Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: Triage and Initial Diagnostic Evaluation of Transient Ischemic Attack and Non-Disabling Stroke

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Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

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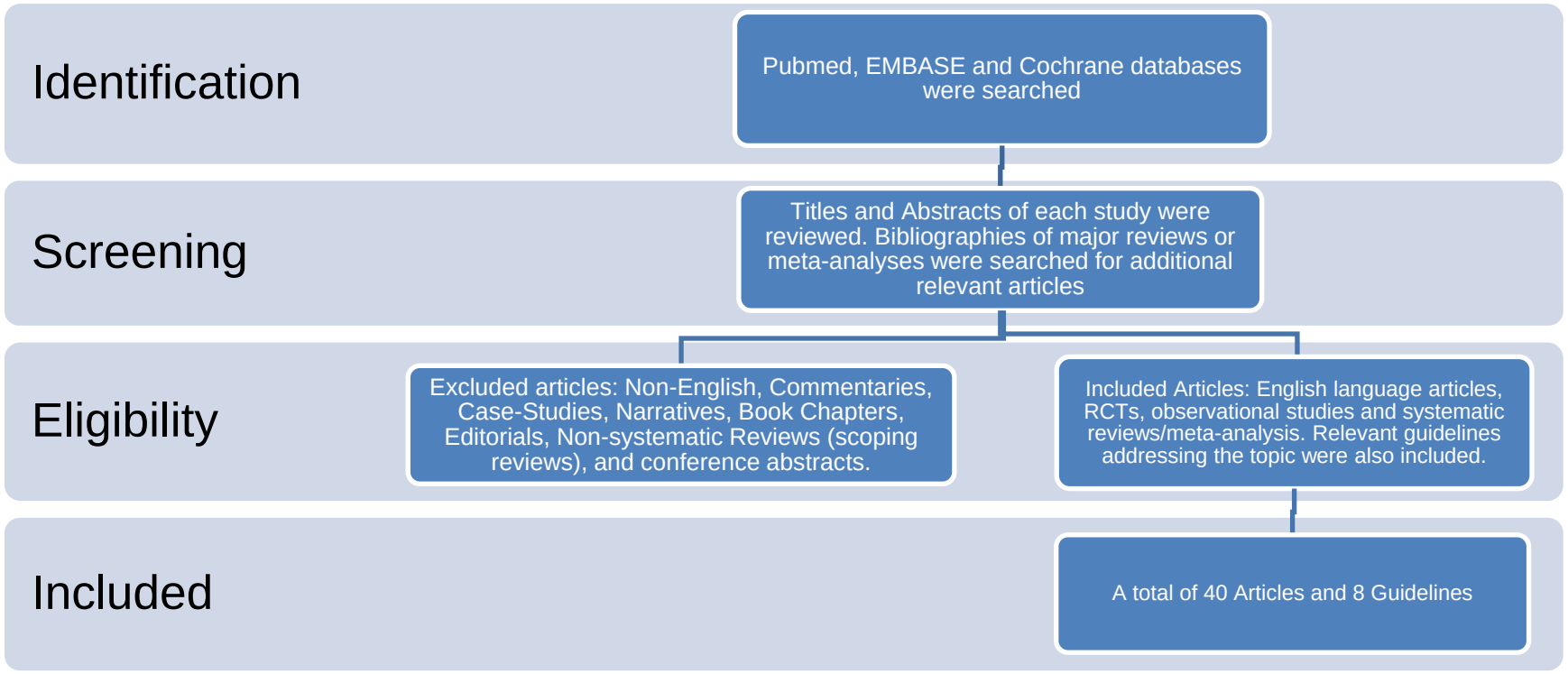
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“minor stroke” OR “TIA” OR “transient ischemic attack”) AND (“outpatient” OR “rapid access” OR “TIA clinic”). 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, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 40 articles and 8 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.** **(selected)**	**Cardiac rhythm assessment** 1. Asymptomatic atrial fibrillation and arrhythmia are very common, screening for atrial fibrillation should be routinely performed in the clinic, the routine checking of pulse should be performed on a patient >65 years of age and a 12-lead ECG should be conducted on patients with abnormalities of pulses (class I, level of evidence A). 2. The Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) or Congestive Heart Failure, Hypertension, Age ≥75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65-74, Female (CHA2DS2-VASc) score is recommended for patients with persistent atrial fibrillation when assessing for the risk of stroke, and used to guide intervention (class I, level of evidence A). 3. In patients with latent stroke who may have embolism, 24hours or long-term and remote cardiac monitoring aiming to find any paroxysmal atrial fibrillation is reasonable (class IIa, level of evidence B). 4. For patients with non-persistent atrial fibrillation or paroxysmal atrial fibrillation/atrial tachycardia (>5.5hours) within 30 days or paroxysmal atrial fibrillation for >30s, stroke prevention treatment in patient with persistent atrial fibrillation may be reasonable (class IIb, level of evidence B). 5. Whether arrhythmias other than atrial fibrillation or paroxysmal supraventricular tachycardia are associated with embolic events is unclear, and any intervention of those arrhythmias to reduce the incidence of embolism is still inadequate, symptomatic treatment can be taken into consideration (class III, level of evidence C).
Consensus statements and recommendations from the ESO Karolinska Stroke Update Conference, Stockholm 11–13 November 2018	**Q1: What is good clinical practice in work up for suspected cardio-embolic cases? Echo and monitoring in all patients?** Recommendation: 1. A good medical history, physical examination, laboratory testing, a 24-h 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE) are the mainstays of cardioembolic source detection (Grade A). 2. Screening of patent foramen ovale (PFO) with bubble test-transcranial Doppler or transoesophageal echocardiogram (TEE) is recommended in patients with embolic stroke of undetermined aetiology despite recommended diagnostic work up, who would be eligible for PFO closure (Grade A). 3. Screening of aortic arch atheroma (AAA) with CTA or TTE is recommended in embolic strokes of undetermined source (ESUS); however, TEE is still the gold standard for AAA evaluation (Grade C). 4. Detection of some minor structural abnormalities on TEE has uncertain therapeutic implications (Grade C). 5. Continuous monitoring of heart rhythm up to 30 days is reasonable in patients with embolic stroke of undetermined aetiology despite recommended diagnostic work up to increase covert atrial fibrillation (AF) detection (Grade A). However, it remains to be firmly established that the increased detection of brief episodes of AF will lead to a reduction in stroke recurrence after adequate treatment (Grade C). 6. Covert AF can be associated with increased brain natriuretic peptide (BNP) and N-terminal-pro-BNP in laboratory tests; atrial ectopic activity, subclinical atrial tachyarrhythmias in Holter–ECG; left atrium enlargement, left ventricular diastolic dysfunction, spontaneous left atrium or left atrial apex (LAA) echo-contrast and low LAA emptying velocities in TTE/TEE. These findings should encourage long-term monitoring in ESUS patients (Grade C).

Guideline	Recommendations
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2018; Mar;49(3):e46-e110**	**6.3. Cardiac Evaluation** 1. Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours. Class I; LOE B-NR. 2. The clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after AIS is uncertain. Class I; LOEIb B-R. 3. In some patients with AIS, prolonged cardiac monitoring to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain. Class IIb; LOE C-EO. 4. Routine use of echocardiography in all patients with AIS to plan subsequent secondary preventive treatment is not cost-effective and is not recommended. Class III: No Benefit; LOE B-NR. 5. In selected patients with AIS, echocardiography to provide additional information to plan subsequent secondary preventive treatment may be reasonable. Class IIb; LOE B-R.
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation.	**Early assessment and diagnosis of TIA** Strong recommendation Updated • All patients with suspected transient ischaemic attack (TIA), i.e. focal neurological symptoms due to focal ischaemia that have fully resolved, should have urgent clinical assessment. • Patients with symptoms that are present or fluctuating at time of initial assessment should be treated as having a stroke and be immediately referred for emergency department and stroke specialist assessment, investigation and reperfusion therapy where appropriate. • In pre-hospital settings, high risk indicators (e.g. crescendo TIA, current or suspected AF, current use of anticoagulants, carotid stenosis or high $ABCD^2$ score) can be used to identify patients for urgent specialist assessment. Strong recommendation New When TIA patients present to primary care, the use of TIA electronic decision support, when available, is recommended to improve diagnostic and triage decisions. Weak recommendation AGAINST New In TIA patients, use of the ABCD2 risk score in isolation to determine the urgency of investigation may delay recognition of atrial fibrillation and symptomatic carotid stenosis in some patients and should be avoided. Strong recommendation Updated All TIA patients with anterior circulation symptoms should undergo early carotid imaging with CT angiography (aortic arch to cerebral vertex), carotid Doppler ultrasound or MR angiography. Carotid imaging should preferably be done during the initial assessment but should not be delayed more than 2 days.

Guideline	Recommendations
	Weak recommendation Updated Patients with TIA should routinely undergo brain imaging to exclude stroke mimics and intracranial haemorrhage. MRI, when available, is recommended to improve diagnostic accuracy. Strong recommendation New Patients with suspected TIA should commence secondary prevention therapy urgently. Strong recommendation New • All patients with TIA should be investigated for atrial fibrillation with ECG during initial assessment and referred for possible prolonged cardiac monitoring as required. • TIA patients with atrial fibrillation should commence anticoagulation therapy early after brain imaging has excluded haemorrhage, unless contraindicated.
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	**Management of TIA – assessment and diagnosis** A- Patients with acute neurological symptoms that resolve completely within 24 hours (i.e. suspected TIA) should be given aspirin 300 mg immediately and assessed urgently within 24 hours by a specialist physician in a neurovascular clinic or an acute stroke unit. B- Patients with suspected TIA that occurred more than a week previously should be assessed by a specialist physician as soon as possible within 7 days. C- Patients with suspected TIA and their family/carers should receive information about the recognition of stroke symptoms and the action to be taken if they occur. D- Patients with suspected TIA should be assessed by a specialist physician before a decision on brain imaging is made, except when haemorrhage requires exclusion in patients taking an anticoagulant or with a bleeding disorder when unenhanced CT should be performed urgently. E- For patients with suspected TIA in whom brain imaging cannot be undertaken within 7 days of symptoms, T2* MRI imaging should be the preferred means of excluding haemorrhage. F- Patients with a confirmed diagnosis of TIA should receive clopidogrel (300 mg loading dose and 75 mg daily thereafter) and high intensity statin therapy (e.g. atorvastatin 20-80 mg daily) started immediately. **Management of TIA – treatment and vascular prevention** A-Patients with non-disabling stroke or TIA should receive treatment for secondary prevention introduced as soon as the diagnosis is confirmed, including: – discussion of individual lifestyle factors (smoking, alcohol excess, diet, exercise); – clopidogrel 300 mg loading dose followed by 75 mg daily; – high intensity statin therapy with atorvastatin 20-80 mg daily; – blood pressure-lowering therapy with a thiazide-like diuretic, long-acting calcium channel blocker or angiotensin-converting enzyme inhibitor.

Guideline	Recommendations
	B- Patients with non-disabling stroke or TIA in atrial fibrillation should be anticoagulated as soon as intracranial bleeding has been excluded and with an anticoagulant that has rapid onset, provided there are no other contraindications. C-Patients with non-disabling stroke or TIA who after specialist assessment are considered candidates for carotid intervention should have carotid imaging performed urgently within 24 hours. D- The degree of carotid artery stenosis should be reported using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. E- Patients with TIA or an acute non-disabling stroke with stable neurological symptoms who have symptomatic severe carotid stenosis of 50–99% (NASCET method) should: – be assessed and referred for carotid endarterectomy to be performed as soon as possible within 7 days of the onset of symptoms in a vascular surgical centre routinely participating in national audit; – receive optimal medical treatment: control of blood pressure, antiplatelet treatment, cholesterol reduction through diet and drugs, and lifestyle advice including smoking cessation. F- Patients with TIA or an acute non-disabling stroke who have mild or moderate carotid stenosis of less than 50% (NASCET method) should: – not undergo carotid intervention; – receive optimal medical treatment: control of blood pressure, antiplatelet treatment, cholesterol reduction through diet and drugs, and lifestyle advice including smoking cessation. G-Patients with recurrent attacks of transient neurological symptoms despite optimal medical treatment, in whom an embolic source has been excluded, should be reassessed for an alternative neurological diagnosis. H- Patients who meet the criteria for carotid intervention but who are unsuitable for open surgery (e.g. inaccessible carotid bifurcation, re-stenosis following endarterectomy, radiotherapy-associated carotid stenosis) should be considered for carotid angioplasty and stenting. I- People who have undergone carotid revascularisation should be reviewed post-operatively by a stroke physician to optimise medical aspects of vascular secondary prevention.
Verma A, Cairns JA, Mitchell LB et al. **2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation.** ***Can J Cardiol* 2014;30(10):1114-1130.** **(selected)**	1. We recommend that all patients with AF or atrial flutter (AFL), whether paroxysmal or persistent, should be stratified using a predictive index for stroke risk (for example, the “CCS algorithm” based on the CHADS2 model) (Strong Recommendation, High-quality Evidence).

Guideline	Recommendations
Easton JD, Saver JL, Albers GW, et al. **Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.** ***Stroke 2009*;40(6):2276-2293.**	Class I Recommendations 1. Patients with TIA should preferably undergo neuroimaging evaluation within 24 hours of symptom onset. MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed (Class I, Level of Evidence B). 2. Noninvasive imaging of the cervicocephalic vessels should be performed routinely as part of the evaluation of patients with suspected TIAs (Class I, Level of Evidence A). 3. Noninvasive testing of the intracranial vasculature reliably excludes the presence of intracranial stenosis (Class I, Level of Evidence A) and is reasonable to obtain when knowledge of intracranial steno-occlusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with noninvasive testing. 4. Patients with suspected TIA should be evaluated as soon as possible after an event (Class I, Level of Evidence B). Class II Recommendations 1. Initial assessment of the extracranial vasculature may involve any of the following: CUS/TCD, MRA, or CTA, depending on local availability and expertise, and characteristics of the patient (Class IIa, Level of Evidence B). 2. If only noninvasive testing is performed before endarterectomy, it is reasonable to pursue 2 concordant noninvasive findings; otherwise, catheter angiography should be considered (Class IIa, Level of Evidence B). 3. The role of plaque characteristics and detection of MESs is not yet defined (Class IIb, Level of Evidence B). 4. ECG should occur as soon as possible after TIA (Class I, Level of Evidence B). Prolonged cardiac monitoring (inpatient telemetry or Holter monitor) is useful in patients with an unclear origin after initial brain imaging and electrocardiography (Class IIa, Level of Evidence B). 5. Echocardiography (at least TTE) is reasonable in the evaluation of patients with suspected TIAs, especially 6. In patients in whom no cause has been identified by other elements of the workup (Class IIa, Level of Evidence B). TEE is useful in identifying PFO, aortic arch atherosclerosis, and valvular disease and is reasonable when identification of these conditions will alter management (Class IIa, Level of Evidence B). 7. Routine blood tests (complete blood count, chemistry panel, prothrombin time and partial thromboplastin time, and fasting lipid panel) are reasonable in the evaluation of patients with suspected TIAs (Class IIa, Level of Evidence B). 8. It is reasonable to hospitalize patients with TIA if they present within 72 hours of the event and any of the following criteria are present:

Guideline	Recommendations
	a. ABCD2 score of ≥3 (Class IIa, Level of Evidence C). b. ABCD2 score of 0 to 2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient (Class IIa, Level of Evidence C). c. ABCD2 score of 0 to 2 and other evidence that indicates the patient's event was caused by focal ischemia (Class IIa, Level of Evidence C).
Stroke Foundation of New Zealand and New Zealand Guidelines Group. Clinical Guidelines for Stroke Management 2010. Wellington: Stroke Foundation of New Zealand; 2010.	Recommendations – location of initial assessment and management • Most people at high risk of stroke following TIA should be transferred urgently to hospital to facilitate rapid specialist assessment and treatment. (European Grade B) • Most people identified at low risk may initially be managed in the community by a general practitioner and should be referred to a specialist clinic and seen within 7 days. • If the treating doctor is confident about the diagnosis, can implement recommended treatments, and has access to brain and carotid imaging within 7 days, then specialist review of people at low risk may not be necessary. Assessment of stroke risk after TIA • All people with suspected TIA should have an assessment of stroke risk using the ABCD2 tool at the initial point of health care contact whether first seen in primary or secondary care. (Australian Grade B, English/Welsh, RCP) • HIGH risk is indicated by any of the following: ○ Active TIA – All people who have symptoms at the time of first contact. (European Grade B) ○ ABCD2 score of 4 or more (English/Welsh, RCP) ○ Other high-risk factors – all people with crescendo TIAs, atrial fibrillation or who are already on anticoagulation, should be managed as high risk regardless of their ABCD2 scores. (NZ TIA) • LOW risk is indicated by any of the following: ○ ABCD2 score of 3 or less – these people are at low risk of early stroke, about one in a hundred by one week and one in thirty by 90 days. (RCP) ○ People who present late (after one week) – after their TIA are at lower risk, as two thirds of early strokes will have already occurred by this period. (RCP) Clinical Assessment and Blood Tests • In patients with TIA, early clinical evaluation, including physiological parameters and routine blood tests (Full blood count, electrolytes, glucose, lipids and creatinine, and in selected patients CRP or ESR) are recommended (European Grade A) Electrocardiography (ECG) • All TIA patients should have a 12-lead electrocardiograph (ECG). (European Grade A) • In TIA patients seen after the acute phase, 24-hour Holter ECG monitoring should be performed when arrhythmias are suspected and no other causes of TIA are found (European Grade A)

Guideline	Recommendations
	Brain Imaging • Patients classified as high risk should have an urgent MRI or CT brain ('urgent' is considered as soon as possible, but certainly within 24 hours). (European Grade A) • Patients classified as low risk should have a MRI or CT brain as soon as possible, but certainly within 7 days. (Australian Grade B) • If MRI is used, the inclusion of DWI and T2* weighted gradient echo sequences is recommended (European Level A) Carotid Imaging • All patients with TIA who are candidates for carotid intervention should have carotid imaging within one week of symptom onset (RCP), and within one working day if at high risk. (English/Welsh, NZ TIA) Cardiac imaging • Echocardiography is recommended in selected patients (European Grade B) Recommendations - for District Health Boards providing TIA Services • A TIA service should be provided by an appropriately resourced, open-access daily specialist outpatient clinic, an inpatient short-stay facility or a combination of these services. In smaller District Health Boards with insufficient population to warrant specialised TIA services this should be by general medical services, using agreed protocols. Recommendations – initial management • All people with TIA who attend emergency departments, out-of-hours medical centres or similar providers soon after TIA must be treated and must not be sent home and simply told to see their GP in due course. (English/Welsh • Clinicians should establish all people with TIA on measures for secondary prevention as soon as the diagnosis is confirmed, including discussion of individual risk factors. (RCP) This should consist of an appropriate individual combination of: o Anti-platelet agent(s) such as aspirin, aspirin plus dipyridamole or clopidogrel o Blood pressure lowering therapy o Statin o Warfarin - if atrial fibrillation or other cardiac source of emboli o Nicotine replacement therapy or other smoking cessation aid. o Treatment must be initiated at first contact. (RCP, English/Welsh)

Evidence Tables

Estimates of Risk of Stroke Recurrence & Predictors

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Estimates of Stroke Following First or Recurrent Stroke					
Flach et al. 2020 **UK** **Retrospective study**	NA	6,052 persons with a first-ever stroke that occurred between 1995-2018. 34% were < 65 years at the time of their first stroke, 42% were > 75 years. 49% were women. 72% were ischemic stroke.	Rates of recurrent stroke and cumulative incidences were stratified by 5-year period of index stroke	**Primary Outcome:** Recurrent stroke, recurrence or death **Secondary Outcomes**: Predictors of stroke	During follow-up, 650 persons had ≥1 stroke recurrence (21.4 per 1000 person-years) after a median of 3 years. Risk of recurrence at 5 years was 18% between 1995 to 1999 dropping to 12% between 2000 and 2004 and remaining at around 10% (9%–13%) for first strokes since 2005. During follow-up, 4035 persons had a stroke recurrence or died (133 per 1000 person-years) after a median of 3 years. Over the whole study period, the frequency of stroke recurrence was 2.2% at 3 months, 5.4% at 1 year, 12.6% at 5 years, and 17.9% at 10 years. Over the whole study period, the frequency of stroke recurrence or death was 24.3% at 3 months, 53.3% at 1 year, 67.7% at 5 years. Age ≥65 years, hypertension, atrial fibrillation and smoking were independent predictors of recurrent stroke. After adjustment for age, severity, and prestroke risk factors, there were no post stroke treatments associated with reduced recurrence; however, treatment on a stroke unit, being seen by a stroke specialist, cholesterol-lowering treatment, antiplatelets, anti-hypertensives and/or anticoagulants, initiated within 3 months of first stroke significantly reduced the risk of a recurrent stroke.
Bergström et al. 2017 **Sweden** **Retrospective**	NA	196,765 persons with ischemic stroke from 1998-2009 included in the Riksstroke Registry. Mean age was 76 years, 50%	The risk of recurrent stroke within the first year after the initial event was compared with risk of ischemic stroke in the general population (matched for age, sex and county, and also included	**Primary Outcome:** Recurrent stroke **Secondary Outcomes**: Predictors of stroke	22.1% of the patients died during the year, of which 19.4% died without experiencing a recurrent ischemic stroke and 8.3% died during hospitalization, compared with 5.9% of persons in the reference group.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
study		were men. 14.6% of persons had sustained a previous stroke.	persons who had a previous history of stroke, n=190,157, mean age was 82.3 years)		The cumulative incidence of recurrent ischemic stroke within the first year was 13.1% in the stroke group compared with 0.5% in the reference group. Predictors of recurrent ischemic stroke included: age >75 years, prior ischemic stroke, prior MI, diabetes, atrial fibrillation without warfarin treatment at discharge, and treatment with diuretics or β-blockers at discharge
Callaly et al. 2016 **UK** **Prospective study**	NA	567 patients ≥18 years who were participants in the North Dublin Population Stroke Study. Mean age was 71 years, 49% were men. 484 patients (85.4%) had suffered a first-ever stroke, while 83 (14.6%) were recurrent stroke, of which 80.1% were ischemic stroke, 10.7% were ICH, 5.1% were SAH and 4.1% were unconfirmed.	Participants, residing in the community or in institutions, who had suffered a new (first-ever or recurrent) stroke during a one-year period (2006) were identified.	**Primary outcome:** Recurrent stroke up to 2 years post event	At 2 years, data were available for 91.4% of participants. Recurrent stroke occurred in 46 patients. The cumulative rate of recurrence was: 5.4% (95% CI 3.7%-7.9%) at 90 days 8.5% (95% CI 6.2%-11.5%) at 1 year 10.8% (95% CI 8.2-14.2%) at 2 years. Recurrence rates were highest for patients with ischemic stroke (11.5%, 95% CI 8.6%-15.3%) at 2 years. 2-year case fatality was 38.6%.
Mohan et al. 2011 **UK** **Systematic review & meta-analysis**	NA	13 studies (n=9,115) from hospital and community-based stroke registries reporting on stroke recurrence following first-ever stroke.	Cumulative risk of reported stroke recurrence was pooled across studies.	**Primary outcome:** Stroke recurrence up to 10 years	The pooled cumulative risk of stroke recurrence after initial stroke was: 3.1% (95% CI, 1.7%- 4.4%) at 30 days (n=8) 11.1% (95% CI, 9.0% -13.3%) at 1 year (n=12) 26.4% (95% CI, 20.1%-32.8%) at 5 years (n=7) 39.2% (95% CI, 27.2%-51.2%) at 10 years (n=4)
Hankey et al. 1998	NA	351 patients with first-ever stroke who had survived for >2 days	Patients were assessed at baseline, 4 months, 12 months and 5 years. Outcome	**Primary outcome:** Stroke recurrence at 5 years	Follow-up data were available at 5 years for 343 patients (98%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Australia **Prospective study**		following hospitalization (1989-1990) participating in the Perth Community Stroke Study. 73% of strokes were ischemic, 10.5% were ICH, 3.8% were SAH and 12.7% of strokes were of undetermined etiology. Mean age was 73 years, 53% were men.	ascertainment was through administrative databases.		During follow-up, 199 patients (58%) had died, 52 (15%) suffered a first recurrent stroke, of which 12 (28%) were fatal within 28 days. Of the recurrent strokes, 37 (71%) were ischemic, 4 (7.7%) were ICH and 11 (21.1%) were of undetermined etiology. 89% of recurrent ischemic strokes occurred in patients with an index event that was ischemic. The 5-year cumulative risk of recurrent stroke was 22.4% (95% CI16.8%-28.1%), with the highest risk (8.8%) during the first 6 months.
Estimates of Stroke Following TIA or Minor Stroke					
Lioutas et al. 2021 **USA** **Prospective study**	NA	14,059 participants from the Framingham Heart Study recruited from 1948 through 2017 and included those from the original cohort, the offspring cohort and the third-generation cohort.	The risk of incident TIA and the risk of stroke after TIA were estimated during 66 years of follow-up (366,209 person-years). A nested matched longitudinal cohort study design was used to estimate the risk of subsequent stroke after the first TIA.	**Primary outcome:** TIA in the incidence cohort and stroke after TIA	435 participants had a first TIA (52.6% women; mean age was 72 years). Crude rate of TIA was 1.19/1,000 person-years. The rate increased with age. Over a median of 8.86 years, 130 participants (29.8%) experienced a stroke, of which 120 were ischemic. Timing of stroke was: Within 7 days 28 (21.5%) Within 30 days 40 (30.8%) Within 90 days 51 (39.2%) >one year 63 (48.5%). Median time to stroke was 1.64 years. Hypertension was the biggest independent predictor of subsequent stroke (OR=5.83, 95% CI, 1.35-25.11). There were 165 strokes among 2,175matched control participants without TIA. The age and sex-adjusted risk of stroke was significantly higher among those with previous TIA (HR=4.81, 95% CI, 3.82-6.06). The increased risk remained after adjusting for common stroke risk factors. The risk of stroke following TIA declined

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					significantly over the study period (original cohort vs. offspring cohort vs. third-generation cohort) for all time periods assessed (within 90 days and one, five and 10 years).
Shahjouei et al. 2020 **USA** **Systematic review & meta-analysis**	Risk of bias was assessed as low in 56 studies and medium in 10 studies	68 studies published from 1971 to 2019, including 223,866 patients with a confirmed TIA who developed an ischemic stroke. Mean age ranged from 42 to 79 years. 42% were men.	The pooled event rate of subsequent ischemic stroke within 2, 7, 30, and 90 days of a TIA, was estimated. The incidences among the population with TIA recruited before 1999 (group A), from 1999 to 2007 (group B), and after 2007 (group C), were compared.	**Primary outcome:** Ischemic stroke at 2, 7, 30, and 90 days	The overall incidences of ischemic stroke were: 2.4% (95% CI, 1.8%-3.2%) within 2 days 3.8% (95% CI, 2.5%-5.4%) within 7 days 4.1% (95% CI, 2.4%-6.3%) within 30 days 4.7% (95% CI, 3.3%-6.4%) within 90 days The group incidences were: within 2 days-3.4% for A, 2.1% for B, and 2.1% for C, within 7 days-5.5% for A, 2.9% for B, and 3.2% for C within 30 days-6.3% for A, 2.9% for B, and 3.4% for C within 90 days-7.4% for A, 3.9% for B, and 3.9% for C
Amarenco et al. 2016, 2018 **France** **Prospective study *TIAregistry.org***	NA	4,583 patients ≥18 years recruited from 61 sites in 21 countries from 1997-2003 with TIA or minor stroke that occurred within the previous 7 days and who were evaluated by a stroke specialist at a high-volume stroke facility. Mean age was 66.1 years, 60.2% were men. 17.6% had previous stroke or TIA. 5-year follow-up: 42 sites had follow-up data on ≥ 50% of their patients at 5 years (n=3847 patients), representing 80.3% of the initial cohort	Data pertaining to the qualifying event were collected at baseline. Thereafter, data related to the occurrence of clinical events, vascular risk factors and medical treatments were collected prospectively at 1,3, and 12 months after stroke and annually for up to 5 years.	**Primary outcome:** Composite of death from cardiovascular causes, nonfatal stroke and nonfatal acute coronary syndrome (MI +/- ST-segment elevation or unstable angina followed by urgent catheterization). **Secondary outcomes** Individual components of the primary outcome, TIA recurrence, death from any cause, and bleeding.	Median duration of follow-up was 27.2 months. 87.6% of patients sought treatment within 24 hours of symptom onset. 5.0% of the patients received a new diagnosis of atrial fibrillation, of which 66.8% (n=133) received anticoagulant therapy before discharge. A carotid stenosis of ≥50% was found in 15.5% of patients, of which 26.9% (n=166) underwent carotid revascularization before discharge. The primary outcome occurred 274 times. The estimate for the event rate was 6.2%, 95% CI 5.5-7.0%. Estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5%, 2.1%, 2.8%, 3.7%, and 5.1%, respectively. Independent predictors of stroke recurrence were: Cerebral infarctions on brain imaging vs. no infarction: HR=2.16; 95% CI, 1.46-3.21, p<0.001 ABCD^2 score of 6-7 vs. 0-3: HR=2.20, 95% CI

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					1.41-3.42, p<0.001) and large-artery atherosclerosis vs. undetermined cause: HR=2.01, 95% CI 1.29- 3.13; p= 0.002). **5-year outcomes** Median duration of follow-up was 5.1 years. The composite primary outcome occurred in 469 patients (cumulative rate, 12.9%; 95% CI 11.8% to 14.1%). Of these events, 235 (50.1%) occurred during the 2nd through 5th years. At 5 years, strokes had occurred in 345 patients (44 fatal strokes) (cumulative rate, 9.5%, 95% CI, 8.5% to 10.5%). Of these events, 149 (43.2%) occurred during the 2nd through 5th years. Death from any cause occurred in 373 patients (10.6%), and any recurrent stroke or TIA in 621 (16.8%). Independent predictors of subsequent stroke included ipsilateral large-artery atherosclerosis, cardioembolism, and a baseline ABCD^2 score ≥ 4.

Investigations/Monitoring for TIA and Non-Disabling Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Detection of Atrial Fibrillation					
Huang et al. 2020 **Taiwan** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☒	826 patients admitted to one of 6 hospitals with acute ischemic stroke, ≥ 65 years, with neither AF history nor any presence of AF on	Patients were randomized 1:1 to receive serial 12-lead ECGs once daily, within 2 days of stroke onset, for five days vs. 24-h Holter monitoring (during their hospitalization).	**Primary outcome:** Newly detected AF	8.4% of patients who received serial ECGs experienced a new episode of AF compared with 6.9% episodes detected using Holter monitoring (OR=1.17, 95% CI 0.69–2.01). The results were similar in the per protocol analysis.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
	ITT: ☑	baseline electrocardiogram at admission. Median age was 76 years, 60% were men. Median baseline NIHSS was 4.			Independent predictors of increased odds of new-onset AF were age >80 years and a history of heart failure, while lacunar infarcts were associated with lower odds.
Tsivgoulis et al. 2019 **Greece** **Systematic review & meta-analysis**	All studies had at least one methodological component with unclear and/or high risk of bias.	4 studies (2 RCTs, [Crystal AF and FIND-AF] and 2 non RCTs) that included a total of 1,102 persons with history of cryptogenic ischemic stroke or TIA. Mean age was 68 years, 41% were women.	The outcomes of persons who received prolonged cardiac monitoring (PCM) were compared with patients who received conventional (non-PCM) cardiac monitoring. 3 trials used implantable cardiac monitoring and one used ambulatory ECG monitoring to provide PCM.	**Primary outcome:** Recurrent stroke and recurrent stroke/TIA during follow-up **Secondary outcomes:** AF detection and anticoagulation initiation	Duration of follow-up ranged from 6 to 30 months. PCM was associated with significantly lower risks of recurrent stroke and recurrent stroke or TIA during follow-up (RR=0.45; 95% CI, 0.21–0.97 and RR=0.49; 95% CI, 0.30–0.81, respectively) AF was detected significantly more frequently in persons who received PCM (RR=2.46; 95% CI, 1.61–3.76). Anticoagulation was initiated more frequently in persons who received PCM (RR=2.07; 95% CI, 1.36–3.17). Results were similar between RCTs and non-RCTs.
Wachter et al. 2017 **Germany** **RCT** ***Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring (FIND-AF)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	398 patients, >60 years admitted with acute ischemic stroke within 7 days of symptom onset, in sinus rhythm at admission and without history of AF, and a premorbid mRS score ≤2. Mean age was 73 years, 40.2% were female.	Patients were randomized to receive prolonged Holter ECG monitoring (10-days) and repeated at 3 and 6 months (n=200) vs. standard care (minimum of 24 hours of cardiac monitoring, n=198)	**Primary outcome:** Detection of newly diagnosed AF/flutter (≥30 sec) within 6 months and before stroke recurrence **Secondary outcomes:** Detection of newly diagnosed AF/flutter within 12 months, recurrent stroke or systemic embolism, and death	At 6 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5%; absolute difference 9%, 95% CI 3.5-14.6, p=0.002; NNS=11). At 12 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 6.1%; absolute difference 7.4%, 95% CI 1.6-13.2; p=0.02; NNS=13). There were no differences between groups in stroke recurrence (2.5 vs. 4.5%, p=0.28) or death (3.0 vs. 4.5%, p=0.45). There were no interactions based on subgroup analyses based on age, sex, baseline NIHSS, CHADS-2 score, symptoms at admission and imaging (lacunar vs. non-lacunar)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Edwards et al. 2016 **Canada** **Retrospective study**	NA	17,398 consecutive patients presenting with first-ever stroke or TIA with motor or speech deficits to the ED of 12 designated stroke centres from 2003-2013 without a known history of AF in sinus rhythm. Mean age was 69 years, 54% were men, 75% of patients presented with a stroke, 25%, a TIA. 79% of patients hospitalized had a mRS score of 0-3.	The use of ambulatory ECG (Holter monitoring and 14-day loop recorders) to detect episodes of AF, was assessed.	**Primary outcome:** The number of patients who received a minimum of 24-hour Holter monitoring within 30 days of index event **Secondary outcomes:** The number of patients receiving single or multiple Holter studies for a maximum cumulative ECG monitoring duration of 24, 48, or >60 hours within 7, 30, or 90 days after index event, the number of patients receiving prolonged ECG monitoring with an event loop recorder within 7, 30, or 90 days after index event	5,318 patients (30.6%, 95% CI 29.8-31.4%) received at least 24-hour Holter monitoring within 30 days of the index event. 2,253 patients (12.9%, 95% CI 12.4-13.5%) underwent 48-hr Holter monitoring within 90 days of the index event. 25 patients (0.1%, 95% CI 0.0-0.3%) underwent >60-hr Holter monitoring within 90 days of the index event. 139 patients (0.8%, 95% CI 0.0-0.0%) underwent monitoring with event loop recording within 90 days of the index event. Factors associated with lower odds of undergoing Holter monitoring within 30 days of index event were: age <75 years, rural residence, moderately disabling stroke (mRS 4-5) and TIA as index event Factors associated with increased odds of undergoing Holter monitoring within 30 days of index event were: pre-morbid independence and admission to a registry hospital
Sposato et al. 2015 **Canada** **Systematic review & meta-analysis**	NA	50 studies, estimating the proportion of patients diagnosed with atrial fibrillation following stroke or TIA, using 8 diagnostic methods: admission ECG, serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, Holter monitoring, mobile cardiac outpatient telemetry, external loop recording,	Sub groups of studies were formed based on 4 phases of cardiac monitoring: emergency room, in-hospital, first ambulatory period and second ambulatory period.	**Primary outcome:** Proportion of patients diagnosed with post-stroke AF	The results from the 13 studies that initiated investigations during the first ambulatory period (phase 3), which used ambulatory Holter monitoring done for 1-7 days, reported an estimated 10.7% (95% CI 5.6-17.2%) of patients were diagnosed with AF. The results from the studies that initiated investigations during the second ambulatory period (phase 4), using mobile cardiac outpatient telemetry (n=5), external loop recording (n=7) or implantable loop recording devices (n=7), reported an estimated 16.9% (95% CI 13.0% - 21.2%) of patients were diagnosed with AF.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		and implantable loop recording. Mean age of included patients was 67 years, 57% were men.			
Gladstone et al. 2014 **Canada** **RCT** ***Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	572 patients ≥55 years without known atrial fibrillation (AF), who had sustained a cryptogenic ischemic stroke or TIA of undetermined cause following standardized testing (including 24-hr ECG), within the previous 6 months. Mean age: 73 yrs. 56% men, 63% of patients sustained an ischemic stroke, 37%, a TIA.	Patients were randomized (1:1) to undergo ambulatory ECG monitoring with a 30-day event-triggered loop recorder or one additional round of 24-hour Holter monitoring (control group).	**Primary outcome:** Occurrences of AF or atrial flutter ≥30 seconds in duration, detected during 90-day follow-up. **Secondary outcomes:** Anticoagulant use at 90 days, AF ≥30 seconds and ≥2.5 minutes in duration, and any AF	Patients were randomized an average of 75 days following qualifying event. The primary outcome was detected more frequently in patients in the enhanced monitoring group (16.1% vs. 3.2%, absolute difference =12.9%, 95% CI 8.0-17.6%, p<0.001, number need to screen [NNS] 8). AF ≥30 seconds was detected more frequently in patients in the enhanced monitoring group (15.5% vs. 2.5%, absolute difference =13.0%, 95% CI 8.4-17.6%, p<0.001, NNS=8). AF ≥2.5 minutes was detected more frequently in patients in the enhanced monitoring group (9.9% vs. 2.5%, absolute difference =7.4%, 95% CI 3.4-11.3%, p<0.001, NNS=14). A higher number of patients in the enhanced monitoring group were treated with anticoagulants (18.6% vs. 11.1%) and switched from antiplatelet to anticoagulant therapy (13.6% vs. 4.7%).
Sanna et al. 2014 **International** **RCT** ***Cryptogenic Stroke and Underlying AF (CRYSTAL-AF)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	441 patients >40 years with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring associated with a cryptogenic symptomatic TIA or cryptogenic ischemic stroke, sustained within 90 days of the event.	Patients were randomized (1:1) to received ECG monitoring on a schedule at the discretion of their treating physician or long-term monitoring with an insertable cardiac monitor (ICM) using the Reveal® XT device, inserted within 10 days of the event.	**Primary outcome:** Time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months **Secondary outcome:** Time to first detection of atrial fibrillation at 12 months of follow-up, recurrent stroke or TIA, and the change in use of	The mean time between the index event and randomization was 38 days. The majority of patients completed 18 months of follow-up. Maximum duration of follow-up was 36 months (n=48). At 6 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (8.9% vs. 1.4%, HR=6.4, 95% CI 1.9- 21.7, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		Mean age: 61 yrs. 63% men		oral anticoagulant drugs For patients for patients in both groups were scheduled at 1, 6, and 12 months.	At 12 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (12.4% vs. 2.0%, HR=7.3, 95% CI 2.6- 20.8, p<0.001). Most patients completed 18 months of follow-up. Maximum duration of follow-up was 36 months (n=48). There were no significant interactions observed in subgroup analysis (age, sex, race or ethnic group, type of index event, presence or absence of patent foramen ovale, and $CHADS_2$. 2.4% of devices were removed due to infection at the insertion site or pocket erosion
Higgins et al. 2013 **UK** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	100 patients admitted within 7 days of ischemic stroke, from 2 centres with no history of AF, presenting in sinus rhythm. Mean age was 65.8 years, 56% were men	Patients were randomized to receive standard practice (SP) investigations or SP + additional investigations, which included 7 days of additional non-invasive cardiac event monitoring. Patients in the SP group underwent cardiac investigations for the detection of AF, at the discretion of the local physician.	**Primary outcome:** Detection of paroxysmal atrial fibrillation (PAF) at 14 and 90 days	The detection of sustained PAF at 14 days was significantly higher in the group that received additional investigations (44% vs. 4%, p<0.001). The detection of any PAF at 14 days was significantly higher in the group that received additional investigations (18% vs. 2%, p<0.05) The detection of sustained PAF at 90 days was not significantly higher in the group that received additional investigations (22% vs. 8%, p<0.09). The detection of any PAF at 90 days was higher in the group that received additional investigations (48% vs. 10%, p<0.001). Significantly more patients that received additional monitoring were started on anticoagulants for AF associated thromboembolic prophylaxis at day 14 (16% vs. 0%, p<0.01) and at day 90 (22% vs. 6%, p<0.05).
Flint et al. 2012 **Prospective study**	NA	239 patients referred for cardiac monitoring, a median of 29 days following ischemic	Cardiac monitoring involved the use of a 30-day electrocardiographic loop recorder (CardioPAL SAVI) that	**Primary outcome:** Number of patients with paroxysmal atrial fibrillation (PAF) detection.	**PAF detection:** 26 patients (11.0%; 95% CI: 7.6% to 15.7%) experienced previously undiagnosed PAF during the 30-day monitoring. 45% of patients had PAF detection within the first

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
US		stroke of unknown cause stroke. Mean age: 64.6 years Exclusion criteria: lacunar/small vessel syndrome, and/or stenosis of greater than 70%.	was mailed to patients for self-setup with guidance over the phone.	**Secondary outcome**: Number of patients with a PAF event longer than 30 seconds.	10 days, 31% from day 11 to 20 and 24% from Day 21 to 30. **Length of PAF:** 16 patients (6.7%) experienced PAF episodes of greater than 30 seconds in duration.
Douen et al. 2008 **Canada** **Prospective study**	NA	144 patients were included (143 patients had serial ECGs completed; 126 patients had Holter monitoring).	Rates of AF detection were compared between the use of serial ECGs (up to 72 hours after admission) and a Holter monitor in an inpatient stroke unit setting.	**Primary outcome**: Detection of AF	No statistically significant difference in detection of AF was found between Holter and serial ECG monitoring. (P=0.25). **Detection of AF**: AF was identified in 15 new patients using serial ECG compared to baseline; a statistically significantly greater rate of diagnosis compared to baseline ECG findings (P=0.001). AF was identified in 9 new patients from baseline assessment using a Holter monitor. Together, serial ECG's and Holter monitoring identified 18 new cases of AF after baseline ECG assessment. Most these cases were identified within 72 hours (83%).
Transesophageal echocardiography (TEE)					
Katsanos et al. 2015 **Greece** **Systematic review & meta-analysis**	NA	35 studies including 5,772 participants with cryptogenic ischemic stroke or TIA who had undergone TEE investigations. Mean age was 54 years, 57% were men.	Cardiac conditions known to be associated with cerebral ischemia were identified using ASCOD criteria, including atherosclerosis, small-vessel disease, cardiac pathology, other causes and dissection	**Primary outcome:** Prevalence of cardioembolic causes	The most common TEE findings were: Atheromatosis in the ascending aorta/aortic arch (51.2%) PFO (43.2%) Complex aortic plaques (14%) Large PFO (19.5%) Atrial septal aneurysm (12.3%) ASA +PFO (14.5%) Conditions associated with cryptogenic ischemia were low including left atrial thrombus (3.0%), spontaneous echo contrast (3.8%) and intracardiac tumors (0.2%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
de Bruijn et al. 2006 **Netherlands** **Prospective study**	NA	231 patients with recent stroke (all types) or TIA of unknown cause. Age: 192 patients were greater than 45 years; 39 patients were less than or equal to 45 years. Exclusion criteria: patients with contraindication to anticoagulation therapy.	All patients had a transesophageal echocardiography (TEE) followed by a transthoracic echocardiography (TTE). Identification of major and minor cardiac sources of embolism were compared between the two diagnostic tools. Subgroup analysis: Analysis also performed separately for patients older than 45 years and younger than 45 years of age.	**Outcomes**: Major (left atrium (LA) cavity thrombus, LA appendage thrombus, left ventrical (LV) thrombus, aortic thrombus, dilated cardiomyopathy, mitral valve stenosis) and minor (mitral valve prolapse, mitral annular calcification, calcified aortic stenosis, patent foramen ovale, spontaneous echo contrast, atrial septal aneurysm, LV aneurysm, aortic aneurysm, false tendon, aortic plaques, other) risk factors for cardiac embolism.	A potential cardiac source of embolism was detected in 55% of patients by TEE vs. 39% by TEE. The detection of possible cardiac sources of embolism was significantly greater using TEE in patients ≤45 years (10/39; P=0.002) and >45 years (80/192; P<0.004).
Metabolic Monitoring					
Kisialiou et al. 2012 **Italy** **Prospective study**	N/A	105 patients admitted with recent ischemic stroke (<24 hours) Mean age: 63.3 years	Patients were assessed for biomarkers on admission: glucose, albumin, TG, TC, LDL, HDL, INR, PTT, platelets, fibrinogen, and erythrocyte sedimentation rate (ESR).	**Outcomes**: Size of ischemic lesion (D1 - <1.5cm; D2 – 1.5 to 3cm; D3 - >3cm; D4 – non confluent dimensions), location (anterior or posterior), stroke severity (NIHSS). Assessment time points: at admission (imaging), 7 days (NIHSS). Analysis were adjusted for age and sex.	**Size of ischemic lesion:** **D1**: Greater odds of having a D1 lesion with a blood Albumin level of 3.4-3.8 compared to less than 2.9 (OR 5.250; 95% CI 1.351 to 20.396) and a triglyceride level of 111-162 compared to less than 78 (OR 9.000; 95% CI 2.487 to 32.567). **D2**: Lower odds of having a D2 lesion with blood albumin levels of 2.9-3.4, 3.4-3.8 and greater than 3.8 compared to a blood albumin level of less than 2.9 (OR 0.227; 0.164; 0.205). **D3**: Greater odds of having a D3 lesion when an ESR of greater than 30 compared to an ESR of less than 10 (OR 5.250), and a fibrinogen level of 368-462 compared to less than 303 (OR 5.500). Lower odds of having a D3 lesion with a platelet value of 256-323 compared to a platelet value of less than 189 (OR 0.059). **D4**: there was no statistically significant association between any of the blood biomarkers and a D4 lesion.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					Location of stroke lesion: No significant association with blood markers. **Stroke Severity**: high values for INR and PTT were associated with worse outcomes on the NIHSS (≥14; ≥7) (P=0.01; P=0.001). Better outcomes on the NIHSS were found when blood albumin levels were higher (P=0.006).
Ferrari et al. 2010 **Austria** **Prospective cohort study (Austrian Stroke Unit registry)**	N/A	8,291 patients with TIA or minor stroke with NIHSS score <4. Median age: 70 years (no deterioration group); 73 years (deterioration group).	Potential predictors of deterioration during stroke unit stay were examined. Predictors included: age, sex, delay in seeking medical attention, risk factors (hypertension, diabetes, hyperlipidemia, smoking status), treatment regime (heparin, platelet inhibitors), complications (acute infection, cardiac decompensation, seizure, hemorrhaging, pulmonary embolism, DVT), and stroke etiology.	**Primary outcome**: Patient deterioration (≥2-point increase in NIHSS score). **Other outcome**: Patient deterioration (≥4-point increase in NIHSS score). Assessment time points: admission to stroke unit, discharge from stroke unit (with 3-month follow-up phone call when necessary).	**Predictors of patient deterioration (≥2-point increase in NIHSS score):** Hypertension: OR=1.5, 95% CI 1.1-2.1; p=0.005). DM: OR= 1.5, 95% CI 1.2 to 2.0; p<0.001). Cardioembolic source: OR= 1.5, 95% CI 1.1-2.2; p=0.014 Macroangiopathy: OR= 2.0, 95% CI 1.4- 2.7; p<0.001) Other known causes: OR=2.4, 95% CI 3.5-7.3 Acute infection: OR=5.1, 95% CI 3.5- 7.3; p<0.001). Cardiac decompensation: OR=4.4, 95% CI 2.3-8.4 **Predictors of patient deterioration (≥4-point increase in NIHSS score):** The same predictors were identified as above, except for cardioembolism, which was not significant.
Langhorne et al. 2000 **UK** **Case-control study**	NA	56 patients with confirmed stroke, onset <24 hours were included assessed and matched per abnormal or normal findings on physiological variables.	Patients with at least one abnormal physiological variable (n=28) were compared with those with normal physiological variables (n=28) obtained during the first 3 days of admission. Patients were matched based on age, initial stroke severity and pre-morbid functioning. Physiological variables measured included: osmolarity, temperature, blood glucose, oxygen saturation.	**Outcomes**: Scandinavian Stroke Scale (SSS) score, change in SSS, neurologic improvement (>3 increase on the SSS), Barthel Index (BI), independence (mRS 0-2), discharge destination. Assessment time point: within 3 days, 7 days for mRS.	Patients with normal physiological variables had a significantly higher median SSS score (54 vs. 45, p=0.04) at day 3. From day 0 to day 3, patients with normal physiological variables had a significantly greater improvement in median SSS score (+6 vs. +2, p=0.02). The number of patients with >3-point improvement in SSS scores at day 3 was significantly higher in the normal physiological group (22 vs. 9, p=0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					The median BI score at day 3 was significantly higher in the normal physiological group (17 vs. 14, p=0.03). At day 7, a significantly greater number of patients in the normal physiological group was independent (17 vs. 10, p=0.03).

Models of Care for Outpatient Management of TIA and Non-Disabling Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Paul et al. 2013 **UK** **Prospective Study**	NA	411 patients with first-ever minor stroke (NIHSS score ≤3 at assessment) who accessed either the stroke clinic (n=250) or acute hospital (n=161) were included. Mean age: Stroke clinic – 72.7 years, Acute hospital – 74.8 years.	Based on data from the Oxford vascular (OXVASC) study. The risk of recurrent stroke was compared between care locations. Regression analysis was used to determine if care location was a significant predictor of care costs at 30 days.	**Primary Outcome:** Risk of recurrent stroke and risk of hospitalization. **Secondary Outcomes**: Length of stay, resource costs. Assessment time points: 1 month, 6 months, 1 year and 5-year follow-up.	Risk of recurrent stroke: There were no significant differences in rates of recurrent stroke between patients seen in hospital compared to the clinic (p=0.61). Risk of hospitalization: There were no significant differences in risk of hospitalization between patients seen in hospital compared to the clinic (p=0.83). Costs of care (based on length of stay) were significantly lower for patients seen in the clinic compared to patients assessed in acute hospital.
Martinez-Martinez et al. 2013 **Spain** **Prospective Study**	NA	282 patients with low-moderate risk TIA (ABCD2 score ≤5) were managed either in-hospital (n=86) or in a TIA clinic (n=125). Mean age: 67.91 years – in-hospital, 65.73 years – TIA clinic.	In hospital evaluation and management included brain imaging, EKG, chest x-ray, echocardiography etc. and subsequent admission to the stroke unit (if TIA suspected) or neurology ward. Patients receiving evaluation and management at the TIA clinic, received a referral from the hospital for next day assessment. A stroke neurologist reassessed patients, including imaging, EKG, echocardiography, etc. Patients	**Primary Outcome:** Risk of recurrent stroke at 7 days and 90 days. **Secondary Outcome:** Cost of hospital stay	There were no significant differences in the 90-day risk of stroke or TIA recurrence between the in-hospital group and the in-clinic group (3.5% vs. 2.4%, p=0.69, 1.2% vs. 2.4%, p=0.65). The percentages of patients in both groups who received investigations (MRI, 24-hr EKG monitoring), procedures (angioplasty, endarterectomy) and medications (antiplatelets, statins, anticoagulants, antihypertensive agents) were similar. A significantly higher percentage of patients in the in-hospital group received echocardiography (70.6% vs. 52.8, p=0.01)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			were admitted to hospital if there were any abnormal findings.		The cost of in-hospital management of TIA was close to 5 times higher than the TIA clinic costs, excluding the costs of diagnostic and laboratory tests.
Luengo-Fernandez et al. 2009 **UK** **Prospective study**	N/A	310 patients with TIA or non-disabling stroke who accessed the EXPRESS clinic during phase I; 281 in phase II. Mean Age: 67% of patients in both cohorts were <80 years old. .	Two prospective cohorts of patients with suspected TIA who were referred (by family doctors) to the EXPRESS TIA clinic during either Phase I or Phase II were included. Phase I of EXPRESS was a weekday only, appointment-based TIA clinic. Phase II of EXPRESS was implemented 30 months later with no appointments necessary – assessment was immediate.	**Primary Outcome:** Risk of stroke at 90 days. **Secondary Outcomes**: Hospital admissions, length of stay, hospital costs, patient disability, death.	There was a statistically significant reduction in the number of strokes at 90 days during Phase 2 vs. Phase 1 (8% vs. 2%, p=0.001) There were no significant differences in the number of hospital admissions between the two groups (p=0.11). Length of stay in hospital and hospital costs were significantly lower in the Phase 2 group compared to the Phase 1 group (p=0.02, p=0.03). The odds of overall disability or death were significantly lower in the Phase 2 group (OR= 0.58, 95% CI 0.34–0.98, p=0.04).
Wu et al. 2009 **Canada** **Case-Control Study**	N/A	189 patients who attended the rapid evaluation unit with TIA, admitted within 24 hours of symptom onset, between March 2002-April 2003 (intervention group) and 392 patients with a discharge diagnosis of TIA who were admitted to the Emergency Room in 2000 (control group) were included. Mean age: Intervention group – 67.5 years, control group – 71.0 years.	Logistic regression analysis was used to determine if being part of the intervention or control group predicted the odds of having a stroke within 90 days.	**Primary outcome**: Occurrence of stroke within 90 days of a TIA.	A higher number of patients in the control group had a recurrent stroke (9.7% vs. 4.7%, p=0.05). Rapid evaluation treatment was associated with significantly reduced odds of stroke recurrence (OR= 0.43, p=0.029). Patients in the intervention group used significantly more resources within 30 days of admission (e.g., ECG, MRI, Echocardiogram, new statin drug, etc.) (p<0.05). The cost of managing patients was also significantly higher for the intervention group CAN$8360 vs. CAN$4820, p<0.001), although the analyses did not control for differences in patient baseline characteristics between the groups.
Rothwell et al.	N/A	591 patients were	The EXPRESS clinic offered	**Primary outcome**:	The risk of recurrent stroke was significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
2007 **UK** **Prospective non-randomized controlled study (based on patients from the Oxford Vascular Study)**		referred to the EXPRESS clinic with TIA or minor stroke. (310 in Phase 1 and 281 in phase 2). Patient age: 33% of patients were ≥ 80 years (Phase 1); 33% ≥ 80 years (Phase 2). Patients were identified from the Oxford Vascular study which recruits patients who have experienced a vascular event and who are registered with one of 63 general practitioners in the UK.	patients more timely access to outpatient services. The clinic required no appointments and treatment was initiated by the patients GP immediately (aspirin and clopidogrel) when possible. Outcomes were compared between phase 1 (non-immediate access) and phase 2 (immediate access) to the EXPRESS clinic.	Recurrent stroke within 90 days, risk of adverse event.	lower in patients who were referred to the clinic during Phase 2 (2.1% vs.10.3%, p=0.0001). The risk of adverse events was significantly lower in Phase 2 (3.6% vs. 11.9%, p=0.0002). The delay in initiating a treatment prescription for patients referred to the clinic was longer in phase 1 (median 20 days) vs. phase 2 (median 1 day).

Components of Care for Outpatient Management of TIA and Non-Disabling Stroke

Study	Referral Source/Hours/Location/Staffing	Assessments				Follow-up
		Imaging	ECG	Echocardiography	Blood Tests	
Benavente et al. 2013 **Spain** **TIA Unit**	1. Urgent care physician 2. 24 hours/day 3. Emergency department of hospital 4. Not specified	☑ (CT – right away) (Transcranial Doppler imaging of brain arteries – if applicable – within one week)	☑ (right away)	☑ (Trans-esophageal ultrasound – if applicable – within one week)	☑ (right away)	Treatment started immediately: 1. Low Molecular weight heparin – 0.1mL/10kg/day 2. Anti-platelets (Aspirin – 100mg, subsequently changed thereafter) 3. Enalapril when blood pressure ≥220/120mmHg 4. Patients with 70-99% stenosis were referred immediately to a surgeon to assess stenting.

						Follow-up visit scheduled with a neurovascular specialist within 15 days, and after 6 and 12 months.
Van Rooij et al. 2012 **The Netherlands** **24/7 TIA-Service**	1. General practitioners 2. 24 hours/7 days per week 3. Acute day ward 4. Specialized nurse (for secondary prevention and education), neurology resident under supervision of a neurologist	☑ (Brain Imaging - MRI or CT - within half day) (Cervical and intracranial arteries - within half day)	☑ (Within half day)	☒ (Not specified)	☑ (Within half day)	Treatment started immediately: 1. Antithrombotic or anticoagulant therapy, antihypertensive and lipid-lowering drugs where applicable. 2. Carotid surgery (>70% stenosis) – within 14 days. 3. Lifestyle modification (smoking, exercise, nutrition) Patients are contacted 2 weeks after initial visit, asked to attend the outpatient clinic after 4 weeks, and consultations are continued as needed. Involvement of the GP is facilitated through written correspondence and active engagement in the patient's treatment plan.
Banerjee et al. 2009 **United Kingdom** **FAST-TIA Clinic**	1. Primary care and in-hospital 2. Weekday only 3. Neurovascular clinic 4. Specialist nurse under the supervision of a neurologist	☑ (CT – same day)	☑ (Same day)	☑ (Trans-thoracic echocardiography – same day when possible)	☑ (Same day)	Treatment started immediately: 1. Lifestyle modification and driving advice provided 2. Anti-platelets (Aspirin – 300mg, subsequently changed thereafter) 3. Patients with 70-99% stenosis were referred immediately to a surgeon to assess stenting. Follow-up visits were scheduled for a week after admission and 3 months later.

Lavallee et al. 2007 **United States** **SOS-TIA Clinic**	1. Family physicians, cardiologists, neurology, ophthalmology, emergency departments 2. 24 hours/7 days per week 3. Neurology department of hospital 4. Nurse (9am-5pm), On duty Neurologist (5pm-9am)	☑ (Brain Imaging - MRI or CT - within 4 hours) (Duplex ultrasonography – within 4 hours) (Transcranial Doppler imaging of brain arteries – within 4 hours)	☑ (Within 4 hours)	☑ (If cardiac source suspected – complete within 4 hours, otherwise not urgent)	☑ (Not urgent)	Referring physician contacted by neurologist to discuss diagnosis and treatment. Summary sent to family doctor with recommended management targets: 1. Blood Pressure (140/90mm Hg, 130/85mm Hg for patients with diabetes) 2. LDL 2.56mmol/L 3. Antithrombotic treatment (300-500mg Aspirin) Patient discharged home.
Rothwell et al. 2007 **United Kingdom** **EXPRESS – Phase I**	1. Primary Care referral *(Appointment only)* 2. Weekday only 3. Hospital outpatient clinic 4. Not specified	☑ (Brain Imaging – CT – same day) (Carotid Ultrasound – within week)	☑ (Same day)	☑ (Trans-thoracic/trans-oesophageal echocardiography – when necessary – within week)	☒ (Not stated)	Report sent to primary care physician and patients told to follow-up with them. Included: 1. Aspirin, or clopidogrel (both if within 48 hours or if at high risk) 2. Simvastatin 3. Anticoagulation therapy
Rothwell et al. 2007 **United Kingdom** **EXPRESS – Phase II**	1. Primary Care referral *(No Appointment necessary)* 2. Weekday only 3. Hospital outpatient clinic 4. Not specified	☑ (Brain Imaging – CT – same day) (Carotid Ultrasound – within week)	☑ (Same day)	☑ (Trans-thoracic/trans-oesophageal echocardiography – when necessary – within week)	☒ (Not stated)	Treatment started immediately: 1. Aspirin (300mg in the clinic): For patients with tiA or stroke 2. Clopidogrel (300mg) *Plus other medication as necessary (based on the protocol above) with a 4-week prescription. Report sent to primary care physician.

Tools for Assessing the Risk of Recurrent Stroke or TIA

Author/ Assessment Tool	Purpose of the tool Details of the validation study	Items and Scoring		Results of validation study
Rothwell et al. 2005 **ABCD Score**	**Purpose**: To determine the 7-day risk of stroke in patients with suspected or definitive TIA.	1) **Age** (>60 years old)	1 point	Diagnostic standard: Occurrence of stroke or TIA within 7 days of index event. <u>Patients with suspected TIA:</u> AUC= 0.91, 95% CI 0.86-0.95
		2) **Blood Pressure** (Systolic >140mm Hg and/or Diastolic ≥90mm Hg)	1 point	
		3) **Clinical Features** (weakness, speech, or other)	1 point (2 points for unilateral weakness)	

	Sample: 188 patients from the Oxford Vascular Study (OXVASC), a cohort of individuals who had experienced an initial or recurrent stroke or TIA.	4) **Duration of symptoms** between 10-59min	1 point (2 points if ≥ 60min)	Patients with probable or definitive TIA: AUC=0.85,95% CI 0.78-0.91 Patients with suspected TIA (not from the OXVASC study): AUC=0.80,95% CI 0.72-0.89 Note: Sensitivity and Specificity not reported.
		Total Possible Score: 6		
Perry et al. 2011 **ABCD^2 Score**	**Purpose**: To determine the 7 and 90-day risk of stroke in patients with suspected or definitive TIA. **Sample**: 2056 patients from the emergency department diagnosed as having a TIA.	1) **Age** (>60 years old)	1 point	Diagnostic standard: Occurrence of stroke or TIA within 7 or 90 days of index event. **Predicting stroke** Patients with Score of **>2** (designated high risk by the American Heart Association): Sensitivity **(7 days)**: 94.7%, 95% CI 82.7-98.5 Specificity **(7 days):** 12.5%, 95% CI 11.2-14.1 Patients with Score of **>5** (designated high risk by original ABCD2 score): Sensitivity **(7 days)**: 31.6%, 95% CI 19.1-47.5 Specificity **(7 days):** 86.9%,95% CI 85.3-88.3 Patients with Score of **>2** (designated high risk by the American Heart Association): Sensitivity **(90 days)**: 96.9%, 95% CI 89.3-99.1 Specificity (**90 days)**: 12.7%,95% CI 11.3-14.3 Patients with Score of **>5** (designated high risk by original ABCD2 score): Sensitivity **(90 days)**: 29.2%,95% CI 19.6-41.2 Specificity **(90 days):** 79.7%,95% CI 77.9-81.4
		2) **Blood Pressure** (Systolic >140mm Hg and/or Diastolic ≥90mm Hg)	1 point	
		3) **Clinical Features** (weakness, speech, or other)	1 point (2 points for unilateral weakness)	
		4) **Duration of symptoms** between 10-59min	1 point (2 points if ≥ 60min)	
		5) **Diabetes**	1 point	
		Total Possible Score: 7		
Meng et al. 2011 **ABCD^2-I Score**	**Purpose**: To determine the 1-year risk of stroke in patients with TIA. **Sample**: 410 patients admitted to hospital with TIA.	1) **Age** (>60 years old)	1 point	Diagnostic standard: Occurrence of stroke or TIA within 1 year of index event. Risk of stroke or TIA: 27.07% **ABCD^2 Score** Patients with high risk of stroke (Score 6-7): AUC= 0.59, 95% CI 0.53 – 0.65
		2) **Blood Pressure** (Systolic >140mm Hg and/or Diastolic ≥90mm Hg)	1 point	
		3) **Clinical Features** (weakness, speech, or other)	1 point (2 points for unilateral weakness)	

		4) **Duration of symptoms** between 10-59min	1 point (2 points if ≥ 60 min)	**ABCD²-I Score** Patients with high risk of stroke (Score 6-7): AUC= 0.77, 95% CI 0.72-0.82 Note: Sensitivity and Specificity not reported.
		5) **Diabetes**	1 point	
		6) **Imaging** (acute DWI hyperintensity)	3 points	
			Total Possible Score: 10	
Song et al. 2013 **ABCD³-I Score**	**Purpose**: To determine the 90-day risk of stroke in patients with TIA. **Sample**: 239 patients presenting to hospital with TIA.	1) **Age** (>60 years old)	1 point	Diagnostic standard: Occurrence of stroke within 90 days of index event. Risk of stroke or TIA: 12.1% **ABCD² Score** ROC Curve 0.694 (0.601 – 0.786) **ABCD³-I Score** ROC Curve 0.825 (0.752 – 0.898) Note: Sensitivity and Specificity not reported.
		2) **Blood Pressure** (Systolic >140mm Hg and/or Diastolic ≥90mm Hg)	1 point	
		3) **Clinical Features** (weakness, speech, or other)	1 point (2 points for unilateral weakness)	
		4) **Duration of symptoms** between 10-59min	1 point (2 points if ≥ 60min)	
		5) **Diabetes**	1 point	
		6) **Imaging** (acute DWI hyperintensity)	3 points	
		7) **Dual TIA** (earlier TIA within 7 days)	2 points	
		8) **Stenosis** of internal carotid artery (ipsilateral **≥50%**)	2 points	
			Total Possible Score: 14	
Fitzek et al. 2011 **ESRS (Essen Stroke Risk Score)**	**Purpose**: To determine the 1-year risk of stroke in patients with acute ischemic stroke. **Sample**: 730 patients presenting to hospital with acute ischemic stroke.	1) **Age** ≥65 years	1 point (2 points if >75 years)	Diagnostic standard: Occurrence of stroke within 1 year of index event. Risk of stroke or TIA: 10.4% Patients with high risk of stroke (Score >2): AUC= 0.59 Note: Sensitivity and Specificity not reported.
		2) Arterial **Hypertension**	1 point	
		3) **Diabetes** Mellitus	1 point	
		4) Previous **Myocardial Infarction**	1 point	
		5) Other **cardiovascular diseases** (not atrial fibrillation)	1 point	
		6) **Peripheral arterial disease**	1 point	
		7) **Smoking** within 5 years	1 point	
		8) Previous **TIA or ischemic stroke**	1 point	
			Total Possible Score: 9	
Kernan et al. 2000	**Purpose**: To determine the 2-year risk of stroke in	1) **Congestive heart failure**	3 points	Diagnostic standard: Occurrence of stroke within 2 year of index event.
		2) **Diabetes**	3 points	
		3) **Prior Stroke**	3 points	

SPI-II (Stroke Prognosis Instrument)	patients with TIA or ischemic stroke **Sample**: Consisted of participants from 4 independent cohorts (current or former trials – WEST, UK-TIA, CAPRIE and NoMaSS)	4) **Age** >70 years	2 points	Pooled risk of stroke or death from all 4 cohorts: Low Risk (Score 0-3) 10%; Middle Risk Group (Score 4-7) 19%; High Risk Group (Score 8-15) 315. **SPI-I Score** AUC=0.59, 95% CI 0.57-0.60 **SPI-II Score** AUC= 0.63,95% CI 0.62-0.65 Note: Sensitivity and Specificity not reported.
		5) **Stroke** (vs. TIA for index event)	2 points	
		6) Severe **hypertension**	1 point	
		7) **Coronary Artery Disease**	1 point	
			Total Possible Score: 15	

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