

Hypothermia for Stroke: call to action 2010

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The European Hypothermia Stroke Research Workshop was held in January 2010, in response to the alarming prospects of a significant increase of stroke expected in the coming years globally. Considering that a minority of patients (around 10%) are currently eligible for thrombolytic treatment, there is a need for an efficacious, cost-effective novel therapy that can be implemented broadly within European health care systems. Accordingly, the primary objective of the workshop was the definition of a research agenda aiming to assess the therapeutic benefits of hypothermia in patients with acute ischaemic stroke. The meeting was organised by the European Stroke Research Network for Hypothermia (EuroHyp) and attended by the representatives of World Stroke Organisation, European Stroke Organisation, Stroke Alliance for Europe, Society for Cryobiology and other organisations – specifically the European Space Agency, and small- and medium-sized enterprises based in EU member states. The participants adopted the ‘Hypothermia for Stroke – Call to Action 2010’, a declaration specifying the priorities for hypothermia research in acute ischaemic stroke. The research programme outlined – a clinical study programme designed to identify and validate therapeutic cooling as a novel treatment providing benefit to a large number of stroke patients – contains a well-integrated series of

Phase II studies aiming to refine the intervention (depth, duration, and mode of cooling; antishivering strategy; patient selection) and a pivotal Phase III clinical trial. The proposed integrated Phase II and III clinical study programme would test the effectiveness of this optimised intervention, and would allow the development of evidence-based Clinical Practice Guidelines describing the optimal use of therapeutic hypothermia as a treatment strategy for stroke.

Key words: acute stroke therapy, clinical trial, hypothermia, intervention, ischaemic stroke, neuroprotection

Background

Stroke is one of the leading causes of death and disability in Europe. As the population in Europe ages, the burden of the disease on society increases. Specifically, the current 38 billion cost per annum is projected to double by 2050 as the number of affected individuals is projected to increase dramatically.

In 1995, a Consensus Meeting on Stroke Management was held in Helsingborg, Sweden, to consider the latest evidence-based knowledge in the management of stroke and to set targets for the following decade. The meeting was arranged jointly by the World Health Organization (WHO) Regional Office for Europe and the European Stroke Council, in collaboration with the European Federation of Neurological Societies, the International Stroke Society, the World Confederation of Physical Therapy–Europe and the World Federation of Occupational Therapists. The meeting resulted in the ‘Helsingborg Declaration on Stroke Management’.

In 2005, the Research Directorate General of the European Commission invited a group of leading European experts in the field of stroke research to provide an overview of the results of European research and to discuss the most promising and important research topics identified. In the context of this European Stroke Workshop, a round-table discussion was organised, aiming to identify the research activities that could potentially result in significant advances in the areas of stroke prevention, treatment and recovery. This meeting resulted in a

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publication entitled 'Stroke Research Priorities for the Next Decade – A Representative View of the European Scientific Community' (1), a document that mentions a recommendation to conduct research on brain-protective treatments, including therapeutic hypothermia.

In 2006, a second Consensus Conference was held in Helsingborg to update the initial recommendations in the light of accumulating evidence, and to set revised targets. This conference was arranged by the International Society of Internal Medicine, endorsed by the European Stroke Council and International Stroke Society and cosponsored by the WHO Regional Office for Europe. It was arranged in collaboration with the European Region of the World Confederation for Physical Therapy and the European Association of Neuroscience Nurses. The patients' organisation Stroke Alliance for Europe also participated.

At the final plenary session, the participants adopted the 'Helsingborg Declaration 2006 on European Stroke Strategies' (2), a statement of the overall aims and goals of stroke management to be achieved by 2015. Crucial to this was the establishment of a research agenda, and an important component of this was the development of new therapies for stroke – including the development of interventions based on therapeutic hypothermia.

In 2008, the Research Directorate General of the European Commission decided to establish a major platform for stroke research, under the umbrella of the European Stroke Network (<http://www.eurostroke-network.info>). This initiative brings together leading researchers, industry, government, the non-profit sector and patient group associations. This network and the associated partnerships between scientists and the broader society illustrate the possibilities existing in Europe for creating World leading research initiatives – successful collaboration, which also seems to be feasible and developing for the major hypothermia stroke research project described below.

The hypothermia stroke research workshop

On 25 January 2010, a Consensus Conference was held in Brussels specifically to give voice to the recommendations of the Stroke Research Workshop held in 2005 and the 2006 Helsingborg Declaration regarding the development of a research agenda to assess the potential therapeutic benefits of hypothermia in patients with acute ischaemic stroke.

The conference was organised by the European Stroke Research Network for Hypothermia (EuroHyp – for more information see <http://www.eurohyp.org>) and was attended by the representatives and delegates of the World Stroke Organisation, European Stroke Organisation, European Stroke Network, Stroke Alliance for Europe, Society for Cryobiology and European Space Agency. Participants also included representatives from small- and medium-sized enterprises based in EU member states.

In addition to discussing and agreeing on the key components of a hypothermia research agenda, the conference took the opportunity for an interim review of progress against some of the goals for 2015 set out in the second Helsingborg declaration,

especially considering the latest evidence generated through the research undertaken since 2006. Thanks to the successes of the European Stroke Research community, a number of the management recommendations contained in the second Helsingborg declaration can now be revised in the light of high-quality data obtained from randomised-controlled trials.

Evolution of selected Helsingborg 2006 recommendations based on new evidences

Thrombolysis

The ECASS III study (PI W. Hacke, Heidelberg) demonstrated that for selected patients, thrombolysis with tPA is also safe and effective when given between 3 and 4.5 h after symptom onset. Further information on efficacy at later time points, in less highly selected patients, or with alternative lytic agents will be available from ongoing Europe led randomised-controlled trials (IST-3, PI P. Sandercock, Edinburgh).

Decompressive hemicraniectomy

Three small European randomised-controlled trials (HAMLET, PI H. B. van der Worp, Utrecht; DECIMAL, PI W. Hacke, Heidelberg, DESTINY, PI M. G. Boussier, Paris) broke new ground by prespecifying a combined interim data analysis. This demonstrated substantial improvements in the survival and functional outcome in selected patients with space-occupying hemispheric infarction.

DVT prophylaxis

The CLOTS I study (PI M. Dennis, Edinburgh) showed no clinically significant benefit of graduated compression stockings in the acute phase of stroke, and these are no longer recommended.

Progress against 2015 goals

Helsingborg Declaration 2006 – Goals for 2015

The goals for management of acute stroke by 2015 are that:

- more than 85% of stroke patients survive the first month after stroke,
- more than 70% of survivors are independent in their activities of daily living by three months after the onset of stroke, and
- all patients with acute stroke who are potentially eligible for acute specific treatment are transferred to hospitals where there is the technical capacity and expertise to administer such treatment.

World Health Organization data suggest that between 2004 and 2007, stroke mortality in the European Union declined from 16.9% to 15.5%, while in the wider European region, it declined from 26.4% to 23.7% (3).

In addition, based on a recent report from Organisation for Economic Co-operation and Development (OECD – Health at a glance, 2009), case-fatality rates for both haemorrhagic and ischaemic stroke have declined by around 15% across the OECD countries between 2002 and 2007 – with all countries

reporting a decrease in both forms of stroke. This indicates a widespread improvement in the quality of stroke care.

At the same time, the European Stroke Facilities Survey, a programme of the European Stroke Initiative, suggests that the minimum standards for acute stroke care are currently met by around 63% of hospitals in Germany and Austria treating acute stroke patients, but by <50% of such hospitals across Europe as a whole (4, 5).

Accordingly, while there is an increase in the number of patients eligible to thrombolysis – thanks to the greater time window of intervention – only a small minority, generally around 10% of the patients with acute stroke, receive this treatment in countries with well-organised acute stroke care (6). Because of this, there is ample need for efficacious, cost-effective therapies that can be implemented in a broad section of the health care systems, across all lower and higher income European Member States and on a global scale as well.

Moderate hypothermia – the lowering of body temperature below normal – has emerged recently as one of the most promising therapeutic interventions, because of a relatively simple application and robust effectiveness in experimental stroke models, as well as in patients with cardiac arrest, hypoxic neonatal encephalopathy and early series and small clinical trials of patients with acute stroke. Hypothermia can therefore be regarded one of the most promising future interventions for the treatment of acute ischaemic stroke.

Recent progress in hypothermia research

Recent years have witnessed significant progress in studies exploring the potential role of temperature management in stroke and related conditions.

Broessner *et al.* (7) (Innsbruck) showed that endovascular normothermia was safe in patients with severe cerebrovascular disease.

The PAIS study (co-PIs D. W. J. Dippel and H. B. van der Worp) showed that paracetamol led to a small reduction in body temperature and was without benefit in unselected patients poststroke, but might have a beneficial effect on functional outcome in patients admitted with a body temperature of 37–39°C (8).

Kollmar *et al.* (9) (Erlangen) showed that induction of hypothermia with the rapid infusion of ice-cold saline and with shivering management with buspirone and pethidine was safe in a stroke population.

Karaszewski *et al.* (10) (Edinburgh and Gdansk) have shown the feasibility of measuring brain temperature in acute stroke patients using MR spectroscopy, and showed that temperature is highest in the ischaemic penumbra, the most attractive target for therapeutic intervention.

Hypothermia stroke research priorities

Based on the hypothermia stroke research completed recently and the learning from recent cardiac arrest hypothermia trials, it is now possible to identify with precision the key research

questions and topics in this domain. Accordingly, the generation of new, in-depth and comprehensive knowledge in the areas described below could lead to the identification of a novel therapy in stroke. This could enable the realisation of the goals specified in the Helsingborg declaration and – most importantly – could provide a relief to the growing number of patients and families who might be exposed to a stroke in the coming years, due to the rapidly ageing population in Europe.

These key research topics discussed and proposed by European Hypothermia Stroke Research Workshop were:

- Generate evidence-based recommendations about the most appropriate cooling protocol.

The efficacy of hypothermia is likely to reflect a balance between beneficial and adverse effects. A research priority is to provide robust data – generated via a well-integrated sequence of Phase II and Phase III trials – on the optimal depth and duration of hypothermia, and the maximum delay to initiation of treatment under which efficacy is still seen (11).

The central objective of this study programme is to generate robust evidence describing the optimal use of therapeutic hypothermia in acute ischaemic stroke. For this to inform the development of European and other international, national and local Clinical Practice Guidelines requires the successful completion of a pivotal, high-quality, well-organised and adequately sized Phase III trial.

- Generate evidence-based recommendations about the patient types who are most likely to benefit from hypothermia treatment. It is likely that different patient groups will be more or less susceptible to some of the adverse effects of cooling. For instance, younger patients may tolerate endovascular cooling to a low temperature in an ICU setting better than the elderly. Research should therefore identify and describe patient subgroups defined by: age, gender, stroke severity, delay to treatment – who should either be excluded from therapeutic hypothermia due to inappropriate risk–benefit ratios or should be treated with less intensive – or different – cooling (regional vs. systemic, for example).

Similarly, research should identify and describe the patients for whom hypothermia might be most beneficial. These recommendations should be formulated in respect of specific hypothermia doses (depth and length of intervention) and patient subgroups. In addition, research should evaluate the interactions between hypothermia and other acute stroke treatments including pharmacological/mechanical thrombolysis within the patient types specified.

- Identify and validate the best temperature-monitoring methodology (or methodologies) for the ischaemic penumbra. Most cooling strategies that have been advocated involve cooling the brain indirectly, through cooling either the whole body or arterial blood as it perfuses the brain. As ischaemic brain tissue has, by definition, impaired perfusion, it is important to be able to demonstrate that the cooling strategies adopted lead to cooling of the target tissue, the ischaemic penumbra. Specifically, a standard brain temperature measurement methodology and body measurement methodology should be validated via comparing the different current options (MRI techniques, ultrasound, bladder, etc.) and identifying the optimum solutions.

This will result in the identification of a peripheral noninvasive temperature measurement strategy that best reflects temperature in the target region of the brain.

- Identify and validate the best vessel-patency monitoring technologies, including precooling diagnostic procedures – considering the scope and specific context of a hypothermia treatment.

Specifically, the feasibility and potential added value of the different diagnostic and monitoring technologies should be assessed: CT angiography, MR angiography, transcranial Doppler ultrasound, etc.

This will allow (1) the issue of any potential interaction of cooling with rates of spontaneous or therapeutic reperfusion to be addressed and (2) the potential identification of patient groups most likely to benefit (i.e., is cooling more effective in patients with established reperfusion at the time of initiation of cooling?).

- Select and validate the best cooling technology – via assessing and considering the side-effects (e.g., shivering) and the overall tolerability and safety profile, in addition to the capacity to deliver the most effective temperature control: speed of cooling, maintenance of cooling and rewarming.

Specifically, the technology validation should include and consider all the options and aspects of therapeutic hypothermia, inter alia: comparison of systemic (surface or endovascular) and regional cooling approaches; complete evaluation of the feasibility and safety aspects; the effect of hypothermia on the immune system; and resistance to infection.

- Recommend and validate an optimised shivering protocol, minimising the adverse effects of the antishivering treatment.

This will allow the adoption of a single protocol for the assessment and management of shivering to be used in a large trial, including different patient subgroups.

- Describe the observed negative effects and validate treatments for the eventual adverse implications of mild therapeutic hypothermia on the immune system.

Describe the effects and associated factors of hypothermia on the incidence and severity of infections such as pneumonia. Define parameters for early detection of infections during hypothermia and identify new treatment and prevention strategies on infections during hypothermia.

- Monitor and evaluate the therapeutic value of blood markers (biomarkers) in hypothermia, especially considering the (a) selection of patients most likely to benefit; (b) exclusion of patients with a high risk of adverse events; (c) ability to use the biomarkers to define the optimal hypothermia dose and (d) validate the use of biomarkers as a surrogate measure of outcome to be used in future clinical trials.

The evaluation of the therapeutic value of blood markers in hypothermia – similar to the generation of evidence-based recommendations about the patient types who are most likely to benefit from hypothermia, requires a clinical study programme, which enrolls an adequately large number of patients (between 1200 and 1500 individuals at minimum, based on the preliminary calculations) in a series of Phase II and Phase III trials.

Participants at the hypothermia stroke research workshop held on 25 January 2010 in Brussels

EuroHYP Executive Committee Members (organisers of the Workshop): Stefan Schwab – President, Jesper Petersson – Vice President, Malcolm R. Macleod – Treasurer, H. Bart van der Worp, Rainer Kollmar, Derk Krieger, Gregor Brössner, Istvan Szabo; Bo Norrving – President, World Stroke Organisation; Werner Hacke – President, European Stroke Organisation; Ulrich Dirnagl – European Stroke Network; Markus Wagner – Stroke Alliance for Europe; Eduardo Martin Moraud – European Space Agency; Mattias Andersson; Steve Cottee; Didier Leys; Marco Biggiogera; Hanne Christensen; Désiré Collen; Anna Czlonkowska; Michele Dileone; Christian Gluud; Manuel Hallen; Joe Harbison; Merce Jourdain; Katja Piironen; Sven Poli; Risto Roine; Julia Schieferstein; Pascal Stammet; Turgut Tatlisuamak; Christoph Testori; Geert Vanhooren; Tadeusz Wieloch.

Dissemination of the 'Hypothermia for Stroke – Call to Action 2010'

The content of this declaration is expected to be presented and disseminated by the sponsoring organisations at their meetings, conferences and teaching events as well as at other international, national and regional stroke conferences.

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