

Abstracts

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Fifty Percent Area Reduction After Four Weeks of Treatment is a Reliable Indicator for Healing—Analysis of a Single-Center Cohort of 704 Diabetic Patients

Coerper S, Beckert S, Kuper MA, et al. *J Diabetes Complications* 2009;23:49-53.

Conclusion: Calculating wound area reduction after 4 weeks is a valid tool to estimate the probability that a diabetic foot wound will heal. A 50% wound area reduction after 4 weeks of therapy indicates likely healing of a diabetic foot wound.

Summary: Subjective and wound-based parameters can be used to document healing of diabetic foot wounds. The only objective wound-based parameters for healing are wound size and ultimate complete wound closure. The authors sought to investigate whether an area reduction >50% with 4 weeks of treatment was associated with long-term probability that a diabetic foot wound would heal.

The authors treated diabetic foot wounds according to an institutional, interdisciplinary wound care protocol. Follow-up was documented using a wound care documentation system and data were analyzed. The probability of healing was assessed with the Kaplan-Meier method, with results expressed as percentage of area reduction. Patients were classified as responders to the protocol when the percentage of wound area reduction reached at least 50% after 4 weeks of treatment, and nonresponders when the percentage area reduction was <50% at 4 weeks. Healing was defined as a percentage area reduction of 100%.

The analyses included 704 patients with a median follow-up of 71 days (range, 2-365 days). Wound duration was 31 days (range, 1-4018 days). Initial wound size was 1.18 cm² (range, 0.1-99 cm²). Bone was involved in the base of the wound in 28%, and in 64.5% both pedal pulses were not palpable. Major amputation rate was 2.8%, and minor amputation rate was 10.2%. Overall probability of healing was 35% after 12 weeks, 41% after 16 weeks, and 73% after 1 year. There were 334 responders (47%) and 370 nonresponders (53%). Responders had a significantly higher probability of healing compared with nonresponders (12 weeks: 52% vs 18%, $P = .0001$; 16 weeks: 47% vs 27%, $P = .0001$; 1 year: 83% vs 65%, $P = .0001$).

Comment: The data suggest that diabetic foot wounds more prone to heal will exhibit a greater healing response early in the course of their treatment. The practical point is that if the wound has not decreased by 50% in area after 4 weeks, an alternative form of wound therapy should be considered.

Plasma Levels of Soluble Tie2 and Vascular Endothelial Growth Factor Distinguish Critical Limb Ischemia from Intermittent Claudication in Patients with Peripheral Arterial Disease

Findley CM, Mitchell RG, Duscha BD, et al. *J Am Coll Cardiol* 2008;52:387-93.

Conclusion: VEGF and sTie2 are increased in critical limb ischemia. sTie2 may be a marker and a cause of critical limb ischemia.

Summary: Patients with peripheral arterial disease (PAD) are at increased risk for cardiovascular mortality. Risk is higher for those patients with critical limb ischemia (CLI) vs those with intermittent claudication (IC). The diagnosis of IC vs CLI is, however, purely clinical. In addition, although a lower ankle-brachial index (ABI) is also a marker for increased cardiovascular mortality, ABI does not distinguish between CLI and IC. A potential biomarker that can distinguish between patients with CLI and IC may therefore be useful in risk stratification in patients with PAD.

The authors are expert in fields of angiogenesis, and it is known that alterations in angiogenic growth factors occur in patients with vascular disease. It is, however, unknown whether these growth factors are altered in the subset of cardiovascular disease patients with PAD or whether these potential alterations in growth factors can correlate with the disease severity. In this study the authors therefore sought to determine whether factors that regulate angiogenesis are altered in PAD and if these alternations exist, whether they are associated with PAD severity.

Plasma was collected from 46 patients with PAD (23 with IC and 23 with CLI) and 23 healthy controls. Plasma angiopoietin-2 (Ang2), soluble Tie2 (sTie2), vascular endothelial growth factor (VEGF), soluble VEGF receptor 1 (sVEGFR-1), and placenta growth factor (PlGF) were measured from the plasma samples. In vitro studies of endothelial cells were also performed with recombinant VEGF to investigate effects on sTie2 production.

Concentrations of sTie2 ($P < .01$), Ang2 ($P < .001$), and VEGF ($P < .01$) were significantly greater in PAD patients compared with controls. No differences were found in PlGF or sVEGFR-1. Plasma Ang2 was increased in both IC and CLI patients compared with controls ($P < .0001$). There were

no differences in levels in patients with IC and CLI. Plasma levels of sTie2 and VEGF were similar in controls and patients with IC, but were increased in patients with CLI ($P < .001$ vs control or IC). Increased sTie2 and VEGF were independent of ABI or standard cardiovascular disease risk factors. Treatment of endothelial cells with VEGF significantly increased sTie2 shedding.

Comment: It is a bit of a stretch to suggest at this time that VEGF and sTie2 have any utility as biomarkers for the large cohort of patients with CLI. If, however, these biomarkers could be used as a predictor of amputation risk in patients with CLI, adjusted for wound size and ABI, that would be useful. The only real conclusion that can come from this study is that plasma levels of sTie2 and VEGF are increased in patients with PAD and are different in those with a clinical diagnosis of CLI vs those with IC. What we really need in the group of patients with CLI is a predictor of short-term amputation risk, and the data here are not sufficient for that degree of risk stratification.

Angina Pectoris is a Stronger Indicator of Diffuse Vascular Atherosclerosis than Intermittent Claudication: Framingham Study

Kannel WB, Evans JC, Piper S, et al. *J Clin Epidemiol* 2008;61:951-7.

Conclusion: Angina pectoris is a stronger predictor of diffuse atherosclerotic cardiovascular disease than intermittent claudication (IC).

Summary: IC is an accepted marker of the presence of diffuse atherosclerosis and conveys an increased risk for mortality, primarily from cardiovascular causes. Angina pectoris, another condition provoked by exertion, however, is generally regarded only as a hallmark of impending myocardial infarction. As an example, the Rose angina questionnaire, a tool for epidemiologic investigation of angina, has been tested chiefly as a predictor of coronary morbidity and mortality. In this study the authors use population-based data from the Framingham Study between 1949 and 1990 to assess relative predictive values of IC or angina pectoris for a cardiovascular disease event. The data from 1949 to 1990 were used because this was a time when few widespread therapies were in use for prevention of cardiovascular disease events.

The prospective cohort of this study consisted of 5209 men and women from Framingham, Massachusetts, who were aged 28 to 62 years at the time of enrollment from 1948 to 1951. For 36 years of follow-up they have received biennial examinations. The incidence of development of cardiovascular disease in the Framingham participants with angina pectoris or IC was determined relative to a reference sample free of cardiovascular disease. There were 95 cardiovascular disease events in the 186 participants with IC, and 206 in the 413 patients with angina pectoris. Adjusting for sex, age, and risk factors, the proportion of the IC group developing other cardiovascular disease was 34%, and the proportion for the angina pectoris group was 43.4%. Compared with the reference sample, the IC group had a 2.73-fold higher age and sex-adjusted 10-year hazard ratio for cardiovascular disease (95% confidence interval [CI], 2.21-3.38). For angina pectoris, the cardiovascular disease hazard ratio was 3.17 (95% CI, 2.73-3.69). The standard risk factor adjustments cardiovascular disease hazard ratios were more elevated for patients with angina pectoris than for those patients with IC. Excess cardiovascular disease was accounted for by risk factors in 34.8% of those with IC and 9.5% of those with angina pectoris.

Comment: Angina and IC are both hallmarks of diffuse atherosclerotic vascular disease. The data indicate that both impart a twofold to threefold increased risk of cardiovascular disease compared with a reference group. It is interesting that the factors increasing risk for clinical events in other vascular territories are not a product of the shared risk factors of patients with IC and those with angina pectoris. Coexistent risk factors only accounted for about 35% of the cardiovascular risk for IC and 9.5% of the hazard associated with angina pectoris. The mechanism of this somewhat unexpected observation is uncertain. It is important to note the Framingham Study has few African Americans or other minority populations. The data presented, therefore, cannot be generalized to the entire United States population.

General and Abdominal Adiposity and Risk of Death in Europe

Pischoon T, Boeing H, Hoffmann K, et al. *N Engl J Med* 2008;359:2105-20.

Conclusions: Abdominal adiposity and general adiposity are both associated with risk of death. Waist circumference and waist-to-hip ratios, in addition to body mass index (BMI), should be used in assessing risk of death related to adiposity.

Summary: Calculations of BMI have been used to assess the association between adiposity and risk of death. The authors sought to determine whether the distribution of body fat contributes to the prediction of death

associated with adiposity. The study used data from patients in the European Prospective Investigation into Cancer and Nutrition (EPIC). The association of waist circumference, waist-hip ratio, and BMI was assessed for risk of death among 359,387 participants in nine European countries. Age was used as the time variable in a Cox regression analysis and was stratified according to study center and age at recruitment. Further adjustments were made for smoking status, alcohol consumption, height, physical activity, and educational level.

During the mean follow-up of 9.7 years, 14,723 participants died. With respect to BMI, the lowest risk of death was observed at a BMI of 25.3 for men and 24.3 for women. Adjusting for BMI, waist-hip ratio, and waist circumference were strongly associated with risk of death. Relative risks among men and women in the highest quintile of waist circumference were 2.05 (95% confidence interval [CI], 1.82-2.33), and 1.78 (95% CI, 1.56-2.04), respectively. The waist-hip ratio relative risk for death for men in the highest quintile was 1.68 (95% CI, 1.53-1.84) and for women was 1.51 (95% CI, 1.37-1.66).

Comment: Adipose tissue, especially adipose tissue associated with visceral fat deposits, can secrete mediators that are likely important in the development of chronic diseases. These mediators are thought to potentiate inflammation that has been associated with respiratory ailments, cancer, and atherosclerosis. Indeed, a recent report suggests the increased risk of death associated with a high BMI is driven by cancer and cardiovascular causes (N Engl J Med 2006;355:779-87). BMI, however, is not the whole story when it comes to the effect of adipose tissue on life span. The study results suggest that in patients with low BMI, measurements of waist circumference or waist-to-hip ratio are more important predictors of the risk of death than the BMI itself. The study also challenges the use of precise cutoff points to define the risk of death associated with abdominal obesity. The risk imposed by the presence of adipose tissue exists essentially as a continuous rather than as a categorical variable, and it now appears important to assess distribution of body fat even in persons of normal weight.

A Predictive Model for Identifying Surgical Patients at Risk of Methicillin-Resistant *Staphylococcus Aureus* Carriage on Admission

Harbarth S, Sax H, Uckay I, et al. J Am Coll Surg 2008;207:683-9.

Conclusions: Surgical patients recently treated with antibiotics, those with recent hospitalizations, and those aged >75 years are at increased risk of being carriers for methicillin resistant *Staphylococcus aureus* (MRSA) on admission to the hospital.

Summary: There are guidelines for control of nosocomial transmission of MRSA (Infect Control Hosp Epidemiol 2003;24:362-86). The spread of MRSA is facilitated by cross-transmission via health care workers' hands and broad-spectrum antibiotic treatment selecting for MRSA. MRSA infections are associated with increased treatment cost and excess morbidity and mortality. MRSA is now present in the community, and patients without previous MRSA infection are being increasingly recognized on admission to the hospital. The authors sought to develop and validate a prediction model to confine surgical patients with previously unknown MRSA who are, in fact, carriers of MRSA on admission to the hospital. The authors used two prospective studies to derive and validate predictors of previously unknown MRSA carriage on admission. There were 13,262 patients (derivation cohort, 3069; validation cohort, 10,193) admitted to the surgery department of Geneva University Hospitals in Switzerland. MRSA carriage at the time of admission increased from 3.2% in 2003 to 5.1% from 2004 to 2006. Of the patients carrying MRSA, 64% were newly identified carriers. Logistical regression analysis identified three independent factors correlated with previously unknown MRSA carriage: (1) recent antibiotic treatment (adjusted odds ratio [OR], 4.5; $P < .001$), (2) history of hospitalization (adjusted OR, 2.7; $P = .03$), and (3) age >75 years (adjusted OR, 1.9; $P = .048$). A score of 0 to 9 points was calculated for these variables. There were 152 patients with a score of <2 points, and previously unknown MRSA carriage was 5% ($n = 8$); 166 had an intermediate score of 3 to 6 points, and previously unrecognized MRSA carriage was 11% ($n = 19$); and 87 had a score >7 points, and previously unrecognized MRSA carriage was 34% ($n = 30$).

Comment: These data indicate most MRSA carriers are unknown at the time of hospital admission. The three variables found to be predictive of unsuspected MRSA infection—previous hospitalization, recent antibiotic use, and age >75 years—are extremely common in patients with vascular disease admitted to the hospital. Vascular surgeons should be aware that many of their patients without previously recognized MRSA infection are very likely to be carriers of MRSA at the time of their admission to the hospital.

Identifying Unprovoked Thromboembolism Patients at Low Risk for Recurrence Who Can Discontinue Anticoagulant Therapy

Rodger MA, Kahn SR, Wells PS, et al. Can Med Assoc J 2008;179:417-26.

Conclusion: Oral anticoagulation therapy can be safely discontinued after 6 months in woman who have zero or one potential predictor of recurrent venous thromboembolism (VTE).

Summary: Optimal duration of anticoagulation after unprovoked VTE is controversial. In this study the authors sought to identify clinical predictors to identify patients at low risk of VTE recurrence after discontinuation of oral anticoagulants.

This was a multicenter prospective cohort study involving 646 patients with a first unprovoked major VTE. Patients were enrolled during a 4-year period, and 600 completed a mean 18-month follow-up. Data were collected for 16 potential predictors of recurrent VTE during the time patients were taking oral anticoagulation therapy (5 to 7 months after initiation). After discontinuation of oral anticoagulation therapy, patients were monitored for recurrent VTE.

During follow-up, 91 confirmed episodes of recurrent VTE were identified (annual risk, 9.3%; 95% confidence interval [CI], 7.1%-11.3%). The annual risk for men was 13.7% (95% CI, 10.8%-17.0%). No combination of clinical predictors could identify a low-risk subgroup of men. Zero or one of the following characteristics were present in 52% of women: D-dimer level >250 mg/L while taking warfarin; body mass index >30 kg/m²; hyperpigmentation, edema, or redness of either leg; or age >65 years. Women with zero or one of these predictors had an annual risk of VTE recurrence of 1.6% (95% CI, 0.3%-4.6%). Women with two or more of these predictors had an annual risk of VTE recurrence of 14.1% (95% CI, 10.9%-17.3%).

Comment: This study is consistent with the previously determined adverse effect of male sex on the recurrence of VTE (Lancet 2006;368:371-8). There are three major points here. First, identification of risk factors after 5 to 7 months of oral anticoagulation therapy is a strong predictor of recurrent VTE. Second, D-dimer levels after stopping oral anticoagulation may not be sufficient to identify patients at low risk of recurrence, whereas D-dimer levels while taking oral anticoagulation may be a strong predictor of recurrent VTE. The point is particularly interesting in that it allows more efficient care of patients. Stopping anticoagulation and testing D-dimer levels 1 month later and subsequently restarting anticoagulation therapy if necessary is impractical and exposes potentially high-risk patients to a period without anticoagulation. Finally, the authors identified a clinical decision rule that identifies women at low risk of VTE.

Intermittent Claudication in Diabetes Mellitus Due to Chronic Exertional Compartment Syndrome of the Leg: An Observational Study of 17 Patients

Edmundsson D, Svensson O, Toolanen G. Acta Orthop 2008;79:534-9.

Conclusion: Chronic exertional compartment syndrome (CECS) of the leg can cause intermittent claudication in patients with diabetes. Fasciotomy provides good results and increased pain-free walking time.

Summary: The authors investigated whether symptoms of claudication could occur in patients with diabetes as a result of chronic exertional compartment syndrome (CECS). The report concerns 17 patients (3 men and 14 women) with a mean age of 39 years (range 18-72 years). All had diabetes mellitus and 12 had type I diabetes mellitus. All had leg pain during walking, relieved at rest, and none had clinical signs of peripheral arterial disease. The mean duration of diabetes was 22 years (range, 1-41 years), and 12 patients had peripheral neuropathy, retinopathy, or nephropathy. Leg muscles were firm and tender on palpation.

Patients were evaluated with scintigraphy and intramuscular pressure measurements during exercise. These evaluations resulted in 16 of 17 patients being diagnosed with CECS. Intramuscular compartment pressures in leg compartments were higher in diabetic patients than in physically active nondiabetic individuals without CECS ($P < .05$). The diagnosis of CECS was made using the following criteria: history of exercised induced pain or symptoms with reproduction of symptoms and pain during a treadmill exercise test; or a combination of intramuscular pressures at rest >15 mm Hg, an intramuscular pressure >30 mm Hg 1 to 2 minutes after the end of the exercise test, or intramuscular pressure >20 mm Hg 5 minutes after the end of the exercise test, all combined with reproduced leg pain. Recommended treatment was fasciotomy of the anterior tibial and peroneal compartment using a 5-cm skin incision halfway between the fibular shaft and the tibial crest in the middle portion of the leg. A 1-cm wide fascial strip was removed during the procedure. Posterior compartments were treated with fasciotomy of the superficial soleus and gastrocnemius muscles as well as the deep posterior compartments.

Fifteen patients were treated with fasciotomy. At surgery the fascia was observed to be thickened and "whitish," and to have a "rubber-like" consistency. After 1 year, 9 patients rated themselves excellent or good in 15 of the 18 treated compartments. Walking times until stopping on the treadmill test increased after surgery from <10 minutes to unlimited time in 8 of the 9 patients who underwent follow-up.

Comment: The authors' small series suggests CECS may be a cause of exercise induced leg pain in patients with diabetes. These patients likely function at different levels than the traditional young athlete with CECS. Nevertheless, the apparent dramatic increase in pain-free walking in the