

SYLLABUS

Marrakesh, Morocco, November 12-17, 2011

XXth WORLD CONGRESS OF NEUROLOGY



SOCIETE MAROCAINE
DE NEUROLOGIE

WCN Education Program
Sunday, 13 November, 2011
14:30-18:00

STROKE

Chairpersons: **José M. Ferro**, *Portugal*
Ka Sing Lawrence Wong, *Hong Kong S.A.R.*

14:30 **PART I**

INTRACRANIAL ATHEROSCLEROSIS

Ka Sing Lawrence Wong, *Hong Kong S.A.R.*

NEUROVASCULAR TREATMENT FOR ACUTE STROKE

Antoni Dávalos, *Spain*

TREATMENT OF SYMPTOMATIC CAROTID STENOSIS

Werner Hacke, *Germany*

16:00 *Coffee Break*

16:30 **PART II**

ORGANIZATION OF ACUTE STROKE CARE

Stephen M. Davis, *Australia*

PREVENTION OF CARDIOEMBOLIC STROKE

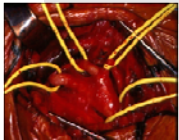
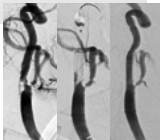
José M. Ferro, *Portugal*

THROMBOLYSIS IN ACUTE ISCHEMIC STROKE

Nils Wahlgren, *Sweden*

Treatment of Symptomatic Internal Carotid Stenoses

The Evidence
Werner Hacke MD PhD FAHA FESC
Heidelberg, Germany

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Disclosures

- No financial disclosures regarding this topic
- I was the principal investigator of SPACE and I am the principal investigator of SPACE II

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Prelude

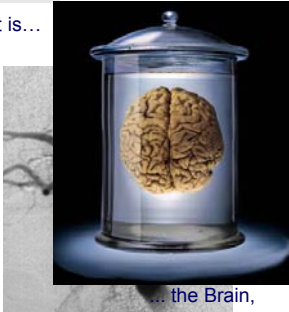
- I assume that we are in agreement about the following statement

The objective of treating carotid stenoses is to prevent *ipsilateral* stroke

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Carotid Interventions

The Target is...



...the Brain,
not the vessel

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Background

- Carotid artery stenoses causes approximately 20% of all ischemic strokes
- Symptomatic carotid artery stenosis have a high recurrence risk
- Endarterectomy (CEA) is the established treatment of choice in symptomatic $\geq 70\%$ ^{NASCET} carotid artery stenosis¹
- Stenting (CAS) was increasingly used and offered as an „established“ alternative to CEA

1: ESO Writing Committee Cerebrovasc Dis (2008); 25:457-507

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Stenting: Evidence

- Until 2006 registries and underpowered RCTs only
 - Best you can say: feasible and relatively safe
- No evidence for equivalence or even superiority
- No such evidence for the use of protection devices
- Some unequivocal indications for stenting include
 - Post-radiation-stenoses
 - Unacceptable surgical risk
 - Surgically unaccessable lesions
 - contralateral palsy of recurrent nerve

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Stenting Registries

- Case series and registries
 - Problem
 - Mostly self-reported results, rarely independent neurological monitoring
 - Comparison of uncontrolled data with results of RCTs
 - What we know
 - It can be done
 - It seems safe
 - No proof of equivalence or superiority so far
(Same is true for protection devices)

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Recent large RCTs

- Trials published after 2006
 - SPACE***
 - EVA-3S*
 - ICST (CAVATAS II**)
 - CREST****

* Mas, NEJM 2006
 ** Brown, Lancet 2010
 *** Ringel, Lancet 2006
 **** Brodt, NEJM 2010

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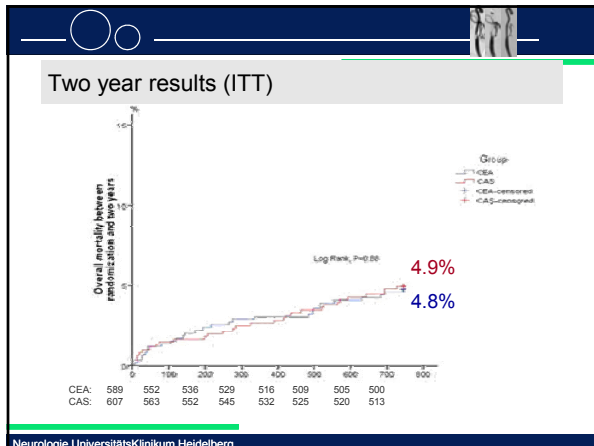
SPACE 1: Results – Primary Endpoint (ITT)

Ipsilateral stroke (any) and death between randomization and day 30

	CAS (599)	CEA (585)
Events	41	37
Percentage	(6.84%)	(6.34%)

Absolute difference (95% CI): 0.51% (-2.37% to 3.39%); p=0.09
 Odds ratio (95% CI): 1.09 (0.69 to 1.72)

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Restenoses

- Assessed at day 7, 30, month 6, 12 and 24
- Based on ultrasound examination
 - no formal criteria for diagnosis of in-stent-restenosis
 - individual experience
 - central reading in process

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Restenoses at 24 months

	CAS	CEA	OR (95% CI)
Intention-to-treat	54 / 607 (8.9%)	23 / 589 (3.9%)	2.40 (1.46 - 3.97)

Two (both after CAS) were symptomatic !

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EVA 3S

- In short:
 - RCT comparing CAS and CEA in symptomatic ACI stenoses
 - Some experience of interventionalists required
 - After 20 patients, DSMC requested standard use of PD (5/20 endpoints without PD)
- Status at termination, required by DSMB
 - 527 patients randomized
 - 261 CAS vs 259 CEA
 - 7 excluded from ITT analysis

Mas NEJM 2007

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EVA 3S - Result primary endpoint

	CAS (N=261)	CEA (N=259)
	25	10
	(9,6%)	(3,9%)

Odds ratio 2,48 (95%CI 1,25 - 4,93)

Study prematurely terminated
November 2005

Mas NEJM 2007

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ICSS: Primary safety end point

	CAS n (%)	CEA n (%)	Hazard ratio (95% CI)	% difference	p
Stroke, MI, or death (ITT)	72 (8.5)	43 (5.1)	1.73 (1.18–2.52)	3.4	0.004

CAS = carotid artery stenting
CEA = carotid endarterectomy
ITT = intention to treat
PP = per protocol

Brown MM et al. European Stroke Conference 2009; May 27, 2009; Stockholm, Sweden.

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ICSS: Primary end point cluster (ITT)

End point	CAS	CEA
Any stroke	65	34
Any myocardial infarction	3	4
Non-stroke, non-MI deaths	7	5

CAS=carotid artery stenting
CEA=carotid endarterectomy

Brown MM et al. European Stroke Conference 2009, May 27, 2009; Stockholm, Sweden.

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ICSS: Primary safety end point (ITT)

72 CAS vs 43 CEA
HR = 1.73 (1.18, 2.52)
120d risk difference = 3.4% (1.0, 5.8)
Log rank p-value = 0.004

Number at risk	0	30	60	90	120
CAS	853	792	753	743	738
CEA	857	822	789	775	768

Brown MM et al. European Stroke Conference 2009, May 27, 2009; Stockholm, Sweden.

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Carotid Stenting trialist' collaboration

Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data

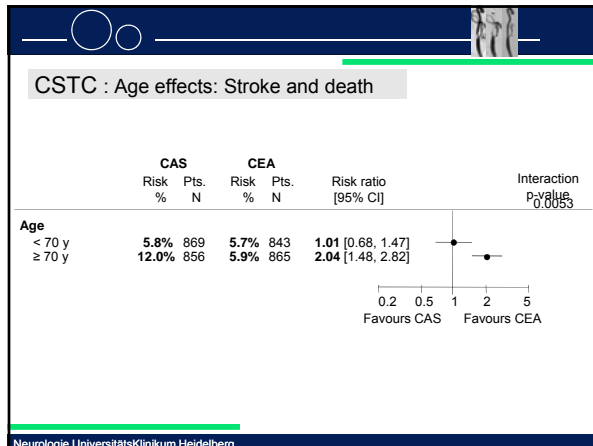
Carotid Stenting Trialists' Collaboration*

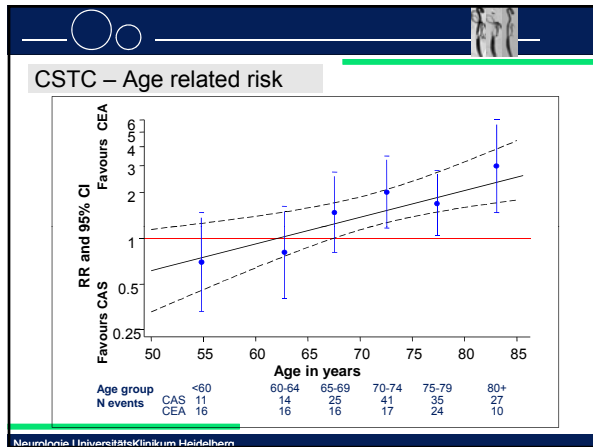
- Single Data joined analysis of SPACE, EVA3S, ICSS
- n=3,433 Patienten

Bonati L... Ringieb P; Lancet (2010); 376: 1062-1073

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Update





Joint analysis: Interpretation

- The short-term outcome is superior after endarterectomy compared with stenting, due to an increased risk of stroke associated with stenting in elderly patients.
- Stenting may be as safe as endarterectomy in younger patients, but determination of the efficacy and ultimate balance between the two procedures requires further data on long-term stroke recurrence.

Bonati et al Lancet 2010 in press

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CREST
Carotid Revascularization Endarterectomy vs. Stenting Trial

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Stenting versus Endarterectomy
for Treatment of Carotid-Artery Stenosis

Thomas G. Brott, M.D., Robert W. Hobson, II, M.D.,* George Howard, Dr.P.H., Gary S. Roubin, M.D., Ph.D., Wayne M. Clark, M.D., William Brooks, M.D., Ariane Mackey, M.D., Michael D. Hill, M.D., Pierre P. Leung, M.D., Alice J. Sheffield, Ph.D., Virginia J. Howard, Ph.D., Wesley S. Moore, M.D., Jennifer H. Voeks, Ph.D., L. Nelson Hopkins, M.D., Donald E. Cullip, M.D., David J. Cohen, M.D., Jeffrey J. Popma, M.D., Robert D. Ferguson, M.D., Stanley N. Cohen, M.D., Joseph L. Blackshear, M.D., Frank L. Silver, M.D., J.P. Mohr, M.D., Brajesh K. Lal, M.D., and James F. Meschia, M.D., for the CREST Investigators†

N Engl J Med 2010 Jul 1;363(1):11-23. Epub 2010 May 26

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CREST- Study Design
Carotid Revascularization Endarterectomy vs. Stenting Trial

- **Study population**
 - 2.502 patients, age mdn 69 y., male 75%
- **Inclusion**
 - asymptomatic Stenosis (n=1.181): $\geq 60\%$ NASCET, $\geq 70\%$ Ultrasound
 - symptomatic Stenosis (n=1.321): $\leq 180d$, $\geq 50\%$ NASCET, $\geq 70\%$ Ultrasound
- **Tx**
 - CAS with Protection (one product only, Cordis) or CEA
- **Primary endpoint**
 - Safety: Stroke, MI, or death w/in 30d
 - Efficacy: Ipsilateral stroke up to 4y

Brott TG et al.: N Engl J Med (2010); 363(1): 11-23

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CREST
long term efficacy (all patients), up to 4 years

Endpoint (ITT-Population)	CAS	CEA	HR (95%CI)	p-value
Stroke, MI, death 30 days + ipsilateral stroke 4y	7,2%	6,8%	1,11 (0,81-1,51)	0,51
Stroke or death 30 days + ipsilateral stroke 4y	6,4%	4,7%	1,50 (1,05-2,15)	0,03
Ipsilateral stroke 4y	10,2%	7,9%	1,40 (1,04-1,89)	0,03

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CREST
Safety, symptomatic patients only, 30 days

Endpoint (ITT-Population)	CAS	CEA	HR (95%CI)	p-Wert
Stroke, MI, death	6,7%	5,4%	1,26 (0,81-1,96)	0,30
Stroke or death	6,0%	3,2%	1,89 (1,11-3,21)	0,02
Stroke	5,5%	3,2%	1,74 (1,02-2,98)	0,04
MI*	1,0%	2,3%	0,45 (0,18-1,11)	0,08

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CREST Periprocedural Risk (Symptomatic Cohort)
1.321 Patients (653 CEA, 668 CAS)

Endpoint	CAS Event Rate	CEA Event Rate	HR (95%CI)	p-value
Stroke MI, Death ^{30d}	6,7%	5,4%	1,26 (0,81-1,96)	p=0,30
Stroke, Death ^{30d}	6,0%	3,2%	1,89 (1,11-3,21)	p=0,02
Stroke ^{30d}	5,5%	3,2%	1,74 (1,02-2,98)	p=0,04
MI ^{30d}	1,0%	2,3%	0,45 (0,18-1,11)	p=0,08

Stroke MI, Death^{30d}
Stroke, Death^{30d}
Stroke^{30d}
MI^{30d}

0% Event rate 10% CAS CEA

Brodt TG et al.: N Engl J Med (2010); 363(1): 11-23

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CREST Criticism

- Combining symptomatic and asymptomatic
- Combining endpoint elements of different importance
- Superiority design
- One company, and potential bias

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Conclusions

- At present, RCTs in patients with symptomatic carotid disease show inferior results of CAS compared to CEA with regard to the risk of stroke or death within 30 days of treatment.
- The safety of carotid stenting needs to be improved and subgroups of patients who could benefit from CAS need to be identified.
- Pending results from ongoing trials and combined analysis, carotid endarterectomy remains the treatment of choice of patients with symptomatic severe carotid stenosis.

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A Final, Very Personal Statement

- What we currently see happen in clinical practice in Europe and the US is not acceptable
 - Asymptomatic patients are persuaded to stenting by cardiologists and radiologists, who claim superiority and low risk
 - They even ask for halting unethical RCTs, and do not take notice of the results
 - It is all about money- they charge for treatment of peripheral vessels
 - Complications are transferred and excluded from the registries

money, no science

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NEUROLOGIE

Thanks for your attention

2011

Organisation of Stroke Services

Marrakesh WCN 2011

Stephen Davis

RMH Stroke Centre
Department of Neurosciences
Royal Melbourne Hospital
University of Melbourne



Stroke – a massive global problem

- Stroke is the most frequent major neurological disease - 20 million/year
- 2nd commonest cause of death worldwide
- Higher mortality than most forms of cancer – 10% within the first months
- High rate of long-term disability
- Increasing incidence and prevalence

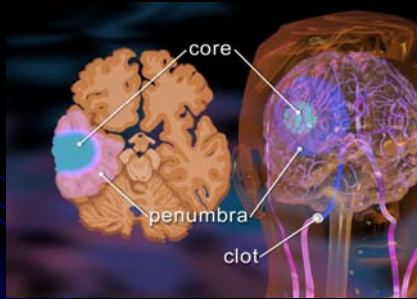


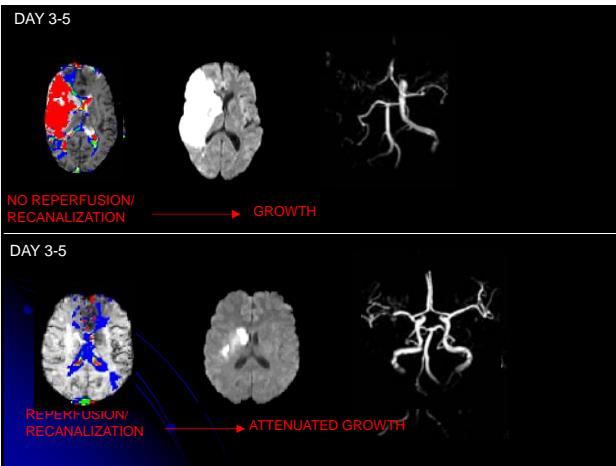
Why are early recognition and diagnosis time-critical?

- Both ischemic stroke and hemorrhagic stroke are dynamic, evolving conditions
- Stroke evolution results in increased lesion volume = worse outcome
- **Therapies for both ischemic stroke and ICH are aimed at limiting stroke growth**



Rescuing the penumbra: the aim of acute stroke treatment





Time is brain – Quantified

Saver J. Stroke 2006;37:263-266

Saver Time Is Brain—Quantified 265

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/216 yards	8.7 h

Every minute counts!

Chain of Recovery

Kennedy et al. Current Neurology and Neuroscience Reports, 2004

- **Recognition**
 - Public education
- **Reaction**
 - Speedy ambulance delivery to emergency department
- **Response**
 - Rapid ED teamwork to assess patient; code stroke
- **Reveal**
 - Urgent CT
- **Rx (treatment)**
 - Stroke unit care, tPA, aspirin, new emerging therapies
- **Rehabilitation**
 - Should start immediately in stroke care unit

If you recognise the signs of **STROKE** act

FAST

Facial weakness

Can the person smile? Has their mouth or eye drooped?

Arm weakness

Can the person raise both arms?

Speech difficulty

Can the person speak clearly and understand what you say?

Time to act fast

If you recognise the signs of stroke, seek immediate medical attention.

The signs of Stroke are:

- Weakness, numbness or paralysis of the face, arm or leg
- Difficulty speaking or understanding
- Dizziness and loss of balance
- Loss of vision
- Headache, usually severe and abrupt
- Difficulty swallowing

Act FAST – seek immediate medical attention.

For more information call **1800 787 653** or visit www.strokefoundation.com.au.



Cincinnati Prehospital Stroke Scale Facial Droop: Have Patient Smile

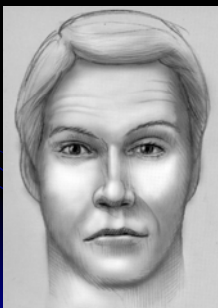


Image Source: NINDS

Arm Drift: Close Eyes & Hold Out Both Arms



Image Source: NINDS

Time is brain

Rapid transport to a stroke centre

- Rapid ambulance transport
- Paramedical diagnostic stroke tools
 - FAST, Cincinnati, LAPS
- Pre-hospital notification valuable
- Potential for ambulance-based therapy
 - Phase 3 in USA using magnesium sulphate



Conditions that mimic stroke

Hand et al. Stroke 2006

Condition	Total Number (%) [†]	Mimics presenting:	
		Within 6 hrs [‡]	After 6 hrs [‡]
Seizure	23 (21.1%)	18 (29.0%)	5 (10.6%)
Sepsis	14 (12.8%)	6 (9.7%)	8 (17.0%)
Toxic / metabolic	12 (11.0%)	6 (9.7%)	6 (12.8%)
Space occupying lesion [§]	10 (9.2%)	3 (4.8%)	7 (14.9%)
Syncope / presyncope	10 (9.2%)	9 (14.5%)	1 (2.1%)
Acute confusional state	7 (6.4%)	3 (4.8%)	4 (8.5%)
Vestibular dysfunction	7 (6.4%)	3 (4.8%)	4 (8.5%)
Acute mononeuropathy	6 (5.5%)	4 (6.5%)	2 (4.3%)
Functional/medically unexplained symptoms	6 (5.5%)	4 (6.5%)	2 (4.3%)
Dementia	4 (3.7%)	2 (3.2%)	2 (4.3%)
Migraine	3 (2.8%)	2 (3.2%)	2 (4.3%)
Spinal cord lesion [¶]	3 (2.8%)	- (0%)	3 (6.4%)
Other [‡]	3 (3.7%)	2 (3.2%)	1 (2.1%)
Total	109 (100%)	62 (100%)	47 (100%)

All strokes (ischemic or hemorrhagic):
admit to a stroke unit



Stroke Care Units

The key components

No age or severity barriers to the benefit

Assessment and monitoring	
Medical	Systematic clinical history and examination Routine investigations—serum biochemistry, haematology, electrocardiogram, CT Investigations in selected patients—carotid doppler, echocardiogram, MRI
Nursing	General care needs, vital signs, swallow assessment, fluid balance, pressure-area risks, neurological monitoring
Therapy	Assessment of impairments and function
Early management	
Physiological management	Careful management of food and fluids (often intravenous saline over first 12–24 h) Monitoring and treatment of infection, pyrexia, hypoxia, hypoglycaemia
Early mobilisation	Early measures to get patient sitting up, standing, and walking
Nursing care	Careful positioning and handling, and pressure-area care Management of swallowing problems Avoidance of urinary catheters if possible
Multidisciplinary team rehabilitation	
Rehabilitation process	Formal multidisciplinary meetings once a week (plus informal meetings) Early rehabilitation, goal-setting, and involvement of carers Close linking of nursing with other multidisciplinary care Provision of information on stroke, recovery, and services
Discharge planning	Early assessment of discharge needs Discharge plan involving patient and carers

Stroke Centres

- **Primary**
 - ED
 - Geographical stroke unit, multidisciplinary team
 - 24 hour CT
 - Use tPA
- **Comprehensive stroke centres**
 - Multimodal imaging MRI, CTP
 - Neurointervention
 - Neurosurgery and vascular surgery
 - Active research program
 - Often telestroke provider



Assessment and Minimisation of Complications

- Hypoxia reduction
- Glycaemia control
- Dehydration prevention
- Neurological & vital sign monitoring
- Chest infection risk reduction
- Deep venous thrombosis minimisation
- Pressure risk management
- Shoulder injury prevention
- Contenance assessment



Why are Stroke Units effective?

- Focused attention on stroke care including:
 - Prevention and early detection / treatment of complications of stroke
 - Prevention of early stroke recurrence by attention to stroke risk factors / secondary prevention strategies
 - Early rehabilitation





Organised inpatient (stroke unit) care for stroke (Review)

Reviewers' conclusions

Stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke. The benefits were most apparent in units based in a discrete ward. No systematic increase was observed in the length of inpatient stay.

SYNOPSIS

Patients who receive organised stroke unit care are more likely to survive their stroke, return home and make a good recovery. Organised stroke unit care is a form of care provided in hospital by nurses, doctors and therapists who specialise in looking after stroke patients and work as a coordinated team. Patients who receive this care are more likely to survive their stroke, return home and become independent in looking after themselves. A variety of different types of stroke unit has been developed. The best results seem to come from those which are based in a dedicated ward.

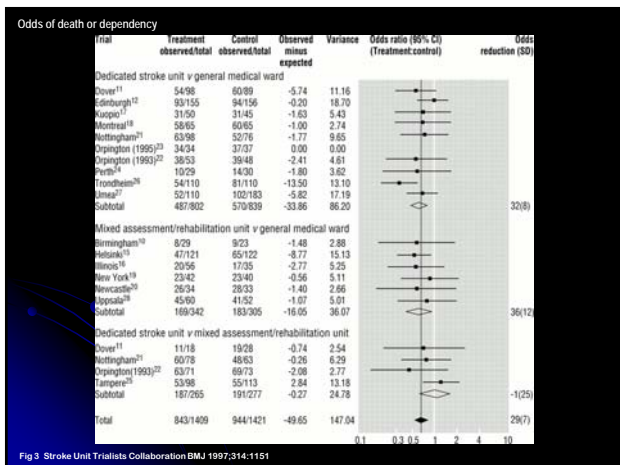


TABLE 4. Length of Hospital Stay and Outcome in Patients Treated at the Stroke Unit and Patients Treated on General Wards

	General Wards	Stroke Unit	P
LOHS, d	55.2 (47.1-63.4)	38.6 (35.7-41.6)	<.0001
LOHS,* d	38.5 (32.2-44.9)	29.6 (27.1-32.0)	.002
LOHS,† d	55.5 (39.4-71.7)	33.5 (28.1-38.9)	.001
LOHS,‡ d	55.1 (45.6-64.6)	40.8 (37.2-44.3)	.0007
Discharged to home	171 (56)	607 (65)	.02
Discharged to nursing home	45 (15)	115 (12)	.02
Died during hospital stay	89 (29)	214 (23)	.02
Case-fatality rate (30 d)	69 (23)	161 (17)	.03
6-mo mortality	106 (35)	258 (28)	.01
1-y mortality	120 (39)	300 (32)	.01

LOHS indicates length of hospital stay. Continuous data are expressed as mean (95% confidence interval). Categorical data are expressed as number of patients (%).

*Excluding patients discharged to nursing home.

†Patients aged ≤70 y.

‡Patients aged >70 y.

Jorgensen et al. Stroke 1995;26:1178-1182.

TABLE 5. Relative Risk of Death, Discharge to Nursing Home, and Discharge to Home After Treatment on the Stroke Unit vs Treatment on General Wards, Independent of Other Influencing Factors

	Relative Risk*	95% CI	P	R
In-hospital mortality	0.50	0.34 to 0.74	<.001	-.12
Case-fatality rate (30 d)	0.45	0.28 to 0.71	<.001	-.12
6-mo mortality	0.57	0.39 to 0.82	.002	-.08
1-y mortality	0.59	0.42 to 0.84	.003	-.08
Discharge to nursing home	0.61	0.38 to 0.98	.04	-.10
Discharge to home	1.90	1.30 to 2.70	<.001	.09

CI indicates confidence interval.

*Relative risk (odds ratio) in patients treated on the stroke unit compared with patients treated on general wards.

Jorgensen et al. Stroke 1995;26:1178-1182.

Number of stroke patients you need to treat in a stroke unit

To prevent one death:

NNT= 22

To prevent one admission to institutional care:

NNT= 14

To prevent one loss of independence:

NNT= 16

Stroke Unit Trialists' Collaboration BMJ 1997;314:1151

Who benefits from SCU?

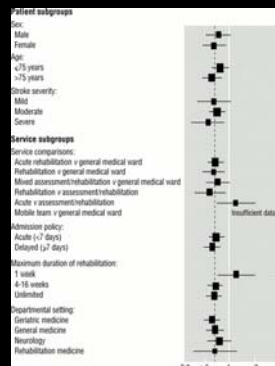
Almost everyone!

gender, age, severity

All types of SCU that provide care lasting >1 week

Benefit most apparent in units based in a discrete ward

Not mobile teams



RMH Comprehensive Stroke Centre

Cochrane Library, 2003

The SCU: the most important intervention for acute stroke

Actual and potential benefits (avoidance of death or disability) of acute interventions for stroke in Australia

Intervention	Absolute risk reduction	Number needed to treat	Estimated proportion of stroke patients treated ¹	Current absolute benefit ² (number of cases)	Potential proportion of stroke patients treated	Potential absolute benefit ³ (number of cases)
Stroke care unit	4% ¹	25 ¹	23%	423	80%	1472
Aspirin ⁴	1.2% ⁴	83 ⁴	70%	387	80%	443
Tissue plasminogen activator ⁵	12.0% ⁵	8 ⁵	<1%	<23	10%	575

¹ From the National Stroke Foundation survey of stroke care unit access, 1998.
² Number of deaths or cases of disability avoided among 40,000 strokes in Australia per year.
³ From the Stroke Unit Trialists' Collaboration.⁶ ⁴ From the International Stroke Trial.⁷
⁵ From the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator trial.⁸

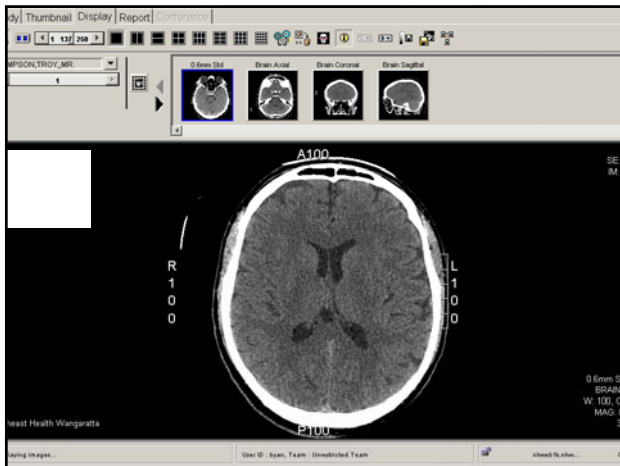
MJA, 2003

RMH Comprehensive Stroke Centre

RMH Telestroke Service



RMH Comprehensive Stroke Centre



T h r o m b o l y s i s v i a T e l e s t r o k e

Schwab et al; Neurology 2007; 69: 898-903

- TEMPIS – Telemedicine Pilot Project for Integrative Stroke Care in Bavaria
- Assessed tPA results in telemedicine vs stroke centre hospitals
- 170 telemedicine, 132 stroke centres
- Mortality and functional outcome after tPA similar

Take home messages Stroke Care Units

- Reduce mortality
- Reduce dependency
- Improve efficiency – reduce LOS
- Facilitate scientific research and health systems research
- Facilitate networking
- Teamwork - morale



