UPDATE

Update in General Internal Medicine

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INTRODUCTION

The aim of this update is to briefly summarize the research articles published in 2008 that we think have the most important implications for General Internal Medicine practice. The wide breadth of General Internal Medicine practice always makes selecting articles a challenging and somewhat subjective process. In selecting articles, we relied heavily on the internal process we routinely use to do this in the Division of General Internal Medicine at Northwestern University. Each month, faculty members review an array of journals and journal aggregators (e.g., ACP Journal Club and Journal Watch General Medicine) to identify potential articles for discussion. A subgroup of the faculty then selects articles that deserve in-depth review and discussion by the entire faculty at our monthly Journal Club. If an article is judged to be particularly important and practice-changing, we then try to use this as a springboard for quality improvement efforts. For this review, we concentrate on eight articles with findings that we think should guide our practice in the future.

CORONARY ARTERY DISEASE

Weintraub WS, Spertus JA, Kolm P, et al., for the COURAGE Trial Research Group. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359:677–87.

Several trials, including an earlier analysis of these COURAGE data, have shown that percutaneous coronary intervention (PCI) does not improve survival or reduce cardiovascular events for patients with stable coronary artery disease compared to optimal medical therapy (OMT) alone.^{1–6} However, the marginal benefit of PCI for anginal symptoms and quality of life has remained unclear. The investigators randomly assigned 2,287 patients with stable coronary disease to PCI plus OMT or to OMT alone. Subjects were not blinded to receipt of PCI versus OMT, and only 1.4% of patients received drug-eluting stents. Medical therapy was indeed close to “optimal” with high

proportions of patients treated with long-acting metoprolol (89%), aspirin (95%) and a statin (89%). Symptoms were assessed using the Seattle Angina Questionnaire (SAQ), and physical and mental functioning were evaluated using the RAND-36. The majority of patients were followed for at least 3 years. During follow-up, 21% of patients in the OMT group crossed over and underwent PCI. Median follow-up was 4.6 years, but all analyses were truncated at 3 years because data were not available for an increasingly large proportion of patients owing to censoring, death or failure to complete the health-status assessments. All analyses were based on intention-to-treat.

At baseline, 22% of patients were free of angina. At 3 months, 53% of the patients in the PCI plus OMT group and 42% in the OMT group were angina-free ($P<0.001$). Over the 3-year follow-up, the proportion of patients without angina gradually increased to 59% in the PCI plus OMT group and 56% in the OMT group, and the difference between the groups ceased to be statistically significant ($P=0.30$). Scores on the SAQ and the RAND-36 showed similar trends over time, with a benefit being seen from PCI for the period between 1 and 24 months, but disappearing by 36 months. For example, angina frequency improved from a mean score of 68 (100-point scale with 100 indicating no angina) to 81 after the 1st month in the PCI plus OMT group compared to a change from 69 to 76 in the OMT group. By 36 months, however, the mean scores were 89 and 88, respectively. There was no significant difference between groups in emotional or social functioning at any time. Patients with more severe angina had a greater benefit from PCI compared to OMT.

Implications for Practice

This study suggests that most patients with stable angina should be managed with aggressive medical therapy instead of PCI. Patients can be reassured that PCI will not decrease their mortality, and with OMT their angina is likely to improve substantially and continue to improve over time. This raises the question of whether patients presenting with stable angina need cardiac catheterization. If a patient has no high risk features on provocative testing (i.e., drop in blood pressure, angina at a low work load, deep ST-segment depression or imaging studies showing large or multiple areas of reversible ischemia) and has normal left ventricular systolic function, perhaps it should become standard-of-care to optimize medical therapy and not perform cardiac catheterization. Those with high-risk features should be catheterized immediately. Patients who feel that they have not achieved adequate control of their angina symptoms within 6 months with OMT should be referred at a later time for catheterization and consideration for revascularization.

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CARDIOVASCULAR DISEASE PREVENTION

Ridker PM, Danielson E, Fonseca FA, et al., for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–207.

Previous studies have shown that individuals with elevated levels of high-sensitivity C-reactive protein (hsCRP) have a higher risk of cardiovascular events than would be predicted by their traditional risk factors alone.^{7–13} However, no studies have shown that treating patients with elevated hsCRP who would not normally be recommended for lipid-lowering therapy is beneficial. This study randomized 17,802 men ≥ 50 years old and women ≥ 60 years old who had (1) no prior cardiovascular disease, (2) LDL cholesterol levels ≤ 3.4 mmol/l (130 mg/dl) and (3) hsCRP levels ≥ 2.0 mg/l to receive rosuvastatin 20 mg daily or placebo. Only 20% of screened study candidates met eligibility criteria. Approximately half of the participants in this study had Framingham risk scores (FRS) above 10%, most were overweight or obese, and 41% had the metabolic syndrome. The primary outcome was the combination of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina or death from cardiovascular cause. The study was stopped early after a median follow-up of 1.9 years because a prespecified difference between groups was reached. The study was funded by the makers of rosuvastatin, and the lead author is listed as a co-inventor on the patent for hsCRP.

Rosuvastatin reduced LDL cholesterol levels by 50% [to a median of 1.42 mmol/l (55 mg/dl)] and hsCRP levels by 37%. Among subjects assigned rosuvastatin, the rate of the primary end point was 0.77 per 100 person-years compared to 1.36 per 100 person-years for subjects assigned placebo (hazard ratio, 0.56; 95% CI, 0.46 to 0.69, $P < 0.00001$). The relative risk reduction was 44%, the absolute risk reduction was 0.59 per 100 person-years, and the number needed to treat at 2 years was 81. All cause deaths were reduced (hazard ratio 0.80; 95% CI 0.67–0.97), but not confirmed deaths from cardiovascular causes (hazard ratio 0.82; 95% CI 0.52–1.27).¹⁴ The rosuvastatin group did not have a significant increase in myopathy or cancer, but did have a higher incidence of physician-reported diabetes.

Implications for Practice

Does the finding that rosuvastatin reduced cardiovascular events among people with elevated hsCRP levels but without hyperlipidemia mean that hsCRP should be used as a screening test for patients who do not meet traditional definitions of hyperlipidemia? We think the answer is no. It is better to think of hsCRP as just one other variable that can be used to help estimate patients' risk of cardiovascular disease, as previous studies suggest.

Clinicians' decisions and their counseling to patients should emphasize *absolute* risk and risk reduction. Despite their relatively favorable lipid profiles, half of patients in the JUPITER study had a FRS above 10% and would already be classified as moderately high risk for coronary events. Measuring hsCRP for someone in this subgroup would usually have little incremental value. Conversely, if a patient has a very low absolute risk based on the FRS (e.g., $< 5\%$), even a high hsCRP would not shift individuals' risk substantially. Thus, an hsCRP test is most useful for patients with a FRS in the 5–9% range who would not otherwise meet treatment criteria, e.g., a

60 year-old male with a total cholesterol of 200 mg/dl, triglycerides of 125 mg/dl, HDL of 50 mg/dl, a calculated LDL of 125 mg/dl and a FRS of 9%. Those who have an hsCRP level above 2.0 mg/l are likely to have a 10-year risk of coronary events above 10%,⁹ a level at which it is reasonable to discuss the benefits of statin therapy even if the LDL cholesterol is < 130 mg/dl.

While hsCRP can be used as another tool to help guide physicians' treatment recommendations and patients' decisions about lipid lowering therapy, until more data are available, patients should be counseled that primary prevention with statin therapy can lower their cardiovascular risk by about 30% rather than the substantially greater reduction reported in JUPITER.¹⁵ The wider availability of very low-cost generic statins should make this therapy highly cost-effective.¹⁶

DIABETES

Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–59.

Randomized controlled trials have demonstrated reduced microvascular complications in patients with type 1¹⁷ and type 2^{18,19} diabetes with strict glycemic control (achieving a hemoglobin A1c level of approximately 7%). Observational studies suggest that the risk of microvascular complications continues to decline down to a hemoglobin A1c below 6% with no apparent threshold. However, the benefits of strict glycemic control for reducing macrovascular complications are not well-defined.

This study included 10,251 patients with type 2 diabetes mellitus and a hemoglobin A1c $\geq 7.5\%$. Participants either (1) were 40 to 79 years old and had known cardiovascular disease, or (2) were 55 to 79 years old and had anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker or obesity). Persons with frequent or recent serious hypoglycemic events or unwillingness to do home glucose monitoring were excluded. Participants were randomized to receive intensive therapy (IT) with an A1c target $< 6.0\%$ or standard therapy (ST) (target A1c from 7.0 to 7.9%). The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. The study was terminated early due to increased mortality in the IT group after a mean of 3.5 years of follow-up.

Within 4 months after randomization, the median A1c had fallen from 8.1% at baseline to 6.7% (interquartile range, 6.2% to 7.2%) in the IT group and to 7.5% (interquartile range, 7.0% to 8.2%) in the ST group with stable median levels of 6.4% and 7.5%, respectively, by 1 year. During follow-up, more patients in the IT group died when compared to the ST group (257 vs. 203; hazard ratio, 1.22; 95% CI, 1.01 to 1.46; $P = 0.04$). At the time of study closure there was no significant difference in the primary outcome between the IT and ST groups (352 events vs. 371 events, respectively; hazard ratio, 0.90; 95% CI, 0.78 to 1.04; $P = 0.16$). However, in pre-specified subgroup analyses the primary outcome was significantly lower in patients in the IT group with no previous cardiovascular disease and in those with a baseline A1c $\leq 8.0\%$ (hazard ratios approximately 0.75). Severe hypoglycemia was much more common in the IT group

(16.2% vs. 5.1% in the ST group; $P < 0.001$), and the mean weight gain was much greater in the IT group (3.5 kg vs. 0.4 kg in the ST group; $P < 0.001$). Polypharmacy and use of the thiazolidinedione rosiglitazone were more common in the IT group.

Implications for Practice

The optimal level of glycemic control must be determined for each patient based on the person's risk of microvascular, macrovascular and hypoglycemic complications. This study, along with ADVANCE²⁰ and the Veteran's Affairs Diabetes Trial,²¹ shows that rapidly intensifying drug therapy to achieve an A1c well below 7.0% does not reduce cardiovascular events over a 3- to 5-year period in patients with longstanding diabetes. Moreover, the higher mortality rate in ACCORD shows the significant risk of this strategy, particularly for older patients and those with established cardiovascular disease. For these individuals, a less intensive A1c goal is usually optimal. However, evidence from these three trials and other observational studies²² suggests that IT may reduce cardiovascular events in younger patients with no previous cardiovascular disease, especially those whose baseline glycemic control is already relatively good ($A1c \leq 8.0\%$). These findings should be considered hypothesis-generating, and randomized controlled trials are needed to determine whether there is a subgroup of patients for whom lowering the A1c to less than 7.0% reduces cardiovascular events and is safe.

HYPERTENSION

Jamerson K, Weber MA, Bakris GL, et al., for the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–28.

The ALLHAT study found that chlorthalidone, lisinopril and amlodipine were equally efficacious primary therapies for hypertension.²³ Most patients, however, require more than one antihypertensive, and few studies have rigorously evaluated which combinations of antihypertensives are most effective.

This randomized, double-blind trial assigned 11,506 patients with hypertension and high cardiovascular risk (i.e., prior coronary event, myocardial infarction, revascularization or stroke; impaired renal function; peripheral arterial disease; left ventricular hypertrophy; or diabetes mellitus) to receive benazepril plus amlodipine or benazepril plus hydrochlorothiazide. Study medications were titrated and additional medications were added as needed to reach a target blood pressure of $<140/90$ mmHg or $<130/80$ mmHg for patients with diabetes or kidney disease. The primary end point was time to a first major cardiovascular event defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest or coronary revascularization. The trial was terminated early after a mean follow-up of 36 months due to a difference in treatment groups, which crossed a prespecified threshold.

Mean blood pressure after dose adjustment was slightly lower in the benazepril-amlodipine group (131.6/73.3 mmHg) than in the benazepril-hydrochlorothiazide group (132.5/74.4 mmHg; $P < 0.001$ for both systolic and diastolic pressures). The primary outcome occurred less often in the benazepril-amlodipine group ($N=552$, 9.6%) than in the

benazepril-hydrochlorothiazide group ($N=679$, 11.8%), an absolute risk reduction of 2.2% and a relative risk reduction of 19.6% (95% CI, 10% to 28%; $P < 0.001$). Results were similar for the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke.

From these data, it cannot be determined whether the benefit in the benazepril-amlodipine group was due to the amlodipine itself or to the small but significantly decreased blood pressure in that group.

Implications for Practice

This study's results provide further evidence contradicting the recommendation that antihypertensive therapy should always include a diuretic unless there are contraindications or comorbidities that provide a compelling reason to use other agents.²⁴ However, one should *not* conclude that diuretics as a class are inferior to calcium channel blockers as second-line agents. One explanation for the discrepancy between these findings and those of ALLHAT is that hydrochlorothiazide (used in ACCOMPLISH) and chlorthalidone (used in ALLHAT) are not equivalent. Chlorthalidone is 1.5 to 2.0 times more potent, has a substantially longer half-life²⁵ and achieves better 24-h blood pressure control²⁶ than hydrochlorothiazide. These differences could lead to better outcomes for chlorthalidone compared to hydrochlorothiazide, although no trials have examined this. Until more data become available, current evidence suggests that when prescribing a diuretic, whether as a first- or second-line agent, chlorthalidone should be the preferred agent. Unfortunately, it is difficult to obtain the lowest dose of chlorthalidone (15 mg), and there are far fewer combination pills containing chlorthalidone.

OSTEOPOROSIS

Tosteson AN, Melton LJ 3rd, Dawson-Hughes B, et al., for the National Osteoporosis Foundation Guide Committee. Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int*. 2008;19:437–47.

To improve the identification of patients with high fracture risk, the WHO developed a fracture prediction algorithm (FRAXTM).²⁷ FRAXTM incorporates age, gender, prior osteoporotic fracture, femoral neck bone mineral density, body mass index, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, parental history of hip fracture, current smoking and alcohol intake to estimate the 10-year risk of hip fracture and 10-year risk of major osteoporotic fracture stratified by country and race. To date, however, there has been no consensus on what level of absolute fracture risk justifies pharmacologic therapy.

This study utilized a Markov-cohort model of annual US age-specific incidence of clinical hip, spine, forearm, shoulder, rib, pelvis and lower leg fractures, costs (in 2005 US dollars) and QALYs to assess the cost-effectiveness of osteoporosis treatment. The baseline study assumptions included a medication cost of \$600/year for 5 years, with treatment decreasing the risk of fracture by 35%. To determine the 10-year hip fracture probability at which treatment became cost-effective, average annual age-specific probabilities for all fractures were multiplied by a relative risk that was systematically varied from 0 to 10 until a cost of \$60,000 per QALY gained was observed for treatment relative to no intervention.

Osteoporosis treatment was cost-effective when the 10-year risk of hip fracture reached 3–5%. Although the *relative* risk at which treatment became cost-effective varied markedly between genders and by race/ethnicity, the *absolute* 10-year risk of a hip fracture at which treatment became cost-effective was approximately 3% for both men and women across all race/ethnicity groups.

The results were particularly sensitive to treatment cost. If the estimated cost of treatment is reduced to \$300 per year, treatment would be cost-effective even when the hip fracture risk was only 1–2%.

Implications for Practice

The FRAX™ risk prediction algorithm should come into routine use to guide decisions about whether to start pharmacologic treatment for osteoporosis. Clinicians should be conservative in treating patients whose absolute 10-year hip fracture risk is less than 3%. However, the FRAX™ does not incorporate all clinical factors that could increase the risk of fall and fracture, such as poor balance or leg weakness. In patients with unmeasured risk factors, treatment of patients with an absolute FRAX™ risk below 3% may be justified.

Future guidelines for osteoporosis are expected to incorporate use of the FRAX™ risk prediction algorithm to decide who should be treated for osteoporosis. This is a rare example of cost-effectiveness data being used to guide clinical practice recommendations, although we should expect to see much more of this in the future.

VENOUS THROMBOEMBOLISM

Verhovsek M, Douketis JD, Yi Q, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med*. 2008;149:481–90.

For patients with unprovoked venous thromboembolism (VTE) randomized trials demonstrate an increased risk of recurrence when anticoagulation is stopped regardless of duration.^{28,29} Previous studies have suggested that patients with an elevated D-dimer may be at increased risk of recurrence.^{30–33}

The authors identified two randomized controlled trials^{33,34} and five prospective cohort studies.^{31,32,35–37} These seven studies included 1,888 patients with a first episode of unprovoked VTE. All patients were anticoagulated for at least 3 months, had D-dimer levels measured 3 weeks to 2 months after stopping anticoagulation, and were followed prospectively for symptomatic recurrence of VTE. All seven studies were of reasonably high quality with regularly scheduled follow-up of at least 12 months (mean close to 2 years), and all had blinded adjudication of outcomes. Only two studies, however, reported the rates of patients lost to follow-up.^{33,36} Six different D-dimer assays were used across the seven studies, and the cutoff for a “positive” D-dimer differed.

Nearly half of patients (N=907, 48%) had a positive D-dimer. The annual risk of VTE recurrence was 8.9% (95% CI, 5.8% to 11.9%) for patients with a positive D-dimer and 3.5% (CI, 2.7% to 4.3%) for patients with a negative D-dimer. Calculating the pooled incidence rate ratio showed that patients with a positive D-dimer have 2.2 times the risk of recurrent VTE compared to patients with a negative D-dimer (CI, 1.65 to 2.94, P=0.002).

Implications for Practice

This carefully conducted systematic review provides much needed assistance in weighing the risks and benefits of long-term anticoagulation for patients with a first unprovoked episode of VTE. Although the optimal timing of measuring D-dimer after stopping anticoagulation is unknown, based on the available evidence for patients in this population, a D-dimer level should be measured 3–8 weeks after stopping anticoagulation. If the D-dimer is elevated according to the manufacturer's cutoff, patients should be advised that they have an 18% chance of recurrence over the next 2 years, which would likely warrant resuming anticoagulation indefinitely. Patients with a negative D-dimer should be advised that they have a 7% chance of recurrence in the next 2 years, and the decision about anticoagulation would have to be individualized. A lower risk of recurrence has been found in patients who are younger, non-obese,³⁸ and female^{39,40} and in those whose veins have recanalized.^{41–43} Ultimately, combining these factors into a clinical prediction rule as these authors suggest may provide the most useful guidance in making a decision about long-term anticoagulation.

COLON CANCER SCREENING

Imperiale TF, Glowinski EA, Lin-Cooper C, et al. Five-year risk of colorectal neoplasia after negative screening colonoscopy. *N Engl J Med*. 2008;359:1218–24.

Although several guidelines recommend a screening colonoscopy every 10 years,^{44–46} this interval is actually extrapolated from case-control studies of sigmoidoscopy.^{47,48} There are no direct controlled-trial data or observational data to support a 10-year interval for screening colonoscopy.

The authors analyzed a registry of 2,436 people aged 50 years and older who had an initial screening colonoscopy that was negative for adenomatous polyps and were offered a routine follow-up colonoscopy 5 years later. After an average of 5.3±1.3 years, 1,256 (51.6%) of subjects underwent repeat screening, and 1,213 (96.6%) of colonoscopies were complete to the cecum. Although the authors attempted to contact the remainder of subjects who did not undergo repeat screening, the response rate was too low to draw any conclusions.

No cancers were found among the patients who were rescreened (upper 95% confidence limit 0.24%), and 201 (16.0%) had polyps, but only 16 (1.3%, 95% CI, 1.21 to 2.15) had an advanced adenoma. Advanced adenomas were defined as tubular adenomas of at least 1 cm, polyps with at least 25% villous features or polyps with high-grade dysplasia. Men were more likely than women to have advanced adenomas (1.8% vs. 0.6%; relative risk 3.31; 95% CI, 1.02 to 10.8). The numbers needed to rescreen to detect one advanced adenoma after 5 years were: 79 (49–137) for all patients, 55 (32–102) for men, and 182 (63–909) for women. These numbers needed to rescreen could change appreciably if the rates of advanced adenomas in the nearly half of patients who were not rescreened differ significantly from the rates among those who were rescreened.

Implications for Practice

The low incidence of advanced neoplasia in this study suggests that the optimal rescreening interval for average risk patients

after a negative initial colonoscopy is longer than 5 years. Since no invasive cancers were found in this study, and since the rate of progression from advanced adenoma to malignancy is unknown, the optimal rescreening interval also remains unknown. Nevertheless, the current recommendation of waiting 10 years to repeat a screening colonoscopy may be too long. Men appear to need screening more frequently than women.

OSTEOARTHRITIS

Englund M, Guermazi A, Gale D, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med*. 2008;359:1108–15.

Although 67–91% of patients with symptomatic osteoarthritis of the knee have evidence of meniscal damage on MRI,^{49–52} a substantial proportion of asymptomatic patients appears to have MRI abnormalities as well.⁵²

Through random-digit dialing, the authors recruited 991 subjects ≥ 50 years of age who were able to ambulate independently. All participants underwent MRI of the right knee, which was read by a single author. Equivocal findings were evaluated by a second reader with good inter-observer agreement (kappa 0.72). Meniscal damage was defined as several types of meniscal “tears” or “destruction.” Subjects also had plain x-rays of the right knee to evaluate for radiographic osteoarthritis and completed a questionnaire about both frequent (on most days) and recent (within the last month) knee pain, aching or stiffness. The questionnaire did not assess the severity or chronicity of knee symptoms.

The overall prevalence of meniscal damage seen on MRI was 35%. This prevalence was greater for men, older patients and those with radiographic osteoarthritis. Among patients with radiographic osteoarthritis, 57/90 (63%) patients with frequent knee symptoms had meniscal tears on MRI; however, so did 46/77 (60%) patients without knee symptoms for an adjusted prevalence ratio of 1.14 (95% CI, 0.90 to 1.45). In contrast, for patients without radiographic osteoarthritis there was a small but significant difference, with 41/127 (32%) of those with frequent symptoms and 146/648 (23%) of those without frequent symptoms having meniscal tears on MRI for an adjusted prevalence ratio of 1.43 (95% CI, 1.08 to 1.90). Overall, 61% of meniscal tears were found in patients who had not had any pain, aching or stiffness in the preceding month.

Implications for Practice

For middle-aged and older patients with osteoarthritis and chronic knee pain, finding a meniscal tear on MRI does not necessarily mean that the tear is responsible for the patient's pain. Therefore, MRIs should be avoided in these patients unless the history and physical exam strongly point toward a large meniscal tear as the etiology of the patient's symptoms. Avoiding an unnecessary MRI may also avert an unnecessary arthroscopy as the benefits of arthroscopy for patients with knee osteoarthritis appear to last no longer than 3 months.⁵³

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