Multimorbidity in Stroke.

Dr Katie I Gallacher, PhD [1]

Dr Bhautesh D Jani, PhD [1]

Dr Peter Hanlon, MSc [1]

Dr Barbara I Nicholl, PhD [1]

Prof Frances S Mair, MD [1*]

1 General Practice and Primary Care, University of Glasgow, 1 Horselethill Road, Scotland, G 12 9LX.

*Corresponding author. Frances.mair@glasgow.ac.uk +44 141 330 8312Cover title:

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Twitter: @FrancesMair ; @gppcglasgow

Introduction

The prevalence of long-term conditions is increasing across the world due to improved treatments for acute conditions and an increase in life expectancy [1, 2]. Importantly, people are now commonly living with multiple long-term conditions and this has important implications for the design and cost of health services [3]. Those with higher numbers of long-term conditions have worse health-related outcomes and use health services more frequently [4, 5]. The presence of multiple conditions adds complexity to disease management, for example disease-disease and disease-drug interactions are more likely to occur. Co-occurring conditions can be concordant i.e. similar in origin and treatment requirements or discordant i.e. apparently unrelated or requiring different treatments [1].

The terms multimorbidity and comorbidity are used frequently in the medical literature, the first commonly defined as the presence of two or more long-term conditions within an individual and the second as the presence of one or more long-term condition alongside an index condition [1, 2, 6]. However, it is widely accepted that there is great variation in definitions and this makes comparison of populations difficult. A recent systematic review of systematic reviews examined definitions and methods of measurement of multimorbidity [7]. The authors reported that multimorbidity is most commonly defined as the presence of two or more conditions within an individual, but there is variation in whether duration, severity, or clustering of conditions are considered. Various options for the measurement of multimorbidity, including weighted and unweighted options, were also examined and the authors concluded that the optimum measure depends on the purpose of the study. So, at the present time there remains no consensus on the optimal approach to measuring multimorbidity. Common measures include the Charlson Comorbidity Index (CCI)[8], Elixhauser [9], and the Cumulative Illness Rating Scale (CIRS) [10]. All are weighted measures,

but Elixhauser can also be used in an unweighted form. The CCI was designed to predict mortality and includes 16 conditions (including cerebrovascular disease and hemiplegia)[8]. Elixhauser is a more extensive measure, it includes 30 acute and chronic conditions and was developed to predict length of hospital stay, hospital charges and in-hospital death [9]. The Cumulative Illness Rating Scale (CIRS) was developed to assess the medical burden of chronic illness, it includes 14 body systems categories [10]. By contrast, the Liu comorbidity index was specifically constructed, from a cohort in Japan, to be used in stroke outcomes research. It includes 41 conditions and is a weighted measure [11]. When choosing a measure, a weighted one that has been validated for the outcome being considered and may be best , but where evidence is weak or multiple outcomes are being examined, then a simple count of conditions may be appropriate [7]. Importantly, a clear reason for choosing a definition and measure should be provided, and it may even be appropriate to include acute conditions, biopsychosocial factors and risk factors in the measure if appropriate for the aim of the study [7]. It is currently unclear what data source is best suited to the measurement of multimorbidity, for example whether routinely collected or self-reported data are more helpful. Traditionally, routinely collected data has been considered to be more valid but this relies on accurate coding by clinicians and risks missing conditions such as depression or chronic pain that are often poorly coded. However, one risk with self-reported data is that it may omit conditions less 'visible' to patients such as chronic kidney disease.

This paper focusses on multimorbidity in stroke. Stroke survivors commonly have comorbid conditions [12], and these may arise due to a variety of biopsychosocial reasons. Many concomitant conditions may be concordant, that is share risk factors and pathological disease processes with stroke for example heart disease, or may predispose an individual to stroke, for example atrial fibrillation (AF). While other co-existing conditions may occur secondary to stroke, for example vascular dementia, or may be entirely unrelated or discordant, for

example breast cancer. When measuring multimorbidity in stroke, how we define comorbidity will affect results, for example inclusion of conditions that are risk factors for stroke will make prevalence of comorbidity high. The recent Academy of Medical Sciences document makes it clear that even if someone only has a cluster of concordant conditions then the person should still be considered multimorbid.

There are several reasons why multimorbidity in stroke merits attention. The additive effect of illness burdens from multiple conditions may contribute to poorer health status, higher risk of mortality, poorer functioning and increased use of health services through several mechanisms ranging from increased treatment burden or workload of healthcare [13] to associated inflammatory processes which may be linked to increased levels of disability [14]. The presence of multimorbidity may interfere with recommended treatments post-stroke, for example by inhibiting participation in rehabilitative therapies. Stroke can reduce a person's capacity to manage health due to physical, cognitive and psychological sequelae, and this can be exaggerated by multimorbidity. For example, a stroke survivor with comorbid peptic ulcer disease may be unable to tolerate anti-platelet medication, or the presence of comorbid rheumatoid arthritis may result in an individual struggling to participate in physiotherapy. Additionally, multimorbidity in stroke is associated with polypharmacy that may enhance the risk of drug-drug interactions, such as anti-platelets taken alongside non-steroidal anti-inflammatory (NSAID) medication increasing bleeding risk.

It is clear that we need to understand the prevalence of multimorbidity in stroke and its association with health-related outcomes, in order to better plan stroke health services. Unfortunately, this is not a straightforward goal, as the way in which we define and measure multimorbidity is likely to impact findings.

This paper aims to examine how multimorbidity has been defined in stroke how prevalence has been measured and how associated health-related outcomes have been studied. We will discuss the implications of our findings for clinical practice and highlight potential research gaps.

Methods

We searched Ovid Medline between Jan 1, 1946 and Feb 19, 2018 for published articles that examined the prevalence of multimorbidity in people with stroke and any associations with health-related outcomes. We used the terms 'stroke' OR 'cerebrovasc*' AND 'comorbid*', OR 'multimorbid*'. For this paper, we focussed on well-conducted, large studies and systematic reviews.

Definition and prevalence of multimorbidity

We found four large, well conducted studies that have provided information on the prevalence of multimorbidity in stroke [12, 15-17]. These are summarised in Table 1. All defined multimorbidity as two or more long term conditions but the conditions that were included varied greatly and only three provided an explanation for choice of conditions[12, 15, 16]. All four examined the prevalence of individual comorbidities, and three also looked at severity of multimorbidity, two by taking a simple count [12, 16]and one by using the CCI [15]. All used administrative data or health records as a data source, none used self-reported data. One study examined older stroke survivors over 66 years [16], and unsurprisingly prevalence of multimorbidity was higher in this study than in the others. Results, shown in Table 1, differed greatly between studies, most likely due to the variation in methods used. One study examined trends in comorbidity over an 18 year period (1994-2011) and found that the proportion of people with stroke who had any comorbidity increased from 40.5% to 47.0%

for ischaemic stroke and 32.0% to 44.7% for haemorrhagic stroke over that time[15]. The existing literature comes from high income nations and there is a lack of data reported from lower or middle-income countries.

There has been limited exploration of prevalence of multimorbidity in stroke in relation to patient demographic and lifestyle factors. One community cohort study in the UK (n= 8751) found higher number of comorbidites in stroke survivors who were female, older, socio-economically deprived, and smokers[12].

Table 1. Large, well-conducted studies that have examined prevalence of multimorbidity in stroke.

Study	Country	Sample	Sample size	Data source	Definition of multimorbidity	Measure of multimorbidity and result	Prevalence of 5 most common comorbidities reported in the paper
Schmidt et al[15]	Denmark	First-time stroke, ≥15 yrs	219,354	Inpatient and outpatient health records	≥ 1 other LTC within 15 yrs prior to stroke, excluding codes during stroke admission. Conditions in CCI chosen plus atrial fibrillation or flutter	Charlson Comorbidity Index: 42.8% ≥1; 18.5% moderate; 13.2% severe; 11% very severe	Atrial fibrillation or flutter 11.0%, cancer 10.9%, diabetes 9.0%, congestive heart failure 8.1%, chronic pulmonary disease 8.1%,
Gruneir et al[16]	Canada	Stroke at least 6 months prior, ≥66 yrs	29,673	Administrative data from health insurance records	≥ 1 other LTC prescription that suggests comorbidity in 5 yrs prior stroke, from 14 highly prevalent / author preferences	Count of conditions: 99.1% ≥1; 51.7% ≥4; 6.5% ≥7	Hypertension 89.9%, arthritis 65.8%, IHD 38.1%, diabetes 35.6%, COPD 30.1%,
Gallacher et al[12]	UK	Diagnosis of stroke or TIA ≥18	35,690	Primary care health records	≥ 1 other LTC from 39 selected for previous research, informed by systematic review. Unknown if predate or postdate stroke	Count of conditions: 94.2 % ≥1 44.5% ≥ 4 10.1% ≥7	Hypertension 60.9%, coronary heart disease 29.5%, painful condition 21.9%, depression 20.7%, diabetes 18.8%,
Johansen et al[17]	Canada	First time stroke ≥20	32,107	Hospital discharge records.	≥ 1 other LTC from 14, unclear why they were selected or if they predate or postdate stroke	None	Hypertension 35%, Diabetes 17%,arrhythmia 15%, IHD 14%, other stroke 12.8%

Associations with health-related outcomes

Mortality

There is evidence that multimorbidity is associated with higher risk of mortality in stroke patients. The relationship between multimorbidity and mortality among stroke patients has been studied for both shorter (in-hospital or within 30 days) and longer (≥6 months) durations of follow-up and results are detailed in Table 2. Most studies have used CCI to measure multimorbidity, which was developed to predict inpatient mortality. In one landmark study involving more than 200,000 stroke patients from the Danish national registry, multimorbidity measured by CCI was consistently found to have a dose-response relationship with 30-day and 5-year mortality risk, over an 18-year period [15]. Other work using this registry has shown that comorbidity, especially cancer and advanced renal or liver disease, increased one year mortality after stroke beyond the combined individual effects of stroke or the comorbidity [18]. Two community studies (in the United States and Spain) found that multimorbidity measured by CCI was a significant predictor of six-month mortality in stroke patients [19, 20]. There is also evidence supporting a relationship between CCI score and risk of long-term mortality in stroke patients. A 29% higher adjusted risk of one-year mortality with each unit increase in CCI, was reported in a study of 960 stroke patients[21]. A CCI score of ≥3 was found to have a higher 3-year and 9-year mortality risk, in a study of 959 stroke patients in Brazil[22].

Table 2. Studies that have examined associations between multimorbidity and mortality.

Study	Country	Study Type	Sample size	Data source	Measure of multimorbidity	Follow-up duration	Key Results
Schmidt et al[15]	Denmark	Cohort	219,354	Hospitalization records	Charlson Comorbidity Index (CCI): 0(none), 1(moderate), 2(severe), 3(very severe)	30 days and 5 years	Stroke patients with very severe comorbidities had a 23.5% and 74.5% mortality risk at 30 days and 5 years respectively, compared to 10.5% and 36.6% for stroke patients with no comorbidities at baseline.
Jimenez et al[19]	Spain	Cohort	175	Hospitalization records	CCI: 0-1 (low),2 or more (high)	6 months	Stroke patients with high CCI had 68.4% greater odds of mortality at 6 months.
Berlowitz et al[20]	US	Cohort	2402	Hospitalization records	3 different methods: CCI, Ambulatory Care Group (ACG, Diagnostic Cost Group (DCG)	6 months	Comorbidity was a significant predictor of all-cause mortality at 6 months for stroke patients, ACGs and DCGs performed better than CCI. The actual effect sizes were not reported.
Goldstein et al[21]	US	Cohort	960	Hospitalization records	CCI: 0-1 (low) 2 or more (high)	1 year	Stroke patients with high CCI at 72% greater odds of mortality at 1 year.
Castro et al [22]	Brazil	Cohort	959	Hospitalization records	CCI: 0(none), 1(moderate), 2(severe), 3(very severe)	3 years, 6 years, and 9 years	Stroke patients with very severe CCI had a hazard ratio of 2.45, 2.87 and 3.18 at 3, 6 and 9 years respectively for all-cause mortality compared to those with CCI=0

Zhu et al[23]	Canada	Cohort	Two samples; Total 5452	Hospitalization records	Elixhauser Index	In-hospital mortality (duration not specified)	Elixhauser index was a significant predictor of in-hospital mortality. The actual effect sizes were not reported.
Gallacher et al[24]	UK	Cohort	8751	Community recruitment	Number of comorbid conditions categorized into: 0,1,2,3,4, 5 or more	7 years	Stroke patients with 5 or more comorbidities had a hazard ratio of 2.38 for all-cause mortality at 7 years, compared to stroke patients with no comorbidities.

Studies using measures other than the CCI, such as The Elixhauser Comorbidity Index have shown a similar relationship between multimorbidity and mortality. In a study of more than 5000 stroke patients in Canada, multimorbidity measured by the Elixhauser Index was associated with a higher rate of in-hospital mortality over the four-year study period [23]. A study involving 8751 UK Biobank participants with stroke measured multimorbidity using a simple count of morbidities (n=42) and found nearly 1.5 times higher risk of mortality in those with two additional comorbidities and an approximately 2.5 times higher risk of mortality in those with ≥5 comorbidities over seven years (Figure 1)[24].

We found four studies that have investigated the influence of number versus type of comorbidities on mortality risk among stroke patients. The Canadian study described above examined the effect of 30 comorbidities in the Elixhauser index on the risk of in-hospital mortality among 5,452 stroke patients. They reported a significant higher risk of death with the presence of congestive heart failure, but the effect of other comorbidities was unclear[23]. The Danish study described earlier compared the effect sizes of 16 comorbidities included in the CCI on mortality risk at 30 days and 5 years [15]. They found a 15% higher mortality risk for presence of diabetes with end-organ damage, 20% for peripheral vascular disease, 25% for chronic pulmonary disease, 35% for congestive heart failure and AF or atrial flutter, 45% for moderate to severe renal disease, and 1.8- to 2.4-fold for mild to severe liver disease, while presence of myocardial infarction and diabetes without end-organ damage was not found to have any significant association. A meta-analysis of 13 studies involving N=59,598 stroke patients [25] found depression after stroke was associated with approximately 20% higher risk of mortality at 2-5 years. This has major implications for the management of

mental health in the stroke population, a largely neglected aspect of stroke recovery [13]. A UK Biobank study with a seven-year follow-up period, explored whether concordant or discordant comorbidity was associated with worse mortality. This study found that the presence of any cardiometabolic comorbidity had similar effect size on the risk of all-cause mortality as did the presence of any non-cardiometabolic comorbidity, compared with no comorbidities in stroke.

Functional outcomes

Given the increasing demand for and limited capacity of rehabilitation services, there is growing interest in factors which may predict functional outcome following stroke and allow more effective targeting of resources [26]. Presence of specific comorbidities can affect functional outcomes following stroke. For example, a meta-analysis of 12 longitudinal cohorts following stroke thrombolysis, comprising 14,801 patients, found that AF was associated with a reduced likelihood of favourable outcome (modified Rankin Scale ≤2) [27]. By the same measure, diabetes mellitus was also associated with poorer functional outcomes following thrombolysis in a meta-analyses of 19 observational or intervention studies [28].

Studies quantifying the relationship between multimorbidity and functional outcomes have reported contradictory findings [19, 20, 26, 29-32]. There is variability both in the choice of scale used to quantify multimorbidity, and in the assessment of functional outcome. A recent systematic review and meta-analysis synthesised the findings of 15 studies assessing the impact of multimorbidity on functional outcome following inpatient stroke rehabilitation [26]. The CCI was the most commonly used measure, with four out of eight studies showing significant associations between a higher CCI and poorer functional outcome. The Liu index was consistently associated with poorer functional status at discharge in three small studies (n=85, 106, and 175, respectively), as was the Comorbidity Severity Index in one study

(n=85), a weighted measure comprising 10 organ systems in which diseases are scored according to effects on functional limitation. The authors meta-analysed seven studies that used the Functional Independence Measure (FIM) to assess discharge functional outcome and included a range of comorbidity indices. These studies were highly heterogeneous, varied in their adjustment for baseline functional status or stroke severity, and had small sample sizes (range 85 to 260). Where more than one comorbidity index was assessed in a single study, the most strongly associated was included in the primary meta-analysis (CCI was excluded in favour of the Liu index), which showed a modest but statistically significant association between multimorbidity and poorer discharge FIM. In a sensitivity analysis including the CCI estimate, the results were no longer statistically significant. However, this analysis excluded the two largest studies to assess the impact of CCI on functional outcome [20, 32], as these did not report FIM at discharge. These two studies are shown in Table 3. One is a large French study of routine data 28,201 patient undergoing inpatient rehabilitation found CCI to be associated with less functional gain, adjusting for baseline functional dependence and length of stay [32]. The other is a study of 2,402 patients undergoing inpatient rehabilitation in the USA that reported the CCI did not improve the overall fit (over age and sex) of models predicting change in FIM [20].

Table 3. Large studies in the systematic review by Kabboord et al examining associations between multimorbidity and functional outcomes excluded from the meta-analysis

Study	Country	Sample	Sample size	Data source	Measure of comorbidity	Functional outcome measure	Method of assessment	Findings
Schnitzler et al[32]	France	Any stroke, admitted for inpatient rehabilitation	28,201	National hospital discharge database	CCI	Physical Dependence Score	Change in physical dependence from admission to discharge from rehabilitation	CCI associated with less functional gain (adjusted for age, sex, rehabilitation setting, stroke type, length of stay, admission physical dependence score)
Berlowitz et al[20]	USA	Inpatient stroke rehabilitation.	2,402	Routine clinical and adminis-trative data	CCI Adjusted clinical groups (ACG) Diagnosis cost groups (DCG)	FIM – change during rehabilitation period.	Model fit including age/sex compared to models including age, sex and each comorbidity score.	No improvement in model fit with CCI or ACG over age/sex alone. Adding DCG to age/sex improved overall model fit for functional gain.

Few studies have assessed the impact of multimorbidity on outcomes at specific time points, with most assessing status at discharge from inpatient rehabilitation. Two small studies have assessed the impact of CCI on modified Rankin Scale at 1 month and 6 months, respectively. These were not included in the systematic review discussed above and are summarised in Table 4. One specifically recruited older patients (mean age 83, n=297) and found no association between CCI and poor outcome after adjusting for stroke severity and premorbid disability [29]. By contrast the other found no association between CCI and poor outcome at 6 months after adjustment for stroke severity [19].

Table 4. Studies assessing associations between multimorbidity and functional outcome at specific time-points rather than discharge from inpatient rehabilitation

Caballero et al[19]	Spain	Ischaemic stroke or intracerebral haemorrhage	175	Assessment 6 months following stroke	CCI	Modified Rankin scale (mRS)	Poor outcome (mRS ≥2) at 6 months	CCI associated with mRS ≥2after adjustment for age, sex, vascular risk factors, and stroke severity)
Denti et al[29]	Italy	First ischaemic stroke	297	Retrospective hospital records	CCI	mRS	Poor outcome (mRS ≥2) at 1 months	CCI not significantly associated with mRS ≥2 at 1 month after adjusting for stroke severity and premorbid disability.

Utilisation and organisation of services

We found little evidence on the associations between multimorbidity in stroke and healthcare utilisation. A Canadian study of older individuals with stroke (N = 29,673) showed that healthcare utilization increased (primary and secondary care, emergency department, home care visits and hospitalisations) with increasing number of comorbidities during the five years post stroke [16]. The majority of healthcare utilisation was for conditions other than stroke at all levels of multimorbidity and was three times higher in those with 8 comorbid conditions compared with those with none. The biggest increases in utilization were for acute care hospitalizations and emergency department visits. Unsurprisingly, associated healthcare costs also increased for those with increasing multimorbidity, and this was mainly explained by an increased use of acute care services [16].

A small Canadian cohort study using clinical and administrative data collected in one hospital over a decade (N=987), showed that having at least one other comorbidity was related to a longer (>7 days) hospital stay for those with a haemorrhagic stroke. This resulted in costlier care, through both diagnostic and rehabilitation stages of care [33]. There were 13 conditions in addition to stroke examined and no explanation was given from the authors as to why they were chosen. Hypertension was the most prevalent comorbidity and independent of all other long-term conditions studied, it was most strongly associated with having a longer stay, and alongside cerebrovascular disease, was linked to the highest overall cost of stay [33]

In a study of approximately 2,200 stroke survivors in Germany, previous stroke, diabetes, symptoms of internal carotid artery stenosis , or a count of >3 comorbidities, were all associated with insurance applications for long-term nursing care within 3.6 years of their

stroke [34]. There were 9 conditions chosen for examination and again no reason was given for their selection.

Discussion

Summary of findings

Multimorbidity in stroke is a growing healthcare challenge with estimates of prevalence ranging from 43% - 94% depending on the definition and measurement used. Prevalence has been estimated to be as high as 99% in those over 66 years.

Multimorbidity in stroke has been reported to be associated with increased short and long-term mortality, however the majority of studies have had a small sample size. The CCI is the most commonly used measure of multimorbidity in studies that examine associations with mortality. It is unclear whether type of comorbidity, for example whether conditions are discordant or concordant, has an influence on mortality. There is some limited evidence to suggest that multimorbidity in stroke survivors is associated with greater stroke severity, lower baseline functional status, longer rehabilitation time, poorer functional gain, lower overall functional status following rehabilitation, longer hospital stays, increased readmission rates, higher overall health care utilisation in the longer term which is associated with increased economic costs. Measures that include assessment of severity of comorbidities appear to be more predictive of functional gain; however, the limited literature to date suggests baseline functional status is consistently the strongest predictor of outcome.

Implications of multimorbidity for clinical practice

The high prevalence of multimorbidity in stroke has important implications for the design of stroke health services. Individuals with multimorbidity are more likely to experience complexity in their healthcare, enhancing risk of non-adherence and disengagement from health services. This may contribute to the poorer outcomes and increased costs reported in

those with multimorbidity and stroke. Stroke rehabilitation trials often exclude those with comorbidity resulting in a lack of evidence about how best to manage these individuals [35]. Current stroke guidelines do not take account of multimorbidity, leaving uncertainty about how best to achieve optimal outcomes in these individuals [36]. Currently, most health systems operate a disease-focussed arrangement that is suboptimal for those with multimorbidity due to poorly co-ordinated care and service fragmentation [13]. Multimorbidity can lead to a considerable workload of healthcare for stroke survivors, defined as treatment burden, which can negatively impact wellbeing [37]. Treatment burden includes the work of making sense of treatments, engaging with others to access services and treatments, attending appointments and investigations, taking medications, enduring treatment side effects, enacting lifestyle changes and self-monitoring activities. For example, individuals with stroke and multimorbidity are expected to attend separate appointments for each condition, often with little communication between clinicians. One potential consequence of multimorbidity is the prescribing of multiple medications (polypharmacy). Polypharmacy is common in stroke, posing potential risks [12], especially with regard to the likelihood of adverse drug reactions (ADRs). There is qualitative evidence that polypharmacy in stroke increases perceived treatment burden, and can be a barrier to adherence [38] but little quantitative evidence about the potential risks of different patterns of polypharmacy.

There is a need for a paradigm shift in our approach to the management of stroke in the context of multimorbidity with a move to prioritise individual patient goals and increased emphasis on understanding each individuals' capacity to self-manage if we are to improve outcomes and reduce resource waste [37, 39]. An individual's capacity to self-manage, particularly in the context of multimorbidity, will vary depending on personal factors, physical and cognitive abilities, social, financial, environmental and wider life circumstances [37]. Delivering more person-centred services that are more likely to meet the needs of those

with stroke and multimorbidity will require greater use of multidisciplinary teams and more emphasis on integrated care approaches across the primary and secondary care interface that can provide better support and respond more appropriately to the needs of these complex individuals. There is a need to shift focus to consider how we can better tailor services to provide the holistic, person-centred care that will be necessary to improve the experiences and outcomes of our increasingly multimorbid stroke populations. It will also be important to include multimorbidity as a key factor when trying to risk stratify those with stroke in hospitals and in the community and when considering the best design and approaches that should be adopted within rehabilitation services.

Evidence gaps and implications for research

The first uncertainty that needs addressed by researchers is how to define and measure comorbidity and multimorbidity in a stroke population. Whether to include risk factors or sequelae of stroke is one important issue, as is whether to use a weighted or unweighted measure. The answers to these questions are likely to vary depending on the purpose of multimorbidity measurement. The wider multimorbidity literature and multimorbidity guidelines described earlier, define multimorbidity as the presence of two or more long term conditions, thus including hypertension or other conditions such as AF which are risk factors for stroke. The published literature to date shows that multimorbidity in stroke has been consistently associated with higher risk of short and longer-term mortality. The published studies included conditions such as hypertension and AF in the morbidity count and both discordant and concordant conditions. Stroke patients with multimorbidity are a heterogenous population and it will be essential to gain a better understanding of modifiable risk factors for multimorbidity and patterns of multimorbidity, for example common clusters of conditions and associations with adverse health outcomes to enable better risk stratification. There is insufficient knowledge about these issues to permit clear recommendations to be made.

International bench marking studies would aid understanding and inform future intervention development and clinical guidelines in this area. However, there will be a need to develop a consensus regarding the optimal approaches to measuring multimorbidity in those with stroke to enable cross country comparisons and more large-scale studies are required, particularly those that aim to understand the role of number versus type of comorbidities on the relationship between stroke, multimorbidity and mortality.

There is a paucity of evidence on the relationship between multimorbidity and functional outcomes, in particular studies examining longer term functional outcomes. Similarly, large, high quality studies are required to better understand the associations between multimorbidity in stroke and healthcare utilisation. The mechanisms underpinning any increased service utilisation should also be explored, for example whether it is due to associated morbidities, polypharmacy or other factors such as frailty that are common in multimorbid populations. Although there is an emerging literature that frailty is associated with multimorbidity [40], even in younger age groups [41], and is important in multimorbid individuals [6], little is known about this in the context of stroke. We found no studies that investigated the impact of multimorbidity on quality of life post-stroke. This should be explored quantitatively and qualitatively in order to inform the future design of stroke services. Development of ways of measuring treatment burden and individual capacity to self-manage those with multimorbidity would aid identification of those are at risk of non-adherence either because of perceptions of being overburdened or limitations in their ability to cope with their burden of illness and the accompanying self-management demands. Polypharmacy is common in multimorbid stroke survivors but we know insufficient about the implications of this and in particular the risks, if any, posed by different patterns of polypharmacy in multimorbid stroke populations. There is also a lack of evidence to inform clinicians about the impact of

interventions for polypharmacy, such as deprescribing medications, on health-related outcomes.

There is uncertainty about how best to manage those with stroke who are multimorbid due to a lack of randomised clinical trials (RCTs) that look specifically at or even explicitly include this patient group. As a result, it is unclear how to best risk stratify or organise services for stroke survivors with multiple conditions. Inclusion of these individuals in RCTs is vital to increase the evidence base for the vast majority of people with stroke. Equally, we know insufficient about the biological mechanisms underpinning multimorbidity in those with stroke. A greater understanding of these issues is important if we are to discover whether there might be any novel therapeutic targets that could be beneficial. Lastly, there is a paucity of evidence about the issues of multimorbidity in stroke from low and middle-income countries, and this should be addressed. Table 5 highlights key research priorities.

Table 5. Research Priorities

To develop a consensus on a standardised approach to the definition and measurement of multimorbidity in those with stroke.
To examine associations between multimorbidity and health-related outcomes (mortality, functional outcomes, health-care utilisation, quality of life) through high quality, large-scale cohort studies.
To examine the influence of patient factors (for example, lifestyle or frailty) or type /clustering of conditions on outcomes in those with multimorbidity and stroke.
To develop measures to better understand the treatment burden experienced by those with stroke and multimorbidity in order to identify targets for intervention.
To examine the risks associated with different patterns of polypharmacy in those with multimorbidity and stroke.
To undertake work with patients, carers and professionals to explore how stroke care services should be designed to better address the needs of people with stroke and multimorbidity.
To include people with multimorbidity in pharmacological and non-pharmacological trials involving people with stroke and to ensure study populations are well described.

Conclusion

Current knowledge of multimorbidity in stroke is limited. The existing evidence gaps need addressed if we are to improve health care delivery and outcomes for the many people with stroke who experience some degree of multimorbidity. Clinical guidelines for those with stroke need to acknowledge the importance of multimorbidity if we are to start to adapt services to better meet the needs of our increasingly complex patients.

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Figure legend - Kaplan–Meier graph of death proportion versus comorbidities (*n*=8,751).

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