FEATURED ARTICLES INCLUDE:

A Methodical Approach to Developing Medical Policy

A Closer Look at Personalized Treatment in the Management of Advanced NSCLC

Novel Diagnostic and Treatment Strategies in the Management of Idiopathic Pulmonary Fibrosis
Patients, Science, and Innovation are the foundation of everything we do. At Celgene, we believe in an unwavering commitment to medical innovation, from discovery to development. Our passion is relentless—and we are just getting started.
A Methodical Approach to Developing Medical Policy
Kara L. Kuntz-Melcavage, PhD, Robert K. Kritzler, MD, and
Amy C. Richardson, MD, MBA ............................................. 5

A Closer Look at Personalized Treatment in the
Management of Advanced NSCLC
H. Jack West, MD .......................................................... 10

Overcoming Current Challenges in the Management of De Novo and Re-
lapsed/Refractory Multiple Myeloma
George Somlo, MD ..................................................... 15

Emerging Pharmacologic Treatments and
Strategies in the Management of Obesity
W. Timothy Garvey, MD, FACE ........................................ 19

New Insights into the Diagnosis and Management
of Venous Thromboembolism
Michael Miller, MD, FACC, FAHA, FNLA ............................ 26

Overcoming Current Challenges in the
Treatment and Management of Hemophilia
Mark T. Reding, MD ...................................................... 32

Update in Pulmonary Hypertension
Deborah Jo Levine, MD ................................................... 36

Best Practices in the Prevention and Management of COPD
David Beuther, MD, FCCP ............................................. 40

Novel Diagnostic and Treatment Strategies in the
Management of Idiopathic Pulmonary Fibrosis
Robert Sussman, MD ................................................... 45

Update in the Management of Type 2 Diabetes:
A Closer Look at Current & Emerging Treatment Strategies
Yehuda Handelsman, MD, FACP, FACE, FNLA .................... 49

Hypertriglyceridemia and Omega-3 Fatty Acids:
Exploring Current and Emerging Treatment Options
Michael Miller, MD, FACC, FAHA, FNLA ............................ 53
Editorial Review Board

Alan Adler, MD, MS
Medical Director
Independence Blue Cross

Devena Alston-Johnson, MD
Medical Director
CIGNA

E. Paul Amundson, MD
Chief Medical Officer
Dakotacare

Linda Ash-Jackson, MD
Medical Director
Hometown Health

Paul Bluestein, MD
Chief Medical Officer
Connecticare

Richard Bock, MD, MBA
Chief Medical Officer
Molina Health Care of California

Anthony Bonagura, MD
Chief Medical Officer
Aetna, Inc.

Salil V. Deshpande, MD
Market Medical Officer
United Healthcare

Michael Fine, MD
Medical Director
Health Net

John K. Fong, MD, MBA
Vice President
Blue Cross Blue Shield of North Carolina

Stephen Friedhoff, MD
Senior Vice President, National Medical Director
Amerigroup/Wellpoint

Ronald Y. Fujimoto, DO, FAAFP
Chief Medical Officer
United Healthcare

Uwe G. Goehlert, MD, MSC, MPH, MBA
Principal
Goehlert & Associates

Steven E. Goldberg, MD, MBA
Vice President of Medical Affairs
Coventry Health Care of Kentucky

Humberto Guerra-Garcia, MD, MPH, FACP
Chief Medical Officer
MMM Healthcare, Inc./PMC Medicare Choice
Puerto Rico

Sarah Gunatilake, MD, DrPH
Professor, Health Science Department
California State University, Long Beach

John W. Heryer, MD, FACS
Medical Director
Blue Cross Blue Shield of Kansas City

Kathy Hudson, PhD
Director, Genetics and Public Policy Center
Johns Hopkins University

Larry L. Hsu, MD
Medical Director
Blue Cross Blue Shield of Hawaii (HMSA)

Stephen Keir, DrPH
Co-Director, Center for Quality of Life Support Care Research
Robert Preston Tisch Brain Tumor Center

John Knispel, MD, CPE, FACOG
Regional Medical Officer
Humana

Karen Knowles, MD
Internal Medicine Physician
HCA/Emcare

Catherine Marino, MD
Chief Medical Officer
MagnaCare

Jeff Martin, PharmD
Clinical Account Director
Innoviant, Inc.

Monte Masten, MD, MBA, MPH
Senior Consultant Health & Group Benefits, Tower Watson

Wesley Mizutani, MD
Director Clinical Research & Chairman Department of Rheumatology Healthcare Partners

Thomas Morrow, MD
Next IT

Barbara Nabit-Stephens, MD, MBA
Medical Director
United Healthcare

Tim Newman, MD
Medical Director
FirstEnergy

Denis O’Connell, MD
Medical Director
Blue Cross Blue Shield of North Carolina

Arik Olson, MD, MBA
Senior Medical Director
CHOICE Health Plans

Gary Owens, MD
Principal
Gary Owens Associates

Philip Painter, MD
Chief Medical Officer
Humana

Mary H. Pak, MD
Medical Director
Unity Health Plans Insurance Corporation

Gary R. Proctor, MD
Chief Medical Officer, Federal Division
ValueOptions, Inc.

Carlos Ramirez, MD
Chief Medical Officer
Valley Baptist Health Plans

Paul Rein, DO
Medical Director
Port Warwick Ambulatory Surgery Center

Kevin Roache, MD, MMM, CPE, FACPE
Vice President Medical Affairs
Peoples Health, Inc.

Joseph Schappert, MD
Chief Medical Officer
PAML

Christine M. Seals, MD
Medical Director
Umpqua Health Alliance

Jacque J. Sokolov, MD
Chairman
SSB Solutions

Scott Spradlin, DO, FACPE, ACOI
Vice President Medical Affairs/Chief Medical Officer
Group Health Plan

William D. Strampel, DO, FACOI
Dean, College of Osteopathic Medicine
Michigan State University

Prentiss Taylor, MD
Corporate Medical Director
Advocate At Work at Advocate
Health Care

Pamella Thomas, MD, MPH, FACOEM
Consulting Medical Director
Wellness Health & Productivity Strategies

Robert A. Ziff, MD, MBA, FACS, CPE
Senior Corporate Medical Director, Medicare
Humana
A Methodical Approach to Developing Medical Policy

Kara L. Kuntz-Melcavage, PhD, Robert K. Kritzler, MD, and Amy C. Richardson, MD, MBA

Summary
Medical coverage policy is a cornerstone for health care management because of the guidance it provides to a managed care organization. Strong medical policy can guide operations throughout a company, ranging from medical coding departments to appeals decisions. Because of their broad impact, the development of medical policies should be careful and include extensive research. Four pillars of evidence, including regulatory, scientific literature, industry standards, and expert opinion, provide a framework on which to base coverage policy research. Having a clear research plan ensures that time spent developing policies is productive, which is essential in a business environment. Approaching research in an organized manner ensures that policies are evidence-based and rational. This report describes an organized approach for evaluating relevant evidence when developing medical policies to guide health insurance decisions.

Key Points
- Medical coverage policy provides a guideline for insurer payment decisions.
- A company can design policies following an organized process.
- Four pillars of evidence provide support for coverage policies.
- Thoughtful design of policies demonstrates that an insurer makes evidence-based decisions regarding policy.

Introduction
MEDICAL COVERAGE POLICIES ARE A NECESSARY component for successful managed care organizations. The jobs of all employees in the organization, from customer service staff to case managers to medical directors, are impacted by medical policies. Therefore, thoughtful policy development yields broad benefits. While policy development can be an arduous task, quality medical policies are a worthwhile investment of resources because of their ability to positively impact workflows throughout an organization. Good medical policies do not arise from arbitrary decisions regarding medical coverage, but rather are the result of thorough research into the scientific, medical, and financial implications of a policy.

The importance of an evidence base for policies has become increasingly apparent as policymakers strive to develop and implement worthwhile and effective policies. Carefully examining evidence when developing medical policies results in policies that are informative and that contribute to organizational success. Approaching policy development with an organized plan is integral for producing positive change.

Our company is a mid-sized managed care organization with three lines of business that cumulatively cover about 350,000 lives. The procedure for developing medical policies at our company has recently been revised and the results of our research into how to write effective and legitimate policies provide an orderly approach for medical policy development.

This paper describes key elements to be examined when developing medical policies that guide coverage decisions about medical treatments, procedures, and devices. Four pillars of evidence are considered when developing medical policies: regul-
Regulatory standards and contractual requirements, scientific literature, practices of other health insurers, and expert opinion (Exhibit 1). Although contractual agreements are the ultimate authority concerning medical coverage for members, medical policies are needed to provide guidance for coverage decisions on which contracts are silent. The four areas described in this paper provide strong guidance and support for policy content.

**Regulatory Standards**

A foremost concern for health insurers is compliance with regulatory standards. Therefore, federal and state regulations that may apply to the policy topic of interest must be explored when developing a policy. Creating a policy that is contradictory to medical coverage allowable or required by law will be confusing for providers and health care workers who are familiar with applicable laws. Ultimately, creating policies that contradict regulatory requirements is futile because the policy will be unenforceable. Any contradictions between a company’s policies and regulatory requirements could damage the credibility of a company.

Health plans that administer benefits for Medicare or Medicaid require knowledge of decisions issued by the Centers for Medicare and Medicaid Services (CMS) regarding coverage of medical procedures for beneficiaries. A good resource for current CMS policy is the official CMS website. From this site one is able to navigate to websites that contain state-specific information regarding Medicaid coverage as well as sites providing coverage information for Medicare. The state of Maryland has a Code of Regulations (COMAR) that is publicly available to provide the most recent information about Medicaid requirements. Similar administrative codes exist for other states. Because Medicaid is a state-specific program, it is necessary to consult examine regulations for the state in which a plan provides coverage.

Federal programs for health insurance possess regulations that are applicable throughout the United States and because of their broad geographic applicability the regulations may differ from state-specific regulations. Two examples of federal health programs are Medicare and TRICARE. Medicare is a well-known program for the nation’s elderly while TRICARE provides access to health care for retired service members and their families. Codes of Regulations unique to these programs exist, and it is important to be aware of program-specific regulations because a failure to comply with the regulations may be punishable in federal court. The library of policies governing TRICARE is rather extensive and navigating the policies is an acquired skill, but it is one worth learning for health plans under TRICARE contracts because of the importance of policy to understanding medical coverage.
Clearly stating how to interpret a company’s medical policy in instances when health plan policies and regulatory policies do not agree is an important safeguard for ensuring that confusion regarding policies does not impact business operations. Our approach has been to include a statement at the beginning of each policy stating that specific benefits, guidelines or regulatory requirements have precedence over the information contained in the policy. Prioritizing contractual agreements over company-wide medical policies makes sense legally as well as financially. The contracts under which health plans are administered emphasize following the guidelines of the organization with whom the contract exists, and receipt of reimbursement for amounts paid is contingent on following the guidelines. Given the underlying business needs of companies that administer insurance, adhering to contracts and subsequently receiving reimbursement is an important practice.

**Scientific Literature**

Published literature is a respected and valued resource to include when developing medical policies. The process of publishing in peer-reviewed journals is rigorous and provides a filter through which only studies of merit will pass. With that being said, the quality of published studies must be assessed to determine how strongly they impact policy contents. At the most desirable end of the spectrum of published studies are randomized-controlled trials that occur at the population level. Case studies that report on a handful of patients are at the other end of the spectrum of desirability. The faults of studies that are underpowered or contain specific parameters can be alleviated when they are included in a meta-analysis. Meta-analyses combine several related studies to produce a report on a particular topic that is based on a large amount of observations.

In addition to peer-reviewed literature, research from companies whose mission is to carefully examine medical technologies is available for review when creating medical policies. Examples of such companies are Hayes, Inc. and Cochrane. An advantage of using information provided by companies such as these is that they routinely survey published literature on a variety of medical topics and are therefore able to provide current topic summaries. Because they devote a large portion of their resources to identifying and evaluating sources related to medical topics, information provided by these companies may be more comprehensive than the knowledge a small group of researchers could gather. Reviews produced by companies devoted to research contain less bias than literature provided by professional organizations or companies, which may have conflicts of interest with particular topics.

**Industry Standards**

Awareness of policies designed by other insurers provides a strategy to stay competitive in the business market while remaining vigilant of patient safety. Major health plans (defined as plans that cover at least 1 million lives) are often at the forefront of updating and revising policies. They maintain their prominence in the policy arena because of the ability to devote a relatively large amount of resources to researching, developing, and updating policies. Fortunately, many health insurers share their medical policies openly via the Internet, so learning about the practices of other insurers merely requires the ability to perform Internet searches. One example of a large insurer who provides publicly available medical policy is Aetna.\(^7\) By navigating to the Medical Clinical Policy Bulletin search page and entering appropriate key words, one is able to locate the most current medical policies developed by Aetna. Other large insurers, such as Blue Cross and Humana, also offer medical policies that are publicly available.\(^8,9\) As the Internet becomes a more integral part of daily life and information is expected by a growing portion of the population, open access to medical policies of insurers is expanding. When one begins to examine medical policies from multiple insurers side-by-side, universal themes begin...
to emerge. Identifying the themes can guide the process of developing and revising medical policy. Topics that are relevant for one's company can be incorporated into policy while a conscious decision can be made to exclude ideas that are not desired in the newly developed policy. The knowledge gained by examining policies from multiple insurers helps to ensure that a policy contains elements that are important for members and providers. Each company must consider the business implications, including potential competitive advantage and/or adverse selection of each policy choice.

**Professional Expert Consultation [and Consensus Statements]**

Individuals who work in the field to which a policy pertains provide important input based on hands-on experience with medical processes and technologies. In addition to providing basic knowledge about the treatment, professionals are aware of practices and problems that may be undocumented. One such example we have encountered is use of Dynasplint® in cancer patients. Review of other insurer’s policies, regulatory standards, and literature suggest that four months is an adequate length of time for coverage of use of this device to treat joint stiffness. However, a medical expert informed our policy committee that Dynasplint® is often used for longer than four months to treat some cancer patients. As a result of that expert input, our policy was modified to allow room for patients who medically require use of Dynasplint® beyond four months to receive coverage.

It is important to understand that, while valuable, the input of experts may be biased. A person who has devoted their life to studying a particular disease may unintentionally inflate the importance of that disease to an insured population. Experts may also have a financial interest in treatments or devices that are relevant for a policy, so a consideration of conflicts of interest may be necessary when soliciting expert input. It is important to balance expert input with the three other types of evidence to develop policies that are credible and efficacious (Exhibit 2). Without considering professional input, one risks developing a medical policy that is not practical and will result in future complications as people have difficulty adhering to the policy. Conversely, a policy based solely on expert input may not be justifiable using evidence other than a person's opinion, which is rarely enough to support a policy that is under scrutiny.

**In Addition to the Four Pillars - Work Flow Matters**

The approach to policy development described in this paper results in a medical coverage policy with strong core attributes. Additional steps are required to fully develop and implement a coverage policy. A financial analysis should be performed alongside the regulatory, literature, and industry research described above. Internal company stakeholders should have an opportunity to share their thoughts about policy content. Gathering company-wide input during the policy development process can help circumvent obstacles that may arise during the implementation process. Even after a policy has been implemented, the work of policy development continues as the impact of a policy on a company’s members and business operations is monitored. Revisions may be necessary for continued improvement to coverage policies.

As health systems gain prominence within the United States, the effect of medical coverage policies on various entities within a health system is becoming a factor of which insurers are increasingly aware. Ideally, entities within a health system will agree on which treatment is most effective, affordable, and tolerable for particular ailments. The convergence of providers, payers, and patients that is occurring alongside the emergence of health systems provides an ideal opportunity for increased dialogue between these entities and the creation of medical coverage policies that are ideal across the system.

**Conclusion**

Medical coverage policies can provide a solid foundation on which a health insurer can flourish. Because of the importance of strong, clear, and relevant medical policies, investing time to thoroughly research and prepare a strong policy is worthwhile for a company. The importance of utilizing a multidimensional approach for policy development has been described by others in reference to general policy development. Similarly, input from stakeholders throughout a health system can be considered when developing medical coverage policies. Examining policy decisions from multiple viewpoints can ultimately result in policies that lead to optimal patient care at reasonable costs. We have developed a methodical approach that includes four pillars of evidence on which to base medical policies for our health plans. This guided approach ensures that medical policies are sensible and relevant for the current health care industry.
References
A Closer Look at Personalized Treatment in the Management of Advanced NSCLC

H. Jack West, MD

For a CME/CEU version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary
The treatment of advanced non-small cell lung cancer (NSCLC) continues to change rapidly with the discovery of numerous genetic mutations driving tumor growth and subsequent development of therapy targeted at these growth factors. Multiple new agents have come to market and more are under study.

Key Points
• Ramucirumab in combination with docetaxel increases progression-free survival and overall survival by one month.
• Afatinib has demonstrated overall survival benefit in tumors with del 19 mutation.
• The combination of erlotinib with bevacizumab is becoming the new standard of care for EGFR mutation-positive patients
• Ceritinib is highly active for ALK-positive disease and has central nervous system activity, but causes adverse effect problems.
• Additional agents and molecularly defined populations are emerging quickly as having targeted therapies.

THERE HAS BEEN SIGNIFICANT PROGRESS during the last few years in the management of advanced non-small cell lung cancer (NSCLC). The focus of this article is what is new in first- and second-line therapy.

At the time of diagnosis, patients are now routinely tested for certain activating genetic mutations including endothelial growth factor receptor (EGFR) and echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase (EML4-ALK) because targeted therapy is available for these mutations. In patients who do not have any identified activating genetic mutation, which is about 85 percent of the NSCLC population, treatment is still chemotherapy based with or without the addition of vascular endothelial growth factor (VEGF) inhibitors which block angiogenesis.

Bevacizumab has been the only VEGF inhibitor available until the recent approval of ramucirumab (Cyramza®) for advanced NSCLC. It is a human IgG1 monoclonal antibody which binds to the VEGF receptor 2 and was previously FDA approved for treating gastric cancer. This agent has similar activity to bevacizumab. Ramucirumab in combination with docetaxel has led to about a 10 percent increase in overall response rate compared with docetaxel alone; the combination led to an improvement in progression-free survival (PFS) and overall survival (OS) of about a month. Although these results were statistically significant, there has been debate about the clinical significance of a one month change. It is also important to factor in toxicity. The addition of ramucirumab to docetaxel modestly increases rates of hematologic toxicities, stomatitis, and peripheral edema. The argument can be made that although the benefits are modest, the toxicities with this agent are not significantly worse than docetaxel alone. The cost of combination treatment also needs to be considered. Ramucirumab addition results in an extra $6,000 per treatment. Options for improving OS in later lines of therapy are very limited, especially for squamous NSCLC, but this agent is not a clear change in standard of care. Ramucirumab in combination with docetaxel
has been FDA approved for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or EML4-ALK genomic tumor aberrations should have disease progression on FDA-approved targeted therapy for these aberrations prior to receiving ramucirumab.

EGFR was the first genetic mutation driving NSCLC to be identified, and it occurs in about 9 percent of cases. The standard of care in the EGFR mutation-positive population has been to start an oral EGFR tyrosine kinase inhibitor (TKI). In the United States, this has been erlotinib, a reversible inhibitor. Afatinib, an irreversible inhibitor, was more recently approved. Afatinib in two studies was shown to improve response rate and PFS in those with EGFR mutations for first-line therapy.2,3 This had previously been shown with erlotinib and gefitinib, which is a reversible inhibitor not used in the U.S. An improvement in OS has not been shown with erlotinib or gefitinib. The afatinib trials found no survival difference for overall intention to treat population. In two trials, there was a trend toward improved OS with afatinib which was not statistically significant. In a combined analysis, in those patients with two activating mutations (del 19 and L858R on exon 21), there was a three-month improvement in OS that was statistically significant.3 The most striking finding was an 11-month difference in OS in the patients with del 19, whereas the L858R population actually had a trend in the other direction. Historically these two populations have been pooled but they appear to have remarkably different outcomes. Examination of data from the trials with erlotinib and gefitinib found the same trend.4 Overall, the L858R population does not respond as well to EGFR TKIs compared with the del 19 population. The OS benefit for del 19 patients is robust and impressive.

Sequence of therapy with EGFR TKIs may be relevant. The L858R population showed PFS benefit but worsened OS when crossed over from chemotherapy to EGFR TKI. It is not clear if an overall survival benefit would be shown with the other agents if all the data were combined and then split out by mutation status.

At this time, it is unknown if one EGFR TKI is any better than the others. A trial comparing afatinib to gefitinib has been completed but not yet published. At least in clinical use, afatinib causes more rash and stomatitis than erlotinib. Clinicians are awaiting publication of comparison trials to help determine the EGFR TKI of choice.

Even though it is effective therapy, patients do not always get an EGFR inhibitor after progression on chemotherapy. In countries where there is third-party coverage for the EGFR inhibitors, over 90 percent of patients receive this additional line of therapy. In countries without such reimbursement, especially China, just 52 percent get crossed over from chemotherapy to an EGFR inhibitor. This is a disturbing finding given that there are efficacious agents that patients are not receiving.

The combination of erlotinib with bevacizumab has been studied but has not been shown to be more efficacious than erlotinib alone for a wide population.5 A few groups do better with the combination including those who are Asian/Pacific Island-

---

**Exhibit 1: Concurrent TKI and Chemo-based Therapy**

<table>
<thead>
<tr>
<th>Disease Burden</th>
<th>D/C targeted Rx</th>
<th>Continue targeted Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKI sensitive</td>
<td>TKI resistant</td>
<td>TKI resistant</td>
</tr>
</tbody>
</table>

---
ers, never smokers, and, of course, those with EGFR mutation. Data support the idea that the combination may well be superior in terms of PFS (6.2 month difference) and possibly OS compared with erlotinib as a single agent in those with or likely to have EGFR mutation.\(^6\) It is notable that addition of bevacizumab increases cost of first-line treatment by approximately $120,000 for 16 treatments when considering acquisition cost alone.

It is a reasonable question to ask whether erlotinib and bevacizumab should be the new standard of care for EGFR mutation-positive patients. A 6.2 month difference in median PFS is impressive and many clinicians, including this author, will be moving to this combination regimen. The unfortunate reality is the threshold for clinical confidence may not be the same as the threshold for third-party coverage. Some may want to see a clinical confirmatory trial, perhaps conducted outside of Japan that shows an OS difference; a confirmatory trial in North America is ongoing.

Unfortunately, as promising as these targeted therapies are in terms of response rates of 70 percent and median PFS of 10 months or longer, the vast majority of patients with advanced NSCLC and genetic mutations will have progression after nine to 12 months. For a very long time, clinicians have had nothing constructive to offer patients with acquired resistance except standard approaches. It is worth stepping back to ask the question, how much progression means there needs to be a change in treatment? Often, treatment with targeted therapy leads to very impressive tumor shrinkage and when progression occurs it could be mild, such as a few millimeters in growth or a new small lung nodule. Many experts would advocate critical evaluation whether the progression seen merits a change in treatment. It may be that continuing the targeted therapy is better than stopping if the alternative is faster progression without it (Exhibit 1). Even when some progression

<table>
<thead>
<tr>
<th>Driver Mutation</th>
<th>Agent(s) with Documented Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation</td>
<td>erlotinib, gefitinib, afatinib</td>
</tr>
<tr>
<td>ALK rearrangement</td>
<td>crizotinib, ceritinib</td>
</tr>
<tr>
<td>HER2 mutation</td>
<td>trastuzumab, afatinib</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>vermurafenib, dabrafenib</td>
</tr>
<tr>
<td>MET amplification</td>
<td>crizotinib</td>
</tr>
<tr>
<td>ROS1 rearrangement</td>
<td>crizotinib</td>
</tr>
<tr>
<td>RET rearrangement</td>
<td>cabozantinib</td>
</tr>
</tbody>
</table>

Exhibit 2: Lung Cancer Mutation Consortium: Incidence of Mutations Detected

A mutation found in 54% of tumors completely tested

- No mutation detected
- KRAS 23%
- EGFR 18%
- EML4-ALK 9%
- MET AMP
- PIK3CA 2%
- BRAF 2%
- AKT1
- NRAS
- MEK 1

- KRAS 23%
- EGFR 18%
- EML4-ALK 9%
is occurring on targeted therapy, many of the cancer cells are still sensitive to the agent. Rapid progression has been shown when patients stop targeted therapy.7

Two leading options in the setting of resistance would be chemotherapy alone or chemotherapy plus targeted therapy. In the face of progression, it may be worth doing a combination of chemotherapy and the targeted agent. One approach used at Dana–Farber is to continue the targeted therapy and add local therapy such as radiation or surgery. One group reported that 45 percent of patients continued without significant progression for greater than three months and 21 percent required no further treatment change for over 12 months.8

This concept of specifically continuing an EGFR inhibitor beyond progression has been studied. In comparing chemotherapy plus gefitinib versus chemotherapy alone, the median PFS was 5.4 months in both arms but there was a difference in median OS (14.8 vs. 17.2 months), favoring not continuing the EGFR TKI.9 Although these results are still incomplete, what many clinicians have been doing may be a mistake and may even be harmful if the difference in OS proves to be statistically significant. Studies with other targeted therapies have not yet been published.

Another option that can be considered in the setting of resistance is to switch targeted agents. In a trial in the setting of acquired resistance with gefitinib or erlotinib, no improvement in OS was found when therapy was switched to afatinib.10 There has been excitement about the combination of afatinib with cetuximab in EGFR–mutated NSCLC refractory to EGFR TKI. In a small study, there was a 30 percent response rate and clinical benefit in 75 percent of those treated with the combination.11

One reason for the lack of success with EGFR TKIs in the setting of resistance is the development of new mutations. A T790M mutation occurs in about 70 percent of tumors with acquired resistance. Two new third-generation EGFR TKIs which appear to be active in patients who have a T790M mutation are under investigation.

AZD9291 is one of the third-generation EGFR TKIs under study. Early data appear promising with a 94 percent response rate in those with the T790M mutation and longer PFS than in those without the mutation. There was a 36 percent response in those who did not have the mutation but had not been exposed to an EGFR TKI before. The response in those without the mutation may just be an effect of receiving an effective therapy. Rociletinib is another agent under study for use in the T790M positive acquired resistance population. Early data from the clinical trials are positive and this agent appears to have a favorable adverse event profile with low rates of rash and diarrhea.

The other major mutation with targeted therapy is EML4–ALK. Crizotinib is standard targeted therapy for those with this mutation, but resistance typically occurs within six to 12 months of starting therapy. Overcoming this resistance is another area of active research.

The first second-generation agent to reach the market is ceritinib (Zykadia®).12 A major benefit of ceritinib over crizotinib is its efficacy for brain metastases. Unfortunately, ceritinib causes a much higher rate of toxicity than crizotinib. At the FDA approved dose, two-thirds of the patients will have increased liver function tests, nausea, diarrhea, and vomiting which leads to discontinuation in 10 percent of patients. It is important to reduce the dose early if these adverse effects occur. There is a temptation to use ceritinib in the first-line setting because the effectiveness appears greater than crizotinib, but it is only approved for the crizotinib refractory or intolerant population. It remains to be clarified whether ceritinib should be used as an earlier line of therapy. A study comparing crizotinib and ceritinib as first-line therapy followed by treatment of choice at progression would be valuable in answering this question. Several additional second-generation ALK inhibitors, including alectinib and AP26113, with much greater effect against native ALK and the many genetic mutations which lead to resistance, are under investigation.

Next-generation sequencing will be fast, accurate, relatively cheap, scalable, and able to detect heterogeneity. This will allow broad testing of patients for a wide array of mutations, unquestionably leading to massive scale identification of theoretically or anecdotally effective, highly expensive targeted therapies to try based on detected abnormalities. In addition to the more common mutations, there are many rarer mutations seen in 2 percent or less of patients with lung cancer (Exhibit 2). Many of these mutations already have targeted therapies, but they may not have been studied in advanced NSCLC.

Conclusion
The treatment of advanced NSCLC is evolving rapidly. Several new agents have been approved in recent years. Ramucirumab for second-line therapy has some documented activity that is statistically significant but is arguable whether a one-month difference in median OS is clinically significant. It is worth bearing in mind that improving OS is hard in advanced NSCLC. Afatinib has demonstrated OS benefit specific in tumors with
del 19 mutation; at this time, it is not known if the benefits seen with afatinib are unique to this agent. Bevacizumab significantly improved PFS in combination with erlotinib for EGFR mutation-positive disease and this combination is likely to become first-line therapy. Ceritinib is highly active for crizotinib-naïve or crizotinib-resistant ALK-positive disease and has central nervous system activity, but toxicity with this agent is challenging. Additional agents and molecularly defined populations are emerging quickly as having targeted therapies. The challenge in the future will be how broadly to define sufficient evidence of efficacy with narrow populations in an era of next-generation sequencing.

H. Jack West, MD, is Medical Director of the Thoracic Oncology Program at the Swedish Cancer Institute in Seattle, WA.

References
9. Mok T. Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after progression on first-line gefitinib: the Phase III, randomised IMPRESS study. ESMO 2014 Congress, Madrid, Spain, Abstract LBA2 PR.
MULTIPLE MYELOMA (MM) IS A CANCER OF the plasma cell characterized by excessive numbers of abnormal plasma cells in the bone marrow. There are approximately 24,000 new cases of MM annually in the United States. The clinical features of MM include bone pain, often with loss of height; constitutional weakness, fatigue, and weight loss; anemia; renal disease; infections secondary to neutropenia and hypogammaglobulinemia; hypercalcemia; hyperviscosity; and neurologic dysfunction secondary to spinal cord or nerve root compression.

MM accounts for 10 to 15 percent of hematologic cancers, making it the second most frequent hematologic malignancy after non-Hodgkin’s lymphoma. It is considered incurable with a current survival of four to six years after diagnosis. It is more common in men and African Americans with a median age at diagnosis of 70 years. Over 70 percent of patients diagnosed with MM had a detectable M protein (monoclonal gammopathy of unknown significance – MGUS) previously.

Depending on genetic markers, patients can be divided into two groups – high and low risk (Exhibit 1). Those with low-risk features have an expected survival greater than six to seven years compared with two to three year survival for those with high-risk features.

Bone marrow stem cell transplant (SCT) is the preferred treatment if the patient qualifies. Previously, chemotherapy with an alkylating agent and corticosteroid-based therapy was used first followed by SCT. The new treatment paradigm includes novel agents in induction, followed by SCT, consolidation, and maintenance therapy.

The goal of treatment is complete or partial response. A complete response is defined as no M protein on immunofixation, absence of soft tissue plasmacytomas, and less than 5 percent plasma cells in bone marrow. A stringent complete response includes those same items plus a normal free light chain ratio and absence of clonal cells in the bone marrow.

Novel agents for MM include immunomodula-
Journal of Managed Care Medicine  |  Vol. 18, No. 3  |  www.namcp.org

...tors [thalidomide (Thalomid®), lenalidomide (Revlimid®), and pomalidomide (Pomalyst®)] and proteasome inhibitors [bortezomib (Velcade®) and carfilzomib (Kyprolis®)]. Other treatment options include chemotherapy, novel agents in combination with chemotherapy combinations, salvage autologous stem cell transplant, allogeneic stem cell transplant, and clinical trials.

In patients who are eligible for SCT, induction is accomplished with combinations of proteasome inhibiting (PI) and/or immune modulatory (ImID) agents. Bortezomib, a proteasome inhibitor, and dexamethasone results in greater progression-free survival (PFS) compared with chemotherapy and has become the standard regimen. Lenalidomide, an immune modulating agent, combined with dexamethasone also provides benefit over chemotherapy. After the SCT, patients are given maintenance therapy. Those who are not eligible for SCT undergo induction chemotherapy with various agents.

Relapse or progression after treatment is common in MM. Exhibit 2 lists the markers of relapse. For those who relapse after initial treatment, primary therapy can be repeated if relapse occurred longer than six months since completion and there are no other contraindications. Exhibit 3 outlines a suggested treatment approach.

Carfilzomib and pomalidomide are two newer agents that are FDA approved for the relapsed/refractory setting. Carfilzomib, a selective irreversible proteasome inhibitor, has been studied in relapsed/refractory MM. Given intravenously, it resulted in a 23.7 percent overall response rate in a heavily pretreated population. The response lasts a median of 3.7 months with overall survival of 13.6 months. The most commonly reported adverse effects with carfilzomib are thrombocytopenia and anemia. The major distinction from bortezomib, a reversible proteasome inhibitor, is a lower rate of peripheral neuropathy.

Pomalidomide, an immunomodulatory lenalidomide analogue, was FDA approved for relapsed/refractory MM in early 2013. When studied in a heavily pretreated population, 31 percent of patients achieved an overall response rate with pomalidomide in combination with dexamethasone. Progression-free survival was four months compared with 1.9 months for dexamethasone alone. Overall survival was also longer with the combination (12.7 vs 8.1 months). Like lenalidomide, cytopenias are the most frequent adverse effects of this agent. Pomalidomide is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on therapy or within 60 days of completion of the last therapy.

Salvage therapy is indicated when there is disease progression following allogeneic or autologous stem cell transplantation, primary progressive disease following initial autologous or allogeneic stem cell transplantation, progressive or relapsing disease after initial induction in patients not eligible for stem

Exhibit 1: Risk Factors in MM

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14); t(6;14)</td>
<td>t(4;14); t(14;16); t(14;20)</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>Del(17p)</td>
</tr>
<tr>
<td>Normal cytogenetics/FISH</td>
<td>Del(1p-) and amp 1p by FISH</td>
</tr>
<tr>
<td></td>
<td>Del(13) by cytogenetics</td>
</tr>
<tr>
<td></td>
<td>Hypodiploidy</td>
</tr>
<tr>
<td></td>
<td>GEP-high-risk signature</td>
</tr>
<tr>
<td></td>
<td>Elevated LDH</td>
</tr>
<tr>
<td></td>
<td>B2 microglobulin</td>
</tr>
</tbody>
</table>

OS = overall survival
t = translocation
FISH = Fluorescence in-situ Hybridization
del = deletion
GEP = gene expression profile
LDH = lactate dehydrogenase
B2 = beta-2

16  Journal of Managed Care Medicine  |  Vol. 18, No. 3  |  www.namcp.org
cell transplantation, or progressive disease following second- or third-line therapy. Salvage therapy is decided on based on prior responses and the duration of response, completion of prior regimen, organ dysfunction which might rule out particular medications, age, and prior transplants.

Numerous supportive therapies are also required to manage MM. Bone disease may require analgesics for bone pain and/or radiotherapy for palliation. Nonsteroidal anti-inflammatory agents should be avoided because of renal effects. Vertebroplasty or kyphoplasty are options for persistent pain. Bisphosphonates are widely used in the management of lytic bone lesions in MM because they inhibit bone resorption by suppressing osteoclast activity. Anemia is common with MM and is typically treated with transfusions and/or blood cell growth factors. An erythropoietin trial can be considered in patients with symptomatic anemia if the hemoglobin is less than 12 g/dL, which is the target of treatment and should not be exceeded. Erythropoietin can also be considered for the non-symptomatic anemia patient if their hemoglobin has fallen below 10 g/dL. Hypercalcemia is treated with rehydration and bisphosphonates. Rehydration and plasmapheresis can be used to manage renal dysfunction and hyperviscosity. Because of their risk of infection, MM patients should receive an annual influenza vaccination.

Adverse effects of treatment also have to be managed. Peripheral neuropathy is a relatively common adverse effect of bortezomib. The pain from neuropathy can be managed with agents such as tricyclic

---

**Exhibit 2: Definitions of Relapse**

- New plasmacytoma or new bone metastatic site
- Increase in bone/plasmacytoma site of > 1cm
- Hypercalcemia
- Progressive anemia
- New or recurrent renal dysfunction
- Reappearance/rise in M protein level or doubling of M protein at 2 consecutive time points

**Exhibit 3: Suggested Treatment Approach for Patients with Relapse or Progressive Disease**

- **Patients with relapse or progressive disease**
  - Transplant-eligible patient
    - Autologous stem cell transplantation
    - Progressive disease
      - Salvage therapy on or off clinical trial
      - Additional autologous stem cell transplant
      - Allogenic stem cell transplant on clinical test
  - Transplant-ineligible patient
    - Salvage therapy on or off clinical trial
    - Palliative care

- **Transplant-eligible patient**
  - Autologous stem cell transplantation
  - Progressive disease

- **Transplant-ineligible patient**
  - Salvage therapy on or off clinical trial
  - Palliative care
antidepressants. Cytopenias, including neutropenia, thrombocytopenia, and anemia, are common with lenalidomide and thalidomide.

Thrombosis is common with MM and the risk is increased by high dose dexamethasone. All patients with MM should be on at least aspirin. For those with two or more risk factors, warfarin or low molecular weight heparin is recommended (Exhibit 4).3

**Conclusion**

Regimens containing lenalidomide or bortezomib have shown efficacy in relapsed/refractory myeloma. Selection of regimens should be a rational process, based upon patient characteristics. Carfilzomib and pomalidomide are useful additions in the relapsed/refractory setting. Many other agents are being assessed in ongoing and planned clinical trials. Supportive care is an important aspect of the care of these patients.

George Somlo, MD, is Professor, Department of Medical Oncology and Therapeutics Research with the City of Hope Comprehensive Cancer Center in Duarte, CA.

**References**


OBESITY IS A CHRONIC DISEASE WITH AN altered physiological and metabolic state which results in increased morbidity and mortality. Like any chronic disease, obesity has genetic determinants. Hundreds of obesity susceptibility genes have been identified which each confer a small increase in relative risk of the disease. Individuals who inherit larger subsets of these genes will have greater risk of obesity in a given environment. In addition to genes, biological factors, environment, and behavior all contribute to body weight (Exhibit 1). Many times obesity is described as a simple thermodynamic equation where there is an imbalance between energy intake and energy expenditure. It is important to remember that in the middle of that imbalance is a human, a biological and behavioral interface which determines how much energy intake will be stored as fat and how much energy expenditure will translate into energy loss and thus weight loss.

Body mass index (BMI) is used to classify the severity of excess body adiposity. The World Health Organization defines overweight as BMI ≥25 kg/m² and obese as BMI ≥30 kg/m². Based on this definition, nearly 70 percent of American adults are overweight or obese.

In terms of increased mortality, there are numerous complications of excess weight (Exhibit 2). The major constellation of complications is cardiometabolic syndrome. In obesity, fat tissue can be inflamed (i.e., “sick fat”) and function abnormally. Abnormal secretion of adipocyte factors leads to cardiometabolic syndrome (insulin resistance, glucose intolerance, hypertension, atherosclerosis, and atherogenic dyslipidemia). There are many adipocyte factors including free fatty acids, leptin, adiponectin, resistin, various interleukins, angiotensinogen, and tumor necrosis factor.

Another area that is dysregulated in obesity is energy or food intake. Food intake is regulated by a number of hormones which are secreted from and

Summary

A great deal has been learned about the pathophysiology of obesity in the last decade and new treatments have come to market that are impelling the evolution of obesity treatment. Benefits and risks of therapy and cost-effectiveness are increased when medical and surgical interventions are targeted to those who would benefit the most - obese patients with complications.

Key Points

• It is not safe or fiscally feasible to treat everyone who is obese with medications or surgery.
• A complications-centric model is needed in the management of obesity as opposed to decisions based primarily on BMI level.
• Risk staging and assessment of obesity-related complications can identify those patients who will most benefit from weight-loss therapy.
• A 10 percent weight loss is sufficient to improve many of the complications of obesity.
interact with the periphery (stomach, fat, intestine, and pancreas), hypothalamus, and the higher cortical centers. The peripherally secreted hormones interact with the hypothalamus to control food intake to maintain normal metabolic homeostasis. Within the hypothalamus, there is an orexigenic pathway that promotes eating and an anorexigenic pathway that reduces intake. In obesity, hormone secretion is geared toward eating more and maintaining a higher equilibrium body weight. This is the reason that many patients fail over the long term with lifestyle interventions. Overall, in obesity, biology protects against weight loss and maintains a high body weight. That is why pharmacotherapy and bariatric surgery need to be used to “trick” the pathways so long-term weight loss can occur.

Obesity is not a lifestyle choice. Greater than 90 percent of obese persons have attempted to lose weight and over 50 percent are currently trying to lose weight. Those who are obese suffer significant discrimination in employment, college admission, romance, medical care, and income.

Treatment of obesity is a three-prong approach of lifestyle intervention, pharmacotherapy, and bariatric surgery. Evidence-based lifestyle interventions include a reduced calorie diet, a healthy meal plan to which the patient can culturally adhere with, very low calorie diets, meal replacements (at least once a day), behavioral intervention (education, motivational interviewing, portion control, resolve psychological problems, etc.), increased voluntary physical activity and reduced sedentary behaviors. These interventions can be put together in a structured program of varying intensities. The obese need the skills and behavior change to induce and maintain weight loss. Lifestyle intervention works and can reduce the progression to diabetes by 58 percent. Early intervention has long-lasting benefits in preventing diabetes. Intensive lifestyle intervention has also been shown to be beneficial, even if the patient already has diabetes. Importantly, lifestyle intervention has to be continued to be beneficial.

Medications help patients who are struggling to achieve health benefits through weight loss and are used as an adjunct to a lifestyle intervention program. The medications essentially reduce appetite to allow patients to be adherent with reduced calorie diets. Addition of a weight-loss medication consistently achieves greater weight loss than that achieved by the lifestyle intervention alone. Long-term use of weight-loss medications can help sustain weight loss. The American Society of Bariatric Physicians, American Association of Clinical Endocrinologists (AACE), and the American Heart Association/American College of Cardiology/The Obesity Society obesity guidelines all advise use of medications for patients who have sufficient health risk, not purely for cosmetic reasons.

Medication is indicated for patients with BMI 25 to 29.9 with at least one obesity-related complication or with BMI ≥ 30. Medications vary regarding efficacy, warnings, cautions, and side effect profiles; this is important for individualization of therapy. Additional data are required for optimal use of medications in long-term treatment. Obesity is a lifelong disease and requires long-term treatment, which may include long-term medication use, and follow-up.

Exhibit 3 lists the available weight-loss agents.
The recently approved agents work within the brain to suppress appetite. Orlistat is the one agent which is different; it blocks fat absorption in the gut. Lorcaserin is a serotonin receptor agonist that has been shown to reduce weight over two years of therapy and is fairly well tolerated. The combination of phentermine and topiramate has been shown effective for weight loss over two years but needs to be titrated slowly to improve patient tolerance. This combination targets two different areas of the brain for reducing food intake. Women of childbearing potential need to have a negative pregnancy test because topiramate, when used in higher doses for seizures, has teratogenic effects. A combination product with naltrexone and bupropion extended release was approved in 2014. Like the other combo, this product works in two different areas of the brain. The product should not be used in patients who require opioid therapy chronically because the nal-trexone will block the effect of narcotics.

Exhibit 4 compares the efficacy of the weight-loss medications from various trials. Phentermine/topiramate appears to be the most efficacious, but all can lead to sufficient weight loss to have a positive metabolic benefit.

The various bariatric surgery procedures are effective in leading to significant weight loss. Bariatric surgery has been shown to reduces mortality in severely obese patients.

Given the high rate of overweight and obesity in the United States, the health care system cannot afford to treat all patients and not all patients need treatment just based on their weight. Thus, therapeutic decisions need to be made to balance efficacy, safety, and cost; optimize benefit to risk ratio; achieve best outcomes; and provide cost-effective care. At this time, BMI typically determines the indication for treatment (i.e., most guidelines are BMI centric). A complications centric guideline has been developed which uses complications and BMI to determine therapy. This approach is a medical model to treat disease; essentially weight loss is being used as a therapeutic modality to treat weight-related complications. Five to 15 percent of starting weight loss was sufficient to have a metabolic benefit.
body weight is a threshold amount of weight loss for preventing complications. For example, weight loss of 10 percent reduces risk of developing diabetes. Weight loss over 10 percent does not provide any additional risk reduction. For other comorbidities, the more the weight loss, the better for reducing HA1C (in those who already have diabetes), blood pressure, lipids, and sleep apnea.

There are obese patients who are metabolically healthy and those who are metabolically unhealthy. Those who are metabolically unhealthy have insulin resistance and high risk for developing T2DM cardiovascular disease secondary to cardiometabolic syndrome. Those who do not have underlying insulin resistance, even if overweight, have a very low risk for T2DM and cardiovascular disease. Overall, insulin resistance is a more important contributor than obesity to cardiovascular risk. Because of this difference in risk, targeting those who are metabolically unhealthy for weight loss with more aggressive treatment is the best strategy.

Identification of those at higher risk of T2DM and CV disease can be done in different ways. The easiest is to identify those with the clinically identifiable risk states of prediabetes or cardiometabolic syndrome. Several indices including the Framingham Risk Score, the Reynolds Risk Score, and the ADA Diabetes Risk Score are also available. More recently commercial diagnostic products including PreDx® (Tethys Bioscience), LP-IR score® (Liposcience), and Quantose IR (Metabolon) have become available. Additionally clinical staging paradigms, Edmonton Obesity Staging System (EOSS) and Cardiometabolic Disease Staging (CMDS) can be used. The CMDS (Exhibit 5) stages obese patients into four groups with increasing risk. Cumulative incidence of diabetes is almost flat in stage 0 patients but increases incrementally from stage 1 through stage 3 over time. Mortality also increases with increasing stage. The simple clinical information in the CMDS can be used to select interventions according to risk. Because of the significant increased risk in stage 2 and 3, managed care may decide that it would be cost effective to use anti-obesity medications in this group.

The AACE has added weight-loss treatments into their prediabetes treatment algorithm. The aim is to not only prevent the development of diabetes but also to improve cardiovascular risk factors. Additionally, weight-loss medications have been added into the diabetes treatment algorithms. All of the weight-loss medications have been studied in patients with diabetes, and the benefits are consistent with lower A1C, less need for conventional diabetes medications, and lower blood pressure and lipids.

BMI-centric guidelines have treatment indications based on BMI with the goal of therapy being to lose a given amount of weight (e.g., 5 to 10%). All patients who meet the BMI criteria are treated. In a complications-centric model, treatment indi-
cations are based on risk, presence, and severity of obesity-related complications. The goal of therapy is to treat or prevent the complications. Using a complication-centric approach, targets the more aggressive treatments to those patients who will derive the most benefit.

There is a paradox in obesity management. There are more effective tools to treat obesity than ever before; yet, overweight, obesity, and the resulting suffering and social costs of the disease are mounting.

There is limited availability and access to many effective therapies including medications and surgery. The uptake of weight-loss medications has not been great, mainly because they are not extensively covered by managed care. In an attempt to resolve this paradox, the AACE sponsored a consensus conference on obesity in 2014. The conference brought together biomedical, government/regulatory, health care, organizations, research, and education stakeholders to answer five questions: 1) What is obesity?, 2) What

---

**Exhibit 4: Comparative Efficacy of Weight-Loss Medications**

All data placebo-subtracted, maximal dose, ITT-LOCF, 1 year, unless otherwise indicated

<table>
<thead>
<tr>
<th>Medication</th>
<th>% Weight Loss from Baseline after 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine/Topiramate</td>
<td>10</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>9</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>8</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>7</td>
</tr>
<tr>
<td>Orlistat</td>
<td>6</td>
</tr>
<tr>
<td>Phentermine</td>
<td>5</td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>4</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>3</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>2</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>1</td>
</tr>
<tr>
<td>Orlistat</td>
<td>0</td>
</tr>
</tbody>
</table>

**Exhibit 5: Cardiometabolic Disease Staging (CMDS)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Risk Factors (healthy obese)</td>
</tr>
<tr>
<td>1</td>
<td>1 or 2 Risk Factors (elevated waist circumference, blood pressure, triglycerides, low HDL-c)</td>
</tr>
<tr>
<td>2</td>
<td>Metabolic Syndrome OR Prediabetes</td>
</tr>
<tr>
<td>3</td>
<td>2 or more out of 3: Metabolic Syndrome, IFG, IGT</td>
</tr>
<tr>
<td>4</td>
<td>End-Stage Cardiometabolic Disease</td>
</tr>
</tbody>
</table>

HDL-C, high density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CVD, cardiovascular disease
options are available for obesity management?. 3) What is the optimal use of therapeutic modalities?. 4) Can the optimal framework be cost-effective?, and 5) What are the knowledge gaps and how can they be filled? One of the concepts that emerged from this conference was that the current diagnosis of obesity (based on BMI) was inadequate, not actionable, and not medically meaningful.25 This was impeding action and preventing people from rallying around this disease to affect it. A meaningful, actionable diagnosis is needed that reflects primary, secondary, and tertiary prevention. Primary prevention is to prevent obesity, secondary treats obesity to prevent disease complications and tertiary treats obesity to ameliorate disease complications. Diagnosis must integrate two components of anthropometric measure (BMI) and an indication of the degree to which excess body weight is affecting the individual (i.e., presence and severity of obesity-related complications). Thus, those with normal weight, in our obesogenic society, need primary prevention. Those who are overweight or obese with no obesity-related complications need secondary prevention. This conference defined obesity stage 1 as a BMI greater than or equal to 25 kg/m2 and presence of one or more mild-moderate obesity-related complications and obesity stage 2 as the same BMI but one or more severe obesity-related complications. Those in stage 1 or 2 require tertiary intervention. Stage 1 treatment would be lifestyle changes and medication and stage 2 would include consideration of bariatric surgery.

Conclusion

Nearly 70 percent of American adults are overweight or obese, and it is not safe or fiscally feasible to treat everyone with medications or surgery. A complications-centric model is needed in the management of obesity as opposed to decisions based primarily on BMI level. Risk staging and assessment of obesity-related complications and obesity stage 2 as the same BMI but one or more severe obesity-related complications. Those in stage 1 or 2 require tertiary intervention. Stage 1 treatment would be lifestyle changes and medication and stage 2 would include consideration of bariatric surgery.

W. Timothy Garvey, MD, FACE, is Professor and Chair, Department of Nutrition Sciences at the University of Alabama at Birmingham and Director, UAB Diabetes Research Center.

References


New Insights into the Diagnosis and Management of Venous Thromboembolism

Michael Miller, MD, FACC, FAHA, FNLA
For a CME/CEU version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary
Treatment of venous thromboembolic events is changing with the availability of novel anticoagulants. Because these agents have advantages related to bleeding and dosing, they are beginning to replace low molecular weight heparin and warfarin for acute treatment and warfarin for secondary prevention. Because the novel agents are not ideal, there are still situations where the older agents are preferred.

Key Points
- Novel anticoagulants have been shown to be noninferior for treatment of VTE compared to traditional treatment.
- The novel anticoagulants have advantages and disadvantages compared with warfarin.
- There is a trend toward using the novel agents for VTE treatment.
- The older agents are still preferred in certain situations.

DEEP VEIN THROMBOSIS (DVT) AND PULMONARY embolism (PE) are collectively referred to as venous thromboembolism (VTE). Each year five million people experience venous thromboembolism worldwide.¹

One in 10 of the more than two million Americans developing DVT annually will die from pulmonary embolism (PE). These 200,000 patient deaths represent more annual deaths than those from breast cancer, AIDS, and traffic accidents combined. Pulmonary embolism is the most common preventable cause of death in the hospital; an estimated 10 percent of inpatient deaths are secondary to PE. Pulmonary embolisms also result in significant costs and morbidity (recurrence, post-thrombotic syndrome, chronic pulmonary artery hypertension). Not only do patients with VTE suffer a 30 percent cumulative risk for recurrence, they are also at risk for the potentially disabling post-thrombotic syndrome. Post-thrombotic syndrome develops in 25 to 40 percent of those who have DVTs, and it leads to permanent disability for 15 million Americans.

Virchow’s triad (Exhibit 1) describes the three main factors that predispose people to thrombosis. Patients can have a provoked or unprovoked VTE event. Pregnancy or leg trauma are examples of states that can provoke an event. Unprovoked VTE is an event without a clear risk factor. Several factors predict risk of recurrence. Primary among these are an unprovoked event and cancer. Secondary factors are a proximal DVT and a second or subsequent VTE. Additional factors that have been investigated for predicting risk are antiphospholipid antibody, male gender, hereditary hemophilia, and residual thrombosis in proximal veins. Exhibit 2 illustrates the risk of recurrence after anticoagulation discontinuation.² DVT recurs in approximately 30 percent of patients after anticoagulation is stopped. It is important to identify the cause of an event because that will help determine the risk of recurrence and the choice of treatment duration to prevent recurrence.

Acute treatment of a VTE episode requires anticoagulation; this has traditionally been done with...
a parenteral anticoagulant. The American College of Chest Physician guidelines recommend low molecular weight heparin (LMWH, once daily) or fondaparinux (Arixtra®) in patients with acute DVT of the leg; but the guidelines have not been updated to include the novel anticoagulants discussed later.2 Local considerations such as cost, availability, and familiarity of use dictate the choice between fondaparinux and LMWH. Secondary prevention is started at the same time as the parenteral anticoagulant. This has traditionally been done with warfarin. The parenteral anticoagulant is discontinued when the international normalized ratio (INR) has been over 2 for more than 24 hours. Until the development of the novel anticoagulants this was the standard of care and is currently still used in the majority of hospitals in the United States. Since the availability of novel anticoagulants, there is a trend toward using these agents.

The duration of secondary prevention anticoagulation is influenced largely by whether the clot was provoked or idiopathic/spontaneous (Exhibit 3). Unprovoked events and multiple events will prompt lifetime use of an anticoagulant. Particularly when indicated for long-term use, warfarin can be difficult to manage and causes sig-
significant bleeding adverse effects. Ideal candidates for warfarin are patients who have renal insufficiency and cannot take the novel agents, are taking a stable dose of warfarin and do not find INR testing burdensome, have access to a self-testing machine, or are concerned about the lack of an evidence-based reversal strategy with the novel agents.

Novel anticoagulant therapy (NOAC) includes multiple agents approved in the last few years with the hope of replacing warfarin and do not find INR testing burdensome, have access to a self-testing machine, or are concerned about the lack of an evidence-based reversal strategy with the novel agents.

Novel anticoagulant therapy (NOAC) includes multiple agents approved in the last few years with the hope of replacing warfarin. Rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa®) all target factor Xa, while dabigatran (Pradaxa®) targets factor IIa. Exhibit 4 compares warfarin and the NOAC agents. In trials evaluating the NOACs for acute treatment of VTE, all four were noninferior to the LMWH/warfarin combination. They also resulted in fewer fatal bleeding events compared with LMWH/warfarin, especially apixaban; but, rates of gastrointestinal bleeding were higher. These agents probably result in a reduced hemorrhagic stroke rate compared with warfarin.

There are significant clinical challenges with the novel agents. No validated tests to measure anticoagulation effect, no established therapeutic range, and no antidote are currently available. Antidotes for bleeding incidents are under investigation. Assessment of compliance is more difficult than with warfarin because there is nothing to objectively measure such as INR. There is potential for unknown long-term adverse events. These agents are more expensive based on acquisition costs, but clinicians must consider overall cost-effectiveness. There is not enough data on the use of NOACs in select patient groups. This includes severe PE or extensive DVT, severe renal or hepatic insufficiency, and high risk of bleeding. Lastly, there is a lack of head-to-head studies comparing the new agents.

**Conclusion**

VTE events are costly and deadly. The novel anticoagulants have been shown to be noninferior for treat-
ment of VTE compared to the combination of LMWH and warfarin and have some significant advantages. The number needed to treat for clinical benefit are large with a probable reduced hemorrhagic stroke rate and reduced rate of fatal bleeding events compared to the traditional combination. The novel agents cause a higher incidence of gastrointestinal bleeds and currently have a significant acquisition cost.

Michael Miller, MD, FACC, FAHA, FNLA is a Professor of Cardiovascular Medicine, Epidemiology and Public Health at the University of Maryland School of Medicine in Baltimore, MD.

References
What’s keeping us from getting somewhere in pancreatic cancer?

Merrimack is actively working to discover and develop new therapies that address the challenges in this disease.

What's keeping us from getting somewhere in pancreatic cancer?

The Biology of Pancreatic Cancer is Complex

Pancreatic Cancer Cells

Compressed Vasculature

Immune-suppressive cells

Extracellular Matrix

Stroma

Pancreatic Cancer Cells

Merrimack is actively working to discover and develop new therapies that address the challenges in this disease.

References:

©2015 Merrimack Pharmaceuticals, Inc. All rights reserved. Printed in USA. June 2015. PP-VDS-US-0023A
HEMOPHILIA IS A CONGENITAL BLEEDING disorder due to deficiency or absence of a coagulation cascade protein. Hemophilia A is a factor VIII deficiency, whereas hemophilia B is a factor IX deficiency but the clinical phenotypes are indistinguishable.

Hemophilia is not common; it only affects about 20,000 Americans. There are more than 500,000 hemophiliacs worldwide. Hemophilia affects all racial and socioeconomic groups equally. As shown in Exhibit 1, the majority of cases are found in the 2 to 19 year age group.1

Genes for factors VIII and IX are located on the X chromosome. Thus, females are carriers and males are affected. There are also high rates of spontaneous mutations; approximately 30 percent of those affected have no family history of hemophilia.

Patients can have mild, moderate, or severe factor deficiency; the severity of bleeding tendency depends on the degree of factor deficiency (Exhibit 2). The major complications of hemophilia are hemarthrosis, deep muscle bleeds, intracranial bleeds, and soft tissue bleeds. Hemarthrosis, primarily involving the ankles, knees, and elbows, is the most common complication and results in joint damage (Exhibit 3). Forty-five percent of those with hemophilia experience their first joint bleed within the first year of life.2,3 Ninety percent have at least one joint bleed by 4 years of age. Ninety percent of those with severe hemophilia have chronic degenerative changes involving at least one joint by age 25. Around forty percent of those with hemophilia report restricted physical activities due to arthropathy.

Since 1968, hemophilia has been treated with factor concentrate infusion. Plasma derived and recombinant factor VIII and factor IX concentrates are available. Because of better screening, there have been no documented cases of viral transmission from factor concentrates in more than 25 years. Factor replacement can be given by self-infusion; the goal of therapy is for every child with hemophilia to learn self-infusion.

Factor replacement is given on demand or as pro-
phylaxis. On demand is treatment of bleeds with factor replacement when bleeds occur. This method is good at stopping bleeds after they start, but does not prevent bleeds. The benefits of on demand administration include fewer infusions, greater patient convenience, and possible lower annual factor consumption and cost. The problems with on demand use include bleeds are not prevented, joint damage is ongoing, end-stage arthropathy is unavoidable resulting in long-term functional disability, and bleeds may become more difficult to control over time. Prophylaxis consists of regular factor administration to prevent bleeds from occurring with a goal of no bleeds. Prophylactic therapy requires frequent infusions, venous access, and time commitment for patients but has been proven to prevent bleeds. Preventing bleeds keeps joints healthy and may delay progression of existing arthropathy. It also provides protection from traumatic and unexpected bleeds.

Prophylactic therapy in children was pioneered in Sweden in the 1960s and became standard of care with introduction of recombinant factor concentrates in the 1990s. It is initiated after the first joint bleed or before age 3. In children, prophylactic therapy has been shown to decrease bleeding frequency and prevent joint damage.

In adults, prophylactic therapy is increasingly used, with support from recent clinical trials. It decreases bleeding frequency and improves quality of life but has not been shown to definitively prevent progression of arthropathy. Children who enter adulthood on regular prophylaxis, with preserved joints, are usually kept on prophylaxis.

Hemophilia carries a significant economic burden with factor concentrates accounting for the majority of the cost of treating hemophilia. Routine prophylaxis for severe hemophilia A, dosed at 25 to 40 IU/kg three times per week, can annually cost an estimated $78,000 to $124,800 for a 5-year-old child and $312,000 to $499,200 for an adult.

There are no comprehensive studies or data to compare the cost-effectiveness of routine prophylaxis to on demand factor use. Factor replacement is very expensive, but so are the long-term costs associated with poorly managed hemophilia.

Unfortunately, some hemophilia patients’ immune systems “see” factor VIII or factor IX as a foreign protein leading to production of antibodies.
Antibodies (inhibitors) directed against factor VIII or factor IX neutralize the procoagulant effect and render standard treatment useless. Development of inhibitors is currently the most serious complication of factor replacement therapy.

Typically inhibitors are seen in those with severe hemophilia but may occur in those with mild or moderate hemophilia, usually after intense factor exposure related to trauma or surgery. Luckily, development of inhibitors is no longer associated with increased mortality. However, in those with inhibitors, bleeding is more difficult to control, devastating joint disease and disability can occur, and major clinical and economic challenges are presented.

Treatment of inhibitor patients is very complicated, extremely expensive, and absolutely requires hemophilia treatment center expertise because these patients are rare and treatment options have significant limitations. The two treatment options are immune tolerance therapy and bypassing agents.

With immune tolerance therapy, factor concentrate is given regularly over a period of time until the body is trained to recognize the treatment product without reacting. When successful, the inhibitors disappear and the patient’s response to factor concentrates returns to normal. The majority of people who undergo this therapy will see an improvement within 12 months, but more difficult cases can take two years or longer. Immune tolerance therapy costs approximately $1 million per patient and is effective.
in 70 percent, but the effects of not trying to overcome inhibitors can be devastating, both clinically and economically.

Bypassing agents, such as activated prothrombin complex concentrates (aPCC) and recombinant factor VIIa (rFVIIa), are used to treat acute bleeding in people with high antibody titers. These agents also have incomplete (75 to 90%) and unpredictable efficacy. No standard laboratory monitoring for this therapy exists and thrombosis is a real risk.

Long-acting factor concentrates have been in development for several years. Extended half-lives result in similar or improved protection from bleeds with fewer infusions. For example, long-acting factor IX has a half-life of 80 to 90 hours compared with 18 to 24 hours for the non-long-acting product. This results in an initial dosing regimen for long-acting factor IX of every seven to 10 days compared with every three days. Several companies have these long-acting factors in development. The first to market were Alprolix® (Factor IX, March 2014) and Eloctate® (Factor VIII, June 2014), which are Fc fusion products where the factor molecule is linked to a protein fragment, Fc, which is found in antibodies. Prophylaxis with these long-acting factors has been shown to significantly reduce bleeds. So far, these long-acting factors appear safe. No anaphylaxis, inhibitors, or thrombotic events have been reported.

With the long-acting factors, it is known they are highly effective for prophylaxis, acute bleeds and surgery with safety comparable to existing products. Their longer half-life allows for fewer infusions to maintain protective factor levels. It is expected that these long-acting factors will result in improved adherence for a greater number of those with hemophilia. It is yet to be determined how other long-acting products in the pipeline will compare to those already approved.

In pediatrics, assuming no new safety concerns appear, less frequent dosing may eliminate the need for central venous catheters. If fewer doses are required, then more doses will actually be received so children on prophylaxis should be better protected.

The use of long-acting factors in adults is a more complicated discussion because the adult population is heterogeneous and will require an individualized approach. Exhibit 4 notes the group of patients most likely to benefit from a switch to long-acting factors. Overall, the long-acting factor products have distinct advantages, but therapeutic and economic implications are not yet fully defined. Managed care can anticipate increasing and widespread use of the long-acting factors.

New in treatment of hemophilia is recombinant porcine factor VIII (Obizur®). Baxter received FDA approval in October 2014 for use in adults with acquired hemophilia; it is hoped the indications for this agent will expand to congenital inhibitor patients.

Gene therapy remains an area of active investigation with clinical trials ongoing. It works in mice and dogs but the scale up to humans has been a challenge; progress is being made. Gene therapy is still expected to be a clinical reality, but not anytime soon.

**Conclusion**

Hemophilia is a rare condition, with a large economic burden on our health care system. Great progress in the management of hemophilia has been made, but there is still work to do. Better treatments for those with inhibitors are desperately needed. New long-acting factor products have distinct advantages, but therapeutic and economic implications are not yet fully defined.

Mark T. Reding, MD, is an Associate Professor of Medicine in the Division of Hematology, Oncology, and Transplantation and Director, Center for Bleeding and Clotting Disorders at the University of Minnesota Medical Center in Minneapolis, MN.

**References**

PULMONARY HYPERTENSION (PH) IS AN observation of elevated pulmonary pressures which encompasses a diverse group of conditions that lead to elevated arterial and/or venous pulmonary pressures. PH is defined hemodynamically as mean pulmonary artery pressure (PAP) greater than 25 mm Hg at right heart catheterization but that does not reveal etiology, pathophysiology, or clinical significance of the increased pressures. PH is very common and can be classified into five groups: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH associated with lung disease, PH associated with chronic thromboembolic disease, and PH with unclear multifactorial mechanisms. The World Symposium on PH provides management guidelines covering diagnostic criteria, classification, treatment algorithms, and prognostic variables.1

PH secondary to left heart disease is the most common type worldwide. This is caused by left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular disease or congenital left heart inflow/outflow obstruction and accounts for about 70 percent of cases. PH secondary to hypoxemic lung disease is caused by chronic obstructive pulmonary disease, interstitial lung disease, other pulmonary diseases with mixed restrictive and obstructive patterns, sleep-disordered breathing such as obstructive sleep apnea, alveolar hypoventilation disorders, chronic exposure to high altitude, and developmental lung diseases. This is another large group.

Chronic thromboembolic pulmonary hypertension (CTEPH) is one type which is curable with surgery and has a specific FDA approved treatment [riociguat (Adempas®), a soluble guanylate cyclase stimulator]. The miscellaneous category includes PH that has other disease states as the cause. The diseases in this group include chronic hemolytic anemias, myeloproliferative disorders, sarcoidosis, neurofibromatosis, vasculitis, Gaucher disease, thyroid disorders, and chronic renal failure.

PAH is very uncommon, accounting for two to six
cases per million in the United States. PAH can be heritable; secondary to drugs and toxins; associated with connective tissue diseases (lupus, scleroderma, etc.), HIV infection, portal hypertension, congenital heart diseases, or schistosomiasis; or idiopathic. In the U.S., methamphetamine is the most common drug-related cause of PAH. Many HIV infected patients are more likely to die from PAH than the HIV infection. PAH is more common in women, but it also affects many men and affects a wide age range.

The pathogenesis of PAH is associated with vascular injury and endothelial dysfunction (Exhibit 1). Initially, this process is thought to be reversible, but eventually the changes become irreversible. Increasing pressures in the pulmonary vasculature lead to increased pressure in the right ventricle, which leads to right ventricle dilation and eventually right sided heart failure. Right ventricle failure is the number one cause of death in patients with PAH. Unfortunately, this is a progressive disease, even with treatment.

Historically, survival with idiopathic PAH has not been great, with less than 50 percent surviving five years after diagnosis. New therapeutic options and research efforts now offer more hope for improving survival.

The severity of PAH is defined by functional limitations. Early in the course of PAH, patients may be largely unaffected in their usual activities (Class I). By the time patients reach Class IV, they are unable to perform any physical activities, and may have dyspnea and fatigue at rest, with an increase in symptoms in reaction to almost any physical activity. Unfortunately, diagnosis delays occur with most patients diagnosed with late symptoms (Class III and IV). The vagueness of the symptoms, particularly early in the disease process, is one of the causes of diagnosis delays. A wide range of signs and symptoms are suggestive of PAH. Dyspnea on exertion is the most common presenting complaint. Fatigue, weakness, angina, and syncope can also occur.

Although many other tests are used in the diagnosis of PAH, a cardiac catheterization is necessary for diagnosis. The catheterization measures cardiac output, capillary wedge pressure, and other factors; excludes systemic to pulmonary shunts; establishes severity and prognosis; and allows for an acute vasodilator challenge. A vasodilator is given and pressures are measured. A decrease in pulmonary artery pressure with cardiac output maintained is considered a positive vasodilator response.
Only about 5 to 6 percent of PAH patients are vasodilator responders, and they do not always remain responsive. Approximately 50 percent will lose response within a year and will require a change in therapy. Patients who do not respond to acute vasodilator challenge should not be treated with CCBs, whereas responders to acute vasodilator challenge may be treated with high dose CCBs. In PAH patients with right heart failure, CCB therapy may worsen the heart failure.

Treatment goals for this disease are numerous, including improving survival, quality of life, hemodynamics, and exercise capacity. Other treatment goals are reducing symptoms and preventing clinical worsening, which results in escalation of therapy, hospitalization, lung transplantation, or death. Ideally, an attempt is made to meet all of these goals with each patient, but that is not always possible. Each PAH case is different and patient response to treatment is variable, so clinicians need to monitor and reevaluate the patient’s condition, working toward meeting these goals. When these goals are met, patients can perform activities of daily living well enough to experience and participate in those things that are important for their own happiness and peace of mind. Our success attaining these goals depends on the severity of the PAH disease, prescribing optimal therapy, response to therapy, and patient compliance with the treatment regimen.

In the day-to-day clinical management of patients with PAH, a variety of clinical assessments are recommended, including a clinical assessment of functional status, six-minute walk test, B-type natriuretic peptide, cardiopulmonary exercise testing, echocardiography, and right heart catheterization. Patients initiating or changing therapy should be more carefully monitored because of the risk of treatment ineffectiveness and the need to rapidly move to alternatives.

In addition to CCB therapy in appropriate patients, several oral, inhaled, subcutaneous, and intravenous therapies are available for reducing symptoms and improving survival (Exhibit 2). Four major categories of therapy are now approved for treatment of PAH. These therapies target endothelial cell dysregulation and smooth muscle cell tone and proliferation. Three major pathways are involved: endothelin, nitric oxide (NO), and prostacyclin pathway. The phosphodiesterase type 5 (PDE-5) inhibitors enhance NO-mediated vasodilation and a soluble guanylate cyclase (sGC) stimulator agent interacts synergistically with available NO to stimulate guanylate cyclase, leading to increased cyclic guanosine monophosphate (cGMP) production.

Exhibit 3 depicts the most recently released evidence-based treatment algorithm for treatment of PAH. The suggested initial approach after the diagnosis of PAH is the adoption of the general measures, the initiation of the supportive therapy, and referral to an expert center. In general if patients have a lower risk profile, oral therapy will be started. Those with a higher risk profile will be started

<table>
<thead>
<tr>
<th>Oral Therapy</th>
<th>Inhaled Therapy</th>
<th>Continuous Parenteral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERAs</td>
<td>PDE-5 Inhibitors</td>
<td>sGC Stimulator</td>
</tr>
<tr>
<td>Ambrisentan (Latairis®)</td>
<td>Sildenafil (Revatio®)</td>
<td>Riociguat (Adempas®)</td>
</tr>
<tr>
<td></td>
<td>Treprostinil (Orenitram®)</td>
<td>Iloprost (Ventavis®)</td>
</tr>
<tr>
<td></td>
<td>Epoprostenol (Flolan®)</td>
<td>Treprostinil (Tyvaso®)</td>
</tr>
<tr>
<td>Bosentan (Tracleer®)</td>
<td>Tadalafil (Adcirca®)</td>
<td>RTS epoprostenol (Veletri®)</td>
</tr>
<tr>
<td>Macitentan (Opsumit®)</td>
<td></td>
<td>Treprostinil (SC or IV)</td>
</tr>
</tbody>
</table>

Exhibit 2: PAH-Specific Treatment Options for Patients Failing Acute Vasoreactivity Testing

Exhibit 3: The most recently released evidence-based treatment algorithm for treatment of PAH.
on intravenous therapy and possibility combination therapy initially.

The effectiveness of the medications selected has to be monitored with adjustments made over time. Therapy should be escalated or changed when there is failure to improve on monotherapy. If the patient has improved, but not to the satisfaction of the patient and/or physician (by objective end points, symptoms, QOL, etc.) or has improved for a period of time, but is now deteriorating, therapy needs to be changed either to another single agent or combination therapy.

In addition to PAH-specific medications, a wide range of supportive measures are also considered standard of care, including supervised exercise program rehabilitation, psychological and social support, training and counseling on infection prevention, and pneumococcal and influenza vaccines. Female patients with PAH should also avoid pregnancy. However, clinicians should be aware that no controlled clinical trials of any of these approaches have been conducted.

Providing the best care possible for patients with PAH is dependent on disease recognition, accurate diagnosis, and appropriate treatment. Clinical practice guidelines and clinical trial evidence continue to evolve rapidly in this field, and keeping abreast of changes is essential. Local practitioners are the front line in recognizing patients with symptoms consistent with PAH. They have established therapeutic relationships with patients, provide continuity of care for multiple comorbid illnesses, and are geographically close to patients' homes. Pulmonary hypertension specialists can provide assistance with diagnostic dilemmas, perform diagnostic procedures, assist with treatment decisions, and offer enrollment in clinical trials. When PAH becomes severe, PH specialists can initiate and manage parenteral medications and can assist with lung transplantation referrals.

**Conclusion**

Differentiating PAH from other types of PH is difficult but important to effectively treat. Evaluation must be methodical and include echocardiography and right heart catheterization. Prognosis improves with therapy, but PAH remains a progressive fatal disease. Therapies and management strategies continue to evolve. Collaborative care with a PH specialist is important.

**References**

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a common, preventable, and treatable disease characterized by persistent, progressive airflow limitation with extrapulmonary effects and comorbidities. The prevalence and burden of this disease is often underestimated. It is the third leading cause of death in the United States. The economic burden in the U.S. alone is $50 billion for direct and indirect costs annually. Two-thirds of COPD costs are driven by exacerbations.

COPD is characterized by airway inflammation, airway fibrosis, and parenchymal tissue destruction. Unlike asthma, the physiologic impact is usually not fully reversible. Eighty percent of COPD cases are due to tobacco smoking. Chronic environmental exposures such as smoke or dust can also contribute. Only 5 percent of COPD cases are attributable to alpha-1 antitrypsin (A1AT) deficiency. Because there is a specific treatment for the deficiency, all COPD patients must be screened for this deficiency.

The dominant, evidence-based guidelines for COPD diagnosis and treatment are the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. These guidelines were last updated in 2013 and have finally caught up to real-world clinicians, by including symptoms in the severity and risk assessment, but now are more complicated. Severity classification and treatment are based on lung function, symptom burden, and history of exacerbations (Exhibit 1).

The diagnosis of COPD is based on spirometry, typical symptoms of dyspnea, cough, and sputum, and a history of appropriate exposure. Spirometry is required for diagnosis but is underutilized in primary care. Less than 50 percent of people labeled with COPD have ever had spirometry. Additionally,
some physicians are hesitant to make the diagnosis due to stigma and misperceptions about the disease. Thus, COPD is overdiagnosed and underdiagnosed.

In addition to being the basis for diagnosis, spirometry is important because the values obtained are important for determining future risk and severity. Airflow severity is based on post-bronchodilator spirometry, which is a challenge in many settings. Because many patients will have a significant bronchodilator response, pre-bronchodilator spirometry overestimates severity. COPD is defined as a forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of 0.7 or less. This value is an arbitrary cutoff that underdiagnoses COPD at young age, and overdiagnoses at older age.

Severity is classified based on the percentage of predicted FEV1. Those who are 80 percent or better of predicted fall in GOLD 1 or mild category. GOLD 2 is 50 to 80 percent of predicted and moderate, and GOLD 3 is 30 to 50 percent of predicted and severe. Lastly, GOLD 4 is less than 30 percent predicted and very severe disease.

The goals of COPD treatment are to reduce impairment by relieving symptoms, improving exercise tolerance, and improving quality of life and reducing risk through prevention of disease progression, prevention and treatment of exacerbations, and reduced mortality. Treatment includes medications, nonpharmacologic therapy, and surgery. Exhibit 1 illustrates how risk based on FEV1% predicted, symptoms, and history of exacerbations are used to select initial medications. Symptom scores are determined using standardized questionnaires. Thus, patients with more severe disease, more exacerbations, or higher symptom scores will be started on more aggressive therapy.

Bronchodilators are central to symptom management with long-acting agents preferred (long-acting bronchodilators, LABAs; long-acting muscarinic
agents, LAMAs). Short-acting agents (SABAs and SAMAs) are used to manage minor symptoms as needed in those with mild disease. Many clinicians are unaware that two-thirds of COPD patients will demonstrate significant FEV1 response to short-acting bronchodilators. Example SABA, SAMA, LABA, and LAMA agents include albuterol, ipratropium, formoterol and salmeterol, and tiotropium, respectively. The bronchodilators have been demonstrated to improve cough, phlegm, dyspnea, and exercise tolerance. The choice of agent is dependent on individual response, adverse effects, and availability. There are increasing individual agents and combinations of long-acting inhaled bronchodilators on the market or coming soon.

The GOLD guidelines recommend inhaled corticosteroids (ICSs) for patients with FEV1 less than 50 percent of predicted and significant symptom burden. These agents improve quality of life, FEV1, and symptoms. Studies have shown ICS added to LABA decreases COPD exacerbations, particularly in those with FEV1 less than 60 percent. But, these studies were performed before the availability of concomitant LAMA therapy. Recently, investigators showed that gradual withdrawal of ICSs in the setting of a LABA/LAMA combination had no adverse effect on severe COPD exacerbations. Most of the time, ICSs are continued in patients for improved symptoms more than to reduce exacerbations.

A phosphodiesterase type 4 (PDE-4) inhibitor is indicated for severe or very severe COPD with poorly controlled chronic bronchitis on maintenance therapy. Roflumilast (Daliresp®) is the only agent currently available. It leads to modest reduction in exacerbations but is very expensive and commonly causes diarrhea and weight loss. The addition of this agent is considered for GOLD category D to LAMA/ICS/LABA or LAMA.

### Exhibit 3: Data Collection for Stable COPD Visit

<table>
<thead>
<tr>
<th>Data Element</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status (pk-yr)</td>
<td>Quality, risk for CT screening</td>
</tr>
<tr>
<td>Spirometry</td>
<td>Quality, GOLD grade</td>
</tr>
<tr>
<td>CAT or mMRC</td>
<td>GOLD grade, billing</td>
</tr>
<tr>
<td>SpO2 and O2 usage</td>
<td>Quality, adherence</td>
</tr>
<tr>
<td>Medication adherence</td>
<td>Adherence</td>
</tr>
<tr>
<td>Exercise status</td>
<td>Should be on med list</td>
</tr>
<tr>
<td>Vaccination status</td>
<td>Quality</td>
</tr>
<tr>
<td>Interval exacerbations</td>
<td>GOLD grade</td>
</tr>
<tr>
<td>Bone density status</td>
<td>Comorbidity</td>
</tr>
<tr>
<td>Advanced directives</td>
<td>Quality, comorbidity</td>
</tr>
<tr>
<td>Mental health screen</td>
<td>Quality, comorbidity</td>
</tr>
</tbody>
</table>

### Exhibit 4: COPD QA Report Card

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Real-Time Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active smoker</td>
<td>Counseling documented, Rx</td>
</tr>
<tr>
<td>No O2 assessment last 12 mos</td>
<td>Medical assistant takes SpO2</td>
</tr>
<tr>
<td>Recent exacerbation</td>
<td>Pulm rehab referral</td>
</tr>
<tr>
<td>Vaccine deficiency</td>
<td>Give upstream of MD visit</td>
</tr>
<tr>
<td>Lung CA screen eligible</td>
<td>Educate, enable, notify MD</td>
</tr>
</tbody>
</table>
fective medication if used carefully, and in the right patients. It is hard to prove the absence of an exacerbation, so the cost and lack of immediate symptomatic benefit is a barrier for many patients using this medication.

A COPD exacerbation is an acute worsening of symptoms beyond day-to-day variation, requiring a change in medication. Exacerbations are difficult to define, can be very mild or life-threatening, and are usually caused by viruses. Given their contribution to overall costs, COPD exacerbations are an excellent target for quality and cost control activities. Smoking cessation, patient medication adherence, pneumococcal and influenza vaccination are all very important in reducing exacerbations. ICS added to LABA reduces exacerbations by 20 to 30 percent; however, as discussed earlier most studies were done in the absence of LAMA. Most severe COPD patients are on triple combination therapy; in these patients, the role of ICS is less clear. LAMA has some evidence of reducing exacerbations alone.

PDE-4 inhibitors reduce exacerbations in severe and very severe COPD, but have significant cost and adverse effects. Macrolides have not consistently demonstrated reduction in exacerbations, but may help select patients. Recurrent airway aspiration is a common cause of exacerbations, thus management of GERD in these individuals can reduce exacerbation frequency. Disease management programs post-exacerbation discharge are rarely integrated with or adopted by the care team, and usually fail for this reason.

One effective strategy to prevent rehospitalization for COPD after an exacerbation is pulmonary rehabilitation. Pulmonary rehabilitation is safe after discharge, improves health status, and reduces recurrent exacerbations. It is indicated for breathlessness walking at own pace, or recent exacerbations. Overall, pulmonary rehabilitation improves exercise capacity, quality of life (QOL), recovery after hospitalization, and survival. It also reduces hospitalizations for COPD, anxiety, and depression.

In addition to pulmonary rehabilitation, other nonpharmacologic therapy is important in managing COPD. Every COPD patient needs to exercise and, where applicable, use oxygen. This is at least as important as medications. COPD patients have unique experiences and needs, particularly with respect to long-term oxygen therapy. Oxygen therapy is recommended for resting partial pressure of oxygen (PAO2) less than 55 or peripheral capillary oxygen saturation (SpO2) less than 88 percent and has been shown to provide a survival benefit in COPD.

Surgical interventions for COPD include lung volume reduction surgery, lung transplant, and bullectomy. A survival benefit in patients with severe upper lobe emphysema and low exercise capacity has been shown with lung volume reduction. Lung transplant improves QOL. Endobronchial interventions under investigation include endobronchial valves and endoscopic lung volume reduction.

Other interventions are important both for preventing exacerbations and slowing disease progression. Smoking cessation can slow progression. Annual influenza vaccine provides a survival benefit. Pneumococcal vaccine is indicated for those age 65 and older but may also be useful in those younger. This vaccine has been shown to reduce the incidence of community acquired pneumonia in those with age < 65 and FEV1 < 40%.

Other comorbidities also need to be addressed. COPD can lead to a vicious cycle of anxiety, dynamic hyperinflation, and dyspnea. Adequately addressing anxiety in severe COPD can be life-changing. Depression, osteoporosis, skeletal muscle dysfunction, and caloric imbalance also need to be addressed. Lung cancer screening is also needed for former or current smokers.

Mortality following a COPD exacerbation can range from 25 to 80 percent. Palliative approaches significantly improve QOL and help caregivers. It is important that end of life care be discussed with all patients. An undesired ICU stay harms the patient, harms the family and caregivers, and unnecessarily drives up health care costs.

National COPD quality metrics include tobacco screening/cessation, spirometry to confirm diagnosis, spirometry evaluation, bronchodilator therapy, influenza vaccination, pneumococcal vaccine for those 65 and older, oxygen saturation annually, and rehabilitation effect on quality of life. No one is measuring whether the clinician customized the approach to the individual patient so they can achieve their goals.

There are many barriers to quality in COPD management. Misdiagnosis, access to spirometry, provider knowledge and guideline adoption, disease heterogeneity, and care fragmentation all impact quality. Patient adherence with treatment is a yet another barrier. The causes of nonadherence may be educational deficits, short-term thinking, medication complexity, cost, adverse effects, poor access to care, or misaligned goals of care.

Additionally, in outpatient care, there are numerous other barriers to quality care. Care occurs across time and in different locations, documentation is not structured, outcomes not clear-cut, the primary outcomes are patient-reported, and the rate of exacerbations may be low. Lastly, traditional measures do not allow for real-time quality intervention. For
example, it is not helpful to clinicians to find out a patient did poorly on influenza vaccination last fall. They need to know during the flu season how the patient is doing.

Exhibit 2 presents a vision for a quality COPD program. In a quality program, much data have to be collected; Exhibit 3 shows what is necessary just for a stable patient visit. It is valuable to go beyond collecting whether someone is a current/former/never smoker to capture actual smoking pack-years. Capturing spirometry discretely aids severity assessment and denominator validation but requires interface between the device and the medical record, or at least manual entry of values. Tracking exacerbations in an individual patient is an opportunity to diagnose triggers, discuss action plan, and re-assess maintenance medications. Bone density status may be difficult to track because of care fragmentation. Most bone density testing is done outside individual clinics or institutions so results are not discretely captured. Based on data collected, providers can be given a QA report card (Exhibit 4). It is important to note that a key mistake would be forcing all of this on the physician which will result in failure to achieve goals, physician dissatisfaction, and patient dissatisfaction. The data collection and acting on the data has to be built into the workflow for this quality of care program to be effective.

**Conclusion**

COPD is a leading cause of death in the U.S. The most recent GOLD guidelines use a matrix based on symptoms, severity, and exacerbations for determining appropriate therapy. Improving the quality of care given to patients with COPD will require collection of additional data and quality improvement in real time to act on the data.

David Beuther, MD, FCCP, is the Chief Medical Information Officer and an Associate Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at National Jewish Health in Denver, CO.

**References**

IDIOPATHIC PULMONARY FIBROSION (IPF) IS A chronic, progressive illness that up until very recently had no approved treatment. It is a form of interstitial lung disease with chronic fibrosing interstitial pneumonia limited to the lungs and associated with the histologic appearance of usual interstitial pneumonia (UIP). In this disease, there is both normal and abnormal lung tissue. The abnormal tissue has fibrotic and not inflammatory changes. There are both idiopathic and non-idiopathic interstitial lung diseases. Non-idiopathic can be occupational (asbestos, silica), granulomatous (sarcoidosis, hypersensitivity pneumonitis), drug induced (amiodarone, nitrofurantoin, cyclophosphamide), connective tissue disease related (rheumatoid arthritis, scleroderma, lupus), inherited, or as the result of pulmonary alveolar proteinosis, cryptogenic organizing pneumonia, malignancy or heart failure. IPF has the absence of a defined etiologic agent and is the most common type of ILD.

The diagnosis of IPF is evolving. Previously, all interstitial lung diseases were considered together. Now they are divided into multiple categories because they respond to treatment differently. It is also misdiagnosed frequently as chronic obstructive pulmonary disease or heart failure.

The current recommended approach to diagnosing IPF is multidimensional and multidisciplinary, comprising clinical, radiologic, and pathologic assessments and relying on the expertise of pulmonologists, pathologists, radiologists, and primary care physicians. The diagnosis of IPF is made based on clinical symptoms, radiographic findings, and lung biopsy.

Dyspnea on exertion is the most prominent presenting symptom of IPF and is usually slowly progressive. A nonproductive cough is also frequently present. Exhibit 1 presents a typical case. A physical exam may reveal “velcro-like” crackles, most prominent at the lung bases, in more than 80 percent of patients. As the disease progresses, rales, clubbing, or cyanosis may develop. A routine laboratory evaluation is often helpful to rule out other causes of interstitial lung disease. Pulmonary function tests

Summary

Although idiopathic pulmonary fibrosis (IPF) is a progressive and lethal disease, two new oral treatments have recently come to market in the United States providing additional hope for those affected. Although the only definitive treatment for this disease is lung transplantation, the new agents have been shown to slow progression.

Key Points

• IPF is a progressive, irreversible, lethal disease.
• Everyone will get worse but when this will occur and how fast is unknown.
• Pirfenidone and nintedanib are two new oral agents that have been shown to slow progression of IPF.
• Lung transplantation is the only definitive treatment.
• Supportive care and management of comorbidities are also important.
typically reveal a restrictive pattern (reduced vital capacity and total lung capacity) and impaired gas exchange. Resting arterial blood gases may be normal; however, exercise typically results in an oxygen desaturation. Patient history is important to the diagnosis to rule out the non-idiopathic form. Chest x-rays may reveal bilateral reticular opacities with a basal predominance. Importantly, however, a normal chest x-ray does not exclude a diagnosis of IPF. Lung biopsy may be necessary to establish the diagnosis when clinical features are atypical. The major purpose of histologic examination is to distinguish IPF from other more treatable diseases.

Although the etiology of IPF is still not understood (hence idiopathic), certain factors have been shown, or are suspected, to be associated with an increased risk of the disease. The most established risk factor for IPF is a family history (defined as at least 2 family members with a confirmed diagnosis of IPF). Other risk factors that have been proposed in some studies include smoking, environmental factors (wood and metal dust), chronic aspiration associated with gastroesophageal reflux disease (GERD), and certain infectious agents. No genetic markers have been identified that could explain familial risk. Several small studies have associated viral agents with an increased risk of IPF, although none have implicated a viral infection as the cause. Some such virus-

### Exhibit 1: Case

71-year-old male with progressive dyspnea on exertion for 2 years. He was previously able to walk > 2 miles; over the past 2 years it decreased to 1/2 mile. Currently, he has difficulty with activities such as dancing and mowing the lawn.

Pulmonary function tests 18 months ago revealed mild obstructive airways disease, but the patient used bronchodilators without much relief of symptoms.

One year prior, he developed “pneumonia” with fever, chills, and a nonproductive cough. The CXR at that time was read as mildly prominent interstitial markings.

#### Patient History
- Smoked 20 pack years
- Denies occupational exposures
- No exposure to birds or mold
- No use of hot tubs

#### Physical Exam:
- BP: 130/80
- Heart rate: 70
- Respiratory rate: 22
- Temperature: 96.9
- Oximetry: 93% on room air
- Lungs: Bibasilar rales

#### Six-minute walk test:
- Oximetry: 96% at rest on RA
- Oximetry dropped to 83% walking on RA
- Significant fibrosis on chest CT

### Exhibit 2: Epidemiology of IPF

![Epidemiology of IPF](image)

---

46 Journal of Managed Care Medicine | Vol. 18, No. 1 | www.namcp.org
es include Epstein-Barr virus, Sendai virus, measles virus, and others.

IPF is not uncommon. There are an estimated 31,000 new cases per year and an estimated 120,000 current patients in the United States. The incidence of IPF increases with age, and the disease is more common in men than women (although gender is not a risk factor), probably owing to the greater prevalence of risk factors in men (Exhibit 2). Patients with IPF are usually over 50 years of age and there is no racial predilection.

Because IPF is a chronic disease that is almost uniformly fatal, the ratio of the prevalence to the incidence can provide a crude indication of the duration of survival after diagnosis (Exhibit 2). The average life expectancy after diagnosis is three to five years. Exhibit 3 shows the common reasons for death in IPF patients from one study.

The traditional view of IPF was that these patients had an almost linear slow decline in pulmonary function and an increase in symptoms. It is now known that acute exacerbations occur, which can cause large declines in function and can possibly be fatal. Acute exacerbations are marked by acute worsening of dyspnea and pulmonary function. Mortality is very high with exacerbations thus they are treated with a trial of high dose steroids and cyclophosphamide (Cytoxan®) but it is not even clear that this works.

The American Thoracic Society treatment guidelines have not been updated recently and still recommend routine treatment with prednisone and cyclophosphamide, the combination of which has been shown to increase mortality and thus should not be used except for treating acute exacerbations. Some of the other interstitial lung diseases do respond to this combination treatment so it is important to have an accurate diagnosis.

Over the years, many different agents have been tried for IPF but until recently none have been effective. In October 2014, the Food and Drug Administration approved two new oral medications for IPF, pirfenidone (Esbriet®) and nintedanib (Ofev®). In addition to the two new medications, clinical trials are still a treatment option.

Pirfenidone’s mechanism of action is unknown; it does block some of the mediators that cause fibrosis. It is an oral medication given three times a day with meals. The side effects include gastrointestinal issues, fatigue, liver function test abnormalities, and photosensitivity. Published trials of this agent have shown that it slows progression of IPF. Unfortunately, none of the studies have been large enough or sufficiently powered to identify if mortality is reduced by pirfenidone.

Nintedanib is a tyrosine kinase inhibitor also given orally, but only twice daily. Diarrhea occurs in about 60 percent of patients; this tends to improve over time. Nausea and liver function abnormalities also occur. Like the other agent, nintedanib has been shown to slow progression of disease. It has also been shown to reduce acute exacerbations and
preserve quality of life. With this agent, the mortality curves in the trials were not statistically different but were separated. Overall, neither of the two new agents have been shown to reverse or cure the disease or alter mortality.

Lung transplantation is the only definitive treatment for the disease. Given that patients with IPF have a dismal prognosis, transplant is a safe and effective treatment to improve their survival and functional status but is not an option for all patients. For very old patients or those who already have another comorbidity likely to end their life, no treatment is an option. These patients would receive supportive care.

There are a few supportive treatment options. Supplemental oxygen is important for those with hypoxemia, particularly on exertion. Patients with IPF benefit from pulmonary rehabilitation. End of life planning is especially important. As shown in Exhibit 3, over a seven-year follow-up period, 60 percent of patients died.

Several comorbidities are commonly present and require management because they complicate IPF. These include pulmonary hypertension, GERD, osteoporosis, deconditioning, and obstructive sleep apnea. About a third of patients will develop pulmonary hypertension; unfortunately the available treatments are not very effective in pulmonary hypertension secondary to IPF. Almost all patients with IPF will need to be on reflux medications because reflux is very common and exacerbates symptoms, particularly cough.

Conclusion
IPF is a progressive, irreversible and lethal disease. Everyone will get worse; however, when this will occur and how fast is unknown. New and future treatments finally offer hope in slowing progression and hopefully reducing mortality.

Robert Sussman, MD, is with Pulmonary and Allergy Associates in Summit, NJ and serves as President and Managing Partner. He is currently the President of the Medical Staff at Overlook Medical Center and the former Chief of the Section of Pulmonary and Critical Care Medicine.

References
Update in the Management of Type 2 Diabetes: A Closer Look at Current and Emerging Treatment Strategies

Yehuda Handelsman, MD, FACP, FACE, FNLA
For a CME/CEU version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.

Summary
Significant advances have been made in managing type 2 diabetes mellitus (T2DM) during the past few years. Therapy is moving toward individualized goals using multiple avenues of therapy including lifestyle modification, combinations of oral agents, and insulin.

Key Points
- Contemporary T2DM care includes identifying individual treatment goals and instituting personalized comprehensive care for people with diabetes.
- It is important to start intensive lifestyle modification while concomitantly starting medications.
- Medications should be chosen based on safety, efficacy and characteristics and should be intensified as needed.
- Insulin should be introduced when appropriate.
- The combination of insulin and GLP-1 agonists can be considered as necessary to improve control and reduce side effects.

ONE AREA OF CHANGE IN THE MANAGEMENT of T2DM has been the individualization of hemoglobin A1C goals, rather than maintaining one goal for all patients. As outlined in Exhibit 1, A1C goals in T2DM are now individualized based on various factors. The overall aim should be to control glucose without causing harm. Age is the least important factor in deciding goals; the underlying comorbidities should determine what an individual’s goal should be.

It is important all patients be prescribed intensive lifestyle modification. Lifestyle modification is aimed at glycemic control, weight loss, and increased physical activity. Rather than begin with lifestyle modification alone, the current standard of care is to simultaneously start lifestyle modifications and medications.

Numerous noninsulin and insulin agents, many of these new in the last 10 years, are available for glycemic control (Exhibits 2 and 3). Many of the oral agents are also available in combinations, particularly with metformin. Two older agents, colesevelam and bromocriptine, have both been “rediscovered” for lowering glucose.

One innovation in diabetes care has been the understanding of the effect of incretins on glucose control, which led to the development of incretin-based therapies. In response to equivalent hyperglycemic stimuli, oral glucose elicits a greater insulin response than intravenous glucose, the incretin effect. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) secreted by L cells in the intestines account for 90 percent of the incretin effect. No therapies targeting GIP have been developed, but two classes of agents working through GLP-1 have reached the market. The GLP-1 agonists act like endogenous GLP-1 and effectively reduce hemoglobin A1C (A1C), may preserve pancreatic beta cell function, promote weight loss, and correct known pathophysiologic defects in T2DM. Importantly, they do not cause hypoglycemia and overall have an excellent safety profile. GLP-1 agonists have been compared to insulin and have similar effect on A1C, 1.1 to 1.2% reduction, but with less weight gain and no episodes of hypoglycemia. For those patients who still have some insulin secre-
tion, many clinicians are prescribing GLP-1 agonists dosed once a week to augment endogenous insulin. The dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the breakdown of endogenously secreted GLP-1 and thus prolong its effect. DPP-4 inhibitor use leads to a 0.6 to 0.8% reduction in A1C. The agents do not cause weight change and are oral, which is an advantage over the injectable GLP-1 agonists.

The thiazolidinediones (TZDs) are making a comeback because it has been shown that they do not cause heart attacks or bladder cancer. Benefits of TZDs include a durable A1C reduction, increases in insulin sensitivity, positive lipid effects, and improvements in nonalcoholic steatohepatitis (NASH).

The sodium-glucose cotransporter (SGLT) inhibitors are the newest agents on the market. These inhibit SGLT1, SGLT2, or both to prevent reabsorption of glucose in the kidneys and intestinal tract. SGLT1 is the primary transporter for absorption of glucose and galactose in the gastrointestinal tract. Reduction of glucose absorption in the proximal intestines leads to more glucose being delivered distally. SGLT2 is expressed in the proximal convoluted tubule (PCT) of the kidney where it reabsorbs greater than 90 percent of filtered glucose. SGLT1 is expressed in the distal PCT and reabsorbs less than 10 percent of filtered glucose. Enhancing glucose excretion in the kidney improves glycemic control, is independent of insulin secretion, and may be pancreas-sparing. There are currently three agents on the market with many more to come. All three inhibit SGLT2; canagliflozin is the only one that weakly inhibits SGLT1. The A1C effect of these agents is reductions of 0.5 to 1.1%. They have also been shown effective in combination with most antihyperglycemics and insulin. Additional benefits of the SGLT inhibitors are a modest reduction in blood pressure (4 to 6 mm Hg), lack of hypoglycemia when used as monotherapy, and modest reduction in weight (3 to 4% of initial weight). An SGLT inhibitor combined with a GLP-1 agonist leads to combined weight loss. These agents are likely to be approved for use in type 1 DM in the future.

Colesevalam is a nonabsorbed polymer that lowers cholesterol levels by binding bile acids in the intestine. Interestingly, it consistently lowers mean A1C by 0.5% when added to metformin-, sulfonylurea-, or insulin-based therapy. The mechanism of action by which it reduces glucose levels has not been elucidated. Bromocriptine, another rediscovered agent, is a dopamine 2 receptor agonist. It increases early morning dopamine receptor activity which is low in T2DM contributing to glucose and lipid dysfunction. Bromocriptine use leads to a 0.6 to 1% reduction in A1C but causes significant dizziness in many patients.

Adding insulin to oral antihyperglycemic medications has become much more common in recent years. This combination improves glycemic control for many patients. When comparing the various insulins, any insulin will lower glucose and A1C and all insulins are associated with some weight gain and some risk of hypoglycemia. Long-acting insulin analogues reduce the incidence of overnight hypoglycemia. Rapid-acting insulin analogues reduce postprandial glucose excursions compared with corresponding human insulins [NPH, Regular]; however, they are associated with more hypoglycemia and weight gain. Although many clinicians and patients are reluctant to start insulin therapy in T2DM, benefits of early insulin use have been shown. In a trial that included subjects with prediabetes or early T2DM with CVD, it was found that starting very early with insulin glargine allowed patients to achieve very low A1C values over seven years (Exhibit 4).3

Many clinicians will combine insulin and GLP-1 agonists. This combination has been studied and negates the weight gain typically seen with insulin alone.4 Additionally, hypoglycemia rates are no higher with the combination compared with insulin alone. Postprandial glucose is also better managed with combination therapy than with insulin alone.

The two major guidelines available for glycemic control include the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE).2,5 These guidelines have many similarities and some differences.

The ADA/EASD guidelines suggest providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.3 Anti-diabetic therapy implementation strategies in this guideline include initial single agent therapy, advancing to dual combination therapy, then advancing to triple combination therapy, and finally transitions to and titrations of insulin.

---

Exhibit 1: Goals For Glycemic Control ADA-AACE

<table>
<thead>
<tr>
<th>A1c Goals – Individualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6.5% to ≤6.9% for most; provided safely</td>
</tr>
<tr>
<td>&lt;6.5% (5%) As close to normal for new, relatively young, healthy; provided safely</td>
</tr>
<tr>
<td>&gt;7% Less stringent for “less healthy” – multiple co-morbidities, labile, short life expectancy</td>
</tr>
</tbody>
</table>

---
The AACE/ACE 2013 diabetes algorithms for glycemic control recommend selecting therapy stratified by A1C level and by A1C-lowering potential. For lower A1C (less than 7.5%), monotherapy can be used. For higher levels, dual or triple therapy should be initiated at the outset to achieve early glycemic control.

Common principles in AACE/ACE and ADA T2DM treatment algorithms are to individualize glycemic goals based on patient characteristics and promptly intensify anti-diabetic therapy to maintain blood glucose at individual targets. The choice of agent(s) should be based on individual patient medical history, behaviors and risk factors, ethnocultural background, and environment. Combination therapy is usually required to achieve glycemic goals and insulin will eventually be necessary for most patients. Self-monitoring of blood glucose is vital for day-to-day management of blood glucose in all patients using insulin and in many patients not using insulin who have tighter glucose goals.

**Conclusion**

Contemporary T2DM care includes identifying individual treatment goals and instituting personalized comprehensive care for people with diabetes. It is important to start intensive lifestyle modification for glycemic control while concomitantly starting medications. Medications should be chosen based on safety, efficacy and characteristics. Patients should be
monitored every three months and have their therapy intensified as needed. Insulin should be introduced when appropriate; patients should be monitored for hypoglycemia and weight gain.

The combination of insulin and GLP-1 can be considered as necessary to improve control and reduce side effects.

Yehuda Handelsman, MD, FACP, FACE, FNLA, is Medical Director and Principal Investigator at Metabolic Institute of America and the current President of the American College of Endocrinology.

References
IN NORMAL TRIGLYCERIDE (TG) METABOLISM, dietary TGs are digested in the stomach and duodenum into monoglycerides and free fatty acids by gastric and pancreatic lipase. Monoglycerides and free fatty acids, along with free cholesterol, are then solubilized in the intestine by bile acid micelles. Once absorbed, they are reassembled into TGs and packaged with cholesterol into chylomicrons, the largest lipoproteins. Chylomicrons are broken down very quickly and the byproducts are taken up by fat and muscle cells for energy. A normal fasting TG level is below 100 mg/dl. Problems occur in those who cannot effectively catabolize chylomicrons. Over time, high levels of TGs and remnant particles build up in the vascular wall, the same as modified low-density lipoprotein cholesterol. It is well known that certain medications lower triglycerides; it has not yet been proven that adding these agents onto statin therapy provides a substantial benefit over statin therapy alone.

Elevated triglycerides are a risk factor for developing heart disease. Although much of the focus of lipid lowering has been on low-density lipoprotein cholesterol, lowering triglycerides is important to reducing risk, particularly for those who also have low high-density lipoprotein cholesterol. Hypertriglyceridemia can include eruptive cutaneous xanthomas, lipemic plasma, lipemia retinalis, and tuberous xanthomas. Xanthomas are most often associated with markedly elevated plasma chylomicrons in cases of familial chylomicronemia. They usually occur in clusters on the skin of the trunk, buttocks or extremities. Lipemia retinalis is a milky appearance of the retinal vessels and pink retina can be seen when plasma triglyceride concentration exceeds 35 mmol/L. Tuberous xanthomas, filled with foam cells, appear as reddish or orange, often shiny nodules, up to 3 cm in diameter. In patients with familial dysbetalipoproteinemia, they usually appear on extensor surfaces such as the elbows. Palmar crease xanthomas are filled with foam cells and appear as yellowish deposits within palmar creases. These skin lesions are pathognomonic for familial dysbetalipoproteinemia.

Summary
Elevated triglycerides are a risk factor for developing heart disease. Although much of the focus of lipid lowering has been on low-density lipoprotein cholesterol, lowering triglycerides is important to reducing risk, particularly for those who also have low high-density lipoprotein cholesterol. It is well known that certain medications lower triglycerides; it has not yet been proven that adding these agents onto statin therapy provides a substantial benefit over statin therapy alone.

Key Points
• Hypertriglyceridemia is associated with increased CV risk.
• The subgroup of those with elevated triglycerides and low HDL-C despite statin therapy appear to benefit the most from triglyceride lowering.
• Omega-3 fatty acids are a safe and effective therapy for TG lowering.
• More data are needed to determine if combination therapy with omega-3 fatty acids is clinically superior to statin monotherapy in hypertriglyceridemia.

IN NORMAL TRIGLYCERIDE (TG) METABOLISM, dietary TGs are digested in the stomach and duodenum into monoglycerides and free fatty acids by gastric and pancreatic lipase. Monoglycerides and free fatty acids, along with free cholesterol, are then solubilized in the intestine by bile acid micelles. Once absorbed, they are reassembled into TGs and packaged with cholesterol into chylomicrons, the largest lipoproteins. Chylomicrons are broken down very quickly and the byproducts are taken up by fat and muscle cells for energy. A normal fasting TG level is below 100 mg/dl. Problems occur in those who cannot effectively catabolize chylomicrons. Over time, high levels of TGs and remnant particles build up in the vascular wall, the same as modified low-density lipoprotein cholesterol (LDL-C).

In the most accelerated cases (TGs >1000 mg/dl), clinical manifestations of primary hypertriglyceridemia can include eruptive cutaneous xanthomas, lipemic plasma, lipemia retinalis, and tuberous xanthomas. Xanthomas are most often associated with markedly elevated plasma chylomicrons in cases of familial chylomicronemia. They usually occur in clusters on the skin of the trunk, buttocks or extremities. Lipemia retinalis is a milky appearance of the retinal vessels and pink retina can be seen when plasma triglyceride concentration exceeds 35 mmol/L. Tuberous xanthomas, filled with foam cells, appear as reddish or orange, often shiny nodules, up to 3 cm in diameter. In patients with familial dysbetalipoproteinemia, they usually appear on extensor surfaces such as the elbows. Palmar crease xanthomas are filled with foam cells and appear as yellowish deposits within palmar creases. These skin lesions are pathognomonic for familial dysbetalipoproteinemia.

Hypertriglyceridemia and Omega-3 Fatty Acids: Exploring Current and Emerging Treatment Options

Michael Miller, MD, FACC, FAHA, FNLA
For a CME/CEU version of this article, please go to www.namcp.org/cmeonline.htm, and then click the activity title.
There are numerous secondary causes of hypertriglyceridemia such as diabetes, alcohol, obesity, pregnancy and several medications, especially steroids, protease inhibitors, beta blockers, and antipsychotic medications. Eliminating or treating these secondary causes can reduce levels.

A triglyceride level below 100 mg/dl is optimal and leads to the lowest risk of heart disease (Exhibit 1).\(^1\) Values of 150 to 200 mg/dl are considered borderline. Values greater than 200 mg/dl lead to a high risk of cardiovascular disease (CVD). The median TG level in the United States is 120 mg/dl. Overall, about 31 percent of American adults have borderline triglyceride levels, while 16 percent have high triglyceride levels. (Exhibit 2).\(^1\) Rates vary among different ethnic groups.

Apolipoprotein C3 inhibits triglyceride hydrolysis and has been implicated in coronary artery disease. Loss of apolipoprotein C3 activity mutations are associated with very low levels of TGs (30 to 40 mg/dl) and low levels of CVD.\(^3,4\) Through a genome-wide association study, 5 percent of the Lancaster Amish were found to be heterozygous carriers of a null mutation. In the population with this mutation and regular physical exercise (5 to 10 miles per day of walking) there is a very low rate of CVD despite a less than “ideal” diet.\(^4\)

It is well known that lowering LDL-C with statins reduces CVD risk about 30 percent but that leaves substantial residual CV risk. Lowering TGs in addition to LDL-C lowering further reduces risk. This has been shown to be an especially important therapeutic strategy in patients after an acute coronary syndrome. Achieving an LDL less than 70 and TG less than 150 mg/dl resulted in the lowest risk of cardiovascular events in this population.\(^5\)
Lifestyle changes can substantially reduce TG levels. Exhibit 3 outlines the percentage benefits of various dietary interventions. Physical activity provides another 20 percent lowering. Taken together, dietary changes and physical activity can invoke a 50 to 60 percent reduction. This is a much better reduction than can be achieved for LDL-C (10%) with lifestyle interventions.

Lipid-lowering medications also reduce TGs. Fibrates and niacin are most effective and can lower levels 20 to 50 percent. Omega-3 fatty acids provide a 10 to 40 percent reduction. The effect of statins on TGs vary from 10 to 30 percent.

Although multiple lipid-lowering therapies are known to lower TGs, outcomes with combination therapy aimed at reducing residual risk by additional lowering of TGs have been mixed. One trial found no difference in major cardiovascular event rates with the combination of statin plus niacin versus statin monotherapy. Subgroup analysis showed that those with high TGs (>200 mg/dl) and low HDL (<34 mg/dl) achieved greater benefit from TG lowering therapies combined with LDL-C lowering therapies. A meta-analysis of fibrate studies has shown this same pattern of a lowering of cardiovascular events in those with high TGs and low HDL.

---

### Exhibit 3: Effects of Nutrition Practices on Triglyceride Lowering

<table>
<thead>
<tr>
<th>Nutrition Practice</th>
<th>TG-Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (5% to 10% of body weight)</td>
<td>20%</td>
</tr>
<tr>
<td>Implement a Mediterranean diet vs a low fat diet</td>
<td>10% - 15%</td>
</tr>
<tr>
<td>Add marine-derived PUFA (EPA/DHA) (per gram)</td>
<td>5% - 10%</td>
</tr>
<tr>
<td>Decrease carbohydrates and 1% energy replacement with MUFA/PUFA</td>
<td>1% - 2%</td>
</tr>
<tr>
<td>Eliminate transfats and 1% energy replacement with MUFA/PUFA</td>
<td>1%</td>
</tr>
</tbody>
</table>

**PUFA = polyunsaturated fatty acid**
**MUFA = monounsaturated fatty acid**
**EPA = Eicosapentaenoic acid**
**DHA = docosahexaenoic acid**

### Exhibit 4: OM-3 FA Combined with Statin Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Lovaza</th>
<th>Vascepa</th>
<th>Epanova</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid inclusion</td>
<td>200 mg/dL ≥ TG &lt; 500 mg/dL</td>
<td>200 mg/dL ≥ TG &lt; 500 mg/dL</td>
<td>Patients with high risk for CV events with 200 mg/dL ≥ TG &lt; 500 mg/dL</td>
</tr>
<tr>
<td>Duration</td>
<td>8 weeks</td>
<td>12 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Treatments</td>
<td>4 g/d plus Simva 40mg</td>
<td>Placebo plus Simva 40mg</td>
<td>4 g/d plus statin</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-29.5*</td>
<td>-6.3</td>
<td>-17.5*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.7</td>
<td>-2.8</td>
<td>1.5*</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-4.8*</td>
<td>-2.2</td>
<td>-5*</td>
</tr>
<tr>
<td>TC</td>
<td>-3.2*</td>
<td>-1.7</td>
<td>-2.2*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>3.4*</td>
<td>-1.2</td>
<td>-1*</td>
</tr>
<tr>
<td>Apo B</td>
<td>-4.2*</td>
<td>-1.9</td>
<td>-2.2*</td>
</tr>
</tbody>
</table>

* Difference from placebo, p < 0.05
§ % ∆ LGSM, p < 0.05

www.namcp.org | Vol. 18, No. 3 | Journal of Managed Care Medicine 55
There is no CV risk benefit of a fibrate in someone without those two lipid issues.

Omega-3 fatty acids are another option for lowering TGs. These can be obtained from plant sources, but the predominant plant omega-3 is alpha-linolenic acid (ALA), which must be converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are the effective omega-3 agents. The amount of conversion in the body is only 10 percent. Obtaining EPA and DHA from fish-derived omega-3 fatty acids is the most efficient way to obtain therapeutic doses.

There is a linear dose response curve between EPA and DHA dose and lowering of TGs. For each 1 gram dose, there will be a 5 to 10 percent reduction. The only study to date that has examined the effects of the combination of statin and omega-3 fatty acids compared to statin monotherapy found that the addition of 1.8 gm/day reduced cardiovascular risk 19 percent. In the subgroup with high TGs (>150 mg/dl in this study) and low HDL (<40 mg/dl), the effect was magnified to over 50 percent.

Available forms of omega-3 fatty acids for supplement and pharmaceutical use are numerous. The formulations sold as supplements are not FDA regulated.

Three pharmaceutical omega-3 products are available that have higher concentrations of EPA/DHA than typical supplement products. All three products are FDA approved for treating very high TG (>500 mg/dl). Omega-3–acid ethyl esters (Lovaza®, generic) is a combination of ethyl esters of omega-3–fatty acids containing 465 mg EPA and 375 mg DHA in a 1-gram capsule. The daily dose of omega-3–acid ethyl esters is 4 g per day taken as a single 4-gram dose or as two 2-gram doses. Icosapent ethyl (Vascepa®) is a 96 percent pure ethyl ester of eicosapentaenoic acid (EPA). The daily dose is 4 g per day taken as two capsules twice daily. Omega-3–carboxylic acids (Epanova®) is a fish oil-derived mixture of free fatty acids, with at least 850 mg of polynsaturated fatty acids, including multiple omega-3 fatty acids, with EPA and DHA being the most abundant). The daily dose of omega-3–carboxylic acids is 2 g (2 capsules) or 4 g (4 capsules) once daily.

Research into omega-3 fatty acids is focusing on two questions: possible differences in bioavailability between those taken orally as “free fatty acids” versus their “ethyl ester” form and any clinical significance in terms of triglyceride reduction. Epanova has been compared to Lovaza in a pharmacokinetic, single-dose evaluation, which showed it had a better absorption and higher bioavailability. There have been no other comparison absorption studies.

Exhibit 4 illustrates the results from short-term trials comparing the addition of each of the three pharmaceutical omega-3 products to statin therapy for lipid lowering. In a population with high TGs, addition provides a consistent non-LDL-C, atherogenic particle lowering (TG, non-HDL-C, and Apo B) and modest increase in HDL-C.

There are two large clinical trials ongoing to examine whether the addition of omega-3 fatty acids provides a clinical benefit in lowering the risk of CV disease. Hopefully, these two trials will provide a definitive answer on whether adding omega-3 produces a significant morbidity or mortality benefit.

Conclusion

Hypertriglyceridemia is associated with increased CV risk. Omega-3 fatty acids are a safe and effective therapy for TG lowering in hypertriglyceridemic patients. Ongoing clinical trials will assess whether combination therapy is clinically superior to statin monotherapy in these patients.

Michael Miller, MD, FACC, FAHA, FNLA is a Professor of Cardiovascular Medicine, Epidemiology and Public Health at the University of Maryland School of Medicine in Baltimore, MD.

References


---

**NAMCP Would Like to Recognize Our Corporate Partners!**

- AbbVie
- Acelity (KCI)
- Acorda
- Actelion Pharmaceuticals US
- Allergan
- Amarin Corporation
- AmerisourceBergen
- Amgen Inc.
- AssureRx Health
- Astellas Pharma US
- Baxalta
- Bayer HealthCare
- Biodesix
- Biogen
- Bioventus, LLC
- Boehringer Ingelheim
- Boston Scientific
- Bristol-Myers Squibb Company
- CVS Caremark
- CardioDx
- Celgene Corporation
- Dendreon
- DiaTech Oncology, LLC
- Eisai
- Exact Sciences Corporation
- Express Scripts
- Foundation Medicine
- GE Healthcare
- Genentech
- Genomic Health
- Genoptix
- Gilead Sciences
- GlaxoSmithKline
- Health Diagnostic Laboratory
- Incyte Corporation
- InSightec
- J & J Health Care Systems
- Janssen Biotech
- Lilly Oncology
- Lilly USA, LLC
- Merck & Co, Inc.
- Myriad Genetic Laboratories
- NanoString Technologies
- Natera
- Novartis Oncology
- Novartis Pharmaceuticals
- Onyx Pharmaceuticals
- Pfizer Inc.
- Primus Pharmaceuticals
- Purdue Pharma, L.P.
- Sandoz Pharmaceuticals
- Sunovion Pharmaceuticals
- Taiho Oncology
- Takeda Oncology
- Teva Pharmaceuticals
- Tolmar Pharmaceuticals
- Valeant Pharmaceuticals
- VITAS Healthcare Corporation
- Veracyte, Inc.
- Vermillion
Caring for cancer differently...

Taiho Oncology, Inc., is focused on bringing novel technology to cornerstone chemotherapies for a wide range of tumor types—including colorectal cancer and a variety of solid tumors. By developing oral oncolytic therapies, we are aspiring to deliver more meaningful moments to patients, and to redefine the way the world treats cancer.

To learn more, please visit www.TaihoOncology.com.
Caring for cancer differently...

It’s all in the delivery

Taiho Oncology, Inc., is focused on bringing novel technology to cornerstone chemotherapies for a wide range of tumor types—including colorectal cancer and a variety of solid tumors. By developing oral oncolytic therapies, we are aspiring to deliver more meaningful moments to patients, and to redefine the way the world treats cancer.

To learn more, please visit www.TaihoOncology.com.

Introducing

TAIHO ONCOLOGY

Making the human connection

© TAIHO ONCOLOGY, INC. 03/2015 All rights reserved. TOI-PM-US-0012
THE NEW NONINVASIVE OPTION FOR AVERAGE-RISK PATIENTS WHO AVOID COLONOSCOPY

Cologuard is the colorectal cancer screening test that uses innovative stool DNA technology to detect cancer with 92% sensitivity and 87% specificity. It's noninvasive and easy to use, with no special preparation required. No wonder patients are excited—and you will be, too.


Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals. Rx only.