Stroke

CLINICAL AND POPULATION SCIENCES

Treatment Restrictions and the Risk of Death in Patients With Ischemic Stroke or Intracerebral Hemorrhage

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BACKGROUND AND PURPOSE: Do-not-resuscitate (DNR) orders in the first 24 hours after intracerebral hemorrhage have been associated with an increased risk of early death. This relationship is less certain for ischemic stroke. We assessed the relation between treatment restrictions and mortality in patients with ischemic stroke and in patients with intracerebral hemorrhage. We focused on the timing of treatment restrictions after admission and the type of treatment restriction (DNR order versus more restrictive care).

METHODS: We retrospectively assessed demographic and clinical data, timing and type of treatment restrictions, and vital status at 3 months for 622 consecutive stroke patients primarily admitted to a Dutch university hospital. We used a Cox regression model, with adjustment for age, sex, comorbidities, and stroke type and severity.

RESULTS: Treatment restrictions were installed in 226 (36%) patients, more frequently after intracerebral hemorrhage (51%) than after ischemic stroke (32%). In 187 patients (83%), these were installed in the first 24 hours. Treatment restrictions installed within the first 24 hours after hospital admission and those installed later were independently associated with death at 90 days (adjusted hazard ratios, 5.41 [95% CI, 3.17–9.22] and 5.36 [95% CI, 2.20–13.05], respectively). Statistically significant associations were also found in patients with ischemic stroke and in patients with just an early DNR order. In those who died, the median time between a DNR order and death was 520 hours (interquartile range, 53–737).

CONCLUSIONS: The strong relation between treatment restrictions (including DNR orders) and death and the long median time between a DNR order and death suggest that this relation may, in part, be causal, possibly due to an overall lack of aggressive care.

Key Words: infarction ■ mortality ■ resuscitation ■ stroke ■ survival analysis

In North American studies, treatment restrictions in the first 24 hours after intracerebral hemorrhage (ICH) have been associated with an increased risk of early death.[1–3] Avoidance of treatment restrictions during the first 5 days after ICH has been associated with a lower 30-day mortality rate than predicted.[4,5] In line with this, American guidelines for the management of ICH advocate aggressive therapy without any treatment restriction in the first days after hospitalization.[6]

However, many uncertainties about the association between treatment restrictions and mortality after stroke remain. First, it is uncertain whether this association is also present in patients with ischemic stroke. Second, the relation between the timing of treatment restrictions and death remains largely unknown. Few studies have investigated the relation between treatment restrictions installed after the first day and clinical outcomes.[7,8] Third, information on the relation between different

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The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.029788.

For Sources of Funding and Disclosures, see page 2689.

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Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
ANH	artificial nutrition and hydration
DNR	do not resuscitate
ICH	intracerebral hemorrhage
mRS	modified Rankin Scale

types of treatment restriction and clinical outcomes is limited.[8] Furthermore, only a small number of studies have assessed the frequency of treatment restrictions in patients with acute stroke in Europe,[9–12] which may be different from that in North America as a result of demographic or cultural differences.

We assessed the frequency and types of treatment restriction in patients with acute ischemic stroke or ICH admitted to the stroke unit of a university hospital in the Netherlands. We also assessed whether any association between treatment restrictions and the risk of death at 90 days is dependent on the timing of their installment.

METHODS

We retrospectively studied consecutive patients with acute ischemic stroke or ICH primarily admitted to the Stroke Unit of the University Medical Center in Utrecht, the Netherlands, between January 2016 and December 2018. Patients were excluded if the final diagnosis was transient ischemic attack, if they were referred from another hospital, or if they were admitted because of elective treatment (eg, carotid endarterectomy). In our center, all stroke patients (including those with ICH) are admitted to the stroke unit, unless mechanical ventilation is required. The study was evaluated by the Medical Ethics Committee of the hospital, and the need for informed consent was waived. To avoid the possibility of unintentionally sharing information that can be used to reidentify private information, individual patient data of this monocenter study will not be made available to other researchers. Methods used in the analysis, such as scripts for statistical packages, are available from the first author upon reasonable request.

Records of eligible patients were manually searched by one investigator (B.K.) and were checked by a second investigator in case of uncertainty (H.R.). Information about patient characteristics (age, sex, ethnicity, and prestroke modified Rankin Scale [mRS]), stroke characteristics (type of stroke, score on the National Institutes of Health Stroke Scale, and Glasgow Coma Scale on admission), and functional outcome (score on the mRS at discharge and at 90 days [±30 days] after stroke onset) was automatically extracted from the patient files and manually complemented with information from the discharge letters. If functional outcome at 90 days was not available, the latest known poststroke mRS score was used. Prestroke comorbidity was quantified according to the Charlson Comorbidity Index.[13]

The date and time of presentation in the hospital and date and time of the installment of treatment restrictions were retrieved from the hospital charts. We coded treatment restrictions as early (installed within 24 hours after hospital admission) or late (installed later). Treatment restrictions were categorized by type on the following ordinal scale: do-not-resuscitate (DNR) order, withhold admission to intensive care unit, withhold curative treatment of complications, and withhold artificial nutrition and hydration (ANH). In principle, treatment restrictions have no effect on patient monitoring, except for no-ANH orders, in which case measurements of vital signs are usually stopped. Whenever possible, the question whether a treatment restriction should be installed is discussed with every patient or the representative on admission to the stroke unit. Treatment restrictions are incremental (eg, a no-intensive-care-unit order is accompanied by a DNR order) and may be extended by the treating physician at any time during the hospital stay, after consultation with the patient or the representative.

For descriptive analyses, we compared the proportions of patients with a treatment restriction between patients with ischemic stroke and patients with ICH by the χ^2 test. In addition, we calculated the median and mean times between hospital admission and treatment restrictions and between treatment restrictions and death (if applicable) and used Kaplan-Meier curves to visualize survival.

The primary outcome was death at 90 days (±30 days). We used a time-to-event analysis and compared the survival time between patients with and those without treatment restrictions. To avoid the inclusion of patients who were already moribund on admission in the analyses of the relation between early treatment restrictions and death at 90 days, we used the date and time 24 hours after hospital admission as the start of survival time (t=0). As a consequence, patients who were already moribund at first presentation in the hospital and died within 24 hours were not included in this analysis, and only patients who survived the first 24 hours with a treatment restriction were compared with those who survived without a treatment restriction. We performed separate analyses for patients with ischemic stroke and for those with ICH and for the 4 types of treatment restriction present at t=0 separately.

To assess the effect of treatment restrictions installed later, we did separate analyses in which t=0 was moved to subsequent days after admission (48 hours, 72 hours, etc) up to 1 week (168 hours) and compared survival time in patients without treatment restrictions to patients with treatment restrictions present at t=0. In this analysis, the treatment restrictions present at t=0 could be a continuation of early treatment restrictions. In an additional analysis, we selected patients with treatment restrictions installed after 24 hours and compared these with patients without treatment restrictions. For all analysis of late treatment restrictions, we excluded patients who had orders to withhold artificial fluid and nutrition in place at t=0, as we considered these patients already moribund at this stage.

We used a Cox regression model, with adjustment for the following variables: age, sex, Charlson Comorbidity Index, type of stroke, National Institutes of Health Stroke Scale, and Glasgow Coma Scale (Eye+Motor score) at admission. Survival time was calculated from t=0 to the moment of death (if within 90 days). If patients survived, they were censored at the date of the final follow-up. If follow-up was missing, patients were censored at the latest known moment they were alive. We expressed associations as crude and adjusted hazard ratios (aHRs) with 95% CIs.

 Stroke. 2020;51:2683–2689. DOI: 10.1161/STROKEAHA.120.029788

RESULTS

Of 1198 patients screened, a total of 576 were excluded from the analysis (Figure I in the Data Supplement). Ninety-four patients were excluded because they were primarily admitted to the intensive care unit. Three-month follow-up was available for 93 of these patients (25 with ischemic stroke and 68 with ICH). Of the ischemic stroke patients, 11 (44%) had died and 6 (24%) had reached functional independence (mRS score 0–2). Of the ICH patients, 51 (75%) had died and 2 (3%) had reached a functional independent state.

Six hundred twenty-two patients fulfilled the inclusion criteria and were included in the main analyses. Treatment restrictions were installed in 226 patients (36%), and in 187 of these patients (83%), treatment restrictions were installed in the first 24 hours. In 43 patients, restrictions were extended during the course of the admission. Treatment restrictions were more prevalent in patients with ICH (51%) than in those with ischemic stroke (32%; $P<0.0001$). Patients with treatment restrictions were older, more often women, more often had prestroke handicap, and had more comorbidity and more severe stroke as illustrated by higher National Institutes of Health Stroke Scale and lower Glasgow Coma Scale scores on admission than patients without treatment restrictions (Table 1). The median time from admission to a DNR order was 3 hours (Table 2). In patients with ICH, 35 of 43 orders (81.4%) to withhold artificial hydration and nutrition were installed within the first 24 hours after hospital admission, versus 8 of 28 orders (28.6%) in patients with ischemic stroke (Table 2).

Twenty-nine patients (14%) with treatment restrictions reached functional independence (mRS score 0—2) at 90 days versus 248 (64%) patients without treatment restrictions (Figure 1). Patients with more extensive treatment restrictions had a higher risk of death and died earlier than those with a DNR order alone (Figure 2). In those who died after a DNR order, the median time between the order and death was 520 hours (Table 3). After installing a no-ANH order, the mean survival time was 52 hours, with 50% of the patients dying in the first 24 hours.

Thirty patients (5%; 4 with ischemic stroke and 26 with ICH) died within the first 24 hours after hospital admission. In 26 (87%) of these patients, death or poor prognosis was perceived imminent after evaluation in the

Table 1. Baseline Characteristics

	Overall (n=622)	Treatment Restriction (n=226)	No Treatment Restriction (n=396)	*P* Value
Ischemic stroke	477 (77%)	152 (67%)	325 (82%)	<0.001
Sex (male)	346 (56%)	100 (44%)	246 (62%)	<0.001
Ethnicity				0.225
White	570 (92%)	208 (92%)	362 (91%)	
Non-White	52 (8%)	18 (8%)	34 (9%)	
Age, y (mean+SD)	68.22 (15.78)	79.19 (9.30)	61.96 (15.30)	<0.001
Prestroke mRS				<0.001
0	276 (44%)	39 (17%)	237 (60%)	
1	88 (14%)	35 (15%)	53 (13%)	
2	95 (16%)	42 (19%)	53 (13%)	
3	73 (12%)	44 (19%)	29 (7%)	
4	45 (7%)	34 (15%)	11 (3%)	
5	5 (1%)	4 (2%)	1 (0.3%)	
Unknown	40 (6%)	28 (12%)	12 (3%)	
Prestroke CCI				<0.001
0	232 (37%)	64 (28%)	168 (42%)	
1	174 (28%)	64 (28%)	110 (28%)	
2	82 (13%)	35 (16%)	47 (12%)	
3	65 (10%)	28 (12%)	37 (9%)	
4	22 (4%)	9 (4%)	13 (3%)	
≥5	47 (8%)	26 (12%)	21 (5%)	
GCS (E+M) at admission (median+IQR)	10 (9–10)	10 (8–10)	10 (10–10)	<0.001
NIHSS at admission (median+IQR)	6 (3–13)	10 (5–18)	5 (2–10)	<0.001

CCI indicates Charlson Comorbidity Index; GCS (E+M), eyes and motor score on the Glasgow Coma Scale; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Table 2. Number and Timing of Treatment Restrictions

	n	Hours From Admission, Median (IQR)	<12 h of Hospital Admission	<24 h of Hospital Admission
All treatment restrictions (n=278)				
DNR	93	3 (2–17)	68 (73%)	76 (82%)
No ICU	94	6 (2–34)	56 (60%)	67 (71%)
No curative treatment	20	6 (2–220)	11 (55%)	11 (55%)
No ANH	71	4 (2–69)	40 (57%)	43 (61%)
Treatment restrictions in ICH patients (n=89)				
DNR	18	3 (2–17)	13 (72%)	15 (83%)
No ICU	21	21 (2–66)	9 (43%)	12 (57%)
No curative treatment	7	6 (2–222)	5 (71%)	5 (71%)
No ANH	43	3 (1–6)	35 (81%)	35 (81%)
Treatment restrictions in ischemic stroke patients (n=189)				
DNR	75	3 (1–17)	55 (73%)	61 (81%)
No ICU	73	5 (2–24)	47 (64%)	55 (75%)
No curative treatment	13	42 (2–220)	6 (46%)	6 (46%)
No ANH	28	55 (1–138)	5 (18%)	8 (29%)

Treatment restrictions are incremental, and only the most extended treatment restriction is shown (eg, no ICU order also includes a DNR order). ANH indicates artificial nutrition and hydration; DNR, do not resuscitate; ICH, intracerebral hemorrhage; ICU, intensive care unit; and IQR, interquartile range.

emergency department, and these patients had immediate withdrawal from any curative treatment. They either died in the emergency department or were admitted to the regular ward for end-of-life care. In those who survived the first day, the presence of any treatment restriction at 24 hours was independently associated with increased mortality at 90 days (aHR, 5.41 [95% CI, 3.17–9.22]), even when patients with no-ANH orders were excluded (aHR, 4.57 [95% CI, 2.62–7.99]; Table 4). Hazard ratios for mortality increased with more extensive treatment restrictions.

The presence of just a DNR order at 24 hours after hospital admission was independently associated with death at 90 days (aHR, 2.46 [95% CI, 1.23–4.92]; Table 4). Of the 72 patients with just a DNR order at 24 hours, 20 had died at 90 days follow-up. Of these, 9 were discharged alive, and relevant information about the causes of their deaths was not available. In the 11 patients who died during hospital admission, none of the deaths could realistically have been avoided by cardiopulmonary resuscitation. Rather, their death was preceded by a gradually deteriorating clinical condition (eg, respiratory insufficiency or progressive loss of consciousness).

In patients with ischemic stroke, all types of early treatment restriction were associated with an increased risk of death at 90 days. In patients with ICH, this association was statistically significant for any treatment restriction after adjusting for baseline confounders but not when no-ANH orders were excluded (Table 4). It should be noted that only 15 patients with ICH had a DNR order only at 24 hours, which is too few to draw conclusions.

We found similar effect sizes when we moved t=0 to subsequent days in the first week after hospital submission (Table I in the Data Supplement). Effect sizes were comparable when we only considered patients with

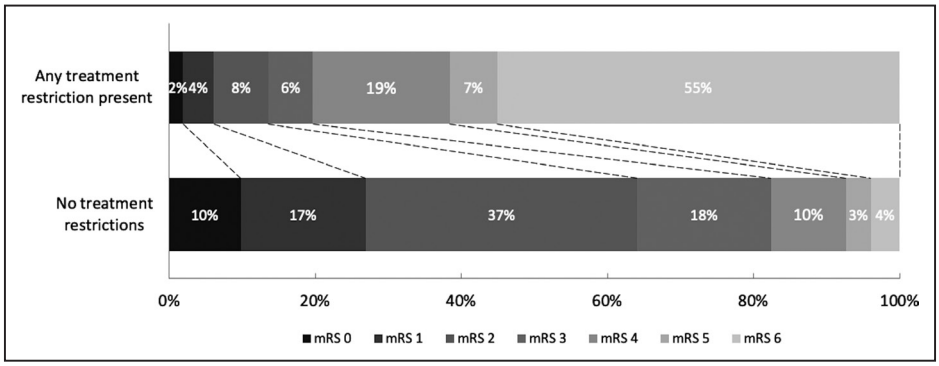

Figure 1. Distribution of score on the modified Rankin Scale (mRS) at 90 d in patients with any treatment restriction present vs no treatment restriction during the entire hospital stay.
Patients with orders to withhold artificial fluids and nutrition are excluded.

 Stroke. 2020;51:2683–2689. DOI: 10.1161/STROKEAHA.120.029788

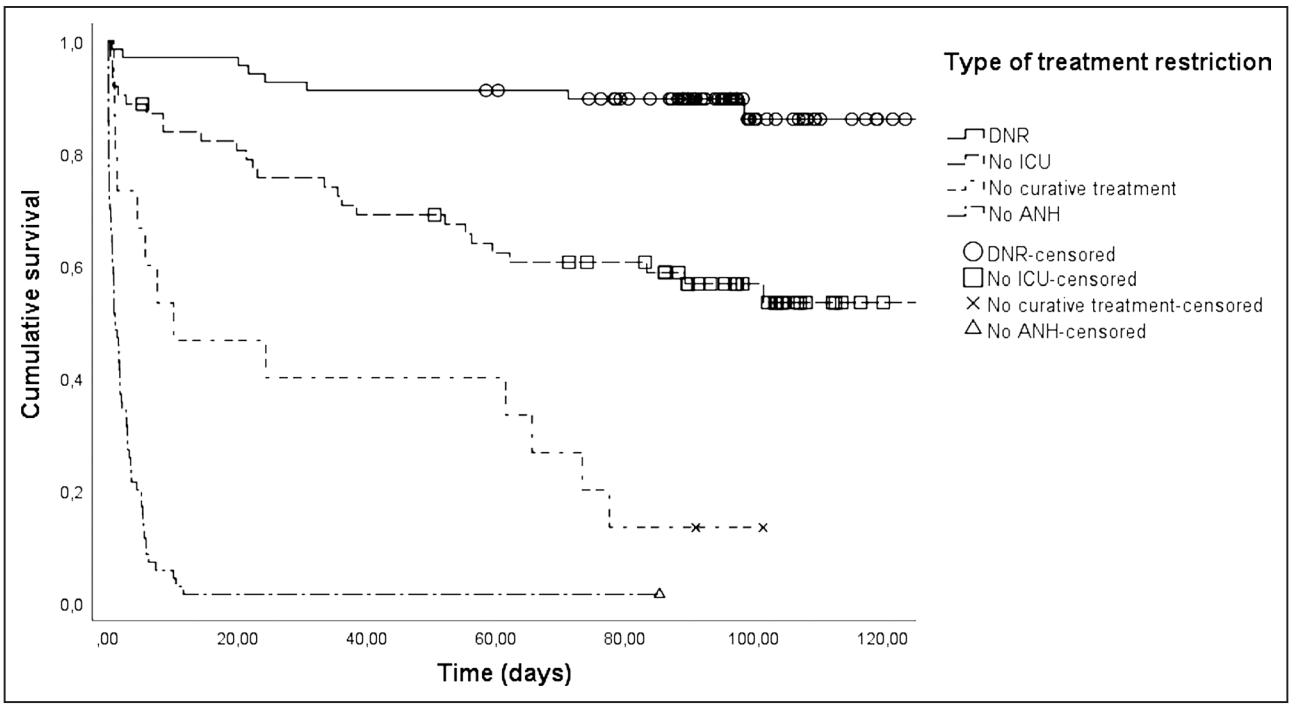

Figure 2. Kaplan-Meijer survival curve for patient with different types of treatment restrictions.
t=0 is the moment of installment of the treatment restriction. In patients with multiple treatment restrictions during hospital admission, only the latest treatment restriction was used. ANH indicates artificial nutrition and hydration; DNR, do not resuscitate; and ICU, intensive care unit.

treatment restrictions installed later than 24 hours (aHR, 5.36 [95% CI, 2.20–13.05]). For late treatment restrictions, patient numbers were too small to perform subgroup analyses based on the type of stroke.

DISCUSSION

In this study, at a stroke unit of a university medical center in the Netherlands, about one-third of the patients admitted with ischemic stroke or ICH had a treatment restriction installed during hospital admission. Having any treatment restriction was independently associated with an increased risk of death at 90 days. The large majority of patients with a DNR or no-intensive-care-unit order survived up to 90 days, and in those who died, the median time from their installment to death was about 3 weeks, demonstrating that these orders were not only placed in patients in whom death was already imminent.

The prevalence of treatment restrictions in our cohort was comparable to that in a study in stroke patients in the United Kingdom (34%),[10] and the prevalence in patients with ICH was comparable to that in an American study (45%)[1] but different from those in Finnish (35.5%)[9] and Chinese studies (8.4%).[14] This may be explained by geographic or cultural differences but also by the use of different definitions of treatment restrictions.

No earlier study has assessed the association between early treatment restrictions and the risk of death in patients with ischemic stroke alone. In these patients, we found that all types of early treatment restriction (even just the installment of a DNR order) were associated with an increased risk of death at 90 days. Not surprisingly, the relation appeared to become stronger with more extensive restrictions. Previous studies focused on the association between treatment restrictions and mortality after ICH. In contrast to these studies,[1,2,12] we found no statistically significant relation

Table 3. Survival Time (Hours) in Patients With Treatment Restrictions Who Died Within 90 Days

	Median (IQR)	Mean (SD)	Minimum	Maximum
All patients				
DNR	520 (53–737)	808 (289)	13	2363
No ICU	537 (66–1327)	741 (138)	8	2435
No curative treatment	182 (33–1477)	618 (208)	21	1862
No ANH	24 (3–78)	52 (8)	0	279

Treatment restrictions are incremental. In patients with multiple treatment restrictions during hospital admission, only the latest treatment restriction was used. ANH indicates artificial nutrition and hydration; DNR, do not resuscitate; ICU, intensive care unit; and IQR, interquartile range.

Table 4. Effect of Stroke Type and Extent of Treatment Restrictions on the Association Between Early Treatment Restrictions (<24 h) and Death at 90 Days

	Death at 90 d		Hazard Ratio (95% CI)	
	Treatment Restriction	No Treatment Restriction	Crude	Adjusted
Full cohort (n=592)				
Any treatment restriction	74/158 (47%)	29/434 (7%)	10.14 (6.58–15.61)	5.41 (3.17–9.22)
DNR+no ICU+no curative treatment	56/140 (40%)	29/434 (7%)	8.15 (5.20–12.79)	4.57 (2.62–7.99)
DNR+no ICU	48/130 (37%)	29/434 (7%)	7.26 (4.57–11.52)	4.10 (2.32–7.26)
DNR	20/72 (28%)	29/434 (7%)	5.05 (2.85–8.93)	2.46 (1.23–4.92)
Ischemic stroke (n=473)				
Any treatment restriction	49/118 (42%)	22/355 (6%)	9.28 (5.59–15.38)	6.59 (3.55–12.22)
DNR+no ICU+no curative treatment	42/111 (38%)	22/355 (6%)	8.20 (4.89–13.77)	6.01 (3.17–11.39)
DNR+no ICU	39/106 (37%)	22/355 (6%)	7.81 (4.62–13.19)	5.63 (2.95–10.73)
DNR	16/57 (28%)	22/355 (6%)	5.56 (2.91–10.59)	3.93 (1.80–8.59)
ICH (n=119)				
Any treatment restriction	25/40 (63%)	7/79 (9%)	11.92 (5.12–27.77)	3.79 (1.16–12.34)
DNR+no ICU+no curative treatment	14/29 (48%)	7/79 (9%)	7.92 (3.19–19.71)	1.50 (0.37–6.17)
DNR+no ICU	9/24 (38%)	7/79 (9%)	5.55 (2.06–14.94)	0.71 (0.13–3.77)
DNR	4/15 (27%)	7/79 (9%)	3.48 (1.02–11.91)	0.17 (0.014–2.08)

Patients who died <24 h are excluded (n=30 for full cohort). Hazard ratios are adjusted for age, sex, CCI, Comorbidity Index, NIHSS at admission, GCS at admission, at stroke type (if applicable). CCI indicates Charlson Comorbidity Index, DNR, do not resuscitate; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; ICU, intensive care unit; and NIHSS, National Institutes of Health Stroke Scale.

between treatment restrictions and mortality at 90 days in ICH patients after adjusting for baseline prognostic factors and when patients with an order to withhold artificial administration of fluids and nutrition were excluded. This may be due to the limited number of patients, in part, caused by the exclusion of patients who died within the first 24 hours of admission.

In addition, most previous studies have only assessed the association between treatment restrictions installed in the first day after hospital admission and mortality at 90 days. We found that this association was comparable for treatment restrictions installed later during the first week after hospital admission. One older cohort study reported increasing in-hospital mortality rates for each successive day on which a DNR order was written during the first 7 days after admission.[7] However, this study did not use a time-to-event analysis, and the increasing mortality rates and effect sizes per day suggest that patients who had died on previous days were still included in the analysis of the consecutive days.

As treatment restrictions are likely to serve as a marker for adverse prognostic factors, we were not surprised to find that functional outcome was worse and survival time was shorter in patients with more extensive treatment restrictions. However, the strong and consistent relationship between the presence of treatment restrictions and death found in our and in previous studies after correcting for important prognostic factors, even when considering only a DNR order, remains remarkable.[1–3,7,15] Our finding that about one-third of patients with a DNR order were functionally independent at 90 days demonstrates that these orders are not exclusively installed in patients with a poor prognosis, and the long survival time in those who died after a DNR order suggests that their installment is not just a preterminal measure in moribund patients. In addition, a previous study that stratified stroke patients by prognostic factors found that the impact of a DNR order on mortality was greatest among patients with a more favorable outcome.[7] In our view, this suggests that the relationship between a DNR order and death may, in part, be causal.

There are several possible other explanations for higher mortality rates in patients with treatment restrictions. Even though we adjusted for prognostic variables, important but unknown confounders for the relationship between treatment restrictions and death may not have been captured. Moreover, treatment restrictions might be a reflection of patient's advanced wishes or family preference to refrain from life-prolonging interventions after a disabling stroke. Unfortunately, we could not use information about advance directives in our analysis, as this is not systematically collected in our stroke database or specifically documented in the hospital charts. However, advance directives are infrequent in the Netherlands: it has been estimated that around 7% of the general population has an advance directive.[16] In addition, a previous study in the Netherlands reported that around 2% of the patients with severe stroke admitted to the stroke unit had a treatment restriction in place before admission.[17]

It has also been suggested that treatment restrictions might be a proxy for overall lack of optimal care, creating a ripple effect with restrictions leading to an overall

 Stroke. 2020;51:2683–2689. DOI: 10.1161/STROKEAHA.120.029788

milieu of nihilism that may influence attitudes of care for patients beyond the DNR orders themselves.[18] Previous studies have demonstrated that patients with intracerebral hemorrhage[9] or ischemic stroke[10] who have a DNR order are less likely to be treated on a stroke unit or by specialist teams and, therefore, may indeed receive less optimal care. There is a potential risk of self-fulfilling prophecies if patients predicted to have a poor outcome have early limitations in care or withdrawal of support and subsequently die.[19,20] It has been emphasized that clinicians should be aware of the limited accuracy of models predicting outcomes after ischemic stroke or ICH and on the potential impact of subsequent early treatment restrictions on the overall aggressiveness of care.[21]

The results of our study should raise further awareness of the potential of an increased risk of death as an undesired side effect of treatment restrictions installed in the early phase after stroke and highlight the importance of avoiding limitations in care beyond that of the treatment restriction itself.

ARTICLE INFORMATION

Received March 13, 2020; final revision received June 26, 2020; accepted July 6, 2020.

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Acknowledgments

We would like to thank Berber Zweedijk, research nurse, for maintaining the University Medical Center Utrecht stroke database and for extracting the data needed for our study.

Sources of Funding

None.

Disclosures

Dr Reinink is supported by the European Union Horizon 2020 research and innovation program (grant agreement No. 634809) as a collaborator of the PRECIOUS trial (Prevention of Complications to Improve Outcome in Elderly Patients With Acute Stroke). Dr van der Worp served as a consultant to Bayer, Boehringer Ingelheim, and LivaNova. The other authors report no conflicts.

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