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Pre-stroke activities of daily living do not predict functional decline after stroke in a cohort of community dwelling older subjects at risk for vascular disease

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HIGHLIGHTS

- Most studies identify pre-stroke impairment of activities of daily living (ADL) as a predictor for post-stroke functional outcome.
- These studies however obtain information retrospectively, with inherent risks of selection and recall bias.
- We found pre-stroke ADL not to be predictive for outcome after stroke in large prospective study, minimizing selection and recall bias.

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ABSTRACT

Background & purpose: Pre-stroke impairment of activities of daily living (ADL) is considered a major determinant for functional outcome after stroke. However, findings are based on studies in stroke patients in which pre-stroke information is gathered retrospectively, with inherent risks of selection and recall bias. The objective of this study was to verify the predictive value of pre-stroke ADL with respect to ADL decline in a large prospective cohort of community dwelling older subjects with known vascular risk factors or vascular disease, thereby minimizing selection and recall bias.

Methods: Within the four-year study follow-up of a cohort including 5,804 community dwelling older subjects from three countries at risk for vascular disease, incident stroke survivors were identified. Incident myocardial infarction (MI) survivors and the remaining study survivors without incident vascular events served as comparison groups. Multivariate logistic regression analyses for each of the aforementioned groups were performed to assess associations between pre-stroke ADL by the Barthel Index (BI) and Instrumental Activities of Daily Living (IADL) scale and risk for ADL decline.

Results: In stroke survivors, neither pre-event BI ($n = 230$, OR 1.00 (95% CI 0.83–1.23)) nor IADL (OR 1.07 (95% CI 0.94 – 1.20)) predicted risk of post-stroke ADL decline in contrast to ADL decline after MI ($n = 443$, OR 0.83 (95% CI 0.70–0.98) and 0.87 (95% CI 0.78–0.97) respectively) and the group without vascular events ($n = 4336$, OR 0.85 (95% CI 0.78–0.92) and 0.87 (95% CI 0.83–0.92) respectively).

Conclusions: In the present prospective cohort of community dwelling older subjects with known vascular risk factors, pre-stroke ADL measured by BI and IADL scale did not predict post-stroke ADL decline.

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1. Introduction

Cardiovascular diseases, encompassing ischemic heart disease and stroke, are major contributors to global disease burden in terms of mortality and disability (Cieza et al., 2021; Vos et al., 2020). Incident vascular events contribute to functional decline in patients with vascular risk factors or pre-existing vascular disease (Kamper et al., 2005). It is estimated that 25%–74% of the stroke survivors experience limitations in activities of daily living (ADL) (Miller et al., 2010). Assessment of the impact of stroke on ADL is of great importance to optimize stroke management (Veerbeek et al., 2011).

Various studies have previously been performed to identify predictors and to construct predictive models for ADL outcome post-stroke. A systematic review showed strong evidence for baseline neurological status, upper limb paresis, and age as predictors for outcome of ADL (Veerbeek et al., 2011). Prospective studies were performed in cohorts of in stroke patients, both ischemic and haemorrhagic in the acute and rehabilitative phase (Bohannon et al., 2002; Counsell et al., 2002; Douiri et al., 2017; Han et al., 2020; Johnston et al., 2000; Quinn et al., 2017; Reid et al., 2010; Tilling et al., 2001; Wagle et al., 2011). Most studies identified pre-stroke ADL to be (strongly) predictive for post-stroke ADL, except for (Douiri et al., 2017) who found pre-stroke BI not to be included in a multivariable prediction model for post-stroke BI in $n = 495$ patients included in a London stroke registry. Studies sample size varied from $n = 92$ (Bohannon et al., 2002) to $n = 330,9$ (Han et al., 2020); a variety of predictor variables and outcome measures were used, encompassing the Oxford Handicap Scale score (Counsell et al., 2002), modified Rankin Scale (mRS) (Han et al., 2020; Quinn et al., 2017; Reid et al., 2010; Tilling et al., 2001; Wagle et al., 2011), Glasgow Outcome Scale (Johnston et al., 2000) and Barthel Index (BI) (Bohannon et al., 2002; Douiri et al., 2017; Wagle et al., 2011) and different analytical approaches were used. However, all studies, although prospective in nature, have in common that pre-stroke ADL was assessed in patients with a stroke, thus retrospectively, which may have introduced selection and recall bias (Podsakoff et al., 2012).

The objective of this study was to verify the predictive value of pre-stroke ADL with respect to ADL decline in a large prospective cohort of community dwelling older subjects with known vascular risk factors or vascular disease but did not yet suffer major vascular events. This study design would allow for a true prospective study, thereby minimizing selection and recall bias.

2. Methods

2.1. Study design and participants

We performed a secondary analysis of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study including 5804 subjects (Shepherd et al., 2002). Detailed information including study design, definitions of outcomes, baseline characteristics and the results of the intervention study are published elsewhere (Ford et al., 2002; Shepherd et al., 2002, 1999).

In short, PROSPER (inclusion from 1997 to 1999) is an international, multicentre, randomised, double-blind, placebo-controlled trial of pravastatin in the prevention of vascular disease in community dwelling older subjects with at least one major risk factor for vascular disease (hypertension, diabetes mellitus or smoking) or with evidence of pre-existing vascular disease (coronary, cerebral, or peripheral). Vascular disease at study entry was defined as physician-diagnosed stable angina or intermittent claudication, ischemic stroke, transient ischemic attack, myocardial infarction (MI), arterial surgery or amputation for vascular disease. Men and women aged 70–82 years were subsequently randomised to either an intervention (pravastatin) or placebo group. During the study, incident vascular events were systematically assessed and recorded by trained nurse-staff. Stroke was defined as (one of the following criteria must be met): (i) rapid onset of focal neurological

deficit lasting ≥ 24 h, (ii) focal neurological deficit mode of onset uncertain but with no plausible evidence of alternative (non-stroke) cause, or (iii) rapid onset of global neurological deficit (e.g. coma) lasting ≥ 24 h with no other plausible non-stroke cause. MI was defined as (one of the following criteria must be met): (i) ischaemic cardiac pain greater than 30 min duration (and/or unexplained acute left ventricular failure) and diagnostic cardiac enzymes, (ii) ischaemic cardiac pain and/or unexplained acute left ventricular failure with both equivocal enzymes and equivocal electrocardiogram, (iii) diagnostic enzymes and equivocal electrocardiogram, (iv) angiographic evidence of occlusion of a major artery with appropriate ventriculographic wall motion abnormality where previous angiogram since randomization showed no such abnormality, or (v) an electrocardiogram at an annual or at an unscheduled visit showing a MI that was not evident on the previous electrocardiogram (Shepherd et al., 2002). Community dwelling older subjects from three countries of which 51.7% were female and 55.8% had vascular risk factors but no known vascular disease, were included. Average follow-up was 39.6 (SD 4.5) months and included recording of all vascular events during this period. The institutional ethics review boards of all centres participating in the PROSPER study approved the protocol, and all participants gave written informed consent. The protocol was consistent with the Declaration of Helsinki.

2.2. Subject selection

For the present study, subjects were identified who survived a stroke during the study within a mean follow-up period of 39.6 months (range 2–48 months). Two comparison groups were constructed: one group of subjects who survived a MI; a second group of remaining study survivors who did not experience any vascular event during the study, i.e. who were not diagnosed with intermittent claudication, angina pectoris or transient ischemic attack during the study period and who underwent no coronary artery bypass surgery, peripheral artery disease surgery or a percutaneous coronary intervention during the study period. Subjects with both stroke and MI during follow-up were included in the stroke group since the selection was first based on stroke survivors.

2.3. ADL assessment

The 20 point Barthel Index (BI, a higher score implies less self-care dependency) measures basic aspects of activity related to self-care and mobility and is widely used, well validated and responsive, populations of community dwelling older people (Hopman-Rock et al., 2019; Wade & Collin, 1988; Wade & Hewer, 1987), although it suffers from a ceiling effect (Huybrechts et al., 2007; Taylor-Rowan et al., 2018). The 14-point Instrumental Activities of Daily Living (IADL, a higher score implies less dependency on the environment) using a modified version of the Older Americans Resource scale questionnaire is more sensitive for changes in the upper region of function (Cohen & Marino, 2000; Cunningham et al., 1993; Fillenbaum & Smyer, 1981; Spector et al., 1987). The questionnaires were completed at baseline and at 9, 18, 30, 36, 39, 42, 45 and 48 months depending on follow up time of each study subject.

2.4. Statistical analysis

For both the stroke and MI group, the nearest available pre-event ADL assessment was defined as the baseline measurement. For the group without vascular events, the baseline measurement was aligned with the median pre-event measurement in both stroke and MI, which was 18 months. For the post-event assessment, data from the final study visit were used to facilitate comparison with the group without vascular events. Calculations were repeated for the nearest available assessment post-event for stroke and MI respectively. Due to skewness of the data to higher scores, subjects were subsequently dichotomised by presence or absence of a post-event decline in BI or IADL score. A post-event decline was defined as a loss of one point or more on aforementioned scales.

Analyses were repeated for a loss of > 2 and > 4 points respectively (the latter only for the stroke group, due to low numbers in the other groups). Subjects with missing data were excluded from the data analysis. Multivariable logistic regression models for BI and IADL decline were constructed for stroke, MI and the group without vascular events respectively. Next to pre-event BI or IADL score, models included previously indicated covariates (Canavan et al., 2014; Cieza et al., 2021), i. e. treatment allocation, age, gender, history of diabetes, history of hypertension, history of any vascular disease, smoking status and follow-up time defined as time in months between pre-event assessment date and the date of the last study visit. P-values of less than 0.05 and 95% confidence intervals not containing the value “1” were considered significant. Statistical analyses were performed with the Statistical Package for Social Sciences (version 19).

3. Results

Of the 5804 subjects, *n* = 782 were excluded from the present analysis, *n* = 233 (4%) survived a stroke (stroke group) and *n* = 453 (9%) a myocardial infarction during the study period (MI group); 4336 subjects who did not experience clinically evident incident vascular disease during the follow up period were included in the group without vascular events (Fig. 1). Post event BI and/or IADL scores were missing in *n* = 3 subjects in the stroke group and *n* = 10 subjects in the MI group; these were excluded from the statistical analyses.

Stroke and MI group had a higher mean age, were more often male and had more co-morbidity, i.e. diabetes mellitus and vascular diseases compared to the group without vascular events. A history of stroke was present in 18% of the subjects in stroke, 12% in MI group and 11% in the group without vascular events; MI in 19% in stroke, 22% in the MI group and 12% in the group without vascular events. Twenty- one patients in the stroke group also experienced an incident MI (Table 1). Within the stroke group, 37% of the subjects (*n* = 85) experienced a post-event BI decline and 43% (*n* = 99) a decline in IADL score; within the MI group, 14% (*n* = 64) experienced a post-event BI decline and 20% (*n* = 88) a decline in IADL score; within the group without vascular events, 13% (*n* = 552) experienced a post-event BI decline and 17% (*n* = 739) a decline in IADL score. Numbers were considerably lower for BI post-event declines of more than 2, respectively 4 points (Table 2).

Both pre-event BI and IADL score predicted a post-event decline in the respective scale in the MI and the group without vascular events, but not in the stroke group (Table 3). Repeating the analysis predicting a BI

Table 1
Characteristics of study subjects with incident stroke, myocardial infarction (MI) and no vascular events.

	Stroke (<i>n</i> = 233)	MI (<i>n</i> = 453)	No vascular events (<i>n</i> = 4336)
Age, mean, years (SD)	75.8 (3.6)	75.6 (3.4)	75.2 (3.3)
Female	111 (48)	189 (42)	2367 (54)
History of diabetes	38 (16)	64 (14)	439 (10)
History of hypertension	129 (55)	277 (61)	2779 (63)
History of vascular disease	123 (53)	258 (57)	1849 (42)
History of stroke or TIA	41 (18)	55 (12)	457 (11)
History of MI	44 (19)	100 (22)	500 (12)
Treatment group	115 (49)	211 (47)	2228 (51)
Current smoker	66 (28)	105 (23)	1117 (25)
Pre-event measurement, median, months [IQR]	18 [9–30]	18 [9–30]	n.a.
Follow-up time, median months [IQR]	18 [11–32]	19 [8–29]	21 [18–24]

All data in numbers (%) unless otherwise indicated. IQR= interquartile range; TIA= transient ischemic attack; MI=myocardial infarction.

post-event decline of > 2 points and > 4 points did not change results. For a decline of > 2 points, stroke: OR 0.86, CI 0.70–1.04; MI: OR 0.67, CI 0.56–0.80; group without vascular events: OR 0.73, CI 0.66–0.80. For a decline of > 4 points, stroke only: OR 0.93, CI 0.79–1.25. When repeating analyze for the nearest available assessment post-event, results were comparable (stroke, BI and IADL respectively: OR 0.98, CI 0.82–1.18 and OR 1.10 CI 0.96–1.25; MI, for BI and IADL: OR 0.87 CI 0.73- 1.03 and OR 0.87, CI 0.78–0.96 respectively).

In the stroke group, only age and follow-up time were significantly predictors for IADL post-event decline. In the MI group, significant predictors were pre-event BI and IADL, age and follow-up time (for IADL only). For the group without vascular events additional predictors were female gender and history of diabetes mellitus and vascular disease (Table 3).

4. Discussion

In a large prospective population based cohort including 5804 community dwelling older subjects at risk for vascular disease, pre-event ADL measured by Barthel Index (BI) and Instrumented Activity of daily living (IADL) was not predictive of risk of post-stroke ADL decline in a group of 233 subjects surviving a stroke during an average study follow

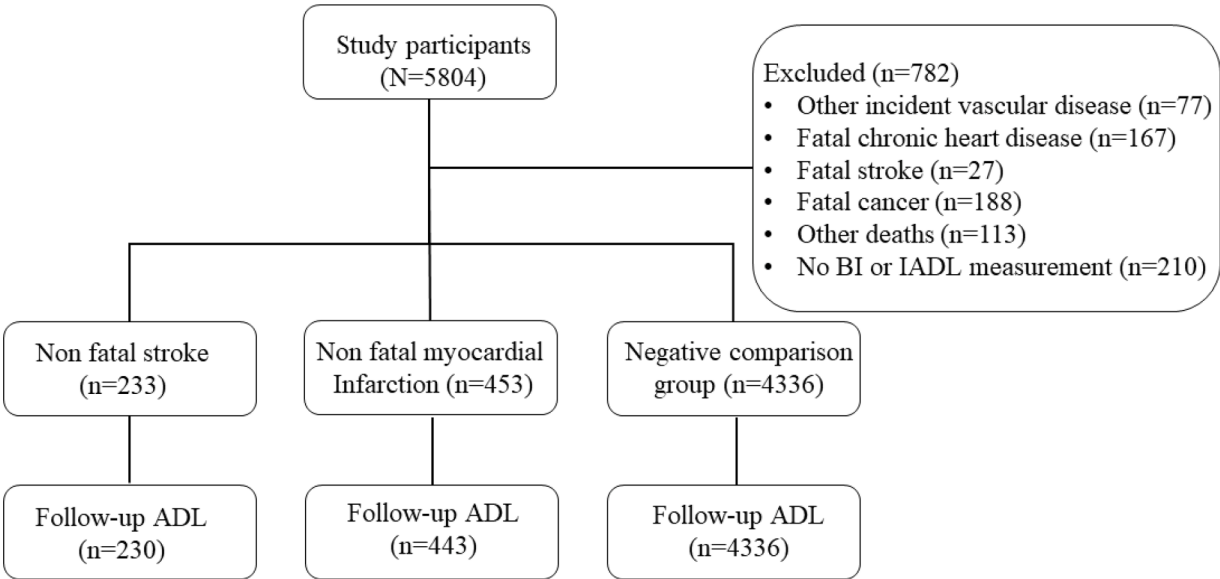


Fig. 1. Study flowchart.

Table 2

Baseline and decline in Barthel Index (BI) and Instrumental Activities of Daily Living (IADL) scores for subjects with incident stroke, myocardial infarction (MI) and no vascular events.

		Stroke (n = 233)	MI (n = 453)	No vascular events (n = 4336)
Pre-event BI	20	180 (77)	374 (83)	3784 (87)
	19	29 (12)	43 (10)	381 (9)
	18	12 (5)	12 (3)	95 (2)
	17	4 (2)	10 (2)	37 (1)
	≤16	8 (4)	14 (3)	39 (1)
Pre-event IADL	14	149 (64)	340 (75)	3610 (83)
	13	25 (11)	40 (9)	391 (9)
	12	15 (6)	23 (5)	161 (4)
	11	13 (6)	15 (3)	86 (2)
	≤10	31 (12)	35 (8)	88 (2)
		n = 230	n = 443	n = 4336
BI decline		85 (37)	64 (14)	552 (13)
> 2 points		50 (22)	32(7)	220 (5)
> 4 points		44 (19)	11 (2)	69 (2)
Range		-6 to 19	-6 to 17	-7 to 20
IADL decline		99 (43)	88 (20)	739 (17)
Range		-6 to 14	-8 to 13	-9 to 14
Range		-6 to 14	-8 to 13	-9 to 14
Range				

All data in numbers (%) unless otherwise indicated. BI= Barthel Index; IADL= Instrumental Activities of Daily Living; MI=myocardial infarction.

up of nearly 40 months, in contrast to 453 subjects surviving a myocardial infarction (MI) and remaining 4336 subjects who survived without clinically manifest incident vascular events.

Present results are generally in contrast with previous prospective studies in stroke patients who generally identified pre-event disability as a predictor for post-event ADL (Bohannon et al., 2002; Counsell et al., 2002; Douiri et al., 2017; Han et al., 2020; Johnston et al., 2000; Quinn et al., 2017; Reid et al., 2010; Tilling et al., 2001; Wagle et al., 2011). Studies were heterogeneous in setting : acute setting, rehabilitation, registry; sample size: ranging from n = 92 (Bohannon et al., 2002) to n = 330,9 (Han et al., 2020); predictor variables and outcome measures (Quinn et al., 2009): Oxford Handicap Scale score (Counsell et al., 2002), modified Rankin Scale (mRS) (Han et al., 2020; Quinn et al., 2017; Reid et al., 2010; Tilling et al., 2001; Wagle et al., 2011), Glasgow Outcome Scale (Johnston et al., 2000) and Barthel Index (BI) (Bohannon et al., 2002; Douiri et al., 2017; Wagle et al., 2011); follow-up time: ranging from 3 months (Johnston et al., 2000) to 13 months (Wagle et al., 2011); analytical methods and validation. This hampers comparison, however, although prospective in nature, all previous studies collected pre-stroke ADL and IADL retrospectively. This is inherent to a study design according to which patients are included after suffering a stroke. Hence, results can be susceptible to selection and recall bias. To

avoid this, subjects should be measured before having a stroke. This requires a fully prospective study with very large study sample and follow-up time in order to ensure a sufficiently high incidence of stroke survivors to allow for meaningful statistical analyses. The present PROSPER study allowed for that, most importantly, because a pre-selection of subjects with vascular risk factors was adopted. This study set-up does imply that subjects who suffered any vascular events, were excluded from participation in PROSPER, hence, the selection of stroke survivors may not be completely comparable with stroke patients encountered in clinical practise, who will to a certain extent have suffered from previous stroke and hence may have lower pre-event ADL and IADL scores. Two previous studies (Counsell et al., 2002; Douiri et al., 2017) included first ever stroke patients, with contradictive results with respect to predictive value of pre-stroke disability. Sample size of the presents study was well within the range of previous studies, median follow-up time of 18 months was longer. However, shifting the assessment as closely as possible to post-event timing, which is equivalent to 3–6 months follow-up, did not changes results. Concerning outcome measures, the present study used the BI which is well validated in stroke research. BI and IADL score are ordinal but non- hierarchical, which forces the use of a dichotomous approach (Lees et al., 2014). The presently used cut point of BI is in accordance with literature (Stroke Unit Trialists' Collaboration, 2007; Kwakkel et al., 2011), were found optimal and in concordance with low cut points for the modified Rankin Scale (mRS,Uytenboogaart et al., 2005, Sep) and in agreement with estimated smallest detectable change (Bouwstra et al., 2019; Hsieh et al., 2007). Sensitivity of the IADL scale is demonstrated by the identification of predictors as age and especially follow-up time. Considering power, sample size falls within the range of previous studies finding associations between pre-stroke ADL and post-stroke ADL and outcome ADL (also compare with Kwakkel et al., 2011). Also note the statistically significant OR's in the MI group in this particular population with a larger group size but lower numbers of subjects with a post-event BI decline.

The BI is of clinical relevance considering its use for prediction and treatment planning in stroke care (Taylor-Rowan et al., 2018). A decline in function defined as a one-point loss on ALD/IADL scales may will work on a population level, but may fall short individual predictions due to measurement uncertainty. Minimal clinical important differences were estimated to range from 1.84 (Hsieh et al., 2007) to 3.6 points (Bouwstra et al., 2019). Repeated analyses in the stroke group with differences of 2 and 4 points did not affect our main conclusion that pre-event ADL does not predict post-event ADL, however, power issues may start to play a role due to low numbers of subjects. Therefore, results of the present study may not directly transfer to individual predictions of outcome.

In contrast to the stroke-group, in both the MI and the group without any incident vascular events, pre-event ADL was predictive for post-event ADL decline. Higher age and longer follow-up time (i.e. the time

Table 3

Baseline predictors (logistic regression analysis) of decrease in Barthel Index (BI) and Instrumental Activities of Daily Living (IADL) in subjects with incident stroke, myocardial infarction (MI) and no vascular events.

	Stroke (n = 230)				MI (n = 443)				No vascular events (n = 4336)			
	BI OR	95% CI	IADL OR	95% CI	BI OR	95% CI	IADL OR	95% CI	BI OR	95% CI	IADL OR	95% CI
Pre-event BI/IADL	1.00	0.83–1.20	1.07	0.94–1.23	0.83	0.70–0.98	0.87	0.78–0.97	0.85	0.78–0.92	0.87	0.83–0.92
Age	0.99	0.91–1.07	1.10	1.02–1.19	1.08	1.00–1.17	1.08	1.01–1.17	1.11	1.07–1.13	1.13	1.10–1.15
Female gender	1.71	0.94–3.13	1.56	0.87–2.82	1.08	0.61–1.90	1.36	0.82–2.25	1.76	1.45–2.15	1.57	1.33–1.87
Follow-up time	0.98	0.96–1.01	1.03	1.01–1.05	1.01	0.99–1.03	1.04	1.02–1.06	1.01	0.99–1.04	1.03	1.00–1.05
History of hypertension	0.53	0.26–1.04	0.79	0.41–1.53	0.99	0.55–1.79	1.24	0.72–2.11	1.20	0.96–1.50	0.98	0.81–1.19
History of diabetes mellitus	0.79	0.31–1.72	1.92	0.91–4.04	1.35	0.64–2.86	1.87	0.97–3.64	1.50	1.12–2.00	1.45	1.12–1.87
History of vascular disease	0.59	0.31–1.11	0.92	0.50–1.68	1.22	0.68–2.19	1.45	0.85–2.47	1.34	1.10–1.63	1.21	1.02–1.45
Current smoker	0.73	0.35–1.54	1.09	0.53–2.23	1.05	0.52–2.13	0.91	0.47–1.73	1.02	0.80–1.31	1.04	0.84–1.30
Treatment group	0.91	0.52–1.60	0.90	0.52–1.56	0.64	0.37–1.11	1.25	0.77–2.04	1.00	0.83–1.20	0.87	0.74–1.02

BI = Barthel Index; IADL = Instrumental Activities of Daily Living; OR = Odds ratio; 95% CI = 95% confidence interval. Significant OR's are in bold. *Models included the following covariates: treatment allocation, age, gender, history of diabetes, history of hypertension, history of any vascular disease, smoking status and follow-up time defined as time in months between pre-event assessment date and the date of the last study visit.

between pre-event and final measurement) associated with a higher risk of IADL decline in all three groups. This is indicative for the functional decline with time and age (Martin & Grotewiel, 2006). In the group without vascular events, female gender and a history of diabetes mellitus or vascular disease were also risk factors for a decline in both BI and IADL. Sex differences are known to play a role in vascular aging (Oneglia et al., 2020) and may also play a role via differences in muscular aging (Doherty, 2001). In the Framingham disability study, it was reported that cardiovascular risk factors may play a role in ADL decline even without overt cardiovascular disease (Pinsky et al., 1985). The present study suggests that in the stroke group, aforementioned decline is overruled by the direct consequences of the brain damage itself. This directly implies that the predictive value of pre-event ADL for post event ADL decline is limited, and should be used with caution for prognosis.

4.1. Study strengths and limitations

The prospective study design including a large number of community dwelling older subjects at risk for vascular disease allowed for minimizing selection and recall bias. Comparison of the stroke group with both a MI group and a group without vascular events, allowed for specific assessment of the effects of disease and time. As included subjects were 75 years or older and had a vascular risk profile; the present cohort may assumed to be valid for the average population at risk for stroke. Study subjects were functioning at a fairly high level; especially for this group, prognosis for returning to the community is very relevant. Widely used and well validated ADL/IADL scales were used, however, limitations in especially concerning inherent measurement inaccuracies prevent from translation of study results to individual predictions. Detailed descriptions of stroke type and their management were not available within PROSPER; variance and bias induced by the latter is expected low with respect to spontaneous neurological recovery post stroke (Kwakkel et al., 2006). Comorbidity only encompassed history of diabetes, history of hypertension and history of any vascular disease. Difference in group sizes between stroke, MI and the group without vascular events may have affected study power. Inclusion of survivors only, may have biased results as deceased subjects were ignored.

5. Conclusions

In the present prospective cohort of community dwelling older subjects with vascular disease or risk factors, activities of daily living as assessed by Barthel Index (BI) and Instrumented Activity of daily living (IADL) score did not predict ADL score after incident stroke survivors in contrast to subjects with incident myocardial infarction and subjects not experiencing any vascular events during study follow-up of nearly 40 months on average. The results of this study in subjects with relatively high initial ADL scores, question the use of pre-event ADL in prognosis and determination of optimal discharge location.

CRediT authorship contribution statement

Annetje M. de Rooij: Writing – original draft, Formal analysis. **Andrea B. Maier:** Writing – review & editing, Supervision, Conceptualization. **Stella Trompet:** Writing – review & editing, Supervision, Project administration. **Carel G.M. Meskers:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The Author(s) declare(s) that there is no conflict of interest. AMR designed the research, performed statistical analyses and drafted the article. ABM and CGM supervised the project, designed the study and drafted the article. ST made critical revisions to the article. Data collection was performed by the PROSPER group.

Data availability

Data of the PROSPER study are available upon request to the PROSPER review board, contact Dr S. Trompet, Department of Internal Medicine, section of Gerontology and Geriatrics, Leiden University Medical centre, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands.

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