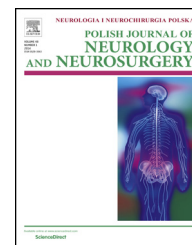


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## Review article

# Consequences of stroke in the light of objective and subjective indices: A review of recent literature



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## ABSTRACT

Despite a significant progress in prevention, treatment and management in the past decades, stroke remains the most common disabling chronic condition in adult population. It may be a source of serious temporary or permanent consequences. These consequences should be recognised and measured for defining and implementation of remedial interventions and for optimum utilisation of health care resources.

The aim of this work was to present sequels of stroke, taking into account objective and subjective indices, as documented in the recent literature of the subject. Selected data on mortality and survival following stroke were presented, the up-to-date literature was reviewed and register-based prospective studies were presented on quality of life (QoL) in post-stroke patients. Systematic reviews and meta-analyses of randomised controlled trials (RCTs) were summed up, related to efficacy of interventions aimed at improving QoL of the patients. Moreover, the studies were reviewed on burden and QoL experienced by caregivers of post-stroke patients and results were summed up of RCT synthesis aimed at reducing the burden and at improving QoL in the caregivers.

The analysed studies indicated that stroke exerts a long-term, negative effect on patients' QoL, promoting a decrease in this measure and burdening a significant proportion of the family caregivers. The applied till now different interventions and programmes targeted at the patients and at their carers analysed in RCTs showed no or modest effects on improving of QoL or reducing the caregiver's burden.

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## 1. Introduction

Worldwide, the absolute number of people with a first-ever stroke increased by 68% in the last decades. Also the number of people who had survived the stroke incidence has increased by 84%. If this trend persists in the year of 2030, 70 million stroke survivors will live in the world [1]. A significant proportion of individuals surviving strokes can expect to face severe health consequences and varying forms of limitations ranging from a shortened life span through temporal or permanent neurological and functional impairments, to limitations in role fulfillment and social participation. Recognition and measurement of these consequences are important both from the theoretical and practical point of view. Especially it may be useful for defining and implementation of preventive, remedial and supportive interventions as well as for optimum allocation of health care resources.

The purpose of this paper was to present multi-dimensional sequelae of stroke, taking into account objective and subjective indices, in the light of recent literature of the subject.

## 2. Sequelae of stroke in the light of objective indices

Traditionally, consequences of stroke and treatment outcomes were evaluated mainly using mortality rates, survival coefficients and indices of neurological or functional deficits. In the last decades stroke mortality rates have declined in several countries, predominantly as an effect of primary and secondary prevention, partly as a result of improved acute stroke care and management. The recently published epidemiological data indicate that between 1990 and 2010 stroke mortality rates fell significantly, on the average by 25%/100 000 globally [1]. In Poland with the unchanged incidence rate, 30 day mortality in first-ever stroke decreased from 43% in 1991/1992 to 14.9% in 2005 and one-year mortality – from 59.7% to 33.1% [2]. These data correspond to indices of survival, according to which one year after stroke 64% patients remain alive, with 43% after 5 years and 24% after 10 years [3].

Despite the proven efficacy of rehabilitation, indices linked to the post-stroke disability have persisted at a similar level for many years [4]. The functional limitations, usually measured using Barthel Index or Rankin Scale affect around 60% of the patients, with the mean of more than ten to 25–30% patients requiring assistance of other person [5,6]. In general population matched for age and co-morbidities this proportion ranges from 5% to 14.5% [6]. Considering types of self-care activities the most pronounced need for care compared with controls pertains transfers in the bathroom [Odds Ratio (OR) = 5.0], dressing (OR = 4.7) and walking out-doors (OR = 5.8) [7]. The number of persons who require care decreases with duration of the post-stroke time. Shortly after stroke a severe or moderate disability can be noted in around 45% of patients, 10 years later in around 11% of patients [3]. It should be mentioned, however, that 10 years after stroke 1 person survives per every 5 affected individuals, on average [8].

Nevertheless, the absolute number of patients who require help in daily life activities will continue to rise. This prognosis

reflects the current facts and demographic trends pointing to senescence of population, and is thought to be the result of the high risk of a recurrent stroke and the linked to it new disability as well as the aforementioned significant reduction in early post-stroke mortality [9].

## 3. Sequels of stroke in the light of subjective indices

### 3.1. Quality of life in post-stroke patients

Beginning at 1990s the traditional, objective indices of stroke consequences and the treatment outcomes have begun to be supplemented by subjective indicators, presenting a patient's perspective and defined as the Patient Reported Outcome (PRO). Among these indices the principal place takes QoL. Its evaluation reflects the result of patient's coping with the disease in various domains of life, perception of symptoms, effects of adjustment or transgressing limitations induced by the illness. The processes cause that the subjective evaluation may significantly differ from the objective one. It was shown that as many as 40% of patients after stroke, participating in randomised clinical trials (RCTs) and manifesting good outcome according to objective indices, suffer from poor QoL [10].

From the beginning, studies on QoL, related to the evaluation of a natural course of diseases and/or treatment outcomes were associated with considerations pertaining a definition of QoL [11]. Several theoretical concepts appeared and subsequently, attempts of their classification. In 2011 the Cochrane Collaboration presented and recommended three main categories of QoL used in clinical trials which took into account: (1) health-related quality of life (HRQoL) covering those aspects of life which undergo significant influence of physical and mental health, (2) quality of life per se including all aspects of life, for example, how an individual lives, where he/she lives and how he/she enjoys in life, (3) quality of life as a subjective bodily and emotional wellbeing [12].

Similar to the problem of definition, following a variability period, a group of tools was defined for evaluation of QoL after stroke, currently in use by most of investigators [13,14]. The tools encompass non-specific scales: SF-36, SF-12 and Euro-QoL-5D, as well as specific scales: Stroke Impact Scale (SIS), Stroke-Specific Quality of Life Scale (SS-QoL) and Stroke Adapted Sickness Impact Profile (SA SIP-30) [15]. For some of the tools, including EuroQoL-5D and SF-36, Health Utility Scores (HUS) were worked out which define the number of years in life, with quality adjusted life years (QALY), for which the scope ranges from HUS = 1 (perfect health), through HUS = 0 (a condition equivalent to being dead according to healthy people) to HUS < 0 (condition that healthy people consider worse than being dead) [16].

First studies on QoL after stroke were mainly cross-sectional. There were few prospective observations but they covered a short period of time (few months to two years) and included relatively small samples [17,18]. These studies showed that stroke causes decrease in QoL and impairs most aspects of patients' functioning. Stroke severity, post-stroke disability and depression, female gender, advanced age and

lack of social support were recognised as the most important determinants of poor life quality [19]. Publications of that period frequently postulated a need for long-term studies, possibly repeated in time, so that QoL could be monitored at all stages of recovery and predictive factors could be verified from a longer perspective of time [17].

In response to that, in 2000s studies began to appear, which presented results of long term research, conducted mainly on the basis of stroke registers, including investigations of “real-time” type, i.e. covering multi-year observation of the patients, beginning at their first stroke through the post-stroke years of life. The studies encompassed or encompass (in cases of continued projects) large groups of few hundred or even few thousand patients. Also, more numerous results of multi-centre RCTs began to appear in which QoL has been an important end-point in the evaluation of clinical efficacy of treatment, rehabilitation or stroke care management [20]. In 2007 an International Stroke Trials Archive (VISTA) was formed which made available for the authors rough, anonymous data of completed RCTs for novel or further detailed exploration, including analysis of life quality [21].

One of the most important longitudinal studies involving QoL assessment is South London Stroke Register (SLSR), targeted at epidemiology, natural course and sequels of stroke, documenting all new first-ever stroke cases in the defined geographical region beginning at 1995. In the study QoL has been evaluated using SF-12. The patients have been examined in months 3rd and 12th after the stroke onset and, subsequently, every year in consecutive post-stroke life [3]. The till now 17-year history demonstrated that QoL within its physical aspects was more or less stable with tendency for significant deterioration in the recent three years of observation. In mental domains the results were similar although a more pronounced fluctuation in time was noted. In both domains patients' QoL was lower (37 and 46 pts, respectively) than in a matched normal population (50 pts., SD = 10) [22].

Another prospective investigation is The Reasons for Geographic and Racial Differences in Stroke (REGARDS), the ongoing study conducted in USA, focused on incidence and analysis of risk factors for stroke and coronary heart disease among 45-year old or older individuals, randomly selected from American population in the years of 2003–2007. An ancillary project to the REGARDS is Caring for Adults Recovering from the Effects of Stroke (CARES). This study examines the long-term psychosocial impact of stroke on a subgroup of stroke survivors registered in REGARDS and on matched stroke-free controls. Furthermore the CARES study allows to compare QoL from the pre-stroke to that of post-stroke period. Similarly to SLSR, QoL has been evaluated using SF-12, with the norm-based score, setting for the general population mean to 50 and the SD to 10. It was shown that QoL in the patients evaluated 9–12 months after the acute hospitalisation deteriorated significantly both in the physical and mental domains, as compared to pre-stroke period and it amounted, respectively, to 46.5 vs. 40.3 and 54.8 vs. 53.4 [23].

The subsequent large prospective investigation is the New Zealand stroke register, entitled the Auckland Regional Community Stroke Study (ARCOS), conducted till now in four consecutive population-based researches covering the years of 1981–1982 (ARCOS I), 1991–1992 (ARCOS II), 2002–2003 (ARCOS

III) and 2010–2015 (ARCOS IV). ARCOS studies are related to epidemiology, stroke outcome and burden in patients, their family caregivers and society. Quality of life of stroke survivors has been evaluated by SF-36. It was found that QoL of the patients registered in the ARCOS over a period 1991–1992, evaluated 6 years after the stroke onset, deteriorated significantly in all eight subscales of SF-36, as compared to the controls matched for age and sex. In the patients the SF-36 scores ranged from 47 to 84, while in the control group from 62 to 93 [7]. In turn, QoL of the patients registered in the ARCOS study of 1981–1982, examined 21 years later did not differ from the age and sex standardised population norms. However, it should be added that out of 626 patients included, after 21 years only 54 individuals remained alive, and these very long survivors at the inclusion to the study were significantly younger and their post-stroke neurological deficit had been less pronounced as compared to those who died earlier [8]. Apart from quantitative evaluations, the ARCOS IV study has included also qualitative analyses, based on in-depth semi-structured interviews performed at 6, 12, 24 and 36 months after stroke. The authors intend to explore issues related to, i.e., perceived impact of stroke, psychological adaptation changes over time, coping strategies applied in life after stroke. The results should soon be available [24].

Next important investigation is the North East Melbourne Stroke Incidence Study (NEMESIS), aimed at evaluation of epidemiological indices in the years of 1998–1999 in north-eastern region of Melbourne and at a long-term evaluation of stroke sequels in persons registered at the time. Health-related QoL was evaluated using health utility score (HUS) developed for the Assessment of Quality of Life Instrument scale (AQoL) [25]. The HUS was found to remain at a similar level at 2, 5, and 7 years after stroke (HUS = 0.47; 0.50; 0.51, respectively) and it was significantly lower than in general population of 70–75-year old individuals (HUS = 0.75). A very low life quality (HUS  $\leq$  0.1) was experienced by 25% of patients at 2 years since stroke, by 20% after 5 years and 23% after 7 years. For comparison, in general population of a similar age less than 3% of people were found to have AQoL score  $\leq$  0.1 [26]. Extremely low quality of life that may be deemed worse than death (HUS < 0) was expressed by 5.8% of patients at 7 years post-stroke [26–28]. The data were confirmed in the other recent assessment, performed within the Efficacy of Nitric Oxide in Stroke Trial, ENOS, with participation of 2569 patients, covering the first three post-stroke months: HUS < 0 was noted in 12.5% patients [29].

Summing up the above presented results of prospective studies of recent years, it can be said that stroke entails long-term deterioration of health related QoL, both as compared to pre-stroke period and to general population norms. Unfavourable patient-reported outcome is relatively common even several years after stroke. This points to the need for systematic evaluation of the stroke survivors and for a systemic medical and social care not only in the early post-stroke period but also for many years thereafter.

### 3.2. Effectiveness of interventions on improving health-related quality of life following stroke

Among independent variables which determine quality of life in stroke survivors one can distinguish unmodifiable and

**Table 1 – Systematic reviews and meta-analyses evaluating effectiveness of various interventions on health related quality of life in stroke survivors published between 2011 and 2014.**

Authors, date	RCT studies <sup>a</sup>	Intervention	Results	HRQoL measure
1. De Chen et al., 2011 [30]	Metaanalysis 9 studies	Exercises	Total effect size Hedges' <i>g</i> 0.32; 95% CI, 0.12–0.51.	SF-36, SF-12, SIS
2. Graven et al., 2011 [31]	Systematic review 9 studies		Insufficient evidence according BES (<50% studies achieved statistical significance)	SA SIP-30, SIP, AQoL, other
3. Graven et al., 2011 [31]	Systematic reviews 3 studies	Leisure therapy	Moderate evidence according BES	SA SIP-30, SIP, NHP
4. Dorstyn et al., 2014 [32]	4 studies		Statistically and clinically significant effect 1 study	SF-36, GWB
5. Lennon et al., 2013 [33]	Systematic reviews 6 studies	Self management programmes	Significant results in favour of the self-management groups 4 studies	SSQoL, SF-36 SA SIP-30, SIS
6. Graven et al., 2011 [31]	2 studies		Insufficient evidence according BES	
7. Graven et al., 2011 [31]	Systematic review 7 studies	Comprehensive, multidisciplinary outpatient or in-home rehabilitation	Strong evidence according BES	SF-36, EuroQoL-5D, VAS, SIP, NHP
8. Fens et al., 2013 [34]	Systematic review 8 studies	Multidisciplinary inpatient or community care	Significant favourable effects 2 studies	SA SIP-30, SF-36, EuroQoL-5D, SSQoL, SIP
9. Graven et al., 2011 [31]	Systematic review 5 studies	Gait and balance rehabilitation	Insufficient evidence	SA-SIP 30, NHP, SIS
10. Graven et al., 2011 [31]	Systematic review 1 study	Information provision	Insufficient evidence	SF-36
11. Peiris et al., 2011 [35]	Metaanalysis 4 studies	Extra physical therapy in acute or rehabilitation settings	SMD: 0.48; 95% CI, 0.29–0.68.	SF-36, Euro-QoL
12. Price et al., 2011 [37]	Systematic review 1 study	Antidepressive pharmacotherapy	Non-significant difference treatment group vs. placebo	SFE

Abbreviations: AQoL – Assessment of Quality of Life Instrument; GWB – General Well Being Scale; NHP – Nottingham Health Profile; SIS – Stroke Impact Scale; SIP – Stroke Impact Profile; SA SIP – Stroke Adapted Sickness Impact Profile; SSQoL – Stroke Specific Quality of life Scale; VAS – Visual Analogue Scale; CI – Confidence Interval; BES – Best Evidence Synthesis; SMD – Standardise Mean Difference.

<sup>a</sup> Only data on quality of life have been extracted from the reviews.

modifiable factors. The modifiable factors, repeatedly documented in short-term and long-term observational studies, include deficit in functional ability, depression and anxiety and lack of social support [19,26,28]. Therefore, it has been postulated that treatment, rehabilitation and other therapeutic interventions should be targeted just at the factors [28]. Efficacy of specific methods or organisational solutions, in line with contemporary standards of clinical practice, should be verified in controlled, possibly randomised investigations. In recent years such RCTs have become increasingly numerous, as proven by increasingly frequent in the literature syntheses of studies, systematic reviews and meta-analyses [30–35].

Summary of the systematic reviews covering recent 4 years presented in Table 1, indicates that most of the studies were focused on the evaluation of efficacy various rehabilitation, supportive and activating programmes. A proportion of the programmes, mainly those with complex and multicomponent interventions, appeared to have a modest positive effect on patients' QoL although the authors' conclusion about the effectiveness of similar programmes were not always consistent because of different measures of efficacy used by different

authors (Table 1: numbers 1, 3, 4, 5, 7, 8, 11). Among the approaches which seems to be beneficial are comprehensive rehabilitation, multidisciplinary care and leisure therapy.

As can be seen in Table 1, a proportion of the programmes, particularly those of a narrow scope of intervention, failed to gain support in scientific evidence (Table 1: numbers 2, 6, 9, 10). The number of pooled analyses, which would allow to draw unequivocal conclusions or practical recommendations, still remains insufficient. Therefore, the need is accentuated for further studies, in particular such which are targeted directly at QoL domains, rather than assuming that QoL will automatically change when relatively narrow functions or basic activities are improved [31].

It is worth noticing that even though depression and anxiety have been repeatedly documented as significant determinants of poor post-stroke QoL [36], until now few RCTs were conducted related to anti-depressive or anti-anxiety treatment or management, which would comprehend QoL as an outcome measure (Table 1: number 12). Unfortunately these studies failed to confirm benefits of the examined interventions [37].



Role of informal social support for QoL, most frequently given by the closest family of the patient, provided a topic for just one systematic review, containing 11 observational studies. The review confirmed importance of the social support in the early and in late post-stroke period but the existing doubts were not clarified, related to significance of sources of the support, its types and mechanisms of action [38]. The authors appeal for further studies, with participation of greater groups of patients, for standardisation of methods in measurement of social support and for application of tools which would allow for simultaneous evaluation of the level, type and source of social support.

### 3.3. Burden and quality of life in caregivers of post-stroke patients

Sequels of stroke are not restricted to the patient, they also affect his/her family or other close persons who take over the care of the patient after his/her discharge from the hospital. The caregivers play an important role in a loved one's recovery from stroke and are expected to care of him/her, to assist in usual activities, to cooperate in rehabilitation, to provide emotional support and to motivate the patient in his/her recovery. The proportion of patients who stay at home following the hospital treatment ranges between 80% and 90% while the time devoted to direct care over the patient ranges from the mean of 5.5–6.4 h a day in Norway and USA to 8.2–9.4 h a day in Poland [39]. The sequels linked to long-term care are measured by assessment of caregiver burden or strain and by evaluation of caregivers' QoL. The latter can be appraised independently of the evaluation of patient's QoL or in parallel, in caregiver/patient pairs, due to the context of occasionally complex interpersonal relations [40,41]. The most frequently applied tools of evaluation include Caregiver Strain Index (CSI) according to Robinson et al. (1983), Zarit Burden Interview (ZBI), according to Zarit et al. (1980) and SF-36 or SF-12 according to Ware et al. (1992) [42,43].

Studies performed in the second half of 1990s and at the beginning of 2000s, mostly cross-sectional observations, demonstrated that a significant burden affected 25% to around 50% of carers within a period of 1 month to 1–2 years after stroke [44]. The studies showed also that QoL of caregivers, evaluated in various domains was, depending on the domain, similar or significantly lower than the comparable in demographic characteristics populations [45,46]. These observations were confirmed in recent reports, including the mentioned above ARCOS studies (New Zealand) [41,47,48]. In the ARCOS research it was revealed in addition that within the first 6 months of caregiving unfavourable changes in the QoL developed in over 50% of carers. They were manifested in reduction of time for the family and social activities, in exhaustion, and deteriorated emotional well-being. Almost 60% of the caregivers reported that life in general had changed for the worse.

In contrast to the studies on QoL in patients, few prospective longer-term observations are available related to carers, although recently a protocol was published of just started multi-centre cohort investigations (Restore4Stroke), with four-fold repeated follow-up assessments in the time after stroke occurrence. The first results of this study can be

expected in two years [49]. The available till now prospective investigations indicate that in the period between 6th and 18th month and between the 1st and the 2nd year following stroke no significant alterations in caregivers' quality of life and burden were noticed [45]. Therefore, it can be concluded that the deterioration takes place during the first months after stroke and thereafter the caregiver burden and QoL persist at a relatively stable level.

The main factors which determine post-stroke negative sequels experienced by the unpaid caregivers include post-stroke neurological and functional deficit, stroke-linked behavioural, emotional, cognitive disturbances in patients, and depression and inadequate or lack of social support in caregivers [50]. The factors which amplify the unfavourable effects of stroke include also insufficient knowledge and competences in provision of care to a person with neurological impairment as well as difficulties in coping with everyday problems linked to the care. In view of the above the need is postulated for professional systemic support, dedicated to caregivers [51].

To support the caregivers different types of training, counselling and psychoeducational programmes have been proposed. Their efficacy was evaluated in RCTs, summed up in systematic reviews. The data synthesis indicate that, apart from certain advantages, e.g. an increased knowledge on stroke and improvement in mood, no significant evidence was obtained for the effectiveness of non-pharmacological interventions in reducing caregiver burden or improving QoL [52,53]. This failure was partially caused by methodological, clinical and statistical heterogeneity of the trials. Therefore, the need is accentuated for continuing studies based on a more rigorous protocols. Also it has been postulated that more RCTs of multifaceted programmes, focused on problem-solving training, during the transitions from hospital to home care, are needed [52,54,55].

The experienced till now inability to obtain scientific proofs for efficacy of interventions targeted at reduction of negative stroke sequels for the caregivers cannot be considered as denying need and sense for developing supportive educational activities, which provide the carers with capabilities and knowledge, allowing to cope with challenges resulting from care over post-stroke patients [54]. To balance the body of knowledge on the negative consequences of long-term caregiving, studies on positive outcomes have begun to appear. They found that family caregivers may experience satisfaction, personal growth and inner strength when they are actively involved in the care of the family member [56].

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## 4. Summary

Despite the progress in diagnosis, treatment and care management, stroke remains to create a great health problem both from the macro perspective and from an individual patient's and his/her family point of view. Evidence for the above is provided by objective indices documenting increase in absolute number of stroke survivors and the linked to this increase in number of patients with disabilities and requiring assistance of other persons. Subjective indices, as reported by the patients indicate that health related QoL after stroke

undergoes long-term reduction in several domains of life. Also in a significant proportion of informal caregivers quality of life becomes deteriorated. Between 25% and 50% of family carers experience a significant burden, which in turn may lead to subsequent unfavourable health consequences and to the break-down of the care and institutionalisation of the patients [54]. Therefore, a number of different types of professional intervention have been suggested for the patients and their caregivers, aimed at alleviating the negative consequences of stroke and at supporting the caregivers in their role. However, the scientific evidence related to their efficacy still remains insufficient and further investigative effort is required both to improve quality of the research and to optimise the interventions.

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### Conflict of interest

None declared.

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### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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