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Stop stroke. Save lives. End Suffering.

Clinical Guidelines for Acute Stroke Management - Supplement

National Stroke Foundation 2007



Australian Government

National Health and Medical Research Council

Introduction

This supplement presents evidence collated to inform the Clinical Guidelines for Acute Stroke Management 2007. Tables present key areas of the guidelines and is organised to reflect the order of the guidelines. The tables are organised by the levels of evidence (i.e. meta-analysis and systematic reviews noted first followed by individual trials and finally observational studies). Each table provides the lead author, a brief description of the sample and the design, a brief description of the intervention or diagnostic criteria, the outcome measures used and a brief conclusion. Readers are recommended to read the original references for more details. Permission has been kindly provided by the Royal College of Physicians London to use and adapt the tables of their 2004 guidelines. Subsequent studies have been added.

Abbreviations

ADL: Activities of daily living	MBS: Modified barium swallow
AF: Atrial fibrillation	MI: Myocardial infarction
ARR: Absolute risk reduction	MRI: Magnetic Resonance Imaging
ASU: Acute stroke unit	MRS: Modified Rankin Score
BSE: Bedside examination	NG: Nasogastric
CI: Confidence interval	NNT: Numbers needed to treat
CCT: Controlled clinical trial	NPV: Negative predictive value
CEA: Carotid endarterectomy	OBS: Observational study
CT: Computed tomography	OR: Odds ratio
DVT: Deep vein thrombosis	OT: Occupational therapist
ESD: Early supported discharge	PE: Pulmonary embolism
FEES: Fiberoptic endoscopic examination of swallowing	PEG: Percutaneous endoscopic gastrostomy
FEESST: Fiberoptic endoscopic examination of swallowing with sensory testing	PPV: Positive predictive value
FIM: Functional Independence Measure	QALYs: Quality adjusted life years
GHQ: General health questionnaire	QOL: Quality of life
GMW: General medical ward	RCT: Randomised controlled trial
GP: General practitioner	rt-PA: Recombinant tissue plasminogen activator
ICH: Intracranial hemorrhage	RR: Risk reduction
INR:	RRR: Relative risk reduction
IQR: Interquartile range	SIP: Sickness impact profile
IV: Intravenous	SLT: Speech and language therapist
LFT: Liver function test	S/R: Systematic review
LMWH: Low molecular weight heparin	SSS: Scandanavian Stroke Score
LOS: Length of stay	TIA: Transient ischaemic attack
M/A: Meta analysis	UFH: Unfractionated heparin
	VFSS: Videofluoroscopic study of swallowing

Contents: Evidence Tables

Table 1: Organisation of stroke care	1
Table 2: Care pathways	3
Table 3: Patient information and education	4
Table 4: Early supported discharge services.....	6
Table 5: Service audit/evaluation/comparison.....	6
Table 6: Pre-hospital care	7
Table 7: Diagnosis of stroke.....	9
Table 8: Transient ischaemic attack.....	11
Table 9: Thrombolysis.....	14
Table 10: Ischaemic stroke and TIA: Antithrombotic therapy in the acute phase	19
Table 11: Intracerebral haemorrhage.....	20
Table 12: General interventions in the acute phase	22
Table 13: Neuroprotective agents	25
Table 14: Dysphagia	29
Table 15: Nutrition after stroke	31
Table 16: Communication	34
Table 17: Incontinence	36
Table 18: Mood	37
Table 19: Prevention of complications: cerebral oedema.....	40
Table 20: Prevention of complications: DVT and PE.....	41
Table 21: Prevention of complications: Pressure care	43
Table 22: Secondary prevention after stroke: Lifestyle/Behavior change.....	44
Table 23: Secondary prevention after stroke: Blood pressure lowering	48
Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy	50
Table 25: Secondary prevention after stroke: Cholesterol lowering	55
Table 26: Secondary prevention after stroke: Carotid surgery	57
Table 27: Concordance with medication	60
Table 28: Discharge planning.....	62
Table 29: Community rehabilitation	62
Table 30: Post-discharge support	64

Table 1: Organisation of stroke care

Source	Design and sample	Intervention(s)	Outcome measures	Conclusions
Stroke Unit Trialists' Collaboration, 2001	M/A; 23 RCTs, n = 2500 patients	Stroke unit care or general medical ward care	Mortality; dependency; institutionalisation; LOS	Stroke unit care reduces mortality and morbidity with no increase in length of stay.
Foley et al, 2007	M/A; 14 trials (5 acute, 4 comprehensive & 5 post acute); n = 3672 patients	Acute stroke unit vs combined acute and rehabilitation care vs rehabilitation care.	Mortality, combined death and dependency and LOS.	Postacute stroke units resulted in greatest reduced odds of mortality, followed by combined then acute units. Combined stroke units were associated with a reduced LOS. All models of care reduced death and disability. Hence all are beneficial but level of benefits differs between models.
Langhorne et al, 2005	S/R 6 trials; n = 1085 patients	Peripatetic stroke care (eg mobile stroke team within a hospital) in comparison to stroke unit and general medical ward care.	Mortality, need for institutional care, dependency, clinical processes (investigations and treatments), delays to clinical processes, ADL scores, mood/depression scores, subjective health or QOL, LOS.	Mobile stroke unit care resulted in greater numbers receiving occupational therapy and swallowing assessment. LOS was not altered. No effect on death, institutionalization or dependence in comparison to general medical ward care. Stroke unit preferred model.
Langhorne and Pollock, 2002	S/R (Descriptive analysis). 11 clinical trials	Descriptive survey of care provided in 11 stroke units that have been shown to be effective.	Structure and organization of unit (i.e. pt inclusion/exclusion criteria, staff mix and staffing levels, communication, education); processes of care (i.e. investigations, drug therapy); discharge planning and follow-up.	Consistent characteristics of effective stroke units include comprehensive assessment of medical problems, careful management of physiological abnormalities, early mobilization, skilled nursing, early establishment of both rehabilitation plan and discharge needs.
Shepperd & Iliffe 2001	M/A; n = 16 trials; various groups, some stroke	Hospital-at-home, early discharge or inpatient hospital care.	Mortality; discharge destination; readmissions; functional outcomes; carer stress; patient & carer satisfaction. Costs	Does not support the development of hospital at home services as a cheaper alternative to inpatient care.
Langhorne et al, 1999	M/A; 4 trials; n = 921 stroke patients	Supported care at home (physical support to avoid hospital admission) vs conventional in-patient care on a general ward.	Death, place of residence, dependency, social activity, psychological outcomes, carer outcomes, patient and care preferences.	No significant difference in mortality, dependency, ADL, subjective health status or mood. There was trend towards patients' preference for home based care. No evidence for radical shift away from hospital based care.
Kalra et al, 2000	RCT, n = 457 acute stroke patients (152 stroke unit, 152 stroke team, 153 domiciliary).	Stroke unit v mobile stroke team on General Medical Ward v Domiciliary management	Mortality; institutionalization and dependency at 1 year.	Decreased mortality and morbidity only seen in stroke unit. Mobile stroke teams not effective. Need geographically located unit and team.
Van der Walt et al, 2005	CCT; n = 200 (100 sequential admissions, 100 historical controls).	Mobile stroke service vs conventional care	Quality indicators (eg DVT prophylaxis, incontinence management, CT brain), LOS, complications and discharge disability.	Mobile stroke service resulted in reduced LOS, and a greater % of patients were independent at discharge. Severe and moderate complications were less in the mobile stroke service group. Adherence to quality indicators such as incontinence management, DVT prophylaxis and early OT.

Table 1: Organisation of stroke care

Source	Design and sample	Intervention(s)	Outcome measures	Conclusions
Blight et al 2000	Case series (Retrospective audit). n = 211 patients referred to neurovascular clinic	One-stop clinic. Examination of the cost-effectiveness of a single consultation to manage people with stroke or TIA	Costs	90% managed with single consultation with potential cost savings
Audebert et al, 2005	Cohort study 12 hospitals, n=106 systemic thrombolyses	Safety analysis of the use of tPA using telemedicine support (two-way conferencing and CT/MRI image transfer) for non-urban hospitals.	In hospital mortality, mortality within 7 days, LOS, symptomatic hemorrhage, onset to admission time, time to treatment	tPA could be administered safely in general hospitals if indicated by teleconference by an experienced neurologist.
Audebert et al, 2006	Prospective cohort study. 12 regional hospitals (n=4727, n=tPA 115) 2 stroke centres (n=1889, n=tPA 110)	Examine the effect of telemedicine on the process of tPA administration in regional hospitals vs stroke centres	Medical history, clinical data, time of onset, time of hospital admission, time of CT scan, administration of tPA, clinical course, NIHSS, blood pressure, mortality, symptomatic hemorrhage	The percentage of patients receiving tPA was twice as high in the stroke centres. No statistical difference in mortality or symptomatic hemorrhage in regional vs stroke centre. Authors suggest the quality of care in the regional hospitals was comparable to the stroke centres.
Hess et al, 2005	Cohort study n = 194 patients (n = 30 tPA)	Evaluation of web-based telestroke tool to provide acute consultations to rural hospitals	NIHSS, onset to treatment time, symptomatic ICH	Authors concluded that patients could be treated safely and rapidly using the consult tool.
Silverman et al, 2005	Retrospective cohort study n=229	Evaluate use of tPA (IV or IA) in regional hospital before transfer to a stroke centre.	Symptomatic hemorrhage, mortality	Symptomatic hemorrhage occurred in one patient (3%), in hospital mortality was 6.1%. 78.8% of patients has a positive outcome. Authors concluded that tPA could be safely initiated before patients were transferred to a stroke centre.
Rymer et al, 2003	Cohort study n= 781 people with stroke, n=142 treated with tPA	To identify if a major centre could work with regional hospitals to increase the use of tPA. Three tPA protocols were used.	Site of origin, mortality, symptomatic hemorrhage rate, admission and discharge NIHSS, time from onset to treatment.	Higher use of tPA than previously reported. Regional hospitals initiated IV tPA in 37.3% of cases. Authors suggest that the use of tPA can be increased when regional hospitals work with a stroke centre.
Candelise et al, 2007	Obs study; n=11572 hospitalized within 48 hours of symptoms	Stroke unit vs conventional ward	In hospital fatality, death after discharge, Rankin score, stroke reoccurrence, new hospital admission, rehabilitation program.	Stroke unit care associated with reduced probability of death or disability by the end of 2 years follow-up.
Cadilhac et al, 2004	Obs study; n=468 patients	Stroke unit vs mobile service vs conventional care	Stroke type and severity, QoL, disability, handicap, satisfaction with service, carer strain.	Greater adherence to process of care in the stroke units. Adherence to process of care was associated with improved mortality and trend towards independence at home.
Wang et al, 2000	Obs study; n=57	Treated with tPA in a tertiary hospital vs a community hospital	NIHSS on admission and discharge, modified Rankin, discharge disposition, intracerebral hemorrhage, mortality	54% of patients given tPA were discharged home. 47% were discharged with no or minimal disability. Complication rates did not appear to differ between community and tertiary hospitals however the result should be interpreted with caution b/c of low patient numbers.

Table 1: Organisation of stroke care

Source	Design and sample	Intervention(s)	Outcome measures	Conclusions
Nguyen-Huynh & Johnston, 2005	Cost-utility analysis	24 hour hospital admission post TIA	Cost effectiveness for quality adjusted life year	Authors concluded that the cost of 24 hours hospitalization was borderline for patients following TIA but cost effective for patients at higher risk of stroke.

Table 2: Care pathways

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Kwan and Sandercock 2004	M/A (3 RCTs n = 340; 12 non random trials n = 1673 patients)	In-hospital care pathways (defined as a plan of care that: (1) involved two or more of the following: assessment, investigation, diagnosis, or treatment; and (2) involved two or more disciplines)	Death; dependency; discharge destination; patient satisfaction and QoL.	No difference between care pathway and control groups for all trials. Possible negative effect on patient satisfaction and QoL. Insufficient evidence to justify routine use.
Naylor et al, 1994	RCT; n = 276 patients aged 70+ years (not stroke specific)	Comprehensive discharge planning protocol for elderly	LOS; readmission; costs of post-discharge care.	Protocol led to shorter admission and fewer readmissions
Odderson et al, 1995	CCT; n = 124; acute stroke admissions; historical controls	Use of a standardised protocol, including dysphagia guidelines	Dysphagia; FIM; aspiration pneumonia; LOS; cost effectiveness.	Aspiration pneumonia risk greatly reduced
Mehdiratta et al, 2006	CCT (historical control); Pre-pathway n=8; Post-pathway n = 47	Introduction of an acute stroke pathway to reduce door to needle time for IV tPA	Door to CT time, door to needle time	Door to CT time and door to needle time were significantly reduced after implementation of the pathway. However the times for the majority of patients were still longer than the recommendations by the NINDS.
Esteve et al, 2004 (Non English paper. Information from abstract only)	CCT (historical control). Pre-pathway n = 69; Post-pathway n = 70	Implementation of a care pathway.	Quality of care indicators, Barthel score, neurological function (Canadian Scale), nosocomial complications, satisfaction, LOS.	Reduction in time from admission to mobilization in the pathway group. No significant differences between groups for quality of care, functional or neurological status. There was a significant reduction of complications in the pathway group.
Taylor et al, 2006	CCT (historical control); Retrospective audit. Pre-pathway n = 77, Post-pathway n = 76	Implementation of a care pathway	LOS, Barthel Index, Modified Rankin Scale, use of investigations, management of specific issues (eg. fever, hypertension) use of secondary prevention strategies (eg. BP lowering, smoking cessation)	No significant difference in LOS. Discharge disposition was similar for both groups. Logistic regression suggested that use of care pathway had an adverse effect on outcome

Table 2: Care pathways

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Asimos et al, 2004	Case series with comparison with historical control (NINDS study); n = 255 code stroke protocol (n = 60 treated with tPA)	Evaluation of a code stroke protocol.	Mortality, Symptomatic intracerebral hemorrhage, Barthel	10% of patients had symptomatic ICH. 3 months post intervention 60% of patients had achieved an excellent neurological outcome. Authors concluded code stroke protocol was feasible and effective to screen for patients to be treated with thrombolysis.
Sattin et al, 2006	Case series; n=103 treated with tPA (n=49 treated within 2 hours; n=54 treated b/w 2-3 hours)	Evaluation of an expedited code stroke protocol.	Primary outcome: symptomatic hemorrhage. Secondary outcome: process of care, safety, 90 day outcome	There were no significant differences in symptomatic hemorrhage between the groups. The processes of care were not different between the groups. Protocol use appears feasible and safe.

Table 3: Patient information and education

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Forster et al 2001	M/A; 9 RCTs; n= 758 patients and carers	Leaflets, booklets, manuals and lectures.	Knowledge about stroke and services; impact on health	Some evidence that information combined with education sessions is more effective than information alone.
Bhagal et al, 2003	S/R; 17 studies; 4 studies for social support, 10 RCTs for family education, 3 studies for leisure therapy; n = 1945 for family education section only. Most studies based in the community.	Evaluate issues for reintegration into the community	Social support, care giver burden and depression, family interactions family education intervention, social and leisure activities post stroke, leisure therapy.	Moderate evidence that improved social support as an intervention improves outcome. Some evidence that family function effects the outcome of stroke. Evidence of a benefit of family education when an educational counseling approach was taken.
Clark et al, 2003	RCT; n = 62 patients and carers (32 intervention; 30 control), rehabilitation unit.	Information package and x3 visits from a social worker x 1 hour.	McMaster family assessment device, BI, Adelaide activities profile, geriatric depression Scale, HADS, Mastery Scale, SF-36	Improved family functioning in the intervention group for patients and carers compared to control. Modest improvement in function (mainly due to family function). There was no significant effect on depression.

Table 3: Patient information and education

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Smith et al, 2004	RCT; n = 170 people with stroke (n = 84 education, n = 86 usual care), n = 70 carers (n = 49 education, n = 48 usual care). Rehabilitation unit.	Stroke information manual and fortnightly education meetings with multidisciplinary team.	Primary outcome: knowledge of stroke and stroke services Secondary: London Handicap Scale, BI, Frenchay Activities Index, HADS, satisfaction (Pound Scale), care mood (General health Questionnaire-28).	No significant knowledge change (positive trend only in intervention). Significant reduction in anxiety in the intervention group at both 3 and 6 months. Increased satisfaction of carers at 6 months with their level of information about allowances. No other significant differences.
Burton et al, 2004	RCT; n=87 intervention, n=89 usual care post discharge	Follow-up by stroke nurse post discharge focused on education and support. (range 0 – 12 months after discharge). Contacts (range 2 – 28).	BI, Nottingham health Profile, Frenchay Activity of Living Index, Beck Depression inventory, Carer Strain Index	Improved emotional and social support. Improved self reported general health at 12 months. Reduced carer strain at 3 months. Less deterioration in physical function between 2-12 months. No other differences.
Boter et al, 2004	RCT n= 536 (n = 263 with stroke & n = 211 carers received standard care, n = 273 patients & n = 230 carers received outreach). Community based.	Outreach nurse intervention: 3 telephone call, x 1 visit	Primary: Satisfaction with stroke care questionnaire, SF-36 Secondary: HADS, readmission, BI, modified Rankin Scale, use of health care services, use of secondary prevention drugs, carer strain index, sense of competence questionnaire, social support list discrepancies	No significant differences for QoL or satisfaction except outreach group scored better for role limitations due to emotional health. Outreach groups scored lower for anxiety and used less rehabilitation resources. No significant differences between carers. Overall this model of education and support not effective.
Kalra et al, 2004	RCT; n = 300 patients and caregivers	Conventional rehabilitation unit care for carers vs care giver training. Training = 3-5, 30-45 minute hands on and educational training sessions.	Stroke sub-type, BI, Frenchay activity index, euroQoL, HADS, Modified Rankin scale Caregivers: demographics, accommodation, health profile, functional status, QoL	Patients whose caregiver had received training had significantly better QoL and mood outcomes. Burden of care, QoL and mood were significantly improved in the caregivers who received training.
Larson et al, 2005	RCT n = 100 spouses (n = 50 education intervention, 50 control). Community based.	Support and education x 6 sessions over 6 months facilitated by specialist nurse.	General QOL, life situation, general well-being, perceived health status	No statistical difference between groups for the outcomes variables. Authors suggested study was effective but only for those attending >4 sessions.
Middelton et al, 2005	RCT; n = 133 carotoid endarterectomy patients (n = 66 intervention, n = 67 control). Community based.	Telephone contact by nurses at 2,6 and 12 weeks post surgery. Education about stroke and stroke risk factors.	Questionnaire: sociodemographics, smoking status, physical activity, BP, cholesterol, knowledge of stroke	Intervention group had improved knowledge of stroke warning signs and self rated changes to lifestyle and diet compared to control. Both groups improved on other measures without difference.
Nir & Weisel-Eichler, 2006	RCT; n = 155 (73 education program, 82 controls), rehabilitation unit.	In-patient rehabilitation usual care vs nursing education intervention. 12 sessions x 2 hours	Assessment of correct use of medications, dietary adherence, FIM, demographic and health characteristics.	Intervention group had greater knowledge of medications (eg shape, dosage and side-effects). However, even in the intervention group knowledge of medications was limited. The intervention group adhered more closely to dietary recommendations.

Table 4: Early supported discharge services

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Early Supported Discharge Trialists, 2005	M/A; 11 trials; n = 1597 selected group of elderly stroke patients (mild to moderate disability)	Early discharge with specialist, community based, multidisciplinary, rehabilitation team	Mortality; place of residence; dependency; satisfaction with services; health status.	The ESD reduces LOS by approx 8 days (P < 0.0001). Overall, benefits in reduced death or dependency and institutionalisation but not in death alone. The greatest benefits were seen in the trials evaluating a co-ordinated ESD team and in stroke patients with mild-moderate disability. Improvements were also seen in patients' extended activities of daily living scores (standardised mean difference 0.12, 95% CI 0.00 to 0.25, P = 0.05) and satisfaction with services (OR 1.60, 95% CI 1.08 to 2.38, P = 0.02) but no statistically significant differences were seen in carers' subjective health status, mood or satisfaction with services. Cost saving of 9-20% with ESD.
Larsen et al, 2006	M/A; 7 studies, n = 1108 patients	Early supported discharge vs conventional rehabilitation	Poor outcomes (referral to nursing home, death), LOS, economic evaluation	Early supported discharge significantly reduced LOS by a mean of 10 days (CI 2.6 – 18 days). The odds ratio for death or institutionalization was also reduced (OR 0.75 (CI 0.46-0.96) NNT=14) as was admission to institution (OR =0.45 (CI 0.31-0.96) NNT=20). Economic analysis showed savings (140 USD) per patient with ESD.

Table 5: Service audit/evaluation/comparison

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Jamtvedt et al 2006	M/A; 118 studies; 9 of the 67 trials focused on health professional behaviour was based in Australia – most based in North America and most involved physicians only.	Audit and feedback with or without concurrent interventions aimed at improving performance.	Objectively measurements of provider performance in a health care setting or health care outcomes (eg. Compliance with guidelines, prescribing patterns or tests ordered). Studies that measured knowledge or performance in a test situation only were excluded.	For dichotomous outcomes: compliance with desired practice varied from a 16 % absolute decrease in compliance to a 70% increase in compliance. For continuous outcomes: the adjusted percent change relative to control varied from a 10 % absolute decrease in compliance to a 68% increase in compliance. Low baseline compliance with recommended practice and higher intensity of audit and feedback were associated with greater effectiveness across studies.
Van der Walt et al, 2005	CCT; n = 200 (100 sequential admissions, 100 historical controls).	Mobile stroke service vs conventional care	Quality indicators (eg DVT prophylaxis, incontinence management, CT brain), LOS, complications and discharge disability.	Mobile stroke service resulted in reduced LOS, and a greater % of patients were independent at discharge. Severe and moderate complications were less in the mobile stroke service group. Adherence to quality indicators such as incontinence management, DVT prophylaxis and early

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Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
				OT.
Cadilhac et al, 2004	Obs study; n=468 patients	Stroke unit vs mobile service vs conventional care	Stroke type and severity, QoL, disability, handicap, satisfaction with service, carer strain.	Greater adherence to process of care in the stroke units. Adherence to process of care was associated with improved mortality and trend towards independence at home.
Irwin et al 2005	Obs; retrospective national audit of service organization and case notes. (n= 4996, 4841 and 5152)	Comparison between 1998, 1999 and 2001/2 audit results	Mortality; Barthel; discharge destination; LOS Proportion of patients managed on stroke unit for over 50% of stay.	Mortality at 7 and 30 days fell by 3% and 5%, respectively. The proportion of hospitals with a stroke unit rose from 48% to 77%. The proportion of patients spending most of their stay in a stroke unit rose from 17% in 1998 to 26% in 1999 and 29% in 2001/02. Improvements achieved in process standards of care between 1998 and 1999 (median change was a gain of 9%) failed to improve further by 2001/02 (median change was 0%). In all three rounds process standards of care tended to be better in stroke units.

Table 6: Pre-hospital care

Source	Design & Sample	Intervention/criteria	Outcome measures	Conclusions
Kwan et al 2004	S/R; 10 studies (all level III and IV studies)	10 non-randomized studies that evaluated interventions that could speed up admission to hospital and administration of rt-PA.	Thrombolysis rate, time from stroke event to admission, door to CT times, stroke to CT times, knowledge	The use of ambulance transport increased, admission delays decreased and the number of patients receiving thrombolysis improved. Emergency medical services, health care professionals and the general public should receive education concerning the importance of early recognition of stroke, emphasizing stroke is a medical emergency.
Kothari et al, 1999	Diagnostic study; 171 convenience sample, 49 with TIA or stroke	Pre-hospital diagnosis by paramedics against final diagnosis by neurologist	Correct diagnosis of stroke or TIA	High reproducibility was observed among prehospital providers for total score and for each scale item: arm weakness, speech, and facial droop (.91, .84, and .75, respectively).

Table 6: Pre-hospital care

Source	Design & Sample	Intervention/criteria	Outcome measures	Conclusions
Bray et al 2005a	Diagnostic study, n=18 paramedics	Validity of the Melbourne Ambulance Stroke Screen (MASS) compared to other prehospital screening tools	Sensitivity, specificity	Paramedics completed 100 MASS assessments for 73 stroke/TIA patients and 27 stroke mimics. The sensitivity of the MASS (90%, 95% CI: 81-96%) showed statistical equivalence to the sensitivity of the CPSS (95%, p = 0.45) and superiority to the LAPSS (78%, p = 0.008). The specificity of the MASS (74%, 95% CI: 53-88%) was equivalent to that of the LAPSS (85%, p = 0.25) and superior to the CPSS (54%, p = 0.007). The MASS is simple to use, with accurate prehospital identification of stroke. It distinguishes stroke mimics, with good recognition of suitable patients for thrombolytic therapy.
Belvis et al 2005	CCT; n=220 (39 in intervention group, 181 in control)	Stroke code feasibility.	Priority by emergency medical services and early notification to hospital emergency departments	Shorter mean time from ED arrival to request for neurologic assessment (4.4 vs. 194.7 min, p < 0.001), from arrival to neurologic examination (12.6 vs. 225.3 min, p < 0.005), and from arrival to performance of brain CT scan (35.5 vs. 120.3 min, p < 0.001), and also in the number of patients treated with thrombolytic agents (19 vs. 4.5%, p < 0.003). There were no differences between groups in the time elapsed from stroke onset to ED arrival.
Bray et al 2005b	CCT; n=61 (18 in intervention group; 43 in control group)	educational intervention and the use of a prehospital stroke tool on the paramedic diagnosis of stroke	Accuracy of stroke diagnosis, knowledge, time from ED arrive to medical review, time from ED arrive to CT	The sensitivity for the FAST study paramedics in identifying stroke improved from 78% to 94% (p = 0.006). There was no change in stroke diagnosis for the non-study paramedics 78% to 80% (p = 0.695). Pre-notification of impending arrival to the emergency department was associated with higher-priority triage in the emergency department, and subsequent shorter times for door to medical review (15 min vs. 31 min, p < 0.001) and door to computed tomography (CT) scanning (94 min vs. 144 min, p < 0.001).
Wojner-Alexandrov et al 2005	CCT; 6 sites/hospitals, Pre-intervention and active-intervention phases with parallel data measurement points were used. N= 6 hospitals.	Accuracy of paramedic diagnosis of stroke increased from 61% to 79%. Admission within 2 hours of symptom onset increased from 58% to 62%. Thrombolysis rates increased in 4 of 6 centers, with 1 post-tPA hemorrhage (3.7%) reported.	Acute stroke therapy requirements	Establishment of stroke centers, combined with accurate paramedic diagnosis and rapid transport, is essential to deliver acute stroke therapy.

Table 6: Pre-hospital care

Source	Design & Sample	Intervention/criteria	Outcome measures	Conclusions
Saver et al 2004	Case series; n=20	Initiation of magnesium sulphate and stroke by paramedics	Adverse events, time to drug admission, functional outcome (Rankin), NIHSS	Paramedics rated patient status on hospital arrival as improved 20%, worsened 5%, and unchanged 75%. Median NIHSS on hospital arrival was 11 in all patients and 16 in patients unchanged since field treatment start. Good functional outcome at 3 months (Rankin 2) occurred in 60%.
Linsberg et al 2006	Obs	Reorganisation of ED moving CT to the ER and streamlining triage by prenotification by emergency medical services, which reduced in-hospital delays and enhanced access to stroke thrombolysis.	Process indicators, numbers receiving thrombolysis	CT delay dropped from 1 hour 3 mins in 1999 to 7 mins in 2004. Door-to-needle time dropped from 1 hour 28 mins to 50 mins, while symptom-to needle time dropped from 2 hours 44 mins to 2 hours 5 mins. From 23 patients in 1999, thrombolysis access was increased to 100 patients in 2004 and 183 patients in 2005.

Table 7: Diagnosis of stroke

Source	Design & Sample	Intervention/criteria	Outcome measures	Conclusions
Wardlaw et al 2004	S/R; Health technology Assessment.	Successful brain imaging strategies for stroke.	Mortality, functional outcomes, accuracy of diagnosis and cost, length of hospital stay and QALY's	Imaging essential to differentiate infarct from haemorrhage. CT did not reliably detect haemorrhage after 8 days after which should use gradient echo MR. The most cost effective strategy is to scan patients immediately on admission.
Goldstein et al 2005	S/R, diagnostic studies	Accuracy of components of clinical assessment	Diagnosis of stroke/TIA	Presence of acute facial paresis, arm drift, or abnormal speech increases the likelihood of stroke (likelihood ratio 5.5). Symptoms associated with high agreement for the diagnosis of stroke or transient ischemic attack vs no vascular event are a sudden change in speech, visual loss, diplopia, numbness or tingling, paralysis or weakness, and non-orthostatic dizziness (average kappa=0.60). Based on examination findings, stroke vascular distribution can be determined with moderate to good reliability (kappa=0.54; 95% CI, 0.39-0.68).

Table 7: Diagnosis of stroke

Source	Design & Sample	Intervention/criteria	Outcome measures	Conclusions
Wardlaw et al 2006	S/R, Health technology Assessment.	To determine whether less invasive imaging tests ultrasound, magnetic resonance angiography, computed tomographic angiography and contrast-enhanced MRA, alone or combined, could replace intra-arterial angiography (IAA).	Cost analysis, stroke, carotid stenosis	In the UK, less invasive tests can be used in place of IAA if radiologists trained in carotid imaging are available. Imaging should be carefully audited. Stroke prevention clinics should reduce waiting times at all stages to improve speed of access to endarterectomy.
Ricci et al, 1991	Obs; n=379 clinical strokes scanned	4 non-stroke lesions on CT scan: 3 malignant tumours and 1 subdural haemorrhage	Stroke incidence	One experienced clinician can usually make diagnosis correctly
Kothari et al, 1995	Obs; n = 446 patients	Diagnosis of admitting doctor compared with discharge diagnosis	Accurate identification of patients with stroke	ED accurately diagnose ICH and SAH (100%). Of the 351 patients with a final discharge diagnosis of ischemic stroke or TIA, 346 were correctly identified by the emergency physicians (sensitivity, 98.6%; PPV 94.8%). 19 patients were diagnosed with stroke or TIA by the emergency physician but had a final discharge diagnosis other than stroke.
Kothari et al, 1997	Obs: 74 stroke patients, and 225 non-stroke	Use of abbreviated neurological scale for triage of stroke patients out of hospital	Correct identification of stroke patients.	Three items identified 100% of stroke patients: facial palsy, motor arm and dysarthria
Martin et al, 1997	Obs; n = 508 referrals with minor stroke or TIA	Agreed TIA/stroke in 373; but vascular area in only 315. No single alternative diagnosis stands out	Stroke incidence	Patients referred for carotid surgery need careful neurological evaluation first
Ferro et al, 1998	Obs; n = 185; general practitioner and admitting doctor stroke diagnoses compared with neurologist-s	44/52 GP diagnoses correct; 169/185 admitting doctor diagnoses confirmed; 3 tumours and 1 subdural	Stroke incidence	Routine clinical diagnosis is robust; absent or unusual history increases error
Kidwell et al 2004	Diagnostic, prospective study. 2 centres, The study was stopped early, after 200 patients were enrolled	MRI v CT for diagnosis of acute cerebral haemorrhage.	Diagnostic accuracy of MRI and CT to detect acute intracerebral hemorrhage.	MRI may be as accurate as CT for the detection of acute hemorrhage in patients presenting with acute focal stroke symptoms and is more accurate than CT for the detection of chronic intracerebral hemorrhage.
Asimos et al 2004	Obs, retrospective review of the hospital CSP registry.	Over 56 months, CSP activation occurred 255 times with 24% of patients treated with tPA	To identify acute ischemic stroke patients and treat them with tPA & compare outcome measures with the National Institute of Neurological Disorders	For community hospitals, ED directed code stroke protocols are a feasible and effective means to screen AIS patients for treatment with thrombolysis.

Table 7: Diagnosis of stroke

Source	Design & Sample	Intervention/criteria	Outcome measures	Conclusions
Morgenstern et al 2004	Diagnostic study, n=13015.	Diagnosis provided by the physician staffing the ED v neurologist who reviewed the patient's source documentation.	Sensitivity and specificity for diagnosis	Physicians practicing in the ED are sensitive (92%) for stroke/TIA diagnosis. The modest positive predictive value (89%) argues for a systems approach with neurology support so that proper decisions regarding acute stroke therapy can be made.
Nor et al 2005	Screening/diagnostic study in EDs. n=343 in development phase and 173 in prospective validation phase	Development and accuracy of ROSIER scale in emergency departments.	Sensitivity, specificity, PPV, NPV	ROSIER scale showed sensitivity of 93% (95% CI 89–97), specificity 83% (77–89), PPV 90% (85–95), and NPV 88% (83–93). Scale useful in helping emergency department staff make appropriate referral to the stroke team.
Hand et al 2006	Diagnostic, prospective study, n=350	Bedside clinical assessment to differentiate stroke and mimics	Diagnosis of stroke or TIA	Final diagnosis of stroke made in 69% of cases. Eight items independently predicted stroke diagnosis: cognitive impairment and abnormal signs in other systems suggested a mimic, an exact time of onset, definite focal symptoms, abnormal vascular findings, presence of neurological signs, being able to lateralize the signs to the left or right side of the brain, and being able to determine a clinical stroke subclassification suggested a stroke.
De Bruijn et al 2006	Diagnostic, prospective study. n=231 with stroke without definite cause	Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) in the management of transient ischemic attack (TIA) and stroke	Presence of cardiac source of event warranting anticoagulation	TEE proved superior to TTE for identification of a cardiac embolic source in patients with TIA or stroke without pre-existent indications. In patients with normal TTE, a cardiac source of embolism was detected by TEE in 40% of patients, independent of age.
Chalela et al 2007	Diagnosis; A single-centre, prospective, blind comparison of non-contrast CT and MRI. n=356	CT v MRI for emergency diagnosis of acute stroke	Infarct and haemorrhagic changes	MRI is better than CT for detection of acute ischaemia, and can detect acute and chronic haemorrhage; therefore it should be the preferred test for accurate diagnosis of patients with suspected acute stroke.

Table 8: Transient ischaemic attack

Source	Design & Sample	Findings	Outcome measures	Conclusions
Redgrave et al 2007	M/A cohort studies; n=19 studies	Positive factors for DWI changes after TIA included symptom duration >60 minutes (OR, 1.50; $P=0.004$), dysphasia (OR, 2.25; $P=0.001$), dysarthria (OR, 1.73; $P=0.03$) and	Correlation of DWI changes with risk factors	Presence of acute ischemic lesions on DWI correlates with several clinical features known to predict stroke risk after transient ischemic attack. Large studies (sample size >1000) needed to determine the independent prognostic value of DWI and its interactions with these clinical

Table 8: Transient ischaemic attack

Source	Design & Sample	Findings	Outcome measures	Conclusions
		motor weakness (OR, 2.20; $P=0.001$). However patient age, sex, HT and diabetes were not associated with the presence of DWI lesions.		characteristics.
Bots et al, 1997	Obs; 7983 people aged 55+; Rotterdam	239 had transient neurological attacks in last 3 years; only 118 were TIAs; both increased with age	Episodes of disturbances in sensibility, strength, speech, and vision that lasted less than 24 hours and occurred within the preceding 3 years	Prevalence of TIAs within 3 years was 1.6/1000 aged 55+; half of all transient neurological attacks are not TIAs
Lemesle et al, 1998	Obs; 283 clinical TIAs on population-based register	25 not TIA: subdural haematoma 12, tumour 8, haemorrhage 5. Of the TIAs 208 (81%) had carotid artery territory and 50 (19%) vertebrobasilar territory TIA. Carotid stenosis > 50% in 87 (34%) cases.	Diagnosis on CT scan within 7 days. Carotid stenosis on cervical carotid Doppler.	Transient neurological symptoms need careful diagnosis and investigation within 7 days.
Johnston et al 2000	Obs; n=1707 patients with TIA assessed in EDs	During the 90 days after index TIA, 180 patients (10.5%) returned to the ED with a stroke, 91 of which occurred in the first 2 days. Stroke or other adverse events occurred in 25.1% in the 90 days.	Stroke, MI, death	Results indicate high short-term risk of stroke and other adverse events among patients who present to an ED with a TIA
Lovett et al 2003	Obs; n= 209 clinical TIAs from population based stroke register	8.6% stroke risk within 7 days from first TIA and 12.0% by 30days	Completed stroke	Much higher early risk of stroke after TIA than previously thought
Clark et al 2003	Obs; n=290 patients with TIA follow up long term (medium 3.8 years)	The 10 year risk of first stroke was 18.8%, MI or death from CHD was 27.8%. 10 year risk of any first stroke, myocardial infarction, or vascular death of 42.8%.	Stroke incidence, MI, CHD, death	Overall risk remains high. Hence secondary prevention measures needed for all patients with TIA.
Douglas et al 2003	Diagnostic case control study. n=322 patients	Head CT was performed in 67% of eligible patients with TIA. Evidence of a new infarct was seen in 4% of patients. A nonischemic cause of TIA symptoms was found in 1.2% patients. During follow-up, 10.9% of TIA patients experienced subsequent stroke.	Head CT and TIA	Evidence of a new infarct on head CT in patients presenting with TIA is associated with increased short-term risk for stroke.

Table 8: Transient ischaemic attack

Source	Design & Sample	Findings	Outcome measures	Conclusions
Hill et al 2004	Obs; n=2285 patients with TIA from register	The risk of stroke after TIA was 9.5% at 90 days and 14.5% at 1 year. The risk of combined stroke, MI or death was 21.8% at 1 year. Hypertension, diabetes mellitus, and older age predicted stroke at 1 year but not earlier.	Stroke, MI, death	
Daffertshoter et al 2004	Obs; n=1380 TIA and 3855 stroke patients in registry	During hospital stay, stroke incidence was 8% for TIA patients (13% at 6 months). 2% of TIA patients died in hospital compared with 9% of stroke patients (P<0.001). 17% TIA compared with 38% IS patients (P<0.05) were dependent at follow-up.	Stroke incidence	Much higher early risk of stroke after TIA than previously thought. TIA patients can have poor outcomes.
Lisabeth et al 2004	Obs; n=612 patients with TIA	Stroke risk within 2 days, 7 days, 30 days, 90 days, and 12 months was 1.64%, 1.97%, 3.15%, 4.03%, and 7.27%, respectively. Stroke risk not influenced by ethnicity, symptoms, or risk factors.	Stroke incidence	Lower incidence than previously reported.
Coull et al 2004	Obs; n = 174 patients after TIA (n87) or minor stroke (n87)	Prospective cohort study of 9 general practices. Risk of reoccurrence 11.5% at 7 days; 15% at 1 mth; 18.5% at 3 months	Risk of recurrent stroke at 7 days, 1 month, and 3 months.	The risks of recurrence were much higher than commonly quoted.
Eliasziw et al 2004	Cohort study; n=603 patients who had a hemispheric TIA related to internal carotid artery disease.	For patients with a first-recorded hemispheric TIA (n = 603), the 90-day risk of ipsilateral stroke was 20.1%, higher than the 2.3% risk for patients with a hemispheric stroke (n = 526). The 2-day risks were 5.5% and 0.0%, respectively.	Stroke occurrence after TIA	Patients who had a hemispheric TIA related to internal carotid artery disease had a high risk of stroke in the first few days after the TIA. Early risk of stroke was not affected by the degree of internal carotid artery stenosis
Wilson et al 2005	Diagnostic study; n=136 patients	Modified version of a questionnaire designed to detect TIA was tested against the gold standard of a specialist assessment	Specificity and sensitivity	Neither postal survey or administered survey had good sensitivity (0.56-0.61) or specificity (0.76-0.81) and hence is not that useful for screening.
Kleindorfer et al 2005	Obs; n=1.3 million. Life-table analyses were used for prognosis.	The incidence rate for TIA was 83 per 100 000. Blacks and men had significantly higher rates of TIA than whites and women. Risk of stroke after	Stroke incidence	There are racial and gender-related differences in the incidence of TIA. Study found a striking risk of adverse events after TIA; however, there were no racial or gender differences predicting these events.

Table 8: Transient ischaemic attack

Source	Design & Sample	Findings	Outcome measures	Conclusions
		TIA was 14.6% at 3 months, and risk of TIA/stroke/death was 25.2%.		
Bray et al 2007	Retrospective case series; n=98 patients with suspected TIA	49% patients with TIA had high risk for stroke (ABCD Score \geq 5). This high-risk group contained all four strokes that occurred within 7 days (sensitivity 100%, specificity 53%, PPV 8%, NPV 100%), and six of seven occurring within 90 days (sensitivity 86%, specificity 54%, PPV 12.5% and NPV 98%).	Stroke incidence	ABCD tool useful for early detection and management of high risk patients with TIA.
Johnston et al 2007	Prospective cohort study; n=2893 (4 settings - primary care, outpatient clinics, and hospital services (emergency departments) in two different countries (UK and USA).	Validation of the ABCD2 tool	Sensitivity/specificity, prognostic	ABCD2, validated well (c statistics 0.62-0.83); overall, 1012 (21%) of patients were classified as high risk (score 6-7, 8.1% 2-day risk), 2169 (45%) as moderate risk (score 4-5, 4.1%), and 1628 (34%) as low risk (score 0-3, 1.0%). Implications: Existing prognostic scores for stroke risk after TIA validate well on multiple independent cohorts, but the unified ABCD2 score is likely to be most predictive. Patients at high risk need immediate evaluation to optimize stroke prevention.

Table 9: Thrombolysis

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Cornu et al 2000	M/A; n = 4 trials, 1292 patients after stroke	Intravenous streptokinase within 6 hours of acute ischaemic stroke	Death or disability	Neutral
Wardlaw et al, 2003	M/A; n = 18 trials, n = 5727 patients	Any thrombolytic treatment	Mortality; dependency; fatal ICH	Thrombolysis increases mortality, but may reduce disability in survivors. IV rTPA needs to be administered in experienced centers in highly selected patients.

Table 9: Thrombolysis

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Graham 2003	M/A n=15 published, open-label studies that broadly followed approved indications and guidelines for tPA use in nonselective patient populations. N=2639 treated patients.	The safety of Intravenous thrombolytic therapy with tPA for acute ischemic stroke.	SICH, mortality, protocol deviation	SICH rate was 5.2%, slightly lower than the 6.4% rate in the NINDS trial. The mean total death rate (13.4%) and proportion of subjects achieving a very favorable outcome (37.1%) were comparable to the NINDS trial results. Protocol deviations were reported in 19.8%. Comparing across studies showed that the mortality rate was correlated with the percentage of protocol violations. Postapproval data support the safety of IV tPA for acute ischemic stroke, especially when established treatment guidelines are followed.
Mielke et al 2004	M/A; 8 trials; n = 1334 patients after stroke	Different doses, routes and agents of thrombolytic treatment within 14 days of stroke onset	Mortality; functional outcome; intracranial haemorrhage	Insufficient evidence to conclude whether lower doses may be safer, or whether any particular agent or route is better than another
ATLANTIS, ECASS AND NINDS RT-pa Study Group 2004	M/A; 6 trials; n = 2775	To assess relationship of interval from stroke onset to start of thrombolysis treatment on outcome at 3 months.	Mortality; NIHSS; Barthel index; modified Rankin scale; at 3 months; intracranial haemorrhage	The sooner rt-PA is given the greater the benefit, especially if started within 90 minutes. Some benefit beyond 3 hours but with added risks.
Engelter et al 2006	S/R of 6 cohort studies, n = 2,244 patients; 477 (21%) aged ≥ 80 years	Cohort studies of tPA in patients $>$ or $<$ 80 years of age	Mortality, mRS, complications, SICH	Significant differences in baseline characteristics to the disadvantage of older patients were present in all studies leading to increased mortality (3.09-time higher 3 month mortality $P < 0.001$) and less likely to have good outcomes (OR = 0.53 $P < 0.001$). The likelihood for 'sICH' (OR = 1.22, $P = 0.34$) was similar in both age groups suggesting safe to include such patients in further RCTs.
Furlan et al.1999	RCT, n=180 pts, acute ischemic stroke $<$ 6hrs from onset with angiographically proven occlusion of the MCA and without major early infarction signs on CT scan	Intra-arterial prourokinase for acute ischemic stroke (PROACT II) 9mg IA r-proUK + heparin -v- heparin	¹ - mRS 0-2 at 90 days ² - % MCA recanalisation, % ICH with neurological deterioration, death	At 90 days 40% of r-proUK and 25% of controls had mRS 0-2 ($p = 0.04$) Recanalisation rate 66% r-proUK, 18% control ($p < 0.001$) ICH with neurological deterioration within 24 hrs 10% r-proUK, 2% controls ($p = 0.06$)
Clark et al. 2000	RCT; n = 142 pts, acute ischaemic stroke $<$ 6 hrs, NIHSS $>$ 3, standard exclusions for thrombolysis but no CT criteria other than haemorrhage	The Alteplase 0-6 hour acute stroke (rt-PA 0.9 mg/kg) vs placebo	¹ - % decrease NIHSS $>$ 4pts at 24 hrs and 30 days, volume of infarct at 30 days ² - multiple	Trial stopped by DMSB because of excess haemorrhage in 5-6 hr group. At 24 hrs 40% of rt-PA and 21% of placebo had improved $>$ 4 pts on NIHSS ($p < 0.02$) but at 30 days 60% rt-PA and 75% placebo ($p < 0.05$). No treatment benefits were seen on secondary outcome measures.

Table 9: Thrombolysis

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Alexandrov et al 2004	RCT, n = 126 pts receiving tPA within 3 hours	Patients receiving tPA within 3 hours PLUS continuous 2-MHz transcranial Doppler ultrasonography (the target group) or placebo (the control group).	recanalization as assessed by transcranial Doppler ultrasonography or dramatic clinical recovery, recovery at 24 hours, mRS at three months, and death at three months.	Complete recanalization or dramatic clinical recovery within two hours after the administration of a t-PA bolus occurred in 49% v 30%; P=0.03). No difference in recovery at 24 hours (44% v 40%). No significant improved outcome at 3 months (mRS 0-1), 42% v 29% (P=0.20).
Daffertshofer et al 2005	Psuedo RCT (alternate allocation), n=26 pts (trial terminated early)	safety of tPA plus low-frequency ultrasound (300 kHz) v tPA alone.	SICH, recanalisation, mortality	The study was prematurely stopped because 5/12 pts from the tPA only group and 13/14 pts treated with the tPA plus ultrasound showed signs of bleeding in MRI (P<0.01). Within 3 days of treatment, 5 SICH occurred within the tPA plus ultrasound group. At 3 months, no outcome differed between both groups.
Ducrocq et al 2005	RCT, n=27 pts (14 IV v 13 IA thrombolysis). Trial terminated due to high mortality rate for both groups.	IA v IV thrombolysis	mRS 0-2, mortality, SICH,	Seven patients (26%) died, 4 in the IV group, 3 in the IA group (SIH in 2, and oedematous infarct in 1). Patients given IVF were treated significantly earlier (4:16 h vs 5:24 h; p=.007). Although IA patients showed greater and earlier improvement there was no significant difference in primary and secondary outcomes.
Macleod et al 2005	RCT, n=16 pts	IA urokinase within 24 h of symptom onset in patients with stroke and angiographic evidence of posterior circulation vascular occlusion	Functional outcome, mortality, adverse events	Imbalance in groups (more severe strokes in treatment arm). A good outcome was observed in 4 of 8 patients who received intra-arterial urokinase compared with 1 of 8 patients in the control group. Need large trial.
Hacke et al 2005	RCT, n=104 pts within 3-9 hours after stroke; 47 involved in part I of trial and 57 involved in part II	Safety and efficacy of IV desmoteplase, administered within 3 to 9 hours of ischemic stroke onset in patients with perfusion/diffusion mismatch on MRI. Part I had fixed doses (25 mg, 37.5 mg, or 50 mg) or placebo. Phase II had lower weight-adjusted doses escalating through 62.5 (mu)g/kg, 90 (mu)g/kg, and 125 (mu)g/kg. (DIAS)	SICH, rate of reperfusion on MRI after 4 to 8 hours, NIHSS, mRS and BI at 90 days	Part 1 was terminated early because of high rates of sICH (26.7%). In Part 2, the sICH rate was 2.2%. No sICH occurred with placebo in either part. Reperfusion rates up to 71.4% (P=0.0012) were observed with desmoteplase (125 (mu)g/kg) compared with 19.2% with placebo. Favorable 90-day clinical outcome was found in 22.2% of placebo-treated patients and between 13.3% (62.5 (mu)g/kg; P=0.757) and 60.0% (125 (mu)g/kg; P=0.0090) of desmoteplase-treated patients. Favorable outcome occurred in 52.5% of patients experiencing reperfusion versus 24.6% of patients without reperfusion.
Furlan et al 2006	RCT; n=37 pts	dose escalation study investigating doses of 90 (mu)g/kg and 125 (mu)g/kg desmoteplase. Eligibility criteria included baseline NIHSS scores of 4 to 20 and MRI evidence of perfusion/diffusion mismatch. (DEDAS)	% reperfusion at 4-8 hours on MRI, SICH, functional outcome at 90 days	At a dose of 125 (mu)g/kg desmoteplase appeared to improve clinical outcome (reperfusion 53%v37% control, good functional outcome 60% v 25%) , especially in patients fulfilling all MRI criteria. Small patient numbers. Confirmed earlier DIAS study.

Table 9: Thrombolysis

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Flint et al 2007	RCT N=80 pts with acute stroke from intracranial ICA occlusion were identified.	Mechanical thrombectomy of acute intracranial ICA occlusion using the Merci Retriever device, alone or in combination with adjunctive endovascular therapy	Rate of ICA recanalisation, mRS of 0 to 2 at 90 days, procedural complications, mortality, haemorrhage rates.	53% had successful ICA recanalization with the Merci Retriever alone and 63% had ICA recanalization with use of the Merci Retriever plus adjunctive endovascular treatment. Good clinical outcome (mRS 0-2) occurred in 39% of patients with ICA recanalization and in 3% of patients without ICA recanalization. Ninety-day mortality was 30% in the recanalized group and 73% in the nonrecanalized group.
Foell et al 2003	Case series with historical control, n=112 cases matched to 168 patients from NINDS trial	tPA in those with pre-existing disability v those without	Mortality, mRS, NIHSS score	Those with pre-existing disability had much higher mortality (33% v 14%). Treated patients appear able to return to their prestroke level of function as often as patients without pre-existing disability.
Szoeke et al 2003	Obs, retrospective audit n=932 patients with ischemic stroke of which 30 received IV tPA	Description of implementation of rtPA.	Treatment rate, protocol violations, SICH, mRS and mortality at 3 months	Eleven patients (37%) had excellent clinical outcomes at 3-month (mRS 0-1), and 15 (50%) were functionally independent (score, 0-2). Mortality rate was 10%. Two patients (7%) had SICH. Treatment deviated from protocol in 7 patients (23%), 5 of whom received tPA over three hours after stroke onset.
Smith et al 2005	Non controlled, prospective, multicentre safety and feasibility study, n=141 pts	Safety and efficacy of a Merci Retriever to open occluded intracranial large vessels within 8 hours of stroke onset in pts ineligible for intravenous tPA	Recanalisation, mortality, mRS at 90 days.	Recanalization was achieved in 48% (significantly higher rates than that expected using an historical control of 18%). Clinically significant procedural complications occurred 7.1% of patients. SICH was observed in 7.8% patients. Good neurological outcomes (mRS < or =2) were more frequent at 90 days in patients with successful recanalization compared with unsuccessful recanalization (46% v 10%; P<0.0001), and mortality was less (32% v 54%; P=0.01).
Inoue et al 2005	Case controlled study, n=91 with 182 matched controls from Japan's Multicenter Stroke Investigator's Collaboration study	Intra-arterial urokinase (IA-UK) thrombolysis in patients with cardioembolic stroke v control	mRS, mortality, adverse events, LOS	A favorable outcome (mRS of 0-2) was more frequently observed in the UK group (50% v 34% p = 0.0124). No difference in the mortality rate (11% v 13%) or LOS (46 v 42 days).

Table 9: Thrombolysis

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Smith 2006	Non controlled, prospective, multicentre safety and feasibility study, n=111 pts	Safety and efficacy of a Merci Retriever to open occluded intracranial large vessels within 8 hours of stroke onset in pts received IV tPA but did not recanalize or who were ineligible for IV tPA	Recanalisation, mortality, mRS at 90 days.	27% received IV tPA before mechanical retrieval. Treatment with the Retriever alone resulted in successful recanalization in 54% and in 69% after adjunctive therapy (IA tPA, mechanical). SICH occurred in 9.0%. Clinically significant procedural complications occurred in 4.5% pts. The SICH rate was 6.7% in pts pretreated with IV tPA and 9.9% in those without (P > .99). Mechanical thrombectomy after IV tPA seems as safe as mechanical thrombectomy alone.
Lindsberg & Mattle 2006	S/R of case series, n=420 Basilar Artery Occlusion pts treated with IVT (76) and IAT (344).	IA v IV thrombolysis for basilar artery occlusion patients	Mortality, dependency, recanalisation	Death or dependency were equally common: 78% v 76% (P=0.82). Recanalization was achieved more frequently with IAT (65% v 53%; P=0.05), but survival rates after IVT (50%) and IAT (45%) were equal (P=0.48). A total of 24% of patients treated with IAT and 22% treated with IVT reached good outcomes (P=0.82).
Sylaja et al 2006	Obs;prospective cohort study n=1135 from Canadian Alteplase for Stroke Effectiveness Study	Patients aged > or = 80 years (n = 270) treated with intravenous tPA were compared with those aged <80 years (n = 865).	SICH, favourable outcome (mRS 0-1), complications	No difference in SICH (4.6% v 4.4%). However less favourable outcomes at 90days (26% v 40%) reflecting other comorbidities such as AF, CHF, hypertension and increased stroke severity.
Bray et al 2006	Obs; Audit of 888 patients with consecutive stroke and TIAs to a 426-bed tertiary bed hospital from March 2003 to October 2005	Description of implementation of rtPA at one site.	Treatment rate, exclusion criteria, protocol violations, SICH, mRS and mortality at 3 months	72 patients received t-PA. If all eligible pts had arrived within 3 h, treatment rate was estimated at 32.5%. Protocol violations occurred in 15 pts. There were seven asymptomatic ICH and one nonfatal SICH. At 3 months, 37% had achieved excellent recovery (mRS 0–1) and 7 (10%) had died.
Wahlgren et al 2007	Obs; n=6483, 285 centres	Observation data of patients treated with tPA in Europe.	Symptomatic (a deterioration in National Institutes of Health stroke scale score of ≥4) ICH type 2 within 24 h and mortality at 3 months.	At 24 h, SICH was 1.7% , 9.5% at 7 days, the proportion with the same condition as per the Cochrane definition was 7.3% compared with 8.6% in the pooled RCTs. The mortality rate at 3 months in SITS-MOST was 11.3% compared with 17.3% in the pooled RCTs. IV alteplase is safe and effective in routine clinical use when used within 3 h of stroke onset, even by centres with little previous experience.

Table 10: Ischaemic stroke and TIA: Antithrombotic therapy in the acute phase

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Berge & Sandercock 2002	M/A 4 trials; n = 16,558 patients	Anticoagulants (UFH or LMWH) vs aspirin started within 14 days	Mortality; symptomatic intracranial haemorrhage	Anticoagulants offered no net advantages over antiplatelet agents. Anticoagulants associated with increased intracranial haemorrhage.
Stam et al 2002	M/A 2 trials; n = 79 patients	Anticoagulation for cerebral sinus thrombosis	Mortality; dependency; major haemorrhage	Anticoagulant therapy associated with reduced risk of death or dependency; appeared safe but very small numbers.
Lyrer et al 2003	M/A; No RCTs found. 26 case series, n = 327 patients	Antithrombotics drugs (antiplatelet drugs, anticoagulation) v placebo in patients with extracranial internal carotid artery dissection	Death; dependency in ADL; rate of intracranial haemorrhage	Case series suggest no difference in outcomes between therapies with very small number of ICH (0.5%). Authors conclude, due to no RCTs or CCTs, there is no evidence to support their routine use for the treatment of extracranial internal carotid artery dissection.
Sandercock et al 2003	M/A 9 trials; n = 41,399 patients	160-300mg aspirin once daily started within 48hrs of stroke.	Mortality; dependency; stroke recurrence; haemorrhagic complications.	Significant decrease in death or dependency at 6 months; treatment increased the odds of complete recovery, and decreased incidence of recurrence stroke and pulmonary emboli. Small excess of symptomatic intracranial haemorrhage.
Gubitz et al, 2004	M/A; n = 21 trials, 23,427 patients	Anticoagulation treatment within first 14 days of acute stroke, or not	Mortality; dependency; PE; DVT; recurrent stroke or intracranial haemorrhage	Reduced rate of DVTs but no other benefit
Sandercock, Counsell & Stobbs, 2005	M/A; n = 6 trials, 740 patients treated within 14 days	Standard heparin or special heparinoid (low molecular weight; LMW)	Mortality; PE; DVT; intracranial or intracerebral haemorrhage	LMW heparinoid associated with fewer DVTs; data otherwise insufficient to draw conclusions
Ciccone et al 2005	M/A; n=2 trials, 414 patients within 6 hours	Glycoprotein IIb-IIIa inhibitors (both using abciximab) v placebo	SICH, mRS, mortality, adverse events	Non-significant reduction of death and dependency combined (OR 0.79) and of death alone (OR 0.67). Non-significant increase of symptomatic intracranial haemorrhages (OR 4.13) and of major extracranial haemorrhages (OR 1.51)..Authors suggest insufficient evidence to draw conclusions.
Ricci, et al 2006	M/A; 3 trials, n = 1002 patients	Use of piracetam for acute ischaemic stroke (within 48 hours)	Death; dependency; haemorrhage.	Possible increase in early death, and no reduction in dependency
Paciaroni et al 2007	M/A; n=7 trials, 4624 patients	Unfractionated heparin or low-molecular-weight heparin or heparinoids), started within 48 hours, with other treatments (aspirin or placebo) in patients with acute ischemic cardioembolic stroke.	Recurrent stroke, mortality, dependency, ICH, adverse events	In patients with acute cardioembolic stroke, early anticoagulation is associated with a nonsignificant reduction in recurrence of ischemic stroke (p=0.09), no substantial reduction in death and disability (p=0.9), and an increased intracranial bleeding (p=0.02).

Table 10: Ischaemic stroke and TIA: Antithrombotic therapy in the acute phase

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Sherman et al 2000	RCT; n = 48 sites, 500 patients with acute stroke. 248 intervention 252 controls	Ancrod within 3 hrs of stroke for 72hrs, followed by 1hr infusions at 96 and 120hrs vs placebo	Survival to day 90 with Barthel 95; death; intracranial haemorrhage	Ancrod group achieved more favourable functional status (p = 0.04), but had more intracranial haemorrhage (p = 0.06).
Rödén Jüllig et al 2003	RCT; n=441 patients with ischaemic stroke within 48 hours	Aspirin (325mg) commenced within 48hours v placebo for 5 days	SSS	No difference in stroke progression (15.9% v 16.7%) or patient outcomes at 3 months.
LaMonte et al 2004	RCT; n=171 patients within 12 hours and NIHSS between 5-22	Argatroban anticoagulation. Initial dose of 100 (mu)g/kg bolus then either continuous IV at 3 (mu)g/kg per minute (n=59) or 1 (mu)g/kg per minute (n=58) adjusted to target aPTTs or placebo (n=54) for 5 days	SICH, adverse events, mortality	SICH not significantly different between groups (high-dose argatroban, 5.1%; low-dose argatroban, 3.4%; placebo, 0%; P=0.18). No significant between-group differences occurred in asymptomatic ICH (7 events), major systemic hemorrhage (no event), or 90-day mortality (13.4% overall).
Hennerici et al 2006	RCT; n = 1222 patients with acute stroke. (608 intervention v 614 placebo)	Ancrod within 6 hrs of stroke vs placebo	Survival to day 90 with Barthel 95; death; intracranial haemorrhage	No difference in functional outcome at 90 days (p = 0.96).

Table 11: Intracerebral haemorrhage

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Prasad & Shrivastava, 1998	M/A; n = 4 trials, 354 patients	Surgery for supratentorial, intracerebral haemorrhage, or routine medical care	Mortality; dependency in ADL	Insufficient data to draw any conclusions; endoscopic evacuation worth investigation
Righetti et al 2004	M/A; n=11 trials	IV Glycerol v control	Mortality, function (mRS), adverse events	Too few data in patients with haemorrhage to draw conclusion.
Feigin et al 2005	M/A; n=8 trials, 5 trails of PICH 206 patients	Corticosteroid therapy patients who die or have a poor outcome at one to six months after the onset of SAH or PICH	Mortality within 6 months, poor outcome within 6 months, adverse events	Too few patients and wide confidence intervals to make clear conclusions.
You & Al-Shahi 2006	M/A; n=4 trials (phase II), 489 patients (373 received drug and 116 placebo)	Haemostatic drugs v placebo within 4 hours (all bar 2 patients received recombinant activated factor VII) NOTE: It was announced that the	Mortality, dependence (mRS), extended glasgow scale, adverse events	Haemostatic drugs appeared to reduce the risk of death or dependence within 90 days of PICH (RR 0.79 (95% CI 0.67 to 0.93)), but not when assessed by the extended Glasgow Outcome Scale (RR 0.90 (95%CI 0.81 to 1.01)). There was a statistically significant excess of arterial thromboembolism

		large phase III trial failed to find benefits. This trial has not been published in full at time of publication.		at 160 mcg/kg rFVIIa. Authors suggest intervention currently cannot provide clear guidelines for clinical practice and further trials needed.
Teernstra et al 2006	M/A; n= 9 trials (8RCT and 1 quasi RCT), 1486 patients	Surgery versus conservative treatment For ICH.	Mortality, dependency	Treatment failed to show a statistically significant reduction in the odds of death (OR: 0.84, 95% CI: 0.67-1.07) in surgically treated patients. Subgroup analysis suggests potential benefits in specific situations with different techniques but these results are not robust and require more primary trial data.
Zuccarello et al, 1999	RCT; n=20 acute ICH	Evacuation, or best medical management	Glasgow Outcome scale at 3 months; Barthel; Rankin and NIHSS	Trend only towards better outcome after early surgery
Kalita et al 2004	RCT, n=29 patients with ICH within 6 days	A single iv infusion of 100 ml 20% mannitol (about 0.3 mg/kg) vs saline	Improvement of GCS, Reduction in SPECT asymmetry, Case fatality at 1 month	No difference in outcomes.
Mayer et al 2005	RCT; n=399 patients with ICH	Recombinant activated factor VII (rFVIIa) v placebo	Mortality, dependence (mRS), extended glasgow scale, adverse events	Significantly reduced hematoma volume growth in rFVIIa groups. Also reduces mortality, and improves functional outcomes at 90 days. Small increase in thromboembolic adverse events.
Mendelow et al 2005	RCT n=1033 patients	Compares early surgery with initial conservative treatment for patients with ICH.	Function, mortality, adverse events	ICH patients in neurosurgical units show no overall benefit from early surgery when compared with initial conservative treatment.
Hayley et al 2005	Combined analysis of 2 RCTs n=3450 (571 with haemorrhage)	gavestinel, a glycine-site antagonist given within 6 hours of suspected ischemic or haemorrhagic stroke.	BI at 3 months, adverse events	Gavestinel is not of substantial benefit or harm to patients with primary intracerebral hemorrhage.
Misra et al 2005	RCT, n=128 ICH randomised within 6 days	Mannitol 20%, 100 ml every 4 h for 5 days, tapered in the next 2 days v control/placebo.	1-month mortality, functional disability at 3 months (BI)	No difference in endpoints.
Secades et al 2006	RCT; n=39 patients with ICH with GCS>8, NIHSS>7	Placebo v 1 g/12 h citicoline for 2 weeks	Adverse events, mRS at 3 months	Citicoline had same rate of adverse events. Authors suggest it seems to be a safe drug in human ICH with a positive trend regarding efficacy.
Qureshi et al 2005	Case series; n=27 patients with ICH and acute hypertension	feasibility and safety of intravenous antihypertensive protocol for acute hypertension (using IV labetalol, hydralazine, or nitroprusside)	Blood pressure, haematoma growth/CT, adverse events, GCS, mRS	Only 2 patients deteriorated. 2/22 patients demonstrated haematoma growth. mRS significantly better for those treated <6hrs compared to those treated 6-24hours after stroke (p=0.03). Protocol appears feasible and safe.

Table 12: General interventions in the acute phase

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Blood Pressure in Acute Stroke Collaboration (BASC), 2001	M/A; n = 5 trials, 218 patients with acute stroke	Deliberate alteration of blood pressure within two weeks of stroke	Mortality, disability, stroke recurrence, discharge destination	Insufficient data to draw any conclusions.
Bennett et al, 2005	S/R; 3 trials, n = 106	Assess the effect of hyperbaric O2 therapy in the treatment of acute ischemic stroke.	Mortality, disability, function.	No evidence to show that hyperbaric O2 therapy used during the presentation of an acute ischemic stroke results in improvement in disability or function.
Willmot et al 2004	S/R, cohort studies; 32 studies n=10982 pts	Review effect of acute high blood pressure and patient outcome.	BP, death or dependency, stroke reoccurrence, hematoma expansion	High BP in acute ischemic stroke or PICH is associated with subsequent death, death or dependency, and death or deterioration.
Gray et al 2006	S/R, 3 trials, 145 pts, 93 in treatment group and 52 in control	effects of Nitric Oxide (NO) donors on systemic hemodynamic measures in patients with acute/subacute stroke.	BP, Pulse Pressure (PP), Heart rate (HR)	Treatment reduces BP, PP, and other derivatives in acute and subacute stroke while increasing HR.
Mistri et al 2006	S/R of non RCTs, 12 trials, n=319 pts with ischaemic stroke	Induced blood pressure in acute phase of stroke v control	BP, adverse events, mortality	Few studies undertaken, but pressor therapy in acute stroke appears feasible and well-tolerated. The benefit and risks in terms of clinical outcomes remains unknown, but intensive monitoring is advised if such therapy is undertaken.
Scott et al, 2000	RCT; n=52 acute stroke patients with glucose 7.0-17.0 mmol/L	Glucose potassium insulin infusion (GKI) or saline infusion	Mortality at 4 weeks.	Administration of GKI safe; no significant effect on glucose; outcomes similar.
Dippel et al 2001	RCT; n = 76 26 = high dose 25 = low dose 25 placebo	Paracetamol 1000mg X 6 per day vs 500mg x 6/day vs placebo. For 5 days.	Temperature at 24hrs; Reduction in body temperature at 1 and 5 days post start of treatment; Modified Rankin at 1 month	Mean temperature at 24hrs 0.4°C lower in high dose group. No other significant differences.
Schrader et al 2003	RCT; (Phase II study) n = 339 patients	Candesartan vs placebo for 10-15% blood pressure reduction in hypertensive patients in acute ischaemic stroke for 7 days and then up to one year.	Mortality, vascular events and side effects	Significant benefit for candesartan group in mortality and number of vascular events. No differences in rate of side effects. Study stopped early due to imbalance in end-points.
Woessner et al 2003	RCT, n=40 pts	6% hydroxyethyl starch (HES) 130/0.4 or crystalloid solution as continuous infusion over 4 days with a total dose of 6.5 liters	hemodynamics (eg. cardiac output, blood pressure, flow velocity with transcranial Doppler) and rheology (hematocrit and plasma viscosity). Laboratory, hemostaseology (including factor VIII) and an adverse event questionnaire.	Continuous infusion (1 ml/min) of HES 130/0.4 or crystalloid solution did not differ regarding safety or hemodynamic efficacy.

Table 12: General interventions in the acute phase

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
LaMonte et al 2004	RCT, n=171 pts within 12 hours and NIHSS score 5-22	Patients received continuous IV argatroban (100 (mu)g/kg bolus) at 3 (mu)g/kg per minute (n=59) or 1 (mu)g/kg per minute (n=58), respectively, adjusted to target activated partial thromboplastin times (aPTTs) or placebo (n=54) for 5 days.	SICH, aPTTs, complications	argatroban at each dose evaluated significantly prolonged aPTTs without increasing ICH or major bleeding although there was 3 events during argatroban infusion and 2 events at 7 days or more after stopping infusion compared to no SICH in control group.
Eames et al 2005	RCT, n=37 pts	double-blind, placebo controlled, parallel group study to bendrofluzide 2.5 mg daily or matching placebo, within 96 h of stroke onset, for a 7-day period	BP, cerebral blood flow velocity, ECG and transcutaneous carbon dioxide levels, pulse interval, BP variability and cardiac baroreceptor sensitivity.	Bendrofluzide is sn ineffective hypotensive agent at the standard dosage.
Singhal et al 2005	RCT, n=16 (9 intervention, 7 control)	Oxygen therapy via high flow facemask for 8 hours v room air in pts with acute stroke (<12 hours) and perfusion-diffusion "mismatch" on MRI.	Stroke scale scores, MRI scans at baseline, 4 hours, 24 hours, 1 week, and 3 months.	Transient improvement of clinical deficits and MRI abnormalities in select patient. Very small numbers.
Emsley et al 2005	RCT, n=34 pts within 6 hours	Recominant human cytokine interleukin receptor antagonist (IL-1ra) IV - 100 mg loading dose over 60 seconds, followed by a 2 mg/kg/h infusion over 72 h v placebo	Adverse events, neutrophil and total white cell counts, C reactive protein	No adverse reactions in any of the 34 patients and positive biological markers indicating treatment is safe and potentially useful.
Abciximab Emergent Stroke Treatment Trial (AbESTT) Investigators 2005	RCT, n=400 pts within 6 hours	0.25 mg/kg intravenous bolus Abciximab followed by a 12-hour infusion at 0.125 (mu)g/kg per minute (maximum 10 (mu)g/min) v placebo	SICH, mRS	SICH within 5 days was diagnosed in 3.6% v 1%. p=0.09. No difference in asymptomatic hemorrhagic transformation rate or function at 3 months.
Kwon et al 2005	RCT, n=135 pts with intracranial artery stenosis (IAS)	cilostazol 200 mg per day or placebo for 6 months	Progression of symptomatic IAS on MRA, clinical events and progression on TCD	Progression of symptomatic IAS in cilostazol group was significantly lower than that in placebo group (P=0.008).
Shibuya et al 2005	RCT, n=160 patients within 48 hours of stroke	60 mg fasudil or a placebo (saline) by intravenous injection over 60 min, twice daily for 14 days	Neurological status at 2 weeks after the start of treatment, clinical outcome at 1 month after the onset of symptoms	Fasudil treatment resulted in significantly greater improvements in both neurological functions (p=0.0013), and clinical outcome (p=0.0015). There were no serious adverse events reported in the fasudil group.
Lodder et al 2006	RCT, 880 pts with acute stroke within 12 hours	diazepam 10 mg or placebo by rectiole, as soon as possible, followed by 10-mg tablets twice daily for 3 days	mRS, BI, adverse events	Point estimates favored diazepam treatment in various analyses (OR 1.14-1.46). Diazepam treatment seems beneficial in cardioembolic infarct patients (OR 2.26-2.65). No difference in adverse events in acute ischemic stroke, but increase in adverse events for patients with ICH.

Table 12: General interventions in the acute phase

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Ullegaddi et al 2006	RCT, n=96 patients with acute stroke	daily oral 800 IU (727 mg) vitamin E and 500 mg vitamin C (n = 24), or B-group vitamins (5 mg folic acid, 5 mg vitamin B(2), 50 mg vitamin B(6), and 0.4 mg of vitamin B(12); n = 24), both vitamins together (n = 24), or no supplementation (n = 24) for 14 days.	plasma or blood vitamin status, plasma total antioxidant capacity (TAOC), malondialdehyde (MDA), tHcy and C-reactive protein (CRP).	Significantly improvements in all outcomes in all three intervention groups. There were no additive or synergistic effects of antioxidants and B-group vitamins together on any outcome measure.
Grey et al 2007	RCT, n=933 pts. Study stopped early due to slow enrolment	Patients presenting within 24 h of stroke onset and with admission plasma glucose concentration between 6.0–17.0 mmol/L were randomly assigned to receive variable-dose-insulin GKI (intervention) or saline (control) as a continuous IV infusion for 24 h.	Mortality at 90 days, avoidance of death or severe disability at 90 days	GKI infusions significantly reduced plasma glucose concentrations (mean difference in glucose 0.57 mmol/L, p<0.001) and blood pressure (mean difference in blood pressure 9.0 mmHg, p<0.0001). Treatment within the trial protocol was not associated with significant clinical benefit (no difference in mortality), although the study was underpowered and alternative results cannot be excluded.
Ronning & Guldvog, 1999	CCT; n = 550 acute stroke patients	Oxygen 3L/min 100%, or air for 24 hours	Death	Higher survival in control group with severe stroke; no other differences
Koenig et al 2006	CCT, n=100 acute stroke patients	Review rate of adverse events with induced hypertension (IH) therapy v control	BP, adverse events	Generally adverse events were similar indicating IH may be safe and a prospective RCT is needed.
Bhalla et al 2003	Obs; n = 364 patients with acute stroke in 6 different European centers (6 months data collection).	Clinical management in the first week of ischaemic stroke.	Survival at 3 months	There was significant variation in acute physiological support in acute stroke across four European centers. 3 month case fatality rates varied from 10 to 28% unexplained by casemix.
Allport et al 2006	Obs; n = 59 acute ischemic stroke	Continuous monitoring in first 72 hours	Blood glucose	On admission, 36% of patients had preexisting diabetes. At 8 hours post stroke 50% of nondiabetic subjects and 100% of diabetic patients were hyperglycemic (≥ 7 mmol/l). This then decreased by 14–16 h poststroke when only 11% of nondiabetic and 27% of diabetic patients were hyperglycemic. A late hyperglycemic phase 48–88 h poststroke was observed in 27% of nondiabetic and 78% of diabetic patients. Thirty-four percent of nondiabetic and 86% of diabetic patients were hyperglycemic for at least a quarter of the monitoring period.

Table 13: Neuroprotective agents

Source	Design & Sample	Intervention	Outcome measures	Conclusions
Berezcki & Fekete, 1997	M/A; n = 1 trial, 33 patients	Use of vinpocetine within 14 days of stroke	Mortality; dependency	Insufficient data to draw any conclusions
Candelise & Ciccone, 2001	M/A; n = 12 trials, 2265 patients	Ganglioside treatment within 15 days of onset	Mortality; dependency.	Insufficient data to draw reliable conclusion but no benefits found for outcomes; may cause Guillain-Barre syndrome
Tirilazad Trialists 2001	M/A; n= 6 trials; 1757 patients with presumed acute ischaemic stroke	Tirilazad mesylate administered within 24 hours of stroke onset.	Mortality; dependency; adverse events	Tirilazad increased odds of being dead or disabled by one fifth. Increased incidence of infusion site phlebitis. No further trials warranted.
Gandolfo et al 2002	M/A; n=5, 3510 patients	Lubeluzole (doses of 5, 10 and 20 mg/day for 5 days) v placebo	Mortality, dependency, adverse events	No difference for either odds of death from all causes (OR=0.93, 95% CI 0.79-1.09) or reduced the odds of being dead or dependent at the end of follow-up (OR=1.04, 95% CI 0.91-1.19). Lubeluzole was associated with a significant excess of heart-conduction disorders (Q-T prolonged > 450 msec) at the end of follow-up (OR=1.43, 95% CI 1.09-1.87).
Muir & Lees 2003	M/A; 36 trials; 11209 patients	Excitatory amino acid antagonists within 24 hours of stroke	Mortality, dependency, complications	There was no evidence of significant benefit or harm from drugs modulating excitatory amino acid action. Reduction of death or dependence by 8% or more has been excluded for gavestinel and lubeluzole, which contribute most of the data for this review.
Bath et al, 2004	M/A; n = 5 trials, 793 patients	Methylxanthines (e.g. pentoxifylline) within one week	Mortality and disability	Insufficient data to draw conclusions
Bath 2004	M/A; n = 5 trials, 191 patients	Prostacyclin or analogue within 7 days of stroke	Mortality	Insufficient data to draw any conclusions
Bath 2004	M/A; n = 2 trials, 119 patients	Theophylline and analogues within seven days of stroke	Mortality; neurological deterioration.	Insufficient data to draw any conclusions
Leonardi-Bee et al 2007	M/A; n = 6 trials; 1274 patients	Naftidrofuryl for acute stroke	Mortality, dependency/disability, blood pressure, adverse events.	No evidence to support use of naftidrofuryl for any outcome measures.
Bath & Sprigg 2007	M/A; n = 6 trials; 177 patients	Colony stimulating factors (including erythropoietin, granulocyte colony stimulating factor and analogues) for stroke	Functional outcome (MRS or BI), death, impairment, deterioration, extension or recurrence, and haematology measures.	Insufficient data to draw any conclusions
Wahlgren et al. 1999 and 2000b	RCT; n = 1360 pts, acute hemispheric infarction < 12 hrs from onset	IV clomethiazole 75mg/kg over 24 hrs or placebo	1 ^o Death, BI at 90 days (proportion > 60). 2 ^o SSS at 90 days	No significant difference overall. Subgroup analysis suggested benefit in TACS

Table 13: Neuroprotective agents

Source	Design & Sample	Intervention	Outcome measures	Conclusions
Clark et al. 1999a	RCT; n = 394 pts with acute ischaemic stroke < 24 hrs from onset, considered to be MCA territory and NIHSS >5	Citicoline 500mg PO OD -v- placebo	1 ^o - BI at 12 weeks 2 ^o - mRS, NIHSS at 12 weeks	No significant difference Post-hoc analysis by baseline NIHSS (not pre-specified) suggested benefit to citicoline in more severe strokes
Wahlgren et al. 2000a	RCT; n = 95 patients who were randomised in CLASS but in whom a CT scan performed after randomisation revealed intracranial haemorrhage rather than infarction.	IV clomethiazole 75mg/kg over 24 hrs or placebo	1 ^o Death, BI at 90 days (proportion > 60). 2 ^o SSS at 90 days	No significant difference - not powered for efficacy. No comment about surgical intervention
Clark et al. 2000	RCT; N = 368 pts, acute ischemic stroke, symptoms < 6 hrs, baseline NIHSS > 4	Nalmefene 60 mg -v- placebo Difference in proportion receiving rt-PA - these patients subsequently excluded from analysis	1 ^o % BI > 60 at 12 weeks or moderate disability or better on GOS	No significant difference
Gusev et al 2000	RCT; n = 200 49 low dose 51 medium dose 50 high dose	Sublingual Glycine vs placebo <6hrs of ischaemic stroke	Mortality; disability; impairment	Neutral
Grotta et al 2001	RCT; n = 45 patients who had received rt-PA (trial stopped early)	Lubeluzole vs placebo	SICH; death; disability	Neutral
Albers et al 2001	RCT; n = 628 Placebo 214 Low dose 200 High dose 214	Aptiganel hydrochloride	Death; disability (modified Rankin at 90 days post stroke); dependency; impairment	Trial stopped early due increased mortality (p = 0.06) in treatment group
Lyden et al. 2001	RCT; n = 200 patients with acute ischaemic stroke who had received rt-PA	IV clomethiazole 75mg/kg over 24 hrs or placebo	1 ^o Death and number of adverse events 2 ^o mRS, BI, NIHSS, SSS at 90 days	No significant difference although 15% dead in clomethiazole group -v- 10% in placebo
Clark et al. 2001	RCT; N = 899 pts, acute ischemic stroke < 24 hrs from onset, considered to be MCA territory and NIHSS >8	Citicoline 1000 mg PO BD -v- placebo	1 ^o - % who improved by > 7 points from baseline on NIHSS 2 ^o % who returned to pre-stroke BI at 12 weeks, % improved 1 or 2 points on Clinician's Global Impression scale at 12 weeks + others	No significant difference Post-hoc analysis using different (not pre-specified) outcome measures suggested benefit to citicoline

Table 13: Neuroprotective agents

Source	Design & Sample	Intervention	Outcome measures	Conclusions
Lyden et al. 2002	RCT; n = 1198 pts, acute ischemic stroke < 12 hrs from onset, classified as TACS	IV clomethiazole 68mg/kg over 24 hrs or placebo	¹ Death, BI at 90 days (proportion > 60). ² mRS at 90 days, CT infarction volume, NIHSS, SSS at 90 days	No significant difference
Kasner et al 2002	RCT; two hospitals, n = 39 patients, <24hrs, NIHSS score >4, white blood cell count < 12 600 cells/mm	The antipyretic effects of acetaminophen in afebrile acute stroke patients.	Temperature, NIHSS score	Early administration of acetaminophen (3900 mg/d) to afebrile patients with acute stroke may result in a small reduction in CBT (0.22 degrees C; p=0.14). Acetaminophen may also modestly promote hypothermia or prevent hyperthermia (non significant results). No difference in NIHSS.
Dippel et al 2003	RCT; n=75 patients with acute ischemic stroke within 24 hours	Paracetamol (acetaminophen; 1000mg) and ibuprofen (400mg) v placebo 6x daily for 5 days	Temperature	Treatment with a daily dose of 6000 mg acetaminophen results in a small, non significant, but potentially worthwhile decrease in body temperature (0.3 degreesC) after acute ischemic stroke, even in normothermic and subfebrile patients.
Otomo et al 2003	RCT; n = 252 patients	Edavarone v placebo for acute ischaemic stroke.	mRS, adverse events	A significant improvement in functional outcome was observed in the Edavarone group as evaluated by the modified rankin scale.
Lees et al 2003	RCT; n=134 patients within 24 hours of stroke	Tolerability of NXY-059 at two doses vs placebo (844 mg/h, n=39; 420 mg/h)	mRS, temperature, BP, mortality, adverse events, plasma concentration	Well tolerated with similar or better function outcomes, mortality and adverse events.
Krams et al 2003	RCT, n=887 ischemic (204 cotreated with tPA) within 6 hours of symptom onset	Dose-response study of UK-279,276 v placebo	SSS, adverse effects,	No benefits found. No difference in adverse events. Trial was terminated early for futility.
De Georgia et al 2004	RCT; pilot study n=40 patients	Endovascular cooling in patients with ischemic stroke	Clinical outcomes were similar in both groups.	Induced moderate hypothermia is feasible using an endovascular cooling device in most patients with acute ischemic stroke. Further studies are needed to determine if hypothermia improves outcome.
Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators 2004	RCT; n=2589 patients within 12hrs of stroke	Magnesium sulphate 16mmol intravenously within 12 hours acute stroke vs placebo	¹ Death at 90 days ² mRS, BI at 90 days	Mortality was slightly higher in the magnesium treated group than in the placebo group. Secondary outcome did not show any treatment effect. Planned subgroup analysis showed benefit of magnesium in lacunar strokes.
Wang et al 2004	RCT; n=14 patients with severe stroke or brain injury	Cooling helmet v no cooling	Temperature, complications	Mean difference was -1.6 degrees C (p<0.0001). Cooling occurred rapidly and only one person (from 8) developed severe complications (bradycardia).
Walters et al 2005	RCT; n=61 patients with ischemic stroke	Does escalation study of AMPA antagonist ZK 200775 v placebo	pharmacokinetics of the compound, NIHSS, haemodynamic parameters	No benefits of treatment at any dose. Potential adverse events recorded (reduction in NIHSS). Authors suggest due to sedative effect no further trials warranted.

Table 13: Neuroprotective agents

Source	Design & Sample	Intervention	Outcome measures	Conclusions
Ladurner et al 2005	RCT; n=146 patients	To explore the safety and preliminary outcome of Cerebrolysin treatment in patients with acute stroke.	Adverse events, BI, cognitive function (Syndrome short test)	No difference in CNS score, BI and the Clinical Global Impressions or adverse events. Significant improvement of cognitive function. Intervention was well tolerated.
Shyu et al 2006	RCT; n=10 patients	Tolerability, safety and efficacy of using granulocyte colony-stimulating factor (G-CSF) in ischemic stroke v placebo	NIHSS, European Stroke Scale (ESS), ESS Motor Subscale, BI all at 12 months.	No adverse events and improved functional outcomes although numbers are very small. Authors conclude treatment is safe and feasible.
Pettigrew et al 2006	RCT; n=92 patients (phase 1, dose escalating study)	Safety and tolerability of arundic acid (ONO-2506) in acute ischemic stroke	NIHSS, adverse events	No difference in adverse events. Possible trend to benefit for doses of 8 mg/kg/h. Further trials warranted.
Lees et al 2006	RCT; n=1772 patients within 6 hours of stroke	IV NXY-059 v placebo NOTE: Subsequent trial (informally reported) which failed to demonstrate any benefits on functional measures.	mRS at 90days, mortality, adverse events, NIHSS, BI	Significant improvement (p=0.038) on mRS for intervention. No difference in adverse event rates or mortality. However no difference in BI (p=0.14) or NIHSS. Authors suggest further data needed to confirm effect.
Palesch et al 2006; and Ginsberg et al 2006	RCT; n=82, phase I dose-escalation study	The safety of high-dose human albumin therapy in ischemic stroke.	Adverse events, functional outcome, dose of albumin	Well tolerated. The probability of good outcome at the highest three ALB doses was 81% greater than in the lower dose and was 95% greater than in the comparable NINDS rt-PA Stroke Study. The tPA-treated subjects who received higher-dose ALB were 3 times more likely to achieve a good outcome than subjects receiving lower-dose ALB, suggesting a positive synergistic effect between ALB and tPA.
Jian et al 2003	Case series; n=50 patients with ischaemic stroke	Induced hypothermia using cooling blankets as well as alcohol and ice bags within 22+/-9h after stroke onset and maintained for 24-72 h; subsequently, patients passively rewarmed over a mean duration of 17 h	Temperature, complications/adverse events, mortality	Complications were frequent thrombocytopenia (70%), bradycardia (62%), and pneumonia (48%). Four patients (8%) died during hypothermia as a result of severe coagulopathy, cardiac failure, or uncontrollable intracranial hypertension. An additional 15 patients (30%) died during or after rewarming because of rebound increase in intracranial pressure (ICP) and fatal herniation.
Lyden et al 2005	Case series, n=18	Intravascular cooling technique using buspirone and meperidine administered prophylactically to suppress shivering.	Safety and feasibility, adverse effects	3 patients managed less than 1.5hrs. Other 15 patients tolerated 12 or 24 hours cooling. Authors suggest technique is feasibility with adequate safety and

Table 14: Dysphagia

Source	Design & Sample	Assessment(s)/management	Outcome measures	Conclusions
Martino 2000	S/R; 10 cohort studies; Adult stroke patients with dysphagia	Comparison of clinical bedside screening with videofluoroscopy.	Screening accuracy: physiological evidence on videofluoroscopy, Aspiration pneumonia, nutritional intake, mortality, length of hospital stay and cost	2 bedside screening tests identified as potential in predicting dysphagia – 50ml water test and reduced pharyngeal sensation. Limited direct evidence for the benefit on health outcomes after screening programs
Perry & Love 2001	S/R 26 studies; 12 studies of screening tools involving 1401 stroke patients with dysphagia	Comparison of swallow screening tools	Validity and reliability of tools.	5 screening tools identified with good specificity (70-100%) but low sensitivity (22-67%).
Doggett et al, 2001	S/R. 4 case series.	Four diagnostic tests of dysphagia – patient reported dysphagia, BSE, FEES, VFSS. Review of reduction in rate of pneumonia	Reduction in pneumonia	The methods assessed were not more effective than a bedside assessment. Small studies.
Ramsey 2003	Review of cohort studies of screening and diagnosis in acute stroke.	Identify methods of swallowing assessment: limitations and merits.	Swallowing assessment methods identified included: videofluoroscopy, pulse oximetry, gag reflex and laryngopharyngeal sensation	Authors concluded bedside examinations of swallowing are safe, however the sensitivity (47-92%) and specificity (59-91%) of the tests are variable. PPV =50-75%, NPV = 70-90%. O2 saturation combined with bedside swallowing assessment useful.
Bath et al 1999	M/A; 6 trials	PEG vs NGT (2 trials; N=49) Swallowing therapy (2 trials; n = 85) Drugs for dysphagia (1 trial; n = 17) Nutritional supplements (1 trial; n = 42)	Nutritional status; Dysphagia; Case fatality; protein and energy intake	Too few studies have been performed, and these have involved too few patients. PEG feeding may improve outcome and nutrition as compared with NGT feeding.
Carnaby et al, 2006	RCT; n = 306 (n = 102 usual care, n = 102 low intensity swallowing/diet, n = 102 high intensity swallowing/diet)	Usual care vs low intensity swallowing compensation strategies and diet modification (x3/week) vs high intensity swallowing strategies and diet modification (daily)	Return to pre-stroke diet, time to return to pre-stroke diet, full recovery of swallowing, dysphagia related medical complications, death, institutionalization, dependence in ADL at 6 months	No significant effect on death or institutionalization. No significant effect on return to normal diet at 6 months post stroke. Trend for increased number who achieved functional swallowing and a decrease in dysphagia related medical complications in the intervention group.
DePippo et al, 1994	RCT; n = 115; patients with mild-moderate dysphagia 3-7 weeks post-stroke	One session explanation and advice, or prescribed diet and monitoring, or diet and therapy	Mortality; pneumonia; dehydration; calorie/nitrogen deficit; recurrent upper airway obstruction.	Explanation and advice as effective as more intensive speech and language therapist involvement
Odderson et al, 1995	CCT; n = 124; acute stroke admissions; historical controls	Use of a standardised protocol including dysphagia guidelines	Dysphagia; FIM; aspiration pneumonia; LOS; cost effectiveness.	Aspiration pneumonia risk reduced greatly
Perry & McLaren, 2003	Prospective quasi-experimental; n = 400	Survey of effect of implementation of nutritional support guidelines	Barthel Index, Body mass Index, infective complications, LOS, discharge destination.	Introduction of guidelines was associated with improvements in practice and selected patient outcomes.
Langmore et al 1991	Diagnostic study 21 subjects	Flexible endoscopic evaluation of swallowing (FEES)	Sensitivity, specificity, positive predictive value and negative predictive	FEES reliable in detecting laryngeal penetration and aspiration (sensitivity >88%); highly sensitivity and

Table 14: Dysphagia

Source	Design & Sample	Assessment(s)/management	Outcome measures	Conclusions
	(9 with stroke)	measured against Videofluoroscopy	value of FEES	specificity for laryngeal penetration and aspiration (92%).
Aviv et al 2000	RCT; n = 139 (n = 61 FEESST; with 78 controls with MBS). 45 of these patients were stroke. Community based.	Dietary and behavioral management guided by the results of MBS or of FEESST,	Pneumonia incidence; pneumonia-free interval	No significant differences in outcome overall. (18.4% v 12%, p=0.2) However, among 45 stroke patients the incidence of pneumonia was lower among FEES group patients (1/21 vs. 7/24, p<0.05).
Smith et al, 2000	Cohort study n = 53	Evaluate predictive value of pulse oximetry and swallowing assessment vs videofluoroscopy for identification of aspiration.	Aspiration, O ₂ desaturation	Assessment of O ₂ desaturation with bedside assessment had a positive predictive value of 95%.
Lim et al 2001	Cohort study; n = 50 patients with acute stroke	50 ml water swallow test, combined with O ₂ saturation measured after each 10ml compared with FEES and SALT assessment	Sensitivity of 2% O ₂ desaturation after 10ml to detect dysphagia; incidence of aspiration pneumonia.	Oxygen desaturation test had a sensitivity of 76.9% and specificity of 83.3%. The 50-ml water swallow test had a sensitivity of 84.6% and specificity of 75.0%. Combined the sensitivity rose to 100% with a specificity of 70.8%.
Leder et al 2002	Cohort study; n = 49 first-time stroke patients was evaluated within 24 hours post-stroke	Clinical swallowing examination (6 identifiers of aspiration risk, i.e., dysphonia, dysarthria, abnormal gag reflex, abnormal volitional cough, cough after swallow, and voice change after swallow), vs FEES	Sensitivity and specificity of clinical assessment compared with FEES.	Clinical examination incorrectly identified 19 subjects with aspiration risk but determined correctly no aspiration risk in 8 patients (sensitivity = 86%; specificity = 30%; false negative rate = 14%; false positive rate = 70%). Need for cost-effective instrumental swallow evaluation.
Chong et al, 2003	Cohort study n = 50	Assessment of dysphagia using water swallow test, O ₂ desaturation and combination of tests compared with fiberoptic examination of swallowing	Aspiration	Water swallow test had a positive predictive value of 81.8%. O ₂ desaturation sensitivity of 55.9% and specificity of 100%. Combined tests had a sensitivity of 94.1% and a specificity of 62.5%. Authors concluded these simple tests are useful for people with stroke.
Wu et al, 2004	Cohort study n = 59	Examination of the validity of the 100ml water swallow test using videofluoroscopy.	Swallowing speed, signs of choking.	Sensitivity of swallowing speed is 85.5% and specificity was 50%. Authors concluded that estimating speed of swallowing is an effective tool for screening for VFSS. Measuring choking during the water swallow test may be useful for monitoring progress of swallow.
McCulloch et al 2005	Cohort study, n = 165	Examination of clinical examinations compared with VSFF	Aspiration.	Some aspects of clinical examinations are certainly helpful in diagnosing aspiration however does not determine quantity of aspiration. Recommend VSFF needed before patient management decisions are made.
Hinchey et al, 2005	Prospective cohort study. 15 health centers n = 2532	Survey of adherence to dysphagia screening assessment.	Adherence to dysphagia screening, % pneumonia,	Adherence to dysphagia screen was higher in hospitals who had a formal screening protocol. Dysphagia screening protocol reduced incidence of pneumonia.

Table 14: Dysphagia

Source	Design & Sample	Assessment(s)/management	Outcome measures	Conclusions
Nishiwaki et al. 2005	Cohort study; 4 hospitals; n=61 patients	Assessment of dysphagia via symptoms of oromotor function (lip closure, tongue movement, palatal elevation, gag reflex, voice quality and motor speech function). Water swallowing test (using 30 mL of water), saliva swallowing test and a VMBS examination.	Sensitivity and specificity of assessment compared to VMBS	Cough/voice change in the water swallowing test was the only variable that was significantly associated with aspiration on VMBS examination (sensitivity=72% and a specificity=67%).

Table 15: Nutrition after stroke

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Hodgkinson, Evans & Wood, 2003	S/R; 17 RCTs	Identify factors that increase risk of dehydration in older people and to assess risk and management of oral fluid intake.	Risk factors (age, gender, incontinence, mobility, mental status), assessment of dehydration 9 intraocular pressure, axillary moisture, biochemical, clinical exam)	No clear determination of risk factors for dehydration. Intake should be at least 1600 ml/ 24 hours to maintain hydration.
Milne et al, 2006	M/A; 55 trials, n = 9187 pts aged over 65	Protein and energy supplementation vs placebo or no supplementation.	Mortality, complications, adverse events, weight change, LOS, arm muscle circumference	Improved survival with supplementation in undernourished people. No significant effect on morbidity, complications or LOS Increase in weight gain with supplementation.
Challiner et al, 1994	RCT; n = 34 elderly stroke patients with dysphagia	Subcutaneous vs IV fluid in hydrating stroke patients	Serum osmolality	No significant differences between the groups.
Norton et al, 1996	RCT; n = 30; dysphagia 14 days post-stroke	Percutaneous endoscopic gastrostomy (PEG) feeding or nasogastric tube feeding	6-week mortality; amount of feed administered; weight; anthropometric measures at follow-up.	PEG associated with better nutrition and better outcome (NB many published criticisms)
Simmons, Alessi & Schenelle, 2001	RCT; n = 63 nursing home residents (not stroke specific)	Evaluate a 3 phase behavioural intervention to increase fluid intake (verbal prompts over 32 weeks)	Between meals fluid intake, serum osmolality, blood urea nitrogen, creatinine	Verbal prompts increased fluid intake in people who were not cognitively impaired. People with cognitive impairment required preference compliance and prompts to increase intake.
The Food Trial Collaboration, 2005a	RCT; n = 4023 (n = 2007 normal diet, n = 2016 oral supplements)	Establish if routine use of oral nutritional supplements improves outcomes after stroke.	Death, poor outcome (Modified Rankin Score grades3-5)	No significant effect of nutritional supplements for people with acute stroke (absolute risk reduction in death 0.7% CI 1.4 – 2.7).

Table 15: Nutrition after stroke

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
The Food Trial Collaboration, 2005b	2 RCTs; n=859 patients across 83 sites in early v avoid trial; n= 321 patients in 47 sites in PEGvNG feeding. Acute dysphagic patients.	Early v late enteral feeding + preferred method of	Death, poor outcome (Modified Rankin Score grades3-5)	Early tube feeding was associated with an absolute reduction in risk of death of 5.8% (95% CI -0.8 to 12.5, p=0.09) and a reduction in death or poor outcome of 1.2% (-4.2 to 6.6, p=0.7). PEG feeding was associated with an absolute increase in risk of death of 1.0% (-10.0 to 11.9, p=0.9) and an increased risk of death or poor outcome of 7.8% (0.0 to 15.5, p=0.05). Hence trend of reduced death but more alive with poorer outcomes. NG preferred in first month after stroke.
Kostadima et al, 2005	RCT; n = 41 (n=20 gastrostomy, n=21 nasogastric) Note: stroke and TBI	Gastrostomy within 24 hours of intubation	Ventilator associate pneumonia, ICU LOS, ICU mortality, duration of mechanical ventilation	People with gastrostomy had a lower frequency of ventilator associated pneumonia than controls. No difference between the groups for mortality, LOS or period of mechanical ventilation.
Hamidon et al, 2006	RCT; n = 23 acute cerebral infarct with dysphagia	Comparison of PEG vs NG for nutritional status and treatment failure.	Upper arm skin fold thickness, mid-arm circumference, serum albumin level	Serum albumin levels were higher in patients with PEG at 4 weeks. No significant differences in anthropometric measures at 4 weeks. Authors concluded PEG feeding was more effective.
Gariballa et al, 2006	RCT; n= 445. Elderly patients with acute admission.	Nutritional support (995kcal of energy and vitamins and minerals) plus normal diet v placebo and normal diet.	6 months disability, non-elective readmission, LOS, discharge destination, morbidity, mortality.	Improvement in nutritional status at 6 months. Reduction in readmission in the supplement group.
Perry & McLaren, 2003	Prospective quasi-experimental; n = 400	Survey of effect of implementation of nutritional support guidelines	Barthel Index, Body mass Index, infective complications, LOS, discharge destination.	Introduction of guidelines was associated with improvements in practice and selected patient outcomes.
Mead et al, 1998	Cohort study; n = 101 (n = 40 acute stroke patients)	Assess the validity and reliability of an observational assessment of nutritional status (underweight, normal, overweight).	Sensitivity and specificity	Sensitivity of ability to assess nutritional status through observation ranged from 64-100% with a specificity of 71-100%.
Whelan et al, 2001	Prospective cohort; n = 24	Assess fluid intake in patients with dysphagia after stroke.	Parenteral, enteral and oral fluid intake, urine output, clinical sequelae	Fluid intake was insufficient. Pre-thickened fluids increased oral intake in patients with dysphagia.
Finestone et al, 2001	Cohort, n = 13, acute stroke patients with dysphagia	Assess if patients with dysphagia receive their estimated fluid requirements (thickened fluids vs enteral feeds supplemented with IV fluids).	Fluid intake	Patients receiving thickened fluids failed to meet their fluid intake requirements whereas patients receiving enteral feeds with IV exceeded their requirements.
Dennis et al, 2003 Food Trial Collaboration	Cohort; n = 3012 Acute stroke patient	Determine the importance of baseline nutritional status on the prediction of long term outcome post stroke.	Modified Rankin Scale, mortality	Undernutrition was associated with decreased survival, functional ability and living circumstances at 6 months post stroke.

Table 15: Nutrition after stroke

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Perry, 2004	Cohort, n = 36 acute stroke patients	Assess nutritional features in patients with communication difficulties	Barthel Index, NIHSS, Eating Disabilities assessment Scale, Anthropometric measures, dietary intake	At 6 months post stroke multiple eating related disabilities persisted and the subjects met 81% of their estimated energy requirements. Authors suggested closer monitoring of nutritional aspects of care is required.
Kelly et al, 2004	Cohort study; n = 102 acute ischemic stroke	Evaluate the relationship between biochemical indices of dehydration and venous thromboembolism after acute stroke.	DVT, pulmonary embolism, Barthel Index	Biochemical indices of dehydration at day 2 post stroke were significantly associated with the development of venous thromboembolism in acute stroke patients.
Lazarus & Hamlyn, 2005	Cohort study; n = 324 (Note: general surgery, neurosurgery, cardiology, urology patients)	Identify incidence of malnutrition, identification and documentation.	Subjective Global assessment Tool, Prevalence of malnutrition, revenue loss under case payment	42.3% of the patients were malnourished. Only 15% of the patients were referred for nutritional assessment.
Jakkola et al, 2005	CCT; n = 200 assessed for malnutrition risk	60ml of 2kcal per ml supplement x 4 /day vs mid-meal supplement.	Mini Nutritional assessment tool, eight, LOS	The intervention group had a significant increase in weight and decreased LOS. Trend towards greater appetite and protein intake.
James et al, 2005	Cohort; n = 919 people with stroke discharged to community or care home.	Describe site variations in the use of enteral feeding and its association with stroke outcomes	FIM (cognitive & motor), severity of illness, discharge destination	Frequency of tube feeding differed between sites. Patients who received tube feeding had lower FIM scores and higher severity of illness. Nutritional support was associated with improved FIM scores.
Horn et al, 2005	Cohort; n = 830 moderate – severe stroke	Assess effect of rehabilitation, neurotropic medications, nutritional support and timing of rehabilitation on outcomes and discharge destination	FIM (motor & cognitive) discharge destination	Enteral feeding was associated with a higher total and motor discharge FIM score for patients with severe stroke.
Esper et al, 2006	Cohort; n = 14 mechanically ventilated patients with intracranial haemorrhage, n = 6 TBI	Determine if the inflammatory state due to intracranial haemorrhage increase the nutritional requirements.	Resting energy expenditure	There was no difference in the resting energy expenditure between the groups in the first week.
Axelsson et al, 1988	Obs; n = 100 acute stroke patients	Observation of nutritional status at admission and discharge	Nutritional status	16% of admitted and 22% discharged patients were malnourished
Finestone et al, 1995	Obs; n = 49 patients in stroke rehabilitation service	Observation of nutritional status at admission, 1 month and discharge.	LOS; Modified Barthel	Malnutrition is common and slows recovery
Davalos et al, 1996	Obs; n = 104 acute stroke patients; assessed nutrition and 1 month disability	16% of admitted and 26% of 1 week surviving patients malnourished; outcome worse	Nutritional parameters; Canadian Stroke Scale; Barthel score at admission and 1 month after stroke.	Malnutrition is common and worsens in first week; may affect outcome
Gariballa et al, 1998	Obs; n = 201 acute stroke patients;	Assessed nutrition and 3 month outcome.	BMI; triceps skinfolds thickness; mid-arm circumference; serum albumen concentration	Malnutrition is common and worsens in first two weeks; may affect outcome. 20-30% malnourished at admission and further deterioration occurred; serum albumin was an independent predictor of death

Table 15: Nutrition after stroke

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Bhalla et al, 2000	Obs; n = 167, acute stroke patients	Assess association of raised plasma osmolality and stroke outcome at 3 months. Identify changes to plasma osmolality in the 1st week post stroke.	Death, Barthel Index	Association between raised plasma osmolality during the first week post stroke and mortality and functional outcome.
FOOD Trial Collaboration 2003	Obs; 2955 stroke patients enrolled for the FOOD trial.	Follow-up in relation to nutritional status and other clinical indicators at admission.	Survival and functional status at 6 months.	Nutritional status early after stroke is independently associated with long-term outcome. Undernourished patients more likely to develop pneumonia, other infections and GI bleed during hospital admission than other patients.
Davis et al, 2004	Obs; n = 185 Acute stroke patients	Identify prevalence of premorbid undernutrition and its association with outcome at 1 month post stroke.	Patient generated subjective global assessment, Modified Rankin Scale, NIHSS, mortality.	Premorbid nutritional was associated with mortality and poor outcome at 1 month post stroke. 16% undernourished on assessment.
Martineau et al, 2006	Obs; n = 73 Acute stroke patients	Identify nutritional status of patients admitted to an acute stroke unit and the association between nutritional status and outcomes.	Patient generated subjective global assessment, LOS, complications, dysphagia	19.2% of acute stroke patients were malnourished. Malnourishment was associated with increased LOS, complications, dysphagia and enteral feeding.

Table 16: Communication

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Whurr et al, 1992	S/R; n = 45 studies; n = 1,336 patients with aphasia	Speech therapy treatment for aphasia	Improvements in function (oral expressive or receptive language; written language; cognitive and psychodynamic function)	Effect of treatment shown (but not all studies were RCTs)
Robey, 1998	S/R; n = 55 studies; n = 1491 patients with aphasia	Speech therapy treatment for aphasia	Within population effect size for measures of outcome used in each study.	Effect of treatment shown (but not all studies were RCTs)
Greener et al, 1999	M/A; 12 trials; n = 1254 adults with aphasia as a result of stroke	Speech and language therapy by trained therapist in any setting	Global rating scales; language tests; psychological tests; pt and carer affective state and satisfaction.	SLT shown to be neither effective nor ineffective
Greener et al 2001	M/A; 10 RCTs; adults with acquired aphasia due to stroke.	Pharmacological interventions for aphasia: piracetam, bifemalane, piribedil, bromocriptine, idebenone, and Dextran 40.	Measures of communication; functional status; adverse events including death.	Main conclusion: that drug treatment with piracetam may be effective in the treatment of aphasia after stroke, but at increased risk of death.

Table 16: Communication

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Sellars et al 2002	S/R; No trials of required quality identified for adults (>16) who became dysarthric following non-progressive brain damage.	Speech & language therapy interventions for dysarthria	Measures of articulation eg Frenchay Dysarthria Assessment; measures of voice; airflow studies; intelligibility; mood; subjective health.	No evidence of good quality clinical trials to support or refute the effectiveness of speech & language therapy interventions for dysarthria
Bhogal, et al 2003	S/R; 10 CCTs; n = 864 pts with aphasia after stroke	Speech and language therapy of varying types, and length of therapy period.	Mean change scores in Token test; PICA; and FCP	Four positive trials in this review provided an average of 8.8 hours of therapy per week for an average of 11.2 weeks (5 hours per week was the minimum intensity of any positive trial). The four negative trials provided an average of 2.0 hours per week for an average of 22.9 weeks. However benefits were noted in only 2 of the 3 outcome measures considered in this review. Overall the definitive benefits of therapy remain uncertain at present, but intense therapy seems more effective than less intense therapy.
Salter et al, 2006	S/R; 10 cohort studies	Evaluation of measurement properties of screening tests used for the assessment of aphasia.	6 instruments were located.	Frenchay Aphasia Screening Test is the most commonly used and most widely evaluated measurement tool. Sensitivity 87%, specificity 80%.
Wertz et al, 1986	RCT; aphasic patients	Clinic treatment by a speech pathologist vs home treatment by a trained volunteer vs deferred treatment	Language measures	Authors suggest treatment by a speech pathologist is effective and there was no detrimental effect for delaying treatment by 12 weeks.
Kagan et al 2001	RCT; n = 40 patients with aphasia, n=40 non-aphasic volunteers All patients with aphasia for 12m or longer	Training of volunteers in Supported Conversation (SCA) vs not	Volunteers: Measure of Supported Conversation for Adults with Aphasia Aphasic patients: social and message exchange skills	Significant changes in interaction and transaction of people with aphasia in treatment group
Engelter et al, 2006	Prospective cohort; n = 269 patients with 1 st ischemic stroke (n = 80 with aphasia)	Assess the incidence and determinants of aphasia attributable to first ischemic stroke	Incidence of aphasia, severity of aphasia	33-52/100,00 are affected by aphasia annually. The risk of aphasia increases by 1 – 7% for each year of age.
Berthier, 2005	Non systematic Review. Stroke patients	Review of therapies including speech-language and pharmacological for the treatment of aphasia		Data from single case studies and case series suggest that donepezil may have a beneficial effect on post-stroke aphasia.

Table 16: Communication

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Pedersen 2004	Cohort study; n = 270 acute stroke patients	Determine type, severity and evolution of aphasia in acute stroke patients and evaluate predictors fro language outcome 1 year post stroke	Frequency of aphasia, severity of aphasia	Global aphasia was present in 32%, Wernicke's = 16%, Brocas = 12%. Severe aphasia was found in 44% of patients. St 1 year follow-up 60% of patients were still aphasic. Predictors of outcome were stroke severity and severity of initial aphasia.
Rose et al, 2005	Pre and post design; n = 12 people with mild to moderate aphasia	Comparison of the comprehension of printed health material vs aphasia friendly printed material.	Comprehension	Aphasia friendly format resulted in an 11.2% increase in comprehension.
Brennan et al, 2005	Obs; n = 9 people with mild to moderate aphasia	Comparison of the comprehension of aphasia friendly paragraphs vs control paragraphs.	Comprehension	People with aphasia comprehended more aphasia friendly paragraphs than control paragraphs.
Hoffman & McKenna, 2006	Observational: n = 57 patients, n = 12 carers	Identify reading ability after stroke and identify the design of information given to patients after stroke.	Rapid assessment of adult literacy, readability	The reading level of material given to patients after stroke was more difficult (11th grade) than their reading level (7-8th grade).

Table 17: Incontinence

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Wallace et al 2003	S/R; 10 trials; n = 1366 incontinent pts, mainly women	Bladder training vs no training (3 trials only) vs drug therapy (in one trial) for urinary incontinence	Improvement in continence levels	Would appear to be helpful but insufficient data for certainty.
Eustice et al 2002	S/R; 5 RCTs; n = 355 incontinent pts mainly women	Prompted voiding for the management of urinary incontinence	No. of incontinent episodes in 24hrs	Inconclusive, evidence of short-term benefit from prompted voiding and from adding the muscle relaxant, Oxybutinin to prompted voiding.
Langhorne and Pollock, 2002	S/R. 11 clinical trials, acute stroke	Descriptive survey of care provided in 11 stroke units that have been shown to be effective.	Structure and organization of unit (i.e. pt inclusion/exclusion criteria, staff mix and staffing levels, communication, education); processes of care (i.e. investigations, drug therapy); discharge planning and follow-up.	Consistent characteristics of effective stroke units include comprehensive assessment of medical problems, careful management of physiological abnormalities, early mobilization, skilled nursing, early establishment of both rehabilitation plan and discharge needs.
Barrett 2003	S/R (14 studies – RCTs, CCTs, Cohort and surveys).	Management of urinary and faecal incontinence	Prevalence and prognosis; staff training; patient perspective; current management patterns.	Demonstrates high prevalence, major impact on patients, poor state of current practice.

Table 17: Incontinence

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Brazzelli et al, 2003	S/R; 6 RCTs; n = 415 patients	Review of absorbent products for the containment of urinary and faecal incontinence	Patient preference; comfort and absorbency	Data too few to provide a firm basis for recommendations.
Coggrave et al 2003	S/R; 7 trials Pts with central neurological diseases.	Management of faecal incontinence: Oral medication (4 trials).	Improved faecal continence	Not possible to draw any recommendation for bowel care in people with neurological diseases from the trials included in this review.
Dumoulin et al, 2005	S/R: 4 RCT, x1 cohort study	Evaluate the effects of behavioral therapies, timed voiding, prompted voiding, bladder retraining, urge suppression, pelvic floor exercises) to treat urinary incontinence.	Continence, reduction in incontinence episodes,	Limited evidence examining effect of behavioral therapies on continence post stroke. No specific evidence examining timed or prompted voiding for people after stroke. Consensus opinion to trial timed and prompted voiding.
Thomas et al, 2005	M/A; 7 RCT, n = 399	Determine optimal method for prevention and treatment of urinary incontinence after stroke. Acupuncture, timed voiding and specialist intervention vs usual care. Oestrogen vs placebo. Oxybutynin vs timed voiding. Sensory motor feedback vs timed voiding.	Urinary urgency, urinary frequency, dependence in ADL.	Some evidence to favour use of continence nurse practitioner compared with usual care for reduction in number of symptoms experienced and severity of leakage at 3 months. Insufficient evidence to evaluate the effect of acupuncture or timed voiding versus usual care, Oxybutynin vs timed voiding and sensory motor feedback vs timed voiding.
Martin et al, 2006	M/A; 129 studies	Identify the diagnostic process of urinary incontinence vs "gold standard" multi-channel urodynamics and construction of an economic model to examine the cost-effectiveness of commonly used tests.	Sensitivity, specificity and odds ration of diagnostic tests.	Authors concluded that the primary studies examining diagnosis of incontinence were poor. Correct diagnosis of incontinence could be made on clinical history alone (sensitivity = .92, specificity = .56). Maintaining a urinary diary appeared to be the most cost-effective diagnostic test.
Wikander et al, 1998	CCT; n = 34 incontinent patients in stroke rehabilitation	Comparison of conventional with FIM governed rehabilitation	ADL; mobility; and mood	20 patients regained continence in FIM governed group compared with 3 in the conventional rehabilitation group.

Table 18: Mood

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Churchill et al 2001	S/R; 50 trials	Psychological treatments for depression including cognitive behavioural therapy (CBT), interpersonal therapy (IPT), psychodynamic therapy (PDT), supportive therapy (ST).	Improved depression post-treatment; non-symptomatic at follow-up; drop-out rate; economic outcomes.	Patients receiving any variant of psychotherapy were significantly more likely to improve to a degree where they were no longer considered clinically depressed. No differences in discontinuation of treatment observed.

Table 18: Mood

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Kimura et al 2003	S/R; 3 studies; n = 27 patients with generalized anxiety disorder (GAD) and depression after stroke. (n = 13 treatment and 14 placebo)	Nortriptyline treatment for patients with comorbid generalized anxiety disorder (GAD) and depression after stroke	Hamilton Rating Scale for Anxiety; Hamilton Rating Scale for Depression; ADL	Patients receiving nortriptyline treatment showed significantly greater improvement; the anxiety symptoms showed earlier improvement than depressive symptoms.
Van der Wurff et al, 2003	S/R; 3 trials	Assess the efficacy and safety of electroconvulsive therapy for the treatment of depression in the elderly.	Depression,	No studies were identified that addressed the purpose of the review. Authors concluded that the 3 identified trials were of poor methodological quality.
House et al, 2004	M/A; 5 trials, n = 103	To evaluate the effect of pharmaceutical treatment on the reduction of emotionalism in people after stroke.	Emotionalism, tearfulness, Psychological laughter and crying scale, depression, cognitive function, ADL, death, adverse events, leaving study early.	Three studies showed a reduction in emotionalism however the confidence intervals were very large. There was also a moderate treatment effect for depression however the confidence intervals were also wider and may have included a negative effect. There was no significant effect on cognition or ADL and no significant differences for death or adverse events.
Anderson, Hackett & House, 2004	M/A; 12 trials, n = 1245	Assess if pharmaceutical or psychological interventions can prevent onset of depression and improve physical and psychological outcome after stroke.	Depression, death, adverse events, leaving the study early.	Some evidence that depression was lower in people treated with anti-depressants. No evidence of benefit of pharmacology on cognitive function, ADL or decreased disability. Some evidence that psychotherapy resulted in a decrease in distress as measured by the GHQ-28. Authors concluded inadequate evidence to support the routine use of pharmacotherapy to prevent depression or improve recovery.
Hackett et al, 2004	M/A; 9 trials, n = 780 stroke patients	Determine if pharmacological, psychological or electroconvulsive therapy treatment in people with depression after stroke improves outcomes.	Depression	Studies had methodological limitations but to date there is no strong evidence of the benefit of pharmacological or psychotherapy for complete remission of depression. Some evidence for a reduction in depression at end of follow-up.
Hackett & Anderson, 2005	S/R: 3 studies population based cohorts n = 492 patients, 8 hospital studies n = 15272, 9 rehabilitation n = 2170	Purpose of review was to identify predictors of depression.	Predictors included: stroke severity, physical disability, cognitive impairment	Only severity of stroke was able to predict likelihood of depression. Insufficient evidence to identify other outcome variables that may be predictive of depression.
Hackett et al, 2005	M/A 51 studies (n = 16302 hospitalized, n = 6031 rehabilitation)	Identification of frequency of depression following stroke in acute medium term and long term stroke survivors.	Frequency of depression	33% of people were depressed following stroke (95% CI 29 – 36%). Authors suggest the frequency of depression may be underestimated due to underreporting of symptoms.

Table 18: Mood

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Niedermaier et al, 2004	RCT; n = 70 acute stroke patients	Examine if mirtazapine given day 1 post stroke prevents depression.	Depression scales, neurological function.	40% of the control group (n = 14) and 5.7% (n = 2) of the intervention group developed depression. Authors concluded mirtazapine is effective in reducing incidence of depression.
Davis et al 2004	Pilot RCT; n = 14 rehabilitation unit	3x1 hour life review sessions.	Zung scale of depression, life satisfaction index	Significantly lower levels of depression (p<0.01) and higher life satisfaction (p<0.01).
Murray et al, 2005	RCT (double blind); n = 123 people with stroke	Assess the effect and tolerability of sertraline vs placebo.	Montgomery-Asberg Depression rating Scale, Emotional distress Scale, QoL, neurological recovery	No differences between the groups for major or minor depressive episodes, short-term or long-term antidepressant effect or neurological recovery. Authors concluded depression improved over time regardless of treatment.
Rampello et al, 2005	RCT; post stroke	Assess effect of reboxetine in patients classified as affected by "retarded" depression post stroke vs placebo.	Beck Depression Inventory, Hamilton Depression rating Scale	Reboxetine showed a good efficacy and safety in stroke patients affected by retarded depression.
Joubert et al, 2006	RCT; n = 87 people discharge from acute stroke unit	Shared-care model vs usual care	Blood pressure, cholesterol, depression, frequency of walking	A greater percentage of people in the intervention group achieved their target blood pressure and cholesterol level and participated in a greater number of weekly walks. Depression was also significantly reduced at 12 months.
Almeida, et al, 2006	RCT; n = 111 acute stroke patients	Sertraline vs placebo for the prevention of depression in non-depressed stroke patients.	Hospital Anxiety and Depression Scale	No significant differences at 24 weeks follow-up. Sertraline was no more effective than placebo and usual care for the prevention of depression in non-depressed stroke patients.
Watkins, 2006	RCT n = 411 patients, n = 207 control, n = 204 intervention)	Usual care vs x4 individual, weekly sessions of motivational interviewing	Proportion of patients with normal mood (28 item general Health Questionnaire). Depression scale (Yale), Barthel Index, beliefs and expectations of recovery (SEQ).	Significant effect for motivational interviewing at 3months and also a protective effect against depression. No significant effect on functional ability, expectations of recovery or death.
Choi-Kwon et al, 2006	RCT; n = 152 people with depression, emotional incontinence or anger proneness post stroke	Fluoxetine vs placebo.	Beck Depression Inventory, Spielberger Trait Anger Scale	More patients in the intervention group dropped out because of adverse events. However the authors concluded that fluoxetine improved emotional incontinence and anger proneness but had no significant effect on depression.
Williams et al, 2007	Prospective RCT; n = 188	Evaluate the effectiveness of "activate-initiate-monitor" care management (medications, monitoring and adjusting treatment) vs usual care.	Hamilton Depression Inventory, PHQ-9.	Care management resulted in a reduction in depression symptoms and greater remission of depression (39%).

Table 18: Mood

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Benaim et al, 2004	Clinical validation of an assessment tool, n = 80	Development of a aphasic depression rating scale for patients during sub-acute stroke.	Validity and reliability	The Aphasic Depression Rating Scale had good content, criterion and construct validity and high test-retest and interrater reliability.

Table 19: Prevention of complications: cerebral oedema

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Qizilbash et al, 2002	M/A; n = 7 trials, 453 patients	Treatment with corticosteroids	Mortality; functional outcome; adverse effects of treatment	No benefit shown, wide confidence intervals, expected adverse effects noted
Asplund et al, 2002	M/A; n = 18 trials, n = 3,119 patients	Haemodilution treatment within 72 hours of stroke	Mortality; dependency; thromboembolic events	No evidence of benefit
Morley et al, 2002	S/R; 5 observation studies, case series and single case studies of people with acute ischemic stroke	Compare medical therapy and decompressive surgery with medical therapy in people with acute ischemic stroke and clinical and radiologically confirmed cerebral oedema.	Death, death or dependency	Available evidence does not support the routine use of decompressive surgery in patients with cerebral infarction complicated by cerebral oedema.
Hofmeijer et al, 2003	S/R; (includes animal studies)	Identify the efficacy of treatment for the reduction of intracranial pressure and brain tissue shifts in people with hemispheric infarct. Osmotherapy, steroids, hypothermia, hyperventilation, surgical decompression, barbiturates.		Insufficient evidence from animal or clinical trials to support the efficacy of treatment to control cerebral oedema and reduce tissue shifts. Hyperventilation may have short term effects but no recent, quality studies are found for patients with stroke.
Righetti et al 2004	M/A; n=10 trials, 945 patients (482 treatment, 463 controls)	Intravenous glycerol within 2 days (1 trial within 4 days)	Mortality and dependency	Possible short-term reduction in mortality. Lack of evidence of benefit in longer term survival does not support the routine or selective use.
Vahedi et al, 2007	M/A; n=3 trials, 93 patients with MCA infarct (2 of the three studies were stopped due to imbalance in endpoint in favour of treatment)	Estimate the effects of decompressive surgery for people with space occupying MCA infarcts.	Modified Rankin Score at 1 year, case fatality at 1 year.	More patients in the decompressive-surgery group had an mRS _{≤4} (75% vs 24%; pooled ARR 51%), an mRS _{≤3} (43% vs 21%; ARR 23%), and survived (78% vs 29%; ARR 50%), indicating NNT =2 for survival with mRS _{≤4} , NNT=4 for survival with mRS _{≤3} , and 2 for survival irrespective of functional outcome. The effect of surgery was highly consistent across the three trials.

Table 19: Prevention of complications: cerebral oedema

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Bereczki et al 2007	M/A; n=3 trials, 226 patients	Mannitol v placebo	Death or dependence (mRS, BI), LOS, mortality, adverse events, QOL	Insufficient data to draw any conclusions

Table 20: Prevention of complications: DVT and PE

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Antiplatelet Trialists Collaboration (APTC), 1994	M/A; n = 10,000 patients with immobility, mostly surgical	Prolonged antiplatelet therapy (75-325 mg aspirin) as prophylaxis for vascular events	Non-fatal MI; non-fatal stroke; or vascular death.	Incidence of DVTs reduced (prevent in 9% of patients) and of PE (prevent in 1.7% of patients)
Amaragiri et al 2003	M/A; 16 RCTs; n = 3211 surgical patients	GCS alone; GCS + another method of prophylaxis	DVT events; PE; mortality	81 (15%) with GCS compared to controls 144 (29%) developed DVT; 18 (3%) with GCS + another method compared to 84(14%) controls. The authors concluded that graduated compression stockings are effective in reducing the frequency of DVT.
Linkins et al 2003	M/A; 29 RCTs & 4 cohort, n = 10757 patients with venous thromboembolism	Purpose was to provide reliable estimates of the clinical impact of anticoagulation related bleeding and risk of intracranial bleeding.	Fatal bleeding, intracranial bleeding	Case fatality rate of major bleeding was 13.4%. Risk of intracranial bleeding was 1.1 per 100 patient years. Authors concluded the impact of anticoagulation major bleeding is considerable.
Mazzone et al 2004	S/R; 2 trials; n = 123 patients after stroke	2 types of compression stockings vs routine care; intermittent pneumatic compression device vs routine care	DVT detected by Doppler, DVT detected by 125-1-fibrinogen scanning, death, adverse outcomes.	No difference in DVT reduction or death in treatment or control groups in either trial. Authors reported there were only 2 small trials that did not provide conclusive evidence for the benefit of physical methods for preventing DVT and therefore there is insufficient evidence to recommend routine use.
van Dongen et al 2004	M/A; 22 RCT, n = 8827 (not specific to stroke patients)	Identify effectiveness of low molecular weight heparin compared with unfractionated heparin for the initial treatment of venous thromboembolism	Venographic assessment, major hemorrhage during treatment, overall mortality at end of follow-up,	Thromboembolism occurred in 3.6% of people treated with low molecular weight heparin compared with 5.4% treated with unfractionated heparin. Reduction in relative size of the thromboembolism was greater in the low molecular weight group. Incidence of hemorrhage was also lower in the low molecular heparin group (1.2% compared with 2.0%).

Table 20: Prevention of complications: DVT and PE

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Roderick et al, 2005	S/R & M/A large number of trials for wide range of patient populations (not specific to stroke)	Assess the benefits of mechanical compression, oral anticoagulants, dextran and regional anesthesia in reducing the risk of DVT and PE.	DVT, PE	Patients undergoing surgery may benefit from mechanical compression as prophylaxis. Patients considered to be at high risk of thromboembolism may benefit from a pharmacological thromboprophylactic agent.
Sandercock, Counsell & Stobbs, 2005	M/A; 6 RCT, n = 740	Compare the effect of low molecular weight heparin or heparinoids with those of unfractionated heparin in people with acute stroke.	Pulmonary embolism during follow-up, death from all causes during follow-up, death from vascular causes during follow-up, intracranial hemorrhage	Authors concluded that low molecular heparin and heparinoids may have greater protection against DVT and pulmonary emboli than unfractionated heparin. However the evidence related to risks was inadequate and there may be an excess of intracranial and extracranial hemorrhages.
Goodacre et al, 2006	M/A; 412 studies of a range of assessments (largest number -142, assessing ultrasound)	Estimate diagnostic accuracy of non-invasive tests for DVT and identify factors associated with variation in diagnostic performance.	Sensitivity and specificity of diagnostic test, costs	CT scan has good sensitivity (89.7%) and specificity (93.8%). Wells score useful to categorise patients risk and guide further tests. D-Dimer useful in suspected cases to confirm absence of DVT (sensitivity 91%, specificity 55%). Plethysmography is less useful (sensitivity 75-91%, specificity 71-93%). CT had excellent sensitivity (95%) and specificity 97% but significant heterogeneity was found. Non-invasive tests generally have worse diagnostic performance when used in asymptomatic patients, compared with use in patients with clinically suspected DVT.
Andre et al 2007	M/A; 29 RCTs and 6 SRs, stroke patients	Review prophylaxis for venous thromboembolism in stroke patients; mechanical devices, paraenteral anticoagulants, aspirin, and other drugs.	DVT, PE	Low molecular weight and unfractionated heparin are partially effective for the prophylaxis of venous thromboembolism after cerebral infarct in selected patients. NNT =2-10. Reduced PE with aspirin based on IST and CAST studies (RR 0.71 (0.52–0.97) but increased major extracranial haemorrhages (fatal or requiring transfusion) – RR 1.69 (1.35–2.13). NNT>300. Mechanical compression maybe effective but more robust data needed.
Diener et al, 2004	RCT; n = 545 acute stroke patients	Comparison of low molecular weight heparin with unfractionated heparin. Certoparin vs unfractionated heparin	Proximal deep vein thrombosis, pulmonary embolism, death related to thromboembolism during treatment	Authors concluded there was non-inferiority for certoparin compared to unfractionated heparin. No difference in NIHSS. Patients treated with certoparin had a decreased incidence of extracranial bleed.
Lacut et al, 2005	RCT; n = 151 Intracerebral hemorrhage	Assess the effect of pneumatic compression to prevent venous thromboembolism. Elastic stockings vs elastic stockings with compression.	Symptomatic venous thromboembolism, death before day 10, death related to pulmonary embolism, asymptomatic DVT	Intermittent compression combined with elastic stocking was effective in reducing risk of asymptomatic DVT; relative risk .29 (CI .08 – 1.00).

Table 20: Prevention of complications: DVT and PE

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Sherman et al, 2007	RCT; n = 1762 acute stroke patients (within 48 hours) unable to walk unassisted	enoxaparin 40 mg subcutaneously once daily v unfractionated heparin 5000 U subcutaneously every 12 h for 10 days (range 6–14). NOTE: No placebo control group.	symptomatic or asymptomatic DVT, symptomatic PE, or fatal PE. Intracranial haemorrhage, major extracranial haemorrhage, and all-cause mortality.	Enoxaparin reduced the risk of DVT by 43% (10% vs 18%; RR 0.57, 95% CI 0.44–0.76, p=0.0001). No difference in overall bleeding (8% both groups) although higher rate of major extracranial bleeding with enoxaparin than with unfractionated heparin (1% vs 0; p=0.015). Overall subcutaneous enoxaparin superior to UFH.
Kelly et al, 2004	Cohort study; n = 102 acute ischemic stroke	Evaluate the relationship between biochemical indices of dehydration and venous thromboembolism after acute stroke.	DVT, pulmonary embolism, Barthel Index	Biochemical indices of dehydration at day 2 post stroke were significantly associated with the development of venous thromboembolism in acute stroke patients.

Table 21: Prevention of complications: Pressure care

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Langer et al, 2003	S/R; 8 RCT	Evaluate the effectiveness of enteral and paraenteral nutrition on the prevention and treatment of pressure ulcers.	Number of pressure ulcers, grade of pressure ulcer.	The studies were generally of poor quality with low subject numbers and high dropouts. For the prevention of pressure ulcers one study found a beneficial effect of nutritional supplements. It is unclear if nutritional supplements are helpful for the treatment of existing ulcers because the follow-up period was too short to detect a clinical outcome.
Cullum et al 2004	M/A; 41 RCT (not specific to stroke)	Support surfaces for pressure sore prevention and treatment	Pressure sore prevention and healing	Specific foam mattresses appear to reduce pressure areas in high risk patients. Effects of higher-tech constant low pressure and alternating pressure for prevention are unclear. Other interventions need further evaluation.
Pancorbo-Hidalgo et al, 2006	S/R; 33 studies (not stroke specific)	Evaluate the effect of risk assessment scales for pressure ulcer prevention and assess the validity and effectiveness of scales as indicator for risk of pressure ulcer.	Sensitivity and specificity of scales. Validity of scales. (Norton Scale, Braden Scale)	No evidence that the use of an assessment scale reduced the incidence of pressure ulcers. Use of assessment scales may have been associated with an increase in the intensity and effectiveness of interventions to prevent pressure ulcers. Braden scale has the best validity and reliability.
Baba-Akbari et al, 2006	M/A; 3 trials, n = 146 (not stroke specific)	Ultrasound vs sham ultrasound, ultrasound & UV vs laser and standard treatment in the healing of ulcers	Ulcer healing rate, cost, QoL, pain, acceptability	Authors concluded there was no evidence to support the effectiveness of ultrasound to assist in the healing of pressure ulcers; however there were very few studies examining this treatment.

Table 21: Prevention of complications: Pressure care

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Jones et al, 1998	RCT; n = 6 wards, 59 nurses, 38 stroke patients; 1000 obs	Two two-hour lectures on stroke and rehabilitation	Nurse knowledge of patient positioning, and patient position	Teaching increased knowledge and changed practice, but effects small
The Food Trial, 2005	RCT; n = 859	Establish whether the timing and route of enteral tube feeding effects the outcome after stroke at 6 months. Enteral feeding vs no tube feed. Percutaneous endoscopic gastroscopy (PEG) vs nasogastric.	Death poor outcome at 6 months	Early tube feeding was associated with a non-significant absolute risk reduction in death. PEG feeding was associated with a non-significant increase in the absolute risk of death.
Forster et al, 1999	CCT; n = 32 nurses, two stroke wards	Training programme: three two-hour sessions	Nurses attitudes.	Improved transfer technique, altered attitudes; but many areas still "poor"

Table 22: Secondary prevention after stroke: Lifestyle/Behaviour change

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Midgley et al, 1996	M/A; 56 trials, n = 1131 hypertensive, 2374 normotensive subjects	Trials with randomised allocation to control and dietary sodium intervention groups and observation of BP	Blood pressure reduction	Decreases in BP larger in trials of older hypertensives, and non-significant in normotensives
Mulrow et al 1998	M/A; 18 RCTs, n = 2611 ambulatory adults with diastolic BP >90mmHg	Weight reducing diet vs normal diet or medication to lower BP.	Weight loss; BP; mortality; cardiovascular events.	3-9% reduction in body weight in wt reducing diet group, with approximately 3mmHg BP reduction.
Hooper et al 2000	M/A; n= 27 trials, 40 interventions 30,901 person years	Reduction or modification in dietary fat vs control. Studies over min 6 months	<u>Primary</u> – mortality; combined CV events. <u>Secondary</u> - risk factor changes; QOL;	Small but potentially important reduction in CV risk in trials longer than 2 yrs. Average salt intake was only reduced by 2 g/day.
Silagy et al 2002	S/R; 110 trials	Nicotine replacement for smoking cessation in different formulations.	Smoking cessation from biochemically confirmed abstinence to 50% self reported reduction.	All forms of commercially available NRT increase quit rate by 1.5-2.0 fold independent of other forms of support and regardless of setting.
Lancaster et al 2002	S/R; 18 trials (3 with randomisation), n = 6,737 smokers	Individual counselling vs minimal contact. 4 studies compared different intensities of counselling	Sustained smoking; abstinence from smoking.	Individual counselling increased likelihood of cessation. OR 1.62 (95% CI 1.35-1.94).

Table 22: Secondary prevention after stroke: Lifestyle/Behaviour change

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Pirozzo et al 2002	M/A; 12 RCTs; obese or overweight (BMI>25kg/m ²) people	Low fat diet vs other type of diet for obesity	Weight loss at 6, 12 and 18 months	No significant difference between low fat and other types of diet for weight loss.
Rice et al 2003	M/A; 20 RCTs, n = 10,289 adult smokers	Nursing interventions for smoking cessation vs normal care	Smoking abstinence (validated biochemically in 15 RCTs) 6-12 months post intervention	Those receiving interventions had increased likelihood of quitting compared to controls.
Jürgens & Graudal 2004	M/A; n=124 trials (57 trials with normal BP; 58 trials mainly Caucasians with raised BP; 8 trials of blacks with normal or raised BP; 1 trial of Japanese.)	Low sodium vs high sodium intake to reduce BP	Blood pressure; plasma renin, aldosterone, cholesterol etc	Reduced sodium intake resulted in lower BP (most obvious in those with high BP: reduction in SBP by -4.18 mm Hg DBp -1.98mmHg in the short-term; the effect was greater in black and Asian patients. Authors suggest low sodium most important for those with high BP and those from black or Asian populations.
Hooper et al 2003	M/A; 3RCTs normotensives (n = 2326); 5 RCTs untreated hypertensives (n=387); 3 trials treated hypertensives (n = 801).	Reduced salt for prevention of cardiovascular disease	Mortality; cardiovascular events; changes in blood pressure	Minimal reductions in BP over longer-term (systolic by 1.1 mm Hg, diastolic by 0.6 mm hg). No difference in mortality. Degree of reduction in sodium intake and change in blood pressure were not related. People on anti-hypertensive medications were able to stop their medication more often on a reduced sodium diet as compared with controls, while maintaining similar blood pressure control.
Thompson et al 2003	M/A; n=12 trials. (4 trials compared dietitian v doctor, 7 trials self-help resources, 1 trial dietitian v nurse v counsellor.	dietary advice given by a dietitian compared with another health professional, or the use of self-help resources, in reducing blood cholesterol in adults.	Cholesterol levels	Dietitian advice better than doctors (-0.25 mmol/L). No difference between dietitian advice and self-help resources (-0.10 mmol/L). No other clear differences.
Poustie et al 2003	S/R. Very few trials (5). Children and adults with Familial Hypercholesterolaemia	Cholesterol lowering diet v other forms of dietary treatment or no dietary intervention	Incidence of IHD and atheromatous disease. Serum LDL, HDL Tg + others	Lack of trial data. No differences could be found between cholesterol lowering diet and other diets for all short term outcomes assessed

Table 22: Secondary prevention after stroke: Lifestyle/Behaviour change

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
He & McGregor 2004	M/A; n=31 trials, n=3022 patients (20 trials with hypertensive patients, 11 trials in normotensive)	Modest salt reduction on blood pressure in individuals with elevated and normal blood pressure. Intervention must be >4weeks.	Net changes in systolic and diastolic blood pressure, and 24h urinary sodium excretion.	In individuals with elevated BP: mean excretion of sodium =4.6 g/day, mean reduction in BP = -5.06 mmHg for systolic and -2.70 mmHg for diastolic. In individuals with normal BP: median excretion of sodium =4.4 g/day of salt, the mean reduction in BP = -2.03 mmHg for systolic and -0.99 mmHg for diastolic. Reducing sodium related to reduction in BP.
Dauchet et al 2005	M/A of cohort studies; 7 studies, 90,513 men, 141,536 women, and 2,955 strokes	Fruit and vegetable consumption and risk of stroke	Intake, stroke, mortality	The risk of stroke was decreased by 11% (RR 0.89) for each additional portion per day of fruit, by 5% (RR: 0.95) for fruit and vegetables, and by 3% (RR: 0.97; NS) for vegetables. The association between fruit or fruit and vegetables and stroke was linear, suggesting a dose-response relationship.
He et al 2006	M/A of cohort studies; 8 studies, 257,551 individuals (4917 stroke events)	Fruit and vegetable consumption and risk of stroke. Average follow up 13 years.	Intake, stroke, mortality	Compared with individuals who had less than three servings of fruit and vegetables per day, the pooled RR of stroke was 0.89 for those with three to five servings per day, and 0.74 for those with more than five servings per day. Subgroup analyses showed that fruit and vegetables had a significant protective effect on both ischaemic and haemorrhagic stroke.
Dickinson et al 2006	M/A; n=6 trials, 483 patients. (MA conducted on 5 trials, 425 patients)	potassium supplementation v control for patients with high BP. Intervention had to be >8weeks.	BP	No statistically significant effect of potassium supplementation on blood pressure
Appel et al 1997	RCT; n=459 patients with systolic BP <160 mm Hg and diastolic BP 80 to 95 mm Hg	Diet rich in fruits and vegetables v diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat v control for 8 wks	BP	The combination diet significantly reduced systolic and diastolic BP by 5.5 and 3.0 mm Hg respectively. Results more pronounced in those with high BP.
de Lorgeril et al 1999	RCT; n=605 patients with MI	Mediterranean-type diet v control to reduce recurrence of MI. Follow up 46 months	Cardiac death and nonfatal MI, unstable angina, stroke, heart failure, pulmonary or peripheral embolism, hospital admission	Mediterranean diet group improved all outcomes (p=0.0001-0.002)
Sacks et al 2001	RCT; n=412 patients with or without high BP	Normal US diet v DASH diet PLUS high, intermediate or low salt for 30 days	BP	A DASH diet in combination with low sodium is most beneficial to lower BP but both lower BP independently.
Brown et al 2001	RCT, n=160 patients with CHD and low HDL but normal LDL	simvastatin plus niacin v vitamins v simvastatin-niacin plus antioxidants v placebo over 3 years.	Coronary stenosis, occurrence of a first cardiovascular event (death, myocardial infarction, stroke, or revascularization).	The frequency of the clinical end point was 24% with placebo; 3% with simvastatin-niacin alone; 21% in the antioxidant-therapy group; and 14% in the simvastatin-niacin-plus-antioxidants group. Authors concluded the use of antioxidant vitamins must be questioned.

Table 22: Secondary prevention after stroke: Lifestyle/Behaviour change

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Brazi et al 2003	RCT; n=11323 patients with previous MI analysed as a cohort	Simple dietary advice to increase the consumption of Mediterranean foods v control	The intakes of the five foods were assessed at baseline, 6, 18 and 42 months. Mortality, CVD, stroke, MI	Subjects generally improved their diet according to the advice given. All foods were associated with a significant reduction in risk of death.
Howard et al 2006	RCT; n=48835 women aged 50-79	Intensive behavior modification in group and individual sessions designed to reduce total fat intake to 20% of calories and increase intakes of vegetables/fruits to 5 servings/d and grains to at least 6 servings/d. The comparison group received diet-related education materials	Mortality, stroke, CHD, risk factor reduction	No difference in risk of CHD, stroke, or CVD in postmenopausal women. Modest effects on CVD risk factors. Authors suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.
Kawachi et al, 1993	Obs; n = 117,006 women aged 30-55 years	To assess the relationship of time since stopping smoking to risk of stroke	Incidence of fatal and non-fatal stroke over 12yrs	The excess risk of stroke among former cigarette smokers largely disappeared 2-4 years after cessation
Wannamethee et al, 1995	Obs; n = 7735 men aged 40-59 years	To examine the effects of giving up smoking, years since cessation and quantity smoked	Incidence of fatal and non-fatal stroke over 12yrs	Smoking cessation is associated with a decreased risk. Complete loss of risk not seen in heavy smokers. Most benefit in hypertensive subjects
Wannamethee et al, 1998	Obs; n = 7142 men aged 40-59 years	To examine the relationship between modifiable lifestyle factors (smoking, physical activity, alcohol intake, and BMI) and survival free of cardiovascular disease	Death from any cause; incidence of stroke, MI or development of diabetes over 15 years	Increased smoking and BMI levels were associated with myocardial infarction, stroke and diabetes. Moderate physical activity was associated with reduced risk
Bak et al 2002	Obs: n=511 patients, 198 were smokers when admitted for stroke	Evaluate the smoking cessation in patients with recent stroke.	Smoking rate	43 patients (21.7%) gave up smoking within 6 months of suffering a stroke. Sex, functional status, and sociodemographic characteristics were independently associated with persistent smoking.
Nagata et al 2004	Cohort (prospective); n=269 stroke patients	Assess sodium intake and death from stroke in a population-based cohort of Japanese men and women	Mortality, sodium intake	Significantly positive associations were also observed between sodium intake and death from both types of stroke although this was clearer in men than women.
Sauerbeck et al 2005	Cohort study; n=405 patients, 112 smokers on admission	Evaluate education for smoking cessation in patients with recent stroke.	Smoking rates	At 3 months, 48 (43%) of the baseline smokers had quit smoking. The number of participants who smoked > 20 cigarettes per day was 31 at baseline versus 7 at 3 months. This change of behavior was independent of baseline characteristics and the level of poststroke disability.

Table 22: Secondary prevention after stroke: Lifestyle/Behaviour change

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Baati et al 2006	Case series; n=2468 patients referred from primary care units and hospitals where treatment options were exhausted	4-week inpatient non-pharmacological risk factor modification programme for individuals with the metabolic syndrome	Risk factor changes: Weight, BP	All risk factor levels for stroke and myocardial infarction decreased. The reduction of weight among men was 4.7kg and 3.8kg among women.. The patients systolic and diastolic blood pressure decreased by 15/10 mm Hg for men and 14/9 mm Hg among women from initial average for the whole population of 148/90 Hg and 146/87 Hg, respectively. A reduction of medication although not a goal was also achieved.
Ovbiagele et al 2006	Obs: cohort study n=2386 patients involved in a RCT	evaluated the role of recent smoking as a prognostic factor following acute ischemic stroke	IMAGES stroke score, poor functional outcomes at day 30 and 90 (defined as Rankin Scale >1 and Barthel Index <95), and survival over the first 3 months	After adjusting for covariates, smokers had independent increased odds of poor 90-day functional outcome, as assessed by Rankin Scale (OR 1.38) and Barthel Index (OR 1.42) at day 90. Smoking status did not affect survival at day 90.
Shaughnessy et al 2006	Obs/survey: n=312 patients with stroke	Evaluate exercise behaviour in patients with stroke		Only 31% exercised four times weekly.

Table 23: Secondary prevention after stroke: Blood pressure lowering

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Midgley et al, 1996	M/A; 56 trials, n = 1131 hypertensive, 2374 normotensive subjects	Trials with randomised allocation to control and dietary sodium intervention groups and observation of BP	Blood pressure reduction	Decreases in BP larger in trials of older hypertensives, and non-significant in normotensives
Blauw et al, 1997	M/A; 13 trials; n = 20,438 participants.	3-Hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor vs randomised placebo controls	Stroke incidence	Combined data suggest HMG-CoA reductase inhibitors prevent stroke in middle age. Need for more trials to determine effect in the elderly
Cutler et al, 1997	S/R; 32 trials; n = 2635 participants	Reducing dietary sodium	Sodium excretion; blood pressure	Effects on lowering blood pressure dependent on substantial lowering of dietary sodium
Crouse et al, 1997, 1998	M/A; 4 trials primary prevention; 8 trials secondary prevention of CHD	Reductase inhibitor monotherapy	Cholesterol levels; stroke incidence.	Significant reduction in expected stroke incidence. Greater for secondary prevention group (32% reduction) than primary prevention (27%)

Table 23: Secondary prevention after stroke: Blood pressure lowering

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Rashid et al 2003	S/R; 7 RCTs; n = 15,527 patients with previous stroke or TIA	Lowering blood pressure to prevent vascular events.	Blood pressure; mortality; stroke; MI; vascular events.	BP lowering reduced stroke, MI and total vascular events (OR 0.76-0.79). No difference on all cause mortality. Vascular prevention was positively associated with the magnitude by which blood pressure was reduced (p=0.002). Clearest data for diuretic & ACE inhibitor or combination. No clear benefits for beta-receptor antagonists.
Post-stroke Antihypertensive Treatment Study (PATS) Collaborative Group, 1995	RCT; n = 5665 patients with a history of stroke or TIA	Antihypertensive treatment for patients with history of stroke/TIA; 2 year follow-up	Stroke recurrence	Blood pressure reduction by 5-2 mmHg reduced incidence of stroke by 29% 1995
Whelton et al, 1998	RCT; n = 975 men and women aged 60-80 with diagnosis of high blood pressure	585 obese: reduced dietary sodium, weight loss, both or usual care; 390 non-obese: reduced sodium or usual care	High BP; starting anti-hypertensive medication; cardiovascular events up to 3yrs post treatment.	Reduced sodium intake and weight loss feasible, effective and safe as non-pharmacological therapy in older persons
Heart Outcomes Prevention Evaluation Study Investigators (HOPE) 2000a,b	RCT; n = 9297 high risk patients with vascular disease or diabetes + one other cardiovascular risk factor (not heart failure)	ACE inhibitor (Ramipril 10mg daily) for mean of 5 yrs v placebo	MI; stroke; death from vascular cardiovascular causes	Ramipril significantly reduces cardiovascular death (by 37%), MI (by 22%) and stroke (by 33%) in high risk patients. The cardiovascular benefit was greater than that attributable to decrease in blood pressure.
PROGRESS 2001	RCT; n = 6105 patients with history of stroke or TIA	Perindopril (ACE inhibitor) 4mg daily v Perindopril 4mg + indapamide (thiazide diuretic) v placebo over 4 yrs.	Total stroke (fatal or non-fatal).	Combination therapy superior to single therapy: reduced BP by 12/5mmHg compared to 5/3mmHg. Stroke risk reduction 43% compared to none discernable; similar reductions achieved in both hypertensive and non-hypertensive patients.
Nazir et al 2004	RCT; n=24 within 2-7 days of ischemic stroke/TIA	Losartan (25 or 50 mg/d) v placebo within 2-7 days post stroke	Adverse events, BP, CBF, GFR	Losartan well tolerated and no patient suffered deterioration in neurological function. A mean reduction in MABP of 9.5 mmHg from 1-12h. Losartan may be introduced within 2-7 days of mild stroke in hypertensive patients in whom significant carotid occlusive disease has been excluded without affecting global or regional CBF, or affecting GFR.
Schrader et al 2005	RCT; n=1405 patients with hypertension and previous stroke in last 24 months	Angiotensin II type 1 receptor antagonist (eprosartan) v calcium antagonist (nitrendipine)	Mortality, CV events, strokes, BP, adverse events	BP reduced similar for both groups (13.2mmHg v 16mmHg). Moreover, already after 3 months, normotensive mean values were achieved, and 75.5% reached values <140/90 mm Hg with the eprosartan regimen and 77.7% with the nitrendipine regimen. During follow-up (mean 2.5 years) lower primary events with eperosartan (p=0.014). Lower CV events (77v101, p=0.06) and strokes (102v132, p=0.03)

Table 23: Secondary prevention after stroke: Blood pressure lowering

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Nazir et al 2005	RCT N=25 within 4-8 days of mild ischemic stroke/TIA and with diastolic BP 70-90mmHg	angiotensin-converting enzyme perindopril (2 or 4 mg/d) v placebo	The effect of angiotensin-converting enzyme perindopril on BP, global and focal cerebral blood flow and glomerular filtration rate in a normotensive acute stroke population.	MABP was reduced within the first 24h with a mean MABP of 9.3 mmHg . Antihypertensive therapy with perindopril may be introduced in the first week after mild ischemic stroke in normotensive patients without affection global or regional CBF or affecting GFR.

Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Antiplatelet Trialists Collaboration (APTC), 1994	M/A; n = 10,000 patients at risk of stroke or TIA	Prolonged antiplatelet therapy (75-325 mg aspirin) as prophylaxis for vascular events.	non-fatal MI; non-fatal stroke; or vascular death.	Overall one-third reduction in death, myocardial infarction and stroke
Hankey et al 2000	M/A; n=4 trials, 22,656 patients with high vascular risk	Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin Aspirin v ticlopidine in three trials (3471 patients) and with clopidogrel in one trial (19,185 patients).	Mortality, stroke, vascular events, adverse events	Modest but significant benefits in preventing serious vascular events in patients at high risk (12%v13%) and specifically in TIA/ischaemic stroke patients; 10.4% v12%) with thienopyridines. Thienopyridines produced a significant reduction in the odds of gastrointestinal haemorrhage and other upper gastrointestinal upset, but a significant increase in the odds of skin rash and of diarrhoea. However, the increased odds of skin rash and diarrhoea were greater for ticlopidine than for clopidogrel. Allocation to ticlopidine, but not clopidogrel, was associated with a significant increase in the odds of neutropenia (2.3% vs 0.8%; OR: 2.7).
Antithrombotic Trialists Collaboration 2002	M/A;n= 287 RCTs; 135,000 pts	Comparisons of antiplatelet therapy v control. Comparisons of different antiplatelet regimens	MI; stroke; vascular death	Daily doses of 75-150mg aspirin seem to be as effective as higher doses for longer-term treatments. Clopidogrel is an appropriate alternative for patients with a contra-indication to aspirin.
Lyrer et al 2003	M/A; No RCTs found. 26 case series, n = 327 patients	Anti-thrombotic drugs (antiplatelet drugs, anticoagulation) v placebo in patients with extracranial internal carotid artery dissection	Death; dependency in ADL; rate of intracranial haemorrhage	Case series suggest no difference in outcomes between therapies with very small number of ICH (0.5%). Authors conclude , due to no RCTs or CCTs, there is no evidence to support their routine use for the treatment of extracranial internal carotid artery dissection.
Sandercock et al 2003	M/A; n=11 trials; 2487 patients	Prolonged anticoagulant therapy following presumed non-cardio-embolic ischaemic stroke or TIA.	Mortality; dependency; haemorrhage	No evidence of effect on death or dependency. Anticoagulation increased fatal intracranial and major extracranial haemorrhage.

Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Jones et al 2004	M/A; n=2 trials, 25787 (CAPRIE & ESPS2 trials)	Compare antiplatelet agents v aspirin for efficiency and cost effectiveness	Stroke, MI, mortality, cost effectiveness	Clopidogrel was marginally more effective than aspirin at reducing the risk of ischaemic stroke, MI or vascular death. MR-dipyridamole in combination with aspirin was superior to aspirin alone at reducing the risk of stroke and marginally more effective at reducing the risk of stroke and/or death but not death alone. MR D+A most cost effective treatment. No conclusions made directly comparing C v D+A.
Tran & Anand 2004	S/R; n= 111 trials, 22 with TIA or stroke (n=30619), 47 with CAD (n=59821), and 42 with PAD (n=9214).	Oral antiplatelet therapy v placebo in patients with stroke, CHD, MI, angina & PVD	Mortality, stroke, MI, vascular events, adverse events	First-line antiplatelet therapy suggested is aspirin for MI; aspirin or clopidogrel for those with TIA or stroke, chronic stable angina, or peripheral arterial disease; and aspirin combined with clopidogrel for those with non-ST-segment elevation acute coronary syndrome. Aspirin combined with dipyridamole is a possible alternative for patients who experience a first episode of TIA or stroke in the absence of clinically apparent CAD. Although ticlopidine has been shown to be of benefit in various vascular conditions, its adverse-effect profile has limited its use.
Gubitz et al, 2004	M/A; n = 21 trials, 23,427 patients	Anticoagulation treatment within first 14 days of acute stroke, or not	Mortality; dependency; PE; DVT; recurrent stroke or intracranial haemorrhage	Reduced rate of DVTs but no other benefit
Sexana & Koudstaal, 2004a	M/A; n = 2 trial, 485 patients	Anticoagulation (INR 1.4-4.0) v aspirin or placebo	Vascular events (recurrent stroke, MI, mortality, embolism)	Anticoagulation reduced the odds of recurrent stroke by two-thirds (OR 0.36) and almost halve the odds of all vascular events (OR 0.55). This benefit is not negated by an unacceptable increase of major bleeding complications (OR 4.32). In the two studies, no intracranial bleeds were identified among patients using anticoagulants (OR 0.13).
Sexana & Koudstaal, 2004b	M/A; n = 2 trial, 1371 patients	Anticoagulation (INR 2.0-4.0) v aspirin (300mg/day) or indobufen (100 or 200 mg BID)	Vascular events (recurrent stroke, MI, mortality, embolism)	Anticoagulants significantly more effective than antiplatelet therapy both for all vascular events and for recurrent stroke. Major extracranial bleeding complications occurred more often in patients on anticoagulants, but the absolute difference was small (0.9-2.8% per year versus 0-0.9% per year). Warfarin did not cause a significant increase of intracranial bleeds.
Serebruany et al 2004	M/A; n=51 trials, 338,191 patients	Bleeding rates in antiplatelet therapy in various groups. 6 sub groups: aspirin (ASA) < 100 mg; ASA > or = 100 mg; dipyridamole, thienopyridines; intravenous and oral GP IIb/IIIa inhibitors.	Bleeding complications	Low-dose aspirin and dipyridamole therapy were associated with the lowest risk of bleeding (3.6% and 6.7%, respectively). The highest rate of bleeding complications (44.6%) was associated with the GP IIa/IIIb inhibitors.
Costa et al 2005	M/A; n = 4 trials, 2944 patients with TIA/stroke and 1 trial, 2275 patients with AMI	Aspirin versus triflusal	composite outcome of vascular events, adverse events	No difference in vascular events between aspirin and triflusal although lower rates of adverse events for triflusal.

Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Algra et al 2006	M/A; n= 5 trials, 4076 patients with TIA or minor stroke	Anticoagulants v antiplatelet for people with presumed arterial origins. Subgroup analysis of intensity of anticoagulation (low=INR 1.4-2.8, medium=INR 2.1-3.6, high=INR 3.0-4.0)	Mortality; dependency at follow-up; recurrent stroke; bleeding events.	Insufficient evidence for routine use medium intensity; high intensity unsafe due to bleeding risk; low intensity no more efficacious than aspirin.
Guo et al 2006	M/A; n=14 trials, 646 patients	Effect of defibrase in China	Neurological deficit score, BI, plasma fibrinogen levels	Neurological deficit score and plasma fibrinogen level difference before and after treatment was significantly different (in favour); p=0.03 and p<0.0001 respectively). Nearly significant difference in BI (p=0.06).
McQuaid & Laine 2006	M/A; 55 trials, 75,005 patients treated with low-dose aspirin, 13,401 with clopidogrel, 11,247 with combined aspirin and clopidogrel, and 30,515 with placebo.	Define the relative and absolute risk of clinically relevant adverse events with aspirin and clopidogrel in patients for CVD prophylaxis.	Adverse events	Low-dose aspirin increases the risk of major bleeding by ~70%, but the absolute increase is modest: NNT = 769 patients to cause one additional major bleeding episode annually. Compared with clopidogrel, aspirin increases the risk of GI bleeding but not other bleeding; however NNT = 883 patients would need to be treated with clopidogrel versus aspirin to prevent one major GI bleeding episode.
De Schryver et al 2006	M/A; 26 trials; n = 19842 patients with coronary artery disease, MI, PAD, stroke, TIA	Dipyridamole in any dose in the presence or absence of other antiplatelet drugs vs no drug or an antiplatelet drug(s) other than dipyridamole.	Vascular death; non-fatal stroke; non-fatal MI	There was no evidence that dipyridamole alone was more efficacious than aspirin. Dipyridamole and aspirin reduced risk of vascular events for people with prior stroke.
CAPRIE Steering Committee, 1996	RCT; n = 19,185 patients with cardiovascular disease (6431 with cerebrovascular disease)	Clopidogrel 75mg/day v aspirin 325mg/day for 1-3 years.	Cluster of ischaemic stroke, myocardial infarction, or vascular death; safety, re-hospitalisation rates, bleeding	Clopidogrel is as effective and safe as medium-dose aspirin. Clopidogrel reduced combined risk of ischaemic stroke, MI or vascular death by 8.7%. Bleeding and gastro-intestinal side-effects were less in the clopidogrel group. Clopidogrel group had significantly fewer re-hospitalisations for ischaemic events or bleeding
Diener et al, 1996 (ESPS 2)	RCT; n = 6602 patients with prior stroke or TIA	Aspirin, dipyridamole slow release, both and neither	Stroke; death.	A combination of aspirin and dipyridimole may be more beneficial than either alone, and dipyridamole may be as effective as aspirin
Stroke Prevention in Reversible Ischaemia Trial (SPIRIT), 1997	RCT; n = 1243 patients with TIA or minor stroke	Aspirin vs anticoagulants (INR 3-4.4; ie higher than normally used in the UK)	Death from all vascular causes; nonfatal stroke; nonfatal MI; or nonfatal major bleeding complication.	Trial stopped owing to excess haemorrhage in the anticoagulant group.

Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Weir et al 2003	RCT; n=1952, 15 hospitals (cluster design)	Computer-based decision support (CDSS) for selecting long-term anti-thrombotic therapy after acute ischaemic stroke v control	Risk reduction (estimated by the CDSS) in ischaemic and haemorrhagic vascular events achieved by long-term anti-thrombotic therapy, and the % of subjects prescribed the optimal therapy identified by the CDSS	With CDSS, the mean RRR attained by prescribing increased by 2.7% units (95%CI -0.3 to 5.7) and the OR for the optimal therapy being prescribed was 1.32 (0.83 to 1.80). Some 55% (5/9) of clinicians believed the CDSS had influenced their prescribing.
Gorelick et al 2003	RCT; n=1809 black patients with ischaemic stroke	Ticlopidine (500 mg/d) v aspirin (650 mg/d)	Recurrent stroke, MI, or vascular death	Trial stopped prematurely due to futility of outcome. Ticlopidine had non significant trend to more adverse events. Authors suggested aspirin is preferred in this patient population.
Culebras et al 2004	RCT; n=429 patients	Aspirin (325 mg/d) v triflusal (600 mg/d)	combined the incidence of vascular death, cerebral ischemic infarction, nonfatal myocardial infarction, or major hemorrhage	No difference in outcomes although haemorrhage rates may be lower.
Diener et al 2004 (MATCH)	RCT; n=7599 patients	Aspirin (75 mg/d) + clopidogrel (75 mg/d) v clopidogrel alone.	Stroke recurrence, mortality, vascular events, adverse events	No difference in incidence of ischemic strokes, MI, or vascular death (15.7% vs 16.7%; RRR, 6.4%; $P=0.24$) but was associated with an increase in the risk of major (2% vs 1%, $P<0.001$) and lifethreatening bleeding (2.6% vs 1.3%; $P<0.001$)
Serebruany et al 2004	RCT, n=40 patients with TIA/stroke without any antiplatelet therapy for 30 days prior	Aspirin (81mg/d) v Aggrenox	Platelet function @ 1, 3, 7, 15 & 30 days	Rapid change in platelet function for both aspirin and aggrenox. Aggrenox superior at 15 and 30 days.
Chimowitz et al 2005 (WASID)	RCT; n=569 patients (trial stopped early)	Aspirin (1300mg/d) v warfarin (INR2.0-3.0) in patients with verified 50 to 99 % stenosis of a major intracranial artery	Stroke, brain hemorrhage, or death from vascular causes other than stroke	Significantly higher rates of death (4.3% v 9.7%, $p=0.02$), major hemorrhage (3.2 vs. 8.3%, $p=0.01$), and MI or sudden death (2.9% v 7.3% $p=0.02$). No difference in the rates of stroke (22.1% v 21.8%). Aspirin should be used for patients with intracranial stenosis.
Serebruany et al 2005	RCT; n=70 patients with ischaemic stroke	Aspirin + clopidogrel v aspirin alone for 1 month.	Platelet studies, hospitalisation, mortality, stroke, vascular events, mortality, adverse events	No hospitalisation, mortality, adverse events recorded at 30 days. A+C had significantly greater inhibition of platelet activity than ASA alone.
Zhao et al 2005	RCT, cross over; n=11 health volunteers and 11 stroke patients	Effects of aspirin, clopidogrel and dipyridamole administered singly and in combination on platelet and leucocyte function each for 2 weeks.	Platelet aggregation, platelet-leucocyte conjugate formation and leucocyte activation were measured ex vivo blinded to treatment.	A+C+D same as A+C. Both superior to other combinations of agents in both volunteers and stroke patients.

Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Bhatt et al 2005 (CHARISMA)	RCT; n=15603 patients at high risk (27% had stroke or TIA)	Aspirin (75-162mg/d) + Clopidogrel (75mg/d) v aspirin (75-162mg/d) + placebo.	¹ First MI, stroke or death from CVD 2 TIA, hospitalisation for angia, vascular procedures	Primary endpoint 6.8% v 7.3% (RR 0.93; P = 0.22). Small reduction in hospitalisation (-1.2%; p=0.04) but small increase in severe bleeding (1.7%v1.3%; p=0.09). Primary end point among patients with multiple risk factors was 6.6% v 5.5% p=0.2) and higher mortality (3.9% v 2.2%; p=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% v 7.9% (RR 0.88; P = 0.046).
Marti-Fabregas et al 2006	RCT; n=28 patients	Aspirin (300 mg/day) v oral anticoagulant (target INR 2-3) in patients with MCA stenosis	Nonfatal CI, nonfatal acute myocardial infarct, vascular death and major hemorrhage	No events in aspirin group but 2 events in anticoagulant group (p=0.48).
ESPIRIT Study group 2006	RCT; n=2738 patients to aspirin (30–325 mg daily) with (n=1363) or without (n=1376) dipyridamole	Aspirin and dipyridamole combined versus aspirin alone for the secondary prevention of vascular events after ischaemic stroke of presumed arterial origin.	Stroke, MI, bleeding rates, adverse events, mortality, CHD	Primary outcome events arose in 13% patients on A+D v 16% on aspirin alone (ARR 1% per yr). Addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or MI of 0.82. Patients on A+D discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache.
Change et al 2006	RCT; n=146 patients with stroke (46 placebo, 45 reduced dose, 49 regular dose)	Dose titration to reduce Dipyridamole-related headache (half dose for first 10 days followed by full dose)	Headaches, adverse events	Headache more commonly reported in full dose compared to either lower dose and placebo (P<0.05). Of the 27 patients who stopped medication 55% sited headaches which was similar for all groups. More people ceased treatment with full strength dose.
ESPIRIT Study group 2007	RCT; n=1068 patients with TIA or minor stroke of arterial origin within last 6 months	Anticoagulants (target INR 2.0–3.0) v aspirin (30–325 mg/d)	death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication	Primary outcome occurred in 19% patients on anticoagulants and in 18% patients on aspirin. Hazard Ratio for ischaemic events was 0.73 (0.52–1.01) and for major bleeding complications 2.56 (1.48–4.43). Hence any benefits are negated by excess bleeding. Trial stopped early due to results of other arm of trial.
Maulaz et al 2005	CCT; n=618 patients	Effect of discontinuation of aspirin therapy as a risk factor for ischemic stroke.(4 weeks prior to even v control of >6months after event)	Rate of discontinuation	The 2 groups had a similar frequency of risk factors, except for coronary heart disease (36% vs 18%; P < .001). Aspirin use had been discontinued in 13 patients and 4 controls. Aspirin interruption yielded an OR for IS/transient ischemic attack of 3.4 (P < .005) after adjustment in a multivariable model.
Hart et al 1999 (SPAF investigators)	Cohort pf RCT. SPAF I,II,III n = 2012 patients in AFon aspirin	Reviews stroke risk factors for those on aspirin only. Stroke risk assessed against risk factors.	Stroke classified as ischaemic or haemorrhagic with CT, or MR or autopsy; assigned by central events committee.	Increased risk of stroke in those on aspirin with 1) increasing age; 2) female sex 3) history of raised BP 4) systolic hypertension 5) Prior TIA and stroke 6) HRT use. Reduced risk if regular moderate alcohol intake (14units).
Dippel et al 2004	OBS; n=60 patients	the lowest dose of aspirin (30 v 50 v 75 v 325)	urinary 11-dehydro-thromboxane-B(2) (uTXB(2)) excretion	In patients with a TIA or nondisabling stroke, a daily dose of 30 mg of aspirin provides sufficient suppression of thromboxane synthesis. No indication of a dose-effect relationship was found.

Table 24: Secondary prevention after stroke: Antiplatelet and anticoagulant therapy

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Volpato et al 2004	OBS; n=17337 patients of which 946 had TIA or stroke admitted to geriatric or medical ward	Description of hospital use of antithrombotic therapy in patients with stroke/TIA		>40% was discharged without antithrombotic prescription. Lower rates in patients with stroke (OR 0.61), presence of anemia (OR 0.70), severe disability (OR 0.48), and cognitive impairment (OR 0.58).
De Schryver et al 2005	OBS, n= 3796 patients from 2 RCTs	Determinants of non-adherence in patients who used aspirin or oral anticoagulation after cerebral ischaemia of arterial origin	NA	For aspirin 18% prematurely stopped treatment, 8% without a clear medical reason (non-adherence). Age \geq 65 years and the use of 300 instead of 30 mg of aspirin were independently associated with non-adherence. Diastolic blood pressure of \geq 90 mmHg and dizziness were associated with better adherence. Of patients on oral anticoagulation 22% stopped at 1 year, 10 % did so because of nonadherence. No statistically significant determinants for non-adherence were identified.
Bhatt et al 2006	OBS: n=67,888 patients in outpatient setting from 44 countries	Baseline prevalence of atherosclerosis risk factors, medication use, and degree of risk factor control.	NA	Atherothrombotic patients throughout the world had similar risk factor profiles: a high proportion with hypertension (81.8%), hypercholesterolemia (72.4%), and diabetes (44.3%). The prevalence of overweight (39.8%), obesity (26.6%), and morbid obesity (3.6%) were similar in most areas. Patients were generally undertreated with statins (69.4% overall; range: 56.4% for cerebrovascular disease to 76.2% for CAD), antiplatelet agents (78.6% overall; range: 53.9% for \geq 3 risk factors to 85.6% for CAD), and other evidence-based risk reduction therapies. Current tobacco use in patients with established vascular disease was substantial (14.4%). Undertreated hypertension (50.0% with elevated BP baseline), undiagnosed hyperglycemia (4.9%), and impaired fasting glucose (36.5% in those not known to be diabetic) were common. Among those with symptomatic atherothrombosis, 15.9% had symptomatic polyvascular disease.

Table 25: Secondary prevention after stroke: Cholesterol lowering

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Amarenco et al 2004	M/A n = >90,000 patients (most related to primary prevention)	Statins v placebo	Stroke (fatal and non fatal), MI, vascular events, LDL-C, adverse events, mortality	The RRR for stroke was 21% (OR 0.79). Fatal strokes were reduced but not significantly by 9% (OR, 0.91). There was no increase in ICH (OR, 0.90). Statin size effect was closely associated with LDL-C reduction. Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 15.6% and carotid IMT by 0.73% per yr.

Table 25: Secondary prevention after stroke: Cholesterol lowering

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
De Dunus et al 2004	M/A; 13 RCTs, n = 49,275 patients	Statin v placebo assessing for risk of liver function abnormalities	LFT, other adverse events	The proportion of patients having LFT abnormalities was low in both groups (statins 1.14% vs placebo 1.05%, OR 1.26, p=0.07). Only fluvastatin was associated with increase in LFT abnormalities. Authors state that pravastatin, lovastatin, and simvastatin at low-to-moderate doses are not associated with a significant risk of LFT abnormalities.
Cholesterol Treatment Trialists' Collaboration 2005	M/A; n = 90 056 individuals in 14 RCTs of statins	Cholesterol lowering drugs (statins) v placebo	Mortality, stroke and heart events, adverse events, LDL cholesterol	The overall reduction of about one fifth per mmol/L LDL cholesterol reduction translated into 48 fewer participants having major vascular events per 1000 among those with pre-existing CHD at baseline, compared with 25 (19–31) per 1000 among participants with no such history. There was no evidence that statins increased the incidence of cancer.
Law and Rudnicka 2006	S/R n = 20 RCTs and other cohort studies, voluntary notifications to national regulatory authorities, and published case reports.	incidence and characteristics of adverse effects in patients treated with statins	Adverse events, mortality	Incidence of rhabdomyolysis was 3.4 (1.6 to 6.5) per 100,000 person-years. Case fatality was 10%. Incidence was higher (4.2 per 100,000 person-years) with lovastatin, simvastatin, or atorvastatin than pravastatin or fluvastatin. The incidence of myopathy was 11 per 100,000 person-years. Fewer liver disease cases in RCTs of statins compared with placebo. RCTs found no excess of renal disease or proteinuria in statin-allocated participants. Very small risk of peripheral neuropathy found in 4 cohort studies. No change in cognitive function from RCTs in elderly patients.
Heart Protection Study 2002	RCT 69 centres. n = 20,536 patients with vascular disease or diabetes mellitus or hypertension (whatever the cholesterol level).	Simvastatin 40mg/day vs placebo for 5 years	Major vascular events (MI, stroke) requiring hospital admission; mortality; and cancer.	All vascular events reduced by approximately a third in patients with arteriosclerotic TIA or stroke on Simvastatin.
Heart Protection Study 2003	RCT n = 20,536 patients – Subgroup analysis of patients with vascular disease or diabetes mellitus or hypertension.	Daily antioxidant vitamin supplementation (Vit E 600mg, Vit C 250mg, B carotene 20mg) vs placebo	Major vascular events (MI, stroke) requiring hospital admission; mortality; and cancer.	These antioxidant vitamins appeared to be safe, but there was no benefit from them at these doses.
Heart Protection Study 2004	RCT; n = 20,536 adults –Subgroup analysis of 3280 patients with cerebrovascular disease, 17,256 with other occlusive arterial disease)	40mg Simvastatin vs placebo (Follow-up results of Heart Protection study patients over 4+ years)	Death; non-fatal MI or stroke; any revascularisation procedure.	Allocation to Simvastatin reduced the rate of ischaemic stroke by one quarter; but no apparent reduction in those with pre-existing cerebrovascular disease. No significant difference in cerebral haemorrhage between treatment groups.

Table 25: Secondary prevention after stroke: Cholesterol lowering

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Amarengo et al 2006	RCT; n= 4731 patients with pre-existing TIA or stroke within 1-6 months and LDL cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known CHD. Mean follow up 4.9 years.	Atorvastatin 80mg v placebo	Fatal and non fatal stroke, mortality, other cardiovascular events, haemorrhage events, adverse events, cholesterol levels	Significantly lower mean LDL cholesterol levels during the trial (1.9 mmol per liter v 3.3 mmol per litre). 11.2% receiving atorvastatin and 13.1% receiving placebo had a fatal or nonfatal stroke (5-year ARR, 2.2%; P=0.03). The five-year ARR of major cardiovascular events was 3.5% P=0.002. The overall mortality rate was similar (P=0.98), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin. Slightly more haemorrhagic events with statin.
Sanossian et al 2006	CCT; n = 92 stroke patients recently admitted for stroke or TIA	Evaluate the effects of in-hospital initiation of statins on 3-month treatment adherence rates and achievement of national guideline target cholesterol goals.	LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglyceride, and non-HDL-C levels, as well as liver enzyme levels.	Hospital initiation of statin therapy yielded high rates of adherence (93%), lowered mean low-density lipoprotein cholesterol levels from 120 to 78 mg/dL and increased the proportion of patients with low-density lipoprotein cholesterol levels lower than 100 mg/dL from 36% to 88% at 3 months (p<0.001).

Table 26: Secondary prevention after stroke: Carotid surgery

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Rothwell et al 1996	S/R, 51 studies (case series, CCT, RCT) reporting outcomes after CEA	CEA	Stroke, mortality	Overall mortality was 1.62% (95% CI, 1.3 to 1.9), and the risk of stroke and/or death was 5.64% (95% CI, 4.4 to 6.9). However, there was significant heterogeneity of risk of stroke and/or death (P < .001). The risk varied systematically with the methods and the authorship of the study. The risk of stroke and/or death was highest in studies in which patients were assessed by a neurologist after surgery (7.7%; 95% CI, 5.0 to 10.2) and lowest in studies with a single author affiliated with a department of surgery (2.3%; 95% CI, 1.8 to 2.7).

Table 26: Secondary prevention after stroke: Carotid surgery

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Cina et al 1999	M/A; 2 trials, n = 5950 patients	Surgery for carotid stenosis compared to best medical treatment	Disabling stroke; death	Carotid endarterectomy reduced the risk of death or disabling stroke in surgically fit patients with measured 50% (NASCET) 70%(ECST) stenosis, by surgeons with low complication rates (<6%)
Westwood et al 2002	M/A; 26 heterogeneous RCTs	Comparison of Magnetic resonance angiography (MRA) v intra-arterial digital subtraction or cut film angiography to screen for carotid stenosis	Performance characteristics of diagnostic test	MRA is accurate for selecting patients for carotid endarterectomy, but the evidence is not robust due heterogeneity of the trials.
Engelter and Lyer 2003	M/A; 6 RCTs n= 907 patients	Safety and effectiveness of antiplatelet after CEA.	Stroke, mortality, complications, adverse effects, MI, TIA, restenosis	Antiplatelet drugs did not significantly change the odds of 'death' but reduce the outcome 'stroke of any cause' in patients undergoing CEA 9p=0.04). There is a suggestion that antiplatelets may increase the odds of haemorrhage, but there are currently too few data to quantify this effect.
Rothwell et al 2003	M/A; 3 RCTs; n = 6092, in 222 centres.	Carotid endarterectomy	Stroke (any cerebral or retinal event with symptoms lasting longer than 24 hours)	Shows a clear benefit for surgery for those with >70% stenosis or greater; marginal in 50-69% stenosis. Surgery increased risk of stroke in <30% stenosis.
Coward et al 2004	M/A; 2 completed RCTs (n=608), 2 RCTs stopped early (n=242), 1 RCT completed with 30 days results (n=307.	CEA v stenting	Mortality, strokes, complications	No significant difference between the odds of death or any stroke at 30 days post procedure (OR 1.26). At one year following procedure, there was no significant difference between the two groups in preventing any stroke or death (OR 1.36). Endovascular treatment significantly reduced the risk of cranial neuropathy (OR 0.12). There was substantial heterogeneity between the trials.
Rothwell et al 2004	M/A; n=5893 patients. Pooled data from ECST and NASCET. 7 predefined subgroup analysis and 7 post hoc analysis.	CEA v medical care	Stroke (fatal and non fatal) risk, mortality, perioperative complications	Sex (p=0.003), age (p=0.03), and time from the last symptomatic event to randomisation (p=0.009) modified the effectiveness of surgery. For patients with >50% NNT = 9 men; 36 women; 5>75 yrs; 18<65 yrs; 5 if within 2 wks; 125 if included after 12 wks. These results were consistent across the individual trials.

Table 26: Secondary prevention after stroke: Carotid surgery

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Chambers and Donnan 2005	M/A, 3 RCTs, n= 5223 patients with asymptomatic carotid stenosis	CEA v medical care	Stroke (perioperative or subsequent), mortality	Despite about a 3% perioperative stroke or death rate, CEA for asymptomatic carotid stenosis reduces the risk of ipsilateral stroke, and any stroke, by approximately 30% over three years. However, the ARR is small (approx 1% per annum over the first few years). CEA appeared more beneficial in men than in women and more beneficial in younger patients than in older patients.
Kopp et al 2003	RCT; n=50 patients undergoing carotid stenting. Outcomes compared to another group n=30 with filter protection.	Standard antithrombotic therapy (n=30) consisting of aspirin, clopidogrel, and heparin v abciximab (n=20).	Whole blood flow cytometry, immunoassay, ischaemic events, NIHSS, complications	Filter protection reduced ischaemic episodes. Trend to improved protection with abciximab v antithrombotic therapy.
Payne et al 2004	RCT, n =100 symptomatic carotid stenosis night before CEA.	Clopidogrel + aspirin (C+A) v aspirin alone	whole-blood flow cytometry, emboli detected by TCD, time from flow restoration to skin closure.	In comparison with placebo, clopidogrel produced a small (8.8%) but significant reduction in the platelet response to ADP (P<0.05). However, in the clopidogrel-treated patients, the time from flow restoration to skin closure was significantly increased (P=0.04), although there was no increase in bleeding complications or blood transfusions
Tytgat et al 2005	RCT, n = 100 patients	One off dose of aspirin (120mg) night before CEA v placebo	Emboli were counted and expressed as emboli rate (ER), bleeding complications	No difference in outcomes.
McKevitt et al 2005	RCT; n = 47 patients undergoing carotid stenting	Clopidogrel + aspirin (C+A) v heparin	30-day bleeding and neurological complications and 30-day stenosis rates	Trend to benefits of C+A for bleeding complications (p=0.35) and 50-100% stenosis rate (p=0.1). Significant benefits in lower neurological complication rates (0% v 25%). Trial stopped prematurely due to complications in heparin group.
Markus et al 2005	RCT, n = 107 with symptomatic carotid stenosis >50%	Clopidogrel + aspirin (C+A) v aspirin alone	microembolic signals (MES) via transcranial Doppler ultrasound (TCD) on day 2 and 7.	Significant reduction in MES 43.8% (C+A) on day 7 v 72.7% of monotherapy patients (RRR 39.8%; P=0.0046). There were 4 recurrent strokes and 7 TIAs in the monotherapy group versus no stroke and 4 TIAs in the dual-therapy group.
SPACE Collaborative Group 2006	RCT, n=1183 within 180 days of stroke	CEA v stenting	30 day mortality and stroke	SPACE failed to prove non-inferiority of stenting compared with CEA for the periprocedural complication rate. (6.84% v 6.34%) Authors suggest results don't justify preference of stenting over CEA.

Table 26: Secondary prevention after stroke: Carotid surgery

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Mas et al 2006 (EVA-3S)	RCT, testing noninferiority; n = 527 (trialled stopped prematurely)	To compare stenting with CEA in patients with a symptomatic carotid stenosis of at least 60%.	30 day mortality and stroke, MI, TIA, cranial-nerve injury, major local complications, and systemic complications within 30 days after treatment	The 30-day incidence of any stroke or death was 3.9% after CEA and 9.6% after stenting ; the RR of any stroke or death after stenting as compared with CEA was 2.5. At 6 months, the incidence of any stroke or death was 6.1% after CEA and 11.7% after stenting (P=0.02). There were more major local complications after stenting and more systemic complications (mainly pulmonary) after CEA, but the differences were not significant. Cranial-nerve injury was more common after CEA than after stenting.

Table 27: Concordance with medication

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Schroeder et al 2004	S/R; 38 RCTs n= 15519 patients	Effectiveness of interventions aiming to increase adherence to blood pressure lowering medication in adults with high blood pressure	Adherence, knowledge	Simplifying dosing regimens increased adherence in seven out of nine studies, with a relative increase in adherence of 8 per cent to 19.6 per cent. Motivational strategies were successful in 10 out of 24 studies with generally small increases in adherence up to a maximum of 23 per cent. Complex interventions involving more than one technique increased adherence in eight out of 18 studies, ranging from 5 per cent to a maximum of 41 per cent. Patient education alone seemed largely unsuccessful.
Schedlbauer et al 2004	S/R; 8 RCTs n=5943 patients	Adherence-enhancing interventions to lipid lowering medication in adults for both primary and secondary prevention of cardiovascular disease in an ambulatory setting	Adherence, selected patient outcomes	Change in adherence ranged from -3% to 25% . Three studies reported significantly improved adherence through simplification of drug regimen, improved patient information/education and reminding . More studies are needed before clear conclusions can be reached.

Table 27: Concordance with medication

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
McGraw 2004	S/R; 2 RCT n= 148 patients (diabetic and hypertensive patients)	Multi-compartment medication compliance devices in promoting adherence among non-adherent adults living at home.	Compliance, patient outcomes	Improved glucose control for diabetic patients in one study. No impact on blood pressure control in hypertensive patients in the other study. Further research needed.
Haynes et al 2005	M/A; 8 RCTs for short term treatments; 49 RCTs for long term treatments	Interventions to improve adherence with medication eg improving convenience; giving information; reminders; counselling	Adherence to prescriptions; knowledge	For short-term treatments, 4 of 9 interventions reported showed an effect on both adherence and at least one clinical outcome. For long-term treatments, 26 of 58 interventions reported were associated with improvements in adherence, but only 18 interventions led to improvement in at least one treatment outcome. Current methods of improving adherence for chronic health problems are mostly complex and not very effective. Further research needed.
Heneghan et al 2006	S/R; 8 RCT, n= 1,137 participants	reminder packaging device with no device in participants taking self-administered medications for a minimum of one month	% of prescribed pills taken, adherence, various outcomes (e.g. BP)	Reminder packing may represent a simple method for improving adherence for patients (e.g. increased % of pills taken). Patient outcomes may be changed although more data is needed.
Schroeder et al 2005	RCT n=245 women and men with uncontrolled hypertension from 21 general practices in Bristol, UK.	There was no evidence of an effect of the intervention on timing compliance at follow-up. There was also no difference at follow-up between the groups with regard to systolic blood pressure or diastolic blood pressure (0.2 mmHg)	To evaluate the effect of nurse-led adherence support for people with uncontrolled high blood pressure compared with usual care.	Adherence to blood pressure medication was much higher than previously reported. There was no evidence of an effect of nurse-led adherence support on medication adherence or blood pressure compared with usual care. Nurse-led adherence support was also more expensive from a primary care perspective.
Ovbiagele et al 2004	CCT, n=144 hospitalised stroke patients and 90 day post discharge follow up	Implementation of secondary prevention strategies prior to discharge.	Utilisation of medications, adherence	Adherence rates in patients without specific contraindications were 100% for antithrombotics, 99% for statins, 92% for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 80% for thiazides. Awareness of the importance of calling 911 in response to stroke was 87%. Adherence to diet and exercise guidelines were 78% and 70%, respectively. Of the 24 smokers, tobacco cessation was maintained in 20 (83%).

Table 28: Discharge planning

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Shepperd et al 2004	M/A; 11 RCTs; n = 5448 medical, surgical and psychiatric cases	Individualised discharge plan vs "normal care"	Mortality; LOS; readmission rates; discharge home; dependency; QoL; satisfaction with care.	Insufficient similarity in outcome measures used so lack of power to identify impact of effectiveness.
Barras, 2005	S/R; 4 RCTs n=906, 7 descriptive studies, n=239	Identify studies that have examined home assessments and the outcome measures that have been used.	personnel present, cost, frequency and when completed, readmission, stakeholder perspective and use of standardized measures.	Authors concluded that there was a paucity of studies examining home assessments. Currently there is insufficient evidence to support the effectiveness of home assessments. There is some evidence to suggest home assessments may influence quality of life and number of falls.
Kalra et al, 2004	RCT; n = 300 patients and caregivers	Conventional rehabilitation unit care for cares vs care giver training. Training = 3-5, 30-45 minute hands on and educational training sessions.	Stroke sub-type, BI, Frenchay activity index, euroQoL, HADS, Modified Rankin scale Caregivers: demographics, accommodation, health profile, functional status, QoL	Patients whose caregiver had received training had significantly better QoL and mood outcomes. Burden of care, QoL and mood were significantly improved in the caregivers who received training.
Dai et al, 2003	Pre and post study n = 112 patients with craniotomy, n = 171 people with stroke	Assess the effects of a nurse designed discharge planning project.	LOS, ADL, rate of nursing home placement, unplanned readmissions, level of satisfaction.	LOS was shorted in the stroke group. No differences between the groups for the other outcomes.

Table 29: Community rehabilitation

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Dekker et al, 1998	S/R; n = 6 trials	Day hospital rehabilitation for stroke	Range of functional measures; mental health; extended ADL; health perceptions.	No conclusions as (a) no definition of DH, (b) varied outcome measures, (c) varied control groups
Forster et al, 1999	S/R; 12 trials; n = 2867	Day hospital vs comprehensive care (5 trials); domiciliary care (4 trials); no comprehensive care (3 trials)	Mortality; institutionalization; disability; global "poor outcome"; use of resources.	Day hospital may be effective for elderly people needing rehabilitation, but has no clear advantage over other comprehensive care.

Table 29: Community rehabilitation

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Britton & Andersson, 2000	S/R; 7 trials, n = 1487 stroke patients	Comparison of home based rehabilitation vs inpatient rehabilitation, day care or out-patient visits.	Cost, depression, QOL, function	No significant differences between the different types of care for outcome. Home based rehabilitation was less expensive than day care. Depression and reduced QOL was common in all groups.
Outpatient Service Trialists 2003	M/A; 14 trials n = 1617 stroke patients resident in the community	Therapy service intervention (physio, OT or MDT working with patients to improve task-oriented behaviour, activity and participation) vs conventional or no care.	Mortality; performance in ADL; institutionalisation	Therapy-based rehabilitation services targeted towards stroke patients living at home appear to improve independence in personal activities of daily living.
Duncan et al 1998	RCT; n = 42 minimally and moderately impaired stroke patients 30-90 days after stroke	Therapist supervised exercises 3 times per week for 8 weeks versus usual care after discharge	Fugl Meyer motor assessment; Barthel; Lawton IADL; SF36 and measures of gait, balance and upper limb function.	Continuing therapy exercises after discharge probably improves mobility.
Holmqvist et al, 2000	Cohort study following an RCT trial comparing ESD with continuing rehab at home to routine rehab i.e. hospital, day-care/out patient care. n = 81 patients followed up 3 months post stroke; n = 78 at 6 months	Tailor-made home rehab programme based on patient's personal interests vs hospital based rehab with review at outpatients or day care. Patients and spouse were interviewed at home at 3 and 6 months post stroke	Sickness Impact Profile. Hours/week carers helped with ADLs. Patient satisfaction.	The rehab at home showed a 50% reduction in length of stay and fewer visits to outpatients compared to hospital rehab. Showed no major differences in use of home help or impact on family. Patient satisfaction was higher in home rehab group
Wolfe et al 2000	RCT n = 43 people with stroke who remained at home. 23 Intervention 20 controls	Rehab at home vs usual care	Barthel; Rivermead ADL; 5-metre time walk; HAD; Mini-mental state; Nottingham Health Profile and Care-Giver strain index.	Community rehabilitation for patients at home is feasible. Larger trial required for clinical and cost effectiveness
Roderick et al 2001	RCT n = 140 patients after stroke aged 55+, who required further rehabilitation after hospital discharge.	Domiciliary vs day hospital rehabilitation after hospital discharge.	6 month Barthel; mortality; recurrent stroke; Rivermead Mobility Index; Frenchay Activities Index; Philadelphia Geriatric Centre Morale scale; SF36.	No significant difference between domiciliary or day hospital care. Total costs similar.

Table 30: Post-discharge support

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Mistiaen & Poot 2006	M/A; 33 studies, n = 5110	Assess the effect of follow-up telephone call in the 1 st month post discharge form hospital.	Psychological outcomes, physical outcomes, other consumer related outcomes, health service relate outcomes.	Some individual studies reported positive effects of telephone follow-up; however there is insufficient evidence to conclude that telephone follow-up is an effective intervention.
Christie & Weigall, 1984	RCT; n = 213 patients late after stroke	Social worker visits 2 yr after stroke (7 in 12 months) to evaluate effect on patient activities and use of services	Katz Index; LOS	No difference in activities score or number of days in hospital
Evans et al, 1988	RCT; n = 206 rehabilitation stroke patients	Nothing vs education, vs education and counselling sessions for carers soon after stroke.	Caregiver knowledge; problem solving; and social resource use at 6 and 12 months.	Education and counselling resulted in better knowledge, more effective problem solving and adjustment at 12 months. No effect on resource use.
Towle et al, 1989	RCT; n = 44 depressed stroke patients at home	Information ± additional social worker support	Use of aids to daily living; EADL; Frenchay Activities Index; use of benefits and services.	No difference in mood, equipment or services
Hansen, 1990	RCT; n = 100 patients with neurological disease	Intensive social assistance at and after discharge	Unmet needs; satisfaction; readmission.	Many unmet needs at discharge. No differences in satisfaction, but readmission less, more problems solved
Friedland & McColl, 1992	RCT; n = 88; stroke patients at home after rehabilitation	Special social support intervention, or nil (normal service)	Social Support Inventory for Stroke Survivors (SSISS); GHQ; Sickness Impact Profile (SIP); Barthel.	No difference in social support or psychosocial function.
Forster & Young, 1996	RCT; n = 240, patients at home after stroke	Specialist nurse visits (6+ over 6 months) or normal services alone	Barthel index; Frenchay activities index; Nottingham Health profile; GHQ-28	No beneficial effect on patient-s disability, social activities, or mood; or carers' stress
Dennis et al, 1997	RCT; n = 417 patients 30 days post-stroke	Family care worker (FCW) or standard care	Barthel index; Frenchay Activities index; GHQ; HAD; social adjustment scale; mental adjustment to stroke scale; satisfaction; carer strain (Pt and carer completed)	FCW group more satisfied; but possible increase in patient helplessness; no other differences detected
Goldberg et al, 1997	RCT; n = 55, community living stroke patients	Assess the effect of home-based case management care in returning to the community	Social activity level	People in the intervention group had significantly increased social activity at six months and there was a trend that the activity remained increased at 1 year.
Mant et al, 2000	RCT; n = 323 patients over 18 years with first or recurrent stroke who had a close family carer. N = 267 carers.	Assigned a Family Support Worker (FSW) within 6 weeks of stroke, nature and interaction was at the FSW's discretion.	At 6 months: <u>Carers</u> - knowledge about stroke; caregiver strain index; GHQ 28, SF 36. <u>Patients</u> - Frenchay activities index; Dartmouth co-op charts; Barthel Index; Rivermead Mobility index; London Handicap Scale; Hospital Anxiety and Depression Score.	Showed significant psycho-social benefits for carers, but no difference to patients in any of the key areas

Table 30: Post-discharge support

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Andersen et al, 2002	RCT (Denmark) n=155 patients with persistent impairments post stroke	3 physician visits vs physiotherapy visits vs control in patients' own home	Readmission rates; mortality; institutionalization at 6 months post discharge; functional ability.	Readmission rates: 26% physician visits; 34% physio visits; 44% control, p = 0.028. Most effective for those with long hospital stay. Non-significant trend to improved functional outcome for intervention groups.
Lincoln et al, 2003	RCT; n = 250 stroke patients	Family Support Officer contacted patient 2 weeks after allocation, provided point of contact, information, helped with discharge, attended case conferences and visited at home to provide support and information for up to 9 months	4 & 9 month assessment; GHQ-12, Barthel Index, Nottingham EADL; patients' knowledge; patients' and carers' satisfaction with information on stroke	Patients - No significant improvement in mood or dependence Carers no improvement in carer strain, Both - significant increases in knowledge and satisfaction with that knowledge.
Clark et al 2003	RCT 62 stroke patients and their spouses	Stroke information package and 3 visits from a social worker trained in family counseling	McMaster Family Assessment device plus measures of disability, mood, SF36 at 6 months	Improved family functioning and social recovery in intervention group. No effect on anxiety, depression, or health status
Hartke and King 2003	RCT 88 caregivers who had been providing care for mean of 3 years	An 8 session psycho-educational telephone group	Measures of burden, mood, loneliness and competence	Little difference between treatment and control groups. Significant increase in competence in intervention group.
Boter et al, 2004	RCT; n= 536 (n = 263 with stroke & n = 211 carers received standard care, n = 273 patients & n = 230 carers received outreach)	Outreach nursing: 3 telephone call, x 1 visit	Primary: Satisfaction with stroke care questionnaire, SF-36 Secondary: HADS, readmission, BI, modified Rankin Scale, use of health care services, use of secondary prevention drugs, carer strain index, sense of competence questionnaire, social support list discrepancies	No significant differences for QoL or satisfaction except outreach group scored better for role limitations due to emotional health. Outreach groups score lower for anxiety and used less rehabilitation resources. No significant differences between carers.
Glass et al, 2004	RCT; n = 291 stroke patients	Assess the effect of family systems intervention (16 sessions) vs usual care on functional recovery	Barthel Index	No significant difference between the groups for functional recovery although there was a trend for improved function in the intervention group.
Tilling et al 2005	RCT; n= 340 stroke patients	The Family support organiser service offers information, emotional support and prevention advice for families and stroke patients	Pt satisfaction; Barthel Score, patient and carer depression (Hospital Anxiety and Depression scales) impact of the stroke on the patient's everyday life (modified version of the Reintegration to Normal Living Index -RNLI), satisfaction with adaptations made to the home and use of social services, satisfaction with stroke care (Pound Satisfaction Scale). Carer strain index.	Patient more satisfied in only 1 of 11 domains (Felt they are listened to). Intervention group received more home help and were less likely to be admitted to hospital with 1 year post stroke. Carers more satisfied in only 1 domain as well (applying for services). No other differences found although study underpowered.

Table 30: Post-discharge support

Source	Design & Sample	Intervention(s)	Outcome measures	Conclusions
Burton 2005	RCT; n = 176, stroke patients discharged to the community	Support and education from a stroke nurse vs usual care	Barthel Index, Nottingham Health Profile, Carer Strain Index, Frenachy Activities of Daily Living	Intervention group had an improved perception of general health, decreased negative emotion and perceived social isolation at 12 months.
Middelton et al, 2005	RCT n = 133 carotoid endartectomy patients (n = 66 intervention, n = 67 control)	Telephone contact by nurses at 2,6 and 12 weeks post surgery. Education about stroke and stroke risk factors.	Questionnaire: sociodemographics, smoking status, physical activity, BP, cholesterol, knowledge of stroke	The intervention group rated their health significantly better at 12 weeks follow-up. Both groups demonstrated an increase in physical activity but there were no significant differences between the groups. People in the intervention group were more likely to report that they had made lifestyle and diet changes at follow-up.
Larson et al, 2005	RCT; n = 100 spouses (n = 47 education intervention, 50 control)	Support and education x 6 sessions	General QOL, life situation, general well-being, perceived health status	No statistical difference between groups for the outcomes variables. Within the education group there was decreased negative well being at 6 months but it returned to baseline at 12 months. Potential benefit for those attending most sessions in subgroup analysis.
Nir & Weisel-Eichler, 2006	RCT; n = 73 education program, n = 82 controls	In-patient rehabilitation usual care vs nursing education intervention. 12 sessions x 2 hours	Assessment of correct use of medications, dietary adherence, FIM, demographic and health characteristics.	Intervention group had greater knowledge of medications (eg shape, dosage and side-effects). However, even in the intervention group knowledge of medications was limited. The intervention group adhered more closely to dietary recommendations.

