CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Cancer-Associated Ischemic Stroke*

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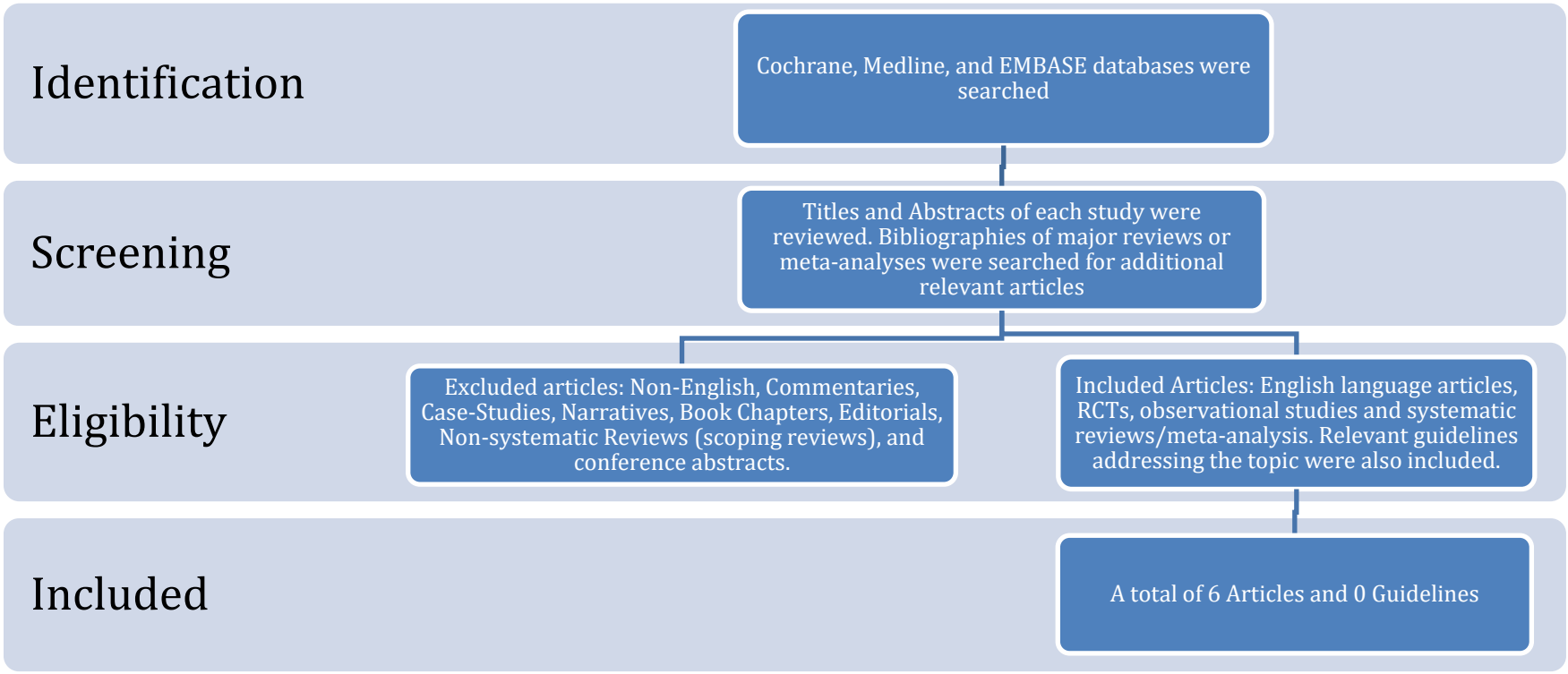
Search Strategy



Cochrane, Medline, and EMBASE databases were search using the terms cancer or malignancy or neoplasm AND stroke. Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review.

Evidence Tables

Relationship between Cancer and Incident Stroke

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Zhang et al. 2021 **China** **Systematic review & meta-analysis**	20 population-based cohort studies involving 10,479,530 participants who were survivors of breast, colorectal, gynecological, head & neck, hematological, lung, melanoma, pancreatic, prostate, stomach and urinary tract cancers.	The risk of stroke in cancer survivors was assessed by comparing their outcomes with those of a non-cancer control group, usually drawn from the general population.	**Primary outcome:** Stroke, ischemic stroke, hemorrhagic stroke	The risk of stroke in cancer survivors was significantly higher compared with the non-cancer group (RR=1.66, 95% CI 1.35-2.04; P<0.001). The risk of ischemic stroke in cancer survivors was significantly higher compared with the non-cancer group (RR=1.53, 1.28–1.84). The risk of hemorrhagic stroke was not significantly increased in cancer survivors. Among cancer types, the risk of stroke was increased significantly for head and neck cancer, hematological cancer, lung cancer, pancreatic cancer and stomach cancer, but not for other cancer types.
Jang et al. 2019 **South Korea** **Retrospective study**	20,707 persons sampled from a population database from 2006-2008 with cancer and 675,594 without cancer. Persons with a history of cancer or stroke between 2002 and 2005 were excluded. Persons in the cancer group were significantly older and a higher percentage were men (51.1% vs. 49.4%).	The incidence of stroke in both groups was examined up to 7 years after cancer diagnosis using both the entire sample and propensity-score matching. Models were adjusted for sex, age, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, heart failure, atrial fibrillation, and medication use (anticoagulant, antiplatelet agent, statin)	**Primary outcomes:** Any stroke, ischemic stroke, hemorrhagic stroke, death	Mean follow-up duration of cancer group was 69.7 months and 82.7 months in the non-cancer group. The cumulative incidence of any stroke was significantly higher in the cancer group (original cohort 3.43% vs.1.07%), as were the cumulative incidences of ischemic stroke (3.10% vs. 0.91%), hemorrhagic stroke (0.46% vs. 0.21%) and death (22% vs. 2.03%). The cumulative incidences of any stroke, ischemic stroke and death were all significantly higher in the cancer group using the matched cohort. The incidence of hemorrhagic stroke was not. Using analyses based on the original sample and the matched cohort, the risk of incident stroke was significantly higher in the cancer group (HR=1.09, 95% CI 1.00-1.18 and HR=1.13, 95% CI 1.02- 1.26, respectively). The risk of ischemic stroke was significantly higher in the cancer group (using both original and matched cohorts), while the risk of hemorrhagic stroke was not.

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				The risk of any and ischemic stroke was significantly higher in persons who received chemotherapy (adj HR= 1.21, 95% CI 1.03–1.41 and adj HR= 1.19, 95% CI 1.01–1.40, respectively).
Navi et al. 2015 **USA** **Retrospective study**	327,389 persons >66 years, with newly diagnosed breast, colorectal, lung, pancreatic, or prostate cancer included in the SEER database from 2001-2009. Mean ages across cancer groups ranged from 75 to 78 years. Cancer stage varied based on type. Most were stage 1 or 2.	The incidence of stroke in persons with cancer was compared with that of a matched cohort (based on age, sex, race, registry, history of hypertension or atrial fibrillation, and Charlson comorbidity index) of persons without cancer, who were identified from the 5% sample of Medicare beneficiaries residing in SEER areas.	**Primary outcome:** Stroke incidence at 3 months, stroke risk at 5 time periods following cancer diagnosis (<1 month, 1-3 months, 3-6 months, 6-9 months and 9-12 months)	Due to differences in survival, median follow-up time was shorter in the cancer cohorts compared to matched controls: 4.3 vs.4.7 years for breast cancer, 2.9 vs. 4.5 years for colorectal cancer, 0.6 vs. 4.5 years for lung cancer, 0.3 s. 4.3 years for pancreatic cancer, and 4.5 vs.4.6 years for prostate cancer. 3-month cumulative stroke incidences of stroke were significantly higher in cancer patients relative to controls for breast cancer (1.5% vs. 1.1%, p<0.001), colorectal cancer (3.3% vs. 1.3%, p<0.001), lung cancer (5.1% vs. 1.2%, p<0.001), and pancreatic cancer (3.4% vs. 1.1%, p<0.001), but not for prostate cancer (1.1% vs. 1.2%, p=0.085). The risk of any stroke was significantly higher in breast cancer patients <1 month (HR=1.71) and 1-3 months (HR=1.17) following cancer diagnosis. The risk of any stroke was significantly higher in colorectal cancer patients <1 month (HR=4.16), 1-3 months (HR=1.80) and 3-6 months (HR=1.37) following cancer diagnosis. The risk of any stroke was significantly higher in lung cancer patients at all follow-up points. HRs ranged from 1.63 at 6-9 months and 7.43 < 1 month after cancer diagnosis. The risk of any stroke was significantly higher in pancreatic cancer patients at all points where patients had survived. <1 month (HR=4.25), 1-3 months (HR=1.80) and 3-6 months (HR=1.37). The risk of any stroke was significantly higher in prostate cancer patients <1 month after cancer diagnosis (HR=1.25), but at no other follow-up periods.

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				The pattern of results for ischemic stroke matched that of risk for any stroke for all cancer types. The pattern of results for hemorrhagic stroke matched that of persons with lung cancer. For other cancers, the risk was significant increased in women with breast cancer at 1-3 months only, increased at all follow-up points for persons with colorectal cancer except at 9-12 months, increased in persons with pancreatic cancer <1 month and 3-6 months and was significantly increased in men with prostate cancer <1 month, 3-6 months and 9-12 months following diagnosis.
Selvik et al. 2015 **Sweden** **Retrospective study**	1,282 patients admitted to a single neurology unit between 2006 and 2011 with acute ischemic stroke and no known history of cancer. Mean age was 71 years, 57% were men.	Patients were followed for a mean of 26.9 months. Information about cancer was obtained using medical records and the Cancer Registry of Norway. Two groups were formed based on cancer status after stroke (newly diagnosed cancer and no cancer). Differences in baseline risk factors and serum markers between groups, were compared. Independent predictors of a cancer diagnosis were identified.	**Primary outcome:** Newly diagnosed cancer	55 patients (4.3%) had 64 cancer diagnoses after stroke. The median time from stroke onset to cancer diagnosis was 14.0 months. 23 patients were diagnosed within 1 year, 13 within 6 months and 9 within 3 months after stroke onset. There were no baseline differences between groups in the proportions of patients with hypertension, atrial fibrillation, diabetes, previous MI, heart disease and smoking. The percentage of patients with previous ischemic stroke was significantly higher in the cancer group (23.6% vs. 13.8%, p=0.04). Mean baseline D-dimers, fibrinogen and C-reactive protein levels were all significantly higher in the cancer group. The risk of cancer detected following ischemic stroke was significantly increased in patients with raised baseline D-dimer levels (HR=1.13, 95% CI 1.1–1.2), smokers (HR=1.59, 95% CI 1.0–2.5) and with advancing age (HR=1.04, 95% CI not provided).
Guo et al. 2014 **Taiwan** **Retrospective study**	564 patients included in either a stroke registration database between 2009 and 2012 (n=516) or a hospital-based database with a stroke diagnosis (n=48).	Patients were divided into 5 subgroups: stroke patients without cancer from the stroke registry (n=430), stroke patients with inactive cancer from stroke registry (n=n=27), stroke patients with active cancer from the stroke registry (n=59), stroke patients with inactive cancer	**Primary outcomes:** Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)	The mean D-dimer level in patients with cancer identified from the stroke registry was significantly higher than that of patients without active cancer (0.66 vs. 5.7 mg/L) and in patients identified in the hospital database (0.60 vs. 10.47 mg/L). Mean fibrinogen and platelet levels did not differ significantly in patients with and without cancer. There was no significant difference in mean D-dimer levels between patients without cancer and those with inactive cancer (p=0.84).

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
		from hospital database (n=9), or stroke patients with active cancer from hospital database (n=39). Demographic and clinical data were compared among the groups. The optimal D-dimer value for predicting cancer in stroke patients was selected using an ROC plot. Different cut-points for D-dimer level to predict cancer was		A significantly higher proportion of active cancer patients had infarctions over multiple territories compared with noncancer patients. 49 patients of 69 with active cancer who were followed up after hospital discharge died within the first year following stroke. At cut-off D-dimer levels of ≥ .55 mg/L, ≥1.55 mg/mL and ≥5.55 mg/mL, using data from patients from the stroke registry and the hospital database, the sensitivities and specificities ranged from 31.6% to 79.6% and 66.7% and 99.6%, respectively. The PPVs and NPVs ranged from 33.5% to 93.9% and 87.4% to 94%. When a D-dimer of ≥.55 mg/L and multiple territory infarctions were used as criteria, the sensitivity, specificity, PPV and NPV were 16.7%, 99.7%, 92.9% and 90.4%.
Zöller et al. 2012 **Sweden** **Retrospective study**	820,491 individuals with a diagnosis of cancer included in a population registry between 1987 and 2008	Standardized incidence ratios (SIRs) for hospital admissions for stroke diagnosed from < 6 months to 10+ years after cancer was first detected, were calculated using observed incidence/expected among the general population without cancer. 34 different cancers were studied.	**Primary outcomes:** Ischemic and hemorrhagic stroke incidence	The SIRs (95% CI) for *ischemic* stroke by follow-up interval were: < 6 months 1.6 (1.5-1.6) 6-12 months 1.1 (1.1-1.2) 1-5 years 1.1 (1.1-1.2) 5-10 years 1.2 (1.2-1.2) 10+ years 1.1 (1.1-1.2) Overall 1.2 (1.2-1.2) The SIRs (95% CI) for *hemorrhagic* stroke by follow-up interval were: < 6 months 2.2 (2.0-2.3) 6-12 months 1.4 (1.3-1.5) 1-5 years 1.3 (1.2-1.3) 5-10 years 1.3 (1.2-1.4) 10+ years 1.2 (1.1-1.3) Overall 1.4 (1.3-1.4) SIRs for ischemic and hemorrhagic stroke with metastases were 1.5 (1.3-1.7) and 2.2 (1.8-2.7), respectively
Taccone et al. 2008	24 patients admitted to a single neurology unit for ischemic stroke	A complete work up was conducted to determine the etiology of stroke and clinical	**Primary outcome:** Stroke etiology and clinical course	59% of patients had no vascular risk factors.

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Belgium **Retrospective study**	between 1991 to 2004, who had an underlying, malignancy. The sample represented 0.4% of all strokes admitted during that time frame. Mean age was 52 years, 62.5% were women.	course. Presumed stroke causes were defined according to preestablished diagnostic criteria. A second workup was performed 6 months later in patients in whom the cause of stroke still could not be determined		After a first stroke, systemic cancer was identified as the most probable cause of the stroke in 4 patients. Stroke causes were disseminated intravascular coagulation (DIC, n=2) and nonbacterial thrombotic endocarditis (NBTE, n=2). In 20 patients, the diagnosis of cancer was only made after a second stroke. In these cases, stroke was presumed to have been caused by arteriosclerosis (n=9), patent foramen ovale with atrial septum aneurysm(n=5), antiphospholipid syndrome (n=2), systemic lupus erythematosus (n=2), and Sneddon's syndrome (n=1). Stroke was considered cryptogenic in one patient. After recurrent stroke, the results of the second workup confirmed the probable origins as atherosclerosis (n=5), embolism (n=9; NBTE n= 7, tumor embolism n=2), DIC (n=3), paraneoplastic vasculitis (n=1), hypercoagulability state (=1) and septic aneurysm (n=1). The mortality was 79% (n=19). Median length of survival was 59 days after stroke. Mean follow-up of surviving patients was 29 months
Risk of Recurrent Stroke in Persons with Cancer				
Navi et al. 2014 **USA** **Retrospective study**	263 patients with active systemic cancer who were diagnosed with an acute ischemic stroke at a single institution from 2005 through 2009. Mean age was 66 years, 51% were men. Median time from diagnosis of underlying cancer to index stroke was 9.7 months	Comprehensive medical records, including all inpatient and outpatient encounters, were reviewed to ascertain outcomes. Additionally, a model was developed to identify independent predictors of recurrent thromboembolism. Potential predictor variables included age, sex, hypertension, adenocarcinoma histology, known systemic metastases, unconventional stroke mechanism, chemotherapy within 30 days, suspected or	**Primary outcome:** Recurrent thromboembolic event defined as a composite of any recurrent ischemic stroke, TIA, MI, systemic embolism, DVT or pulmonary embolism (PE).	Stroke etiology was unknown in 51% of patients. Stroke mechanisms according to TOAST criteria comprised 22% cardioembolism, 15% large-artery atherosclerosis, 8% small-vessel occlusion, and 5% other determined causes. Median survival was 84 days. 87% of patients were followed up until death. There were 117 cases of recurrent thromboembolism, which occurred in 90 patients: 40 DVTs, 36 recurrent ischemic strokes, 17 PEs, 13 MIs, 10 cases of systemic embolism, and one TIA. The cumulative prevalences of recurrent ischemic stroke were 7%, 13% and 16% at one, 3 and 6 months.

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
		confirmed nonbacterial thrombotic endocarditis, and lung cancer.		Adenocarcinoma histology was the only independent predictor of recurrent thromboembolism (HR=1.65, 95% CI 1.02 –2.68). 65% of patients were discharged on an antithrombotic agent.

Cancer-Associated Hypercoagulation and Ischemic Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lee et al. 2017 **South Korea** **Prospective study *Optimal Anticoagulation Strategy In Stroke related to Cancer (OASIS-Cancer) study***	NA	268 patients admitted to a single institution between January 2006 and July 2015, with an acute ischemic stroke and active systemic cancer. Median age was 66 years, 59.3% were men. Stroke etiology was of unknown origin in 71.6% of patients	Routine anticoagulation studies (D-dimer, PT, aPTT, fibrinogen and platelet counts) were conducted to assess possible hypercoagulopathy. Antithrombotic treatments were initiated, as required. During hospitalization, plasma D-dimer level was serially monitored after the start of the anticoagulation treatment. The pre-treatment and post treatment plasma D-dimer levels were divided into quartiles and their independent relationship with overall and 1-year survival was examined.	**Primary outcome:** Overall and one-year mortality	Overall, median survival was 109 days. The mortality was 18.3% at 1 month, 44.4% at 3 months, 60.1% at 6 months, and 71.6% at 1 year. Baseline D-dimer levels were: Q1: <2.08 µg/mL (25.1%) Q2: 2.08–9.06 µg/mL (24.7%) Q3: 9.06–23.26 µg/mL (25.5%) Q4: >23.26 µg/mL (24.7%) When Q3 and Q4 groups were combined, the risks of overall and one-year mortality were increased significantly compared with group 1 (reference). HR=2.19, 95% CI, 1.46–3.31 and 2.70, 95% CI 1.68–4.35, respectively after adjustment for stroke mechanism, age, NIHSS score, primary cancer type, cancer histology (adenocarcinoma vs others), and atrial fibrillation. Among a subgroup of 113 patients in D-dimer groups 3 and 4 who were treated with anticoagulants, D-dimer levels were reduced (median of 8.17 µg/mL). Post-treatment D-dimer level was independently associated with poor 1-year survival (adjusted HR=1.03; 95% CI, 1.01–1.05 per 1 µg/mL increase, p= 0.015) but not with overall survival. After discharge from hospital, a D-dimer level of 3.17 µg/mL was identified as the cut-point, above which the

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					risk of death within one month was increased significantly (OR=1.07, 95% CI, 1.04–1.10 per 1 µg/mL increase, p<0.001). The authors suggested that increased coagulation could be a marker of increased cancer activity, effectiveness of antithrombotic treatment, or both.
Schwarzbach et al. 2012 **Germany** **Case-control study**		140 patients admitted to a single stroke centre from 2002-2011 following ischemic stroke, with an active and malignant cancer. Mean age was 73 years,	Clinical assessment and diagnostic workup were performed according to a standardized stroke protocol. The etiology and risk factors of stroke, types of cancer, deep vein thrombosis/pulmonary embolism, D-dimer levels, and diffusion-weighted imaging lesion patterns were compared to an age- and sex-matched control group. Patients with cancer with a conventional stroke etiology and patients with an unidentified and/or cancer-associated stroke etiology were analyzed separately.	**Primary outcomes:** D-dimer levels, DVT, PE	A definite/probable stroke etiology was identified in significantly more patients without cancer (73% vs. 52% with cancer, p<0.001). The prevalence of DVT and PE was significantly higher in patients with cancer (8% vs. 1%, p<0.01) and in patients with cancer with an unidentified and/ or cancer-associated stroke etiology compared with patients with cancer with a definite/ probable stroke etiology (15% vs. 1%, p<0.01). Mean D-dimer levels were significantly higher in patients with cancer vs. persons in the control group (7.64 vs. 5.36 µg/mL, p<0.05), in persons in the cancer group with a stroke of undetermined etiology compared with patients in the control group with a conventional etiology (6.15 vs. 1.39 µg/mL, p<0.001). Mean D-dimer levels were also significantly higher in patients with cancer with metastases compared with cancer patients without, and in persons with lung, pancreatic, and gastric cancers vs. other cancers). A significantly higher percentage of persons in the control group had hypertension and hyperlipidemia (88% vs. 77% and 44% vs. 27%, respectively), but there were no differences in smoking or diabetes (22% vs. 16% and 33% vs. 33%).

Antithrombotic Treatment

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Kawano et al. 2019 **Japan** **Retrospective study**	NA	59 patients admitted to a stroke unit between 2014 and 2017 with known or newly diagnosed active cancer. Mean age was 75.5 years, 42% were men. Median NIHSS score was 3.	The clinical outcomes of persons on long-term subcutaneous heparin following discharge from hospital were compared with those who discontinued heparin therapy	**Primary outcome:** Stroke recurrence	49 patients were diagnosed with cancer prior to stroke, 10 patients were diagnosed with cancer afterwards. 27 patients had received anticoagulation therapy before stroke (atrial fibrillation, n=11, DVT, n =11, and previous ischemic stroke n = 5). 47 patients received continuous intravenous heparin therapy, while 19 initiated subcutaneous heparin following hospital discharge. Of the 19 patients, 9 discontinued therapy, of whom 3 had a recurrent ischemic stroke. No patients who continued heparin therapy had a recurrent stroke. There was no significant difference in 1-month survival between patients with and without subcutaneous heparin therapy (100% vs. 89%, p =0 .47). The main reasons that the 40 patients were not treated with subcutaneous heparin therapy were: palliative care, multiple metastases, hemorrhagic complications, cardiorespiratory instability, and a final diagnosis of conventional stroke mechanisms. The median D-dimer levels at pretreatment and 8 days after treatment were 3.9 mg/mL and 1.9 mg/ml, respectively.
Navi et al. 2018 **USA** **Pilot RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT:☑	20 patients (40 planned) aged 18 to 85 years with active solid or hematological cancer who had sustained an ischemic stroke within the previous 4 weeks. Median age was 70 years, 75% were women. 15% had a previous stroke. Median	Patients were randomized1:1 to receive subcutaneous enoxaparin (1 mg/kg twice daily) or oral aspirin (81-325mg/d) for 6 months	**Primary outcome:** Feasibility, bleeding and thromboembolic events	6 patients randomized to receive enoxaparin crossed over to use aspirin after a median of 6 days, during follow-up (aversion to injection, n=5, cost n=2). One year after enrollment, 3 patients in the aspirin group had nonfatal gastrointestinal bleeding, 1 patient in the enoxaparin group had nonfatal pulmonary hemorrhage. One patient in the aspirin group had nonfatal MI, 1 patient in the enoxaparin group had fatal recurrent AIS.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		NIHSS score was 2. 49 patients were eligible for inclusion			
Jang et al. 2015 **South Korea** **Retrospective study**		79 patients with cancer-associated stroke, who presented within 7 days of symptom onset and were treated with either enoxaparin (1.0 mg/kg, n=29) or warfarin (target INR of 2-3, n=50) for prevention of recurrent stroke. Median age was 65 years. 53% were men.	The changes in D-dimer levels following treatment with an antithrombotic were compared between groups and independent predictors of D-dimer levels ≥10 μg/mL following treatment, identified.	**Primary outcomes:** Recurrent stroke, major bleeding events	Mean duration of follow-up was 4.9 months. The proportions of patients in each group with traditional stroke risk factors did not differ significantly (hypertension, diabetes, hyperlipemia, smokers, coronary artery disease). Median D-dimer, platelet and fibrinogen levels did not differ between groups. There was one recurrent stroke in the enoxaparin group and 8 in the warfarin group (p=0.25). The incidence of major bleeding events was similar between groups (6.9% enoxaparin v 10.0% for warfarin; p = 0.960). After a median of 8 days of treatment the mean D-dimer level decreased significantly in patients treated with enoxaparin (from 17.06 μg/mL to 3.88 μg/mL) but did not fall following treatment with warfarin (17.78 μg/mL to 17.42 μg/mL). Independent predictors of high D-dimer levels were treatment with warfarin (HR= 12.95, 95% CI 2.89–57.94), systemic metastasis (HR=18.8, 95% CI 69–207) and adenocarcinoma (HR= 2.41, 95% CI 0.43–13.44).

Abbreviations

CA: concealed allocation	CI: confidence interval	HR: hazard ratio
ITT: intention-to-treat	OR: odds ratio	ROC: Receiver Operator Curve
NNTH: number needed to harm		RR: relative risk
RRR: relative risk reduction		

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