ABSTRACTS

Malignancies, prothrombotic mutations, and the risk of venous thrombosis

Blom JW, Doggen CJM, Osanto S, et al. JAMA 2005;293:715-22.

Conclusion: There is an increased risk of venous thrombosis in patients with cancer. The risk is greatest in the first few months after diagnosis and in the presence of distal metastasis. Patients also with Factor V Leiden and prothrombin 20210A mutations have even higher risk.

Summary: This is a report of the Multiple Environmental and Genetic Assessment (MEGA) of Risk Factors for Venous Thrombosis Study. MEGA is a case controlled population based study evaluating risk of venous thrombosis with various risk factors. This report details risk of venous thrombosis with cancer and the joint effects of cancer and selected genetic mutations predisposing to venous thrombosis. Patients were identified at 6 anticoagulation clinics in the Netherlands between March 1, 1999, and May 31, 2002. Patients included were those 18-70 years of age with a first time diagnosis of pulmonary embolism or lower extremity deep venous thrombosis. Control patients, (partners of the patients with venous thrombosis) were also utilized in the study. Both patients and controls received a questionnaire to evaluate acquired risk factors for venous thrombosis. Once anticoagulation therapy had been discontinued for three months, patients and controls were interviewed and blood taken for analysis of Factor V Leiden and prothrombin 20210A mutations.

In patients with malignancy, the overall risk of venous thrombosis was increased 7 times (odds ratio [OR], 6.7; 95% CI, 5.2-8.6). The highest risk was present in patients with hematologic malignancies (OR 28.0, 95% CI, 4.0-199.7). Risk was also substantially increased in patient with gastrointestinal cancers (OR 18.9; 95% CI, 4.6-77.8), and patients with pulmonary malignancies (OR 24.8; 95% CI, 3.4-181.1). Risk was highest in the first several months following malignancy diagnosis (adjusted OR 53.5; 95% CI, 8.6-334.3). In patients with cancer the presence of distal metastatic disease further increased the risk of venous thromboembolism (VTE) compared to patients without metastatic disease (adjusted OR, 19.8; 95% CI, 2.6-149.1). The combination of cancer and Factor V Leiden mutation increased the risk of VTE 12 times compared to patients with Factor V Leiden mutation and no diagnosed malignancy. Results were similar for patients with and without cancer with respect to the prothrombin 20210A mutation.

Comment: The data raises the question as to whether patients with cancer should be screened for Factor V Leiden and prothrombin 20210A mutation and treated with prophylactic anticoagulation therapy if a mutation is present. Also the question arises whether prophylactic anticoagulation is indicated in patients with malignancies associated with an especially high risk for VTE. The cost effectiveness of such strategies and the ultimate ability of such strategies to prolong life or improve quality of life are clear in patients with cancer who are undergoing surgery or active chemotherapy (ACTA Haematol 2001;106:73-80). There is currently no data to suggest routine prophylaxis for VTE in all cancer patients would be effective. However, the results of the current study suggest certain subgroups of patients with cancer should be studied more closely for potential benefit of routine VTE prophylaxis.

Perioperative beta-blocker therapy and mortality after major non cardiac surgery

Lindenauer PK, Pekow P, Wang K, et al. N Engl J Med 2005; 353:349-61.

Conclusion: Perioperative beta-blocker therapy reduces risks of in-hospital death in high-risk patients undergoing major non-cardiac surgery.

Summary: The authors conducted a retrospective cohort study of patients ≥18 years of age undergoing major non-cardiac surgery in the years 2000 and 2001 in 329 hospitals in the United States. The aim was to assess the use of perioperative beta blockers and their effects on in-hospital mortality as used in routine clinical practice. Propensity scoring matching was used to adjust for differences in patients who received and who did not receive perioperative beta blockers. In-hospital mortality was compared using multivariable logistic modeling. Surgical procedures were categorized using available DRG software. The procedure was considered major if the median length of stay by diagnostic group exceeded two days. Information was recorded regarding age, sex, race, ischemic heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, diabetes, hyperlipidemia and hypertension. Other perioperative medications such as angiointensin converting enzyme inhibitors, calcium channel blockers, and antiplatelet agents and methods of venous prophylaxis were also recorded. Contraindications to beta blocker therapy were assessed.

There were 782,969 patients analyzed; 85% apparently had no contraindication to beta blockers. 18% (n = 122,338) received beta blocker therapy in the first two hospital days. Fourteen percent of patients had a revised cardiac risk index (RCRI) score of 0 and 44% had a score of 4 or higher. Risk of death related to perioperative beta-blocker treatment varied directly with cardiac risk. In 580,665 patients with a RCRI score of 0 or 1 there was no benefit from perioperative beta-blockers. Among patients with a RCRI score of 2, 3, or 4, adjusted odds ratio for death in the hospital were 0.88 (95% CI, 0.8 to 0.98), 0.71 (95% CI, 0.63 to 0.80), and 0.58 (95% CI, 0.50 to 0.67), respectively.

Comment: Only approximately 51,000 of the patients analyzed in this study underwent a vascular surgical procedure. Nevertheless, vascular patients generally have increased cardiac risk and the results of this study support strongly the use of beta blockers in patients with high cardiac risk. There is no question that the perioperative use of beta-blockers as a routine in vascular surgical patients without contraindications to beta blocker therapy should be standard practice.

Carotid plaque pathology: Thrombosis, ulceration, and stroke pathogenesis

Fisher M, Paganini-Hill A, Martin A, et. al. Stroke 2005;36:253-57.

Conclusion: Carotid plaque ulceration and thrombus are more prevalent in symptomatic patients.

Summary: This was a microscopic analysis of carotid plaques surgically removed from patients enrolled in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and in the Asymptomatic Carotid Atherosclerosis Study (ACAS). Microscopic plaque morphology was compared in patients with and without stroke symptoms ipsilateral and contralateral to the plaque. The presence of calcification, thrombus, and ulceration were used to characterize the plaques. There were a total of 241 subjects from whom plaques were obtained with 128 subjects having no history of stroke symptoms, 80 subjects with symptoms ipsilateral to the plaque and 33 with symptoms contralateral to the plaque. Of the subjects, 170 had been enrolled in ACAS and 71 in NASCET.

Ulceration of the plaque was more common when the plaque was removed from a symptomatic patient than when the plaque was obtained from an asymptomatic patient (36% versus 14%; $P < 0.001$). The frequency of ulceration was similar in plaques associated with ipsilateral (34%) and contralateral symptoms (42%). Thrombus was more common in plaques removed from patients with both ipsilateral symptoms and ulceration. Calcification was not associated with stroke symptoms.

Comment: This is another indirect attempt trying to determine which plaques in asymptomatic patients may have a greater propensity to produce stroke. The authors conclusions are not new, not unexpected, and add very little to what is already known or suspected. There continues to be great interest in characterizing surgically removed plaques. What is needed is a preoperative marker of plaque virulence that is sufficiently sensitive and powerful to improve selection of patients with asymptomatic carotid stenosis for a prophylactic carotid intervention.

Soluble CD40L and cardiovascular risk in asymptomatic low-grade carotid stenosis

Novo S, Basili S, Tantillo R, et al. Stroke 2005;36:673-75.

Conclusion: High levels of soluble CD40L are associated with an increased risk of cardiovascular events in patients with asymptomatic minimal carotid stenosis.

Summary: C-reactive protein, IL-6, and CD40L have all been shown in prospective studies to predict the risk of development of cardiovascular disease. In addition, soluble CD40L (sCD40L) has been shown to be associated with features of high-risk plaques. This investigation focused on whether sCD40L can predict risk of cardiovascular events in patients who have known minimal asymptomatic carotid plaques.

The authors studied 42 patients with asymptomatic low-grade carotid stenosis and 21 control patients without evidence of carotid stenosis. All patients had at least one major cardiovascular risk factor. Measurements were made of C-reactive protein (CRP), IL-6, and sCD40L. Subjects were followed up every 12 months with a median follow up of 8 years. No patient was lost to follow up.

There were 14 patients (33%), who experienced a vascular event (4 non fatal myocardial infarctions, 2 strokes and 4 transient ischemic attacks). In addition, 2 patients developed intermittent claudication and 2 had a need for a percutaneous revascularization procedure. Patients with cardiovascular events had higher median values of sCD40L (9.1 versus 5.6 ng/mL; $P < 0.02$), than those who did not have a cardiovascular event. Overall, the patients with minimal asymptomatic carotid plaquing had higher CRP, IL-6 and sCD40 levels than controls ($P < 0.0001$). Cox regression analysis indicated only sCD40L levels ($P = 0.003$), were independently predictive of cardiovascular risk.