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CME MOC

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Interpreting ISCHEMIA

Short QT and sudden cardiac death

Steroids and osteoporosis

Devices that lower blood pressure

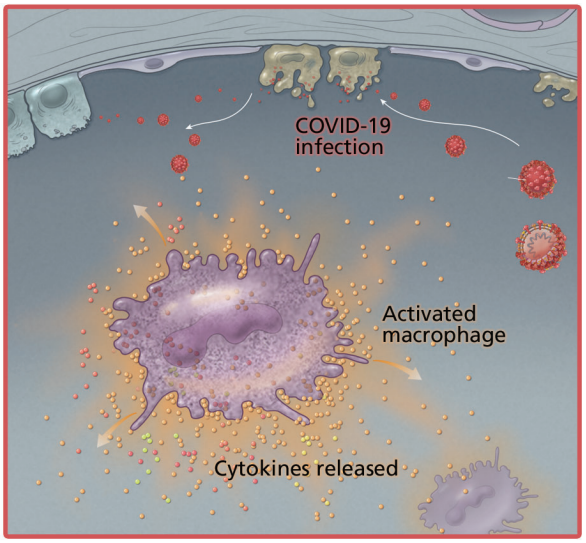
Documentation and Medicare

Mönckeberg medial sclerosis

A firm lesion on the thigh

COVID-19
Brief perspectives from the front line

- Cytokine storm: Prospects for treatment
- Clinical presentation and course of COVID-19
- More at Curbside Consults www.ccjm.org



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Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 1950 Richmond Rd., TR404, Lyndhurst, OH 44124.

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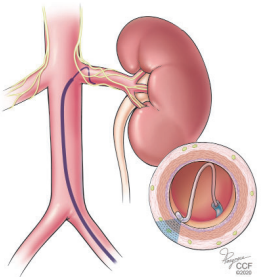

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Cytokines and the still-baffling clinical biology of COVID-19

Although it seems like forever, we are only months into the COVID-19 pandemic, so it should really be no surprise that there are huge gaps in our understanding of the infection and its treatment. It took decades before we developed effective therapies for HIV, hepatitis B, and non-A non-B hepatitis. But this is different. It feels different. It was on us like a tidal wave, and we are now inundated with new data 24/7. Clinical descriptions of new syndromes linked to coronavirus infection and results of small randomized and larger observational studies appear online ahead of print, and alerts are forwarded to our inboxes in a constant stream, not to mention what we hear in the nightly news. Every medical center seems to be scrambling to conduct emergent clinical trials comparing novel treatments with "usual care," but "usual care" of COVID-19 patients is also changing at a rapid pace.

With all this information, it seems we should know more than we do about how to manage the very sick. But it even in a pandemic affecting such a large number of patients in a short window of time, with many of them experiencing measurable outcome events, well-done randomized treatment trials take time to orchestrate and complete. When morbidity and mortality of hospitalized patients is high, with no known effective therapy, the usual care of patients will likely include multiple unproven medications in an attempt to turn the tide of their infection. This can dramatically complicate the analysis of observational studies. Plus, this virus drives a complicated pathobiology.

The clinical expression and course of COVID-19 are pleomorphic and, thus far, are not easily predicted. There are asymptomatic infected individuals who are nonetheless shedding virus, and presymptomatic individuals seemingly even more infective. Most patients experience a mild to modest illness with some combination of fatigue, gastrointestinal symptoms, anosmia, and respiratory symptoms. But some, perhaps after 5 to 10 days, have a second phase of illness characterized by markedly worsened respiratory symptoms due to severe and progressive viral pneumonia. And within this latter group, some experience a dramatic clinical downturn with variable cardiopulmonary collapse, high fevers, and hypercoagulability associated with laboratory markers consistent with what has been called cytokine storm, macrophage activation syndrome (MAS), or in some other settings, hemophagocytic lymphohistocytosis (HLH). The similarity to these latter syndromes, which often respond to agents directed against the cytokines interleukin 1 (IL-1) (anakinra, canakinumab) or interleukin 6 (IL-6) (tocilizumab, sarilumab), has led to empiric use of these agents and to the initiation of multiple formal clinical trials, as discussed by Dr. Len Calabrese in this issue of the *Journal* (page 389).

But it is not as simple as patients experiencing cytokine storm just having worse disease, characterized by immune overreactivity, which needs to be quelled by blocking the culprit immune hormone. The primary culprit contributing to the progressive lung dysfunction and damage is not certain. Is it all immune damage? Or is the contin-

doi:10.3949/ccjm.87b.07020

ued persistence of coronavirus playing a direct or indirect role through continued activation of primordial components of the immune system? And is the hyperinflammatory response the body's last-ditch effort at controlling the virus, in which case blocking it might (in the absence of an effective antiviral therapy) be counterproductive? Hence the need for well-done, controlled, and randomized clinical trials.

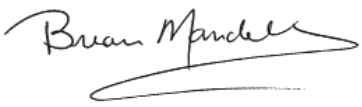
The respective significance of active viral infection and replication vs effects of ultra-high levels of inflammatory mediators (IL-1, IL-6, granulocyte-macrophage colony-stimulating factor) on lung damage and multisystem failure remains to be delineated. Elevated levels of IL-6 and downstream markers of cytokine effects (eg, ferritin) have been associated with death, but this association doesn't prove that it is not the persistence of viral replication and viral products that are in fact contributing to the ongoing elaboration of these cytokines as well as to direct damage to lung tissue.

The biology is complicated. This novel coronavirus has been shown to increase synthesis of IL-1 by stimulating its precursor pro-IL-1 as well as activating the intracellular inflammasome cascade that cleaves active IL-1 from its precursor. Additionally, there are studies that indicate the virus can antagonize the initial host antiviral mechanisms involving interferon generation and natural killer cell-mediated destruction of viral infected cells, resulting in persistence of replicating virus. This latter effect can mimic the rare genetically influenced primary HLH syndromes. Thus, blocking specific cytokines may not be sufficient therapy, unless the virus itself can also be eliminated.

Adding to this complexity, there are studies demonstrating that IL-6 can play an important antiviral role and also can be a positive influence on repair and remodeling following experimental inflammatory lung injury induced in animals by endotoxin or bleomycin.

A lack of an answer to how best to treat patients with severe COVID-19 is not the same as having a lack of information. The latter continues to grow, the former will hopefully follow. Certainly, identifying a potent antiviral agent will help enormously, and I'd expect an antiviral will work synergistically with anticytokine strategies in patients with severe disease. In the meantime, we await clinical results and biochemical analyses from the several prospective trials under way, while wading through the minefields of many well-intentioned but compromised, complicated, and hard-to-interpret observational studies.

If after reading the Calabrese article you are interested in reading more about the fascinating biology of the immune response to this virus that is so rapidly unfolding, I refer you to 2 other well-referenced reviews,[1,2] and more articles about COVID-19 in general are available at our COVID-19 Curbside Consults section at www.ccjm.org.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

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Clinical presentation and course of COVID-19

ABSTRACT

Information about the clinical presentation and course of COVID-19 is evolving rapidly. On presentation, cough and fever predominate, but extrapulmonary symptoms are also common; in some patients, loss of sense of smell may be an early but favorable sign. The mortality rate varies widely in different reports but should become clearer as more data are collected. Risk factors for severe disease and death include comorbid conditions such as hypertension, cardiovascular disease, diabetes mellitus, and chronic obstructive pulmonary disease. Other implicated factors include older age, obesity, end-stage renal disease, and a higher neutrophil-lymphocyte ratio.

KEY POINTS

Patients with COVID-19 who have ground-glass opacities, consolidative opacities, increased inflammatory markers, older age, and comorbid conditions have been shown to have increased risk of ventilation and death.

Anosmia may be a sign of favorable infection outcome.

Those with obesity, hypertension, or underlying lung or heart disease tended to do worse in studies of mortality and severity.

For predictive markers, the neutrophil-lymphocyte ratio, Sequential Organ Failure Assessment score, and CURB-65 score may correlate with worse disease.

doi:10.3949/ccjm.87a.ccc013

Relatively few studies are available that show the symptoms, course, and prognostic factors of COVID-19 disease, but the data are evolving rapidly. The disease affects not only the lungs, but also other organ systems. Patients with comorbidities are most vulnerable. Novel symptoms and markers of risk continue to be identified.

FEVER AND COUGH PREDOMINATE BUT OTHER SYMPTOMS ARE COMMON

Zhou et al[1] reported the characteristics and outcomes of 191 patients hospitalized for COVID-19 in 2 hospitals in Wuhan, China. Fever was present in 94%, cough in 79%, sputum production in 23%, myalgia in 15%, and diarrhea in 5%; 54 patients died.

Others (reviewed by Lai et al[2]) cite similar numbers, with some variation in less-specific symptoms, such as myalgia in up to 43.9% of patients and diarrhea in up to 10.1%.

Arentz et al[3] described 21 patients admitted to the intensive care unit with COVID-19 in Evergreen Hospital in Kirkland, WA. Symptoms included cough in 11, shortness of breath in 17, and fever in 11. In the intensive care unit, 15 patients required mechanical ventilation, 8 developed severe acute respiratory distress syndrome (ARDS), and 11 died.

Jin et al[4] reported that 74 (11%) of 651 COVID-19 patients in Zhejiang province in China had at least 1 gastrointestinal symptom (nausea, vomiting, or diarrhea). Other symptoms included sore throat in 99 (15%) fatigue in 119 (18%), shortness of breath in 27 (4%), headache in 67 (10%), cough in 435 (67%), and fever in 130 (20%).

Rodriguez-Morales et al[5] performed a systematic review and meta-analysis that includ-

ed 656 patients. The most common symptoms were fever (reported in 88.7% of cases), cough (57.6%), dyspnea (45.6%), myalgia or fatigue (29.4%), sore throat (11.0%), headache (8.0%), and diarrhea (6.1%).

On radiography, 25% of patients had unilateral chest opacities, and 72.9% had bilateral opacities; 68.5% had ground-glass opacities on computed tomography.

On laboratory testing, 43.1% had lymphopenia, 58.3% had high C-reactive protein levels, and 57% had high lactate dehydrogenase levels.

Outcomes included death in 15.9%, discharge in 38.1%, acute respiratory distress syndrome (ARDS) in 7.1%, and secondary infection in only 1.6%.

Kim et al[6] reported on the first 28 cases of COVID-19 in Korea. The median age was 40 years, 15 patients were male, 28.6% had cough, 28.6% had sore throat, 25% had fever, and 10.7% had diarrhea, but 2 patients had no symptoms. Nearly half (46.4%) of the patients had infiltrates on chest radiography, and 88.9% had infiltrates on computed tomography. Six patients (21%) were hypoxic, but none required mechanical ventilation.

In general, the majority of patients present with fever, cough, dyspnea, and elevated C-reactive protein, with or without elevated lactate dehydrogenase. Less-common symptoms include diarrhea, nausea, vomiting, sore throat, headache, and fatigue.

Loss of smell an early but favorable sign

Anosmia, or olfactory loss, has been reported as an early sign of COVID-19.

Yan et al,[7] at the University of California San Diego, reviewed the cases of 169 patients with laboratory-confirmed COVID-19 infections, of whom 128 had olfactory and gustatory data available; 26 were hospitalized. The investigators performed univariate and multivariate logistic regressions to identify risk factors for hospital admission and anosmia.

Hospital admission was strongly associated with intact smell and taste, older age, diabetes, and parameters associated with respiratory failure. Anosmia was independently associated with outpatient care (adjusted odds ratio [OR] 0.09, 95% confidence interval [CI] 0.01–0.74). The finding of pulmonary infiltrates or pleural effusion on chest radiography was independently associated with admission (adjusted OR 8.01, 95% CI 1.12–57.49).

This implicates anosmia as a sign of mild clinical course and reinforces radiographic abnormalities as a predictor for a worse clinical course.

WHO SURVIVES COVID-19?

Wang et al[8] reviewed the cases of 1,012 patients who were admitted to the hospital in China because they had positive results on polymerase chain reaction testing but were not critically ill. Only 4.5% had hypertension, 2.7% had diabetes mellitus, 1.5% had cardiovascular disease, and 2.0% had respiratory disease at baseline. Their median age was 50 (interquartile range 39–58, total range 16–89). Three percent of the patients had no symptoms, 75.2% had fever, 18% had chills, 5.6% had rhinorrhea, 52.4% had cough, 15% had headache, and 15% had diarrhea. Median admission length of stay was 10 days (interquartile range 7–14).

Computed tomography of the chest showed large ground-glass opacities in 508 patients and large consolidated opacity in 54 patients. None of the patients died.

In essence, fewer comorbid conditions indicates better prognosis, but more research needs to be done to show the true prognostic factors for those who do well.

Novel symptoms and markers of risk continue to be identified

WHO DIES OF COVID-19?

Deaths in COVID-19 have been attributed to multiple organ failure with ARDS, cardiac injury, acute kidney injury, and shock.[5]

The mortality rate may be variable when patient admission criteria are not standardized: ie, if the threshold for admission is lower, then the mortality rate will be lower. This may also reflect testing bias, as the cause of death may not be attributed to SARS-CoV-2 if the patient went untested or died at home without a clear diagnosis after discharge.

Pooled analysis of 278 patients in Wuhan, China,[2] showed that 72 (26%) required intensive care unit admission, 56 (20%) developed ARDS, 23 (8%) required invasive mechanical ventilation, and 9 (3%) required extracorporeal membrane oxygenation for refractory hypoxemia. Hemodynamic shock was seen in

6.8% of patients, and the mortality rate was 4% to 15%. The median time of death from first symptoms was 14 days.[2]

Zhou et al[1] compared survivors of COVID-19 and those who died of it with univariate and multivariate logistic regression models used to determine significant differences. Compared with survivors, patients who died were statistically significantly more likely to have:

- Older age (median age 69 vs 52)
- Comorbidities such as hypertension, diabetes, coronary heart disease, and chronic obstructive lung disease (67% vs 40%)
- Tachypnea (63% vs 16%)
- A higher Sequential Organ Failure Assessment (SOFA) score[9] (4.5 vs 1.0)
- A higher CURB-65 score (**c**onfusion, **u**rea, **r**espiratory rate, **b**lood pressure, age ≥ **65**)[10] (2.0 vs 0.0)
- A higher white blood cell count (9.8 vs 5.2 × 10^9/L)
- A lower lymphocyte count (0.6 vs 1.1 × 10^9/L)
- A lower platelet count (165 vs 220 × 10^9/L)
- Lower serum albumin (29.1 vs 33.6 g/L)
- Higher alanine aminotransferase (ALT) (40.0 vs 27.0 U/L)
- Serum creatinine > 133 µmol/L (1.5 mg/dL) (9% vs 2%)
- Higher creatine kinase (39.0 vs 18.0 U/L)
- Elevated high-sensitivity cardiac troponin I (22.2 vs 3.0 pg/mL)
- Longer prothrombin time (12.1 vs 11.4 seconds)
- Higher D-dimer levels (5.2 vs 0.6 µg/mL)
- Higher serum ferritin levels (1,435.3 vs 503.2 µg/L)
- Higher interleukin 1 (11.0 vs 6.3 pg/mL)
- Procalcitonin ≥ 0.6 ng/mL (25% vs 1%)
- Radiographic consolidation (74% vs 53%)
- Ground-glass opacity (81% vs 67%)
- Bilateral pulmonary infiltrates (83% vs 72%).

Deaths are due to multiple organ failure with ARDS, cardiac injury, acute kidney injury, and shock

Li et al[11] examined the records of 25 patients who died. Their ages ranged from 55 to 100 years. Initial laboratory testing showed the following median values:

- ALT 24 U/L
- Aspartate aminotransferase 37 U/L
- Albumin 3.2 mg/dL
- Blood urea nitrogen 9.29 mmol/L (26 mg/dL)
- Creatinine 66 µmol/L (0.75 mg/dL)
- Hypersensitive troponin I 316 ng/mL
- White blood cell count 11.01 × 10^9/L
- Neutrophil count 10.41 × 10^9/L
- Lymphocyte count 0.52 × 10^9/L
- Procalcitonin 0.36 (ng/mL)
- C-reactive protein 91.1 mg/L
- Lactate 3.35 mmol/L.

The median course of disease was 9 days (range 4–20 days). Mechanical ventilation was needed in 23 patients, 16 patients had hypertension, 10 patients had diabetes, and 8 patients had heart disease.

Cummings et al[12] performed a prospective cohort study of 257 critically ill patients with laboratory-confirmed COVID-19 in New York City. The most common comorbidity was hypertension (63%), followed by obesity (46%) and diabetes (36%). Of the 257 patients, 203 received mechanical ventilation for a median of 18 days (interquartile range 9–28 days), 170 required vasopressors, and 79 needed renal replacement therapy. The median time to in-hospital deterioration was 3 days (interquartile range 1–6).

In total, 101 patients died. A multivariable Cox model identified the following as independently associated with in-hospital mortality:

- Older age (adjusted hazard ratio [aHR] 1.31 per 10-year increase [95% CI 1.09–1.57])
- Chronic cardiac disease (aHR 1.76 [1.08–2.86])
- Chronic pulmonary disease (aHR 2.94 [1.48–5.84])
- Higher interleukin 6 levels (aHR 1.11 per decile increase [1.02–1.20])
- Higher D-dimer levels (aHR 1.10 per decile increase [1.01–1.19]).

Overall, patients with older age, baseline lung or heart disease, and radiographic opacities are more likely to develop progressive COVID-19 infection and to die. Data indicate that those who present with higher CURB-65 and SOFA scores tend to do worse as well.

CAN WE PREDICT SEVERE DISEASE?

Comorbid conditions

Wang et al[13] performed a meta-analysis of 34 reports, many of which are included in this

review. The following comorbid diseases were associated with severe COVID-19:

- Hypertension (odds ratio [OR] 2.92, 95% CI 2.35–3.64, I^2 45.2% [indicating moderate heterogeneity])
- Cardiovascular disease (OR 3.84, 95% CI 2.90–5.07, I^2 3.5%)
- Chronic kidney disease (OR 2.22, 95% CI 1.14–4.31, I^2 38.1%)
- Chronic liver disease (OR 0.86, 95% CI 0.42–1.75, I^2 0%)
- Diabetes (OR 2.61, 95% CI 2.05–3.33, I^2 39.2%).

Radiographic progression

Liu et al[14] performed a retrospective cohort study of computed tomography of pneumonia lesions in early hospitalization to predict progression to severe illness. The researchers used artificial intelligence algorithms to measure ground-glass opacity volume, semiconsolidation volume, and consolidation volume of both lungs in 134 patients with confirmed COVID-19 in Shanghai, China, of whom 19 (14.2%) were severely ill.

Changes on computed tomography from day 0 to day 4 had the best predictive value for developing severe illness, with a hazard ratio of 1.39 (95% CI 1.05–1.84) for ground-glass opacity volume and 1.67 (95% CI 1.17–2.38) for consolidative volume.

Neutrophil-lymphocyte ratio

Pereira et al,[15] in Spain, evaluated the characteristics of 60 pregnant women with SARS-CoV-2 infection, of whom 75.5% presented with fever and cough, 37.8% reported dyspnea, and 68.6% required hospital admission; however, more than half of the admissions were for delivery. The most common laboratory findings were lymphopenia, thrombocytopenia, and elevated C-reactive protein. A neutrophil-lymphocyte ratio less than 3 appeared to be the most sensitive marker of disease improvement, with relative risk of 6.6.

Liu et al[16] investigated laboratory markers as predictors of critical illness, finding that patients with a neutrophil-lymphocyte ratio of 3.13 or higher and age 50 or older had a higher tendency to progress into critical illness (P = .0004). However, they did not report a hazard ratio associated with their Cox proportion hazards regression analysis. They do report that area under the receiver operator curve was 0.867 for the neutrophil-lymphocyte ratio. This study involved 61 patients in their derivation cohort and 54 patients in a validation cohort.

Obesity

Hajifathalian et al[17] performed a retrospective chart review of 770 COVID-19 patients in New York City. Their mean body mass index was 29 kg/m^2, and 277 patients had a body mass index greater than 30. The obese patients were more likely to present with fever, cough, and shortness of breath, and they had a significantly higher rate of intensive care unit admission or death (relative risk 1.58, P = .002).

Acute liver injury

Phipps et al[18] performed a retrospective cohort study of acute liver injury in patients undergoing testing for SARS-CoV-2 in New York City. Of 3,381 patients tested, 2,273 had positive results and 1,108 had negative results. Those who tested positive had higher median initial and peak ALT levels than those who tested negative. Of those who tested positive, those with the highest peak ALT levels were most likely to need intensive care, intubation, or renal replacement therapy and to die in the hospital.

An artificial intelligence program measured pneumonia volume

Hemodialysis

Goicoechea et al[19] reported the outcomes of 36 patients on hemodialysis in Spain who were hospitalized for COVID-19. Over the course of 1 month, 11 patients (31%) died, and 18 (including the 11 who died) had a worsening of their clinical status, defined as an increase in oxygen requirement of more than 4 liters and radiographic worsening.

Nonsurvivors had significantly longer time on dialysis than survivors, higher lactate dehydrogenase levels (490 vs 281 U/L), higher C-reactive protein levels (18.3 vs 8.1 mg/dL), and lower lymphocyte counts (0.38 vs 0.76 × 10^9/L). The median time on dialysis for both groups was 29 months; 19 patients had arteriovenous fistulas and 17 patients had permanent central venous catheters.

6.5 MILLION CASES AND COUNTING

At the time of this writing, the US Centers for

Disease Control and Prevention is reporting 1,842,101 US cases and 107,029 deaths, resulting in a 5.8% mortality rate.[20] The World Health Organization has listed 6,515,796 confirmed cases with 387,298 deaths, which results in a mortality rate of 2.6%.[21] As testing improves and becomes more widely available, these numbers should settle on the true mortality rate; however, they continue to fluctuate.

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Cytokine storm and the prospects for immunotherapy with COVID-19

ABSTRACT

Knowledge about the pathobiology of SARS-CoV-2 as it interacts with immune defenses is limited. SARS-CoV-2 is spread by droplets that come into contact with mucous membranes. COVID-19 is characterized by 2 or 3 stages: most patients who recover experience 2 stages of illness commencing with an asymptomatic or paucisymptomatic incubation period, followed by a nonsevere symptomatic illness lasting for several weeks, occurring in about 80% of those infected. In the remainder, a third phase marked by a severe respiratory illness, often accompanied by multisystem dysfunction, coagulopathy, and shock is observed. This phase of the illness is characterized by hypercytokinemic inflammation and is often referred to as "cytokine storm." While the immunopathogenesis remains unclear, prospects of treating this severe phase of the illness with immunotherapy are evolving, with some treatments showing promise.

As we learn about COVID-19, we recognize that there are gaping holes in our knowledge of the pathobiology of SARS-CoV-2 as it interacts with our immune defenses. Epidemiologically, we know that most people, especially young and healthy ones, do quite well at defending themselves from this infection and that even those with severe disease tend to recover without sequelae. We also know that not everyone has a relatively benign disease course and that risk factors for progression are dominated by age and comorbidities, especially cardiovascular disease, diabetes, and obesity.

While some of these clinical findings seem to have face-validity, others are not so clear. Why is age such a dominant risk factor, but on the other hand, why do some young, otherwise seemingly healthy individuals succumb to the infection? We do not yet have complete answers to these questions.

THREE STAGES OF DISEASE

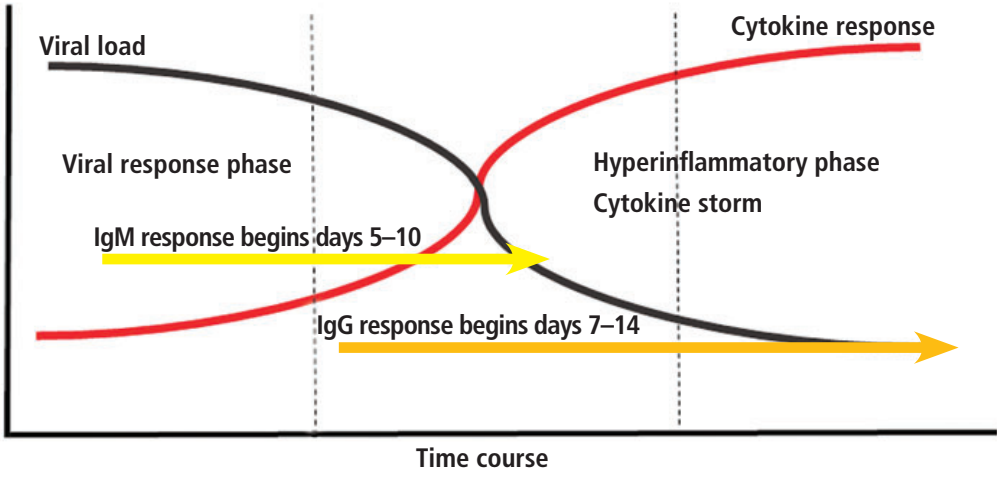
To tackle this problem, we must first examine what is known about the interaction between the pathogen and the host immune system. SARS-CoV-2 is spread by droplets that come into contact with mucous membranes. Interestingly, not all individuals who are exposed acquire the infection. Once a person is infected, the disease progresses through 2 or 3 main stages (**Figure 1**).

Stage 1 is an asymptomatic or paucisymptomatic incubation period in which there is a high level of viral shedding in the upper respiratory tract. Implicitly, this stage marks engagement of the innate immune system as the initial mode of host defense.

Dr. Calabrese has disclosed financial interests (consulting, teaching, and speaking) with AbbVie, Bristol Myers Squibb, Crescendo Biologics, GlaxoSmithKline, Genentech/Roche, Horizon Therapeutics, Janssen, Novartis, and Pfizer.

doi:10.3949/ccjm.87a.ccc008

	Stage 1 Asymptomatic	Stage 2 Nonsevere symptomatic	Stage 3 Severe respiratory-inflammatory
Immune response over time: **Self-limiting in 80%** **Severe in 15%–20%** **Fatal in 1%–2%**	**Innate immune activation** Viral engagement of PAMPs Low type 1 IFN	**Adaptive immune activation** Generation of specific antibodies and T-cell response Release of DAMPs	**Cytokine release syndrome** IL-1, IL-6, TNF, GM-CSF, IFN-gamma, others Coagulopathy Complement



DAMPs= damage-associated molecular patterns; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IgM = immunoglobulin M; IL-1 = interleukin 1; IL-6 = interleukin 6; PAMPs = pathogen-associated molecular patterns; TNF = tumor necrosis factor

Figure 1. Three stages of COVID-19 disease.

Stage 2 is a period of nonsevere symptomatic illness in which viral loads peak approximately 5 days after symptom onset.[1] At this stage adaptive immunity is engaged, allowing development of specific T- and B-cell responses required to end the infectious process. The disease ends in stage 2 in approximately 80% of infected individuals.

Finally, **stage 3** is characterized by severe respiratory illness with progressive pneumonitis that may or may not lead to respiratory failure, which, in its final stages causes diffuse alveolar damage. Stage 3 is also frequently attended by progressive fever, multiorgan dysfunction, hypercoagulability, and shock.[2]

Immunologically, SARS-CoV-2 infects cells that express the angiotensin-converting enzyme 2 receptor, including cells of the respiratory tract, endothelial cells, and likely hematopoietic cells, including macrophages. With full engagement of the integrated immune response, the development of neutralizing antibodies is believed to be a critical event in recovery as well as the generation of virus-specific T-cell responses, ultimately leading to viral clearance.[3]

Attempts to correlate the stages of clinical disease described above with SARS-CoV-2 viral loads from respiratory secretions, blood, and tissues have yielded conflicting results. Some patients with advanced disease have high viral loads while others do not.[4]

WHY DO SOME PATIENTS GO ON TO STAGE 3?

Why host antiviral defenses fail and why some patients go on to stage 3 is not yet clear, but attempts to reconcile these findings suggest that this progression may be driven by ongoing viral infection. In support of this hypothesis is a recent study documenting that SARS-CoV-2 infection actually induces a low interferon response, an immune pathway critical for antiviral defense, while at the same time inducing

a strong inflammatory response, thus creating a perfect storm of continued viral replication and unbridled inflammation.[5,6]

The clinical state of patients with stage 3 disease is characterized by hypercytokinemic inflammation. This syndrome has variably been referred to as "cytokine storm." The cytokine storm of COVID-19 bears similarities to other conditions that are also referred to under this umbrella, including primary hemophagocytic lymphohistiocytosis (HLH), as well as secondary forms such as macrophage activation syndrome (MAS) and secondary HLH, which are often encountered in the setting of autoimmunity, cancer, or viral infections.[7,8] In COVID-19, and unlike in MAS or secondary HLH, the primary target organ is the lung, leading to an acute respiratory distress syndrome. While stage 3 COVID-19 is not secondary HLH or MAS, it does share features both clinically and pathologically.[5]

Recently, a variant of this cytokine storm has been described in children with COVID-19 and has been dubbed *multisystem inflammatory syndrome in children* (MIS-C).[9]

Laboratory features are quite similar among these disorders, with marked elevations of acute-phase reactants (eg, C-reactive protein, ferritin), lymphopenia, coagulation defects, and elevated levels of numerous inflammatory cytokines; prominent among them are interleukin 6 (IL-6), IL-1, IL-2, IL-7, IL-17, granulocyte macrophage-colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF).[10]

Why there is an increased incidence of this inflammatory late-stage complication in select young individuals and more frequently in patients who are elderly and in those with comorbidities is poorly understood. Interestingly, though, in a study attempting to further understand why otherwise-healthy individuals can die from viral illness, 30% of patients dying from H1N1 influenza were found to carry single copies of genes commonly encountered in patients with HLH,[11] suggesting a link between immune predisposition to HLH and outcome. We can also postulate that the chronic low-grade inflammation and an increase in self-reactivity that characterize the aging immune system also may contribute. Importantly, recent studies have shown that immunologic aging proceeds at different rates in different individuals; thus, mere chronologic age is, not surprisingly, a relatively crude predictor of COVID-19 progression.[12]

TABLE 1

Immunotherapeutic strategies for COVID-19

Kinase inhibitors
Tofacitinib, baricitinib, ruxolitinib, others

Targeted therapy
Inhibitors of interleukin 1 (IL-1), IL-6, tumor necrosis factor, and granulocyte macrophage colony-stimulating factor; interferon gamma

Tolerogenic therapies
T-cell regulators, low-dose IL-2

Cellular therapies
Natural killer cell therapies, antiplasmacytoid dendritic cell, others

Passive therapy
Intravenous immune globulin, immune plasma, specific antibodies

Nonspecific therapies
Glucocorticoids, calcineurin inhibitors, mammalian target of rapamycin inhibitors

IMPLICATIONS FOR THERAPY

From a therapeutic perspective, there is a clear need for an effective antiviral agent that can prevent viral infection in exposed individuals and limit tissue damage in those with established disease (stages 1 and 2).

Despite gaping holes in our knowledge, treatment is evolving

In stage 3, in the absence of any effective antiviral therapy, we are relegated to supportive care. It is at this stage that the experimental use of agents designed to limit tissue damage driven by uncontrolled inflammation is being investigated. Given the similarities between stage 3 COVID-19 and other hypercytokinemic states, a variety of nonspecific immunosuppressive strategies have been proposed, such as glucocorticoids, hydroxychloroquine, colchicine, and other immunomodulators, as well as Janus kinase inhibitors and a number of targeted therapies directed at pivotal cytokines (**Table 1**). For now, the experience with such agents largely consists of anecdotal case reports and small clinical trials.[13]

As of this writing, more than 900 clinical trials of various therapeutics for COVID-19 are registered at clinicaltrials.gov. Agents that have been proposed or are in use include anti-

IL-1, anti-IL-6, anti-GM-CSF, and anti-TNF drugs, and Janus kinase inhibitors. A conceptual framework of such therapies is displayed in **Table 1**.

Anti-IL-6 and anti-IL-1 agents: Center stage for COVID-19 stage 3 disease

Among these therapies, agents that target IL-6 have perhaps generated the greatest enthusiasm. Numerous IL-6–targeting agents are being tested in COVID-19 including those targeting the IL-6 receptor (tocilizumab, sarilumab) and those targeting IL-6 itself (siltuximab, clazakizumab, and sirukumab). Two of these agents—tocilizumab (NCT04320615) and sarilumab (NCT04315298)—are already in advanced stages of multicenter randomized control trials, and data should be forthcoming soon.

Interest in IL-6 is strong, as it is a pleomorphic cytokine produced by both hematopoietic and viscerosomatic cells and has far-reaching effects on immune function and diverse nonimmune physiologic processes.[14] It is a key upstream driver of inflammation and has been successfully targeted therapeutically. IL-6 also has been shown to be a predictor of respiratory failure.

The disease ends in stage 2 in about 80% of infected individuals

Of particular relevance for stage 3 COVID-19 disease, targeting IL-6 with tocilizumab is now indicated for treatment of cytokine storm accompanying chimeric antigen receptor (CAR)-T-cell therapy.[15] Clinical support for advancing the study of IL-6 inhibition in COVID-19 has come from a variety of sources, including anecdotes from now-widespread off-label use of tocilizumab, case reports, and small series[16] in which rapid reversal of laboratory and clinical parameters were reported. Balancing enthusiasm for such a strategy is the known pivotal role of IL-6 in host defense, particularly in defense against respiratory viruses.[17]

IL-1 is another inflammatory cytokine that could potentially be targeted to treat various cytokine storm syndromes. IL-1 is an upstream mediator of inflammation and is produced by the NLPR3 inflammasome; it has been incriminated in the pathogenesis of COVID-19, having been detected in lung tissue by a variety of techniques.[18]

As of this writing, 3 small nonrandomized case series have demonstrated benefit of IL-1 inhibition in COVID-19.[18,19] The largest of these series,[19] while suffering from the use of a retrospectively derived comparator group, demonstrated meaningful improvement in reducing the need for mechanical ventilation with the use of anakinra, a human IL-1 receptor antagonist. Anakinra has a short half-life, a large therapeutic window, and a well-established safety profile, and can be given by subcutaneous and intravenous routes.[18] Large prospective trials are now under way and results are eagerly awaited.

Safety concerns

Above all, there are serious considerations regarding untoward toxicity. Paramount among safety considerations is the potential for targeted therapies to suppress the host's immune response and further limit failing antiviral defenses. Theoretically, the short-term use of such agents is likely to be less immunosuppressive than observed in long-term clinical use, but this hypothesis remains unproven. Concerns regarding the use of Janus kinase inhibitors is of particular note since they can further serve to suppress type I and III interferons, which are critical in antiviral defense.[20] Also critical is the potential risk associated with the timing of therapy. Administering treatment too early may compromise antiviral immunity, while waiting too long may risk irreversible organ damage.

Other novel therapies

Other novel therapies used alone or in combination include targeting GM-CSF, granulocyte-colony stimulating factor, and Janus kinase. These have been reviewed or mentioned in several excellent narrative reviews.[5,8,13,21]

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Firm lesion on the lateral thigh

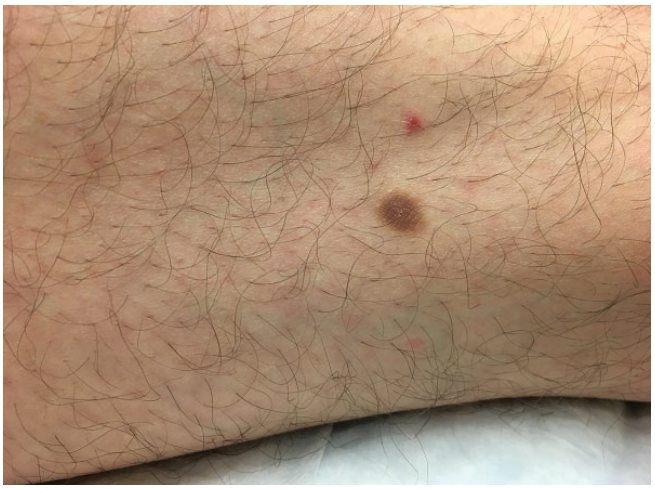

Figure 1. A hyperpigmented nodule on the lateral thigh.

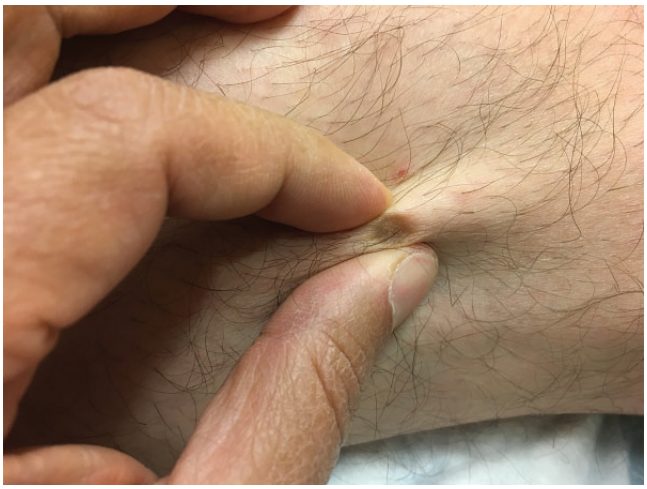

Figure 2. Retraction with lateral compression.

A 41-year-old man presented with concern about a lesion he had first noticed 6 years earlier

A 41-year-old man presented with concern about a lesion on the right lateral thigh that he had first noticed 6 years earlier. The lesion had not changed since that time.

There was no history of trauma or infection to the area. He reported no weight loss, and he said he had not noticed similar lesions elsewhere.

Physical examination revealed a firm, nontender, hyperpigmented nodule (7 mm × 9 mm) on the lateral aspect of his right thigh (**Figure 1**). There was no surrounding erythema or warmth. Lateral pressure on the sides of the lesion produced a depression ("dimple" sign) (**Figure 2**).

Based on the clinical picture and physical examination, the diagnosis of dermatofibroma was made.

THE DIFFERENTIAL DIAGNOSIS

Firm, hyperpigmented, macular or nodular skin lesions are prevalent and seen in a number of conditions (**Table 1**).

Dermatofibroma (fibrous histiocytoma) is a benign proliferation of collagen fiber and other mesenchymal cell lines, likely in response to local inflammation or trauma.[1]

Dermatofibromas are more common in women and typically develop between ages 20 and 50.[1,2] They often present as smooth, slow-growing, firm, tan to reddish brown papules or nodules less than 1 cm in diameter that classically dent on compression.[1–3] They are mostly asymptomatic and may appear anywhere on the body, though 20% are on extremities.[1–3] Lesions are typically darker in color in the center and lighter toward the perimeter.[1–3]

Lentigo maligna is a premalignant melanocytic nevus that may be considered melanoma in situ in its most advanced stages.[4] It has a high risk of progression to invasive melanoma.[4] Lesions typically present on sun-exposed skin such as the head or neck.[4] They appear as heterogeneous asymmetric macules with irregular borders that grow centrifugally.[4] Ultraviolet light examination with a Wood lamp can show extension of the lesion far beyond the pigmented borders.[4]

Treatment is typically by surgical excision with borders greater than 7 mm and

doi:10.3949/ccjm.87a.19107

TABLE 1

Differential diagnosis of a firm, hyperpigmented, macular skin lesion

Condition	Characteristics
Lentigo maligna	Irregular asymmetric pigmented macules that grow centrifugally
Dermatofibrosarcoma protuberans	Similar to dermatofibroma, but larger, irregular border, deeper skin invasion
Seborrheic keratosis	Shiny ("oily"), well-demarcated macule or papule, "stuck-on" appearance
Epidermoid inclusion cyst	Flat or raised flesh-colored cystic lesion; often has dark central punctum; size varies; may spontaneously drain
Dermatofibroma	Slow-growing, firm, tan to reddish-brown papules, < 1 cm, that "dimple" to lateral compression

histopathologic examination of the margins, though radiation and topical imiquimod may be used in specific circumstances.[4]

Dermatofibrosarcoma protuberans is a malignant neoplastic lesion, more common in women and darker-skinned individuals age 30 to 50.[5] It can present as an asymptomatic, slow-growing, violaceous nodule or plaque, more often on the trunk or upper extremities.[5] It is typically larger than a dermatofibroma, with an irregular border and deeper palpable skin invasion.[3] Diagnosis is typically by excisional biopsy.[5] Though it has a low metastatic potential, it can have a great capacity for local invasion and destruction.[5]

Treatment requires excision with exhaustive histopathologic examination of boundaries for tumor cells, either by Mohs micrographic surgery or wide local excision.[5] Adjuvant and neoadjuvant therapies such as radiation and imatinib may also be used in cases refractory to excision or with extensive invasion.[5]

Seborrheic keratosis is a common benign skin tumor that becomes increasingly common with age, though lesions can present at any age.[6] They can be pigmented and so may be mistaken for dermatofibroma, but they do not dimple to lateral compression.[6] They typically present as sharply demarcated ovoid macules or papules 1 cm in diameter and with a shiny ("oily") appearance.[6] They classically appear raised and "stuck on" to the skin.[1,6] Obvious seborrheic keratoses may be monitored, but questionable lesions should be diagnosed with shave excision or curettage and histopathology.[6]

Epidermoid inclusion (sebaceous) cyst is a common cystic lesion that can be flat or raised, with size ranging from a few millimeters to a few centimeters.[1] They often have a dark central punctum, which occasionally drains.[1] They are benign and should be removed only if they cause symptoms such as frequent infection or for cosmetic reasons.[1]

MANAGEMENT OF DERMATOFIBROMA

Most dermatofibromas do not require treatment unless they show signs of malignant progression such as a change in quality or rapid growth.[1,2] It is essential to distinguish them from the far more malignant dermatofibrosarcoma protuberans, as well as melanoma and other malignant lesions. Irregular borders or substantial palpable depth of invasion through skin should prompt excisional biopsy for definitive diagnosis.[3]

Most dermatofibromas do not require treatment unless they show signs of malignant progression

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Mönckeberg medial sclerosis

A man with chronic kidney disease presents with pain and ulceration of the fingers

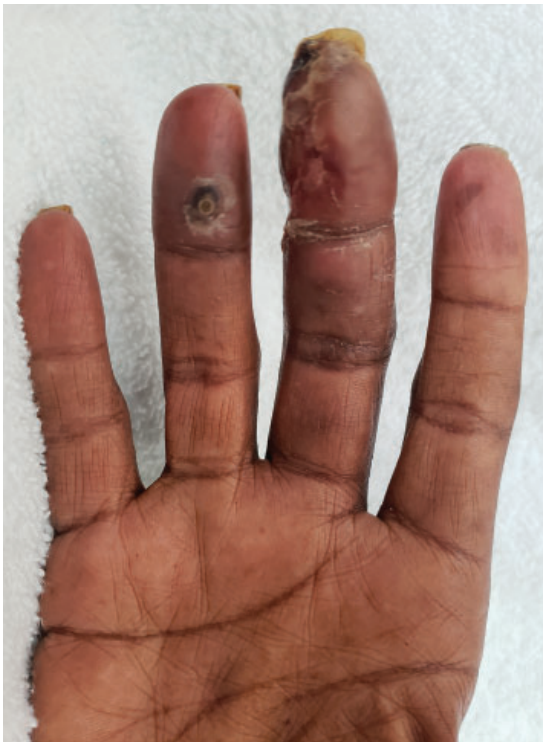

Figure 1. Physical examination revealed purplish discoloration and ulceration of the third and fourth fingertips.

A 59-year-old man presented to the emergency department with pain and ulceration of several fingers on the right hand. He reported no history of trauma. His medical history was significant for chronic kidney disease, coronary atherosclerosis, ischemic cardiomyopathy, and hypertension. He described antecedent pain and discoloration for 1 week, followed by blistering of the fingertips, which became ulcerated 2 days ago. He reported strict adherence to hemodialysis (performed via a tunneled catheter) and medications, including aspirin, clopidogrel, and atorvastatin.

doi:10.3949/ccjm.87a.19085

On examination, the third and fourth fingers of his right hand were purplish with distal ulcerations, worse on the tip of the middle finger (**Figure 1**). Palpation revealed absent radial and ulnar pulses in the right wrist and diminished radial and ulnar pulses in the left. His hands were markedly colder than his upper arms, and the right hand was colder than the left. Suspecting acute limb ischemia, we started systemic anticoagulation with heparin infusion.

Plain radiography of the hands (**Figure 2A**) revealed extensive vascular calcifications of the radial and ulnar arteries with no bony abnormalities. The calcifications were parallel and linear, typical of the "railroad-track" appearance that characterizes Mönckeberg medial sclerosis when the affected vessel is viewed longitudinally. Arterial Doppler ultrasonography found scattered areas of concentric calcified atherosclerotic disease. Computed tomography (CT) angiography confirmed diffuse circumferential calcification. Conventional angiography (**Figure 2B**) bilaterally revealed diminutive radial arteries with significantly delayed flow and occlusion of the ulnar artery bilaterally. The right distal radial artery had severe stenosis.

The vascular stenosis was not amenable to percutaneous intervention, and there were no adequate revascularization options. The right third and fourth digits and the left third digit were amputated. Medical management at discharge included a phosphate binder, vitamin D, a calcimimetic, and an aldosterone antagonist. Antiplatelet and statin therapy were continued. The frequency of hemodialysis was increased.

MÖNCKEBERG MEDIAL SCLEROSIS

The differential diagnosis for digital ischemia is broad, including arterial thromboembolism, vasoconstrictive drug use or disorders, vasculitis, infectious ulceration, Raynaud phenom-

enon, and arterial stenosis. In patients with arteriovenous fistulas, steal syndrome can precipitate ischemia. In this case, there was no evidence of steal syndrome on the more-affected side.

In general, vascular calcifications are characterized by mineral deposits in the walls of arteries, and occur as one of two types:

Intimal layer calcification occurs in atherosclerosis and is characterized by diffuse arterial involvement with late calcifications.

Medial layer calcification occurs in several diseases, of which Mönckeberg medial sclerosis is the most common.[1] It typically involves discrete vascular territories with early calcification.

Mönckeberg medial sclerosis is believed to be driven by hyperphosphatemia[2] and is frequently associated with diabetes and chronic kidney disease. Sclerosis tends to localize to the arteries of the extremities.

The diagnosis is supported by findings on plain radiography (**Figure 2A**) or B-mode ultrasonography (with distinct echogenic granules located in the abluminal layers of the arterial walls), and is confirmed with an ankle-brachial index greater than 1.[1] Recent research into medial layer calcifications has shown it to be an active process initiated and regulated by a variety of molecular signaling pathways.[1]

Compared with treatments for intimal layer calcifications, those for medial layer calcifications in general, and specifically for Mönckeberg medial sclerosis, are less well studied and effective. In patients with a documented disorder of phosphate homeostasis (typically chronic kidney disease with a mineral and bone disorder, as is the case for this patient), prevention and treatment includes phosphate binders, low-dose vitamin D, calcimimetics, magnesium, bisphosphonates, sodium thiosulfate, and aldosterone antagonists.[3–5] In patients with skin lesions suggesting calciphylaxis, the recommended combined medical and surgical treatment includes the following:

- Lowering the calcium and phosphate concentrations
- Increasing the frequency of hemodialysis
- Giving intravenous thiosulfate
- Hyperbaric oxygen
- Wound care
- Debridement of necrotic tissue.[6]

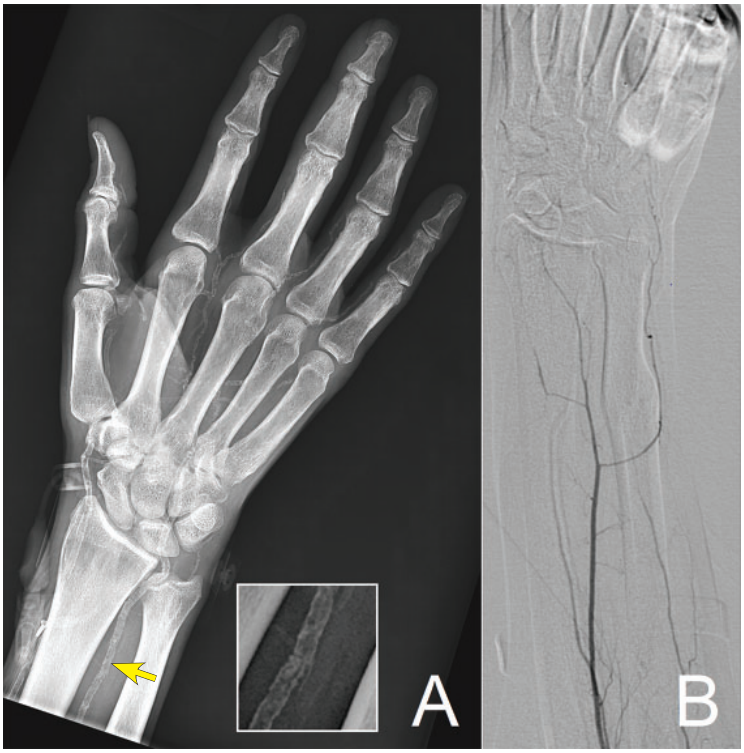

Figure 2. Plain radiography (A) and conventional angiography (B) demonstrated a "railroad-track" pattern (ulnar artery at arrow magnified in the inset), with severe arterial calcifications and a smooth endothelial interface, features typical for Mönckeberg medial sclerosis.

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does a short QT interval increase the risk of cardiac death in healthy people?

A: In healthy people without symptoms, a short QT interval by itself does not necessarily increase the risk of sudden cardiac death and may in fact be a normal variant. However, it may warrant further investigation to determine if the patient is at risk.[1–3]

Most agree that a QTc < 330–340 ms is diagnostic of short QT syndrome

CORRECTING THE QT INTERVAL

The corrected QT interval (QTc) should be calculated. However, this should not be done when the patient is in tachycardia or bradycardia (using long-term electrocardiographic monitoring or beta-blockers if needed) to prevent the use of the Bazett formula at heart rates in which its correction is not linear and may lead to overestimation or underestimation of QTc values.[2] Furthermore, in patients with short QT syndrome, the physiologic abbreviation of the QT interval during tachycardia can be blunted (pseudonormalization of the QT interval) with failure to prolong the QT interval at slower heart rates, which contributes to the poor performance of correction formulas with heart rates above 100 beats/min or below 60 beats/min.

WHAT IS NORMAL?

The definition of the lower limit of the normal QT interval is a matter of debate. Mason et al[4] analyzed the electrocardiograms of 79,743 healthy people (including babies and children) and found that a QTc value 2 standard deviations below the mean was 350 ms in males and 360 ms in females. Many cardiac society guidelines deem that a QTc less than those values should be considered short, and a QTc interval less than 330 to 340 ms should be considered extremely short.[1,2,4,5]

doi:10.3949/ccjm.87a.19090

Applying the cutoff of 2 standard deviations, the prevalence of a short QT interval is around 2%.[4] Although this cutoff is sensitive, it takes in a large number of people who are not really at risk, and it does not necessarily predict arrhythmogenic potential.[6]

Proposed diagnostic criteria for short QT syndrome

The threshold of 360 ms is considered diagnostic of short QT syndrome if it is accompanied by 1 or more of the following:

- Pathogenic mutation
- Family history of short QT syndrome
- Family history of sudden death before age 40
- Survival of an episode of ventricular tachycardia-ventricular fibrillation (VT-VF) in the absence of heart disease.

Most experts agree that even without any of these factors, a QTc shorter than 330 to 340 ms is diagnostic of short QT syndrome, as such values are very rare in a healthy population.

DIFFERENTIAL DIAGNOSIS

Diagnosing short QT syndrome can be challenging, owing to the overlapping QT range of at-risk and healthy populations. Patients with short QT syndrome with normal QT interval have been reported, but in most cases, the QTc interval is less than 360 ms.

Assess for acquired causes first

Acquired causes of short QT interval should be considered first. Potential causes of nongenetic QT shortening include:

- **Hypercalcemia, hyperkalemia, acidosis, and hyperthermia**[7]
- **Drug effects**, eg, from digitalis,[8] nicorandil (through activation of adenosine triphosphate [ATP]-sensitive potassium

channels),[9] isavuconazole (through inhibition of L-type calcium channels),[10] and lamotrigine[9]

- **Effect of acetylcholine and increased vagal tone,** through activation of acetylcholine-sensitive potassium channels. This leads to deceleration-dependent shortening of the QT interval (ie, paradoxical QT interval shortening with a decrease in heart rate instead of lengthening)[11]
- **Effect of catecholamines,** through beta-adrenoceptor-induced activation of ATP-sensitive potassium channels[12]
- **Myocardial ischemia** through activation of ATP-sensitive potassium channels[12]
- **Ventricular fibrillation,** possibly related to increased intracellular calcium[13]
- **Androgen use**.[14]

Genetic causes

After considering possible acquired causes of short QT syndrome, the proposed diagnostic criteria discussed above should be satisfied before evaluating for a genetic cause.[1,2,6]

Short QT syndrome can be caused by a rare inherited genetic channelopathy associated with markedly shortened QT intervals and a structurally normal heart. Electrocardiography usually shows short or absent ST segments, tall and narrow T waves, marked shortening of the interval from the J point to the T peak (< 120 ms), and the signature sign of short QT intervals in the precordial leads.

Ion channel defects associated with short QT syndrome may be caused by mutations in potassium channels (KCNH2, KCNQ1, KCNJ2), calcium channels (CACNA1C, CACNB2, CACNA2D1), or carnitine channels (SLC22A5), leading to an abnormal acceleration of repolarization. This predisposes patients to the risk of reentry and hence atrial arrhythmias, ventricular arrhythmias, and sudden cardiac death. Often, patients with calcium channel mutations have a Brugada syndrome pattern on electrocardiography in addition to a short QT interval, either spontaneously or in response to a drug challenge with a class I antiarrhythmic agent.[15]

MANAGEMENT

A short QTc interval (330–360 ms) in isolation—ie, in the absence of pathogenic mutations, family history, or clinical history criteria proposed for the diagnosis of short QT syndrome—may not be associated with an increased risk of sudden cardiac death. Such patients are classified as having a low probability for the diagnosis of short QT syndrome and observation is recommended, providing that other acquired causes of short QT interval have been excluded.[1–3]

For patients who satisfy the proposed diagnostic criteria for short QT syndrome, the optimal strategy of primary prevention is unclear. Placement of an implantable cardioverter-defibrillator (ICD) or prescribing quinidine or sotalol may be considered on an individual basis in patients without symptoms but with a strong family history of sudden cardiac death and evidence of short QTc in some of the victims; otherwise, observation is recommended.[1,2]

For patients with short QT syndrome who survived cardiac arrest or have spontaneous sustained VT with or without symptoms, ICD implantation is recommended.[1–3] Quinidine or sotalol should be considered in patients who qualify for an ICD but have a contraindication or refuse one.[1,3] Finally, isoproterenol infusion can be useful in short QT syndrome with VT-VF storm.[3]

Referral for electrophysiologic study is not recommended for sudden cardiac death risk stratification or arrhythmia risk prediction.[1,3]

In patients with short QT syndrome, genetic testing should be considered. Those determined to have a mutation causative for short QT syndrome should have genetic counseling, and first-degree relatives should undergo mutation-specific genetic testing.[3]

A cutoff of 360 ms does not necessarily predict arrhythmogenic potential

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The role of ISCHEMIA in stable ischemic heart disease

ABSTRACT

Although it is well established that adding early revascularization to optimal medical therapy reduces mortality and recurrent myocardial infarction in acute coronary syndrome, there is less convincing evidence to guide intervention in stable ischemic heart disease. This review summarizes the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial, which investigated whether there is benefit from initial catheterization and possible revascularization in addition to optimal medical therapy in patients with at least moderate ischemia on stress testing.

KEY POINTS

ISCHEMIA randomly assigned 5,179 patients with moderate or severe ischemia to an initial invasive strategy plus optimal medical therapy, or optimal medical therapy alone.

Over a median of 3.2 years, there was no significant difference between the 2 groups in the incidence of the primary outcome (a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable, angina, heart failure, or resuscitated cardiac arrest) or in a number of important secondary outcomes.

Decisions regarding treatment of stable ischemic heart disease must remain individualized.

Dr. Ellis has disclosed speaking, teaching, consulting, or serving on an advisory committee for Medtronic.

doi:10.3949/ccjm.87a.20033

The current American College of Cardiology and American Heart Association guidelines recommend coronary angiography as a "reasonable" approach (class IIA indication) in patients with suspected stable ischemic heart disease in whom the clinical characteristics and noninvasive testing indicate a high likelihood of severe coronary artery disease.[1] However, uncertainty has persisted about whether to pursue an initial invasive approach as opposed to optimal medical therapy alone.

See related commentary, page 410

This review summarizes the recent International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial, which investigated whether there is benefit from initial catheterization and possible revascularization in addition to optimal medical therapy in patients with at least moderate ischemia on stress testing.

VARIABLE FINDINGS IN EARLIER TRIALS

Observational studies have suggested that myocardial perfusion imaging may help to risk-stratify patients with stable ischemic heart disease and identify those who may benefit from revascularization.[2,3] Patients with mild ischemia have been shown to have a good prognosis with optimal medical therapy alone, while those with moderate or severe ischemia seem to have survival benefit when treated with percutaneous coronary intervention (PCI) in addition to optimal medical therapy.

However, subsequent randomized controlled trials cast doubt on this notion and raised questions regarding the ideal initial management of stable ischemic heart disease.

These trials have not shown a reduction in the rates of death or cardiovascular events with PCI compared with optimal medical therapy alone.[4–6] On the other hand, PCI has been shown to reduce the rates of urgent or unplanned revascularization and spontaneous myocardial infarction, and improve angina symptoms and quality of life.[4–6]

The trials of stable ischemic heart disease treatment have been very heterogeneous in terms of design, patient selection, mode of revascularization, and medical therapies, leading to several limitations in their generalizability and applicability to current practice.

One of the main limitations was the inclusion of a broad population of patients with and without objective evidence of ischemia and without a specific threshold of required ischemia on a stress test. Patients with moderate or severe ischemia were more rarely included, based on earlier observations that the severity of ischemia may be associated with increased mortality, and revascularization may be associated with better prognosis.[2,3]

While the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed no improvement in the primary outcome of all-cause mortality and nonfatal myocardial infarction with PCI,[4] a substudy showed that PCI plus optimal medical therapy was associated with a greater reduction in inducible ischemia on follow-up myocardial perfusion imaging, and those who experienced a reduction in ischemia had a lower unadjusted risk of death or myocardial infarction.[7] However, in this substudy, 70% of the participants had only a small amount of ischemia (< 10%), and with risk adjustment the reduction in death and myocardial infarction was not significant.[7]

In previous trials, medical therapy consisted primarily of antianginal medications rather than modern disease-modifying agents

The COURAGE substudy,[7] along with the prior observations by Hachamovitch et al,[2] again suggested potential benefit from revascularization with more significant ischemia. Nevertheless, this evidence should be used with caution, given its retrospective nature and that it comes from a substudy of a larger trial.

Further complicating the picture, in earlier trials the patient's coronary anatomy was often known before randomization, and this knowledge may have introduced bias in patient selection by limiting the inclusion of patients who had significant angiographic coronary artery disease, such as those with proximal left anterior descending or multivessel disease.[4] More specifically, physicians and patients may have been reluctant to participate in a randomized trial, knowing that the coronary angiogram showed significant coronary artery disease.

Additionally, the invasive approach in previous trials was quite variable, ranging from balloon angioplasty to bare-metal stents and first- and second-generation drug-eluting stents. These trials did not use the newest-generation drug-eluting stents, which are associated with improved outcomes. Also omitted in many studies was the use of newer invasive intravascular techniques to assess the hemodynamic significance of intermediate lesions, such as fractional flow reserve, instantaneous wave-free ratio, intravascular ultrasonography, and optical coherence tomography, which assist with the appropriate selection of lesions requiring intervention and improve revascularization outcomes.[5]

In the previous trials, optimal medical therapy consisted primarily of antianginal medications rather than modern disease-modifying agents such as aspirin, statins, beta-blockers, and renin-angiotensin-aldosterone system inhibitors, which are now considered the foundation of medical therapy and lead to better outcomes.

Lastly, the trials were open-label, and the control groups did not undergo sham procedures, which may have introduced bias regarding the true beneficial effect of PCI in reducing angina. The Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA),[8] the only randomized trial that used a sham procedure, showed no difference in exercise time in patients with stable angina undergoing PCI compared with medical therapy. This finding suggests that PCI may be associated with a placebo effect.[8]

Meta-analyses of stable ischemic heart disease treatment have also reported variable findings. For example, Gada et al[9] performed a meta-analysis that showed a reduction in all-cause mortality with addition of PCI to optimal medical therapy. This meta-analysis included 3 randomized controlled trials

(COURAGE Nuclear Substudy, the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 trial, the Swiss Interventional Study on Silent Ischemia Type II), that enrolled 1,557 patients with stable ischemic heart disease and objective evidence of myocardial ischemia by noninvasive imaging tests or fractional flow reserve.[5,7,10]

Bangalore et al[11] found a reduction in spontaneous myocardial infarctions with PCI compared with optimal medical therapy alone at the expense of periprocedural myocardial infarctions, resulting in no difference overall.

In a meta-analysis by Stergiopoulos et al,[12] PCI plus optimal medical therapy was not associated with a reduction in death, myocardial infarction, unplanned revascularization, or angina compared with optimal medical therapy alone, but again, the severity of ischemia was quite variable among the different studies.

Over the past decade, PCI technology and technique have improved, and so have invasive outcomes. Similarly, improvement in primary and secondary prevention of cardiovascular disease with disease-modifying, rather than purely symptom-controlling medications, has led to equipoise and brought into question the utility of routine revascularization in stable ischemic heart disease. As a result, current practice varies widely, with many centers using stress perfusion imaging and the severity of ischemia to guide revascularization. This uncertainty set the stage for a new large randomized controlled trial in patients with stable ischemic heart disease and high-risk ischemic features.

ISCHEMIA TRIAL DESIGN

The purpose of ISCHEMIA was to evaluate if a routine initial invasive approach with cardiac catheterization and possible revascularization provides any additional benefit compared with optimal medical therapy alone in patients who have symptoms of stable ischemic heart disease and evidence of moderate or severe ischemia on stress testing.

Exclusion criteria included heart failure with reduced ejection fraction (left ventricular ejection fraction < 35%), New York Heart Association class III or IV symptoms, hospitalization for heart failure within 6 months, coronary artery bypass grafting (CABG) or PCI within 1 year, or acute coronary syndrome within 2 months. Also excluded were patients with "severe angina despite maximal medical therapy," Canadian Cardiovascular Society class III angina of recent onset, or class IV angina, or who were "very dissatisfied" with medical management.[13]

From July 26, 2012, through January 31, 2018, investigators enrolled 8,518 patients and randomized 5,179 to optimal medical therapy alone vs optimal medical therapy plus an initial invasive approach, with coronary angiography followed by PCI or CABG based on decisions made by the heart team.

Most of the patients underwent blinded coronary computed tomographic (CT) angiography before randomization to exclude left main artery stenosis (≥ 50%) and ensure the presence of significant coronary artery disease (≥ 50% stenosis in a major epicardial vessel for those undergoing stress imaging and ≥ 70% stenosis in a proximal or mid vessel for those undergoing exercise tolerance testing).[13,14]

Of the 3,339 excluded patients, 12.9% had unprotected left main disease, 36.4% did not have obstructive coronary artery disease on CT angiography, and 40.4% did not have moderate or severe ischemia based on core laboratory assessment.[15]

Over the past decade, PCI has improved, and so has medical therapy

Owing to slow enrollment, a protocol amendment in January 2014 permitted the inclusion of patients with exercise-induced ischemic electrocardiographic changes without adjunctive imaging. The inclusion criteria were also expanded to patients who demonstrated 5% or more ischemia on nuclear perfusion imaging at low levels of exertion (≤ 7 metabolic equivalents).[13]

The primary end point was originally defined in 2012 as the composite of cardiovascular death and myocardial infarction. Due to low event rates, the primary end point was expanded in 2018, just 7 months before enrollment completion, to also include resuscitated cardiac arrest, hospitalization for unstable angina, and hospitalization for heart failure.[16] The myocardial infarction events included both spontaneous and periprocedural infarctions. The definitions of periprocedural myocardial infarctions (PCI- and CABG-related) included elevation in cardiac biomarkers and

electrocardiographic changes according to the most recent proposed definition of clinically relevant myocardial infarction after revascularization, from the Society for Cardiovascular Angiography and Interventions.[15,17]

POPULATION CHARACTERISTICS

The median age of the study participants was 64. Among the participants, 23% were women, and 66.3% were white. Regarding history, 73.4% had hypertension, 41.8% had diabetes, 57.4% had a history of smoking, and 19.2% had a history of myocardial infarction. Regarding angina frequency, 43.9% of the patients reported having angina monthly, 19.5% weekly, 2.3% daily, while 34.4% reported no angina in the month prior to randomization and 10.3% had no history of angina.[14]

Most of the patients were receiving optimal medical therapy by contemporary standards at baseline (94.1% were receiving antiplatelet drugs, 94.8% statins at any dose, 36.7% high-intensity statins, 4.1% ezetimibe, 80.4% beta-blockers, and 66% angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). As for other antianginal medications, long-acting nitrates were used in 32.3%, calcium channel blockers in 30.5%, and ranolazine in 5% of the patients.[14]

Outcomes did not differ significantly between the two treatment groups

Regarding coronary artery disease, 75% of the patients qualified on the basis of stress imaging tests (nuclear myocardial perfusion imaging in 49%, stress echocardiography in 21%, cardiac magnetic resonance imaging in 5%). According to core laboratory interpretation, 44.8% of those with stress imaging tests had severe ischemia, 41% had moderate, 8.1% had mild, and 6% had no ischemia or the test was uninterpretable.[14,15]

The remaining 25% of the patients qualified on the basis of abnormal exercise tolerance testing. For these patients, stricter criteria were applied for their participation, including history of angina, an interpretable resting electrocardiogram, exercise-induced 1.5-mm ST-segment depression in 2 leads or 2-mm ST-segment depression in 1 lead or 1.5-mm ST elevation in a noninfarct territory occurring at early stages of the exercise tolerance test, and at least 70% stenosis in a coronary artery serving a large myocardial region based on CT angiography (proximal or mid left anterior descending, proximal or mid right coronary artery, or proximal left circumflex artery).[14,15]

RESULTS

Over a median follow-up period of 3.2 years, cardiac catheterization was performed in 96% of the invasive treatment group and 28% of the optimal medical therapy group. Indications for catheterization in the optimal medical therapy group included suspected or confirmed events (13.8%), medical therapy failure (3.9%), and nonadherence (8.1%). Coronary revascularization was performed in 80% of the invasive therapy group (74% PCI, 26% CABG) and 23% of the medical therapy group. Of the 20% of the invasive therapy group who did not undergo revascularization, two-thirds had insignificant disease on angiography and the other third had extensive coronary artery disease not suitable for any mode of revascularization.[15]

Outcomes

Outcomes did not differ significantly between the 2 treatment groups.

The composite primary outcome (cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) occurred in 13.3% of the invasive therapy group vs 15.5% of the optimal medical therapy group (hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.80–1.08, $P = .34$) (**Figure 1A**).

The major secondary end point (cardiovascular death or myocardial infarction occurred in 11.7% vs 13.9% (HR 0.90, 95% CI 0.77–1.06, $P = .21$) (**Figure 1B**).

Death from any cause occurred in 6.5% vs 6.4%, which were low rates ($P = .67$) (**Figure 1C**).

Myocardial infarction rates were similar (HR 0.92, 95% CI 0.76–1.11, $P = .38$) (**Figure 1D**). However, there were more periprocedural infarctions (HR 2.98, 95% CI 1.87–4.74, $P < .01$) and fewer spontaneous infarctions (HR 0.67, 95% CI 0.53–0.83, $P < .01$) in the invasive therapy group.

Hospitalizations. The invasive therapy group had fewer hospitalizations for unstable angina (HR 0.50, 95% CI 0.27–0.91, $P = .02$), but more hospitalizations for heart failure (HR 2.23, 95% CI 1.38–3.61, $P < .01$).

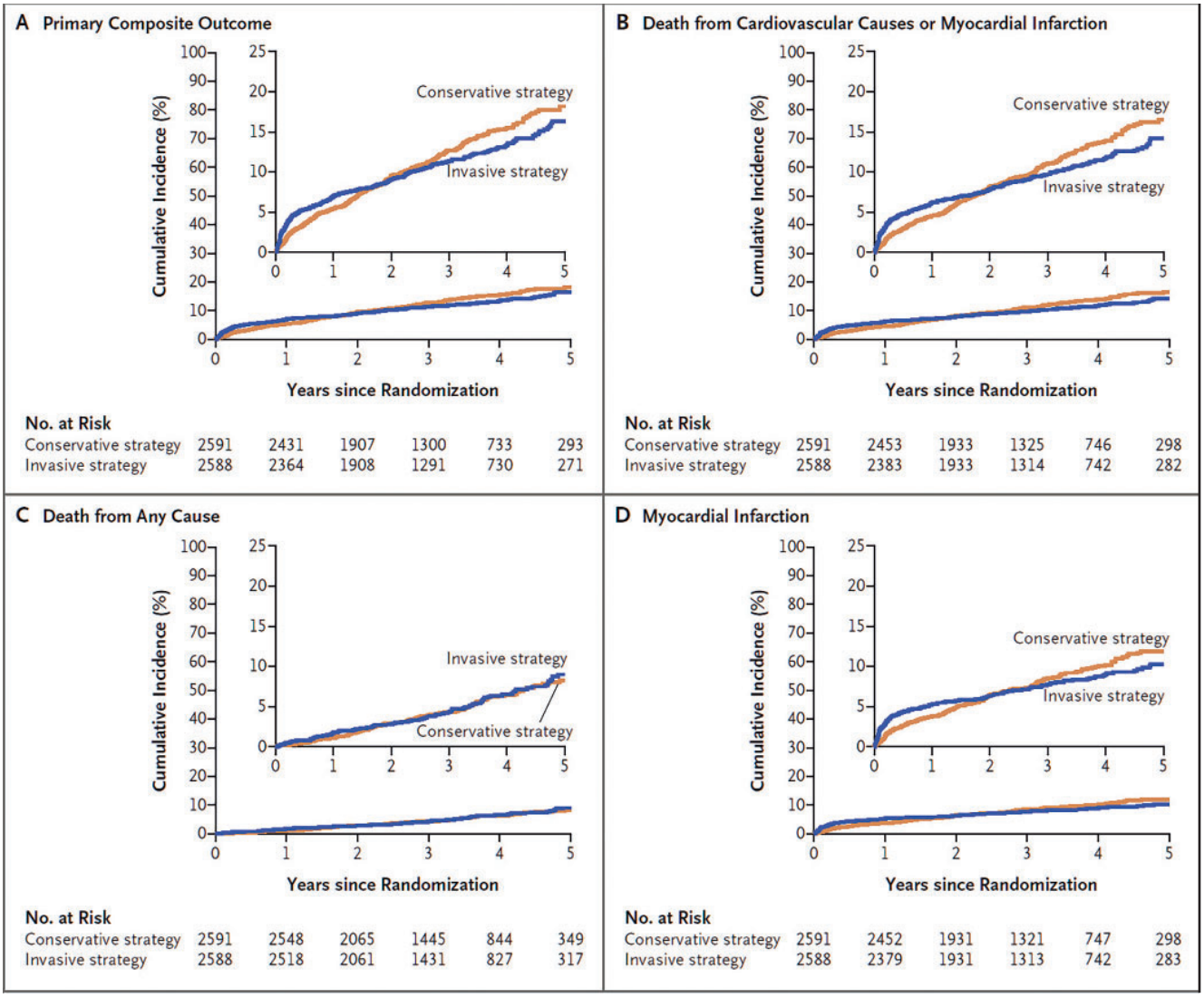

Figure 1. Time-to-event curves in the ISCHEMIA trial. The primary composite outcome consisted of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest.

Stroke and resuscitated cardiac arrest rates were similar between the 2 groups.[15]

Angina. The invasive therapy group experienced more reduction in angina frequency at 3 months than the optimal medical therapy group. In terms of quality of life, patients with moderate or severe ischemia and frequent angina (daily, weekly, or monthly) had better angina control with the invasive strategy.[15]

The outcomes were similar between the 2 groups irrespective of the type of stress modality used, severity of ischemia, or extent of coronary artery disease on CT angiography.[15]

STRENGTHS OF THE TRIAL

ISCHEMIA was the first large randomized controlled trial in the field of stable ischemic heart disease to include mainly patients with moderate to severe ischemia on stress testing as well as anatomic evidence of coronary ar-

tery disease based on CT angiography. Various forms of stress tests were used to quantify ischemia, including nuclear myocardial perfusion imaging, stress echocardiography, stress magnetic resonance imaging, and exercise electrocardiography, with the inclusion criteria for the latter being stricter, as described above.

Unlike previous trials, ISCHEMIA did not require the coronary anatomy to be angiographically defined before randomization, thus reducing possible selection bias. Moreover, up-front knowledge of coronary anatomy could increase the risk of ascertainment bias among providers and patients by potentially increasing reported events and crossovers in the optimal medical therapy group.

Although the coronary anatomy was not fully defined, most of the patients were screened with CT angiography before randomization to exclude significant left main artery disease and to ensure the presence of coronary artery disease in an effort to minimize the inclusion of patients with false-positive stress tests. Based on CT angiography, most patients had evidence of high-risk coronary artery disease, as reflected in the disease of multiple vessels in 79%, left anterior descending artery in 86.8%, and proximal left anterior descending artery in 46.8%.[14,15]

Groups who were excluded represent a significant portion of patients seen in daily practice

One of the main strengths of ISCHEMIA was the use of contemporary revascularization strategies: 98% of the patients in the PCI group received latest-generation drug-eluting stents, and 93% in the CABG group received arterial grafts. Additional evaluation of intermediate lesions was performed with the use of the most advanced available technology in the catheterization laboratory (fractional flow reserve, instantaneous wave-free ratio, intravascular ultrasonography), although their use was relatively limited.[18]

LIMITATIONS OF THE TRIAL

Although ISCHEMIA was originally designed to include only patients with moderate or severe ischemia on stress imaging, challenges with recruitment led to the inclusion of patients with less ischemia as well as patients who met only the exercise tolerance testing criteria.[13] In fact, 14.1% of patients who underwent stress imaging and 9% of those who underwent exercise tolerance testing had mild or no ischemia or an uninterpretable stress test based on core laboratory assessment.[14] This was addressed by the authors, who found no effect on the primary outcome in an analysis of heterogeneity of treatment effect.[15] Exercise electrocardiographic testing without imaging was also used more often (in 24.5%)[14] than in contemporary practice, in which imaging modalities are generally preferred for the assessment and quantification of ischemia.

Perhaps also related to poor enrollment was the inclusion of patients with no angina (10.3%) and patients who had not had angina within the month before randomization (34.4%).[14] While this certainly represents a subset of patients who undergo stress testing (eg, during preoperative assessment in patients who cannot accomplish 4 metabolic equivalents), it is unclear whether those without symptoms or those whose symptoms have subsided are at the same risk as those with active or more significant burden of angina. More importantly, if this subset of patients with minimal symptoms overlapped considerably with those with mild or no ischemia, they may represent a low-risk population and their inclusion may have attenuated the potential benefit of an invasive strategy.

A second limitation of the study was the large proportion of outcome events that were myocardial infarctions, either periprocedural or spontaneous. This in part was due to low mortality rates relative to the rates of myocardial infarction and the other measures included in the composite primary outcome. Early on, rates of periprocedural myocardial infarction were higher in the invasive treatment group, but later, rates of spontaneous myocardial infarction were higher in the optimal medical therapy group. While these rates are combined in the outcome of total myocardial infarctions, the authors state that a preliminary analysis of ISCHEMIA data supports the findings of previous studies showing that spontaneous myocardial infarction is associated with higher morbidity and mortality rates than periprocedural myocardial infarction.[15,19] Furthermore, given the trends noted in the time-to-event curves, the 2 groups may continue to diverge in the primary composite outcome, with lower rates in the invasive

therapy group. Therefore, longer follow-up is warranted to fully understand the prognostic implications of the different spontaneous and periprocedural myocardial infarction rates between the 2 groups.[20]

A third and probably the most important limitation is the applicability of ISCHEMIA results to current practice. Changing the primary end point to include "softer" and more subjective clinical end points such as hospitalization for heart failure or unstable angina, as well as including patients with less ischemic burden than originally planned, raises concerns about the trial's applicability to clinical practice and ability to answer the main study question.

Additionally, only 22.6% of the study participants were women, and women were more often excluded for having less ischemia on stress testing and less obstructive coronary artery disease on CT angiography.[14]

Importantly, patient groups who were excluded, such as those with heart failure, significant angina, or revascularization within a year, represent a significant portion of patients with stable ischemic heart disease symptoms encountered in daily clinical practice.

Several features of the ISCHEMIA trial were not completely addressed in its publications or supplementary materials. For example, more information is needed about the use of intravascular ultrasonography or physiologic measures such as instantaneous wave-free ratio or fractional flow reserve in guiding coronary interventions in the invasive group. The appendix reports only generally on fractional flow reserve, stating that it was used in 20.3% of patients in the invasive therapy group in their initial catheterization, but does not detail how that influenced treatment decisions.[18] Although these strategies are not routinely used in most PCI cases, the benefit from their use in reduction of major adverse cardiovascular events and improvement in interventional outcomes has been well established.[21,22]

Finally, a comparison between the PCI and CABG subgroups of the invasive therapy group in terms of patient characteristics, severity and location of coronary lesions, completeness of revascularization, and outcomes is not included in the publication.

CLINICAL IMPLICATIONS

Based on the findings of the trial, the utility of stress testing in the assessment of stable ischemic heart disease is brought into question, as the presence of moderate or severe ischemia did not seem to lead to severe adverse outcomes regardless of invasive or conservative approach. Additionally, the trial shows the weaknesses of these assessments as tools to reliably diagnose obstructive coronary disease; a modest proportion (21%) of patients did not have 50% or greater stenosis on CT angiography, showing the differences between anatomic evidence of epicardial coronary artery disease and physiologic evidence of ischemia.[14] This finding could also be related to the inclusion of patients with mild or no ischemia as described above. Furthermore, about 15% of patients in the invasive group did not have obstructive coronary artery disease on angiography, highlighting the significant rate of false-positive stress tests.[15]

As noted, an important group that was excluded was patients with left main stenosis of 50% or more on CT angiography (7.5% of the patients who underwent this test).[14] By virtue of this protocol, an anatomic study (CT angiography or cardiac catheterization) would be necessary for a patient undergoing evaluation for stable angina in order to exclude left main disease. This may lead to more providers obtaining anatomic studies initially, potentially at the expense of stress testing, in the evaluation of patients with stable angina. While outside the scope of this review, available data about the use of CT angiography in suspected stable ischemic heart disease have not shown improvement in "hard" clinical outcomes compared with functional stress testing, although it led to fewer "unnecessary" catheterizations showing no obstructive coronary artery disease.[23]

The findings of the trial have brought into question the utility of stress testing in assessment of stable ischemic heart disease

Therefore, the optimal sequence of diagnosing obstructive coronary artery disease and evaluating stable coronary disease is in question. Given the false-positive rate of functional stress tests and need to exclude left main stenosis, up-front evaluation with CT angiography may be warranted in many cases.

When significant left main disease has been excluded, the provider should addition-

ally ensure that the patient is similar to the population enrolled in ISCHEMIA, taking into account the other exclusion criteria. If that is the case, proceeding with either an initial invasive strategy or conservative approach will then require an informed decision that will vary based on individual patient factors after risk/benefit discussion.

CONCLUSIONS AND FUTURE DIRECTIONS

The results of ISCHEMIA are consistent with those of previous trials in patients with stable ischemic heart disease, suggesting that despite a reduction in symptoms, angina-related hospitalizations, and spontaneous myocardial infarction, there is no clear survival benefit from an initial invasive strategy compared with optimal medical therapy alone after a follow-up period of 3.2 years, even in patients with moderate or severe ischemia.

Taking into account the limitations described above, it is not apparent that the results of this trial will significantly alter the current practice of stable ischemic heart disease management. Deciding between an initial invasive vs a conservative approach in patients who present with stable angina has been—and should continue to be—individualized, based on patient preference, angina severity, ability to tolerate optimal doses of antianginal therapy, availability of diagnostic testing, and risk of procedural complications associated with coronary interventions.

Future studies will need to address the optimal sequence and selection of noninvasive testing to better risk-stratify patients presenting with symptoms of stable ischemic heart disease. Identifying patients who may benefit from an initial invasive approach as well as the optimal management of the patient groups not included in ISCHEMIA should be the focus of future randomized trials.

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COMMENTARY

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Stable coronary artery disease: Intervene or not?

Stable coronary artery disease needs a patient-centered approach; one size does not fit all

When the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial[1–3] was presented at the American Heart Association meeting in November, 2019, it generated multiple headlines in major news sources. CNN covered the story by saying, "For heart disease, meds may work as well as invasive surgery, major trial shows."[4] *The Washington Post* published a story entitled "Stents and bypass surgery are no more effective than drugs for stable heart disease, highly anticipated trial results show."[5]

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Neither these nor other similar headlines accurately convey the current body of evidence regarding the role of coronary revascularization in patients with coronary artery disease. The benefits of early revascularization in reducing mortality and reinfarction risk have been well established in patients who have unstable angina at rest, acute myocardial infarction, and significant unprotected left main coronary artery disease.[6–9] However, since the publication of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[10] in 2007, we have also known that patients with stable angina or ischemia do not experience a reduction in the risk of death, myocardial infarction, or cardiac arrest with percutaneous coronary intervention. Importantly though, percutaneous coronary intervention is associated with better relief of ischemic symptoms and quality of life than medical therapy alone.

Here, we describe the design, results, and limitations of the recent ISCHEMIA trial[1–3] and how its findings confirm and expand our existing understanding of the role of coronary revascularization in patients with stable ischemic syndromes.

doi:10.3949/ccjm.87a.20048

ISCHEMIA TRIAL DESIGN AND METHODOLOGY

The ISCHEMIA trial[1–3] was a randomized trial that compared, in a 1-to-1 ratio, an initial invasive or conservative treatment strategy in 5,179 patients with stable coronary artery disease with moderate or severe ischemia by noninvasive stress testing.

The key exclusion criteria were:

- Significant unprotected left main coronary artery disease (≥ 50% stenosis)
- Estimated glomerular filtration rate less than 30 mL/min/1.73 m^2
- New York Heart Association class III or IV heart failure
- Recent myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting
- Severe left ventricular dysfunction (ejection fraction < 35%)
- Intolerable angina at baseline.

All patients received guideline-directed optimal medical therapy. Coronary computed tomography was performed to exclude left main disease unless the coronary anatomy was previously defined. Patients with renal dysfunction did not undergo coronary computed tomography. The invasive strategy group underwent coronary angiography followed by revascularization within 1 month after randomization.

The primary end point of the trial was a composite of cardiovascular death, nonfatal myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure,

or resuscitated cardiac arrest. The key secondary end points in North American participants were a composite of cardiovascular death and nonfatal myocardial infarction, angina, and measures of quality of life and health economics.

Concurrent studies were performed in patients with advanced chronic renal failure[11] and nonobstructive coronary artery disease with inducible ischemia.

TRIAL RESULTS

It took over a decade for the trial investigators to enroll 8,518 patients after screening nearly 26,000 candidates.

Of these 8,518 patients, 3,339 were excluded for various reasons, eg:

- 1,350 did not have moderate or severe ischemia on stress testing
- 1,218 did not have obstructive coronary artery disease
- 434 had left main coronary artery disease.

Coronary computed tomography was performed in 73% of patients.

Most (77%) of the patients were men, and the median age was 64. About 40% had diabetes mellitus. Most (90%) had a history of stable angina, and 29% had progressive angina in the previous 3 months, while 34.3% had no angina in the previous 4 weeks. Moderate to severe ischemia was documented in 87%. Nearly everyone in the trial was receiving a statin and aspirin, nearly 60% had a low-density lipoprotein cholesterol level less than 70 mg/dL, and 77% had a systolic blood pressure lower than 140 mm Hg.

Among patients randomized to the invasive strategy, approximately 80% underwent revascularization, of whom 25% underwent surgical revascularization (using the internal mammary artery in 92%). Most of the percutaneous coronary interventions were performed using second-generation drug-eluting stents (n = 1,329).

In the conservative strategy group, 28% of the patients ultimately underwent cardiac catheterization and revascularization for suspected or confirmed events (13.8%), optimal medical therapy failure (3.9%), or nonadherence (8.1%).

In the invasive strategy group, conventional coronary angiography confirmed triple-vessel disease (≥ 50% stenosis on quantitative coronary angiography) in 39.6% of the patients. More than one-third of the patients had proximal left anterior descending lesions (≥ 50% stenosis on quantitative coronary angiography). Fractional flow reserve-guided revascularization was performed in 20.3% of the cases. More than 400 patients in the invasive-strategy group underwent no revascularization, as a large proportion (221) of them had nonobstructive coronary artery disease. Coronary anatomy was found to be unsuitable for revascularization in 111 patients, and 28 patients preferred not to undergo revascularization.

Outcomes

After a median follow-up of 3.2 years, the event rates in the invasive vs conservative strategy groups did not differ significantly for the primary outcome (hazard ratio [HR] 0.93, 95% confidence interval [CI] 0.80–1.08) or cardiovascular death or myocardial infarction (HR 0.90, 95% CI 0.77–1.06).

However, the rate of spontaneous myocardial infarction was lower in the invasive strategy group (HR 0.67, 95% CI 0.53–0.83), as was the rate of hospitalization for unstable angina (HR 0.50, 95% CI 0.27–90). The rate of periprocedural myocardial infarction was higher in the percutaneous coronary intervention group than in the medical therapy group (HR 2.98, 95% CI 1.87–4.74), although periprocedural myocardial infarctions have been shown to have less prognostic importance (unless associated with Q waves or creatine kinase-MB > 10 times the upper limit of normal) than spontaneous myocardial infarctions.[12]

This finding raises the intriguing possibility of the benefit of revascularization in reducing spontaneous myocardial infarctions beyond symptom improvement in this patient population. However, spontaneous myocardial infarction was not a prespecified end point and thus must be regarded as a hypothesis-generating result that requires further validation. Moreover, the greater incidence of spontaneous myocardial infarction did not affect overall mortality, at least over the median 3.2 years of follow-up. Long-term follow-up might shed more light on the impact of spontaneous myocardial infarction on mortality and whether

More than a decade was needed to enroll 8,518 patients, after screening nearly 26,000 candidates

the rates of myocardial infarction continue to diverge between the 2 treatment groups over time. It would also be interesting to see the characteristics of the spontaneous myocardial infarction in each cohort, especially if they were large or complicated.

Results in patients with chronic kidney disease

The ISCHEMIA-CKD trial[11,13] assessed the same hypothesis as the ISCHEMIA trial in 777 patients with renal dysfunction (end-stage renal disease on dialysis or estimated glomerular filtration rate less than 30 mL/min/1.73 m^2). The findings were similar to those of the ISCHEMIA trial, although the incidence of stroke was higher with the invasive strategy (HR 3.76, 95% CI 1.52–9.32), as was the rate of death or new dialysis (HR 1.48, 95% CI 1.04–2.11). Interestingly, the invasive approach was beneficial in individuals with severe inducible ischemia.

Quality of life

The burden associated with medical therapy and recurrent symptoms is not inconsequential. Frequent trips to outpatient clinics and emergency departments for recurrent symptoms and inability to participate in cardiac rehabilitation and exercise and weight-loss programs impair quality of life in patients with coronary artery disease.[14] Multiple previous trials[10,15] have shown improvement in quality of life after percutaneous coronary intervention in patients with stable angina.

In the ISCHEMIA trial,[3] patients randomized to invasive therapy had significantly greater improvements in disease-specific health status (angina symptoms, functional status, and quality of life) than those in the conservative treatment group.

While differences in health status were only modest in the overall trial population, this was driven by the fact that 35% did not have angina at baseline, and 44% had angina only 1 to 3 times per month. A minority of the trial population, only 20%, were severely symptomatic with daily or weekly angina. Not surprisingly, patients who were asymptomatic or minimally symptomatic at baseline had little or no change in symptom status over follow-up. In contrast, patients with moderate to severe symptoms at baseline had substantial improvements in angina frequency and quality of life with revascularization compared with conservative management, benefits that were sustained over the 36-month observation period. Similar findings were observed in the ISCHEMIA-CKD trial.[3,16]

The impact of complete revascularization, the mode of revascularization, and invasive functional assessment are yet to be explored in the ISCHEMIA trial

LIMITATIONS OF THE ISCHEMIA TRIAL

Due to slow recruitment and lower-than-expected event rates, the primary end point was changed from cardiovascular death or nonfatal myocardial infarction to a composite of cardiovascular death, nonfatal myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest. Although this modification was a prespecified contingency and was enacted before the trial was unblinded, it raises questions regarding whether additional end points like resuscitated cardiac arrest or heart failure are relevant to percutaneous coronary intervention in stable coronary artery disease.

More relevant to the interpretability of the trial was that patients with lower ischemia burden (5%) and abnormal exercise tolerance testing were included to increase enrollment, potentially diluting the results of the trial. Nearly 13% of the invasive strategy group had nonobstructive coronary artery disease and did not require revascularization.

Moreover, as noted in the discussion above on quality of life, only a small proportion of patients were severely symptomatic with the potential to experience substantial improvements in quality of life and angina frequency.

Finally, the impact of complete revascularization, mode of revascularization, and invasive functional assessment are yet to be explored in the ISCHEMIA trial.

INVASIVE PHYSIOLOGY ASSESSMENT IN STABLE CORONARY ARTERY DISEASE

Findings from trials using the instantaneous wave-free ratio (IFR),[17,18] or fractional flow reserve (FFR)[19–21] have suggested that these functional measurements of hemodynamic significance may help identify patients for whom revascularization is best suited.

FAME 2. The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 (FAME 2) randomized trial[15] found

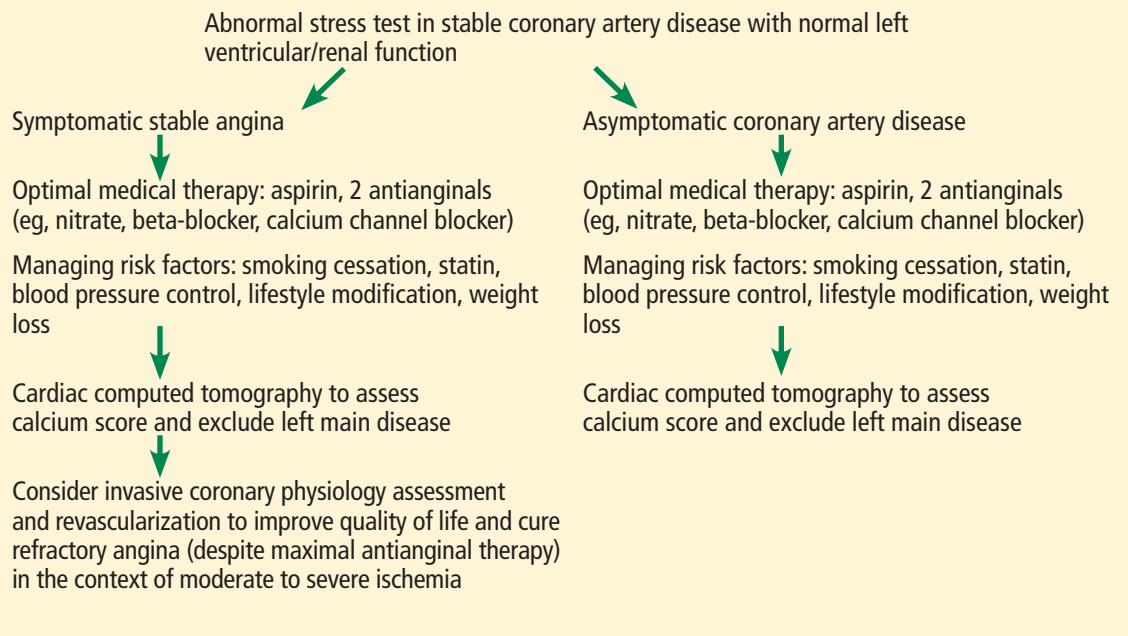

Figure 1. Algorithm for management of stable coronary artery disease.

that in patients with stable angina and FFR 0.80 or less, percutaneous coronary intervention reduced the rate of death, nonfatal myocardial infarction, and urgent revascularization at 5 years compared with medical therapy, a benefit driven by a reduction in the rate of urgent revascularization. Patients deferred for revascularization based on a nonsignificant FFR value of more than 0.80 had a good long-term prognosis.

Similar to the ISCHEMIA trial findings, the FAME 2 trial[15] also demonstrated a trend in which percutaneous coronary intervention was associated with a nearly significant reduction in myocardial infarction at 5 years (HR 0.66, 95% CI 0.43–1.00) compared with medical therapy.

The RIPCORD trial (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?)[22] evaluated the routine use of pressure wire assessment during coronary angiography and demonstrated a drastic difference in decision- making before and after pressure wire assessment.

This finding provided the hypothesis for the RIPCORD 2 trial,[23] which will evaluate all patients undergoing catheterization for elective indications and urgent stabilized non-ST-elevation acute coronary syndromes with a routine pressure wire. The primary outcome measures are economic and quality of life. This trial will shed more light on FFR-guided angiography and steer further trials in this arena targeting hard end points.

ONE SIZE DOES NOT FIT ALL

Revascularization improved quality of life and reduced angina frequency

The population of the ISCHEMIA trial[1–3] was heterogeneous and included patients with or without symptoms, assessed with various imaging tests proving ischemia. Importantly, the trial excluded patients with intolerable angina. The results were consistent with those of previous trials, and percutaneous coronary intervention had no survival benefit in patients with stable coronary artery disease without severe left main disease.

Importantly, however, revascularization did improve quality of life and reduce angina frequency in moderately or severely symptomatic patients. Moreover, rates of spontaneous myocardial infarction and hospitalizations for unstable angina were lower in the invasive treatment group. Based on the trial findings, tools can be developed that would predict the possible advantages and disadvantages of each management strategy in individual patients.

The ISCHEMIA trial[1–3] does not change the indication for revascularization in stable coronary artery disease that has been estab-

lished so far. Revascularization should be reserved to treat individuals with refractory angina and moderate to severe ischemia to improve the quality of life. The ISCHEMIA trial[1–3] results do not apply to patients with significant unprotected left main disease, ischemic cardiomyopathy, or acute coronary syndromes.

Figure 1 is a suggested algorithm for managing patients with stable angina. The ISCHEMIA trial provides added reassurance that patients without symptoms with an abnormal stress test can be treated noninvasively once left main disease is excluded.

Stable coronary artery disease needs a patient-centered approach, and one size does not fit all. Management should take into consideration the clinical history, impact on quality of life, risk factors, and the burden of ischemia. A multidisciplinary approach and up-front, frank discussion is necessary regarding an invasive strategy, contemplating the risk and benefits.

KEY POINTS

- The ISCHEMIA trial indicates that patients who have stable coronary artery disease, an abnormal stress test, and no left main disease can be medically managed safely without invasive treatment.
- Cardiac computed tomography is useful to exclude left main disease.
- The ISCHEMIA trial results are relevant to stable coronary artery disease and do not apply to significant unprotected left main disease, ischemic cardiomyopathy, and acute coronary syndromes.
- Interestingly, rates of spontaneous myocardial infarction and hospitalizations for unstable angina were lower in the invasive treatment group than in the conservative management group. However, further research is necessary to confirm this finding at a large scale.
- Revascularization continues to be beneficial in patients with refractory angina and moderate to severe ischemia to improve the quality of life.

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REVIEW

CME MOC

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Glucocorticoid-induced osteoporosis: Insights for the clinician

ABSTRACT

Glucocorticoids cause significant bone loss, predominantly affecting trabecular bone, with consequent fragility fractures. The risk of fractures is related to the dose and duration of glucocorticoid use, but an increased risk may be observed even at low doses and even in the first month of treatment. Steps to prevent or treat osteoporosis should be considered in all patients who take the equivalent of prednisone at a dose of 2.5 mg or more per day for 3 or more months.

KEY POINTS

The Fracture Risk Assessment tool (FRAX) includes a yes-or-no question about glucocorticoid use, but the formula is based on a medium dose, and the FRAX score should be adjusted upward in patients on high doses and downward in patients on lower doses.

Lifestyle modifications and optimization of calcium and vitamin D intake are recommended for all patients on long-term glucocorticoid therapy.

Bisphosphonates are the first-line drugs for patients at moderate or high fracture risk, based on proven efficacy, safety, and low cost.

Zoledronate (intravenous), teriparatide, and denosumab are second-line options for patients at high risk of fracture on glucocorticoids who cannot tolerate oral bisphosphonates.

Dr. Magrey has disclosed board membership and consulting for Eli Lilly and board membership, consulting, teaching, and speaking for Novartis.

doi:10.3949/ccjm.87a.19039

Glucocorticoids are associated with a variety of adverse effects including osteoporosis, with fractures occurring in as many as 50% of long-term users.[1] A meta-analysis[2] has shown strong correlations between cumulative dose and loss of bone mineral density, and between daily dose and risk of fracture. The relative risk of fracture is significantly increased even with daily doses as low as 2.5 mg of prednisolone,[3] and depends on duration of therapy; daily oral prednisone therapy for 3 to 6 months or more has been shown to increase the risk of bone loss in most studies.[4,5] After glucocorticoids are discontinued, the fracture risk gradually decreases to baseline but may be only partially reversible.[4,5] The problem affects a great many people, as these drugs are used to treat a variety of inflammatory diseases, and the estimated prevalence of oral use is more than 1% in the United States and United Kingdom.[6–8]

In 2017, the American College of Rheumatology (ACR) published guidelines for preventing and treating glucocorticoid-induced osteoporosis, with recommendations and algorithms for assessing and categorizing fracture risk, both initially and on follow-up.[9] This review summarizes the 2017 ACR recommendations, as well as advances in treatment since then.

HOW GLUCOCORTICOIDS DAMAGE BONE

Bone loss in patients taking glucocorticoids has 2 phases, with rapid loss in the first several months to 1 year followed by a further slower and progressive decline.[10] The loss is predominantly from trabecular bone, with marked changes in the lumbar spine, but the femoral neck and other sites are also affected.[2] Even

at relatively low doses, such as prednisone 2.5 mg daily, glucocorticoids have been shown to cause more than an 8% decrease in trabecular bone mineral density after just 20 weeks of therapy.[11]

Glucocorticoids damage bone though several mechanisms:

By increasing bone resorption. Initial bone loss is caused by increased bone resorption resulting from upregulation of RANK ligand and suppression of osteoprotegerin.[12,13] Further, glucocorticoids inhibit gonadotropin secretion, so that serum levels of androgen and estrogen are lower, also causing bone resorption. They also decrease calcium absorption in the intestines, antagonize vitamin D, and decrease renal calcium reabsorption, all resulting in a secondary hyperparathyroid state.[14]

By decreasing bone formation. In cell cultures, glucocorticoids at high doses decrease bone formation by inhibiting osteoblast proliferation, increasing rates of apoptosis of osteoblasts.[15] They also have been shown to suppress *Wnt* gene expression in a dose-dependent manner, which in turn suppresses osteogenesis.

By decreasing bone vascularization, likely by reducing production of vascular endothelial growth factor by osteoblasts, creating areas of necrosis.[16] That may explain why reduction in bone strength is greater than that due to reduced bone mass alone.[17]

Risk begins with daily doses as low as 2.5 mg

RISK FACTORS AND FRAX

Other risk factors can contribute to bone loss in patients taking glucocorticoids. Nonmodifiable risk factors include advanced age, white race, female sex, early menopause, low weight or body mass index, previous fragility fracture, history of rheumatoid arthritis, and a family history of hip fragility fracture. Modifiable risk factors include low calcium or vitamin D intake, estrogen deficiency, immobility, cigarette smoking, and excessive alcohol or caffeine intake. Other comorbid disorders contributing to bone loss must also be taken into account.[18]

The fracture risk calculation

Released in 2008 by the World Health Organization, the Fracture Risk Assessment Tool (FRAX; https://www.sheffield.ac.uk/FRAX/index.aspx) has been validated and is commonly used in clinical practice. It calculates the 10-year probability of a major fracture of the spine, forearm, hip, or shoulder, and the 10-year probability of a hip fracture. The FRAX models were developed from population-based cohorts from different countries of the world and are further subcategorized by race. It requires the following information:

- Age or date of birth
- Sex
- Weight
- Height
- Bone mineral density of the femoral neck (optional, but recommended for greater accuracy[19]).

Yes-or-no answers are required for:

- Previous fragility fracture
- Hip fracture in a parent
- Smoking status
- Glucocorticoid use (prednisolone ≥ 5 mg/day or the equivalent, for > 3 months)
- Diagnosis of rheumatoid arthritis
- Alcohol intake of 3 units per day or more
- Disorders associated with secondary osteoporosis–eg, type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or early menopause (before age 45), chronic malnutrition or malabsorption, and chronic liver disease.

FRAX risk adjustment for glucocorticoid dose

The FRAX score for a patient using glucocorticoids is based on a medium dose. Hence, it may underestimate the actual fracture risk in people on higher doses and overestimate the risk in people on lower doses.

Kanis et al[20] devised a simple FRAX adjustment (**Table 1**) based on glucocorticoid dose and age. For example, for those receiving higher doses of glucocorticoids (prednisolone ≥ 7.5 mg/day or equivalent), the adjusted risk of major osteoporotic fracture is 15% higher in the 60-to-70 age group and 20% higher in the 40-to-50 age group compared with unadjusted risk. The FRAX score can also be adjusted without regard for age, as follows:

In patients on medium doses (eg, prednisolone 2.5 to 7.5 mg/day) no adjustment to the FRAX risk is needed.

In patients on low doses (eg, prednisolone < 2.5 mg/day), multiply the unadjusted FRAX

TABLE 1

Adjustment in FRAX score by glucocorticoid dose and age

Dose		Age 40	50	60	70	80	90	All
	For hip fracture risk							
Low[a]	Multiply FRAX score by:	0.60	0.60	0.50	0.40	0.70	0.70	0.65
High[b]	Multiply FRAX score by:	1.25	1.25	1.25	1.20	1.10	1.10	1.20
	For major osteoporotic fracture risk							
Low[a]	Multiply FRAX score by:	0.80	0.80	0.85	0.80	0.80	0.80	0.80
High[b]	Multiply FRAX score by:	1.20	1.20	1.15	1.15	1.10	1.10	1.15

[a]Prednisolone < 2.5 mg/day or equivalent.
[b]Prednisolone ≥ 7.5 mg/day or equivalent.

Based on information in reference 20.

risk of a major osteoporotic fracture by 0.80, and multiply the unadjusted risk of a hip fracture by 0.65.

In patients on high doses (eg, prednisolone ≥ 7.5 mg/day), multiply the unadjusted FRAX risk of major osteoporotic fractures by 1.15, and multiply the unadjusted FRAX risk of hip fractures by 1.20.

Example. A 66-year-old woman with rheumatoid arthritis has been taking prednisone 10 mg for 4 months and is expected to continue this dose. According to the unadjusted FRAX score, her 10-year hip fracture risk is 0.9%. This should be multiplied by 1.2 (a 20% increase), yielding an adjusted FRAX score of 1.08%. The adjustment for glucocorticoid dose suggests that this patient should be treated, as her 10-year risk of hip fracture is now higher than 1% (moderate risk).

FRAX caveats

FRAX cannot be used to estimate the risk of fracture in patients younger than 40. Moreover, FRAX results are partly based on hip bone mineral density (if available), while glucocorticoid use results in more significant loss from the spine (trabecular bone) than from the hip, so the FRAX score may underestimate the true fracture probability.[19]

For patients with discordant bone mineral density in the hip vs the lower spine, the Foundation for Osteoporosis Research and Education's 10-year risk calculator can be used (https://riskcalculator.fore.org/).

FRACTURE RISK CATEGORIES

The ACR[9] stratifies the risk of fracture in glucocorticoid users into 3 categories:

Low fracture risk

- Patients age 40 and older with adjusted FRAX risk of less than 10% for major osteoporotic fracture or less than 1% for hip fracture
- Patients under age 40 who do not have risk factors other than glucocorticoid exposure.

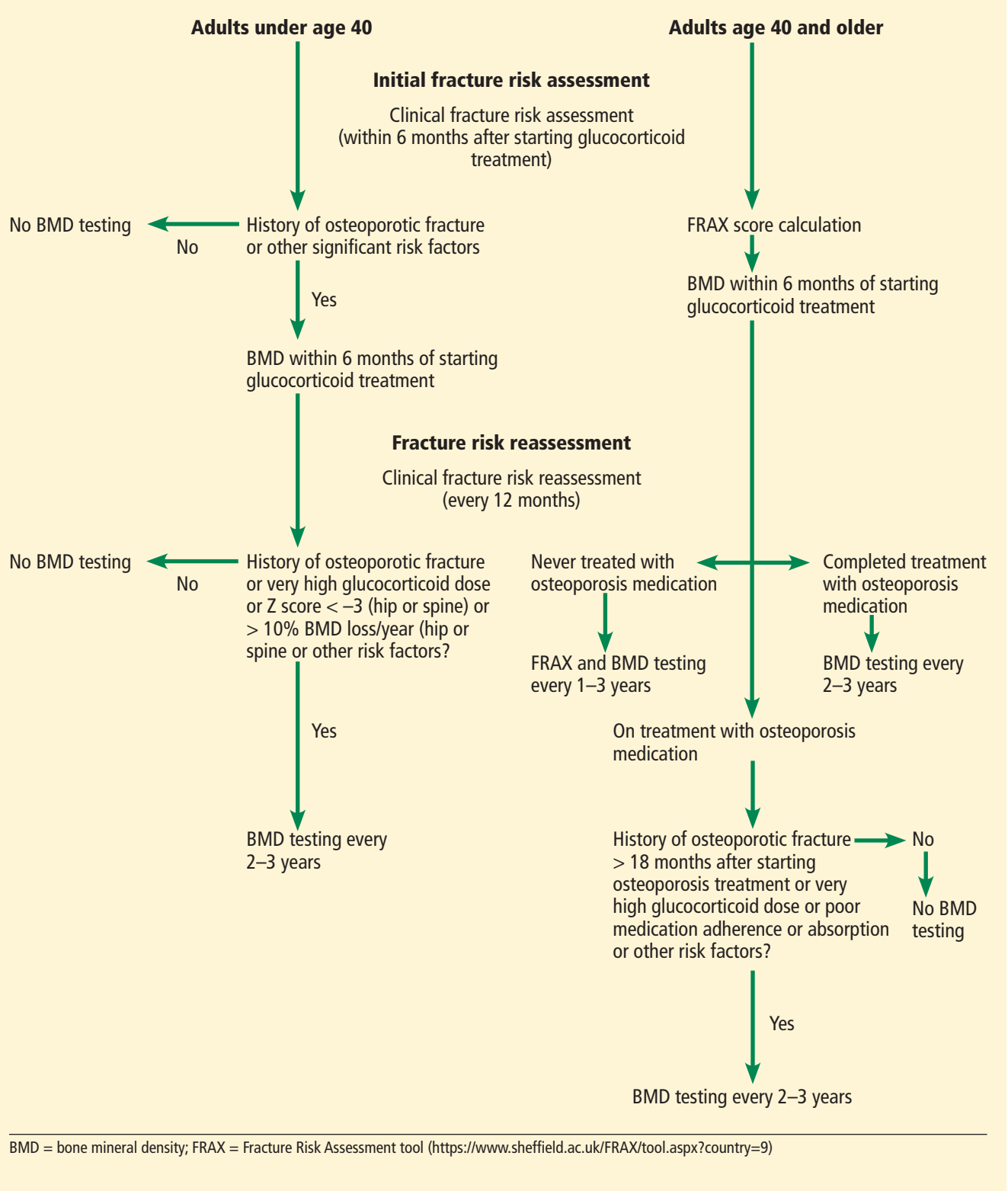
Moderate fracture risk

- Patients age 40 and older whose adjusted FRAX risk of major osteoporotic fracture is 10% to 19%, and whose risk of hip fracture is 1% to 3%
- Patients under age 40 on glucocorticoids taking 7.5 mg or more daily for at least 6 months, and either hip or spine bone mineral density Z score below –3, or rapid bone loss of at least 10% at the hip or spine over 1 year.

High fracture risk

- Patients of any age with a history of osteoporotic fracture
- Patients age 40 and older whose T score

Bone is lost rapidly in the first year, followed by a further, slower, progressive decline



BMD = bone mineral density; FRAX = Fracture Risk Assessment tool (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9)

Figure 1. An algorithm for initial fracture risk assessment and reassessment in adult patients, based on current guidelines.

Adapted from information in reference 9.

(hip or spine) is –2.5 or lower (in men age 50 and older, and in postmenopausal women)
- Patients with adjusted FRAX risk 20% or higher for major osteoporotic fracture or 3% or higher for hip fracture.

Adults age 30 and older on a very high dose of glucocorticoids (eg, prednisone ≥ 30 mg daily and > 5-g cumulative dose over the past year) are included in the moderate-to-high-risk group for treatment.

INITIAL RISK ASSESSMENT

The initial fracture risk assessment for an adult includes a detailed history reviewing the risk factors for osteoporosis and details of glucocorticoid use including dosages, frequency, and duration. Modifiable, nonmodifiable, and secondary causes of osteoporosis should be reviewed as appropriate, including fall risk.

Physical examination should include weight, height (looking for a decrease), and thorough evaluation of limbs and spine, checking for signs of fracture (bony deformities, spinal tenderness, and kyphosis).

The initial evaluation should be done as soon as possible, but preferably within 6 months after starting glucocorticoid treatment (**Figure 1**).[9]

For adults younger than 40, bone mineral density should be measured as soon as possible or within 6 months after starting glucocorticoids if they are at high fracture risk (due to prior osteoporotic fractures) or have other significant osteoporotic risk factors.

For adults 40 and older, the FRAX score should be calculated as soon as possible or within 6 months after starting glucocorticoids and should include the bone mineral density if this testing is available.

REASSESSING FRACTURE RISK

Every year, a comprehensive evaluation including fracture risk assessment should be completed for patients on glucocorticoids to determine how frequently the bone mineral density needs to be tested (**Figure 1**)[9]:

Adults younger than 40 should undergo bone mineral density testing every 2 to 3 years if any of the following features are present:
- High fracture risk (prior osteoporotic fractures)
- High-dose glucocorticoids (eg, prednisone 30 mg or more daily, and cumulative dose 5 g per year)
- Bone mineral density Z score –3 or less (hip or spine)
- Bone mineral density loss from the hip or spine 10% or more per year, or other significant osteoporotic risk factors.

Adults age 40 and older should be reevaluated based on treatment status. Those on glucocorticoids who have never started osteoporosis treatment (except for vitamin D and calcium) should have their FRAX score calculated, with bone mineral density testing if possible, every 1 to 3 years. Those on glucocorticoids who have completed osteoporosis treatment, or on glucocorticoids and currently on osteoporosis treatment with risk factors for higher fracture risk (including fracture that occurs after 18 months of treatment), should undergo bone mineral density testing every 2 to 3 years.

Additionally, adults age 40 and older should undergo more frequent bone mineral density testing if on high initial doses (eg, prednisone ≥ 30 mg daily and cumulative dose of 5 g per year) or if at high fracture risk due to prior osteoporotic fracture. Bone mineral density testing can be done closer to every 3 years for patients on lower doses of glucocorticoids and without any other osteoporotic risk factors or who have higher bone mineral densities.

Evaluate as soon as possible, preferably within 6 months after starting glucocorticoid treatment

RECOMMENDATIONS FOR TREATMENT

The ACR[9] made its 2017 recommendations after rating the evidence of benefit vs harm for the different treatment options and thoroughly reviewing the literature, after which an expert panel of rheumatologists and internists reached a decision by consensus. Most of the recommendations were conditional, owing to uncertain evidence.

For all:
Lifestyle, calcium, and vitamin D

All adults taking the equivalent of prednisone 2.5 mg or more daily for 3 or more months should incorporate lifestyle changes to optimize their bone density, eg, follow a healthy

TABLE 2

Treatment based on age and fracture risk

Fracture risk	Treatment
Low	Calcium and vitamin D
Moderate or high	Calcium and vitamin D
	and
	An oral bisphosphonate
	or one of the following (in order of preference)
	An intravenous bisphosphonate
	Teriparatide
	Denosumab
	Raloxifene (postmenopausal women)

Based on information in reference 9.

diet, maintain a normal weight (body mass index), stop smoking, limit alcohol intake to less than 3 units/day, engage in low-impact weight-bearing exercises, and take measures to prevent falls.

Intravenous zoledronic acid is superior to oral bisphosphonates and may be preferable in certain patient groups

In addition, these patients should optimize their calcium and vitamin D intake.[9] Vitamin D helps increase osteoblastogenesis and intestinal absorption of calcium, and glucocorticoids counteract this.[21] A meta-analysis disclosed that vitamin D and calcium supplementation prevented bone loss at the lumbar spine and forearm in glucocorticoid-treated patients; the effect was modest but clinically and statistically significant.[22] The recommended daily vitamin D intake is about 600 to 800 international units, with a serum level 20 ng/mL or higher as the goal. Calcium intake, preferably through diet, should be in the range of 1,000 to 1,200 mg daily.

The recommendations for lifestyle, calcium intake, and vitamin D intake are conditional due to indirect and low-quality evidence in glucocorticoid users.

PHARMACOLOGIC TREATMENT

The guidelines[9] recommended pharmacologic treatment in addition to the above measures in patients at moderate or high risk of fractures, including patients of any age who have had a previous osteoporotic fracture.

An oral bisphosphonate is the first choice, intravenous bisphosphonate the second choice, teriparatide the third choice, and denosumab the fourth (**Table 2**). This ranking was based on the opinions of the ACR guideline voting panel. The panel recommended oral bisphosphonates as a first choice and parenteral bisphosphonates as a second choice after comparing data about absolute fracture reduction, harms (toxicity and inconvenience of daily injections), and costs (**Table 3**). A purely evidence-based ranking was not possible since the number of comparative studies was small.

Bisphosphonates

A Cochrane review of 27 randomized controlled trials[23] found high-quality evidence that bisphosphonates reduce the risk of vertebral fractures in glucocorticoid-induced osteoporosis, with data extending to 24 months of use, and prevent bone loss at both the lumbar spine and femoral neck. The effect of glucocorticoids on nonvertebral fractures was minimal to none.

Alendronate has been shown to increase bone mineral density in both the lumbar spine and hip in patients taking glucocorticoids and also to reduce the rate of new vertebral fractures.[24–27]

Risedronate similarly was shown in a randomized, placebo-controlled trial to significantly increase bone mineral density.[28]

Intravenous bisphosphonates (eg, zoledronic acid, pamidronate) have also been shown to significantly reduce the rates of nonvertebral fractures, vertebral fractures, and hip fractures.

A meta-analysis of 8 randomized, placebo-controlled trials involving 13,335 patients showed that treatment with zoledronic acid significantly reduced the incidences of nonvertebral fractures, vertebral fractures, and hip fractures. Zoledronic acid was also associated with significant improvement in bone mineral density in the lumbar spine, total hip, femoral neck, and trochanter.[29] However, the incidence of any adverse event was higher in the zoledronic acid group than in the control group.

A randomized controlled trial[30] showed that intravenous zoledronic acid was superior to risedronate in increasing the bone mineral density of the lumbar spine for both treatment and prevention of osteoporosis.

Oral bisphosphonates are cost-effective and considered first-line agents for glucocorticoid-induced osteoporosis. However, intravenous zoledronic acid is superior to oral bisphosphonates and may be preferable in certain patient groups if better compliance is required or fracture risk is high.[8]

Teriparatide

Teriparatide is a synthetic analogue of parathyroid hormone that activates the Wnt/beta-catenin pathway in osteoblasts, thereby increasing bone formation. Since inhibition of bone formation is a key mechanism in glucocorticoid-induced osteoporosis, anabolic agents such as teriparatide may be pivotal in its treatment.

Compared with alendronate in treating glucocorticoid-induced osteoporosis in a 36-month randomized controlled trial,[31] teriparatide was associated with greater increases in bone mineral density in the spine, hip, and femoral neck and with fewer new vertebral fractures. Also, a meta-analysis in 2016 showed teriparatide was efficacious in preventing vertebral fractures in glucocorticoid users.[32]

Despite data that teriparatide reduces the risk of radiographic vertebral fractures more than bisphosphonates do, the 2017 ACR guidelines[9] recommended it as a second option after bisphosphonates, in view of its higher cost and its inconvenient route of administration (daily injections).[33] However, we recommend that it be considered as a first-line option in patients who have at least one grade 2 or higher (on a scale of 1 to 4) vertebral fracture, based on literature review.

Bone is rapidly lost after teriparatide is discontinued, so an antiresorptive agent should be started soon thereafter if appropriate.[25]

Denosumab

Denosumab is a fully humanized monoclonal antibody against RANK ligand with a potent antiresorptive effect, resulting in higher bone mineral density at the lumbar spine and total hip and lower risk of new fractures in patients on glucocorticoids.[34]

TABLE 3

Considerations regarding osteoporosis medications

Oral bisphosphonates
Preferred because of safety, low cost, and lack of evidence of superior antifracture benefits from other osteoporosis medications
Avoid in patients with gastroesophageal reflux disease or esophagitis
Intravenous bisphosphonates
Higher risk with intravenous infusion (than with oral bisphosphonate therapy) of hypersensitivity reaction, acute-phase reaction (influenza-like illness), hypocalcemia
Longer half-life
Consider for better adherence, given no weekly pill burden
Teriparatide
Expensive; burden of therapy with daily injections
Limited to 2 years of therapy
Caution in patients with urolithiasis
Denosumab
Lack of safety data in premenopausal women
Hypersensitivity reaction, infection risk

Based on information in reference 9.

The safety and efficacy of denosumab in treating glucocorticoid-induced osteoporosis were evaluated in the 12-month primary analysis of a 2-year, randomized, multicenter, double-blind, parallel-group, active-controlled study in 795 patients.[35] Patients received either oral risedronate 5 mg daily or denosumab 60 mg subcutaneously every 6 months for 1 year. Denosumab was noninferior (the primary outcome) and superior (a secondary outcome) to risedronate at 1 year in its effect on lumbar bone mineral density in patients who had been on glucocorticoids for at least 3 months or even less than 3 months. Given these findings, denosumab can be used in patients in whom bisphosphonates are contraindicated.

A post hoc analysis revealed that the vertebral fracture rate increased to the level seen in the untreated population after denosumab was discontinued, which needs to be kept in mind when choosing this treatment.[36]

The US Food and Drug Administration has approved denosumab for treating glucocorticoid-induced osteoporosis in men and women at high risk of fractures who are either initiating or continuing glucocorticoids in a daily dosage equivalent to 7.5 mg or more of prednisone and are expected to remain on them for at least 6 months. (This approval came after the ACR guidelines were written.)

TREATMENT IN SPECIAL POPULATIONS

The ACR guidelines included recommendations for initial treatment in special populations.[9]

Women

In women at moderate to high risk who have childbearing potential, treatment is recommended for those who do not plan on becoming pregnant while receiving osteoporosis medication and are either sexually inactive or using birth control.

- Treat with an oral bisphosphonate rather than calcium and vitamin D alone
- Second-line therapy is teriparatide
- For patients at high risk for whom oral bisphosphonates and teriparatide are not appropriate, consider intravenous bisphosphonates or denosumab (in that order of preference), but consider the potential fetal risks with both options.

These recommendations are conditional, based on low-quality evidence. They have been extrapolated from other treatment groups.

In women who are pregnant:

- Optimize calcium, vitamin D, and lifestyle modifications
- No other osteoporosis medications are recommended in this group, given the lack of safety data.

Teriparatide is a second-line option, in view of its cost and inconvenient route of administration

Young patients

In adults age 30 or older receiving high-dose glucocorticoids (eg, initial dose of prednisone 30 mg per day or higher and cumulative dose higher than 5 g in 1 year):

- Treat with an oral bisphosphonate rather than calcium and vitamin D alone
- Treat with an oral bisphosphonate rather than an intravenous bisphosphonate, teriparatide, or denosumab
- If bisphosphonates are not appropriate, other treatments are available (**Table 2**). These recommendations are conditional.

Organ transplant recipients

For adults with organ transplants who are treated with glucocorticoids, treatment is the same as for everyone else (**Table 2**) if the glomerular filtration rate is at least 30 mL/minute and there is no evidence of metabolic bone disease. Renal transplant patients should be evaluated by a metabolic bone disease expert.

The ACR and others[9,37] did not recommend denosumab in transplant patients due to lack of safety data when used along with other immunosuppressive medications. However, in a study in 63 organ transplant recipients (15 diabetic patients who received simultaneous kidney and pancreas transplants, 34 patients who received kidney transplants, and 14 patients with liver grafts), denosumab was well tolerated (without serious adverse effects or infections). It improved bone mineral density in the lumbar spine and proximal femur, proving to be a successful option for transplant patients.[38]

FOLLOW-UP TREATMENT RECOMMENDATIONS

No studies have evaluated the duration of osteoporosis treatment in glucocorticoid-induced osteoporosis. The 2017 ACR guidelines, however, have provided some framework for treatment duration.

In adults age 40 and older taking an oral bisphosphonate, switching the therapy is conditionally recommended if a fracture is sustained after at least 18 months of treatment or if bone mineral density loss is greater than 10% per year. If the treatment failure is from poor absorption or adherence, then intravenous bisphosphonates should be considered.

For adults age 40 and older who have completed 5 years of oral bisphosphonate treatment and are at moderate or high risk of fracture, treatment can be:

- Continued
- Switched to an intravenous bisphosphonate if there is an absorption or adherence problem
- Switched to another class of medication.

Adults age 40 and older on osteoporosis medication, calcium, and vitamin D whose glucocorticoid treatment is stopped and at low risk should discontinue the medication. However, calcium and vitamin D should be contin-

ued. These recommendations are conditional.

Adults age 40 and older on osteoporosis medication, calcium, and vitamin D whose glucocorticoid treatment has stopped and at moderate or high risk should complete the osteoporosis medication treatment. This recommendation is conditional for moderate-risk patients but strong for high-risk patients.

SUMMING UP

Glucocorticoid-induced osteoporosis is a major cause of bone loss and consequent fragility fractures. Despite high risk of fractures and comprehensive recommendations for treatment, most patients on glucocorticoids are not treated for it.

In addition to lifestyle modifications, pharmacologic treatment is recommended in both men and women taking glucocorticoids based on dose and duration of use. The first-line agents continue to be oral bisphosphonates. Intravenous bisphosphonates, teriparatide, and denosumab are recommended for patients with high risk for fractures or unable to tolerate oral bisphosphonates.

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Optimize your documentation to improve Medicare reimbursement

ABSTRACT

There's nothing more frustrating than not getting credit for work performed. Physicians often leave large amounts of compensation on the table, because even though services were provided, insurance payers do not recognize the work due to suboptimal documentation. This problem is especially apparent in preventive medicine and wellness visits with adult and geriatric patients, and results in physician services being undervalued. This article outlines specific documentation requirements for receiving full credit for the work already provided by most primary care physicians.

KEY POINTS

Billing for outpatient evaluation and management has 5 levels, determined by 3 elements: the history, physical examination, and medical decision-making. In a new patient, all 3 elements must meet the criteria for a given level to be compensated at that level, but in an already established patient, only 2 of the 3 need to.

It is important to classify geriatric visits into 2 separate categories: the new wellness visit and the standard office visit.

Many clinics have adopted screening questions to assess patients' overall health, which patients can answer by filling out a form while waiting for their visit.

To receive compensation for a preventive service, 3 components must be documented: the amount of time spent counseling, the Current Procedural Terminology code, and the linked diagnosis.

doi:10.3949/ccjm.87a.19116

Geriatric patients are complex. The typical older adult is more likely to suffer from severe end-stage diseases, adverse effects of polypharmacy, and lack of social support, resulting in poorer overall outcomes. The goal for the primary care physician is to address as many of these complaints as possible in an efficient matter, while documenting and billing appropriately for procedures to ensure that taking care of the geriatric population remains a cost-effective endeavor.

This article provides clear templates and instructions to ensure all geriatric services rendered are properly billed and coded for and briefly reviews general medical billing in the outpatient setting.

OVERVIEW OF GENERAL MEDICAL BILLING IN OUTPATIENTS

The Current Procedural Terminology (CPT) codes used in outpatient billing for evaluation and management are typically divided into 5 levels for new patients (99201–99205) and established patients (99211–99215), determined by the number of topics documented in the history, physical examination, and medical decision-making.

For a new patient, all 3 sections must meet the criteria for the level in order to bill for the corresponding level (**Table 1**).[1,2] For instance, if the history and the physical examination are documented to a level 3 standard, and the medical decision-making is documented to a level 4 standard, then the overall visit will count as a level 3, despite the medical decision-making, because the history and physical were not documented at the level 4 standard.[1] (A new patient is defined as one who has nev-

Glossary

AWV–Annual Wellness Visit

CPT—Current Procedural Terminology

E/M—evaluation and management

HPI—history of present illness

IPPE—Initial Preventive Physical Examination

PFSH—past medical, family, and social history

ROS—review of systems

RVU—Relative Value Unit

er been seen by a physician in your group, or as a patient who has not been seen in 3 years.)

In an already-established patient, only 2 of the 3 areas need to meet the documentation criteria in order to bill at a specific level (**Table 2**). For example, if the history and examination meet the criteria for level 4, and the medical decision-making meets the criteria for level 3, the note can still be billed as a level 4.

As a side note, billing based on time is an acceptable alternative. However, significantly more time (30 minutes) is required to bill at a level 3, which is typically completed in the 15-minute patient time slot allotted in most clinics. When billing based on time, the history, examination, and medical decision-making do not need to hit the required level of documentation.[1,2]

Optimization can dramatically increase RVUs for services that most physicians already provide

GERIATRIC BILLING: DETERMINING THE VISIT TYPE

It is important to classify geriatric visits into 2 separate categories: the new wellness visit and the standard office visit. This is essential because while a large portion of preventive services (depression screening, advance care planning, smoking cessation, sexually transmitted diseases screening, alcohol counseling, weight counseling, and heart disease counseling) can be administered at either category of visit, a cognitive assessment is only billable during a wellness visit or a specific visit for cognitive assessment.[2] See **Table 3** for the complete inclusion criteria.

However, if the patient presents for a wellness visit with a separate chief complaint, it is also allowable to "split-bill" the visit as both a wellness and standard visit as long as 2 separate notes exist for the encounter. The caveat is that a patient can only be billed for a wellness preventive visit once per year, but split billing can often dramatically increase the Relative Value Units (RVUs) generated by a single wellness visit.

THE ANNUAL WELLNESS VISIT

The annual wellness visit (AWV) is an incentive visit provided by Medicare. Many people refer to the AWV as "the yearly physical," which is a misconception. The AWV is simple, and its main focus is to perform a health risk assessment and create a personalized prevention plan.

There are 2 billable codes for an AWV: G0438—initial annual wellness visit, which can only be assigned once in a patient's life, and G0439—subsequent annual wellness visit.[3] Of importance, certain documentation is required to bill for these codes (**Table 4**).

As a side note there is a "Welcome to Medicare" visit code (G0402) that is considered an Initial Preventive Physical Examination (IPPE) and not a billable code for AWV. The IPPE is covered only once within the first 12 months of Medicare Part B enrollment. The goal of the IPPE is essentially to review medical and social history along with health promotion, education, disease prevention, and detection. The initial AWV (G0438) can be offered 12 months after the patient received the IPPE or 12 months after the patient was enrolled under Medicare Part B. A subsequent wellness visit (G0439) can be offered annually.[2,4]

For more detailed information see: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/AWV_Chart_ICN905706.pdf.

This may seem like a lot of documentation, but with appropriate staff coordination, previsit data collection, and appropriate templates it will not take more than 20 minutes with documentation included.[3,4] **Table 5** is a sample note with the required documentation to bill for an annual wellness visit.

COGNITIVE ASSESSMENT

Cognitive assessment is an examination to evaluate a person's cognitive level, remain-

TABLE 1

New patient office visit evaluation and management codes

	Requirement (all 3 must be at the billed level)						
	History			Examination	Medical decision-making	Time	
Level	HPI	ROS	PFSH	Organ systems	Diagnoses/complexity/risk	(minutes)	RVUs
Level 1 (N1) 99201	1–3	None	None	1	Straightforward	10	0.48
Level 2 (N2) 99202	1–3	1	None	2–7 (no detail)	Straightforward	20	0.93
Level 3 (N3) 99203	≥ 4	2–9	1–2	2–7 (with detail)	Low complexity	30	1.42
Level 4 (N4) 99204	≥ 4	≥ 10	3	≥ 8	Moderate complexity	45	2.43
Level 5 (N5) 99205	≥ 4	≥ 10	3	≥ 8	High complexity	60	3.17

HPI = history of present illness; PFSH = past medical, family, and social history; ROS = review of systems; RVU = Relative Value Unit

TABLE 2

Established patient office visit evaluation and management codes

	Requirement (at least 2 of the 3 must be at the billed level)						
	History			Examination	Medical decision-making	Time	
Level	HPI	ROS	PFSH	Organ systems	Diagnoses/complexity/risk	(minutes)	RVUs
Level 1 (E1) 99211	1–3	None	None	1	Problem-focused	5	0.18
Level 2 (E2) 99212	1–3	1	None	1	Straightforward	10	0.48
Level 3 (E3) 99213	≥ 4	1	None	2–7	Low complexity	15	0.97
Level 4 (E4) 99214	≥ 4	2–9	1	2–7 (with detail)	Moderate complexity	25	1.5
Level 5 (E5) 99215	≥ 4	≥ 10	2–3	≥ 8	High complexity	40	2.11

HPI = history of present illness; ROS = review of systems; PFSH = past medical, family, and social history; RVU = Relative Value Unit

ing abilities, and capacity to function. It can be provided to any patient who exhibits any signs or symptoms of cognitive impairment,[3] in either a wellness visit or a specific cognitive assessment visit (see below).

Several standardized tests are available to be used by any eligible medical provider (physicians, nurse practitioners, clinical nurse specialists, and physician assistants). Some acceptable tools to assess cognition are the Mini-Cog, Montreal Cognitive Assessment, Mini-Mental State Examination, Saint Louis University Mental Status Examination, Memory Impairment Screen, and AD8 Dementia Screening Interview.[5,6]

Specific cognitive assessment visit

For geriatric patients with suspected cognitive dysfunction, a specific cognitive assessment visit (CPT 99483) can be performed. The cognitive assessment visit is a stand-alone visit code and it can be cobilled with wellness visits or preventive services, but not with a standard office visit.[5,7,8] It is recommended that if a cognitive assessment is performed, the entire visit should be billed as a cognitive assessment (3.44), as the total number of RVUs generated exceeds a new patient level 5 visit (3.17). The cognitive assessment visit requirements are not the same described in the AWV (**Table 5**). See **Table 6** for the required elements that need to be documented in order to code CPT 99483.[5]

For more detailed information see: www.alz.org/careplanning/downloads/cms-consensus.pdf.

MAXIMIZING PREVENTIVE SERVICES

Regardless of the chief complaints, many clinics have adopted automatic screening questions or quality metrics to assess patients'

TABLE 3

Billable preventive services

Service	Wellness visit	Standard office visit	Cognitive assessment visit
Cognitive assessment	Yes	No	Yes
Advance care planning	Yes	Yes	No
Depression screen	Only if patient is established (G0439; not with G0402 or G0438)	Yes	Yes
Smoking cessation	Yes	Yes	Yes
Alcohol screening	Yes	Yes	Yes
Alcohol counseling	Yes	Yes	Yes
STD counseling	Yes	Yes	Yes
Cardiovascular counseling	Yes	Yes	Yes
Weight counseling	Yes	Yes	Yes

G0439 = subsequent annual wellness visit code; G0402 = welcome to Medicare visit code; G0438 = initial annual wellness visit code; STD = sexually transmitted disease

TABLE 4

Required documentation for an initial annual wellness visit

- Demographic data
- Self-assessment of health status
- Psychosocial risks
- Behavioral risks
- Activities of daily living
- Instrumental activities of daily living
- Updated personal and family history
- Substance use disorder assessment
- List of current health care providers and suppliers
- Documentation of weight, height, body mass index, and blood pressure
- Detection of cognitive impairment during visit (direct observation or third-party information helps)
- Depression screening
- Functional ability and level of safety (ability to successfully perform activities of daily living, fall risk assessment, hearing impairment screening, home safety assessment)
- Update all screenings recommended by US Preventive Services Task Force and vaccines recommended by US Centers for Disease Control and Prevention
- Action plan for any identified risks

For more detailed information see: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/AWV_Chart_ICN905706.pdf

overall health, such as body mass index monitoring, screening for smoking and alcohol use, or even "health vital signs" such as asking patients to estimate how much exercise they perform in a week. Often, these screening questions are given to the patient on a paper form to fill out while waiting for the doctor's visit.[6,7] The reason these monitoring metrics are included is to maximize the billing for any particular encounter.

To optimize potential for billable preventive services, annual wellness screening paperwork should include questions regarding depression, alcohol use, tobacco use, sexually transmitted disease risk factors, and cardiovascular risk factors. A positive answer on any of these screens should prompt a brief discussion during the encounter with the appropriate billing code and time documented. The reason for including these questions on the AWV is that many counseling services can only be billed for once a year.[7,8]

To maximize preventive services, wellness visits should be set for at least a 30-minute time slot, not only to manage whatever chief concern the patient brings, but also to address as many positive screening questions as possible. Furthermore, having more time in the wellness visit allows for overlapping counseling such as smoking cessation, cardiac risk factor counseling, and alcohol cessation to ensure the time criterion is met for each topic. See **Table 7** for the requirement time for each billable code, RVU value, and the required interval of time before each service can be billed for again.

TABLE 5

Annual wellness visit template

Reason for visit

Chief complaint

Subjective narrative

Review of systems
"Please refer to patient-completed questionnaire (previsit template with checkboxes)."

Past medical history (diagnoses and dates)

Past surgical history

Family history

List of medications

Socioeconomic history

Substance use disorder assessment

Occupational history

Tobacco use

Recent hospitalizations

Objective
Vital signs, weight, height, body mass index
Physical examination
Vision and hearing evaluation
"Pertinent lab results and tests in the record were reviewed with the patient and a copy was provided to the patient as needed."

Assessment of any cognitive impairment

General appearance

Mood and affect

Input from others

Notes and plan

Depression screening (PRIME MD-PHQ2)
Refresh note if PHQ-9 was completed
Follow-up plan for depression

Functional ability
Does the patient exhibit a steady gait?
How long did it take the patient to get up and walk from a sitting position?
Is the patient self-reliant (can the patient do their own laundry, prepare meals, do household chores)?
Does the patient handle his or her own medications?
Does the patient handle his or her own money?
Is the patient's home safe (eg, good lighting, handrails on stairs and bath)?
Did you notice or did patient express any hearing difficulties?
Did you notice or did patient express any vision difficulties?
Were distance and reading eye charts used?
Notes and plan

Advance care planning
Was patient offered the opportunity to discuss advance care planning?
If no, did you provide information on advance directives?
Notes and plan

Smoking cessation counseling

Electrocardiogram results
Required only in initial AWV

Vaccines

Screening recommendations

Assessments and plan

DOCUMENTING FOR PREVENTIVE VISITS

To receive compensation from Medicare for a preventive service, 3 components must be documented,[8] ie, the amount of time spent counseling, the CPT code, and the linked diagnosis. This will improve Medicare reimbursement for the preventive services that a primary care physician regularly provides. However, these services are not exclusive to primary care physicians: they can be billed for by any medical specialist as long as they are properly documented and not billed by another physician (usually the primary care physician) in the specific required interval for that service. For example, if a primary care physician documents and bills for a particular service after a subspecialist does, the primary care physician won't get reimbursed.

For more detailed information see: https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/index.

The time documented in the services requiring time attestation cannot overlap be-

TABLE 6

Cognitive assessment visit: Required elements

Cognition-focused evaluation including a pertinent history and examination

Medical decision-making of moderate or high complexity

Functional assessment (eg, basic and instrumental activities of daily living), including decision-making capacity

Use of standardized instruments for staging of dementia (eg, Functional Assessment Staging Test [FAST], Clinical Dementia Rating [CDR])

Medication reconciliation and review for high-risk medications

Evaluation for neuropsychiatric and behavioral symptoms, including depression, with use of standardized screening instrument(s)

Evaluation of safety (eg, home), including motor vehicle operation

Identification of caregiver(s), caregiver knowledge, caregiver needs, social supports, and the willingness of caregiver to take on caregiving tasks

Development, updating or revision, or review of an advance care plan

Creation of a written care plan, including initial plans to address any neuropsychiatric symptoms, neurocognitive symptoms, functional limitations, and referral to community resources as needed (eg, rehabilitation services, adult day programs, support groups) shared with the patient and/or caregiver with initial education and support

Typically, 50 minutes are spent face to face with the patient, family, or caregiver

For detailed information see: https://www.alz.org/careplanning/downloads/cms-consensus.pdf

tween the time for the standard office visit and the time for other preventive services. See **Table 8** for examples of time attestation.

REIMBURSEMENT FOR CARE PROVIDED

The role of the primary physician is to provide comprehensive care to the individual. But often, the care provided is not reflected in the Medicare reimbursement as a result of incomplete or inadequate documentation. While initially daunting, proper optimization of the clinic visits to include previsit screening questions, increased time slots for wellness visits, and note templates with prebuilt preventive coding can dramatically increase the RVUs generated for services that most physicians already provide.

TABLE 7

Billing and documentation criteria for preventive services

Service	CPT code	RVUs	Time (minutes)	Recommended diagnosis	Required interval	Other requirements
Cognitive assessment	99483	3.44	None	None	180 days	Cognitive Assessment Template Not the same cognitive assessment described in the AWV
Advance care planning	99497	1.5	15–45	None	None	Document discussion, outcomes, and signed forms
	99498	1.40	> 45			
Depression screening	G0444	0.18	≤ 15	713.31: Encounter for screening for depression	365 days	
Smoking cessation	99406	0.24	3–10	Several[a]		
	99407	0.50	> 10			
Alcohol screening	G0442	0.18	> 15	Any alcohol use code	365 days	Patient must be having adverse effects from use
Alcohol counseling	G0443	0.45	> 15	Any alcohol use code	4 sessions per year	Patient must have positive alcohol screen
STD counseling	G0445	0.45	> 30	Several[b]	180 days	Document education and skills provided
Cardiovascular counseling	G0446	0.45	> 15	713.6: Screening for cardiovascular disease	365 days	Must include intensive behavioral counseling to promote a healthy diet for adults with hyperlipidemia, hypertension, advancing age, and other known risk factors for cardiovascular and diet-related chronic diseases If a patient has a current diagnosis of hyperlipidemia and/or hypertension, the diagnosis codes for these diseases should be used instead of Z13.6; screening codes cannot be used if the patient already has a confirmed diagnosis
Weight counseling	G0447	0.45	> 15	BMI > 30.0 kg/m^2 and weight-related diagnosis must be documented	Month 1: weekly Months 2–6: biweekly Monthly thereafter	Goal-oriented behavior

[a]For example, F17.210: Nicotine dependence, cigarettes, uncomplicated; F17.220: Nicotine dependence, chewing tobacco, uncomplicated; Z87.891: Personal history of nicotine dependence.

[b]For example, Z11.3: Encounter for screening for sexually transmitted infection; Z11.59: Encounter for screening for other viral disease; Z72.89: Other problems related to lifestyle; Z72.51: High-risk heterosexual behavior; Z72.52: High-risk homosexual behavior; Z72.53: High-risk bisexual behavior.

For detailed information see: https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/index.

TABLE 8

Time attestation for 2 services

Advance care planning

This is a time code. You must enter in the number of minutes spent on advance care planning.

Example: "I spent ___ minutes with the patient on advance care planning."

You may also state "I have spent > 16 minutes on advance care planning."

Template suggestion: "I spent ___ minutes with the patient in counseling and discussion of goals of care, code status, and advance directives as detailed in the assessment and plan (excluding visit time and annual wellness visit time)."

Depression screening

This is a time code. You must enter in the number of minutes spent on depression screening

Example: " ___ minutes were spent on depression screening."

You must enter in the minutes on each patient.

Template suggestion: "I spent ___ minutes with the patient on screening and counseling about depression (excluding advance care planning and annual wellness visit time)."

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REVIEW

CME MOC

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Procedures and devices to treat resistant hypertension in chronic kidney disease

ABSTRACT

Treatment of resistant hypertension is a challenge, especially in patients who have chronic kidney disease. The choice of medications may be limited in this group, making the possibility of device-based therapies attractive. We explore 4 devices and procedures available to treat this vexing issue.

KEY POINTS

Placing a shunt between the iliac artery and iliac vein (arteriovenous coupling) relieves the arterial pressure hemodyamically; this approach is experimental.

Catheter ablation of sympathetic nerve endings in the renal artery leads to less activation of the renin-angiotensin-aldosterone system and lower blood pressure; this procedure is experimental as well.

A third experimental approach to lowering blood pressure is stimulation of the carotid baroreceptors with an implanted pacemaker or stent device.

For patients with renal artery stenosis, percutaneous revascularization with stent placement can be considered; the current American College of Cardiology/American Heart Association guidelines give the procedure a class IIa recommendation.

Dr. Rader has disclosed consulting for ReCor Medical.

doi:10.3949/ccjm.87a.19099

Nonpharmacologic, device-based antihypertensive treatments show potential, but, except for stenting of the renal arteries in patients who have renal artery stenosis, all remain experimental. Researchers have focused on patients with chronic kidney disease (CKD) and resistant hypertension, a group at high risk, in whom the benefit may justify the risk and cost of the treatment.

See related editorial, page 444

Nonpharmacologic procedure-based treatments that could in theory provide a permanent cure would be welcome in this group of patients. We discuss the role of several procedure-based treatments, ie, arteriovenous coupling, renal sympathetic denervation, baroreflex activation, and renal percutaneous revascularization in the management of resistant hypertension (**Table 1**).

RESISTANT HYPERTENSION IS COMMON IN CKD

Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of 3 antihypertensive agents of different classes (1 of which is a diuretic) at their maximum tolerated doses, or controlled blood pressure with the use of 4 or more agents.[1]

The prevalence of true resistant hypertension is difficult to ascertain, and patients suspected of having it should undergo a meticulous search for reversible causes (**Table 2**).

CKD, defined by the presence of kidney damage or decreased kidney function for 3 or more months irrespective of the cause,

TABLE 1

Advantages and limitations of antihypertensive procedures

Type of procedural therapy	Advantages	Limitations
Arteriovenous coupling	Improves measures of arterial stiffness Reduces overall systemic vascular resistance Increases cardiac output and arterial blood oxygen content	Development of venous iliac stenosis proximal to the anastomosis Potential risk of restenosis, and need for antithrombotic therapies Compression stockings need to be used after device insertion Potential for high-output cardiac failure
Renal denervation therapy	Potential reduction of increased sympathetic activity Percutaneous ambulatory procedure	Lacks a procedural end point Variable effects on blood pressure due to variability in degree of denervation achieved
Baroreflex activation therapy	Attenuates overall sympathetic activation Potential for neurohormonal modulation	Need for subcutaneous internal pulse generator with some systems Heterogeneity in the response to carotid sinus stimulation Requirement of surgical neck dissection Potential of nerve injury with residual deficit
Renal artery stenting	Potential to avoid surgery to treat stenosis Rapid improvement of global renal ischemia with bilateral lesions Potential to lessen sudden cardiac disturbance syndromes	Discordance between procedural success and clinical improvement Risk of contrast-induced nephropathy Need for surveillance for stent restenosis Complications related to femoral access

presents a unique challenge in patients with resistant hypertension.[2–4] The prevalence of apparent treatment-resistant hypertension in this group is estimated to range from 23% to 42%, and it is associated with worse prognosis.[5–7] Maintaining normal blood pressure can be difficult, given features that are common in CKD such as accelerated atherosclerosis, fluctuating volume status, inability to use the full spectrum of antihypertensive medications due to increased adverse effects, and related nonadherence issues.[8] The task is made more challenging by the revised hypertension guidelines,[2] which encourage clinicians to target blood pressure below 130/80 mm Hg in patients with CKD.

ARTERIOVENOUS COUPLING

Peripheral arteriovenous fistulae created for hemodialysis access are known to reduce vascular resistance. Based on this principle, there have been efforts to add a low-resistance, high-compliance venous tract parallel to the high-pressure systemic arterial circulation to reduce arterial resistance and pressure.[9]

The ROX coupler (ROX Medical, San Clemente, CA) is a device placed between the distal iliac vein and artery to create a central arteriovenous anastomosis (**Figure 1**).

Trial of arteriovenous coupling

In an initial trial,[10] 44 patients were randomly assigned to receive the device and 39 were assigned to receive normal care. Six months lat-

TABLE 2

Possible causes of difficult-to-treat hypertension

Suboptimal antihypertensive therapy
Nonadherence
Lifestyle choices (eg, high-sodium diet, smoking)
Dietary indiscretion
Over-the-counter medications and supplements
Older age
Intravascular and extracellular volume expansion
Primary hyperaldosteronism
Renal artery stenosis
Renal parenchymal disease
Obstructive sleep apnea
Coarctation of the aorta
Cushing disease
Hyperparathyroidism
Pheochromocytoma

er, office systolic blood pressure had dropped by a mean of 26.9 (standard deviation 23.9) mm Hg in the device group ($P < .0001$) and by 3.7 (21.2) mm Hg in the control group ($P = .31$).

There was no deterioration in renal function at 6 months, though patients with advanced CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) were excluded from the study.[10] However, the trial lacked a sham treatment control group, treatment adherence was not verified, and proximal venous stenosis developed in nearly 29% of the intervention group, tempering the positive results.[11]

A subsequent trial was planned that would have included a control group undergoing a sham procedure, but it seems to have been terminated by the sponsor.[12]

Prospects for arteriovenous coupling

It remains unclear at this stage if arteriovenous coupling has the potential to become a mainstream procedure.

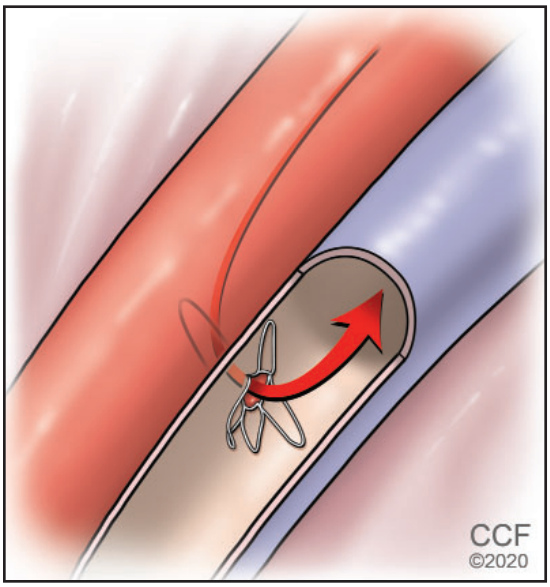

Figure 1. A percutaneously placed device creates an arteriovenous anastomosis.

RENAL SYMPATHETIC DENERVATION

Hyperactivity of the sympathetic nervous system is known to be a major factor in sustaining resistant hypertension. Curtailing this hyperactivity to better control blood pressure is a potential treatment for resistant hypertension.[13,14] With this view, catheter-based devices have been developed to ablate the sympathetic afferent and efferent nerves of the renal artery by radiofrequency or ultrasound energy (**Figure 2**) or by transarterial injection of caustic substances.[15]

Guidelines encourage clinicians to target blood pressure < 130/80 mm Hg in patients with CKD

Trials of renal sympathetic denervation

Despite success in early studies, subsequent trials have had discouraging results.[16] Pooled data from 3 sham-procedure-controlled trials of first-generation devices showed no significant reduction in blood pressure on summary treatment estimates (weighted mean difference 2.23 mm Hg, 95% confidence interval [CI] –4.70 to 0.25 mm Hg; $P = .08$).[17]

Most of these trials excluded patients with eGFRs lower than 45 mL/min/1.73 m^2, but even so, renal denervation did not seem to have a major deleterious effect on renal function. In the non-sham-controlled SYMPATHY trial (N = 139), the average eGFR was 77 ± 19 mL/min/1.73 m^2 at baseline and declined by 1.5 (−3.1 to 0.1) mL/min/1.73 m^2 at 6 months, with no difference between the

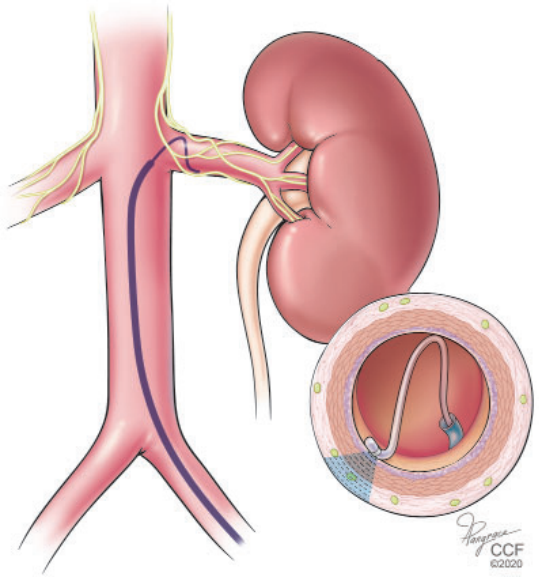

Figure 2. Renal artery denervation is performed using an intra-arterial catheter.

groups receiving renal denervation and usual medical care.[18,19]

A subsequent sham-controlled trial set out to include participants with low eGFR, but only 3% of the denervation treatment group had eGFRs between 30 and 45 mL/min/1.73 m^2; most (92%) had eGFRs higher than 60. There was no detectable change in renal function after the procedure.[20]

It is unclear at this stage if arteriovenous coupling has the potential to become a mainstream procedure

In recent sham-controlled trials, novel second-generation devices seemed to hold promise. In the SPYRAL HTN-ON MED and OFF-MED trials,[21,22] renal denervation using the Symplicity Spyral device (Medtronic, Dublin, Ireland) led to statistically significant and clinically meaningful blood pressure reduction at 6 months; the mean 24-hour systolic blood pressure had dropped by 7.0 mm Hg (95% CI –12.0 to –2.1; P = .0059). Patients with eGFR less than 45 mL/min/1.73 m^2 were excluded, but no patient in the entire cohort had a serum creatinine elevation greater than 50%, and no new or worsening renal failure was reported.

The RADIANCE-HTN SOLO trial[23] showed that renal denervation with the Paradise system (ReCor Medical, Palo Alto, CA) reduced daytime ambulatory systolic blood pressure in 74 patients (8.5 vs 2.2 mm Hg; P < .0001). While patients with eGFR less than 40 were not recruited, there were no significant changes in eGFR between the treatment groups (adjusted mean difference –0.6, 95% CI –4.4 to 3.2, P = .75).

Cost-effectiveness of renal denervation

Geisler et al[24] calculate that the discounted lifetime incremental cost-effectiveness ratio for renal denervation therapy is $3,071 per quality-adjusted life-year, and the 95% credible interval for incremental cost-effectiveness ratio is $31,460 per quality-adjusted life-year.

Chowdhury et al[25] report that over a lifetime at the current estimated costs, renal denervation it would be cost-effective only if it were targeted to patients whose 10-year predicted cardiovascular risk was at least 13.2% initially.

Prospects for renal denervation

Improvement in the design of renal denervation delivery could overcome some of the procedural setbacks of earlier trials. This, and better selection of patients, may lead to acceptable results of renal denervation in the near future. Experience suggests that patients who have mild CKD may tolerate this treatment well. However, well-designed, adequately powered trials to evaluate the long-term efficacy and safety of second-generation renal denervation technology in patients with resistant hypertension with all stages of CKD are needed to validate the safety of this treatment in CKD.

BAROREFLEX ACTIVATION THERAPY

Another approach to reducing sympathetic tone to help control blood pressure is electric stimulation of the carotid sinus baroreceptors.[26] The first-generation Rheos system (CVRx, Minneapolis, MN) consisted of a pacemaker unit implanted subcutaneously in the infraclavicular position along with electrodes leading to both carotids.[27]

Studies of baroreflex activation therapy

Early studies using the Rheos system in 383 patients showed that substantial blood pressure reduction was maintained over a follow-up of 6 years.[28] Patients on dialysis were generally excluded from these trials, and those with CKD made up only a small portion of the cohort (< 15%).

In a follow-up study of 236 patients from

the Rheos Pivotal trial, the mean eGFR decreased from 92 ± 20 mL/min at baseline to 87 ± 22 mL/min at 6 months in the active therapy group and to 85 ± 23 mL/min in the control group (P = .589). Given the drop in eGFR in both groups, this decrease could merely represent the normal decline of renal function over time. In the relatively small subgroup of patients with an eGFR less than 60 mL/min (n = 18, mean eGFR 49 ± 8 mL/min), renal function remained stable over a 12-month observation period.[29]

The second-generation Neo system (also from CVRx), which uses a smaller electrode, was developed to mitigate some of the procedure-related complications such as cranial nerve injuries associated with the use of first-generation Rheos.

In a pilot study in 23 patients with CKD and resistant hypertension who were treated with the second-generation Neo system, there was a significant decrease in the mean arterial blood pressure (116.9 ± 20.9 mm Hg before vs 104.2 ± 22.2 mm Hg after the procedure). Patients who had stage 3 or 4 CKD experienced a greater reduction in proteinuria, and the eGFR remained stable in the treated patients despite the reduction of systemic blood pressure.[30]

The MobiusHD device (Vascular Dynamics, Mountain View, CA), another second-generation device, is a catheter-delivered self-expanding intracarotid implant designed to activate the baroreflex (**Figure 3**).[31] In its first study in humans, it seemed successful in reducing blood pressure, and a larger trial designed to evaluate the safety and effectiveness of the MobiusHD device is actively enrolling patients.[31,32] Again the long-term efficacy and safety of second-generation baroreflex activation devices in patients with resistant hypertension and CKD of all stages is yet to be verified in large randomized controlled trials.

Cost-effectiveness of baroreceptor stimulation

Borisenko et al[33] calculate that baroreceptor stimulation therapy generates 1.66 additional life-years and 2.17 additional quality-adjusted life years at an incremental cost of €16,891 compared with continued medical management in a simulated cohort of 50-year-old patients at high risk of end-organ damage. Baroreceptor stimulation was estimated to be cost-effective compared with optimal medical treatment with an incremental cost-effectiveness ratio of €7,797 per quality-adjusted life year.

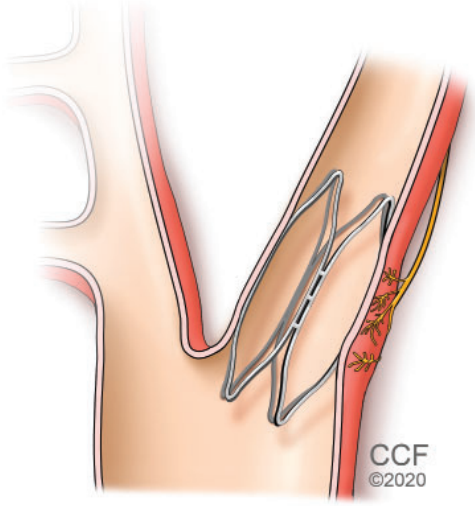

Figure 3. A percutaneously placed implant is designed to stimulate the carotid baroreceptors and thus lower blood pressure.

However, an independent assessment by the Norwegian Institute of Public Health noted that based on incremental cost-effectiveness ratio levels and after adjusting the model to account for important shortcomings in the submitted analysis related to clinical effect and health-related quality of life, the incremental cost-effectiveness ratio rises well above the level that has been considered cost-effective in Norway.[34]

Trials are needed to validate the safety of renal denervation therapy in CKD

RENAL ARTERY STENTING

Renal artery stenosis compromises blood flow to the kidneys, activating the renin-angiotensin-aldosterone axis and causing hypertension. In more than 90% of cases, renal artery stenosis is due to atherosclerosis, usually affecting the ostial part of the renal artery.[35]

Clinicians are encouraged to suspect renal artery stenosis and to look for it in patients with resistant hypertension, as it has been noted to be present in up to 24% of these patients.[36] Risk factors and specific clinical presentations that raise suspicion for renal artery stenosis are presented in **Table 3** and **Table 4**.

TABLE 3

Causes of renal artery stenosis

Atherosclerosis
Fibromuscular dysplasia
Nephroangiosclerosis (hypertensive injury)
Diabetic nephropathy (small-vessel)
Renal thromboembolic disease
Atheroembolic renal disease
Aortorenal dissection
Renal artery vasculitis
Trauma
Neurofibromatosis
Thromboangiitis obliterans
Scleroderma
Extrinsic compression

TABLE 4

Clues to the presence of renal artery stenosis

Onset of hypertension before age 30
Onset of severe hypertension after age 55
Resistant hypertension
Hypertensive urgencies
New renal impairment after starting angiotensin-converting enzyme inhibitor therapy

Clinicians are encouraged to suspect renal artery stenosis in patients with resistant hypertension

Optimal medical therapy remains the preferred treatment of atherosclerotic renal artery stenosis. Major society guidelines emphasize optimal medical therapy with blockade of the renin-angiotensin-aldosterone axis to confer survival benefit in these patients.[37]

However, clinicians and researchers have long hoped that procedural intervention could relieve renal artery stenosis, cure the hypertension, and eliminate the burden of lifelong medical therapy. Pioneering work by Grüntzig et al[38] with balloon angioplasty of renal artery stenosis showed significant relief of hypertension. The subsequent development of vascular stents led to percutaneous revascularization by stenting as the preferred technique to resolve renal artery stenosis (**Figure 4**).[39]

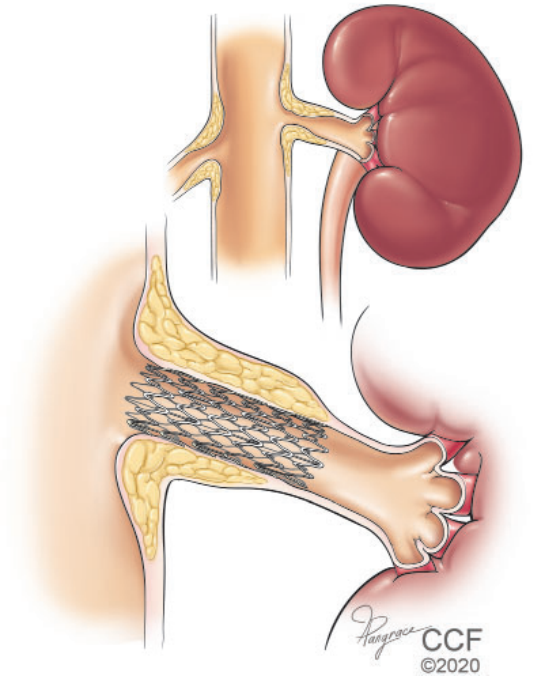

Figure 4. Stenting is reasonable for treating resistant hypertension in patients with significant renal artery stenosis.

Early case series and registries seemed to validate the utility of percutaneous resvascularization as a treatment for renal artery stenosis. In a nonrandomized single-arm study of 202 patients (with 241 total lesions), percutaneous resvascularization lowered the mean systolic blood pressure from 162 mm Hg at baseline to 145 mm Hg at 9 months (P < .0001), while the eGFR remained nearly the same at 58 vs 57 mL/min/1.73 m^2 (P = .38).[40]

However, these results could not be replicated in various subsequent randomized controlled trials.[41] Analysis of 8 trials, which included 2,223 patients, showed that renal artery revascularization was not associated with a change in systolic blood pressure from baseline when compared with medical therapy (weighted mean difference 0.12, 95% CI −0.97 to 1.21, P = .83). Moreover, revascularization was not associated with a reduced incidence of adverse cardiovascular or renal outcomes, and the results seemed similar when restricted to 5 stent-only trials.[41]

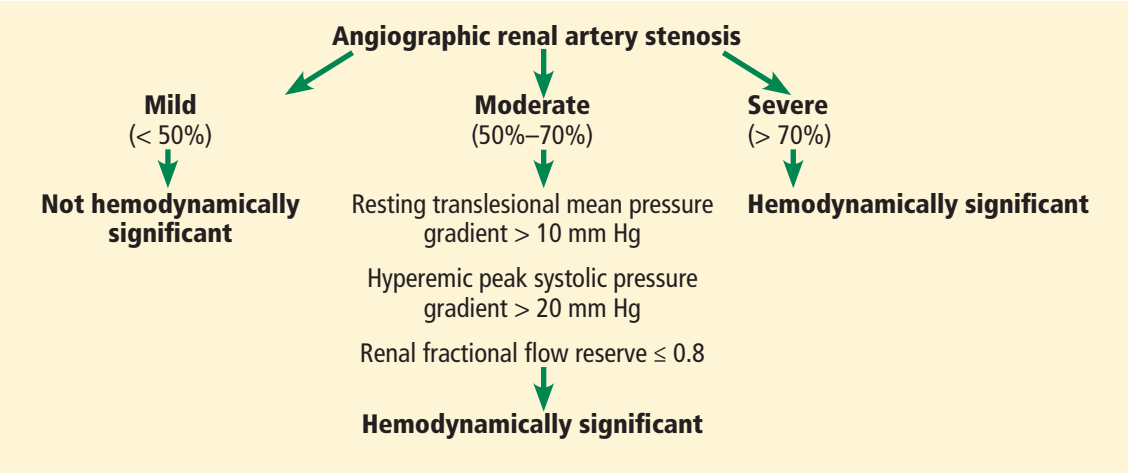

Figure 5. Hemodynamic significance of angiographic renal artery stenosis.

However, the randomized controlled trials may not tell the whole story. Design flaws, patient selection, and enrollment bias in various published trials may limit their clinical applicability, especially in patients who might benefit the most.[42]

There hence seems to be a broad expert consensus that certain groups of patients with severe renal artery stenosis should be treated with revascularization. The current American College of Cardiology/American Heart Association guidelines on the management of peripheral arterial disease give the procedure a class IIa recommendation (level of evidence B), stating that percutaneous revascularization "is reasonable" for patients with hemodynamically significant renal artery stenosis and resistant hypertension.[37,43] Similarly, a Society for Cardiovascular Angiography and Interventions statement also suggests percutaneous revascularization may be considered as appropriate care in patients with significant renal artery stenosis and resistant hypertension.[44]

Figure 5 presents diagnostic criteria for significant renal artery stenosis and outlines when percutaneous revascularization can be considered.

Renal outcomes after percutaneous revascularization have varied. In one of the largest randomized controlled trials to date, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL study), with 947 patients in total, the rates of end points were similar between the percutaneous revascularization group and the medical therapy-only group at 43 months of follow-up, including death from renal causes (2 cases vs 1, $P = .6$), progressive renal failure (77 vs 89, $P = .34$), and need for permanent renal replacement therapy (16 vs 8, $P = .11$).[45]

In the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial,[46] with 806 randomized patients, the rate of progression of renal impairment was slightly slower in the revascularization group than in the medical group (-0.07×10^{-3} L/µmol/year vs -0.13×10^{-3} L/µmol/year; $P = .06$) over 5 years of follow-up. Over the same time, the mean serum creatinine level was 1.6 µmol/L lower in the revascularization group than in the medical therapy group.

Thus, percutaneous revascularization for renal artery stenosis seems to have a reasonable renal safety profile even in patients with CKD.

Percutaneous revascularization for renal artery stenosis seems to have a reasonable renal safety profile even in patients with CKD

Cost-effectiveness of percutaneous revascularization

In a German study[47] analyzing the cost-effectiveness of medical therapy, percutaneous transluminal angioplasty with and without a stent, and surgery for the therapy of renal-artery stenoses in hypertensive patients, the average reimbursed treatment cost per patient after 3 years was as follows:

- €9,121 for medication
- €17,164 for surgery
- €14,670 for percutaneous angioplasty
- €8,437 for stenting.

This resulted in cost-effectiveness ratios

per event-free patient at 3 years as follows:

- €51,752 for medical treatment
- €36,454 for surgery
- €78,766 for percutaneous angioplasty
- €11,663 for stenting.

The researchers concluded that a strategy of primary stent implantation is more cost-effective than stand-alone balloon dilatation.[47]

THESE TREATMENTS MAY PROVE USEFUL

Nonpharmacologic treatments for resistant and difficult-to-treat hypertension in patients with CKD may prove to be useful. Percutaneous revascularization may be considered in patients with resistant hypertension and underlying renal artery stenosis.

Ongoing trials have demonstrated the efficacy and safety of newer renal denervation and baroreflex activation devices, but more data are needed regarding treating the difficult subgroup of hypertensive patients who have CKD of all stages. The concept of reducing pill burden and increasing medication adherence remains attractive and has a large potential for improving outcomes in this high-risk group.

We would like to emphasize that except for renal artery stenting, the therapies discussed here remain experimental and are not approved by the US Food and Drug Administration for routine clinical use except as part of clinical trials.

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EDITORIAL

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Device-based therapies for resistant hypertension in chronic kidney disease: The continuing quest for a cure

Device-based therapies have shown promise, but many questions still need clarification

Hypertension can be a cause or consequence of chronic kidney disease (CKD), in which sodium retention and volume expansion, increased activity of the renin-angiotensin system, and increased sympathetic nervous system activity can all contribute to raising blood pressure. Resistant hypertension, which is associated with a higher risk for adverse outcomes, is overrepresented in CKD. An analysis from the CRIC (Chronic Renal Insufficiency Cohort) study showed a high prevalence of apparent treatment-resistant hypertension in CKD (about 40%), with a 38% increase in risk for adverse cardiovascular events and 28% increase in risk for adverse renal events.[1] This underscores the importance of blood pressure control in this population, and novel therapeutic strategies should be explored.

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In this issue, Gajulapalli et al[2] review device-based therapies (renal denervation, baroreflex activation and amplification therapy, arteriovenous coupling, and renal artery stenting) in the treatment of resistant hypertension in CKD.

While clinical trials of device-based therapies have shown promise, many questions still need clarification. Additionally, as noted in the article, most device trials excluded patients with moderate-to-severe CKD (stages 3b, 4, and 5) and patients with end-stage kidney disease. In analyzing these trials, some important considerations need to be kept in mind.

doi:10.3949/ccjm.87a.20092

RENAL DENERVATION

The concept of renal denervation is arguably the most exciting new frontier for device-based therapies.

However, in resistant hypertension, the large SYMPLICITY HTN-3 renal denervation trial did not show benefit in a group undergoing this therapy compared with a sham procedure group.[3] Methodologic concerns with this study and questions related to ablation technique led to more-refined trial designs.

The SPYRAL HTN-ON MED[4] and OFF-MED[5] trials used second-generation multielectrode radiofrequency ablation devices, and the RADIANCE-HTN SOLO trial[6] used an endovascular ultrasound device, all of which showed significant blood pressure reductions in the denervation group. It should be noted that the SPYRAL HTN-OFF MED and RADIANCE-HTN SOLO trials were done in patients not taking antihypertensive medications, and SPYRAL HTN-ON MED was done in patients taking up to 3 antihypertensive medications, which does not necessarily constitute resistant hypertension; the mean number of antihypertensive medications in the denervation group was 2.2.

Unblinded trials like DENERHTN in resistant hypertension showed significantly more blood pressure reduction when renal denervation was combined with stepped-up medication therapy, but there was no sham procedure group in this study.[7]

Meta-analyses of randomized trials of renal denervation showed reductions in 24-

hour ambulatory blood pressure, with a mean difference of –4.02/–2.05 mm Hg compared with controls, and a mean difference of –3.65/–1.71 mm Hg when the analysis was restricted to sham-controlled randomized trials, suggesting a modest effect size.[8,9] No subgroup analysis for CKD was done in these trials.

There are limited data on renal denervation in CKD with resistant hypertension. A small study in 15 patients with stage 3 or 4 CKD (mean estimated glomerular filtration rate [eGFR] 31 mL/min/1.73 m^2) showed significant reduction in office blood pressure and ambulatory nighttime blood pressure, but not in 24-hour ambulatory blood pressure or ambulatory daytime blood pressure.[10] The REGINA RDN study in 25 patients with stage 3 or 4 CKD (mean eGFR 37 mL/min/1.73 m^2) did not show a significant change in 24-hour ambulatory blood pressure, although there was significant reduction in office blood pressure.[11]

It is reassuring that available data do not suggest an unfavorable renal safety profile with denervation. A 3-year follow-up from the Global SYMPLICITY registry, which is a database of real-world patients treated with renal denervation, did not find a decline in CKD exceeding what would be expected in hypertensive CKD patients.[12]

Besides limited data in CKD patients, there are other unanswered questions with renal denervation:

Who are the optimal candidates? Response to renal denervation has been variable, and to date there are no good predictors of response that would enable optimal patient selection.

How much ablation is enough? There is no method to verify adequacy of ablation in real time.

Is the effect durable? Long-term efficacy (beyond 3 years) is as yet unknown. Could reinnervation occur, and what are the possible physiologic effects of this?

Is it safe in the long term? While the reported safety profile so far is reassuring, could there be longer-term deleterious vascular effects?

Will it improve cardiovascular outcomes? While cardiovascular outcomes could be extrapolated from effects of lower blood pressure, no studies of renal denervation have directly examined cardiovascular outcomes.

BAROREFLEX AMPLIFICATION

Baroreflex amplification therapy is the other device-based therapy of interest, with endovascular deployment of a self-expanding nitinol device in the carotid sinus that increases vessel radius and amplifies baroreceptor signaling. (An earlier concept used an electrical device to stimulate the baroreceptors.)

CALM-FIM_EUR, a proof-of-principle study, showed significant lowering of 24-hour ambulatory blood pressure, but patients with moderate to severe CKD were excluded from this study (the average eGFR was 83 mL/min/1.73 m^2).[13] Results from the CALM 2 study are awaited, although this trial also excluded patients with eGFR less than 45 mL/min/1.73 m^2.

ARTERIOVENOUS COUPLING

The coupler device, which creates a central arteriovenous fistula connecting the distal iliac vein and artery to reduce arterial resistance and pressure, is no longer in development.[14]

In summary, device-based therapies for resistant hypertension hold promise, but more research is needed, particularly in patients with advanced CKD. These therapies remain investigational in the United States and are not currently approved by the US Food and Drug Administration for clinical use.

Renal denervation may be the most exciting new device-based therapy

RENAL ARTERY STENTING

As Gajulapalli et al note,[2] angioplasty with stenting for atherosclerotic renal artery stenosis remains a matter of controversy, and recent trials did not show differences in cardiovascular outcomes, mortality, or progression of CKD with stenting compared with medical therapy alone (although the CORAL trial showed a modestly greater blood pressure reduction in the stent group).[15] In our practice, we consider stenting for hemodynamically significant renal artery stenosis only in certain circumstances, including resistant hypertension with blood pressure that remains uncontrolled despite optimal and intensive medication therapy.[16]

HOW SHOULD RESISTANT HYPERTENSION BE MANAGED?

The management of resistant hypertension

TABLE 1

Approach to treatment-resistant hypertension

1 Confirm the diagnosis

Blood pressure should be measured in an out-of-office setting using either ambulatory monitoring or home blood pressure monitoring to confirm diagnosis and to ascertain possible white coat effect.

2 Carefully review medications

Review of medications should include over-the-counter medications such as nonsteroidal anti-inflammatory drugs and herbal medications, if any.

3 Explore the possibility of nonadherence to medications

Nonadherence may be cost- or side-effect-related or due to complexity of regimen and poor understanding of medications.

4 Reinforce lifestyle modifications

Guidelines for nonpharmacologic therapy from the American Heart Association and American College of Cardiology include a low-sodium diet, physical activity, weight management, and limited alcohol intake. Of note, although increased intake of dietary potassium is recommended for hypertension, this would not be feasible for patients with chronic kidney disease, who are prone to hyperkalemia.

5 Assess for secondary causes of hypertension

6 Ensure optimal doses and combination of antihypertensive medications

Use thiazide-like diuretics such as chlorthalidone instead of hydrochlorothiazide.

Use loop diuretics in states of volume overload or when the estimated glomerular filtration rate is less than 30 mL/min/1.73 m^2.

Dual renin-angiotensin blockade with angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker is not recommended for hypertension as it has not been shown to improve cardiovascular outcomes or blood pressure control, and increases risk for acute kidney injury.

Consider addition of spironolactone as a fourth-line agent; this may require use of potassium binding agents in patients to prevent hyperkalemia.

Further stepwise treatment could include addition of beta-blockers, alpha-blockers, centrally acting alpha agonists, and direct vasodilators.

Complex treatment regimens should take into account the possibility of increased side effects and risk of nonadherence, and care should be individualized, with close monitoring of renal function and electrolytes.

7 Refer to a hypertension specialist

should follow a stepwise approach (**Table 1**), and should prompt investigation for secondary causes, including possible renal artery stenosis.

Spironolactone as a fourth-line agent

Spironolactone has been shown to be beneficial as a fourth-line agent in resistant hypertension.[17] A small Spanish trial (DENERVHTA) found that spironolactone lowered 24-hour ambulatory blood pressure more than did renal nerve denervation.[18] The larger Czech PRAGUE-15 study showed similar 24-hour ambulatory blood pressure reduction at 6 months with renal denervation compared with medication therapy that included spironolactone, and numerically better blood pressure reduction at 1 and 2 years in the group that was able to tolerate and continue spironolactone.[19]

In CKD, the use of spironolactone may be more likely to cause hyperkalemia, especially when combined with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Newer gastrointestinal cation exchanger potassium-binding agents

have been shown to be effective in enabling patients with CKD and resistant hypertension to take spironolactone with less hyperkalemia.[20]

DEVICES WOULD BE ATTRACTIVE

Complex treatment regimens increase the possibility of side effects and risk of nonadherence, and device-based therapies would seem an attractive option especially in these patients. While this is certainly an area of opportunity, available data do not support recommendations for device therapy in this group (yet).

Resistant hypertension in CKD presents a dual challenge for management, and randomized trials are needed in resistant hypertension across the CKD spectrum to better assess the efficacy of device-based therapies and comparative outcomes with antihypertensive drug combinations.

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ABP MOC: Successful completion of this CME activity, which includes participation in the activity and individual assessment of and feedback to the learner, enables the learner to earn up to 1.0 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABP MOC credit.

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ABS MOC: This activity qualifies for 1.0 self-assessment credit toward Part 2 of the American Board of Surgery (ABS) Maintenance of Certification (MOC) Program.

Please note: It is the participant's responsibility to self-report their participation to the American Board of Surgery, per board policy.