MAYO CLINIC

Clinical Update

Current Trends in the Practice of Medicine

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Renal Sympathetic Denervation for Treatment of Resistant Hypertension

The Challenge

It is estimated that between 30% and 40% of adults are currently affected by hypertension. Although there are numerous safe and effective antihypertensive drugs available for treatment, from 20% to 30% of adults being treated do not have adequate control of their hypertension, and this number is growing. Approximately 13% of adults with hypertension are considered to be treatment resistant because their hypertension is uncontrolled despite taking a 3-drug regimen that includes a diuretic. Not surprisingly, factors such as cost, adverse effects, drug interactions, and noncompliance play a role in limiting the effectiveness of current therapies.

Looking Back in Time for Answers

The search for a solution to this dilemma led researchers to look back in history. A 1931 publication documented that surgically disrupting the sympathetic nerves connecting the kidneys with the central nervous system, via a procedure called splanchnicectomy, helped reduce blood pressure. The use of surgical procedures (splanchnicectomy and even nephrectomy) to treat severe hypertension continued through the early 1950s, until medical therapies became widely available.

Decades later, with the incidence of drug-resistant hypertension rising and the availability of less invasive techniques, researchers began looking at interventions with renewed interest. With catheter-delivered radiofrequency ablation already in use for the treatment of complex ventricular arrhythmias, certain cancers, and other disorders, this option is now being studied as a possible intervention for resistant hypertension.

Points to Remember

- Between 20% and 30% of adults being treated for hypertension with medications do not achieve adequate blood pressure control.
- Researchers are exploring whether ablation of the renal sympathetic nerves using catheter-delivered radiofrequency energy is an effective intervention for uncontrolled hypertension.
- Mayo Clinic is enrolling patients in the Symplicity HTN-3 trial, a multicenter study of the safety and effectiveness of renal denervation in subjects with uncontrolled hypertension.

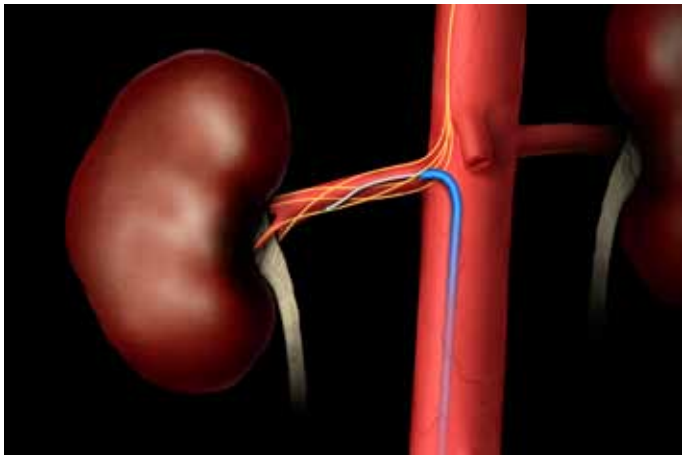


Figure. *During denervation, a catheter is introduced via the femoral artery and positioned in the renal artery under fluoroscopic guidance. The device design allows for continuous blood flow throughout the treatment, which provides cooling of the artery wall. The catheter is torquable, allowing the user to easily rotate the device to treat different segments of the vessel.*

How Catheter-Based Denervation Works

During a catheter-based denervation procedure, the physician places a standard 6F sheath in the femoral artery with the patient under local anesthesia, and advances an electrode-tipped catheter into the renal artery with fluoroscopic guidance. Once positioned, the catheter delivers low-level radiofrequency energy through the renal artery wall to disrupt the surrounding renal nerves, working in a spiral pattern to avoid single segment injury. Both left and right renal arteries are treated, and the total procedure time is 30 to 40 minutes (Figure).

Early Results

Early studies in animals and in humans suggested that the renal nerves play a role in blood pressure regulation. A series of pilot studies as well as a clinical trial (Symplicity HTN-2) involving patients with uncontrolled hypertension then showed that a catheter-based system can safely denervate the kidney and produce notable and sustained reductions in blood pressure.

The Symplicity HTN-2 trial, conducted in Australia and Europe, involved 106 patients who were randomly assigned to either the treatment group (receiving renal denervation and maintenance of baseline medications) or the control group (maintenance of baseline medications). Participants were patients with uncontrolled hypertension who had office-based systolic blood pressure of 160 mm Hg or higher despite treatment with 3 or more antihypertensive medications. Published in November 2010, the trial showed a –32/–12 mm Hg change for the renal denervation group at 6 months, compared with a +1/0 mm Hg change for the control group ($P<.001$), with no adverse device effects and no serious device- or procedure-related complications. These blood pressure changes, observed 6 months after intervention, have also been observed to persist at 2 years in the latest follow-up study. Additionally, data from these studies suggest an improvement in glycemic control with the intervention.

Table. Symplicity HTN-3 Trial: Renal Denervation in Patients With Uncontrolled Hypertension

Inclusion criteria:

- Age 18-80 years
- Office systolic blood pressure≥160 mm Hg on ≥3 medications, including a diuretic
- Glomerular filtration rate >45 mL/min
- No history of renal artery stenosis

Exclusion criteria:

- Type 1 diabetes mellitus
- Chronic oxygen use
- Primary pulmonary hypertension
- Pregnancy
- Known secondary cause of hypertension

Patient flow:

- Two screening visits over 2 weeks to confirm resistant hypertension
- Angiography in catheterization lab
- Randomization on table to denervation or angiography alone (2:1)
- Follow-up visits at 1, 3, and 6 months
- 3-4 more visits over next 2 years
- Sham group offered denervation at 6 months

For more information or to enroll a patient in the Symplicity HTN-3 study, please contact the study coordinator at 507-266-3802.

What's Next? Symplicity HTN-3

Mayo Clinic has been selected to participate in the Symplicity HTN-3 trial, a multicenter, prospective, single-blind, randomized controlled study of the safety and effectiveness of renal denervation in patients with uncontrolled hypertension. This study will enroll approximately 1,060 subjects into the screening phase, of whom approximately 530 will be randomized. Subjects who meet all criteria after the screening period will undergo a renal artery angiogram to evaluate renal artery anatomy, and eligible subjects will be randomly assigned at a 2:1 ratio to either the intervention group or the control group (Table).

Intervention group subjects will receive the renal denervation procedure and continue baseline antihypertensive medications without changes for 6 months. Control group subjects will undergo angiography alone (sham procedure) and continue baseline antihypertensive medications without changes for 6 months, after which they will have the option to have the renal denervation procedure. Subjects will be unaware of their randomization assignment because of a combination of conscious sedation, sensory isolation, and lack of familiarity with procedural details and duration.

New data from the Symplicity HTN-3 trial will help establish whether therapeutic renal denervation using a catheter-based approach is a safe and effective therapy for patients with uncontrolled hypertension. To schedule a consultation for evaluation and treatment of a patient with resistant hypertension, please call 507-284-9991. To enroll a patient in the Symplicity HTN-3 study, please call 507-266-3802.

Endarterectomy vs Stenting: CREST Study Compares Patient Outcomes

For more than 50 years, endarterectomy has been the standard alternative to medical therapy for patients with extracranial carotid stenosis who are in need of revascularization. Available since the early 1990s, carotid angioplasty with stent placement first emerged as a less invasive treatment option for high-risk patients in whom surgery was contraindicated. As the use of stenting has expanded beyond high-risk patients, the need to compare the outcomes associated with these 2 procedures laid the groundwork for the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST). A randomized treatment trial with 2,502 patients from 117 participating institutions in the United States and Canada, CREST is the largest such study conducted.

Study participants included men and women in need of a revascularization procedure. Half were asymptomatic and half were symptomatic, defined as having evidence of a transient ischemic attack, amaurosis fugax, or minor nondisabling stroke involving the carotid artery within 180 days of entering the study. Eligible patients were randomly assigned to undergo either endarterectomy or stenting.

Points to Remember

- The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) compared the outcomes associated with carotid endarterectomy and carotid stenting in patients with carotid artery occlusive disease.
- The rate of stroke, myocardial infarction, and death was the same for these 2 procedures in the 30 days after they were performed. Stroke was lower after surgery (4.1% vs 2.3%), and myocardial infarction (MI) was lower after stenting (1.1% vs 2.3%).
- Both endarterectomy and stenting are designed to prevent stroke. At 4 years of follow-up, they were equally effective.
- Patients older than 70 years had better outcomes with endarterectomy, and those younger than 70 years fared better with stenting.

CREST Outcomes

Published CREST results showed that both procedures were associated with similar rates of the outcome measure. Configured as a primary composite end point, the outcome measure was ipsilateral stroke, myocardial infarction (MI), or death. Neurologic and cardiac functions were assessed at the periprocedural period (within hours after the procedure and 1 month later) and at 6-month intervals for the 4-year duration of the study (Figure on page 4).

According to the CREST study leaders at Mayo Clinic, the combined stroke and mortality rates associated with both procedures were extraordinarily low, and the outcomes were the best ever reported in a randomized trial that evaluated these outcomes. The rate of stroke was 4.1% in the endarterectomy group and 2.3% in the stenting group. The rate of MI was 2.3% in the endarterectomy group and 1.1% in the stenting group.

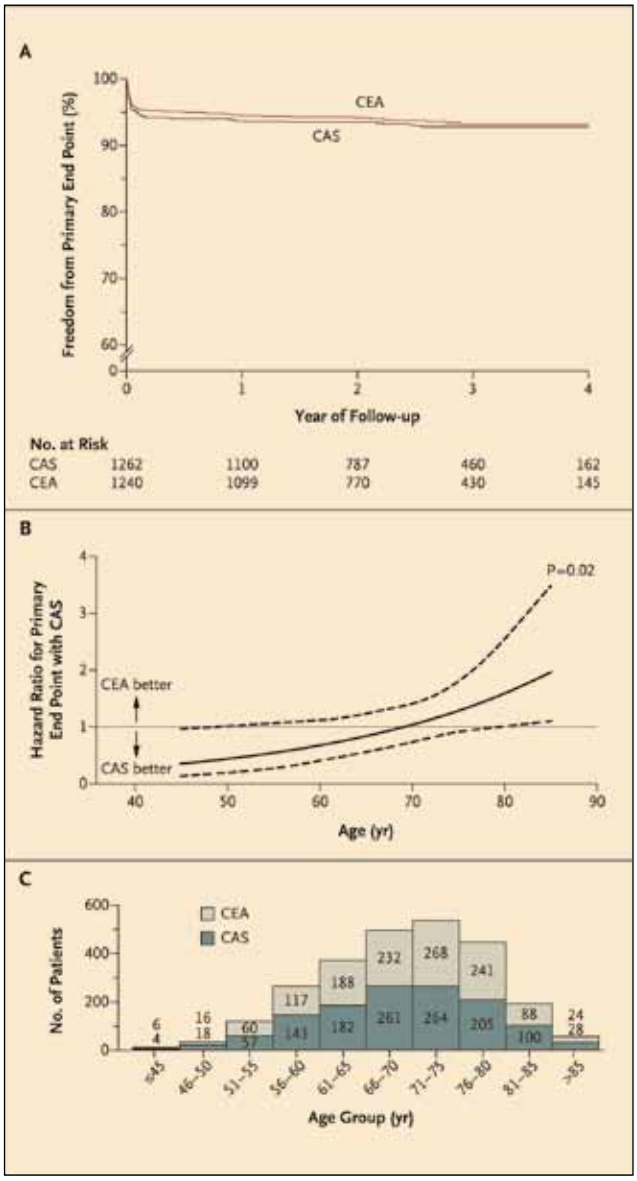
Age-Related Differences

CREST found that patients older than 70 years had better outcomes with endarterectomy, and those younger than 70 years fared better with stenting. Mayo researchers believe that these findings could be explained, in part, by blood vessel deterioration (vascular tortuosity, calcification) frequently found in persons older than 70 years. During endarterectomy, the presence of plaque in other parts of the arterial system does not pose as great a challenge because the surgeon interrupts the blood flow below and above the narrowed areas.

Another possible explanation is that elderly patients may also be less able to form a vascular bypass through collateral circulation in response to a plaque-based occlusion. Mayo researchers are now examining the angiograms of the study population to see if vascular health is associated with poorer outcomes for stenting in patients older than 70 years.

Benefits of Multispecialty Collaboration

The CREST findings highlight the advantage of treating carotid stenosis with a multidisciplinary team approach in which all options are considered. Today, every patient who comes to Mayo Clinic with carotid stenosis is assessed by a collaborative team that includes a neurologist, a surgeon (either vascular or neuro), and an interventionalist (neuroradiologist or interventional



cardiologist). This team approach helps patients learn about the different treatment options and removes any perception of potential operator bias.

Ten-Year Follow-up Study Funded

Although endarterectomy has been shown to reduce stroke risk 10 years after the procedure, a question arising from the CREST results is the long-term durability of stenting. The National Institutes of Health is funding a Mayo Clinic–led 10-year, multi-institutional follow-up study to compare the long-term outcomes of both procedures.

Figure. *Primary end point according to treatment group. The primary end point was a composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 4 years after randomization. A, Kaplan-Meier curves for patients undergoing carotid artery stenting (CAS) and those undergoing carotid endarterectomy (CEA) in whom the primary end point did not occur, according to year of follow-up. B, Hazard ratios for the primary end point, as calculated for the CAS group vs the CEA group according to age at the time of the procedure. The hazard ratios were estimated from the proportional hazards model, with adjustment for sex and symptomatic status. Dashed lines indicate the 95% confidence intervals. C, Numbers of patients in each group in whom the primary end point occurred during the study, according to age group. Adapted from Brott et al.* N Engl J Med. *2010;363(1):11-32. Used with permission.*

Preserving Fertility in Cancer Survivors

Of the estimated 1.5 million men and women in the United States who will receive a diagnosis of cancer this year, 10% are younger than 45 years and 1% are younger than 20 years. Overall 5-year relative survival rates for this group are excellent—nearly 80%—and ongoing improvements in cancer treatment likely will continue to increase survivorship.

More than 75% of patients who are 35 years old and childless at the time of their cancer diagnosis desire children in the future. Although cancer therapy can be lifesaving, treatment sequelae can be considerable and may include premature gonadal failure or infertility, thus creating an important quality-of-life issue for these individuals.

Fertility preservation refers to therapies that promote or retain fertility for patients undergoing medical treatments that otherwise could jeopardize future childbearing ability. Conditions where fertility preservation may be considered include malignancies, autoimmune disorders such as lupus erythematosus, certain hematologic disorders such as vasculitis or aplastic anemia, and any other medical condition where the disease itself or its long-term management may impair fertility. Risk of permanent reproductive damage varies with the type, dose, and site of therapy rendered, as well as the patient's age at the time of treatment. In general, chemotherapy that is not cell cycle specific, such as alkylating agents (eg, cyclophosphamide), has the highest risk of causing permanent gonadal damage. Likewise, pelvic

irradiation poses a greater risk for gonadal damage than irradiation to distant sites.

Options for fertility preservation vary by age and sex. Prepubertal males and females have limited options, primarily the collection and cryopreservation of gonadal tissue for later use. The tissue can then be autologously transplanted or thawed and matured in vitro for use with in vitro fertilization. Both of these approaches should be considered experimental. Although there are rare case reports of births after partial or whole ovary transplantation, to date there are no reported live human births from immature gametes retrieved from cryopreserved gonadal tissue.

For postpubertal males, one of the most familiar and long-standing fertility preservation strategies is sperm banking. Cryopreserved sperm can be used years—even decades—after initial storage, for either insemination into a female partner or in vitro fertilization.

Postpubertal females may elect to undergo embryo or oocyte cryopreservation (Figure). Although the first human birth from cryopreserved oocytes occurred in the mid 1980s, recent improvements in cryopreservation technique have made it a more viable treatment option.

Points to Remember

- Fertility preservation may be considered for patients with malignancies, autoimmune disorders such as lupus erythematosus, certain hematologic disorders such as vasculitis or aplastic anemia, and other medical conditions where the disease or its long-term management impairs fertility.
- Risk of permanent reproductive damage varies with the type, dose, and site of therapy rendered, as well as the patient's age at the time of treatment. In general, chemotherapy that is not cell cycle specific and pelvic irradiation have the highest risk of causing permanent gonadal damage.
- Recent advances in cryopreservation technique have made cryopreservation of sperm, oocytes, and embryos a more viable treatment option.

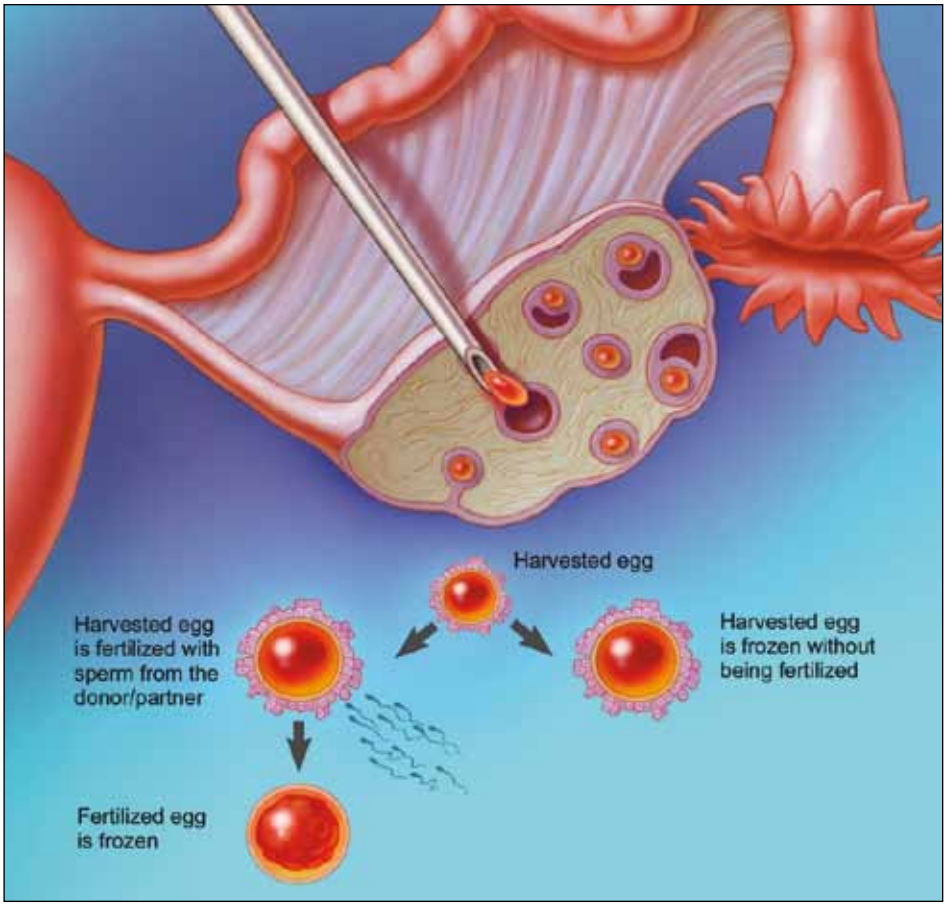


Figure. *Cryopreservation of oocyte or embryo. For oocyte cryopreservation, the mature eggs are cryopreserved immediately. For embryo creation, mature oocytes are combined with sperm, and the embryos are cryopreserved.*

Today, more than 70% of oocytes can survive the cryopreservation process, and pregnancy rates—although lower than with conventional in vitro fertilization—are reasonable.

Cryopreservation of either the oocyte or the embryo typically involves administering exogenous human gonadotropins for approximately 10 to 12 days. During this time, serial estradiol levels and ultrasonography help monitor follicular growth. When follicles are large enough to contain mature oocytes, human chorionic gonadotropin is given to mimic the natural preovulatory surge of luteinizing hormone, which causes the maturing oocytes to resume meiosis and prepare for ovulation. Shortly before ovulation, the oocytes are retrieved with a needle attached to a vaginal ultrasonographic probe.

For oocyte cryopreservation, the mature eggs are cryopreserved immediately; for embryo creation, mature oocytes are combined with sperm and cryopreserved after fertilization is confirmed. In either case, the oocytes or embryos can be used months or even years in the future.

Patients considering fertility preservation should be counseled, when possible, that fertility preservation should be initiated before receiving chemotherapy or any other fertility-jeopardizing treatment. Before making a final decision regarding fertility preservation, each patient should also receive risk-benefit counseling that addresses his or her individual prognosis and understand the experimental status of some of the available strategies.

MeTeOR Study: Comparing Arthroscopy to Nonoperative Therapy for Meniscal Tears in Patients With Osteoarthritis of the Knee

The Challenge

Each year in the United States more than 300,000 knee arthroscopies are performed for patients who have both a meniscal tear and osteoarthritis in the same compartment of the knee. Yet the frequency with which this treatment is performed belies considerable uncertainty that surrounds outcomes associated with its use.

According to orthopedic surgeons at Mayo Clinic, the challenge starts in the consultation room, when a patient presents with, for example, medial-sided knee pain. If the patient has a medial meniscus tear and concomitant medial compartment osteoarthritis, determining the source of the pain is difficult. Is it the meniscus, or the arthritis?

This ambiguity is problematic because meniscal tears and osteoarthritis tend to respond differently to arthroscopy. Data show that while arthroscopy is effective in treating meniscal tears without osteoarthritis, it is highly ineffective for treating advanced osteoarthritis of the knee.

MeTeOR to Clarify Treatment

What is the best course of treatment when both conditions are present? Currently physicians tell these patients that outcomes associated with knee arthroscopy are unpredictable if both meniscal tear and concomitant osteoarthritis are present. However, a new federal study is generating comparative effectiveness research data that will help answer the question. Mayo Clinic was selected as 1 of the 7 advanced orthopedic centers involved in the Meniscal Tear With Osteoarthritis Research (MeTeOR) study, a large, randomized, multicenter trial sponsored by the National Institutes of Health (NIH). According to participating Mayo researchers, the data provided by this study will clarify indications for arthroscopy vs nonoperative treatment in these patients and help physicians identify which knee symptoms and clinical and intraoperative variables predict good and bad outcomes following arthroscopy (Figure).

Points to Remember

- Outcomes associated with knee arthroscopy are unpredictable if both meniscal tear and osteoarthritis are present.
- The Meniscal Tear With Osteoarthritis Research (MeTeOR) study is a large, randomized, multicenter trial sponsored by the National Institutes of Health and designed to clarify indications for arthroscopy vs nonoperative treatment.

About MeTeOR

MeTeOR is the first study of its size to evaluate patients who have both a symptomatic meniscal

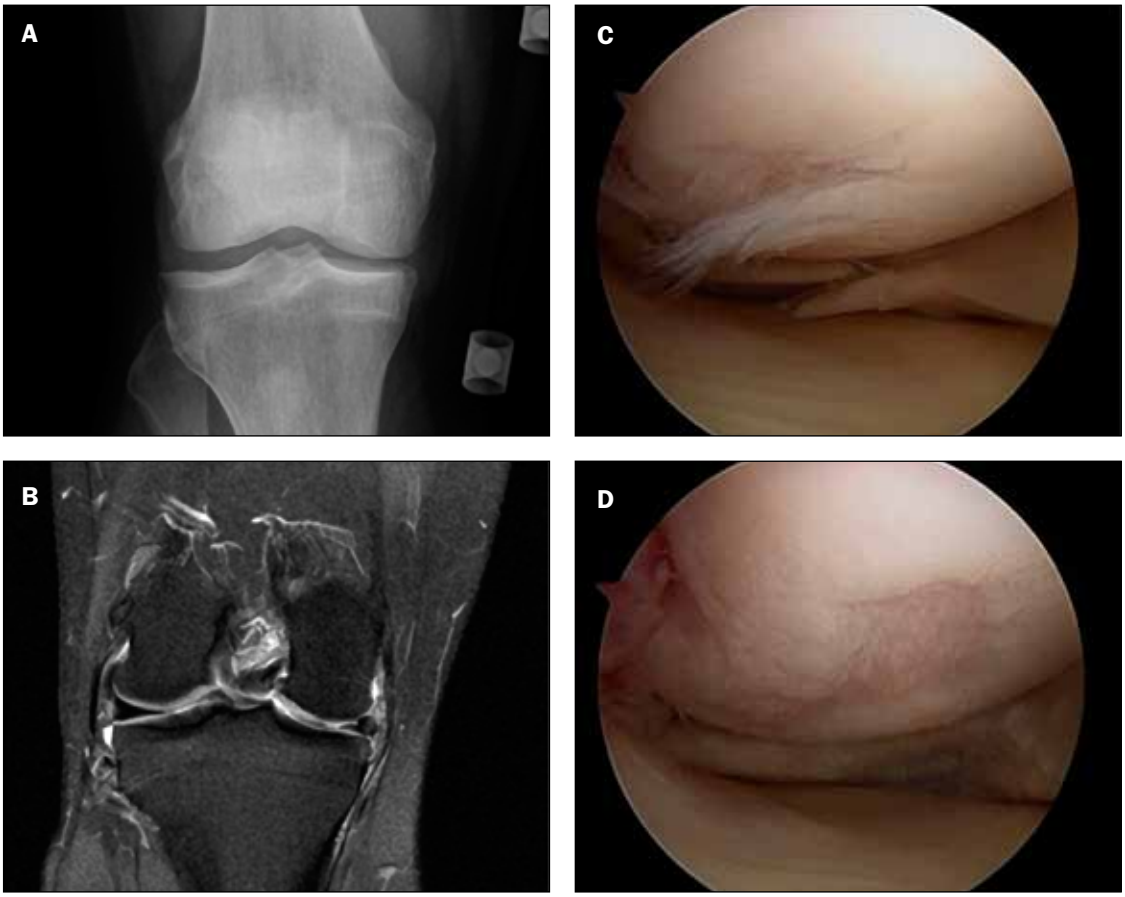


Figure. *A, Standing x-ray showing medial compartment joint space narrowing (medial osteoarthritis). B, MRI showing medial meniscal tear and cartilage thinning of the femoral condyle. C, Intraoperative scope image of large cartilage flap and large meniscal tear. D, Intraoperative scope picture of cartilage débrided and meniscal tear resected.*

tear characterized by mechanical symptoms such as knee catching, locking, or buckling, as well as mild to moderate osteoarthritis. Arthritic pain is typically described in nonmechanical terms, such as "dull" and "achy." But those distinctions are also problematic, because patients often report both types of pain.

MeTeOR has enrolled more than 340 patients older than 45 years who have these 2 knee conditions and are otherwise healthy. They have been randomly assigned to 1 of 2 arms of the trial to evaluate the effects of arthroscopy compared with nonoperative treatment such as standard physical therapy. To eliminate bias, specialists follow a standard protocol (Table).

Mayo Clinic's 3 investigators are excited and optimistic about the potential of MeTeOR to improve patient care. They believe that the trial that will change clinical practice because of the volume of procedures done for this particular problem and because it has never been studied this effectively.

Table. MeTeOR at a Glance

Enrollment goal: 340 by February 2011
Mayo Clinic contribution to total enrollment: 80 patients

Centers involved: 7 US advanced orthopedic centers, sponsored by NIH

Randomized to 2 arms: Arthroscopy vs nonoperative treatments. These may include physical therapy, use of anti-inflammatory drugs, intra-articular cortisone injections, activity modification, braces.

Main inclusion criteria:

- Age >45 years
- Presence of symptomatic meniscal tear with mechanical indicators such as locking, buckling, catching
- Presence of mild to moderate osteoarthritis on MRI
- No comorbidities, not pregnant

Main exclusion criteria:

- Age ≤45 years
- Presence of advanced osteoarthritis on MRI
- Chronically locked knee
- Previous knee surgery, recent viscosupplementation injection
- Poor health, pregnancy

Crossover option available?

In selected cases, after 6 months of nonoperative participants, patients may be allowed to cross over to the surgical arm.

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Clinical Update

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Education Opportunities

33rd Annual Practice of Internal Medicine
April 30-May 4, 2012, Rochester, MN
This course will focus on the management of a variety of medical issues seen in areas of gastroenterology, infectious diseases, general internal medicine, rheumatology, geriatrics, emergency medicine, pulmonary, endocrinology, cardiology, neurology, and women's health.

ENT for the Primary Care Provider
May 18, 2012, Rochester, MN
The 2012 ENT for the Primary Care Physician Symposium is designed to update primary care providers on the diagnosis and treatment of common ear, nose, and throat problems. This year's symposium features a choice between 2 breakout sessions: "Hands-on Training in the Diagnosis and Treatment of Benign Paroxysmal Positional Vertigo" or "Pediatric ENT Emergencies: What Needs Action Now or Later?"

19th Annual Nicotine Dependence Conference
May 21-23, 2012, Rochester, MN
The 19th Annual Mayo Clinic Nicotine Dependence Conference offers a range of topics, including care of patients with mental illness, issues specific to women, and the physiologic mechanisms and clinical correlations of smoking and pain. In addition to an update on the risks and benefits of using FDA-approved, nonnicotine medications for treating tobacco dependence, the conference offers a presentation about "e-cigarettes" and some of the myths and controversy surrounding their use.

Hot Topics in Neurology and Neurologic Surgery for the Primary Clinician
June 7-8, 2012, Rochester, MN
This course provides education on interventional therapies that have evolved over the past 10 years to treat various neurologic and neurosurgical conditions.

19th Annual Clinical Reviews and Primary Care Update
June 25-29, 2012, Amelia Island, FL
Clinical Reviews and Primary Care Update consists of lectures, discussions, and workshops on topics of general interest in various areas of medicine. Medical staff from Mayo Clinic provide reviews and updates in the areas of cardiology, dermatology, endocrinology, gastroenterology, infectious diseases, internal medicine, neurology, urology, pulmonology, nephrology, and hematology/oncology.

To register or for additional information, please call 800-323-2688, e-mail cme@mayo.edu, or visit www.mayo.edu/cme.

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