Health Composite Scores from the 12-item Short-Form Health Survey. Those randomized to the intervention group increased their 6-minute walk distance in meters significantly (357.4 to 399.8 vs 353.3 to 342.2 for those in the control group; mean difference, 53.5; $P < .001$). There were also increases in maximum treadmill walking time (intervention, 7.91 to 9.44 minutes vs control, 7.56 to 8.09 minutes; mean difference, 1.01 minutes; $P = .04$). Accelerometer-measured physical activity over 7 days also increased in the intervention group vs the control group ($P = .03$). There were also significant improvements in the Walking Impairment Questionnaire distance score ($P = .003$) and Walking Impairment Questionnaire speed score ($P = .004$).

Comment: The study indicates that home-based exercise can be effective in patients with PAD. It does not indicate that home-based exercise has equal effectiveness to supervised exercise programs, because the two were not directly compared. Nevertheless, until supervised exercise becomes a benefit of insurance coverage, the data should encourage physicians to recommend home-based exercise therapy in their patients with PAD.

Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study

Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. JAMA Intern Med 2013;173:743-52.

Conclusions: Glucocorticoid use increases the risk of venous thromboembolism (VTE).

Summary: It is known that excess endogenous cortisol increases VTE risk. Whether this risk applies to exogenous use of glucocorticoids is unclear, however, potentially clinically important. The authors point out that in Denmark, the country of origin of this study, 3.5% of the population redeemed a prescription for systemic glucocorticoids in 2010 (Danish Medicines Agency). Given the incidence of VTE and the prevalence of glucocorticoid use, any association between VTE and glucocorticoid use has important implications. The authors therefore decided to examine the association between exogenous glucocorticoid use and VTE. This was a population case-control study using a nationwide database from Denmark. The authors identified 38,765 VTE cases from the period of January 1, 2005, through December 31, 2011. Risk matched sampling by birth year and sex was used to select 387,650 controls from the general population. The VTE diagnosis date for the case was the index date for cases and matched controls. Patients who had filled a glucocorticoid prescription were classified by the time the prescription was filled, ≤90 days, 91 to 365 days, and >365 days before the index VTE date. Such patients were classified as present, recent, and former users of glucocorticoids, respectively. Present users were subdivided into new (first-ever prescription <90 days before the index date) and continuing users (others). Analysis was performed using conditional logistic regression adjusted for VTE risk factors to estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for glucocorticoid users vs nonusers. VTE risk was increased by systemic glucocorticoids in present (adjusted IRR, 2.31; 95% CI, 2.18-2.45), new (3.06; 2.77-3.38), continuing (2.02; 1.88-2.17), and recent (1.18; 1.10-1.26) users but not in former users (0.94; 0.90-0.99). Adjusted IRR increased from 1.00 (95% CI, 0.93-1.07) for a prednisolone-equivalent cumulative dose of ≤10 mg to 1.98 (95% CI, 1.78-2.20) for >1000 to 2000 mg, and to 1.60 (95% CI, 1.49-1.71) for doses >2000 mg. New use of inhaled (adjusted IRR, 2.21; 95% CI, 1.72-2.86) and intestinal-acting (adjusted IRR, 2.17; 95% CI, 1.27-3.71) glucocorticoids also increased VTE risk.

Comment: Of course, many of the disease processes for which glucocorticoids are prescribed may, in themselves, increase VTE risk. However, this extensive analysis found increased risk for not only systemic glucocorticoids but also inhaled and intestinal-acting glucocorticoids, and a causal link is further suggested by higher risk with new users, and with higher doses. These observations, along with adjustment for confounding variables, strongly suggest that the authors' conclusion is correct that glucocorticoid use increases the risk of VTE.

Ambulatory Blood Pressure Changes After Renal Sympathetic Denervation in Patients with Resistant Hypertension

Mahfoud F, Ukena C, Schmieder RE, et al. Circulation 2013;124:132-40.

Conclusions: Office blood pressures are reduced and relevant aspects of ambulatory blood pressure (BP) monitoring (APBM) are improved after renal sympathetic denervation in patients with true-treatment resistant hypertension.

Summary: Hypertensive patterns and methods of assessing BP appear to be important in the relationship between hypertension and cardiovascular morbidity and mortality. Guidelines recommend ABPM for patients with resistant hypertension. This is to exclude pseudohypertension and accurately assess BP control according to treatment. ABPM, with 24-hour day-and-night average BP values, correlates better than office BP values with hypertensive or diabetic end-organ damage (Mancia G et al, Hypertension 2000;36:894-900). In addition, nighttime BP correlates more closely with cardiovascular morbidity and mortality than daytime BP (Fagard RH et al, Hypertension 2008;51:55-61). Finally, high nighttime BP and non-dipping patterns of hypertension have been associated with increased sympathetic activity in hypertensive patients (Grassi G et al, Hypertension 2008;52:925-31). Renal sympathetic denervation (RDN) reduces office systolic and diastolic BPs in patients with resistant hypertension (Esler MD et al, Lancet 2010;376:1903-9). The purpose of this study was to investigate the effects of RDN on out-of-office BP using 24-hour ABPM. The study represents the largest cohort of patients with true resistant and pseudoresistant hypertension analyzed thus far. A total of 346 uncontrolled hypertensive patients were separated according to daytime ambulatory BP monitoring into 303 with true resistant BP (office systolic BP [SBP] 172 ± 22 mm Hg; 24-hour SBP 154 ± 16 mm Hg) and 43 with pseudoresistant hypertension (office SBP 161 ± 20.3 mm Hg; 24-hour SBP 121 ± 20 mm Hg). Patients were from 10 centers and were studied at 3, 6, and 12 months of follow-up after RDN. In follow-up, office SBP was reduced by 21.5/23.7/27.3 mm Hg, office diastolic BP by 8.9/9.5/11.7 mm Hg, and pulse pressure by 13.4/14.2/14.9 mm Hg (n = 245/236/90; *P* for all <.001), respectively, at 3, 6, and 12 months. In patients with true treatment resistance, there was a significant reduction with RDN in 24-hour SBP (−0.1/−10.2/−11.7) and minimum SBP (−6.0/−9.4/−13.1 mm Hg; $P < .001$) at 3, 6, and 12 months, respectively. In pseudoresistant patients, RDN had no effect on ambulatory BP; however, office BP was reduced to a similar extent. RDN was equally effective in reducing BP in different subgroups of patients. Office SBP at baseline was the only independent correlate of BP response.

Comment: The study addressed concerns that RDN might not as effectively reduce ambulatory BP as it does office BP. Results of the study are not entirely unexpected. The Symplicity study of resistant hypertension and RDN did not specifically exclude pseudoresistant hypertension (Esler MD et al, Lancet 2010;376:1903-9). However, only ~12% of the patients in the Symplicity study apparently had pseudoresistant hypertension. As treatment with RDN for resistant hypertension potentially moves toward application out of clinical trials, it will be important for clinicians to be aware that only patients with truly resistant hypertension, and not those with "white-coat syndrome," be considered for RDN.

Endovascular Repair Versus Open Repair of Ruptured Abdominal Aortic Aneurysms: A Multicenter Randomized Controlled Trial

Reimerink JJ, Hoornweg LL, Vahl AC, and the Amsterdam Acute Aneurysm Trial Collaborators. Ann Surg 2013;258:248-56.

Conclusions: There is no difference in outcome of treatment of ruptured abdominal aortic aneurysm (RAAA) in rates of death and severe complication for those patients treated with endovascular (EVAR) or open repair (OR).

Summary: In recent years, treatment of RAAA with EVAR has emerged as an alternative to OR. Support for the hypothesis that EVAR reduces mortality in patients with RAAA vs those treated with OR comes from observational and population-based studies (Veith FJ, Ann Surg 2009;250:818-24; and Giles KA, J Endovasc Ther 2009;16:554-64). However, to date, no significant randomized trial data has been available comparing EVAR vs OR for RAAA. A single previous trial was terminated after randomizing 32 patients (Hinchliffe RJ et al, Eur J Vasc Endovasc Surg 2006;32:506-13). The Amsterdam Acute Aneurysm Trial was designed with the hypothesis that EVAR would reduce mortality and severe complications compared with OR for treatment of RAAA. The study was conducted in the greater Amsterdam area (1.24 million inhabitants and 10 hospitals). Three hospitals, consisting of two academic medical centers and a teaching hospital, were trial centers for this study. The trial centers provided alternating around-the-clock RAAA service. The other seven regional hospitals agreed to participate in the trial by transferring patients with suspected RAAA to one of the trial centers if possible. They also provided data on all patients who presented with an RAAA. After diagnosis, anatomic suitability for EVAR based on computed tomography angiography and clinical suitability for OR was documented by the vascular surgeon and the radiologist. Patients suitable for both were then randomized. All patients in the trial region with proven RAAA were included in a prospective parallel cohort. The primary end point of the study was the composite of death and severe complications at 30 days. Between April 2004 and February 2011, 520 patients were identified with RAAA. Of these patients, 365 were excluded from potential randomization because of anatomy unfavorable for EVAR, another 71 were not evaluated by computed tomography scan, and 54 were not referred to a trial center. This left 155 with favorable anatomy who could potentially be randomized. An additional 39 patients, however, were excluded as unfit for OR (n = 16),

for logistical problems (n = 11), severe hemodynamic instability after computed tomography angiography (n = 7), or refused surgery (n = 5). This left 116 patients for randomization. The primary end point rate was 42% for EVAR and 47% for OR (absolute risk reduction, 5.4%; 95% confidence interval [CI], −13% to 23%]. The 30-day mortality was 21% in patients assigned to EVAR compared with 25% for OR (absolute risk reduction, 4.4%; 95% CI, −11% to 20%). The mortality was 30% (95% CI, 26%-35%) in all surgically treated patients in the nonrandomized cohort and was 26% (95% CI, 20%-32%) in patients with unfavorable anatomy for EVAR treated by OR at trial centers.

Comment: The 30-day mortality for open repair in this study was <30%, considerably lower than the 48.5% postulated before the study. A subanalysis by the authors suggests that excluding patients highly unstable for OR was not the reason for the unanticipated low operative mortality of OR. It appears that OR in centers of excellence may be a better operation for RAAA now than in the past. A combination of the improved OR for RAAA and the large percentage of patients with RAAA unsuitable for conventional EVAR suggests the effect of EVAR on overall outcomes for treatment of RAAA may be less, and perhaps considerably less, than previously suggested.

Long-Term Clinical Effectiveness of Supervised Exercise Therapy Versus Endovascular Revascularization for Intermittent Claudication from a Randomized Clinical Trial

Fakhry F, Rouwet EV, den Hoed PT, et al. Br J Surg 2013;100:1164-71.

Conclusions: Over the long-term, supervised exercise therapy (SET)-first or endovascular revascularization (ER) therapy-first treatment strategies are equally effective in improving the quality of life and functional performance in patients with intermittent claudication. There are significantly higher numbers of total invasive interventions in the ER-first group. This supports a SET-first treatment strategy for intermittent claudication.

Summary: SET and ER both improve walking performance and quality of life in patients with intermittent claudication (Spronk S et al, Radiology 2005;235:833-42; and Watson L et al, Cochrane Database Syst Rev 2008;CD000990). The Comparing Exercise Therapy with Angioplasty for Claudication (CETAC) Trial (Spronk S et al, Radiology 2009;250:586-95) and a systematic review comparing ER and SET for treatment of intermittent claudication concluded that SET and ER were equally effective after 12 months (Frans FA et al, Br J Surg 2012;99:16-28). The current report represents an attempt to provide longer follow-up of the CETAC trial to provide an estimate of long-term clinical effectiveness of a SET-first or an ER-first treatment strategy for patients with intermittent claudication. CETAC was a single-center randomized trial that compared SET vs ER as the initial treatment for patients with intermittent claudication. A total of 151 patients were randomly assigned to SET (n = 75) or ER (n = 76). After a median follow-up of ~7 years (range, 0.07-9.17 years), there were 17 deaths in the SET group and 15 in the ER group. Completeness of long-term follow-up was 71% in the SET group and 84% in the ER group (36 patients available for review in the SET group and 47 in the ER group). Outcome measures were functional performance (pain-free maximum walking distance, ankle-brachial pressure index), quality of life, and the number of secondary interventions measured at baseline and at ~7 years of follow-up. Repeated-measurement and Kaplan-Meier methods were used for data analyses. Data were analyzed on an intention-to-treat basis. After 7 years, functional performance ($P < .001$) and quality of life ($P < .005$) improved after both SET and ER. The number of secondary interventions was higher in the SET group ($P = .001$). The total number of endovascular and surgical interventions (primary and secondary) was significantly higher with the ER-first strategy, 64 interventions in the SET group and 121 in the ER group ($P < .001$). There were two minor amputations in the SET group and three major amputations in the ER group.

Comment: The study has some limitations in that not all patients were available for long-term follow-up, and the mortality and attrition rate decreased the power to detect small differences between the SET and ER groups. In addition, the authors did not collect information on regular exercise performed after the trial. Only endovascular and surgical procedures were considered secondary interventions. Nevertheless, the study still strongly argues that to minimize total procedures in patients with intermittent claudication, a SET-first rather than ER-first treatment strategy is preferred.

Systematic Review of Exercise Training or Percutaneous Transluminal Angioplasty for Intermittent Claudication

Frans FA, Bipat S, Reekers JA, et al. Br J Surg 2012;99:16-28.

Conclusions: The combination of percutaneous transluminal angioplasty (PTA) and exercise therapy (ET) may be superior to ET or PTA alone for treatment of intermittent claudication.

Summary: One goal in patients with intermittent claudication is to improve their walking distance with the thought that this will subsequently improve their quality of life. Percutaneous transluminal angioplasty (PTA), surgery, drugs, and exercise therapy (ET) all can improve symptoms in patients with intermittent claudication. Systematic reviews have demonstrated superiority of supervised ET (SET) over unsupervised ET for both increasing pain-free and maximum walking distance (Bendermacher BL et al, Cochrane Database Syst Rev 2006;CD005263; and Wind J et al, Eur J Vasc Endovasc Surg 2007;34:1-9). A Cochran review (Fowkes FG et al, Cochrane Database Syst Rev 2000;CD000017) indicted that there was greater short-term benefit with PTA than with exercise in patients with intermittent claudication but that the effect was not sustained after 1 to 2 years. A second review found medical treatment (home or SET, plus risk factor modification) resulted in longer walking distances than PTA at 1 to 2 years (Wilson SE, Ann Vasc Surg 2010;24:498-502). The authors noted that since this review, six additional randomized clinical trials have compared PTA and ET during the past 5 years. They therefore decided to perform a systematic review to summarize the results of all randomized clinical trials comparing PTA with ET therapy. Their goal was to obtain the best estimate of the relative effectiveness of these two approaches. They performed a systematic review of relevant randomized clinical trials identified from MEDLINE, Embase, and Cochrane Library Databases. To be included in the review, the trial had to compare PTA with ET in patients with intermittent claudication secondary to aortoiliac or femoral popliteal occlusive disease, or both. There were 258 initial articles identified with 11 (reporting data on eight trials) meeting inclusion criteria. There was one trial with isolated aortoiliac obstruction, three trials with femoropopliteal disease, and five with combined lesions. Two trials compared PTA with advice for ET, 4 trials compared PTA with SET, 2 trials compared PTA plus SET with SET alone, and 2 trials compared PTA plus SET with PTA alone. The authors concluded that heterogeneity precluded pooling of the data even though the end points in most trials were walking distance and quality of life. Their analysis indicated the effectiveness of PTA and ET was equivalent, although PTA plus ET provided greater improvement of walking distance and some domains of quality of life analysis compared with PTA alone or ET alone.

Comment: The article does indeed provide a good summary of the most up-to-date information currently available on the effectiveness of ET and PTA in patients treated for intermittent claudication. The data suggest that SET and PTA can both be effective in improving walking distance in patients with claudication. Neither therapy is perfect. ET is noninvasive, seemingly relatively inexpensive, and with less risk compared with PTA. However, PTA may be more universally applicable and more quickly effective than ET. Eventual failure rates are high with PTA treatment of femoral popliteal disease, but angioplasty of infrainguinal arteries is a moving target, with improvements of percutaneous techniques, such as drug-eluting balloons and stents, potentially shortly down the road. Two important questions not addressed in this study include the cost effectiveness of each treatment strategy and the potential for each treatment strategy to convert patients from claudication to critical limb ischemia with therapy failure.