterol by 50%, 60%, and can be useful for patients whose LDL is very elevated but where statins and ezetimibe don't do the trick, or in patients who are statin intolerant who can't go on just ezetimibe. These are agents that are very well tolerated, (with) very few side effects other than injection site reactions.

These are branded; they are expensive. That's the major barrier in terms of their use and what's limited their uptake. But, perhaps in the future, as more PCSK9 inhibitors enter clinical practice — several are being tested and are in development — that might lower the costs. A lot of interesting things (are) going on, but in terms of what's actionable right now, certainly the algorithm beyond lifestyle modification would be statin, ezetimibe and PCSK9 inhibitor.

Busch: As a provider, (there's) nothing more fun than calling the patient who's on the PCSK9 to tell them their LDL is lower than their grandchild's LDL. I like making that phone call to tell someone that their LDL is in one digit, which is incredible, and (PCSK9 inhibitors) almost always work.

Patel: ***We've talked a lot about LDL and tools we have there. Dr. Bhatt, let's talk about triglycerides. You led the REDUCE-IT trial, and very rarely do I get to hear it from the primary source. Can you talk to us about REDUCE-IT and what that means from a clinical practice standpoint?***

Bhatt: Focusing on triglycerides is an important aspect of cardiovascular risk reduction. We've been focusing on LDL; indeed, the world of cardiovascular risk reduction has been very LDL-centric, and rightly so. But there are other cardiovascular risk factors, even in the lipid domain. Triglycerides are one of them, and that's based on

several different lines of evidence. Lots of science now (supports) that triglycerides, much like LDL, are directly causal or directly atherogenic, though to be scientifically precise it's triglyceride-rich lipoproteins more than just what we measure in terms of triglycerides per se. But regardless, they do appear to have an independent effect on cardiovascular risk above and beyond LDL cholesterol.

How to modulate that risk has also been a source of debate. In the REDUCE-IT trial, we studied patients with elevated triglycerides. Patients had to have elevated triglycerides above about 135 or so milligrams per deciliter and less than 500 milligrams per deciliter.

So in that range, we enrolled patients. About 70% of them were stable, about another 30% are high risk, primary prevention, but specifically were those patients with diabetes and at least one additional cardiovascular risk factor. That was the overall population. We followed 8,000 patients for an average of about five years. We randomized them to icosapent ethyl or to a placebo.

Just to say a quick word about what icosapent ethyl is: It's an omega-3 fatty acid, a prescription medicine, not a supplement. Icosapent ethyl is a medicine that had already been approved for triglyceride reduction based on a trial called Marine for patients with high triglycerides, over 500, to hopefully prevent pancreatitis. But we were studying it in patients with a lower level of triglycerides, not to see if it'll prevent pancreatitis but rather to see if it would reduce cardiovascular events.

What we found with this drug was a significant reduction in cardiovascular events — about a 25% reduction in ischemic events, specifically a 26% reduction in death from cardiovascular causes, heart attacks, stroke, so important cardiovascular end points with large risk reductions.

That's the overall trial. I think it was very representative of clinical practice. Dr. Busch was one of the leading enrolls of patients in the trial. I think it reflects real world practice, that these weren't some carefully selected patients. These were just patients at high cardiovascular risk (who) happened to have elevated triglycerides. Certainly, the trial does support measurement of triglycerides to identify patients who would be candidates for icosapent ethyl to reduce cardiovascular risk.

Patel: ***I did want to mention a recent approval of bempedoic acid. I know it exists as monotherapy and in combination. Dr. Busch, what's the role of that in your toolbox?***

Busch: Bempedoic acid blocks the pathway to generate cholesterol in the liver higher up than where a statin does. Basically, it stops cholesterol synthesis within the liver, the liver is hungry for cholesterol, and upregulates the LDL receptors, which is what Brown and Goldstein won the Nobel Prize for in the 1980s.

It works higher in the pathway but, interestingly, it is not activated in the muscle, even though it's activated in the liver, so that it doesn't affect the muscle cholesterol, and so there's very little myopathy with the drug. The potential side effects are few. It can raise uric acid a little bit, so you must be cautious if you give it to someone who's had gout in the past, and there are very rare cases of muscle rupture.

There's no outcome study yet. The outcome study is in progress, fully recruited. It's called the Clear Outcome study. Interestingly, about that outcome study, the patients are either on no statin or very low-dose statin, very different than all the other trials. In the PROVE-IT trial, they were all on a statin. In the PCSK9 studies, they were on statins, and obviously (in) the statin outcome studies they were on statins. This will be one of the first studies in someone on no or low-dose statin where a drug that is not a statin should show benefit.

> ***"What we found with [icosapent ethyl] was a significant reduction in cardiovascular events: about a 25% reduction in ischemic events; specifically, a 26% reduction in death from cardiovascular causes, heart attacks, stroke, so important cardiovascular end points with large risk reductions."***
>
> **Deepak Bhatt, M.D., M.P.H.**

Bhatt: The data to date for bempedoic acid look good in terms of safety and efficacy, especially for that statin-intolerant patient, and when combined with ezetimibe it seems to be respectable reductions in LDL cholesterol. Of course, in the cardiovascular community, we're often looking for outcome trials, and there's an ongoing outcome trial. I think many cardiologists are really waiting for that before jumping on board. ■

Interchangeable insulin biosimilars: A game changer in diabetes management

EndoView
ENDOCRINOLOGY NETWORK®

Welcome to this special EndoView and PharmacyView presentation, brought to you by *Medical Economics*® and *Endocrinology Network*®.

The first interchangeable insulin biosimilar approved by the US Food and Drug Administration (FDA), insulin glargine-yfgn (Semglee) has the potential to transform care and reduce costs for many insulin users. The following transcript features a conversation between a pharmacist and a practicing clinician discussing how the historic approval of insulin Semglee affects patients using insulin as well as next steps for the diabetes care team. The transcript was edited for length and clarity.

The guests for this special presentation of EndoView and Pharmacy View are:

Diana Isaacs, Pharm.D., Clinical Pharmacy Specialist and the Remote Monitoring Program Coordinator, Cleveland Clinic, Cleveland, OH

Thomas Blevins, M.D., Endocrinology, Diabetes & Metabolism Specialist, Texas Diabetes and Endocrinology, Austin, TX

To view the entire video program, go to:

by **Patrick Campbell** Senior Editor

Pathophysiology of Diabetes and Need for Insulin Therapy

Diana Isaacs, Pharm.D.: ***I want to start off by asking you to briefly describe the pathophysiology of diabetes and the whole rationale for insulin therapy?***

Thomas Blevins, M.D.: Thank you for asking. This is interchangeability, which we're going to get to as a big deal. But pathophysiology, of course, in type 1 diabetes is straightforward. People don't make insulin and therefore they need insulin replacement and as a hormone replacement treatment and we use basals and bolus and we use insulin pumps and things like that. So, they have to have insulin and if they're using multiple daily injection, then they're going to need to have a basal insulin. We'll talk more about those in a minute. Now, in Type 2 diabetes, many people don't need insulin at all. They don't make enough insulin as you all know. We do use insulin in those who can't control with other means. So, we use basal, we use the bolus pre-meal. Sometimes we need basal alone to give them just that supplemental amount, to give them just enough to get the control that we want. So, two different pathophysiologies, both need insulin and not everyone with type 2, of course, needs insulin.

Isaacs.: Could you ***provide us with maybe a brief historic overview of the current FDA-approved basal insulins?***

Blevins: I was in training in the 1980s and medical school starting in the 70s. So, I've seen, as many of us have, quite a bit of evolution. We had long-acting insulins like Ultralente, where most people don't even know what that is nowadays. Don't even try to know, by the way — let me give you that advice. It was like once

a day. For the most part though, we used an insulin, the Neutral Protamine Hagedorn (NPH), which was a protamine-based insulin that was really more of an intermediate-acting insulin. We called it basal. The way we used it, back then, it was an art and a science, but a little more art than science sometimes because with NPH you had to use multiple doses to get any kind of a leveling in the background. NPH was a true mess. It would peak in about six to eight hours and then it kind of dropped off after about 14 to 16 or 16 to 18 hours depending on the dose.

Then about 20 years ago or so came detemir, which is a once-a-day insulin. It's an insulin that we still use now. Then, along came glargine, insulin glargine. You add a glycine to a chain of insulin and 2 arginine to the B chain and you have an insulin that lasts longer. So, the once-a-day glargine came along and that was a big, huge change for us. We had much more predictable usage of basal, a much better basal.

I would say that glargine is probably the most commonly used basal around the world at this point. I think that's true. Now, around 2005 or so, we get degludec, which is the Tresiba, and then that we get the U300 glargine and we got that about 10 or 15 years ago now. So, we've had a nice evolution.

Interchangeable Biosimilar Insulin

Isaacs: I want ***to switch gears and talk about biosimilars now. So, we have insulin glargine-yfgn*** **(*Semglee*)*, which is the first interchangeable biosimilar ever approved by the FDA. So, I'm hoping you can define for our audience what a biosimilar is and just maybe talk through, how the FDA approves biosimilars and how these compare to the original reference product.***

Blevins: I'd be happy to talk about that. This is really important for the audience to understand. First, let me throw out a couple definitions. So, a biologic is essentially a pharmaceutical agent created in living cells and that's what we're dealing with here. Insulin is a biologic. Making a biologic is a very complicated process, it's not like making a generic statin or a generic other kind of medicine. A biosimilar is a biologic medicine that's considered to be highly similar to the reference biologic and with no clinically meaningful or notable significant differences in terms of the safety and purity as well as potency.

Now, we're talking about insulin glargine and the reference glargine will always be Lantus, the Sanofi Lantus insulin. So, anytime somebody wants to do a biosimilar glargine, they're going to reference to the original, essentially what is Lantus. Another point is that a biosimilar is an approved version of a biologic medicine that with identical amino acid structure sequencing to the originator, which would, again, be the reference. The intent is to make it as close as possible in every way to the reference biologic and biologics are complex. Therefore, biosimilars are complex proteins.

The approval process for a biosimilar requires that the company that desires approval of their biosimilar to go to the FDA with data from their agent that shows that the pharmacokinetic and pharmacodynamic data is very similar and they also have to show mitogenicity. They have to look at things that are from really the bench to the clinic. Then, they need to do the large, not terribly large, but large studies with people, in this case, who have of type 1 or type 2 diabetes and show that the insulin is highly similar in terms of efficacy, safety, and even immunogenicity. So, those are the standards set by the FDA. So, the Viatris people had to do that. That's what Eli Lilly had to do when they got their Basaglar approved too.

Isaacs: So, what ***exactly though, is an interchangeable product? Are there any other biosimilars out there that also have this status of being interchangeable?***

Blevins: In the insulin world, you may be surprised to hear that there has been no insulin, until now, approved as an interchangeable insulin. Now, Semglee has received that approval. What the FDA requires is that a company do studies that show that you get the same clinical result as the reference product. There can also be no diminished efficacy, no sign of safety issues, and no sign of difference in immunogenicity. The FDA encourages switching studies. That's a study where you take people with type 1 or type 2 diabetes and you put one group on the reference product, the originator like Lantus, and you put other people on the new product. Then, you treat them for periods of perhaps 3 months at a time, switch them to the other side, see if there is any difference, and then you switch them back. As long as the safety, efficacy, and all of that are highly similar, then you have a chance of getting approved. I suspect there'll be others down the road. This is a big, big deal.

Isaacs: I would ***love to hear a little bit about these clinical studies that were done to really support that Semglee can be interchanged with the reference product.***

Blevins: Remember, you have to study these biosimilars in humans with diabetes. There's an INSTRIDE 1 in type 1, INSTRIDE 2 in type 2, and then, INSTRIDE 3, which that is the study that helps get the interchangeability. I'll talk about each one.

So, INSTRIDE 1 included 558 people with type 1 diabetes, and this is a study where a group will be put on reference product and another is going to be put on the biosimilar. They were then followed for a period of 52 weeks. The outcomes of interest in that trial included A1C changes and hypoglycemia but we'll talk about that more it in a minute. INSTRIDE 2 included 560 people with type 2 diabetes and these are people that need basal insulin. Again, they're comparing the reference product to the biosimilar.

Let's talk about INSTRIDE 1. When you look at the A1C data, there was no difference between the start and the finish of the study between the groups. So, the A1Cs were the same from start to finish in this group of people type 1 diabetes. If you look at the fasting plasma glucose, it's the same. There was no significant difference for the A1C. So, bottom line here is noninferiority in A1C results. I mentioned the fasting glucose, but incidence of adverse events, serious adverse events, and incidence of hypoglycemia were also similar, with no clinically meaningful differences between treatment groups. So, that's the type 1 diabetes study. In the type 2 diabetes study, if you look at the A1C changes at week 12 and week 24, between the 2 insulins there was no significant difference. If you look at safety and adverse events, hypoglycemia, glargine dose over time, it's very similar. So, again, no clinically significant or meaningful differences between the reference and biosimilar. There were immunogenicity studies done in the INSTRIDE 1 and INSTRIDE 2 studies, looking at anti-drug antibodies. Long story short, the INSTRIDE 1 and 2 studies over the time period is looked at, which was 50-week data in INSTRIDE 1 and 24-week data in type 2 and no significant cross-reactive, anti-drug antibody presence between the biosimilar and reference product.

The INSTRIDE 3 trial is the switching study and, briefly, the way this study worked is that people were taken from the INSTRIDE 1 study and they were offered to continue on into this switch study. So, a group is left on reference insulin glargine throughout the time period of the study, which was 36 weeks, and another group was given the biosimilar for 12 weeks, then given the reference insulin for 12 weeks, then given the biosimilar for 12 weeks.

So, the results there again showed that there was no significant difference between the treatment groups when it came to A1C during the different treatment periods. Additionally, there was no difference in fasting glucose and immunogenicity looked very similar too. So that's the data that shows us that we can have the confidence and the FDA has the confidence that a pharmacist can change without us saying "It's OK", because we have an insulin extremely similar in every way that we talked about. So that, I think, is a big deal.

Isaacs: That was *such a good summary of the different studies. I'm curious how you think that this may affect things in terms of formulary and price considerations in the marketplace with insulin.*

Blevins: It's really interesting. I think the biologics are never going to be as cheap as generics because, even though they're biosimilars, they're still very complicated and the way to make them is not inexpensive. The pricing can be quite a bit lower potentially. I'm not going to give numbers right now because they change all the time and I'm not sure they're totally accurate every time, but considerably lower cost.

Now, then comes the complexity of the formularies and sometimes the formularies have different pricing that they can offer or they can get from pharmaceutical companies. Then comes the idea of translating this data into practice. Will doctors feel comfortable? In general, I think it's safe to say biosimilars are less expensive, making them more affordable, and making access better, which is huge in here in the US and around the world too.

Making a good insulin, a really good basal insulin, available to everyone that needs it is very important. Lots of people have diabetes and the number of people with diabetes is not going to get smaller. It's going to be greater and greater everywhere. So, I think there's a real potential for cost saving which is really important.

From a practitioner standpoint, I'm pretty happy about that because every time a patient switches from a type of insulin to another based on formula even though it's the almost same insulin, I have to prove it and the formula says, "we prefer this over the other", then I have to approve what my staff does and it costs us a ton of time. If someone could just change up the pharmacy, I'll say "Yes, go for the one that has the best price," and I'm very confident that the quality is good, they're interchangeable based on the data, and the FDA agrees. ■

Follow-Up VISIT from PER® Physicians' Education Resource, LLC

3 Things You Should Know About CKD in Primary Care

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To learn more about this topic, including information on the management of CKD in primary care, go to ***gotoper.com/go/ckd21***

Release Date: January 1, 2022
Expiration Date: January 1, 2023

Learning Objectives:

- Describe recommended diagnostic practices for chronic kidney disease (CKD) in patients with type 2 diabetes (T2D)
- Identify CKD as a unique disease with high risk of cardiovascular and renal comorbidities
- Evaluate the efficacy and safety of nonsteroidal mineralocorticoid receptor antagonists and other therapies under investigation for the treatment of patients with CKD

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This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals Inc.

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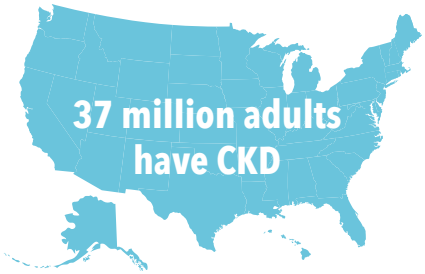
Chronic kidney disease (CKD) causes the gradual loss of kidney function over time. The prevalence of CKD is steadily rising; however, 96% of patients with early kidney disease (stages 1 and 2) do not know they have CKD. Of all patients with severely reduced kidney function (stage 4) who are not on dialysis, 48% are unaware of their condition.[1] Early detection and treatment can prevent progression, and novel therapies, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and nonsteroidal mineralocorticoid receptor antagonists (MRAs), have shown renoprotective benefits in clinical trials.[2,3] Here are 3 things you should know about the management of CKD in primary care.

1 More than 1 in 7 adults in the US have CKD.

CKD is defined as the presence of abnormalities of kidney structure or function for three or more months, irrespective of cause.[4] An estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 or the presence of one or more markers of kidney damage for more than three months provides the diagnosis. These markers include:

- albuminuria (albumin-to-creatinine ratio [ACR] 30 mg/g or greater)
- urine sediment abnormalities
- electrolyte and other abnormalities due to tubular disorders
- abnormalities detected by histology
- structural abnormalities detected by imaging
- a history of kidney transplantation

An estimated 15% of adults in the US, or 37 million people, have CKD.[5] Diabetes is one of the primary causes of CKD, which develops in as many as 40% of patients with diabetes.



2 As renal function declines, the risk of CVD increases.

As CKD progresses, complications and comorbidities become more likely. CKD increases the chances of cardiovascular disease (CVD). Even small decreases in eGFR are associated with an increased risk of CV events, including CV mortality.[6] The high morbidity and mortality in patients with CKD is not fully accounted for by traditional risk factors such as age, diabetes mellitus, dyslipidemia, family history, hypertension, hyperuricemia, obesity, tobacco use, and male gender.[7]

Specific risk factors for kidney impairment include albuminuria, anemia, mineral and bone disorders, malnutrition, toxic metabolites, endothelial dysfunction, inflammation, and oxidative stress. Multiple studies indicate that patients with CKD undergo accelerated aging, which precipitates the appearance of pathologies, including CVD, which are usually associated with advanced age.[8]

3 Agents are now approved to help slow CKD progression.

Several SGLT2 inhibitors have been proven to slow the progression of kidney disease in patients with and without T2D. Currently, four SGLT2 inhibitors are approved by the United States Food and Drug Administration (FDA): canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.[3]

SGLT inhibition can slow kidney disease progression

The CREDENCE trial assessed renal outcomes in patients with T2D and albuminuric CKD on maximally tolerated doses of an angiotensin converting enzyme inhibitor or angiotensin-receptor blocker therapy. Patients were randomized to receive canagliflozin 100 mg daily or placebo. The relative risk of the kidney-specific composite end point of end-stage renal disease (ESRD), doubling of serum creatinine, or death from renal causes was reduced by 34% (HR, 0.66; 95% CI, 0.53-0.81), and the relative risk of ESRD was reduced by 32% (HR, 0.68; 95% CI, 0.54-0.86).[9]

Empagliflozin was shown in the EMPA-REG OUTCOME trial to not only reduce CV outcomes, but also to slow CKD progression. In total, 7020 patients with T2D were randomized to receive empagliflozin (10 mg or 25 mg) or placebo, in addition to the standard of care.[10] Although not specifically powered to detect renal outcomes, a significant benefit was noted regarding incident or worsening nephropathy, progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, and composite worsening of nephropathy.[11]

The DAPA-CKD trial investigated the use of dapagliflozin in CKD. In this trial, 4304 patients with an eGFR between 25 and 75 mL/min/1.73m^2, and a urine ACR of 200 to 5000 mg/g were assigned to receive dapagliflozin 10 mg or placebo once daily. After 2.4 years, the trial was stopped early due to efficacy in reducing the primary composite end point of a sustained decline in eGFR by at least 50%, ESRD, or death from renal or CV causes (9.2% vs 14.5%; HR, 0.61; 95% CI, 0.51-0.72).[12]

Ertugliflozin is the newest SGLT2 inhibitor, and its CV safety was evaluated in the VERTIS CV trial; patients were randomized to receive ertugliflozin 5 mg or 15 mg daily. Although ertugliflozin did not provide composite CV benefit, as seen in the other approved SGLT2 inhibitors, the renal benefit appeared to be on par with that seen in previous studies of this class. The initial renal composite outcome for worsening nephropathy, defined as death from renal causes, dialysis or transplant, or doubling of serum creatinine, was not significantly different between ertugliflozin and placebo (HR, 0.81; 95.8% CI, 0.63-1.04).[13]

Nonsteroidal MRAs have been developed as adjunctive therapies to reduce the risks of CKD and CVD in patients with T2D. The FIDELIO-DKD trial assessed the efficacy and safety of finerenone in patients with CKD and T2D. In this trial, 5734 patients with CKD and T2D received finerenone or placebo.[14] Patients had a uACR of 30 to less than 300 mg/g, an eGFR of 25 to less than 60 mL/min/1.73 m^2, and diabetic retinopathy; or a uACR of 300 to 5000 mg/g and an eGFR of 25 to less than 75 ml/min/1.73 m^2. Treatment with finerenone resulted in a lower risk of CKD progression and CV events compared with placebo. Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively). Following these results, finerenone was approved by the FDA in July 2021 for CKD associated with T2D.[15]

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CME POST-TEST QUESTIONS

1 Which of the following is true regarding American Diabetes Association screening guidelines for chronic kidney disease (CKD) in patients with type 2 diabetes (T2D)?

- **A** In patients with cardiovascular disease (CVD) risk factors (ie, obesity, hyperlipidemia and/or hypertension), urinary albumin level and estimated glomerular filtration rate (eGFR) should be assessed every 2 years.
- **B** Patients who maintain a hemoglobin A1C (HbA_{1C}) level under 7.0% can be screened with a urinary albumin level and eGFR every 5 years.
- **C** Regardless of CVD risk factors, patients should be instructed to sporadically check for proteinuria in first-morning specimens using a reagent strip device and report to their provider when the level exceeds 300 mg/L.
- **D** Urine albumin-to-creatinine ratio and eGFR should be assessed annually, at minimum, in all patients with T2D.

2 Which of the following is a criterion for a diagnosis of CKD?

- **A** A urine albumin-to-creatinine ratio of 45 mg/g or more
- **B** Abnormalities of kidney structure or function present for longer than 6 months
- **C** An eGFR < 60 mL/min/1.73 m^2
- **D** An abnormal kidney biopsy

3 Which of the following statements is true regarding the FIDELIO-DKD trial that evaluated the nonsteroidal mineralocorticoid antagonist (MRA) finerenone versus placebo?

- **A** Treatment-emergent adverse events were greater with the use of finerenone than with placebo.
- **B** Enrolled patients had an eGFR > 60 mL/min
- **C** Hyperkalemia leading to permanent discontinuation occurred in less than 1% of the treatment group.
- **D** Treatment with finerenone resulted in a lower risk of CKD progression and cardiovascular events compared with placebo.

To learn more about this topic, including information on the management of CKD in primary care, go to ***gotoper.com/go/ckd21***

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Addressing Influenza
IN THE **COVID-19** ERA

Interseasonal levels of influenza have fallen to historic lows. Some patients are now complacent about health risks from an infection. Others, in the wake of the COVID-19 pandemic, have vaccination burnout. In this *Medical Economics*® Around the Practice series, Tina Tan, MD; John J Russell, MD; Stephan Foster, MD; and Charles Vega, MD; discuss how to educate patients on the importance of influenza vaccines, consider the lasting impacts of COVID-19, and examine case scenarios reflecting challenges physicians are likely to face this season. **Explore the series now!**

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