

## **Value of Treatment by Comprehensive Stroke Services for the reduction of critical gaps in acute stroke care in Europe**

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### **Running Title**

Value of Treatment of unmet needs in stroke care

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### **Conflicts of Interest**

Alastair Webb: none

Ana Catarina Fonseca: none

Eivind Berge: none

Gary Randall: none

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### **Informed consent**

The corresponding author (Geert Vanhooren) affirms that this is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

### **Ethical Approval**

Not required.

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### **Contributorship**

This study was coordinated as part of the European Brain Council (EBC) Value of Treatment Initiative, with representation from the European Stroke Organisation, Stroke Alliance for Europe and the European Association of Neurologists. Geert Vanhooren chaired the Stroke Working Group and coordinated the project. Alastair Webb coordinated the patient pathway analysis, Emilia Nivelles and Vincent Thijs performed the economic analysis, Alastair Webb performed the systematic literature search. Alastair Webb and Ana Catarina Fonseca drafted the manuscript. All authors participated in the EBC Expert Round Table discussions and edited the manuscript.

### **Key Words**

Acute stroke care

Value of treatment

Care pathway

Economic analysis

## **Abstract**

### **Background**

Stroke is the second leading cause of death and dependency in Europe and costs the EU >€30 billion, yet significant gaps in the patient pathway remain and the cost-effectiveness of comprehensive stroke care to meet these needs is unknown.

### **Methods**

The European Brain Council Value of Treatment Initiative combined patient representatives, stroke experts, neurological societies and literature review to identify unmet needs in the patient pathway according to Rotterdam methodology. Cost-effectiveness of Comprehensive Stroke Services was determined by a Markov model, using UK cost data as an exemplar and efficacy data for prevention of death and dependency from published systematic reviews and trials, expressing effectiveness as Quality Adjusted Life-Years (QALYs). Model outcomes included total costs, total QALYs, incremental costs, incremental QALYs and the incremental cost-effectiveness ratio (ICER).

### **Results**

Key unmet needs in the stroke patient pathway included inadequate treatment of atrial fibrillation, access to neurorehabilitation and implementation of Comprehensive Stroke Services. In the Markov model, full implementation of Comprehensive Stroke Services was associated with a 9.8% absolute reduction in risk of death or dependency, at an intervention cost of £9,566 versus £6,640 for standard care, and long-term care costs of £35,169 per 5.1251 QALYs vs £32,347.40 per 4.5853 QALYs, resulting in an ICER of £5,227.89. Results were robust in one-way and probabilistic sensitivity analyses.

### **Conclusion**

Implementation of Comprehensive Stroke Services is a cost-effective approach to meet unmet needs in the stroke patient pathway, to improve acute stroke care and support better treatment of atrial fibrillation and access to neurorehabilitation.

## Introduction

Stroke is the second leading cause of death,<sup>1</sup> third leading cause of disability-adjusted life-years worldwide,<sup>2</sup> the leading cause of acquired disability in Europe,<sup>2</sup> and a major cause of dementia.<sup>3</sup> The number of stroke events in Europe is projected to rise from 1.1 million in 2000 to 1.5 million per year by 2025.<sup>4, 5</sup> Twenty-five per cent of strokes occur in young people of working age, resulting in more prolonged impairment, greater dependency and significant loss of productivity. Recent analyses have estimated a marked inflation in the societal cost of stroke, with a total cost to 32 European countries in 2017 of €60 billion, including €27 billion in direct costs, €5 billion in social care costs and €29 billion in informal care and loss of productivity.<sup>6</sup> The Action Plan for Stroke in Europe<sup>7</sup> has set ambitious targets to optimise stroke care in Europe for the next decade. However, to achieve these targets it is vital to identify which interventions have the greatest potential to improve clinical outcomes and whether such large scale reorganisations of clinical systems are sufficiently cost effective to be feasible in a resource-limited healthcare environment.

Stroke patients make a long journey from health, to acute illness, intensive investigation and treatment, followed by a long road to recovery, adaptation and reintegration back into society. This pathway presents complex challenges at each stage, where gaps in care provision can occur. In the past 20 years, there have been particular advances in acute stroke treatment and the development of streamlined services. Comprehensive stroke services<sup>8</sup> provide a mechanism for delivering and coordinating all steps of the stroke pathway, from acute reperfusion (thrombolysis<sup>9</sup> and mechanical thrombectomy<sup>10</sup>) to early multidisciplinary rehabilitation after stroke,<sup>11</sup> optimal investigation (vascular imaging, prolonged cardiac monitoring<sup>12</sup>), rapid initiation of secondary prevention<sup>13</sup> and transition into rehabilitation (inpatient rehabilitation, early supported discharge<sup>14</sup>). However the cost-effectiveness of comprehensive stroke services in different healthcare settings is uncertain.

The European Brain Council 'Value of Treatment' initiative was established to identify current gaps in delivery of stroke care, the cost of these gaps and the value of resulting interventions. We report the results of a patient pathway analysis to identify these gaps and the cost-effectiveness of delivery of Comprehensive Stroke Services, the currently recommended strategy to meet these needs. Based on these results we propose recommendations that can improve stroke care through the delivery of evidence based interventions.

## Methods

### ***Care Pathway Analysis***

To describe the unmet needs along the patient pathway, we used research methodology defined by the Rotterdam Institute of Health Policy and Management<sup>15</sup>. We gathered data from literature review, consulted stroke experts, patients' associations and neurological scientific societies.

### ***Economic Analysis***

From the care pathway analysis, we identified which potential interventions had the greatest potential impact on clinical care. Therefore, a combined decision tree and Markov model was developed to describe the experience of patients *after stroke*. The model was used to estimate total costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) of full implementation of treatment services for acute ischemic stroke. The model follows patients with ischemic stroke, with transitions between health states in 6-month cycles, defined by treatment status and disability level (modified Rankin Scale 3-5), from the acute phase until a 20 year horizon (Figure 1). Primary stroke outcomes (death or dependency at end of primary assessment, usually 3 - 6 months) were sourced from Cochrane collaboration data<sup>11, 14, 16, 17</sup> or other relevant meta-analyses.<sup>10</sup> Interventions included stroke units,<sup>11</sup> thrombolysis with alteplase,<sup>9, 16</sup> endovascular clot retrieval,<sup>10</sup> early aspirin use,<sup>18</sup> early carotid artery endarterectomy,<sup>19</sup> rhythm monitoring for atrial fibrillation<sup>17</sup> and subsequent treatment with anticoagulants.<sup>20</sup> Expert opinion was used to assess the maximally achievable rate of intervention if services were available 24/7, supported by SSNAP audit data,<sup>21</sup> assuming no barriers to access these treatments (table 1), with disability associated utility values, event-related utility decrements<sup>22</sup> and recurrent stroke rates derived from the literature.<sup>3, 23</sup> The model assumed that: recurrent stroke events would be treated in the same way and incur similar costs as first events, the risk of recurrent stroke was conservatively 4%/year in both arms; Mortality in dependents is higher than mortality in independents (which is higher than general population); that over the time course patients with recurrent stroke will remain in the originally assigned group (intervention versus control), assuming low rates of migration to alternative health care systems.

See figure 1.

The model was adapted to the UK setting due to availability of data by using national all-cause mortality rates, local resource use data, and local unit costs, with care without stroke services as the relevant comparator. Costs were calculated using the healthcare payer perspective, and included all direct medical costs borne by the National Health Service (NHS), updated to 2015 costs using the consumer price index. Average length of stay was updated to UK average length of stays in 2015. Stroke unit costs were modelled by costing uniform frequencies of allied health units and stroke specialist time to each patient. The medical resource consumption per year after the first six months period was £1938 in the independent state and £5782 in the dependent state.<sup>22</sup> The UK National Institute for Clinical Excellence (NICE) defines an intervention as cost-effective if the costs are less than £30,000 per QALY.

One-way sensitivity analyses were conducted on the base case model to identify parameters having a major influence on the ICER with a probabilistic sensitivity analysis to evaluate the uncertainty around the ICERs related to uncertainty in clinical inputs, cost inputs, utility values, and time horizon. Input parameters were varied within reasonable ranges with expert input. Costs and outcomes are discounted by 3.5% annually.

### ***Literature Search***

We searched PubMed for relevant source data between inception and 31<sup>st</sup> Dec 2016 with the terms (“Cost” OR “Cost-effective” OR “Cost-effectiveness”) AND (“Stroke” OR “Stroke Unit”). Following review of all relevant abstracts, all reports potentially reporting the cost or cost-effectiveness of stroke units or any specific stroke intervention were reviewed in full (AW). UK national guideline bodies (NICE, Scottish Intercollegiate Guidelines Network), governmental reports ([gov.uk](http://gov.uk)) and audits ([Sentinel Stroke National Audit Programme \(SSNAP\)](#), National Audit Office) were searched.

### **Expert Round Table Discussion**

Policy recommendations were formulated by an expert round table discussion, as a part of the European Brain Council Value of Treatment Initiative, with formulation of a Stroke Working Group in collaboration with the European Stroke Organisation and the European Academy of Neurology. Biannual face-to-face meetings were held from 2015-2017, with subdivision of the working group into Care Pathway and Economic Analysis working groups, before formulation of policy recommendations.

## Results

### *Care Pathway Analysis*

To identify unmet needs in delivery of stroke care and delivery of optimal care, we assessed the Patient Pathway for acute stroke from rapid acute assessment, appropriate acute treatment, prevention of further vascular events (secondary prevention), ideally delivered through a comprehensive stroke service, followed by transition to appropriate rehabilitation, with efficacy of treatment critically dependent on the time from stroke onset. Every step of the patient trajectory from symptom onset to the start of treatment within the hospital should be optimized with a shorter delay from onset of symptoms to reperfusion, which is vital to return to a functional state, including rapid investigation and initiation of secondary prevention. During and after the acute phase, targeted rehabilitation is needed to reduce the remaining deficits to a minimum and to reintegrate stroke victims into normal life. We identified three areas through group consensus following literature review representing significant gaps in implementation of effective interventions:

- 1) **Low implementation of comprehensive stroke services:** Comprehensive stroke services are integrated systems of multi-disciplinary units devoted to care for patients with stroke, providing a wide range of proven interventions, from acute reperfusion therapies (thrombolysis, mechanical thrombectomy), to early rehabilitation and secondary prevention.<sup>9-11</sup> Treatment in stroke units has been shown to reduce the risk of death and disability, and ESO strongly recommend the establishment of stroke units in all centres caring for stroke patients.<sup>8</sup> Still, the implementation of stroke unit care is inadequate across Europe due to cost barriers, lack of appropriately trained staff and limited provision of specialised facilities, despite strong evidence for its clinical effectiveness.<sup>24</sup>
- 2) **Inadequate treatment of atrial fibrillation (AF):** Patients with atrial fibrillation have a five-fold increased risk of ischemic stroke and AF is estimated to be responsible for approximately 15% of all strokes, which could be avoided through improved detection and use of available drugs.<sup>17</sup> Although oral anticoagulation after ischemic stroke in patients with AF is recommended by the European Stroke Organisation, many patients do not receive such treatment. In the UK, only



53% of patients with atrial fibrillation identified at high risk are receiving anticoagulants,<sup>12</sup> with similarly low rates of prescription in Poland (41%), and Greece (41%).<sup>24</sup>

- 3) Limited access to rehabilitation:** Many stroke survivors experience functional deficits that make them dependent on others for their daily tasks. Rehabilitation enables people with disabilities to regain physical, intellectual, psychological and/or social function.<sup>14</sup> The early rehabilitation process from a stroke should be initiated in a stroke unit. However, it is rarely complete when it is time to leave hospital. Although it has been showed that continued rehabilitation after discharge during the first year after stroke reduces the risk of disability, only very few clinical trials have been conducted in this field.<sup>14</sup> Therefore, many of the recommendations for treatment in this field are weak, and investment in funding of research in this area is essential.

### ***Economic Analysis***

The economic analysis focussed upon the first identified unmet need, implementation of comprehensive stroke services, as the ESO recommended intervention and a focus supporting delivery of the other needs. The base case estimates and assumptions underlying this analysis are shown in *Supplementary Table 2*. Full implementation of acute ischemic stroke treatments (table 1) to the maximum extent possible led to an absolute risk reduction in death or dependency of 9.8% (table 1). The rate of dependency in the intervention group was 25.9% versus 29.8% in the group in which none of the interventions was performed. Mortality rates were 11.8% versus 14.4%. The average cost of intervention was £9,566 versus £6,640 in the standard of care group (table 1). The base case analysis demonstrated the long-term costs of standard of care was £32,347.40 for 4.5853 QALYs, compared to the cost of interventions of £35,169.85 per 5.1251 QALYs, resulting in incremental costs of the intervention over a 20 year horizon of £2,822.45 with incremental QALYs of 0.5399. This yielded an ICER of £5,227.89 .

The one-way sensitivity analysis (Figure 2) demonstrated that higher age, low rates of the independent state at six months and higher costs of intervention had the predominant impact on the incremental cost effectiveness ratio (ICER), whilst time horizon, utility of the dependent state and variation of the cost of the independent state after stroke had no major impact. The ICER did not exceed the 30,000/QALY in any sensitivity analysis. Utilizing the most pessimistic input parameters remained cost-effective despite

important variations in critical model input parameters such that in the probabilistic sensitivity analysis the intervention was dominant (cost-beneficial) in 1.9% of scenarios, non-dominant in 0.2 and cost-effective in 98% (figure 3).

### ***Literature Search***

To validate the results of the economic analysis in both the UK and in other countries, and identify the impact of additional interventions not able to be included in the model, we performed a literature search. The literature search identified 5737 abstracts, of which 641 abstracts were potentially relevant from the title, and 244 papers were reviewed in full. Of these, 34 papers related to the absolute cost of stroke in a specific region without addressing effectiveness of the stroke unit as an intervention, whilst 14 papers directly reported measures of cost-effectiveness of stroke units (supplemental table 2). Our estimate of the impact of multiple interventions is comparable to previous estimates of the cost-effectiveness of establishing stroke units, although individual analyses varied in the number and degree of provision of individual interventions (Supplemental Table 2), with an ICER per QALY ranging from overall cost saving to stroke unit provision being dominated by alternative models. All the above cost-effectiveness analyses were published prior to the widespread recognition of mechanical thrombectomy as standard of care. However, recent cost-effectiveness analyses demonstrate that mechanical thrombectomy is highly cost-effective, and potentially cost-saving, in a broad range of healthcare settings (supplemental table 3), consistent with its effect within our economic model.

There were two estimates of the cost-effectiveness of widespread systematic changes in service organisation in the UK. In 2007, the National Stroke Strategy resulted in an increase in provision of stroke units, early supported discharge and a small increase in thrombolytic treatment rates.<sup>25</sup> Cost-effectiveness analyses by the National Audit Office demonstrated an ICER of £5500 per QALY for implementation of this multi-component strategy, whilst increasing stroke unit availability alone to 100% was cost-effective at an ICER of £7249 per QALY. Subsequently, in 2010, all stroke units in London were reorganised into 8 centralised hyper-acute stroke units with diversion of potential stroke patients by ambulance services, significantly increased rates of thrombolytic treatment, streamlined investigation, and transfer to local acute stroke units for early rehabilitation within 72 hours. In a real-life patient cohort, this was associated with a £811 cost saving per patient.

### ***Expert Round Table Discussion: Policy Recommendations***

Policy recommendations were developed by expert round table discussion utilising the care pathway, the economic analyses, and the result of the literature search:

**Improve primary and secondary prevention of Stroke** Population-based initiatives are required to improve primary prevention of stroke, through control of hypertension and identification of individuals with asymptomatic AF. After a stroke, patients should be monitored to detect asymptomatic AF, for example with long-term heart rate monitoring. Once AF is detected, patients should receive oral anticoagulant therapy, unless there are clear contraindications.

**Foster implementation of comprehensive stroke services** Stroke units should be established in all centres caring for stroke patients through national policy initiatives, supported by a requirement for stroke unit certification through the ESO program. Strategic plans are required to improve access to comprehensive stroke centres that provide sophisticated facilities for reperfusion therapies. This requires developing current centres to provide comprehensive services through increased facilities and targeted training programs to expand clinical teams with the appropriate skills.

**Improve access to timely and effective rehabilitation** Access to timely and individualized rehabilitation should be available to all stroke patients, through development of acute stroke units, early supported discharge where appropriate<sup>14</sup> and close collaboration and efficient transition to rehabilitation services matched to patient need.

The Expert Round Table discussion resulted in a number of policy recommendation, specifically to enhance provision of stroke units in the short-term, and development of facilities and personnel for provision of comprehensive stroke services in the medium to long term (Panel 1).

## Discussion

The complexity of acute stroke care and variation in service needs at each stage of the patient pathway results in multiple care gaps, specifically in the lack of access to high-quality acute stroke care (stroke units, revascularisation therapies), effective diagnosis and treatment of atrial fibrillation and transition to specialist neurorehabilitation. Gaps in care can be improved by development of stroke units, in line with the European Stroke Organisation guidelines, linked to rehabilitation services. The economic analysis confirmed that a model of comprehensive stroke unit care, based upon UK healthcare, is cost-effective with an estimated ICER of £5,227.89. This was robust to sensitivity analyses and was similar compared to other modelling studies in Europe and studies measuring the cost-effectiveness of service reorganisation in the UK.

The economic analysis is consistent with previous studies demonstrating the cost-effectiveness of individual components of the multi-component intervention of a comprehensive stroke service, including thrombolysis, rapid assessment of TIA/minor stroke,<sup>26</sup> detection of atrial fibrillation, initiation of appropriate anticoagulation, and endovascular thrombectomy for large proximal occlusions (supplemental tables 1-2). The closest equivalent studies assessed the effect of stroke units,<sup>11</sup> but these studies are primarily based upon clinical care prior to 2010, and were only minimally affected by the impact of mechanical thrombectomy. We also identified previous analyses that demonstrated the cost-effectiveness of mechanical thrombectomy. The delivery of such comprehensive stroke services could be through a single comprehensive stroke centre, or through a decentralised service with local acute stroke units, or through regional comprehensive stroke centres functioning within a hub-and spoke model, dependent upon local geographical factors. Since the completion of the VOT Initiative, tele-stroke services have become much more widespread, with formal cost-effectiveness analyses reported in non-UK health care systems,<sup>27</sup> and observational evidence for their additional cost-effectiveness when added to current UK services,<sup>28</sup> although with insufficient data available from the UK to include this in the Markov model. Similarly, development of telerehabilitation services provides an opportunity to enhance access and cost-effectiveness of neurorehabilitation.

The analysis was sensitive to age, increasing cost of intervention and low rates of independence after an event. These UK-based results were consistent with published reports from other European countries (France, Netherlands, Sweden, Spain and Denmark), but its applicability in lower

mean income European countries is less certain. Therefore, the development of a comprehensive stroke service in these countries may not be cost-effective. However the interventions could be even more cost-effective in European regions where the population age and costs of intervention are lower.

There are limitations to this study. First, we focused on the outcomes of dependency and death instead of more fine grained improvements in disability ratings. These shifts in disability may produce additional cost-savings as direct economic costs increase for each step in the modified Rankin scale. Second, the benefits of other subacute interventions like AF detection with early anticoagulation, as identified in the care pathway analysis, extend beyond the six month mark, but only their acute effects were modelled here. Thirdly, our model did not consider the costs required to achieve the desired targets of implementation. For instance, we did not model the costs to increase and maintain rates of thrombolytic treatment by public campaigns or the capital costs of investment to provide new capacity for interventions such as thrombectomy, or to reorganise stroke services. These costs will vary significantly according to regional systems, but even within the relatively expensive UK economy the costs were offset by cost-savings associated with service reorganisation.<sup>16</sup> Fourthly, the model assumes that the included interventions are summative, whereas it is possible that improvements in death and disability from one intervention would apply to the same patient group as another intervention and therefore the total benefit of multiple interventions would be less than the expected benefit from each intervention. However, the estimates of the effectiveness of these interventions are largely derived from randomised clinical trials performed in advanced stroke services where the interventions tested have been provided in addition to excellent stroke care.

### ***Policy implications for development of stroke services in Europe***

The European Stroke Organisation has recently defined the services that would be expected from an acute stroke service.<sup>8</sup> However, the large variability in availability of acute stroke units represents a significant gap in care. Access to highly specialised units providing mechanical thrombectomy poses a very significant challenge in direct care costs, capital costs for development of facilities and training of adequate staff, such that even more affluent healthcare systems are currently unable to meet the demand for this intervention. To increase provision of comprehensive stroke services will require significant policy directives and capital investments, but the resulting long-term benefits

justify it in both the short-term and the long-term. There is also a widespread lack of provision of specialist neurorehabilitation services, limited integration with acute stroke services and limited use of prolonged cardiac monitoring in either primary or secondary prevention. We therefore suggested a number of policy initiatives, specifically to enhance provision of stroke units in the short-term, and development of facilities and personnel for provision of comprehensive stroke services in the medium to long term (see Panel).

### ***Conclusion***

In summary, significant gaps exist in the care pathway of patients with acute stroke, from acute stroke management, to identification and treatment of atrial fibrillation to integration into rehabilitation. Development of comprehensive stroke services has the potential to meet these challenges to improve clinical outcomes and were cost-effective in a model based upon the UK healthcare system. This is consistent with previous reports in other European nations, but there is limited data in many regions. Based upon an expert round table discussion, we present policy recommendations to improve cost-effective provision of stroke services in Europe, to help prioritise implementation of the Action Plan for Stroke in Europe recommendations.

### **In Memoriam**

It is with great sadness that we pay tribute to our friend and colleague, Prof Eivind Berge, who recently passed away. He was a key member of the stroke working group for the VoT team, always ready to contribute with great insight and enthusiasm. His outstanding contributions to stroke research always reflected his commitment to research excellence, a rigorous scientific approach and a recognition of the clinical questions that needed answering to reduce the burden of stroke on our patients, leaving behind a legacy that will last. His friendship and contribution to our further understanding of stroke care will be greatly missed by us all.

**Panel:** Recommendations for development of comprehensive stroke services referring to the Stroke Action Plan 2018-2030 (European Stroke Organisation)<sup>7</sup>

1. National definitions of the ideal level of provision of stroke services, modelled on the European Stroke Organisation definition of comprehensive stroke services<sup>8</sup>
2. National definition of the minimum expected level of stroke services.<sup>8</sup>
3. Establishment of regional stroke strategies and national stroke plans, as a part of the Action Plan for Stroke in Europe 2018-2030 from the European Stroke Organisation.
4. Establishment of sufficient posts and training programs for stroke physicians / neurologists, stroke nurses and interventional neuroradiologists.
5. Investment in facilities to expand availability to mechanical thrombectomy.
6. Integration of acute stroke services with longer term inpatient rehabilitation services and community based rehabilitation, including early supported discharge schemes.<sup>14</sup>
7. Increased availability of prolonged cardiac monitoring after stroke to identify atrial fibrillation.
8. Investment in research to optimise methods of service development, provision of comprehensive stroke centres and transition to rehabilitation.

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