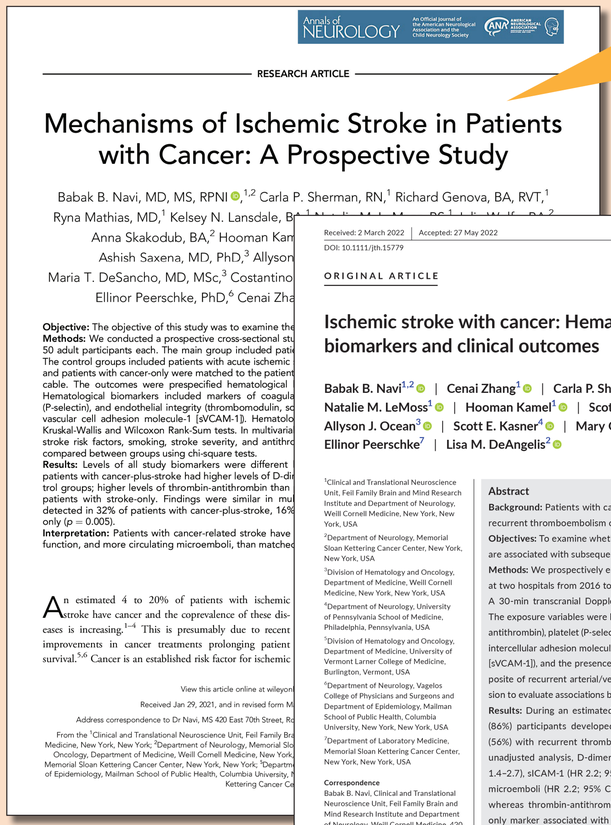
Weill Cornell Medicine | NewYork-Presbyterian

Neurovascular Ultrasound Lab

An Investigative Clinical Site

MOST Study

We found that in a prospective study, patients with active cancer and acute ischemic stroke have higher markers of coagulation, platelet, and endothelial activation, and more circulating microemboli than matched controls. These data implicate hypercoagulable and embolic processes in the pathogenesis of ischemic stroke in patients with solid tumor cancer. Future studies should evaluate whether these biomarkers can predict the risk of incident and recurrent stroke and the response to antithrombotic treatment in patients with cancer. Meanwhile, clinicians should explore prothrombotic and embolic pathophysiologies in patients with cancer and stroke, especially when the stroke mechanism is undetermined after standard evaluation.



Annals of NEUROLOGY — An Official Journal of the American Neurological Association and the Child Neurology Society

RESEARCH ARTICLE

Mechanisms of Ischemic Stroke in Patients with Cancer: A Prospective Study

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Objective: The objective of this study was to examine the
Methods: We conducted a prospective cross-sectional study
50 adult participants each. The main group included patients
The control groups included patients with acute ischemic
and patients with cancer-only were matched to the patient
cable. The outcomes were prespecified hematological
Hematological biomarkers included markers of coagula
(P-selectin), and endothelial integrity (thrombomodulin, so
vascular cell adhesion molecule-1 [sVCAM-1]). Hematolo
Kruskal-Wallis and Wilcoxon Rank-Sum tests. In multivaria
stroke risk factors, smoking, stroke severity, and antithro
compared between groups using chi-square tests.
Results: Levels of all study biomarkers were different
patients with cancer-plus-stroke had higher levels of D-di
trol groups; higher levels of thrombin-antithrombin than
patients with stroke-only. Findings were similar in mu
detected in 32% of patients with cancer-plus-stroke, 16%
only ($p = 0.005$).
Interpretation: Patients with cancer-related stroke have
function, and more circulating microemboli, than matched

An estimated 4 to 20% of patients with ischemic stroke have cancer and the copresence of these diseases is increasing.[1–4] This is presumably due to recent improvements in cancer treatments prolonging patient survival.[5,6] Cancer is an established risk factor for ischemic

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ORIGINAL ARTICLE

Ischemic stroke with cancer: Hematologic and embolic biomarkers and clinical outcomes

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Abstract

Background: Patients with cancer and acute ischemic stroke (AIS) face high rates of recurrent thromboembolism or death.

Objectives: To examine whether hematologic and embolic biomarkers soon after AIS are associated with subsequent adverse clinical outcomes.

Methods: We prospectively enrolled 50 adults with active solid tumor cancer and AIS at two hospitals from 2016 to 2020. Blood was collected 72–120 h after stroke onset. A 30-min transcranial Doppler (TCD) microemboli detection study was performed. The exposure variables were hematologic markers of coagulation (D-dimer, thrombin-antithrombin), platelet (P-selectin), and endothelial activation (thrombomodulin, soluble intercellular adhesion molecule-1 [sICAM-1], soluble vascular cell adhesion molecule-1 [sVCAM-1]), and the presence of TCD microemboli. The primary outcome was a composite of recurrent arterial/venous thromboembolism or death. We used Cox regression to evaluate associations between biomarkers and subsequent outcomes.

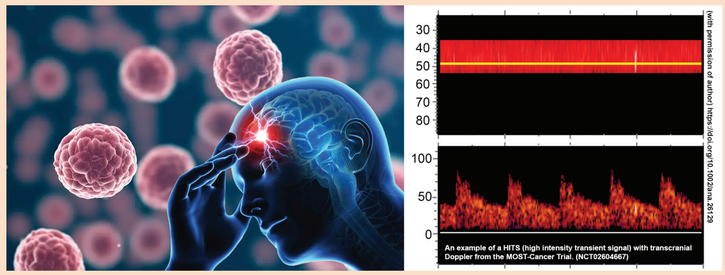
Results: During an estimated median follow-up time of 48 days (IQR, 18–312), (86%) participants developed recurrent thromboembolism or death, including (56%) with recurrent thromboembolism, of which 13 were recurrent AIS (2[illegible] unadjusted analysis, D-dimer (HR 1.6; 95% CI 1.2–2.0), P-selectin (HR 1.9; [illegible] CI 1.4–2.7), sICAM-1 (HR 2.2; 95% CI 1.6–3.1), sVCAM-1 (HR 1.6; 95% CI 1.2 [illegible].1), and microemboli (HR 2.2; 95% CI 1.1–4.5) were associated with the primary outcome, whereas thrombin-antithrombin and thrombomodulin were not. D-dimer was the only marker associated with recurrent AIS (HR 1.2; 95% CI 1.0–1.5). Results were generally consistent in analyses adjusted for important prognostic variables.

Conclusions: Markers of hypercoagulability and embolic disease may be associated with adverse clinical outcomes in cancer-related stroke.

KEYWORDS
biomarkers, neoplasms, stroke, thrombophilia, thrombosis

Manuscript Handled by: Sabine Eichinger Final decision: Sabine Eichinger, 27 May 2022

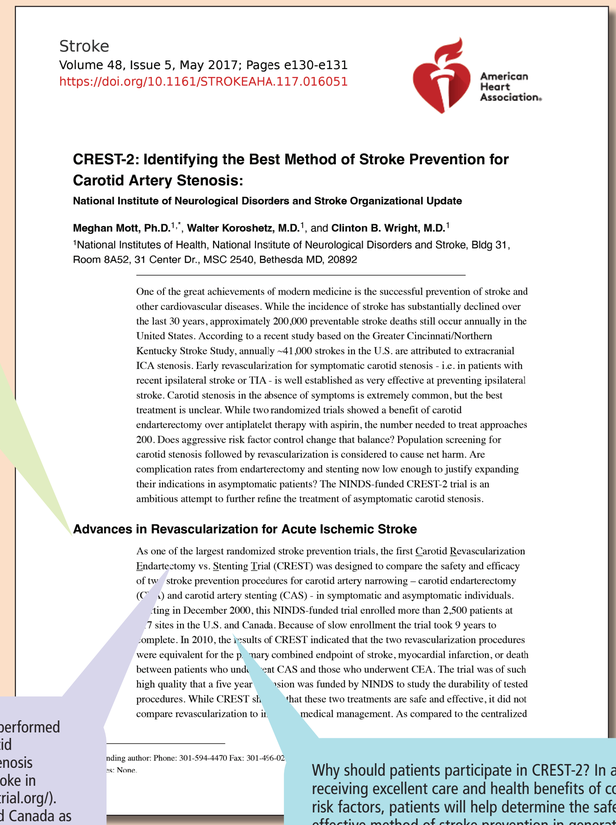
The WCM Neurovascular Ultrasound Lab was one of the two investigative sites for the MOST Study, performing microemboli detection exams.



An example of a HITS (high intensity transient signal) with transcranial Doppler from the MOST-Cancer Trial. (NCT02604667)

CREST-2 Trial for Stroke Prevention

As one of the largest randomized stroke prevention trials, the first Carotid Revascularization Endartectomy vs. Stenting Trial (CREST) was designed to compare the safety and efficacy of two stroke prevention procedures for carotid artery narrowing – carotid endarterectomy (CEA) and carotid artery stenting (CAS) - in symptomatic and asymptomatic individuals.



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https://doi.org/10.1161/STROKEAHA.117.016051

American Heart Association.

CREST-2: Identifying the Best Method of Stroke Prevention for Carotid Artery Stenosis:
National Institute of Neurological Disorders and Stroke Organizational Update

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One of the great achievements of modern medicine is the successful prevention of stroke and other cardiovascular diseases. While the incidence of stroke has substantially declined over the last 30 years, approximately 200,000 preventable stroke deaths still occur annually in the United States. According to a recent study based on the Greater Cincinnati/Northern Kentucky Stroke Study, annually ~41,000 strokes in the U.S. are attributed to extracranial ICA stenosis. Early revascularization for symptomatic carotid stenosis - i.e. in patients with recent ipsilateral stroke or TIA - is well established as very effective at preventing ipsilateral stroke. Carotid stenosis in the absence of symptoms is extremely common, but the best treatment is unclear. While two randomized trials showed a benefit of carotid endarterectomy over antiplatelet therapy with aspirin, the number needed to treat approaches 200. Does aggressive risk factor control change that balance? Population screening for carotid stenosis followed by revascularization is considered to cause net harm. Are complication rates from endarterectomy and stenting now low enough to justify expanding their indications in asymptomatic patients? The NINDS-funded CREST-2 trial is an ambitious attempt to further refine the treatment of asymptomatic carotid stenosis.

Advances in Revascularization for Acute Ischemic Stroke

As one of the largest randomized stroke prevention trials, the first Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) was designed to compare the safety and efficacy of two stroke prevention procedures for carotid artery narrowing – carotid endarterectomy (CEA) and carotid artery stenting (CAS) - in symptomatic and asymptomatic individuals. Starting in December 2000, this NINDS-funded trial enrolled more than 2,500 patients at [illegible]7 sites in the U.S. and Canada. Because of slow enrollment the trial took 9 years to complete. In 2010, the results of CREST indicated that the two revascularization procedures were equivalent for the primary combined endpoint of stroke, myocardial infarction, or death between patients who underwent CAS and those who underwent CEA. The trial was of such high quality that a five year [illegible]sion was funded by NINDS to study the durability of tested procedures. While CREST showed that these two treatments are safe and effective, it did not compare revascularization to [illegible] medical management. As compared to the centralized

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[illegible]s: None.

Markers of hypercoagulability and embolic disease may be associated with adverse clinical outcomes in cancer-related stroke.

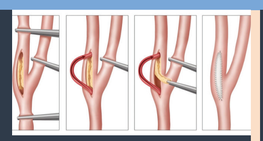
Clinicians should be aware that patients with active cancer and AIS (acute ischemic stroke) have considerably higher rates of major thromboembolic events or death than patients with stroke only or cancer only, and that markers of hypercoagulability and embolic disease likely portend an increased risk for adverse clinical outcomes in cancer-plus-stroke patients. Of the biomarkers we studied, D-dimer, a ubiquitous blood test and marker of coagulation, was the most robust predictor for recurrent AIS after cancer-related stroke. Future studies should validate these results in larger cohorts and different settings, adjust for additional covariates, and investigate whether different cancer and stroke treatments can influence the studied biomarkers and their association with clinical outcomes, especially recurrent AIS and other thromboembolic events, which may be more modifiable outcomes than death in cancer-plus-stroke patients.

An estimated 100,000 carotid procedures, either surgical or stenting, are performed in the U.S. every year, the majority in asymptomatic individuals. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) is designed to determine the best method of preventing stroke in asymptomatic individuals with severe carotid stenosis (http://www.crest2trial.org/). Started in December 2014, CREST-2 is being conducted across the U.S. and Canada as two parallel multi-center randomized, observer-blinded endpoint clinical trials. One trial will assess treatment differences between intensive medical management alone compared to CEA plus intensive medical management. The parallel trial will assess treatment differences between intensive medical management alone compared to CAS plus intensive medical management.

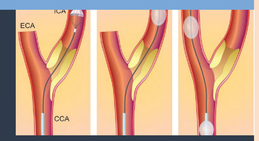
Why should patients participate in CREST-2? In addition to receiving excellent care and health benefits of controlling risk factors, patients will help determine the safest and most effective method of stroke prevention in generations to come. In addition, both CEA and CAS are expensive at roughly $15,000 per procedure, and CREST-2 will help clarify if such costs are justified compared to intensive medical management.

CREST-2 offers three
STROKE PREVENTION OPTIONS

1 Medical Management



2 Carotid Endarterectomy + Medical Management



3 Carotid Artery Stenting + Medical Management

We are an official CREST-2 Study Center Location

Dr. Dana Leifer, MD — Principal Investigator at Weill Cornell Medicine-New York Presbyterian Hospital