Intravenous tPA may improve functional outcomes in acute ischemic stroke even if given within 3 to 4.5 hours after symptom onset.

**Background:** Intravenous tissue plasminogen activator (tPA) is known to provide significant benefit in ischemic stroke up to 3 hours after symptom onset. Recent data suggest that there may be benefit within a 3- to 4.5-hour window, but exact treatment effect is not known.

**Objective:** To estimate the benefit of tPA in ischemic stroke 3 to 4.5 hours after symptom onset.

**Design:** Meta-analysis of randomized, controlled trials (RCTs).

**Methods:** The meta-analysis included data from all available RCTs (>100) of IV tPA for ischemic stroke with outcome data on patients who received therapy within 3 to 4.5 hours of symptoms. All analyses were performed on an intention-to-treat basis. Outcomes included 90-day global functional outcome (based on 3 individual outcome scales: modified Rankin scale [mRS] 0 to 1, NIH Stroke Scale [NIHSS] 0 to 1, and Barthel Index ≥95), 90-day functional outcome on the mRS, and mortality.

**Results:** Patients treated with tPA within 3 to 4.5 hours in the European Cooperative Acute Stroke Study (ECASS) -1 (n=234), ECASS-2 (n=265), ECASS-3 (n=821), and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial (n=302) were included, with a total of 1622 patients. Mean age varied from 64.7 to 65.5 years; median NIHSS ranged from 10 (ECASS-3) to 15 (ECASS-1). Median time to treatment ranged from 3 hours, 50 minutes (ECASS-1) to 4 hours, 1 minute (ATLANTIS). Treatment within 3 to 4.5 hours was associated with an increased chance of 90-day favorable global outcome (OR, 1.31; \( P =0.002 \)) and outcome on the mRS (OR, 1.31, \( P =0.01 \)) without a significant increase in mortality (OR, 1.04; \( P =0.83 \)). In a separate meta-analysis that excluded ECASS-1 (in which a higher-dose tPA was used), the odds of a favorable outcome were slightly lower (OR, 1.27 and 1.28 for global outcome and mRS, respectively), and the odds of mortality decreased (1.04 to 0.87), although this was not significant (\( P =0.46 \)).

**Conclusions:** IV tPA administered within 3 to 4.5 hours is beneficial and increases the odds of a favorable 90-day outcome by 31% without increasing mortality.

**Reviewer's Comments:** This article is important for hospitalists who care for patients with acute ischemic stroke. All studies included were similar in design, and time to treatment was well matched. From pooled data, it appears that there is no association between treatment and mortality; however, in 2 of 4 studies, mortality odds were substantially higher (with statistical significance in 1), although the authors attribute these discrepancies to chance effect. (Note that one of the authors is employed by Boehringer Ingelheim, a manufacturer of tPA.) While this analysis appears to support the idea that tPA may be beneficial in stroke treatment even if administered slightly outside the 3-hour window, the odds of a favorable 90-day outcome decrease with increased time from symptom onset, and early treatment remains the goal. (Reviewer-Anneliese M. Schleyer, MD).

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Keywords: Stroke, Tissue Plasminogen Activator

Print Tag: Refer to original journal article
In patients aged ≥65 years with syncope, the highest yield and cost-effective workup includes a history and exam, orthostatic vital signs, ECG, telemetry, and troponin I.

**Background:** Syncope is a common reason for admission to the hospital. Some clinicians order multiple diagnostic studies to determine the cause of the syncope. The clinical yield and cost-effectiveness of this practice is unknown.

**Objective:** To determine the clinical yield and cost for tests ordered in the management of older patients with syncope.

**Design:** Retrospective cohort study. **Methods/Participants:** Consecutive patients aged ≥65 years with a discharge diagnosis of syncope from 2002 to 2006 at one academic medical center were included. Researchers reviewed the medical records to determine (1) how often different tests were ordered to evaluate the syncope, (2) how often tests determined the diagnosis or changed management, and (3) the cost per test that affected the diagnosis or management (using billing records).

**Results:** 2106 patients were included. The most commonly ordered tests were ECG (99%), telemetry (95%), cardiac enzyme tests (95%), and head CT (63%). The yield of diagnostic testing was poor, as the following tests determined the cause or impacted management <5% of the time: cardiac enzymes, CT scans, echocardiography, carotid ultrasound, and EEG. Notably, recording the postural blood pressure changes was infrequently done (38% of patients) but had a substantial diagnostic yield, leading to a diagnosis in up to 25% of cases. Telemetry and ECG also had a reasonable yield. The cost for each test performed that changed the diagnosis or management ranged from a low of $17 for postural blood pressure to $32,973 for EEG. The most cost-effective tests seemed to be postural blood pressure, telemetry, ECG, and troponin I alone.

**Conclusions:** This retrospective cohort study of elderly patients with syncope reveals that many of the cardiac and neurologic tests commonly ordered have low yield and are not cost effective. The highest yield and most cost-effective tests to determine the diagnosis of or change in management of syncope were postural blood pressure, ECG, telemetry, and troponin I alone.

**Reviewer’s Comments:** Many patients with syncope currently get a “shotgun” approach to their diagnosis—a standard list of tests regardless of their clinical presentation. This creative study tried to help determine the highest yield and most cost-effective workup of syncope in patients aged ≥65 years. In line with prior evidence, most of the diagnostic tests for syncope are very low yield (changing diagnosis or management <5% of the time). In patients ≥65 years old with syncope, we should instead focus on a good history and physical exam and supplement with postural blood pressure, ECG, telemetry for 24 hours, and troponin I. The other possible tests should probably be ordered in patients with specific clinical suspicion after the history and physical exam. (Reviewer-Bradley A. Sharpe, MD).

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Keywords: Syncope, Diagnostic Tests, Cost-Effectiveness

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Acute Biliary Pancreatitis--Early ERCP vs Conservative Therapy

Early Endoscopic Retrograde Cholangiopancreatography in Predicted Severe Acute Biliary Pancreatitis: A Prospective Multicenter Study.

van Santvoort HC, Besselink MG, et al:

Ann Surg 2009; 250 (July): 68-75

In patients with severe acute biliary pancreatitis and cholestasis, early ERCP is associated with fewer complications than conservative therapy.

**Background:** There is a growing consensus that there is benefit to early endoscopic retrograde cholangiopancreatography (ERCP) in patients with severe acute biliary pancreatitis (ABP) and concomitant cholangitis. The role of early ERCP in severe ABP without cholangitis remains unclear.

**Objective:** To examine whether early ERCP (defined as ERCP within 72 hours of symptoms), compared to conservative therapy, is associated with a reduced risk of complications and mortality in patients with predicted severe ABP without cholangitis.

**Design/Participants:** A subset of patients with predicted severe ABP was evaluated from a larger cohort of patients with acute pancreatitis from all causes. Patients in this study had to meet prespecified criteria for acute pancreatitis, as well as criteria for a diagnosis of ABP within 72 hours of symptom onset. All patients with evidence of cholangitis were excluded, and the cohort was divided into those with and without cholestasis. All patients were managed with nasojejunal enteral feeds and without antibiotics. The decision to perform ERCP was left to the treating physician. Patients with ERCP within 72 hours of the onset of symptoms were assigned to the "early ERCP group."

**Methods:** The authors looked at the end points of complications and mortality during a patient's hospital stay and over a 90-day follow-up. The end points of patients in the early ERCP group and the conservative management group were compared, and patients with and without cholestasis were evaluated separately.

**Results:** 153 patients met inclusion criteria, 78 (51%) with cholestasis and 75 (49%) without. In the group with cholestasis, 52 patients (67%) underwent early ERCP, and the others were managed conservatively. After adjustment for disease severity by admission APACHE II score, early ERCP was associated with a lower risk of overall complications, including pancreatic necrosis and a nonsignificant reduction in mortality. In those without cholestasis, 29 patients (39%) underwent early ERCP, and the remaining patients had conservative management. For patients without cholestasis, there was no difference in the incidence of complications or mortality between the 2 management groups.

**Conclusions:** In patients with ABP with cholestasis, early ERCP is associated with fewer complications and a nonsignificant reduction in mortality.

**Reviewer's Comments:** In contrast to previous conflicting trials examining the utility of early ERCP in ABP, this study had a large-enough cohort that different subgroups could be studied. The separation of patients with and without cholestasis appears to be a key factor in the significant findings of this study and has good biological plausibility. ERCP, although potentially beneficial, is not without risks and should be reserved for those who will benefit. (Reviewer-Michelle Mourad, MD).

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Keywords: Pancreatitis, ERCP

Print Tag: Refer to original journal article
**H. pylori Eradication May Reduce Gastric Cancer Risk**

*Meta Analysis: Can Helicobacter pylori Eradication Treatment Reduce the Risk for Gastric Cancer?*

Fuccio L, Zagari RM, et al:

Ann Intern Med 2009; 151 (July 21): 121-128

In a meta-analysis of 6 randomized, controlled trials, *Helicobacter pylori* eradication decreased the incidence of gastric cancer risk by 35%.

**Background:** Although *Helicobacter pylori* infection is known to be a risk factor for gastric cancer, it is unclear whether eradication decreases the cancer risk.

**Objective:** To analyze existing randomized, controlled trials in pooled fashion with the goal of determining whether *H. pylori* eradication decreases the risk of gastric cancer.

**Design:** Meta-analysis.

**Methods:** Studies were identified from a literature search, clinical trial registers, and abstract searches. Inclusion criteria included randomization and comparison of an *H. pylori* eradication group to an untreated *H. pylori*-positive group, with citation of the number of gastric cancer cases seen during follow-up. Ongoing and unpublished studies were included. Two investigators reviewed all studies and extracted data on study design, number of subjects, demographic characteristics and risk factors of patients enrolled, details of eradication therapy and diagnostic testing, and histologic and pathologic results. Using an intention-to-treat analysis, relative risks (RR) for gastric cancer in the eradication and untreated groups were compared and then pooled to produce a cumulative RR.

**Participants:** 6695 *H. pylori*-positive patients (mean age, 42 to 51 years) from China, Japan, and Colombia were followed up for 4 to 10 years (median, 6 years).

**Results:** 7 randomized, controlled trials published between 2000 and 2008 were included for analysis, with 1 trial later excluded for heterogeneity. Inter-reviewer agreement was good. Gastric cancer was diagnosed in 37 of 3388 patients (1.1%) in the eradication group and 56 of 3307 (1.7%) in the untreated group. Eradication rates ranged from 73% to 88.9% in the eradication group and 5% to 15.2% in the untreated group. Pooled analysis revealed an RR of gastric cancer for patients in the eradication group of 0.65 and, in subgroup analysis, an RR of 0.66 for progression of preneoplastic lesions.

**Conclusions:** In this meta-analysis, *H. pylori* eradication appears to decrease the risk of gastric cancer. Major limitations of this analysis include a small number of randomized, controlled trials, with most based in Asia (potentially limiting generalizability) and lack of double blinding in most studies. Observation and outcome biases were not seen. Future large-scale trials are unlikely.

**Reviewer's Comments:** This study strengthens the rationale for screening for and treating *H. pylori* in high-risk populations, both geographic and clinical. As hospitalists, we frequently test for *H. pylori* in patients with gastritis or ulcer disease. However, in my experience, these serologies are often pending at the time of discharge. In ensuring that eradication therapy is initiated during hospitalization or that pending results are communicated to the ambulatory setting, hospitalists may aid in decreasing the cancer risk. For an action so small, that is no small thing. (Reviewer-Jennifer Best, MD).

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Keywords:*Helicobacter pylori* Infection, Gastric Cancer, Eradication, Risk

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In patients who require vancomycin, clinicians should use the appropriate dose initially and then monitor serum trough levels closely, especially in serious MRSA infections.

**Background:** Vancomycin is commonly used to treat infections—in particular, those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). There is a clear relationship between serum vancomycin concentrations and treatment success in serious MRSA infections. There is also considerable confusion about the need for and timing of monitoring serum vancomycin concentrations.

**Objective:** To recommend appropriate vancomycin dosing and monitoring of serum concentrations.

**Design:** Consensus expert guidelines.

**Methods:** Experts from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists reviewed the available literature regarding vancomycin pharmacodynamics, efficacy, and toxicity. These experts established 6 guidelines for the optimal dosing and monitoring of vancomycin.

**Results:** Initial vancomycin dosing should be based on actual body weight and not estimated ideal body weight. Trough serum vancomycin concentrations are the best measure of the therapeutic effectiveness of vancomycin and should be obtained immediately before the fourth dose. For all patients, trough serum vancomycin concentrations should always be maintained at >10 mg/L to avoid the development of *S. aureus* resistance. In serious MRSA infections (endocarditis, bacteremia, hospital-acquired pneumonia, or meningitis), trough serum concentrations of 15 to 20 mg/L are optimal. There are no data to support monitoring of peak vancomycin concentrations to determine toxicity, as there is no evidence that correlates serum vancomycin concentration with either nephrotoxicity or ototoxicity. For patients receiving >5 days of vancomycin therapy, a steady-state trough level should be determined weekly or more frequently in those with changing renal function.

**Conclusions:** Vancomycin is commonly used in the treatment of gram-positive infections, and adequate serum concentrations are essential. Clinicians should follow these simple expert guidelines in the use of vancomycin.

**Reviewer's Comments:** These expert guidelines simplify recommendations about the dosing and monitoring of vancomycin and should be used by clinicians and pharmacists in the inpatient setting. Probably the most important recommendation is that we should aim for a trough concentration of >10 mg/L in all patients but 15 to 20 mg/L in those with serious MRSA infections. In addition, there is no indication for measurement of peak serum vancomycin levels. (Reviewer-Bradley A. Sharpe, MD).

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Keywords: Vancomycin, Guidelines, Methicillin-Resistant *Staphylococcus aureus*

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Oral Factor Xa Inhibitors May Become Standard of Care for ACS—Just Not Yet

Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor, in Combination With Antiplatelet Therapy After Acute Coronary Syndrome: Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial.

APPRAISE Steering Committee and Investigators:

Circulation 2009; 119 (June 9): 2877-2885

Oral factor Xa inhibitors will hopefully someday supplant their current injected counterparts, but their utility in ACS is still unproven and may be associated with bleed risk.

**Background:** Oral anticoagulation with vitamin K antagonists has been shown to be beneficial in the secondary prevention of acute coronary syndrome (ACS), but these drugs have a very narrow therapeutic window and an elevated bleeding risk. Whether oral anticoagulants can be utilized successfully with modern antiplatelet therapy in secondary prevention is unknown.

**Objective:** To evaluate the safety and efficacy of an oral factor Xa inhibitor, apixaban.

**Design/Participants:** Prospective, international, randomized, double-blind, placebo-controlled, dose-escalation trial of apixaban plus antiplatelet therapy in 1715 patients presenting with ACS.

**Methods:** Patients with ACS were randomized to placebo or 1 of 4 doses of apixaban in addition to standard ACS treatment.

**Results:** Apixaban at doses of 10 mg twice a day or 20 mg once a day caused a >2-fold increased risk of hemorrhage compared to placebo that resulted in discontinuation of these 2 arms of the study. Apixaban 2.5 mg orally twice a day or 10 mg once daily had a trend toward reduction in ischemic events with an increased, dose-dependent increased risk of hemorrhage, particularly in patients on dual antiplatelet therapy for the 2.5-mg twice-daily dose (HR, 1.78; 95% CI, 0.91 to 3.48) and the 10-mg once daily dose (HR, 2.45; 95% CI, 1.31 to 4.61).

**Conclusions:** Apixaban has a trend toward decreasing ischemic events in patients who present with ACS at the expense of dose-related increasing risk of hemorrhage, particularly in those on dual antiplatelet therapy.

**Reviewer's Comments:** Oral factor Xa antagonists are in development and may prove as efficacious as Coumadin but without the concomitant need for frequent blood monitoring. Apixaban is intriguing in that not only is it an oral medication, but it also has a half-life of only about 12 hours. In addition, it is cleared nonrenally yet provides anticoagulation that pilot studies seem to indicate is on par with low-molecular-weight heparins in the prevention of venous thromboembolism. That being said, this study raises concerns that hemorrhage—whether major hemorrhage (such as bleeding into a body cavity) or minor bleeding (such as ecchymoses) may limit this drug's utility, at least when used in addition to antiplatelet therapy for ACS. Given the huge burden that both ACS and anticoagulation have in clinical practice, hospitalists need to remain aware of drugs that are in development and could rapidly move into clinical practice. (Reviewer-Jason Persoff, MD).

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Keywords: Oral Anti-Xa Inhibitor, Anticoagulation, Acute Coronary Syndrome

Print Tag: Refer to original journal article
Capsule endoscopy is not sensitive for the detection of colorectal polyps, advanced adenomas, or cancer in patients with known or suspected disease compared with colonoscopy.

**Background:** Capsule endoscopy has been shown to be feasible and safe for visualizing the colon. Performance of this test for detecting colorectal lesions relative to colonoscopy has not been well defined.

**Objective:** To compare the performance of capsule endoscopy for detecting polyps, adenomas, and cancer with colonoscopy in patients with known or suspected colorectal disease.

**Design:** Prospective, multicenter study.

**Participants/Methods:** 320 patients from 8 European centers. Patients were aged ≥18 years with known colonic disease (history of colorectal cancer or adenomatous polyps with 3+ years since last colonoscopy, colonic abnormalities on imaging, or ulcerative colitis) or aged ≥50 years with suspected/symptomatic colonic disease and were scheduled for colonoscopy. All patients underwent colon preparation; capsule endoscopy was performed without insufflation or sedation. Patients underwent colonoscopy after capsule endoscopy.

**Results:** Among study patients, 45% were women, and 55% were men. The mean age was 59 years (range, 22 to 84 years). Thirty-five percent of patients had known colonic disease; in 65%, disease was suspected. The sensitivity of capsule endoscopy was 64% and 73% for detecting polyps and advanced adenomas ≥6 mm, respectively. The sensitivity for cancer detection was 74%. Specificity ranged from 74% for cancer detection to 97% and 98% for polyps and advanced adenomas ≥10 mm in size, respectively. Sensitivity was significantly higher in patients with good/excellent colon preparation with limited impact on specificity. For patients with advanced adenomas, for example, sensitivity was 88% with good colon preparation versus 44% if preparation was poor. Most adverse events were associated with colon preparation rather than the procedures themselves. Mean capsule transit time was 4 hours, 51 minutes.

**Conclusions:** Capsule endoscopy is a safe but insensitive test for detecting colonic polyps, advanced adenomas, and colorectal cancer compared with colonoscopy. The adequacy of colon preparation significantly affects test sensitivity.

**Reviewer’s Comments:** This is a well-designed multicenter trial that reviews capsule endoscopy for case findings of colorectal lesions in patients with known or suspected disease. In a busy hospitalist practice that may include symptomatic patients aged ≥50 years, the time for test completion is reasonable; however, excellent colon preparation is necessary (and often a challenge), and follow-up colonoscopy (or additional testing) would still be required if capsule endoscopy was unrevealing. There may be a role for this test in patients who cannot or are unwilling to undergo colonoscopy. Capsule cost and expertise required for image review were not discussed in this article. (Reviewer-Anneliese M. Schleyer, MD).

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Keywords: Capsule Endoscopy, Colonoscopy, Colorectal Cancer, Polyps

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The Long and Short of the Long PR Interval

Long-Term Outcomes in Individuals With Prolonged PR Interval or First-Degree Atroventricular Block.

Cheng S, Keyes MJ, et al:

JAMA 2009; 301 (June 24): 2571-2577

The prolonged PR interval is not so benign in this populational study from the Framingham dataset, and correlates with increased risk for atrial fibrillation, pacemaker need, and all-cause mortality.

Background: Prolongation of the PR interval (PRI) >200 ms (first-degree AV block) has long been thought to be a benign electrocardiographic finding.

Objective: Using the Framingham Heart Study data, the authors determined the potential long-term health risks of PR prolongation.

Methods: 11th biennial examination of the original cohort (1968-1971) and the first offspring cohort (1971-1974), for a total of 7575 participants from the Framingham dataset.

Results: A total of 124 patients had prolonged PRI >200 ms. These patients were compared to those with a nonprolonged PRI. Patients with a prolonged PRI were statistically older (mean age, 55 vs 46 years) and included more males (73% vs 56%). They also tended to have a higher prevalence of hypertension, diabetes, valvular disease, prior ischemic coronary disease or congestive heart failure, and slower baseline heart rates. Patients in the prolonged PRI cohort experienced increased risks of future atrial fibrillation (multivariate-adjusted HR, 2.06; 95% CI, 1.36 to 3.12; \( P <0.01 \)), future need for pacemaker implantation (HR, 2.89; 95% CI, 1.83 to 4.57; \( P <0.01 \)), and all-cause mortality (HR, 1.44; 95% CI, 1.09 to 1.91; \( P =0.01 \)).

Conclusions: Prolongation of the PRI, particularly when using the definition of first-degree AV block of >200 ms, portends worse outcomes with increased risk of future atrial fibrillation, pacemaker implantation, and increased all-cause mortality.

Reviewer's Comments: Life comes at you fast sometimes—and if that means your PRI is slow, then life may be faster than you'd like. Prolonged PRIs appear to confer an increased risk of downstream rhythm derangements (atrial fibrillation and need for implantation of a pacemaker) and also seem to confer an increased risk of death. Therefore, if the Framingham data are correct, then shorter is better—meaning shorter PRI, because life can be too short if your PRI is long. Confusing? The clinical importance of this new "sure to lose sleep over this" issue for patients and physicians does little to clarify what can be done to avoid these adverse outcomes. Note that the statistics remained similar for patients with PRI prolongation regardless of whether they were taking a nodal-blocking drug such as a beta-blocker. This study has a lot of drawbacks (not the least of which was the small number of patients with baseline PRI prolongation). Also, there are countless mechanisms that can prolong the PRI, and not all of them are pathological. Therefore, this popularly circulated article on newsgroups and national news probably should be viewed as curious but not overwhelmingly concerning. And that's the long and short of it. (Reviewer-Jason Persoff, MD).

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Keywords: Prolonged PR Interval, Long-Term Mortality

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The LEFt prediction rule shows promise, but requires independent validation prior to widespread clinical application.

**Background:** Pregnant patients have been excluded from previous studies in which diagnostic strategies for deep venous thrombosis (DVT) have been evaluated. Furthermore, it is uncertain how accurate clinicians are in determining pretest probability of DVT in pregnancy.

**Objective:** To measure the accuracy of subjective pretest probability for DVT in symptomatic pregnant patients, as assigned by expert clinicians, and to identify clinical variables that might alter pretest probability in this setting.

**Design:** Cross-sectional study based at 5 Canadian hospitals between March 2000 and April 2007.

**Methods:** Patients with suspected DVT were evaluated by experts who assigned a clinical pretest probability (low/medium/high) and noted the presence of 11 variables of interest. Patients then underwent compression ultrasonography. Those with DVT were treated with unfractionated or low-molecular-weight heparin. Those without DVT were followed up for 3 months for the outcome of interest. Test characteristics (sensitivity, specificity, and negative predictive value) of clinician pretest probability were calculated. Univariate analysis identified variables independently associated with DVT, and these were then submitted for multivariate analysis, in which the LEFt prediction rule was based, and then internally validated. The LEFt rule stands for "symptoms in the left leg (L), calf circumference difference ≥2 cm between asymptomatic and symptomatic legs (E), and first trimester presentation (Ft)."

**Participants:** 194 pregnant outpatients were referred with suspected first DVT. Patients with previous venous thromboembolism or symptoms of pulmonary embolism were excluded.

**Results:** 17 DVTs were identified over 8 years. Six variables were independently associated with DVT: left leg symptoms ($P = 0.003$), ≥2-cm calf difference ($P = 0.001$), first trimester ($P < 0.001$) of pregnancy, alternative diagnosis ($P = 0.012$), redness ($P = 0.03$), and warmth ($P = 0.008$). Adding the 3 weakest variables failed to strengthen a prediction rule that considered the 3 strongest variables: symptomatic left leg (OR, 44.28), ≥2-cm calf difference (OR, 26.89), and first trimester of pregnancy (OR, 53.43). All 17 patients with DVT had at least one of these predictors. Patients classified as having a low pretest probability by experts had a 1.5% prevalence of DVT, whereas those classified as moderate or high had a prevalence of 24.6%.

**Conclusions:** Expert clinicians successfully identified patients at "low" versus "nonlow" pretest probability of DVT. The LEFt prediction rule may further improve accuracy of diagnosis but requires independent validation. The study's most important limitation is a small number of outcomes. Other limitations include lack of expert blinding to the objective Wells rule and the use of ultrasound, rather than venography, as the diagnostic standard.

**Reviewer's Comments:** This is an outpatient study; therefore, no conclusions should be drawn about the performance of these variables in a hospitalized population. Furthermore, the average hospitalist may be less skilled in assessing the pretest probability of DVT than these investigators—hence, the desirability of a simple, well-validated prediction rule. This study represents one step toward this goal but will not be sufficient in isolation. (Reviewer-Jennifer Best, MD).

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**Keywords:** Deep Venous Thrombosis, Venous Thromboembolism
In high-risk patients with non-ST-elevation MI, age ≥60 years, ST-depressions on ECG, and positive enzymes, early angiography (<24 hours) is better than delayed intervention (>36 hours).

**Background:** Prior evidence has shown that, in patients with non-ST-elevation myocardial infarction (NSTEMI), early invasive angiographic intervention improves outcomes. Yet, it is not clear how "early" the intervention should be.

**Objective:** To determine the optimal timing of coronary angiography and revascularization in patients with acute coronary syndromes (ACS) without ST-segment elevation.

**Design:** Randomized, controlled, multicenter trial.

**Methods/Participants:** Patients were enrolled if they presented with unstable angina or NSTEMI and had at least 2 of 3 criteria indicative of increased risk: age ≥60 years, ECG evidence of ischemia, and/or positive cardiac enzymes. The study protocol made recommendations to managing physicians for all patients to receive appropriate adjunctive therapies (anti-coagulation, beta-blockage, etc.). Patients were randomized to early intervention (angiography within 24 hours of admission) or delayed intervention (angiography at least >36 hours after admission).

**Results:** 3031 patients were randomized. On average, those in the early intervention group underwent angiography at 14 hours, while those in the delayed group underwent angiography at 50 hours. At 6 months, no statistical difference was found in the composite outcome of death, new MI, or stroke, although there was a trend toward a benefit in the early intervention group (9.6% vs 11.3%; HR, 0.85; 95% CI, 0.68 to 1.06). For a secondary outcome of death, MI, or refractory ischemia, there was a statistical benefit in the early intervention group (9.5% vs 12.9%; \( P = 0.003 \)); this benefit was primarily due to much less refractory ischemia. Notably, in subgroup analysis, there was a clear benefit for early intervention for the primary and secondary outcomes in the highest-risk patients — those with ECG evidence of ischemia or positive cardiac enzymes.

**Conclusions:** For most patients with ACS without ST-segment elevation, there is no difference in outcomes between early intervention (within 24 hours) and late intervention (>36 hours). In the highest-risk patients, there is a benefit to early intervention.

**Reviewer's Comments:** Multiple prior large, randomized, controlled trials have shown that, in patients with unstable angina or NSTEMI, intervening (angiography) within the first 3 days is better than waiting > 7 days. This well-done study helps determine the definition of "early." Overall, for most patients, the optimal timing is whenever it is safe and feasible to perform cardiac angiography within the first 72 hours. For the highest-risk patients, those with clear ECG evidence of ischemia and/or positive cardiac enzymes, "time is muscle," and we likely should get them to catheterization as quickly as possible (at least within the first day). (Reviewer-Bradley A. Sharpe, MD).

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Keywords: Acute Coronary Syndrome, Unstable Angina, Non-ST-Elevation MI, Early Intervention

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