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EVALUATION FOR CANCER IN PATIENTS WITH SYMPTOMATIC DVT

Reference Cornuz J, Pearson SD, Creager MA, Cook EF, Goldman L. Importance of findings on the initial evaluation for cancer in patients with symptomatic deep venous thrombosis. Ann Intern Med 1996; 125:785-93.

Clinical question **What clinical evaluation for cancer is appropriate in patients with idiopathic deep venous thrombosis (DVT), and what is their risk of developing cancer during the follow-up period if it is not found at the time of the original hospitalization?**

Background There is a well-documented association between cancer and DVT but how aggressively a physician should pursue the evaluation of cancer has not been well studied.

Population studied The study population was composed of 989 patients referred for venous sonography during a 3-year period at a tertiary care teaching hospital. Of these patients, 92% were outpatients at the time of their venous study. An additional 4811 patients had venous sonography during this period at the study site but were excluded because they had known risk factors for DVT, were undergoing sonography as part of an evaluation for pulmonary embolism, were undergoing the sonograms in follow-up, were lost to follow-up, refused to participate, or had prior evaluations for cancer.

Study design and validity The investigators used a retrospective cohort design based on chart review. Demographic information and the results of the initial clinical examinations at the hospital were collected from the records using a standardized instrument; patients were contacted when outcomes could not be determined by review of medical records. The duplex venous sonograms were performed by the same laboratory using both compressibility of the lower extremity vein and venous flow augmentation. Abnormalities on all imaging studies were confirmed by two observers, and the sonogram was used as the gold standard. The subsequent risk of cancer in those thought to be free of cancer at the time of initial DVT evaluation was calculated by comparing their incidence of cancer with the incidence of cancer in patients referred for venous sonography but found not to have clot.

This design raises concerns about the reliability and validity of the clinical data. While data were extracted from charts in a systematic fashion, we have no way of knowing if these data were collected by the clinicians in a systematic fashion. It could be that physicians were much more likely to pursue signs and symptoms related to cancer if the physician suspected that cancer was present. Workup bias can easily arise in retrospective studies and distort associations.

Outcomes measured The primary outcomes were the incidence of cancer at the time of initial diagnosis of DVT and during the subsequent follow-up period (median of 34 months) after the diagnosis of DVT.

Results Cancer was diagnosed in 16 of 136 patients with DVT (12%; 95%CI= 6% to 17%) at the time of their index hospitalization. The risk increased with the age of the patient and with tobacco use. Of the 120 patients who were not found to have cancer, 3 (2.5%) were discovered to have cancer during the follow-up period. The same incidence of cancer occurred in patients referred for venous ultrasonography but found to be clot-free during the follow-up period. The authors concluded that a comprehensive medical history, physical examination, routine laboratory testing, and chest radiography (CXR) were sufficient for screening those patients with new DVTs who needed further evaluation for detecting cancer. Six of the 16 patients with cancer had an abnormal CXR compared with 2 of the 120 patients without cancer (positive likelihood ratio [LR+] = 22.5, negative likelihood ratio [LR-] = 0.64). The presence of anemia or leukocytosis had greater sensitivity but lower specificity (LR+ = 2.4, LR- = 0.19). Patients with no positive findings on the history, physical examination, CXR, or complete blood count (CBC) were found to be free of cancer during the hospitalization.

Recommendations for clinical practice **A significant number of patients with new DVTs and no obvious risk factors for DVT have cancer (12%). The risk of developing cancer for patients with**

DVT who are found to be cancer-free at the time of their DVT is the same as in patients without DVT (~2.5%). A careful history, physical examination, CBC, and CXR form a reasonable minimal assessment for occult malignancy. However, because of the retrospective nature of this study and the small number of patients with cancer and DVT, these results should not be considered definitive, and additional tests might be warranted based on clinical judgment. Prospective cohort studies using a predetermined set of tests would provide a more definitive answer.

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Fluoxetine and Amitriptyline in the Treatment of Fibromyalgia

Reference Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheumatol 1996; 39:1852-9.

Clinical question **How effective are amitriptyline and fluoxetine, alone or in combination, in the treatment of fibromyalgia?**

Background Clinical trials evaluating the treatment of fibromyalgia have shown only modest results. Various medical regimens have been studied, including both tricyclic antidepressants and selective serotonin reuptake inhibitors. This study evaluated the therapeutic value of drugs from both classes (fluoxetine and amitriptyline), alone or in combination.

Population studied Patients who met the classification criteria of the American College of Rheumatology for fibromyalgia were recruited by rheumatologists in a tertiary care referral center. Criteria for eligibility included no current or past history of other systemic illnesses, age within the range of 18 to 60 years, and a willingness to discontinue all central nervous system active medications, nonsteroidal antiinflammatory drugs, and analgesics 1 week prior to the start of the study. At the intake visit, each patient had to have a score of ≥ 30 (maximum 100) on the visual analog scale (VAS) for pain and a score of ≤18 on the Hamilton Rating Scale for Depression (eliminating patients with depression). All patients were white, 90% were women, and 71% were married.

Study design and validity Patients were randomized in a double-blind crossover fashion to one of four treatment groups: (1) placebo in the morning and amitriptyline 25 mg at bedtime; (2) fluoxetine 20 mg in the morning and placebo at bedtime; (3) fluoxetine 20 mg in the morning and amitriptyline 25 mg at bedtime; or (4) placebo in the morning and placebo at bedtime. Each of the four trial periods was 6 weeks in duration, separated by a 2-week washout period. Patients were evaluated at the beginning and end of each trial period by rheumatologists unfamiliar with the patients or their treatment assignments.

Thirty-one patients were initially enrolled and 19 (61%) completed the study. Five patients (1 receiving fluoxetine, 3 receiving fluoxetine and amitriptyline, and 1 receiving placebo) cited an adverse drug reaction as the reason for dropping out of the study. Four patients (3 receiving fluoxetine and 1 during the washout period) cited increased symptoms as the reason. Three patients withdrew for various other reasons. Because of the statistical strength of the crossover design where each patient served as his or her own control, a pre-study power analysis indicated that only 20 patients would be necessary for statistical significance.

Outcomes measured Primary outcomes measured included a manual tender point examination score, results from the Fibromyalgia Impact Questionnaire (FIQ) and the Beck's Depression Inventory (BDI), and a VAS for pain, global well-being, sleep disturbance, fatigue, and feeling of refreshment upon awakening. Assessments were performed by examining both clinicians and the patients themselves.

Results There was statistically significant improvement, compared with placebo, for both amitriptyline and fluoxetine, as measured by the FIQ and VAS for pain, global well-being, and sleep. Improvement with the combination of drugs was twice that of either agent used alone. Nonstatistically significant improvement was noted for the other variables, with the exception of the tender point scores. Further analysis ensured that the 2-week washout period was sufficient to avoid crossover contamination from previous medications. Similar to the group mean scores, individual patients also improved most with the combination of drugs, and patients receiving placebo fared the worst.

Recommendations for clinical practice **Treatment with both amitriptyline and fluoxetine resulted in significant improvement in Fibromyalgia Impact Scores as well as scores for global well-being, pain, and sleep. The combined regimen was more effective than either drug alone. Major concerns of the study include a small sample size (19 patients), short follow-up (6 weeks), and a high dropout rate (nearly one third of patients withdrew due to adverse drug effects or worsening symptoms). Family physicians treating patients**

with fibromyalgia should consider the combination therapy of amitriptyline and fluoxetine unless otherwise contraindicated.

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Prevention of NSAID-Induced GI Mucosal Injury

Reference Koch M, Dezi A, Ferrario F, Capurso L. Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury. Arch Intern Med 1996; 156:2321-32.

Clinical question **Should misoprostol or an H_2 blocker be coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent gastrointestinal mucosal injury?**

Background Although NSAIDs are commonly prescribed by family physicians, their use triples the risk for developing severe adverse gastrointestinal (GI) events. This meta-analysis assessed the effectiveness of misoprostol or H_2 blockers as preventive agents when coadministered with NSAIDS.

Studies reviewed Clinical trials published between January 1970 and December 1994 were identified by searching both MEDLINE and relevant review articles. Inclusion criteria were: (1) endoscopy performed before NSAID treatment; (2) no evidence of ulcer initially; (3) random allocation with a placebo arm; and (4) NSAIDS given for at least 5 days.

The search found 24 articles describing 4325 patients. Referral patterns were not described, but subjects appeared to be representative of those seen by family physicians. About 16% were healthy volunteers, and the rest were patients with acute musculoskeletal disease, osteoarthritis, or rheumatoid arthritis. All patients were over 18 years of age; the proportion of elderly was not specified. Most trials were short term (<2 weeks) and *H pylori* status was not described. A variety of NSAIDs were used and drug dosages were not specified. The H_2 blockers studied were ranitidine and cimetidine. Daily misoprostol dosages ranged from 200 to 800 µg.

Study design and validity This article does not review trials comparing the two agents; rather, it pools the data comparing each agent against a placebo. In this context, the literature search, data extraction, assessment of quality and heterogeneity (variations between the different studies), and publication bias and analysis were adequate. Particular strengths were: (1) inclusion of only randomized trials, which decreases heterogeneity and minimizes the impact of unmeasured confounding variables, such as presence of *H pylori;* (2) the use of three independent reviewers to extract information about the studies; and (3) the use of a number-needed-to-treat (NNT) analysis, which allows assessment of clinical impact. The major weakness was the lack of sensitivity analyses on methods quality, duration of treatment, patient age, or specific drug dosages.

Outcomes measured The main endpoints measured were the number of subjects in which gastric ulcers, gastric lesions (>5 erosions or 1 ulcer), duodenal ulcers, and duodenal lesions appeared. Ulcer disease is the key outcome, as the clinical significance and natural history of erosions is unclear. Other serious patient-oriented outcomes such as GI tract bleeding, hospitalization, treatment costs, side effects, and patient satisfaction were not reported.

Results Misoprostol use significantly reduced the rate of gastric ulcers both in short-term (rate difference [RD] -13%; 95%CI, -26% to -1%) and long-term (RD -8%; 95% CI, -18% to -1%) NSAID treatment, for an NNT = 8 and 12.5, respectively. By contrast, H_2 blockers were not found to reduce the rate of gastric ulcers with either short-term or long-term trials. For duodenal ulcers, both H_2 blockers and misoprostol significantly reduced the risk in the long-term trials, but neither result was clinically significant (NNT = 42 and 29, respectively), and neither agent had an effect on short-term trials. Results were not modified significantly whether normal subjects or patients were studied, although there were no studies on long-term prevention with normal subjects.

Recommendations for clinical practice **This study provides modest evidence that misoprostol has a clinically significant effect on preventing gastric ulcers when NSAIDS are given. This effect stands in sharp contrast to H_2 blockers, which seem to have minimal preventive value. Neither misoprostol nor H_2 blockers have a significant effect on preventing duodenal ulcers.**

Given the variation in results between the different studies, the lack of information about dosage, side effects, symptoms, serious patient-oriented outcomes, and the natural history of gastric erosions, as well as the lack of comparative trials, this information must be taken as preliminary. The methods and findings of this meta-analysis are, however, strong enough that family physicians should consider using misoprostol in patients at high risk for complications resulting from NSAID therapy—specifically, patients older than 75 years of age or with a history of peptic ulcer disease or upper GI tract bleeding. The drugs should be coadministered as soon as possible, since the risk of

adverse events is highest during the first weeks of NSAID treatment. Misoprostol will soon become available in a generic formulation.

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Parents and Pediatric Procedures

Reference Bauchner H, Vinci R, Bak S, Pearson C, Corwin MJ. Parents and procedures: a randomized controlled trial. Pediatrics 1996; 98:861-7.

Clinical question **What effect does parental presence have during the performance of pediatric procedures?**

Background Most parents prefer to be present when their child undergoes a routine medical procedure. Some clinicians believe that parents are more likely to interfere with the performance of the procedure than they are to help by comforting the child. These clinicians are often reluctant to allow parents to be present during procedures.

Population studied Eligible subjects included all children under 3 years of age requiring a routine procedure (venipuncture, intravenous cannulation, or uretheral catheterization). Patients were from a large urban pediatric emergency department. Fewer than 10% of the patients were white, and two thirds were from single-parent families. Nearly 70% of the children had previously been seen in the same emergency department.

Study design and validity To enhance the parental calming benefits and minimize the potential for interference during the procedure, the authors designed a simple intervention to teach the parents how to be more effective comforters. Designing an objective measure of efficacy for such an intervention is difficult. The authors chose to use a complex digital analysis of the child's cry. Previous studies have shown a correlation between degree of pain and results of the cry analysis.

Parents were randomly assigned to one of three groups. Parents randomized to the intervention group were present during the procedure. Prior to the procedure, researchers gave these parents brief but concrete instructions on comforting their child. In the first control group, parents were present during the procedure but did not receive instruction. In the second control group, parents were not present during the procedure.

Randomization took place before investigators approached parents to obtain informed consent. Thus, parents knew to which group they had been assigned before they had to decide whether or not to participate. Many of the parents assigned to the not-present control group refused to participate. Of the 572 patients who were randomized, 431 agreed to participate: 153 in the intervention group; 147 in the present-not-taught group; and 131 in the not-present group.

Outcomes measured Two different methods were used to quantify the child's degree of pain: a digital analysis of the child's cry, and a subjective estimate of pain on a simple 3-point scale (severe, moderate, little) by the child's parent and the clinician performing the procedure. Secondary outcomes included difficulty in performance of the procedure, parent and clinician anxiety, and parent satisfaction with care.

Results There were no significant differences between the groups in any of the three measures of pain experienced by the child. Parents not present during the procedure reported more anxiety than those who were present. This result may be biased because those parents who were randomized to the not-present group and chose not to participate in the study may have been less anxious than those choosing to participate. Although the difference was not statistically significant, parents assigned to the intervention group tended to be more satisfied with care. Parental presence or absence during the procedure did not have a significant impact on the performance of the procedure or the clinicians' anxiety.

Recommendations for clinical practice **The ill child undergoing a routine pediatric procedure does not seem to derive any benefit or harm from having parents present. The clinicians' ability to successfully complete procedures was not affected by parental presence, and parents who were present were less anxious than those who were not. Intervening to enhance the comforting skills of the parents did not reduce procedure-associated pain. Family physicians should encourage parents who want to be present to stay during procedures. This study does not address the issue of parental presence during more invasive or more critical procedures.**

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Oral Terbutaline After Parenteral Tocolysis

Reference Lewis R, Mercer BM, Salama M, Walsh MA, Sibai BM. Oral terbutaline after parenteral tocolysis: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 1996; 175:834-7.

Clinical question **Does oral terbutaline, given after successful intravenous tocolysis for preterm labor, prolong pregnancy?**

Background Use of intravenous beta-agonists or magnesium chloride can temporarily stop preterm labor, but oral beta-agonists given as maintenance therapy have not been shown to prolong pregnancy. Because of weaknesses in past studies, many physicians still believe that oral agents may have some beneficial effect.

Population studied Eligible subjects included consenting women with a gestational age between 24 and 34 completed weeks admitted with preterm regular uterine contractions and documented cervical change. Patients were excluded if they had chorioamnionitis, vaginal bleeding consistent with placental abruption, medical contraindications to terbutaline, preterm premature rupture of membranes, or a maternal or fetal indication for immediate delivery. Two hundred women were enrolled; although not clearly stated, it appears that they came from an urban university hospital service population. The number of eligible women refusing to enter the study was not reported.

Study design and validity All patients were given parenteral tocolysis and then randomized in a double-blind fashion to receive either terbutaline (5 mg 5 times a day) or an indistinguishable placebo. Patients were monitored for compliance and clinical status 1 to 2 times weekly in the antenatal clinic. Compliance rates were not reported. There was no significant difference between the two groups for age, race, gestational age, cervical dilation or effacement, or risk factors for preterm delivery.

Patients with recurrent preterm labor were restarted on parenteral tocolytics. If labor was successfully stopped they were restarted on the same study medication. After a second recurrence of preterm labor, patients were restarted on the physician's choice of medication and removed from the study. It is not stated how many women were dropped from the study for this reason. Biased results could have occurred as a result of more women on placebo having recurrent labor and thus being dropped from the final analysis. The terbutaline and placebo groups were similar, however, in regard to the percentage with at least one episode of recurrent preterm labor (20% vs 16%, respectively).

Outcomes measured The primary outcome measured was delivery within 7 days of randomization. Secondary outcomes were delivery at <37 weeks' gestation, incidence of recurrent preterm labor, and neonatal outcome including birthweight, neonatal intensive care unit admissions, and neonatal illness.

Results There was no significant difference between the women treated with terbutaline and those treated with placebo for any of the study outcomes. Eighteen percent of women receiving terbutaline gave birth within 7 days compared with 24% of those receiving placebo, a nonsignificant difference. Sixty-three percent of women in both groups had preterm delivery. A post hoc analysis (after the results were obtained) of the data evaluating only the 96 women randomized at less than 32 weeks' gestation did show a statistically significant prolongation of the pregnancy with terbutaline therapy. No information was given to judge whether this was clinically significant. This kind of post hoc data analysis is an unreliable way to evaluate study results.

Recommendations for clinical practice **The current study agrees with the findings of numerous other reports, including a second trial reported in the same journal issue.[1] Oral beta-agonists given as maintenance therapy after intravenous tocolysis fail to prolong pregnancy. In addition, previous reports (including one meta-analysis) have not shown a reduction in patient-oriented outcomes including neonatal morbidity and mortality. These drugs are well known to have bothersome and potentially serious side effects.**

Family physicians should continue to use intravenous tocolytics as these can prolong delivery by 2 to 3 days, enough time for corticosteroids to become effective or for transfer to another center. No oral drug has been shown to be effective, however, for maintenance therapy. Until further information is available, physicians should strongly consider not using oral terbutaline.

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Treatment of Late-Stage HIV Infection

Reference Saravolatz LD, Winslow DL, Collins G, et al. Zidovudine alone or in combination with didanosine or zalcitabine in HIV-infected patients with the acquired immunodeficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. N Engl J Med 1996; 335:1099-1106.

Clinical question **Is zidovudine (AZT) in combination with didanosine (DDI) or zalcitabine (DDC) better than zidovudine alone in preventing AIDS-defining events or death?**

Background Current evidence indicates that zidovudine as a single agent is not optimal therapy in any stage of HIV infection. The Delta study showed that therapy with zidovudine in combination with a second reverse transcriptase inhibitor prolongs life compared with zidovudine monotherapy in HIV-infected persons with CD4 counts between 50 and 350.[1] This study by Saravolatz and colleagues was very similar to the Delta trial, except that patients in this study had somewhat more advanced disease.

Population studied 1102 HIV-infected patients 13 years of age or older who had a previous AIDS-defining condition, a CD4 count less than 200, or CD4 cells less than 15% of the total lymphocyte count. The 77% of patients who had taken zidovudine previously had done so for a median of 12 months. Four percent had taken didanosine previously, and 2% had taken zalcitabine previously.

Study design and validity This was a randomized, double-blinded, placebo-controlled trial. Patients were allocated to receive zidovudine plus placebo, zidovudine plus didanosine, or zidovudine plus zalcitabine. Patients were followed up for an average of 35 months, and fewer than 3% in each group were lost to follow-up. Many patients, however, stopped taking the study drugs at their own or their physician's request; only about 60% of the time was spent taking the assigned drugs. Other anti-retroviral agents were not available for much of the study period. Appropriately, the investigators analyzed the patients by the group to which they were randomly assigned (ie, this was an "intention-to-treat" analysis).

Outcomes measured The primary outcome measure was the rate of either disease progression or death. The investigators defined disease progression as the first occurrence of an AIDS-defining condition (in the 70% of patients who had never had one). In patients who had already had an AIDS-defining condition, the endpoint was death.

Results Overall, there were no differences in outcome between the treatment groups, but patients receiving combination therapy were more likely to experience adverse effects. In patients who had not received prior zidovudine therapy, each combination was better than zidovudine monotherapy: in the zidovudine-didanosine group, 50% died or developed an AIDS-defining condition compared with 52% in the zidovudine-zalcitabine group and 58% in the zidovudine monotherapy group (the difference between each combination therapy and zidovudine monotherapy was statistically significant). In patients who had never received zidovudine, 13 patients would need to be treated with the zidovudine-didanosine combination, or 17 patients with zidovudine-zalcitabine, to prevent one death or AIDS-defining condition at the end of 3 years. Patients who had been receiving zidovudine for less than 12 months also had slightly better outcomes if they received combination therapy, compared with zidovudine monotherapy.

Recommendations for clinical practice **In zidovudine-experienced patients with a CD4 count of less than 200, or who have previously had an AIDS-defining condition, continuing AZT or adding DDI or DDC offers little or no clinical benefit. Other evidence suggests that at least two other drugs should be used instead (two reverse transcriptase inhibitors and, possibly, a protease inhibitor for those patients who can adhere to a complex regimen[2]). In AIDS patients who have never received AZT, AZT in combination with DDI or AZT in combination with DDC is preferable to AZT alone. HIV viral load is an important prognostic indicator and should be used to assess the virologic response to therapy.[3]**

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Cardiac Troponin T Levels in Acute MI

Reference Ohman EM, Armstrong PW, Christenson RH, et al, for the GUSTO-IIa investigators. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med 1996; 335:1333-41.

Clinical question **Do cardiac-specific troponin T levels predict prognosis in the setting of acute myocardial ischemia?**

Background Standard criteria for diagnosing myocardial infarction (history of chest pain, electrocardiography, and the measurement of creatinine kinase MB [CK-MB] levels) are often insufficient to determine etiology and prognosis at presentation. Cardiac troponin T (tn-T), the tropomyosin-binding protein of car-

diac muscle, can be distinguished from that of skeletal muscle; elevated tn-T levels have been found in the setting of acute myocardial injury and are postulated to be a marker of poor prognosis.

Population studied Patients presented within 12 hours of the onset of chest discomfort, and had abnormal ECGs consisting of ST-segment elevation or depression, T-wave inversion, or left bundle branch block. Patients with renal dysfunction, recent stroke, or contraindications to anticoagulation were excluded. The pretest likelihood of acute myocardial infarction (AMI) was quite high: 72% were eventually diagnosed with AMI.

Study design and validity This study was a prospective observational substudy within a multicenter randomized trial; the primary trial has also been published.[1] This substudy examined single blood levels of tn-T and CK-MB measured a median of 5.1 hours after the onset of symptoms. Treating physicians were blinded to these experimental values, but did have locally determined CK-MB levels. Patients all received aspirin and either heparin or hirudin, a similar anticoagulant. Patients with ST-segment elevation also received either streptokinase or tissue plasminogen activator (tPA). Other treatments were at the discretion of the treating physicians. ECGs, biochemical markers, and the endpoints of death or infarction were all analyzed independently and blindly. However, since a rise in serial CK-MB levels is a part of the "gold standard" used to diagnose MI, treating physicians could not be blinded to these values. It is probably not fair to compare CK-MB and tn-T for predicting outcome, because of the possibility that patients with elevated CK-MB levels might have been treated more aggressively when tn-T levels were not available.

Outcomes measured The primary endpoint was a composite of death, infarction, reinfarction, bypass surgery, or angioplasty within 30 days. Secondary endpoints included the individual endpoints used in the composite as well as cardiogenic shock, congestive heart failure, atrioventricular block, and ventricular tachycardia, or fibrillation.

Results For predicting AMI or the composite primary endpoint, tn-T was no better than CK-MB. For predicting death within 30 days in this very high risk population, the initial tn-T level had a higher sensitivity than the initial CK-MB level (68% vs 48%), with a similar specificity (66% vs 69%), positive predictive value (12% vs 10%), and negative predictive value (96% vs 95%). The prognostic value of tn-T remained significant whether CK-MB was high or low.

Recommendations for clinical practice **Cardiac troponin T (tn-T) is an intriguing new biochemical marker for cardiac injury. In this study, patients presenting with suspected AMI and elevations of tn-T were at increased risk for death, even when controlled for CK-MB levels and ECG abnormalities. However, the predictive value was low; only 12% of those with an abnormal troponin-T level died. Other studies have shown similar results with cardiac troponin I.[2] Whether knowing the tn-T level will lead to more effective strategies for managing patients with acute myocardial ischemia still needs to be proven. Despite these problems, the study raises very interesting questions for further study, including the difficulty of defining a true gold standard for the diagnosis of AMI.**

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Cardiac Troponin I Levels in Unstable Angina and Non-Q Wave AMI

Reference Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335: 1342-89.

Clinical question **Can cardiac troponin I (tn-I) be used as a predictor of short-term mortality in patients with unstable angina and non-Q wave acute myocardial infarction (AMI)?**

Background Cardiac troponin I (tn-I) is a cardiac-specific marker that is found in the circulation as a result of myocardial necrosis. It is less sensitive in the first 12 hours for AMI (sensitivity 25% at 0 to 6 hours, 93% at 6 to12 hours, and 95% to 100% at >12 hours) than myoglobin or CPK-MB,[1] but remains elevated for 7 to 10 days after a cardiac event. This study examines whether elevated serum tn-I is a predictor of short-term mortality in patients with "acute coronary syndromes."

Population studied Patients (N=1404) with documented evidence of coronary artery disease (CAD; criteria not specified in article), chest pain lasting at least 5 minutes but less than 6 hours, no AMI within 21 days, no angioplasty in the last 6 months, no thrombolytics in

the last 72 hours, no evidence of left bundle branch block, and a "nontreatable" cause of angina (criteria not specified in article).

Study design and validity The authors ran tn-I levels on frozen serum collected for a previous trial and retrospectively examined outcomes in these patients. Of the 1404 specimens, 573 had detectable levels of tn-I defined by the authors as greater than 0.4 ng/mL. They then compared mortality at day 42 in the group with an elevated tn-I level with mortality in the group with tn-I levels of <0.4 ng/mL.

The choice of 42 days as time endpoint limits the applicability of this study since it addresses only the first 6 weeks after a qualifying cardiac event. Another concern is that the patients who were enrolled in this trial had "documented evidence of CAD" and "nontreatable" causes of angina (neither term is defined in this paper). How these patients compare with other "rule-out AMI" patients is unclear.

Outcomes measured The primary outcome was mortality at 42 days after non-Q wave AMI or chest pain secondary to unstable angina.

Results Of the 1404 patients, 2.1% died within the first 42 days after enrolling in the study. Of the 573 patients with an elevated tn-I, 3.7% died; of those with a normal tn-I, only 1% died. As the tn-I level increased, so did the mortality; absolute risk of mortality was 1.7% (95% CI, 0.5 to 6.7) for a tn-I level from 0.4 ng/mL to 1.0 ng/mL and 7.5% (95% CI, 2.6 to 23.0) for a tn-I level greater than 9.0 ng/mL. This relationship was independent of CK-MB, age at enrollment, electrocardiographic changes, and other cofactors. Thus, tn-I was an independent predictor of mortality. However, note that the confidence interval of the 0.4 ng/mL to 1.0 ng/mL group includes one. Therefore, individuals in this group may or may not have an increased mortality.

Recommendations for clinical practice **This study suggests that tn-I can be used to help stratify the risk of death in patients with documented cardiac disease who have unstable angina or a non-Q-wave AMI. However, even with the highest level of tn-I, 42-day mortality was only 7.5% (95%CI, 2.6% to 23%). An elevated tn-I may be useful to determine which patients warrant further investigations to determine the presence and extent of CAD. While it would be helpful to demonstrate that investigations prompted by an abnormal tn-I save lives as a result of more aggressive management, this study does not address this question. Also, the generalizability of this study is limited because all study patients had "documented evidence of CAD," which is not always the case among patients admitted to "rule-out AMI."**

Our understanding (and the "gold standard") of what constitutes an AMI should evolve in response to this and similar studies. Essentially, what the presence of tn-I in the circulation defines is the group of patients who have had enough cardiac ischemia to have cell death. The long-term prognostic and management significance of these biochemically defined AMIs remains to be determined.

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