PRECISE4Q

PREDICTIVE MODELLING IN STROKE

DELIVERABLE

Project Acronym: **Precise4Q**

Grant Agreement number: **777107**

Project Title: **Personalised Medicine by Predictive Modelling in Stroke for better Quality of Life**

D1.1 – SoA on knowledge and literature concerning stroke risk factors, prognosis and outcomes

Revision: 1.0

Authors and Contributors	Alejandro García Rudolph (GUT); David Sánchez Pinsach (GUT); Eloy Opisso Salleras (GUT); Sara Laxe García (GUT); Joan Saurí Ruiz (GUT); Vince Istvan Madai (CUB); Dietmar Frey (CUB)			
Responsible Author	Alejandro García Rudolph		**Email**	agarciar@guttmann.com
	Beneficiary	GUT	**Phone**	+34 93 497 77 00-2265

Project co-funded by the European Commission within **H2020-SC1-2016-2017/SC1-PM-17-2017**		
Dissemination Level		
PU	Public, fully open	X
CO	Confidential, restricted under conditions set out in Model Grant Agreement	
CI	Classified, information as referred to in Commission Decision 2001/844/EC	

Revision History, Status, Abstract, Keywords, Statement of Originality

Revision History

Revision	Date	Author	Organisation	Description
0.1	27.07.2018	Alejandro García Rudolph	Guttmann	Final content draft
1.0	30.07.2018	Malte von Tottleben	Empirica	Style and layout revision

Date of delivery	Contractual:	31.07.2018	Actual:	30.07.2018
Status	final ☒ /draft ☐			

Abstract (for dissemination)	To better understand the specific needs - especially the unmet needs addressed in deliverable D1.2 - the herewith presented report provides an overview of the current state-of-the-art in the literature concerning knowledge about stroke risk factors (incl. genetics), prognosis and outcomes after interventions. This will help the consortium in identifying the most relevant clinical challenges and needs for each patient journey phases. The main medical concept of PRECISE4Q is to target four different stages of stroke in the life trajectory in a novel precision medicine approach. For model building this information is crucial. Feature selection is an integral part of model building and will implement domain knowledge from this report for selection the fitting subset of clinical features for each built model.
Keywords	State of the art, risk factors, prognosis, outcomes, prevention, acute, sub-acute, rehabilitation, reintegration

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

Table of Content

Executive Summary

To better understand the specific needs - especially the unmet needs addressed in deliverable D1.2 - the herewith presented report provides an overview of the current state-of-the-art (SoA) in the literature concerning knowledge about stroke risk factors (incl. genetics), prognosis and outcomes after interventions. This will help the consortium in identifying the most relevant clinical challenges and needs for each patient journey phases..

The main medical concept of PRECISE4Q is to target four different stages of stroke in the life trajectory in a novel precision medicine approach.

First stage is Prevention, considering that more than 77% of stroke events are first time events. Former epidemiologic studies have identified major overarching causes of stroke such as hypertension, cigarette smoking, diabetes, dyslipidemia, atrial fibrillation and carotid stenosis. While general recommendations can be given to patients to treat these conditions, it is currently unknown how a given patient is individually affected by these risk factors. Importantly, most of the risk factors are currently undertreated in the population.

In the Acute Treatment phase, regardless of advances in the therapy of ischemic stroke in the past decades, the overall therapy success is still poor. For thromboembolic stroke, the most favourable current treatment paradigm is the time-based dissolution of the obstructing blood clot by a drug. Unfortunately, up to 20% of patients arrive with an unknown time from stroke onset, and most patients present too late in the hospital to receive treatment. However, the optimal treatment strategy for an individual patient remains unknown. Additionally, what challenges the treatment of stroke patients is that the causes are highly heterogeneous.

Multitude of different stroke rehabilitation concepts and methods has been developed to date. However, from an evidence-based perspective only very few general proven recommendations exist: a) Specialized rehabilitation is useful, b) early rehabilitation and mobilization is useful and c) higher intensities of therapy are useful. Beyond this, it is unclear which therapy options lead to better rehabilitation outcome, i.e. which therapies are best suited for the individual patient. Since the rehabilitation success can make the difference between the need for 24/7 care or independency, there is dire need to identify individual factors and therapy options to allow specifically tailored rehabilitation for optimal outcome after stroke.

Finally, Reintegration is the long-term outcome after stroke. After acute treatment and rehabilitation, reintegration success is measured by the patients' reintegration into their family, communities and workplaces. Self-esteem, depressive symptoms, social support satisfaction and other parameters are important. Such psycho-social parameters, together with functional rehab outcome, comprise long-term stroke outcome picture, e.g. by determining social integration, return to the work force and work performance.

For model building this information is crucial. Feature selection is an integral part of model building and will implement domain knowledge from this report for selection the fitting subset of clinical features for each built model.

1 Scope and Purpose

Ischemic stroke is the death of brain tissue due to the sudden lack of blood supply. Most strokes are the result of sudden obstruction of brain vessels by a blood-clot, i.e. thromboembolism. Approximately 900.000 Europeans suffer an ischemic stroke each year (Bejot et al, 2016). About 25% of men and 20% of women can expect to suffer a stroke if they live to be 85 years old (Meairs et al, 2006). The overall mortality of stroke is up to 30% (Bejot et al, 2016) making stroke a leading cause of death in developed countries. Moreover, up to half of the surviving patients remain permanently disabled (Hankey et al, 2003). The high mortality and the rates of disability due to stroke make it a tremendous medical and socio-economic burden in Europe. In other areas of the world (for example China, where a significant part of the world population lives) stroke incidence is rising (Yong et al, 2013).

Thus, PRECISE4Q sets out to minimise the burden of stroke for the individual and for society. It will create multi-dimensional data-driven predictive simulation computer models enabling – for the first time – personalised stroke treatment, addressing patient's needs in four stages: prevention, acute treatment, rehabilitation and reintegration.

To better understand the specific needs - especially the unmet needs - the herewith presented report provides an overview of the current state-of-the-art in the literature concerning knowledge about stroke risk factors (incl. genetics), prognosis and outcomes after interventions. This will help the consortium in identifying the most relevant clinical challenges and needs for each patient journey phases. For model building this information is crucial. Feature selection is an integral part of model building and will implement domain knowledge from this report for selection the fitting subset of clinical features for each built model.

2 Prevention

One of the most promising approaches to reduce the effects of stroke on individual health and healthcare systems is to prevent stroke. More than 77% of stroke events are first time events (http://standardofcare.com/Strokes).Former epidemiologic studies have identified major overarching causes of stroke such as hypertension, cigarette smoking, diabetes, dyslipidemia, atrial fibrillation and carotid stenosis (Goldstein et al, 2011). While general recommendations can be given to patients to treat these conditions, it is currently unknown how a given patient is individually affected by these risk factors. Importantly, most of the risk factors are currently undertreated in the population. Likely, this can be attributed to the lack of personalized treatment incentives. Nevertheless, knowledge about the the epidemiology of stroke allows optimized streamlining of the development of individualized models that will ultimately lead to personalized treatment regimes. Thus, in the following the current SotA regarding the epidemiology of stroke and stroke prevention is summarized.

2.1 Modifiable vs. Unmodifiable Risk Factors

Risk factors for primary stroke can be divided into modifiable and non-modifiable risk factors. While both are crucial for building predictive models, the distinction is very important, since modifiable risk factors allow the development of interventions. Only by specific and individualized interventions strategies can the ultimate goal of PRECISE4Q, a reduction in the incidence of stroke be achieved.

2.1.1 Non modifiable risk factors

Non-modifiable risk factors are age, sex, ethnicity and genetics (Boehme et al, 2017).

Age

Age is a main risk factor of stroke. However, while stroke is known to occur with high frequency in the elderly (>65 years) - the mean age at stroke being 69.2 years (Boehme et al, 2017) - latest analyses show that stroke occurrence is increasing in the young population (Bejot et al, 2016). In extrapolation, by 2025 more than 1.5 million strokes are expected to occur in Europe each year, increasingly targeting younger people (Bejot et al, 2016).

Sex

Sex is known to play a role in the pathophysiology and in the phenotype of stroke. With regards to stroke occurrence, men are generally heavily favoured (m/f ratio=1.33), however, in mid-life and above the age 85 year, stroke is more common in women (Haast et al, 2012). However, even though the incidence favors men, due to their higher life-span, more stroke occur in women than in men (Roger et al, 2012). Higher stroke risks in mid-life and younger populations for women can be explained by risks related to pregnancy and the post-partum state, as well as other hormonal factors, such as use of hormonal contraceptives (Boehme et al, 2017). In terms of stroke mortality, stroke mortality is lower in women until the age of 65, whereas in the age group above 65 the mortality of women is higher (Haast et al, 2012).

Ethnicity

Disparities owing to ethnical differences are well reported in the literature. Increased risk for stroke has been reported for African Americans, Latino Americans and American Indians (Boehme et al, 2017). However, it is important to mention that these correlations might not not be fully causal, but at least partially due to bias. Here, a higher incidence of stroke related risk factors for minorities has been reported (Boehme et al, 2017). Thus, socio-economic reasons might be a main driving force behind the reported ethnical differences.

Genetic factors
Genetic factors play an important role in the development of stroke, as shown by partial heritability (30% risk increase due to family history), but are challenging to identify and quantify due to high heterogeneity of stroke causes and populations (Boehme et al, 2017). One can distinguish between single gene disorders, where stroke is the primary or important manifestation of the diseases and genetic variants associated with ischemic stroke. The former include diseases like CADASIL, CARASIL, sickle cell disease, Fabry disease and others (Boehme et al, 2017). Regarding the latter, few works have explored associations; however, several reports have shown associations between stroke and the ABO blood type gene. Other gene loci were also identified, but here the disease mechanisms are unclear and are a focus of investigation (Boehme et al, 2017).

2.1.2 Modifiable risk factors

Modifiable risk factors are the main targets of prevention as they can be treated or changed leading to possible intervention strategies. One can distinguish between “classic” risk factors, which have been strongly established epidemiologically (O´Donnel et al, 2010), and emerging new risk factors, which might lead to possible new interventions in the future (Boehme et al, 2017).

Established risk factors

Hypertension
Hypertension leads to increased risk of stroke and the incidence of hypertension increases with age (Chobanian et al, 2003). Thus, treatment of hypertension is an effective measure to reduce stroke risk. However, hypertension treatment is still far from optimal in developed countries and low-income countries have the highest prevalence of elevated blood pressure (http://www.who.int/features/qa/82/en/). Recent new strategies are looking into novel ways to assess this biomarker. For example, the variability in blood pressure measurements over time may be a better predictor of risk than the static snap shot measurements done today (Rothwell et al, 2010).

Diabetes
Diabetes is an independent strong risk factor for stroke and stroke accounts for 20% of deaths in diabetics (Boehme et al, 2017). The increase in diabetes prevalence in the younger populations might be explanatory for the overall increasing incidence of stroke in younger people (Kissela et al,2005).

Carotid Stenosis
Another modifiable risk factor is large vessel atherosclerotic disease, mostly presenting as stenosis of the internal carotid artery. It was shown that in asymptomatic with greater than 60% carotid stenosis and low perioperative risk, carotid endarterectomy (CEA) is protective of stroke (Boehme et al, 2017). Novel therapies try to focus less on the lumen width, but on functional imaging to determine plaque vulnerability, which might be a much better dynamic predictor of stroke risk (Kips et al, 2008).

Atrial Fibrillation
Atrial fibrillation is one of the largest risk factors for stroke. The current model of blood clot generation due to the stasis of blood in the left atrium is currently challenged, however, leading to the need for new models for the relation of atrial fibrillation and stroke (Boehme et al, 2017). Nonwithstanding, the treatment of atrial fibrillation can substantially reduce the risk for stroke. Under-treatment of atrial fibrillation is currently still a major public health problem, both in developed (Wilke et al, 2015) and developing countries (Al-shamkhani et al, 2018).

Dyslipidemia and metabolic syndrome
Elevated levels of LDL-cholesterol are associated with higher stroke risk, while high levels of HDL-cholesterol seem to have a protective effect. Study data, whether LDL-lowering interventions have a

protective effect are conflicting. For a comprehensive overview, see (Boehme et al, 2017). Better established is the combination of elevated lipids in combination with obesity, pre-hypertension and pre-diabetes coined metabolic syndrome. Here, the combination of several stroke-related risks lead to a generally elevated stroke risk (Najarian et al, 2006). Importantly, regarding obesity new markers like the waist-to-hip ratio may play a more important role than the classic BMI (O´Donnel et al, 2010).

Substance abuse

Cigarette smoking is a well known independent risk factor for ischemic stroke, with a dose-response relationship between pack-years and and stroke risk (Bhat et al, 2008). Also, other substances such as cocaine, heroin, amphetamines and others are associated with increased risk of stroke, especially in younger patients (de los Rios et al, 2012).

Novel risk factors and stroke triggers

Less well established - currently investigated - risk factors are chronic inflammation and acute and chronic infections as well as air pollution, vitamin B deficiency, heart failure (Boehme et al,2017 Kim et al,2018) Hankey et al, 2018). Another important new area of stroke research is the investigation of stroke triggers. Stroke triggers bridge the gap between the presence of stroke risk factors and the situation, where stroke manifests (“why now”-question of stroke) (Boehme et al, 2017). Potential stroke triggers are infections, ranging from smaller infections to sepsis, surgeries, traumas, pregnancy, drug abuse and mental stress (Elkind et al, 2007).

2.2 Interventions for stroke prevention

We have summarized the current status regarding stroke risk factors above. Interventions that can be deduced from the modifiable risk factors in stroke are discussed primarily from an epidemiological and public health point of view (Goldstein et al, 2011). Interventions are analyzed on the population level both in terms of the interventions themselves (e.g. Saraiva et al, 2018) as well as their health-economic outcome (e.g. Zhang et al, 2017). Prevention strategies focused on the individual patient in terms of personalized medicine are lacking (Kim et al, 2015). One reason is that current personalized approaches have focused on individualized management programs run by doctor’s offices and outpatient clinics (Kim et al, 2015). These, however, are expensive and logistical challenges, as they require multiple sessions with highly qualified staff. Regional lack of centres that can provide such programs as well as limited mobility of patients are challenging for such programs. Here, risk calculation tools with disease management functions embedded into smart phone applications can be a viable alternative (Kim et al, 2015). Such an approach is highly promising, since according to some reports 90% of the stroke risk can be explained by 10 risk factors (O´Donnel et al, 2010), thus optimal management of a few risk factors could reduce the stroke risk significantly-

3 Acute Stroke therapy and outcome

Although there have been advances in the treatment of ischemic stroke, overall therapy success is still poor. For thromboembolic stroke, the most favourable current treatment paradigm is the time-based pharmacological dissolution or the mechanical extraction of the obstructing blood clot (Powers et al, 2018). Unfortunately, up to 20% of patients arrive with an unknown time from stroke onset, and most patients present too late in the hospital to receive treatment (Meairs et al, 2006). Additionally, what challenges the treatment of stroke patients is that the causes are highly heterogeneous. Thus, each patient suffering a stroke is an individual representation of the disease entity stroke. Current treatment paradigms, however, do not consider individual differences. Also, physicians presented with the clinical cases are bad in predicting the outcome of stroke patients (Ntaios et al, 2016). This suggests that stroke care could be significantly improved by more personalized risk calculation, outcome prediction and therapeutic recommendations, i.e. by precision medicine. A precision medicine approach in stroke would entail determining individual factors influencing the outcome after stroke. This would lead to informed choice of therapeutic interventions and a more rational allocation of resources. Overall, a reduction of stroke mortality and disability with consecutive reduction of healthcare costs could be expected.

However, in contrast to primary and secondary prevention, only few works have dealt with the statistical prediction of stroke outcome and best treatment so far. In the following we will summarize the background and the current state of predictive models in stroke.

3.1 Precision Medicine in Acute Stroke

Precision medicine is a form of health care that emerged in the past years that relies on data, algorithms and precision molecular tools to offer individualized care for patients (Dzau et a, 2016l). It gives insight into mechanisms of disease, treatment and prevention. By treating the patient as an individual the attending physician is able to consider variations in pathophysiology, genome and anatomical variances. This will improve outcomes and reduce healthcare costs. Precision medicine has been successfully used so far in oncology to find genetic mutations and is now considered for a variety of different fields (Hinman et al, 2017). Its use in stroke is now emerging as more and more pathophysiological data becomes available. Stroke has a complex pathophysiology comprising medical and environmental factors and is therefore a suitable candidate for precision medicine Different types of data like clinical and imaging data are available for ischemic stroke. Additionally, given its high prevalence, a lot of data is routinely acquired and can be made available. A precision medicine approach can therefore integrate this data and offer higher for treatment decision making and outcome prediction (Dzau et al, 2016 Hinman et al, 2017).

Precision medicine relies on the aggregation, integration and analysis of data in a computational "learning network" (Dzau et al, 2016). It therefore needs interdisciplinary cooperation at the crossroads of medicine, statistics and engineering. One particularly promising approach is the use of machine learning artificial intelligence (Dzau et al, 2016 Hinman et al, 2017). Another promising approach is the biophysiological modelling of pathophysiological phenomena, also called mechanistic modelling. Since both have unique advantages it has been suggested that hybrid modelling - the combination of mechanistic modelling and machine learning - will be the method to allow truly personalized medicine, especially in complex biological systems (Diaz et al, 2013).

3.2 Hybrid Modelling in Acute Stroke

Hybrid modelling is the combined use of mechanistic and machine learning models. Hybrid modelling combines the better of two worlds: i) the simulation based possibilities of mechanistic models with ii) the predictive versatility of machine-learning models. The most often used combination is called "staged methods". These involve a two-step modelling process. A mechanistic model is used to transform some or all the input data into a new feature space and then machine learning is applied to the transformed data. In some ways, the mechanistic models in these architectures can be understood as new smart inputs for the ML trained models. Not surprisingly, hybrid modelling is a big focus for example of European Research Council (ERC) funding, e.g. in the Discipulus project (Diaz et al, 2013). Hybrid modelling is thus probably the most promising approach to achieve true precision medicine in acute ischemic stroke. However, it relies on the availability of both biophysiological and machine learning models for stroke.

3.3 Bio-physiological Modelling in Stroke

Several mechanistic bio-physiological models have been suggested accounting for disruption of blood flow in the brain, reduced oxygen in the brain, and cell damage (Duval et al, 2002). Also, the influence of spreading depression on cell death has been investigated (Chapuisat et al, 2008). Together these mechanistic models can describe the time-evolution of key risk factors in normal conditions, and in response to different treatments, such as diet, exercise, and medication (Lundengard et al, 2016).

In addition to these initial models, the Charité team led by Dietmar Frey has developed a bio-physiological model of brain perfusion (manuscript in preparation). This model integrates individual patient-specific imaging data and boundary conditions (e.g. blood pressure, intracranial pressure, etc.). It computes flow volumes, velocities, and perfusion pressures for different brain areas. This is the first brain circulation model that integrates individual stroke patient data and enables simulation of brain blood flow and perfusion based on vascular pathology such as stenosis and occlusion. The model has the advantage that it can be adapted to individual patient data derived from medical neuroimaging sources. The model also allows incorporating vessel segments into the model/planar graph to examine their effect in the cerebral vasculature and/or to supplement missing medical data/information. Taken together, the tool provides a dynamic and individualised simulation model for the brain circulation integrating individual patient data and enabling simulation of blood flow and perfusion in stroke.

Importantly, this model is based on routine clinical imaging. Thus, it is able to provide individual data for a precision medicine approach without the necessity of additional time-consuming and even potentially harmful approaches used today in perfusion imaging.

However, while this mechanistic models can incorporate some of the features available in current dataset and predict the time-evolution of key biomarkers in a patient-specific manner, there are still many pieces of data that these mechanistic models cannot make use of. Using fusion methodologies, the outputs of our mechanistic model along with the data not accommodated models will need to be combined with machine learning approaches to create hybrid stroke model. This will allow precise personalized predictions for stroke treatment and outcome.

3.4 Predictive Modelling of Stroke Outcome

Machine learning is an overarching term for computer algorithms which can infer patterns from data without specific programming to recognize these patterns. It can produce abstract conclusions from different types of raw data from heterogeneous, large data sets (Mamoshina et al, 2016). In machine learning, an algorithm is taught to use the data to analyze different factors and to make predictions. Like the human brain, algorithms can recognize patterns and classify information. Except that the algorithm can consider more data than a human brain ever could while being faster and more accurate (Mamoshina et al, 2016).

While still being a new modality in medicine, machine learning has shown success in different fields. It powers advertising, self-driving cars and processes in different scientific domains such as astronomy, biology or physics. Healthcare is the next logical application where machine learning could reap enormous benefits for doctors, researchers and patients.

Machine learning has already been used for example in oncology, where it can serve as a predictor for different cancers by analysing genomes and amino acid sequences to find cancer-causing variants. Machine learning image recognition skills have also been applied to the field of radiology and pathology. Recently, a state-of-the-art machine learning algorithm was shown to diagnose pneumonia in chest x-rays with higher accuracy than human radiologist (Rajapurkar et al, 2017).

First efforts have already been made to apply machine learning techniques to the pathology of stroke.

They can be divided into 3 categories. Predictions based on clinical data, predictions based on imaging data and predictions based on meta-data, e.g. clinical scores.

3.4.1 Predictions based on clinical data

Khosla et al. [15] examined 16 clinical features such as age, blood pressure, medication etc. using a machine learning approach to predict the occurrence of ischemic stroke [15]. In another work – focusing on mechanical thrombectomy – the authors found age, NIHSS and collateral status to be predictive for 3-month outcome (AUC: 0.76). A similar study for endovascular treatment found NIHSS, intracerebral haemorrhage and age to the three most predictive factors (Asadi et al, 2014). Weimar et al found age, arm paresis and NIHSS to be most predictive for stroke outcome with accuracy over 80% (Weimar et al, 2002).

3.4.2 Predictions based on imaging data

Forkert et al. predicting functional outcome by lesion mapping and the use of support vector machines with an accuracy of 85% [14].

3.4.3 Predictions based on meta-data

Parsons et al explored the use of the ASPECTS-score and found that a score above 6 points was better in prediction the final outcome than native CT and CT-angiography (Parsons et al, 2005). Next to this, they found age and NIHSS to be predictive for stroke outcome. Researchers working on data from the DEFUSE study developed a 5-item scale to predict stroke outcome after middle-cerebral-artery infarction (Vora et al, 2011). The 5 independent predictors of stroke outcome were age, NIHSS, infarct volume, admission white cell blood count and presence of hypoglycaemia; combination of these factors in a scale further improved the prediction (AUC: 0.91). Another score is the DRAGON-Score (Strbian et al, 2013). In a very large collective of over 4000 patients with both anterior and posterior circulation the score achieved an AUC of around 0.83. The THRIVE-c score was validated in a huge database of over 12000 patients and achieved and AUC of 0.74 for the prediction of stroke outcome.

3.4.4 Combined predictions

Hand et al combined MR diffusion weighted imaging with clinical parameters for the prediction of stroke outcome. They found that only two clinical parameters, age and the NIHSS were predictive of stroke outcome (AUC: 0.73) (Hand et al, 2006). Bentley et al combined CT-imaging and clinical predictors for outcome prediction (Bentley et al, 2014). The most predictive factors were NIHSS, thrombolysis, and gender (age was on 5th place) with an AUC of 0.74. Eilaghi et al combined perfusion parameters and clinical parameters for prediction and found improved performance when combining the parameters with AUCs around 0.80 (Eilaghi et al, 2014).

3.5 Conclusion

Most approaches so far targeted on a single type of input, neuroimaging, clinical data or scores. A few authors combined features extracted from imaging with clinical features. All in all, the achieved AUC and/or accuracy ranged between 0.7 and 0.8. We can support these values by internal – yet unpublished data – where we achieved an accuracy of over 80% in a cohort of 1200 acute stroke patients using purely clinical data. We can also corroborate the importance of age and NIHSS as predictors, which were the two most influential features in our own analysis. To our knowledge only very few works have ever attempted to use pure imaging features for the prediction of stroke outcome (see above). A reason here was the lack of proper methodologies to extract relevant features directly from the images. Mostly hand-crafted features were used so far like scores or the infarct volume. Here, new techniques – like auto-encoder manifold learning (Feng et al, 2018) – have the potential to extract features directly from images that can be used together with clinical features for improved predictions. Also, in stroke, the pathophysiology is diverse. To achieve precision medicine, different data has to be evaluated including neuroimaging and clinical data. Thus, a logical next step is the combination of available features from clinical and imaging sources with bio-physiological modelling, i.e. hybrid modelling.

Taken together, the availability of both bio-physiological models as well as established machine learning tools in stroke, calls for the development of hybrid models to predict the outcome after stroke. In PRECISE4Q we will use such models which will be a big step towards the achievement of true precision medicine in stroke.

4 Rehabilitation

The impairments associated with a stroke show a wide diversity of clinical signs and symptoms. Disability, which is multifactorial in its determination, varies according to the degree of neurological recovery, the site of the lesion, the patient's premorbid status and the environmental support system.

The clinical consequences of stroke are classified based upon the anatomical regions(s) of the brain affected. This leads to dividing the brain into: 1) the cerebral hemispheres, where all but the posterior hemispheres are supplied by the carotid or anterior circulation, left and right side, and 2) the brain stem and posterior hemispheres (which are supplied by the vertebral basilar or posterior circulation). There is a large degree of specialization within the brain with different neurologic functions divided amongst the two hemispheres and the brainstem. The clinical picture of a stroke depends upon which specialized centres have been damaged with subsequent loss of the specialized neurological function they control. However, this schematic view of the brain is in many ways too simplistic. Brain functioning occurs in an integrated fashion. Even a simple activity, such as bending over to pick up an object, requires the integrated function of the entire central nervous system. When damage occurs in one region of the brain, not only are those specialized centres associated with the impaired region affected, but also the entire brain suffers from loss of input from the injured part.

4.1 Neurological Recovery

Recovery after a stroke is a complex process combining:

1. Spontaneous Recovery. It is defined as recovery of neurological impairments. These are determined primarily by the site and extent of the stroke. As a general rule, the severity of the initial deficit is inversely proportional to the prognosis for recovery. The majority of neurological recovery occurs within the first 1- 3 months. Afterwards recovery may occur much more slowly for up to one year. The course of recovery is a predictable phenomenon; it is initially very rapid and then negatively accelerates as a function of time (Skilbeck et al. 1983) studied 92 stroke survivors with a mean age of 67.5 years (range= 36-89) at final assessment, either 2 or 3 years after stroke. The majority of recovery was reported within the first 6 months, with continued but non-statistically significant recovery after 6 months. This type of recovery is still largely if not completely independent of rehabilitation and is discussed further later on.

2. Functional or Adaptive Recovery. Functional deficits are often referred to as disabilities and are measured in terms of functions such as activities of daily living. Functional recovery is defined as improvement in mobility and activities of daily living; it has long been known that it is influenced by rehabilitation. This recovery depends on the patient's motivation, ability to learn and family supports as well as the quality and intensity of therapy. Functional recovery is highly influenced by neurological recovery but is not dependent on it.

4.2 Time Course of Recovery

Peak neurological recovery from stroke occurs within the first one to three months. A number of studies have shown that recovery may continue at a slower pace for at least 6 months; with up to 5% of patients continuing to recover for up to one-year. This is especially true with patients who are severely disabled at the time of initial examination (Ferrucci et al. 1993, Kelly-Hayes et al. 1989).

Progress towards recovery may plateau at any stage of recovery with only a very small percentage of those with moderate to severe strokes (about 10%) achieving "full recovery". The return of motor power is not synonymous with recovery of function; function may be hampered by the inability to perform skilled coordinated movements, apraxias, sensory deficits, communication disorders as well as cognitive impairment. Functional improvements may occur in the absence of neurological recovery (Duncan and Lai 1997). Functional recovery (the ability to do activities despite limitations) and improvement in communication may continue for months after neurological recovery is complete.

4.3 Prognosis of Recovery

(Alexander 1994) noted that the two most powerful predictors of functional recovery are initial stroke severity and age. Stroke severity is by far the most predictive factor.

4.3.1 Stroke severity as predictor

The best predictor of stroke outcome is initial clinical assessment of stroke severity. This correlates with the length of time to maximal neurological and functional recovery. (Garraway et al. 1980) first proposed the concept of 3 bands of stroke patients based upon stroke severity during the acute phase:

1. Mild Strokes: Few deficits, early FIM score (1st 5-7 days) > 80, (Stineman et al. 1998) defined as motor FIM > 62; rehab gains limited by "ceiling" effect.

2. Moderately Severe Strokes: Moderate deficits, conscious with significant hemiparesis, early FIM 40-80 or motor FIM 38-62; make marked gains in rehab and 85% discharged to community.

3. Severe Strokes: Severe deficits, unconscious at onset with severe paresis or serious medical comorbidity, early FIM < 40 or motor FIM < 37; slower improvement, unlikely to achieve functional independence (unless young) and smallest likelihood of community discharge.

(Jorgensen et al. 1995a) studied 1,197 acute stroke patients in what is referred to as the Copenhagen Stroke Study. Impairments were classified using the Scandinavian Neurological Stroke Scale (SSS) and functional disability was defined according to the Barthel Index (BI). Neurological recovery occurred on average two weeks earlier than functional recovery. In surviving patients, the best neurological recovery occurred within 4.5 weeks in 80% of the patients, while best ADL function was achieved by 6 weeks. For 95% of the patients, best neurological recovery was reached by 11 weeks and best ADL function within 12.5 weeks. (Jorgensen et al. 1995c) reported that best walking function was reached within four weeks for patients with mild paresis of the affected lower extremity, six weeks for those with moderate paresis and 11 weeks for severe paralysis. Consequently, the time course of both neurological and functional recovery was strongly related to both initial stroke severity and functional disability. (Jorgensen et al. 1995a), found two-thirds of all stroke survivors have mild to moderate strokes and are able to achieve independence in ADL.

4.3.2 Age as recovery predictor

Recovery is faster and occurs to a greater extent in younger individuals with a stroke. This correlates with decline in ability to form neurological connections with aging. There is also a small but significant effect of age on functional recovery.

In a cohort study of 2219 patients, (Kugler et al. 2003) studied the effect of patient age on early stroke recovery. The authors found that relative improvement decreased with increasing age: patients younger than 55 years achieved 67% of the maximum possible improvement compared with only 50% for patients above 55 years ($p < 0.001$). They also found that age had a significant but relatively small impact on the speed of recovery with younger patients demonstrating a slightly faster functional recovery ($p < 0.001$). The authors concluded that although age had a significant impact it nevertheless was a poor predictor of individual functional recovery after stroke and could not be regarded as a limiting factor in the rehabilitation of stroke patients. However, younger patients did demonstrate a more complete recovery.

4.4 Reviews of Stroke Rehabilitation Efficacy

While the benefits of a stroke rehabilitation service may seem obvious, determining the impact of this treatment is difficult, due to problems with study design and methodology (lack of randomization, inappropriate control group selection, failure to blind assessors, difficulty in controlling for all possible confounders) and difficulties inherent to stroke rehabilitation (controlling for spontaneous neurological recovery, daily fluctuation in individual function, and difficulties in measuring functional outcomes). Despite these difficulties, earlier comparative studies demonstrated patients cared for by specialized stroke rehabilitation teams had lower one-year mortality, achieved greater gains in activities of daily living by discharge, and were less likely to be in a nursing home at follow-up (Anderson et al., 2009). However, pre-selection of patients and concerns about observer bias raised concerns over the validity of these findings.

4.4.1 The Effectiveness of Stroke Rehabilitation

Systematic reviews and meta-analyses have been conducted to evaluate the effectiveness of stroke rehabilitation compared to conventional care. All identified reviews provided evidence of a benefit of specialized stroke care. For example:

The Canadian Coordinating Office of Health Technology Assessment (CCOHTA) conducted a review of stroke unit care compared to care on a general medical ward (Noorani et al., 2003). The review was confined to RCTs published from 1995 to July 2002, which yielded six RCTs including a total of 1,709 patients with an average age of 76 years. Stroke unit care was associated with a reduction in the odds of death (OR 0.60, 95% CI 0.42-0.86), an outcome that was recorded in all studies, and the estimated number needed to treat to prevent one death was 11 (range, 7-25). There was also an increase in the odds of return to living at home among the four studies in which the outcome was evaluated (OR 1.42 95% CI 1.05-1.92). In the three trials where it was recorded, the median Barthel Index score was one point higher after 12 months among patients in stroke units (13.9, range 8-17) compared to the scores of patients in general medical wards (12.9, range 6-16.8) in the three trials that evaluated the Barthel Index. There was also a non-significant reduction in the need for institutional care of patients from stroke units at follow-up (OR 0.64), as reported in the six trials that evaluated this outcome (Noorani et al., 2003).

Given that the evidence for organized stroke units was mainly derived from clinical trials, it is worth considering whether the positive results were applicable in routine clinical practice. Results from population-based studies using administrative datasets showed similar findings to the clinical trials. In Finland, an adjusted hazard ratio for death in stroke unit versus no stroke unit for men and women was 0.79 and 0.83, respectively (Terent et al., 2009). In Scotland, an absolute risk difference of 3% for survival and 5% for home discharge was reported for stroke units (Langhorne et al., 2010a).

A systematic review on observational studies of stroke units was performed to determine whether the benefits seen in previous trials were generalizable to clinical practice (Seenan et al., 2007). Comparisons were conducted between stroke units and alternative interventions (i.e. conventional care on a general medical, neurology ward, or mobile stroke team). For patients receiving stroke unit care, there was a significant reduction in the odds of death (OR 0.79, 95% CI 0.73-0.86) and odds of death or poor outcome (OR 0.87, 95% CI 0.80-0.95) at one year post stroke. A subsequent review employed Bayesian analysis to investigate the impact of organized stroke units and demonstrated a similar reduction in mortality (O'Rourke & Walsh, 2010). The review evaluated the available evidence while adjusting for the heterogeneity and bias in non-randomized studies.

4.4.2 Cost-Effectiveness of Stroke Rehabilitation

While stroke unit care has been associated with improved outcomes, it has been assumed that they are a more costly intervention. As a result, there has been a proliferation of studies evaluating costs and cost-effectiveness of this form of care. Stroke represents a significant economic burden in developed countries, and so estimating costs and cost-effectiveness associated with stroke care is fraught with uncertainty. Stroke recovery and residual disability are highly variable, the contribution of informal caregivers is often ignored, and costing the discrete components of care provided within institutions is difficult. These factors and others limit the generalizability of the results of most studies. However, the results from several studies suggest that stroke unit care may in fact be cost-effective when compared to other interventions.

4.5 Reviews of Secondary prevention risk factors

The secondary prevention of stroke includes strategies used to reduce the risk of recurrence among patients who had previously presented with a stroke or TIA. Management strategies, which should be specific to the underlying aetiology, include risk factor modification, the use of antithrombotic or anticoagulant drugs, surgery and endovascular treatments.

The risk of stroke recurrence is as high as 25% within the first 2 years. Up to 40% of survivors of a stroke of TIA will have a stroke within 5 years. A second stroke can potentially reverse the benefits of stroke rehabilitation. Reintegration

The key to secondary prevention of stroke is to treat risk factors for an additional stroke. These include:

- High blood pressure (HBP)
- Atrial fibrillation (AF)
- Congestive heart failure/cardiomyopathy
- Smoking
- Dyslipidemia
- Diabetes
- Carotid stenosis
- Obstructive Sleep Apnoea

4.5.1 Hypertension

Hypertension is the most powerful risk factor after age. High blood pressure has high prevalence and is easily modifiable. Stroke mortality and incidence have declined over past 5 decades is partially attributable to better hypertension management. Risk of stroke rises proportionally with increasing systolic and diastolic blood pressure. The treatment of hypertension comes with a relative risk reduction of 42-48%. There is moderate evidence that antihypertensive therapy post stroke is associated with reduction in risk of functional disability and dependence. There is strong evidence that ACE-inhibitors (other than Captopril) are associated with a reduced risk of stroke (HOPE/PROGRESS). There is strong evidence that the addition of a Ca-antagonist (Diltiazem) to an antihypertensive regimen decreases the risk of stroke (Hansson et al. 2000). Most patients with hypertension will require 2 or 3 drugs to achieve blood pressure control. Preferred combinations include ACE inhibitor/diuretic, ARB/diuretic, ACE inhibitor/CCB and ARB/CCB. The treatment regimen will be dictated by patient's considerations and tolerance.

4.5.2 Diabetes

Diabetics have increased susceptibility to atherosclerosis, hypertension, obesity and hyperlipidemia. The relative risk of ischemic and hemorrhagic stroke for diabetics is 1.5-3.0. The risk of recurrent stroke is also significantly higher among patients with diabetes. Diabetic stroke patients have higher risk of death and disability in the first 28 days after stroke "FINNSTROKE study". Diabetic stroke patients are less likely to be discharged home from acute care, and less able to ambulate independently at the time of discharge. Tight glycemic control reduces microvascular complications (nephropathy, neuropathy, and retinopathy) but has not yet been shown to reduce stroke.

4.5.3 Hyperlipidemia

Recent studies have shown an association between serum cholesterol and thrombotic stroke but it has not been established that it is an independent predictive risk factor for stroke. Elevated total serum cholesterol, triglycerides, and LDL appear to be associated with an increased risk of ischemic stroke. The Cholesterol Treatment Trialists (2008) meta-analysis of 14 statin trials showed a dose-dependent relative reduction in cardiovascular disease with LDL lowering. There is strong evidence that statins are an effective treatment to lower cholesterol and reduce risk of stroke/TIA. There is strong evidence that intensive therapy may be more effective than less intense therapy in reducing the risk for ischemic stroke events. Statins have been shown to reduce the risk of stroke by 30% in patients with CAD despite serum cholesterol levels. Statins have been used for treating patients post MI and have been shown to reduce the risk of stroke by 24-34%. Statin therapy has been associated with increased risk for hemorrhagic stroke.

4.5.4 Homocysteine

Homocysteine is a sulpher-containing amino acid. It has been linked to atherosclerotic vascular disease including stroke. Normal serum levels of homocysteine are 5-15 mmol/L, greater than 16 abnormal. Elevated levels of homocysteine may be attributable to deficiencies in folic acid, vitamin B6 and vitamin B12, as well as old age (over 70 years), renal insufficiency, drinking more than 4 cups of coffee per day, alcohol use, smoking and physical inactivity. Plasma homocysteine levels are inversely correlated with red cell level of folate, vitamin B12 and vitamin B6. Supplementation with folic acid, vitamins B6 and B12 is associated with significant reductions in plasma homocysteine levels (tHcy) up to one year from baseline.

4.5.5 Carotid Stenosis

7-10% of men and 5-7% of women over the age of 65 have more than 50% internal carotid artery stenosis. The rate of ipsilateral stroke in significant carotid artery stenosis is 1-2% annually. Carotid stenosis should be measured by CTA alone or two concordant non-invasive imaging modalities such as MRA and carotid ultrasound or digital subtraction angiography (DSA).

4.5.6 Apnoea

Obstructive sleep apnoea (OSA) should be considered a risk factor for stroke and has also been shown to be present in many patients following a stroke (Evidence Level B). Patients who have experienced a stroke or TIA should be screened for the presence of sleep apnoea symptoms using a validated sleep apnoea screening tool. Patients with symptoms suggestive of sleep apnoea on screening should be referred to a sleep specialist.

4.6 Medical Complications

Numerous studies have investigated the incidence of medical complications after stroke of multiple etiologies in a variety of settings, including acute care, inpatient rehabilitation, and after discharge. These studies report varying rates of medical complications. The discrepancies in medical complication rates is likely multifactorial, including different study designs, varying diagnostic criteria for medical complications, pre-selection of complications to be studied, different patient selection methods, differences between the acute care and inpatient rehabilitation setting, and inherent differences in the populations studied, such as country of origin. Moreover, potential sources of bias can confound the accurate reporting of complications. Retrospective identification of complications, case note retrieval bias (i.e. obtaining information about patients who may have deceased earlier), and inter-observer bias (i.e. the ability of one or more observers to accurately retrieve medical information from patient records) may be factors contributing to the variability of complication reporting (Davenport et al., 1996).

In a single-centre prospective cohort study of 1029 patients in inpatient stroke rehabilitation in Chicago, USA, (Roth et al. 2001) reported that 75% of patients experienced at least one medical complication during their inpatient rehabilitation stay. UTIs, depression, falls, soft tissue pain, and elevated blood pressure were the most common complications; 19% of patients required transfer back to acute care for the management of medical complications. In this study, patients most likely to experience a complication post stroke were those with greater severity of stroke and a history of hypertension. Both (McLean 2004) and (Kitisomprayoonkul et al. 2010) found UTIs, depression, and musculoskeletal pain to be common, but they reported much lower frequency of certain medical events than in other studies, specifically pneumonia, seizures, gastrointestinal disturbances, and pressure ulcers.

In a prospective study of 133 patients admitted to an inpatient stroke rehabilitation centre in Nova Scotia, Canada (McLean, 2004) reported that 67% of patients experienced at least one complication post stroke, and 25% experienced two or more complications. The most frequently reported complications in their study were depression (26%), shoulder pain (24%), falls (20%), and UTIs (15%). The author also suggested that certain patient characteristics such as age, disability before stroke onset, and stroke severity may predict the likelihood of complications post stroke. In a prospective study of 118 patients admitted to inpatient rehabilitation in Bangkok, Thailand, (Kitisomprayoonkul et al. 2010) found that 70.3% of patients experienced at least one medical complication. Depression was the most commonly reported complication, occurring in 56.6% of patients. The only consistent predictive factor for complications post stroke between these studies was initial severity of stroke (Kitisomprayoonkul et al., 2010; McLean, 2004; Roth et al., 2001).

4.6.1 Bladder Dysfunction Post Stroke

Few investigators have examined the prevalence of Urinary Incontinence past the acute and subacute stage of stroke. (Brittain et al. 2000) reported that a significantly higher proportion of community-dwelling individuals who experienced a stroke had more urinary symptoms compared to those that had never had a stroke (64% vs. 32%); the difference was statistically significant even after adjusting for differences in age and sex between groups. Those who experienced stroke were 1.77 times more likely to experience urinary symptoms than those who did not, and twice as many individuals post stroke reported that their urinary symptoms were moderate to severe. As well, more individuals who experienced stroke reported a significant impact of urinary symptoms on lifestyle.

The risk factors for UI post stroke vary by study, which may reflect diverse patient populations, different evaluation time post stroke, and different definitions of UI. However, some common themes emerge with regards to stroke and personal factors that increase risk of UI post stroke. In a prospective cohort study, (Pizzi et al. 2014) studied 106 patients admitted to a neurorehabilitation service after ischemic stroke. The authors found that UI developed in 79% of patients and that it was strongly associated with lower functional status or greater stroke area, as measured by the Functional Independence Measure (FIM). Similarly, (Gelber et al. 1993) found that patients with UI had lower Barthel Index and Modified Barthel Index scores at admission and discharge, and were more likely to have aphasia. In a prospective study of 423 patients with ischemic or hemorrhagic stroke admitted to inpatient rehabilitation, (Ween et al. 1996) found that UI was associated with lower FIM scores, poorer motor function, and the presence of dysphagia. The authors found that small vessel, also known as lacunar, strokes had the lowest rates of UI and that pre-existing comorbidities were not predictive of UI. As well, UI was strongly associated with slower and reduced extent of recovery post stroke compared to continent controls.

In a retrospective case control study, the Overactive Bladder Symptom Score (OABSS) was used to examine the prevalence and risk factors of post-stroke overactive bladder in 500 patients with chronic stroke (Itoh et al. 2013). Patients were stratified by the presence or absence of symptoms for overactive bladder (OAB), and independent risk factors for OAB were examined using logistic regression methods. Patients with symptoms of OAB had significantly lower health-related quality of life compared to patients who did not report any symptoms of OAB. This study found that 73% of patients with symptoms of OAB had never been treated for their symptoms, despite relatively high OABSS scores (mean 7.1), indicating significant burden of symptoms. Unlike previous studies, (Itoh et al. 2013) did not find that motor deficits or sensory disturbances were predictive of UI.

Several of the studies reviewed above outlined negative patient consequences associated with UI and its sequela: UTIs; higher risk of skin breakdown; higher risk of falls; poorer health-related quality of life; slower and reduced extent of recovery; likelier discharge to a long-term care facility; and prolonged hospitalization (Gelber et al., 1993; Ifejika-Jones et al., 2013; Mehdi et al., 2013; Pizzi et al., 2014; Ween et al., 1996). Despite the negative effects on patients and their caregivers, (Itoh et al. 2013) found that many patients with significant symptoms had never been treated for their UI.

4.6.2 Bowel Dysfunction Post Stroke

(Kovindha et al. 2009) reported that incontinence of bowel and bladder (double incontinence) occurred in 33% of patients at admission to a rehabilitation unit and persisted in 15.1% at discharge. As well, (Brittain et al. 2006) reported that major faecal incontinence was 4.5-times more prevalent among patients post stroke compared with controls. A variety of risk factors for faecal incontinence have been identified including stroke location, stroke severity, and functional limitations. Total anterior infarction has been identified as an independent predictor of the presence of faecal incontinence (Barrett, 2002).

(Harari et al. 2003) found that problems with toilet access and constipating drugs were modifiable risk factors post stroke. The authors also found that the most powerful predictor of faecal incontinence in the first few days post stroke was the initial level of consciousness and stroke severity.

Constipation post stroke has not been well studied. The prevalence is unclear, likely due to high variability in the diagnostic criteria for constipation in stroke research. (Harari et al. 2004) reported that 66% of patients screened for their interventional study suffered from constipation. A similar percentage of affected patients (66%) was reported by (Robain et al. 2002) among patients in stroke rehabilitation. In general, constipation is thought to be a consequence of poor fluid intake, use of constipation-inducing medications, poor dietary fibre intake, decreased mobility, and increased dependence, rather than as a direct effect of stroke (Winge et al., 2003). Mild cases can be treated by correcting some of these abnormalities, such as ensuring adequate hydration, and with interventions, such as stool softeners or pro-kinetic agents.

4.6.3 Venous Thromboembolism Post Stroke

Deep vein thrombosis (DVT) is a potentially life-threatening condition in which blood clots form in the deep veins of the body. Venous thromboembolism (VTE) occurs when these clots embolize, or break free, and travel through the body's circulatory system. VTE is life-threatening when it enters the lungs, at which point it is clinically recognized as pulmonary embolism (PE), or when it embolizes to other areas, leading to focal ischemia.

The prevalence of DVT among patients admitted for rehabilitation is lower than in acute care, ranging from 12 to 40%, depending on the provision of anticoagulants, mobility status, and method of detection used (Wilson & Murray, 2005). The incidence of DVT diagnosed during rehabilitation is lower still, ranging from 5% to 11% (Harvey et al., 2004).

(Brandstater et al. 1992) evaluated two studies of 118 patients who were screened for DVT before admission to inpatient rehabilitation post stroke. The authors reported 31% of patients admitted to rehabilitation units had a DVT, and the mean time between stroke onset and screening was 45 days (Sioson et al., 1988).

Using venography, (Cope et al. 1973) reported a DVT prevalence of 31% in patients admitted to a stroke rehabilitation centre. (Miyamoto and Miller 1980) screened patients with I-125 fibrinogen, a precursor to D-dimer, an average of 9 days following admission to stroke rehabilitation and found a 29% prevalence of DVT.

Like DVT, the incidence of PE post stroke varies widely between studies; estimates range from 0.8% at 2 weeks to 39% at 10 days (Dickmann et al., 1988). A review of the Registry of the Canadian Stroke Network in 2013 by the Stroke Outcomes Research Canada Working Group reported a similar incidence of PE (Pongmoragot et al., 2013).

(Skaf et al. 2005) observed an increased rate of PE, DVT, and VTE in patients with hemorrhagic stroke relative to ischemic stroke, which may reflect decreased use of DVT prophylaxis in this population due to the concerns for increased bleeding risk. Using a multivariable regression model, (Kelly et al. 2004) identified advanced age and a Barthel Index ≤9 as the two major risk factors for the development of DVT two days post stroke.

4.6.4 Seizures Post Stroke

Seizures are episodes of abnormal electrical activity in the brain, which have been described as “the clinical expression of excessive, hypersynchronous discharge of neurons in the cerebral cortex.” (Wiebe & Butler, 1998). Given that strokes alter the brain parenchyma, they are a known structural risk factor for the development of seizures (Cordonnier et al., 2005). There is considerable variability in the reported incidence and timing of post-stroke seizures (PSS), and the impact of PSS on subsequent outcomes is unclear. While some studies reported that seizures were an independent risk factor for mortality (Hamidou et al., 2013), other studies failed to replicate these findings (Labovitz et al., 2001). As well, the risk of mortality associated with PSS may no longer be significant once adjusting for stroke severity and comorbidity (Hamidou et al., 2013).

In comparison to earlier studies, recent reports reveal less variability in the risk of post-stroke seizures (PSS). The average risk of PSS is 10% within 9-10 years post stroke, and well-conducted prospective studies report a 5-year cumulative incidence of 11.5% (Burn et al., 1997). At least two studies suggested a higher incidence of PSS (15-17%) in patients in rehabilitation units (Kotila & Waltimo, 1992; Paolucci et al., 1997). It is not clear whether this finding reflects ascertainment bias, in which seizures are less likely to be missed in these closely observed patients, or a true increased seizure risk in this population, possibly related to greater stroke severity in inpatient rehabilitation.

Several studies have examined risk factors for stroke to aid in identifying patients who are at increased risk of developing seizures post stroke. Despite considerable variability in the definitions and methodology between studies, common risk factors have emerged from the literature: cortical strokes, severe strokes, greater disability, and younger age. Stroke type may also predict seizure development, with hemorrhagic strokes being more likely than ischemic strokes (Alvarez et al., 2013a).

4.6.5 Osteoporosis Post Stroke

Osteoporosis is a disease of decreased bone mass, quantified as diminished bone mineral density (BMD). It is associated with significant complications, including hip fractures and mortality (Carda et al., 2009). In a group of patients admitted for inpatient stroke rehabilitation, (Watanabe, 2004) found that 40% already had osteoporosis. These findings highlight the importance for screening for bone loss in patients post stroke. Unfortunately, few stroke management guidelines include recommendations regarding post-stroke osteoporosis (Borschmann et al., 2012).

During the first year post stroke, subjects can lose from 3.6% to 17% of their BMD (Carda et al., 2009). Considerable evidence suggests that loss of BMD preferentially occurs in paretic limbs (De Brito et al., 2013; Pang et al., 2013), even when controlling for disuse (Pang et al., 2013). For instance, Hamdy et al. (1993) reported a significant difference in BMD for both the affected upper limb (7.95%) and lower limb (3.42%) when compared to the non-affected limbs. As well (Beaupre and Lew, 2006) found that the loss of BMD in the affected arm within the first year post stroke for some patients was equal to more than 20 years of bone loss for similar aged healthy individuals. These finding underscore the difference in clinical presentation of osteoporosis post stroke: upper limbs are disproportionately affected compared to the usual osteoporosis pattern for individuals without stroke (Carda et al., 2009). Even in patients without lower limb paresis, the ability to ambulate independently and low BMD are closely linked (Schnitzer et al., 2012).

4.6.6 Central Pain States Post Stroke

CPSP is a specific type of neuropathic pain that is thought to be due to stroke-related injury to pathways or brain centres involved in pain processing (de Oliveira et al., 2012; Henry et al., 2008). In this condition, pain and sensory abnormalities occur in the parts of the body that correspond to the stroke lesion (Klit et al., 2009). In 40-60% of patients, the onset of pain occurs more than one month after the stroke (Hansson, 2004).

Neuropathic pain such as CPSP creates challenges for involvement in rehabilitation (Cioni & Meglio, 2007). CPSP is caused by lesions located within nociceptive neuronal circuits that pass through the spinothalamic pathways at a higher level within the CNS (Katayama et al., 1998). Patients with CPSP commonly do not respond to other medical treatments and are usually resistant to opioid and nonsteroidal anti-inflammatory drug treatments. Though functional magnetic resonance imaging has increased understanding and specific localization of neuropathic pain, pharmacological treatments have made little improvement in pain reduction (Lazorthes et al., 2007).

4.6.7 Fatigue Post Stroke

Fatigue is a subjective term and there is no universally accepted definition (Choi-Kwon & Kim, 2011; Van Eijsden et al., 2012). Abnormal or pathological fatigue has been characterized as a state of general tiredness or weariness unrelated to exertion levels that is usually not ameliorated by rest (De Groot et al., 2003).

A variety of risk factors for PSF have been identified: depression, chronic pain, sleep disorders, functional disability, neurological impairment, and certain medications; female sex and older age also emerged as independent predictors of fatigue in predictions models (Feigin et al., 2012; Hoang et al., 2012; Mead et al., 2011). Patients with post-stroke pain were reported to have higher fatigue scores, although pain is not required nor necessarily comorbid with PSF (Tang et al., 2015). Currently, controversy exists as to whether there is a causal relationship between depression and fatigue.

4.7 Predictors of Stroke Rehabilitation Outcomes

Following stroke, all individuals need care, support, and education, but not all need formal rehabilitation. Approximately 20% of individuals fully recover functional independence by 2 weeks post stroke (Kelly-Hayes et al., 1988). It is estimated that another 20% have such severe functional deficits that they are expected to remain non-ambulatory and continue to require assistance with activities of daily living (ADLs) irrespective of rehabilitation efforts (Pfeffer & Reding, 1998). In the cases of severe stroke, the age of the patient and the presence of a caregiver (Pereira et al., 2014; Pereira et al., 2012) dictates whether rehabilitation will alter the discharge destination or improve function of all abilities to a substantial degree. Between these extremes are individuals with varying degrees of disability, for whom the goal should be to identify the best possible match between their needs and the capabilities of available rehabilitation facilities.

(Alexander, 1994) noted that the most powerful predictors of functional recovery are initial stroke severity and the patient's age. This finding has been confirmed by (Stineman et al., 1998) and (Stineman and Granger, 1998), although the effect of age diminishes for patients with less initial disability (FIM>60- 65), leaving stroke severity as the most powerful predictor. Discharge to inpatient rehabilitation was found to be associated with older age, greater length of stay in intensive care, higher therapy costs, and living in a country of lower poverty; the opposite was true for each of these factors for patients discharged home (Gregory & Han, 2009). Similarly, factors such as older age, impaired cognition, lower functional level, and urinary incontinence were found to be predictors of increased inpatient rehabilitation (Winstein et al., 2016).

A cluster analysis by (Buijck et al., 2012) revealed two groups of patients who had received rehabilitation at a skilled nursing facility; those in fair condition and those in poor condition upon admission. These clusters were based on balance, gait, arm function, ADL performance, and neuropsychiatric complaints. Nearly half (46%) of patients in the poor condition cluster were able to be discharged to assisted-living or an independent living program, implying that these discharge destinations are attainable despite stroke severity. In a study of 189 patients with severe stroke admitted to a specialized interdisciplinary stroke rehabilitation unit, (Pereira et al. ,2014) found that only one patient of the 123 discharged home did not have a caregiver, indicating a near zero likelihood of being discharged home if a caregiver was not present. Moreover, those patients with a caregiver achieved higher FIM gains during stroke rehabilitation than those without a caregiver.

A systematic review with 27 studies found that admission functional level (FIM or BI), stroke severity (National Institutes of Health Stroke Scale; NIHSS), dysphasia, impulsivity, neglect, previous stroke, and age were significant predictors of functional ability after inpatient stroke rehabilitation (M. J. Meyer et al., 2015). Data from four countries showed that baseline NIHSS score was essential for predicting good outcome after stroke, with age also being an important predictor (Rost et al., 2016).

5 Reintegration

While the majority of stroke survivors return to live in the community, re-integration may be an enormous challenge. The ability to return to an acceptable lifestyle, participating in both social and domestic activities is important for perceived quality of life.

In this section we review main factors arising after discharge from hospital care or rehabilitation into the community. These include social support, impact of caregiving on informal carers, family functioning, provision of information and education, leisure activities, driving and return to work.

5.1 Social Support

While the majority of stroke survivors return to live in the community, re-integration based on the resumption of activities of daily living and the adoption of successful psychosocial roles may be an enormous challenge (Palmer & Glass, 2003). The ability to return to an acceptable lifestyle, participating in both social and domestic activities has been found to be important for patient satisfaction and perceived quality of life post stroke (Clark & Smith, 1999b; Jaracz & Kozubski, 2003; Kim et al., 1999; Mayo et al., 2002).

A study by (Boden-Albala et al.,2005) reported that social isolation following first stroke is significantly associated with the risk for recurrent stroke or death where social isolation was defined as "knowing fewer than three people well enough to visit with in their homes". The authors suggested that social isolation may be related to poor outcome via stress, depression, poor treatment compliance and decreased participation in healthy activity.

While the quality of life of stroke survivors may be lower than that of comparison groups within the general population, it may be influenced, positively, by the presence of social support. Functional status has been demonstrated to be of considerable importance in the quality of life of stroke survivors; however, the degree of social support an individual receives may moderate the effect of disability and handicap on that individual's quality of life (Gottlieb et al., 2001; Kim et al., 1999). In a large observational study, (Shao et al. 2014) found that physical functioning, optimism, and social support were significantly related to well-being, and correlated significantly with the meaning of life. In addition, it has been found that the size of social networks and their perceived quality or effectiveness affect the quality of life post stroke (Mackenzie & Chang, 2002). (Hilari et al. 2010) demonstrated that both the perception of loneliness and satisfaction with one's social networks influence the development of psychological distress over time. Individuals with larger social networks who also perceive them to be effective in supporting them may have a better quality of life. (Haslam et al. 2008) demonstrated that individuals affiliated with a greater number of social groups prior to stroke may be more likely to maintain a larger number of these existing affiliations. Maintenance of group membership, rather than establishing new affiliations, may be important to well-being. However, maintenance of existing memberships may be threatened by cognitive impairment.

In a single RCT by (Kim et al., 2014), a community walking program that incorporates the social aspect of participating as a group, was evaluated to determine its effectiveness at improving walking function. Results suggest that when compared to the usual care group that did not receive this intervention, the walking group did significantly better on the ambulation outcomes. Although both groups received standard rehabilitation at the same intensity, the intervention group received additional walking exercises which the control group did not. Therefore, the results must be interpreted with caution as the effect observed may not be due to the social aspect of the program but rather due to the increased intensity of the physical exercise.

5.2 Family

Family members providing care for stroke survivors are often required to sacrifice their personal needs to meet those of the stroke survivor. Smith et al. interviewed 90 caregivers one year following stroke (Smith et al., 2004). In that study, carers reported spending 7 days per week in the provision of care and almost half (47.8%) of the 90 caregiver participants reported spending more than 160 hours per week in caregiving activities. It is hardly surprising that reports have suggested that more than 25% of carers under the age of 65 either reduce the number of hours they spend at work or leave their employment entirely in order to juggle the many demands of providing care for their loved one which may have dire effects on the financial wellbeing of the family (Grant et al., 2004c). In a recent study, (Ko et al. 2007) reported that a substantial proportion (36%) of working caregivers either reduced the number of hours they worked, or left their jobs entirely to care for their family member.

The most commonly identified effects of caregiving on the caregiver include increased caregiver stress, strain or burden, decreases in perceived health (both physical and mental), social contact and activity, increased risk for depression, and an overall decrease in quality of life. Many of these, such as caregiver health status, depression and lack of social contact, are also identified as factors influencing other consequences of caregiving. Reports concerning the influence of patient characteristics vary with the effect in question. The presence of stroke-related impairments such as aphasia, are often cited as having a significant impact on caregivers. A systematic review by (Grawburg and colleagues 2013) found that caregivers of patients with aphasia are affected at all levels of their health – body functions, activities and participation (based on the ICF framework). Age, severity of stroke, and functional status and cognitive status of the patient are other factors reported as influencing caregiver outcomes.

The increased risk for depression associated with caregiving is substantial. Many carers' experience social isolation, depression, loneliness, helplessness, fatigue and burnout in the process of carrying for a loved one with a stroke (Chow & Tiwari, 2014). Within the literature, the prevalence of caregiver depression has consistently been documented as higher in stroke caregivers (37% to 52%), when compared to non-caregiving populations (12% to 16.5%) (Simon et al., 2009;). However, many of the stroke caregiving studies have relatively small sample sizes and may suffer from weaknesses associated with the use of opportunistic samples with self-selection biases (Han & Haley, 1999).

In addition to health-related challenges, caregivers encounter financial challenges either because of a loss of job due to the increased caregiving demand, or to a loss of income due to the patient's stroke (Cecil et al., 2013). Many caregivers report having financial concerns which can further deteriorate other aspects of a caregivers' wellbeing. For instance, (McLennon et al., 2014) showed that depression was associated with lower financial wellbeing. Financial hardship largely due to increases in expenditure for the patient and the loss of income, was found to contribute to carers stress (Chow & Tiwari, 2014).

5.3 Leisure activities

A reduction of social and leisure activity is common post stroke. (Niemi et al. 1988) noted that stroke patients in their survey reported 80% deterioration in leisure domains. (Belanger et al. 1988) reported that, 6 months after returning home, fewer than 50% of the 129 stroke patients included in their sample participated in regular physical activities, and more than 50% did not participate in leisure activities outside of the home.-

O'Connell et al. found that the decline in participation in leisurely events was a consequence largely attributed to other non-stroke related factors such as transport difficulties, health issued unrelated to stroke, losing interest in the activities previously undertaken, fatigue, and physical limitations (O'Connell et al., 2013). Activities such as listening to music and reading for pleasure were often declined due to poor eyesight, headaches and lack of concentration (O'Connell et al., 2013). Patients also had a decreased interest in artistic events such as attending the cinema, musical performances, concerts, dancing, and singing, although, Jean et al. indicates that listening to music may decrease depression scores (Jean et al., 2013).

In order to promote the early identification of stroke survivors at risk for social inactivity, researchers attempted to create a simple rule to be used in the prediction of social inactivity as assessed on the Frenchay Activities Index (Schepers et al., 2005). Using information obtained on admission to rehabilitation, the proposed instrument had a sensitivity of 82% and specificity of 76% (AUC = 0.85) for the prediction of social inactivity/activity at one-year post stroke. It should be noted that interpretation of FAI scores should be undertaken with caution (Salter et al., 2005; Schepers et al., 2005). Many of the items on the scale are related to housework activities, which are undertaken by women in a traditional household model. This may result in an inflation of FAI scores among women and a corresponding depression of FAI scores among men (who may never have engaged in these activities). Further evaluation of this predictive aid is required.

Community-based, group exercise has also been examined for its possible social benefit. While effective in improving physical function as well as satisfaction with physical performance, evidence regarding the impact of group exercise on participation outcomes is less clear. On the other hand, factors such as perceived recovery, the amount of retained activities, and community reintegration have been found to predict perceived participation (Eriksson et al., 2013). Marital status however, was not a significant predictor of perceived participation (Eriksson et al., 2013). The severity of a patient's depression was also significantly associated with limited community participation and low social support (J. H. White et al., 2014). In an observational study, (Le Dorze et al. 2014) identified several factors that facilitated or impeded participation in patient with aphasia.

5.4 Driving

Inability to drive is associated with disruption in lifestyle, an inability to participate in the community, resume pre-stroke roles or maintain independence and autonomy (White et al., 2012). Resumption of driving, although perceived as a relief, may be accompanied by a lack of confidence (White et al., 2012). Stroke patients who do not resume driving report that this decision negatively impacted social activities and wellbeing (Mackenzie & Paton, 2003). Similarly, (Finestone et al. 2010) reported that driving is significantly associated with community reintegration one year following stroke ($p<0.001$, adjusted for health status). However, the ability to drive is dependent on good vision and reflex response, quick decision-making and keen attentiveness, which may be compromised by perceptual, cognitive and physical disorders that often accompany stroke (Tan et al., 2011).

Tasks that are frequently repeated and are closely associated to personal autonomy, like driving, may be incorporated as an aspect of self-concept (Scott et al., 2009). Most normal, driving, adults believe that they are much better drivers than they are, despite evidence to the contrary. The same may be true of individuals with stroke; however, self-assessment of driving ability following stroke may also be affected by impaired cognition and self-awareness (Scott et al., 2009). (Patomella et al. 2008) assessed the driving ability of 38 individuals approximately 1 year following stroke using a driving simulator, an assessment of awareness of driving disability and a stroke driver screening assessment (Patomella et al., 2008). The majority of patients (75%) demonstrated at least one major discrepancy between performance and awareness indicating that there had been at least one major mistake made of which the patient was entirely unaware. (Scott et al. 2009) reported that stroke survivors demonstrated significant bias in estimating their driving ability when compared to the "average driver". This bias in favour of their own ability was less noticeable when they were asked to compare themselves to their significant other, although they tended to compensate by elevating the ability of their companion. In addition, when asked to identify important factors in making a decision about driving, stroke survivors identified only one domain, convenience, while significant others felt that cognitive abilities, physical function and professional advice were important. Conversely, a recent study by (Stapleton et al. 2012) found that self and proxy ratings of driving ability were significantly correlated with each other and both ratings correlated well with on road driving assessments completed by a professional (Spearman's correlation coefficient = 0.497 (stroke survivor) p= 0.005; Spearman's correlation coefficient = 0.614 (proxy) p= 0.005). Despite demonstrable deficits, many stroke survivors make decisions regarding their driving without professional advice and/or evaluation (Fisk et al., 1997). A recent study (Finestone et al., 2009) reported that 41.7% of individuals with a valid license, who drove prior to their assessment, failed their first evaluation.

5.5 Return to Work

Observational studies suggest that while many stroke survivors may be capable of working, a substantial proportion do not return to work or must alter their hours of work or place of employment to do so (Vestling et al., 2003). In a large, prospective, population-based study, (Busch et al. 2009) reported that a significant proportion of independent (53%) and active (39%) individuals who had been employed prior to stroke did not return to work one year following the stroke event. However, resuming employment may have a positive impact on quality of life and well-being for both the individual with well-being and his/her spouse (Gabriele & Renate, 2009).

A stroke patients' return to work is dependent on factors such as age (Busch et al., 2009), functional ability (Gabriele & Renate, 2009), motor weakness or muscle strength (Sreedharan et al., 2013), type of employment (e.g. white vs. blue collar) (Hackett et al., 2012) level of education and income (Gabriele & Renate, 2009), and post-stroke duration (Maaijwee et al., 2014) such that younger, more independent individuals with better muscle strength and motor control with more education who were employed in high-paying, white-collar professions are more likely to return to work in the months and years following a stroke event. Other identified factors influencing return to work include the presence of aphasia (Tanaka et al., 2014), apraxia or other cognitive impairments (Kauranen et al., 2012), diabetes (Busch et al., 2009), fatigue (Andersen et al., 2012), or psychiatric morbidity (Glozier et al., 2008), length of stay in hospital or rehabilitation (Trygged et al., 2011) and size of employing business enterprise (Hannerz et al., 2012) . Although identified as influential in several studies, the role of gender in return to work remains unclear (Busch et al., 2009).

In-patient stroke rehabilitation is perceived, by stroke survivors of working age as being aimed at restoring bodily function and promoting function in activities of daily living rather than supporting a return to the workplace (Medin et al., 2006). (Chan, 2008) reported that the majority (55%) of individuals receiving employment services from a community-based agency were successful in returning to paid employment (Chan, 2008). However, these individuals tended to change type of employment from blue to white collar jobs. Reasons for poor outcome included need for further rehabilitation, failure to return for assessment and being unfit for work.

5.6 Factors influencing Community Reintegration

Stroke patients discharged from hospital care can face numerous challenges upon their return to the community. Oftentimes, the discharge goals of health care professionals do not align with those of the patients. Current evidence suggests that patients prioritize returning to "normality" and resuming previous roles while health care providers focus on the effects of specific interventions once discharged into the community (Wood et al., 2010). This misalignment can curtail rehabilitation outcomes and impede reintegration within the community. It is therefore crucial that rehabilitation specialists also target potential barriers to community reintegration prior to discharge such that patients can be better prepared to confront potential barriers within the reintegration process.

Primary effects of stroke are related to the barriers encountered resulting from the direct physical and cognitive impairments associated with stroke (Walsh et al., 2015). Many of the studies revealed overall physical limitations such as communication deficits (Alaszewski et al., 2007), fatigue (White et al., 2012), cognitive and memory impairments (Alaszewski et al., 2007), loss of mobility and motor function, and limited capacity to perform fundamental functions (Alaszewski et al., 2007).

Perseverance, along with other personality traits such as hope, optimism, determination, competitiveness, resilience and initiative were found to play an important role in integration success (White et al., 2012) Completing meaningful tasks and goals such as returning to work, home, or driving where described as powerful motivators in the first year post stroke (Robison et al., 2009). Stroke survivors that accept the change in their abilities and adapt to their post-stroke selves are found to better integrate within the community (Kubina et al., 2013). On the other hand, negative emotional factors such as loss of control, self-consciousness, reduced self-esteem and confidence (Wood et al., 2010), as well as overwhelming feelings of fear, anxiety, anger and frustration (Barnsley et al., 2012) were found to have the opposite effect, thus negatively impacting one's ability to return in the community.

Social environments that foster a sense of support and belonging allow stroke patients to increase their motivation of participating in group activities (Erikson et al., 2010). Important sources of social support are family members and close friends which can provide substantial practical and emotional support (Barnsley et al., 2012). However, stroke patients can also experience feelings of dependency from family members which have a negative effect on the patients' wellbeing and can cause stress (Wood et al., 2010) and tension in relationships (Dickson et al., 2008).

Other factors that can negatively impact community reintegration relate to a lack of accessibility and limited access to various community centres due to environmental constraints (Gustafsson & Bootle, 2013). Patients have reported environmental barriers from unsafe sidewalks to a lack of accessible entrances that prevent them from leaving their homes. Such constraints become even more apparent for individuals living in rural communities where the nearest accessible centres are located at a significant distance. Transportation challenges can also isolate stroke survivors and thus impede the process of reintegration. Not surprisingly, driving was reported to be the most important facilitator of community reintegration and accessibility (Barnsley et al., 2012).

6 Conclusions

In this report we provide an overview of the current state-of-the-art in the literature concerning knowledge about stroke risk factors (incl. genetics), prognosis and outcomes after interventions. This will help the consortium in identifying the most relevant clinical challenges and needs for each patient journey phases.

The main medical concept of PRECISE4Q is to target four different stages of stroke in the life trajectory in a novel precision medicine approach. Therefore, in this report we have summarized the current status regarding stroke risk factors, prognosis and outcomes in each stage.

Interventions that can be deduced from the modifiable risk factors in stroke are discussed primarily from an epidemiological and public health point of view. Interventions are analysed on the population level both in terms of the interventions themselves as well as their health-economic outcome. Prevention strategies focused on the individual patient in terms of personalized medicine are lacking. One reason is that current personalized approaches have focused on individualized management programs run by medical doctors' offices and outpatient clinics. These, however, are expensive and logistical challenges, as they require multiple sessions with highly qualified staff. Regional lack of centres that can provide such programs as well as limited mobility of patients are challenging for such programs. Here, risk calculation tools with disease management functions embedded into smart phone applications can be a viable alternative. Such an approach is highly promising, since according to some reports 90% of the stroke risk can be explained by 10 risk factors, thus optimal management of a few risk factors could reduce the stroke risk significantly-.

In the acute phase, most approaches so far targeted on a single type of input, neuroimaging, clinical data or scores. A few authors combined features extracted from imaging with clinical features. All in all, the achieved AUC and/or accuracy ranged between 0.7 and 0.8. We can support these values by internal – yet unpublished data – where we achieved an accuracy of over 80% in a cohort of 1200 acute stroke patients using purely clinical data. We can also corroborate the importance of age and NIHSS as predictors, which were the two most influential features in our own analysis. To our knowledge only very few works have ever attempted to use pure imaging features for the prediction of stroke outcome (see above). A reason here was the lack of proper methodologies to extract relevant features directly from the images. Mostly hand-crafted features were used so far like scores or the infarct volume. Here, new techniques – like auto-encoder manifold learning– have the potential to extract features directly from images that can be used together with clinical features for improved predictions. Also, in stroke, the pathophysiology is diverse. To achieve precision medicine, different data has to be evaluated including neuroimaging and clinical data. Thus, a logical next step is the combination of available features from clinical and imaging sources with bio-physiological modelling, i.e. hybrid modelling. Taken together, the availability of both bio-physiological models as well as established machine learning tools in stroke calls for the development of hybrid models to predict the outcome after stroke. In PRECISE4Q we will use such models which will be a big step towards the achievement of true precision medicine in stroke.

The secondary prevention of stroke includes strategies used to reduce the risk of stroke recurrence among patients who had previously presented with a stroke or TIA. Management strategies, which should be specific to the underlying aetiology, include risk factor modification, the use of antithrombotic or anticoagulant drugs, carotid surgery, and endovascular treatments. The present review provided information on risk factors such as hypertension, diabetes, hyperlipidemia, the role of infection, lifestyle modification (diet, smoking, use of alcohol, physical activity) as well as treatment for atherosclerosis and cardiac abnormalities (e.g. atrial fibrillation) and reperfusion techniques. Besides, numerous studies have investigated the incidence of medical complications after stroke of multiple etiologies in a variety of settings, including inpatient rehabilitation, and after discharge. These studies report varying rates of medical complications. The discrepancies in medical complication rates is likely multifactorial, including different study designs, varying diagnostic criteria for medical complications, pre-selection of complications to be studied and different patient selection methods.

While the majority of stroke survivors return to live in the community, re-integration may be an enormous challenge. The ability to return to an acceptable lifestyle, participating in both social and domestic activities is important for perceived quality of life. Finally, in the present review we examined issues arising following discharge from hospital care or rehabilitation into the community. These include social support, impact of caregiving on informal carers, family functioning, provision of information and education, leisure activities, driving, sexuality and return to work.

7 References

Alaszewski, A., Alaszewski, H., Potter, J., & Penhale, B. (2007). Working after a stroke: survivors' experiences and perceptions of barriers to and facilitators of the return to paid employment. Disability and rehabilitation, 29(24), 1858-1869.

Alexander MP. Stroke rehabilitation outcome. A potential use of predictive variables to establish levels of care. Stroke 1994; 25:128-134.

Al-Shamkhani, W., Ayetey, H. & Lip G. Atrial fibrillation in the Middle East: unmapped, underdiagnosed, undertreated Expert Review of Cardiovascular Therapy
Volume 16, 2018 - Issue 5

Andersen, G., Christensen, D., Kirkevold, M., & Johnsen, S. P. (2012). Post-stroke fatigue and return to work: a 2-year follow-up. Acta Neurol.Scand., 125(4), 248-253

Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. Stroke 2009; 40:2068-2072.

Alvarez, V., Rossetti, A. O., Papavasileiou, V., & Michel, P. (2013a). Acute seizures in acute ischemic stroke: does thrombolysis have a role to play? Journal of Neurology, 260(1), 55-61.

Asadi H, Dowling R, Yan B, Mitchell P (2014) Machine Learning for Outcome Prediction of Acute Ischemic Stroke Post Intra-Arterial Therapy. PLoS ONE 9(2): e88225. doi:10.1371/journal.pone.0088225

Barnsley, L., McCluskey, A., & Middleton, S. (2012). What people say about travelling outdoors after their stroke: a qualitative study. Australian Occupational Therapy Journal, 59(1), 71-78.

Barrett, J. A. (2002). Bladder and bowel problems after stroke. Reviews in Clinical Gerontology, 12(3), 253-267.

Beaupre, G. S., & Lew, H. L. (2006). Bone-density changes after stroke. Am.J.Phys.Med.Rehabil., 85(5), 464-472.

Béjot, Y., Bailly, H., Durier, J. and Giroud, M. “Epidemiology of stroke in Europe and trends for the 21st century,” Presse Médicale, vol. 45, no. 12, Part 2, pp. e391–e398, Dec. 2016.

Belanger, L., Bolduc, M., & Noel, M. (1988). Relative importance of after-effects, environment and socio-economic factors on the social integration of stroke victims. Int.J.Rehabil.Res., 11(3), 251-260.

Bentley P., Ganesalingam J, Carlton Jones AL, Mahady K, Epton S, Rinne P, Sharma P, Halse O, Mehta A, Rueckert D. Prediction of stroke thrombolysis outcome using CT brain machine learning. Neuroimage Clin. 2014 Mar 30;4:635-40. doi: 10.1016/j.nicl.2014.02.003. eCollection 2014

Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women
Stroke. 2008 Sep; 39(9):2439-43.

Boden-Albala, B., Litwak, E., Elkind, M. S., Rundek, T., & Sacco, R. L. (2005). Social isolation and outcomes post stroke. Neurology, 64(11), 1888-1892.

Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. Circulation research. 2017;120(3):472-495. doi:10.1161/CIRCRESAHA.116.308398

Borschmann, K., Pang, M. Y. C., Bernhardt, J., & Iuliano-Burns, S. (2012). Stepping towards prevention of bone loss after stroke: A systematic review of the skeletal effects of physical activity after stroke. International Journal of Stroke, 7(4), 330-335.

Brandstater, M. E., Roth, E. J., & Siebens, H. C. (1992). Venous thromboembolism in stroke: literature review and implications for clinical practice. Arch.Phys.Med.Rehabil., 73(5-S), S379-S391.

Brittain, K. R., Perry, S. I., Peet, S. M., Shaw, C., Dallosso, H., Assassa, R. P., Williams, K., Jagger, C., Potter, J. F., & Castleden, C. M. (2000). Prevalence and impact of urinary symptoms among community-dwelling stroke survivors. Stroke, 31(4), 886-891.

Brittain, K., Perry, S., Shaw, C., Matthews, R., Jagger, C., & Potter, J. (2006). Isolated urinary, faecal, and double incontinence: Prevalence and degree of soiling in stroke survivors. J.Am.Geriatr.Soc., 54(12), 1915-1919.

Buijck, B. I., Zuidema, S. U., Spruit-van Eijk, M., Geurts, A. C., & Koopmans, R. T. (2012). Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study. Int J Geriatr Psychiatry, 27(7), 734- 741

Burn, J., Dennis, M., Bamford, J., Sandercock, P., Wade, D., & Warlow, C. (1997). Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. BMJ., 315(7122), 1582-1587.

Busch, M. A., Coshall, C., Heuschmann, P. U., McKevitt, C., & Wolfe, C. D. (2009). Sociodemographic differences in return to work after stroke: the South London Stroke Register (SLSR). J.Neurol.Neurosurg.Psychiatry, 80(8), 888-893.

Carda, S., Cisari, C., Invernizzi, M., & Bevilacqua, M. (2009). Osteoporosis after stroke: a review of the causes and potential treatments. Cerebrovasc.Dis., 28(2), 191-200.

Cordonnier, C., Henon, H., Derambure, P., Pasquier, F., & Leys, D. (2005). Influence of pre-existing dementia on the risk of post-stroke epileptic seizures. J.Neurol.Neurosurg.Psychiatry, 76(12), 1649-1653.

Cope, C., Reyes, T. M., & Skversky, N. J. (1973). Phlebographic analysis of the incidence of thrombosis in hemiplegia. Radiology, 109(3), 581-584.

Cioni, B., & Meglio, M. (2007). Motor cortex stimulation for chronic non-malignant pain: current state and future prospects. Operative Neuromodulation, 45-49.

Chan, M. L. (2008). Description of a return-to-work occupational therapy programme for stroke rehabilitation in Singapore. Occup Ther Int., 15(2), 87-99.

Chapuisat G.,. Dronne M. A, Grenier E., Hommel M., Gilquin H., and Boissel J. P., A global phenomenological model of ischemic stroke with stress on spreading depressions, Prog. Biophys. Mol. Biol., vol. 97, no. 1, pp. 4–27, May 2008

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure., National High Blood Pressure Education Program Coordinating Committee. JAMA. 2003 May 21; 289(19):2560-72

Choi-Kwon, S., & Kim, J. S. (2011). Poststroke fatigue: an emerging, critical issue in stroke medicine. International Journal of Stroke, 6(4), 328-336.

Chow, C., & Tiwari, A. (2014). Experience of family caregivers of community-dwelling stroke survivors and risk of elder abuse: a qualitative study. Journal of Adult Protection, 16(5), 276-293.

Clark, M. S., & Smith, D. S. (1999b). Psychological correlates of outcome following rehabilitation from stroke. Clin Rehabil., 13(2), 129-140

Cecil, R., Thompson, K., Parahoo, K., & McCaughan, E. (2013). Towards an understanding of the lives of families affected by stroke: a qualitative study of home carers. Journal of Advanced Nursing, 69(8), 1761-1770.

Chow, C., & Tiwari, A. (2014). Experience of family caregivers of community-dwelling stroke survivors and risk of elder abuse: a qualitative study. Journal of Adult Protection, 16(5), 276-293.

Davenport, R. J., Dennis, M. S., Wellwood, I., & Warlow, C. P. (1996). Complications after acute stroke. Stroke, 27(3), 415-420.

De Groot, M. H., Phillips, S. J., & Eskes, G. A. (2003). Fatigue associated with stroke and other neurologic conditions: Implications for stroke rehabilitation. Arch.Phys.Med.Rehabil., 84(11), 1714-1720.

De Brito, C. M. M., Garcia, A. C. F., Takayama, L., Fregni, F., Battistella, L. R., & Pereira, R. M. R. (2013). Bone loss in chronic hemiplegia: A longitudinal cohort study. Journal of Clinical Densitometry, 16(2), 160-167

de los Ríos F, Kleindorfer DO, Khoury J, Broderick JP, Moomaw CJ, Adeoye O, Flaherty ML, Khatri P, Woo D, Alwell K, Eilerman J, Ferioli S, Kissela BM. Trends in substance abuse preceding stroke among young adults: a population-based study. Stroke. 2012 Dec;43(12):3179-83. doi: 10.1161/STROKEAHA.112.667808. Epub 2012 Nov 15

de Oliveira, R. A. A., de Andrade, D. C., Machado, A. G. G., & Teixeira, M. J. (2012). Central poststroke pain: somatosensory abnormalities and the presence of associated myofascial pain syndrome. BMC neurology, 12(1), 89.

Díaz V., Viceconti M.,. Stroetmann V, and Kalra D., Discipulus Roadmap, 2013

Dickmann, U., Voth, E., Schicha, H., Henze, T., Prange, H., & Emrich, D. (1988). Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. Klin.Wochenschr., 66(23), 1182-1183.

Dickson, S., Barbour, R. S., Brady, M., Clark, A. M., & Paton, G. (2008). Patients' experiences of disruptions associated with post-stroke dysarthria. International Journal of Language & Communication Disorders, 43(2), 135-153.

Duncan PW, Lai SM. Stroke recovery. Topics Stroke Rehabil 1997; 4(17):51-58.

Duval V., Chabaud S., Girard P., Cucherat M., Hommel M., and. Boissel J. P, Physiologically Based Model of Acute Ischemic Stroke, J. Cereb. Blood Flow Metab., vol. 22, no. 8, pp. 1010–1018, Aug. 2002.

Dzau V. J. and G. S. Ginsburg, “Realizing the Full Potential of Precision Medicine in Health and Health Care,” JAMA, vol. 316, no. 16, pp. 1659–1660, Oct. 2016.

Eilaghi A., d'Esterre CD, Lee TY, Jakubovic R, Brooks J, Liu RT, Zhang L, Swartz RH, Aviv RI. Toward patient-tailored perfusion thresholds for prediction of stroke outcome. AJNR Am J Neuroradiol. 2014 Mar;35(3):472-7. doi: 10.3174/ajnr.A3740. Epub 2013 Oct 10.

Elkind, MSV Why now? Moving from stroke risk factors to stroke triggers. Current Opinion in Neurology: February 2007 - Volume 20 - Issue 1 - p 51–57 doi: 10.1097/WCO.0b013e328012da75

Erikson, A., Park, M., & Tham, K. (2010). Place integration through daily activities 1 year after stroke. OTJR: Occupation, Participation and Health, 30(2), 68-77.

Eriksson, G., Baum, M. C., Wolf, T. J., & Tabor Connor, L. (2013). Perceived Participation After Stroke: The Influence of Activity Retention, Reintegration, and Perceived Recovery. American Journal of Occupational Therapy, 67(6)

Feng Y., Zhang L., Mo J. Deep Manifold Preserving Autoencoder for Classifying Breast Cancer Histopathological Images. IEEE/ACM Trans Comput Biol Bioinform. 2018 Jul 23. doi: 10.1109/TCBB.2018.2858763. [Epub ahead of print]

Ferrucci L, Bandinelli S, Guralnik JM, Lamponi M, Bertini C, Falchini M, Baroni A. Recovery of functional status after stroke. A post-rehabilitation follow-up study. Stroke 1993; 24:200-205.

Finestone, H. M., Guo, M., O'Hara, P., Greene-Finestone, L., Marshall, S. C., Hunt, L., Biggs, J., & Jessup, A. (2010). Driving and reintegration into the community in patients after stroke. PM.R., 2(6), 497-503.

Feigin, V. L., Barker-Collo, S., Parag, V., Hackett, M. L., Kerse, N., Barber, P. A., Theadom, A., & Krishnamurthi, R. (2012). Prevalence and predictors of 6-month fatigue in patients with ischemic stroke: a population-based stroke incidence study in Auckland, New Zealand, 2002-2003. Stroke, 43(10), 2604-2609

Fisk, G. D., Owsley, C., & Pulley, L. V. (1997). Driving after stroke: driving exposure, advice, and evaluations. Arch.Phys.Med.Rehabil., 78(12), 1338-1345.

Finestone, H. M., Marshall, S. C., Rozenberg, D., Moussa, R. C., Hunt, L., & Greene-Finestone, L. S. (2009). Differences between poststroke drivers and nondrivers: demographic characteristics, medical status, and transportation use. Am J Phys Med Rehabil., 88(11), 904-923

Goldstein, L. B. et al. Guidelines for the Primary Prevention of Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 42, 517–584 (2011)

Gustafsson, L., & Bootle, K. (2013). Client and carer experience of transition home from inpatient stroke rehabilitation. Disability & Rehabilitation, 35(16), 1380-1386.

Gregory, P. C., & Han, E. (2009). Disparities in postacute stroke rehabilitation disposition to acute inpatient rehabilitation vs. home: findings from the North Carolina Hospital Discharge Database. Am J Phys Med Rehabil, 88(2), 100-107.

Garraway WM, Akhtar AJ, Hockey L, Prescott RJ. Management of acute stroke in the elderly: follow-up of a controlled trial. Br Med J 1980; 281:827-829 (b).

Gelber, D. A., Good, D. C., Laven, L. J., & Verhulst, S. J. (1993). Causes of urinary incontinence after acute hemispheric stroke. Stroke, 24(3), 378-382.

Gottlieb, A., Golander, H., Bar-Tal, Y., & Gottlieb, D. (2001). The influence of social support and perceived control on handicap and quality of life after stroke. Aging (Milano.), 13(1), 11-15.

Gabriele, W., & Renate, S. (2009). Work loss following stroke. Disability & Rehabilitation, 31(18), 1487-1493.

Glozier, N., Hackett, M. L., Parag, V., & Anderson, C. S. (2008). The influence of psychiatric morbidity on return to paid work after stroke in younger adults: the Auckland Regional Community Stroke (ARCOS) Study, 2002 to 2003. Stroke., 39(5), 1526-1532.

Grant, J. S., Weaver, M., Elliott, T. R., Bartolucci, A. R., & Newman, G. J. (2004c). Sociodemographic, physical and psychosocial factors associated with depressive behaviour in family caregivers of stroke survivors in the acute care phase. Brain Inj., 18(8), 797-809.

Grawburg, M., Howe, T., Worrall, L., & Scarinci, N. (2013). Third-party disability in family members of people with aphasia: A systematic review. Disability and rehabilitation, 35(16), 1324-1341

Haast, R. A., Gustafson, D. R. & Kiliaan, A. J. Sex Differences in Stroke. J. Cereb. Blood Flow Metab. 32, 2100–2107 (2012)

Hackett, M. L., Glozier, N., Jan, S., & Lindley, R. (2012). Returning to paid employment after stroke: the Psychosocial Outcomes In StrokE (POISE) cohort study. PLoS ONE [Electronic Resource], 7(7)

Han, B., & Haley, W. E. (1999). Family caregiving for patients with stroke. Review and analysis. Stroke, 30(7), 1478-1485

Hand PJ, Wardlaw JM, Rivers CS, Armitage PA, Bastin ME, Lindley RI, Dennis MS. MR diffusion-weighted imaging and outcome prediction after ischemic stroke. Neurology. 2006 Apr 25;66(8):1159-63. Epub 2006 Mar 8.

Hankey G. J, “Long-Term Outcome after Ischaemic Stroke/Transient Ischaemic Attack,” Cerebrovasc. Dis., vol. 16, no. Suppl. 1, pp. 14–19, 2003.

Hankey GJ. B vitamins for stroke prevention. Stroke Vasc Neurol. 2018 Jun 6;3(2):51-58. doi: 10.1136/svn-2018-000156. eCollection 2018 Jun

Hannerz, H., Ferm, L., Poulsen, O. M., Pedersen, B. H., & Andersen, L. L. (2012). Enterprise size and return to work after stroke. J Occup Rehabil, 22(4), 456-461

Hansson, P. (2004). Post-stroke pain case study: clinical characteristics, therapeutic options and longterm follow-up. Eur.J.Neurol., 11 Suppl 1, 22-30.

Hamidou, B., Aboa-Eboulé, C., Durier, J., Jacquin, A., Lemesle-Martin, M., Giroud, M., & Béjot, Y. (2013). Prognostic value of early epileptic seizures on mortality and functional disability in acute stroke: The Dijon Stroke Registry (1985-2010). Journal of Neurology, 260(4), 1043-1051.

Harari, D., Coshall, C., Rudd, A. G., & Wolfe, C. D. (2003). New-onset fecal incontinence after stroke: prevalence, natural history, risk factors, and impact. Stroke, 34(1), 144-150.

Harari, D., Norton, C., Lockwood, L., & Swift, C. (2004). Treatment of constipation and fecal incontinence in stroke patients: randomized controlled trial. Stroke, 35(11), 2549-2555.

Harvey, R. L., Lovell, L. L., Belanger, N., & Roth, E. J. (2004). The effectiveness of anticoagulant and antiplatelet agents in preventing venous thromboembolism during stroke rehabilitation: a historical cohort study. Arch.Phys.Med.Rehabil., 85(7), 1070-1075.

Haslam, C., Holme, A., Haslam, S. A., Iyer, A., Jetten, J., & Williams, W. H. (2008). Maintaining group memberships: social identity continuity predicts well-being after stroke. Neuropsychol.Rehabil., 18(5-6), 671-691.

Henry, J. L., Lalloo, C., & Yashpal, K. (2008). Central poststroke pain: an abstruse outcome. Pain Research and Management, 13(1), 41-49.

Hoang, C. L., Salle, J. Y., Mandigout, S., Hamonet, J., Macian-Montoro, F., & Daviet, J. C. (2012). Physical factors associated with fatigue after stroke: an exploratory study. Top.Stroke Rehabil., 19(5), 369-376

Hilari, K., Northcott, S., Roy, P., Marshall, J., Wiggins, R. D., Chataway, J., & Ames, D. (2010). Psychological distress after stroke and aphasia: the first six months. Clin Rehabil., 24(2), 181-190.

Hinman J. D. et al., Principles of precision medicine in stroke, J. Neurol. Neurosurg. Psychiatry, vol. 88, no. 1, pp. 54–61, Jan. 2017.

Itoh, Y., Yamada, S., Konoeda, F., Koizumi, K., Nagata, H., Oya, M., & Suzuki, N. (2013). Burden of overactive bladder symptom on quality of life in stroke patients. Neurourology & Urodynamics, 32(5), 428-434.

Ifejika-Jones, N. L., Peng, H., Noser, E. A., Francisco, G. E., & Grotta, J. C. (2013). Hospital-acquired symptomatic urinary tract infection in patients admitted to an academic stroke center affects discharge disposition. Pm & R, 5(1), 9-15.

Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: The Copenhagen Stroke Study. Arch Phys Med Rehabil 1995; 76:27-32 (a).

Jaracz, K., & Kozubski, W. (2003). Quality of life in stroke patients. Acta Neurol.Scand., 107(5), 324-329.

Jean, F. A., Swendsen, J. D., Sibon, I., Feher, K., & Husky, M. (2013). Daily life behaviors and depression risk following stroke: a preliminary study using ecological momentary assessment. J Geriatr Psychiatry Neurol, 26(3), 138-143

Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. Arch Phys Med Rehabil 1995; 76:406-412 (c).

Katayama, Y., Fukaya, C., & Yamamoto, T. (1998). Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J.Neurosurg., 89(4), 585-591.

Kauranen, T., Turunen, K., Laari, S., Mustanoja, S., Baumann, P., & Poutiainen, E. (2012). The severity of cognitive deficits predicts return to work after a first-ever ischaemic stroke. Journal of Neurology, Neurosurgery and Psychiatry, 84(3), 316-321.

Kelly-Hayes M, Wold PA, Kase CS, Gresham GE, Kannell WB, D'Agostino RB. Time course of functional recovery after stroke: The Framingham Study. J Neurol Rehabil 1989; 3:65-70.

Kelly-Hayes, M., Wolf, P. A., Kannel, W. B., Sytkowski, P., D'Agostino, R. B., & Gresham, G. E. (1988). Factors influencing survival and need for institutionalization following stroke: the Framingham Study. Arch Phys Med Rehabil, 69(6), 415-418.

Kim W and Kim E. Heart Failure as a Risk Factor for Stroke. J Stroke. 2018 Jan;20(1):33-45. doi: 10.5853/jos.2017.02810. Epub 2018 Jan 31.

Kim, P., Warren, S., Madill, H., & Hadley, M. (1999). Quality of life of stroke survivors. Qual.Life Res., 8(4), 293-301.

Kim, M., Cho, K., & Lee, W. H. (2014). Community Walking Training Program Improves Walking Function and Social Participation in Chronic Stroke Patients. Tohoku Journal of Experimental Medicine, 234(4), 281-286.

Kim J, Thrift A, Nelson M, Bladin C, Cadilhac D. Personalized medicine and stroke prevention: where are we? Volume 2015:11 Pages 601—611 Vascular Health and Risk Management Journal

Kips J.G., Segersa P., Van Bortel L.M. Identifying the vulnerable plaque: A review of invasive and non-invasive imaging modalities Artery Research Volume 2, Issue 1, February 2008, Pages 21-34

Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, Gebel J, Shukla R, Broderick JP Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study
Diabetes Care. 2005 Feb; 28(2):355-9

Kitisomprayoonkul, W., Sungkapo, P., Taveemanoon, S., & Chaiwanichsiri, D. (2010). Medical complications during inpatient stroke rehabilitation in Thailand: a prospective study. J.Med.Assoc.Thai., 93(5), 594-600.

Klit, H., Finnerup, N. B., & Jensen, T. S. (2009). Central post-stroke pain: clinical characteristics, pathophysiology, and management. The Lancet Neurology, 8(9), 857-868

Kotila, M., & Waltimo, O. (1992). Epilepsy after stroke. Epilepsia., 33(3), 495-498.

Kovindha, A., Wattanapan, P., Dejpratham, P., Permsirivanich, W., & Kuptniratsaikul, V. (2009). Prevalence of incontinence in patients after stroke during rehabilitation: a multi-centre study. J.Rehabil.Med., 41(6), 489-491.

Ko, J. Y., Aycock, D. M., & Clark, P. C. (2007). A comparison of working versus nonworking family caregivers of stroke survivors. J.Neurosci.Nurs., 39(4), 217-225.

Kubina, L. A., Dubouloz, C. J., Davis, C. G., Kessler, D., & Egan, M. Y. (2013). The process of re-engagement in personally valued activities during the two years following stroke. Disability & Rehabilitation, 35(3), 236-243.

Kugler C, Altenhoner T, Lochner P, Ferbert A; Hessian Stroke Data Bank Study Group ASH. Does age influence early recovery from ischemic stroke? A study from the Hessian Stroke Data Bank. J Neurol 2003; 250(6):676-681.

Langhorne, P., Lewsey, J. D., Jhund, P. S., Gillies, M., Chalmers, J. W., Redpath, A., Briggs, A., Walters, M., Capewell, S., McMurray, J. J., & MacIntyre, K. (2010a). Estimating the impact of stroke unit care in a whole population: an epidemiological study using routine data. J Neurol Neurosurg Psychiatry, 81(12), 1301-1305.

Lazorthes, Y., Sol, J., Fowo, S., Roux, F., & Verdie, J. (2007). Motor cortex stimulation for neuropathic pain. Operative Neuromodulation, 37-44.

Labovitz, D. L., Hauser, W. A., & Sacco, R. L. (2001). Prevalence and predictors of early seizure and status epilepticus after first stroke. Neurology, 57(2), 200-206.

Le Dorze, G., Salois-Bellerose, É., Alepins, M., Croteau, C., & Hallé, M.-C. (2014). A description of the personal and environmental determinants of participation several years post-stroke according to the views of people who have aphasia. Aphasiology, 28(4), 421-439.

Lundengård K.et al., Mechanistic Mathematical Modeling Tests Hypotheses of the Neurovascular Coupling in fMRI, PLoS Comput. Biol., vol. 12, no. 6, Jun. 2016

Maaijwee, N. A. M. M., Rutten-Jacobs, L. C. A., Arntz, R. M., Schaapsmeerders, P., Schoonderwaldt, H. C., van Dijk, E. J., & de Leeuw, F.-E. (2014). Long-term increased risk of unemployment after young stroke: A long-term follow-up study. Neurology, 83(13), 1132-1138.

Mackenzie, A. E., & Chang, A. M. (2002). Predictors of quality of life following stroke. Disabil.Rehabil., 24(5), 259-265.

Mackenzie, C., & Paton, G. (2003). Resumption of driving with aphasia following stroke. Aphasiology, 17(2), 107-122.

Mamoshina, A. Vieira, E. Putin, and A. Zhavoronkov, Applications of Deep Learning in Biomedicine, Mol. Pharm., vol. 13, no. 5, pp. 1445–1454, May 2016.

Mayo, N. E., Wood-Dauphinee, S., Cote, R., Durcan, L., & Carlton, J. (2002). Activity, participation, and quality of life 6 months poststroke. Arch.Phys.Med.Rehabil., 83(8), 1035-1042.

Mead, G. E., Graham, C., Dorman, P., Bruins, S. K., Lewis, S. C., Dennis, M. S., & Sandercock, P. A. (2011). Fatigue after stroke: baseline predictors and influence on survival. Analysis of data from UK patients recruited in the International Stroke Trial. PLoS.One., 6(3)

Meairs S. et al., "Stroke Research Priorities for the Next Decade – A Representative View of the European Scientific Community," Cerebrovasc. Dis., vol. 22, no. 2–3, pp. 75–82, 2006.

Medin, J., Barajas, J., & Ekberg, K. (2006). Stroke patients' experiences of return to work. Disabil.Rehabil., 28(17), 1051-1060.

McLennon, S. M., Bakas, T., Jessup, N. M., Habermann, B., & Weaver, M. T. (2014). Task difficulty and life changes among stroke family caregivers: relationship to depressive symptoms. Archives of Physical Medicine & Rehabilitation, 95(12), 2484-2490.

McLean, D. E. (2004). Medical complications experienced by a cohort of stroke survivors during inpatient, tertiary-level stroke rehabilitation. Arch.Phys.Med.Rehabil., 85(3), 466 469.

Meyer, M. J., Pereira, S., McClure, A., Teasell, R., Thind, A., Koval, J., Richardson, M., & Speechley, M. (2015). A systematic review of studies reporting multivariable models to predict functional outcomes after post-stroke inpatient rehabilitation. Disabil Rehabil, 37(15), 1316-1323

Mehdi, Z., Birns, J., & Bhalla, A. (2013). Post-stroke urinary incontinence. International Journal of Clinical Practice, 67(11), 1128-1137.

Miyamoto, A. T., & Miller, L. S. (1980). Pulmonary embolism in stroke: prevention by early heparinization of venous thrombosis detected by iodine-125 fibrinogen leg scans. Arch.Phys.Med.Rehabil., 61(12), 584-587

Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study Arch Intern Med. 2006 Jan 9; 166(1):106-11.

Niemi, M. L., Laaksonen, R., Kotila, M., & Waltimo, O. (1988). Quality of life 4 years after stroke. Stroke, 19(9), 1101-1107

Noorani, H. Z., Brady, B. K., McGahan, L., Teasell, R., Skidmore, B., & Doherty, T. (2003). Stroke rehabilitation services: Systematic reviews of the clinical and economic evidence.

Ntaios G., Gioulekas F., Papavasileiou V., Strbian D., Michel P., ASTRAL, DRAGON and SEDAN scores predict stroke outcome more accurately than physicians. European Journal of Neurology, Volume23, Issue11 November 2016 Pages 1651-1657

O'Connell, C., Cassidy, A., O'Neill, D., & Moss, H. (2013). The aesthetic and cultural pursuits of patients with stroke. Journal of Stroke & Cerebrovascular Diseases, 22(8)

O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010 Jul 10;376(9735):112-23. doi: 10.1016/S0140-6736(10)60834-3. Epub 2010 Jun 17.

O'Rourke, K., & Walsh, C. (2010). Impact of stroke units on mortality: a Bayesian analysis. Eur J Neurol, 17(2), 247-251.

Palmer, S., & Glass, T. A. (2003). Family Function and Stroke Recovery: A Review. Rehabilitation Psychology, 48(4), 255.

Pang, M. Y. C., Zhang, M., Li, L. S. W., & Jones, A. Y. M. (2013). Changes in bone density and geometry of the radius in chronic stroke and related factors: A one-year prospective study. Journal of Musculoskeletal Neuronal Interactions, 13(1), 77-88.

Paolucci, S., Silvestri, G., Lubich, S., Pratesi, L., Traballesi, M., & Gigli, G. L. (1997). Poststroke late seizures and their role in rehabilitation of inpatients. Epilepsia, 38(3), 266-270.

Parsons M.W., Pepper EM, Chan V, Siddique S, Rajaratnam S, Bateman GA, Levi CR. Perfusion computed tomography: prediction of final infarct extent and stroke outcome. Ann Neurol. 2005 Nov;58(5):672-9.

Patomella, A. H., Kottorp, A., & Tham, K. (2008). Awareness of driving disability in people with stroke tested in a simulator. Scandinavian Journal of Occupational Therapy, 15(3), 184-192.

Pizzi, A., Falsini, C., Martini, M., Rossetti, M. A., Verdesca, S., & Tosto, A. (2014). Urinary incontinence after ischemic stroke: clinical and urodynamic studies. Neurourology & Urodynamics, 33(4), 420-425.

Pongmoragot, J., Rabinstein, A. A., Nilanont, Y., Swartz, R. H., Zhou, L., Saposnik, G., Investigators of Registry of Canadian Stroke, N., & University of Toronto Stroke Program for Stroke Outcomes Research Canada Working, G. (2013). Pulmonary embolism in ischemic stroke: clinical presentation, risk factors, and outcome. Journal of the American Heart Association, 2(6)

Powers, W.J., Rabinstein, A. A., Ackerson, T., Adevoe, O.M., Bambakidis N.C., Becker K., Summary of acute ischemic stroke guidelines 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Pereira, S., Foley, N., Salter, K., McClure, J. A., Meyer, M., Brown, J., Speechley, M., & Teasell, R. (2014). Discharge destination of individuals with severe stroke undergoing rehabilitation: a predictive model. Disabil Rehabil, 36(9), 727-731.

Pereira, S., Graham, J. R., Shahabaz, A., Salter, K., Foley, N., Meyer, M., & Teasell, R. (2012). Rehabilitation of individuals with severe stroke: synthesis of best evidence and challenges in implementation. Top Stroke Rehabil, 19(2), 122-131.

Pfeffer, M. M., & Reding, M. J. (1998). Stroke rehabilitation. In R. B. Lazar (Ed.), Principles of Neurological Rehabilitation (pp. 105-119). New York: McGraw Hill.

Rajpurkar P. et al., CheXNet: Radiologist-Level Pneumonia Detection on Chest X-Rays with Deep Learning, ArXiv171105225 Cs Stat, Nov. 2017

Robain, G., Chennevelle, J. M., Petit, F., & Piera, J. B. (2002). [Incidence of constipation after recent vascular hemiplegia: a prospective cohort of 152 patients]. Rev.Neurol.(Paris), 158(5 Pt 1), 589-592

Richards, L. G., Stiers, W., Zorowitz, R. D., American Heart Association Stroke Council, C. o. C., Stroke Nursing, C. o. C. C., Council on Quality of, C., & Outcomes, R. (2016). Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke, 47(6).

Robison, J., Wiles, R., Ellis-Hill, C., McPherson, K., Hyndman, D., & Ashburn, A. (2009). Resuming previously valued activities post-stroke: who or what helps? Disability and rehabilitation, 31(19), 1555-1566.

Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: Heart disease and stroke statistics--2012 update: A report from the american heart association. Circulation. 2012;125:188–197. [PubMed]

Rost, N. S., Bottle, A., Lee, J. M., Randall, M., Middleton, S., Shaw, L., Thijs, V., Rinkel, G. J., Hemmen, T. M., & Global Comparators Stroke, G. c. (2016). Stroke Severity Is a Crucial Predictor of Outcome: An International Prospective Validation Study. J Am Heart Assoc, 5(1)

Roth, E. J., Lovell, L., Harvey, R. L., Heinemann, A. W., Semik, P., & Diaz, S. (2001). Incidence of and risk factors for medical complications during stroke rehabilitation. Stroke, 32(2), 523-529.

Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension Lancet. 2010 Mar 13; 375(9718):895-905.

Salter, K., Jutai, J. W., Teasell, R., Foley, N. C., Bitensky, J., & Bayley, M. (2005). Issues for selection of outcome measures in stroke rehabilitation: ICF activity. Disability & Rehabilitation, 27(6), 315-340.

Saraiva JFK. Stroke Prevention with Oral Anticoagulants: Summary of the Evidence and Efficacy Measures as an Aid to Treatment Choices. Cardiol Ther. 2018 Jun;7(1):15-24. doi: 10.1007/s40119-018-0106-1. Epub 2018 Feb 27

Scott, C. A., Rapport, L. J., Coleman Bryer, R., Griffen, J., Hanks, R., & McKay, C. (2009). Self-assessment of driving ability and the decision to resume driving following stroke. Journal of Clinical and Experimental Neuropsychology, 31(3), 353-362.

Schepers, V. P., Visser-Meily, A. M., Ketelaar, M., & Lindeman, E. (2005). Prediction of social activity 1 year poststroke. Arch.Phys.Med.Rehabil., 86(7), 1472-1476.

Schnitzer, T. J., Harvey, R. L., Nack, S. H., Supanwanid, P., Maskala-Streff, L., & Roth, E. (2012). Bone Mineral Density in Patients With Stroke: Relationship With Motor Impairment and Functional Mobility. Topics in stroke rehabilitation, 19(5), 436-443.

Seenan, P., Long, M., & Langhorne, P. (2007). Stroke units in their natural habitat: systematic review of observational studies. Stroke, 38(6), 1886-1892.

Shao, J., Zhang, Q., Lin, T., Shen, J., & Li, D. (2014). Well-being of elderly stroke survivors in Chinese communities: mediating effects of meaning in life. Aging & Mental Health, 18(4), 435-443.

Simon, C., Kumar, S., & Kendrick, T. (2009). Cohort study of informal carers of first-time stroke survivors: profile of health and social changes in the first year of caregiving. Soc.Sci.Med., 69(3), 404-410.

Sioson, E. R., Crowe, W. E., & Dawson, N. V. (1988). Occult proximal deep vein thrombosis: its prevalence among patients admitted to a rehabilitation hospital. Arch.Phys.Med.Rehabil., 69(3 Pt 1), 183-185.

Skaf, E., Stein, P. D., Beemath, A., Sanchez, J., Bustamante, M. A., & Olson, R. E. (2005). Venous thromboembolism in patients with ischemic and hemorrhagic stroke. Am.J.Cardiol., 96(12), 1731-1733.

Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. J Neurol Neurosurg Psychiatry 1983; 46:5-8.

Smith, Lawrence, M., Kerr, S. M., Langhorne, P., & Lees, K. R. (2004). Informal carers' experience of caring for stroke survivors. J.Adv.Nurs., 46(3), 235-244.

Stapleton, T., Connolly, D., & O'Neill, D. (2012). Exploring the relationship between self-awareness of driving efficacy and that of a proxy when determining fitness to drive after stroke. Aust Occup Ther J, 59(1), 63-70.

Sreedharan, S. E., Unnikrishnan, J. P., Amal, M. G., Shibi, B. S., Sarma, S., & Sylaja, P. N. (2013). Employment status, social function decline and caregiver burden among stroke survivors. A South Indian study. Journal of the Neurological Sciences, 332(1-2), 97-101.

Stineman, M. G., Fiedler, R. C., Granger, C. V., & Maislin, G. (1998). Functional task benchmarks for stroke rehabilitation. Arch Phys Med Rehabil, 79(5), 497-504.

Stineman, M. G., & Granger, C. V. (1998). Outcome, efficiency, and time-trend pattern analyses for stroke rehabilitation. Am J Phys Med Rehabil, 77(3), 193-201

Stineman MG, Granger CV. Outcome, efficiency, and time-trend pattern analyses for stroke rehabilitation. Am J Phys Med Rehabil 1998; 77:193-201.

Strbian D., Seiffge D.J., Breuer L., Numminen H., Michel P, Meretoja A, Coote S, Bordet R, Obach V, Weder B, Jung S, Caso V, Curtze S, Ollikainen J, Lyrer PA, Eskandari A, Mattle HP, Chamorro A, Leys D, Bladin C, Davis SM, Köhrmann M, Engelter ST, Tatlisumak T. Validation of the DRAGON score in 12 stroke centers in anterior and posterior circulation. Stroke. 2013 Oct;44(10):2718-21. doi: 10.1161/STROKEAHA.113.002033. Epub 2013 Aug 8.

Tang, W.-K., Lau, C. G., Mok, V., Ungvari, G. S., & Wong, K.-S. (2015). Insomnia and health-related quality of life in stroke. Topics in stroke rehabilitation, 22(3), 201.

Tanaka, H., Toyonaga, T., & Hashimoto, H. (2014). Functional and occupational characteristics predictive of a return to work within 18 months after stroke in Japan: implications for rehabilitation. International Archives of Occupational & Environmental Health, 87(4), 445-453.

Tan, K. M., O'Driscoll, A., & O'Neill, D. (2011). Factors affecting return to driving post-stroke. Ir.J.Med.Sci., 180(1), 41-45.

Terent, A., Asplund, K., Farahmand, B., Henriksson, K. M., Norrving, B., Stegmayr, B., Wester, P. O., Asberg, K. H., & Asberg, S. (2009). Stroke unit care revisited: who benefits the most? A cohort study of 105,043 patients in Riks-Stroke, the Swedish Stroke Register. J Neurol Neurosurg Psychiatry, 80(8), 881-887.

Trygged, S., Ahacic, K., & Kareholt, I. (2011). Income and education as predictors of return to working life among younger stroke patients. BMC.Public Health, 11, 742.

Van Eijsden, H. M., Van De Port, I. G. L., Visser-Meily, J. M. A., & Kwakkel, G. (2012). Poststroke fatigue: Who is at risk for an increase in fatigue? Stroke Research and Treatment

Vestling, M., Tufvesson, B., & Iwarsson, S. (2003). Indicators for return to work after stroke and the importance of work for subjective well-being and life satisfaction. J.Rehabil.Med., 35(3), 127-131.

Vora N.A., Shook SJ, Schumacher HC, Tievsky AL, Albers GW, Wechsler LR, Gupta R. A 5-item scale to predict stroke outcome after cortical middle cerebral artery territory infarction: validation from results of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study. Stroke. 2011 Mar;42(3):645-9. doi: 10.1161/STROKEAHA.110.596312. Epub 2011 Jan 27.

Walsh, M. E., Galvin, R., Loughnane, C., Macey, C., & Horgan, N. F. (2015). Factors associated with community reintegration in the first year after stroke: a qualitative meta-synthesis. Disability and Rehabilitation, 37(18), 1599-1608.

Watanabe, Y. (2004). An assessment of osteoporosis in stroke patients on rehabilitation admission. Int J Rehabil Res., 27(2), 163-166.

Wilke, T., Groth,A., Pfannkuche, M., Harks, O., Fuchs, A., Maywald, U. and Krabbe, B. Real life anticoagulation treatment of patients with atrial fibrillation in Germany: extent and causes of anticoagulant under-use. Journal of Thrombosis and Thrombolysis. July 2015, Volume 40, Issue 1, pp 97–107

Wood, J. P., Connelly, D. M., & Maly, M. R. (2010). 'Getting back to real living': a qualitative study of the process of community reintegration after stroke. Clinical Rehabilitation, 24(11), 1045-1056

Ween, J. E., Alexander, M. P., D'Esposito, M., & Roberts, M. (1996). Incontinence after stroke in a rehabilitation setting: outcome associations and predictive factors. Neurology, 47(3), 659-663.

Weimar C , Ziegler A, König IR, Diener HC. Predicting functional outcome and survival after acute ischemic stroke. J Neurol. 2002 Jul;249(7):888-95.

Winge, K., Rasmussen, D., & Werdelin, L. M. (2003). Constipation in neurological diseases. J.Neurol.Neurosurg.Psychiatry, 74(1), 13-19.

Wilson, R. D., & Murray, P. K. (2005). Cost-effectiveness of screening for deep vein thrombosis by ultrasound at admission to stroke rehabilitation. Arch.Phys.Med.Rehabil., 86(10), 1941-1948.

Wiebe, S., & Butler, J. (1998). Longterm Complications in Stroke. Physical Medicine and Rehabilitation: State of the Art Reviews, 12(3).

White, J. H., Miller, B., Magin, P., Attia, J., Sturm, J., & Pollack, M. (2012). Access and participation in the community: a prospective qualitative study of driving post-stroke. Disabil.Rehabil., 34(10), 831-838.

White, J. H., Attia, J., Sturm, J., Carter, G., & Magin, P. (2014). Predictors of depression and anxiety in community dwelling stroke survivors: a cohort study. Disability & Rehabilitation, 36(23), 1975-1982.

Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., Deruyter, F., Eng, J. J., Fisher, B., Harvey, R. L., Lang, C. E., MacKay-Lyons, M., Ottenbacher, K. J., Pugh, S., Reeves, M. J.,

Yong, H; Foody, J ; Linong, J ; Dong, Z ; Wang, Y ¶; Ma, L ‖; Meng, HJ , Shiff, S ; Dayi, H. A Systematic Literature Review of Risk Factors for Stroke in China. Cardiology in Review: March/April 2013 - Volume 21 - Issue 2 - p 77–93 doi: 10.1097/CRD.0b013e3182748d37

Zhang D, Wang G, Joo H. A Systematic Review of Economic Evidence on Community Hypertension Interventions. Am J Prev Med. 2017 Dec;53(6S2):S121-S130. doi: 10.1016/j.amepre.2017.05.008.